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Formal Intramolecular (4 + 1)-Cycloaddition of Dialkoxycarbenes: Control of the Stereoselectivity and a Mechanistic Portrait

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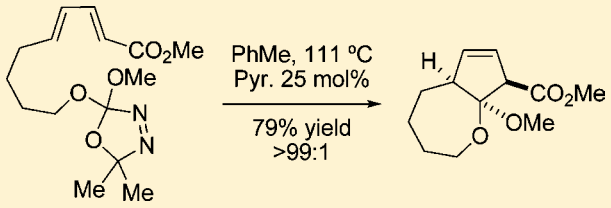
Supporting Information

ABSTRACT: The stereoselective synthesis of 5−5, 6−5, and 7−5 fused *O*-heterocyclic compounds is reported. The key reaction is a formal intramolecular (4 + 1)-cycloaddition involving a dialkoxycarbene and an electron-deficient diene where the stereoselectivity is dependent on the length of the tether. An analysis of the stereochemical outcome of this reaction sheds light on its complex mechanistic picture. High-level calculations were used to support the proposed mechanistic portrait.



INTRODUCTION

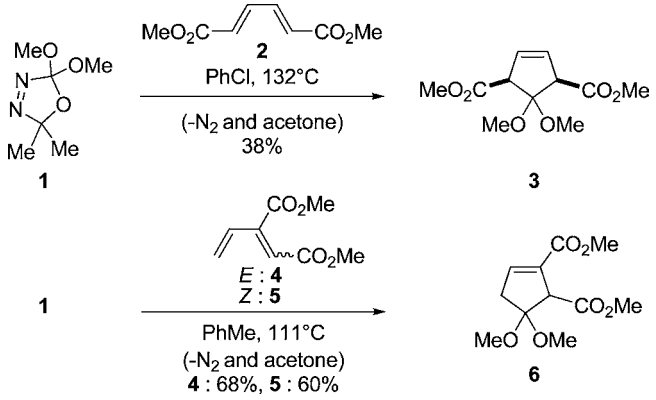
Since the discovery of the Diels−Alder reaction in 1928,[1] the [4 + 2]-cycloaddition has gained tremendous popularity among synthetic chemists because it gives rise to complex six-membered carbo- or heterocycles from structurally simpler starting materials by the direct formation of two C−C bonds with control of up to four stereocenters.[2] Its reliability and the easy prediction of its structural and stereochemical outcome have helped make this reaction an essential tool in organic synthesis.

Like its six-membered ring counterpart, the concerted (4 + 1)-cycloaddition[3] between a carbene and a diene is a cheletropic reaction allowed by the frontier molecular orbitals theory.[4] In principle, this reaction enables the stereoselective synthesis of cyclopentene derivatives with control of up to three stereocenters. In practice, however, examples of concerted (4 + 1)-cycloadditions are very scarce in the literature and are not general, usually involving one pair of a particular carbene and diene.[5] The high and sometime unusual reactivity[6] of free carbenes may explain why this transformation has been little exploited in the field of organic chemistry. Another reason is the difficulty in controlling the chemoselectivity of carbenes for the cycloaddition reaction, particularly given their known propensity to preferentially give cyclopropane products instead of (4 + 1)-cycloadducts when reacting with 1,3-dienes.[7−9] Fisher carbene complexes give mostly cyclopropanation products with electron-poor dienes.[10] Given the ubiquity of five-membered rings in natural and pharmaceutical products,[11] synthetic chemists have dedicated much attention toward developing alternative methodologies to circumvent the important limitations of the concerted (4 + 1)-cycloaddition, namely, the poor yields of cycloadducts obtained and the low tolerance of the carbene for spectator functional groups.[5]

Among the alternative methods, the cyclopropanation of 1,3-dienes followed by a vinylcyclopropane rearrangement emerged as one of the most effective formal (4 + 1)-annulation strategies. By using to their advantage the apparent predilection of carbenes for cyclopropanation of 1,3-diene over the (4 + 1)-cycloaddition, Hudlicky,[12] Danheiser,[13] and others set the foundation for the stereoselective synthesis of cyclopentenes.[14] The incorporation of one carbon unit such as carbon monoxide,[15] isocyanides,[16] diazomethane,[17] ylides,[18] various carbenoids,[19] or nucleophilic carbenes[6f,8,20,21] into 1,3-dienes have equally met with some degree of success to yield (4 + 1)-cycloadducts in good yields.

Using Warkentin's 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines as a source of dialkoxycarbenes,[22] our research group reported the discovery of a (4 + 1)-annulation that demonstrated the ability of nucleophilic carbenes to stereoselectively add to electron-deficient dienes, either intermolecularly or intramolecularly.[8,20] The intermolecular version gave modest yields and worked best when the diene was activated by the presence of two electron-withdrawing groups (Scheme 1).

Scheme 1. Examples of Stereoselective Intermolecular (4 + 1)-Cycloadditions



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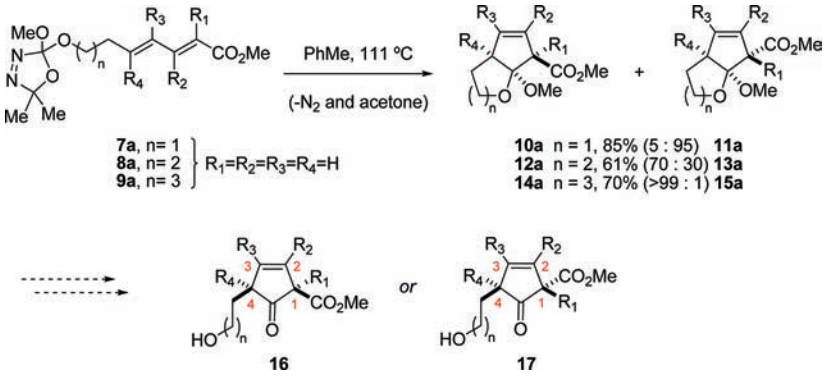
Scheme 2. Examples of Stereoselective Intramolecular (4 + 1)-Cycloadditions



The intramolecular reaction proved far more promising, affording good to high yields of bicyclic *O*-heterocycles **10a**–**15a** and showing good potential for the efficient synthesis of 3-cyclopenten-1-ones **16** or **17**, where the stereoselectivity at the 1- and 4-positions is controlled by the length of the tether (Scheme 2).

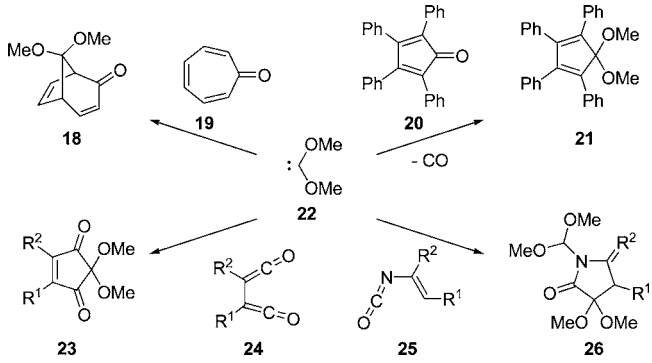
We report herein an in-depth study of the scope and mechanism of this unique intramolecular (4 + 1)-cycloaddition involving dialkoxycarbenes and electron-deficient dienes. Our study encompasses a wide range of parameters that were varied with the aim of acquiring knowledge on the generality, usefulness, and stereochemical predictability of the reaction. The observed stereoselectivities and the proposed mechanistic picture of the (4 + 1)-cycloaddition were also supported by computational calculations.

The most striking aspect of the reactions shown in Scheme 2 was the complete reversal of stereoselectivity observed in going from the 5–5 (**10a**:**11a** = 5:95) to the 7–5 fused bicyclic system (**14a**:**15a** = >99:1), with the 6–5 fused bicyclic system (**12a**:**13a** = 70:30) being an intermediate case. Clearly, we needed to better understand the reasons behind this behavior in order to better predict the stereochemical outcome of the reaction. Although we had suggested in a previous publication that a change in mechanism could be at the origin of this selectivity reversal,[8] the present study provides mechanistic insights that speak to the contrary.

Generation and Prior (4 + 1)-Cycloadditions of Dialkoxycarbenes. Since the first use of dimethoxycarbene (DMC) **22** by Hoffman and co-workers in the 1960s,[23] dialkoxycarbenes have been known to act as nucleophiles and to react with various electrophiles such as carbonylated compounds (anhydrides, acyl chlorides, ketones, esters, ketenes, and isocyanates), thiocarbonyles, and imines and with various alkenes, alkynes, and cumulenes.[22,24] Few formal (4 + 1)-cycloadditions with DMC have been reported and involve tropone **19** or tetraphenylcyclopentenedione **20**,[25] substituted bis-ketenes **24**,[26] and vinylisocyanates **25** (Scheme 3).[27] Yet, carbene **22** gave cyclopropane derivatives in low yield when reacted with 1-phenyl- or 1,1-diphenyl-1,3-butadiene.[25]

Fundamental studies and synthetic applications of dialkoxycarbenes have been constrained for a long time by the difficulty in generating them. The thermolysis of norbornadiene derivatives[28] or the thermolysis or photolysis of 3,3-dialkoxydiazirines[29] proved problematic, either because they produce large amounts of byproduct or because they are known to be explosive. Furthermore, the synthesis of these carbene precursors is not

Scheme 3. Formal (4 + 1)-Cycloadditions of Dimethoxycarbene



trivial. Warkentin's oxadiazolines, such as **1** or **7a**–**9a**, have greatly simplified this task for the generation of dialkoxycarbenes: they are easily prepared from simple precursors (*vide infra*) and produce only volatile and innocuous byproduct (N_2 and acetone).[22] Moreover, the nature of the oxadiazoline can be easily changed to alter the thermolysis temperature.[30]

To illustrate how oxadiazolines are easily prepared, a typical example is given in Scheme 4. In the presence of a catalytic amount of acid, primary alcohols will substitute the acetate on **29** in good yield, as was the case of alcohols **27** and **28**, affording the corresponding oxadiazoline in 87% and 90% yields, respectively. Besides being a reliable source of the dialkoxycarbene, the oxadiazoline also proved to be a tolerant functional group. It withstands temperatures of up to 80–85 °C and is unreactive toward many nucleophilic or basic reagents. For more details on the complete synthesis of all precursors, see the Supporting Information.

■ RESULTS AND DISCUSSION

Dienes tethered to the oxadiazoline moiety with a three-carbon chain (**8**) gave 6–5 bicyclic products **12** and **13** upon thermolysis (cf. Scheme 2). They were the starting point of our investigation on the effect of the nature and length of the tether on the stereochemical outcome of the reaction. We first revisited the thermolysis of diene **8a** in more details because its moderate diastereoselectivity contrasted with the high stereoselectivities obtained with the two- and the four-carbon tethered dienes **7a** and **9a**, respectively.[20] Note that in all observed products **10a**–**15a** the relative stereochemistry of the ring fusion is *cis*.[31]

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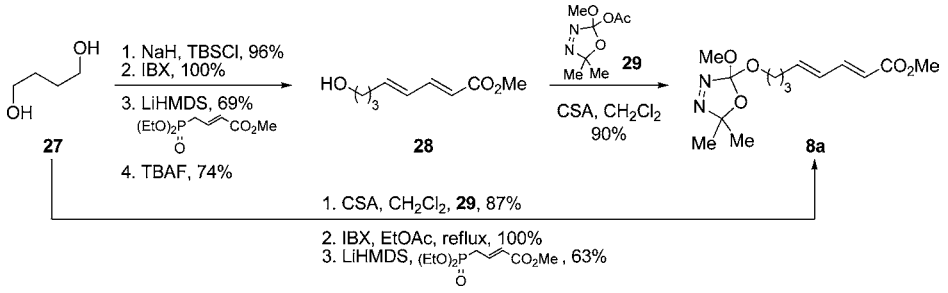
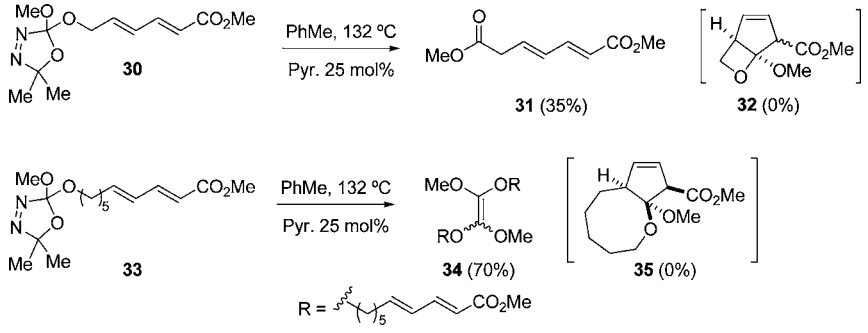
Scheme 4. Typical Preparation of a Cycloadduct Precursor



Scheme 5. Attempted Formation of Oxabicyclic Compounds 32 and 35



After careful re-examination of the reaction conditions, cycloadducts **12a** and **13a** were obtained with a significant increase in yield and a slight increase in ratio using pyridine as an additive (84% vs 61%, **14a**:**15a** = 70:30 vs 75:25). These reaction conditions also gave higher yields for the 5−5 (86% vs 85%, **10a**:**11a** = 5:95) and the 7−5 oxabicyclic compounds (79% vs 70%, **14a**:**15a** = >99:1).

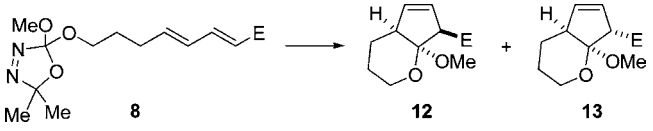
The (4 + 1)-cycloaddition could not be extended to the formation of 4−5 or 8−5 oxabicyclic compounds (Scheme 5). Thermolysis of diene **30** failed to give any of the desired product **32** and gave ester **31** as the only identifiable product in 35% yield.[32f]

The formation of the unstable dimer **34** (70%[33]) in the case of diene **33** (Scheme 5) is somewhat surprising in light of the efficiency and yield with which the 7−5 bicyclic compound **14a** was formed. Entropy is probably to blame for this difference, but we were nevertheless expecting at least some product **35** to be formed given that even intermolecular reactions give 20−65% of the desired cycloadducts.[8,20]

Remarkably, many activating groups proved to be compatible with the high reactivity of dialkoxycarbenes as shown by the good yields of the expected (4 + 1)-cycloadducts obtained upon thermolysis of dienes **8a**−**h** (Table 1, entries 1−5 and 8). The conversion of aldehyde **8d** into products **12d** and **13d** was excellent (Table 1, entry 4), though their isolated yields were low due to their instability. Compounds **12d** and **13d** easily shed methanol to give cyclopentadiene **36** (Figure 1).

The only low-yielding (4 + 1)-cycloaddition resulting from the thermolysis of nitrodiene **8f** (Table 1, entry 6) was likely due to the acidity of the allylic protons[34] coupled with the basicity of the carbene (estimated pK_a values for dimethoxycarbene = 11−16).[35] This gives rise to competing acid−base reactions.[36] We were unable to identify any specific insertion products in the present case, but we had shown in the past that dimethoxycarbene inserts into the acidic proton of nitromethane.[37]

Table 1. Effect of the Nature of the Electron-Withdrawing Group on the Intramolecular (4 + 1)-Cycloaddition



Entry	Diene **8**	E	Conditions[a]	Yield of **12**+**13** (%)[b]	Ratio **12**:**13**[c]
1	**8a**	CO_2Me	A	84	75:25
2	**8b**	SO_2Ph	A	79	91:9
3	**8c**	CN	A	77	82:18
4	**8d**	CHO	C	49[d] (85[e])	60:40
5	**8e**		A	74	67:33
6	**8f**	NO_2	A	23	63:37
7	**8g**	$CONEt_2$	B	44[f]	58:42
8	**8h**	CF_3	C	46 (>70[e])	92:8

[a]All reactions were performed on 0.25−0.50 mmol scale at 0.01−0.04 M with 25 mol % of pyridine. Condition A: PhMe, 111 °C, 20 h. Condition B: PhCl, 132 °C, 5 h. Condition C: PhMe, 160 °C (sealed tube) 15 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Product **36** was also isolated in 12% yield after flash chromatography [e]Conversion determined by ^{1}H NMR spectroscopy. [f]Product **37** was also obtained in 17% proportion as measured from the ^{1}H NMR of the crude reaction mixture.

The transient dialkoxycarbene generated from the thermolysis of amide **8g** led to a complex mixture of compounds, of which **12g** and **13g** were isolated in moderate yield (Table 1, entry 7). Surprisingly, product **37** (Figure 1) was observed in

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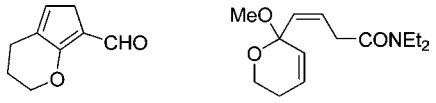


36 37

Figure 1. Side products resulting from the thermolysis of dienes **8d** and **8g**.

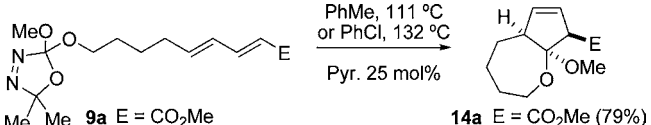
significant amounts (17%[33]).[38] The *Z* configuration of the acyclic double bond in **37** was established from the observed coupling constant between the olefinic protons (11.5 Hz). At this point, it is hard to explain the difference in reactivity of amide **8g** compared to ester **8a**, but it seems that amides are in general a poor choice of activating group for this cycloaddition.[39]

The volatility of **12h** and **13h** is thought to be in part responsible for the loss in yield of the thermolysis of trifluoromethyl-substituted diene **8h** (Table 1, entry 8).[40] Its conversion was judged to be much higher by ^{1}H NMR. The high observed stereoselectivity illustrates the potential of inductivity-based (as opposed to resonance-based) electron-withdrawing groups to activate a diene moiety toward cycloaddition with a nucleophilic carbene. Given the increasing importance and impact of fluorinated compounds in the pharmaceutical, agrochemical, and materials industries,[41] the (4 + 1)-cycloaddition may prove useful to diastereoselectively install a trifluoromethyl group on a five-membered ring.

From all of the cases shown in Table 1, a trend emerges: the stronger the electron-withdrawing group on the diene, the lower the diastereoselectivity (resonance-based electron-withdrawing ability: CF_3 < SO_2Ph/CN < $CONEt_2$/CO_2Me < RCOR < RCHO < RNO_2). The trifluoromethyl group is the least capable of stabilizing a negative charge and gives the highest diastereoselectivity, while modest selectivities are obtained with the aldehyde and nitro functionalities.

By contrast, the stereoselectivity of reactions leading to 7−5 bicyclic compounds remained unaffected by the variation of the nature of the electron-withdrawing group. Using optimized reaction conditions, all carbene precursors shown in Scheme 6 nicely gave >95% of **14a−c** as single diastereomers.

Scheme 6. Effect of the Nature of the Diene's Electron-Withdrawing Group on 7−5 Bicyclic Systems

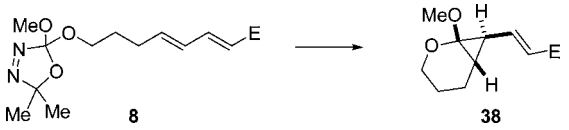


9a E = CO_2Me
9b E = SO_2Ph
9c E = CN

14a E = CO_2Me (79%)
14b E = SO_2Ph (54%)
14c E = CN (79%)

That at least one electron-withdrawing group is required for the (4 + 1)-cycloaddition to proceed was also unambiguously established. When electronically unactivated diene **8i** was thermolyzed, cyclopropane **38i** was isolated in 81% yield. Interestingly, at lower temperature, dienes **8g−h** led to the formation of isolable bicyclic cyclopropanes **38g−h** (Table 2, entries 1−2). Inspired by the work of Carboni, Carreaux, and Hall,[42] we thought that a successful cycloaddition reaction of **8j** would have led to a (4 + 1)-cycloadduct bearing an allylic boronic ester that could further participate in allylboration of

Table 2. Formation of Cyclopropanes 38g−j from Dienes 8g−j



8 **38**

Entry	Diene **8**	E	Conditions[a]	Yield of **38** (%)
1	**8g**	$CONEt_2$	A	68[b]
2	**8h**	CF_3	A	63[c]
3	**8i**	$CH_2OTBDPS$	B	81[c]
4	**8j**		A	78[b]

[a]All reactions were performed on 0.25−0.50 mmol scale at 0.01−0.04 M with 25 mol % of pyridine. Condition A: toluene, 111 °C, 20 h. Condition B: PhCl, 132 °C, 5 h. [b]Conversion determined by ^{1}H NMR spectroscopy. Any attempts of purification resulted in complete degradation of the product. [c]After flash chromatography on silica gel.

carbonyl compounds. However, thermolysis of diene **8j** afforded only cyclopropane **38j**. Note that heating either **38i** or **38j** to 160 °C did not lead to any amount of the corresponding (4 + 1)-cycloadducts.

Moving the electron-withdrawing group to the 2-position (dienes **39** and **41**) led surprisingly to the sole formation of 5−3 and 6−3 bicyclic compounds **40**[33] and **42** as single diastereomers in excellent yields (Scheme 7). However, lengthening the tether (diene **43**) afforded a 6% yield of (4 + 1)-cycloadduct **45** along with cyclopropane **44**. It should be noted that the *trans*-fusion between the seven- and five-membered rings in compound **45** is observed for the first time after dozens of cycloadditions we have carried out. The implication of the observed stereoselectivity will be discussed in the mechanistic section of the paper.

Cyclopropanes **38g−j**, **40**, **42**, and **44** are relatively stable compounds, interesting both from a structure and reactivity standpoint.[43] This intramolecular process could provide a new efficient way to construct dialkoxyvinylcyclopropanes that would subsequently undergo vinylcyclopropane-cyclopentene rearrangements (to give formally (4 + 1)-cycloadducts),[14l,44] [5 + 2] cycloadditions,[45] radical-mediated ring-opening reactions,[46] and a host of other reactions that we will investigate in due course.

Transposing the electron-withdrawing group at the 3-position of the diene had a profound effect on the stereochemical results (Scheme 8). First, cycloadducts **47** and **49** were obtained in good yields with complete stereoselectivity starting from dienes **46** and **48**, respectively. While the isolation of a single diastereomer **47** was consistent with the stereochemical outcomes shown in Scheme 2 (1-substituted diene **7a**), the isolation of **49** as the only adduct was quite stunning in two respects: a mixture of isomers was anticipated, and diastereomer **49** was expected to be a minor product.

Thermolysis of diene **50** led to the formation of three compounds, which we identified as cycloadducts **51a**, **51b**, and **52**, in 20%, 34%, and 17% yields, respectively (Scheme 8).

Higher structural complexity is always desirable, and it is of synthetic relevance that chiral quaternary carbon centers could be created on the cyclopentene scaffold with stereoselectivities superior to the analogue **8a**. We were delighted to find that thermolysis of **53** resulted in the formation of the

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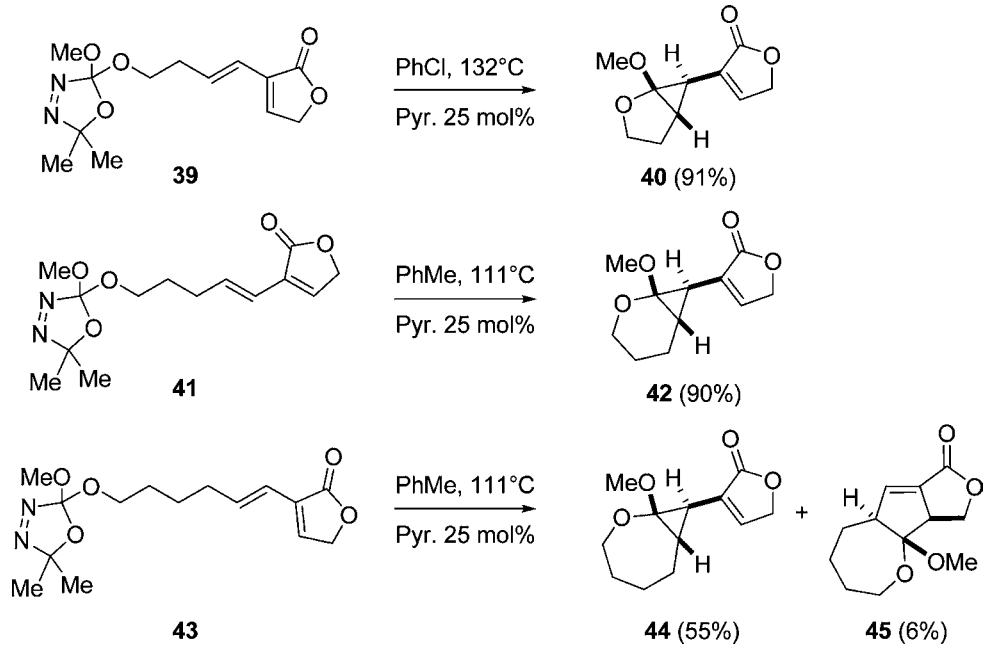
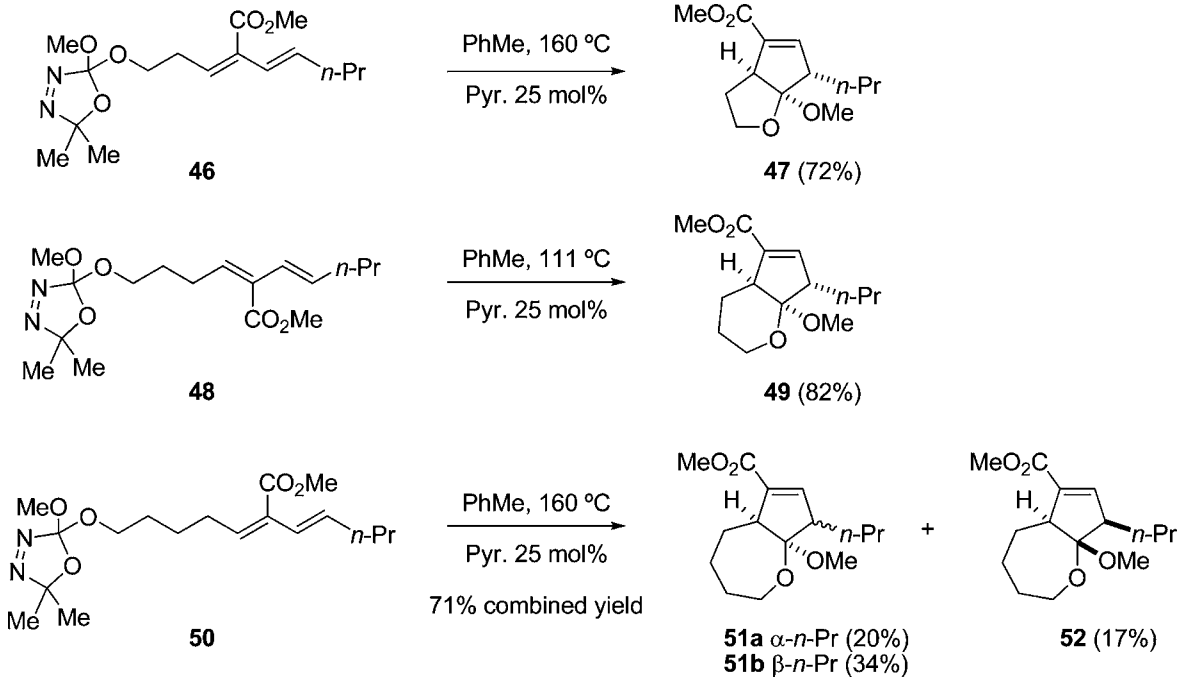
Scheme 7. Thermolysis of 39, 41, and 43, Having an Electron-Withdrawing Group at the 2-Position



Scheme 8. Thermolysis of 46, 48, and 50, Having an Electron-Withdrawing Group at the 3-Position



corresponding cycloadducts **54** and **55** in decent yield and in a ratio of 81:19 (Scheme 9). We were also excited, despite a moderate 44% yield, about the highly stereoselective formation of **57** from oxadiazoline **56**. In addition, the corresponding cyclopropane **59** was isolated in 12% yield as a 70:30 mixture of stereoisomers at C-3. As depicted in scheme 9, the temperature required to accomplishing the (4 + 1)-annulation depends on the position of the methyl group.

Mechanistic Studies. Mechanistic studies of this (4 + 1)-cycloaddition is unfortunately complicated by the fact that the rate-determining step is the ring opening of the 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline **60** in the generation of carbene **61** (Scheme 10).[47] Once generated, the highly reactive singlet[48] carbene **61** reacts immediately with the diene moiety, one way or another, to eventually lead to the formation of the (4 + 1)-cycloadducts **62**. The concentration of the free carbene during the thermolysis is thus likely to be low.

We elected to use stereochemistry as a probe to gain mechanistic insights on this reaction. We are well aware that the stereochemistry of the product cannot be used to draw a complete picture of the mechanism of the transformation of **61** into **62**. However, coupled with evidence of the presence or the absence of key intermediates, it can help answer questions about the concertedness of bond-forming and bond-breaking events.

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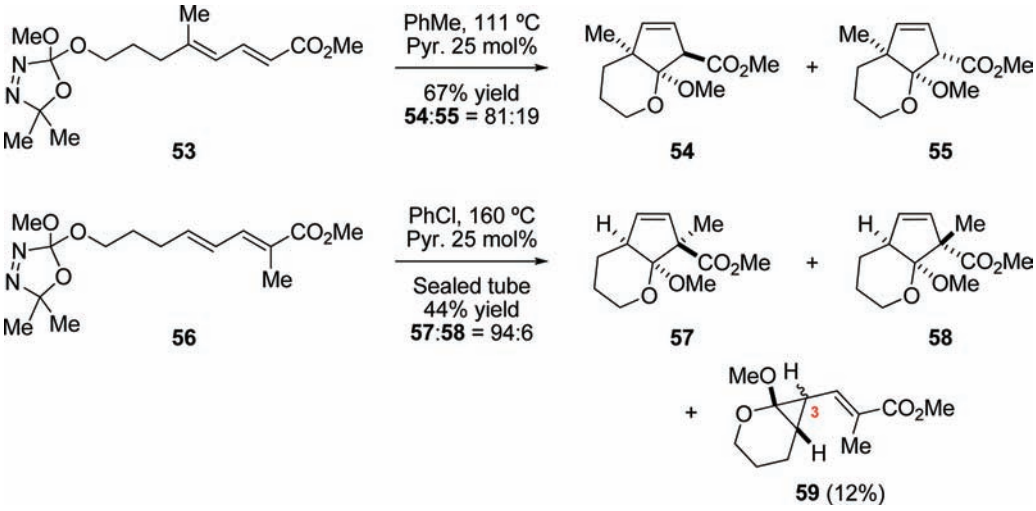
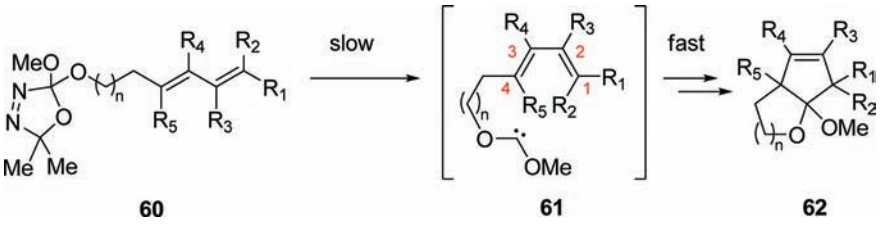
Scheme 9. Formation of Cyclopentenes with Chiral Quaternary Carbons



Scheme 10. Thermolysis of 2,2-Dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines 60 and Formation of Cyclopentenes 62



At the onset of our studies on the intramolecular (4 + 1)-annulation of electron-rich carbenes with electron-deficient dienes, we considered all mechanistic possibilities that allowed the formation of bicyclic cyclopentenes **62** from the corresponding carbene **61**. Although examples of concerted (4 + 1)-cycloadditions are quite scarce in the literature, we believed that a concerted mechanism remained possible (Scheme 11, top). This cheletropic reaction is allowed according to the Frontier Molecular Orbital theory[49] and would produce either the cycloadduct **62a** or **63** from transition states **TS61a** or **TS61b**, respectively.

Another accessible mechanism is the isomerization of a vinylcyclopropane to the corresponding cyclopentene, the product of a formal (4 + 1)-cycloaddition. The dialkoxycarbene **61** could react stereospecifically with the alkene,[50] via transition state **TS-61c**, to give vinylcyclopropane **64**, which could then rearrange via three distinct pathways to yield (4 + 1)-cycloadducts **62a**, **62b**, or **63** (Scheme 11, center).[14] If intermediate **64** participates in a concerted [1,3]-sigmatropic rearrangement with inversion of configuration at the migrating center, adduct **63** will result. Conversely, the collapse of the zwitterion **65** would provide cycloadducts **62a** or **62b**.[51] Note that the rearrangement of the intermediate resulting from a radical ring opening of **64**, albeit possible,[52] is unlikely to operate due to the donor–acceptor nature of the studied vinylcyclopropanes.[53] Finally, a complete ionic mechanism (**61** → **65** → **62**) must also be considered as a possible competing pathway for the (4 + 1)-cycloaddition (Scheme 11, bottom). Any one or a mixture of the proposed pathways for each substrate may be operative and thus lead to diastereomeric cyclopentenes **62a**, **62b**, or **63**. We will show that different substrates follow a complex array of possible and energetically close mechanistic pathways that are greatly influenced by the architecture of the substrate. The following discussion on the mechanism is divided into sections according to the position of the electron-withdrawing group on the diene.

As mentioned in the previous section, dienes with a methyl ester at position 1 experience a profound change in stereoselectivity when the length of the chain tethering the carbene to the diene is varied. Indeed, a complete reversal of stereoselectivity was observed in going from the 5–5 (**10a**:**11a**) to the 7–5 fused ring system (**14a**:**15a**) with the 6–5 fused ring system (**12a**:**13a**) being an intermediate case (Scheme 12). Each pair of diastereomeric cycloadducts are stereochemically stable, either upon further heating or when resubmitted to the initial reaction conditions. Therefore, we can conclude that, at the very least, the last step in the overall mechanism is irreversible. We can confirm that this is the case for all cyclopentene adducts found in the present study, and this important issue can be considered solved.

Cycloadduct **11a** (corresponding to **62b** in scheme 11) was clearly not produced by a concerted (4 + 1)-cycloaddition, but what of cycloadduct **14a** (corresponding to **62a** in Scheme 11)? Could the lengthening of the tether provoke a change from an ionic to a concerted mechanism? Or did the tether length simply influence the selectivity via conformational biases? Lastly, are vinylcyclopropane intermediates **64a–c** involved, and if so, what role do they play in this diastereoselective process?

We started by tackling the question of whether intermediate cyclopropanes **64a–c** were involved in the overall process or not. For the transformation of **7a–9a** to **10a–15a** under the conditions shown in Scheme 12, cyclopropanes were never detected. A computational study of all the available reaction pathways for **7a–9a** was carried out, and the formation of a cyclopropane intermediate was found to be favored by calculations (Figure 2). The common reaction solvent is

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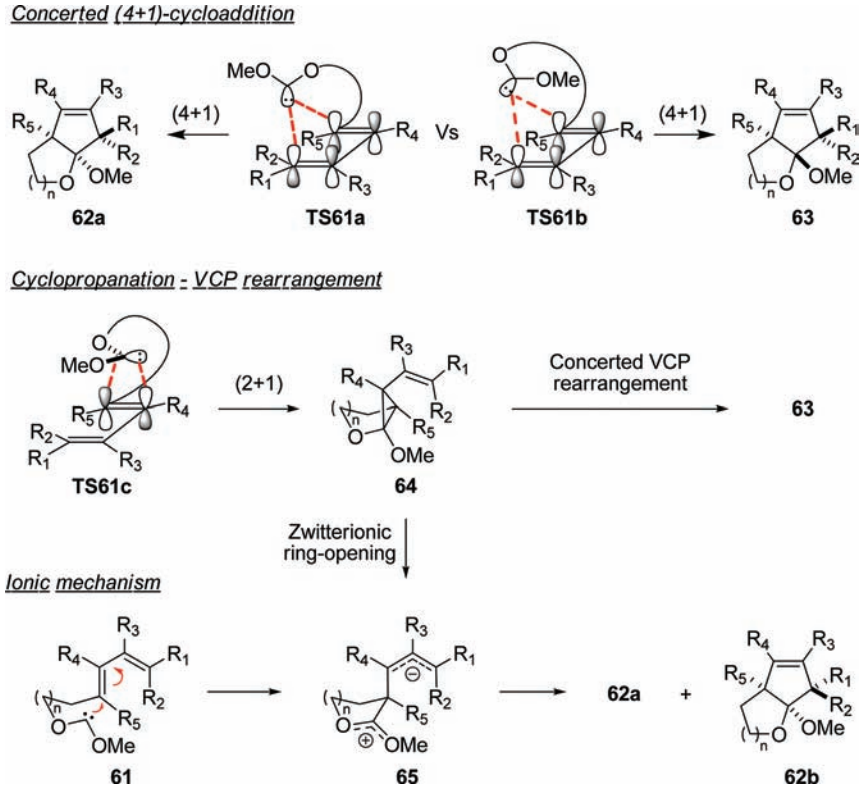
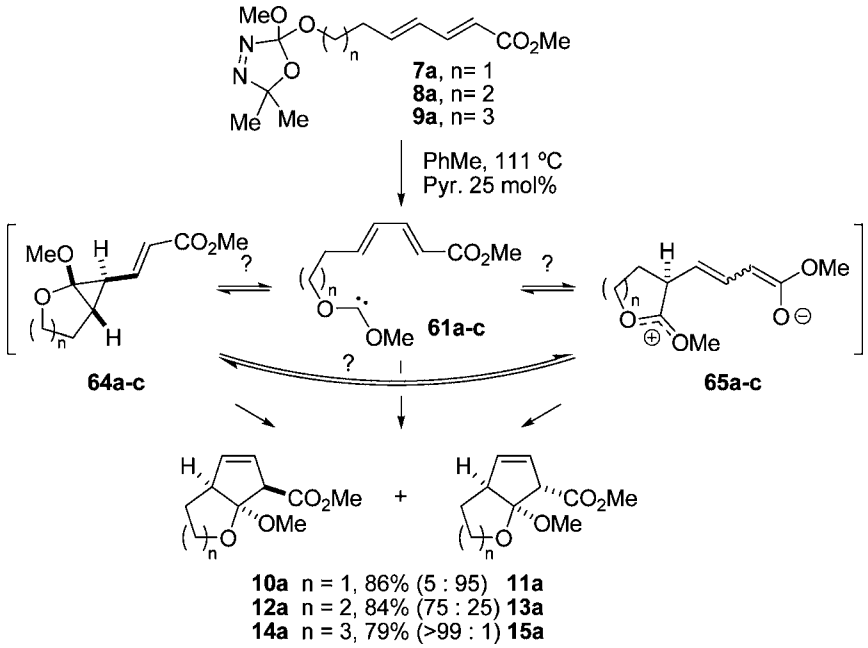
Scheme 11. Mechanistic Pathways for the (4 + 1)-Cycloaddition of Carbenes 61



Scheme 12. Stereoselective Intramolecular (4 + 1)-Cycloadditions of Dienes 7a–9a



toluene. Due to its nonpolar nature, we considered that optimization of the structures in the gas phase was adequate. A thorough analysis of the reaction pathways did not lead to any concerted (4 + 1)-cycloaddition transition structure. Analysis of the process gave evidence of the initial formation of the vinylcyclopropane intermediate. It was found that the reaction proceeds by an initial conjugate addition of the carbene on C-4 of the diene ester moiety (Figure 2 top).[54] In all cases, this addition was found to occur with a preference of 2 kcal/mol on the *s-trans* conformation of diene **7a–9a**. The formed adducts then preclude the direct formation of (4 + 1)-cycloadducts **10a–15a**, as rotation around the C2–C3 bond is strongly disfavored due to the delocalization of the anionic ester moiety.[55]

Analysis of the vibrational mode of the imaginary frequency clearly shows a unique bond-forming event (conjugate addition) in transition structures **TS65a–c**. IRC calculations were carried out to determine if a stable zwitterionic intermediate could be found following the addition. In all

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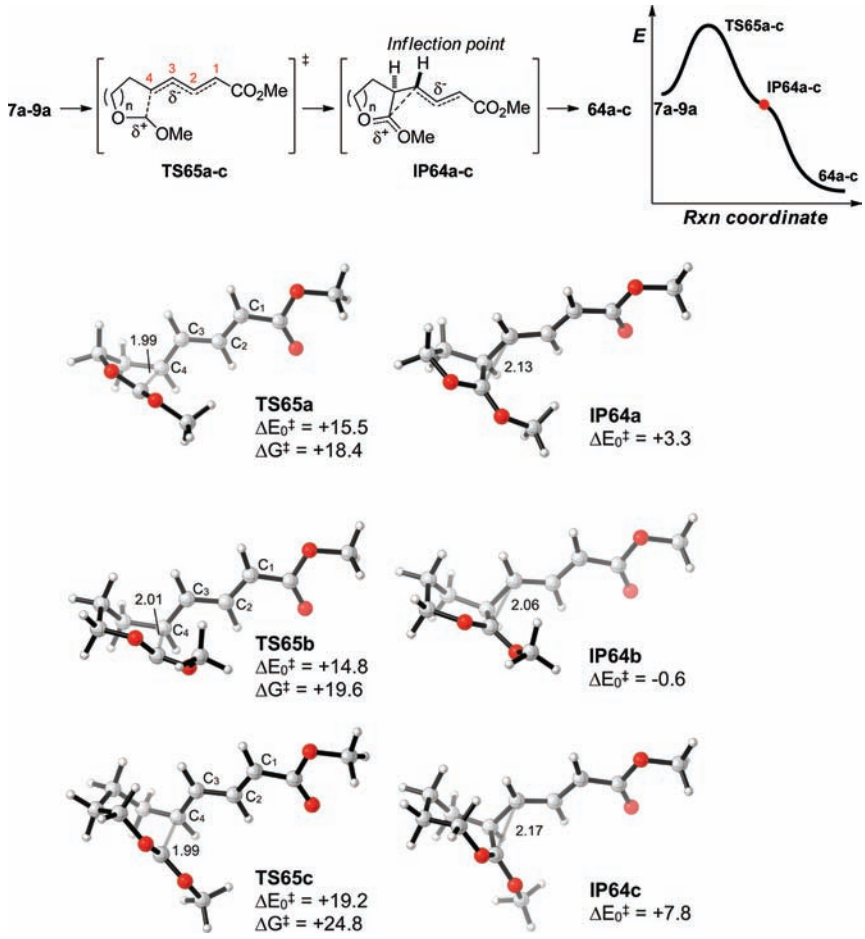
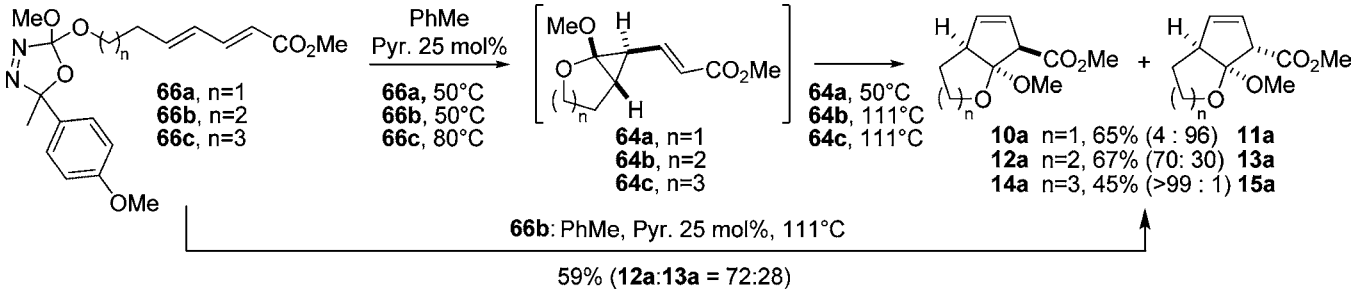


Figure 2. B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) optimized conjugate addition TSs and PES inflection points obtained from IRC calculations on respective TSs. Relative energies reported in kcal/mol with respect to the corresponding most stable conformation of the free carbene.

Scheme 13. Generation of Cyclopropanes 64a−c at Low Temperature



these cases, a rapid collapse to the corresponding vinylcyclopropanes **64a−c** was obtained. These are clear examples of two-step no-intermediate processes.[56] Inspection of the inflection point that follows the initial transition structure showed structures **IP64a−c** with a partially formed bond between $C_{carbene}$ and C-3, leading to the cyclopropane. Optimization of these transition structures using a solvation model (i.e., PCM/Toluene) resulted in almost identical structures and no stable intermediates on the calculated IRC paths. This is an evidence of the reliability of gas phase calculations for this study.

With this in mind, we considered that the required temperature for the thermolysis of the 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines **7a−9a** (>100 °C) may have been too high to allow the observation of cyclopropanes **64a−c**. We thus turned to a modified version of these oxadiazolines, namely, the 2,2-dialkoxy-5-methyl-5-(*p*-methoxy)phenyl-Δ^3-1,3,4-oxadiazolines **66a−c**, which undergo cycloreversion at approximately 50 °C (Scheme 13).[30b−d] When dienes **66a−c** were heated in toluene at temperatures ranging from 50 to 80 °C, the unstable and moisture-sensitive **64a−c** were observed and characterized as single diastereomers. Importantly, heating these cyclopropanes in toluene converted them into the corresponding (4 + 1)-cycloadducts **10a−15a** with almost identical stereoselectivities as the reactions reported in Schemes 2 and 12. Cyclopropane **64a** readily rearranged at 50 °C, while **64b** and **64c** necessitated higher rearrangement temperatures. The reactivity trend of cyclopropanes **64a−c** seems to be directly related to ring strain of the 5, 6 and 7−3 bicyclic systems. As a control experiment, we thermolyzed **66b** directly

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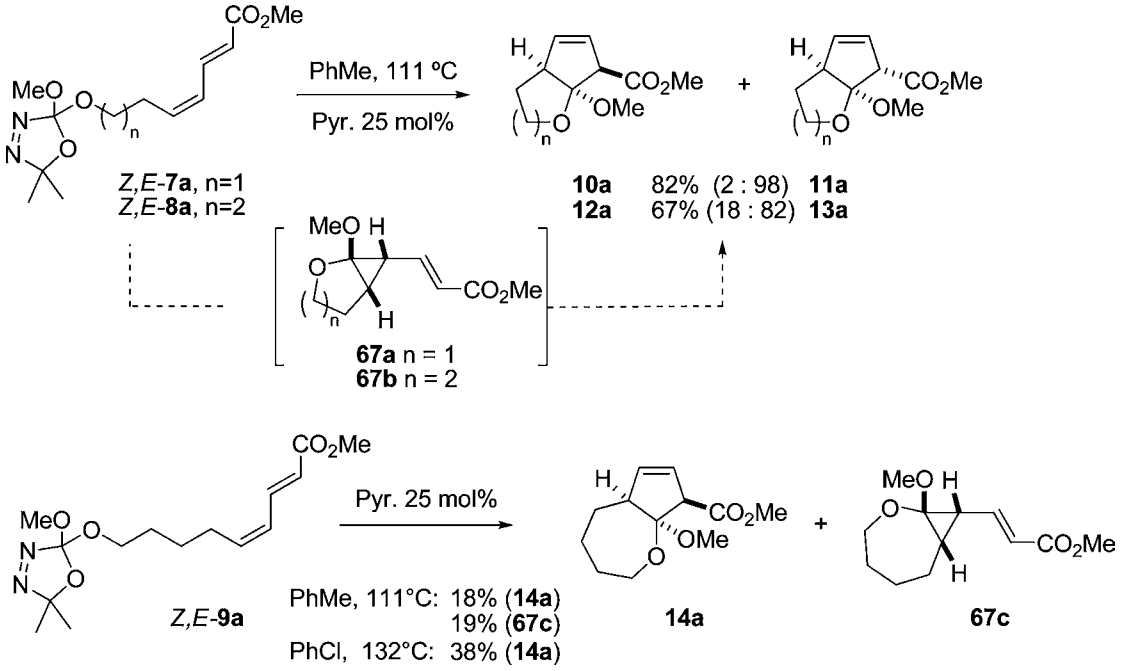
Scheme 14. Thermolysis of Dienes *Z,E*-7a−9a



at 111 °C and observed nearly the same yield and ratio of products **12a** and **13a** as for the thermolysis of **8a** or **64b**. Aside from the small difference in yields, attributable to the relative instability of dienes **66a−c** and vinylcyclopropanes **64a−c** at high temperature, these experimental results are in accordance with computational findings and support very strongly the implication of cyclopropanes in the mechanism of formation of (4 + 1)-cycloadducts.

We surmised that the stereochemistry of the vinylcyclopropane intermediates **64a−c** had a direct influence on the stereochemistry of the (4 + 1)-cycloadducts. To prove or disprove this hypothesis, we decided to examine the effect that the double bond geometry in the starting diene would have on the ratio of cycloadducts. Changing the geometry at the 3,4-position of the diene should led to the cyclopropanes epimeric to **64a−c**, namely, cyclopropanes **67a−c** (Scheme 14). The thermolysis of *Z,E*-**7a−9a** gave interesting results. While both *Z,E*-**7a** and *Z,E*-**9a** led to very similar ratios of cycloadducts as per dienes *E,E*-**7a** and *E,E*-**9a**, respectively (cf. Scheme 12), only diene *Z,E*-**8a** afforded a complete reversal of stereoselectivity. We repeated these experiments several times, and the reported ratios were constant and reproducible. Moreover, the isolation of cyclopropane **67c** in 19% yield as a single stereoisomer was evidence of the stereospecificity of the (2 + 1)-cycloaddition reaction. This was the first time a dialkoxycyclopropane did not rearrange readily at 111 °C. Thermolyzing *Z,E*-**9a** at a higher temperature (PhCl, 132 °C) gave **14a** (38%) as the only isolable bicyclic adduct. When comparing cyclopropanes **64c** and **67c**, it seems that the stereochemistry of the cyclopropane intermediate has an important effect on its rate of rearrangement.[57]

At this time, we can put forth the following hypotheses: (1) the thermolysis of substrates bearing an electron-withdrawing group at position 1 of the diene, led to the corresponding carbenes, which undergo a stereospecific cyclopropanation to give **64a−c** or **67a−c** depending on alkene geometry (Scheme 15); (2) the fact that we observed cycloadducts **10a−15a** with *cis* ring junctions precludes a concerted vinylcyclopropane rearrangement as a possible pathway for their formation (cf. Scheme 11, center); (3) in the case of intermediates **64a** and **67a** (leading to 5−5 fused bicyclic systems) and **64c** and **67c** (leading to 7−5 fused bicyclic systems), the cyclopropane ring opens to a zwitterion (**65a** or **65c**) and free bond rotation occurs before its stereoselective collapse to the corresponding cycloadduct **11a** and **14a**, respectively (Scheme 15, $k_{rot} > k_1$ or k_2).

Yet, the selectivity switch in going from diene **7a** to **9a** still puzzled us. A further conundrum was why a selectivity switch was observed in going from *E,E*-**8a** to *Z,E*-**8a** (leading to 6−5 fused bicyclic systems) but not in the case of *E,E*-**7a** to *Z,E*-**7a** or *E,E*-**9a** to *Z,E*-**9a**. A free equilibration of the different rotamers of zwitterion **65b** is excluded on the basis that the same ratios of products should have been obtained regardless of double bonds geometries in the starting diene. The only possibility left is that the cyclopropanes **64b** and **67b** open to different rotamers of zwitterion species **65b** that collapse at a rate competitive with bond rotation ($k_{rot} < k_1$ or k_2) (each may open to give zwitterionic species *E*-**65** (Scheme 15), but the *trans* internal double bond prevents cyclization). Although experimental data gave us many hints on the reaction mechanism, we were still unable at this point to explain the discrepancy in the stereochemical outcomes for the rearrangement of **64a−c** and **67a−c**, the implication of their corresponding zwitterions **65a−c**, and the fundamental origin of the stereoselectivities. We thus had recourse to high level calculations.

Optimization of transition structures leading to both cycloadducts **10a**, **12a**, **14a** and **11a**, **13a**, **15a** were done to help us understand this rather drastic selectivity difference (Scheme 15, k_1 vs k_2) for the 5−5, 6−5, and 7−5 fused bicyclic systems with an ester at C-1. The existence of diradical species was investigated, and they were found to be either nonexistent (singlet) or highly disfavored (triplet). It was possible to find and characterize well-defined polar transition structures for the formation of all (4 + 1)-cycloadducts (Figure 3). These transition structures possess relative free energies lower than

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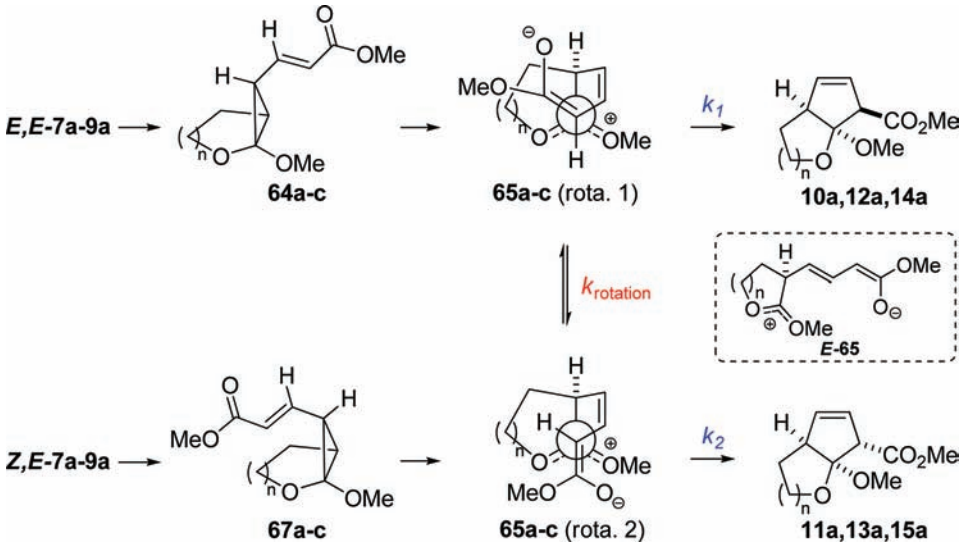
Scheme 15. Competitive Rates for the Rearrangements of 64a–c and 67a–c



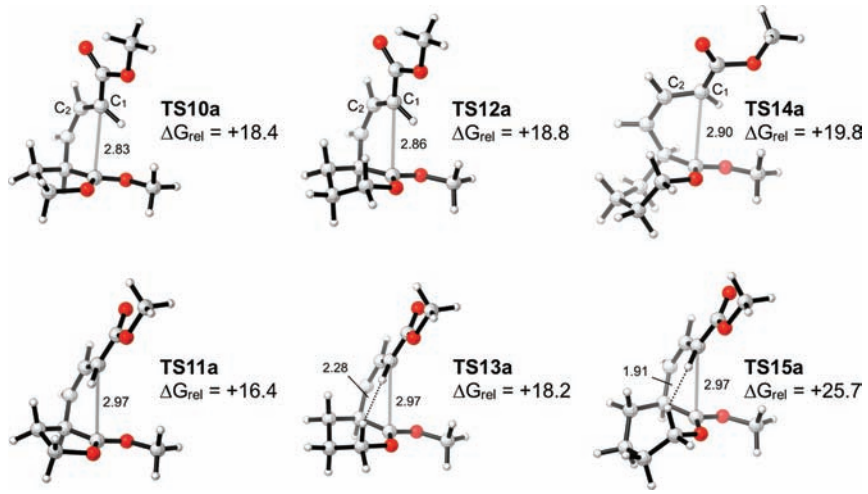


Figure 3. B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) optimized cyclization TSs, leading to **10a, 12a, 14a** (a) and **11a, 13a, 15a** (b). Relative energies reported in kcal/mol with respect to the respective most stable conformation of the free carbene.

their related conjugate addition step (cf. Figure 2, **TS65a–c**). *This is evidence that the initial addition of the free carbene is irreversible*. A notable feature of all transition states in Figure 3 is their "early" character with the forming bond length ranging from 2.83 to 2.97 Å. IRC calculations were performed on these TS structures to ensure their connection to the final products and determine if there was the existence of stable zwitterionic intermediates (**65a–c**). **TS10a** and **TS11a** both led to a common intermediate **65a** through the IRC calculations, via a barrier-less rotation process. A more thorough geometric optimization of **65a**, however, led to a very flat potential energy surface near the transition states and an almost barrier-less closure to the cyclopropane **67a**. IRC of **TS12a** also shows a very flat surface with no stable zwitterionic intermediate. Interestingly, IRC of **TS13a** directly connects **67b** to **13a**, with no intermediate. The same type of behavior was found for both **TS14a** and **TS15a**, which show paths that directly connect **64c** to **14a** and **67c** to **15a**, respectively. These results clearly indicate the transient nature of intermediates **65a–c** and the possible dynamic effects that could prevent equilibration between rotamers 1 and 2 of **65a–c** (Scheme 15). They could even be perceived as concerted [1,3] sigmatropic rearrangements with retention of configuration. Such forbidden processes have been previously rationalized by stabilization though the "subjacent orbital effect".[58] However, in the cases described in the current study, the stabilization can be explained by charge delocalization, as observed by the highly polar nature of the transition structures. This is reminiscent of oxyanion-accelerated vinyl cyclopropanes rearrangements reported by Danheiser et al.[59]

To evaluate this possibility, the free energy barriers for the isomerization of vinylcyclopropanes **64a–c** to the corresponding cycloadducts were compared (Table 3). The barriers of isomerization for **64a** are lower than the corresponding barriers for **64b–c**. This is in good agreement with the experimental results obtained for the reactions of **64a–c** (cf. Scheme 13), as **64a** readily converts to **11a** at 50 °C, whereas **64b** and **64c** need a higher temperature (111 °C) to react.

The correlation between theory and experiment for selectivities observed in the rearrangement of **64a** is very good (Table 3, entries 1 and 2). The computed value of 2.1 kcal/mol, which predicts a 6:94 ratio for **10a** and **11a**, is almost

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Table 3. Computed B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) Free Energy Barriers and Differences for the Isomerization of Vinyl Cyclopropanes 64a−c to the Corresponding Cyclopentenes[a]

entry	TS	$\Delta G_{iso}^{\ddagger}$	$\Delta\Delta G^{\ddagger}$	calcd ratio	exptl ratio[b]
1	**TS10a**	27.6	+2.1	6:94 (**10a**:**11a**)	5:95 (**10a**:**11a**)
2	**TS11a**	25.5			
3	**TS12a**	30.5	+0.6[c]	31:69 (**12a**:**13a**)	75:25 (28:72)[d] (**12a**:**13a**)
4	**TS13a**	29.9			
5	**TS14a**	31.0	−5.8	>99:1 (**14a**:**15a**)	>99:1 (**14a**:**15a**)
6	**TS15a**	36.8			

[a]Free energy barriers calculated relative to the corresponding vinylcyclopropanes **64a−c**. [b]Ratio observed in toluene (cf. Scheme 3). [c]$\Delta\Delta E_{ZPE}^{\ddagger}$ = −0.1 kcal/mol. [d]Ratio observed in acetonitrile (see discussion on solvent effect later in this article).

identical to the experimental ratio of 5:95 obtained at 111 °C, which corresponds to a $\Delta\Delta G_{iso}^{\ddagger}$ of 2.3 kcal/mol. Here, the stereoselectivity can be explained by a small conformational bias in the transition structures: in **TS10a**, the vinylogous ester enolate chain is pseudo equatorial on the five-membered ring, causing a torsion (22°) of the C1−C2 bond to accommodate orbital alignment to form the bond; at the opposite, in **TS11a**, the vinylogous ester enolate moiety can remain planar during the bond-forming event. Scan of the C1−C2 bond on a model system indicates that this torsion can account for as much as 1.7 kcal/mol, in good agreement with the observed difference.

Additionally, the energy difference (5.8 kcal/mol) computed for the isomerization of **64c** predicts a ratio of >99:1, in good agreement with experimental observations (Table 3, entries 5 and 6). Due to the extra degree of freedom of the seven-membered ring, it is possible in **TS14a** to position the vinylogous ester enolate in a pseudoaxial fashion, enabling cyclization without any torsion in the π-system. In contrast, a severe interaction developing between the C-1 vinylic proton and the ring residue can be found in **TS15a**. Furthermore, the seven-membered ring needs to adopt a higher energy conformation to position the vinylogous ester enolate in a pseudo equatorial fashion. Summation of both factors can explain the observed stereoselectivity.

For the rearrangement of **65b**, a competition of two factors occurs: as was the case for **TS10a**, there is also a destabilizing torsion of the C1−C2 bond in the vinylogous ester enolate π-system of **TS12a**; in **TS13a**, a severe interaction is developing between the C-1 vinylic proton and the axial hydrogen on the six-membered ring. Both effects compete to lead to a small energy difference between both transition structures (0.6 kcal/mol). The zero-point energy barrier difference ($\Delta\Delta E_{ZPE}^{\ddagger}$) is almost nonexistent (−0.1 kcal/mol). IRC calculation on **TS12a** shows a very flat surface, whereas IRC on **TS13a** shows a direct connection between **67b** and **13a**.[55] By taking into account the flat nature of the TSs, PES and the small energy difference between **TS12a** and **TS13a**, we believe that we are observing here a dynamic effect.[60] On the basis of the least motion principle,[61] **64b** will lead preferentially to **12a** and **67b** will lead to **13a**, respectively. This would account for the difference between the experimental (75:25) and predicted (31:69) ratios (Table 3, entries 3 and 4). The slight energetic preference for **TS13a** could even explain why a better selectivity is observed experimentally for the reaction of *Z*,*E*-**8a** (Scheme 14) compared to *E*,*E*-**8a** (Scheme 12). This is well represented by the IRC of **TS13a**.[55]

We have previously established that the stereoselectivity in the thermolysis of analogues of *E*,*E*-**8b−e**, where the ester group is replaced by other electron-withdrawing groups, decreased when the electron-withdrawing power of the group increased (cf. Table 1). We believe that activating groups better at stabilizing the negative charge in zwitterion **65b** favor the equilibrium between the two rotamers (cf. Scheme 15), leading to an overall less stereoselective process.

Another way to confirm the influence of the stabilization of zwitterion **65b** was to probe the effect of solvent on the product ratio obtained from the thermolysis of diene *E*,*E*-**8a**. Although many solvents or additives are incompatible with the intermediate dialkoxycarbene and cannot be used (nitromethane,[35,62] alcoholic solvents,[36b] and other nucleophilic solvents[63,64]), a reversed ratio of 28:72 was obtained in acetonitrile for **12a** and **13a**. This value is nearly identical to the calculated one (cf. Table 3, entries 3 and 4). A more detailed study of the effect of solvents and additives can be found in the Supporting Information. These experiments support the notion that the dynamic effect observed in toluene is not seen in polar media: the increased stability of the zwitterion **65b** decreases k_1 and k_2 to the benefit of k_{rot} and allows an equilibrium between the different rotamers of **65b**, which then collapse preferentially to **13a** (cf. Scheme 15). Conversely, heating *E*,*E*-**7a** and *E*-*E*-**9a** in acetonitrile gave the same ratios of products as per in toluene (24% and 21% yields,[65] respectively). It appears that k_1 and k_2, in the case of **65a** and **65c**, are lower than k_{rot} in polar or apolar solvents.

The results obtained from the thermolysis of methyl-substituted diene **56** at lower temperature (Scheme 9 vs Scheme 16) further demonstrate that the stereoselectivity of the (4 + 1)-cycloaddition is dictated by the difference in cyclization rate of a zwitterion intermediate (like **65b**) and the rate of bond rotation (similar to Scheme 15, k_{rot} vs k_1 and k_2). At 111 °C, only cyclopropane **59** was isolated as a 77:23 mixture of stereoisomers.[54] When diene **59** or cyclopropane **59** was heated to 160 °C, bicyclic adducts **57** and **58** (44%, **57**:**58** = 94:6 ratio) were formed along with recovered cyclopropane **59** (12%) as a 70:30 mixture of diastereomers (cf. Scheme 9). Epimerization of **59** at C-3 occurs presumably because the rate of cyclization into bicyclic adducts **57** or **58** is slow and the zwitterionic species may revert back to cyclopropane after bond rotation.[51,66] By opposition, the stereoselectivity observed for the thermolysis of **53** (cf. Scheme 9, 67%; **54**:**55** = 81:19) is similar to the one obtained from diene *E*,*E*-**8a** (75:25). It is believed that the methyl substituent in a remote position from the reacting center has a negligible effect on the stereoselectivity.

Computational analysis of the reaction of **56** indicates that the transition structures **TS57** and **TS58**, leading to **57** and **58**, respectively, possess relative free energies higher than that of the initial conjugate addition **TS59** (Figure 4). This could explain the epimerization of **59** and the lower yield of adducts **57** and **58**. Indeed, the possible reversibility between the free carbene, the zwitterion, and cyclopropane **59** would be accompanied by alternative degradation pathways. The high stereoselectivity, here, stems from a kinetic preference for **TS57** due to the severe interaction between the vinylic methyl group and the ring residue and the larger C1−C2 torsion on vinylogous ester enolate π-system present in **TS58** (Figure 4).

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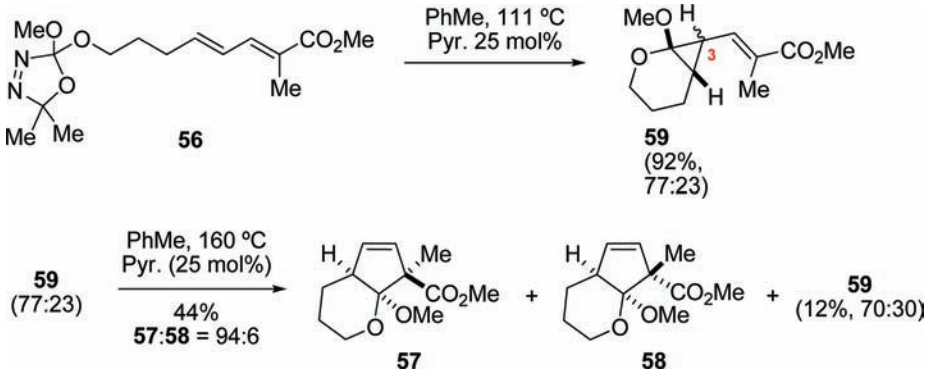
Scheme 16. Results from the Thermolysis of Diene 56 at Lower Temperature



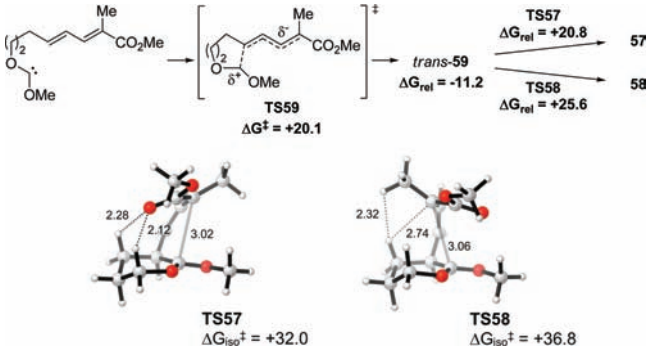


Figure 4. B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) optimized cyclization TSs, leading to **57** and **58**. Relative energies (ΔG_{rel}) reported in kcal/mol with respect to the respective most stable conformation of the free carbene. Isomerization barriers ($\Delta G_{iso}^{\ddagger}$) reported with respect to *trans*-**59**.

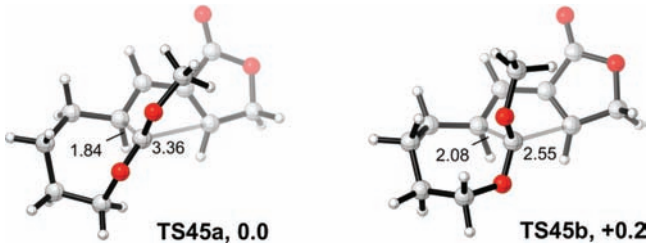


Figure 5. B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) optimized (4 + 1)-cycloaddition TSs leading to **45**. Free energies reported in kcal/mol with respect to **TS45a**.

Unlike cyclopropanes **64a–b**, compounds **40** and **42**, which possess an activating group at C-2, have no driving force to open into a zwitterionic species and are thus thermally stable. We rapidly dismissed the idea that cycloadduct **45** would come from the thermal rearrangement of vinylcyclopropane **44** when resubmission of the latter to the reaction conditions or to higher temperatures failed to give any of compound **45** (cf. Scheme 7). *This provides strong experimental evidence that* **45** *may be the product of a truly concerted (4 + 1)-cycloaddition.* Contrary to 1-substituted dienes, a concerted (4 + 1)-cycloaddition could be advantaged by the stabilizing effect at the transition state of electron-withdrawing groups at the C-2/C-3 position.[67] We have been able to optimize and characterize *in silico* two transition structures that also support this assertion (Figure 5). In the case of **TS45a**, a two-step no-intermediate process was found to account for **45**. The almost equi-energetic **TS45b** showed a truly concerted process that was confirmed by analysis of the IRC and the vibrational mode of the imaginary frequency. The particular stereochemistry of the *trans* ring-junction of **45**, which had never been observed up to now in this study, might result from a conformational preference where the methoxy group of the dialkoxycarbene is directed inside the developing tricyclic structure.

Recall that moving the activating group at C-3 on the diene resulted in several changes in the stereoselectivity of the annulation and revealed a yet more complex mechanistic picture. Thermolysis of dienes **46** and **48** gave bicyclic cyclopentenes **47** and **49** in 72% and 82% yield, respectively, both as single diastereomers (cf. Scheme 8). The thermolysis of diene **50** (PhMe, 160 °C, 15 h) resulted in the unselective formation of diastereomers **51a**, **51b** and **52** in 20%, 34%, and 17% yield, respectively.

We initially assumed that the corresponding cyclopropanes were intermediates in the mechanism of this formal (4 + 1)-cycloaddition. However, heating **46** at 111 °C instead of 160 °C gave yet another surprising result: the cyclic orthoester **69** (70%[54]) was formed as the major compound (Scheme 17). This orthoester probably resulted from a cyclization of the corresponding zwitterionic species **72**, themselves originating either from the opening of the corresponding cyclopropanes or from a conjugated addition of the carbene to the electron-deficient alkene. Recourse to the aromatic oxadiazoline **68**[30b–d] and heating to 50 °C was necessary to investigate the formation of the cyclic orthoester in the case of the 6–5 bicyclic system. In this case, only orthoester **70** (74%[54]) was obtained, and no trace of the corresponding cyclopropane or the (4 + 1)-cycloadduct **49** was detected. Lastly, when diene **50** was thermolyzed in PhCl at 132 °C, orthoester **71** was the major isolated product (65%[54]) along with compound **52** (10%).

We attempted to confirm that orthoesters **69–71** were the exclusive source of (4 + 1)-products. The conversion of orthoester **69** into its corresponding *O*-heterobicycle required temperature as high as 160 °C. Yields of products and ratios were nearly identical as per when diene **46** was heated directly to 160 °C. Again, the 6–5 bicyclic system behaved differently than the other bicyclic systems and gave decomposition products in a reproducible manner when orthoester **70** was submitted to heat. We have no explanation for this behavior yet. Thermolysis of diene **50** for a short period of time (PhMe, 160 °C, 1.5 h) led to a mixture of orthoester **71** and cycloadducts **51a**, **51b**, and **52** in 35%, 13%, 22%, and 17% yield, respectively. Importantly, the relative amount of product **52** (17%, Schemes 8 and 17) did not change when heating was continued further to 160 °C (15 h), while the yields of **51a** and

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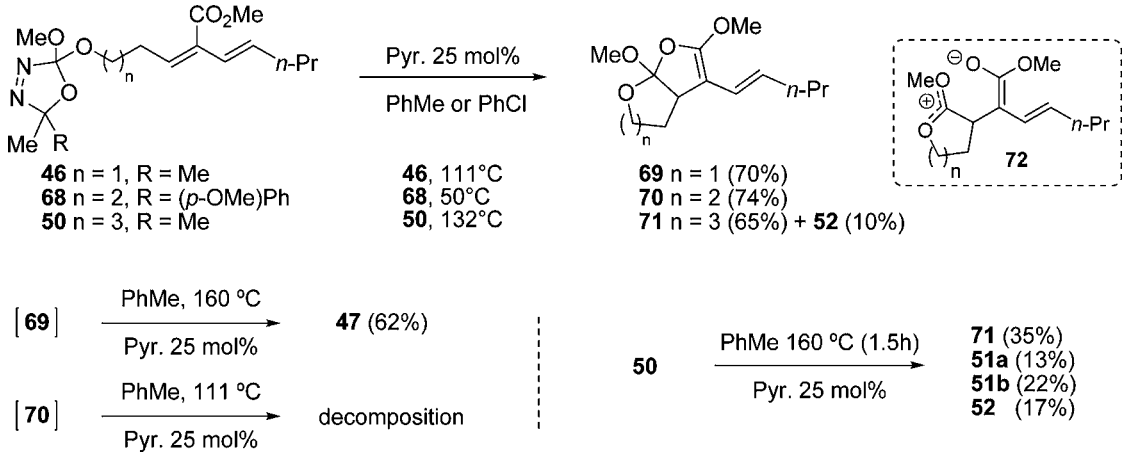
Scheme 17. Results from the Thermolysis of 46, 68, and 50



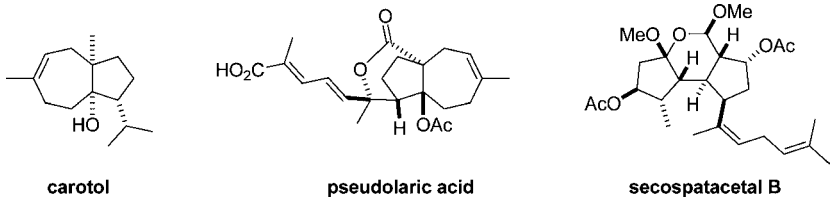


Figure 6. Three natural products that are targeted for synthesis.

51b increased gradually. Orthoester **71** is thus not the source of cycloadduct **52**.

The global picture for the thermolysis of 3-substituted dienes can now be summarized in two points: (1) in accord with Davies' findings,[68] the diastereocontrolled formation of cycloadducts **47**, **49**, **51a**, and **51b** would stem from a kinetic facial selectivity of the zwitterion **72**. The latter, in our case, initially and reversibly, form the corresponding orthoesters **69**–**71**; (2) cyclopentene **52** (7–5 fused ring system) is *formed from a concerted (4 + 1)-cycloaddition*. The *trans* ring junction, as in **45**, seems to be a structural characteristic of cycloadduct arising from an intramolecular concerted (4 + 1)-cycloaddition.

CONCLUSION

We have shown that dialkoxycyclocarbenes can react with many dienes bearing various electron-withdrawing groups at two different positions to lead to (4 + 1)-cycloadducts in good yields and good-to-excellent stereoselectivities. We demonstrated that the intramolecular (4 + 1)-cyclization is a useful and valuable reaction that allows access to stereodefined fused bicyclic ring systems. The creation of adducts bearing a quaternary center is a definite highlight of this work.

We have shown that the mechanistic portrait of the intramolecular reactions of dialkoxycarbenes with electron-deficient dienes is complex. Many of the mechanistic pathways available to the free carbenes are close in energy, and small changes in the substrate affect which one is followed. Nevertheless, most carbenes react via the initial formation of a cyclopropane, which then opens to a zwitterion that closes again to the desired cyclopentene products with stereoselectivities that depend on the substrate. We have provided evidence of a truly concerted intramolecular (4 + 1)-cycloaddition in two examples (dienes **43** and **50**), each case featuring the formation of a 7–5 fused bicyclic system. It seems that a *trans* ring junction is obtained in such cases as opposed to a *cis* ring junction when a zwitterionic intermediate is involved. How to favor the concerted pathway over the others is not obvious at this point, but it might be desirable to be able to do so in order to improve the stereochemical predictability of the reaction.

We are currently investigating a chiral nonracemic version of the cycloaddition and plan to use it to prepare the natural products carotol,[69] pseudolaric acid A,[70] and secospatacetal B[71] (Figure 6).

ASSOCIATED CONTENT

Supporting Information

Characterization and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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