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Inter- and Intramolecular [4 + 1]-Cycloadditions Between Electron-Poor Dienes and Electron-Rich Carbenes

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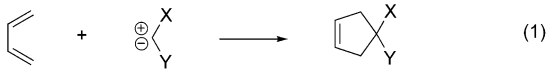
The [4 + 1]-cycloaddition between a carbene **2** and a diene **1** to give a cyclopentene derivative is, in a sense, the five-membered ring equivalent of the Diels−Alder reaction (eq 1).



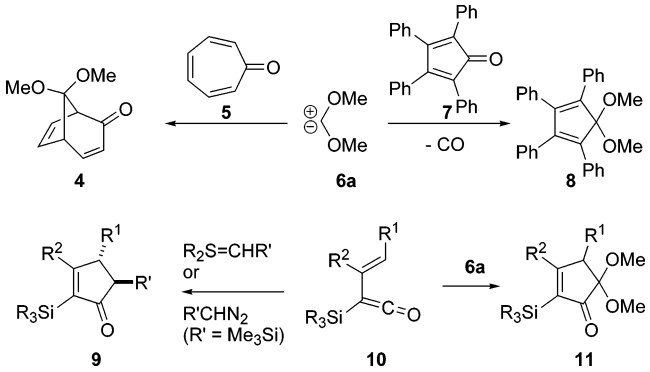
1 2 3 (1)

Given the ubiquity of five-membered carbo- and heterocyclic substructures in natural products, one would expect the [4 + 1]-cycloaddition, like the Diels−Alder reaction, to count among the most powerful reactions in the arsenal of the synthetic chemist. On the contrary, this reaction has few precedents. Lilienblum and Hoffmann reported such an intermolecular cheletropic reaction between dimethoxycarbene **6a** and tropone **5** or tetracyclone **7** (Scheme 1).[1] The same carbene also added to tetrazines[2] and to 4,4-bis(trifluoromethyl)-1,3-diazabutadiene.[3] More recently, Rigby established that **6a** added to vinyl isocyanates to give five-membered ring lactams.[4] In addition, dimethoxy carbene **6a** reacts with silyl-substituted vinyl ketenes **10** (Scheme 1).[5] The latter also react with sulfur ylids or trimethylsilyldiazomethane to give **9**.[6]

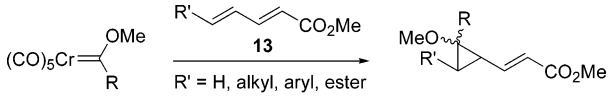
Examples of [4 + 1]-cycloadditions between a carbene and a simple diene are rare.[7] The main reason is the known propensity of carbenes and carbenoids to give cyclopropanation products with alkenes and 1,3-dienes.[8] For example, dimethoxycarbene gave cyclopropane derivatives in low yield with 1-phenyl- and 1,1-diphenyl-1,3-butadiene.[1] Fisher carbene complexes **12** gave mostly cyclopropanation products with electron-poor dienes (Scheme 2).[9] On the basis of the precedented rearrangement of vinylcyclopropanes,[10] Hudlicky[11] and Danheiser[12] established a two-step protocol that converted 1,3-dienes to cyclopentene derivatives.

Warkentin and co-workers studied extensively the chemistry and mechanistic aspects of dialkoxy carbenes and related bis-heteroatom carbenes.[13] One of the easiest methods to generate such carbenes is through the thermal decomposition of appropriately substituted oxadiazolines **15** (Scheme 3).[13,14] We were surprised to find that dialkoxycarbenes **6a** and **6b** added efficiently to electron-poor diene **17** to give the corresponding cyclopentene adducts **18a** and **18b** in 67 and 60% yields, respectively. Cyclopropane products were not detected, although they could be intermediates (vide infra). Dienes **19a**,**b** gave cyclopentanone acetals **20a**,**b** as single diastereomers in 38% and 29% yield, respectively. The latter reaction gave a crude product with a clean NMR that indicated complete conversion of the diene **19b**, but the products were somewhat unstable. The two methyl ether groups in **20a** gave different ^{1}H NMR signals, indicating a cis stereochemistry of the two esters in **20a**. The stereochemistry of **20b** was assumed to be the same as **20a**. Diene **21** reacted efficiently also, as judged by NMR, but gave cyclopentadiene **22** in 30% yield after purification on silica gel. Vinylcyclohexene and other electron-rich dienes, such as Danishefsky's diene, did not react with **6a**.

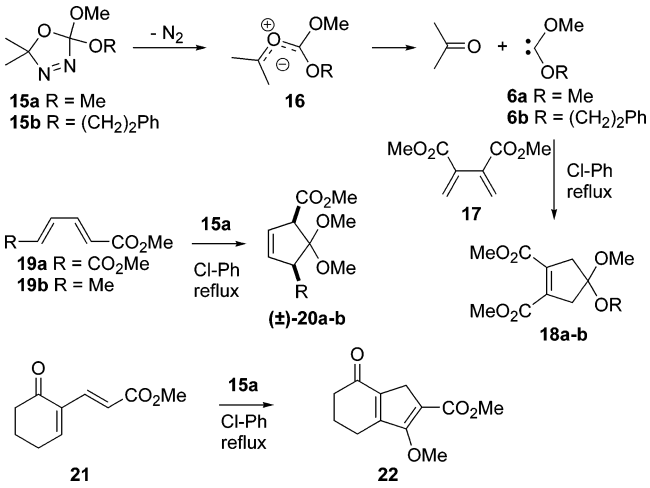
Scheme 1. Examples of [4 + 1]-cycloadditions



Scheme 2. Fisher Carbenes **12** Give Mostly Cyclopropane Products with Electron-Poor Dienes



Scheme 3. Intermolecular [4 + 1]-Cycloadditions of Electron-Deficient Dienes with Dialkoxy Carbenes



At this point, we were convinced that an intramolecular version of this annulation reaction could lead to useful polycyclic structures in improved yields. We are not aware of prior examples of such intramolecular [4 + 1]-cycloaddition aside from a fortuitous reaction observed by Warkentin and co-workers.[15]

We prepared dienes **23a**−**c**, which were coupled to oxadiazoline **15c** using an improved reaction condition (Scheme 4).[16] Heating to reflux the resulting oxadiazolines **24a**−**c** in toluene in carefully washed glassware gave good yields of the bicyclic adducts **25a**−**c** and **26a**−**c** (Scheme 4). Oxadiazoline **24a** gave a 5:95 mixture of diastereomeric adducts **25a** and **26a** in 85% yield, while acetals

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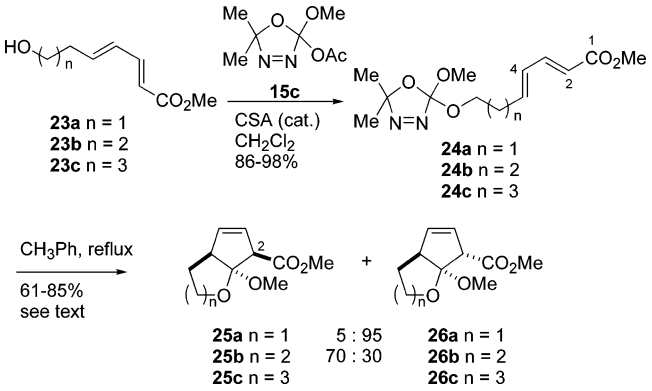
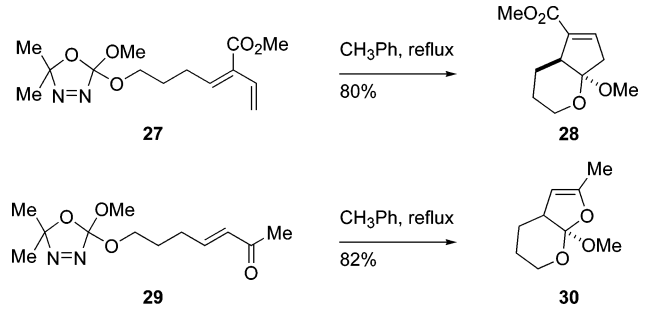
Scheme 4. Preparation of Bicyclic Adducts **25a**−**c** and **26a**−**c**



Scheme 5. Preparation of Bicyclic Acetal **28** and Orthoester **30**



25b and **26b** were isolated in a ratio of 70:30 in 61% combined yield. Reduction of the ester in **26a**, **25b**, and **26b** to the primary alcohol and subsequent derivatization into the corresponding *p*-nitrobenzoate ester allowed assignment of their stereochemistry on the basis of single-crystal X-ray diffraction analyses. Oxadiazoline **24c** led to a single diastereomer, although we could not yet unambiguously assign its stereochemistry.

Heating **27** gave diastereomerically pure **28** in 80% yield along with 16% of a carbonate, a frequent byproduct of the thermolysis of oxadiazolines in general (Scheme 5).[13] We were also pleased to see that [4 + 1]-annulation was possible with enone **29** to give a bicyclic ortho ester **30** in 82% isolated yield.

The mechanism of this annulation process is not clear at present. Carbene **6a** is nucleophilic and generally reacts with electrophiles to form zwitterionic intermediates.[4a,13] Our results seem to indicate that this may not always be the case. While it is tempting to assume a general stepwise mechanism for these [4 + 1]-annulation reactions on the basis of the formation of both isomers **25** and **26**, the isolation of **20a**,**b** as single isomers is indicative of a concerted process. In that regard, we have prepared the (2*Z*,4*E*)-isomer of **24a**, and it does not give any observable amount of **25a** or **26a** under the same reaction conditions as per (*E*,*E*)-**24a**. Instead, several decomposition products were reproducibly obtained. We would expect a stepwise process to be independent of the geometry of the C2-double bond in **24a**. Moreover, it is difficult to explain the reversal in selectivity in the cycloadditions of the carbenes derived from **24a** and **24b**, even if the cyclizations were entirely reversible. Further probing into the mechanism of this reaction is ongoing in our laboratories.

In conclusion, we have shown that electron poor dienes and oxadienes participate in [4 + 1]-cycloadditions with dialkoxy carbenes. The intramolecular reactions are the first examples of this kind and lead to useful bicyclic structures. We are presently expanding this methodology to include nitrogen[17,18] and sulfur[5,19,20] atoms as well as probing into the mechanistic aspects of the reaction.

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Supporting Information Available: Experimental and ^{1}H NMR spectra of all new compounds and syntheses and characterization of **23a**−**c** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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