J|A|C|S
COMMUNICATIONS

Intramolecular [1 + 2] and [3 + 2] Cycloaddition Reactions of Cyclopropenone Ketals

Paresma R. Patel and Dale L. Boger*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received January 21, 2010; E-mail: boger@scripps.edu

The disclosure of the reversible thermal generation of π-delocalized singlet vinylcarbenes from cyclopropenone ketals first emerged from an examination of the cycloaddition reactions of the parent unsubstituted cyclopropenone ketals.[1] This resulted in the discovery of the thermal [1 + 2],[2] [3 + 2],[3] and [3 + 4][4] cycloaddition reactions of singlet π-delocalized vinylcarbenes, which complement the [4 + 2][5] cycloaddition reactions of the cyclopropenone ketals themselves, providing a rich series of reactions whose course could be controlled by a combination of the choice of substrate and the reaction conditions (Figure 1).[1,6]

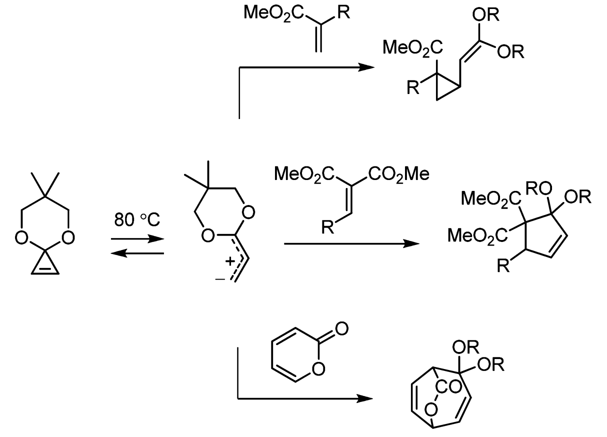
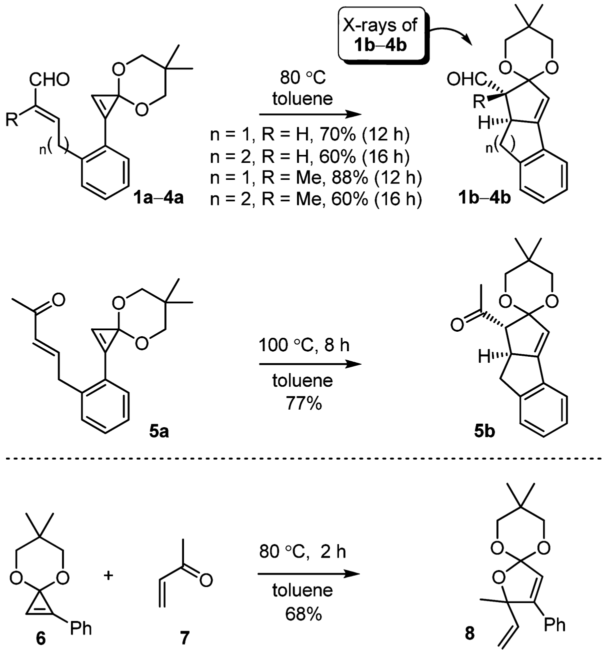


Figure 1. Generation and intermolecular cycloaddition reactions of a π-delocalized singlet vinylcarbene.

A key element that emerged from the studies was the reversibility of the thermal π-delocalized singlet vinylcarbene generation that insures its eventual productive trapping by an electron-deficient substrate. In preceding studies, only intermolecular cycloadditions had been examined, with a focus on understanding the underlying mechanistic questions posed by the observed reactions.[1,6] Herein, we report the first intramolecular thermal cycloaddition reactions of cyclopropenone ketals that permit the nature of the substrate tethering and the stereoelectronic (orbital alignment) features of the reactions to control the reaction course, providing additional mechanistic insights into these unique thermal reactions. Examined herein are the reactions of a cyclopropenone ketal tethered to an electron-deficient olefin bearing a single electron-withdrawing substituent. Whereas the intermolecular reactions provide only the olefin addition products derived from an endo-selective [1 + 2] cycloaddition,[2] the intramolecular variants provide either [1 + 2] or [3 + 2] cycloadducts in reactions that depend on the reaction conditions, the alkene activating substituent, and the nature of the tethering. In addition to providing key mechanistic insights into the thermal [3 + 2] cycloaddition, they were also found to proceed under conditions that reflect the ease and regioselectivity of the cyclopropenone ketal cleavage[7] for π-delocalized singlet vinylcarbene generation.

Substrates exploring two variations on the tether (alkyl or aryl) were examined.[8] The most remarkable combination of structural features that impacted the reactivity was observed with substrates **1a**−**5a** bearing an aldehyde- or ketone-substituted electron-deficient olefin and an aryl cyclopropenone ketal substituent built into the linking tether (Scheme 1).

Scheme 1

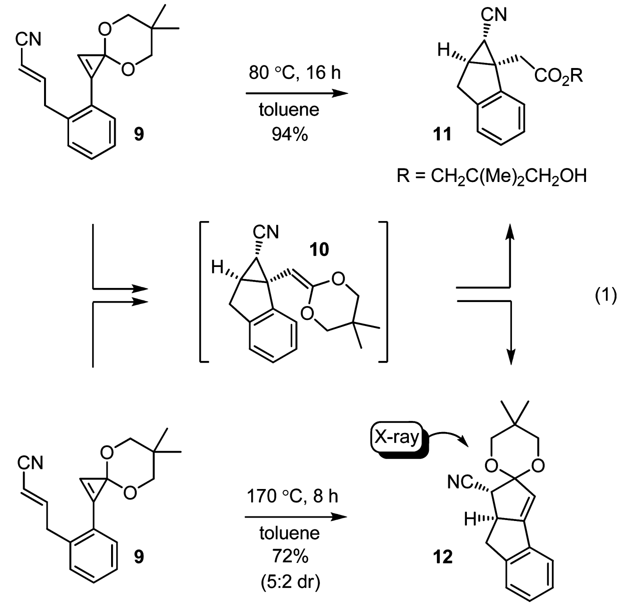


Simply warming a solution of **1a** in toluene at 80 °C for 12 h directly provided the [3 + 2] cycloadduct **1b** in good yield (70%) as a single diastereomer whose structure and stereochemistry were confirmed by X-ray analysis[9] (Scheme 1). Extension of the tether by one carbon (**2a**), resulting in a four- versus three-atom linker, similarly provided the [3 + 2] cycloadduct **2b** (X-ray[9]) directly in good yield (60%, 16 h, 80 °C). Further substitution of the electron-deficient olefin with a methyl group (substrates **3a** and **4a**) resulted in diastereospecific generation of the [3 + 2] cycloadducts **3b** and **4b**, respectively, with good conversion (88 and 60%, 12−16 h, 80 °C) as single diastereomers (X-ray[9]) in which the stereochemistry of the substrate olefin was maintained in the product. Similarly, the ketone substrate **5a** directly provided the [3 + 2] cycloadduct **5b** in excellent yield (77%) under comparable mild thermal reaction conditions (100 °C, 8 h; Scheme 1). The reaction course observed with substrates **1a**−**5a** is remarkable in two respects. First, the reactions directly provide the [3 + 2] cycloadducts under mild thermal reaction conditions and likely entail an intermediate thermal

10.1021/ja103933n

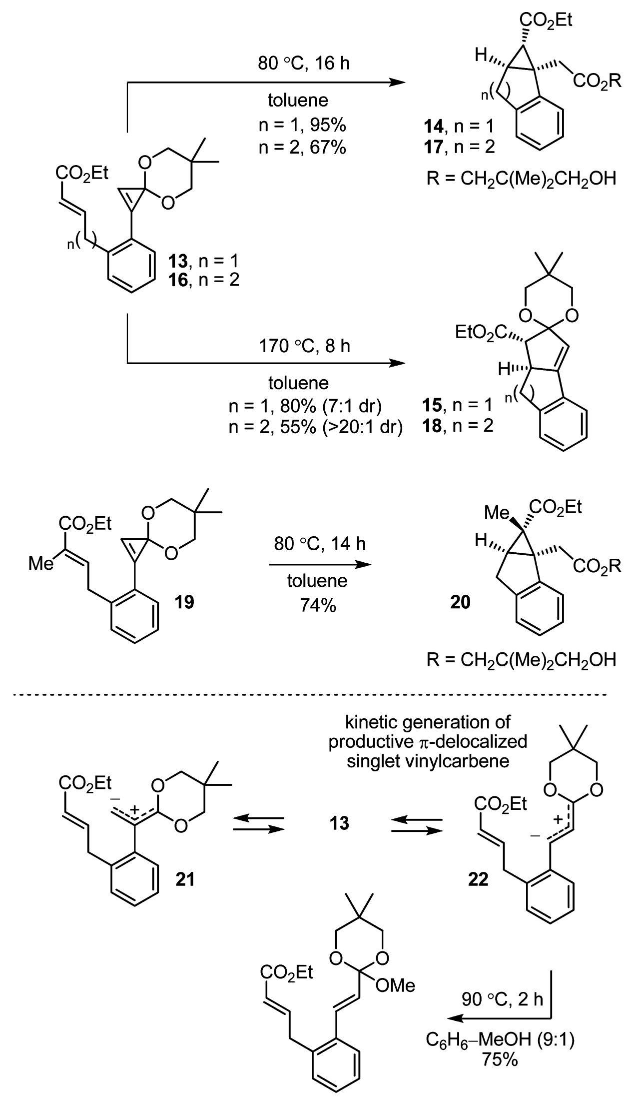
vinylcyclopropane rearrangement that proceeds with unprecedented ease.[10] Just as significantly, the intramolecular tethering of the substrates precludes the otherwise preferred intermolecular carbonyl addition of the thermally generated π-delocalized singlet vinylcarbene.[3b] Representative of this preference, the intermolecular reaction of the phenyl-substituted cyclopropenone ketal **6** with methyl vinyl ketone (**7**) cleanly provides only the carbonyl addition product **8** (80 °C, 2 h, 68%) without the detection of olefin addition products, despite the propensity of the electrophilic double bond of **7** to dominate its reactivity (Scheme 1).

Highlighting the unique reactivity of **1a**−**5a**, substrate **9** incorporating a nitrile-substituted electron-deficient olefin cleanly provided cyclopropane **11** (94%) upon reaction at 80 °C in toluene for 16 h, affording the product derived from an endo [1 + 2] cycloaddition of the thermally generated singlet π-delocalized vinylcarbene and hydrolysis of the ketene acetal **10** upon aqueous workup (eq 1). Moreover, warming either a solution of **10** (generated in situ at 80 °C, 16 h) or a solution of **9** in toluene at 170 °C (8 h, 72%) directly provided the [3 + 2] cycloadduct **12** (X-ray[9]) arising from initial [1 + 2] cycloaddition of the thermally generated singlet π-delocalized vinylcarbene followed by vinylcyclopropane rearrangement. In addition to defining the mechanism responsible for the [3 + 2] cycloaddition reaction of such substrates, the comparison of **1a**−**5a** with **9** underscores the remarkable activating properties of the aldehyde or ketone substituent for the ensuing vinylcyclopropane rearrangement.[10]



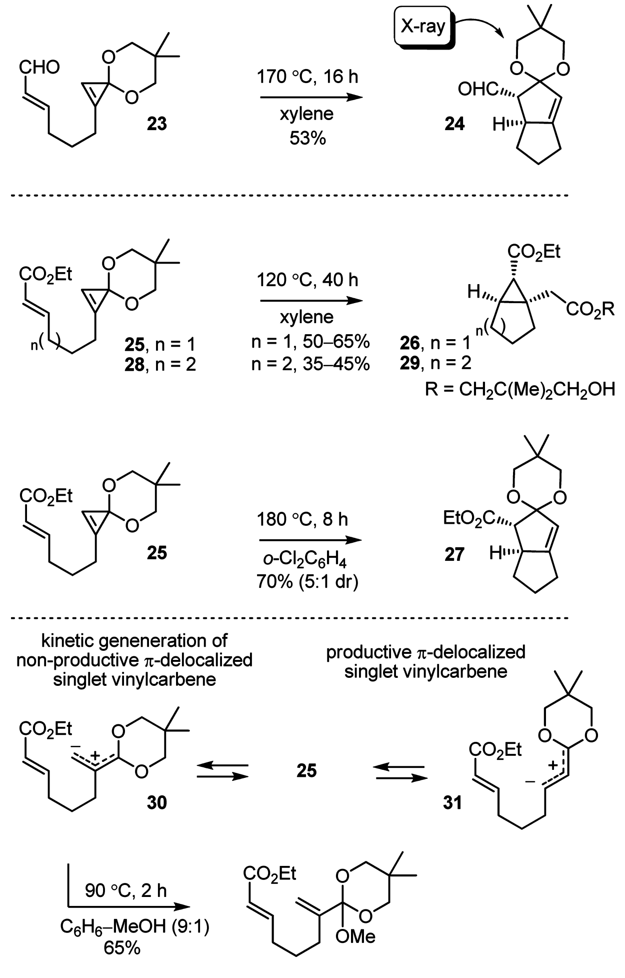
Similarly, substrates **13** and **16** bearing an ethyl ester substituent on the tethered olefin selectively provided the endo [1 + 2] cycloadducts **14** (95%) and **17** (67%), respectively, as single diastereomers when warmed at 80 °C for 16 h in toluene (Scheme 2). The reaction of substrate **16** with the longer four- versus three-atom linker (**13**) was slower but effective (67 vs 95%), and substitution of the double bond with an additional methyl substituent (**19**) did not alter the course or endo diastereoselectivity of the reaction, exclusively providing **20** (74%) containing a quaternary center incapable of epimerization. Only a trace of the [3 + 2] cycloadduct **15** (<4%) was detected under the conditions (80 °C, 16 h) that provided **14** (Scheme 2). Upon reaction at 170 °C for 8 h in toluene, **13** and **16** cleanly provided the corresponding [3 + 2] cycloadducts **15** and **18** in 80% (7:1 dr) and 55% (>20−30:1 dr), respectively. In the case of **13**, where the reaction was examined in detail, warming the intermediate vinylcyclopropane generated in situ (80 °C, 16 h) at 170 °C (8 h) also provided the [3 + 2] cycloadduct **15**, whereas warming a solution of substrate **13** at 175 °C for only a brief period (10 min) provided the [1 + 2] cycloadduct **14** (70%) along with only a small amount of the [3 + 2] cycloadduct **15** (8%). Collectively, these results indicate that the initial vinylcyclopropane [1 + 2] cycloadduct is an intermediate en route to the [3 + 2] cycloadduct **15**. In view of the diastereospecific reactions of **3a** and **4a**, it should also be noted that the partial loss of stereochemistry with the [3 + 2] cycloadduct **15**, as well as **12**, may reflect partial epimerization of the products under the thermal conditions rather than definitive evidence of a stepwise vinylcyclopropane rearrangement, since warming a solution of pure **15** to 170 °C led to slow epimerization (8:1 dr at 1 h). Finally, kinetic trapping of the π-delocalized vinylcarbene generated from **13** (C_6H_6/MeOH, 90 °C, 2 h) revealed regioselective cleavage preferentially leading to **22** that result from phenyl stabilization of its allyl cation and contribute to the facility of the cycloaddition reactions.

Scheme 2



Analogous to the behavior of **1a**−**4a**, substrate **23** bearing an alkyl-substituted cyclopropenone ketal, a straight-chain alkyl tether, and an aldehyde-substituted electron-deficient olefin directly provided a single diastereomer (X-ray[9]) of the [3 + 2] cycloadduct **24** (53%) but required more vigorous reaction conditions (170 °C, xylene, 16 h) (Scheme 3). The effect of the alkyl tethering was examined in detail with the ethyl ester substrates **25** and **28**. Because of the lower reactivity, it was more difficult to develop conditions that cleanly provided only the initial [1 + 2] cycloadducts. Thus, **25** and **28** provided the products **26** and **29**, respectively, in more modest conversions and required higher temperatures and longer reaction times (120 °C, 40 h vs 80 °C, 16 h) for observation of the initial endo [1 + 2] cycloaddition. However, warming a solution of **25** at the higher reaction temperature of 180 °C (o-$Cl_2C_6H_4$, 8 h) cleanly provided the corresponding [3 + 2] cycloadduct **27** in good yield (70%) (Scheme 3). Terminating this latter reaction conducted at the higher reaction temperature (180 °C) at shorter reaction times (4 and 1 h) led to isolation of increasing amounts of the [1 + 2] cycloadduct **26** (25 and 55%, respectively) with accompanying lower conversions to **27** (63 and 21%, respectively) indicating that the reaction proceeds by initial [1 + 2] cycloaddition of the thermally generated π-delocalized singlet vinylcarbene followed by vinylcyclopropane rearrangement to provide **27**. Because of the higher reaction temperatures required for the initial [1 + 2] cycloaddition in this series, it was not possible to define conditions that cleanly provided the [1 + 2] cycloadducts without significant generation of the [3 + 2] products. Responsible in part for this behavior, kinetic trapping of the π-delocalized singlet vinylcarbene derived from **25** (C_6H_6/MeOH, 90 °C, 2 h) revealed preferential regioselective cleavage to provide isomer **30**, requiring the reversible and slower occasional generation of **31** for productive partitioning into the reaction cascade (Scheme 3). In contrast, direct conversion to the [3 + 2] cycloadducts occurred cleanly, although it required the higher reaction temperature (180 °C) and proceeded at rates and conversions comparable to those for the phenyl-tethered substrates.

Scheme 3



The first study defining the scope of the intramolecular cycloaddition reactions of cyclopropenone ketals tethered to olefins bearing a single electron-withdrawing substituent has been described herein, which explored the cyclopropenone ketal substitution, two variations of the linking tether (alkyl or aryl), and the impact of the olefin electron-withdrawing substituent. The most effective combination of structural features was observed with substrates bearing an aldehyde- or ketone-substituted electron-deficient olefin and an aryl cyclopropenone ketal substituent built into the linking tether. Unlike the intermolecular reactions, such substrates not only now participated in olefin addition reactions rather than the otherwise preferred carbonyl addition reactions by virtue of the constraints imposed by the linking tether, but they were also found to directly provide [3 + 2] cycloadducts in excellent yields under mild thermal reaction conditions (80−100 °C). Less activated substrates bearing an ester- or nitrile-substituted olefin provided intermediate cyclopropanes derived from endo [1 + 2] cycloaddition of the thermally generated singlet π-delocalized vinylcarbene under mild thermal conditions (80−100 °C) or cleanly provided the [3 + 2] cycloadducts at higher reaction temperatures (170−180 °C) required to promote the intermediate vinylcyclopropane rearrangement. In addition to defining a two-step mechanism leading to the [3 + 2] cycloaddition products, the cycloaddition cascade of the aldehyde and ketone substrates was found to entail vinylcyclopropane rearrangements that proceed with unprecedented ease.[10] Examination of additional intramolecular cycloaddition reactions of cyclopropenone ketals and the exploitation of the remarkable facility (80 °C) with which the intramolecular [3 + 2] cycloaddition of a thermally generated π-delocalized singlet vinylcarbene proceeds with selected substrates are in progress.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA042056) and the Skaggs Institute for Chemical Biology. P.R.P. is a Skaggs Fellow.

Supporting Information Available: Full experimental details and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695–6713.
(2) (a) Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611–5614. (b) Tokuyama, H.; Yamada, T.; Nakamura, E. *Synlett* **1993**, 589–591.
(3) (a) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805–807. (b) Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 5615–5619. (c) Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.* **1987**, *65*, 32–40. (d) Boger, D. L.; Wysocki, R. J., Jr. *J. Org. Chem.* **1988**, *53*, 3408–3421.
(4) (a) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425–3427. (b) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713–6719.
(5) (a) Albert, R. M.; Butler, G. B. *J. Org. Chem.* **1977**, *42*, 674–679. (b) Boger, D. L.; Brotherton, C. E. *Tetrahedron* **1986**, *42*, 2777–2785. (c) Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453–3458. (d) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452–12459. (e) Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, *122*, 12169–12173. For a [5 + 2] cycloaddition, see: (f) Delgado, A.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2002**, *4*, 3091–3094.
(6) Reviews: (a) Boger, D. L.; Brotherton-Pleiss, C. E. *Adv. Cycloaddit.* **1990**, *2*, 147–219. (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295–1326.
(7) Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5523–5530.
(8) Although not the topic of this communication, the substrate preparations (see the Supporting Information) revealed the robust nature of cyclopropenone ketals and indicated that they can be carried through a range of reactions (e.g., Bu_4NF, CrO_3-pyr_2 or TPAP, Wittig reaction, Negishi coupling) that may otherwise appear challenging.
(9) The X-ray data have been deposited with the Cambridge Crystallographic Data Centre under the following accession codes: **1b**, CCDC773877; **2b**, CCDC775265; **3b**, CCDC776316; **4b**, CDCC776318; major diastereomer of **12**, CDCC762696; minor diastereomer of **12**, CCDC773876; **24**, CCDC776317.
(10) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. *Org. React.* **1985**, *33*, 247–335.

JA103933N