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

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Abstract

The first intramolecular thermal reactions of cyclopropenone ketals are reported enlisting substrates tethered to an electron-deficient olefin bearing a single electron-withdrawing substituent. Whereas the intermolecular variants of the reactions provide only the products of an endo selective [1 + 2] cycloaddition or a carbonyl addition reaction of a thermally generated π -delocalized singlet vinylcarbene, 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 reaction for such substrates, they were also found to proceed under conditions that reflect the ease and regioselectivity of the cyclopropenone ketal cleavage for π -delocalized singlet vinylcarbene generation. The most effective combination of structural features that impact the reactivity was observed with substrates bearing an aldehyde or ketone substituted electron-deficient olefin and incorporating an aryl cyclopropenone ketal substituent built into the linking tether. Simply warming a solution of such substrates in toluene at 80–100 °C directly provided the [3 + 2] cycloadducts in excellent yield (60–88%) under mild thermal reaction conditions.

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 that 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}

A key element to emerge from the studies was the reversibility of the thermal π -delocalized singlet vinylcarbene generation that insures its eventual productive trap by an electron-deficient substrate. In preceding studies, only intermolecular cycloadditions were 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

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Supporting Information Available: Full experimental details are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 cleavage⁷ for π -delocalized singlet vinylcarbene generation.

Substrates that explore two variations on the tether (alkyl or aryl) were examined.⁸ The most remarkable combination of structural features that impact 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).

Simply warming a solution of **1a** in toluene at 80 °C (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-ray⁹ (Scheme 1). Extension of the tether by one carbon (**2a**), constituting 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 olefins with a methyl group (substrates **3a** and **4a**) resulted in diastereospecific generation of the [3 + 2] cycloadducts **3b** and **4b** in good conversion (88% and 60%, 12–16 h, 80 °C) and as single diastereomers (X-rays)⁹ in which the stereochemistry of the substrate olefin is maintained in the product. Similarly, the ketone substrate **5a** directly provided the [3 + 2] cycloadduct **5b** in excellent yield (77%) under comparable and mild thermal reaction conditions (100 °C, 8 h, Scheme 1). The reaction course observed with the 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 vinylcyclopropane rearrangement that proceeds with a previously 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 for the electrophilic double bond of **7** to dominate its reactivity (Scheme 1).

Highlighting the unique reactivity of **1a–5a**, the substrate **9** incorporating a nitrile substituted electron-deficient olefin cleanly provided the cyclopropane **11** (94%) upon warming at 80 °C in toluene (16 h), resulting from 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-rays),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 comparisons of **1a–5a** with **9** underscores the remarkable activating properties of the aldehyde or ketone substituent for the ensuing vinylcyclopropane rearrangement.¹⁰

(1)

Similarly, substrates **13** and **16** bearing an ethyl ester substituent on the tethered olefin selectively provided the endo [1 + 2] cycloadducts **14** (95%) or **17** (67%), respectively, as single diastereomers when warmed at 80 °C in toluene (16 h) (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, providing exclusively **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). When warmed at 170 °C in toluene (8 h), **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 the 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, both results indicate that the initial vinylcyclopropane [1 + 2] cycloadduct is an intermediate en route to the [3 + 2] cycloadduct **15**. Given 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** at 170 °C leads to slow epimerization (dr 8:1 at 1 h). Finally, kinetic trap of the π -delocalized vinylcarbene generated from **13** (C₆H₆–MeOH, 90 °C, 2 h) revealed regioselective cleavage preferentially leading to **22**, resulting from phenyl stabilization of its allyl cation and contributing to the facility of the cycloaddition reactions.

Analogous to the behavior of **1a–4a**, the substrate **23** bearing an alkyl substituted cyclopropanone ketal, a straight chain alkyl tether, and an aldehyde substituted electron-deficient olefin provided directly 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*-Cl₂C₆H₄, 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 h and 1 h) led to isolation of increasing amounts of the [1 + 2] cycloadduct **26** (25% and 55%, respectively) with the 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 a vinylcyclopropane rearrangement to provide **27**. In this series and because of the higher reaction temperatures required for the initial [1 + 2] cycloaddition, 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 trap of the π -delocalized singlet vinylcarbene derived from **25** (C₆H₆-MeOH, 90 °C, 2 h) revealed preferential regioselective cleavage to provide the isomer **30**, requiring the reversible and occasional generation of **31** for productive partitioning into the reaction cascade (Scheme 3). In contrast, direct conversion to the [3 + 2] cycloadducts occurs cleanly, albeit requiring the higher reaction temperature (180 °C), and proceeds at rates and conversions comparable to the phenyl tethered substrates.

The first study defining the scope of the intramolecular cycloaddition reactions of cyclopropenone ketals tethered to olefins bearing a single electron-withdrawing substituent were detailed exploring the cyclopropenone ketal substitution, two variations on 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 their intermolecular reactions, such substrates now not only participate 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 an unprecedented ease.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. Although not the topic of this communication, the substrate preparations (Supporting Information) revealed the robust nature of the cyclopropanone ketal and indicate that it can be carried through a range of reactions (e.g., Bu_4NF , $\text{CrO}_3\text{-pyr}_2$ or TPAP, Wittig reaction, Negishi coupling) that may otherwise appear challenging.
9. The X-rays have been deposited with Cambridge Crystallographic Data Centre: **1b** (CCDC773877), **2b** (CCDC775265), **3b** (CCDC776316), **4b** (CDCC776318) **12** major diastereomer (CDCC762696), **12** minor diastereomer (CCDC773876), **24** (CCDC776317).
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Figure 1.
Generation and intermolecular cycloaddition reactions of a π -delocalized singlet vinylcarbene.

Scheme 1.

Scheme 2.

Scheme 3.