ORGANIC LETTERS

2010
Vol. 12, No. 15
3540−3543

Intramolecular Diels−Alder Reactions of Cyclopropenone Ketals

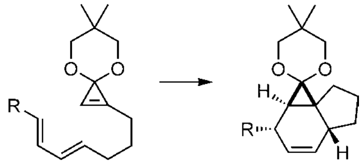
Paresma R. Patel and Dale L. Boger*

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

boger@scripps.edu

Received June 16, 2010

ABSTRACT



The first intramolecular cycloaddition reactions of cyclopropenone ketals with tethered electron-deficient, electron-rich, and neutral 1-substituted dienes are reported, constituting inverse electron demand, normal, and neutral Diels−Alder reactions, that provide exclusively the exo [4 + 2] cycloaddition products without the intervention of [1 + 2], [3 + 2], or [3 + 4] cycloadducts in reactions whose courses do not depend on the reaction conditions, the diene activating substituent, or the nature of the tethering.

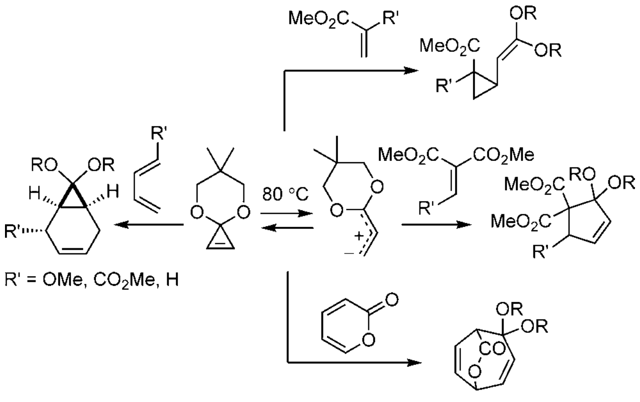


Figure 1. Intermolecular reactions of cyclopropenone ketals.

The examination and anticipated exploitation of the Diels−Alder reactions of the parent unsubstituted cyclopropenone ketals led to the discovery of the reversible thermal generation of π-delocalized singlet vinylcarbenes from cyclopropenone ketals.[1] This resulted in the disclosure 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 these studies was the capability of cyclopropenone ketals to participate in normal, inverse electron demand, or neutral Diels−Alder reactions with equal facility. Although a well-founded explanation of this behavior can be derived from a FMO analysis of the reactions,[5b] it is also

---

(1) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

(2) (a) Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611. (b) Tokuyama, H.; Yamada, T.; Nakamura, E. *Synlett* **1993**, 589.

(3) (a) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. (b) Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 5615. (c) Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.* **1987**, *65*, 32. (d) Boger, D. L.; Wysocki, R. J., Jr. *J. Org. Chem.* **1988**, *53*, 3408.

(4) (a) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425. (b) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713.

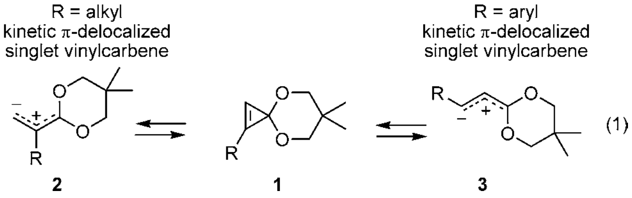
(5) (a) Albert, R. M.; Butler, G. B. *J. Org. Chem.* **1977**, *42*, 674. (b) Boger, D. L.; Brotherton, C. E. *Tetrahedron* **1986**, *42*, 2777. (c) Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453. (d) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452. (e) Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, *122*, 12169. For a [5 + 2] cycloaddition, see: (f) Delgado, A.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2002**, *4*, 3091.

(6) Reviews: (a) Boger, D. L.; Brotherton-Pleiss, C. E. In *Advances in Cycloaddition*, Vol. 2; Curran, D. P., Ed.; JAI Press: Stamford, CT, 1990; pp 147−219. (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295.

10.1021/ol101375a

intuitively easy to understand on the basis of the release of cyclopropene ring strain energy (ca. 25 kcal/mol) in the course of the [4 + 2] cycloaddition reactions that supersedes the electronic features of the reactions. In preceding studies, only the intermolecular cycloaddition reactions were examined with a focus on understanding the underlying mechanistic questions posed by the observed reactions.[1,6] Herein, we report the examination of the first intramolecular [4 + 2] cycloaddition reactions of cyclopropenone ketals with tethered, 1-substituted dienes that permit an assessment of the impact of the substrate tethering on the reaction course conducted with the intention of providing additional mechanistic insights into these unique thermal reactions. A key question we wished to address was whether the cyclopropenone ketal tethering to a 1-substituted diene would lead to competitive intervention of cycloaddition reactions of a thermally generated π-delocalized singlet vinylcarbene.[7] Analogous to the intermolecular reactions that provide only the products of an exo selective [4 + 2] cycloaddition with 1-substituted dienes,[1,5] the intramolecular variants were found to only provide the analogous exo Diels−Alder products without the intervention of [1 + 2], [3 + 2], or [3 + 4] cycloadducts in reactions that do not depend on the reaction conditions, the diene activating substituent, or the nature of the tethering.

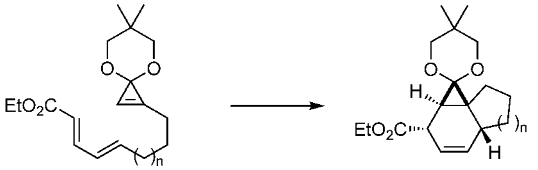
Substrates that explore two variations on the linking tether (alkyl or aryl) were examined.[8] Although not discussed in detail herein, alkyl substitution favors thermal cleavage of the cyclopropenone ketal **1** to provide the 2-substituted π-delocalized singlet vinylcarbene **2**, whereas aryl substitution favors a regioselective ring-opening reaction to provide the 3-substituted π-delocalized singlet vinylcarbene **3** potentially increasing the rate of its subsequent cycloaddition reaction with the type of substrates explored herein (eq 1).[6,7,9]



2 **1** **3**

The intramolecular Diels−Alder reaction was examined in greatest detail with the substrates **4a** and **5a** bearing an alkyl cyclopropenone ketal substituent, a straight chain three or four atom alkyl tether, and an electron-withdrawing 1-ethoxycarbonyl substituent on the tethered diene that could activate the system for trap of a thermally generated π-delocalized singlet vinylcarbene (Scheme 1).

Scheme 1



4a, n = 1
5a, n = 2

4b, n = 1
5b, n = 2

compd	temp	solvent	time	product	yield
4a, n = 1	25 °C	CH_2Cl_2	24 h	**4b**	15%
4a, n = 1	25 °C	C_6H_6	24 h	**4b**	89%
4a, n = 1	25 °C	C_6H_6	48 h	**4b**	94%
4a, n = 1	45 °C	CH_2Cl_2	8 h	**4b**	78%
4a, n = 1	45 °C	C_6H_6	12 h	**4b**	75%
5a, n = 2	45 °C	CH_2Cl_2	24 h	**5b**	25%
5a, n = 2	60 °C	C_6H_6	24 h	**5b**	56%
5a, n = 2	60 °C	C_6H_6	64 h	**5b**	78%

Substrate **4a** bearing the three atom linker, which underwent the intramolecular [4 + 2] cycloaddition effectively even at 25 °C, reacted distinguishably and expectedly faster than the substrate **5a** containing a four atom linker, the nonpolar solvent benzene proved to be more effective than the more polar aprotic solvent CH_2Cl_2, and warming (45−60 °C) the solutions containing either **4a** or **5a** only led to formation of the Diels−Alder products faster, but without the detection of carbene derived addition products. Importantly, both substrates proved to be superb participants in the intramolecular Diels−Alder reaction providing a single (exo) diastereomer.

Without efforts at optimization, a series of additional substrates **6a**−**9a** containing the three atom straight chain alkyl linker were examined that bear an alternative electron-withdrawing substituent (−CN), a conjugated aryl substituent (−Ph), no substituent representing an unactivated diene (−H), or an electron-donating substituent (−OBn) reflecting the full spectrum of potential 1-substituted dienes (Scheme 2). In many instances, the [4 + 2] cycloaddition reaction proceeded with such facility that the products were observed to form under conditions used to install or purify the diene, making it difficult to secure pure substrate and to accurately monitor the rate of product formation. Nonetheless, we could qualitatively establish that both **6a** and **9a** (R = CN or OBn), constituting either an electron-deficient or electron-rich diene, react at similar rates and slightly faster than either **7a** or **8a** (R = Ph or H). Thus, similar to observations made in the study of the intermolecular reactions,[1,5] a tethered cyclopropenone ketal participates equally well in an exo diastereoselective intramolecular normal or inverse electron demand Diels−Alder reaction. Moreover, it even effectively reacts with unactivated dienes (e.g., **8a**) that typically are difficult to employ in a conventional Diels−Alder reaction and does so under remarkably mild reaction conditions (C_6H_6, 45 °C, 12 h, 72%).

Notably, the unsubstituted alkyl chains used to link the dienophile with the diene in the substrates above do not represent the most effective tethering strategy and may be viewed as a series that significantly challenges the reaction

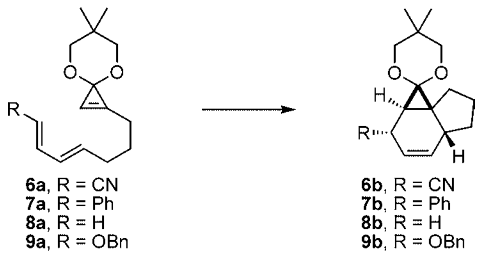
---

(7) Patel, P. R.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8527.

(8) Although not the topic of this communication, the substrate preparations (Supporting Information) revealed the robust nature of the cyclopropenone ketal, indicating that it 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) Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5523.

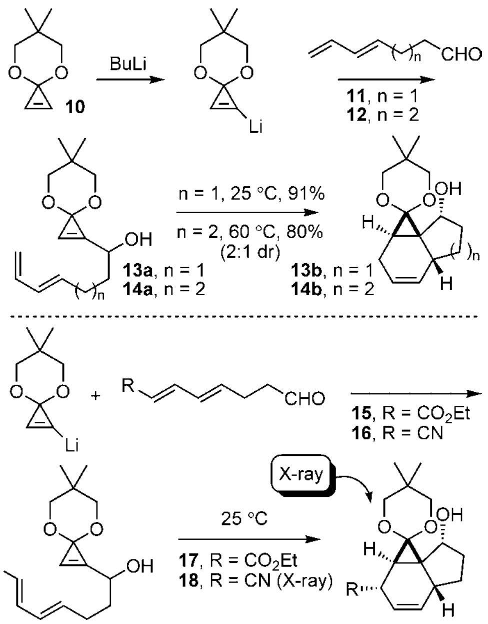
Scheme 2



compd	temp	solvent	time	product	yield
6a, R = CN	25 °C	C_6H_6	36 h	**6b**	86%
7a, R = Ph	60 °C	C_6H_6	20 h	**7b**	94%
8a, R = H	45 °C	C_6H_6	12 h	**8b**	72%
9a, R = OBn	25 °C	C_6H_6	16 h	**9b**	85%

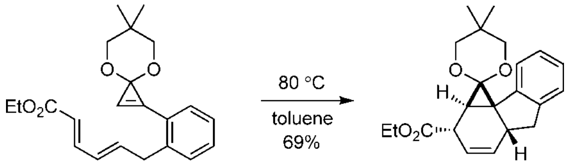
potential. Substitution on the linking chain or introduction of unsaturation into the linking chain is often used to further accelerate the rate of such intramolecular reactions. One such series that contains a substituted linking alkyl chain was examined in the course of our studies as a result of the approach used to prepare the tethered substrates (Scheme 3). Lithiation of the parent cyclopropenone ketal **10** followed by addition to the aldehydes **11** and **12** containing an unsubstituted and unactivated diene provided the substrates **13a** and **14a** containing a three and four atom alkyl linker bearing a secondary alcohol substituent. Substrate **13a** with the three atom linker now participated in the intramolecular exo Diels–Alder reaction at room temperature even though it represents the reaction of an unactivated diene (benzene, 14 h, 91%) to provide the product **13b** in superb yield and as a single detectable diastereomer. Substrate **14a**, containing the longer four atom alkyl linker, provided the product **14b** derived from exo selective [4 + 2] cycloaddition with the unactivated diene, but as a 2:1 mixture of alcohol diastereomers in good yield (80%, benzene, 60 °C, 18 h). Efforts to extend this approach to the preparation of substrates containing activated 1-substituted dienes (R = CO_2Et or CN) and a three atom linker failed to provide the isolated substrates and simply provided the resulting subsequent exo Diels–Alder products **17b** and **18b** as single detectable diastereomers. Cycloadduct **18b** was obtained as a crystalline product whose structure and stereochemistry were established with a single crystal X-ray structure determination[10] that served to confirm the assignments made herein based on spectroscopic properties.

Scheme 3



To date, we have briefly examined a single example of a tethered 1-substituted electron-deficient diene bearing an ethoxycarbonyl group (ethyl ester) and incorporating an aryl cyclopropenone ketal substituent in the linking tether (Scheme 4). In initial efforts to potentially observe competitive cycloadducts derived from the thermally generated π-delocalized singlet vinylcarbene (see **3**, eq 1), substrate **19** was warmed in toluene at 80 °C (12 h) under conditions demonstrated to lead to reversible carbene formation[7] but was found to provide only **20** (69%) derived from the intramolecular exo Diels–Alder reaction.

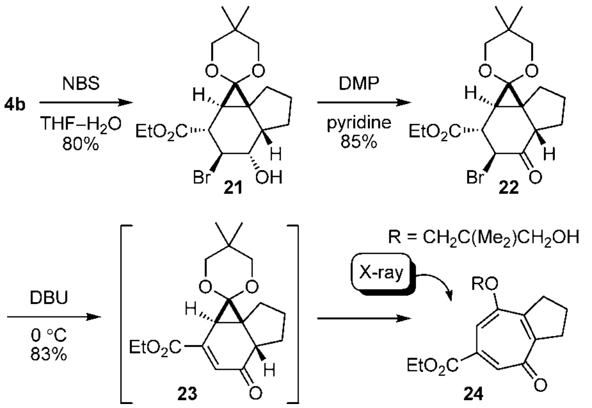
Scheme 4



19 **20**

Finally, and representative of the synthetic utility of the intramolecular [4 + 2] cycloaddition reaction, the cycloadduct **4b** was converted to the tropone **24** in 3 steps (Scheme 5). Thus,

Scheme 5



---

(10) A single crystal X-ray structure determination of **18b** confirmed the structural and stereochemical assignment (CCDC763497). A single crystal X-ray structure determination of **24** confirmed the structural assignment (CCDC763498).

regioselective bromohydrin formation (NBS, THF−H_2O, 80%), alcohol oxidation to the ketone **22** (DMP, pyr, 85%), and base-catalyzed elimination of HBr and in situ enolization (DBU, CH_2Cl_2, 0 °C, 45 min, 83%), resulting in rearrangement of the intermediate norcaradiene to the corresponding cycloheptatrienone ketal and subsequent tautomerization, provided the crystalline tropone **24**, whose structure was confirmed with a single crystal X-ray structure determination.[10]

The first intramolecular cycloaddition reactions of cyclopropenone ketals with tethered electron-rich, electron-deficient, and neutral 1-substituted dienes were reported and constitute normal, inverse electron demand and neutral Diels−Alder reactions that proceed under mild reaction conditions and provide exclusively the exo [4 + 2] cycloaddition products in reactions whose course do not depend on the reaction conditions, the diene activating substituent, or the nature of the tethering. Significantly, the reactions proceed without the intervention or trap of thermally generated π-delocalized singlet vinylcarbenes in [1 + 2], [3 + 2], or [3 + 4] cycloaddition reactions.[7]

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA042056) and the Skaggs Institute for Chemical Biology. We thank Dr. Raj Chadha (The Scripps Research Institute) for the X-ray crystal structures. P.R.P. is a Skaggs Fellow.

Supporting Information Available: Full experimental details, compound characterizations, and two X-ray structures are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101375A