

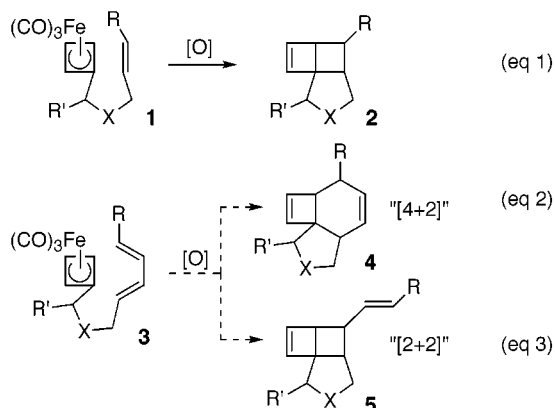
Intramolecular Cycloadditions between Cyclobutadiene and Dienes

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The use of ring strain is a proven strategy in facilitating the construction of complex molecules.¹ As there are only a few methods to generate cyclobutenes,² developing new means to produce this functionality could provide unique opportunities in synthesis. Recently, we reported that cyclobutadiene underwent an effective intramolecular cycloaddition with olefins to afford highly functionalized cyclobutene-containing products (eq 1).³ To expand further the scope and utility of this reaction, we report herein the first intramolecular cycloadditions between cyclobutadiene and various dienes to provide novel, cyclobutene-containing products (eqs 2 and 3).⁴ Considering the known intermolecular chemistry between these functional groups,⁵ we expected that the formal "[4 + 2]" product **4** (eq 2) would predominate over the "[2 + 2]" cycloadduct **5** (eq 3).⁶



The preparation of the substrates⁷ and their subsequent cycloaddition chemistry are summarized in Table 1. Treatment of dienyl ether **8** with ceric ammonium nitrate (CAN) in acetone at room temperature, in fact, provided a 1:2:6

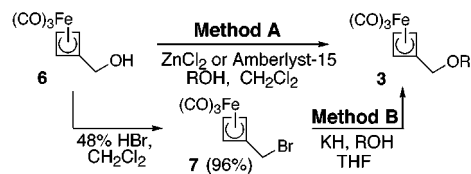
Table 1. Intramolecular Cyclobutadiene–Diene Cycloadditions

Entry	Substrate	(yield, ^a method ^b)	Cycloadducts ^c	Yield ^a (ratio)	
(1)		8 (73%, A)			75% (1:2.6 9 : 10)
(2)		11 (73%, A)			66%
(3)		13 (80%, B)			45% (3.5:1 14 : 15)
(4)		16 (74%, B)			61%
(5)		18 (87%, A)	No desired cycloadduct observed		
(6)		19 (55%, A)			66%
(7)		21 (71%, B)			41%
(8)		23 (65%, A)			32% ^d

^a Isolated yields. ^b See ref 7 and Supporting Information for substrate syntheses. ^c Reaction conditions: CAN (4–5 equiv), acetone (1–2 mM), rt, 15–20 min. ^d MeOH, CAN (55 equiv), reflux, slow addition.

mixture of [4 + 2] (**9**) and [2 + 2] (**10**) cycloadducts (entry 1). A possible explanation for these results was that the rate of formation of the [2 + 2] product was significantly faster than that of the [4 + 2] reaction and that the majority of compound **9** was formed through a subsequent Cope rearrangement of cycloadduct **10** (Scheme 1).⁸ In this regard, we found that heating the [2 + 2] product **10** to 130

(7) Cycloaddition substrates **3** were prepared through either of two procedures: Method A: Direct etherification of hydroxymethyl cyclobutadieneiron tricarbonyl **6** with various dienols was accomplished with either, substoichiometric amounts of ZnCl₂ (Kim, S.; Chung, K. N.; Yang, S. *J. Org. Chem.* **1987**, *52*, 3917), or Amberlyst-15, 4 Å molecular sieves (Braun, A.; Toupet, L.; Lellouche, J.-P. *J. Org. Chem.* **1996**, *61*, 1914), (Method B: For Lewis acid sensitive dienes, conversion of **6** to bromomethyl cyclobutadieneiron tricarbonyl **7** (Grubbs, R. H.; Pancoast, T. A.; Grey, R. A. *Tetrahedron Lett.* **1974**, *28*, 2425), followed by treatment with the appropriate potassium alkoxide, also afforded the desired cycloaddition precursors **3**.



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(1) For example, see: (a) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (c) Hirst, G. C.; Johnson, Jr., T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992. (d) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610. (e) Crimmins, M. T.; Wang, Z.; McKerlie, L. A. *J. Am. Chem. Soc.* **1998**, *120*, 1747.

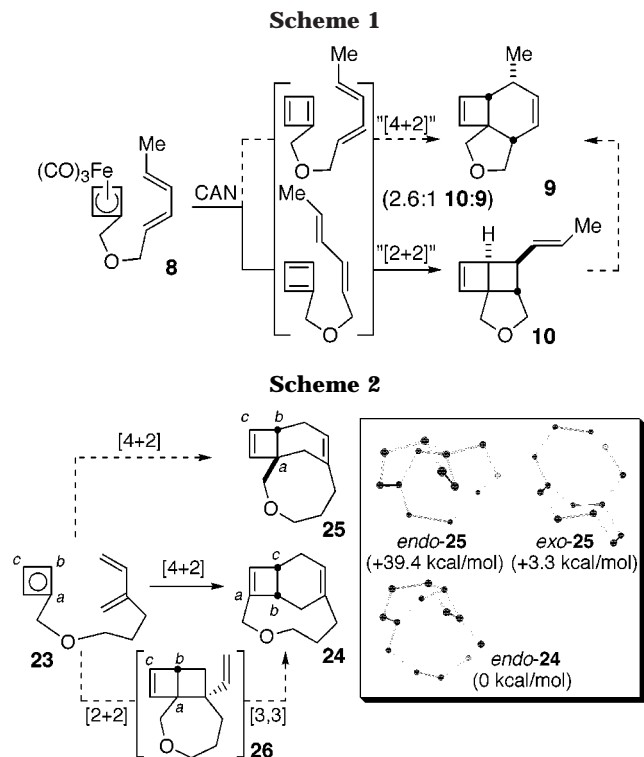
(2) For representative examples, see: (a) Kowalczyk, B. A.; Smith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379. (b) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459. (c) Gourdel-Martin, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166. (d) Liu, F.; Negishi, E.-I. *Tetrahedron Lett.* **1997**, *38*, 1149. (e) Negishi, E.-I.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveira, A., Jr.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325 and references therein. (f) Durst, T.; Breau, L. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 675–697.

(3) (a) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196. (b) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478.

(4) For an overview of iron-complexed cyclobutadienes and their reactions, see: Efraty, A. *Chem. Rev.* **1977**, *77*, 691.

(5) For examples of intermolecular cycloadditions between dienes and cyclobutadiene, see: (a) Watts, L.; Fitzpatrick, J. D.; Pettit, R. *J. Am. Chem. Soc.* **1966**, *88*, 623. (b) Barborak, J. C.; Pettit, R. *J. Am. Chem. Soc.* **1967**, *89*, 3080. (c) Paquette, L. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 5735. (d) Paquette, L. A.; Hefferon, G. J.; Samodral, R.; Hanzawa, Y. *J. Org. Chem.* **1983**, *48*, 1262.

(6) The terms "[4 + 2]" and "[2 + 2]" are used to describe the product connectivity and are not meant to imply a mechanistic pathway for the reaction.

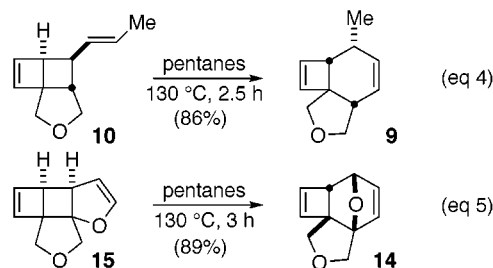


$^{\circ}\text{C}$ in pentane provided the observed [4 + 2] cycloadduct **9** in 86% yield (eq 4). It is, therefore, possible that during the course of the cycloaddition some cerium intermediate catalyzed a room temperature-rearrangement of the [2 + 2] adduct **10** to provide the [4 + 2] product **9**.^{8c} However, oxidative cycloaddition of substrate **13** in the presence of compound **10** provided cycloadducts **14** and **15**, as well as recovered **10**, with no trace of the [4 + 2] product (**9**). Since cycloadduct **10** did not rearrange to compound **9** under the reaction conditions, it appeared that products **9** and **10** were formed independently and concurrently in the cycloaddition reaction. In any event, based on the thermal rearrangement (eq 4), as well as NMR analyses,⁹ we assigned the relative stereochemistry of cycloadduct **9** to be consistent with an *endo* cycloaddition process.

Since substituents might influence the mode of cycloaddition, substrate **11** was prepared to decrease hindrance about the diene, as well as to separate the allylic oxygen and diene by one methylene group.¹⁰ As shown in Table 1, whereas cycloaddition of substrate **8** provided both the [2 + 2] and the [4 + 2] products (entry 1), cycloaddition of the homologated compound **11** afforded only the [4 + 2] compound **12** in 66% yield (entry 2).

We next investigated cycloadditions between cyclobutadiene and aromatic compounds. While the furanyl¹¹ (**13**, entry 3) and anthracenyl substrates (**16**, entry 4) underwent intramolecular cycloadditions, neither the naphthyl (**18**, entry 5) nor the phenyl substrates (not shown) afforded any of the desired cycloadducts. In the case of furanyl substrate **13**, a 3.5:1 mixture of compounds **14**:**15** was obtained in 45% yield. As in the earlier example (entry 1), heating the [2 + 2] product **15** resulted in the stereospecific formation of the *endo* [4 + 2] cycloadduct **14** in 89% yield (eq 5).

Substrates **19** and **21** were designed to investigate regio- and diastereoselectivity of the cycloaddition in substituted



systems (entries 6 and 7). Oxidation of **19** afforded only compound **20** where the cycloaddition occurred away from the methyl substituent on the cyclobutadiene. Compared to entry 3, it is also noteworthy that no [2 + 2] product was observed in this transformation. As shown in entry 7, cycloaddition of **21** produced cyclobutene **22** as a single diastereomer, albeit in moderate yield.

Compound **23** (entry 8)¹² was prepared to investigate the feasibility of a type II intramolecular Diels–Alder reaction.¹³ Subjecting of **23** to the usual oxidative conditions yielded only a trace amount of an intramolecular cycloadduct; however, slow addition of substrate **23** to a refluxing methanolic solution of a large excess of CAN (i.e., 55 equiv) resulted in a relatively low yield of the unexpected cycloadduct **24**. If the energy differences in the transition states to form the expected cycloadduct **25** and observed product **24** are reflected in the stability of the cycloadducts, it may be of relevance to note that the conformational minima of compound **25** in an *endo* or *exo* geometry are significantly higher in energy than the *endo* conformation of isomer **24** (Scheme 2).¹⁴ Alternatively, we cannot rule out the possibility that compound **24** was formed through the [2 + 2] cycloadduct **26** which experiences a facile Cope rearrangement under the refluxing methanolic reaction conditions.

In summary, we have demonstrated a new intramolecular cycloaddition between cyclobutadiene and a variety of tethered dienes to afford novel, cyclobutene-containing cycloadducts. Further studies on the scope of this reaction, as well as subsequent transformations of the highly functionalized cycloadducts for the efficient construction of molecular targets of significance are in progress.

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Supporting Information Available: Experimental procedures and data on new compounds (31 pages).

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(9) See Supporting Information for COSY and NOE interactions indicating relative stereochemistry of cycloadducts.

(10) For the preparation of 3,5-hexadien-1-ol, see: (a) Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317. (b) Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 5274.

(11) For representative examples of intramolecular Diels–Alder reactions involving furan, see: (a) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5853. (b) Jung, M. E.; Kiankarimi, M. *J. Org. Chem.* **1998**, *63*, 2968. (c) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.

(12) For the synthesis of 4-methylene-5-hexen-1-ol, see: von Bertele, E.; Schudel, P. *Helv. Chim. Acta* **1967**, *255*, 2445.

(13) For example articles on type II intramolecular Diels–Alder reactions, consult: (a) Shea, K. J.; Wise, S.; Burke, L. D.; Davis, P. D.; Gilman, J. W.; Greeley, A. C. *J. Am. Chem. Soc.* **1982**, *104*, 5708. (b) Shea, K. J.; Burke, L. D.; England, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 860. (c) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248.

(14) Molecular mechanics calculations were carried out using the SYBYL force field supplied with MacSpartan (Wavefunction, Inc, Irvine, CA).

(8) For reviews on Cope rearrangements, see: (a) Rhoads, S. J.; Raulins, N. E. *Org. React.* **1974**, *22*, 1. (b) Zielger, F. E. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 875–898. (c) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (d) Hudlicky, T. Fan, R. Redd, J. W. Dadamasetti, K. G. *Org. React.* **1991**, *41*, 1. (e) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 785–873.