Intramolecular Cycloadditions between Cyclobutadiene and Alkenes

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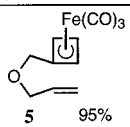
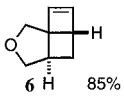
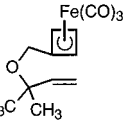
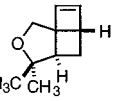
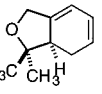
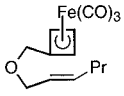
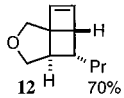
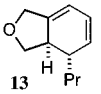
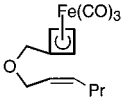
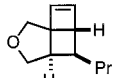
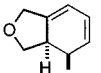
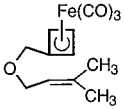
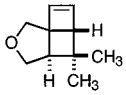
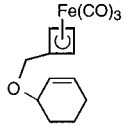
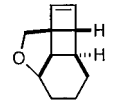
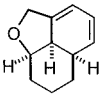
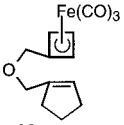
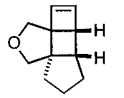
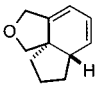
Cross metatheses of strained rings with acyclic olefins offer concise new solutions toward the syntheses of natural and unnatural products.[1] Securing the full value of these cross metatheses and related processes, however, requires the development of more efficient entries into highly functionalized cyclobutene-containing substrates. In this regard, we report herein the first intramolecular cycloadditions between cyclobutadiene and unactivated olefins to produce novel cyclobutene-containing systems. The utility of this transformation is illustrated by the conversion of the cyclobutene-containing cycloadducts into 1,3-cyclohexadiene-containing ring systems.

Over the last three decades, theoretical, structural, and reactivity studies have provided a rich understanding of the chemistry of cyclobutadiene.[2] The synthetic utility of this reactive functionality, however, has been exploited to a lesser extent. A important exception is the use of cyclobutadiene in [4 + 2] cycloadditions,[3] where a range of *activated* cycloaddition partners have been employed (*e.g.,* benzoquinones, phenylacetylene, dibenzoylacetylene, norbornadiene).[4] Considering the prevalence of cyclobutadiene cycloadditions, it is interesting to note that, to the best of our knowledge, there have been no reports of cycloadditions between cyclobutadiene and simple, unactivated olefins.[5]

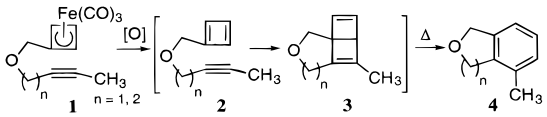
In view of our need for improved pathways to biologically active agents,[6] we chose to examine whether an *intramolecular* cycloaddition with *unactivated* alkenes is a feasible transformation. As illustrated in Scheme 1, there has been one report of an intramolecular transformation where cyclobutadiene was shown to react with tethered alkynes to produce Dewar benzene-containing cycloadducts (**3**, $n = 1,2$).[7] Without isolation these cycloadducts were then converted to the aromatic systems (**4**, $n = 1,2$).

Table 1. Intramolecular Cyclobutadiene−Olefin Cycloadditions

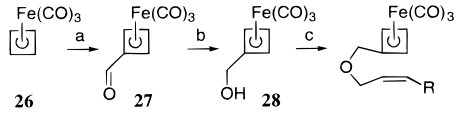
Entry	Substrate[a]	Cycloadduct[b]	Thermal Product[b]
(1)			
	5 95%	**6** 85%	**7** 85%
(2)			
	8 67%	**9** 92%	**10** 86%
(3)			
	11 98%	**12** 70%	**13** 97%
(4)			
	14 95%	**15** 64%	**16** 80%
(5)			
	17 78%	**18** 70%	**19** 92%
(6)			
	20 85%	**21** 60%	**22** 51%
(7)			
	23 85%	**24** 65%	**25** 88%

[a] Isolated yields from alcohol precursor **28**. [b] Isolated yields.

Scheme 1



Scheme 2[a]



[a] (a) *N*-methylformanilide, $POCl_3$; (b) $NaBH_4$; (c) H^+, alcohol.

The substrates prepared to examine intramolecular cyclobutadiene cycloadditions with unactivated alkenes are illustrated in Table 1 (substrates, entries 1−7). As shown in Scheme 2, alcohol **28**, used to construct these cycloaddition substrates, was prepared through the formylation of an iron tricarbonyl-complexed cyclobutadiene (tricarbonyl(η^4-cyclobutadiene)iron, **26**),[8] followed by reduction of resulting aldehyde **27**.[9] While the desired allylic ether-containing substrates are obtainable through displacement of iron-complexed (cyclobutadienyl)-methyl bromide with the requisite allylic alkoxides, a more

(1) (a) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610−9611. (b) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411−412.

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(3) (a) Ward, J. S.; Pettit, R. *J. Am. Chem. Soc.* **1971**, *93*, 262−264. (b) Pearson, A. J. *Iron Compounds in Organic Synthesis;* Academic Press: London, 1994; p 83−84.

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(5) For examples of selective cycloadditions to activated olefins, see: (a) Mehta, G.; Reddy, S. H. K. *Tetrahedron Lett.* **1991**, *32*, 4989−4992. (b) Mehta, G.; Reddy, S. H. K.; Reddy, D. S. K. *Tetrahedron Lett.* **1991**, *32*, 6399−6402.

(6) Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114−1115.

(7) Grubbs, R. H.; Pancoast, T. A.; Grey, R. A. *Tetrahedron Lett.* **1974**, 2425−2426.

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convenient route to the cycloaddition substrates was realized by exploiting the ability of the iron complex to stabilize an α-carbonium ion. In a manner similar to dicobalt hexacarbonyl−alkynyl complexes,[10] the desired cyclobutadienyl ethers are obtained readily when **28** and the corresponding allylic alcohols are treated with catalytic acid.[11]

Since intermolecular cycloadditions of **26** with unactivated olefins afford only cyclobutadiene oligomerization products, high dilution conditions (*i.e.*, <5 mM) were thought to be required for a selective intramolecular reaction. As illustrated in Table 1, oxidation of the cyclobutadiene−iron complexes at high dilution did indeed provide efficient intramolecular cycloadditions (cycloadducts, entries 1−7).[12] It is of particular interest that, unlike the related intermolecular processes, these cycloadditions do proceed with unactivated olefins. While other conditions to unmask the reactive cyclobutadiene functionality were examined,[13] a cerium ammonium nitrate(CAN)-mediated oxidation provided superior results.

Tolerance for sterically encumbered alkenes in this transformation is evident with the cycloaddition of substrate **23**, where two adjacent quaternary centers are established on the newly formed four-member ring (**23** → **24**) of the cycloadduct. Interestingly, oxidation of substrates possessing a conformationally restricted tether, such as **20**, provides mainly oligomeric products. Fortunately, at higher temperatures and shorter reaction times (*e.g.*, 55 °C for 2 min) formation of the desired intramolecular cycloaddition product (*i.e.*, **21**) is significantly favored over undesired processes.

The stereochemical assignments of the cycloadducts illustrated in Table 1 are supported by ^{1}H NMR coupling constants, as well as NOE and chemical correlation studies.[14] For example, whereas cycloadduct **15** displays an NOE between the methylene protons on the propyl substituent and one of the tetrahydrofuranyl protons, the tetrahydrofuranyl protons of cycloadduct **12** show NOEs only to protons on the cyclobutane ring. Overall, the relative stereochemistry of the cycloaddition appears to be governed by expected thermodynamic preferences in forming cyclobutane-containing fused-ring systems.[15]

An important issue of whether the alkene stereochemistry is preserved during the cycloaddition is addressed with entries 3 and 4. If the reaction is stepwise, as might be the case given the oxidative nature of the transformation,[16] the stereochemical integrity of the tethered olefin in substrates **11** and **14** may be lost through freely rotating radical or carbocation intermediates. If these freely rotating intermediates are involved in the mechanism, molecular mechanic calculations suggest that cycloaddition of both **11** and **14** should favor the formation of **15**. Since substrates **11** and **14** provide only cycloadducts **12** and **15**, respectively, a concerted mechanism appears to be operative.

To extend the utility of the intramolecular cyclobutadiene cycloadditions beyond our need in ring-opening cross metatheses, the cyclobutene-containing cycloadducts shown in Table 1 were heated in pentane or benzene to provide novel 1,3-cyclohexadiene-containing substrates (thermal products, entries 1−7).[17] This method complements other intramolecular cycloadditions/extrusions strategies which provide cyclohexadiene-containing bicyclic ring systems.[18]

In summary, this work, describing the first intramolecular cycloadditions of cyclobutadienes with unactivated olefins, provides a new strategy for the synthesis of functionalized cyclobutene-containing substrates. In addition, the cyclobutene-containing compounds can be used for the preparation of 1,3-cyclohexadiene-containing systems. For the rapid preparation of functionalized medium ring-containing systems, selective ring-opening cross metatheses of the cyclobutene-containing cycloadducts will be the subject of future studies.

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Supporting Information Available: Experimental procedures and spectrographic data are provided for all new compounds (17 pages). See any masthead page for ordering and Internet access instructions.

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(10) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214.

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(12) Typical cycloaddition conditions: An acetone (4 mM, −5 °C) solution of the iron−cyclobutadiene substrate was treated with CAN (4 equiv) for 15 min. The reaction was then diluted with water, and the product was extracted into pentane. After the organic layer was dried with Na_2SO_4, the crude product was used directly in the next step. Alternatively, concentration of the organic layer followed by silica gel chromatography provided analytically pure material.

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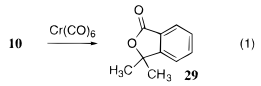
(14) Structural assignments are supported further through the following transformations. Koala bear metabolite derivative **29** (Southwell, I. A. *Tetrahedron Lett.* **1975**, 1885−1888) was obtained when **10** was subjected to a $Cr(CO)_6$/*t*-BuOOH (eq 1). In a related fashion, the independent DDQ oxidation of **13** and **16** to the same aromatic product supports the diastereotopic relationship between **13** and **16**.



(1)

(15) Eliel, E. I.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994; Chapter 11.

(16) Schmittel, M.; Wöhrle, C. *J. Org. Chem.* **1995**, *60*, 8223−8230.

(17) Typical thermolysis conditions: The cycloadduct in pentane (0.01 M) was heated under an Ar atmosphere in a sealed tube (220 °C, 90 min). Removal of the solvent followed by silica gel flash chromatography yielded the thermal product.

(18) For related examples, see: (a) Noguchi, M.; Kakimoto, S.; Kajigaeshi, S. *Chem. Lett.* **1985**, 151−154. (b) Noguchi, M.; Kakimoto, S.; Kawakami, H.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.***1986**, *59*, 1355−1362.