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Intramolecular Cycloadditions of Cyclobutadiene with Olefins

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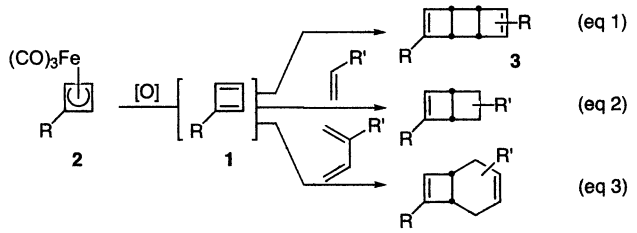
Abstract: Intramolecular cycloadditions between cyclobutadiene and olefins can provide highly functionalized cyclobutene-containing products. The outcome of the reaction depends on the nature of the tether connecting the two reactive partners in the cycloaddition. Electronically unactivated olefins attached to cyclobutadiene through a three-atom, heteroatom-containing tether yield successfully the desired cycloadducts, whereas the corresponding substrates without a heteroatom linkage or with a longer tether are less prone to undergo the intramolecular cycloaddition. Calculations were used to help uncover some of the factors that influence the course of the cycloaddition. Successful intramolecular reactions usually require either electronic activation of the dienophile, conformational restriction of the tether, or a slower oxidation protocol. In general, a facile intermolecular dimerization of cyclobutadiene is the major process that competes with the intramolecular cycloaddition.

Introduction

Cyclobutadiene (**1**, R = H) is a highly reactive, antiaromatic species[1] that undergoes rapid and facile dimerization (**1** → **3**, eq 1).[2] Nevertheless, cyclobutadiene has been observed at low temperatures (i.e., 8 K, noble gas matrix),[3] inferred through Rebek's three-phase test,[4] and isolated inside Cram's hemicarcerand molecular container.[5] The reactivity of cyclobutadiene can be modulated, however, through coordination to a metal center.[6] The metalloaromatic[7] tricarbonylcyclobutadiene iron complex [$C_4H_4Fe(CO)_3$] (**2**, R = H), for example, has sufficient stability to tolerate a wide range of transformations without disrupting the cyclobutadiene functionality, including electrophilic aromatic substitution reactions,[8] deprotonation of the cyclobutadiene ring hydrogen(s) followed by trapping with electrophiles,[9] and Pd(0)-catalyzed C−C and C−N bond forming reactions.[10] In general, the iron tricarbonyl complexes survive acidic, basic, and reducing environments, as well as some mild oxidizing conditions. Treatment of these complexes with cerium ammonium nitrate (CAN), however, can oxidize the iron and liberate free cyclobutadiene.[11] To a lesser extent, $FeCl_3$ and $Pb(OAc)_4$ have also been used for this purpose.[11] When cyclobutadiene is generated in the presence of olefins and dienes, an intermolecular cycloaddition can lead to a variety of cyclobutene-containing adducts (eqs 2 and 3).[11]



We envisioned that an *intramolecular* reaction between cyclobutadiene and olefins could offer substantial control over

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⊥ Current address: Infinity Pharmaceuticals, 650 Albany St., Boston, MA 02118.

(1) (a) Maier, G. *Angew. Chem.* **1974**, *86*, 491. (b) Deniz, A. A.; Peters, K. S.; Snyder, G. J. *Science* **1999**, *286*, 1119. (c) Bally, T.; Masamune, S. *Tetrahedron* **1980**, *36*, 343.
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(7) Bursten, B. E.; Fenske, R. F. *Inorg. Chem*. **1979**, *18*, 1760.
(8) For reviews on cyclobutadienylmetal complexes, see: Efraty, A. *Chem. Rev*. **1977**, *77*, 691 and references therein.
(9) Bunz, U. *Organometallics* **1993**, *12*, 3594 and references therein.
(10) For Stille type couplings, see: (a) Bunz, U. H. F.; Enkelmann, V. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1653. (b) Wiegelmann, J. E. C.; Bunz, U. H. F.; Schiel, P. *Organometallics* **1994**, *13*, 4649. For C−N bond forming reactions, see: Wiegelmann-Kreiter, J. E. C.; Enkelmann, V.; Bunz, U. H. F. *Chem. Ber*. **1995**, *128*, 1055.

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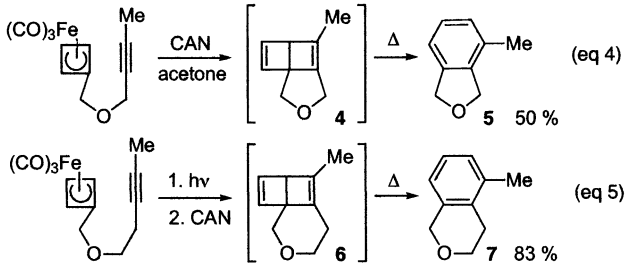
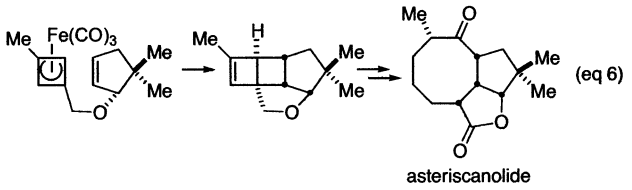
chemo-, regio-, and stereoselectivity issues in these cycloadditions. Furthermore, the intramolecular variants could yield a unique and rapid access into highly functionalized, cyclobutene-containing cycloadducts. The strain associated with these cycloadducts should provide novel opportunities for improved access to several types of challenging synthetic targets.[12]

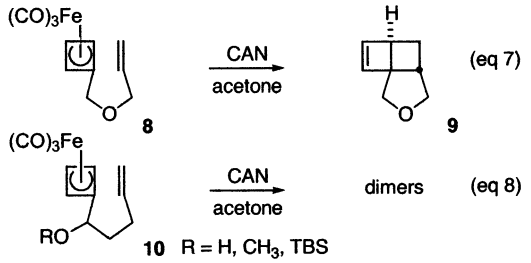
In support of the intramolecular reaction, Grubbs and coworkers have shown that cyclobutadiene reacts with tethered alkynes to yield aromatic systems (eqs 4 and 5).[13] Presumably, these reactions proceed through the desired cyclobutene-containing Dewar benzene-intermediates (**4** and **6**), but rearrange upon mild heating during the workup to the observed aromatic products.



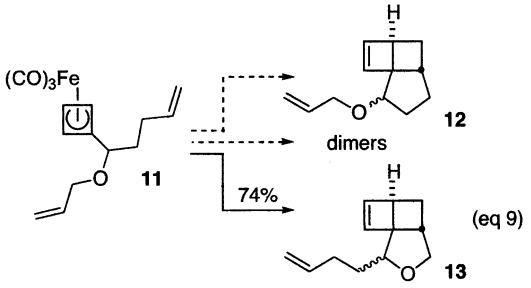
Our preliminary studies have demonstrated the feasibility of intramolecular reactions of cyclobutadienes with olefins.[14] Moreover, we have shown that the resulting highly strained cycloadducts provide unique and effective entries into seven- and eight-membered ring systems.[15] The concise nine-step synthesis of asteriscanolide, featuring an intramolecular cyclobutadiene cycloaddition, is illustrative (eq 6).[12]



While offering effective access to functionalized cyclobutenes, our results indicate that the success of these cycloadditions is dependent on the nature of the tether connecting the two reactive cycloaddition partners. For example, when **8** is treated with CAN, cycloadduct **9** is generated in 85% yield (eq 7); however, the identical oxidation of complex **10** yields only cyclobutadiene dimers without any of the desired intramolecular cycloaddition (eq 8). Because it was unclear whether the ether tether of substrate **8** serves to facilitate the intramolecular cycloaddition



or the secondary hydroxyl or ether functionality adjacent to the cyclobutadiene moiety in compound **10** inhibits the reaction, substrate **11** was prepared to address this reactivity question. Oxidation of complex **11** generates cycloadduct **13** in 74% yield as a 3:1 mixture of diastereoisomers (eq 9). Evidently, this example suggests that the intramolecular cycloaddition with CAN tolerates a substituent adjacent to cyclobutadiene and, moreover, *requires* the ether linkage to proceed.



Examining and understanding the subtle, yet critical effect of tether composition in the intramolecular cycloaddition is necessary to exploit fully the utility of the methodology. *Along these lines, our studies of the factors that influence the intramolecular cycloadditions of cyclobutadienes with olefins are reported herein.* In particular, the influence of tether length and substituents, as well as the stereochemistry and electronic properties of the cycloaddition partners in the intramolecular cycloadditions, are described. In conjunction with experimental studies, theoretical density functional calculations using B3LYP/6-31G(d) were performed to quantify specific effects of the tether and olefin substitution on the relative ease of intra- and intermolecular cycloadditions of cyclobutadiene.

Results and Discussion

Oxidative Decomplexation of $(CO)_3$Fe-Cyclobutadiene Complexes. The major competing side reaction in the intramolecular cycloadditions is the dimerization of cyclobutadiene (eq 1). In general, minimizing the concentration of free cyclobutadiene will serve to favor the intramolecular process over the facile intermolecular side reaction. For substrates predisposed toward the intramolecular pathway, a cerium ammonium nitrate (CAN) oxidation of the iron complex provides the desired cycloadducts rapidly in acceptable yields (5 equiv of CAN, acetone, [1−2 mM] iron complex, room temperature, 15 min). For substrates less prone to undergo the intramolecular reaction, a slower trimethylamine-*N*-oxide (TMAO) oxidation affords better yields of the desired cycloadducts (8−20 equiv of TMAO, acetone, [2−20 mM] iron complex, reflux, 6−24 h). In either case, excess oxidant is usually required for complete consumption of the starting complex. Even under high dilution and slow oxidation conditions, particularly poor cycloaddition substrates

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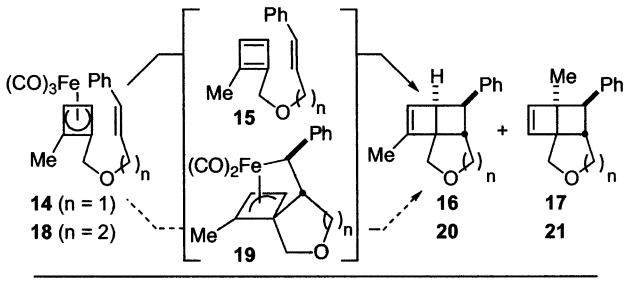
(15) (a) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478. (b) Randall, M. L.; Lo, P. C.-K.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534. (c) Lo, P. C.-K.; Snapper, M. L. *Org. Lett.* **2001**, *3*, 2819. (d) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152.

Table 1. Cycloadditions of Chiral Cyclobutadiene Complexes



entry	SM (% ee)	conditions[a]	yield	product ratio (ee)
1	**14** (35%)	CAN	66%	**16**:**17** = 16 (0%):1 (0%)
2	**14** (35%)	TMAO	55%	**16**:**17** = 14 (0%):1 (0%)
3	**18** (35%)	CAN	48%	**20**:**21** = 1 (0%):1 (0%)
4	**18** (35%)	TMAO	54%	**20**:**21** = 1 (0%):1 (0%)

[a] CAN (room temperature, 2 mM, 15 min); TMAO (56 °C, 20 mM, 6 h).

(see below) are unable to compete with the rapid intermolecular dimerization. Nevertheless, the TMAO oxidative conditions generally yield more favorable intramolecular cycloadditions for a broader range of substrates.

Clearly, the more that is understood about the mechanism of the intramolecular cycloaddition, the better the reaction outcome can be predicted. One longstanding concern has been the role of iron in the cycloaddition. Previous studies on intermolecular cycloadditions with olefins and intramolecular cycloadditions with alkynes have indicated that the iron does not play a stereochemical role in the CAN-promoted cycloadditions.[13]

As shown in Table 1, our findings support the conclusion that both the CAN- and the TMAO-promoted intramolecular cycloadditions of cyclobutadienes with olefins likely proceed through liberation of a free cyclobutadiene, without involvement of a chiral iron complex. Specifically, when enantiomerically enriched disubstituted complexes **14** and **18** (both 35% ee) were treated with either CAN or TMAO under the usual reaction conditions, a regioisomeric mixture of *racemic* cycloadducts was obtained (**16**:**17**, **20**:**21**). These results suggest the intramolecular cycloaddition involves an achiral cyclobutadiene species such as cyclobutadiene **15** (i.e., not **19**).

Three-Atom Heteroatom-Containing Tethers. Our initial investigation focused on substrates containing a three-atom tether between the cyclobutadiene and the olefinic partner. Table 2 summarizes the results of these cycloadditions with an *ether*- or *amine*-containing linkage. Electronic activation of the olefins is not necessary for these intramolecular cycloadditions to proceed efficiently. The transformation yields the cyclobutene-contained cycloadducts in moderate to excellent yields (20−93%). Entries 2 and 3 indicate that the reaction proceeds stereospecifically, results that are consistent with a concerted cycloaddition of cyclobutadiene reacting from the rectangular singlet ground state.[16]

The cycloaddition clearly tolerates sterically encumbered olefins, as illustrated in entry 5. In this example, two adjacent quaternary carbon centers (C1, C2) are generated simultaneously in the newly formed cyclobutane **31**. The kojic acid-derived

Table 2. Intramolecular Cycloadditions with Three-Atom Heteroatom-Containing Tethers

entry	substrate	cycloadduct	method[a]	yield[b]
(1)	**22** R_1=R_2=H	**23**	A	85%
(2)	**24** R_1=*n*-Pr, R_2=H	**25**	A	64%
(3)	**26** R_1=H, R_2=*n*-Pr	**27**	A	70%
(4)	**28** R_1=R_2=Me	**29**	A	70%
(5)	**30**	**31**	A	65%
(6)	**32**	**33**	A	90%
(7)	**34**	**35**	A	35% (4.5:1.0 dr)
(8)	**36**	**37**	A B C	20% 49% 64%
(9)	**38** R=SO_2*p*-Tol	**39**	A	93%
(10)	**40** R= allyl	**41**	A	70%

[a] Reaction conditions: method A, CAN (5 equiv), acetone (1−2 mM), room temperature, 15 min; method B, CAN (10 equiv), DMF (1 mM), 80 °C, 5 min; method C, TMAO (10 equiv), acetone (45 mM), reflux, 12 h. [b] Isolated yields.

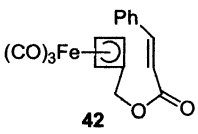
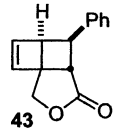
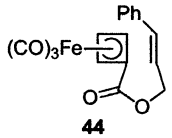
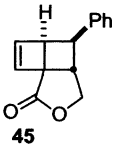
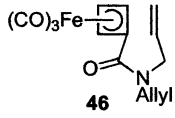
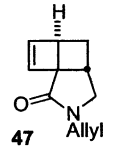
substrate **32** (entry 6) was prepared to study the possibility of a competing intramolecular "[5 + 2]" cycloaddition.[17] Under the typical reaction conditions, however, the "[4 + 2]" (cyclobutadiene functioning as a diene) cycloadduct **33** was obtained exclusively in 90% yield. The possibility of employing an allene as a cycloaddition partner was also investigated; subjection of substrate **34** to CAN afforded a mixture of diastereomeric cyclobutene cycloadducts **35** (4.5:1 dr), albeit in only 35% yield (entry 7).

The disubstituted complex **36** (entry 8), which was used in the total synthesis of (+)-asteriscanolide,[12] was less prone to undergo the desired intramolecular cycloaddition under the typical CAN-promoted reaction conditions, presumably due to additional ring strain. The yield for this cycloaddition was improved when the reaction was carried out in DMF at 80 °C (20 → 49%). To improve further the reaction, several other oxidants were screened. Trimethylamine *N*-oxide (TMAO) was found to promote an efficient intramolecular cycloaddition of complex **36** at higher concentrations (i.e., 45 mM), without

(16) (a) Dewar, M. J. S.; Gleicher, G. J. *J. Am. Chem. Soc.* **1965**, *87*, 3255. (b) Reeves, P.; Henery, J.; Pettit, R. *J. Am. Chem. Soc.* **1969**, *91*, 5888. (c) Reeves, P.; Devon, T.; Pettit, R. *J. Am. Chem. Soc.* **1969**, *91*, 5890. (d) Balkova, A.; Bartlett, R. J. *J. Chem. Phys.* **1994**, *101*, 8972.

(17) (a) Rodriguez, J. R.; Rumbo, A.; Castedo, L.; Mascarenas, J. L. *J. Org. Chem.* **1999**, *64*, 4560. (b) Wender, P. A.; Mascarenas, J. L. *Tetrahedron Lett.* **1992**, *33*, 2115. (c) McBride, B. J.; Garst, M. E. *Tetrahedron* **1993**, *49*, 2839.

Table 3. Intramolecular Cycloadditions of Carboxylate Derivatives

entry	substrate	cycloadduct	method[a]	yield[b]
(1)	 **42**	 **43**	A B C	55% 70% 88%
(2)	 **44**	 **45**	A D	0%[c] 0%[c]
(3)	 **46**	 **47**	A D	47% 30%

[a] Reaction conditions: method A, CAN (5 equiv), acetone (1−2 mM), room temperature, 15 min; method B, CAN (5 equiv), CH_3CN (1 mM), room temperature, 15 min; method C, CAN (10 equiv), DMSO:H_2O (1:1), room temperature, 15 min; method D, TMAO (8−10 equiv), acetone (20 mM), reflux, 12 h. [b] Isolated yields. [c] 20−30% starting material recovered, as well as 65% *trans*-cinnamyl alcohol.

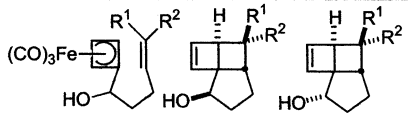
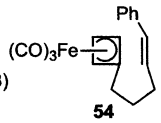
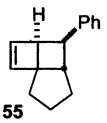
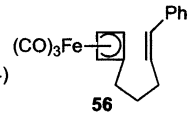
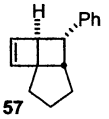
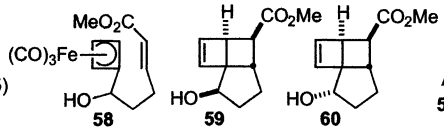
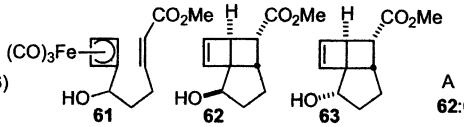
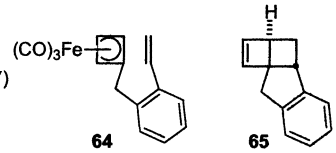
formation of cyclobutadiene-dimer byproducts. The reaction was carried out in refluxing acetone for 6−12 h with excess oxidant to give the desired cycloadduct **37** in 64% yield. The fact that the transformation can be carried out at a higher concentration and requires longer reaction times to consume starting materials suggests that the reactive cyclobutadiene is generated more slowly as compared to under the CAN conditions, and, hence, self-dimerization of cyclobutadiene is kept to a minimum.

To expand the scope of the cycloaddition methodology, nitrogen-tethered intramolecular cycloadditions were examined. Concerned that free amines may undergo oxidation, the sulfonamide complex **38** was prepared for the initial studies. Subjection of **38** to the CAN-promoted reaction conditions afforded the desired cyclobutene cycloadduct **39** in 93% yield (entry 9, Table 2). Under similar conditions, the *N*,*N*-diallylamine complex **40** also afforded the corresponding cyclobutene **41** as the major product in 70% yield (entry 10). Again, electronic activation of the dienophile does not appear to be essential for the cycloaddition. These results suggest that oxidation of the amine is either slower than oxidative liberation of the cyclobutadiene ligand or the nitrogen is protected under the moderately acidic CAN reaction conditions.

We next investigated intramolecular cycloadditions of iron complexes linked to olefins through a carboxylate-containing tether (Table 3). Subjection of ester **42** to the typical CAN reaction conditions afforded the desired lactone **43** in 55% yield (entry 1). The yield of the reaction appears to be dependent on solvent, with the polar mixture of DMSO:H_2O (1:1) giving the best results (88% yield).[18] When the ester functionality is transposed as in complex **44**, however, none of the desired cyclobutene lactone **45** was obtained with either the CAN- or the TMAO-based oxidations. Moreover, incomplete consumption of starting material was encountered (70−80% conversion), and *trans*-cinnamyl alcohol (∼65%) was recovered upon aqueous workup, suggesting that hydrolysis of the ester occurred

(18) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469.

Table 4. Intramolecular Cycloadditions with Three-Atom All-Carbon Tethers

entry	substrate	cycloadduct	method[a]	yield[b] (dr)
(1)	**48** R^1 = Et, R^2 = H	 **49** : **50**	A B	trace 49% **49:50** (2.9:1.0)
(2)	**51** R^1 = H, R^2 = *n*-Pent	**52** **53**	A or B	trace
(3)	 **54**	 **55**	A B	53% 55%
(4)	 **56**	 **57**	A B	trace 53%
(5)	 **58** **59** **60**		A	92% **59:60** (2.3:1.0)
(6)	 **61** **62** **63**		A	66% **62:63** (2.5:1.0)
(7)	 **64** **65**		C	34%

[a] Reaction conditions: method A, CAN (5 equiv), acetone (1−10 mM), room temperature, 15 min; method B, TMAO (10 equiv), refluxing acetone (20 mM), 6−8 h; method C, CAN (10 equiv), refluxing acetone:CH_2Cl_2 (7:1, 1 mM), 3 min. [b] Isolated yields.

under the reaction conditions. The corresponding *N*,*N*-diallylamide complex **46**, on the other hand, afforded cyclobutene **47** in modest yield under either CAN or TMAO reaction conditions (entry 3, Table 3).

Three-Atom Tethers, All-Carbon Linkage. We also investigated the feasibility of intramolecular cycloadditions of cyclobutadiene complexes bearing all-carbon tethers. While heteroatom-containing three-atom tether substrates undergo efficient CAN-promoted cycloadditions, the all-carbon tether substrates, such as **48** and **51** (entries 1 and 2, Table 4, as well as **10**, eq 7), fail to undergo an efficient intramolecular cycloaddition under similar reaction conditions. These findings suggest that under fast oxidative decomplexation of the iron complex by CAN, intermolecular dimerization of the cyclobutadiene competes with the intramolecular process even under high dilution reaction conditions. When the reaction was carried out using a slower oxidant TMAO, however, the desired cycloadducts were obtained as a mixture of diastereomers in 49% yield (**49**:**50** = 2.9:1).

There are numerous differences between the heteroatom- and the all-carbon-containing tethers that could account for this reactivity difference. The ability of the oxygen in the tether to

coordinate to Lewis acidic species may influence the course of the reaction. However, as will be described in the theoretical section, calculations on the corresponding transition states indicate that the shorter C−O bond lengths and compressed C−O−C bond angles may play a role favoring the intramolecular cycloaddition process.[19]

One way to enhance the intramolecular Diels−Alder reaction is to electronically activate the dienophile (i.e., lower LUMO) through conjugation with a phenyl group. As shown in entry 3 of Table 4, treatment of the *trans*-phenyl substrate **54** with CAN or TMAO affords the desired cycloadduct **55** in 53−55% yield, with no indication of intermolecular side products. The *cis*-phenyl isomer **56**, however, failed to undergo the desired intramolecular cycloaddition under CAN reaction conditions. With the slower oxidant TMAO, the corresponding cyclobutene cycloadduct **57** was obtained in 53% yield (entry 4). These findings suggest that secondary orbital interactions between the cyclobutadiene and the dienophile, enjoyed in the *trans*- but not the *cis*-isomers, may be helpful, but are not required for a favorable intramolecular process. In addition, while electronic activation of *trans*-olefin substrates (**48** or **54**) is not essential for a successful intramolecular cycloaddition, some activation is necessary for the corresponding *cis*-olefin isomers (complex **51** vs **56**).

Changing the substituent on the olefin from a phenyl to an ester group provides additional electronic activation of the olefin (i.e., further lowers LUMO) and increases the efficiency of the intramolecular cycloaddition. For example, treatment of *trans*-methyl ester complex **58** with CAN (2 mM, room temperature) affords the diastereomeric cycloadducts (**59**:**60** = 2.3:1) in 92% yield (entry 5, Table 4). A similar yield was obtained when this reaction was carried out at higher concentrations. In comparison, oxidative decomplexation of the corresponding *cis*-methyl ester **61** under high dilution (CAN, 2 mM, room temperature) affords the diastereomeric cycloadducts in a somewhat lower yield (66%, **62**:**63**/2.5:1, entry 6). These results suggest that, while secondary orbital interactions between two reacting partners in *trans*-isomers could favor the intramolecular cyclizations, electronic activation of either the *cis*- or the *trans*-dienophile is an overriding factor in favoring the intramolecular reaction.

Another way to favor the intramolecular cycloaddition relative to competitive intermolecular processes is to limit the degrees of freedom of the tether. The conformationally restricted and electronically activated complex **64** (entry 7, Table 4), however, affords cyclobutene **65** in only 34% yield in refluxing acetone:CH_2Cl_2 [7:1] (CAN, 1 mM, 3 min). *These results (as well as those reported below) indicate a limitation on using functionality within the connecting tether to activate the olefin toward cycloaddition.*

As mentioned, substrates with all-carbon, three-atom tethers that possess electronic activation of the dienophile *external* to the connecting tether undergo a facile intramolecular cycloaddition (entries 5 and 6, Table 4), especially under the faster oxidative decomplexation conditions of CAN. Given these observations, we investigated the feasibility of cycloadditions involving electronically activated enone substrates, where the carbonyl functionality is part of the tether (i.e., internal with respect to the olefin, Table 5). Subjection of complexes **66**, **68**, or **70** under typical (acetone, 1 mM, room temperature) or more vigorous (refluxing acetone, acetonitrile, dioxane) CAN reaction conditions did not afford any of the desired ketone cycloadducts (entries 1−3, method A, Table 5); in all cases, only cyclobutadiene dimers were detected.

Table 5. Cycloadditions with Enone Substrates

entry	substrate	cycloadduct	method[a]	yield[b]
(1)	**66** R = Ph	**67**	A B	0% 70%
(2)	**68** R = *n*-Pent	**69**	A B	0% 51%
(3)	**70** R = *t*-Butyl	**71**	A B	0% 27%
(4)	**72** R =CO_2Me	**73**	A	91%
(5)	**74** R = Ph	(**67**)[d]	C	70%(100%)[c]
(6)	**75** R = *n*-Pent	(**69**)[d]	C	57%(75%)[c]
(7)	**76** R = *t*-Butyl	(**71**)[d]	C	29%(95%)[c]
(8)	**77**	**78**	A	83%

[a] Reaction conditions: method A, CAN, acetone (1 mM), room temperature; method B, TMAO, acetone (5−20 mM), reflux; method C, CAN, MeOH (1 mM), room temperature. [b] Isolated yields. [c] Overall yield from the corresponding enone $C_4H_4Fe(CO)_3$ substrate; the number in parentheses represents percent conversion during ketalization of enones **66**, **68**, and **70**. [d] Isolated as the corresponding ketones **67**, **69**, and **71**.

The failure of these CAN-promoted intramolecular cycloadditions can be attributed perhaps to disfavorable torsional and angle strains associated with the tethered carbonyl in the transition state of the requisite rotamer for the cycloaddition. A way to resolve this limitation is to convert the ketone into an sp^3-hybridized functional group. In this regard, we prepared the dimethyl ketal complexes **74**−**76**. Not only would the dimethyl ketal help to release any strain associated with the tethered carbonyl, it would also increase the population of the reactive rotamer through Thorpe−Ingold and reactive rotamer effects.[18] Subjection of the dimethyl ketal complexes **74**−**76** to the CAN-promoted cycloaddition conditions (MeOH, 1 mM, room temperature) indeed afforded the corresponding dimethyl ketal cycloadducts, which, with the exception of the phenyl cycloadduct derived from **74**, were difficult to isolate without some hydrolysis of the ketal functionality. In practice, these adducts were subjected to a mild deprotection protocol (SiO_2/10% aqueous oxalic acid, CH_2Cl_2, room temperature), yielding the corresponding ketone cycloadducts **67**, **69**, and **71** in 20−70% yield for the three steps (entries 5−7, Table 5). It is interesting to note that under these deprotection conditions, no rearrangements associated with carbonium ion character adjacent to the cyclobutane ring were observed.

(19) Jung, M. E.; Kiankarimi, M. *J. Org. Chem.* **1998**, *63*, 2968.

Along the same lines, a *gem*-dialkyl substituent on the tether should increase the population of the reactive conformer for the cycloaddition. In this regard, while phenyl enone substrate **66** failed to give the desired cycloadduct under CAN-promoted reaction conditions, the dimethyl phenyl enone substrate **77** afforded the corresponding ketone adduct **78** in 83% yield (entry 8, Table 5).

When an additional electron-withdrawing group ($-CO_2Me$) is present on the dienophile, such as in complex **72**, the corresponding cyclobutene cycloadduct **73** is obtained in high yield (91%, entry 4). When the slower oxidant TMAO is used in refluxing acetone, enone complexes **66**, **68**, and **70** underwent the desired [4 + 2] cycloadditions, affording the corresponding cyclobutene cycloadducts **67**, **69**, and **71** in 27−70% yields (entries 1−3, method B, Table 5). Substrates bearing a bulkier substituent on the olefin, such as the *tert*-butyl group in complex **70**, required higher dilutions (5 mM) and longer reaction times, and only a 27% yield of cycloadduct **71**, together with significant amounts of the corresponding cyclobutadiene dimers, was obtained (entry 3, method B, Table 5).

In general, the success of intramolecular cycloadditions of three-atom-tethered iron cyclobutadiene complexes depends on several factors. Electronic activation of the dienophile, favorable secondary orbital interactions (*trans*-olefin), restrictions in the degrees of freedom of the connecting tether, and/or incorporation of a geminal substitution along the tether all serve to facilitate the intramolecular cycloaddition when the fast oxidant CAN is employed. In cases lacking *some* of these favorable elements, the slower oxidant TMAO may be used to accomplish the desired transformation.

Four-Atom Heteroatom-Containing Tethers. Inserting an additional atom in the tether to generate a four-atom connection between the cycloaddition partners increases the degrees of freedom and number of possible nonproductive rotamers, which can result generally in a less efficient intramolecular process. Under typical CAN oxidation conditions, complex **79** failed to undergo the desired cycloaddition (entry 1, method A, Table 6); only dimers were obtained as judged by the ^{1}H NMR spectrum of the reaction mixture. On the other hand, switching to the slower TMAO oxidation leads to the formation of some of the corresponding cyclobutene cycloadduct **80** (entry 1, method B). Optimization of the reaction conditions provides a modest 22% yield of cycloadduct **80**. When the dienophile is activated, such as in *trans*-phenyl complex **81**, the cycloaddition proceeds more smoothly, affording the corresponding cycloadduct **82** under either CAN (63%) or TMAO (55%) reaction conditions (entry 2). More activated dienophiles, such as in *trans*-methyl ester complex **83**, also provide the desired cyclobutene **84** in a 65% yield (entry 3) under CAN-promoted reaction conditions. These results suggest that electronic activation of the reacting dienophile in the four-atom tether substrates is essential for a successful and synthetically useful intramolecular cycloaddition.

While activated *trans*-olefinic substrates afford the cyclobutene adducts in reasonable yields, the *cis*-isomers undergo a much less efficient intramolecular cycloaddition. For example, subjection of *cis*-phenyl substrate **85** (entry 4) or *cis*-methyl ester **87** (entry 5) to CAN did not result in the formation of the intramolecular cycloadducts; in each case, only dimers were obtained. Under the TMAO-promoted reaction conditions (1 mM, refluxing acetone, 24 h), complex **85** afforded a 17% yield of cycloadduct **86**. Interestingly, under these reaction conditions, the *cis*-methyl ester substrate **87** gave two cycloadducts (**88**:**89**/3:1; entry 5) in a modest 21% yield. The major cycloadduct (**88**) was the product of a Type II intramolecular cycloaddition.[20]

Table 6. Intramolecular Cycloadditions with Four-Atom Ethereal Tethers

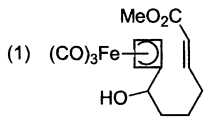
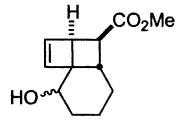
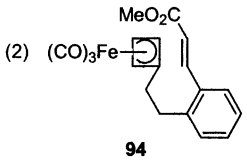
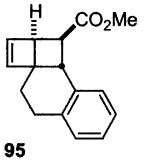
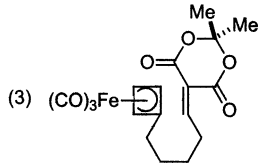
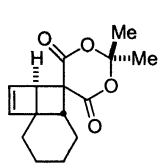
entry	substrate	cycloadduct	method[a] (yield[b])
(1)	**79** R = Et	**80**	A (0%), B (22%)
(2)	**81** R = Ph	**82**	A (63%), C (55%)
(3)	**83** R = CO_2Me	**84**	A (65%)
(4)	**85**	**86**	A (0%), B (17%)
(5)	**87**	**88** / **89**	A (0%), B (21%); **88**:**89** (3.3:1.0)
(6)	**90**	**91**	A (0%), B (30%)

[a] Reaction conditions: method A, CAN, acetone (1 mM), room temperature, 15 min; method B, TMAO (20 equiv), refluxing acetone (1 mM), 24 h; method C, TMAO (8 equiv), refluxing acetone (20 mM), 6 h. [b] Isolated yields.

A role for the beneficial secondary orbital interaction is also consistent with the *trans*-olefinic substrates undergoing the intramolecular cycloaddition in higher yields as compared with the corresponding *cis*-olefin-containing compounds. Nevertheless, there may be additional unfavorable steric interactions in the transition state of the *cis*-isomers that may also slow the intramolecular reaction relative to competitive intermolecular processes. Complex **90**, which has both a *cis*- and a *trans*-substituent on the pendent olefin, was prepared to help differentiate between these effects. If it is the favorable electronic interactions of the *trans*-substituent that lead to a successful intramolecular cycloaddition, then **90** should cyclize smoothly. Alternatively, if the *cis*-substituent suffers unfavorable steric interactions in the transition state, then the intramolecular reaction will suffer relative to competitive intermolecular processes. Subjecting complex **90** to the CAN cycloaddition conditions did not result in the formation of any of the desired cyclobutene cycloadduct; again, only the corresponding cyclobutadiene dimers were obtained. With TMAO (1 mM, refluxing acetone, 24 h), cyclobutene cycloadduct **91** was obtained, albeit in only 30% yield (entry 6, Table 6). These findings suggest that while activation (i.e., primary and secondary orbital

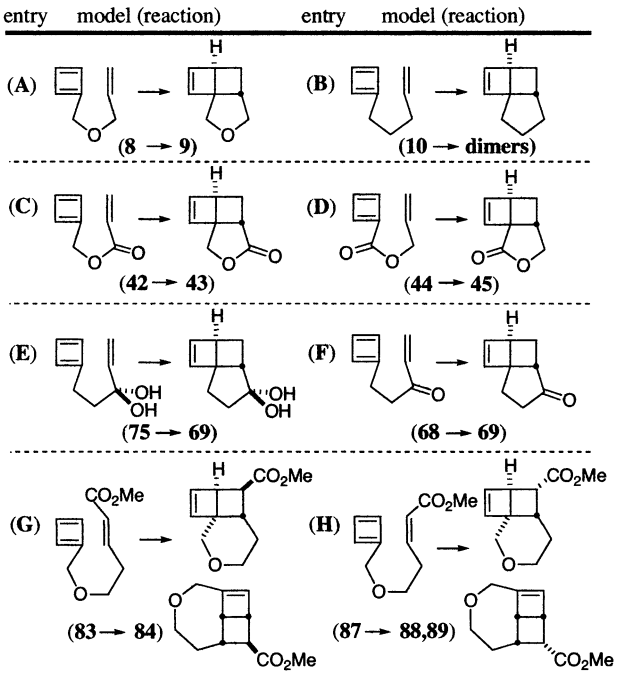
(20) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 821 and references therein.

Table 7. Cycloadditions with Four-Atom All-Carbon Tethers

entry	substrate	cycloadduct	method[a]	yield[b]
(1)	 **92**	 **93**	A	<5%
(2)	 **94**	 **95**	A	88%
(3)	 **96**	 **97**	A	33%[c]

[a] Reaction conditions: method A, CAN (5 equiv), acetone (1 mM), room temperature. [b] Isolated yields. [c] The yield represents a two-step sequence: Knovenagel condensation of the corresponding iron aldehyde with Meldrum's acid followed by CAN-promoted cycloaddition.

Table 8. Transformations Used To Examine Transition States



interactions) of four-atom tether substrates is essential for efficient cycloadditions, steric factors (i.e., nonbonded interactions) also play a significant role in dictating the outcome of the reaction.

Four-Atom Tethers, All-Carbon Linkage. Intramolecular cycloadditions between cyclobutadiene and olefins connected through an all-carbon four-atom tether were also examined (Table 7). All studies involving these substrates were performed using CAN to promote the oxidative decomplexations and intramolecular cycloadditions.

Unlike the electronically activated three-atom tether methyl ester **58** (entry 4, Table 4), the corresponding four-atom tether substrate **92** afforded only a trace of the expected cycloadduct **93** under identical reaction conditions (entry 1, Table 7). Resorting to refluxing acetone or CH_3CN did not improve the intramolecular cycloaddition. When the tether was rigidified by incorporation of a phenyl ring as in complex **94**, however, the desired cycloadduct **95** was obtained in 88% yield (entry 2). Evidently, restricting the degrees of freedom in the four-atom tether favors the intramolecular process, presumably by increasing the relative population of the reactive conformer.

The failure of methyl ester **92** to undergo efficient intramolecular cycloaddition prompted us to investigate further the effects of electronic activation of the tethered olefin. We reason that structural modifications to the dienophile that decrease the HOMO−LUMO gap of the cycloaddition partners could outweigh the extra entropic freedom of the longer tether. On the basis of this assumption, substrate **96** was prepared via a Knovenagel condensation of the corresponding four-carbon-tethered aldehyde. Because of the reactivity of **96** toward Michael additions, the compound was subjected to the typical CAN-promoted cycloaddition conditions without rigorous purification. The reaction proceeded to give the corresponding cyclobutene cycloadduct **97** as the only isolable monomeric product in 33% yield for the two steps (entry 3, Table 7).

These studies suggest that the intramolecular cycloadditions of all-carbon four-atom-tethered substrates require strongly activated dienophiles to compete favorably with the intermolecular cyclobutadiene dimerization process. In addition, unlike the three-atom-tethered examples, the incorporation of a rigid group in the four-atom tether, such as a phenyl ring, which decreases conformational freedom, can improve the efficacy of the intramolecular process.

Theoretical Calculations. Geometry optimizations were performed for all reactants, transition structures, and products using RB3LYP/6-31G(d) as implemented in Gaussian 98.[21] When an unrestricted wave function was found to be more stable, a reoptimization was performed using UB3LYP/6-31G(d). All stationary points were characterized with frequency calculations.

As shown in Table 8, the calculations focused on four pairs of model systems, each corresponding to a set of specific experimental reactions. In each pair, the first entries (**A**, **C**, **E**, **G**) model a reaction in which the intramolecular cycloaddition was successful, whereas the second systems (**B**, **D**, **F**, **H**) model an apparently similar reaction in which intermolecular dimerization, instead of intramolecular cycloaddition, was the major process. Entries **A** and **B** specifically address the reactivity of an ether versus an all-carbon tether. Systems **C** and **D** examine the effect of transposing the three-atom carboxylate tether. Systems **E** and **F** probe the consequence of changing an sp^3-

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

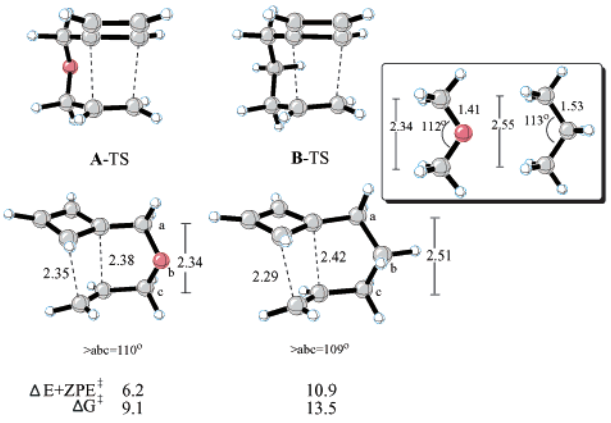
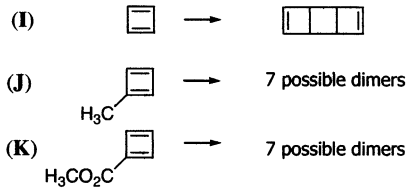


Figure 1. Calculated transition states for reactions **A** and **B**.

hybridized carbon in the tether to an sp^2 carbon. Systems **G** and **H** study the influence of *E* versus *Z* stereochemistry of four-atom-tethered alkenes.

Because cyclobutadiene dimerization is the major competing side reaction, several other model systems were examined computationally. Using systems **I** through **K**, we established the influence of alkyl and carboxylate substituents.



The transition structures for intramolecular [4 + 2] cycloaddition for systems **A** and **B** are shown in Figure 1. Two sets of energies (relative to the reactant) are provided for each transition structure. The first energy value (ΔE + ZPE‡) is the calculated electronic energy with zero point energy correction. The second energy value ($\Delta G^{\ddagger}$) is the calculated free energy at 25 °C. Free energies were computed for the conversion of global minimum to transition state.

A comparison of **A**-TS and **B**-TS reveals that the intramolecular cycloaddition is more favorable with the ether tether as compared to the all-carbon tether ($\Delta\Delta G^{\ddagger} = 4.4$ kcal/mol). **A**-TS is more synchronous than **B**-TS, and the incipient five-membered ring is more fully formed in **A**-TS. To evaluate the structural features of these two transition states, two additional sets of calculations were performed.

First, the ideal bond lengths of a cyclobutadiene-alkene [4 + 2] transition structure were determined in the *absence* of a tether. Examples of such transition structures are shown in Figure 2. In the case of cyclobutadiene plus ethylene, a concerted, synchronous TS is found.[22] The bond lengths clearly illustrate that this is a prototypical [4 + 2] transition structure, and not a [2 + 2] transition structure. Substitution of a methyl group on either the alkene or the cyclobutadiene leads to an increase in asynchronicity and activation energy. Methylcyclobutadiene plus propene has the most asynchronous TS, and its electronic activation barrier (ΔE + ZPE‡ = 14.7 kcal/mol) is higher than either of the intramolecular cases **A**-TS or **B**-TS (6.2 and 10.9 kcal/mol, respectively). Methyl substitution has a significant effect on the activation barrier of the intermolecular cycloaddition and is partly due to a decrease in thermodynamic driving

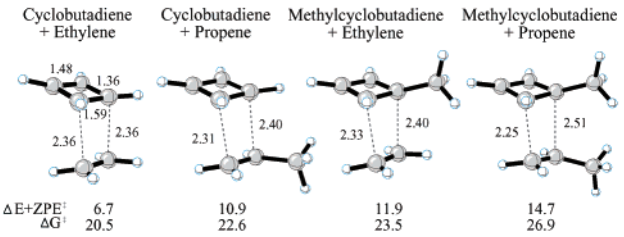


Figure 2. Transition state geometries for intermolecular cycloadditions between substituted cyclobutadienes and olefins.

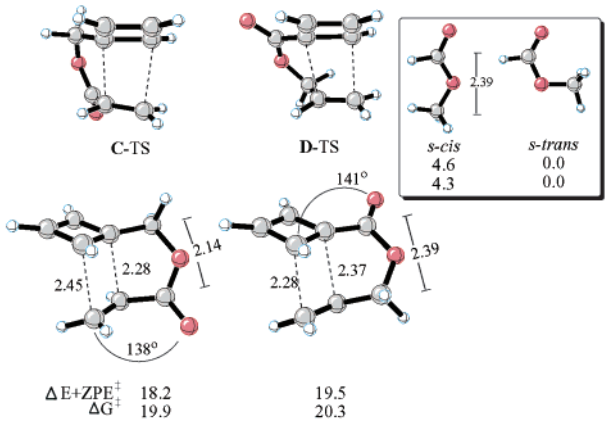


Figure 3. Calculated transition states for reactions **C** and **D**.

force along the series. For example, the ΔG_{rxn} changes from −42.1 kcal/mol (cyclobutadiene + ethylene) to −39.4, −37.8, and finally −33.8 kcal/mol (methylcyclobutadiene + propene).

The second additional set of calculations involved a simple comparison of dimethyl ether and propane (see inset Figure 1) to the ether tether and the three-carbon tether. The optimized geometry of dimethyl ether is very similar to that of the ether tether in **A**-TS. On the other hand, the optimized geometry of propane deviates from that of the all-carbon tether in **B**-TS. It appears that **B**-TS is more asynchronous and higher in energy than **A**-TS because the natural length of the propyl tether is longer than the natural length of the ether tether. This is partially compensated for by a compression of the ∠*abc* in **B**-TS, but only at the expense of angle strain that destabilizes the TS. Note the difference in tether lengths arises from C−O and C−C bond length differences.

The above calculations corroborate experimental results obtained for reactions of **8** and **10**. Assuming that the rate of dimerization is approximately equal for both systems, we expect a reactant with an ether tether would produce more of the desired intramolecular adduct.

Figure 3 compares three-atom ester tethers connected in two ways. The **C**-TS and **D**-TS have very similar energies ($\Delta\Delta G^{\ddagger}$ = 0.4 kcal/mol) with **C**-TS being slightly favored. These two transition structures are significantly higher in energy than either **A**-TS or **B**-TS; this is counterintuitive because we generally expect electron-withdrawing groups (such as an ester) to activate a [4 + 2] cycloaddition. However, as shown in the box on the right of Figure 3, the ester tether is too short to connect the

(22) A stepwise, diradical mechanism was also studied. The rate-limiting step for the diradical pathway was the addition of ethylene to cyclobutadiene to form a diradical intermediate. This transition structure had the following energy using UB3LYP/6-31G(d): ΔE + ZPE‡ = 12.0 kcal/mol, $\Delta G^{\ddagger}$ = 22.5 kcal/mol.

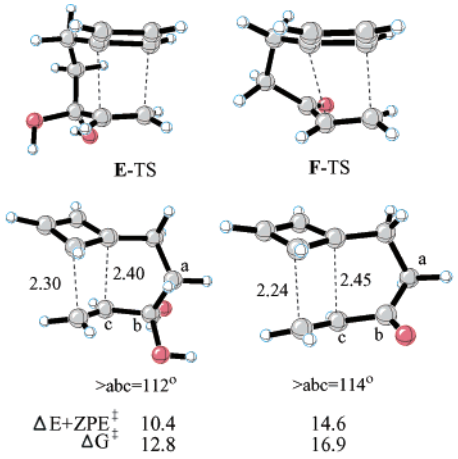


Figure 4. Calculated transition states for reactions **E** and **F**.

reacting groups without strain, and the ester is forced into the unfavorable *S-cis* conformation in the TS.[23]

The similar activation energies for **C** and **D** appear to contradict the experimental results in which a carboxylate-tethered compound **42** gives a high yield of desired product but a carboxylate-tethered compound **44** gives none of the desired product. It is possible that the conjugation of the cyclobutadiene to the carbonyl retards the oxidation process; consequently, ester hydrolysis occurs faster than the intramolecular cycloaddition. The cyclobutadiene-Fe(CO)$_3$ might also activate the ester toward nucleophilic attack. In addition, the phenyl substituent on the olefin may also influence the relative reactivity of this system. These calculations show, nevertheless, that there is no inherent difference in cycloaddition reactivity between **C** and **D**; the ester tethers increase the activation energy substantially because they are too short to be accommodated without strain in the transition state, and the *syn*-conformer is unfavorable.

Transition structures **E**-TS and **F**-TS illustrate clearly that an sp^3-hybridized carbon of a ketal can be incorporated more easily into the three-atom tether than an sp^2-hybridized carbon of a ketone (Figure 4). The activation energy for **E**-TS, $\Delta G^{\ddagger} =$ 10.4 kcal/mol, and the lengths of the forming σ bonds are similar to those of **B**-TS, which is expected because both tethers are composed of three sp^3 carbons. Replacing the hydrate functionality (model for ketal) with the corresponding ketone introduces significant angle strain into the [4 + 2] transition structure, resulting in **F**-TS being 4 kcal/mol higher in energy than **E**-TS. The additional strain induced by the ketone is reflected in the compressed angle of the ketone ($\angle abc = 114°$). These calculations support the experimental result that dimethyl ketal complexes (**74**−**76**) undergo the intramolecular cycloaddition more readily than their ketone analogues (**66**, **68**, **70**).

Because systems **G** and **H** have a longer tether (four atoms instead of three), two intramolecular cycloadditions are now feasible. These two reactions are known as Type I and Type II intramolecular cycloadditions. Figure 5 shows the four relevant transition structures for systems **G** and **H**. In each case, conformational searches were performed to determine the lowest energy conformation of the tether. **G**-TS-I and **H**-TS-I are the lowest energy conformations corresponding to Type I, and **G**-TS-II and **H**-TS-II are the lowest energy conformations

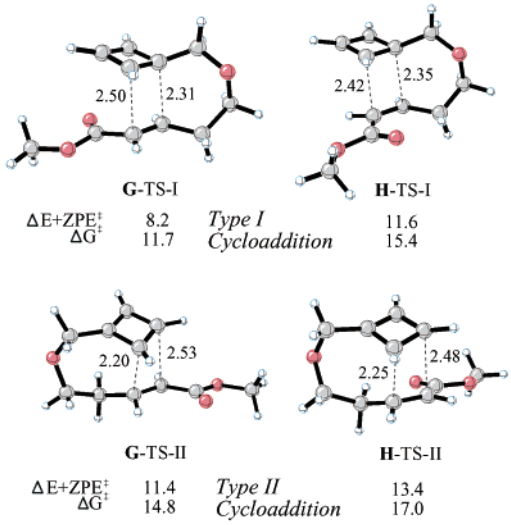


Figure 5. Calculated transition states for reactions **G** and **H**.

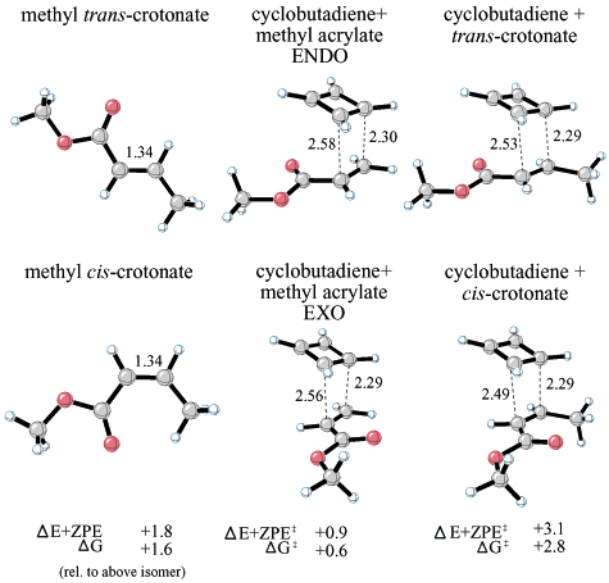


Figure 6. Calculated energy differences between *endo*- and *exo*-geometries, as well as olefin stereochemistry in cycloaddition transition states.

corresponding to Type II. For each system, the Type I transition structure is lower in energy than the Type II transition. The results for **G** are consistent with the experimental results shown for the reaction of **83** in which only the Type I cycloadduct was isolated. On the other hand, the calculations for **H** appear to disagree with the experimental observation that the product ratio of Type I to Type II cycloadduct was 1.0:3.3. The second important trend is that the *E*-alkene **G** leads to lower energy transition structures as compared to the *Z*-alkene **H**. This result is consistent with the experimental finding that **83** gives relatively high yields of the desired adduct relative to dimerization, whereas **87** gives relatively poor yields of cycloadduct relative to dimerization.

As a quantitative measure of the factors that contribute to the energy differences between the *cis* and *trans* systems, calculations on simplified systems were done (Figure 6). The first comparison is between *cis*- and *trans*-methyl crotonate, and the *cis*-isomer is found to be 1.6 kcal/mol higher in energy than the *trans*-isomer. The second comparison is between an *endo*

(23) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938.

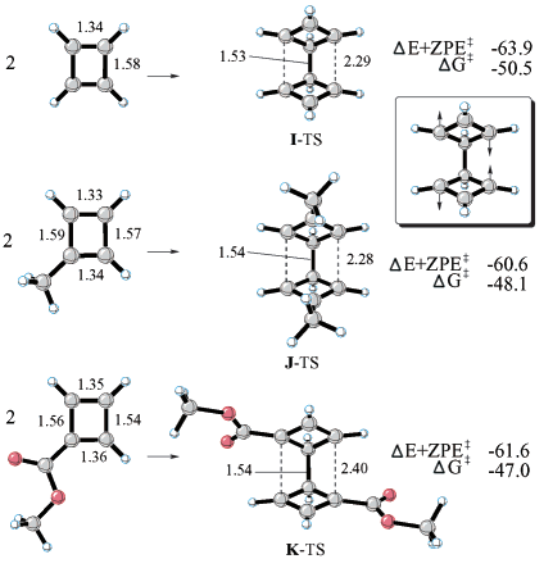


Figure 7. Transition states for dimerization of substituted cyclobutadienes.

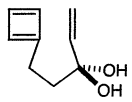
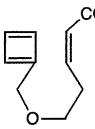
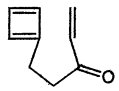
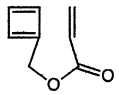
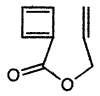
versus and *exo* cycloaddition involving methyl acrylate as the dienophile. The *endo* orientation is preferred by only 0.6 kcal/mol relative to the *exo* orientation in the [4 + 2] transition state. Third, the transition states involving *trans*-crotonate versus *cis*-crotonate differ by 2.8 kcal/mol. This indicates that approximately 0.6 kcal/mol of additional strain in the transition state can be attributed to the *cis*- versus the *trans*-configuration.

Because cyclobutadiene dimerization is the major competing side reaction, the energetics of the bimolecular process were also probed. The dimerizations of three model systems (cyclobutadiene, methylcyclobutadiene, and methyl cyclobutadienecarboxylate) are illustrated in Figure 7. Only the singlet energy surface was explored because singlet cyclobutadiene has been calculated to be significantly lower in energy than the triplet. Bartlett's MRCCSD(T) + ZPE calculations indicate that the rectangular singlet ground state is 12.5 kcal/mol below the triplet. Even at the square geometry, the singlet state is 8.8 kcal/mol lower in energy than the triplet state.[24]

The discussion begins with the dimerization of parent cyclobutadiene, which was studied previously with HF calculations.[2] The most striking feature of the dimerization transition structure is that is does not resemble a typical [4 + 2] cycloaddition. It actually resembles the Cope transition state, and the motion associated with the imaginary frequency is highlighted in Figure 7. This is similar to the dimerization of cyclopentadiene,[25] in which a bispericyclic transition structure leads to the formation of only one σ bond. A subsequent valley ridge inflection breaks the C_2 symmetry by mixing in the Cope TS, and either the [4 + 2] or the [2 + 4] cyclopentadiene dimer is formed. The main difference for the cyclobutadiene dimerization is that there is no barrier to formation of the first σ bond.

Similar transition structures are found for methylcyclobutadiene and methylcyclobutadiene-carboxylate. One additional complication is that the methyl or ester groups can adopt various substitution patterns about each four-membered ring. A total of seven dimers are possible for each system, and one is shown in Figure 7 as a representative example. The nature of the substituent has very little effect on the activation free energy

Table 9. Predicted Relative Rates of Cycloadditions

model	cyclobutadiene	$\Delta G^{\ddagger}$	$k_{trans}(s^{-1})$	cycloaddition results
A		9.1	1.3×10^{6}	*HIGH YIELD*
G		11.7	1.6×10^{4}	
E		12.8	2.6×10^{3}	
				DIFFUSION CONTROLLED DIMERIZATION $10^{8}M^{-1}S^{-1}$ X $[10^{-5}]M$
B		13.5	7.8×10^{2}	
H		15.4	3.2×10^{1}	
F		16.9	2.5×10^{0}	*LOW YIELD*
C[a]		19.9	1.6×10^{-2}	
D		20.3	8.1×10^{-3}	

[a] Calculations predict no intramolecular cycloadditions, but experimentally a good yield of cycloadduct **43** is obtained from **42**.

of the dimerization. On the basis of these calculations, dimerization of monosubstituted cyclobutadiene is expected to be barrierless and, therefore, diffusion controlled.

Table 9 summarizes the predicted rate constants at room temperature, using the computed values of $\Delta G^{\ddagger}$ found here and transition state theory.[26] The table orders the reactions according to increasing activation free energy. From the calculated activation barriers for systems **A**−**H**, the experimental yields can be explained if the rate of cyclobutadiene dimerization is slower than the intramolecular cycloadditions of **A**, **G**, and **E**, but faster than the intramolecular cycloadditions of **B**, **H**, **F**, **C**, and **D**. The intramolecular cycloadditions **A**, **G**, and **E** occur in good yields, while dimerization appears to be the major reaction for **B**, **H**, **F**, **C**, and **D**. This suggests that the first-order rate constant for cyclobutadiene dimerization under diffusion control in acetone is approximately 10^3 s^{-1}, which allows for reaction **E** to produce intramolecular cycloadducts but for reaction **B** to produce mainly dimer. The value of 10^3 s^{-1} appears low because the bimolecular diffusion rate constant is expected to be on the order of 10^8 M^{-1} s^{-1} (the typical diffusion rate constant in water) and the $Fe(CO)_3$-cyclobutadiene complex is present in millimolar concentration. However, assuming that free cyclobutadiene is reacting as it is formed and that only 10^{-5} M is present at any given time during the reaction, the diffusion rate could

(24) Balková, A.; Bartlett, R. J. *J. Chem. Phys.* **1994**, *101*, 8972.
(25) Caramella, P.; Quadrelli, P.; Toma, L. *J. Am. Chem. Soc.* **2002**, *124*, 1130.
(26) The first-order rate constants were evaluated using the Eyring equation: $k = (k_b T/h) \exp(-\Delta G^{\ddagger}/RT)$.

be 10^{-3} s^{-1}, so that the fastest intramolecular cycloadditions, such as **A**, **G**, and **E**, can compete with dimerization.

Conclusions

Oxidative decomposition of iron-cyclobutadiene complexes with CAN or TMAO liberates free cyclobutadiene, which can be trapped intramolecularly with various olefins to afford potentially useful and highly functionalized cyclobutene-containing cycloadducts. Generally, cyclobutadiene complexes that fail to undergo the intramolecular cycloadditions under the CAN-promoted reaction conditions (room temperature, acetone or MeOH, 1 mM) react to afford the corresponding cycloadducts when the slower oxidant, TMAO, is employed (acetone, 1−40 mM, 56 °C, 12−24 h). Electronically unactivated olefins, connected through a three-atom etherate tether, have successfully trapped the free cyclobutadiene to give [4 + 2] cycloadducts in good yields. With four-atom ether tether substrates, on the other hand, electronic activation and *trans*-configuration of the tethered olefin are required for an efficient intramolecular cycloaddition. Unactivated *trans*-olefin or activated *cis*-olefin complexes afford only moderate yields of the corresponding cyclobutene cycloadducts under TMAO-promoted cycloaddition conditions.

In the carbocyclic series of substrates, electronically activated three-atom-tethered *cis*- and *trans*-olefins efficiently trap the free cyclobutadiene under fast CAN reaction conditions, providing good yields of the corresponding cycloadducts. On the other hand, enone substrates, where the carbonyl group is part of the tether, require one of the following: (1) conversion of the carbonyl group into a dimethyl ketal functionality, (2) incorporation of an additional external electron withdrawing group (i.e., CO_2Me), (3) geminal dialkyl substituents in the tether, or (4) employment of TMAO as a slower oxidant. Furthermore, substrates with unactivated dienophiles connected through a three-atom tether require the use of TMAO. Incorporating rigid functional groups into the tether, as well as the presence of strongly activated dienophiles, are essential for efficient CAN-promoted intramolecular cycloadditions of four-atom, all-carbon tether substrates.

Theoretical considerations of the transition states in these cycloadditions provide useful insight into the factors influencing the course of the reaction. Moreover, the calculations offer a means to predict the success of the intramolecular cycloadditions versus competing intermolecular dimerization processes. The information and understanding offered by these studies should help advance further the methodology, as well as promote its application toward new challenges in synthesis.

Experimental Section[27]

General Procedure for Cyclobutadienyl Etherification. Sulfuric acid (0.20 equiv) was added to a solution of the tricarbonyl[η^4-(hydroxymethyl)cyclobutadiene] iron (1 equiv) in the allylic alcohol (solvent) at 0 °C. The reaction was judged complete by TLC usually after approximately 90 min at 0 °C. CH_2Cl_2 was added to the reaction along with H_2O and $NaHCO_3$ (aq). The organic layer was separated, and the aqueous layer was back-washed with CH_2Cl_2. The combined organic layers were then dried over Na_2SO_4 and concentrated. The resulting ether was purified by silica gel chromatography.

General Procedure for Cyclobutadienyl Alkylation. Tricarbonyl-[η^4-(methoxymethyl)cyclobutadiene] iron (1.0 equiv) was dissolved in CH_2Cl_2 (0.5 M) under an Ar atmosphere at room temperature with stirring, resulting in a yellow homogeneous solution. Addition of the enol silyl ether (1.3 equiv) followed by boron trifluoride-diethyl etherate (1.1 equiv) resulted in a dark brown solution. The reaction mixture was stirred for 0.5 h and quenched with saturated $NaHCO_3$ (aq). The reaction mixture was diluted with CH_2Cl_2 and poured into a separatory funnel containing water and CH_2Cl_2, the organic layer was separated, and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were then washed with brine and dried with anhydrous sodium sulfate. The solution was filtered, concentrated under vacuum, and purified by silica gel column chromatography. All compounds were stored under a N_2 atmosphere at −20 °C.

Intramolecular Cyclobutadiene Cycloaddition Methods. The intramolecular cycloadditions were promoted by oxidative removal of the iron from its corresponding cyclobutadiene ligand according to one of the following methods:

Method A (CAN-Promoted Cycloadditions). To a solution of the iron complex (1.0 equiv) under a N_2 atmosphere in either HPLC-grade acetone or MeOH (1−3 mM) was added CAN (5.0 equiv) as a solid over 3 min at room temperature. The resulting orange solution was stirred for 10 min, and then quenched with saturated $NaHCO_3$ and transferred to a separatory funnel containing Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O (2×). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$/K_2CO_3, filtered and concentrated in vacuo, and purified by silica gel flash column chromatography.

Method B (TMAO-Promoted Cycloadditions). To a solution of the iron complex (1.0 equiv) under a N_2 atmosphere in HPLC-grade acetone (1−40 mM) was added a portion of TMAO (4−10 equiv) all at once. The resulting reaction mixture was refluxed for 6 h, treated with a second portion of TMAO (4−10 equiv), and refluxed for an additional 6−18 h. Once all of the starting material has been consumed as judged by TLC and GC, the resulting brown suspension was cooled to room temperature and then transferred to a separatory funnel containing Et_2O and saturated $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$/K_2CO_3, filtered, concentrated, and purified by silica gel chromatography.

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Supporting Information Available: Experimental procedures, data on new compounds, and computational results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0203162

(27) See the Supporting Information for general experimental and computational methods as well as details about specific compounds.