CYCLOBUTADIENEIRON TRICARBONYL:
SYNTHETIC ACCESS TO AN ANTI-AROMATIC SYSTEM AND ITS USE IN SYNTHESIS

Reported by Tyler W. Wilson November 10, 2005

INTRODUCTION

Cyclobutadiene has captured the imagination of chemists for over a century, and this simple molecule has had an impact in many fields of chemistry. Unfortunately, synthetic chemists have often over-looked cyclobutadiene as reagent that might be used at the bench, because of its extreme reactivity and instability. However, the metal complexes of cyclobutadiene that were developed in the 1960's by Rolland Pettit and others furnish a stable form of the molecule that is suitable for synthetic endeavors. A brief introduction to the structure of cyclobutadiene and its current uses in synthesis are presented in this review.

CYCLOBUTADIENE

Structure

Application of simple Huckel molecular orbital theory to the square geometry of cyclobutadiene gives one bonding orbital, two degenerate non-bonding orbitals, and one anti-bonding orbital (Figure 1). Filling electrons into the molecular orbitals results in either a square singlet or a square triplet state, and many questions have been raised as to which is the true ground state of cyclobutadiene. The question had remained one of purely theoretical speculation until recently when experimental and spectroscopic evidence suggested that cyclobutadiene is much more dynamic in nature than originally thought.[1]

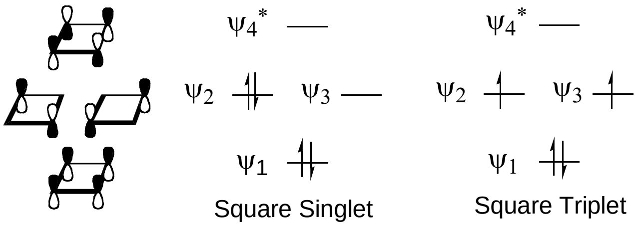
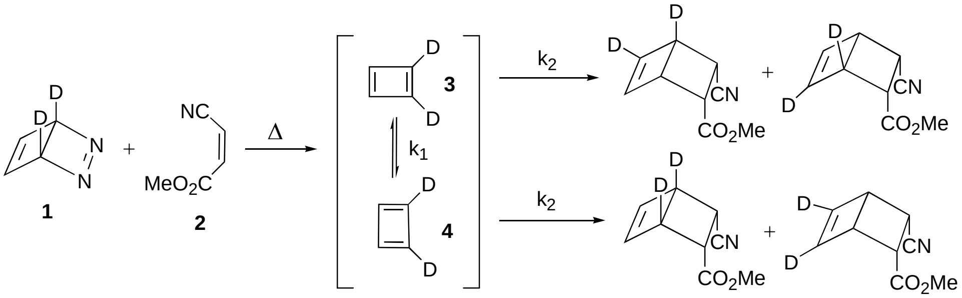


Figure 1: Molecular orbital and Energy level Diagrams of Cyclobutadiene

For example, Carpenter and co-workers prepared the deuterium labeled azo compound **1** and studied its decompostion to cyclobutadiene in the presence of a trapping agent methyl (*Z*)-3-cyanoacrylate (Scheme 1).[2]

Scheme 1:



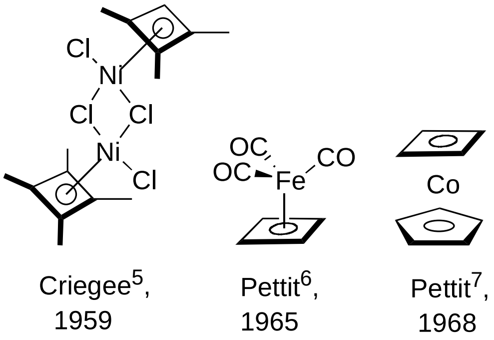
The study suggested that cyclobutadiene exists not as a square, but as two rapidly interconverting rectangles **3** and **4**. The calculated energy difference between these two forms is in the range of 8.3 – 14.0 kcal/mol.[3]

METAL COMPLEXES OF CYCLOBUTADIENE:

Background

In 1956 H.C. Longuet-Higgins and L.E. Orgel published a paper that hypothesized the existence of stable cyclobutadiene metal complexes.[4] The authors' argument was based on the observation that the singly occupied e_g orbitals of cyclobutadiene was of the correct symmetry for π-bonding to a metals d_{zx} and d_{zy} orbitals. This landmark publication opened the door for the synthesis of cyclobutadiene metal complexes and many examples followed (Figure 2).

Figure 2: Representative Metal Complexes of Cyclobutadiene



Criegee[5], 1959

Pettit[6], 1965

Pettit[7], 1968

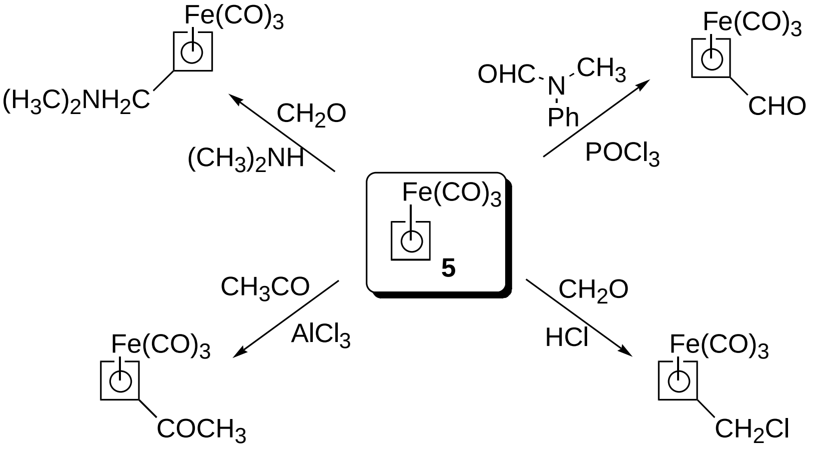
Of particular interest to organic chemists was the cyclobutadieneiron tricarbonyl. Pettit showed that when the complex was treated with an oxidizing agent free cyclobutadiene was liberated and dimerization products could be islolated. This allowed for the first time in synthesis the use of cyclobutadiene as a reagent.

CYCLOBUTADIENEIRON TRICARBONYL

Electrophilic Substitutions

Petitt and co-workers showed that cyclobutadieneiron tricarbonyl will undergo a number of different electrophilic substitution reactions, similar to ferrocene or benzene (Scheme 2).[8] Although these reactions are not particularly interesting in terms of mechanism or theory, they do highlight the aromatic character of the cyclobutadieneiron tricarbonyl and serve as useful methods for derivatizing the parent structure.

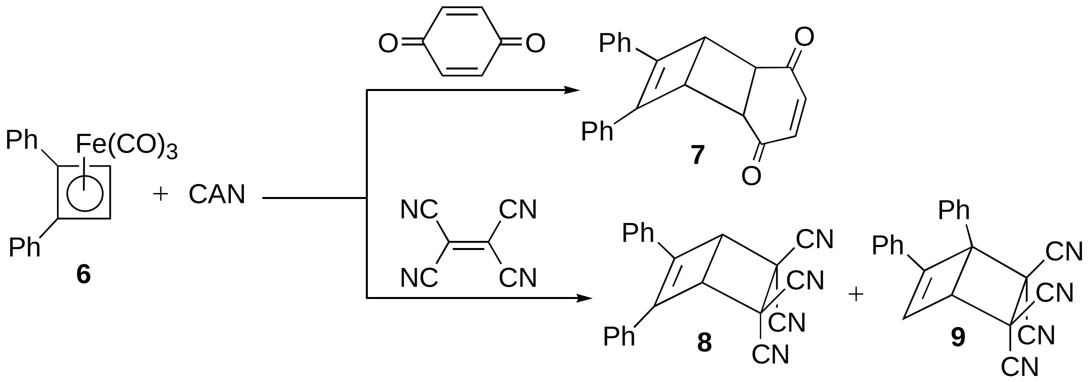
Scheme 2:



Intermolecular Cycloadditions

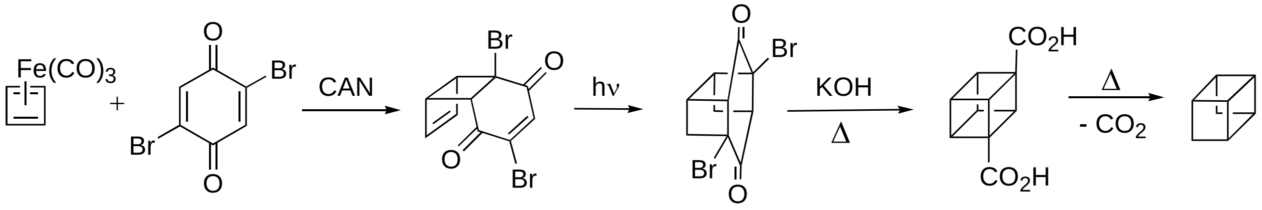
Petitt has studied the product distribution for the Diels-Alder reaction of cyclobutadiene and shown that it is greatly affected by the nature of the dienophile (Scheme 3).[9] The authors found that when the more reactive dienophile tetracyanoethylene was used two regio-isomeric products **7** and **8** were formed in a ratio of 7:1. This study provided some of the first experimental evidence for the rectangular structure of cyclobutadiene.

Scheme 3:



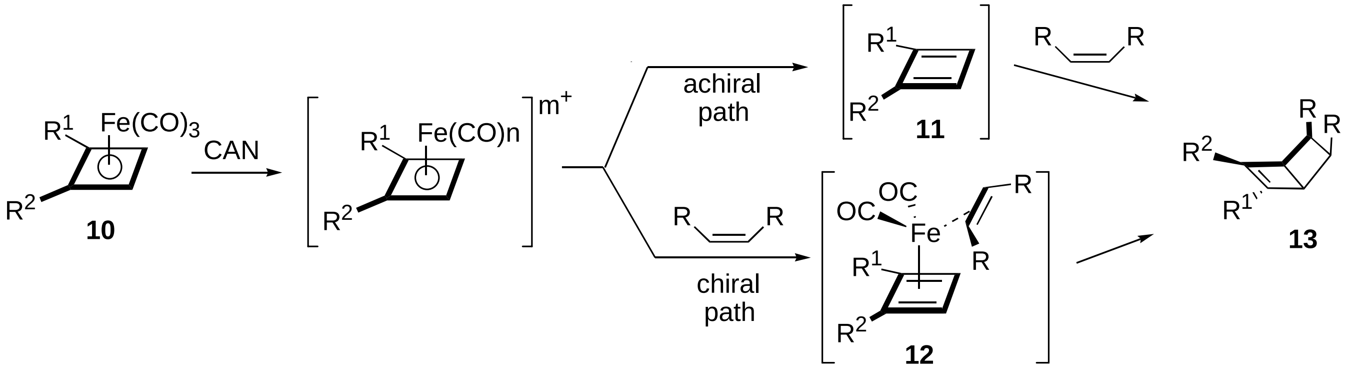
Pettit and co-workers showcased the utility of the intramolecular cycloadditons of cyclobutadiene with a concise synthesis of the highly strained molecule cubane (Scheme 4)[10].

Scheme 4



Grubbs and Schmidt independently studied the stereochemistry of the intermolecular cycloaddition to determine if the reaction was occurring through a free cyclobutadiene or within the coordination sphere of the metal.[11,12] The experiment required the starting material **10** be optically pure and each author reported a different method to resolve the racemic complexes with moderate to high er. The authors each concluded that the reaction occurred through an achiral intermediate **11** because only racemic products were recovered. Further support for the intermediacy of a free cyclobutadiene was reported by Rebek, who applied a three phase test to the reaction.

Scheme 5

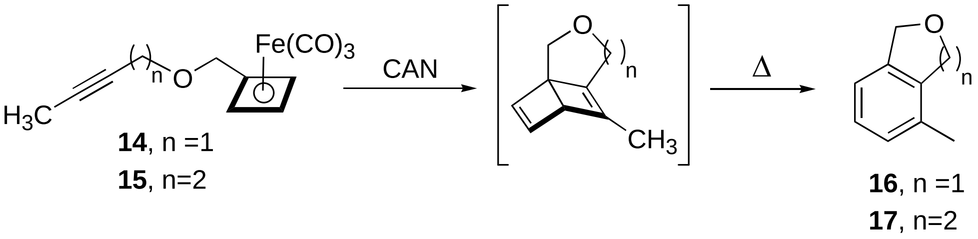


Intramolecular Cycloadditions

One significant draw back to the intermolecular cycloadditions is that a competition develops between capture of the dienophile and dimerization of the cyclobutadiene. Houk has shown with computational studies that the potential energy barrier for dimerization of cyclobutadiene is approximately zero, so the reaction is essentially diffusion controlled.[13] To overcome the low energy dimerization pathway one either has to use a very reactive dienophile, or a tether.

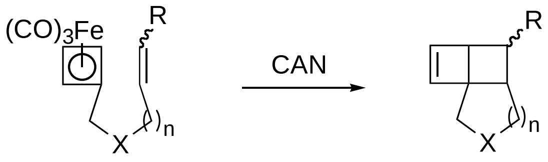
Grubbs and co-workers published the first example of a tethered intramolecular cycloaddition with cyclobutadieneiron tricarbonyl (Scheme 6).[14] The direct cyclization product of this [4 + 2] reaction is a dewar benzene, which is not thermally stable and rearranges to the observed aromatic products.

Scheme 6



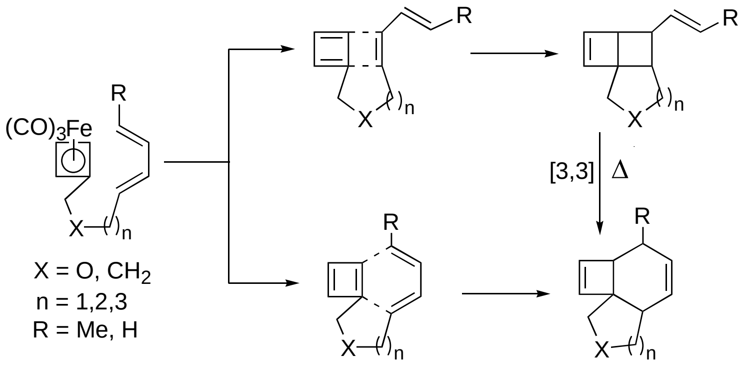
Following this work Snapper and co-workers published a thorough study of intramolecular cycloadditions of cylclobutadiene with tethered dienophiles.[15] The authors wanted to address what factors favored cycloaddition over dimerization. The study included varying the tether length and bite angle as well as a wide variety of cyclic and acyclic dienophiles. An important finding from this study that has greatly increased the scope of the cylcoaddition is that the yield of the reaction for unactivated dienophiles can be greatly increased by the use of the slower oxidizing agents such as trimethylamine-N-oxide.

Scheme 7



Cyclobutadiene can serve as either the diene or dienophile component in a Diels-Alder reaction. Snapper and co-workers have investigated what determines this mode of reactivity by setting up a competition experiment as shown in Scheme 8.[16] Through a systematic study of the tether length, bite angle and atomic composition the authors were able to determine what factors govern the different modes of reactivity. Additionally, the authors reported a method of converging the product distributions to a single adduct through a [3,3] rearrangement making this a very powerful method for the synthesis of functionalized ring systems.

Scheme 8

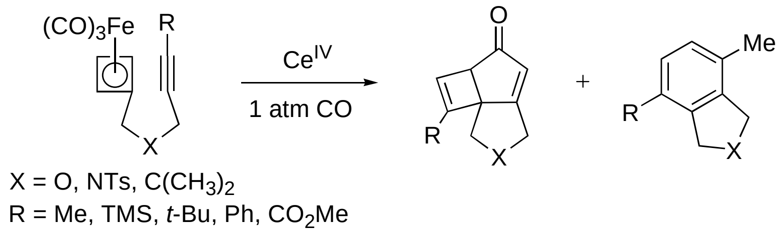


Cycloadditions with CO Insertion

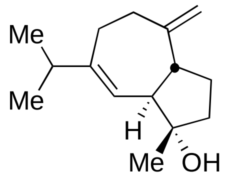
[2 +2 +1]

During Grubbs initial study of intramoleuclar cycloadditons of tethered alkynes he noted the formation of a minor product that resulted from CO insertion.[17] When the reaction was repeated with an optically pure substrate the reaction yielded a product that retained some of the asymmetry of the starting material. Grubbs concluded from this result that the insertion was occurring to a cyclobutenoid intermediate that was still bound to the Iron. Although this was an interesting result the conversion was very low and no further attempts were made by Grubbs to optimize the reaction conditions. Snapper and co-workers have recently shown that the CO insertion product can be obtained in high yield by slow addition of oxidant.[18] In addition, the authors surveyed a number of different tethered alkynes and concluded that electron deficient alkynes prefer the [4 +2] pathway (Scheme 9).

Scheme 9



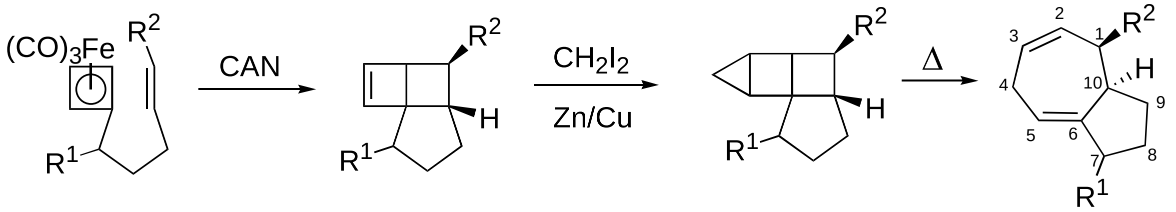
Accessing the 5-7 Ring System



alismol

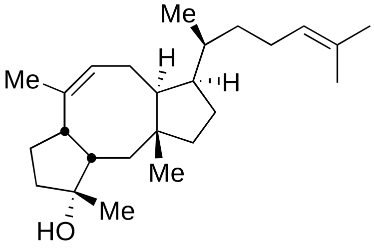
The 5-7 ring systems are common to many natural products targets such as alismol. Snapper and co-workers have shown that this ring system can be quickly assembled via the cyclopropanation/fragmentation of highly functionalized cylobutenes (Scheme 11).[19] The authors report high selecetivity for the cycloproponation using a modified Simmons-Smith reagent. The electrocyclic ring opening of the strained ring resulted in an inversion of the stereochemistry at C-10, and the authors propose a mechanism that is consistent with this result.

Scheme 11



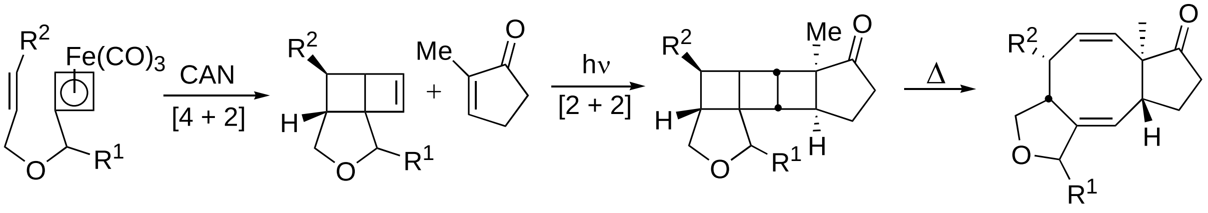
Accessing the 5-8-5 Ring Systems:

Snapper and co-workers have also recently shown that the 5-8-5 ring system can be easily assembled in as few as six steps. The authors' impetus for developing this methodology is seen in the highly functionalized 5-8-5 rings of the natural products such as ophiobolin F.[20] The synthesis of the 5-8-5 system begans with a [4 + 2] cycloadditon of the tethered cylcobutadiene, followed by a [2 + 2] photocycloaddition and finally thermolysis to give the 5-8-5 ring system (Scheme 12). The authors noted an interesting dependence how the configuration of R^2 influened the stereochemistry of the resulting 5-8-5 ring system.



ophiobolin F

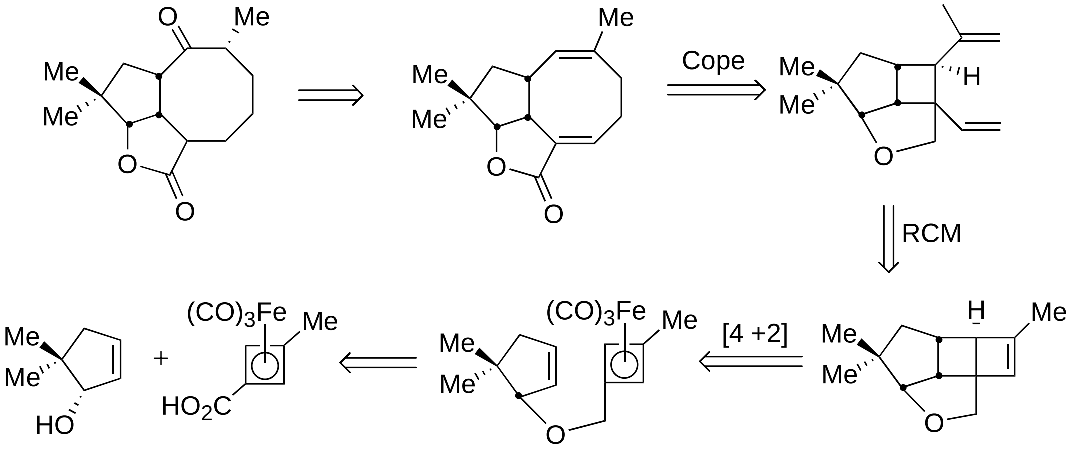
Scheme 12



Applications in Total Synthesis

Snapper and co-workers have demonstrated the utility of the intramolecular cyclobutadiene cycloadditon with a concise nine-step synthesis of (+)-asteriscanolide. The core of the natural product ring system was set by an intramolecular Diels-Alder reaction with a tethered cyclobutadiene, followed by ring opening metathesis to give the cis-diene, which was transformed to the cyclooctadiene through a cope rearrangement (Scheme 13).[21]

Scheme 13



CONCLUSION

Cyclobutadieneiron tricarbonyl is a powerful tool for synthetic chemists because it allows the controlled release of an extremely reactive molecule that can be used to generate high-energy intermediates. Further manipulation of these intermediates can result in the facile formation of very elaborate ring systems in just a few steps. Many challenges are still present though such as biasing the molecules ability to react as a diene or a dienophile, as well as out competing the dimerization pathways. More exciting though is the possibility of harnessing the ability of the metal center to mediate the course of the reactions and direct the introduction of stereochemistry.

References:

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