Angewandte
Chemie

DOI: 10.1002/anie.200501100

Intramolecular [2+2+1] Cycloadditions with (Cyclobutadiene)tricarbonyliron**

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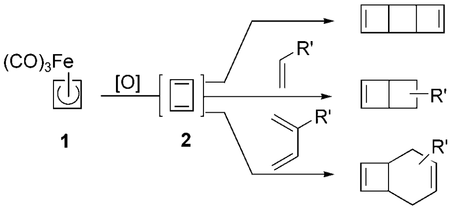
Oxidative decomplexation of (cyclobutadiene)tricarbonyliron (**1**) is a convenient method for the generation of free cyclobutadiene (**2**).[1] Once released from the metal, this reactive, antiaromatic species can undergo rapid dimerization [Eq. (1)]. When cyclobutadiene is generated in the presence of olefins or dienes, intermolecular cycloadditions can occur which lead to various cyclobutene-containing adducts [Eqs. (2) and (3)].

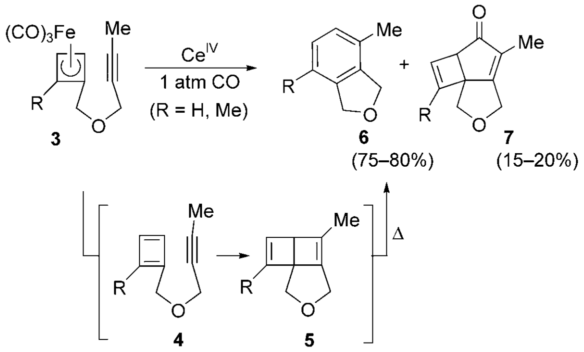


(1)

(2)

(3)

In 1974, Grubbs et al. studied intramolecular cycloadditions between cyclobutadiene and tethered alkynes [e.g., Eq. (4)].[2] The major product isolated from this reaction was compound **6**, which presumably was generated through rearrangement of the Dewar benzene cycloadduct **5**. In



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[**] We thank the National Institute of General Medical Sciences (National Institutes of Health, GM62824) for financial support. We are grateful to Schering-Plough for support from their X-ray facility.

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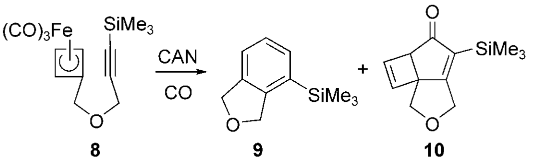
addition, a minor amount of ketone **7** was also obtained.[3] Elegant studies with chiral, nonracemic iron complexes (such as **3**, R = Me) suggested that **5** was formed through a [4+2] cycloaddition of a metal-free intermediate **4**, whereas the generation of cycloadduct **7** appeared to involve a more participative role for the ironcarbonyl component.

Given the synthetic utility of intramolecular cycloadditions of cyclobutadiene,[4] coupled with the established usefulness of the fused-ring system found in **7**,[5] we sought to develop this intramolecular cyclobutadiene [2+2+1] cycloaddition (the Pauson–Khand reaction) into an effective methodology.[6] Specifically, our goals were to improve the efficiency of the [2+2+1] cycloaddition and expand the substrate scope of the reaction.[7] Our preliminary steps towards these objectives are reported herein.

Our first aim was to improve the yield of the carbonylative cycloaddition process. We reasoned that a slower rate of oxidation of the iron complex in the presence of carbon monoxide would favor the iron-mediated Pauson–Khand reaction over the oxidative release of free cyclobutadiene required in the Diels–Alder reaction. Our initial efforts focused on the cycloaddition of alkyne **8** [Eq. (5)]. After optimization of the reaction conditions (solvent, oxidant, reaction temperature, rate of addition of oxidant, CO pressure, and additives), we were able to improve the yield of adduct **10** obtained from the Pauson–Khand reaction from 15 to 60%, while minimizing the formation of the Diels–Alder product **9**. Further optimization of the workup, combined with the use of purified ammonium cerium(IV) nitrate (CAN),[8] increased the efficiency of the [2+2+1] cycloaddition to provide ketone **10** in 77% yield.[9]



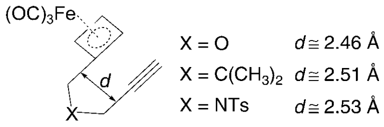
(5)

The investigation of additional substrates is summarized in Table 1. Under the optimized Pauson–Khand conditions, the original Grubbs alkyne **11** afforded the [2+2+1] cycloadduct **12** in 91% yield (entry 2). Likewise, the sterically hindered *t*Bu alkyne **13** underwent [2+2+1] cyclization to provide **14** in 78% yield (entry 3). On the other hand, the cycloaddition of electron-deficient alkynes, such as **15**, did not undergo the desired [2+2+1] cycloaddition, but instead only generated the [4+2] cycloadduct **16** (entry 4).

On the basis of the emerging trend of electron-rich alkynes performing efficiently in this cycloaddition, we expected aryl alkynes to act similarly. In this regard, the oxidation of a *p*-methoxyphenyl alkyne **17** generated the desired [2+2+1] cycloadduct **18** in 71% yield as well as the [4+2] cycloadduct **19** in 20% yield (entry 5). Similar results were seen with a phenyl alkyne substrate **20**, which provided the [2+2+1] cycloadduct **21** in 69% yield, along with **22** in 24% yield (entry 6). Furthermore, it was demonstrated that terminal alkynes, such as **23**, will also take part in the Pauson–Khand reaction, as cycloadduct **24** was obtained in 60% yield (entry 7).

We next examined the influence of the tether functionality on the course of the cycloaddition. We replaced the oxygen atom in the tether with a *gem*-dimethyl group, thereby taking advantage of the reactive rotamer effect in the cycloaddition.[10] Oxidative carbonylation of the propargyl methyl ether **25** led to the desired [2+2+1] cycloadduct in 55% yield as a mixture of hydroxy diastereomers (β/α = 1.8:1), with only a trace amount of the [4+2] cycloadduct (entry 8). In contrast, a phenyl alkyne **27** delivered a Pauson–Khand product **28** that favored the opposite diastereoselectivity (β/α = 1:3) in 57% yield of combined product, as well as the Diels–Alder product **29** in 30% yield (entry 9). When the hydroxy group of **25** was protected as a MOM ether to generate **30**, oxidation resulted in the formation of the [2+2+1] cycloadduct **31** as a single diastereomer in 62% yield (entry 10). The sensitive role of the tether functionality in these cycloadditions was further demonstrated in entry 11 (compare with entries 6 and 9): oxidation of the *p*-toluenesulfonate-protected amine **33** favored the formation of the [4+2] cycloadduct **35** over the [2+2+1] cycloadduct **34**.

Previous studies have indicated that the intramolecular [4+2] cycloaddition of cyclobutadiene is sensitive to distortions imparted by the tether functionality on the transition-state geometries.[4c,d] The Pauson–Khand cycloadditions presented above also appear to be influenced by the geometry of the tether group. Although the transition state in the iron-mediated Pauson–Khand reaction is unclear at this time the span, or "bite size", of the tether group does correlate with the ratio of [2+2+1]/[4+2] cycloadducts obtained. The identity of the atoms used to connect the cyclobutadiene and the alkyne units can provide different idealized ground-state geometries (Scheme 1). Thus, the energetic cost of the distortion in each of these systems in their respective cycloaddition transition states may be different.



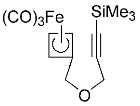
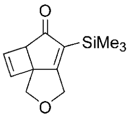
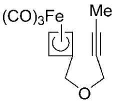
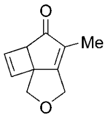
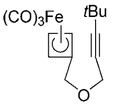
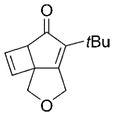
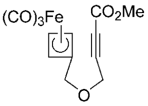
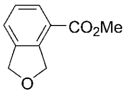
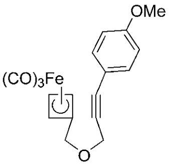
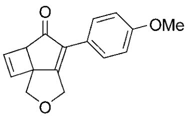
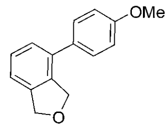
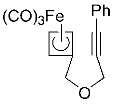
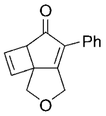
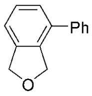
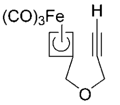
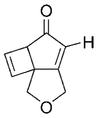
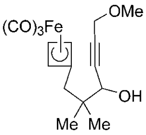
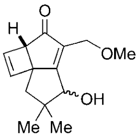
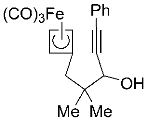
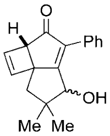
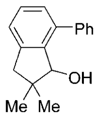
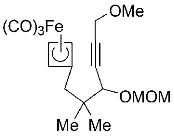
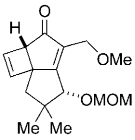
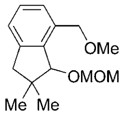
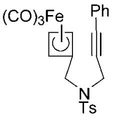
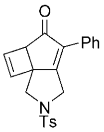
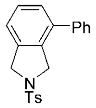
Scheme 1. Composition and geometry of the tether.

The results of the cyclization reactions for phenyl alkynes **20**, **27**, and **33** showed that an increase in the distance between the alkyne and the cyclobutadiene units disfavors the Pauson–Khand process relative to the Diels–Alder reaction. The cycloaddition of **20** (X = O), in which the ether tether allows a closer relationship between the reactive functionalities, provided the highest ratio of [2+2+1]/[4+2] cycloadducts (**21**/**22** = 2.9:1, entry 6). On the other hand, the *p*-toluenesulfonate amide linker in **33** (X = NTs) increases the distance between the alkyne and cycloabutadiene units, thus leading to an unfavorable ratio of [2+2+1]/[4+2] cycloadducts (**34**/**35** = 0.5:1, entry 11). Substrate **27**, with a *gem*-dimethyl linker (X = $C(CH_3)_2$), has a bite size between that of **20** and **33** and, accordingly, provided an intermediate ratio of products (**28**/**29** = 1.9:1, entry 9).

In addition to the influence of the tether geometry, there are also diastereoselectivity questions regarding the cycloaddition reactions of the hydroxy-substituted *gem*-dimethyl substrates **25**, **27**, and **30**. The mechanism of the [2+2+1] cycloaddition needs to be considered to gain insight into these trends (Scheme 2).[3] Conversion of alkyne **36** into the Pauson–Khand product **37** is likely to involve several steps. Depending on the reversibility of the steps, the diastereomeric control observed could result from favorable hydrogen-bonding interactions (entry 8) or unfavorable allylic strain (entries 9 and 10) in intermediates such as **38**. The importance of this latter interaction was particularly evident in the cyclization of the MOM-protected substrate **30**, where only diastereomer **31** was observed (entry 10).

In summary, we have developed a cyclobutadiene [2+2+1] cycloaddition that allows the efficient preparation of highly functionalized cyclobutene-containing systems in synthetically useful yields. In this process, the tricarbonyliron functionality, which usually serves to protect the cyclobutadiene against unwanted side reactions, also mediates a [2+2+1] cycloaddition with various alkynyl side chains. Both electronic and steric factors were found to influence the course of the reaction. Further studies will focus on expanding the scope of the cyclobutadiene [2+2+1] cycloaddition, as well as evaluating the transformation in the syntheses of targets of interest.

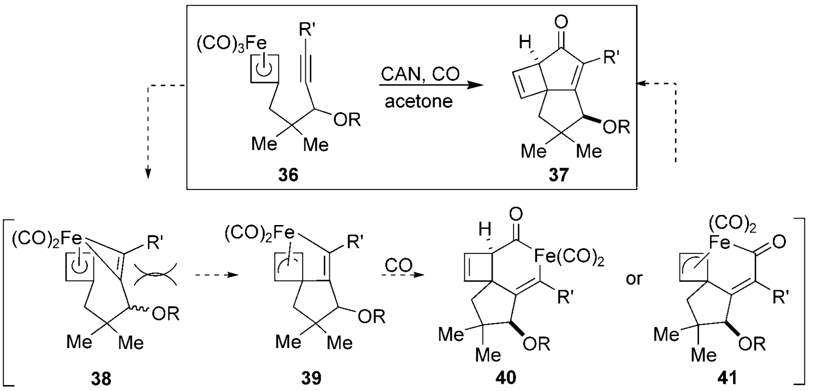
Table 1: Intramolecular [2+2+1] cycloadditions.[a]

Entry	Alkyne	[2+2+1] Cycloadduct	Yield [%][a]	[4+2] Cycloadduct	Yield [%][a]
1			77	–	–
2			91	–	–
3			78	–	–
4		–	–		67
5			71		20
6			69		24
7			60	–	–
8			55[b]	–	–
9			57[c]		30
10			62		21
11			29		63

[a] An average of the two highest yields of isolated product. [b] $\beta/\alpha = 1.8:1$. [c] $\beta/\alpha = 1:3$. MOM = methoxymethyl. Ts = *p*-toluenesulfonate.

Received: March 28, 2005

Keywords: alkenes · alkynes · cycloaddition · cyclobutadiene · intramolecular reactions



Scheme 2. Diastereoselectivity observed in the [2+2+1] cycloaddition.

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[9] Representative cycloaddition procedure: Carbon monoxide was bubbled through a solution of (cyclobutadiene)tricarbonyliron in acetone for 20 min, and then the solution was stirred in an atmosphere of carbon monoxide at room temperature for the remainder of the reaction. A solution of CAN (5 equiv) in acetone was added over 3.0 h by syringe pump to the reaction mixture. At the conclusion of the slow addition, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then concentrated under vacuum (to remove the acetone). The aqueous solution was extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried over $MgSO_4$, and the organic solvent was removed under vacuum. The cycloaddition product was then purified by chromatography on silica gel.

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