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Cycloisomerization

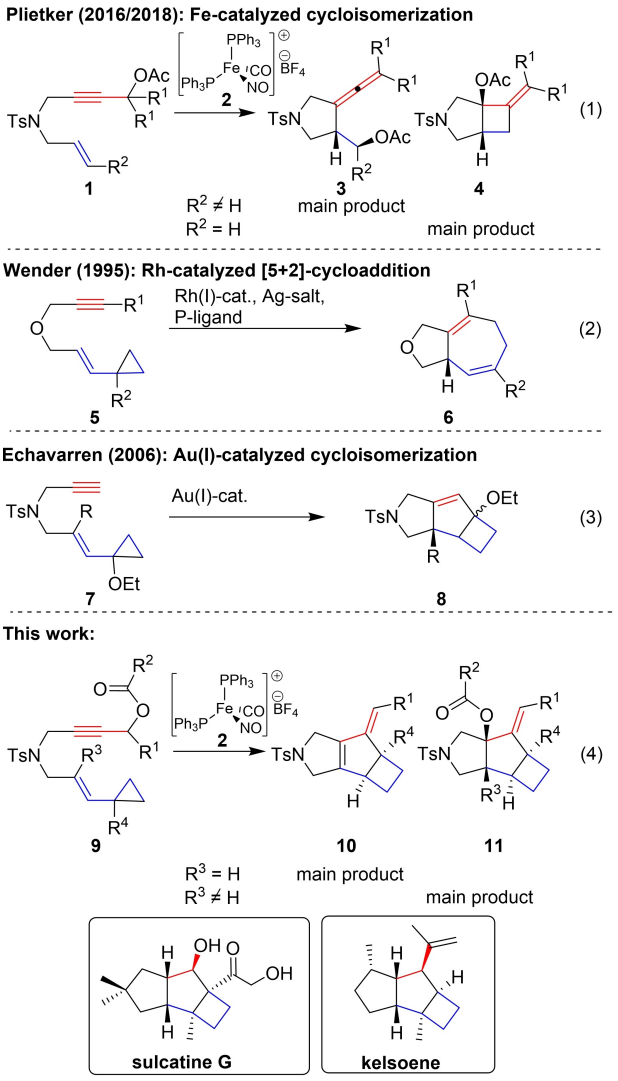
Iron-Catalyzed Cycloisomerization and C–C Bond Activation to Access Non-canonical Tricyclic Cyclobutanes

*Frederik Kramm, Franziska Ullwer, Benedict Klinnert, Min Zheng, and Bernd Plietker**

In memory of Professor Klaus Hafner

Abstract: Cycloisomerizations are powerful skeletal rearrangements that allow the construction of complex molecular architectures in an atom-economic way. We present here an unusual type of cyclopropyl enyne cycloisomerization that couples the process of a cycloisomerization with the activation of a C–C bond in cyclopropanes. A set of substituted non-canonical tricyclic cyclobutanes were synthesized under mild conditions using $[(Ph_3P)_2Fe(CO)(NO)]BF_4$ as catalyst in good to excellent yields with high levels of stereocontrol.

Cycloisomerizations allow the construction of complex annelated ring systems from readily available simple starting materials. The significance of the research activities is reflected in the number of reports on this particular type of skeletal rearrangements.[1] While Rh-[2] and Ir-complexes[3] clearly dominated this field of chemistry, the advent of defined Au^I-complexes as π-Lewis acid catalyst opened up a totally new direction in this field.[4] Recently, we reported that the cationic 16-electron Fe^0-complex $[(Ph_3P)_2Fe(CO)(NO)]BF_4$ **2** acts as a π-Lewis acid catalyst redox-neutral cycloisomerizations of enyne acetates or aryl allenyl ketones [Eq. (1), Scheme 1].[5] Cycloisomerizations of cyclopropyl-substituted enynes such as **5** were pioneered through a couple of landmark reports by Wender[6a–c] or Shintani/Hayashi[6d] using Rh-complexes to provide products of a formal [5+2]-cycloaddition [Eq. (2), Scheme 1]. The fact that Au^I-complexes act as π-Lewis-acid was used by Echavarren in a remarkable study on cycloisomerizations of cyclopropyl-substituted enynes such as **7** [Eq. (3), Scheme 1].[7] In sharp contrast to the Rh-catalysis the cycloisomerization does not deliver the [5+2]-cycloaddition product but rather the product of a cycloisomerization-Prins-cyclization to give fused 5,5,4-tricyclic product **8** [Eq. (3), Scheme 1].



Scheme 1. Transition metal catalysed cyclizations of enynes and cyclopropyl-substituted enynes.

We envisioned a comparative study on cyclopropyl-substituted enynes to be a perfect litmus test to verify or

[*] Dr. F. Kramm, Dr. F. Ullwer, M. Zheng, Prof. Dr. B. Plietker
Institut für Organische Chemie, Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)
B. Klinnert, M. Zheng, Prof. Dr. B. Plietker
Lehrstuhl für Organische Chemie I, Fakultät Chemie und Lebensmittelchemie, TU Dresden
Bergstraße 66, 01069 Dresden (Germany)
E-mail: bernd.plietker@tu-dresden.de

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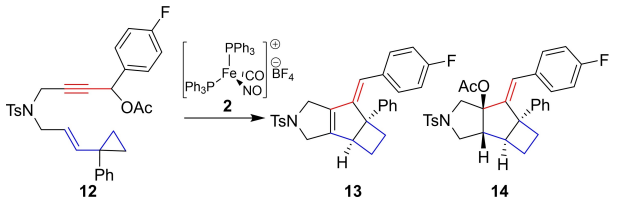
falsify our understanding of the catalytic activity of $[(Ph_3P)_2Fe(CO)(NO)]BF_4$ toward enynes. Herein, we report that the cationic Fe-complex $[(Ph_3P)_2Fe(NO)(CO)]BF_4$ catalyzes the cycloisomerization-C–C-bond activation of cyclopropyl-substituted enynes to complex tricyclic n,5,4-scaffolds that are present in natural products like sulcatine G or kelsoene [Eq. (3), Scheme 1].

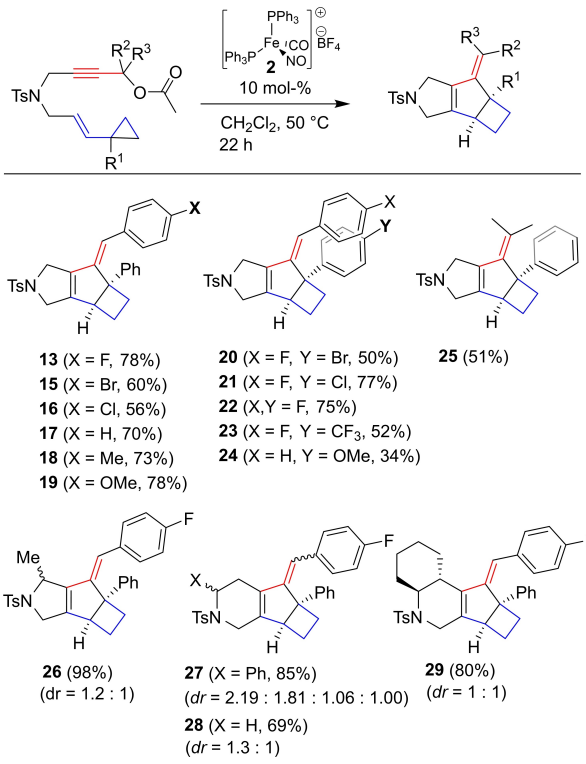
Based on our previous work, we initiated this study by treating cyclopropyl enyne **12** with the Fe-complex under the conditions that proved successful in our previous studies (Table 1). While initial attempts to employ simple unactivated cyclopropanes (R^4 = H, Me) or alkoxide-substituted cyclopropanes (R^4 = OTBS) did not show any conversion, aryl-substituted cyclopropanes like **12** showed good reactivity already under mild conditions in dichloromethane at 50 °C leading to a mixture of allylic acetate **14** or diene **13** (entry 1, Table 1).

Table 1: Catalyst optimization.[a]



Entry	Catalyst [mol-%]	Solvent/T [°C]	**13**[b]/**14**[b]
1	**2** (10)	CH_2Cl_2/50	80 %/–
2	**2** (2)	CH_2Cl_2/50	40 %/35 %
3	**2** (3)	CH_2Cl_2/50	43 %/33 %
4	**2** (3)	CH_2Cl_2/30	60 %/34 %
5	–	CH_2Cl_2/50	–
6	HBF_4 (2)	CH_2Cl_2/50	decomp.

[a] Reaction conditions: All reactions were performed on a 0.2 mmol scale in dry solvent (1 mL) under a N_2-atmosphere for 22 h. [b] Yields determined by ^{19}F NMR using 4,4′-difluorobenzophenone as internal standard.

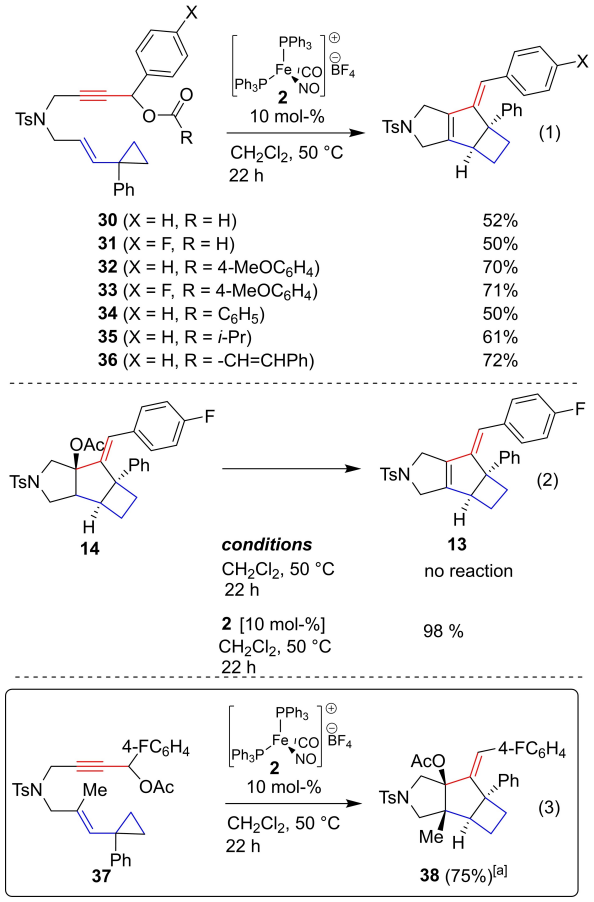


Scheme 2. Scope of the Fe-catalyzed cycloisomerization-elimination.[9]

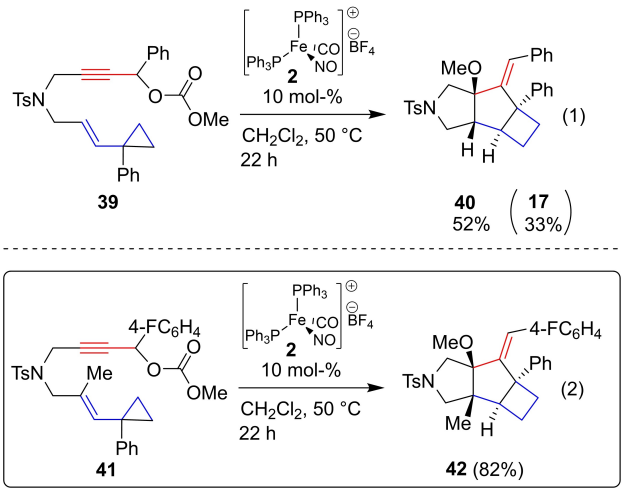
Diene **13** was isolated in good yields as the only product. Upon decreasing the catalyst loadings down to 3 mol-% good conversions even at a temperature of 30 °C were possible, however, diene **13** was formed as a by-product alongside with allylic acetate **14** [entries 3 and 4, Table 1, Eq. (2), Scheme 3].[8] Control experiments showed that the reaction is indeed Fe-catalyzed (entries 5 and 6, Table 1).

The cycloisomerization-elimination proved to be broadly applicable (Scheme 2). A variety of different cyclopropyl-substituted enynes were transformed into the corresponding fused tricyclic cyclobutanes in good to high yields. While in all reported cases the yields based on recovered starting materials are exceeding 90 %, in some cases the formation of the allylic alcohol due to hydrolysis of the allylic ester moiety was observed to a minor amount. Importantly, halides, ethers, and amides are tolerated. Propargyl- but also homopropargylamides can be employed and thus allow for variation of the ring sizes, or upon use of higher substituted homopropargylic amides the formation of even tetracyclic structures like **29** in good yields. The nature of the *p*-substituent Y has a significant impact on the yield (products **13**–**19** vs. products **20**–**24**, Scheme 2). Whereas +M-substituents increase the yield of products **13**–**19**, which is indicative for the need to stabilize partial positive charge during the activation of the propargylic acetate, the opposite is true for the *p*-substitution of the aryl-group at the cyclopropane moiety (products **20**–**24**, Scheme 2). This points into the direction of a catalyst-controlled C–C-bond activation of the cyclopropane rather than a carbocationic (Wagner–Meerwein-type) ring-opening reaction.

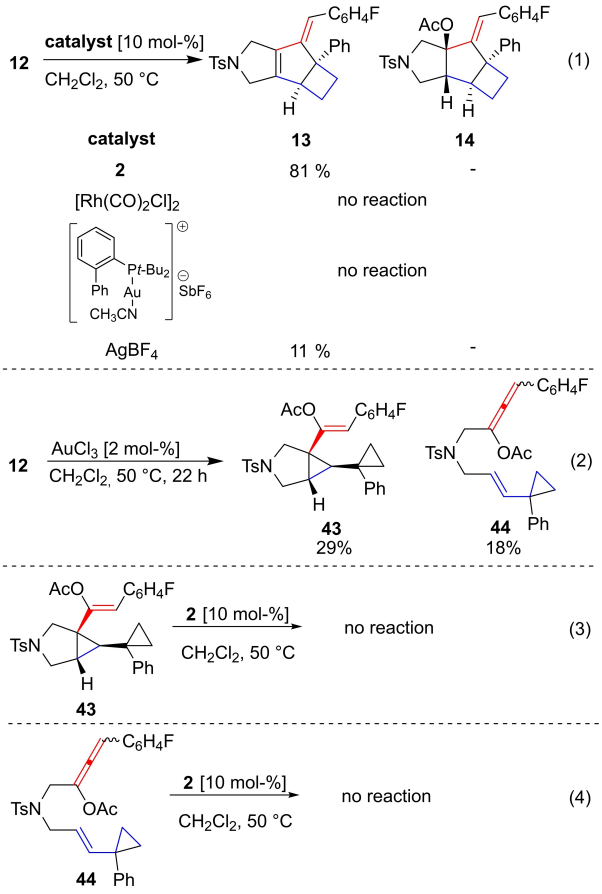
As the formation of dienes **13**–**29** follows a two-step mechanism of cycloisomerization and subsequent elimination [Eq. (2), Scheme 3][8] we were wondering whether a variation of the ester moiety in the starting material might allow to slow down the elimination process and hence would provide an access to the corresponding allylic acetate (Scheme 3). Consequently, various propargylic esters **30**–**37** were prepared and subjected to the reaction conditions. Gratifyingly, in all cases the starting material was converted indicating that apart from pivalate these ester groups are compatible with the cycloisomerization conditions, however, in all cases a fast elimination to diene **13** or **17** was observed [Eq. (1), Scheme 3]. At this point we were wondering whether the Fe-complex actually catalyzes the fast elimination. Indeed, subjecting allylic acetate **14** to the reaction conditions in the presence or absence of catalyst **2** led to either quantitative elimination to **13** or to no reaction, respectively [Eq. (2), Scheme 3]. Consequently, trisubstituted olefin **35** which is not prone toward elimination undergoes the cycloisomerization in 75 % yield to diastereomerically pure acetate **36** [Eq. (3), Scheme 3].



Scheme 3. Fe-catalyzed cycloisomerization-elimination—influence of the ester and olefinic moiety. [a] Partial hydrolysis of the ester to the corresponding tertiary alcohol **40** was observed. Combined yield after acetylation of the crude product.[9]



Scheme 4. Fe-catalyzed decarboxylative cycloisomerization.[9]



Scheme 5. Control experiments.

In transition metal catalyzed Tsuji–Trost-type allylations allylic alkylcarbonates are highly reactive. In contrast to the use of allylic acetates, the leaving group can undergo a fast decarboxylation to give the corresponding alkoxide which acts as a base or nucleophile. Gratifyingly, the use of propargylic alkylcarbonates as starting materials slowed down the elimination process. Employing propargylic carbonate **37** we were able to isolate ether **38** in 52 % yield as a single diastereomer along with diene **17** as by-product [Eq. (1), Scheme 4]. The use of trisubstituted olefin **39** led to the formation of the respective allylic ether **40** in 82 % yield and with exclusive diastereoselectivity [Eq. (2), Scheme 4].

Although a detailed description of mechanistic scenarios at the current state of research is not possible and needs further investigations, we performed additional experiments to gain some further information on potential pathways (Scheme 5). Different catalysts were tested [Eq. (1), Scheme 5]. While $(Rh(CO)_2Cl)_2$ did not work, we were surprised to find Echavarren's Au^I-complex to be inactive, too [Eq. (1), Scheme 5]. The use of $AgBF_4$ did provide access to product **13** in moderate yields.[10] The use of $AuCl_3$ led to conversion of starting material, however, allene **44** and cyclopropane **43**, in which the cyclopropyl-moiety remained unaffected, were isolated in moderate yields [Eq. (2), Scheme 5]. As we considered both products to be potential intermediates in this transformation, we subjected them to the reaction conditions but did not find any conversion [Eq. (3) and (4), Scheme 5]. Based on these findings, our previous experimental results in related cycloisomerizations[5a,c] and the fact that +M-substituents at

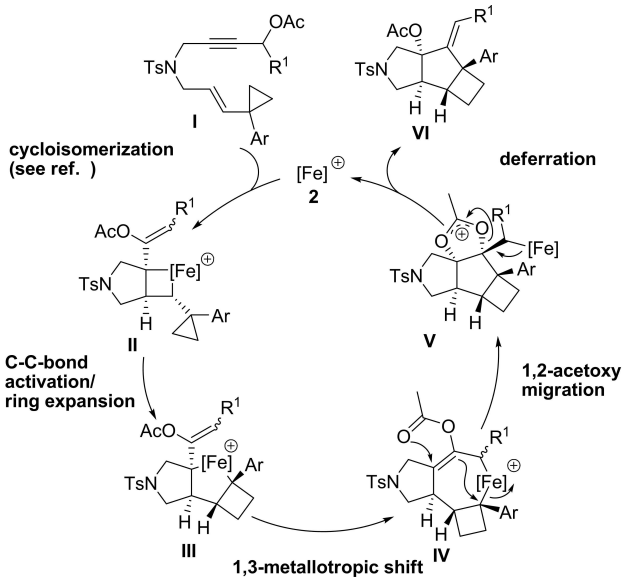


Figure 1. Mechanistic model for Fe-catalyzed cycloisomerization.

the propargylic aromatic unit promote the reaction whereas +M-substituents in the arylcyclopropane moiety decrease the conversion (Scheme 2) we propose the following mechanistic scenario as a working hypothesis (Figure 1).

The cationic Fe-complex coordinates to the alkyne moiety leading to the cyclopropyl-substituted metallcyclobutane intermediate **II**. The fact that +M-substituents in the arylcyclopropane moiety decrease the conversion does not support the hypothetical formation of a free carbocationic intermediate, hence, it seems as if the cationic Fe-center fosters **II** to undergo a metal-centered C–C-bond activation ring expansion process with release of ring-strain to give ferracyclobutane **III**. 1,3-Metallotropic shift within the exocyclic vinylacetate unit provides access to the ferracycloheptane **IV** that upon 1,2-acetoxy migration and deferration leads to the observed product **VI** and recycled catalyst **2**.

We report here a cycloisomerization-C–C-bond activation of enyneacetates featuring a vinylcyclopropane moiety. Catalytic amounts of the readily accessible cationic Fe-complex $[(Ph_3P)_2Fe(CO)(NO)]BF_4$ mediate this transformation under mild conditions to give fused tricyclic cyclobutanes in good to high yields. Depending on the substitution pattern either 1,3-dienes or allylic acetates were observed. Interestingly, amongst the different noble metal type catalysts tested only $AgBF_4$ showed a similar reactivity albeit at significantly lower yields.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Cyclobutanes · Cycloisomerization · Cyclopropanes · Iron Catalysis · Rearrangement

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[8] Kinetic ^{19}F NMR experiments revealed that indeed allylic acetate **14** is formed at a very high conversion rate as the initial product which under the reaction conditions undergoes a fast elimination to diene **13**. Details are found in the Supporting Information.

[9] Deposition Numbers 1961122 (for **17**), 1961124 (for **38**) und 1961123 (for **40**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[10] The fact, that Fe-complex **2** shows a reactivity profile comparable to Ag(+I)-salts is striking and we are currently trying to understand the fundamental electronic features of this complex through in-depth spectroscopy and quantum chemistry.

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