Angewandte Chemie

Cycloheptane Syntheses

DOI: 10.1002/anie.200801738

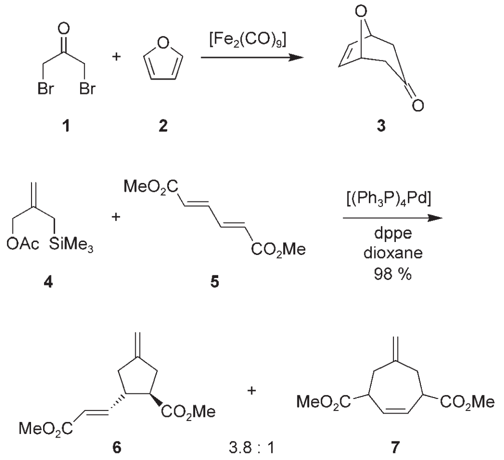
Seven-Membered Rings by Cyclization at Transition Metals: [4+3], [3+2+2], [5+2]

*Holger Butenschön**

carbocycles · cobalt · coordination chemistry · cyclization · transition metals

Transition metal complexes facilitate unusual reactions in their coordination sphere that are usually not possible outside this environment. Among these reactions, cyclizations of high-energy unsaturated compounds, such as alkynes, allenes, or strained small ring compounds, have always been prominent. Nowadays some of these reactions are successfully applied in organic synthesis. In this context, the Pauson–Khand reaction,[1–5] which is the formation of cyclopentenones from an alkene, an alkyne, and CO, deserves mention, as does the [2+2+2] cyclization of alkynes,[6–13] which currently enjoys an impressive renaissance as a result of current contributions from the groups of Tanaka, Shibata, Aubert, Deiters, and Heller.[14–21] Regarding their atom economy, cyclizations of these types fundamentally differ from the equally important ring closing metathesis reactions, which produce equimolar amounts of ethene or 2-butyne in addition to the desired reaction products. Although the Pauson–Khand reaction and [2+2+2] cyclization lead to five- or six-membered rings, which are frequently present natural products, cyclization reactions which result in other ring sizes have also been developed. These include interesting syntheses of seven-membered rings, which, according to a review article by Lautens et al.,[22] are much less common than many other transition-metal-mediated cyclizations, and which were the subject of a Highlight in *Angewandte Chemie* as early as 1995.[23]

Cyclization reactions leading to seven-membered rings require a differentiation between [4+3], [3+2+2], and [5+2] cyclizations. In 1979, Noyori summarized contributions about reactions of α,α'-dibromoketones, such as **1**, with dienes in the presence of stoichiometric amounts of $Fe_2(CO)_9$ leading to cycloheptenones. These reactions are thought to proceed via an iron-coordinated oxyallyl intermediate, which reacts in a [4+3] cyclization reaction with the diene to give the seven-membered ring. If furan (**2**) is used, the primarily obtained oxabicyclic cycloheptenones, such as **3**, can easily be ring-opened with formation of the respective tropone derivatives.[24] The cycloaddition of allyl cations with dienes has since developed into a general synthetic method.[25] Other important [4+3] cyclizations were published in the eighties by Trost et al., who succeeded in the formation of trimethylenemethane intermediates from 2-[(trimethylsilyl)methyl]allyl acetate (**4**) in the presence of palladium(0) catalysts. The reaction with electron-poor dienes, such as **5**, afforded methylenecycloheptene **7** in addition to vinyl-substituted methylenecyclopentene **6** (Scheme 1).[26,27]



Scheme 1. [4+3] cyclizations. dppe = bis(diphenylphosphino)ethane.[24,26]

In 1995, Stryker and Schwiebert first succeeded in synthesizing a cycloheptane with [3+2+2] cyclization by in situ reaction of cationic iridium complexes obtained from triflate **8** with terminal or internal alkynes, affording cycloheptadienyl complexes. The reactions gave reasonable yields of 40–78 %; the reaction of **8** with deca-2,8-diyne (**9**) to give **10** was particularly successful, with a yield of 94 % (Scheme 2).[28] Further investigations with the cheaper catalyst metal cobalt showed that (η^3-allyl)(η^5-pentamethylcyclopentadienyl)cobalt(III) triflates, such as **11**, allow the formation of cycloheptatrienyl complexes like **13** by reaction with ethyne (**12**) or other terminal alkynes, when noncoordinating solvents such as dichloromethane were applied (Scheme 2). The cycloheptadienyl complexes thus obtained can be trapped

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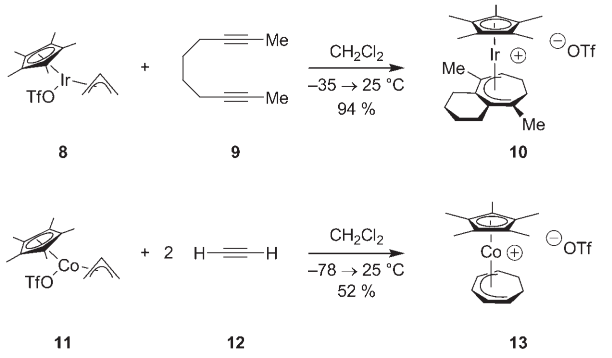
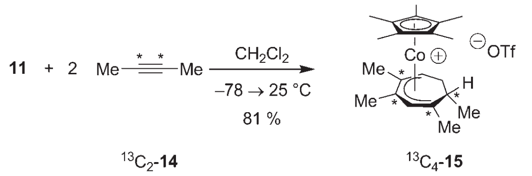
[*] Prof. Dr. H. Butenschön
Institut für Organische Chemie
Leibniz Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-762-4661
E-mail: holger.butenschoen@mboc.oci.uni-hannover.de
Homepage: http://www.oci.uni-hannover.de/AK_Butenschoen/startseite.htm



Scheme 2. [3+2+2] cyclizations.[28,29]

with nucleophiles such as malonates to give the corresponding cycloheptadiene complexes, which allow for an easy decomplexation of the cycloheptadiene ligands.[29]

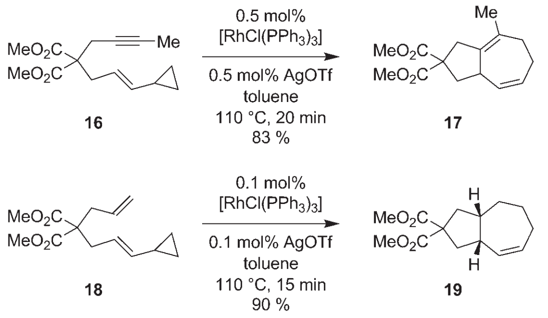
For [3+2+2] cyclizations, it is reasonable to assume a stepwise process, in which the allyl substituent reacts in the first step with an alkyne molecule giving a pentadienyl system, which combines with the second alkyne molecule by cyclization to form the product. However, the reaction of **11** with 2-butyne, which gives **15** in 81 % yield, shows that the process is more complicated in reality. One explanation is to assume either a methyl migration or a fundamental reconstruction of the carbon framework before or after the cyclization takes place. Stryker et al. observed the formation of $^{13}C_4$-**15** in 81 % when using the doubly-labeled $^{13}C_2$-2-butyne ($^{13}C_2$-**14**), thereby showing that the methyl groups stay bound at the ^{13}C atoms, which excludes the first explanation (Scheme 3).[30]



Scheme 3. [3+2+2] Cyclization with doubly ^{13}C-labeled 2-butyne ($^{13}C_2$-**14**).[30]

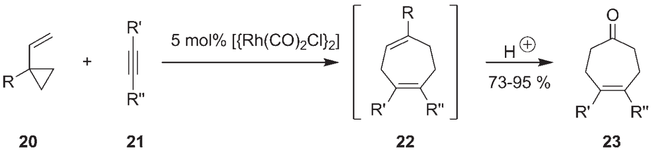
(Allyl)(hexamethylbenzene)ruthenium triflates also allow [3+2+2] cyclizations to cycloheptadienyl complexes; however, depending on the reaction conditions, other reaction products are observed as well.[31]

[5+2] cyclizations can start from various C_5 building blocks. In the mid 1990's, Wender et al. demonstrated that vinylcyclopropane derivatives are suitable C_5 building blocks, which, in the presence of catalytic amounts of rhodium(I) complexes, react with alkynes to give cycloheptadienes.[32] For example, the reaction of the alkynyl-substituted vinylcyclopropane derivative **16** in the presence of 0.5 mol % of the Wilkinson catalyst $[RhCl(PPh_3)_3]$ and 0.5 mol % of silver triflate in boiling toluene leads in an intramolecular [5+2] cyclization in 83 % yield to the bicycle **17**.[33,34] Later it was shown that the reaction is also successful with the corresponding alkenyl-substituted vinylcyclopropane **18**; in the presence of only 0.1 mol % of the same catalyst and 0.1 mol % of silver triflate, the cycloheptene **19** is formed (Scheme 4).[35] Similar results were achieved with allenyl-substituted vinylcyclopropanes.[36] The formation of the seven-membered rings by these reactions was understood to be the result of reductive elimination reactions from the corresponding rhodacyclooctenes or rhodacyclooctadienes, respectively.



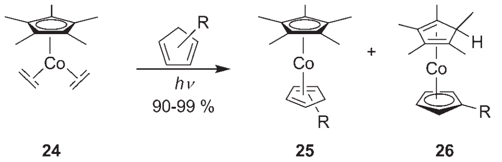
Scheme 4. Intramolecular rhodium-catalyzed [5+2] cyclizations of alkynyl- or alkenyl-substituted vinylcyclopropanes.[33,35]

A short time later, using $[\{Rh(CO)_2Cl\}_2]$ as catalyst, the intermolecular reaction was realized in which 1-(*tert*-butyldimethylsilyloxy)-1-vinylcyclopropane (**20**, R = OSi*t*BuMe$_2$) reacted with terminal and with internal alkynes **21**, via the silyl enol ether **22** (not isolated), to give 4-cycloheptenones **23** in yields of up to 93 % (Scheme 5).[37] Later it was shown that, instead of the silyl ether,1-(2-methoxyethoxy)-1-vinylcyclopropane (**20**, $R = OCH_2CH_2OMe$) may be used as well.[38] More recent developments of this reaction, which, in a somewhat simplified manner is sometimes termed a homo-Diels–Alder reaction, include vinylcyclopropane derivatives without an activating 1-oxy substituent, and reactions in water as the solvent.[39,40] Based on theoretical calculations, the differences between alkenes, alkynes, and allenes in [5+2] cyclization reactions with $[\{Rh(CO)_2Cl\}_2]$ as the catalyst were recently explained by the reductive elimination to be less facile in the case of the reaction with alkenes.[41] In another recent paper, Yu et al. describe a so-called [(5+2)+1] cyclization, in which a vinylcyclopropane and an intramolecular alkene moiety combine along with an additional CO molecule, leading to formation of a cyclooctenone.[42]



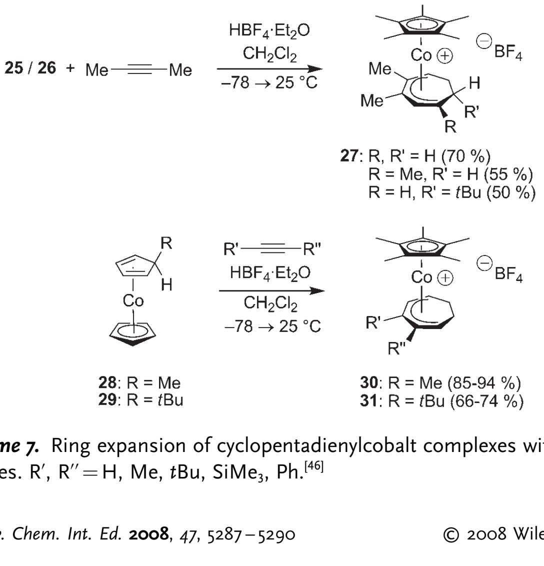
Scheme 5. Intermolecular catalyzed [5+2] cyclizations of 1-substituted vinylcyclopropanes with alkynes. R = OSi*t*BuMe$_2$, OCH_2CH_2OMe, CO_2Me, Ph, CH_2OMe, CH_2OH, Pr, $SiMe_3$; R', R'' = H, CO_2Me, Ac, CH_2OMe, Me_3Si, CH_2OH, alkyl, alkenyl.[37–39]

[5+2] cyclizations with pentadienyl complexes leading to cycloheptane derivatives were first reported by Kreiter et al. Irradiation of tricarbonyl(η^5-2,4-dimethylpentadienyl)manganese(I) in THF at 208 K in the presence of an excess of dimethyl butynedioate or diphenylethyne afforded the respective cycloheptadienyl complexes in 12 % and 11 % yield, respectively, by alkyne insertion.[43–45] Although the cyclizations starting from vinylcyclopropanes have attracted considerable attention for some time, the use of pentadienyl complexes now comes into focus as a result of two recent publications by Stryker et al. The starting point is the photochemical ligand exchange of the two ethene ligands of bis(ethene)(η^5-pentamethylcyclopentadienyl)cobalt(I) (**24**) by cyclopentadiene with formation of (η^4-cyclopentadiene)(η^5-cyclopentadienyl)cobalt(I) complexes in 90–99 % yield. Such reactions involve a reversible hydrogen transfer from the cyclopentadiene to the cyclopentadienyl ligand, resulting in the formation of complexes **25** and **26** (Scheme 6).[46]



Scheme 6. Formation of cyclopentadiene complexes **25** and **26** by photochemical ligand exchange from **24**. R = H, Me, *t*Bu.[46]

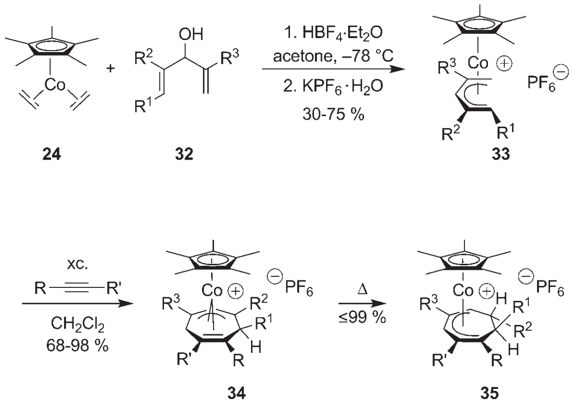
Upon protonation of the mixture of **25** and **26** with tetrafluoroboric acid in the presence of 2-butyne, a ring expansion of the less highly substituted five-membered ring is observed with formation of the cationic cycloheptadienyl complex **27**, which is formed in 50–70 % yield (Scheme 7). Further investigations with methyl or *tert*-butyl-substituted (η^4-cyclopentadiene)(η^5-cyclopentadienyl)cobalt complexes **28** and **29** indicate that this is a general reaction type, yielding cyclopentadienyl complexes **30** and **31** in 66–94 % yield, respectively (Scheme 7). Although the reaction mechanism is not yet fully understood, the authors suggest a cyclopentenylcobalt intermediate with an agostic hydrogen atom, from which, by addition at the alkyne, a vinylcyclopentene intermediate is formed, which then reacts to the product.[46]



Scheme 7. Ring expansion of cyclopentadienylcobalt complexes with alkynes. R′, R″ = H, Me, *t*Bu, $SiMe_3$, Ph.[46]

After the investigations of Stryker and Dzwiniel had shown that a ring expansion of η^5-cyclopentadienylcobalt complexes to cycloheptadienyl complexes was feasible, the question was raised as to how far it would be possible to perform a [5+2] cyclization starting from acyclic η^5-pentadienyl complexes, which are in principle accessible in much larger variety than their cyclic analogues. η^5-Pentadienyl complexes are of fundamental interest in catalysis because of their possible change in hapticity to η^3 or η^1 along with formation of vacant coordination sites.[47,48] In a recent publication, Stryker et al. have faced this challenge and report on the formation of (η^5-pentadienyl)(η^5-pentamethylcyclopentadienyl)cobalt complexes and their [5+2] cyclization to cycloheptadienyl complexes.[49]

1,4-Alkadien-3-oles **32** react in reasonable yields with bis(ethene)(η^5-pentamethylcyclopentadienyl)cobalt (**24**) and $HBF_4{\cdot}Et_2O$ to the cationic, air-stable pentadienylcobalt complexes **33**. With an excess of alkyne, these are transformed under mild reaction conditions to the cycloheptadienyl complexes **34**, which, remarkably, form under kinetic reaction control as the unconjugated η^2,η^3-isomers, which were at the time unknown. Upon heating, isomerization to the thermodynamically more stable η^5-cyclopentadienyl complexes **35** occurs. The reactions afford products in excellent yields, usually in the range of 91–99 % (Scheme 8).



Scheme 8. [5+2] cyclization of the acyclic η^5-pentadienyl complex **33** with alkynes. R^1, R^2, R^3 = H, Me, Et, Ph; R, R′ = H, Me, Pr, OEt, $SiMe_3$.[49]

As a mechanistic explanation, the authors assume a partial decomplexation of the pentadienyl ligand ($\eta^5 \rightarrow \eta^3$) thereby creating the vacant coordination site required for alkyne complexation. Subsequent coupling of the coordinated allyl part of the pentadienyl ligand with the coordinated alkyne followed by a recomplexation of the alkene part of the pentadienyl ligand and a ring closure leads to the isolable η^2,η^3-cycloheptadienyl complex **34**. Because of the similarity to the Nazarov cyclization of divinyl ketones, the authors term this as an "interrupted Nazarov cyclization" with trapping of the cationic intermediate before the ring closure by cyclization with the alkyne.

In summary, the synthesis of cycloheptane derivatives by cyclization of unsaturated building blocks at transition metals has developed from the well-established [4+3] via some

[3+2+2] to versatile [5+2] cyclizations of vinylcyclopropanes, or more generally, pentadienyl systems. The high degree of development that has been achieved ushers interesting applications in the synthesis of complicated target structures involving cycloheptane moieties. Future challenges include the stereocontrol of the reaction and the development of more catalytic [5+2] cyclizations, for instance with alkenes instead of alkynes.[50]

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[50] Note added in proof (May 29, 2008): After the submission of this manuscript another important paper on [5+2] cycloaddition of vinylcyclopropanes appeared: P. Liu, P. H.-Y. Cheong, Z.-X. Yu, P. A. Wender, K. N. Houk, *Angew. Chem.* **2008**, *120*, 4003–4005; *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 3939–3941.