chromium(III) 2,4-pentanedionate ([Cr(acac)$_3$], 0.1M) in an ordinary 5-mm ϕ NMR tube. The ^{13}C NMR spectrum was measured on a JEOL EX-270 spectrometer at 68 MHz and operated with 9-s relaxation delay and gated decoupling without NOE (160 transients, 0.6 s acquisition time). The spectra were referred to the resonance for TMS. ^{13}C NMR spin-lattice relaxation times (T_1) were measured by using the inversion recovery method at 298 K (16 data points, 16 scans per point). The T_1 values for methyl and carbonyl groups attached to the resin were shorter than 1 s in the presence of [Cr(acac)$_3$] and 12 s and 29 s in the absence of the relaxation agent.

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Single-Step Construction of a Nine-Membered Carbocycle by a New [4+4+1] Cycloaddition[**]

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There is much interest in medium-sized, that is, eight- to eleven-membered, carbocycles because they are often an important structural feature of biologically active compounds. From the synthetic point of view, however, construction of medium-sized ring systems is a formidable objective due to unfavorable entropy factors as well as energy barriers inherent to cyclization (generally ascribed to arising angle strain, bond opposition (Pitzer) strain, and transannular interactions).[1, 2] Especially scarce are methods for the preparation of nine-membered carbocycles,[3] the development of which remains an important challenge in organic chemistry.

Vinylallene has been described to act as a versatile four-carbon unit in metal-catalyzed [4+1][4] and [4+2] cycloaddition[5] reactions. We expected that the use of an appropriate metal catalyst capable of simultaneous multiple coordination of vinylallene would make it possible to incorporate two or more molecules of vinylallene in the resulting skeleton in a single operation. Here we report a palladium-catalyzed [4+4+1] cycloaddition reaction which provides a new route to nine-membered carbocycles. To the best of our knowledge, this is the first example of a [4+4+1] cycloaddition.[6] While our approach presently requires certain substitution in the substrate, we believe that this new reaction may eventually lead to a useful strategy for the construction of nine-membered rings.

A solution of vinylallene **1** in THF was stirred under an atmosphere of carbon monoxide in the presence of 5 mol% palladium(0) catalyst at 30°C. The reaction mixture was stirred for 43 hours, and vinylallene **1** was consumed to afford a sole product. From the spectroscopic data the structure was concluded to be the symmetrical nine-membered ketone **2**, as depicted in Scheme 1. The cyclic compound **2**, isolated in 87% yield, was assembled from two molecules of vinylallene **1** and one molecule of carbon monoxide. Vinylallene **1** coupled at the 1-position in a head-to-head manner, providing the two four-carbon units. Cheletropic incorporation of carbon monoxide between the 4-positions furnished the nine-membered ketone **2** as a [4+4+1] cycloadduct.

Vinylallene **3** also underwent an analogous [4+4+1] cycloaddition reaction to afford **4** as a solid in 61% yield (Scheme 2). Although the ketone gradually decomposed on exposure to light, careful recrystallization from ether/hexane generated single crystals suitable for X-ray crystallography,[7]

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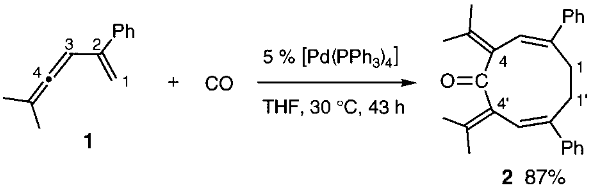
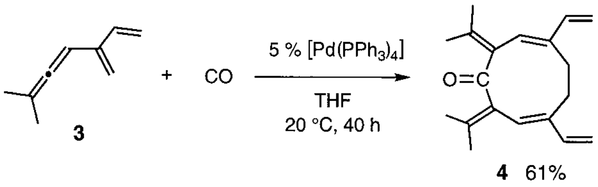


Scheme 1. Palladium-catalyzed [4+4+1] cycloaddition of **1** and carbon monoxide.



Scheme 2. Synthesis of the nine-membered cyclic ketone **4**.

which unambiguously established the nine-membered-ring structure (Figure 1). Whereas the NMR data of **4** conformed to the symmetrical structure, significant deformation was

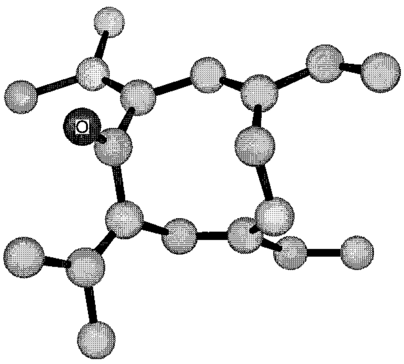
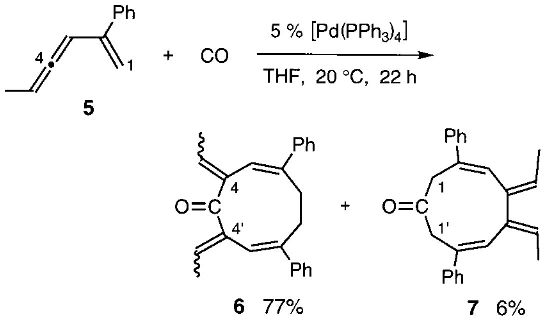


Figure 1. Molecular structure of **4** in the crystal (hydrogen atoms omitted for clarity).

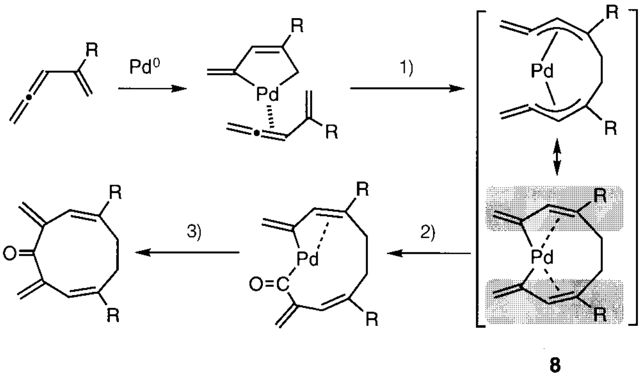
observed in the solid state. On one side of the carbonyl group (the top half in Figure 1) the triene skeleton fits on a plane and is in full conjugation, but the triene unit severely deviates from the carbonyl plane. On the other side (the bottom half in Figure 1) the triene skeleton is divided into the exocyclic α,β-unsaturated carbonyl system and the remaining 1,3-diene system in terms of conjugation. Presumably the deformation reduces the steric congestion around the carbonyl group.

In the case of vinylallene **5** (Scheme 3), the [4+4+1] cycloadducts were obtained as a mixture of regio- and stereoisomers. In the dominant regioisomer (**6**), isolated in 77 % yield, carbon monoxide was inserted between the sp^2 carbon atoms (4-positions), as is the case with **2** and **4**. The major regioisomer consisted of three stereoisomers with respect to the orientation of the two methyl groups of the exocyclic double bonds (outward–outward:outward–inward:inward–inward = 5:92:3).[8] Besides the major regioisomer (**6**), **7** was obtained as the minor regioisomer (6 % yield), in which carbon monoxide was inserted between the sp^3 carbon atoms (1-positions). Interestingly, both of the methyl groups of **7** face outward, probably for steric reasons.



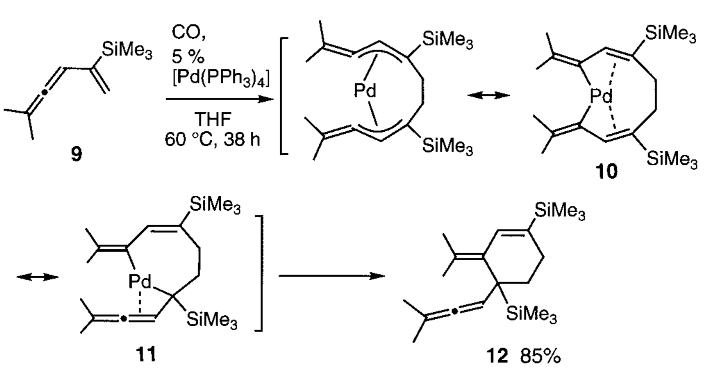
Scheme 3. Synthesis of the nine-membered cyclic ketones **6** and **7**.

A plausible mechanism to explain the formation of the nine-membered cyclic ketones **2**, **4**, and **6** is given in Scheme 4. A five-membered palladacycle is initially formed by the reaction of a molecule of vinylallene with the palladium(0) catalyst. Another molecule of vinylallene binds to the palladium center at the allene site. A carbon–carbon bond is formed between the 1-positions producing a bis(π-allyl)-palladium intermediate.[5a] Among its resonance contributors, the σ-di(alkenyl)palladium form **8** would be of greater importance because it gains stabilization by the extended conjugation from the exocyclic C–C double bond through the endocyclic C–C double bond to the pendant unsaturated R (phenyl or vinyl) substituent. Insertion of carbon monoxide into the Pd–C$_{sp^2}$ bond and subsequent reductive elimination would afford a nine-membered cyclic ketone.



Scheme 4. Plausible mechanism of the [4+4+1] cycloaddition (substituents at the allenyl terminus omitted for clarity). 1) C–C bond formation, 2) CO insertion, 3) reductive elimination. Sections in the shaded boxes are conjugated.

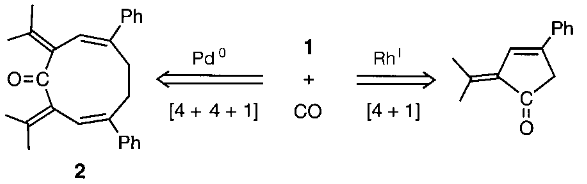
For comparison, an analogous reaction was carried out with vinylallene **9**, which has a trimethylsilyl group as the pendant R substituent, and hence, no extended conjugation could be expected. With **9**, not a nine-membered carbocycle but the six-membered [4+2] cycloadduct **12** was formed exclusively (Scheme 5).[5a] In this case the σ-di(alkenyl)palladium form **10** might be less predominant due to the lack of stabilization by conjugation, and the other contributor (**11**) is liable to direct reductive elimination affording an easy-to-form, six-membered ring prior to insertion of carbon monoxide. This result, standing in marked contrast to the reactions with the vinylallenes **1**, **3**, and **5**, lends support to the mechanistic



Scheme 5. Palladium-catalyzed [4+2] cycloaddition of **9** and CO. The reaction from **11** to **12** proceeds with reductive elimination.

interpretation that the extended conjugation with the pendant R substituent is crucial for the formation of the nine-membered carbocycle.

An unprecedented [4+4+1] cycloaddition is realized by a palladium(0)-catalyzed carbonylation with vinylallenes lacking coordinative heteroatom functionalities. Palladium(0) serves as a template to set three components in an array for a cycloaddition otherwise impossible to achieve. The usefulness of this new reaction is validated by the fact that nine-membered carbocycles that are normally difficult to form are constructed in a single chemical operation with good atom economy,[9] a concept which has gained in interest in organic synthesis. Although the full potential of the new cycloaddition reported here awaits exploration, it is clearly demonstrated that [4+4+1] is a viable mode. Finally, it should be noted that the present reaction with the palladium(0) catalyst provides a remarkable contrast to that with rhodium(I):[4d,e] palladium(0) drives the [4+4+1] cycloaddition to give a nine-membered adduct, whereas rhodium(I) promotes [4+1] cycloaddition producing a five-membered adduct from the same vinylallene and carbon monoxide (Scheme 6).



Scheme 6. Contrast in the assembly modes of cycloadditions mediated by Pd^0 and Rh^I catalysts.

Experimental Section

2: A mixture of $[Pd(PPh_3)_4]$ (54 mg, 47 μmol) and 5-methyl-2-phenyl-1,3,4-hexatriene (**1**, 160 mg, 940 μmol) in THF (3 mL) was stirred under an atmosphere of carbon monoxide at 30 °C for 43 h. The reaction mixture was passed through a pad of Florisil to remove the insoluble materials. The eluent was concentrated to dryness under vacuum, and the residue was subjected to column chromatography (silica gel, ether/hexane (1/10)) to afford **2** (150 mg, 87 %) as a white solid. ^1H NMR ($CDCl_3$, 200 MHz): $\delta =$ 1.88 (s, 6H), 2.04 (s, 6H), 2.80 (s, 4H), 6.47 (s, 2H), 7.15–7.30 (m, 10H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): $\delta = 22.4$, 22.5, 30.2, 126.6, 127.0, 128.3, 136.3, 141.1, 141.3, 144.5, 203.1; IR (neat): $\tilde{\nu} = 1670$, 1590 cm^{-1}; HRMS *m/z* calcd for $C_{27}H_{28}O$: 368.2140; found: 368.2121; elemental analysis calcd for $C_{27}H_{28}O$: C 88.00, H 7.66; found: C 87.74, H 7.71.

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[7] **4**: $C_{19}H_{24}O$, $M_r = 268.4$, monoclinic, space group $P2_1/a$, $a = 11.295(7)$, $b = 15.972(8)$, $c = 10.006(6)$ Å, $\beta = 113.72(3)^\circ$, $V = 1652.7(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.08\ g\,cm^{-3}$, $\mu = 0.601\ cm^{-1}$. Intensity data were collected on a Mac Science DIP2000 diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 71.069$ pm), using an imaging plate area detector with an oscillation mode. From a total of 16928 observations, 2796 unique reflections were processed by a MAC-DENZO program. The structure was solved by direct methods and refined by full-matrix least squares to $R = 0.066$ ($R_w = 0.073$) for 1169 reflections [$I > 3.0\sigma(I)$], using the Crystan GM program package. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were observed or calculated and refined isotropically with a fixed C–H distance of 0.96 Å. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102096. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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