4730 J. Org. Chem. **1994**, 59, 4730−4732

Facile Formation of Seven- and Eight-Membered Cycloalkenes via Catalytic and Cyclic Carbopalladation of Allenes

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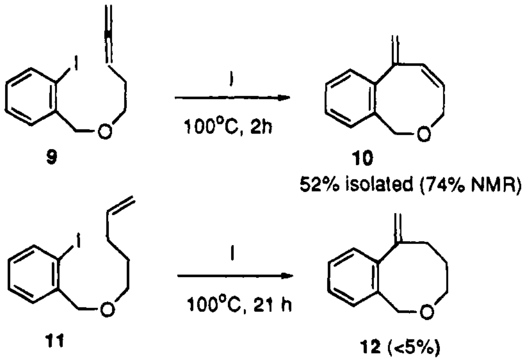
Received June 13, 1994®

Summary: Cyclization of allene-containing aryl and alkenyl halides under the influence of a catalytic amount of a Pd−phosphine complex, *e.g.*, Cl$_2$Pd(PPh$_3$)$_2$, proceeds via carbon−carbon bond formation at the central carbon atom of the allene moiety, providing a novel and facile route to seven- and eight-membered cycloalkene derivatives.

In conjunction with our studies directed toward the development of cyclic carbopalladation[1,2] we became interested in the use of allenes. The presence of two alkene moieties in an allene offers the possibility of two exo-mode[3] cyclization paths shown in Scheme 1. In view of the known intermolecular carbopalladation of allenes[4] which has been shown to give allylpalladium derivatives, path ii may be predicted to be favored over path i. On the other hand, the Pd-catalyzed cyclization of aminoallenes[5] has been shown to give alkenylpalladium species. The ring formed via path i is smaller than that via path ii by one atom, which could also be an important factor in determining the course of the reaction. Herein we report what appear to be the first examples of intramolecular cyclic carbopalladation of allenes.

Treatment of **1a**[6] with 5 mol % of Cl$_2$Pd(PPh$_3$)$_2$, K$_2$CO$_3$ (5 equiv), and EtOH (10 equiv) at the concentration of 0.05 M in DMF at 100 °C for 5 h cleanly afforded a seven-membered ring **2**[7] in 70−75% yield (~60% isolated). Although the putative allylpalladium intermediate **3** can, in principle, give two regioisomeric conjugated dienes **2** and **4**, the extent of formation of **4** was <2%. The bromo analogue **1b** reacted similarly to give **2** in 71% NMR yield. The most noteworthy feature of the reaction is the virtual absence (<1−2%) of six-membered ethers, such as **5**, that can be formed via **6**. Since the formation of allenes via dehydropalladation of alkenylpalladium species is known to be unfavorable,[1g,h] it is possible that **6** might be formed without producing six-membered ethers as final products. With the hope of trapping **6** by carbonylation the cyclization reaction of **1a** was carried out in the presence of CO (1 atm) and MeOH (10 equiv) in place of EtOH under otherwise identical conditions. The product consisted of **2** obtained in 74% NMR yield and the premature esterification product **7** (20% NMR yield). The extent of formation of **8** was <2%. Although we[1f,8] and others[2d] have demonstrated that cyclic carbopalladation of alkenes and alkynes is a viable route to seven-membered rings, preferential formation of seven-membered rings over six-membered rings is unprecedented.

The results described above prompted us to examine competitions between seven- and eight-membered rings. The reaction of **9**[6] under the conditions I at 100 °C for 2 h gave **10**[7] in 74% NMR yield (52% isolated) without producing detectable amounts of seven-membered ethers. Unlike the cases of seven-membered ring formation, cyclic carbopalladation of alkenes has not been readily applicable to the synthesis of eight-membered rings.[8b,9] In accord with this generalization, the reaction of **11**[6] under the conditions I at 100 °C for 21 h did not give the expected product **12** (<5%, if any).



9 **10**

52% isolated (74% NMR)

11 **12** (<5%)

As indicated by these results and those that follow, facile formation of seven- and eight-membered rings via carbopalladation of allenes appears to be quite general. Conversion of **13**−**16**[6] into **17**−**20**[7] in the yields shown in parentheses indicates the applicability of the reaction to the synthesis of carbocycles. Both aryl and alkenyl

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[1] For some of our earlier papers, see: (a) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289. (b) Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (c) O'Connor, B.: Zhang, Y.; Negishi, E.; Luo, F. T.; Cheng, J. W. *Tetrahedron Lett.* **1988**, *29*, 3903. (d) Zhang, Y.; O'Connor, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5588. (e) Negishi, E.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 291. (f) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (g) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (h) Review: Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323.

[2] For other seminal papers, see: (a) Narula, C. K.; Mak, K.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792. (b) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073. (c) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. See also: Trost, B. M. *Acc. Chem. Res.* **1990**, *23*. 34. (d) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133. (e) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.

[3] The great majority of cyclic carbopalladation has been shown to involve an exo-mode cyclization. For a discussion of an apparent endo-mode cyclic carbopalladation, see: Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091.

[4] (a) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 4505. (b) For a review, see: Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867. (c) Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.

[5] (a) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Malloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652. (b) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *57*, 6377.

[6] The starting ethers were prepared from the corresponding allenols and benzyl bromides in THF at room temperature using NaH as a base. For the preparation of allenols, see: Olsson, L. I.; Claesson, A. *Acta Chim. Scand. B* **1977**, *31*, 614. The malonate derivatives were prepared by two-step alkylation with the corresponding bromides and NaH. Conversion of allenols into bromides was carried out using PBr$_3$. For the conversion of cyclopentanone into 1-bromo-2-(bromomethyl)-cyclopentene in three steps, see: Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789.

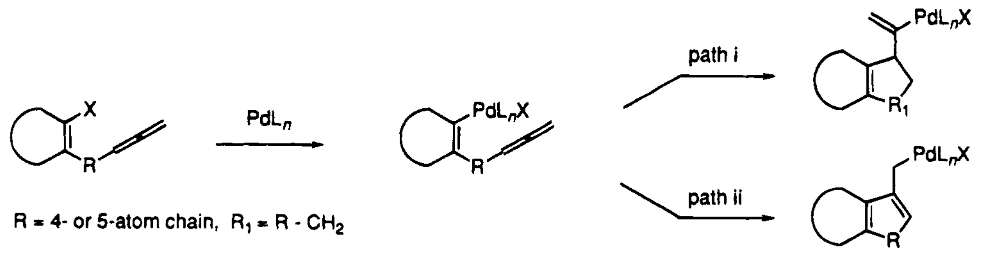
[7] All isolated cyclization products were fully identified by the usual spectroscopic means including high resolution mass spectrometry.

[8] (a) Negishi, E.; Nguyen, T.; O'Connor, B.; Evans, J. M.; Silveira, A., Jr. *Heterocycles* **1989**, *28*, 55. (b) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507.

[9] For successful preparation of a structurally rigid eight-membered ring, see: Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253.

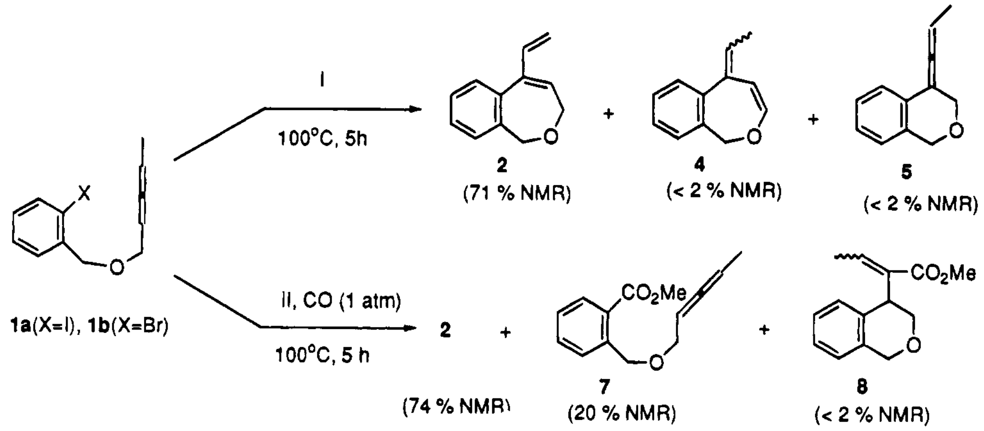
0022-3263/94/1959-4730$04.50/0

Scheme 1



R = 4- or 5-atom chain, R$_1$ = R - CH$_2$

Scheme 2



1a(X=I), 1b(X=Br)

2 (71 % NMR)

4 (< 2 % NMR)

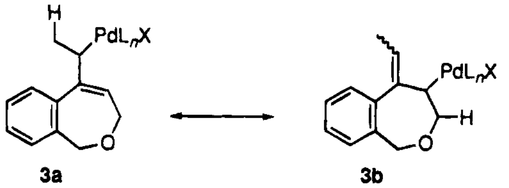
5 (< 2 % NMR)

2 (74 % NMR)

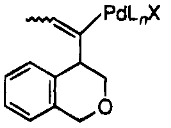
7 (20 % NMR)

8 (< 2 % NMR)

I = 5% PdCl$_2$(PPh$_3$)$_2$, K$_2$CO$_3$ (5 equiv), EtOH (10 equiv), DMF. II = I except that MeOH is used instead of EtOH.



3a **3b**



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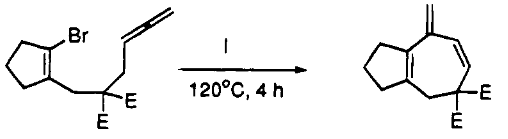
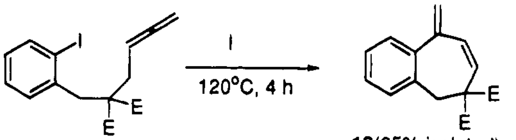
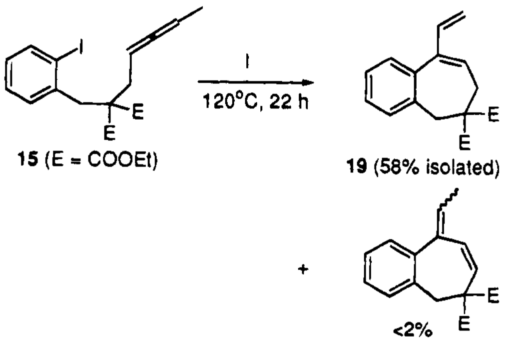
halides participate in the reaction. Conversion of **13** into **17** represents a novel route to hydrazulenes.



13 (E = COOEt) **17** (58% isolated)

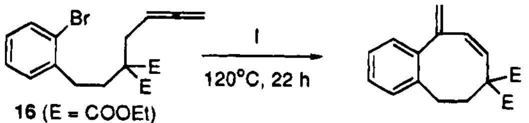


14 (E = COOEt) **18**(65% isolated)



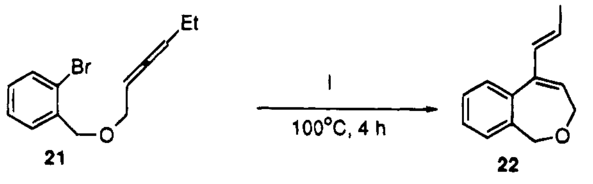
15 (E = COOEt) **19** (58% isolated)

<2%

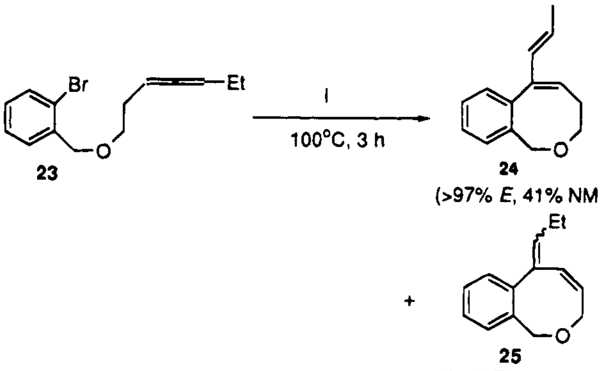


16 (E = COOEt) **20** (56% isolated)

In the seven-membered ring formation, 1,4-elimination is highly regioselective to give nearly exclusively alkenyl-substituted cycloheptadienes, *i.e.*, **2**, **19**, and **22**,[7] in cases where two regiochemical modes of elimination are possible. On the other hand, the regioselectivity of elimination in the eight-membered ring formation does not appear to be high, as suggested by the results shown below. It is also noteworthy that the formation of **22** and **24**[7] was >97% stereoselective, providing preferentially the *E* isomer.



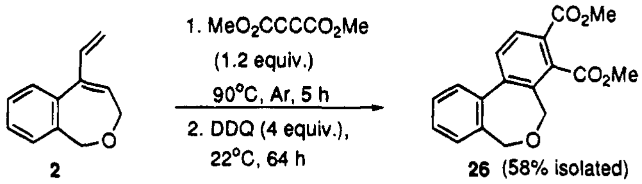
21 **22** (>97 % *E*, 61 % isolated)



23 **24** (>97% *E*, 41% NMR)

25 (66% *Z*, 35% NMR)

The potential utility of the reaction described herein in the synthesis of seven- and eight-membered rings is evident. Conversion of **1** into **26**[7] via cyclic carbopalladation–Diels–Alder reaction–oxidation represents a novel route to fused tricyclic biaryls. Further development of this promising cyclization methodology is in progress.



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26 (58% isolated)

Acknowledgment. We thank the National Institutes of Health (GM 36792) for support of this research. We also thank Johnson Matthey for a loan of $PdCl_2$.

Supplementary Material Available: A representative procedure for cyclic carbopalladation and spectral data for all isolated cyclization products (**2**, **10**, **17**–**20**, **22**, **24**–**26**) (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.