J. Org. Chem. 1989, *54*, 2507-2508

Palladium-Catalyzed Cyclization of Benzyl Halides and Related Electrophiles Containing Alkenes and Alkynes as a Novel Route to Carbocycles[1]

Guang-zhong Wu, Frédéric Lamaty, and Ei-ichi Negishi*

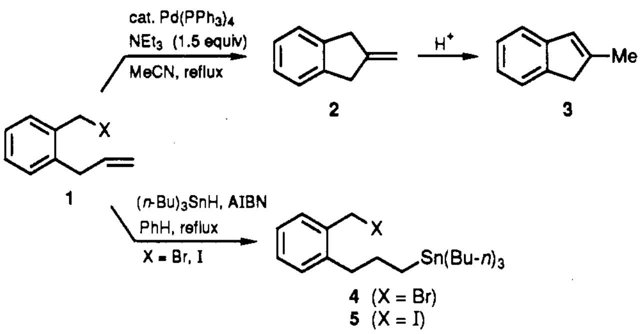
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received April 3, 1989

Summary: Treatment of benzyl halides and related electrophiles containing alkene and alkyne groups with a catalytic amount of Pd complexes, such as $Pd(PPh_3)_4$, provides the corresponding cyclization products containing five- through seven-membered rings often with retention of the alkene regiochemistry.

Sir: In recent years, both radical cyclization reactions,[2] especially those involving Sn-promoted cyclization of organic halides,[3] and cyclic carbopalladation reactions[4,5] have been developed as tools for the preparation of carbocycles and heterocycles. Although these two methodologies display some similar features, they are also complementary to each other in many other respects. Conspicuously absent in the radical cyclization methodology[2,3] is the use of benzyl halides and related electrophiles as radical precursors, even though a recent paper by Stork[3] has indicated that allyl derivatives can participate in cyclization. This and the virtual absence of investigation of benzylpalladation of alkenes and alkynes in the literature[6] aroused our interest in exploring cyclic benzylpalladation as a potential tool for cyclization.

Scheme I



We now report that cyclic benzylmetalation of alkenes and alkynes catalyzed by palladium complexes, such as $Pd(PPh_3)_4$ and $Cl_2Pd(PPh_3)_2$, can indeed proceed cleanly and in high yields, producing five- through seven-membered cyclic compounds. Noteworthy among other features is the unexpectedly high alkene regiospecificity. These features combine to make the Pd-catalyzed benzylpalladation a cyclization tool of considerable promise. The results herein presented vis-a-vis our failures to effect a related cyclization reaction of alkene-substituted benzyl halides under radical cyclization conditions (vide infra) may represent a point of departure from the parallelism observed between the Pd-catalyzed and radical-promoted cyclization methodologies.

In a representative test case, *o*-allylbenzyl chloride (**1a**) was treated with 5 mol % of $Pd(PPh_3)_4$ in the presence of 1.5 equiv of NEt_3 in refluxing MeCN for 1 h. The reaction was remarkably regioselective and produced in 95% GLC yield (82% isolated) 2-methyleneindan[7] (**2**). The amount of 2-methylindene (**3**) was <1%. Examination of the effects of leaving groups on the conversion of **1** into **2** has revealed that Cl, Br, and OMs can be satisfactory leaving groups, whereas OAc and OCO_2Me are not. With the iodide (**1c**), the formation of the undesired **3** accompanies that of **2** even during the first 5 min (ca. 20% of the total amount). Thus, the yields of **2** and **3** observed with various leaving groups as well as the reaction times are as follows: Br (82, <1, 0.5 h), I (64, 18, 0.5 h), OMs (60, <1, 1 h), OCO_2Me (26, 23, 5 days), and OAc (<1, <1, 2 days). A subtle difference between Cl and Br became more apparent when the reaction times were prolonged. Under the standard reaction conditions, the yields of **2** and **3** from the bromide observed after 1 h were 68 and 17%, respectively, whereas little regioisomerization was observed with the chloride even after 3 h under the comparable conditions. Since treatment of **2** with 0.2 equiv of 7.5 M HBr in refluxing MeCN completely isomerized it into **3** in >90% yield within 1 h, it is possible that the observed regioisomerization is catalyzed by acids rather than Pd complexes. In accord with this notion, 7.5 M HCl induced isomerization of **2** to **3** only to the extent of 35% under comparable conditions.

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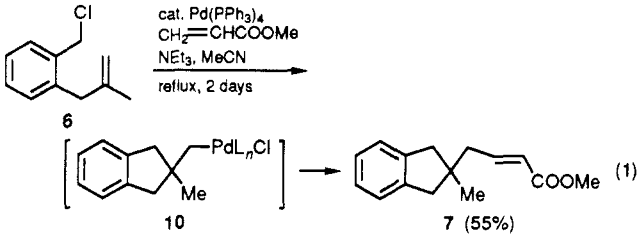
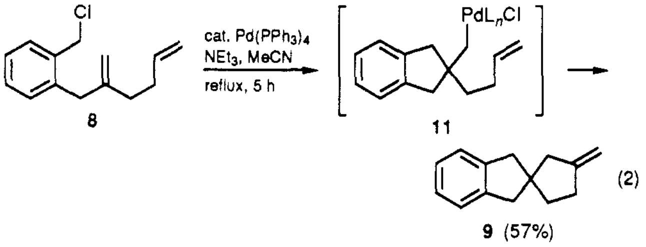
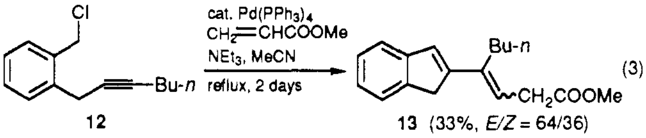
In sharp contrast with the results presented above, attempts to induce cyclization of **1a** under typical radical cyclization conditions involving its treatment with $(n\text{-Bu})_3SnH$ (1.2 equiv) and 6 mol % of AIBN in refluxing benzene^{3i-k} led only to the recovery of **1a** in ca. 90% after 16 h. Interestingly, the corresponding bromide (**1b**) and iodide (**1c**) did react to the extents of 34 and 46%, respectively. However, the compounds isolated in 30 and 32% yields were hydrostannation products **4** and **5**, respectively. No cyclization products were formed under the reaction conditions used.

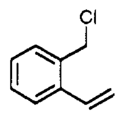
The highly contrasting results shown in Scheme I suggest that the Pd-catalyzed reaction most probably does not proceed via radical cyclization. That the cyclization reaction most likely proceeds via an alkylpalladium intermediate formed by cyclic benzylpalladation is indicated by the results of the cyclization reaction of **6** in the presence of methyl acrylate, producing **7** in 55% yield as well as by a >99% regiospecific conversion of **8** into **9** in 57% (68% GLC) yield. Most probably, presumed intermediates **10** and **11** respectively participate in subsequent intermolecular and intramolecular carbopalladation processes. Similarly, the Pd-catalyzed reaction of **12** with methyl acrylate gave a 64:36 mixture of the *E* and *Z* isomers of **13** in 33% yield.







The scope and the potential synthetic utilities of the cyclic benzylpalladation reaction are further indicated by the reactions shown in eq 4–7. As these results indicate, five- through seven-membered carbocycles are readily formed, although our brief attempts to cyclize **14** and **15** under similar conditions have not so far been successful. Conversion of **16** into **17** and that of **22** into **23** are both 99% regiospecific, although cylization of **18** and **20** producing cyclohexene derivatives was not regiospecific. The required benzyl derivatives described in this paper are obtainable either via benzylation of appropriate organometals containing Li and Mg or via allylation of aryl Grignard reagents. A subtle but apparent difference between cyclic benzylpalladation and allylpalladation^{5m-p} should be noted. All of the currently known examples of the latter are those that can readily attain a six-centered transition state for the Pd–ene process. Furthermore, all our attempts to induce cyclic allylpalladation in cases where only a four-centered, rather than six-centered, transition state might be readily attainable have uniformly failed. On the other hand, six-centered transition states appear to be highly strained and unlikely in all of the successful cases herein reported. We suggest the cyclic benzylpalladation, like aryl- and alkenylpalladation, most likely proceeds via a four-centered transition state.



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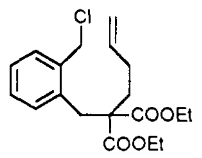

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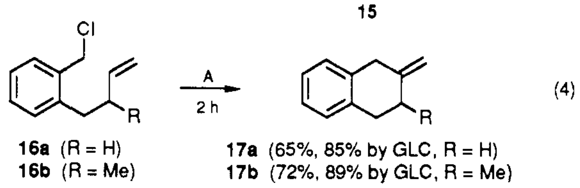

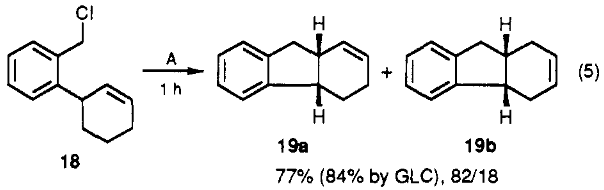

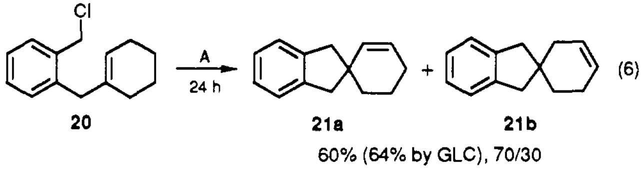

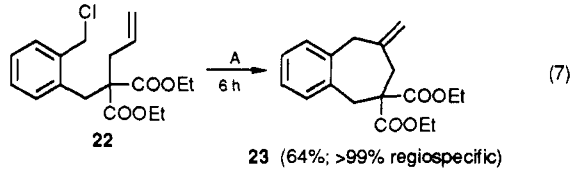

A = 5 mol % $Pd(PPh_3)_4$, NEt_3 (1.5 equiv.), MeCN, reflux.

The following procedure of the preparation of **23** via **22** is representative. To NaH (0.73 g of 60% suspension in mineral oil, 18.2 mmol) suspended in 20 mL of THF were sequentially added at 25 °C ethyl allylmalonate (3.31 g, 16.5 mmol) and α,α'-dichloro-*o*-xylene (3.76 g, 21.5 mmol) in 10 mL of THF. After quenching with water and the usual extractive workup, distillation provided 2.8 g (50%) of **22**. Treatment of 0.68 g (2 mmol) of **22** with 0.12 g (0.1 mmol) of $Pd(PPh_3)_4$ and NEt_3 (0.30 g, 3 mmol) in refluxing MeCN (4 mL) for 6 h followed by an extractive workup and purification by column chromatography (silica gel, 80:20 hexane–ether) afforded 0.39 g (64%) of **23**: IR (neat) 1734 (s), 1646 (m), 1264 (s), 1236 (s), 1198 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.20 (t, J = 7 Hz, 6 H), 2.77 (s, 2 H), 3.37 (s, 2 H), 3.54 (s, 2 H), 4.13 (q, J = 7 Hz, 4 H), 4.92 (s, 1 H), 4.96 (s, 1 H), 7.05–7.2 (m with a peak at 7.11, 4 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.09, 38.22, 41.86, 42.28, 56.85, 61.49, 114.89, 126.69, 127.79, 128.71, 131.18, 135.71, 139.90, 141.85, 171.19; high-resolution MS calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1518.

Acknowledgment. We thank the National Institutes of Health (Grant GM 36792) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank French Ministere des Affaires Etrangeres for providing Frédéric Lamaty with a fellowship (bourse Lavoisier, 1987–1988).

Supplementary Material Available: Experimental details for **1a–c**, **2**, **3**, **4a**, **5–9**, **12–15**, and **16–23** (5 pages). Ordering information is given on any current masthead page.