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Communications

Palladium-Catalyzed Annulation of 1,4-Dienes Using *Ortho*-Functionally-Substituted Aryl Halides

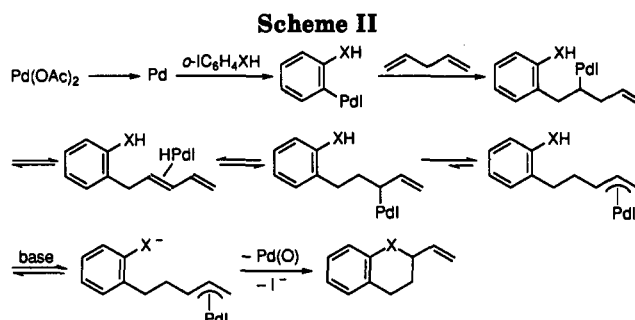
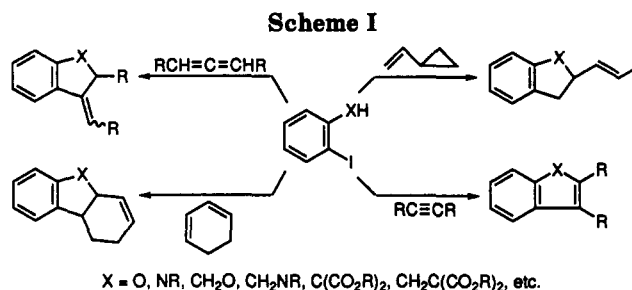
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Summary: The palladium-catalyzed annulation of 1,4-dienes by aryl halides bearing *ortho*-heteroatoms and carbanion-stabilizing groups affords monocyclic and bicyclic 6-membered ring heterocycles and carbocycles in high yields by a process involving arylpalladium formation and addition to the diene, palladium migration, and intramolecular π -allylpalladium displacement.

Annulation processes are among the most important in organic synthesis, though few are very general with regard to the different types of compounds that successfully undergo annulation. However, the palladium-catalyzed annulation of 1,2-¹ and 1,3-dienes,² unsaturated cyclopropanes and cyclobutanes,³ and alkynes⁴ by aryl halides bearing *ortho*-substituted heteroatoms or carbanion-stabilizing groups affords a convenient, very versatile, new route to a wide variety of heterocycles and carbocycles (Scheme I). A number of useful new synthetic processes have already recently taken advantage of the unique ability of palladium to migrate along carbon chains.⁵ We hereby report the successful combination of these two processes to provide a synthetically useful annulation of 1,4-dienes.



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(4) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* 1991, 113, 6689 and references cited therein. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* 1990, 109, 567.

(5) For some recent references see: (a) Larock, R. C.; Lu, Y.-D.; Bain, A. C.; Russell, C. E. *J. Org. Chem.* 1991, 56, 4589 and references cited therein. (b) Larock, R. C.; Leung, W.-Y. *J. Org. Chem.* 1990, 55, 6244. (c) Söderberg, B. C.; Akermark, B.; Chen, Y.-H.; Hall, S. S. *J. Org. Chem.* 1990, 55, 1344.

Using the following general procedure, the annulation of a wide variety of 1,4-dienes has been achieved, as summarized in Table I. Palladium acetate (5 mol %), the aryl halide (0.5 mmol), the base (1.75 mmol for heteroannulation), *n*-Bu₄NCl (0.5 mmol), the 1,4-diene (2.5 mmol), DMF (1 mL), and 5 mol % PPh₃ (where indicated in Table I) were heated under N₂ for the appropriate time, and the reaction mixture was worked up using ether and saturated aqueous NH₄Cl, dried, and chromatographed. Carboannulation reactions were run on half this scale using 1.25 mmol of base.

Table I. Palladium-Catalyzed Annulation of 1,4-Dienes

entry	aryl halide	1,4-diene	reaction condns ^a	product(s) ^b	% isolated yield (ratio)	entry	aryl halide	1,4-diene	reaction condns ^a	product(s) ^b	% isolated yield (ratio)
1			-, NaHCO ₃ 100 °C, 1 d		70	8			-, Na ₂ CO ₃ 100 °C, 3.5 d		65
2			-, Na ₂ CO ₃ 100 °C, 1 d		67	9			+, Na ₂ CO ₃ 100 °C, 2 d		75
3			-, Na ₂ CO ₃ 100 °C, 1 d	 +	71 (7:1)	10			-, Na ₂ CO ₃ 100 °C, 2 d		73 ^c
4			+, Na ₂ CO ₃ 100 °C, 2 d		82	11			-, Na ₂ CO ₃ 100 °C, 3 d		55
5			-, K ₂ CO ₃ 100 °C, 1.5 d		69 ^c	12			-, NaOAc 60 °C, 7 d		73
6			-, K ₂ CO ₃ 100 °C, 1.5 d		70	13			-, Na ₂ CO ₃ 60 °C, 5 d		85 ^c
7			-, Na ₂ CO ₃ 100 °C, 2 d		52	14			-, NaOAc 60 °C, 5 d		64

^a Reaction conditions: presence or absence of 5 mol % PPh₃ (+ or -), base used, temperature, time. ^b All products gave appropriate ¹H and ¹³C NMR, IR, and mass spectral or elemental analysis data. ^c Diene is an *E/Z* mixture.

The annulation of 1,4-dienes by *o*-iodophenols produces benzopyrans (entries 1–4). The reaction gives high yields when run at 100 °C in the presence or absence of PPh₃ and using sodium bicarbonate or carbonate as the base. Three different dienes have been utilized. 1,4-Pentadiene and 5-methyl-1,4-hexadiene gave high yields of a single isomer (entries 1, 2, and 4), but 3-methyl-1,4-pentadiene afforded an isomeric mixture in which the side product appears to be that shown in entry 3, although it is not obvious how it is formed mechanistically.

In general, cleaner reactions were observed when the *o*-iodophenols were replaced by *o*-iodoaniline (entries 5–8). Only minor amounts of side products were observed, even when 3-methyl-1,4-pentadiene was employed. The analogous tosyl derivative also affords the corresponding nitrogen heterocycles in high yields (entries 9–11).

The carboannulation of 1,4-dienes can also be effected in excellent yield (entries 12–14). Best results have been obtained by running these reactions at a lower temperature (60 °C) for longer reaction times (5–7 days).

As indicated in Table I, a wide variety of 1,4-dienes can generally be employed in this annulation process. Arylation occurs cleanly on the least substituted double bond of the diene, and nucleophilic attack provides exclusively the six-membered ring product. No eight-membered ring products have ever been observed. It is noteworthy that

the carboannulation of 2,4-dimethyl-1,4-pentadiene (entry 12) yields only the *trans*-substituted carbocycle. Especially exciting is the observation that even the strained bicyclo[3.3.1]non-2-ene ring system can be produced in good yield by this methodology (entry 14).

Mechanistically, this 1,4-diene annulation process appears to proceed as shown in Scheme II. Precedent exists for each step. The final, nucleophilic displacement of palladium from the π -allylpalladium intermediate may proceed by backside or frontside displacement, presumably depending on the nature of the nucleophile. Clearly, formation of the bicyclic carbon system present in entry 14 requires frontside attack on palladium, followed by reductive elimination, an unusual process for stabilized carbanions, but one observed previously in the carboannulation of cyclic, 1,3-dienes.^{2b}

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Supplementary Material Available: General experimental procedure and spectral data for all products (6 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.