Synthesis of Allylic Alcohols via Palladium-Catalyzed Cross-Coupling of Vinylic Epoxides and Aryl or Vinylic Halides and Triflates[†]
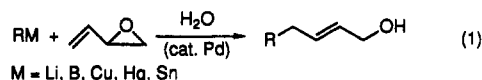
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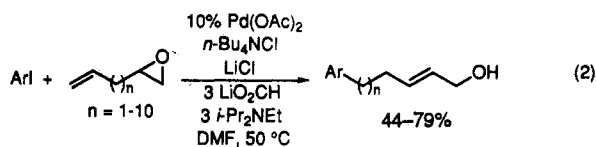
Summary: Palladium acetate in the presence of sodium formate, n-Bu$_4$NCl, and diisopropylethylamine catalyzes the cross-coupling of vinylic epoxides with aryl or vinylic halides and triflates to form allylic alcohols in good yield.

The ring-opening of vinylic epoxides by organometallics of lithium, magnesium, boron, and particularly copper has provided a valuable approach to allylic alcohols (eq 1).[1]

$$RM + \text{/}\!\!\!\diagup\!\!\!\bigtriangleup\!\!\text{O} \xrightarrow[\text{(cat. Pd)}]{H_2O} R\diagdown\!\diagup\!\diagdown\!\diagup\text{OH} \qquad (1)$$

$$M = \text{Li, B, Cu, Hg, Sn}$$

Palladium catalyzes the analogous cross-coupling of organomercurials,[2] -boranes,[3] and -stannanes.[4]

We have been interested in replacing these organometallic reagents by more readily available organic halides and triflates. Indeed, we have recently reported that palladium catalyzes the cross-coupling of aryl halides, but not vinylic halides, and olefinic epoxides in which the two functional groups are separated by anywhere from one to 10 carbons (eq 2).[5] This reaction is presumed to proceed

$$\text{ArI} + \underset{n=1-10}{\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown\!\!\text{O}} \xrightarrow[\substack{3\ \text{LiO}_2\text{CH} \\ 3\ i\text{-Pr}_2\text{NEt} \\ \text{DMF, 50 °C}}]{\substack{10\% \text{ Pd(OAc)}_2 \\ n\text{-Bu}_4\text{NCl} \\ \text{LiCl}}} \underset{44-79\%}{\text{Ar}\diagdown\!\diagup\!\diagdown\!\diagup\text{OH}} \qquad (2)$$

by oxidative addition of the aryl halide to palladium(0), subsequent arylpalladium addition to the carbon–carbon double bond, palladium migration, ring-opening, and palladium alkoxide reduction by the formate salt.

In attempting to extend this procedure to vinylic epoxides, we were concerned about the known propensity of such epoxides to react with palladium(0) to form π-allylpalladium species which can undergo attack by various nucleophiles[6] including formate[7] or rearrange to
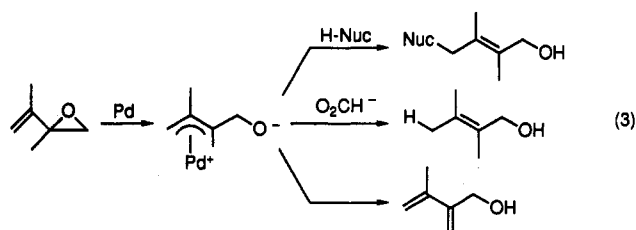
dienols or unsaturated carbonyl compounds[8] (eq 3). If competitive, such a process would circumvent the desired allylic alcohol formation.

After examining our earlier procedure for olefinic epoxides and numerous variations thereof on the reaction of aryl iodides and vinylic epoxides, we have found that good yields of the desired allylic alcohols can be achieved by employing 10% Pd(OAc)$_2$, 5 equiv of NaO$_2$CH, 2 equiv of n-Bu$_4$NCl (TBAC), 3 equiv of i-Pr$_2$NEt, 5 equiv of vinylic epoxide, and 1 equiv of organic halide or triflate in N,N-dimethylacetamide (2 mL per 0.5 mmol of organic halide or triflate) at 80 °C for 1 day. The reactions of a variety of vinylic epoxides and organic halides or triflates have been examined using this procedure, and the results are summarized in Table I.

A wide variety of aryl iodides may be employed in this process. The best yields are obtained using electron-rich arenes. Aryl halides bearing electron-withdrawing substituents give significantly lower yields. The problem appears to be either dimerization to a biaryl[9] or reduction of the intermediate arylpalladium species by the formate salt[10] in competition with alkene insertion.

To our pleasant surprise, unlike our earlier process for the arylation of olefinic epoxides[5] which failed with vinylic halides, vinylic iodides and triflates react with vinylic epoxides under the present procedure to produce dienols in good yield. With vinylic iodides, best results are obtained using the less hindered vinylic iodides. Although we have not optimized the reaction conditions for vinylic triflates, the one example studied (entry 15) afforded a modest yield of the desired dienol using the same procedure as that used for the organic iodides.

The yields vary significantly with the structure of the vinylic epoxide. When aryl halides are employed 3,4-epoxy-3-methyl-1-butene (entries 1–4) and 3,4-epoxy-3-methyl-1-pentene (entry 5) were found to give significantly higher yields than 3,4-epoxy-1-butene (entry 6), while 3,4-epoxy-2-methyl-1-butene (entry 7) with a more substituted

† Dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

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Table I. Palladium-Catalyzed Cross-Coupling of Vinylic Epoxides and Organic Halides or Triflates[a]

entry	epoxide	organic halide or triflate	product	% isolated yield[b]	E/Z ratio[c]
1				70	69:31
2				75	60:40
3				65	59:41
4				41	63:37[d]
5				72	52:48
6				51	73:27
7				24	41:59
8				85	50:50
9				37	64:46
10				62	55:45[e]
11				91	72:27
12				77	77:23
13				61	72:28
14				71	50:50
15				45	78:22

[a] See the text for the standard reaction conditions. [b] Yields based on the organic halide or triflate as the limiting reagent. [c] Determined by integration of the 300-MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxyl group. [d] Only 1 equiv of NaO_2CH was used. [e] Reaction time is 2 days.

carbon–carbon double bond gave quite low yields. In the latter case, it is assumed that the increased steric hindrance to alkene insertion now favors one or more of the side reactions suggested previously. However, with vinylic halides, the yields obtained from 3,4-epoxy-1-butene (entries 11–13) are usually higher than those obtained from

3,4-epoxy-3-methyl-1-butene (entries 8–10) or 3,4-epoxy-3-methyl-1-pentene (entry 14), and 3,4-epoxy-2-methyl-1-butene failed to give any product when allowed to react with (E)-1-iodo-1-hexene.

The stereochemistry of this process is noteworthy. The stereochemistry of the vinylic halide is retained during

cross-coupling. However, when using aryl or vinylic halides, there is only modest control of the stereochemistry in the newly generated carbon–carbon double bond. The stereoselectivity depends on the structure of the vinylic epoxide employed. Disubstituted double bonds are usually generated in approximately a 3:1 *E/Z* ratio. Trisubstituted double bonds are produced with stereoselectivities ranging from zero to approximately 2:1. The stereoisomer favored, however, depends on the substitution pattern of the epoxide. The stereoselectivity observed is generally similar to that found in the cross-coupling of these same epoxides with most organometallics. Only our earlier palladium-catalyzed coupling of vinylic or arylmercurials and vinylic epoxides proceeds with high stereoselectivity.[2]

The mechanism of this process is assumed to be similar to that suggested earlier by us for the cross-coupling of olefinic epoxides and aryl halides,[5] except that no migration of palladium down the carbon chain is necessary.

This type of cross-coupling process is also quite general for the ring-opening of vinylic oxetanes to homoallylic alcohols[11] and vinylic azetidinones to 3-alkenamides.[12]

Supplementary Material Available: The general experimental procedure and spectral characterization of all products (12 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.

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