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PALLADIUM-CATALYZED INTERMOLECULAR ALLYLIC ARYLATION OF CYCLOALKENES

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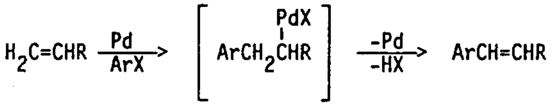
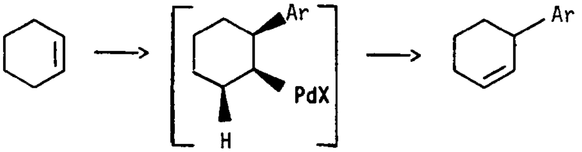
Summary: Aryl halides and cycloalkenes undergo palladium-catalyzed, intermolecular, allylic cross-coupling in excellent yields under exceptionally mild reaction conditions.

The Heck palladium-catalyzed cross-coupling of aryl halides and acyclic alkenes has proven to be a valuable approach to substituted styrenes (eq. 1).[1-4] The reaction proceeds



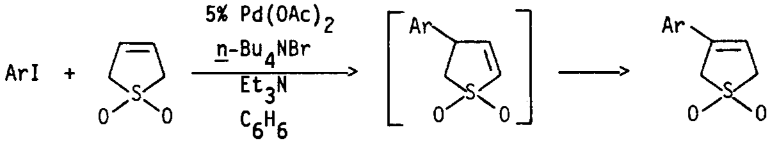
$$H_2C{=}CHR \xrightarrow[ArX]{Pd} \left[ArCH_2\overset{\overset{PdX}{|}}{C}HR \right] \xrightarrow[-HX]{-Pd} ArCH{=}CHR \qquad (1)$$

via syn addition of an arylpalladium species to the carbon-carbon double bond, followed by the syn elimination and subsequent decomposition of a palladium hydride. Analogous reactions of cyclic alkenes would be expected to afford allylic cross-coupling products (eq. 2). Indeed,



(2)

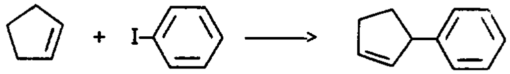
such reactions have been reported using palladium reagents and organomercurials,[4-16] aryl diazonium salts,[17] aryl amines (plus nitrites),[18] aryl sulfinate salts,[19] and aryl[20-23] or heterocyclic[13,24] halides. The organomercurial and arylsulfinate reactions require stoichiometric amounts of palladium, and frequently afford mixtures of regioisomers (presumably due to palladium hydride addition-elimination reactions) in low overall yield. The reactions of aryldiazonium salts and amines (plus nitrites) can be effected using palladium in only catalytic amounts, but they afford bad isomeric mixtures. Organic halides are clearly the most attractive starting materials since they are readily available and should require only catalytic amounts of palladium. However, the early examples of such reactions all employed elevated temperatures, tended to generate isomeric mixtures and employed only six-membered ring cycloalkenes. The recent report by Harrington and DiFiore[23] on the facile, intermolecular, palladium-catalyzed arylation of sulfolene (eq. 3) and two recent intramolecular variations[25,26] of this reaction using aryl halides prompt us to report at this time an exceedingly mild, catalytic procedure for the allylic cross-coupling of aryl halides and a



(3)

wide variety of cycloalkenes, which affords a single product in excellent yield.

As a model system, we have explored the cross-coupling of cyclopentene and iodobenzene (eq. 4). We have examined various modifications of Jeffrey's catalyst system [cat. Pd(OAc)$_2$,



(4)

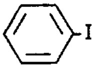
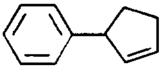
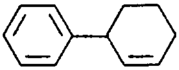
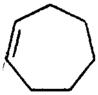
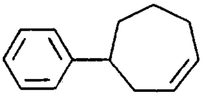
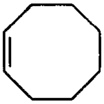
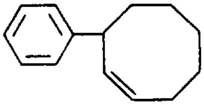
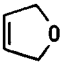
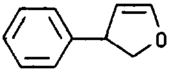
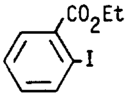
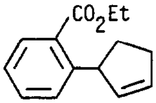
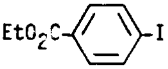
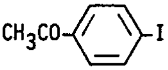
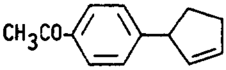
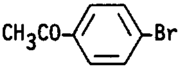
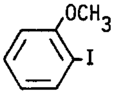
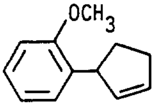
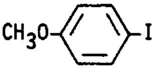
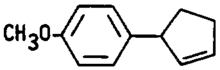
n-Bu$_4$NCl, carbonate or bicarbonate bases, DMF][27-29] and found the base and solvent employed to be critical to the yield and overall rate of the reaction. Alkali metal acetates in DMF have proven superior to all other combinations examined, including carbonate bases and triethylamine. Using 2.5% Pd(OAc)$_2$, three equivalents of KOAc, five equivalents of cyclopentene and one equivalent of n-Bu$_4$NCl in DMF *at room temperature*, we have been able to prepare 3-phenylcyclopentene in *quantitative* yield! While we have generally employed an excess of the readily available cycloalkene, one can employ lesser amounts with satisfactory results. For example, iodobenzene and 1.5 equivalents of cyclopentene afforded an 81% yield of allylic product in only 12 hours at room temperature.

These reaction conditions have proven effective for the cross-coupling of a wide variety of aryl halides and cycloalkenes as summarized in Table I. Cycloalkenes of ring size 5 through 8 are readily accommodated (entries 1-5), but cyclohexene gave a higher yield when NaOAc was used as the base (entry 2) and cyclooctene gave a cleaner reaction with CsOAc (entry 4). Most surprising was the observation that cycloheptene gave the homoallylic isomer, 4-phenylcycloheptene, exclusively (entry 3)! We are presently examining ways to overcome this problem. Under identical reaction conditions (KOAc as base) the following relative reactivities of the cycloalkenes were observed: cyclopentene > cyclooctene > cycloheptene > cyclohexene.

A variety of aryl halides can be successfully employed in these arylation reactions. Contrary to Harrington's conclusions,[23] electron-withdrawing substituents, whether in the *ortho* or *para* positions, do not particularly deactivate the arene towards substitution (entries 6-9), but electron-donating groups slow the reaction and tend to require slightly higher reaction temperatures (entries 10, 11). On the other hand, we too have found that nitro groups are incompatible with this reaction. While phenyl bromide has proven virtually inert under these reaction conditions, aryl bromides bearing electron-withdrawing groups (entry 9) can be employed.

It is important to note that these reactions can be scaled up with only a slight increase in reaction time or temperature being necessary to complete the reaction. For example, 3-phenylcyclopentene can be prepared on a 50 mmol scale in 87% distilled yield when the reaction of phenyl iodide and cyclopentene is run for 3.5 days at room temperature. Similarly, ethyl

Table I. Palladium-Catalyzed Intermolecular Arylation of Cycloalkenes[a]

entry	aryl halide	cycloalkene	base	reaction conditions	product	% yield[b]
1			KOAc	2 d, 25°C		100(89)
2			NaOAc	5 d, 25°C		88(70)
3			KOAc	6 d, 25°C		99(95)
4			CsOAc	2 d, 25°C		100(85)
5			NaOAc	4 d, 25°C		91(78)
6			KOAc	0.5 d, 25°C		77(74)
7				3.5 d, 25°C		90(85)
8				4.5 d, 25°C		96(94)
9				2 d, 80°C		87
10				1 d, 80°C		(78)
11				3 d, 80°C		(67)

[a] ArX (0.5 mmol), cycloalkene (2.5 mmol), $Pd(OAc)_2$ (2.5%), $\underline{n}$-Bu_4NCl (0.5 mmol), base (1.5 mmol), DMF (1 ml).

[b] Yield by gas chromatographic analysis (isolated yield).

o-iodobenzoate and cyclopentene afford the cross-coupled product in 90% distilled yield when run on a 10 mmol scale.

It is evident that this mild, catalytic arylation process should find considerable application in organic synthesis. We are presently examining the regio- and stereoselectivity of this process, as well as looking at intermolecular alkynylation and vinylation processes.

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