J. Org. Chem. **1991**, *56*, 4589–4590

Palladium-Catalyzed Coupling of Aryl Iodides, Nonconjugated Dienes, and Carbon Nucleophiles by Palladium Migration

Richard C. Larock,* Yong-de Lu, and Anjali C. Bain

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Charles E. Russell

Department of Chemistry, Muhlenberg College, Allentown, Pennsylvania 18104

Received January 14, 1991 (Revised Manuscript Received April 10, 1991)

Summary: Aryl iodides, nonconjugated dienes, and carbon nucleophiles react in the presence of a palladium catalyst to give good yields of coupled products apparently formed by arylpalladium generation and addition to the less substituted end of the diene, palladium migration down the carbon chain to form a π-allylpalladium intermediate, and carbanion displacement of the palladium moiety.

Synthetic methodology, which allows for a rapid increase in molecular complexity, is extremely valuable in organic chemistry, particularly when it generates more than one new carbon–carbon bond at a time, accommodates considerable functionality, and is broad in scope. We report here just such a process involving the palladium-catalyzed coupling of aromatic iodides, nonconjugated dienes, and carbon nucleophiles (eq 1).[1,2] Our preliminary results are summarized in Table I.

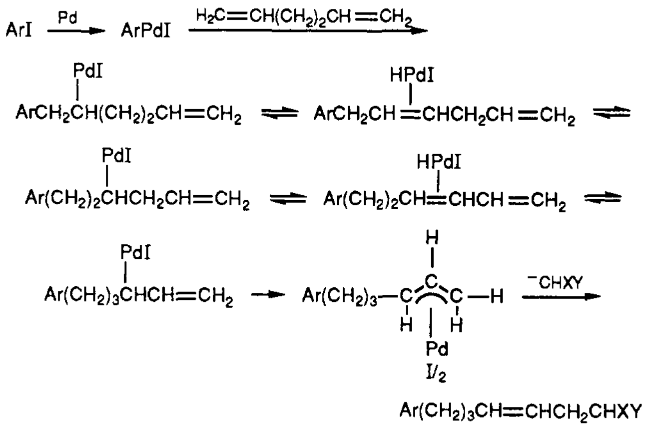
$$\mathrm{ArI} + \mathrm{H_2C{=}CH(CH_2)_\mathit{n}CH{=}CH_2} + \mathrm{H_2CXY} \xrightarrow[\text{base}]{\text{cat. Pd(0)}} \mathrm{Ar(CH_2)_{\mathit{n}+1}CH{=}CHCH_2CHXY} \quad (1)$$

$$\mathrm{X, Y = COR, CO_2R, CN}$$

The coupling of iodobenzene, 1,5-hexadiene, and diethyl malonate was chosen as a model system. After examining the effect on the yield of a variety of solvents (1:1 EtOH/DMSO, DMF, 1:1 DMF/DMSO, HMPA, DMSO), bases (Et_3N, KO_2CH, KOAc, Na_2CO_3, K_2CO_3, $KHCO_3$, $NaHCO_3$), palladium catalysts ($PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$), temperatures (60–120 °C), and the presence or absence of n-Bu_4NCl and systematically varying the stoichiometry (see entries 1–7), we arrived at the following optimal procedure. Sodium bicarbonate (1.25 mmol), n-Bu_4NCl (0.55 mmol), bis(dibenzylideneacetone)palladium(0) (5%, 0.025 mmol), aryl iodide (0.50 mmol), diene (1.00 or 2.50 mmol), the potential carbon nucleophile (1.00 or 2.50 mmol), and DMSO (1 or 2 mL) were heated under nitrogen at 80 °C until the aryl iodide had disappeared. The reaction mixture was worked up using ether and saturated aqueous ammonium chloride and dried and the product purified by flash chromatography. All compounds gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral or elemental analysis data.

This process is remarkably versatile, giving good yields for a variety of carbon nucleophiles. It works well for acyclic or cyclic dienes with anywhere from 1 to 10 carbons between the carbon–carbon double bonds (entries 13–17) and accommodates electron-rich (entry 18) or electron-poor (entry 19) aryl halides, as well as heterocyclic halides (entries 20 and 21). Phenyl bromide and triflate do not react, however.

Scheme I



These reactions presumably proceed by oxidative addition of the aryl halide to Pd(0), arylpalladium addition to one of the carbon–carbon double bonds, palladium migration to form a π-allylpalladium intermediate, and carbanion displacement of the palladium moiety as illustrated in Scheme I.

The oxidative addition of aryl halides to Pd(0) and subsequent olefin insertion are well-known processes.[3] Only products arising from regioselective syn insertion of the less substituted double bond are observed (entry 15). Careful spectroscopic examination of the products provides no evidence of aryl addition to the internal carbon of the carbon–carbon double bond of the diene as sometimes is observed in related reactions.[4]

We have previously reported the unique ability of organopalladium compounds generated by the transmetallation of organomercurials to add to the carbon–carbon double bond of nonconjugated dienes and migrate palladium along the carbon chain to form π-allylpalladium compounds.[5,6] However, the elimination of palladium hydride in that process and its subsequent reaction with

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[1] For the related coupling of an aryl halide, a 1,4-diene, and a secondary amine to form aryl 1,3-dienes and allylic amines in less than 50% yields, see: Bender, D. D.; Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1984**, *47*, 1278.

[2] For related palladium-promoted 1,4-additions of carbon moieties to 1,3-dienes, see: (a) Uno, M.; Takahashi, T.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1987**, 785. (b) Lebedev, S. A.; Lopatina, V. S.; Beletskaya, I. P. *Metallorg. Khim.* **1989**, *2*, 624; *Chem. Abstr.* **1989**, *111*, 231969z. (c) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807. (d) Uno, M.; Takahashi, T.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 647.

[3] (a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, Heidelberg, New York, 1980. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985.

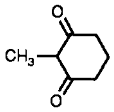
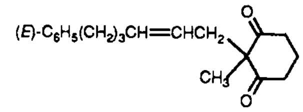
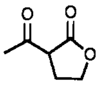
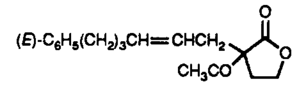
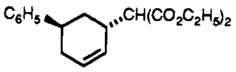
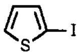
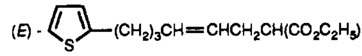
[4] See for example: (a) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. K. *Tetrahedron Lett.* **1989**, *30*, 6629. (b) Larock, R. C.; Leung, W.-Y. *J. Org. Chem.* **1990**, *55*, 6244.

[5] (a) Larock, R. C.; Takagi, K. *J. Org. Chem.* **1984**, *49*, 2701. (b) Larock, R. C.; Takagi, K. *Tetrahedron Lett.* **1983**, *24*, 3457.

[6] For other recent examples of palladium migration processes, see ref 4 and: (a) Söderberg, B. C.; Åkermark, B.; Chen, Y.-H.; Hall, S. S. *J. Org. Chem.* **1990**, *55*, 1344. (b) Åkermark, B.; Söderberg, B. C.; Hall, S. S. *J. Org. Chem.* **1989**, *54*, 1110. (c) Söderberg, B. C.; Åkermark, B.; Hall, S. S. *J. Org. Chem.* **1988**, *53*, 2925. (d) Åkermark, B.; Söderberg, B. C.; Hall, S. S. *Organometallics* **1987**, *6*, 2608. (e) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399. (f) Larock, R. C.; Takagi, K. *J. Org. Chem.* **1988**, *53*, 4329. (g) Larock, R. C.; Song, H.; Kim, S.; Jacobson, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 834. (h) Larock, R. C.; Leuck, D. J. *Tetrahedron Lett.* **1987**, *28*, 5291. (i) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407. (j) Albéniz, A. C.; Espinet, P.; Jeannin, Y.; Philoche-Levisalles, M.; Mann, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 6594.

0022-3263/91/1956-4589$02.50/0

Table I. Palladium-Catalyzed Coupling of Aryl Iodides, Nonconjugated Dienes, and Carbon Nucleophiles

entry	aryl-iodide	diene	equiv	carbon nucleophile	equiv	time (h)	product	% isolated yield
1	C_6H_5I	$H_2C{=}CH(CH_2)_2CH{=}CH_2$	1	$H_2C(CO_2C_2H_5)_2$	1	24	(*E*)-$C_6H_5(CH_2)_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$	29
2			1		2	24		68
3			2		1	48		65
4			2		2	12		82
5			2		5	12		76
6			5		2	12		62
7			5		5	12		82
8			2	$NCCH_2CO_2C_2H_5$	2	12	(*E*)-$C_6H_5(CH_2)_3CH{=}CHCH_2CH(CN)CO_2C_2H_5$	32
9			5		5	12		81
10			2		2	12		72
11			5		5	12		64
12			5		5	12		64
13		$H_2C{=}CH(CH_2)_4CH{=}CH_2$	5	$H_2C(CO_2C_2H_5)_2$	5	12	(*E*)-$C_6H_5(CH_2)_5CH{=}CHCH_2CH(CO_2C_2H_5)_2$	66
14		$H_2C{=}CH(CH_2)_{10}CH{=}CH_2$	2		5	24	(*E*)-$C_6H_5(CH_2)_{11}CH{=}CHCH_2CH(CO_2C_2H_5)_2$	52
15		$H_2C{=}CH(CH_2)_2C(CH_3){=}CH_2$	5		5	36	(*E*)-$C_6H_5(CH_2)_3CH{=}C(CH_3)CH_2CH(CO_2C_2H_5)_2$	60
16			2		2	12		84
17			5		5	12		88
18	*p*-$CH_3OC_6H_4I$	$H_2C{=}CH(CH_2)_2CH{=}CH_2$	5		5	12	(*E*)-*p*-$CH_3OC_6H_4(CH_2)_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$	54
19	*p*-$CH_3COC_6H_4I$		5		5	8	(*E*)-*p*-$CH_3COC_6H_4(CH_2)_3CH{=}CHCH_2CH(CO_2C_2H_5)_2$	56
20			2		2	12		55
21			5		5	12		59

the starting diene to form a second, different π-allylpalladium product detracted from the procedure and suggested a potentially major limitation in synthetic applications of that methodology. Fortunately, only minor amounts of aryl diene or $CH_3(CH_2)_{n+1}CH{=}CHCH_2CHXY$ side products arising from such a process are observed under our reaction conditions, even though the reaction is run in the presence of a base, carbanions, and a very polar solvent, any of which might have been expected to displace a palladium hydride from any of the intermediate palladium hydride diene π-complexes. It is indeed noteworthy that palladium can apparently reversibly migrate up and down even very long carbon chains without noticeable formation of aryl dienes or any significant decrease in the yield of the coupled product.

This migration process no doubt proceeds by a series of reversible palladium hydride syn eliminations and readditions as judged by the exclusive formation of the trans product from 1,4-cyclohexadiene (entries 16 and 17). The high stereospecificity of the migration process has been noted previously.[6a–d,g,j,7]

Finally, the well-established[3] backside displacement of palladium from π-allylpalladium compounds by stabilized carbanions generated from the β-dicarbonyl compounds and α-cyano ester by proton abstraction by the weak base sodium bicarbonate results in the observed product. Only products of carbanion attack at the remote end of the carbon chain are observed. All products consist exclusively of the *E* isomers shown in the table, even when a trisubstituted double bond is formed (entry 15).

We are presently examining analogous reactions using a variety of heteroatom-containing nucleophiles and possible applications to the synthesis of natural products and will report those results shortly.

Acknowledgment. We gratefully acknowledge the National Institutes of Health and the Donors of The Petroleum Research Fund, administered by the American Chemical Society for their financial support and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for the palladium used in this project.

Supplementary Material Available: Representative experimental procedure and characterization of all new compounds prepared (6 pages). Ordering information is given on any current masthead page.

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