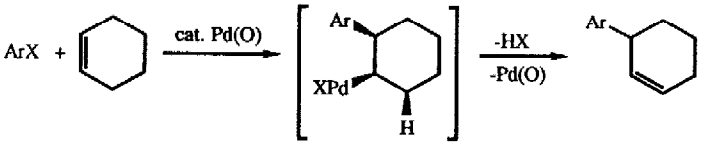
Tetrahedron Letters,Vol.30,No.20,pp 2603-2606,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

IMPROVED PROCEDURES FOR THE PALLADIUM-CATALYZED INTERMOLECULAR ARYLATION OF CYCLIC ALKENES

Richard C. Larock,* William H. Gong and Bruce E. Baker
Department of Chemistry, Iowa State University, Ames, Iowa 50011

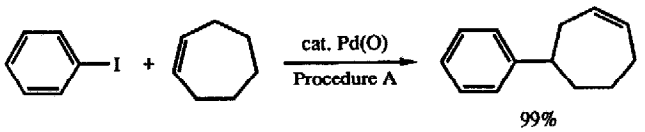
Summary: Improved procedures for the palladium-catalyzed, intermolecular, allylic cross-coupling of aryl halides and cyclic alkenes inhibit double-bond isomerization and accommodate many important functional groups.

The palladium-catalyzed cross-coupling of aryl halides and *acyclic* alkenes provides a very valuable route to substituted styrenes.[1-4] The analogous reaction of *cyclic* alkenes[5-9] has received much less attention since early reports employing only six-membered ring cycloalkenes indicated that this reaction usually required elevated temperatures and tended to generate mixtures of double-bond regioisomers (eq. 1). Recent work in our laboratories[10]



(1)

(Procedure A: 0.5 mmol ArX, 2.5 mmol cycloalkene, 2.5% $Pd(OAc)_2$, 0.5 mmol n-Bu_4NCl, 1.5 mmol KOAc, 1 ml DMF) and others[11] (10 mmol ArX, 10.5 mmol sulfolene, 5% $Pd(OAc)_2$, 10 mmol n-Bu_4NBr, 12.5 mmol Et_3N, 5 ml benzene) has indicated that in the presence of tetra-n-butylammonium halides and an appropriate base the room temperature reaction of a variety of aryl halides and cyclic alkenes can afford high yields of a single regioisomer. Those earlier reports[10,11] indicated that ether, ketone and ester functionality were readily accommodated, but Harrington and DiFiore observed that 1-iodo-4-nitrobenzene failed to react.[11] The major products of this latter work were rearranged 3-arylsulfolenes. We noted the isolation of 4-phenylcycloheptene as the sole product from the reaction of iodobenzene and cycloheptene (eq. 2).[10] These early

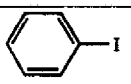
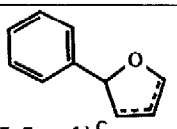
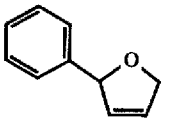
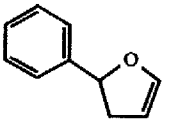
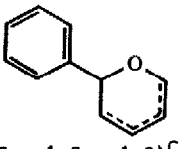
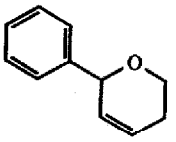
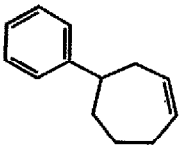
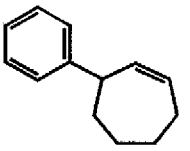
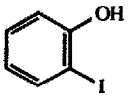
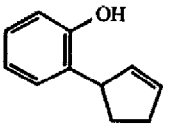
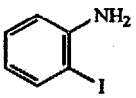
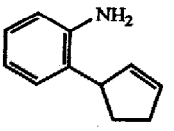


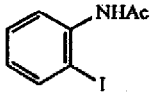
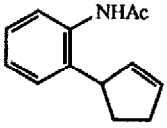
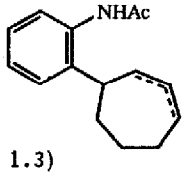
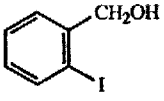
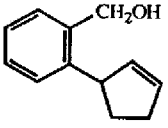
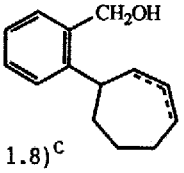
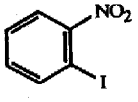
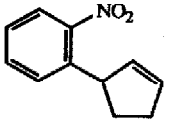
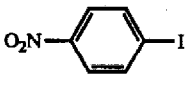
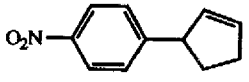
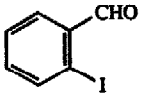
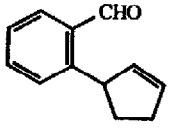
(2)

difficulties and similar more recent observations of ours have encouraged us to reexamine this reaction in the hopes of finding an improved procedure which would overcome these problems.

We now wish to report two procedures which overcome virtually all of the aforementioned difficulties. We have examined the use of Ag_2CO_3 and PPh_3 (Procedure B: 0.5 mmol ArX, 2.5 mmol cycloalkene, 3-4% $Pd(OAc)_2$, 9% PPh_3, 1.0 mmol Ag_2CO_3, 6 ml CH_3CN at 80°C) which has

Table I. Palladium-Catalyzed Intermolecular Arylation of Cycloalkenes

entry	aryl halide	cycloalkene	procedure	time (h)	temp. (°C)	product(s)	% isolated yield
1			A[a]	12	25	 (5.7 : 1)[c]	100[b]
2			B	48	80		98[b]
3			C	24	80		76
4			A[a]	144	25	 (3.9 : 1.0 : 1.0)[c]	71
5			B	48	80		96
6			A	144	25		99
7			B	24	80		99
8			A	142	80		42
9			B	48	80		0
10			C	96	80		66
11			A	108	80		6
12			B	120	80		0
13			C[d]	168	80		52[e]

14			A	48	80	many products	0
15			B	120	80	--	0
16			C	24	80		76
17			C	24	80	 (1 : 1.3)	80
18			A	120	80		0
19			B	120	80		0
20			C	24	80		99
21			C	24	80	 (1 : 1.8)[c]	99
22			A	96	80		0
23			B	48	80		70
24			C	24	80		90
25			A	96	80		0
26			B	48	80		52
27			C	24	25		85
28			A	168	25		0
29			B	120	80		0
30			C	24	80		87

[a]NaOAc used as the base. [b]Yields determined by gas chromatography. [c]Allylic : homoallylic : other isomer. [d]5% Ph_3P and 3 equiv Et_3N were used. [e]Yield based on recovered starting material.

previously proven quite successful in inhibiting double bond isomerization in *intramolecular* versions of this reaction[12,13] and we have looked at the effect of catalytic amounts of PPh_3 in this reaction (Procedure C: same as Procedure A plus 2.5% PPh_3). A comparison of all three procedures A-C is summarized in Table I.

The following conclusions can be drawn with regard to the three procedures. Procedure B inhibits isomerization where that has been a major problem before with Procedure A (compare entries 1 and 2, 4 and 5, 6 and 7). Procedure B fails to solve most of the problems encountered using Procedure A and functionally-substituted aryl halides, except where *ortho*- or *para*-nitro groups are involved (compare entries 22 and 23, 25 and 26). The addition of just catalytic amounts of Ph_3P to Procedure A (Procedure C) dramatically improves the results from a wide variety of functionally-substituted aryl halides, including those containing either electron-donating groups (compare entries 8 and 10, 11 and 13, 14 and 16, 18 and 20) or electron-withdrawing groups (compare entries 22 and 24, 25 and 27, 28 and 30). While it is not obvious why this should be so, the effect is remarkable. Unfortunately, Procedure C does not solve the isomerization problems encountered using Procedure A (see entries 3, 17 and 21). In fact, in one case Procedure C actually promotes isomerization (compare entries 1 and 3).

In conclusion, it would appear that these two new procedures solve many of the problems of isomerization and functional group incompatibility encountered using previous procedures. One can anticipate many further applications of this chemistry in the synthesis of complex molecules and natural products.

Acknowledgment. Financial support of this research by the National Institutes of Health (GM 40036) and generous loans of palladium acetate by Johnson Matthey, Inc. and Kawaken Fine Chemicals, Ltd. are deeply appreciated.

References

1. J. Tsuji, "Organic Synthesis with Palladium Compounds", Springer Verlag, New York (1980).
2. R. F. Heck, Organic Reactions **27**, 345 (1982).
3. R. F. Heck, "Palladium Reagents in Organic Synthesis", Academic Press, New York (1985).
4. R. C. Larock, "Organomercury Compounds in Organic Synthesis", Springer Verlag, New York (1985).
5. N. A. Cortese, C. B. Ziegler, Jr., B. J. Hrnjez and R. F. Heck, J. Org. Chem. **43**, 2952 (1978).
6. I. Arai and G. Doyle Daves, Jr., J. Org. Chem. **44**, 21 (1979).
7. C.-M. Andersson, A. Hallberg and G. Doyle Daves, Jr., J. Org. Chem. **52**, 3529 (1987).
8. Y. Tamaru, Y. Yamada and Z. Yoshida, Tetrahedron **35**, 329 (1979).
9. I. Arai and G. Doyle Daves, Jr., J. Org. Chem. **43**, 4110 (1978).
10. R. C. Larock and B. E. Baker, Tetrahedron Lett. **29**, 905 (1988).
11. P. J. Harrington and K. A. DiFiore, Tetrahedron Lett. **28**, 495 (1987).
12. M. M. Abelman, T. Oh and L. E. Overman, J. Org. Chem. **52**, 4130 (1987).
13. R. C. Larock, H. Song, B. E. Baker and W. H. Gong, Tetrahedron Lett. **29**, 2919 (1988).

(Received in USA 19 January 1989)