JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 11
1986

The Product-forming Step in Palladium-catalysed Methoxycarbonylation of Organic Halides

David Milstein

Central Research & Development Department, E. I. du Pont de Nemours & Company, Experimental Station, Wilmington, DE 19898, U.S.A.

Use of trimethylphosphine–palladium complexes renders the product-forming step in palladium-catalysed methoxycarbonylation of benzyl chloride or iodobenzene rate-determining and allows for its direct observation; the product-forming step is alcoholysis of an acylpalladium complex and not reductive elimination of a methoxycarbonylpalladium intermediate.

Although mechanistic information relevant to the synthetically useful Pd-catalysed alkoxycarbonylation of organic halides to esters[1—7] (equation 1) is available, a central question, the nature of the product-forming step, still remains to be resolved. Here we present results bearing on this problem.

$$R^1X + CO + R^2OH + B \xrightarrow{Pd^0} R^1CO_2R^2 + BH^+X^- \quad (1)$$

B = base (usually a tertiary amine)

Reaction (1) can proceed by two main mechanisms (Scheme 1), both involving oxidative addition of the organic halide to Pd^0 as the first step. Path (a) proceeds by CO insertion into the Pd–C bond followed by base-assisted alcoholysis of the acylpalladium complex, whereas in path (b) an alkoxycarbonylpalladium complex is generated and forms the ester by reductive elimination. Precedents for steps in both processes are known. CO insertion into Pd–C bonds to form acylpalladium complexes in inert solvents[3,8—10] (*i.e.* not in alcohol–base) and their alcoholysis[3,11] have been demonstrated, whereas formation of a methoxycarbonylpalladium complex under conditions similar to those employed in methoxycarbonylation of alkyl halides is known[12] (equation 2).

$$(PPh_3)_2PdCl_2 + CO + MeOH + NEt_3 \rightarrow trans\text{-}ClPd(PPh_3)_2CO_2Me + HNEt_3^+Cl^- \quad (2)$$

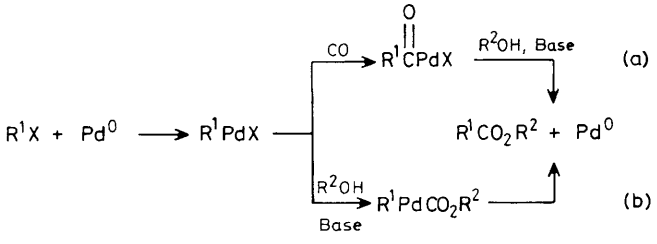
Upon treatment of $PhCH_2Pd(PPh_3)_2Cl$ with methanol, triethylamine (NEt_3), and CO (50 lb in^{-2}) methyl phenylacetate is formed, but no intermediates could be isolated or observed. Since nucleophilic attack on an acylpalladium complex should be retarded by an increase in the electron density on the metal, and since C–C bond formation by reductive elimination from Pd^{II} is preceded by phosphine dissociation,[13] we reasoned that utilization of the small, basic PMe_3 ligand instead of PPh_3 may render the product-forming step, whatever it may be, rate-determining and allow for intermediate isolation.

trans-$PhCH_2Pd(PMe_3)_2Cl$
(1)

trans-$PhCH_2COPd(PMe_3)_2Cl$
(2)

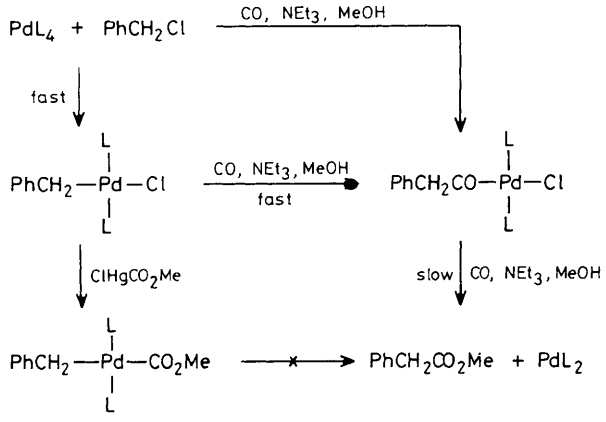
$PhCH_2Pd(PMe_3)_2CO_2Me$
(3)

Addition of a stoicheiometric amount of benzyl chloride to a solution of $Pd(PMe_3)_4$[14] in pentane at 0 °C resulted in instantaneous formation of *trans*-$PhCH_2Pd(PMe_3)_2Cl$ **(1)**† which was isolated by filtration at −40 °C. Treatment of **(1)** with CO (50 lb in^{-2}) in methanol–Et_3N (1 : 1 v/v) at 25 °C for 3 h resulted in quantitative formation of *trans*-$PhCH_2COPd(PMe_3)_2Cl$ **(2)**† with no detectable $PhCH_2Pd(PMe_3)_2CO_2Me$ **(3)**. Heating of this solution at 80 °C for 1 h resulted in quantitative formation of $PhCH_2CO_2Me$, accom-



Scheme 1. Phosphine ligands are omitted for clarity.

† This compound is fully characterized based on ^1H and ^{31}P n.m.r. and i.r. spectra, and elemental analysis.



Scheme 2. L = PMe_3. All steps are essentially irreversible.

panied by $Pd(PMe_3)_4$ and Pd metal [formed by disproportionation of $Pd(PMe_3)_2$]. When (**2**) was partially decomposed under an atmosphere of ^{13}CO under the same conditions, there was no incorporation of ^{13}CO into the recovered complex or the product ester, demonstrating the irreversibility of the CO insertion reaction into Pd–C. Complex (**2**) can be also directly and quantitatively obtained by reaction of $Pd(PMe_3)_4$ with $PhCH_2Cl$ and CO in methanol–NEt_3 at 25 °C, again with no trace of (**3**). *trans*-$PhCH_2Pd(PMe_3)_2CO_2Me$ (**3**)† was prepared separately by treatment of (**1**) with $ClHgCO_2Me$ at 25 °C. It is thermally stable and heating at 80 °C does not result in reductive elimination of $PhCH_2CO_2Me$. All these observations taken together (Scheme 2) indicate that path (a) involving rate-determining methanolysis‡ of (**2**) is operative and not (b). In fact, (**2**) is the only Pd complex observed by ^{31}P n.m.r. spectroscopy under actual catalysis conditions [50 lb in^{-2} CO, 80 °C, MeOH–NEt_3, 1 : 1, $PhCH_2Cl$: $Pd(PMe_3)_4$, 50 : 1].

‡ Although the details of the alcoholysis process are not dealt with here, it can, in principle, proceed by nucleophilic attack at the acyl ligand or at the metal. Reductive elimination of acyl chloride prior to alcoholysis is not likely in these relatively electron-rich systems. We could not detect, for example, any acetyl chloride upon heating *trans*-$MeCOPd(PMe_3)_2Cl$ at 80 °C under high vacuum.

Similar results are obtained when iodobenzene is used instead of benzyl chloride. Oxidative addition yields *trans*-$PhPd(PMe_3)_2I$† which reacts with CO at 25 °C in methanol–NEt_3 to form *trans*-$PhCOPd(PMe_3)_2Cl$† exclusively, which in turn forms $PhCO_2Me$ at 80 °C. Thus, the acylpalladium mechanism for alkoxycarbonylation is probably quite general,§ with possible exceptions being reactions involving palladium complexes containing Pd–C bonds of low aptitude for migratory insertion, such as π-allylpalladium compounds.[15]

Received, 20th November 1985; Com. 1643

References

1 A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3318.
2 J. K. Stille and P. K. Wong, *J. Org. Chem.*, 1975, **40**, 532.
3 M. Hidai, T. Hikita, Y. Wada, Y. Fujikura, and Y. Uchida, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2075.
4 T. A. Weil, L. Cassar, and M. Foa' in 'Organic Synthesis *via* Metal Carbonyls,' Vol. 2, eds. I. Wender and P. Pino, Wiley, New York, 1975, p. 517.
5 M. Mori, K. Chiba, N. Inotsume, and Y. Ban, *Heterocycles*, 1979, **12**, 921.
6 A. Cowell and J. K. Stille, *J. Am. Chem. Soc.*, 1980, **102**, 4193.
7 K. E. Hashem, J. B. Woell, and H. Alper, *Tetrahedron Lett.*, 1984, **25**, 4879.
8 K. Kudo, M. Sato, M. Hidai, and Y. Uchida, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 2823.
9 P. E. Garrou and R. F. Heck, *J. Am. Chem. Soc.*, 1976, **98**, 4115; M. Sugita, J. V. Minkiewicz, and R. F. Heck, *Inorg. Chem.*, 1978, **17**, 2809.
10 J. K. Stille and K. S. Y. Lau, *J. Am. Chem. Soc.*, 1976, **98**, 5841.
11 J. K. Stille, L. F. Hines, R. W. Fries, P. K. Wong, D. E. James, and K. Lau, *Adv. Chem. Ser.*, 1974, **132**, 90.
12 M. Hidai, M. Kokura, and Y. Uchida, *J. Organomet. Chem.*, 1973, **52**, 431.
13 A. Gillie and J. K. Stille, *J. Am. Chem. Soc.*, 1980, **102**, 4933; F. Ozawa, T. Ito, Y. Nakamura, and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1868.
14 W. Kuran and A. Musco, *Inorg. Chim. Acta.*, 1975, **12**, 187.
15 D. Milstein, *Organometallics*, 1982, **1**, 888.

§ One has to keep in mind that a different mechanistic pathway may be operative with ligands other than PMe_3.