Observation of Stable and Transient Intermediates in Palladium Complex-catalysed Cross-coupling Reactions

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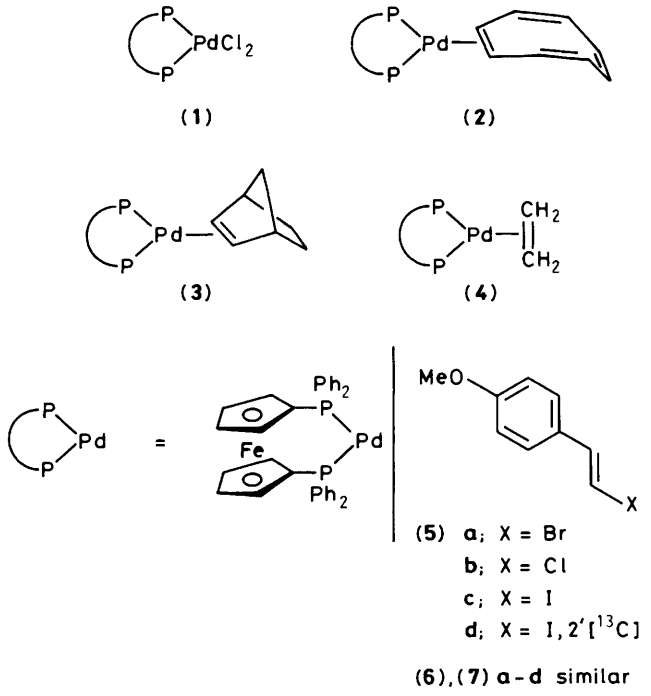
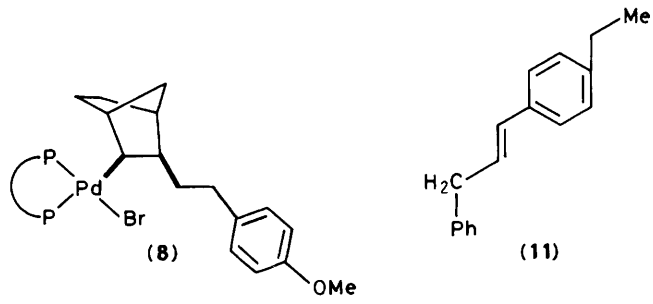
Complexes of 1,1′-bis(diphenylphosphino)ferrocene corresponding to the separate steps of cross-coupling have been identified and related to the catalytic cycle.

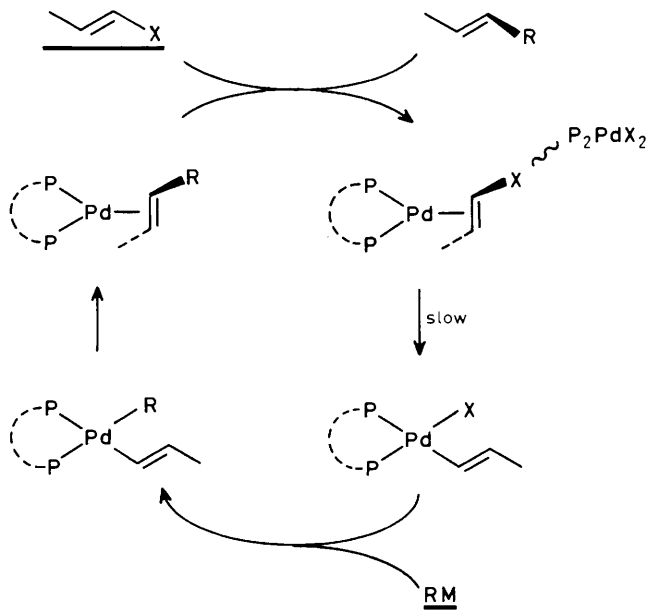
The coupling of unsaturated halides and organometallic reagents catalysed by Ni or Pd complexes is of wide utility.[1] It proceeds by the pathway outlined in Scheme 1, with sequential addition of the electrophile and the nucleophile to the metal. Mechanistic studies have revealed potential complexity in the reaction of model compounds, through *cis–trans* biphosphine isomerisation and oxidative or associative routes for the C–C bond forming step.[2] We report new work on a system closely related to the most effective catalysts,[3] which defines the catalytic cycle.

Complex (**1**)[3] reacts with dilithio (cyclo-octatetraenide) in tetrahydrofuran (thf) at −78 °C to give the unstable η^2-complex (**2**);† the alkene is readily displaced by norbornene or

† ^{31}P *n.m.r. data* (p.p.m.) for intermediates in thf: (**2**) δ 10.6 (−70 °C); (**3**) δ 11.5 (−70 °C); (**4**) δ 12.0 (−70 °C); (**6a**) δ 11.7, 11.1, J_{PP} 15 Hz (−60 °C); (**6b**) δ 11.6, 11.2, J_{PP} 17.5 Hz (−70 °C); (**7a**) δ 24.9, 6.3, J_{PP} 29 Hz (−80 °C); (**7c**) δ 17.2, 5.0, J_{PP} 29 Hz, J_{CP} 125, 5 Hz (−70 °C); (**8**) δ 30.7, 3.5, J_{PP} 53 Hz (30 °C); (**9a**) δ 11.9, 10.9, J_{PP} 29 Hz (−70 °C); (**10b**) δ 16.6, 10.9, J_{PP} 24 Hz, $J_{CP'}$ 86 Hz (−20 °C).







Scheme 1. General mechanism for catalytic cross-coupling.

Table 1. ^{13}C Labelling experiments. Isotopic distribution in reactant (**5d**) (R), product 2',4-dimethoxystilbene (P), and iodovinyl complex (**7d**) (C) compared to predictions for palladium(II) and palladium(IV) routes.

					% Calculated			
					Pd^{II}		PD^{IV}	
Turnovers	Initial %		Final %					
	C	R	C	P	C	P	C	P
1.86	99	1	16	45	17	46	40	33
1.34	1	99	66	51	73	45	48	63
0.38	1	99	37	<10	31	17	17	54
0.43	14	99	42	35	43	30	30	61
0.48	69	1	42	56	43	55	55	31

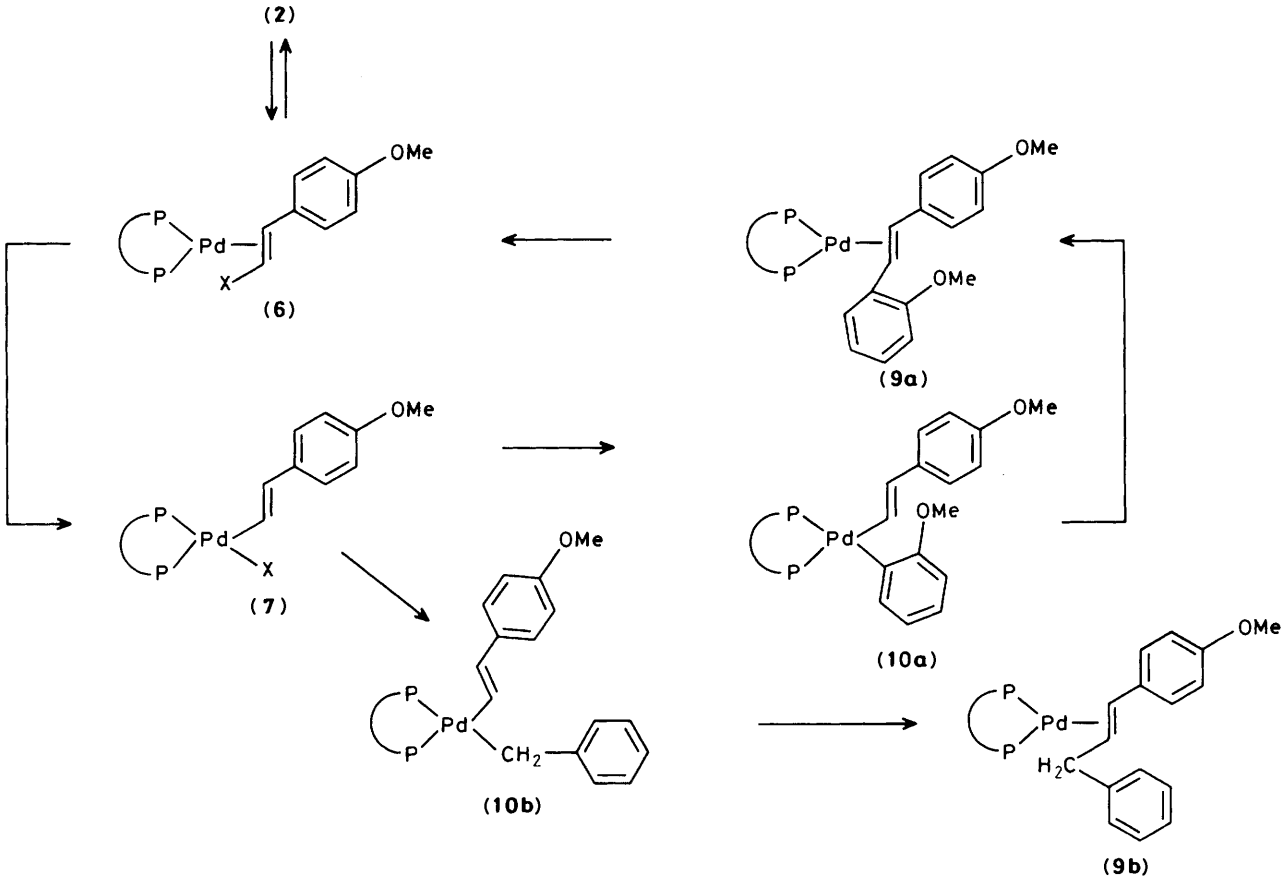
C_2H_4 giving respectively (**3**) or (**4**). The latter can be isolated below room temperature.[4] In the presence of *E*-2'-*p*-methoxystyryl bromide (**5a**),[5] complex (**2**) is in reversible equilibrium with the alkene complex (**6a**) at −40 °C. At or above −20 °C, this rearranges cleanly to the η^1,η^1-vinyl bromide complex (**7a**). The rate of this rearrangement was shown to be independent of the concentration of halide (**5a**). When the norbornene complex (**3**) is employed in the same sequence, further reaction takes place to give the double insertion product (**8**). C–C Insertion reactions of norbornene into palladium complexes have been observed previously.[6] Both (**7a**) and (**8**) are isolable and have been fully characterised.

This rapid vinyl halide rearrangement step (**6**)→(**7**) is strongly dependent on the halogen. With chloride (**5b**), only the η^2-alkene complex (**6b**) is formed, which is stable in solution up to 60 °C. From the corresponding iodide (**5c**)[7] the η^1,η^1-complex (**7c**) is formed rapidly at −60 °C and the presumed intermediate alkene complex cannot be observed.

When complex (**7a**) was reacted with excess of an *o*-methoxyphenylmagnesium bromide solution in thf at −80 °C, and monitored by ^{31}P n.m.r., the resonances of starting material disappeared immediately. The new product is the η^2-alkene complex (**9a**), and the coupled product can be displaced by cyclo-octatetraene to complete the formal catalytic cycle. The structure of (**9a**) was confirmed by its reconstitution using an authentic sample of 2,4'-dimethoxystilbene. Entirely similar results were observed with other arylmagnesium halides, forcing the conclusion that the expected intermediate (**10a**) is too unstable to be observed at −80 °C (Scheme 2).

In the reaction of $PhCH_2MgCl$ with complex (**7a**) the desired intermediate (**10b**) was observed, and only undergoes C–C elimination on warming to −15 °C. The benzylpalladium bond in (**10b**) was proved using ^{13}C-labelled Grignard reagent, and the coupling product (**11**) was isolated in good yield.

Taken together these experiments indicate but do not prove that the catalytic cycle proceeds through successive formation of (**6**), (**7**), (**10**), and (**9**). Firm evidence is derived from an isotope partitioning experiment.[8] Authentic [2'-^{13}C]-*E*-2'-*p*-methoxystyryl iodide was prepared from the aldehyde and $^{13}CHI_3$,[7] and converted into the ^{13}C-labelled vinyl iodide complex (**7d**). This was reacted with a defined excess of *o*-methoxyphenylmagnesium bromide and unlabelled vinyl iodide (**5c**) in thf at 0 °C such that all the palladium was present in the form of complex (**7**) at the end of the reaction. Similar coupling experiments were conducted with complex (**7c**) and labelled iodide (**5d**).



Scheme 2. Intermediates observed by ^{31}P and ^{13}C n.m.r. spectroscopy.

The ^{13}C-label contents of regenerated complex and stilbene product were determined accurately by n.m.r. techniques and are recorded in Table 1. Results were compared with computer-calculated predictions for alternative pathways based on an iterative program.[7]‡ They demonstrate that the vinyl complex (**7**) is a true catalytic intermediate which breaks down without the intervention of a second molecule of vinyl halide [*i.e.* through palladium(IV) intermediates],[9] an alternative which had been widely discussed.

A simple *cis* elimination from a 16e-palladium intermediate is in best accord with experiment, at least for vinyl–aryl coupling. Future work will examine the particular case of asymmetric cross-coupling.

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‡ Programming details, suitable for an HP 85, are available from the authors.

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