Transient and Stable Intermediates in Cross-Coupling Reactions

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Transient and stable intermediates in cross-coupling reactions

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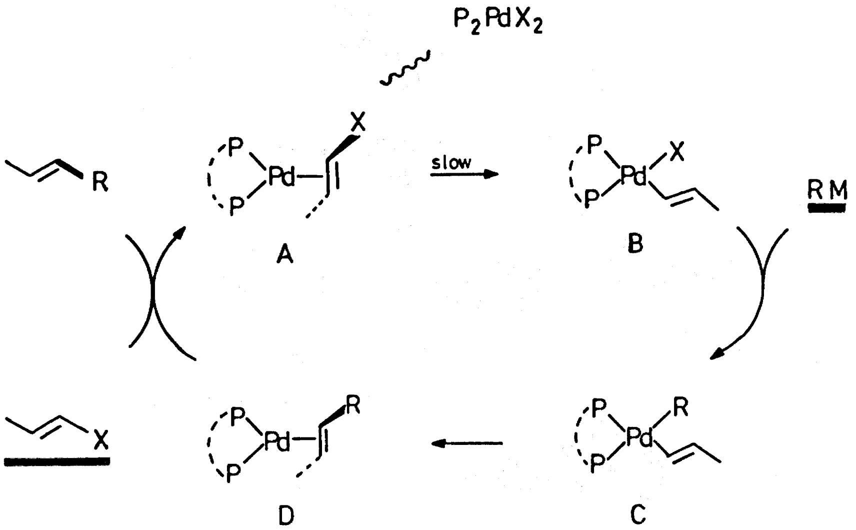
The mechanism of catalytic cross coupling mediated by palladium complexes has been examined. This has involved the successful *in situ* generation of a biphosphine palladium(0) species, and then observation of the sequential formation of an η^2-olefin complex and an η^1-alkenyl bromide complex on addition of an alkene. The latter is a stable isolable species, which reacts rapidly with added arylmagnesium halides; only the η^2-olefin complex is observed after this step at −80 °C. The contribution of these intermediates to the catalytic cycle of cross coupling was tested, employing a ^{13}C-labelled alkenyl iodide, and determining the label distribution in both palladium complex and product. On this basis it was demonstrated that the η^1-alkenyl iodide is a true intermediate in cross coupling, and the reaction cycle occurs without the intervention of a second molecule of substrate.

Platinum complexes are more stable than their isostructural palladium analogues. All the intermediates in a slow but sustainable catalytic cycle have been characterised in solution. Oxidative addition of the alkenyl bromide is profoundly accelerated by one-electron oxidizing agents.

Introduction

Catalytic asymmetric synthesis of C–C bonds has been demonstrated by the Kyoto group and others (Hayashi *et al.* 1986; Cross & Kellogg 1984; Consiglio *et al.* 1986). The basic principle of their experiment is that a racemic Grignard reagent, usually benzylic, is permitted to react with an alkenyl halide in the presence of a nickel or palladium complex with an optically active



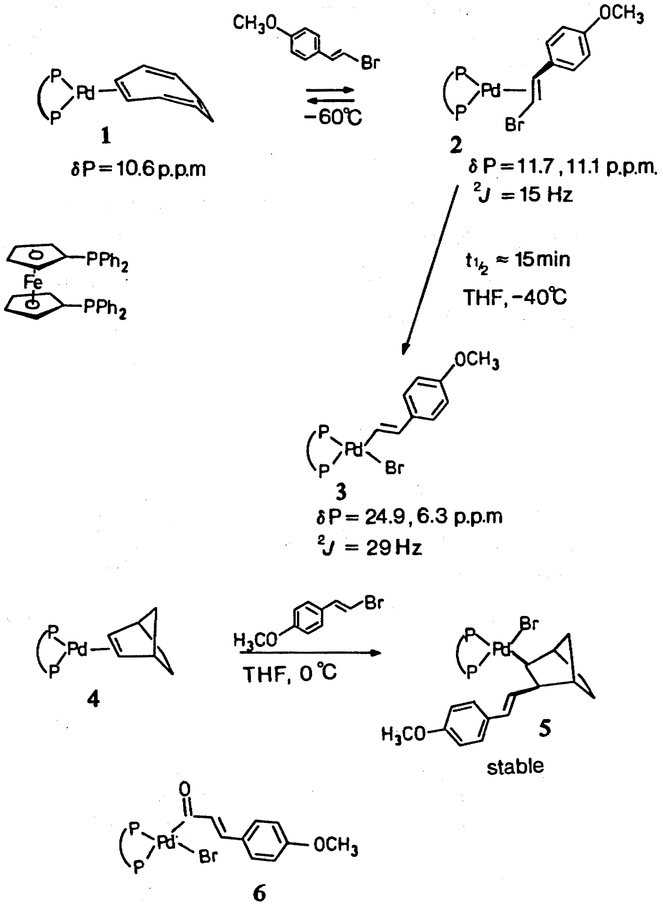
Scheme 1. A scheme for the catalytic cycle of cross coupling proceeding through η^2-alkenyl halide complex A, its rearrangement product B, an η^1,η^1-intermediate C and the complexed product D.

ligand. The most effective example is an amino acid derived from or based on an α-ferrocenylphosphine amine.

Because the reaction has substantial potential, not yet realized in more than one or two cases (allylsilanes are the only products which can be formed in more than 90% enantiomer excess) a thorough mechanistic study seemed worthwhile. We report the first findings of that study, providing information on intermediates in the catalytic cycle for a simple achiral model case. A general reaction scheme is indicated in scheme 1. Three of the four intermediates indicated in the scheme have been observed but the dialkylpalladium species C remains elusive because internal rearrangement is rapid at −80 °C.

Observation of palladium-bound intermediates

The first problem to be surmounted was generation of a suitable palladium(0) complex *in situ*, from which the preparation of catalytic intermediates could be initiated (Hodgson *et al.* 1987). The choice of ligand was dictated by the range and effectiveness demonstrated for *bis*-1,1′-diphenylphosphinoferrocene (Hayashi *et al.* 1984). It forms a stable palladium(II) dibromide that can be reduced *in situ* by $C_8H_8Li_2$ at low temperatures giving the cyclooctatetraene complex **1** (scheme 2) stable in solution at low temperatures. This reacted in turn

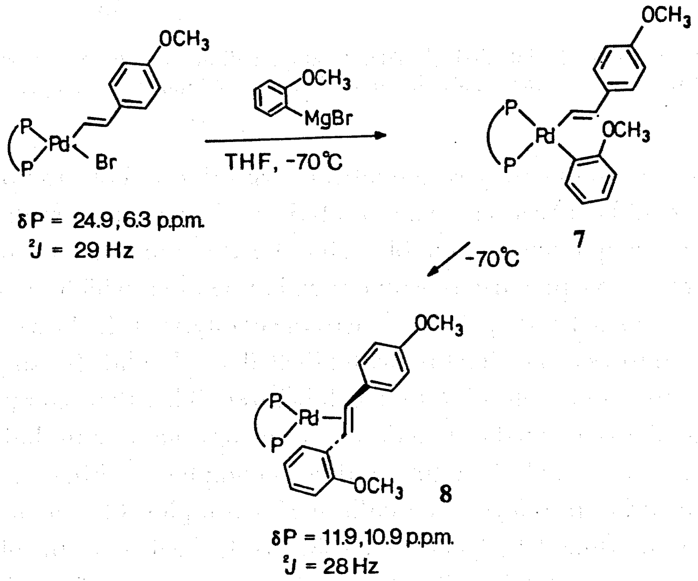


Scheme 2. The observation of intermediates in palladium-catalysed cross coupling with 1,1′-bis(diphenylphosphino)ferrocene as ligand. The alkenyl bromide complexes **3** and **5** are stable and isolable; other species are labile.

with *E*-2′-bromo-4-methoxyphenylethene to give first the η^2-olefin complex **2** at −60 °C and then the alkenyl bromide **3** complex resulting from insertion at slightly higher temperatures. The latter proved to be a stable isolable complex that has been fully characterized. The alkenyl iodide analogue of complex **2** was not observed, because the oxidative addition reaction occurred too rapidly and the intermediate was consumed faster than it was formed. In contrast, the corresponding η^2-chloro-olefin complex showed no tendency to rearrange, even under forcing conditions.

Cyclo-octatetraene was readily displaced from palladium in **1** by addition of norbornene, giving a new olefin complex **4**. When this was employed in the alkenyl bromide reaction, the final product contained a coordinated norbornene-derived alkyl residue **5**. There are precedents for the insertion of norbornene into a palladium–carbon bond (Amari *et al.* 1985) and similar behaviour was observed in the present series with carbon monoxide to give **6**. Neither ethylene nor cyclo-octatetraene showed any tendency to react in this manner. A probable pathway involves the displacement of bromide and coordination of norbornene, followed by *cis*-ligand migration and bromide return.

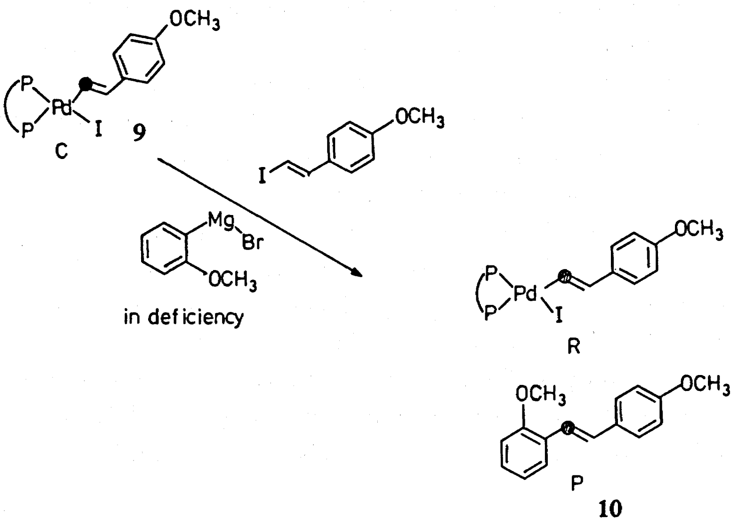
The isolation of an η^1-alkenyl bromide complex **3** led us to entertain hopes that the dialkyl complex **7** (scheme 3) would be amenable to study. Reaction of **3** with an excess of the arylmagnesium bromide led only to the η^2-alkene complex **8**, even at −70 °C. Similar observations were made with a variety of related Grignard reagents, from which it was concluded that the aryl alkenyl palladium species **7** has only transient existence at −70 °C so that the rearrangement to **8** has a very low activation energy. Work is continuing in an attempt to pin down this critical transient species, or closely related complexes.



Scheme 3. Attempted formation of the palladium dialkyl species **7** and observation of its easy rearrangement.

^{13}C-LABELLED REACTANTS

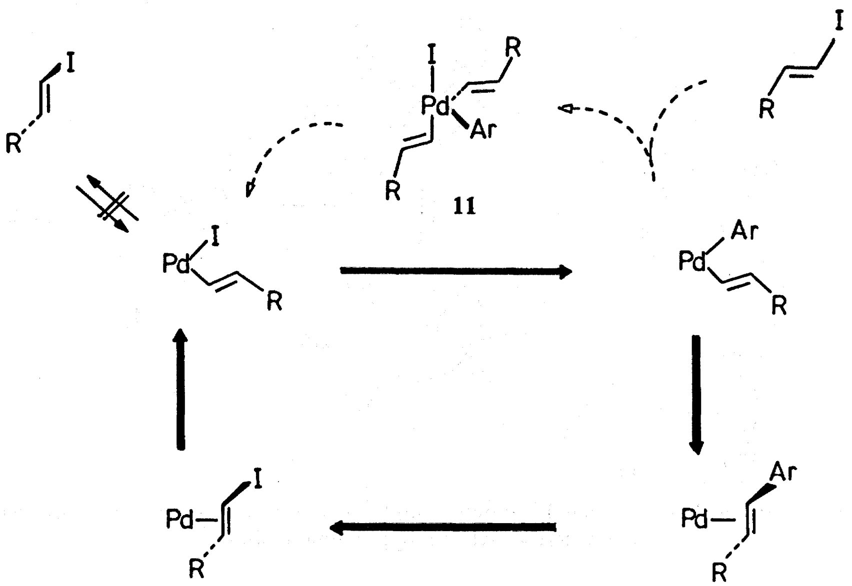
The previous section describes conditions under which three of the four putative intermediates in the catalytic cycle of scheme 1 may be observed, and their interconversion studied. This makes it reasonable to propose their intervention under catalytic conditions, but does not constitute proof; other pathways might be available for catalysis. Further insights were gained by employing the labelled reactant *E*-2′-[^{13}C]-2′-iodo-4-methoxyphenylethene, prepared from [^{13}C]iodoform and *p*-anisaldehyde according to the recently published procedure (Baker *et al.* 1988; Takai *et al.* 1986; Siegel & Seebach 1980). The logic of the experiment is demonstrated in scheme 4. The ^{13}C-labelled complex is reacted with both Grignard reagent and unlabelled substrate, such that at the end of the catalytic reaction there is ^{13}C-label in both the recovered complex **9** and the product **10**. Accurate assays were developed for the measurement of isotope content in both of these by NMR methods. The reverse experiment was also carried out, employing ^{13}C-labelled substrate and unlabelled complex.



SCHEME 4. Demonstration that the labelled η^1-alkenyl iodopalladium complex **9** is a true intermediate in catalysis (0.4–2.0 turnovers), and that a palladium(II)⟷palladium(0) cycle operates; see table 1.

With a relatively short span of catalysis, the label distribution in both the palladium complex and the product is readily measured. The catalytic cycle may be simulated by numerical integration techniques, employing reasonable values for the rate constants of individual steps; the final numbers are not particularly sensitive to values chosen, which are extrapolated from ^{31}P NMR observations reported earlier. Reference to the catalytic cycle shown in scheme 5 makes the consequences of catalysis clear. Starting with labelled vinyl iodide **9** a single traversal of the catalytic cycle leads to a molecule of **9** that is label-free. This then competes with labelled molecules on an equal basis for further reaction with the arylmagnesium halide. Alternatively, the vinyl iodide could intervene by reacting with aryl complex **7**, either by alkenyl exchange, or through oxidative addition to form a palladium(IV) complex **11**, which then breaks down to complex **9** and the product **10** (Byers *et al.* 1986, 1987). Mechanisms of this type give an entirely different prediction of label distribution in both **9** and **10**. A further alternative possibility is that reaction takes place predominantly outside the coordination sphere; the palladium species serves as an electron-transfer relay and does not participate directly. This predicts that label will not be transferred from complex **9** to product **10**. To safeguard the validity of experimental observations it was demonstrated that there is no exchange of label between the alkenyl iodide and complex **9** on the timescale of the experiment.

The results are recorded alongside predicted label distributions for different mechanisms in



Scheme 5. The mechanistic possibilities tested by experiments reported in table 1.

Table 1. Carbon-13 label distribution in a series of limited-turnover experiments together with the predicted label distribution for Pd^{II} and Pd^{IV} intermediates

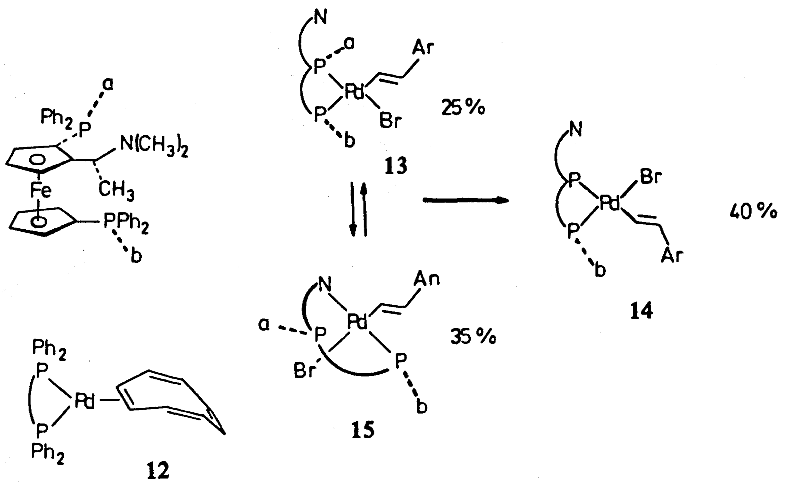
	initial (%)		final (%)		Pd^{II} (%)		Pd^{IV} (%)	
turnovers	C	R	C	P	C	P	C	P
1.86	99	1	16	45	17	46	40	33
1.34	1	99	66	51	73	45	48	63
0.38	1	99	37	< 10	31	17	17	54
0.43	14	99	42	35	43	30	30	61
0.48	69	1	42	56	43	55	55	31

Abbreviations: C, complex; R, reactant; P, product.

table 1. This endorses the view that the stepwise catalytic cycle of scheme 5, in which the alkenyl iodide complex **9** is a true catalytic intermediate, provides a viable explanation for the reaction mechanism.

Optically active biphosphine complexes

Ferrocene-based ligands have been among the most successful in asymmetric cross-coupling chemistry, and are readily prepared (Hayashi *et al.* 1984). In the manner previously described, the cyclo-octatetraene complex **12** was prepared *in situ* and reacted with the now familiar alkenyl bromide. Its chemical behaviour was quite different, for the η^2-olefin complex proved transient, even at −70 °C. Three species were apparent in comparable proportions at low temperatures, and their structures were assigned by comparison with the homologous complexes formed from ^{13}C-labelled alkenyl iodide. Two of these, **13** and **14**, are the expected diastereomeric η^1-alkenyl bromides, formed without much selectivity. The third species is a *trans*-alkenyl bromide **15**, with the phosphine of the substituted ring replaced by amine in the coordination sphere. The intervention of this type of species in cross coupling had not been recognized previously, and raises interesting questions about the origin of enantioselectivity. Complexes **14** and **15** appear to be in equilibrium at lower temperatures but above 0 °C both are completely transformed into complex **13**, within experimental error (scheme 6).



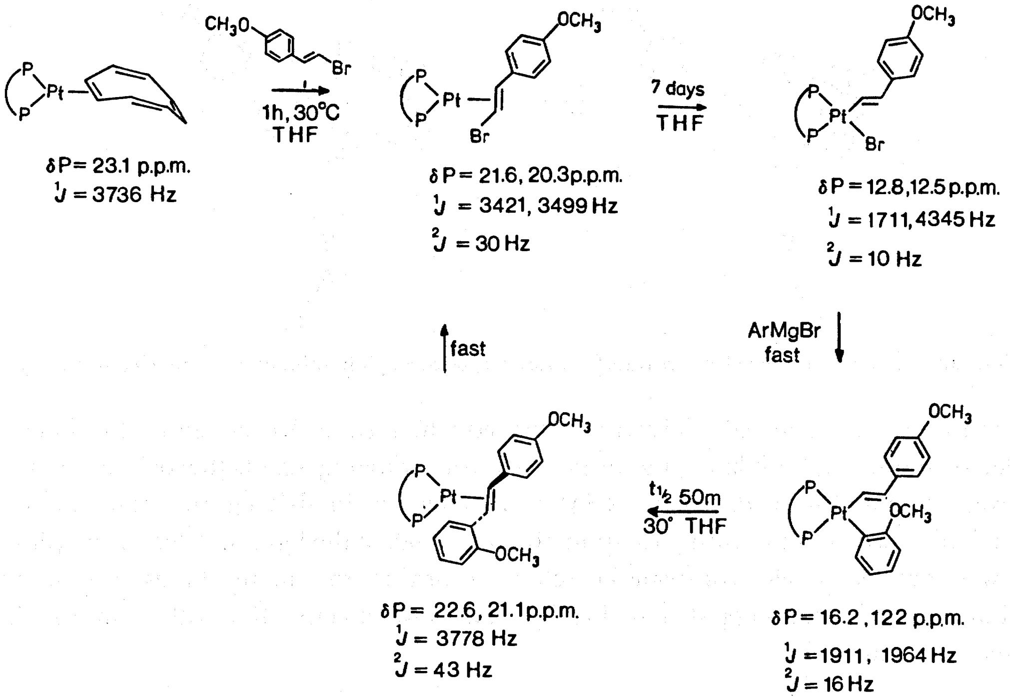
Scheme 6. Intermediate η^1-alkenyl bromide complexes observed at low temperatures with a chiral ferrocenyl aminophosphine ligand.

Reaction of either arylmagnesium or benzylmagnesium halides with this mixture of complexes at −70 °C gave only the cyclo-octatetraene derived species **12**, and not the initial olefinic product of cross-coupling. Evidently η^2-olefin complexes have lower stability in this series, both towards displacement and rearrangement.

CATALYSIS BY ORGANOPLATINUM COMPLEXES

The availability of η^2-ethylene platinum complexes possessing a chelate biphosphine (Brown *et al.* 1984; Parker & Taylor 1987) encouraged us to examine cross-coupling intermediates in the platinum series. A particular incentive was then to characterize the transient η^1-aryl η^1-alkenylmetal species, which proved to be elusive in palladium chemistry. Following the previously established protocols, the cyclo-octatetraene complex **16** derived from bis-1,1′-diphenylphosphino-ferrocene was prepared *in situ* and reacted with alkenyl bromide (scheme 7). Displacement was significantly slower than with the corresponding palladium complexes, but complete after an hour at 30 °C. The stable, isolable alkenyl bromide **17** rearranged very slowly indeed in THF, but reaction nevertheless proceeded to completion over a week at ambient temperature, giving complex **18**, which is fully characterized. As expected, this reacted rapidly with arylmagnesium halide to give complex **19**. On the basis of a great deal of precedent this was expected to be stable at ambient temperature (Braterman *et al.* 1976*a*, *b*, 1977; Hackett & Whitesides 1987). It proved to be otherwise and was observed to decompose cleanly to complex **20** over an hour or so. This is far higher reactivity towards reductive elimination than has ever been observed in dialkylplatinum chemistry. It may arise from a fortunate combination of chelate biphosphine and unsaturated alkyl groups. Whatever the reason, a complete catalytic cycle has been formally established because complex **20** can be converted back into complex **17** by olefin–olefin displacement.

These results suggested that sustainable catalysis could be carried out with platinum complexes. This proved to be the case; and starting with the appropriate ethylene complexes, 50 turnovers of catalysis could be achieved over a couple of days in refluxing THF (table 2). In each case the product was cleanly isolated without contamination from homo-coupled

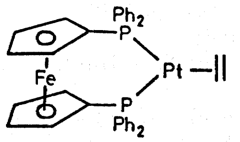


Scheme 7. A cycle involving organoplatinum intermediates, which have much greater stability than their organopalladium counterparts.

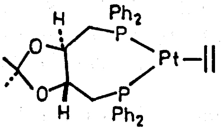
Table 2. Examples of *trans*-stilbene formation via platinum-complex-catalysed cross coupling

(Solvent = THF; yields = 90–98 %; 2 mol % catalyst.)

R1	R2	reaction conditions	catalyst
p-methoxyphenyl	*p*-fluorophenyl	48 h, 65 °C	A
p-methoxyphenyl	*o*-methoxyphenyl	48 h, 65 °C	A
p-methoxyphenyl	6-methoxy-2-naphthyl	48 h, 65 °C	A
p-methoxyphenyl	*p*-fluorophenyl	19 h, 65 °C	B
p-methoxyphenyl	*p*-fluorophenyl	4 days, room temp.	B



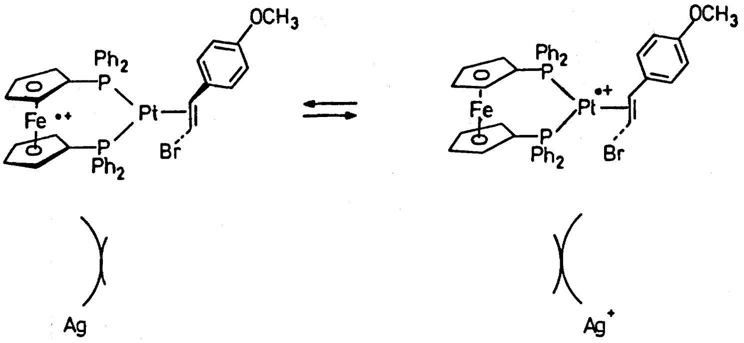
A



B

product. Control experiments established that no reaction occurred in the absence of the platinum catalyst. It was felt prudent to employ high-purity magnesium for the reaction, because it was demonstrated that one-electron oxidants could also catalyse the reaction. The scope and limitations of platinum-catalysed cross coupling is being actively pursued.

A major drawback to the application of platinum complexes in catalytic cross coupling relates to the slowness of individual stages, particularly the rearrangement exemplified by conversion of **17** into **18**, and the elimination of **19** to give **20**. It was surprising to discover that the first of these two steps proceeded very readily in CH_2Cl_2, about 10^3 times faster than in THF. Because the solvent is known to oxidize sensitive platinum(0) complexes, an electron-



Scheme 8. A postulate for electron-transfer catalysis; ferrocenylphosphines as a one-electron relay.

transfer process was suspected. This was confirmed when it was discovered that traces of silver ion or ferrocinium ion, both known to be one-electron oxidizing agents towards organometallic complexes (Magnuson *et al.* 1980, 1983) were effective in driving the reaction in THF solution. This raises an interesting question about the role of the ligand. A ferrocenylphosphine might well act as an electron-transfer relay, according to the mechanism of scheme 8. Preliminary experiments suggest that this ligand is more effective than others in assisting the oxidative addition step.

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