Although the volume selection in this first in vivo demonstration was achieved with a simple surface coil, **3** can be used as a thermometer in other, more sophisticated localization schemes.[23] Since the a transversal relaxation time (T_2) of the methoxy protons is approximately 10 ms, short spin-echo pulse sequences may be used for volume selection. The longitudinal relaxation time (T_1) of the methoxy protons is 47 ms in bovine plasma, which allows short repetition times. The high sensitivity and precision of the Pr[MOE-DO3A] thermometer could be used to generate images representing temperature distribution[24] in order to identify and localize regions of abnormal metabolic activity or to monitor temperature during thermal energy therapy (for instance, laser-induced interstitial thermotherapy, hyperthermia).

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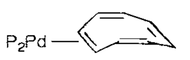
Characterization of Reactive Intermediates in Palladium-Catalyzed Arylation of Methyl Acrylate (Heck Reaction)**

John M. Brown* and King Kuok (Mimi) Hii

Among palladium-catalyzed reactions available to the synthetic organic chemist, the Heck reaction has enjoyed widespread use. This stems in part from the variety of circumstances in which coupling occurs with high yield and regioselectivity,[1] and in part from successful application to asymmetric synthesis.[2] The coupling reaction often requires forcing conditions, and optimization has proceeded by empirical methods, with a bewildering variation of base, solvent, and catalysts. Since mechanistic information is rather lacking, we have begun a project with an emphasis on the characterization of true catalytic intermediates in solution for the case of a bis(phosphane)palladium catalyst.

Much recent work employed organotriflate electrophiles[3] or organohalides in the presence of silver salts, which has led to the presumption that cationic palladium intermediates are involved. In the first instance we studied the addition of aryl triflates to the organopalladium complex **1**, which had been previously used in mechanistic work on catalytic cross-coupling.[4] The reaction is fairly slow at −25 °C and did not give rise to the desired product (vide infra). For this reason the fully characterized aryl halide complexes **2**–**4** were treated with silver triflate in THF at −78 °C, and the products examined by ^{31}P NMR after removal of silver salts by low-temperature centrifugation. In each case an AB quartet was observed in the range −60° to −35 °C, although only the product from **4** was stable at higher temperatures. In that case rapid isolation at 0 °C gave a yellow ionic solid (specific molar conductivity, Λ_m = 4.91 S cm^{-1} mol^{-1} (THF, −20 °C))[5] with an electrospray MS (m/z 873) that corresponds to the Ar{P$_2$Pd}$^+$ ion with the predicted isotope pattern. In all three cases the low-temperature ^{31}P NMR spectrum in THF exhibited characteristic broadening of both signals, more evident in the high-field partner. The reaction with complex **2** was investigated in most detail. On cooling from −40 °C, the ^{31}P NMR spectrum at 101.3 MHz in THF broadened and then separated below the coalescence region of about −70 °C into two distinct AB systems: At −98 °C the chemical shifts for spin system (A) were δ_P = 35.4 and 13.5



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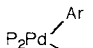
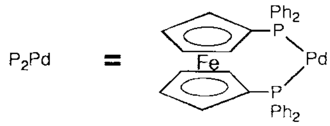


2, Ar = Ph, X = I

3, Ar = 4-MeOC$_6$H$_4$, X = I

4, Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$, X = Br



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($J = 30$ Hz), and those for spin system (B) $\delta_P = 34.8$ and 16.0 ($J = 30$ Hz); the ratio of signal intensities was about 1:2. Assuming a dissociative exchange mechanism we calculated a rate constant k_{ex} of 800 s^{-1} at -70 °C (Fig. 1). The identity of the second complex was defined by addition of H_2O to the sample, which shifts the equilibrium towards spin system (A). These observations are consistent with a fast exchange between solvates **5** and **6** (giving rise to signals (A) and (B) respectively, Scheme 1). Since the concentration of H_2O is low, its binding constant to Pd is concomitantly high:[6] $K_{aq} \approx 500$ M^{-1} has been estimated from the titration of the THF solution of the triflate derived from **2** with 1% H_2O in THF. When dimethylformamide (DMF) (1–3 µL) was added to a sample of the triflate salt derived from **4** (0.02 M in THF) at -78 °C, a single nondynamic species, ($\delta_P = 15.3$ and 37.1, $J = 27$ Hz) was observed, which can be attributed to structure **7**. An important recent study of the addition of aryl triflates to $[(PPh_3)_nPd^0]$ complexes concluded that the main species produced was an ionic *trans*-$[Ar(PPh_3)_2Pd^+]$ complex; the existence of strongly bound DMF complexes was noted.[7]

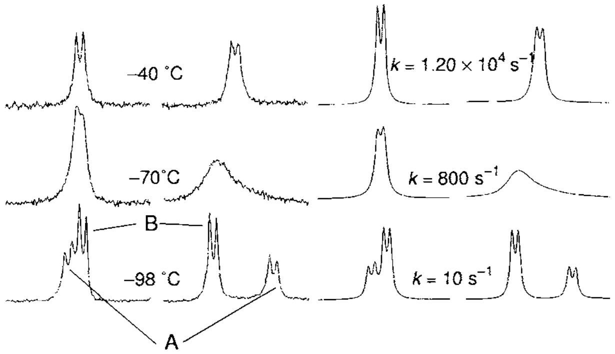
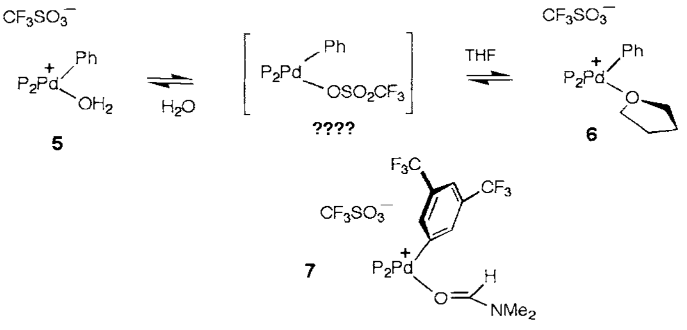


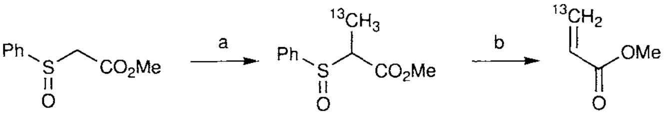
Fig. 1. The observed (left) and simulated (right) $^{31}P\{^1H\}$ NMR spectra for the equilibrium between solvate complexes **5** and **6**; simulation was carried out with the program gNMR.



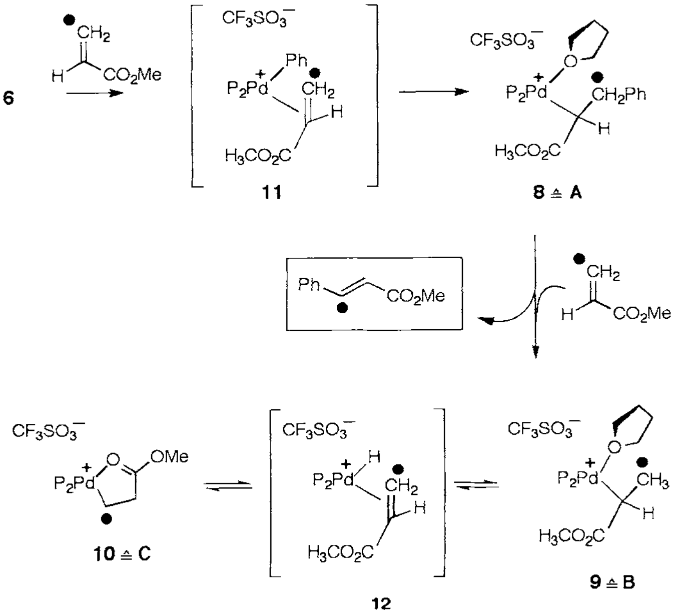
Scheme 1. Solvation equilibria for arylpalladium cations.

Alkenes, including norbornene, methyl acrylate, 2,3-dihydrofuran, and 2,5-dihydrofuran, reacted with the triflate complexes at low temperatures. For the most part, this was manifested by changes in the ^{31}P NMR first to form a new AB quartet, and then by decomposition around -30 °C. The most clear-cut results were obtained with an excess of methyl acrylate. At -60 °C, there is a slow pseudo-first-order conversion of complex **6** ($k_{obs} = 2.35 \times 10^{-4}$ s^{-1} with 20-fold excess of methyl acrylate; **5**:**6** = 1:3) into a new species A ($\delta_P = 42.5$, 20.8, $J = 33$ Hz). The rate is slower at lower concentrations of methyl acrylate, and also when H_2O (1.5 equiv) is added, indicating a pre-equilibrium competition between alkene and solvent for the labile coordination site.[8] If the sample is then warmed to -40 °C, a further transformation takes place, which results in the formation of **B** ($\delta_P = 41.4$ and 20.6, $J = 37$ Hz). This intermediate is in turn converted into C ($\delta_P = 40.4$ and 17.5, $J = 35$ Hz), and that product is stable to 0 °C. Electrospray MS of **C** isolated as the bromide (m/z 746) indicated the basic structural elements ($H_2C{=}CHCO_2Me$ and $\{P_2Pd\}H^+$). Direct electrospray MS whilst **A** was still present indicated the structural elements $H_2C{=}CHCO_2Me$ and $\{P_2Pd\}Ph^+$. The ^1H NMR spectrum indicated concomitant formation of *E*-methyl cinnamate as the only organic product at -40 °C, which was confirmed by its isolation.

In order to identify the various transient species, a new synthesis of [3-^{13}C] methyl acrylate was developed (Scheme 2).[9] Reaction of an excess of this labeled compound with complex **6** (Scheme 3) clearly showed that **A** was the Pd alkyl **8** ($\delta(^{13}C) = 35.3$, $J_{C,P} = 4$ Hz for the ^{13}C nucleus *trans* to the P atom). In similar manner complex **B** was shown to have structure **9** ($\delta = 13.6$; $J_{C,P} = 5$ Hz), and **C** to be the regioisomeric complex **10** ($\delta = 30.8$; $J_{C,P} = 85$ Hz). Complexes **8** and **9** both disappear rapidly when 2,4,6-trimethylpyridine is added to the solution at the appropriate stage, but complex **10** is robust to this treatment. The rearrangement is intermolecular and occurs via the unobserved hydride complex **12**, since addition of unlabeled methyl acrylate to the reaction after **8** had disappeared led to the equilibrium distribution of ^{13}C-label in the ultimate product **10**. No other species except *E*-methyl cinnamate ($\delta = 145.5$) were detectable by ^{13}C NMR spectroscopy. Two ^{31}P NMR spectra



Scheme 2. Synthesis of ^{13}C-labeled methyl acrylate. a) NaH, 1,3-dimethylhexahydro-2-pyrimidinone (DMPU), THF, 0 °C then $^{13}CH_3I$, 51% yield; b) 125 °C, 2 h, 74% yield.



Scheme 3. Heck intermediates observed by heteronuclear NMR spectroscopy. The complex **12** exchanges acrylate ligands with the acrylate pool. The labeled C atom is indicated as •C.

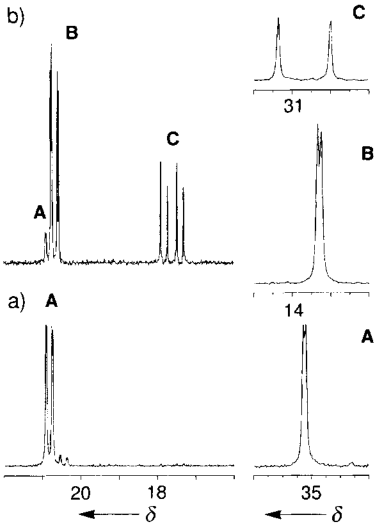
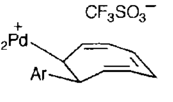


Fig. 2. Left : the high-field region of the $^{31}P\{^1H\}$ NMR spectrum of the reaction between the solvate species **5**/**6** and 3-$\{^{13}C\}$ methyl acrylate a) after about 2 h at −60 °C and b) after warming to −40 °C and holding for a further hour. The $^{13}C\{^1H\}$ NMR spectra of the three intermediates **A**–**C** recorded in the same experiment are reproduced on the right.

recorded in the course of a single experiment are shown in Figure 2; at −40 °C the separation of the stages **A** through **B** to **C** is less clear than at −60 °C.

With this information in hand, the structure of the initial species formed from complex **1** and 3,5-$(CF_3)_2C_6H_3OTf$ was investigated. At −30 °C, the now familiar AB type ^{31}P NMR spectrum ($\delta_P = 12.6$ and 32.8, $J = 29$ Hz) developed cleanly over an hour, and the electrospray MS in MeOH indicated that the probable structure of the new complex was **13** (*m*/*z* 873; $\{P_2Pd\}^+ + Ar + C_8H_8 + MeOH$). In this case the initially formed migration product is stabilized by the absence of a feasible *β*-elimination pathway.



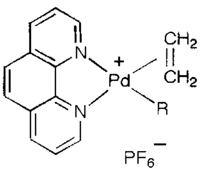
13

These observations clarify several features of the Heck reaction catalyzed by bis(phosphane)palladium complexes:

a) The Pd aryl triflate complex, already shown to be cationic in the PPh_3 series, is also ionized in chelate complexes, and solvent molecules rapidly exchange at the labile coordination site.

b) Traces of water can alter the composition of the initial ionic Pd complex, since its binding constant is high. Influences of water on the Heck reaction have been noted.[10]

c) The putative η^2-alkene complex **11** cannot be observed at −60 °C, thus putting a conservative upper limit of $\Delta G^{+} \approx 14$ kcal mol^{-1} on the barrier for the C–C bond-forming step under these conditions. In a search for intermediates in the Pd-catalyzed copolymerization of propene and CO, complexes **14** and **15** were characterized by low-temperature NMR spectroscopy, and ΔG^{+} values of 18.5 and 19.4 kcal mol^{-1} were measured for respective migration of Me and Et groups.[11]



14, R = CH_3

15, R = C_2H_5

d) The aryl migration is completely regiospecific; the only product is *E*-methyl cinnamate, the expected outcome of a Heck reaction. The elimination step generates an unseen Pd–H intermediate, which adds regiospecifically to methyl acrylate to give a new alkyl complex **9**.

e) The initially formed complex **9** then rearranges cleanly to the more stable, primary alkyl regioisomer, for which a chelate form with coordinated ester carbonyl group is likely (**10**).[12] A precedent for such a rearrangement by reversible *β*-hydride transfer to Pd has already been established, although the precursor of the stable alkyl complex was not observed in the previous case.[13] In addition, a Pt analogue of complex **10** formed by Pt–H insertion into methyl acrylate has been demonstrated.[14]

In summary, a key intermediate of the Heck reaction was characterized in a catalytically viable system, and the alkene elimination step then observed directly. A stoichiometric amount of base is widely employed in catalysis, and its likely function is seen to be the deprotonation of a hydridopalladium complex to regenerate the oxidative addition precursor; otherwise this may intercept the alkene as observed here. Future work will endeavour to clarify the role of base, to define the enantioselective variant, and to pursue the elusive η^2-alkene complex, which could not be observed here.

Experimental Procedure

The ^{13}C-labeled methyl 2-phenylsulfinylpropanoate was prepared as an (R^*R^*)/(R^*S^*) mixture from $^{13}CH_3I$ according to the general procedure in Ref. [9] and purified by chromatography on silica (1:1 ethyl acetate:petroleum). Yield 51%, ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C) $\delta = 8.6, 9.3$, ($^1J(C,H) = 131$, $^2J(C,H) = 3.5$ Hz from ^1H NMR). Thermolysis was carried out in a Kugelrohr apparatus at 125 °C for 2 h under A. Yield 74%, $\delta_C = 130.8$, $^1J(C,H) = 160$, 160.6, $^2J(C,H) \approx 0$ Hz.

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