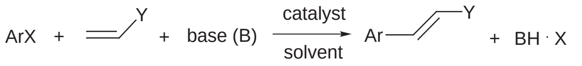
Highly active, stable, catalysts for the Heck reaction; further suggestions on the mechanism

Bernard L. Shaw,*† Sarath D. Perera and Elaine A. Staley

School of Chemistry, University of Leeds, Leeds, UK LS2 9JT

Tri(1-naphthyl)phosphine gives palladacycles which are very active catalysts for Heck reactions; mechanisms based on a Pd^{II}–Pd^{IV} cycle are proposed and a new, very efficient method of separating the product from the catalyst has been devised, which involves treatment with cyanide ion.

The Heck alkenation reaction [eqn. (1)] is very important in



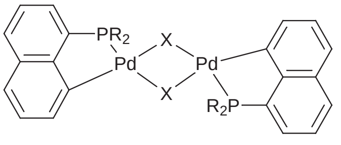
(1)

organic synthesis with many applications. Frequently, a Heck catalyst has been generated *in situ* from Pd(OAc)$_2$ and a tertiary phosphine, L = PPh$_3$ or P(C$_6$H$_4$Me-*o*)$_3$. This is assumed to give some PdL$_2$, which forms part of a catalytic cycle involving Pd^0–Pd^{II}. Recently, highly efficient catalysts using cyclopalladated P(C$_6$H$_4$Me-*o*)$_3$ have been reported.[1*a,b*] One of us has suggested a quite new mechanism for such catalyses with reversible nucleophilic attack on Pd^{II}-coordinated alkene being a key step in the promotion of oxidative addition of ArX, in a Pd^{II}–Pd^{IV} catalytic cycle.[2] Previously, as part of an extensive study on the effects of steric compression, we found that 1-naphthylphosphines could give particularly stable metallacycles,[3] with metallation in the 8- or *peri*-position. We have now found tri(1-naphthyl)phosphine (PNp$_3$) cyclopalladates to give very stable palladacycles, which are excellent catalysts for Heck reactions.

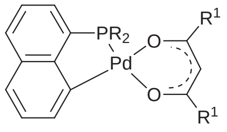
On heating PNp$_3$ with Pd(OAc)$_2$ in toluene the metallacycle **1a** was obtained. **1a** showed broad NMR spectra at 25 °C, probably due to exchange at the bridging acetates; the spectra sharpened at −60 °C. Broad NMR spectra were similarly found for the palladacycles prepared from Pd(OAc)$_2$ and P(C$_6$H$_4$Me-*o*)$_3$.[1*a*] We treated **1a** with acetylacetone and converted it into the mononuclear acetylacetonate **2a** which showed sharp NMR spectra at 25 °C. **2a** can be more conveniently made by treating [Pd(acac)$_2$] with PNp$_3$ in hot benzene. **2b** was similarly prepared from PNp$_3$ and [Pd(hfacac)$_2$]. We have similarly cyclopalladated P(C$_6$H$_4$Me-*o*)$_3$ to give **3a** and **3b**. All these new palladacycles have been fully characterised.

The palladacycles **1a**, **2a** and **2b** are excellent catalysts for Heck reactions. Some of our catalytic results are summarised in Table 1. Thus treatment of iodobenzene with styrene at 120 °C for 5 days using 10^{-4} mol% catalyst **2b** gave stilbene in 65% isolated yield, *i.e.* a turn over number (TON) of 650 000. No palladium metal was formed and the final reaction solution was extremely pale yellow. Treatment of iodobenzene with methyl acrylate at 95 °C for 13 days using 5×10^{-5} mol% of catalyst **2b** gave methyl cinnamate with a TON of 1 120 000, the highest turnover number yet reported for a Heck reaction; with 10^{-3} mol% catalyst reacting at 95 °C for 5 d we isolated methyl cinnamate in 88% yield with a TON of 88 000. Herrmann and Beller's catalysts gave TONs of up to 100 000, or in the presence of much NBu$_4$Br as promoter, 1 000 000; NBu$_4$Br is expensive and we tried to achieve high TONs without it. 4-Bromoacetophenone reacted with styrene at 125 °C over 7 h to give 4-acetylstilbene in 94% isolated yield using catalyst **1a** (entry 5); similarly with 4-bromocyanobenzene (entry 6). Bromobenzene, a relatively inactive bromide, gave a 77% yield of stilbene after reacting with styrene at 115 °C for 30 h using catalyst **2b** (entry 7). In entry 8 we used sodium acetate as the base and the acetylacetonate catalyst **2a**. Examples of catalyses using **3a** and **3b** are also given. The entries given in Table 1 all refer to isolated yields of crystalline products. Apart from entry 3, where column chromatography was used, and entry 1, the products were separated from the palladium catalyst using an extraction process that we have devised. This depends on the enormous affinity of palladium for cyanide ion: the formation constant for [Pd(CN)$_4$]$^{2-}$ is *ca.* 10^{52}.[4] The extraction process works very well for the examples given in Table 1.‡

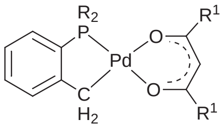
We suggest a mechanism for the Heck reactions catalysed by **1a**, **2a** or **2b** which is analogous to that proposed by one of us[2] for Heck reactions. The mechanism involves Pd^{II}–Pd^{IV}, with the alkene coordinating to the Pd^{II} being reversibly attacked by a nucleophile, such as OAc$^-$, acac$^-$, OH$^-$, Br$^-$ or I$^-$, to give a negatively charged alkyl species **5** in which the Pd^{II} is electron rich and oxidatively adds ArX. Loss of nucleophile regenerates the coordinated alkene and migration of Ar from Pd^{IV} to coordinated alkene followed by β-hydrogen migration, gives the product ArCH=CHY and removal of HBr by the base regenerates the Pd^{II} catalyst of type **1**, (see Scheme 1).



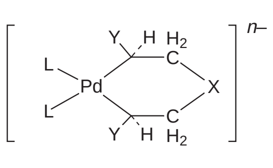
1a R = naphthyl, X = OAc
1b R = naphthyl, X = I
1c R = naphthyl, X = Br



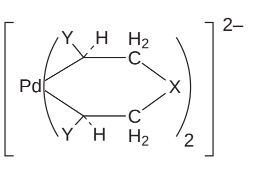
2a R = naphthyl, R^1 = Me
2b R = naphthyl, R^1 = CF$_3$



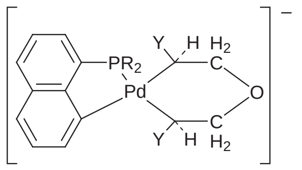
3a R = *o*-tolyl, R^1 = Me
3b R = *o*-tolyl, R^1 = CF$_3$



10a X = OC(=O)O
10b X = O



11a X = OC(=O)O
11b X = O



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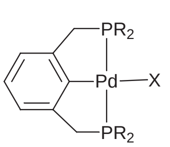

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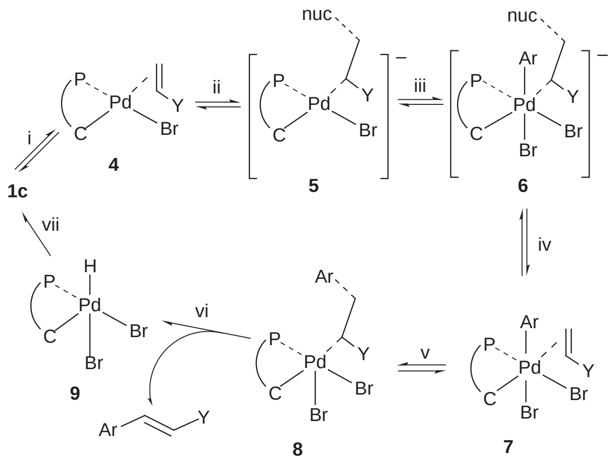
Table 1 Selected results of the Heck reactions catalysed by palladium chelates[a]

Entry	Aryl halide[b]	Alkene	ArX/alkene mmol/mmol	Catalyst/mmol	Time (T/°C)	Yield (%) (TON)
1	PhI	sty	10/12.5	**2b** (10^{-5})	5 d (120)	65 (650 000)
2	PhI	sty	10/12.5	**2b** (10^{-3})	17 h (95)	78 (7800)
3	PhI	mac	10/10	**2b** (5×10^{-6})	13 d (95)	56 (1 120 000)
4	PhI	mac	10/10	**2b** (10^{-4})	5 d (95)	88 (88 000)
5	bab	sty	2/2.6	**1a** (5.2×10^{-3})	7 h (125)	94 (180)
6	bcb	sty	2/3	**1a** (5.2×10^{-3})	7 h (125)	85 (165)
7	PhBr	sty	10/12.5	**2b** (10^{-2})	30 h (115)	77 (770)
8	PhI	sty	2/2.2	**2a** (10^{-2})	24 h (95)	56 (115)
9	PhI	sty	2/3	**3a** (7×10^{-3})	8 h (95)	83 (240)
10	PhI	sty	10/12.5	**3b** (10^{-2})	4 h (95)	90 (900)
11	PhI	mac	2/2.2	**2a** (1.9×10^{-3})	24 h (95)	72 (760)

[a] Except for entry 8, an equivalent amount of tri-(*n*-butyl)amine to the aryl halide was used as base; in entry 8, 4 mmol of sodium acetate was used. The catalyst was dissolved in dmf, *e.g.* 1 cm^3 in entry 1. Experimental details available upon request from the authors. [b] bab = 4-bromoacetylbenzene, bcb = 4-bromocyanobenzene, sty = styrene, mac = methyl acrylate.

In the so-called exceptionally mild 'Jeffrey' conditions for effecting a Heck reaction, *viz* [Pd(OAc)$_2$], an aryl iodide and an alkene such as CH_2=CHY reacting in dmf at *ca.* 30 °C in the presence of sodium hydrogen carbonate or potassium carbonate, with much added NBu_4Cl as phase-transfer catalyst, very good yields are obtained. One of us suggested that the remarkable ability of aryl iodide to oxidatively add to Pd^{II} at such as low temperature arises because HCO_3^- or CO_3^{2-} attacks two coordinated alkenes to give chelated dialkyl species **10a** and **11a**, X = CO_3.[2] **11a** is an 'ate' complex with an extremely electron-rich palladium. We now suggest that under these conditions the bridging group X could be an oxygen atom, formed from water + base attacking two coordinated alkenes, *i.e.* **10b** and **11b**. Water is known to promote Heck reactions including under Jeffrey conditions.[5] We suggest that one function of the large cations such as NBu_4^+ is to help stabilise in solution large anions such as of type **10** or **11** and analogous species from palladacycles. Because of the beneficial effect of water we deliberately did not dry our reagents nor the dmf solvent (⩾0.1% water). Electron rich 'ate' complexes of iron(II) or cobalt(II) *e.g.* $[FeMe_4]^{2-}$ or $[CoMe_4]^{2-}$, react with a series of vinyl bromides, such as β-bromostyrene, even at −78 °C, undergoing oxidative addition/reductive elimination:[6] 'ate' complexes of Pd^{II}, Ni^{II} and Pt^{IV} are known. We also suggest that attack on two-coordinated alkenes by H_2O + base could give **12**, as an electron rich Pd^{II} complex which oxidatively adds ArX and which could participate in a catalytic cycle similar to that shown in Scheme 1. Recently, the very stable and sterically hindered chelates of type **13** have been shown to be very stable catalysts for Heck reactions giving very high TON but requiring high reaction temperatures (140 °C) even with iodides.[7] We suggest a mechanism similar to that shown in Scheme 1 for catalyses by **13**.



Scheme 1 Proposed mechanism for the Alkenation reaction using a palladacycle of type **1** or **2** and an aryl bromide. After several cycles the bromide **1c** will be formed and is used in the Scheme. i, CH_2=CHY; ii, reversible attack by nucleophile (OAc^-, Br^-, $acac^-$ or OH^-); attack is shown on the terminal carbon atom but it could be on the internal carbon; iii, oxidative addition of ArBr; iv, loss of nucleophile; v, migration of Ar to terminal carbon; vi, β-hydrogen elimination; vii, removal of HBr by base.

Notes and References

† E-mail: b.l.shaw@chem.leeds.ac.uk

‡ For entry 5 the reaction mixture was dissolved in CH_2Cl_2 (10 cm^3) and the organic layer washed successively with water, with a solution of NaCN (2 mg) in water (5 cm^3), with 2 M HCl, and finally with water; evaporation and crystallisation from MeOH gave the product;. similarly for the other entries. For syntheses involving methyl acrylate, diethyl ether was used in the work up. Preliminary work suggests that the treatment with NaCN gives a little PNp_3 but the main product seems to be a rapidly interconverting mixture of sodium salts of type $[Na^+]_n[Np_2PC_{10}H_6Pd(CN)_{n+1}]^{n-}$ which is not soluble in CH_2Cl_2 or Et_2O, is very soluble in MeOH and presumably sufficiently soluble in dilute aqueous NaCN; very small quantities are involved, typically μg of Pd.

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