Letter

Speculations on new mechanisms for Heck reactions

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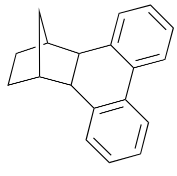
A mechanism for the olefination reaction is proposed, involving Pd^{II}/Pd^{IV}, in which a key step is reversible nucleophilic attack on the Pd^{II}-coordinated olefin to give an electron-rich σ-alkyl- or, with carbonate, a chelated σ-dialkyl-complex, which then oxidatively adds the organic halide *e.g.* ArX. Loss of nucleophile, migration of Ar from Pd^{IV} to coordinated olefin, β-hydrogen elimination and loss of HX then gives the product of olefination and regenerates the Pd^{II} catalyst.

The Heck olefination reaction is very important in organic synthesis and is the subject of many reviews.[1a–e] There are several variations on the Heck olefination reaction but most commonly an organic halide RX, R = aryl, alkenyl or benzyl, X = I or Br, is reacted with an olefin of type $CH_2{=}CHY$, Y = CO_2R, Ar, CN or COR in the presence of a palladium catalyst and a base (B). The catalyst is frequently generated *in situ*, *e.g.* from $Pd(OAc)_2$ and a tertiary phosphine, L = PPh_3 or $P(o\text{-}MeC_6H_4)_3$. This is assumed to give a mixture of PdL_x, x = 4, 3 or 2. It has been suggested that PdL_2 reacts with RX to give $RXPdL_2$, which then loses another L and complexes to $CH_2{=}CHY$. After addition of R—Pd across C=C and β-hydrogen elimination, RHC=CHY and BH^+X^- are produced and PdL_2 is regenerated. The catalyst system is an extremely complex mixture and frequently some metallic palladium is formed. As has been pointed out recently,[1c,e] this mechanism has not been proven and assumptions have been made. Various halides, such as alkali-metal halides, $NBu^n{}_4Cl$ or $NBu^n{}_4Br$ have been shown to promote Heck reactions; it is thought that halide ion interacts with Pd and promotes the oxidative addition of RX. Typically, 1–5 mol% of Pd catalyst is used which means that the maximum turnover numbers (TON) are only 100–20.

An important advance in this area was the discovery that metallacycles of type **1** are extremely good catalysts for Heck olefination reactions, better than anything used previously, giving essentially quantitative yields and turnover numbers of 100 000, or in the presence of much $NBu^n{}_4$ Br as promoter 1 000 000.[2a,b] Usually no palladium is formed and a catalyst **1**, *e.g.* with X = Br, is recovered unchanged.[2a] Herrmann and co-workers could not detect any Pd^0 in their systems and could not rule out a redox system involving Pd^{II}/Pd^{IV} but could not detect any aryl–Pd^{IV} species. It seems extremely likely that these catalyses involve Pd^{II}/Pd^{IV} chemistry and not Pd^0. Herrmann and co-workers[2a,b] report that a complex of type **1** does not add an aryl bromide and nothing happens until the olefin, such as $CH_2{=}CHCO_2Bu^n$ or $CH_2{=}CHPh$, is added, when catalysis starts. The new mechanism given below explains why the olefin promotes the oxidative addition of the aryl bromide to palladium(II).

Alkyl– or aryl–palladium(IV) complexes are still uncommon and much less stable than alkyl- or aryl-derivatives of platinum(IV), which are well known. It is established that alkyl substituents on Pt^{II} greatly increase the reactivity towards oxidative addition,[3] *e.g.* $[PtI_2(PEt_3)_2]$ does not add MeI whereas $[PtMeI(PEt_3)_2]$ adds MeI reversibly and rather weakly to give $[PtMe_2I_2(PEt_3)_2]$[4] and there are many examples of dialkyl-substituted platinum(II) complexes oxidatively adding an organic halide to give stable Pt^{IV} complexes.[3] Not surprisingly therefore, the introduction of alkyl- or aryl-substituents on Pd^{II} has been shown to increase the tendency towards oxidative addition, although not many examples are known and the Pd^{IV} products are thermally unstable. An early example was the oxidative addition of MeI to $[PdMe_2(bipy)]$ (bipy = bipyridyl) to give $[PdMe_3I(bipy)]$.[5a] Some work with palladium, bicyclo[2.2.1]heptene and aryl bromides is thought to involve organopalladium(IV) complexes. Treatment of norbornene (bicyclo[2.2.1]heptene) with PhBr, $KOBu^t$ and a Heck catalyst gives **2**. Good evidence has been obtained that a Pd^{II} species **3** (L = PPh_3) undergoes oxidative addition of PhBr to give a Pd^{IV} species **4** and this is an intermediate step in the formation of **2**; some *para*-substituted bromobenzenes react similarly.[5b–d] Thus the presence of one alkyl, one aryl and two triphenylphosphine ligands makes Pd^{II} able oxidatively to add bromobenzene at quite a low temperature (110 °C). The Pd^{II} species **3** with L_2 = phenanthroline, oxidatively adds 4-nitrobenzyl bromide and the resultant six-coordinate Pd^{IV} species, although unstable, has been characterised.[5d]



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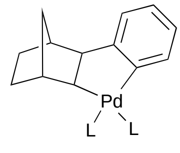

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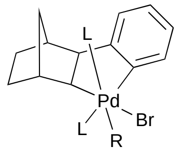

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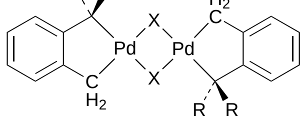
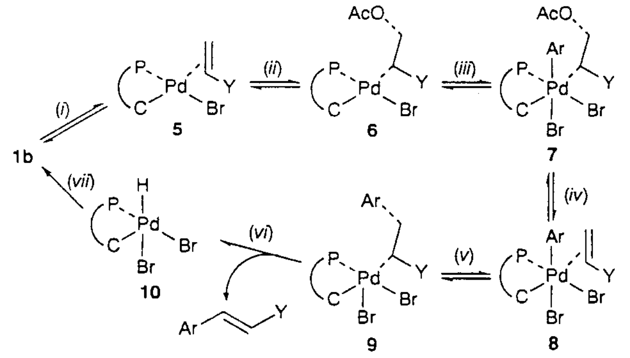
As mentioned above, catalysts of type **1** do not react with aryl bromides and nothing happens until the olefin is added.[2a] This seems surprising at first since coordination of an olefin to Pd^{II} would not be expected to increase the tendency towards oxidative addition, an important factor being back coordination from d to π* orbitals on the olefin removing electron density from the metal. However, an olefin on coordination to Pd^{II} or Pt^{II} becomes susceptible to nucleophilic attack; either *exo* attack or intramolecular addition of Pd—X to coordinated C=C; in such a process the olefin is converted into a σ-alkyl substituent. The many examples in which nucleophiles or substituents X do this include OC(=O)R, OH, OR, H_2O, NH_2R, NR_3 or Cl, adding to a C=C of a monoolefin, or to a C=C of 1,5-, 1.4-, 1.3- or 1,2-diolefins; these additions are frequently fast and *reversible*.[6] Specific examples of attack on coordinated C=C are: (*i*) by a carboxylate ion or carboxylic



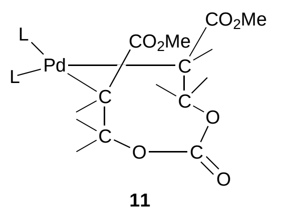
1a X = OAc, R = $o\text{-}MeC_6H_4$
1b X = Br, R = $o\text{-}MeC_6H_4$



Scheme 1 Proposed new mechanism for the olefination reaction. The new features are that the Pd^{II} metallacycle **1b** is coordinated by the olefin, which then undergoes nucleophilic attack to give a σ-alkyl complex; by way of example, acetate ion is the nucleophile involved. The resultant electron-rich Pd^{II} complex then undergoes oxidative addition with an aryl bromide, or some other organic halide, to give a Pd^{IV} complex. This then loses acetate ion to regenerate coordinated olefin and, after migration of aryl from Pd to olefin, β-hydrogen elimination and removal of HBr by the base (acetate ion) gives the required product, ArCH=CHY, and the Pd^{II} metallacycle catalyst **1b** is reformed. **6** and **7** are anionic. (*i*) CH_2=CHY. (*ii*) Reversible attack AcO^-; attack is shown on the terminal carbon atom but it could be on the internal carbon. (*iii*) Oxidative addition of ArBr. (*iv*) Reversible loss of AcO^-. (*v*) Migration of Ar to terminal carbon. (*vi*) β-hydrogen elimination (*vii*) Removal of HBr by AcO^- .

acid in vinyl ester exchange,[7] (*ii*) by an alcohol in vinyl ether exchange, such exchanges are fast even at −40 °C using $[PdCl_2(NCPh)_2]$ as catalyst,[8] (*iii*) by OH or H_2O in the conversion of ethene to acetaldehyde (the Wacker process)[9,10] or (*iv*) by acetate ion in the presence of copper and oxygen to give vinyl acetate.[1d,e,10] Most examples of such attack involve oxygen donating nucleophiles but chloride ion can attack buta-1,3-diene coordinated to palladium, rapidly and reversibly, and the so-called 'butadiene palladous chloride' was shown to be an η^3-chlorocrotyl complex.[11a] Chloride similarly attacks coordinated allene to give an η^3-2-chloroallyl complex;[11b] this is also reversible. There are many other examples of attack on olefins coordinated to Pd^{II} or Pt^{II} including attack by primary, secondary or tertiary amines.[6] I suggest therefore that in Heck-type catalysis by a metallacycle **1b**, the first step is coordination of the olefin CH_2=CHY to give **5** (see Scheme 1) and the coordinated olefin is then attacked by a nucleophile, in this case acetate ion to give **6** containing an alkyl–palladium bond in addition to the one in the metallacyclic ring. Two σ-donating carbon atoms and the electron-donating phosphine make the palladium sufficiently reactive oxidatively to add ArBr, giving **7**. Reversible loss of $^-$OAc then regenerates the coordinated olefin in complex **8**, and migration of the aryl group from palladium to the CH_2= carbon occurs, giving **9**. A β-hydrogen migration to palladium liberates ArCH=CHY and the base removes HBr from Pd^{IV} to give the Pd^{II} complex **1b**, completing the cycle. Thus I am suggesting that the acetate ion has a *dual function*: (*i*) to remove HBr, and (*ii*) to convert coordinated olefin to a σ-alkyl group, since this would promote oxidative addition of ArBr, generally considered to be the rate-determining step in Heck reactions. Other nucleophiles could similarly attack the coordinated olefin, reversibly, to give a σ-alkyl group and activate the Pd^{II} towards oxidative addition; such nucleophiles could include RCO_2^-, CO_3^{2-}, HCO_3^-, OH^-, H_2O, Cl^-, Br^-, I^-, F^-, primary, secondary or tertiary amines, *etc.*

Similar attack on a coordinated olefin to give a σ-alkyl might be involved in the so-called 'Jeffery' conditions for effecting a Heck reaction.[12a–d] In such a reaction $Pd(OAc)_2$ and an aryl iodide or alkenyl iodide plus an olefin such as CH_2=$CHCO_2Me$ in dimethylformamide are reacted together at about 30 °C in the presence of solid sodium bicarbonate or potassium carbonate; NBu_4Cl is added as phase-transfer catalyst. No tertiary phosphine need be added. Very good yields of ArCH=$CHCO_2Me$ are obtained under these exceptionally mild conditions. It seems very unlikely indeed that Pd^0 is involved in these reactions and therefore I suggest that olefinic carbons of two Pd-coordinated methyl acrylates are attacked (stepwise) by HCO_3^- or CO_3^{2-} to give an *electron rich* palladium(II) complex **11** containing a *chelating dialkyl ligand* incorporating an organic carbonate group, *i.e.* the attack on C=C is like that of other oxygen donating nucleophiles such as acetate ion but carbonate attacks two C=C bonds. The ligands L in **11** could be solvent, CH_2=$CHCO_2Me$, Br *etc.* Because of the chelate effect, which typically can increase a stability constant by a factor of more than 1000, attack by bicarbonate/carbonate on two more coordinated CH_2=$CHCO_2Me$ ligands might give the extremely electron-rich tetra-alkyl 'ate' complex **12**. Complexes **11** or **12** then undergo oxidative addition of aryl iodide under the very mild 'Jeffery' conditions. After reversible loss of the carbonate ions the Ar migrates from Pd to the coordinated olefin (methyl acrylate) and Pd—H elimination occurs from the Pd^{IV} complex to give ArCH=$CHCO_2Me$ *etc.* Isomers of **11** or **12** could be formed depending on which olefinic carbon is attacked, whether the coordinated CH_2=$CHCO_2Me$ groups are parallel or antiparallel and which prochiral face of C=C is attacked. Bicycloheptadiene, coordinated to Pt^{II}, has been shown to undergo attack by methanol (methoxide) on *both* C=C double bonds to give a chelating dialkyl ligand coordinated to Pt^{II}.[13]



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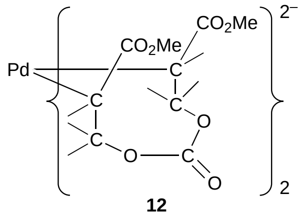

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It seems likely that some metallacycle is formed when Heck catalysts are generated *in situ* by treating $Pd(OAc)_2$ with $P(o\text{-}MeC_6H_4)_3$ or, possibly, PPh_3 and that this is sufficient to explain much of, or all of, the catalytic activity, *i.e.* the catalytic cycle involves Pd^{II}/Pd^{IV} and not Pd^0/Pd^{II}. Spencer[14] showed that a catalytic system generated *in situ* from $P(o\text{-}MeC_6H_4)_3$, $Pd(OAc)_2$, with sodium acetate, gave turnover numbers in the range 65 000–134 000 with CH_2=CHR and reactive aryl bromides.[14] One would expect the extra tertiary phosphine used for *in situ* formation of a catalyst system might slow down catalysis since it would react with a metallacycle of type **1** to block coordination sites.

I suggest the nucleophilic attack on coordinated olefins coupled with oxidative addition reactions could generate other new kinds of organometallic and catalytic reactions.

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Received 21*st November* 1997; *Paper* 7/09028E;