

Palladium catalyzed C–C and C-heteroatom bond formation reactions

Irina .P. Beletskaya

Department of Chemistry, Moscow State University, Moscow 119899, RUSSIA

Abstract: The application of palladium catalyzed reactions, such as cross-coupling, Heck arylation, carbonylation, to the preparation of various classes of organic and organoelement compounds is discussed. Special attention is given to catalytic reactions in water and aqueous solutions.

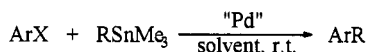
During the last two decades transition metal complex catalysts and reagents have virtually invaded the domain of organic synthesis, and provided a basis for numerous incredible achievements (ref. 1). Palladium complexes play one of the major roles in this spectacular development, as can be readily seen from numerous publications on the use of palladium catalysis in organic synthesis (ref. 2).

Zerovalent palladium catalyzes such reactions as cross-coupling with C–C and C-heteroatom bond formation, carbonylation, leading to various oxygen-containing compounds (aldehydes, ketones, carboxylic acids and their derivatives etc.), arylation and vinylation of olefins by aryl (vinyl) halides or triflates. The reactions driven by zero-valent palladium are usually described by a catalytic cycle involving the oxidative addition of Pd(0) to organic halide with the formation of organopalladium intermediate, which further may react with an organometallic compound by transmetalation, or undergo an insertion of carbon monoxide, or add to the double bond. Next, the respective intermediate either undergoes a reductive elimination in the case of cross-coupling, or β -hydride elimination as in Heck reaction, or is cleaved by a nucleophile as in carbonylation to yield the final product with the regeneration of active zero-valent palladium.

Carbon-carbon bond formation in cross-coupling reactions

The derivatives of various metals (Mg, Zn, Cu, Hg, B, Sn) (ref. 3), as well as anions including heteroatom anions were studied in cross coupling reactions with organic halides. Organotin, organomercury, and organozinc reagents were used in the reactions with acyl halides.

The reaction with organotin (the *Stille* reaction) was shown to proceed well with palladium catalysts without phosphine ligands, e.g. $\text{PdCl}_2(\text{MeCN})_2$ or $[(\eta^3\text{-allyl})\text{PdCl}]_2$, etc. Such reactions are usually much faster than the reactions catalyzed by phosphine complexes, which allows the use of simpler solvents - THF, acetone, or even benzene and ether - in place of commonly used HMPA, DMF, and DMSO. The same is valid for the reactions with acyl halides.



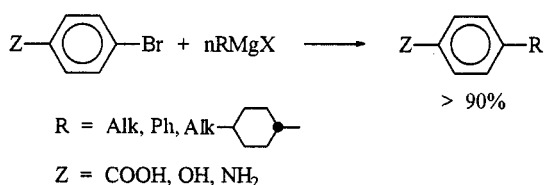
R = Ar, Het, vinyl, $\text{PhC} \equiv \text{C}$

"Pd" = Li_2PdCl_4 , $(\text{MeCN})_2\text{PdCl}_2$, $(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2$, $\text{Pd}(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3$

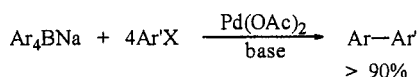
solvent = HMPA, DMSO, DMF, THF, Me_2CO

The reactions with organomercuric compounds can be highly selective in the presence of phosphine complexes of palladium and iodide-ion as nucleophilic co-catalyst. In this case both diorganomercurials R_2Hg , and monoorganomercurials are reactive. The reaction of acyl halides with hexaalkyldistannanes was applied for the synthesis of diketones.

Cross-coupling of Grignard reagents with aryl halides bearing substituents with acidic hydrogens (carboxy, hydroxy, or amino-groups) can be realized if Grignard reagent is taken in excess equivalent to the number of removable protons. Cheaper Grignard reagents like ethylmagnesium bromide can be used for proton removal. These reactions are highly selective if $\text{PdCl}_2(\text{dppf})$ is used as a catalyst.

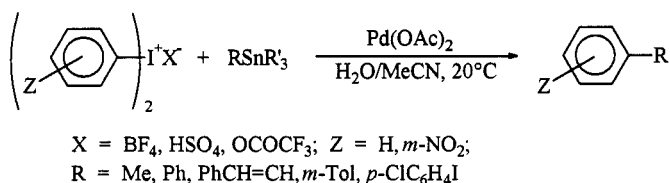


All four aryl groups are transferred to the product in the reaction with tetraarylbates in water:

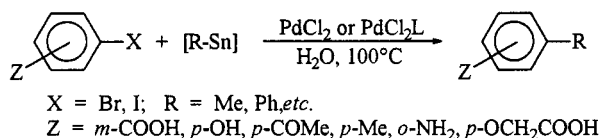


If both reagents are water soluble the reaction is very fast and shows extremely high catalytic efficiency, expressed by enormous turnover ratios, which is quite uncommon for palladium catalysis where the catalyst is almost never used in less than 0.1 mol% loads. For example, in the reaction with *m*-bromobenzoic acid the amount of catalyst PdCl_2 was reduced to 0.0004 mol% without any degradation of the almost quantitative product yield. In this case the turnover ratio was as high as 250,000. The reaction in water is so efficient, that even *p*-chlorobenzoic acids gives a high yield of the cross-coupling product. Palladium black can be used as an efficient catalyst precursor in this process with water-soluble aryl iodides. For aryl halides which are insoluble in water the reaction can be performed in aqueous DMF. It is very important to note that the addition of water to DMF is essential to achieve good yields of products. For example, in the phenylation of *p*-nitroiodobenzene catalyzed by PdCl_2 the yield is 10% in DMF, but 77% in DMF - H_2O (2:1) for the same reaction time.

If aryldiazonium, or, better, more reactive diaryliodonium salts are taken in place of aryl halides cross-coupling reaction in aqueous solutions can be realized even for organotin reagents. Note, that in aqueous solution even the chloride salt of aryldiazonium can be easily used (ref. 9).

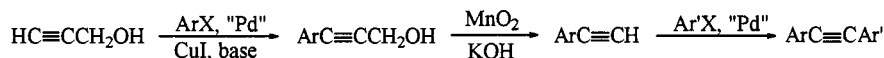


Water-soluble organotin derivatives $\text{K}_n[\text{RSn(OH)}_{3+n}]$, which are formed in situ from RSnCl_3 in aqueous alkalies turned out to readily react with even water-insoluble aryl halides in the presence of palladium chloride complex with hydrophilic monosulfonated triphenylphosphine (ref. 10). However, if the aryl halide is also water-soluble, the reaction readily proceeds with palladium chloride without any phosphine ligands.

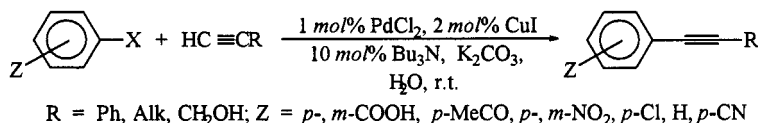


Cross-coupling reactions with terminal acetylenes

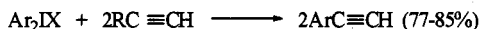
The palladium catalyzed reaction of aryl and vinyl halides with terminal acetylenes actually presents a special case of cross-coupling. This reaction takes place in the presence of bases and often requires copper(I) salts as co-catalysts. Earlier, we have used this reaction for the preparation of terminal acetylenes by arylation of propargylic alcohol with subsequent oxidation of the intermediate by manganese dioxide. By applying a second cross-coupling reaction unsymmetrical tolanes can be obtained in a *one pot* method.



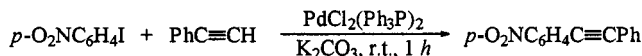
The preparation of terminal acetylenes, and two-step cross-coupling leading to unsymmetrical tolanes can be achieved in aqueous solvents or neat water in the case of water-soluble reagents by using calcium carbide as a source of both acetylene and base generated *in situ*. Various liquid crystalline materials, e.g. 4-cyano-4'-alkoxytolanes (with normal alkyls of C_3 - C_{10} series) were obtained by this approach in 86-88% yields. Terminal acetylenes are most conveniently obtained in water as solvent with 10 mol% of Bu_3N and K_2CO_3 as a base, catalyzed by $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ - CuI. In this system the reaction is very fast, and besides, the isolation of final products is markedly facilitated (ref. 11).



Aryldiazonium salts can also be used as arylating agents under such conditions.



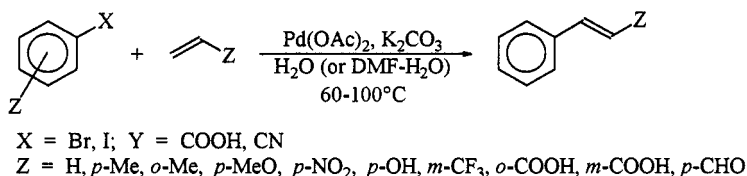
As in the case of cross-coupling with tetraarylboration, the addition of small amount of water leads to a dramatic acceleration of this reaction.



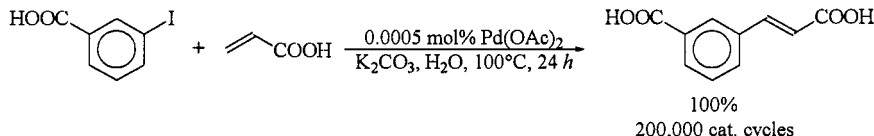
DMF - 0%; DMF - H₂O (9:1) - 98%; DMF - H₂O (1:1) - 65%

Heck reaction

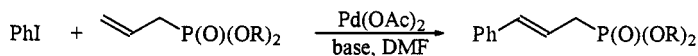
Similarly to the cross-coupling reactions of arylboronic acids and tetraphenylborates, the Heck reaction with water-soluble olefins can be performed in aqueous solvents, and water-soluble aryl halides readily react in neat water (ref. 12).



In the case when both reagents are soluble in water, a very small amount of palladium catalyst is needed to drive the reaction to completion. Very huge turnover ratios are observed.

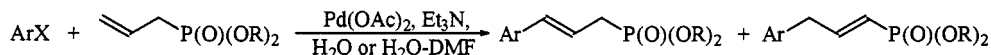


As in cross-coupling reactions, a dramatic acceleration of Heck arylation is induced by the addition of water, as can be seen from the comparison of two runs performed under otherwise identical conditions except for the presence of water. For example, for the reaction of bromobenzene with acrylic acid the yield of cinnamic acid is only 12% in DMF, but as high as 95% in DMF - H₂O (9:1). Similar trends are observed for the reactions in which both reagents are insoluble in water (ref. 13).

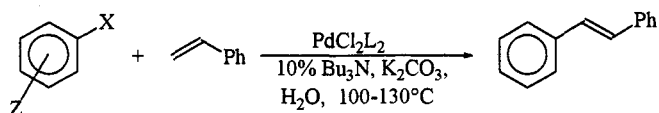


DMF - 0%; DMF-H₂O (9:1) - 91%

The use of aqueous solvents may in some cases have an effect on the selectivity. Thus, in the arylation of diethylallylphosphonate by aryl halides the reaction in water gives predominantly γ -arylallylphosphonate, while the reaction in the presence of triphenylphosphine or DMF leads to γ -arylpropenylphosphonate. DMF and Ph₃P are likely to interfere with the intramolecular coordination of palladium and phosphonate oxygen, and thus, change the site of β -hydride elimination (ref. 13).



The reactions with olefins which are insoluble in water, e.g. styrenes, are best carried out in water in the presence of 10% Bu₃N and K₂CO₃ with PdCl₂(Ph₃P)₂ as a catalyst for water-insoluble aryl halides, and Pd(OAc)₂ for water-soluble halides (ref. 14).



Diaryliodonium salts readily arylate olefins in water. In the reaction with acrylic acid both aryl groups of iodonium salt are transferred to the product, while for reaction with water-insoluble styrene only one aryl group is used.

Carbonylation of aryl halides

Carbonylation of organic halides in the presence of either an organometallic compound or another nucleophile can be formally described as a combination of three fragments $\text{R}^+ + \text{CO} + \text{R}'^-$.

In the presence of organotin, organomercuric, organoboron, or organoaluminum compounds carbonylation gives unsymmetrical ketones (ref. 3).



We have shown that the use of ligandless palladium catalyzes the carbonylation with organotin compounds under very mild conditions (1 atm CO, r.t.). Alkylmercury halides react only with aryl halides bearing electron-withdrawing substituents in the presence of iodide ions (ref. 3). This reaction may serve as a convenient alternative for Friedel-Crafts acylation, especially in the case when direct electrophilic substitution gives low yields or altogether fails. In some cases the use of organoaluminum or organoboron compounds may be advantageous.

In the presence of other nucleophiles carboxylic acid derivatives, e.g. esters or amides, may be formed.



The respective derivatives of tin, such as Bu₃SnOMe and Bu₃SnNR₂ can be used in such reactions.

Aromatic anilides can be obtained by the carbonylation of aryl halides in the presence of anilines, though anilines bearing strong electron-withdrawing substituents like nitro-group are unreactive. Similarly, in the presence of phenols aryl esters of benzoic acids are formed. Even better results were obtained with pre-formed phenolates (ref. 15).

The carbonylation in the presence of water presents a special interest. We have shown that carbonylation of various aryl iodides containing both electron-donor and electron-withdrawing substituents can be performed in strongly aqueous solvents in the presence of Pd(OAc)₂ giving the corresponding benzoic acids in high yields (ref. 16). For the carbonylation of water-insoluble aryl bromides under such conditions phosphine ligands are required. The carbonylation of water-soluble aryl iodides, e.g. *p*-iodobenzoic acid, requires very small amounts of catalyst. Turnover ratios as high as 100,000 can be easily achieved.

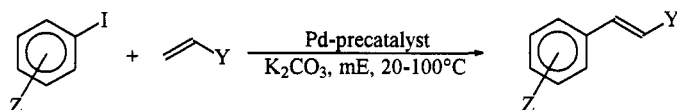
Reactions in aqueous solubilized systems

Environmental and safety gains of the replacement of organic solvents by water are obvious and indisputable. Therefore, even a mere possibility to perform palladium catalyzed and other reactions in aqueous media is fairly appealing. Though, as is clearly seen from previous discussion, water and strongly aqueous media are applicable if at least one of the reagents is hydrophilic, this restriction is not fatal. We have discovered that even the reactions with all strongly hydrophobic reagents can be successfully carried out in aqueous solubilized systems. The latter are microheterogeneous systems formed by a well-balanced compound amphiphiles capable of spontaneous dispersion of huge amounts of either hydrophobic materials in water, or water in hydrophobic liquids (ref. 17). We have shown that solubilized systems of various kinds including direct microemulsions of oil-in-water type, ideally balanced bicontinuous Winsor III systems, inverted microemulsions of water-in-oil type (Winsor II systems), and swollen micelles of nonionic surfactants near the phase inversion point can serve as versatile media for various palladium catalyzed reactions. A typical microemulsion is formed by mixing together 1.5 mmol of surfactant, 6 mmol of aliphatic alcohol with chain length of 2-6 carbon atoms, and 5 ml of water. Such microemulsion is usually capable to serve as reaction medium for 2-5 mmol loads of hydrophobic substrates.

Carbonylation of iodoarenes to benzoic acids can be easily achieved in microemulsions formed by ionic surfactants, such as sodium dodecylsulfate (SDS) and cetyltrimethylammonium bromide (CTMAB) in the presence of simple palladium salts and potassium carbonate as a base. Anionic surfactants were generally more efficient. Another approach used readily accessible nonionic surfactants, the derivatives of oligoethyleneglycol (*Brij-35*, *Igepal-CO* series, etc.). Such surfactants with long polyoxyethylene chains (35-100 units) taken in very small amounts (as low as 0.1%) are capable of bringing iodobenzene to take part in palladium catalyzed carbonylation in water (ref. 18). Surfactants with shorter polyoxyethylene chains are inefficient.

Arylation of diphenylamine (ref. 19) and cross-coupling of aryl iodides with terminal acetylenes (ref. 20) were achieved in cationic microemulsions in the presence of palladium and copper salts.

Heck arylation of olefins is very readily achieved in microemulsions of both anionic and cationic kinds.



Pd precatalyst = PdCl_2 , $\text{Pd}(\text{OAc})_2$, or Pd sol

Z = H, Cl, Me, OMe, NO_2 , COOMe, etc.; Y = Ph, COOEt, 4- $\text{C}_6\text{H}_4\text{N}$

mE = surfactant - ROH - H_2O (R = all C_2 - C_6 alkyls)

surfactant = $\text{C}_{12}\text{H}_{25}\text{OSO}_3\text{Na}$, $\text{C}_{16}\text{H}_{33}\text{SO}_3\text{K}$, $\text{C}_{16}\text{H}_{35}\text{NMe}_3\text{Br}$, $\text{C}_n\text{H}_{2n+1}\text{COOK}$ (n = 9-17)

We have noticed a strong influence of the nature of main surfactant on the yields of arylation product. Thus, anionic surfactants with sulfate and sulfonate head groups required the presence of phosphine ligands to give high yields. On the other hand the reactions in microemulsions based on cationic surfactant took place with simple palladium salts without the need to add phosphine ligands. Later it was shown that such anionic surfactants as alkali salts of fatty acids were even more efficient than cationic surfactants. Moreover, the yields were highly sensitive to the length of hydrocarbon chain, with the best results observed for long-chain carboxylates (C_{15} to C_{17}). Microheterogeneous solubilized system was shown to play a major role in preventing the deactivation of palladium by promotion of the formation of very fine palladium sol, in which palladium metal remains reactive. Palladium sol is likely to grow and stay in interface layers of the solubilized system. Further coalescence of palladium microparticles into large inactive particles is blocked by surfactant aggregates. Such systems enable one to perform reactions with very low loads of palladium, and turnover ratios of 10,000 - 50,000 and higher are common for the reactions under consideration.

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