An Advantageous Use of Palladium Compounds in Organic Synthesis

THE FORMATION OF CARBON-CARBON BONDS

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Palladium has a rich organometallic chemistry which has developed over the past twenty-five years. While palladium is not unique in its ability to carry out a wide range of carbon-carbon bond forming reactions, its versatility has resulted in an increasing effort being made towards the use of palladium reagents in organic synthesis in academic and industrial research laboratories. This will result in increased industrial applications of these compounds in the organic chemicals sector.

Most of the organic reactions which use palladium compounds involve the interconversion of palladium(II) and palladium(0), that is between the d^4 and d^0 electronic states. This occurs as the reaction sequence usually involves oxidative addition to, and reductive elimination from, the metal centre as necessary steps. Two general types of use have emerged for palladium co-ordination compounds in organic reactions. The first is in catalytic reactions where turnover numbers in excess of 100:1 substrate:palladium are achieved, and the second is as a reagent in stoichiometric reactions. The latter has arisen as a consequence of the facile decomposition of palladium(0) complexes to the metal. For products with a high added value this approach can be cost effective, in that palladium is much cheaper than platinum or rhodium, and high recoveries of palladium can be achieved. Thus the cost of the compound should be regarded as having two components: a manufacturing cost, which in effect is a running cost, and secondly an investment in palladium metal which can, to a large extent, be regarded as a capital investment. It should be noted that in a number of cases it has been possible to change what was initially a stoichiometric reaction into one which is catalytic, by the use of a co-oxidant. The classic example of this is in the Wacker process for the conversion of ethylene to acetaldehyde.

While the redox behaviour of palladium plays an important role in its relevance to organic synthesis, there are at least three other characteristics which enrich the organic chemistry of palladium.

[a] The facile rearrangement of trihapto (h') into monohapto (h') ally1 complexes, which creates co-ordinative unsaturation at the metal centre and enhances reactivity.
[b] The ability of nucleophile to attack at either metal or ligand sites selectively.
[c] The kinetic lability of palladium-carbon monoxide species which enables carbon monoxide to insert into other palladium-carbon bonds.

This article will address the organic chemistry which can be achieved using palladium complexes, and the nature of the palladium reagents or catalysts.

Palladium compounds are particularly useful for the elaboration of alkenes and alkenic compounds in a number of different ways. The generation of a variety of functional groups from vinyl halides or main group metallovinylic compounds is illustrated in Figure 1.

Arenes can be directly coupled to alkenes containing electron withdrawing groups such...
Fig. 1 Vinyl halides or main group metallovinyllic compounds may be reacted with palladium(II) or palladium(0) complexes to generate vinyllic palladium intermediates. These can undergo nucleophilic attack with cyanide or thiolate groups, for example to incorporate functionalities at the vinyllic position. Reaction with alkenes or alkynes can generate conjugated dienes or enelyne systems, and carbonyl species can be formed with carbon monoxide or acyl bromides.

that arylation occurs at the least substituted alkenic carbon. The reaction can be made catalytic by using palladium(II) acetate under an oxygen atmosphere in the presence of copper(II) acetate or silver acetate. Intramolecular attack of an arene on an alkene can be used in the formation of a fused ring system.

A variation on this theme is the coupling of aryl organometallics with organic halides (aryl or vinyllic). This route provides a means of forming 1-aryl-1-alkenes, 1-aryl-2-alkenes, \( \beta \)-haloethylarenes and \( \beta \)-arylaldehydes and ketones. It has been used in the synthesis of chiral styrenyl derivatives as shown in Figure 2 (1), and also in the synthesis of the antiestrogenic tamoxifen (2). A practical limitation to the utility of this route is the inability to obtain the desired organometallic starting material. A number of organometallics such as those of lithium, magnesium or aluminium are unable to tolerate a range of functionalities on either the organometallic or organic halides. For other base metals, such as boron, zinc or zirconium it is often not possible to synthesise the desired organometallic. The palladium...
catalysed coupling of allyl halides to vinylic or aryl organotin compounds has shown tolerance to functional groups (ester, nitrile, alcohol or aldehyde).

The catalyst used is Pd(dba)$_2$:2PPh$_3$, where dba is dibenzylideneacetone. In the absence of palladium the reaction is not regioselective, but when palladium is present the cross-coupling takes place in high yield with retention of geometry in the vinylic partner (3). When the reaction is carried out under a moderate pressure of carbon monoxide then the carbonyl insertion product is obtained.

A generally useful method of obtaining arylated alkenes is through the palladium catalysed coupling of aryl halides with alkenes. The particular advantages of this system are:

[i] The reaction normally proceeds in one step with high regioselective and stereoselective control.

[ii] The reaction occurs under mild conditions and is not affected by water or air, however if organophosphines are present an inert atmosphere should be used.

[iii] The reaction is tolerant of most functionalities.

Recently it has been shown that reasonable rates of reaction can be achieved for the arylation of non-electron deficient alkenes, for
Fig. 3 The stepwise allylic coupling of bifunctional monomers allows the construction of complex molecules because of the high regio and stereoselective control which palladium(0) complexes exert on the reaction. Thus the total synthesis of coenzyme Q10 has been achieved using tetrakis(triphenylphosphine)palladium(0) as the catalyst.
example but-3-en-2-ol using palladium acetate as a catalyst in the presence of triethylamine. The amine appears to act as a neutral ligand; it significantly enhances the rate of arylation and also inhibits the formation of palladium metal (4).

An alternative reaction which has attracted a great deal of attention is the incorporation of carbon functionalities at the allylic group through the nucleophilic attack of carbanions on allylic acetates.

This reaction was initially established for relatively simple molecules, but the extremely high regioselective and stereoselective yields which have been achieved has meant that the reaction can be applied sequentially to the synthesis of complex molecules, such as ubiquinone 10 or coenzyme Q10, as illustrated in Figure 3 (5). Variations in this reaction have made it possible to synthesise juvenile hormone (6), and carbonylation at the allylic position has been used in the preparation of manoalide, Figure 4 (7).

**High Selectivity to the Larger Ring Size**

Trost, who pioneered the early work on allylic alkylation with Moritani, has applied the procedure to annulation reactions (8). An important feature of the palladium catalysed reaction is that ring closure normally results in high selectivity to the larger ring size, whereas other cyclisation procedures favour the formation of the most stable ring size. Furthermore this procedure is particularly useful for the construction of odd numbered rings, such as (i), and this can be avoided by the use of a palladium(0) catalyst which is attached to a macroreticular polymer support containing organophosphine functionalities. Using this system it has been possible to construct a 26 membered macrolide ring (ii), which has antifungal and antibiotic properties.

![Diagram](ii)

It is also possible to bring about ring closure using oxygen or nitrogen nucleophiles rather than carbon. Isomerisation of an amine nucleophile catalysed by a palladium(0)-bis(diphenylphosphino)butane complex has been used to bring about cyclisation in the synthesis of inandenin-12-one, a spermidine alkaloid (iii).

![Diagram](iii)

The formation of heterocycles by the use of palladium reagents, typically palladium acetate in acetic acid, is related in some respects to macrocycle synthesis (9). Some illustrations of this are given in Figure 6, where amine and oxo groups can be incorporated, as well as carbonyl or amide functions. It is also possible to convert diphenylamine or diphenylether to the corresponding carbazole or oxazole species. These types of bond forming reactions are relevant to the formation of the mitomycin skeleton (iv) where these compounds are used as antibiotics or anticancer agents. Recently lysergic acid...
For this step in a synthesis of manoalide, a bis(dibenzylideneacetone)palladium triphenylphosphine catalyst is used, and the reaction proceeds under carbon monoxide at a pressure of 3 bars. Carbon monoxide inserts into the allyl-chloride bond and the acyl group couples to the cyclopentadienyl moiety with the elimination of tributyltin-chloride.

The coupling of molecules with leaving groups such as acetate or trimethylsilyl (TMS) at the allylic position with mono, di or trienes permits the formation of 5, 7 or 9 membered rings via [2 + 3], [4 + 3] or [6 + 3] cycloadditions. Odd membered rings are not readily accessible by other routes.

The palladium assisted intramolecular nucleophilic attack of a heteroatom at an alkenic carbon atom permits the formation of heterocycles such as indoles, quinolines and furans.
a pharmacologically active ergot alkaloid has been prepared through the intermediate (v), (10).

Having described the types of reaction that are possible using palladium reagents, it is worth considering the nature of these reagents. Palladium(II) chloride has limited value as a reagent due to its lack of solubility: it is very slightly soluble in water and most organics, but soluble in N,N-dimethyl formamide and hydrochloric acid. As a relatively simple salt, palladium acetate provides an attractive alternative in that it does not possess chloride ions which can cause problems of poisoning and corrosion. In addition it does have a significant solubility in organic solvents such as toluene, acetic acid and alcohols.

Nitrile complexes such as trans-bis(benzonitrile)dichloropalladium(II) or trans-bis(acetonitrile)dichloropalladium(II) are soluble in many organic solvents and provide convenient precursors to species of the type [PdCl₂L₂], where L is an organophosphine. Thus trans-bis(triphenylphosphine)dichloropalladium(II), which is commercially available, has found widespread use as a catalyst or reagent, principally because of the wide availability of triphenylphosphine, which has popularised its use as a ligand in combination with a platinum group metal compound. However, the judicious choice of other phosphanes or diphosphanes can lead to significant improvements in selectivity.

Advantages of in situ Catalyst Preparation

The other class of palladium compounds which are widely employed are those of palladium(0) as exemplified, in particular, by tetrakis(triphenylphosphine)palladium(0). A drawback to the use of this compound is that it is sensitive to air, and also to heat and light, both in solution and in the solid state. Consequently some decomposition can occur on storage, and adequate precautions must be taken if the preformed complex is used. However, it is possible to prepare the complex in situ, one method for this being the reduction of trans-bis(triphenylphosphine)dichloropalladium(II) using hydration or a basic alcoholic media in the presence of excess triphenylphosphine, although yields of the palladium(0) product are rarely quantitative. A more convenient precursor is tris(dibenzylideneacetone)dipalladium(0), Pd₂(dba)₃L (L = dba or solvate). This compound is stable in the solid state and yet in solution the dibenzylideneacetone ligand is labile and is readily displaced by phosphanes to give [PdLₙ] species (L = phosphane, n = 2-4).

A further feature of this chemistry which has not been utilised to date is that it is possible to modify the solubility of the tris(dibenzylideneacetone)dipalladium(0) by placing substituents on the arene fragment of the ligand.

If an in situ method of catalyst preparation is used then adequate time must be allowed for the desired compound to preform, prior to carrying out the organic transformation. An additional benefit of the in situ method is that it is generally possible to screen a number of catalysts in a cost effective manner, in order to optimise a specific reaction.

Summary and Conclusions

This article has dealt mainly with the formation of carbon-carbon bonds and has excluded other important palladium catalysed reactions such as oxidation and carbonylation for which an extensive literature exists. The regiospecific and stereospecific control which can be exerted in palladium-mediated reactions is impressive, and will undoubtedly result in more industrial applications of palladium in the synthesis of complex organic molecules. It is also anticipated that there will be greater opportunity to use palladium reagents in the synthesis of chiral molecules.
References
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Palladium as an Aid in Trace Analysis of Food

Palladium has become established as one of the most widely applicable chemical modifiers in electrothermal atomic absorption spectrophotometry (ETAAS). Its applications have recently been extended to the determination of lead, cadmium and tin in food slurries.

In ETAAS a volume of sample is introduced into a small furnace—usually a graphite tube—and heated in stages to remove the solvent, decompose the sample matrix and finally produce a cloud of atoms in the central zone of the furnace. These atoms absorb light selectively, permitting the ultra-trace determination of metals. Chemical modifiers are added to the sample solution to avoid the loss of the elements of interest during the decomposition stage.

Palladium appears to act by forming compounds, for example Pb,Pd, which are more thermally stable than the base metal alone.

A recent report from the University of Strathclyde, Glasgow, describes the extension of this work to the determination of lead in slurries of freeze-dried foodstuffs (S. Lynch and D. Littlejohn, “Palladium as a Chemical Modifier for the Determination of Lead in Food Slurries by Electrothermal Atomisation Atomic Adsorption Spectrometry”, J. Anal. At. Spectrom., 1989, 4, (2), 157–161). Detection limits of 200 ng/g have been reported. Promising results have also been obtained for cadmium and tin. Palladium appears to have considerable potential in this area.

Plasma-Enhanced Vapour Deposition of Thin Rhodium Films

Thin films of platinum and of palladium have been prepared successfully by plasma-enhanced chemical vapour deposition, and now the use of this method for the formation of thin rhodium films has been reported (A. Etspieler and H. Suhr, “Deposition of Thin Rhodium Films by Plasma-Enhanced Chemical Vapor Deposition”, Appl. Phys. A., 1989, 48, (4), 373–375).

Dicarbonyl-2,4-pentadionato-rhodium(I) was vapourised from a vessel whose temperature could be changed to achieve the required vapour pressure of the organometallic compound and was then carried into the reaction vessel, through the upper electrode, by a flow of argon or a mixture of argon and hydrogen. The rate of deposition and the properties of the rhodium film depend upon a number of parameters including the temperature of the source, the temperature of the substrate, the partial pressure of the organometallic, and the hydrogen content of the carrier gas.

It was found that a source temperature of 50°C gave the best results; increasing the substrate temperature from 30°C to 150°C increased the rhodium content of the deposit from 86 to 96 per cent and lowered its resistivity by a factor of four. Hydrogen in the carrier gas also resulted in a further increase in the rhodium content of the film. The lowest resistivity value determined for these thin rhodium films was 23μΩcm, compared to 4.5μΩcm for pure bulk rhodium at a temperature of 20°C.

Plasma-enhanced chemical vapour deposition using organometallic is thus a suitable technique for preparing rhodium thin films, especially on three-dimensional and temperature sensitive substrates.