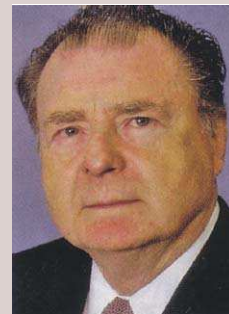# Cobalt and Palladium Reagents in Organic Synthesis: The Beginning

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A Retrospective

Abstract: A personal account of the discovery and initial development of organocobalt and organopalladium chemistry. R. F. Heck, Professor Emeritus, University of Delaware, Newark DE, USA.

In 1956, after completing my graduate training and post-doctoral work in physical organic chemistry, I entered the employment of the Hercules Powder Co. (now Hercules, Inc.) at their research center in Wilmington, Delaware. I joined a group of chemists working on the development of a commercial process for producing polyethylene and polypropylene employing the recently discovered Ziegler–Natta catalysts. This work required me to learn the literature on transition-metal chemistry and to do laboratory work with air-sensitive and unstable organometallic compounds. While I accomplished little of scientific value in the two years that I was in this program, the experience prepared me for my next assignment. The next project I was given by my supervisor, Dr. David Breslow, was a rather unusual one. He said, "Do something with transition metals." I had the opportunity to choose a project that I thought would benefit the company.

At this time, 1958, organotransition-metal chemistry was just beginning. Only a few cyclopentadienyl, alkyl, and carbonyl complexes of the metals were known and very little chemistry had been done with these compounds. There were several important commercial processes being used at that time, however, which employed transition metals as catalysts. All of these had been discovered by empirical methods and nothing was known about the chemistry involved. I decided to begin my new project by trying to determine the mechanism of one of these important reactions in the hope that this knowledge would suggest new chemistry to study.

The commercial process I chose to study was the hydroformylation reaction, which was also known as the Oxo reaction in Germany where it had been discovered by Otto Roelen in 1938.[1] The reaction involved a cobalt-catalyzed combination of carbon monoxide and hydrogen with an alkene at elevated temperature (~120 °C) and pressures (~800–1000 psi) to form aldehydes. For example, 1-hexene in the reaction produced a mixture of about 70%

heptanal and 30% 2-methylhexanal in high yields. The catalyst for the reaction was generally added as cobalt oxide, carbonate, acetate or similar compounds. It was known that the cobalt compounds were converted into the well-known dicobalt octacarbonyl under the reaction conditions. Studies carried out by Professor Walter Hieber of the Technische Hochschule in Munich at about this time also suggested that the very unstable (at room temperature and atmospheric pressure) cobalt hydrocarbonyl, $HCo(CO)_4$, would be present in the catalytic reaction as well.[4]

A brief report appeared in the literature in 1953 by a research group under Irving Wender[2] at the U.S. Government Bureau of Mines Labs in Pittsburgh, which suggested that cobalt hydrocarbonyl was the actual catalyst in the hydroformylation reaction. Since the decomposition of $HCo(CO)_4$ was probably second order in cobalt, reactions of the compound could be studied at 25 °C in dilute solution if they were relatively fast. The Wender group added 1-hexene dropwise to an excess of a solution of $HCo(CO)_4$ at room temperature and found the same 70:30 mixture of heptanal and 2-methylhexanal as was obtained catalytically. They did not offer a reasonable explanation for their results. During my previous work with transition-metal-catalyzed alkene polymerization, there was the idea by some that transition-metal hydrides might be involved as initiators of polymer formation by first undergoing addition to the alkenes to form alkyl transition metal complexes presumably bonded also to aluminum chloride or other metal halides employed as catalyst components. This step would then be followed by insertion of multiple alkene units to form long-chain metal alkyls, which ultimately eliminate polyalkene and reformed the metal hydride catalyst. There was no experimental evidence to support this idea at that time but it was known that some non-transition hydrides, such as those of boron and aluminum, would add to alkenes.

This proposal led me to believe that the hydroformylation probably also began with a hydride addition of $HCo(CO)_4$ to the alkene presumably in both possible directions to explain the formation of two isomeric aldehydes in the reaction. The next step was not obvious at the time. As it happened, I had noticed a paper by a group working at the Ethyl Corporation on some hydrocarbon-soluble manganese carbonyl derivatives, probably made to test as antiknock agents. The group, Coffield, Koziekowski and Closson,[3] for reasons not given, placed methylmanganese

pentacarbonyl in solution in an autoclave, pressured it up with carbon monoxide, shook it for a while and isolated the product. The product turned out to be acetylmanganesepentacarbonyl (Equation 1).

$$Me-Mn(CO)_5 \xrightarrow{\;CO\;} Me\overset{O}{\underset{}{\|}}\!\!-\!\!Mn(CO)_5$$
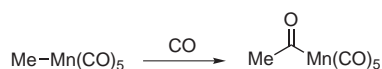
Equation 1

To my knowledge, this was the first recognized carbon monoxide insertion reaction. Of course, its generality was not known or even suggested at this time. It appeared to me, however, as the probable next step in the hydroformylation reaction, presuming cobalt would react as manganese did. If this were the case, then all that would be needed to complete a reasonable mechanism for the hydroformylation reaction would be a reduction of the acyl–cobalt bond by either hydrogen or the other potential reductant known to be present, $HCo(CO)_4$. Thus, the following mechanism was formulated with two possible final steps (shown with only one of the two isomers expected, Scheme 1).
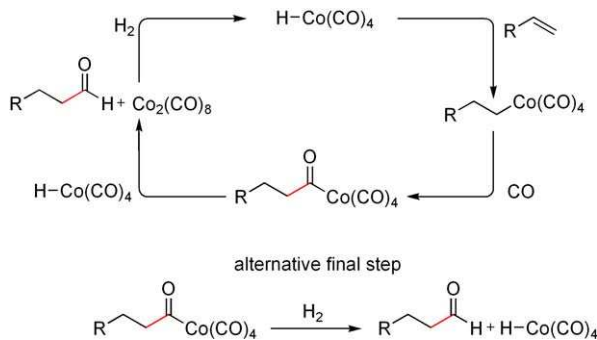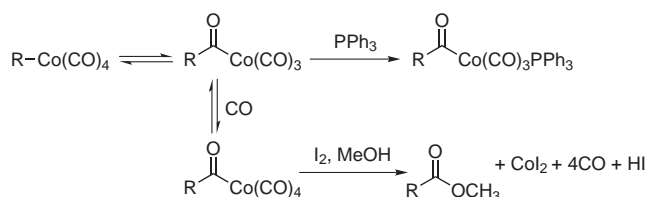
Scheme 1

My next move was to show that the proposed steps would actually occur as shown with isolated, pure, cobalt carbonyl derivatives at low temperatures where they were stable enough to be isolated and identified.

Fortunately, at about this time, Walter Hieber had just reported the preparation of the very unstable methyl cobalttetracarbonyl.[4] The compound was prepared by the reaction of sodium cobalttetracarbonyl with methyl iodide. The yellow-orange compound was not only very readily oxidized by air, but in the pure state, it decomposed rapidly well below 0 °C. Hieber established the formula of the compound but did no further chemistry with it or any other cobalt alkyls.

I prepared methyl cobalttetracarbonyl as Hieber reported and found that it reacted rapidly with carbon monoxide even at 0 °C and one atmosphere to form acetyl cobalttetracarbonyl as predicted by analogy with the manganese reaction. Another important discovery was that the commonly employed ligand, triphenylphosphine, would react easily with alkyl and acyl cobalttetracarbonyls to give

much more stable (though still oxidizable in air) and less soluble monophosphine derivatives. This allowed me to isolate and characterize organocobalt complexes more easily. The alkyl cobalttetracarbonyls turned out to react with triphenylphosphine to form acyl cobalttricarbonyltriphenylphosphine complexes as products and the acyl cobalttricarbonyltetracarbonyls gave the same products with loss of carbon monoxide (Scheme 2). The kinetics of the PPh_3 reaction with acyl cobalttetracarbonyls were subsequently studied and found to be first order in the cobalt compound but zero order in PPh_3, indicating that the loss of a coordinated carbonyl group from the acyl cobalttetracarbonyl is the rate-determining step. Thus, a 16-electron acyl cobalttricarbonyl species is an intermediate in the PPh_3 reaction and probably in the CO reaction as well.
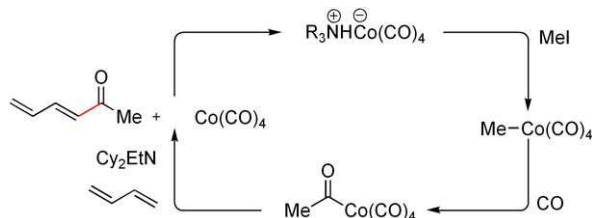
Scheme 2

When a solution of $HCo(CO)_4$ was allowed to react at 0 °C with a large excess of 1-pentene for 15 minutes and an excess of triphenylphosphine was added, evaporation of the solution left a yellow solid whose spectrum indicated that it was a mixture of alkyl cobalttricarbonyltriphenylphosphines. Cleavage of the products with iodine in methanol gave a solution containing roughly equal amounts of methyl hexanoate and methyl 2-methylpentanoate, demonstrating that $HCo(CO)_4$ adds rapidly to alkenes. This was the first experimental proof of this reaction. The rapid reduction of acyl cobalttetracarbonyls with cobalt hydrocarbonyl and with hydrogen at above 500 psi at room temperature was also found to occur, providing evidence for the proposed mechanism (Scheme 2).

The next task was to use this information to find profitable applications of this new chemistry. My approach was to see what else, besides hydrogen and $HCo(CO)_4$, the acyl and alkyl cobaltcarbonyls would react with.

Ethylene reacted rapidly with acetyl cobalttetracarbonyl at 0 °C and one atmosphere but a non-stoichiometric amount was absorbed, as I recall about 2.5 moles of ethylene were taken up per mole of acetyl cobalttetracarbonyl. The IR spectrum of the reaction mixture showed several new carbonyl absorptions. I did not pursue this apparently complex reaction further, since, in the meantime, I had discovered, while exploring the chemistry of the alkyl cobaltcarbonyls, that 1,3-butadiene reacted selectively with the acetyl cobalttetracarbonyl to give a single product, π-1-acetylmethylallyl cobalttricarbonyl.[5]

This reaction turned out to be very general and nearly all conjugated dienes and alkyl or acyl cobalttetracarbonyls would undergo the reaction. It was then found that the organic ligand could be eliminated by reacting the com-

plexes with a tertiary amine under carbon monoxide at room temperature. Furthermore, the reaction became catalytic in cobalttetracarbonyl anion with a stoichiometric amount of a tertiary amine. Dicyclohexylethylamine was used to avoid any possible coordination of the amine with cobalt intermediates. Thus, acyl chlorides or alkyl halides and CO reacted with conjugated dienes in the presence of a few mol% of the cobalt carbonyl anion and a stoichiometric quantity of the tertiary amine to form dienones in good yields (Scheme 3).[6]
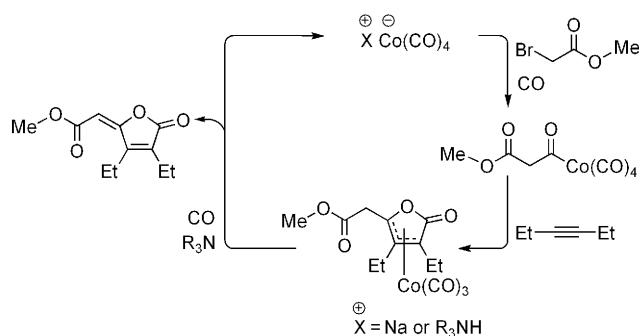

Scheme 3

Similarly, it was found that acyl cobalttetracarbonyls would add to alkynes at 25 °C or less to form 1,2-adducts which immediately cyclized by way of a 1-acyl-2-tricarbonylcobaltacyl intermediate, ultimately forming a π-allylic cobalt tricarbonyl complex of a γ-lactone (Scheme 4).[7]
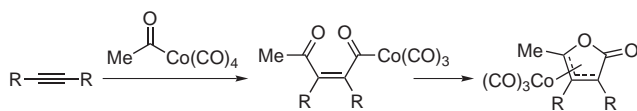

Scheme 4

In an analogous reaction using methyl bromoacetate and CO, 3-hexyne underwent reaction with NaCo(CO)$_4$ and dicyclohexylethylamine, but the expected γ-lactone-cobalt intermediate underwent base-catalyzed elimination of HCo(CO)$_4$ to form a γ-dienolactone as a major product (Scheme 5).[6]

Scheme 5

A similar addition reaction was found with α,β-unsaturated carbonyl compounds to give 1-acyloxy-π-allylic cobalt complexes and CO (Equation 2).[8]
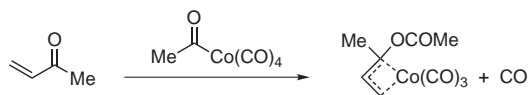

Equation 2

In spite of the discovery of the above chemistry, I had no immediate ideas on how to employ it profitably for Hercules. Therefore, my research then took a new direction.

In the laboratory across the hall from me at Hercules worked another chemist, named Pat Henry. He had been studying the mechanism of the commercially important "Wacker Process", the palladium chloride catalyzed oxidation of ethylene with oxygen (air) to acetaldehyde.[9]

One step of his mechanism interested me, particularly. In this step, Pat proposed that an intermediate β-hydroxyethylpalladium chloride species decomposed by the elimination of dichloropalladium hydride anion (Cl$_2$PdH$^-$) forming acetaldehyde. There was the widespread belief at this time that transition-metal–carbon bonds were quite weak and easily decomposed by homolytic cleavage. This belief arose because attempts to prepare compounds such as dimethylpalladium, dimethylnickel, methylcobalt or trimethyliron all failed. Henry's proposal of the decomposition occurring by a β-hydrogen elimination raised the doubt in my mind that maybe the metal–carbon bond wasn't so weak but that decomposition may occur preferably by other mechanisms. I decided to try an experiment to see what would happen if an organopalladium compound without β-hydrogens was prepared in the presence of something else – perhaps it could react with something other than another group on the metal. The first experiment I tried was to add phenylmercuric acetate to a stirred solution of lithium tetrachloropalladate in acetonitrile at 0 °C under an atmosphere of ethylene. An immediate reaction occurred. Palladium metal precipitated and ethylene gas was rapidly absorbed (about one mole per mole of palladium). Analysis of the reaction mixture showed that about an 80% yield of styrene and 10% of *trans*-stilbene had been formed (Scheme 6)!
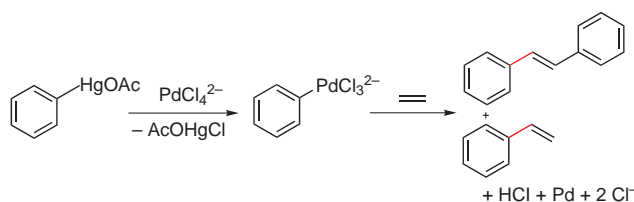

Scheme 6

This was a very exciting result! A new method of carbon–carbon bond formation under very mild conditions had been found. Further study showed the reaction to be very general and tolerant of all important functional groups.[10] Unfortunately, there were obvious problems that would keep the reaction from ever becoming generally useful. While a wide variety of arylmercurials with nearly all functional groups could be made by direct electrophilic

mercuration and used successfully stoichiometrically, this reaction was not only expensive, but the use of highly toxic mercurials was a severe deterrent. We found that aryltin compounds could also be used, but most substituted derivatives were not readily available. The need for a stoichiometric amount of a palladium salt was also prohibitive. A solution to the problem was suggested by a literature report.[11]

This report, and subsequent ones, showed that air-stable arylpalladium-bistriphenylphosphine halides could be prepared by warming tetrakistriphenylphosphinepalladium(0) with iodobenzene, bromobenzenes or even chlorobenzenes (Equation 3).
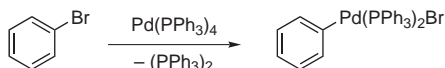
Equation 3

The next question was, would finely divided palladium metal do the same and give the reactant needed for reaction with alkenes? While separately prepared palladium powder did work with iodobenzene, it was found more convenient to simply add a palladium(II) salt, which was reduced by the excess alkene in the reaction mixture. The reaction went poorly, however, until it was found that addition of a base such as triethylamine in a stoichiometric amount gave a high yield of the expected product, catalytically in palladium.[12] This catalytic form of the reaction is shown in Scheme 7.
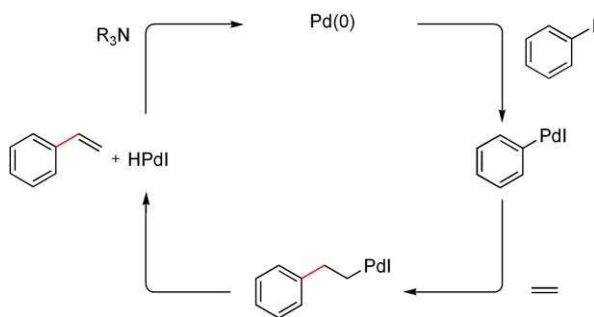
Scheme 7

This reaction was discovered independently in Japan at about the same time by Mizoroki;[13] however, he did not appear to appreciate the significance of it since he did not report any further work on it. We looked at several examples of the reaction but soon found, as Mizoroki apparently had as well, that the reaction was mainly limited to aryl iodides. Since it was known, as noted in Equation 3, that tetrakistriphenylphosphinepalladium would react with bromobenzene to give the phenylpalladiumbistriphenylphosphine bromide, a solution to getting bromobenzene to react well could be to simply add triphenylphosphine to the reaction mixture. Indeed, this worked such that many aryl bromides reacted, catalytically, with a variety of mono- and disubstituted alkenes.

However, it was soon found that aryl bromides with strongly electron-donating substituents such as *p*-bromophenol reacted very poorly.

After considerable study, we found that the problem was due to aryl bromides having strongly electron-donating substituents undergoing a palladium-catalyzed quaternerization reaction with the triphenylphosphine ligands. This ultimately removed the triphenylphosphine ligands from the metal and palladium metal alone did not react well with the aryl bromide under these conditions.

We soon found a solution to this problem. We needed only to substitute tri-*o*-tolylphosphine (or other *o*-substituted triarylphosphines) for the triphenylphosphine to prevent the migration of the aryl group on palladium to an unhindered arylphosphine ligand and stopping the reaction. We were thus able to get a wide variety of aryl and vinyl iodides and bromides to react with any mono- or di- and even some trisubstituted alkenes normally. Aryl chlorides, however, generally reacted poorly or not at all. Still, the reaction has proved to be very convenient and useful for preparing a wide variety of aryl alkenes and dienes.[14] Recently, Fu[15] found it was possible to get arylchlorides to react well by the use of the more basic phosphines, tri-*tert*-butylphosphine as a ligand.

The reaction occurs to add the vinyl or aryl group from the bromide or iodide exclusively, or at least mainly, to the less substituted (hindered) carbon of the double bond. The only known exception occurs with unsubstituted vinyl alkyl ethers or amides where the reverse direction of addition is favored.

The catalyzed addition of aryl bromides to *cis*- and *trans*-alkenes is stereospecific. The major products formed are explainable on the basis of a mechanism involving a *syn*-addition of the aryl palladium bromide followed by a *syn*-elimination of the hydrido-palladium bromide.[16]

Vinyl halide additions to mono-, di- or trienes provide convenient routes to conjugated polyenes. Cyclic products are formed if a vinyl bromide group can form a five- or six-membered ring by reacting with an appropriately placed double bond in the same molecule. In cases where conjugated diene-palladium hydrido-halide π-complexes are formed as intermediate species, π-allylic palladium products are formed. These are stable up to at least 100 °C and must be decomposed by using a nucleophilic secondary amine rather than triethylamine as the base, in which case allylic amine products are formed catalytically (Scheme 8).[14,]
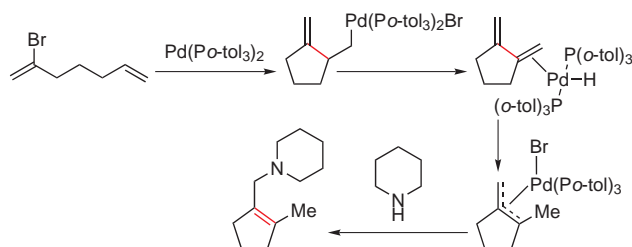

Scheme 8

Terminal alkynes, also, were found to react with aryl and vinyl halides using a palladium triarylphosphine catalyst to form aryl or vinyl alkynes (Scheme 9).[17,]
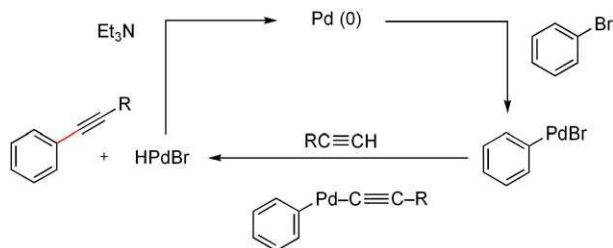
Scheme 9

The same reaction was found by Luigi Cassar at about the same time.[18] Subsequently, Sonogashira fount that copper salts catalyzed some of these reactions.[19] I then turned my attention to another palladium-catalyzed reaction. Many examples of the dimerization of 1,3-butadiene to a mixture of isomeric octatrienes by numerous palladium complexes were known, but I was more interested in reports by two independent groups that the dimerization reaction led to a mixture of 1,6- and 1,7-octadienes by employing a π-allylic palladium acetate dimer catalyst combined with a triarylphosphine, formic acid and triethylamine.[20,21] Two things interested me about this reaction. Could isoprene be dimerized selectively to a natural product structure with use of the proper phosphine co-catalyst, and what else could be reduced besides the central double bond in octatriene with this catalyst system?

We found that, indeed, isoprene could be dimerized catalytically in about 80% yield to a mixture of 3,7-dimethyl-1,6- and -1,7-octadienes, monoterpene-type structures employing tri-*o*-tolylphosphine in the catalyst (Equation 4).[22]
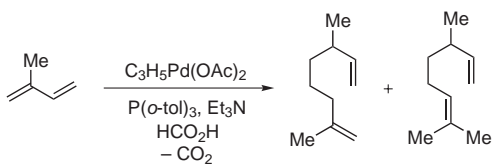

Equation 4

Unfortunately, even an 80% yield does not compete with Mother Nature because of the problem of separating 20% of other dimethyloctadiene isomers, also formed.

We then turned our attention to the use of the catalyst system as a hydrogenation catalyst. We soon found that nearly any palladium compound or even palladium on carbon would catalyze reductions with formic acid and triethylamine. In fact, we were able to catalytically reduce just about anything with HCO_2H/Et_3N that could be reduced with low-pressure hydrogen (<~2 atm) and the same catalyst. Thus, *o*-bromonitrobenzene was reduced

with one molar equivalent of 98%, commercially available, formic acid in triethylamine solution with a palladium on carbon catalyst to nitrobenzene selectively, while with three equivalents of formic acid and a platinum on carbon catalyst the nitro group was reduced selectively (Scheme 10).[23]
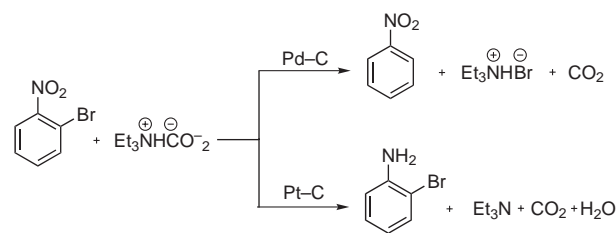
Scheme 10

Similarly, α,β-double bonds to carbonyl groups were reduced selectively in the presence of other unsaturation.

More useful was the finding that triple bonds could be easily reduced to *cis*-double bonds in high yield, employing normal, commercially available palladium on carbon as catalyst (Equation 5).[24]
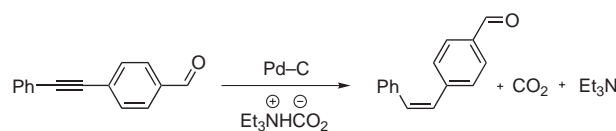
Equation 5

Apparently, the triethylammonium formate is stable in the presence of the catalyst unless there is a reducible material present, since quantitative reductions occur with all of the formic acid added.

Carbonyl groups directly bound to aromatic rings were also reduced by $HCO_2^-Et_3NH^+$ analogously to the reduction with hydrogen gas.

The formic acid–amine reducing system has two major advantages over hydrogen gas reduction. Most importantly, it is safer because with air, flammable and explosive hydrogen is not involved. No free hydrogen (or carbon monoxide) is produced in the formic acid reductions. Only carbon dioxide is evolved. Secondly, quantitative, partial reductions are very easy to carry out simply by adding the calculated amount of 98% liquid formic acid to the amine, the catalyst, and the substance to be reduced. The reaction is complete when CO_2 evolution ceases. This procedure avoids the necessity of removing the hydrogen gas as soon as the partial reduction is complete to prevent over-reduction. Of course, there is no need to control temperature carefully either (usually) to correct for the vapor pressure of the solvent.

This completes a brief summary of the most important results I obtained during more than 32 years of research. Recent reviews on palladium-catalyzed reactions are available.[25a,b]

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