Reviews

The use of palladium complexes in highly selective multistep organic synthesis*

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Palladium complexes are versatile catalysts for the selective construction of organic molecules. The use of a model system containing a norbornyl—palladium bond stable toward β-hydrogen elimination allows the formation of a variety of molecules. Carbon monoxide is a particularly advantageous building block in these multistep reactions, because it helps to induce the formation of various types of carbon—carbon bonds. Some palladium-catalyzed multistep reactions, which proceed in sequence and have a common initial step, *i.e.*, oxidative addition, are described.

Key words: palladium catalysis; multistep reactions; formation of C—C bonds; carbon monoxide.

The achievement of metal-catalyzed multistep organic syntheses is one of the main goals pursued in our studies. The principle that is followed in based on the stepwise construction of an organic molecule through coordination of small molecules around a metal center and their consecutive transformations. The metal—carbon bond formed initially determines the choice of the next partner, which, in its turn, after association and reaction, determines the incorporation of new molecules or groups, and the process goes on until the metal is expelled. However, to achieve this objective, it is necessary to use substrates and ligands that do not readily undergo elimination when they become bonded to the metal. It is well known,[1] for example, that β-hydrogen elimination often occurs from alkyl—metal bonds. Therefore, it has been necessary for our study to find an initial process meeting the condition of stability toward reductive elimination. The model system chosen, which is based on the reaction of norbornene, an organic halide RX, and palladium(0), satisfies the above-mentioned requirement.[2]

As shown in Scheme 1 (non-reacting ligands are omitted for clarity), the reaction consists of the oxidative addition of the organic halide to Pd^0 followed by coordination and insertion of norbornene, which leads to a *cis,exo* adduct. This means that both the Pd and the R groups are located on the same side of the bridge of the norbornyl unit. These compounds are rather resistant to β-H elimination.[3] Their stability is due to the fact that they do not possess any β-hydrogen *cis* to palladium that could be readily eliminated. In fact, reactions of this type proceed according to the well known Heck mechanism[4] and consist of two steps: *cis* addition of the

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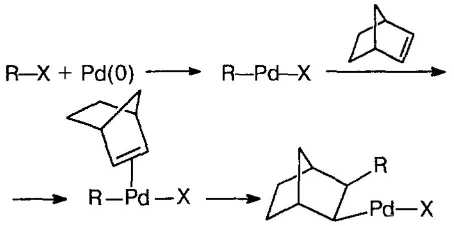
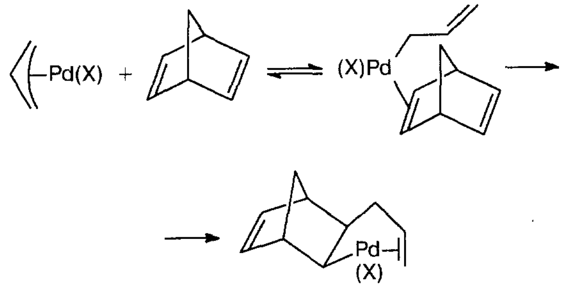
Scheme 1



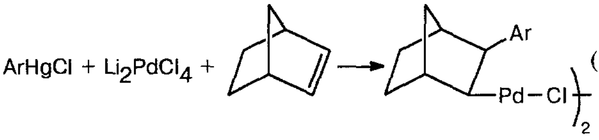
organopalladium species to the double bond and *cis* elimination of the hydridopalladium complex to give the substituted olefin. In this case, the rigid *trans* configuration of the β-H and Pd atoms hampers the elimination of hydridopalladium halide.

Several complexes of this type are known. Representative examples are shown in Eqs. (1),[5] (2),[6] (3),[7] and (4).[8]

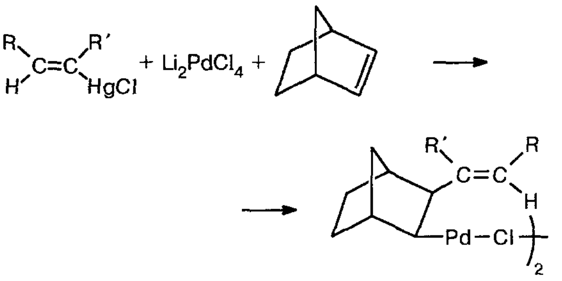


(1)

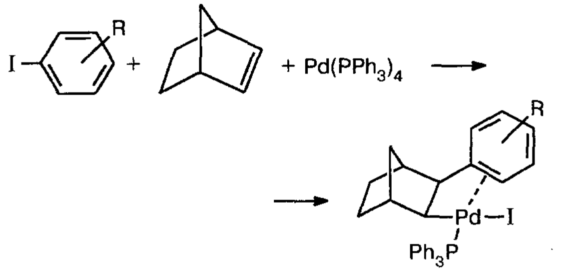
X is hexafluoroacetylacetonate



(2)



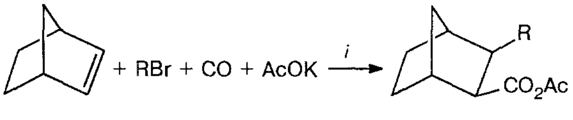
(3)



(4)

Though these compounds are stable toward β-H elimination, they readily undergo other reactions, particularly coupling and insertion reactions depending on the conditions and the ligands and substrates present in the reaction mixture. Further transformations of these complexes are multistep processes that can follow various pathways.

The reactions of organic bromides such as styryl, aryl, or benzyl bromides with norbornene in the presence of an alkali metal carboxylate and $Pd(PPh_3)_4$ as the catalyst, under an atmospheric pressure of carbon monoxide, and in anisole as the solvent gave the corresponding anhydrides (Eq. 5).[9]

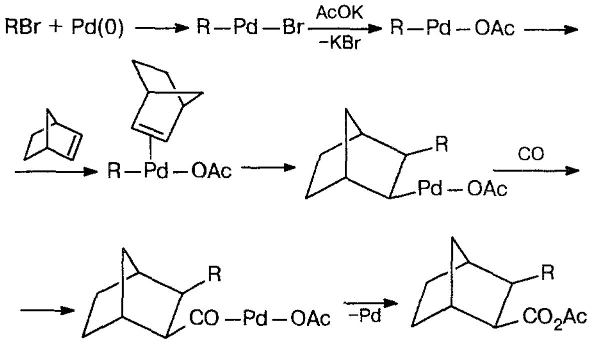


(5)

i. 0.5 % $Pd(PPh_3)_4$, 80 °C, 8 h, anisole

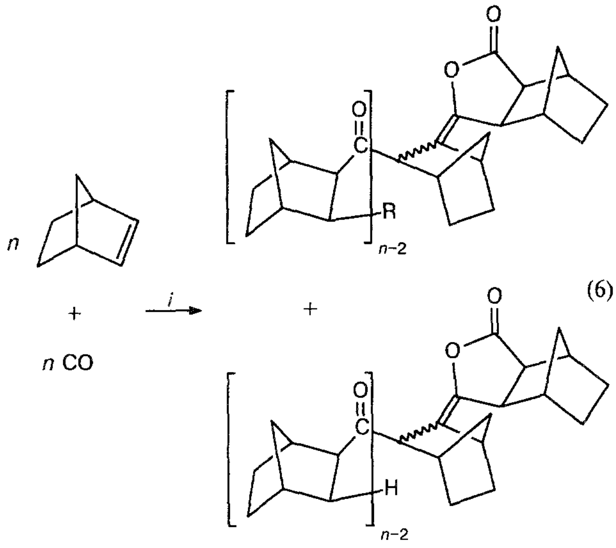
The catalytic cycle involves the steps that are shown in Scheme 2 in a simplified way.

Scheme 2



Once the norbornyl—palladium bond is formed according to the previously described pathway (Scheme 1), coordination and insertion of CO occur, and the resulting acyl palladium intermediate undergoes nucleophilic attack by the carboxylate anion and the corresponding mixed anhydride is formed. Since it is known that bromides can exchange with acetates, we assume that at a certain point of the process, the acetate group becomes coordinated to the metal. However, direct nucleophilic attack by the carboxylate anion at the acyl group also cannot be ruled out. The important role played by the carboxylate anion in closing the catalytic cycle is confirmed by the fact that in the absence of a carboxylate anion, this reaction follows a completely different course leading to a norbornene-CO copolymer (Eq. (6)).[10]

This time the acyl palladium intermediate does not undergo nucleophilic attack by the carboxylate anion, and another molecule of norbornene can be inserted to



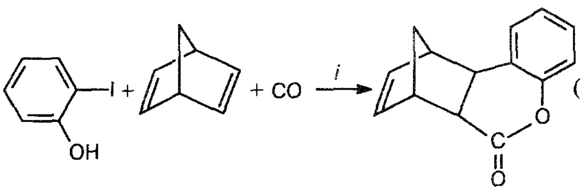
(6)

i. $R\cdot Pd\cdot X$, Na_2CO_3, 80 °C, anisole

afford a norbornyl palladium species, which again inserts CO. The reaction proceeds further with alternating insertions of norbornene and CO to give a polyketone with *cis,exo* substituted norbornane units. Termination occurs when an exocyclic unsaturated lactone forms through the interaction between the final inserted CO molecule and the previous one. A palladium hydride species is also formed, which can start a new catalytic cycle leading to a series of hydride-initiated copolymers. Thus, the reaction product is a mixture of two types of copolymers, one of which results from initiation by the R group and the other results from hydride initiation. Spectroscopic studies suggest that the copolymers have stereoregular structures, except for the last unit, whose stereochemistry is disrupted through enolization.

The copolymerization of olefins and CO to give polyketones has been the subject of both industrial and academic research.[11] As shown by the patent literature, the alternating copolymers are of considerable industrial interest. It has been found by Drent and coworkers (the Shell company)[12] that this sort of copolymerization of olefins and carbon monoxide occurs efficiently in the presence of cationic palladium complexes with bidentate phosphines as ligands. These catalysts make it possible to prepare high-molecular-weight copolymers, which can be used as starting materials for other types of functionally substituted copolymers with special properties. Recently a series of papers[13] has been published devoted to the investigation of the separate steps of palladium-catalyzed polymerization: the insertion of CO into a metal—alkyl bond and the insertion of an alkene into the resulting metal—acyl bond. The use of strained cyclic olefins such as norbornene and norbornadiene and bidentate nitrogen-containing ligands made it possible to isolate new complexes formed by the successive insertion of the alkene and CO. The norbornyl or norbornadienyl moieties were always found *cis,exo*-substituted. We shall come back to this point later.

It is well known that alcohols or phenols readily attack a Pd—C(acyl) bond to yield esters. The reaction of *o*-iodophenol with norbornadiene and CO in the presence of $Pd(PPh_3)_4$ as the catalyst, in anisole as the solvent, and at atmospheric pressure gives the lactone in a 90 % yield (Eq. 7).

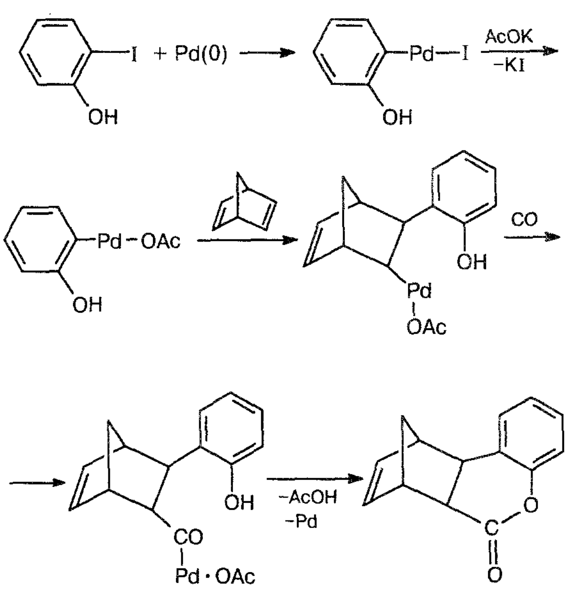


(7)

i. 1.5 % $Pd(PPh_3)$, AcOK, 80 °C, 4 h, anisole

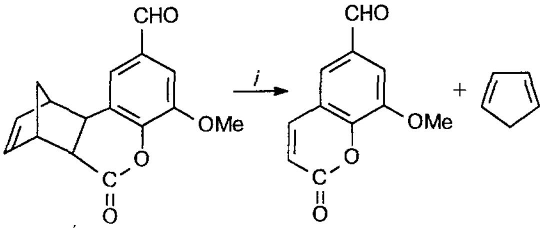
As shown in Scheme 3 (non-reacting ligands are omitted), the final reaction product results from the initial oxidative addition of iodophenol to Pd^0 followed by the successive insertion of norbornene and CO. An intramolecular nucleophilic attack by the phenolic OH group leads to the formation of the lactone.

Scheme 3



The reaction was also carried out with iodophenols containing various functional groups, including the formyl group. Iodovanillin was converted into the corresponding lactone in a 56 % isolated yield.[14]

An interesting feature of these compounds is that they undergo a retro-Diels—Alder reaction to yield coumarins under very mild conditions. Coumarins can be obtained in almost quantitative yield by heating the corresponding lactones in anisole at 150 °C for 3 h. So this new synthesis provides a method for preparing coumarins containing various substituents in the aromatic ring. The coumarin derived from iodovanillin had not been reported previously.

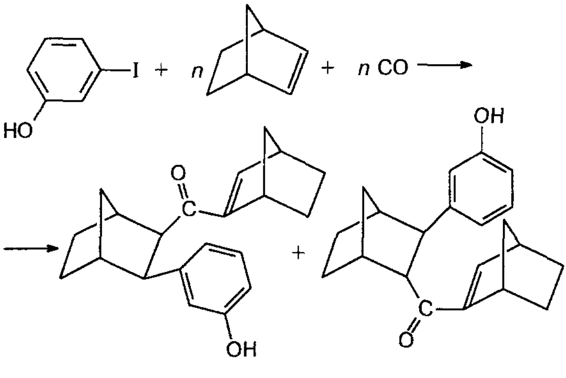


(8)

i. 150 °C, 3 h, anisole

We wondered at this point whether the insertion of new molecules of a strained olefin and CO could lead to the formation of larger rings.

For this purpose, *m*-iodophenol was used instead of the *ortho* isomer,[15] in order to move the OH group responsible for the final elimination step leading to the ring closure away from the reaction center. When the reaction was carried out at 80°C in anisole at an atmospheric pressure of carbon monoxide and in the presence of potassium acetate, cyclic oligomers containing 5—6 norbornyl—CO units were formed only in poor yields, since in this case, the reaction proceeded according to a different pathway (Eq. (9)).

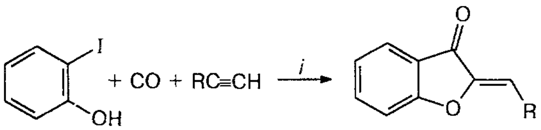


(9)

exo, exo 2 stereoisomers: *exo, endo*

As Eq. 9 indicates, despite the fact that β-H elimination in the system is hampered, the reaction yields compounds containing double bonds in the norbornyl units. A mixture of three isomers in a 1 : 1 : 0.5 ratio was obtained. One of the major isomers was identified by X-ray diffraction analysis as the *cis,exo* compound, while the two others were *exo,endo* stereoisomers, as shown by ^{1}H NMR spectroscopy. The presence of *endo* isomers suggests an *exo* to *endo* isomerization possibly through a base-catalyzed enolization process. However, the question arises, why do we obtain two diastereomers for the *exo,endo* compounds and only one for the *exo,exo* compounds? This fact can only be interpreted by assuming that in the absence of enolization, the norbornene unit always inserts the same face into the growing polymer. Our hypothesis has been recently confirmed by van Koten and coworkers, who succeeded in isolating a palladium-bonded norbornene—CO oligomer whose X-ray structural study showed that the norbornyl units are *syn*-arranged with respect to each other.[13b]

The reactions considered up to now proceed according to a pathway involving the initial insertion of a strained olefin and the subsequent insertion of CO. When an acetylenic compound such as phenylacetylene, rather than norbornene, was used, the reaction took a different course leading to the closure of a five-membered ring. The reaction of *o*-iodophenol, phenylacetylene, and CO under the previously described conditions occurred according to a pathway leading to the formation of aurone in an 86 % yield, mostly as the *Z*-isomer (Eq. (10)).[14]



(10)

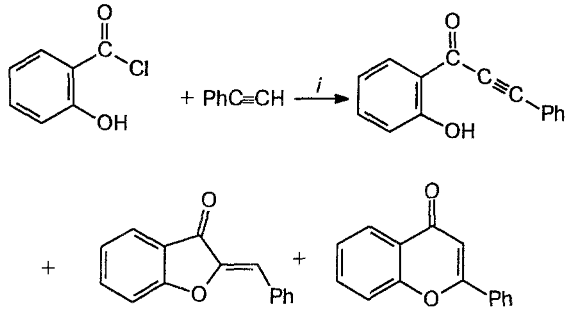
i. 1.5 % Pd(PPh$_3$)$_4$, AcOK, 80 °C, 24 h, anisole

Aliphatic alkynes were also used, but the corresponding cyclic products were obtained only in low yields due to their instability in the presence of palladium-containing species. It is noteworthy, however, that these compounds have not been reported previously.

The mechanism proposed for these reactions is presented in Scheme 4 referring to the formation of aurone (non-reacting ligands are omitted). The oxidative addition of *o*-iodophenol to Pd^0 followed by coordination and insertion of CO leads to the acyl palladium intermediate. The replacement of iodide by the phenylacetylene anion gives a new intermediate, and then the product of the coupling of the two palladium-bonded organic groups is formed, and the Pd^0 is recovered. However, the reaction does not stop at this stage. In fact, the formation of aurone implies further oxidative addition of the OH group to Pd^0, intramolecular insertion of the acetylene fragment into the Pd—O bond, and reductive elimination of palladium. It should be noted that *cis* addition of the phenoxy- and hydridopalladium groups to the triple bond must give the *E* isomer, whereas the aurone isolated was in the *Z* form. It is likely that the *E* isomer formed initially is rapidly converted into the more stable *Z* form.

In order to confirm this mechanism and gain access to various classes of heterocyclic compounds we carried out the reaction of salicyloyl chloride with *o*-iodoaniline, instead of *o*-iodophenol (Eq. (11)).[16]

As can be seen from Eq. 11, the main product of the reaction of salicyloyl chloride with phenylacetylene is the acyclic ketone obtained in 56 % yield together with two cyclization products: aurone and flavone (19 and 14 % respectively). The overall yield is rather high, in



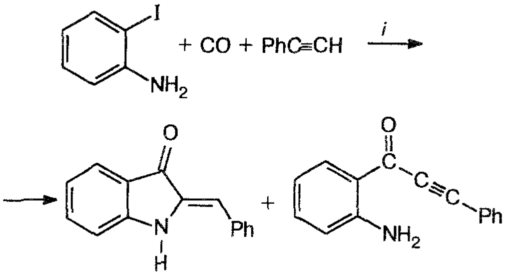
(11)

i. 2 % $Pd(dba)_2$, $N(C_8H_{17})_3$, 50 °C, 6 h, anisole

spite of the fact that reaction conditions for this substrate are rather crucial. In fact, the expected reaction does not occur in the presence of palladium complexes containing phosphine ligands. The best results were obtained using Pd^0 complexes such as $Pd(dba)_2$ with trioctylamine as the ligand. The quantity and type of amines play a significant role in the selectivity of the process. The reaction occurs efficiently only in a narrow temperature range. The yield of the reaction products decreases both above and below 50 °C.

The preparation of the acetylenic ketone containing an *ortho* hydroxyl group offers a useful starting point for further syntheses. The acetylenic ketone is known to undergo cyclization to give aurone and flavone. These products were obtained by the action of temperature and a base or an acid.[17] Pd^0 complexes with triarylphosphines catalyze cyclization yielding only aurone according to the pathway proposed previously for the one-pot reaction.[16]

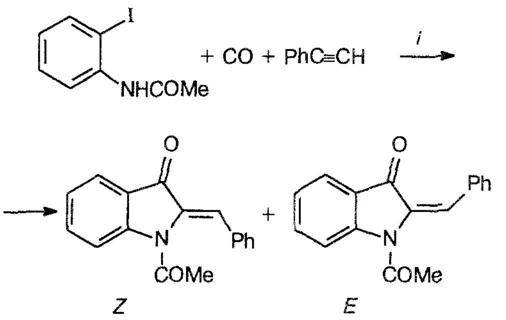
In the reactions with acetylenes and CO, *o*-iodoanilines behave similarly to *o*-iodophenols (Eq. (12)).[18]



(12)

i. 4 % $Pd(PPh_3)_4$, AcOK, 80 °C, 23 h, anisole

The reaction gives an indoxyl derivative and an open-chain compound in a 92 % overall yield. The indoxyl compound is obtained exclusively in the *Z* form, which is also the preferred form for aurone. However, if the nitrogen atom bears a substituent, for example, an acetyl group, steric effects determine the formation of the *E* isomer, along with the *Z* isomer.

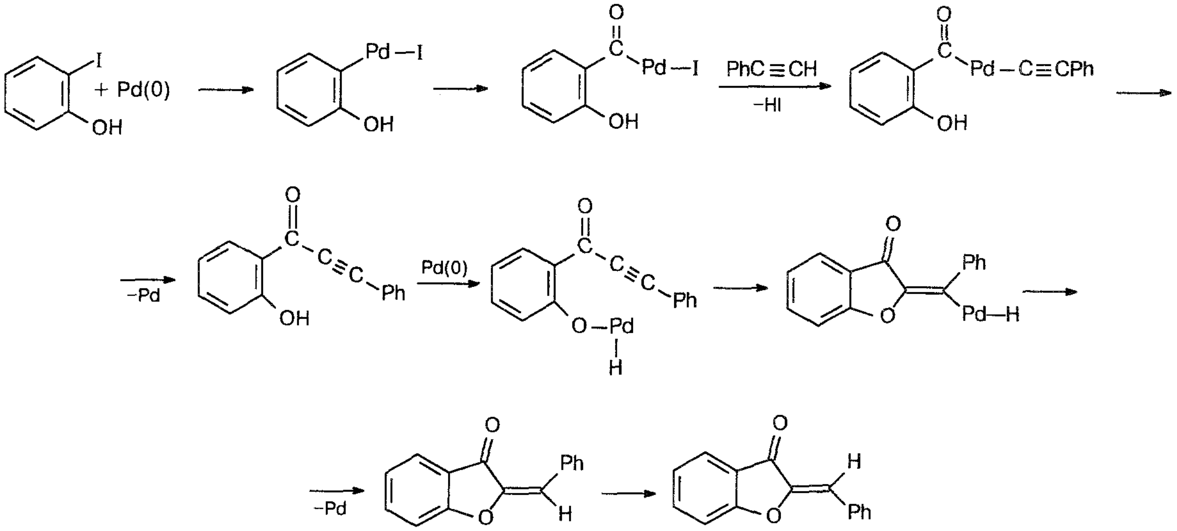


(13)

i. 4 % $Pd(PPh_3)_4$, AcOK, 80 °C, 23 h, anisole

The molar ratio between the *E* and *Z* forms varied from 2 : 1 after 14 h at a degree of conversion of the

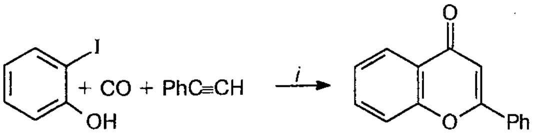
Scheme 4



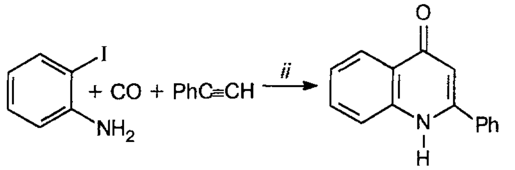
starting acetylaniline of 73 %, to 1 : 2 after 23 h at complete conversion. The *E* compound is formed at the beginning of the reaction under kinetic control. In this case, its isomerization to the more stable *Z* form is slow due to the presence of the acetyl group; therefore the mixture of the reaction products contains a higher proportion of the *E* isomer than that present at thermodynamic equilibrium. The latter was found to be about 2.5 : 1.

At this point, the result of the cyclization of *o*-iodophenol to *Z*-aurone is worth recalling. The explanation for the formation of the *Z* isomer, rather than the *E* isomer (which would be expected from the *cis* addition of the palladium complex), was the isomerization of the initially formed *E* compound. In the case of substituted *o*-iodoanilines, the *E* isomer becomes so stable that it can be easily isolated, and its isomerization into the *Z* isomer slowly occurs with time. Thus, we obtained indirect evidence for the postulated isomerization process.

Various cyclization pathways to give six-membered rings have been reported for reactions involving *o*-iodophenol or *o*-iodoaniline carried out under similar conditions (reactions (14) and (15)).[19]



(14)



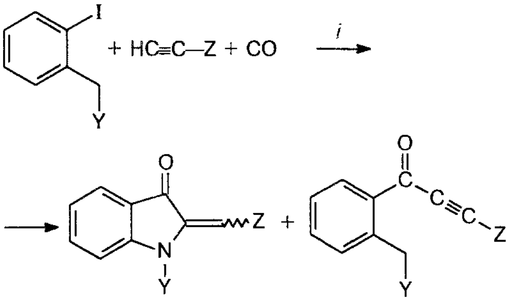
(15)

i. 1 % $PdCl_2(dppf)$, Et_2NH, 120 °C, 2 h, 20 atm

ii. 5 % $PdCl_2(PPh_3)_2$, Et_2NH, 120 °C, 6 h, 20 atm

The best results have been achieved at 120 °C with diethylamine as the solvent. In this case, the yields of the products were 81 to 90 %. Catalysts both containing and not containing phosphine ligands were used. The process is probably very dependent on the presence of the base.

To extend the scope of the reactions under consideration we used aryl iodides containing activated *ortho*-CH_2 groups instead of OH or NH_2 groups. These transformations are presented below (Eq. (16), Y = ester or amide, Z = aryl or substituted aryl).[20]

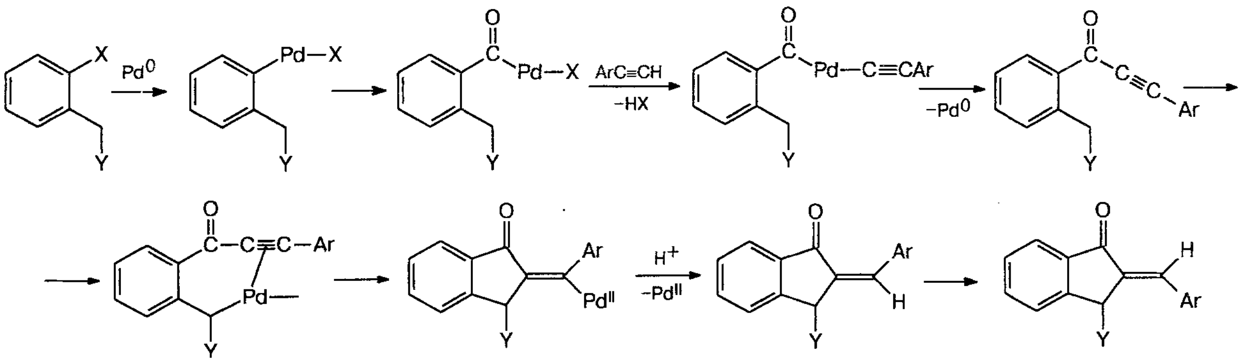


(16)

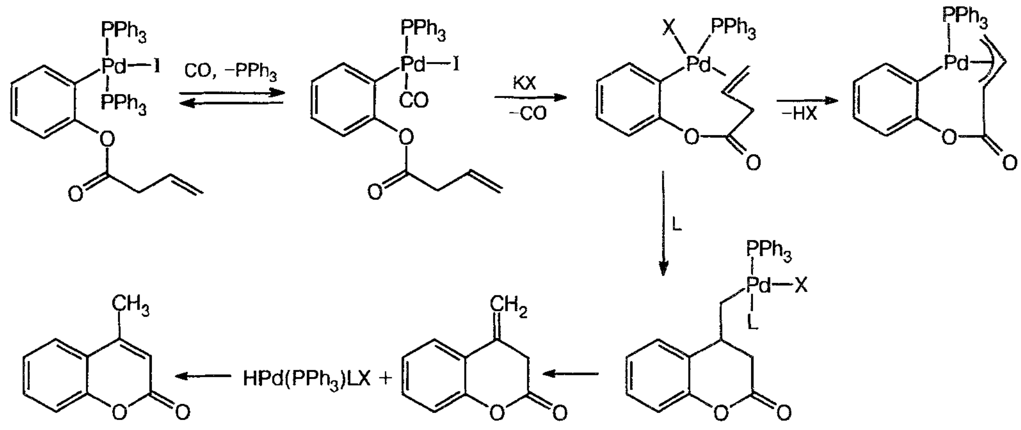
i. Pd-cat., –HI

In fact, two reactions occur in sequence; one of these yields an open-chain alkynyl ketone, and the other results in ring formation. The process occurs efficiently at 80 °C in the presence of $Pd(PPh_3)_4$ and potassium acetate and at an atmospheric pressure of CO in anisole to give *Z* and *E* isomers together with their acyclic precursor, which in some cases was isolated as the main product. Compounds with various substituents at the methylene group and various acetylenes were used in the reaction. The ratio between the reaction products, *viz.*, the open-chain ketone and the *E* and *Z* isomers of the cyclic product, depends on the nature of the substituents at the CH_2 group. The mechanism of this reaction (Scheme 5, non-reacting ligands are omitted) implies a sequential process involving the oxidative addition of

Scheme 5



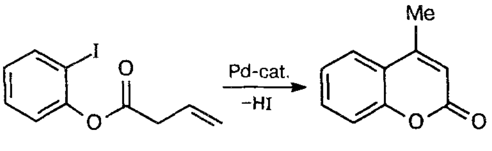
Scheme 6



aryl iodide to Pd^0, CO insertion, replacement of the iodide by the alkynyl group, and the C—C coupling to afford alkynyl ketone. Since the open-chain ketone can also be obtained selectively, we studied the conditions of the cyclization reaction to give the five-membered ring separately. It was found that the conversion of the open-chain ketone into the five-membered ring is catalyzed by Pd^{II} compounds, for example, bis(triphenylphosphine)palladium acetate, whereas Pd^0 complexes do not work. This allowed us to conclude that the cyclization is not due to oxidative addition but implies deprotonation of the CH_2X group to give a compound with a Pd—C(alkyl) bond able to attack the coordinated alkyne. Thus, the subsequent step should involve the nucleophilic attack on the alkyne by the activated carbon. The base, potassium acetate, present in the reaction mixture is unable to cause cyclization. Pd^0 catalyzes the first step, while cyclization requires a Pd^{II} compound. This brings up the question, how can the Pd^{II} species form? Under the reaction conditions, such compounds as the arylpalladium iodide involved in the catalytic cycle can disproportionate to give a diarylpalladium complex with phosphine and palladium iodide. As we have previously pointed out, in some cases, both the *E* and *Z* isomers of the reaction product have been isolated. The initially formed cyclic compound is the *Z* isomer. The *E* isomer could result from isomerization catalyzed by various compounds present in the reaction mixture.

So far we have seen that catalysis by palladium complexes is an efficient tool for cyclization reactions starting from some *ortho*-substituted aryl iodides. Now catalytic syntheses of 4-methyl- and 4-alkynylcoumarins from *o*-iodophenol alkenoates will be described.

4-Methylcoumarin results from a palladium-catalyzed intramolecular reaction (Eq. 17).[21]



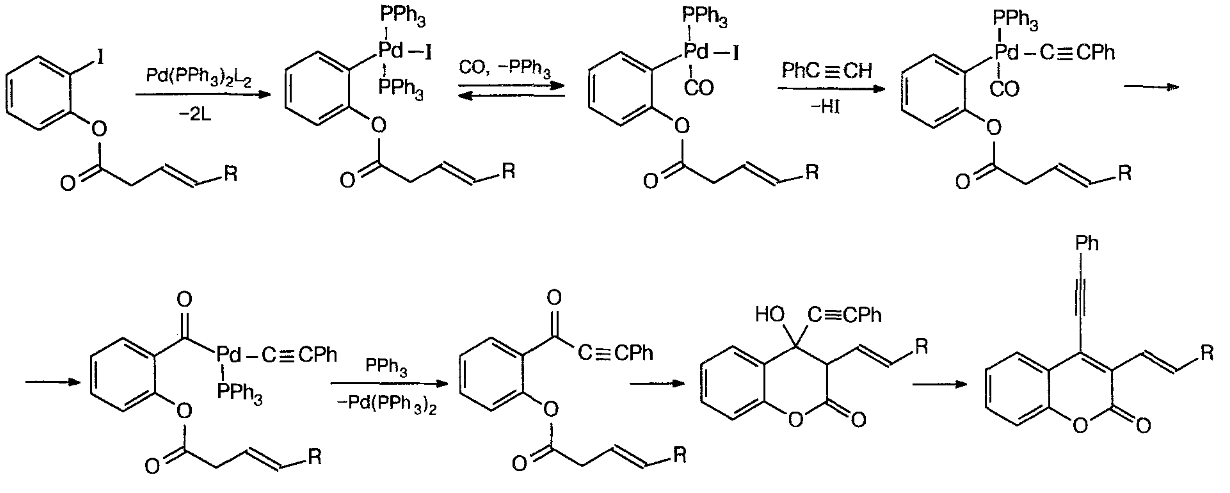
(17)

The reaction readily occurs under mild conditions in the presence of a suitable promoter that favors the insertion of the double bond and simultaneously prevents isomerization of the butenoate with the transfer of the terminal double bond to a more stable position allowing conjugation. At 80 °C, in the presence of $Pd(PPh_3)_4$ and a promoter such as benzonitrile, phenylacetylene, or methyl acrylate, in anisole, and at an atmospheric pressure of carbon monoxide, 4-methylcoumarin can be obtained in a yield of more than 85 %. When the reaction was carried out in the absence of CO and a promoter, *o*-iodophenyl crotonate was formed as the main product, and the yield of 4-methylcoumarin was less than 10 %.

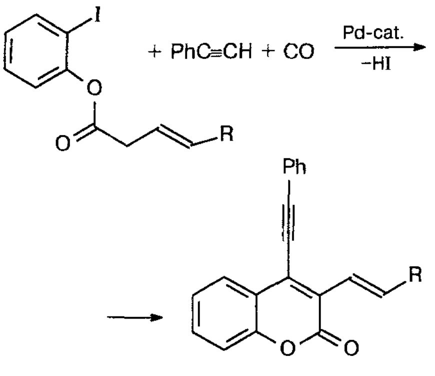
According to Scheme 6, CO replaces one triphenylphosphine molecule, which facilitates the coordination of the double bond of the butenoate moiety (with the displacement of CO). The role of the promoter is probably that it quickly occupies a coordination site in the palladium complex. This circumstance would stabilize the product resulting from the migration of the aryl group on the butenoic double bond and, at the same time, it would prevent the formation of an η^3-allyl complex. We also wondered whether this task could be performed by chelating phosphines. However, it turned out that in the presence of diphenylphosphinoethane, the reaction is arrested owing to the stability of the chelates toward dissociation. Diphenylphosphinopropane and diphenylphosphinobutane, whose complexes are more prone to dissociation, also gave poor results, probably due to the fact that not only dissociation, but also reassociation to stabilize the ring formed by insertion is necessary. In both cases, benzonitrile is necessary for a catalytic reaction to occur. Diphenylphosphinoferrocene, which has a rigid structure and can readily dissociate and reassociate, also exerts a catalytic action without benzonitrile, but in this case, extensive isomerization occurs. The best results were obtained with triphenylphosphine, CO, and benzonitrile.

It has already been mentioned that phenylacetylene in combination with CO also can act as a promoter of the cyclization of *o*-iodophenyl 3-butenoate. These spe-

Scheme 7



cies are known to react with aryl groups to give aryl alkynyl ketones. The possibility of these transformations under the conditions of the synthesis of 4-methylcoumarin is confirmed by the fact that when the butenoic chain has a terminal substituent, another pathway is followed, leading to a 4-alkynylcoumarin (Eq. (18)).[22]



(18)

Thus, two competing processes are at work and the preference for the former appears to be determined by the ability of the double bond to coordinate palladium. The result can be explained according to Scheme 7.

The formation of the acetylenic ketone should proceed according to the pathway that we postulated previously. The subsequent steps involve nucleophilic attack by the activated methylene group on the carbonyl group followed by dehydration.

In conclusion, it should be noted that the methods described here can be quite useful although they require delicate control of the reaction conditions. This is a general feature of transition metal chemistry: synthetic procedures are much simpler and milder than the conventional procedures in the organic chemistry, but slight modifications in the structure of the substrate or in the metal environment may cause substantial changes in the course of the reaction.

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