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Review

Recent developments of palladium(0) catalyzed reactions in aqueous medium☆

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Abstract

Palladium cross-coupling reactions: Heck, Sonogashira, Tsuji-Trost, Suzuki, Stille as well as protecting group chemistry in aqueous media are presented. The excellent compatibility of water-soluble palladium catalysts offer new opportunities (mild conditions, new selectivity). In most of the reaction catalyzed by palladium in water described in this review, careful selection of reaction conditions, co-solvents and catalysts, is very important for long life catalyst and new selectivities. The palladium catalyzed reactions with water-soluble phosphines (e.g. sulfonated phosphines) provide advantages of the two phase aqueous system: easy separation of the products and recycling the expensive palladium. This technique has increased the potential of modern palladium catalysis. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Aqueous media; Cross coupling reactions; Palladium; Recycling

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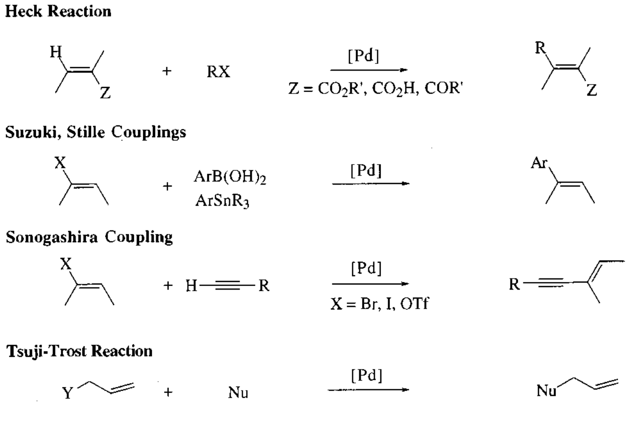
1. Introduction

Through the past three decades, homogeneous catalysis has undergone a considerable amount of progress in the field of organic synthesis [1]. Among the large panel of transition metals frequently used, palladium has a predominant role [2]. Organopalladium complexes are fairly stable and non-toxic, which explains the recent development of efficient industrial processes [3] including palladium-promoted steps. One of the major contributions of zero-valent palladium catalysts in organic synthesis is the formation of carbon–carbon bonds through many coupling reactions presented in Scheme 1.

To date, synthetic organic chemists have used palladium catalysts in a number of useful transformations. Many reviews and books have been published involving the use of palladium catalysts [1,2,4–6]. Nevertheless,



Scheme 1.

☆ Sharing the delight of working on organometallic chemistry, we dedicate this article to Professor J. Tsuji for his invaluable contribution in this field.

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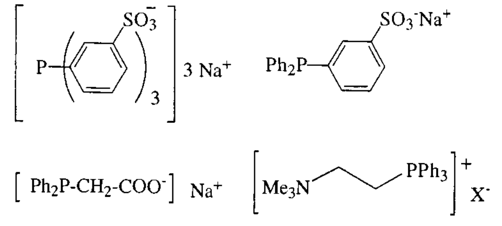
one of the major drawbacks of homogeneous metal catalysis lies in the separation of the reaction product from the catalyst, which requires costly procedures. A solution to this problem consists in using water-soluble ligands which once complexed to the metal make the catalyst poorly soluble in organic media [7], and combine the advantages of homogeneous and heterogeneous catalysis. In addition, the use of water may have positive effects such as increasing selectivity and catalytic efficiency.

However until recently, palladium-promoted reactions in aqueous media, with water-soluble catalysts were still unexplored. The development of water-soluble catalysts offers several advantages for industrial production: easy separation of the product from the catalyst, high reactivity, recycling of catalyst. The present review will discuss some of recent developments and applications of palladium catalysis in aqueous medium.

1.1. Palladium catalysts used in aqueous medium

It has been shown that the commercially and relatively inexpensive palladium acetate without phosphine ligand catalyzes cross-coupling reactions in aqueous medium or neat water [8].

Phosphines can be converted into water-soluble derivatives by introduction of polar groups, including carboxylate, sulfonate and ammonium:



Sulfonated triphenylphosphines are the most commonly used as water-soluble ligands, with which palladium goes into aqueous phase and catalytic reaction proceeds therefore in water. A preformed water-soluble palladium(0) has been prepared using triphenyl (mono *m*-sulfonated phenyl) phosphine, TPPMS. This catalyst fully characterized has been successfully used in various cross-coupling reactions [9]:

$$Na_2PdCl_4 + Ph_2P(m\text{-}C_6H_4SO_3Na) \xrightarrow{\text{Zn dust}} Pd[Ph_2P(m\text{-}C_6H_4SO_3Na)]_3$$

Another useful and versatile water-soluble catalytic system was generated in situ from the mixture of $Pd(OAc)_2$ and *m*-trisulfonated triphenylphosphine (TPPTS) in a 1:4 ratio affording spontaneously an active palladium(0) complex. The fourth TPPTS ligand reduces Pd(II) to palladium(0) with the formation of *m*-trisulfonated triphenylphosphine oxide. This in situ generation of water palladium(0) species is a very convenient preparative method for catalytic reactions. Thus, in this way, $Pd(TPPTS)_2$ can be generated using $Pd(OAc)_2$ or $PdCl_2$ and TPPTS in a 1:3 ratio and must be used immediately.

$$Pd(OAc)_2 + 4P(m\text{-}C_6H_4SO_3Na)_3 \xrightarrow{\text{in situ}} Pd[P(m\text{-}C_6H_4SO_3Na)_3]_3 + O{=}P(m\text{-}C_6H_4SO_3Na)_3$$

This transformation has been established through a series of kinetic and ^{31}P-NMR experiments [10]. This system is an excellent catalyst for various cross-coupling reactions (Heck, Sonogashira, Suzuki) as well as π-allylpalladium chemistry [11,12]. The TPPTS ligand is much more soluble in water than the monosulfonated ligand (TPPMS) (1100 g l^{-1} at 20°C instead of 80 g l^{-1}). The extremely high solubility of this phosphine ensures the hydrophilic properties of palladium zero-valent catalyst.

More recently, $Pd(OAc)_2$ has been used for the preparation of water-soluble palladium(0) containing guanidinium phenylphosphine [13].

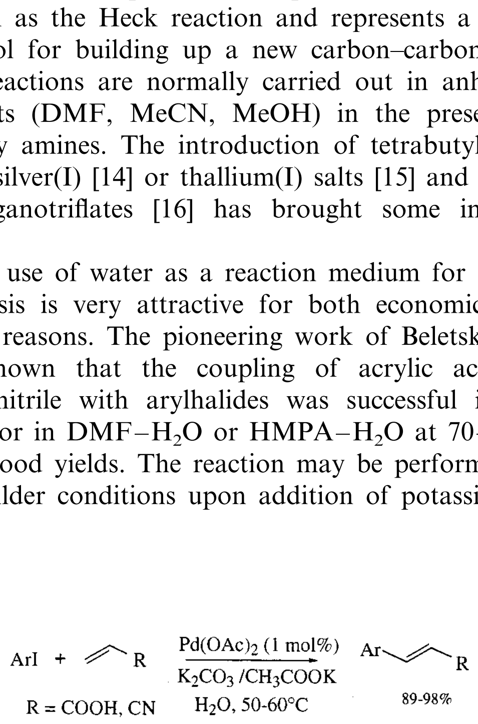
2. Reactions

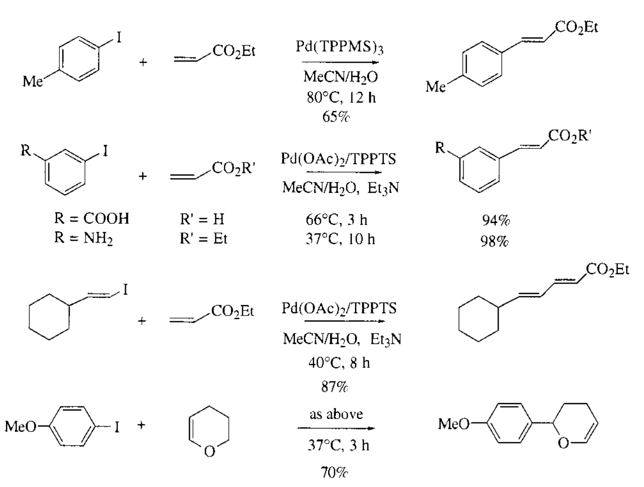
2.1. Vinylation and arylation of alkenes: Heck reaction

2.1.1. Intermolecular reactions

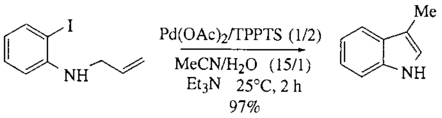
The addition of vinyl or aryl halides with various alkenes in the presence of palladium catalysts is known as the Heck reaction and represents a powerful tool for building up a new carbon–carbon bond. The reactions are normally carried out in anhydrous solvents (DMF, MeCN, MeOH) in the presence of tertiary amines. The introduction of tetrabutylammonium silver(I) [14] or thallium(I) salts [15] and the use of organotriflates [16] has brought some improvements.

The use of water as a reaction medium for organic synthesis is very attractive for both economical and safety reasons. The pioneering work of Beletskaya [8] has shown that the coupling of acrylic acid and acrylonitrile with arylhalides was successful in neat water or in DMF–H_2O or HMPA–H_2O at 70–100°C with good yields. The reaction may be performed under milder conditions upon addition of potassium acetate:

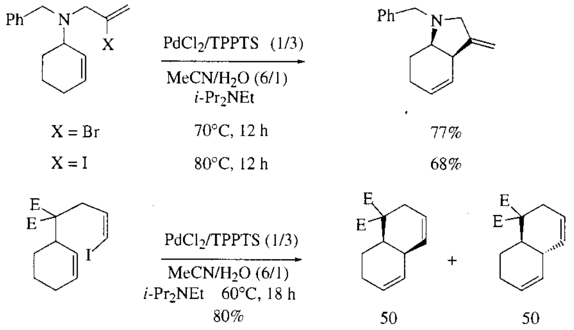




Scheme 2.

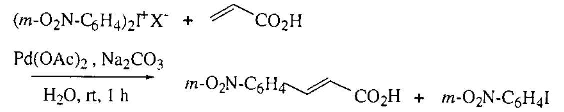


Scheme 3.



Scheme 4.

If diaryliodonium salts are used as arylating agents of acrylic acid, the reaction can be carried out at room temperature:



Reactions involving water-insoluble substrates can be efficiently performed in water, in the presence of a combination of an alkali metal carbonate and a quaternary ammonium salt [17].

Heck reactions were also conducted in homogeneous aqueous medium (acetonitrile–water) in the presence of preformed $Pd(TPPMS)_3$ catalyst [9] or with $Pd(TPPTS)_3$ catalyst [10] produced in situ from 2.5% $Pd(OAc)_2$ with 5% of *m*-sulfonated triphenylphosphine (TPPTS). The reaction proceeded in a better yield. The coupling was generally complete within several hours at temperature between 25–60°C. α,β-Unsaturated esters or acids were obtained with good to excellent yields. Under the same conditions, the coupling of aryl iodides with cyclic alkenes (3,4-dihydropyran, cyclohexene and cyclopentene) proceeded at room temperature to give a single aryl adduct in 70–91% yield (Scheme 2). With 3,4-dihydropyran, it is noteworthy that the conditions afforded solely the thermodynamic product. More recently, cationic guanidino phosphines in combination with palladium acetate have been found effective catalyst for Heck reactions in aqueous medium [18].

Thus, the Pd(0)/TPPTS was a good catalyst for Csp^2–Csp^2 coupling under mild conditions; crude products were obtained on pure form by simple filtration.

2.1.2. Intramolecular Heck reactions

The intramolecular Heck reaction is used as key step in numerous natural product syntheses [19]. Using the $Pd(OAc)_2$-TPPTS catalyst in a homogeneous aqueous phase (water-acetonitrile), the *o*-iodo-*N*-allylaminobenzene cyclized very rapidly at room temperature to produce the 3-methylindole in quantitative yield [11] (Scheme 3).

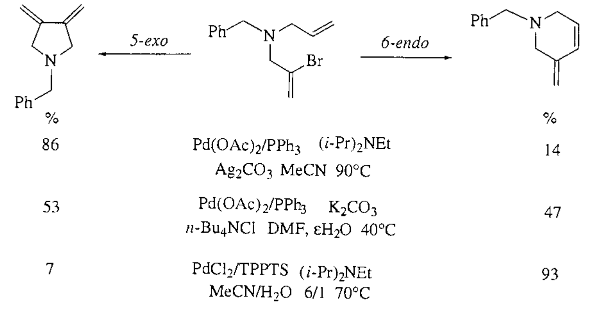
Both iodide and bromide amino precursors derived from cyclohex-2-ene underwent smooth cyclization giving the corresponding fused bicyclic products in good yields. In some cases, $PdCl_2$ as Pd(II) salt was more efficient; triethylamine or diisopropylethylamine could be used as base [20]. When the halogen was branched on the internal position of the double bond, only *cis* heterocycles or carbocycles were formed, whereas an equimolar mixture of *cis* and *trans* diastereomers was observed when the iodine atom was on the terminal carbon of the double bond (Scheme 4).

In addition, when substrates were likely to cyclize via an *exo* or *endo* process, the *exo* mode cyclization was observed in many cases. However, the regioselectivity strongly depends on the catalytic species and the change from 5-*exo* to 6-*endo* preference was recently reported for the intramolecular carbo-palladation of 1,6-enynes by modifying the catalyst [21].

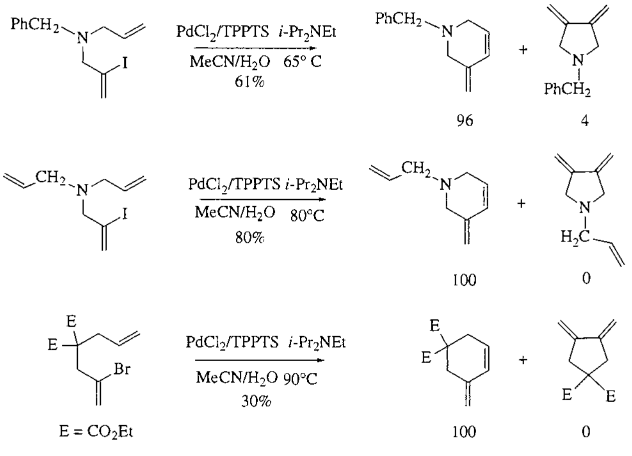
In the standard anhydrous conditions, in the presence of $Pd(OAc)_2$, PPh_3, Ag_2CO_3 and diisopropylethylamine, the 5-*exo*-trig cyclization was observed; meanwhile under phase transfer conditions, a tendency to reverse the *exo* preference was observed. Finally, the hydrosoluble palladium(0) catalyst afforded a total inversion of selectivity in favor of 6-*exo* cyclization (Scheme 5).

These results were in agreement with the cyclization of highly functionalized enamides where the unexpected *endo* process was observed using phase transfer conditions [22].

Similarly, nitrogen substrates that are likely to undergo both 5-*exo*-trig and 6-*endo*-trig cyclization, reacted in the presence of Pd(0)/TPPTS in aqueous



Scheme 5.



Scheme 6.

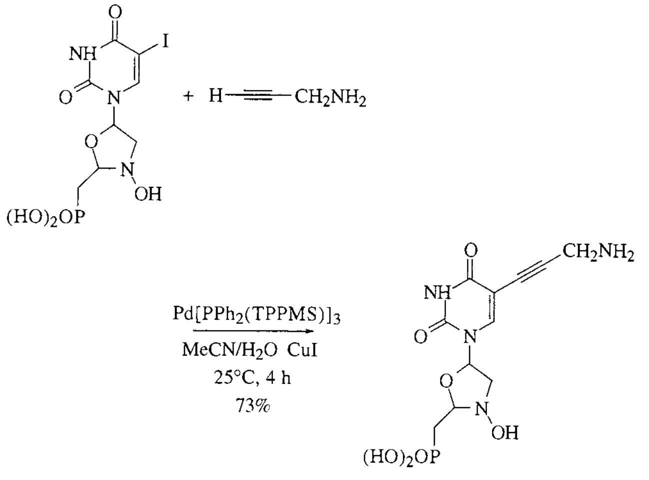
medium to give a six membered ring in fair to good yields [20] (Scheme 6).

These aqueous conditions have therefore offered the opportunity to reverse the usual *exo* process, affording the *endo*-products. Thus, by proper choice of reaction medium, it is possible to obtain either the *endo* or the *exo*-ring closure starting from the same precursor.

2.2. Cross-coupling reactions of terminal alkynes with vinyl and aryl halides

Palladium catalyzed reactions of terminal alkynes with aryl or vinyl halides are usually conducted in non aqueous media with a base as scavenger for hydrogen halide [23]. Copper(I) iodide is a particularly effective co-catalyst allowing the reaction to occur under mild conditions [4k].

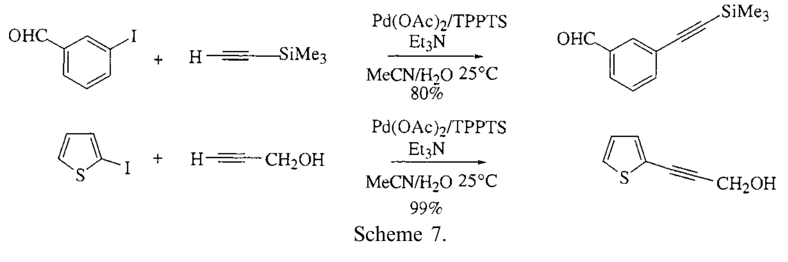
The hydrosoluble catalyst Pd(TPPMS)$_3$ prepared by Calsalnuovo [9], was effective in the cross-coupling of a wide range of acetylenes with unprotected nucleosides, nucleotides and amino acids in 50% aqueous acetonitrile solution with a Cu(I) promoter:



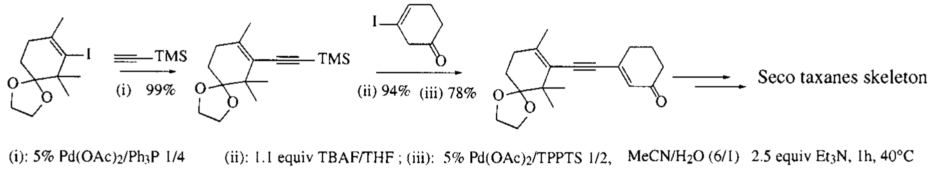
The synthetic versatility of this methodology was illustrated in an alternative synthesis of the T-505, part of a family chain-terminating nucleotide reagents used in automated DNA sequencing and labeling.

The Pd(OAc)$_2$-TPPTS catalyst efficiently catalyzed coupling of iodoaromatics and vinyl halides [11] with a variety of terminal alkynes in acetonitrile/water solution (6/1) at room temperature in a few hours without any Cu(I) promoter. High yields were observed and interestingly, in these cross-coupling reactions, the catalyst was tolerant of a wide range of functionalities such as sulfur which is not poisonous to the catalyst (Scheme 7).

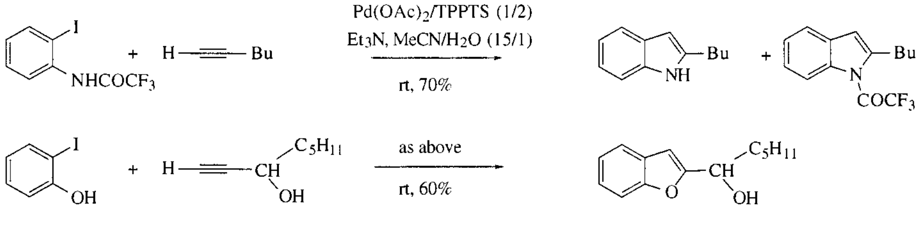
Based on theses Csp^2–Csp coupling, an approach to the tricyclic structure of taxanes has been accomplished in our laboratory [24]. The key elements of the strategy involved a sequential Sonogashira reaction between first the protected iodoketone and trimethylsilylacetylene then, after deprotection of trimethylsilyl group, with 3-iodocyclohexenone to generate the two carbon atoms C-9 and C-10 of the taxane skeleton. The first cross-coupling failed under aqueous conditions, standard anhydrous conditions afforded the coupling product in 99% yield, whereas the second one proceeded smoothly using aqueous conditions (Scheme 8).



Scheme 7.



Scheme 8.



Scheme 9.

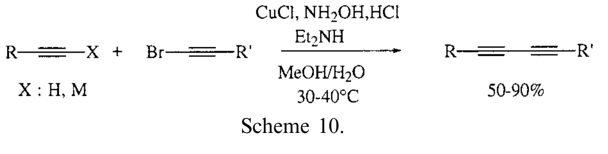
The synthesis of indoles and furans via the two-step Csp^2–Csp coupling/intramolecular cyclization sequence has been studied for a long time, and at the beginning, harsh reaction conditions were used in the presence of Cu(I) species. In the presence of the water-soluble catalyst $Pd(OAc)_2$/TPPTS, this sequential two-step reaction proceeded under very mild conditions (room temperature) without Cu(I) [10]. When the amino function was activated by a trifluoroacetyl group, a complete cyclization was observed. Benzofuran derivatives were prepared with the same strategy in moderate to good yields (Scheme 9).

This method is very easy to handle since the catalyst and the base are eliminated by simple water treatment affording, after extraction, very clean crude products.

2.3. *Cross-coupling of alkynes–alkynes*

Symmetrical diyne molecules have been synthesized by an Csp–Csp coupling reaction for a long time by the use of stoichiometric or catalytic quantities of Cu(I) [25]. The synthesis of unsymmetrical diynes has been described in the 1950's by Cadiot and Chodkiewicz [26] who developed a Csp–Csp coupling between acetylenic bromides and terminal alkynes or alkynyl cuprates in organoaqueous medium (Scheme 10).

Very few Csp–Csp coupling methods using organopalladium catalysts have been described in the literature [4]. The water-soluble catalyst formed in situ from $Pd(OAc)_2$ and TPPTS, again has proved its efficiency in these sp–sp coupling reactions without any copper(I) promotor. In aqueous acetonitrile and in the presence of triethylamine (two and a half equivalents), various alkynyl iodides, easily prepared from the corresponding alkynes have been coupled with functionalized terminal alkynes under very mild conditions. The corresponding alkynes were obtained with moderate yields [10] (Scheme 11).

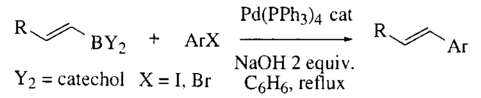


Scheme 10.

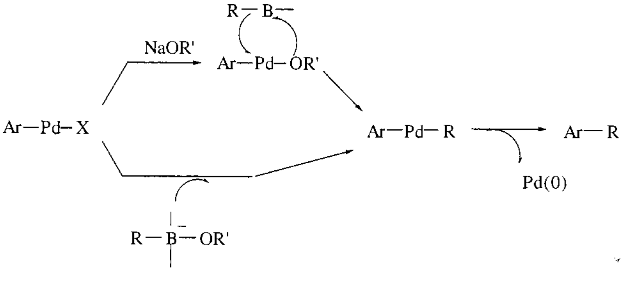
Thus, under very mild conditions, the water-soluble catalyst allowed Csp–Csp cross-coupling without any copper(I). Furthermore, silylated diynes could be useful nucleophilic precursors for the preparation of new materials.

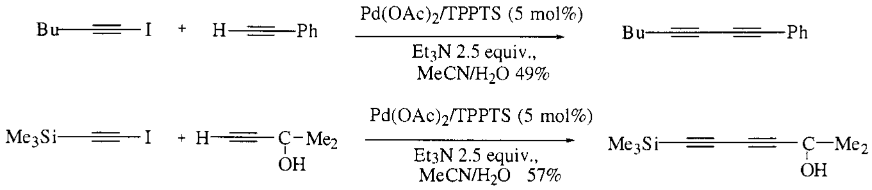
2.4. *Reactions of organohalides with boronates and boronic acids: Suzuki coupling*

The palladium-catalyzed cross-coupling reaction of organometallic reagents with halides was an important synthetic method for regio- and stereoselective bond formation between unsaturated carbon atoms. This coupling of alkenyl and aryl boranes or boronic acids (the Suzuki reaction) was catalyzed in organic solvents by $Pd(PPh)_4$ in the presence of an inorganic base:

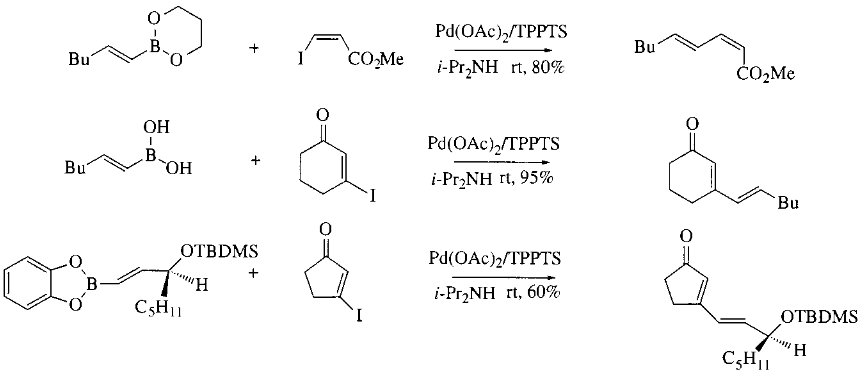


It has been suggested that, during the transmetalation step, the role of the base is probably to increase the nucleophilicity of the organic group on boron atom or to form the alkoxy palladate from arylpalladium halide [40]:



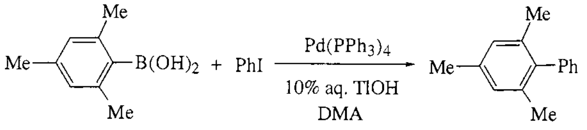


Scheme 11.

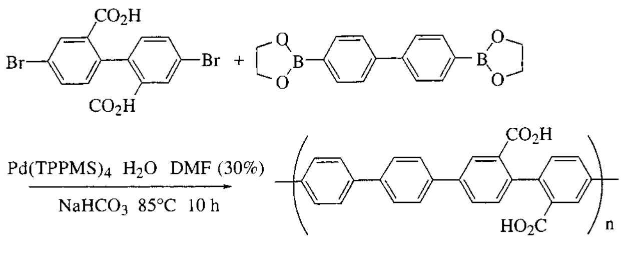


Scheme 12.

As organoboron compounds are often stable to protolytic decomposition by water, it seems attractive to perform the Suzuki reaction in water. An extensive study of this reaction under anhydrous and aqueous conditions was carried out, little difference could be noticed between these conditions [27]. On the other hand, in the case of hindered boronic acids such as mesityl boronic acid, the reaction proceeded with aqueous thallium hydroxide, under very mild conditions giving biphenyl derivatives in 92% yield:



Polyphenylene polymers can be prepared by Suzuki coupling. For instance, the preparation of poly(*p*-quaterphenylene-2,2′-dicarboxylic acid) was carried out using the water-soluble phosphine TPPMS associated with palladium and aqueous $NaHCO_3$ [28]:

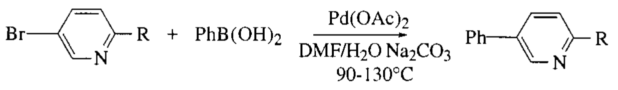


The cross-coupling of phenylboronic acid with *p*-iodoanisole has shown that in acetonitrile–water (3/1) with a catalytic amount of hydrosoluble catalyst (Pd/TPPTS 2.5 mol%), the inorganic bases such as K_2CO_3, $Ba(OH)_2$ or Cs_2CO_3 were inefficient, while triethylamine and diisopropylamine led to the biphenyl product in good yield [29]. A better yield was observed with diisopropylamine compared to triethylamine.

Under these optimized conditions, the coupling of functionalized alkenyl boronic acids or esters with iodoesters or iodoketones afforded the functionalized dienes or trienes in good to excellent yields at room temperature (Scheme 12).

The nature of the boronic derivatives, boronic acid or ester did not affect the yield. Moreover, an high stereoselectivity was observed. The coupling of (*E*)-hex-1-enyl-boronic acid with 3-iodocyclohexenone gave (*E*)-3-(hex-1-enyl)cyclohexenone. Interestingly, under the standard conditions, the chiral center of an alkenyl boronate was not affected during the reaction with 3-iodocyclopentenone. The Suzuki-coupling performed with the water-soluble catalyst $Pd(OAc)_2$/TPPTS was therefore very efficient with high stereoselectivities. It has occurred under mild conditions which have some advantages for the preparation of α,β-unsaturated esters with (*Z*) geometry [29]. In addition, the catalyst was cleanly eliminated.

A new procedure to the powerful Suzuki coupling was phosphine-free palladium catalysis. The reaction of aryl boronic acids with water-soluble organic halides has been carried out at room temperature in the presence of palladium(II) salts ($Pd(OAc)_2$, $PdCl_2$) and inorganic bases (e.g. K_3PO_4, NaOAc, K_2CO_3, etc.) [30]. This ligandless reaction with water-insoluble aryl halides proceeded in aqueous DMF at elevated temperature in good yields as shown in the cross-coupling of 3-bromopyridines with phenylboronic acid:

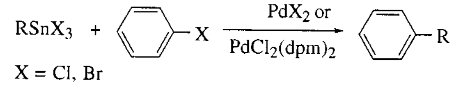


2.5. Cross-coupling with organostannanes

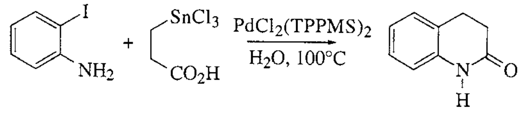
Organotin compounds are used for cross-coupling of aryl, alkenyl and alkylstannanes with aryl, vinyl halides or pseudo halides (the Migita–Kosugi–Stille reaction) [31].

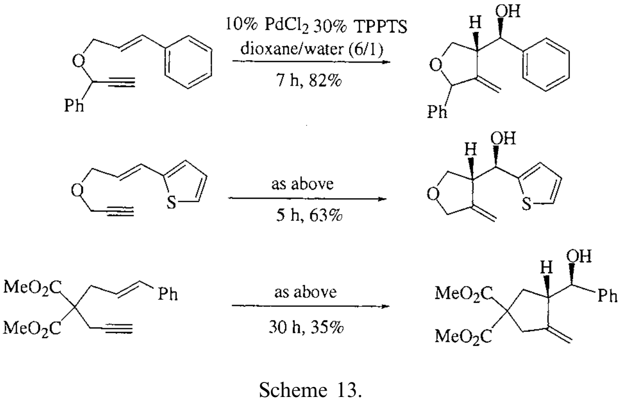
$$R^1SnR_3 + R^2-X \xrightarrow{Pd(0)} R^1-R^2 + XSnR_3$$

The cross-coupling of stannanes requires palladium catalysts containing phosphines. Unsymmetrical organotin compounds containing three alkyl groups (butyl or methyl) are used, and the fourth group which was transferred was alkynyl, aryl or allyl. Thus, the utilisation of only one of the four organic radicals, led to the formation of toxic R_3SnX. A solution to this ecological problem would be the use of monosubstituted compounds $RSnX_3$. Thus, $RSnX_3$ can be used in aqueous medium and reacted with aryl iodides or bromides in the presence of palladium catalysts [32]:



This reaction was carried out using β-trichlorostannylpropionic acid and *o*-iodoaniline for the preparation of heterocycles:

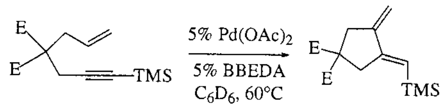




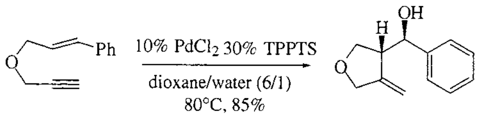
Scheme 13.

2.6. Reactions of 1,6-enynes

The cycloisomerization of 1,6-enynes has been extensively developed by Trost in the middle of the 1980’s [21]. These reactions were carried out by using Pd(0) or Pd(II) in association with a catalytic amount of phosphine and a carboxylic acid affording an efficient access to 1,3-dienes that could be engaged in subsequent Diels–Alder reactions:

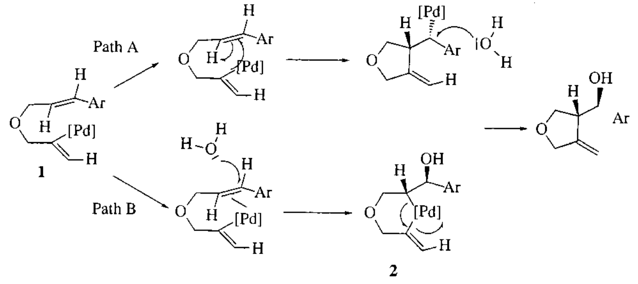


Using $PdCl_2$/TPPTS in an homogeneous mixture of dioxane–water in 6/1 ratio and in absence of acetic acid, the readily available cinnamyl propargyl ether underwent the cyclization to give a 3-hydroxytetrahydrofuran derivative as a single diastereomer in 85% yield.

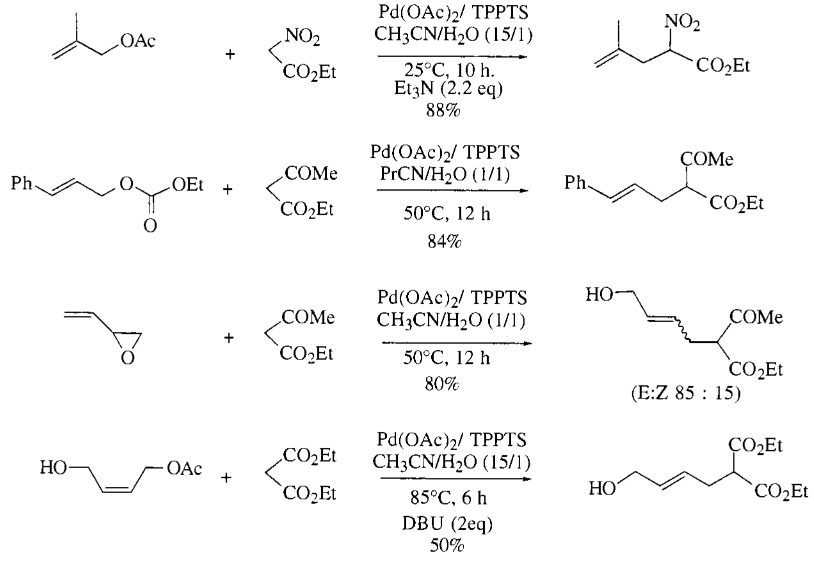


These conditions were applied to various substrates [33]. The phenyl group could be substituted by a thienyl group and carbocycles could be also obtained with moderate yield (Scheme 13).

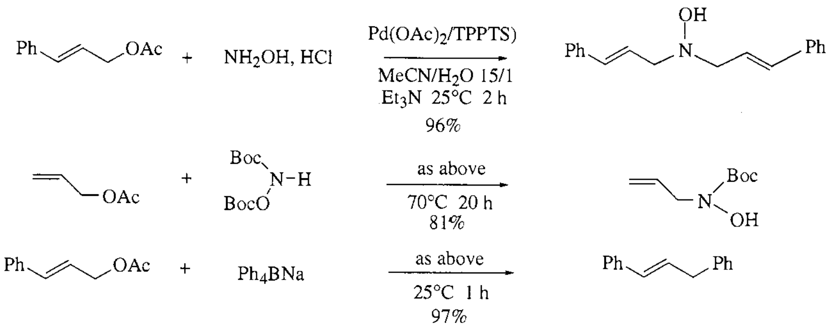
The precise mechanism is not established yet. The formation of a single isomer can be rationalized by two alternative mechanisms starting from the same intermediate **1**. Path A requires the *syn* addition of the palladium species on the double bond, followed by benzylic water substitution. This *anti* addition process accounts for the relative *syn* configuration of the hydrogen atom and the hydroxyl group. Path B consists of a Wacker-type process including *anti* nucleophilic attack of water on the double bound, formation of the six-membered palladacycle **2**, and reductive elimination leading to the same relative stereochemistry:



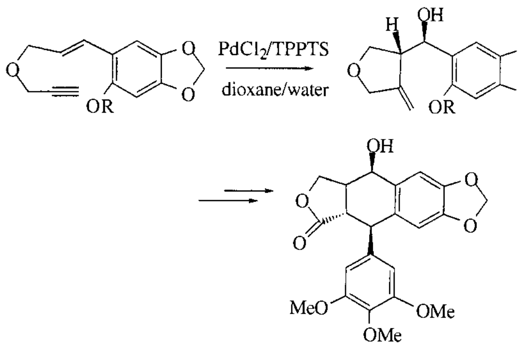
The ease of availability of acyclic substrates has made this atom-economical reaction a very practical approach for the construction of podophyllotoxins skeleton [34]:



Scheme 14.



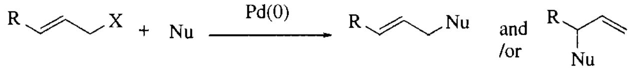
Scheme 15.



2.7. Reactions of allylic compounds via π-allylpalladium complexes

2.7.1. Allylic substitution

Palladium allylic substitution, first realized as a stoichiometric reaction, was later developed in a catalytic version and was probably the most widely used palladium methodology in organic synthesis [2]. A wide range of carbonucleophiles (stabilized and non stabilized) as well as heteronucleophiles reacted with allylic substrates:



Several allylic substrates reacted with stabilized nucleophiles using the palladium associated with the trisodium salt of the tri(*m*-sulfonylphenyl)phosphine (TPPTS) [11]. It is remarkable that, in most cases, the nucleophile reacted in water without transformation into the enolate by addition of base. The allylic allylation proceeded under neutral conditions using allylic carbonates and vinyloxiranes giving substituted compounds in good yields with nucleophiles such as acetoacetate and ethylmalonate. Cinnamyl carbonate gave a single regio and stereoisomer with *E* configuration. Alkylation of 3,4 epoxybut-1-ene regiospecifically led to the formation of a mixture of *E* and *Z* isomers (85:15). Alkylation of acetate required the presence of a base such as triethylamine or better DBU (1,8-diazabicyclo-5,4,0-undec-7-ene) (Scheme 14).

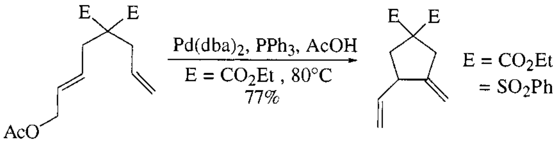
Some nucleophiles, other than carbon stabilized nucleophiles, were allylated. Secondary amines, primary amines (*n*-butylamine, 1,1-diethyl propargylamine, methylbenzylamine, etc.) reacted equally well using the palladium(0)-TPPTS system in acetonitrile–water. The hydroxylamine used as hydrochloride salt gave the bis allylated product in almost quantitative yield. The *N*,*O*-Boc protected hydroxylamine cleanly afforded the monoallylated product. With sodium tetraphenylborate, only one of the four phenyl radicals was transferred as shown in Scheme 15.

Other stabilized carbonucleophiles as well as heteronucleophiles reacted equally well [12] using the Pd(0)TPPTS system as shown in Scheme 16.

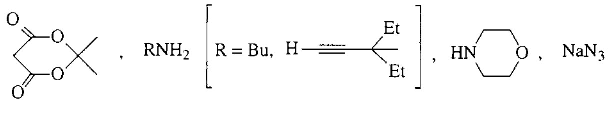
The use of water-soluble palladium(0)-TPPTS ligand in the presence of a water-insoluble nitrile such as butyronitrile or benzonitrile makes the system biphasic allowing easy separation of the catalyst from the product during the work-up. After completion of the reaction, the catalyst stays in the aqueous phase and can be recycled without substantial loss of activity. All types of nucleophiles including carbon as well as heteronucleophiles allowed an easy recycling [12].

2.8. Intramolecular reactions of alkenes

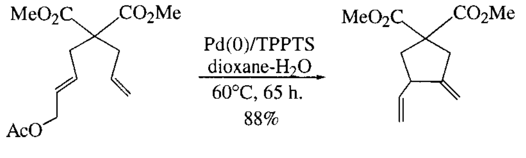
Intermolecular insertions of alkenes into π-allylpalladium have been reported recently [35]. The intramolecular version has been extensively developed by Oppolzer and proceeded smoothly to give a wide range of cyclic compounds after β-elimination. Numerous useful synthetic examples have been reported [36].



This intramolecular ene-palladium reaction has been realized under milder condition in aqueous medium using water-soluble Pd(0)-TPPTS catalyst without any additive (acetic acid) and in better yield [37] (Scheme 17).



Scheme 16.

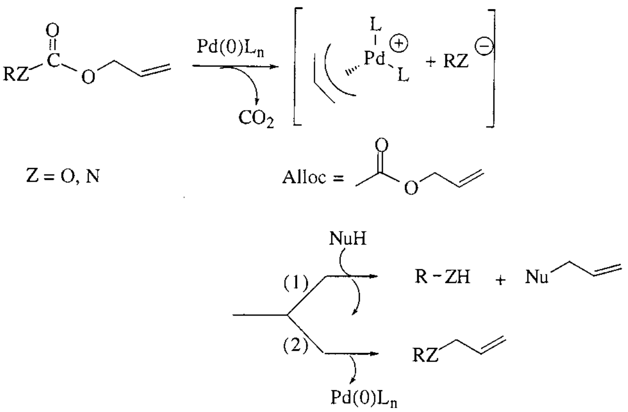


Scheme 17.

3. Protecting group chemistry

3.1. Principle

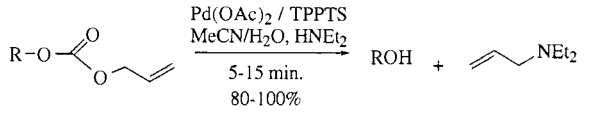
Among the usual protecting groups for amino, hydroxyl and carboxylic functions, the allyloxycarbonyl (Alloc) and allyl moieties were largely developed over the past 20 years, since a methodology using π-allylpalladium complexes was introduced for their cleavage [38].



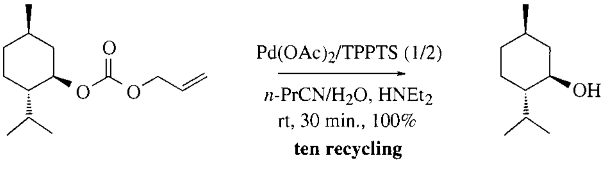
In the literature, various conditions involving different allyl scavengers such as formic acid [39], morpholine [40], tributyltin hydride [41] or potassium-2-ethylhexenoate [42] have been reported in anhydrous media. Nevertheless, these systems suffered some limitations, in particular for the deprotection of secondary amines which led to the competitive *N*-allylation (path 2). Although recent progress was achieved, using silylated amines [43] or phenyltrihydrosilane [44] as nucleophiles, a simple and inexpensive method for the cleavage of allyl carbamates derived from secondary amines seemed to be of great interest. The water-soluble catalyst generated in situ from $Pd(OAc)_2$ and the sulfonated phosphine TPPTS [10] allowed smooth and selective removal of allyl and Alloc groups, in the presence of diethylamine as the allyl scavenger, in homogeneous ($MeCN/H_2O$) or biphasic (*n*-$PrCN/H_2O$) media [45].

3.2. Deprotection of alcohols and carboxylic acids: recycling

The use of 2% Pd(0) species and an excess of diethylamine as the allyl trapping agent led to the fast deprotection of primary and secondary alcohols in homogeneous medium.



The reaction of protected Alloc menthol proceeded smoothly in a two-phase system *n*-$PrCN/H_2O$, and the



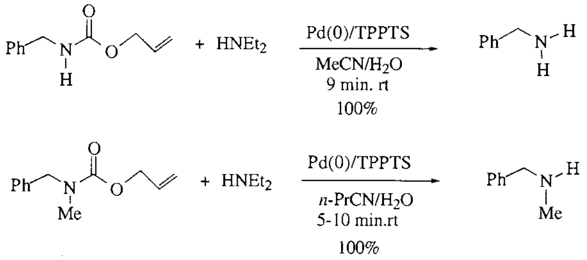
Scheme 18.

water-soluble catalyst could be recycled up to ten times, with no loss of efficiency, providing a major asset from an industrial view point [45]. In addition, the use of diethylamine as a cheap allyl scavenger is very attractive since both the excess of nucleophile and the *N*-allyldiethylamine by-product are simply removed by evaporation, affording, after aqueous work-up, very clean crude products (Scheme 18).

The same procedure was also successful for the cleavage of allylic esters in homogeneous medium. The mild conditions were compatible with other sensitive molecules such as cephalosporin, which was deprotected using 5% of the catalyst, with 93% yield. Moreover, other protecting groups remained untouched under these conditions as shown in the deprotection of a highly polyfunctional molecule, precursor of the west part of ambruticine [46] (Scheme 19).

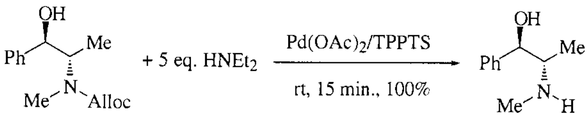
3.3. Deprotection of primary and secondary amines: recycling

The cleavage of allyl carbamates derived from primary amines under treatment with 2% Pd(0) catalyst and two and one fifth equivalents of the nucleophile, has been realized smoothly, within a short reaction time. However, with *N*-Alloc-*N*-protected secondary amines, the competitive *N*-allylation process occurred preferentially [45]. The reaction was totally selective in a biphasic system, the deprotection was carried out in n-PrCN/H_2O (6/1) medium, with 5 mol% of Pd(0) catalyst, affording the free secondary amine quantitatively without any undesired *N*-allylated product (Scheme 20).



Scheme 20.

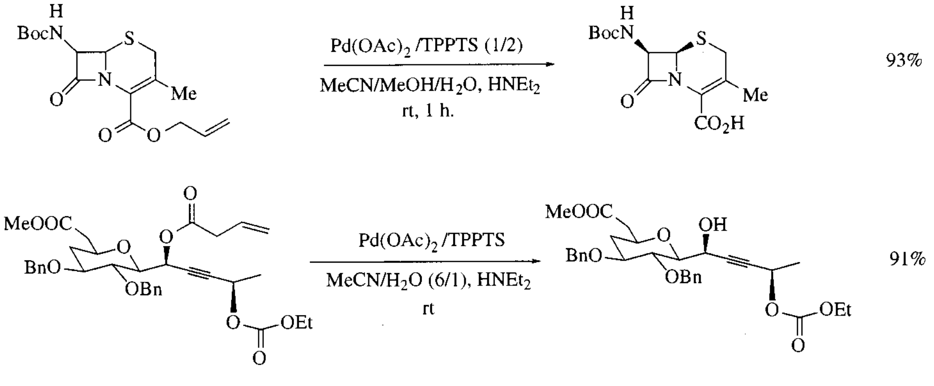
Therefore the use of a two-phase system offered therefore an efficient alternative for the total removal of allyl carbamates derived from secondary amines, avoiding the competitive *N*-allylation. It is reasonable to think that in such a biphasic medium there is almost no contact between the catalyst present in the aqueous phase and the deprotected substrate liberated in the organic layer, resulting in an enhanced selectivity toward the deprotective process. Other protected secondary amines, for instance (1*R*,2*S*)-*N*-allyloxycarbonylephedrine, have reacted equally well upon treatment with a 5-fold excess of $HNEt_2$.



This efficient and unexpensive methodology thus has allowed the removal of allyl and allyloxycarbonyl groups from various substrates and the particularly mild conditions were compatible with polyfunctionalized molecules. Moreover, both Pd(0) catalyst and the *N*-allyl diethylamine by-product were easily separated from the free alcohols, amines and carboxylic acids which were recovered in almost pure form.

3.4. Chemoselective removal (e.g. allyl versus dimethyallyl) of allylic protecting groups

The chemoselective cleavage of allylic compounds was achieved by tuning the reaction conditions; sub-



Scheme 19.

strate/catalyst ratio, homogeneous or biphasic conditions.

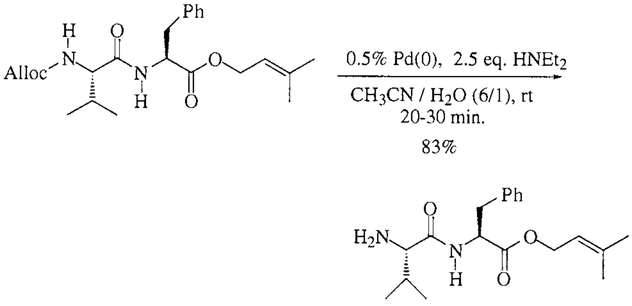
The deprotection proceeded with high selectivity, on the one hand in homogeneous medium between allyl and dimethylallyl groups by using a small quantity of Pd(0) species, and on the other hand in biphasic system between allyl and substituted allylic groups. Thus, it was possible to adjust these conditions in order to selectively deprotect doubly protected difunctional substrates.

For instance, the selective deprotection was achieved on a base sensitive cephalosporin; with 2.5% of the water-soluble catalyst, the Alloc moiety was selectively removed to give the dimethylallyl carboxylate within 30 min, and then the carboxylic acid was quantitatively recovered using 5% Pd(0). These selective deprotection reaction conditions on amino acids were then applied with success for the cleavage of the *N*-allyloxycarbamate of the L-proline without affecting the carboxylic acid protected by the dimethylallyl moiety (Scheme 21). Moreover, the reaction occurred without any trace of the competitive *N*-allylation process on the secondary amine [45c].

3.5. Application to the synthesis of peptides in solution

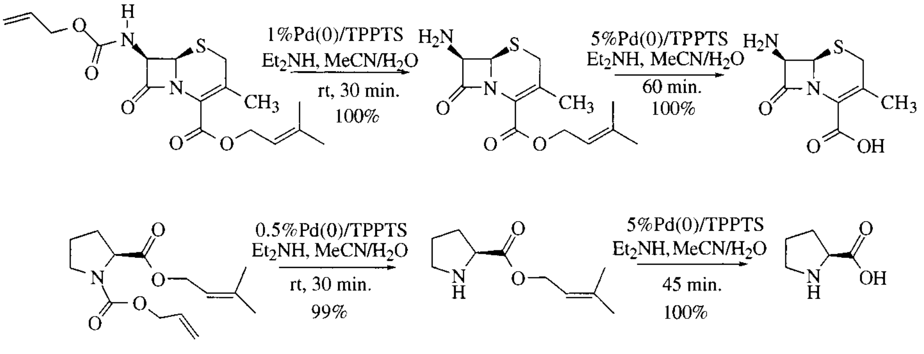
Having developed a powerful methodology for the chemoselective deprotection of *N*-allyloxycarbonyl-*O*-dimethylallyl-α-aminoesters in the presence of the water-soluble $Pd(OAc)_2$/TPPTS system, we applied these conditions to the synthesis of tetrapeptides. The assembling of the dipeptide was carried by repetition of the sequence; selective cleavage of the terminal allyl carbamate/peptide coupling, avoiding any intermediate purification. This strategy was illustrated through the preparation of tetrapeptides [47]. The classical coupling agents TBTU [48] or the cyclic propylphosphonic anhydride PPA [49] were used and it was possible to eliminate the by-products by either acidobasic or simple aqueous treatment, to provide very clean crude coupled compounds (Scheme 22).

The following step consisted in the selective deprotection of the terminal amine moiety of the dipeptide. This reaction is a critical step of the sequence since the deprotected amino group can react with the terminal ester to produce diketopiperazine derivatives. In the presence of 0.5% of the water-soluble Pd(0) species, the terminal allyl carbamate was selectively removed, without any formation of the undesired cyclized by-product. Within very short reaction time, the amino free dipeptide was obtained in 83% yield and was of very good purity after simple aqueous work-up.

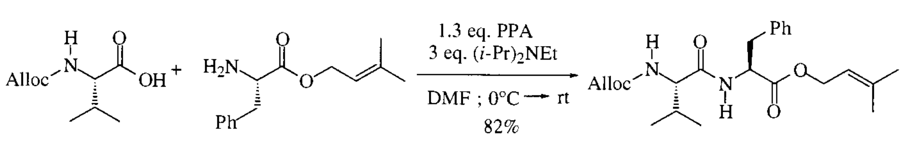


The synthesis of tetrapeptides was then achieved according to this methodology. An illustrative example is shown in Scheme 23, L-valyl-L-phenylalanyl-*O*-dimethylallyl was coupled with *N*-allyloxycarbonyl-L-valyl in the presence of TBTU as the coupling reagent.

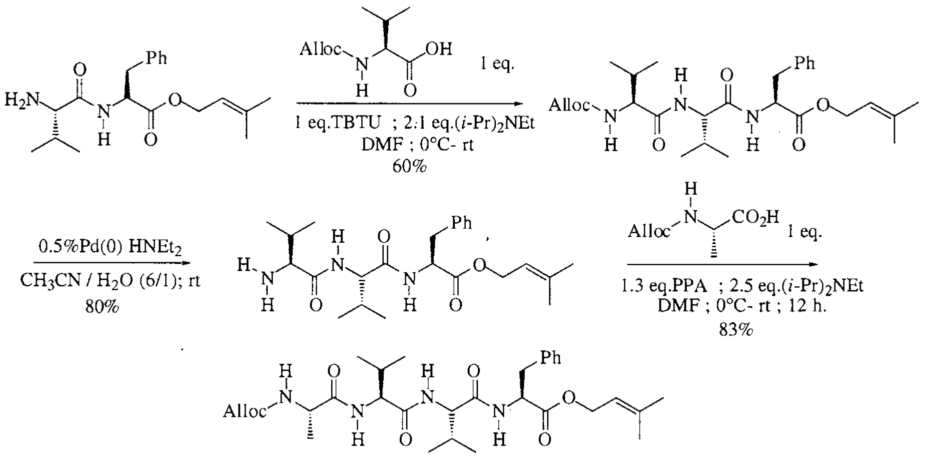
A rapid methodology was thus developed for the preparation of peptides in solution, using the selective



Scheme 21.



Scheme 22.



Scheme 23.

removal of an allyl carbamate in the presence of a substituted allylic ester, promoted by the water-soluble Pd(OAc)$_2$/TPPTS catalytic system [47]. This technique proved to be efficient for the synthesis of peptides that could be used as building fragments for the assembling of larger molecules. As no purification was required throughout the elongation, these conditions were suitable for industrial process since the coupling and deprotection steps could be carried out in large scale and short reaction times.

4. Conclusions

Since the development of the Ruhrchemie–Rhone Poulenc process using a modified water-soluble rhodium complex in the hydroformylation methodology, the concept of transition metal catalysis in water is now commonly used. The excellent compatibility of palladium catalysts, phosphine free or containing water-soluble phosphines, which was not expected even by experts in catalysis, has increased the potential of modern palladium catalysis.

In most of the reactions catalyzed by palladium in water described in this article, careful selection of reaction conditions, co-solvents and catalysts is very important for long life catalyst and new selectivities. The palladium catalyzed reactions with water-soluble phosphines (e.g. sulfonated phosphines) provides advantages of the two phase aqueous system, easy separation and recycling of the expensive palladium. It seems that the use of water will become increasingly popular in the future for fine synthetic chemistry in industry and at universities.

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