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Mini review

A new frontier in the metal-catalyzed cross-coupling reaction field. The palladium-promoted metal–carbon bond formation. Scope and mechanism of a new tool in organometallic synthesis

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Abstract

The synthetic uses and the investigation of the reaction mechanism of the Pd-catalyzed metal–carbon bond-formation process are accounted. Preparations of simple σ-metal metal acetylides of type M–C≡C–R (M = Fe, Ru, Mo, W; R = H, Alkyl, Ph), homo and heterobimetallic complexes of type M–C≡C–Thiop–C≡C–M′ (Thiop = 2,5-thiophene; M, M′ = Fe, Ru, Mo, W), polymetallaacetylide tethers of type M–C≡C–Thiop–C≡C–M′(η^5-Cp)–C≡C–Thiop–C≡C–(η^5-Cp)M′–C≡C–Thiop–C≡C–M (M = Re, Mn; M′ = Fe), and metallaacetylide polymers of type $[–M–C≡C–Ar–C≡C–]_n$ (Ar = 2,5-thiophene, 1,4-phenylene) are reported. By the use of properly designed model substrate principal intermediates (i.e. oxidative addition, transmetalation) involved in the catalytic cycle have been isolated and fully characterized. Kinetic and spectroscopic studies of the reaction mechanism have evidenced that, depending from the reaction conditions, the transmetalation step may proceed by two pathways: (i) in concentrated solutions of the complex of oxidative addition ($\cong 10^{-2}$ M), transmetalation occurs through the formation of the intermediate species which is an associative complex between the substrate and the organostannane (associative mechanism). (ii) When transmetalation is performed using the complex of oxidative addition in lower concentrations ($\cong 10^{-4}$ M), the reaction proceeds through formation of a highly-reactive solvent-coordinate species (dissociative mechanism). These results are showing clear analogies with mechanistic studies of the carbon–carbon coupling process, thus with the use of these model substrates, a unique opportunity to investigate factors affecting the metal–carbon bond formation reaction is offered, as well as the possibility to shed light on unclear aspects of the carbon–carbon coupling itself, a phenomenon of paramount importance in synthetic organic chemistry. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Metal acetylides; Poly(aryleneethynylene); Poly(metallaaryleneethynylene); Palladium catalysis; Stille coupling; Reaction mechanisms

1. Introduction

The research work we are going to describe in this paper has a very precise starting date that is the beginning of August 1988, when one of the authors (Lo Sterzo) received a letter by John K. Stille announcing his surprise, and requesting for an explanation, upon obtaining a totally unexpected result from the X-ray structural determination of one of his samples [1]. Just a few weeks before, after a long post-doctoral stay, Lo Sterzo had left his research group to return to Italy, leaving some reaction products to be examined. One of them was a polymetallic complex that, according to the synthetic route adopted, was expected to be the dicobalt hexacarbonyl derivative of the bimetallic 1,2-bis(cyclopentadienyl)ethynyl framed complex **4**; however, the X-ray structural determination revealed that an isomeric structure (**5**) was instead obtained (Scheme 1). This led Lo Sterzo to realize that during the synthetic process a rearrangement had occurred: thus, instead of a Cp–I moiety (**1**) an Fe–I moiety (**2**) was formed, and as a consequence the Pd-catalyzed coupling with the trimethyltinacetylide derivative (**3**), and the subsequent reaction with $Co_2(CO)_8$ has led to the formation of complex **5** instead to that of the 1,2-bis(cyclopentadie-

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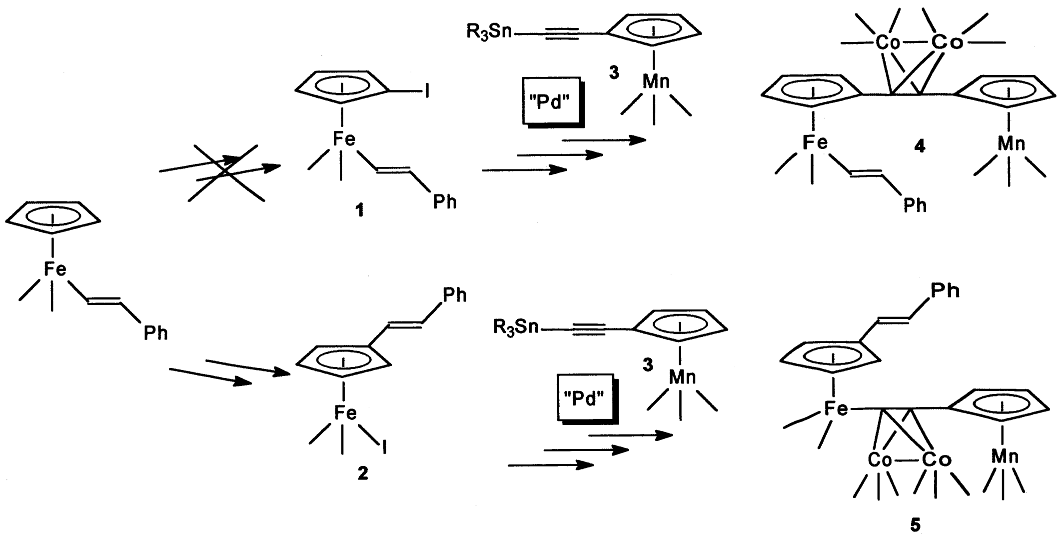


Scheme 1.

nyl)ethynyl framed complex **4** [2]. On considering this result, Lo Sterzo was lucky enough to perceive that the accidental formation of **5** was suggesting the existence of a new and intriguing scenario, widening the synthetic possibilities offered by the palladium catalysis, i.e. the possibility to achieve a Pd-promoted coupling of metal halides and organostannanes.

In this work, we will try to describe the most rewarding consequences we were granted upon devoting attention to this unexpected result. Having recently reported [3] the novel synthetic applications made possible by exploiting these results, in the present work we will only shortly summarize the synthetic aspects, mainly reporting on mechanistic studies.

2. Synthetic aspects

2.1. Preliminary studies

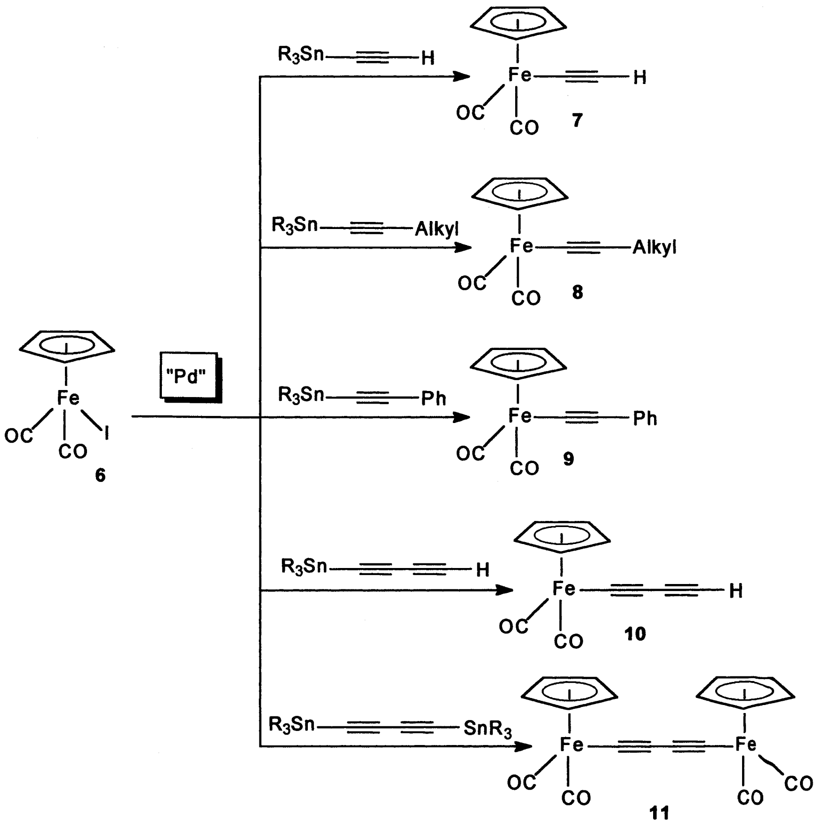
The intuition that the formation of **5** had occurred by an unprecedented Pd-promoted process was readily rewarded by the encouraging results obtained upon a preliminary screening of the reactivity of the commercially available (η^5-C_5H_5)Fe(CO)$_2$I (**6**) with a series of organostannanes in the presence of a catalytic amount of $(Me_3CN)_2PdCl_2$ in DMF (typical Stille conditions [4]). The corresponding iron acetylide complexes (η^5-C_5H_5)Fe(CO)$_2$C≡CR (**7**–**11**) were obtained in moderate to good yields [5] (Scheme 2).

These results clearly demonstrated that, in analogy to the behavior of organic electrophiles, an iron–iodide moiety, in the presence of palladium, may undergo a cross-coupling reaction with an organostannane ending with the formation of an iron–carbon bond. Subsequently we increased the number of transition metal iodides to study under conditions of palladium catalysis, and the ruthenium, molybdenum and tungsten iodide complexes **12**–**14** were thus reacted with representative organostannanes in the presence of palladium catalyst (Scheme 3). All reactions performed well and the corresponding metal σ-acetylides **15**–**23** were smoothly formed [6].

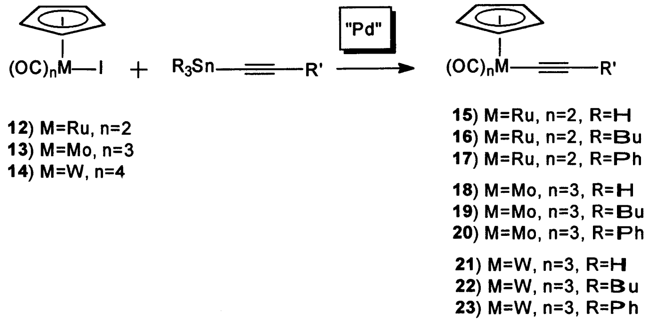
2.2. Metallaacetylide dimers and oligomers

Since compounds **15**–**23** are model and building blocks of highly ethynylated organometallic structures, a subject of relevant interest in material science, we decided to explore the use of this novel synthetic procedure for the preparation of more elaborated compounds such as bimetallic complexes with metal centers spaced by a bis(ethynyl)aromatic module. The reaction of the cyclopentadienyl metal iodides **6** and **12**–**14** with 2,5-bis[(tributyltin)ethynyl]thiophene (**24**) in the presence of zerovalent palladium led to the symmetrical functionalization with metals of both acetylenic termini of the bis(etynyl)thiophene spacer [7] with formation of the homo-bimetallic derivatives **25**–**28** (Scheme 4a). More challenging was the preparation of the corresponding hetero-bimetallic derivative **37** that was achieved [8] by the stepwise introduction of the two different metal centers on the acetylenic termini of the bis(etynyl)thiophene spacer (Scheme 4b).

It is worth noting that the synthetic path leading to the hetero-bimetallic complex **37** is based on three different uses of Pd-catalysis. Complex **30** is formed by the Heck [9]–Cassar [10]–Sonogashira [11] ethynylation reaction, complex **32** is formed by the Stille [4] coupling, and complexes **34** and **37** have been formed by our Pd-catalyzed metal-carbon bond formation procedure [3]. The unique potential offered by the combined uses of



Scheme 2.



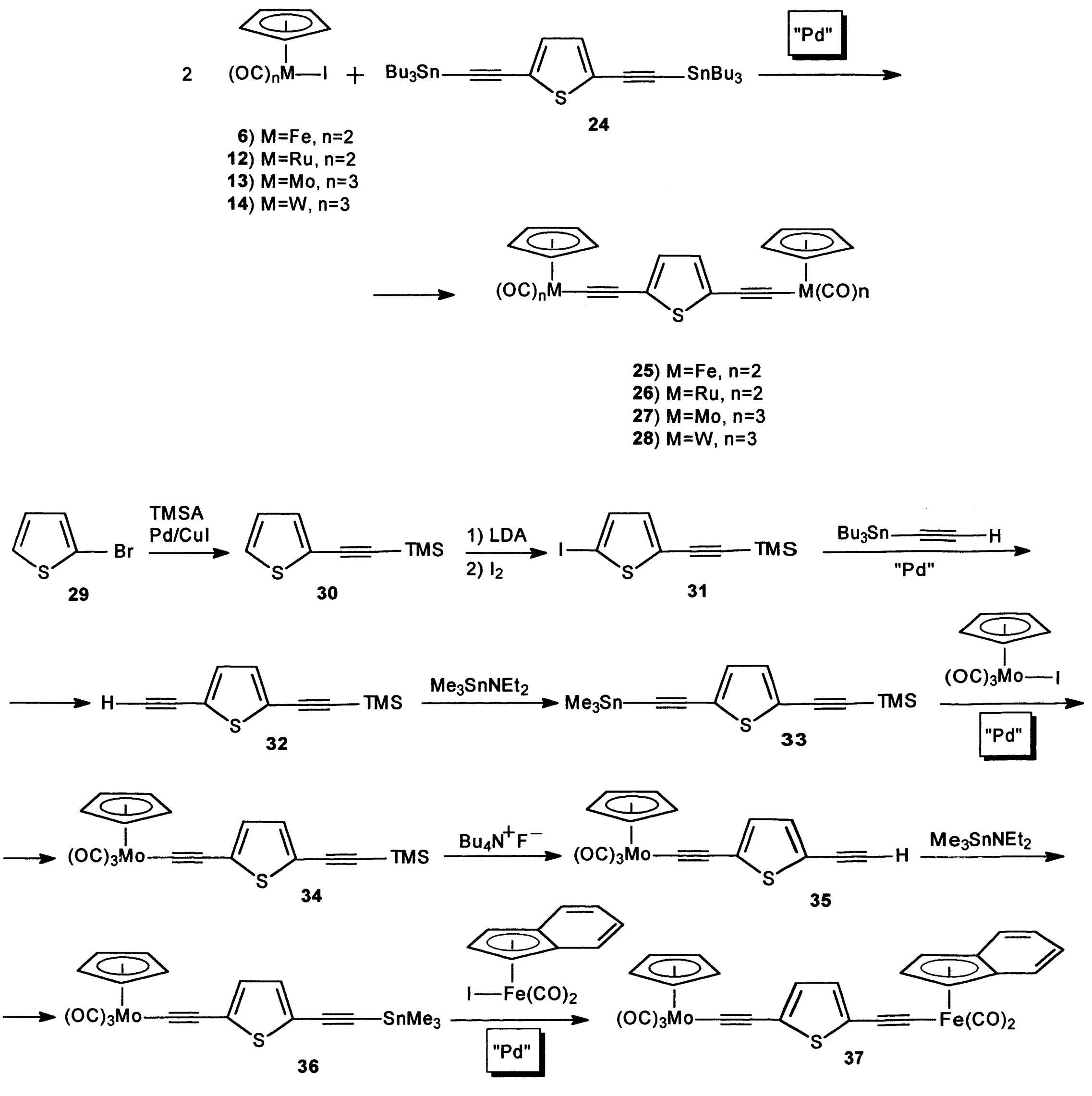
Scheme 3.

these different Pd-catalyzed processes for the construction of highly elaborated polymetallaacetylide blocks was further demonstrated [12] by the preparation of the polymetallaacetylide tethers **44a** and **44b** (Scheme 5).

2.3. Organic and organometallic highly ethynylated polymers

At this point we were ready to test this synthetic manifold with the preparation of organometallic polymers having a backbone composed of conjugated polyynes and transition metals. These materials are of relevant interest in material science in view of their promising liquid crystalline, magnetic, optical, and electronic properties [13]. While undertaking this new task, we discovered a new and convenient synthetic protocol to form tributyltinethynyl aromatic derivatives, i.e. the nucleophilic coupling partners to be used both in the Stille ethynylation reaction and in our Pd-catalyzed metal–carbon bond formation procedure. This transformation consists of an original one-pot route straightforwardly leading from aromatic halides to the corresponding tributyltinethynyl aromatic derivatives and, further, to their direct use to form organic and organometallic polymers. This novel approach to highly ethynylated materials has been named the extended one-pot (EOP) procedure [14]. In this procedure formation of the tributyltin acetylides does not require isolation of the difunctionalized alkyne precursors and polymerization is straightforwardly carried out in the same pot where tributyltin acetylides were formed. In Fig. 1 three EOP pathways (path a_1, path a_2 and path b) are outlined, respectively, leading to (i) poly(arylene-ethynylene) co-polymers [14] $[-Ar-C{\equiv}C-Ar'-C{\equiv}C-]_n$ (path a_1), or (ii) poly(arylene-ethynylene-co-metalla-ethynylene) [15] $[-Ar-C{\equiv}C-M(L)_m-C{\equiv}C-]_n$ (path a_2) and (iii) poly(arylene-ethynylene) homo-polymers [16] $[-Ar-C{\equiv}C-]_n$ (path b).

All EOP procedures (path a_1, path a_2 and path b) consist of three straightforward steps which are carried out consecutively in the same reaction pot, just by



Scheme 4.

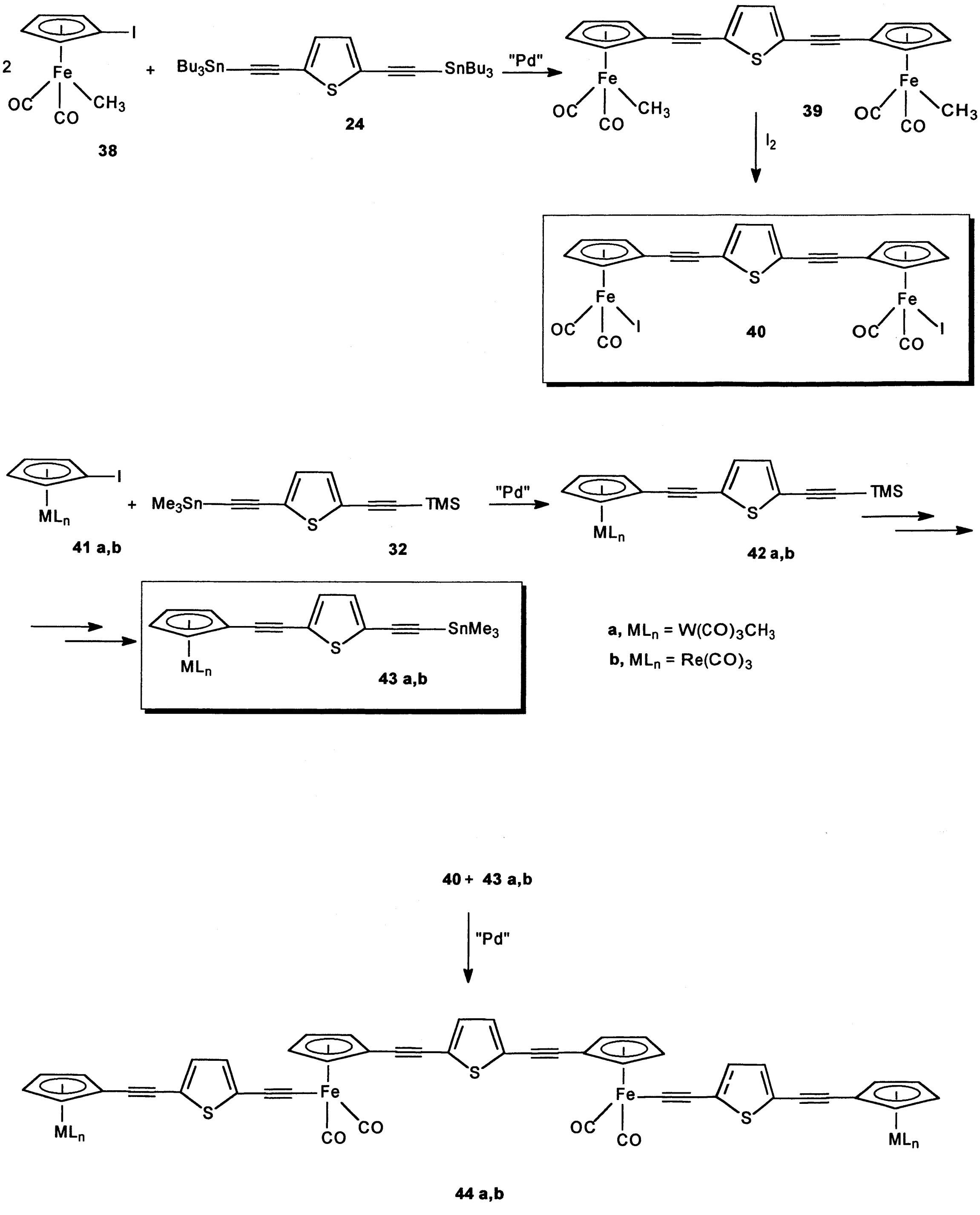
adding reactants sequentially up to the formation of the polymeric product. Path a_1 and path a_2 procedures differ from path b by the fact that, under the conditions of path a_1 and path a_2, co-polymers (either organic or organometallic) are obtained, while under the conditions of path b homo-polymers are obtained.

2.3.1. *Path a_1 and path a_2: formation of organic or organometallic co-polymers*

In step 1, a diiodoaromatic compound (I–Ar–I) is reacted with two equivalents of tributyl(ethynyl)tin ($Bu_3SnC{\equiv}CH$) in the presence of Pd^0. In this reaction the diethynylaromatic compound (H–C≡C–Ar–C≡C–H) is formed along with two equivalents of Bu_3SnI side product. To this mixture two equivalents of LDA are added causing deprotonation of the terminal acetylenic functionalities and their recombination with the Bu_3SnI side product to form the corresponding tin acetylide (Bu_3Sn–C≡C–Ar–C≡C–$SnBu_3$) (step 2). Following this transformation, alternatively a second diiodoaromatic compound (I–Ar′–I) (step 3—path a_1) or a metal diiodide compound (I–M–I) (step 3—path a_2) is added to the reaction mixture; and by a second Pd^0-promoted process the corresponding poly(arylene-ethynylene) co-polymers $[-Ar-C{\equiv}C-Ar'-C{\equiv}C-]_n$ (path a_1), or poly(arylene-ethynylene-co-metalla-ethynylene) $[-Ar-C{\equiv}C-M(L)_m-C{\equiv}C-]_n$ (path a_2) are formed.

2.3.2. *Path b: formation of homo-polymers*

By reacting, in a 1:1 stoichiometric ratio, a diiodoaromatic compound (I–Ar–I) and tributylethynyltin (Bu_3Sn–C≡C–H) in the presence of Pd^0 a mixture of the diethynylaromatic compound (H–C≡C–Ar–C≡C–H), the iodo(ethynyl)aromatic compound (I–Ar–C≡C–H), and unreacted diiodoaromatic (I–Ar–I), along with an equivalent amount (per equivalent of ethynyl group



Scheme 5.

reacted) of Bu_3SnI is obtained (step 1). Treatment of this mixture with an equivalent amount of LDA, while leaving the I–Ar moieties unaffected, allowed recombination of the ethynyl moieties with Bu_3SnI to form a mixture of I–Ar–C≡C–$SnBu_3$, Bu_3Sn–C≡C–Ar–C≡C–$SnBu_3$, and unchanged I–Ar–I. Thereafter, the Pd catalyst still being active, it is sufficient to warm up this mixture to achieve formation of the corresponding homo-polymers $[–Ar–C≡C–]_n$.

Fig. 2 shows representative examples (**45**–**50**) of the polymers prepared [14–16] by the use of the three EOP routes outlined in Fig. 1. Organic homo-polymers and co-polymers **45**–**48** are well soluble in common solvents (CH_2Cl_2, $CHCl_3$, THF), their molecular weights esti-

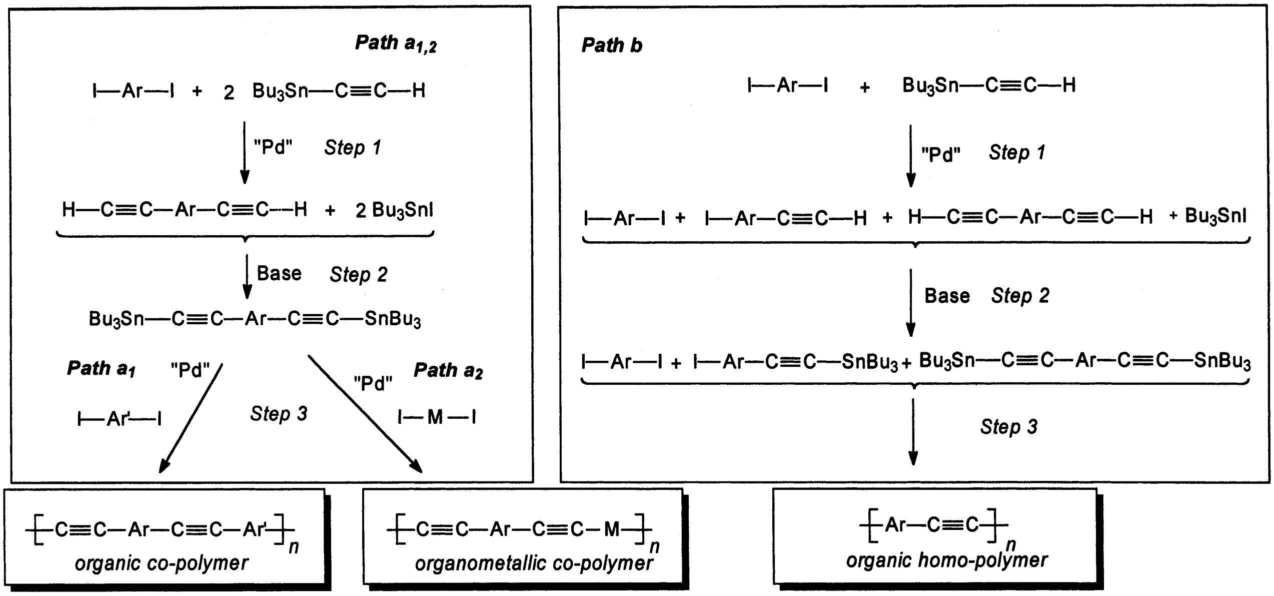
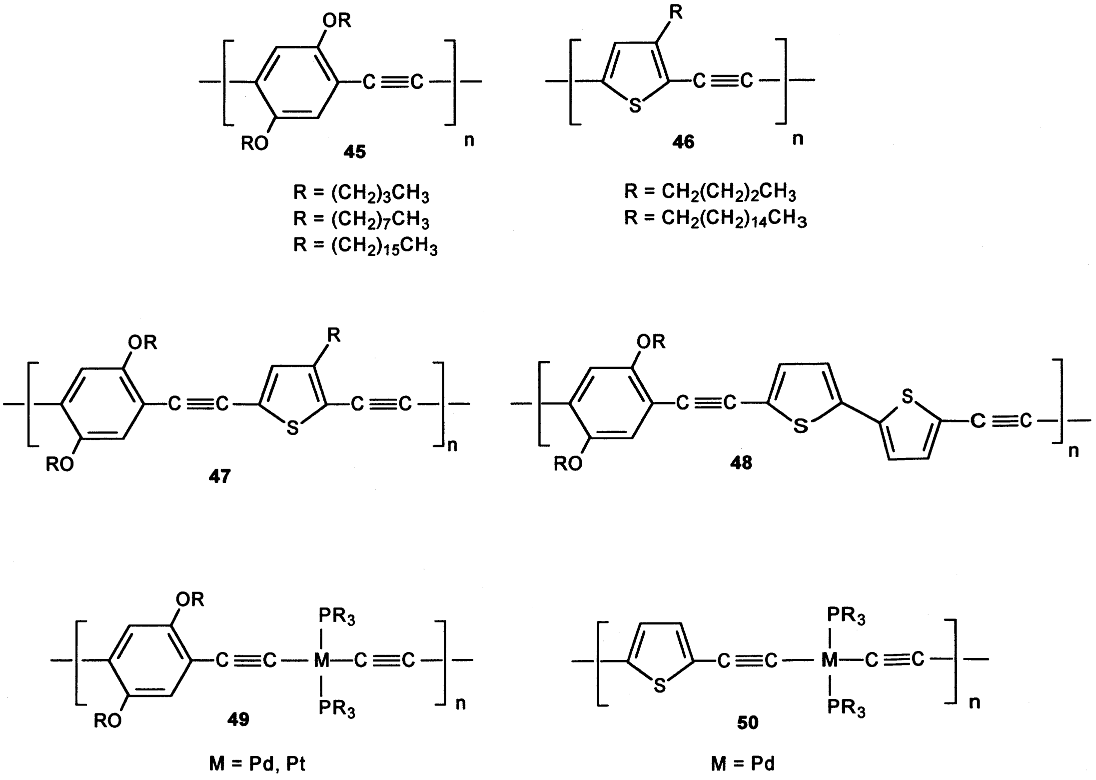


Fig. 1. Different uses of the EOP procedure.

mated by GPC accounts for chain lengths in the range of 23–45 repeating units [14,16]. In contrast we only obtained short chains oligomers for the organometallic materials **49**, **50** [14,15]. Nevertheless, since in conjugated polymers electronic and photoactive properties tend to saturation over a chain length of 10–20 units, the perspective of using these materials for electronic applications are not compromised.

At the end of the overall process, the polymeric material is isolated by simple precipitation and washing with appropriate solvents. From the rinsing solution the final Bu_3SnI side product may be recovered by distilla-



45

R = $(CH_2)_3CH_3$
R = $(CH_2)_7CH_3$
R = $(CH_2)_{15}CH_3$

46

R = $CH_2(CH_2)_2CH_3$
R = $CH_2(CH_2)_{14}CH_3$

47

48

49

M = Pd, Pt

50

M = Pd

Fig. 2. Polymers prepared by EOP procedure.

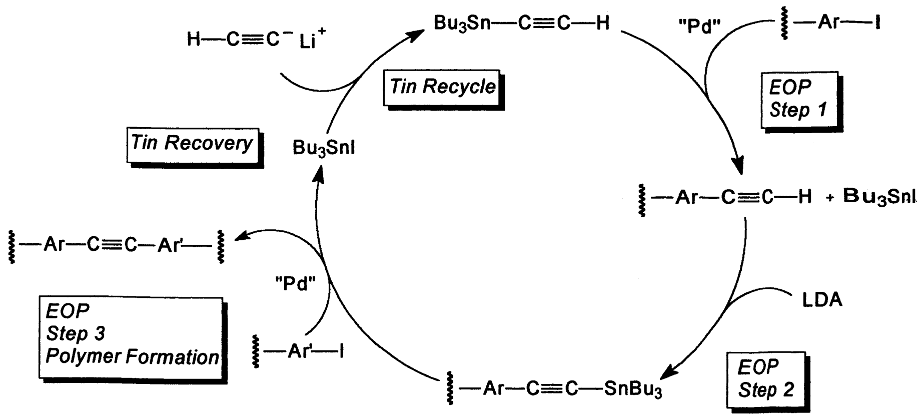


Fig. 3. The tin cycle in the use of EOP procedure.

tion and reused, to form new tributyl(ethynyl)tin ($Bu_3SnC{\equiv}CH$) (the reactant that introduces the alkyne moiety into the polymer) thus allowing a practically complete recycling of the tin reagent (Fig. 3).

In comparison with current procedures to prepare organic and organometallic ethynylated polymers [17], the key aspects of the process depicted in Fig. 3 are: (1) the polymers are accessed without the otherwise mandatory need of purification and handling of aromatic difunctionalized terminal alkynes. (2) Since tin acetylides are formed by reuse of the Bu_3SnI generated as by-product in step 1, no extra instable and toxic tin reagents are needed to form these key intermediates. (3) The recovery and the recycle of the tin reagent allow the overcome of the major drawback of the Stille reaction, that is the environmental concern related with the use of toxic and costly organostannanes [18]. In this respect we believe that our EOP synthetic protocol is in accord not only with the desirability of Stille protocols catalytic in tin [19], but also with the 'Atom Economy' concept recently developed by Trost [20], and the design of environmentally benign chemical processes [21].

At the end of this section it is worth to mention the attention that our Pd-catalyzed process for the formation of metal–carbon bond has received. Liu [22], Cotton [23] and Fischer [24] have made use of the coupling of metal–halides and trialkyltinacetylides in the presence of Pd to form σ-metal acetylides. In particular these studies have shown that the Ru–Cl and the M–Br (M = Mn, Re) moieties are also active partners in this Pd-catalyzed coupling process.

3. Study of the reaction mechanism

3.1. Mapping the milestones of the catalytic cycle

3.1.1. Oxidative addition

Along with the exploration of the synthetic potential of the Pd-catalyzed M–C bond formation, we also decided to investigate the mechanism of this special catalytic behavior of palladium, and we begun searching for possible analogies with the mechanism of the apparently related Pd-catalyzed C–C coupling phenomenon (Stille coupling) which is outlined in Fig. 4 [4].

The catalytic cycle consists of: (i) oxidative addition of the electrophile to zerovalent palladium; (ii) transmetalation with an organotin compound; (iii) *trans*-to-*cis* isomerization of R ligands; and (iv) reductive elimination to yield the coupled product.

It must be noted that, although single intermediates and segments of this picture have been studied independently and characterized in a number of cases [25], yet (apart of the work presented in this account) no example has ever been reported of a single reaction that has allowed the mapping of the overall catalytic cycle. Moreover, a number of recent reports reveals that a more complicated mosaic underlies this simplified picture [26]. However, these new findings do not rule out this Scheme that still remains a useful model to refer to, in order to explain key features of the cross-coupling

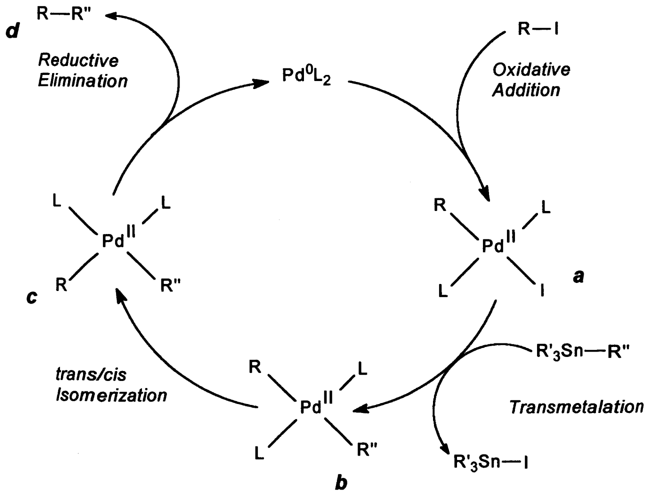


Fig. 4. Catalytic cycle of the Pd-promoted carbon–carbon (C–C) bond formation process.

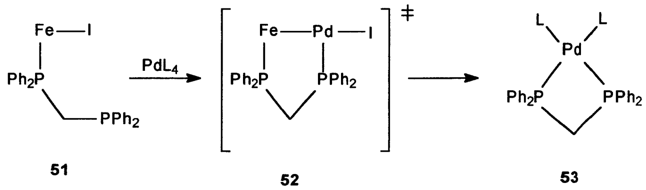
of organotin compounds with organic electrophiles. The first approach was then to seek for a parallel with the mechanism operating in the Stille coupling reaction [4] initiated by the oxidative addition of an electrophile to a palladium(0) complex. If this parallel is true, in the present case the zerovalent palladium complex should insert into the M–I bond with formation of the M–Pd–I moiety (Eq. (1)).

$$\mathrm{M{-}I} + \mathrm{Pd^0} \longrightarrow \mathrm{M{-}Pd{-}I} \qquad (1)$$

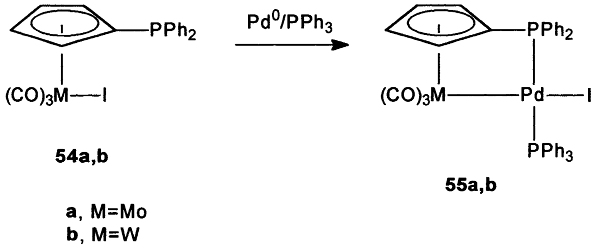
M = Fe, Ru, Mo, W

Considering the excellent ability of the cyclopentadienyl metal iodides of type (η^5-C_5H_5)$M(CO)_nI$ (M = Fe, Ru, Mo, W) to undergo the Pd-catalyzed coupling with organostannanes (Scheme 3), in a series of preliminary experiments we reacted $CpFe(CO)_2I$ with a stoichiometric amount of the complex $Pd(PPh_3)_4$ under standard coupling conditions [27], but only formation of $CpFe(CO)(PPh_3)I$ and $CpFe(PPh_3)_2I$, generated by phosphine replacement of the CO ligand on the starting iron complex was observed. We have therefore used the bis(dibenzylideneacetone) complex $Pd(dba)_2$ in order to avoid the inconvenience caused by PPh_3, but it was only possible to monitor the consumption of starting materials without detection and/or isolation of intermediates or products. In order to increase chances to isolate or at least to detect any possible product formed by oxidative addition of the Fe–I moiety to zerovalent palladium, we decided to prepare a model substrate bearing, in a mono-ligated fashion, the bis(diphenylphosphino)methane (dppm) ligand, with one of the phosphorus groups bound to iron and the other phosphorus group pending as a dangling appendix prone to trap the palladium in the event of its insertion into the Fe–I moiety (Scheme 6). Unfortunately, under these conditions the only Pd-containing products observed were deriving from the complete removal of dppm from iron and its rearrangement around palladium (**53**).

The idea of designing a substrate bearing a free coordinating arm able to stabilize the Pd after its insertion into the M–I moiety was further pursued with the preparation of the diphenylphosphinocyclopentadienyl complexes **54a** and **54b** (Scheme 7), expecting that in the eventual formation of the M–Pd–I moiety, the palladium center might benefit of a stabilizing chelating effect exerted by the diphenylphosphine sidearm which, being covalently linked to Cp, will not suffer the risk of being removed from the stable molecular framework of complexes **54a**,**b**. This hypothesis proved to be correct and both complexes **54a**,**b** reacted rapidly with a stoichiometric amount of the zerovalent palladium complex, $Pd(PPh_3)_4$ or $Pd(dba)_2$, in THF at room temperature to form the corresponding M–Pd–I species **55a**,**b** [27b] (Scheme 7). In the case of the reaction with $Pd(dba)_2$, an equivalent amount of PPh_3 was added to the reaction mixture in order to provide the ancillary ligand needed to stabilize the product.



Scheme 6.



Scheme 7.

Although complexes **55a**,**b** proved to be quite delicate materials, they were isolated and fully characterized. With their formation it has been then possible to establish that Mo–I and W–I moieties can oxidatively add to zerovalent palladium to form the corresponding M–Pd–I species; indeed these transformations can be viewed as an oxidation of Pd^0 to Pd^I by Mo^{II} and W^{II}, that in turn are reduced to Mo^I and W^I, respectively. In this respect, the electrophilicity of the M–I functionality in $CpM(CO)_nI$ (Cp = η^5-cyclopentadienyl; M = Fe, Mo, W) complexes has been demonstrated previously by their ability to oxidatively add zerovalent mercury with formation of the M–Hg–I array. Moreover, several literature reports account for the insertion of palladium and, more generally zerovalent Group 10 metals, into organomercurials and organometallic derivatives of Group 14 elements. Also complexes containing Pd inserted between a transition metal and a halide such as M–Pd–X (M = transition metal; X = Cl, Br, I) have been reported [27b] (Eq. (2)), and in some cases their formation has been rationalized as an oxidative addition of M–X moieties to Pd^0. The process outlined in Scheme 7 is thus closely comparable with the oxidative addition step triggering the Pd-catalyzed carbon–carbon coupling (intermediate **a** in Fig. 4).

$$\mathrm{R_nMX} + \mathrm{M'} \longrightarrow \mathrm{R_nMM'X} \qquad (2)$$

M = Hg, Si, Ge, Sn, Pb
X = halogen
M' = Pt, Pd, Ni

3.1.2. Transmetalation

In order to investigate the ability of complexes **55a**,**b** to perform further steps of the palladium-promoted coupling process, their reaction with trialkyltinacetylides $R_3SnC{\equiv}CPh$ (R = Me, Bu) was studied. Although the starting materials were consumed rapidly, any attempts to isolate reaction products failed. However, observation by ^{1}H- and ^{31}P-NMR provided persuasive evidences that a transmetalation process was indeed occurring (Scheme 8).

In particular, upon formation of **56a**, in the ^{31}P-NMR spectrum the two non-equivalent phosphorus atoms of **55a** appearing as two doublets at 41.6 and 20.2 ppm. ($J_{P-P} = 454$ Hz)] changed into two new doublets at 39.3 and 28.6 ppm ($J_{P-P} = 454$ Hz). The unchanged value of the coupling constant indicates that the *trans* geometry is retained in the new species. In addition, formation of Me_3SnI, detected by GC-MS, confirmed the occurrence of the transmetalation process.

Encouraged by the clear spectroscopic evidences for the formation of **56a**, we were urged to design a more suitable model that would also allow the isolation of the transmetalation product.

We turned thus our attention to the use of a substituted η^5-Cp ligand that, while maintaining the key presence of the chelating diphenylphosphino arm, was bearing bulky substituents that would make the products more robust and easier to handle. This idea was pursued by using the η^5-(1-diphenylphosphino-2,4-diphenyl)cyclopentadienide ligand **60**, relying on the expectation that, without altering the reactivity pattern under investigation, the introduction of two phenyl groups into the Cp ring could impart a certain degree of kinetic stabilization to these otherwise thermodynamically unstable intermediates.

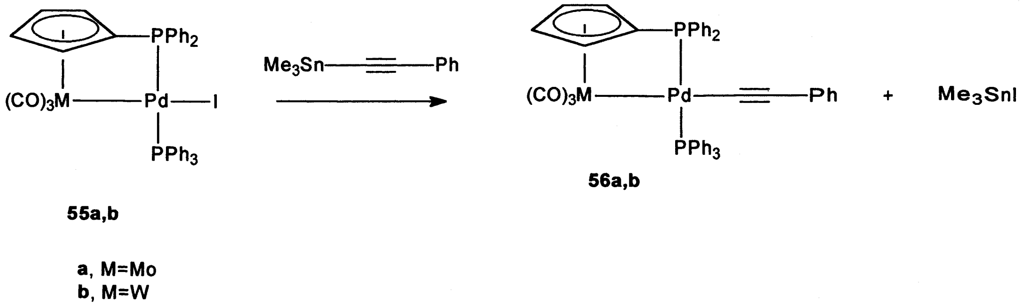
Complexes **62a**,**b** were obtained straightforwardly by the procedure outlined in Scheme 9 [28]. In the case of **62b** it was also possible to determine the molecular structure by single crystal X-ray analysis (Fig. 5).

As it was for **54a**,**b**, complexes **62a**,**b** smoothly reacted with $Pd(PPh_3)_4$ or $Pd(dba)_2/PPh_3$ in THF to form complexes **63a**,**b** as a consequence of the oxidative addition of the corresponding Mo–I and W–I moieties to zerovalent palladium (Scheme 10). However, in the present cases yields were very high and the products showed to be quite stable. The solid state structure of **63b** was determined by X-ray diffraction methods. In Fig. 5 the plots of **62b** and **63b** with thermal ellipsoids are shown.

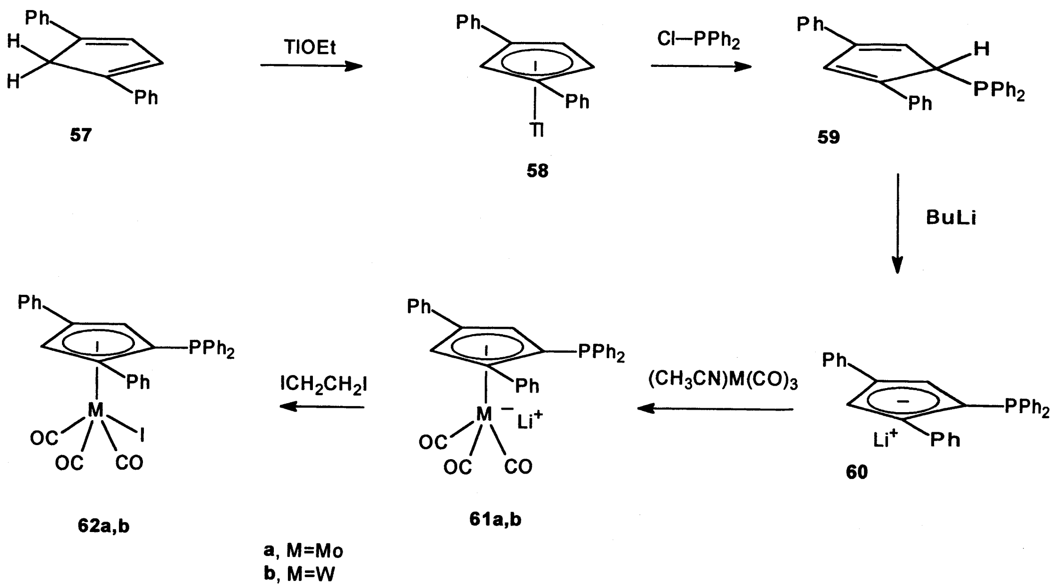
Once the oxidative addition process was clearly confirmed with the isolation of complexes **63a**,**b**, we took advantage of the easy access and of the improved robustness of such important intermediates to gain further support for the occurring of the transmetalation process that, in the reaction of complexes **56a**,**b** with organostannanes, was only envisioned by NMR spectroscopy (Scheme 8).

Both the Mo–Pd and the W–Pd complexes **63a**,**b** showed a good reactivity toward a series of phenylethynyltrialkyltin derivatives affording the corresponding products of transmetalation; however, isolation of complexes **64a**,**b** required some precautions (Scheme 11).

Although ^{31}P-NMR analysis clearly indicated that, in DMF, by the action of the organostannane the initial oxidative addition complexes (**63a**,**b**) were quantitatively transformed into new products, attempts to obtain the pure products of transmetalation **64a**,**b** by column chromatography always ended with the recovery of a product of molecular rearrangement, later revealing an intriguing structure and reactivity [29], and a consistent amount of the starting materials **63a**,**b**, the latter formed by the reverse reaction between **64a**,**b** and Bu_3SnI. Avoiding chromatography, isolation of the products of transmetalation was efficiently achieved by removal of the DMF solvent, dissolution of the residue in THF and subsequent addition of pentane, which caused precipitation of **64a**,**b**. Formation of the products of transmetalation **64a**,**b** represented clearly an important forward step toward the identification of critical intermediates along the catalytic cycle of the Pd-promoted metal–carbon bond formation and, as well, further analogies with the related carbon–carbon bond formation process have been confirmed (intermediate **b** in Fig. 4). Moreover, in complexes **64a**,**b** the metal center M and the acetylide (namely, the two partners to be coupled),



Scheme 8.

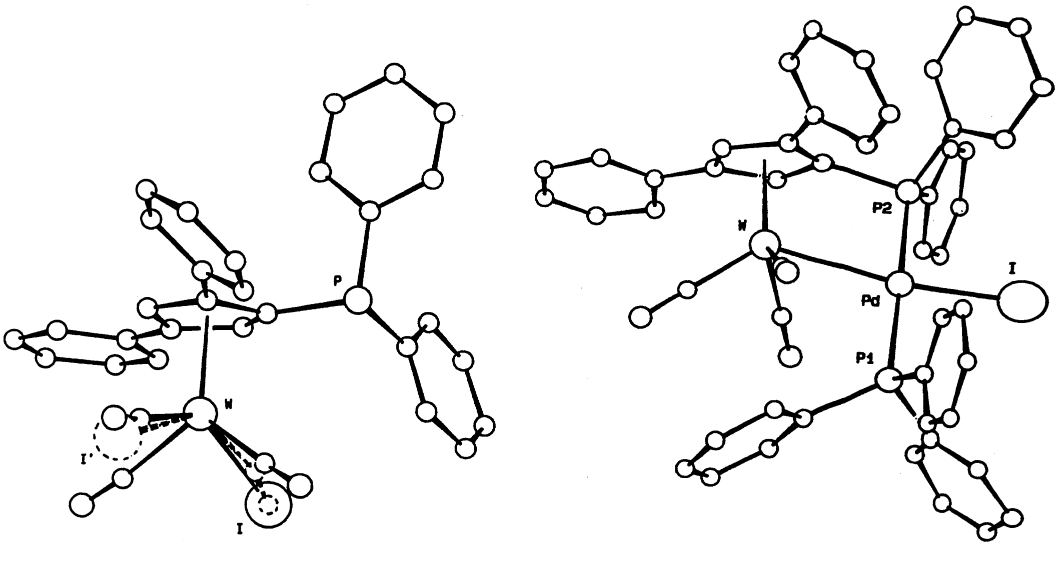


Scheme 9.

although joined by the interposition of palladium, already constitute a single molecular unit, and the completion of the coupling process, through the *trans*-to-*cis* isomerization and the reductive elimination steps is expected to be an overall downhill energetic pathway.

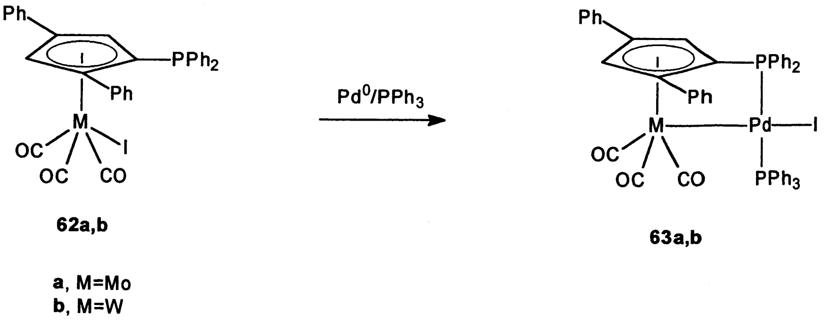
3.1.3. *Trans-to-cis isomerization and reductive elimination*

Preliminary studies concerning the possibility of inducing *trans*-to-*cis* isomerization in complexes **64a**,**b** followed by reductive elimination were carried out by ^{31}P-NMR spectroscopy. A pure sample of **64a** in DMF-d_7 displays, at room temperature, a ^{31}P-NMR spectrum consisting of two doublets at 39.3 and 28.6 ppm ($J_{P-P} = 454$ Hz), the typical pattern for two non-equivalent phosphorus lying in a *trans* fashion in a square planar complex. This situation remains unchanged as long as the sample is maintained at room temperature; however, upon raising the temperature to 323 K, a new set of doublets at 34.4 and 24.3 ppm, of smaller coupling constant ($J_{P-P} = 66$ Hz), appears in the spectrum, suggesting the occurrence of a *trans*-to-*cis* isomerization process (Scheme 12). However, shortly after, the spectrum evolved in a more complicate pattern, clearly

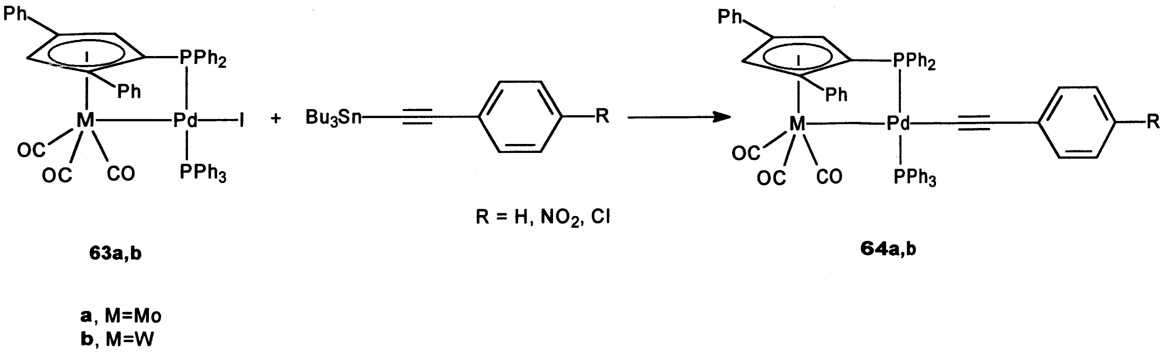


62b **63b**

Fig. 5. Drawings of the molecular structures of complexes **62b** and **63b**.



Scheme 10.



Scheme 11.

indicating dispersion of material through different processes which cannot be attributed to reductive elimination [30].

Evidently, the efficient coordinating effect exerted by the diphenylphosphine side arm on the palladium center of complexes **63a**,**b** and **64a**,**b**, if on one hand has allowed stabilization (and thus isolation) of the oxidative addition and transmetalation intermediates, on the other hand it settles palladium in such a strong chelating environment that, although allowing the *trans*-to-*cis* isomerization process, it is preventing the release of palladium and thus the reductive elimination process.

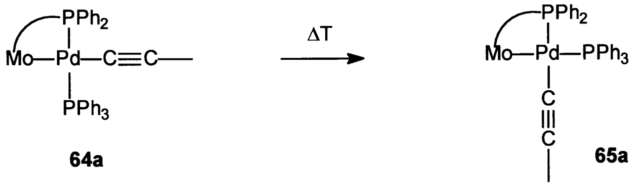
The aim of inducing reductive elimination led us to search for conditions that would favor the release of palladium from **65a**, and to this end we decided to perform the *trans*-to-*cis* isomerization in the presence of dppe [31]. Under these conditions dppe efficiently exerted a scavenging effect on Pd, inducing the reductive elimination process leading to the formation of **66a** (Scheme 13).

A definitive proof of the critical interplay of species **62a**, **63a** and **64a** in the catalytic process leading to **66a** was obtained by reacting **64a** with an equivalent amount of **62a**. The existence of two simultaneous processes was detected by ^{31}P-NMR spectroscopy (Fig. 6).

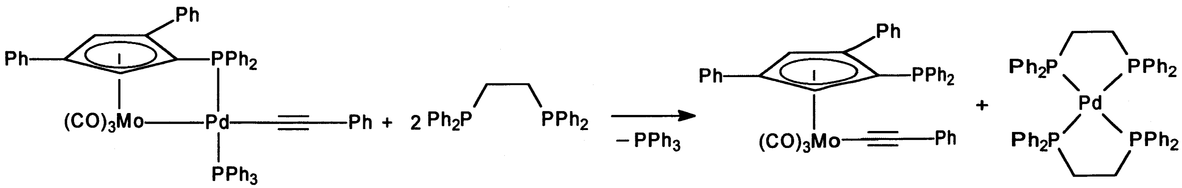
Palladium was extracted from **64a** to give **66a** by reductive elimination. Simultaneously, the Mo–I moiety of **62a** captured the palladium released from **64a** forming the oxidative addition product **63a**. The core of the catalytic turnover consists of these combined processes, as depicted in Fig. 6. These results while providing a mechanistic rationale for the palladium-catalyzed cross-coupling reaction between metal halides and organostannanes, are also demonstrating that the overall phenomenon occurs through a sequence of events closely comparable to the principal steps of the palladium-promoted cross-coupling process forming carbon–carbon bonds (Fig. 4).

3.2. An insight into the transmetalation step

During the search of suitable conditions that might help the reductive elimination process on the transmetalation intermediates **64a**,**b** to occur (Scheme 13), we also considered the opportunity of using an excess of the tin acetylide as scavenging agent for Pd and, on pursuing this investigation, an intriguing mechanistic detail came unexpectedly to light. In consideration that the transmetalation reaction usually requires an excess of tin acetylide ($Bu_3SnC{\equiv}CR$) [31], we decided to carry



Scheme 12.



64a **66a**

Scheme 13.

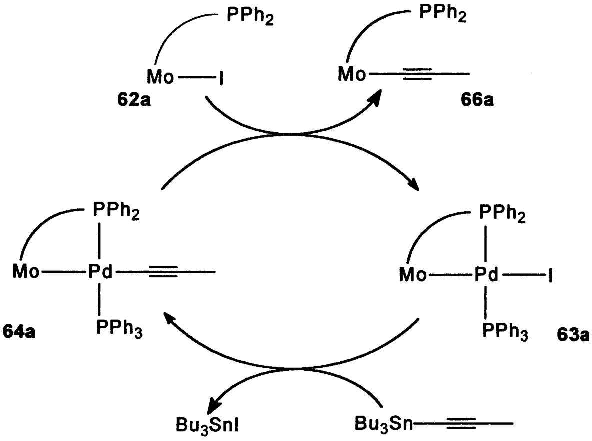


Fig. 6. Combined processes in which palladium is extracted from **64a** to give **66a** by reductive elimination and simultaneously is inserted into Mo–I of **62a** to form the oxidative addition complex **63a**.

out the preparation of **64a** using a strong excess of tin acetylide. The expectation was that, following the transmetalation and the thermally induced *trans*-to-*cis* isomerization, the excess alkyne might favor (through coordination) the release of palladium from **65a**; thus the overall process from **64a** to **66a** might be straightforwardly observed.

3.2.1. P-NMR spectroscopy. A unique tool to monitor the catalytic cycle

The reaction of **63a** with a tenfold excess of (phenylethynyl)tributyltin (**67**) was thus carried out in an NMR tube in DMF-d_7 at room temperature and followed by ^{31}P-NMR. In Fig. 7 are reported the spectroscopic variations accounting not only the transmetalation process (traces b–d), but also for the *trans*-to-*cis* isomerization (trace e) and the reductive elimination (trace f) events. Moreover, in order to fully display the unique opportunities offered by this spectroscopic technique in the study of these processes, the spectrum of the parent complex **62a** (trace a) is reported.

The ^{31}P-NMR of **62a** appears as a simple sharp singlet at −18.9 ppm (trace a). The ^{31}P-NMR spectra of **63a** (trace b) clearly accounts for the structural variations taking place with the introduction of the Pd and its ancillary PPh_3 on **62a** (Scheme 10). In **63a** the two non-equivalent phosphorus atoms bonded to palladium in *trans* configuration give rise to a simple first-order AB splitting pattern, that produces two sets of doublets, centred at 41.6 and 20.2 ppm, respectively, with a coupling constant of 454 Hz.

Upon carrying the transmetalation reaction of **63a** with $Bu_3SnC{\equiv}CPh$ (**67**) using a tenfold excess of the tin acetylide, the presence of a transient species was detected by the appearance of two doublets at 36.0 and 29.0 ppm ($J_{P-P} = 10$ Hz), respectively, which persisted until complete conversion of **63a** into **64a** occurred (traces b–d). The fact that this intermediate is observed only in the presence of a large excess of the tin reagent suggests that it is an adduct between complex **63a** and the tin acetylide. This species appears only during the time of conversion of **63a** into **64a** and is not detected at the end of the reaction. The strong variation of the ^{31}P-NMR coupling constants, from ca. 450 Hz of complexes **63a** or **64a** to 10 Hz (see expansion in trace c), indicates that the phosphorus ligands are still bound to the palladium center in the intermediate, while a severe change of the coordination geometry occurs during the trasmetalation. On the basis of these facts, a tentative description of the intermediate complex is shown in Fig. 8 as the five-coordinate structure **68**.

After completion of the transmetalation process (30 min), the temperature was increased to 353 K and after few minutes the *trans*-to-*cis* isomerization process was detected by the appearance of the two doublets at 34.4 and 24.3 ppm ($J_{P-P} = 66$ Hz) (trace e). Upon prosecuting warming, after 24 h the presence of a singlet at −20.2 ppm due to **66a** accounted the accomplishment of the reductive elimination process (trace f). In the spectrum reported in trace f the PPh_3 released from **64a**, upon formation of **66a**, appears as a broad peak at −4.5 ppm.

3.2.2. The disclosure of two alternative mechanisms

Taking advantage of the clear insight into the transmetalation process allowed by the use of ^{31}P-NMR spectroscopy and, because of the critical importance of this step along the overall Pd-catalyzed process, we decided to undertake a detailed kinetic study of this phenomenon by means of ^{31}P-NMR and UV–vis spectroscopic techniques. Experiments were carried out in DMF at 25 °C using complex **63a** in the concentration range 10^{-2}–10^{-4} M and at least a tenfold excess of

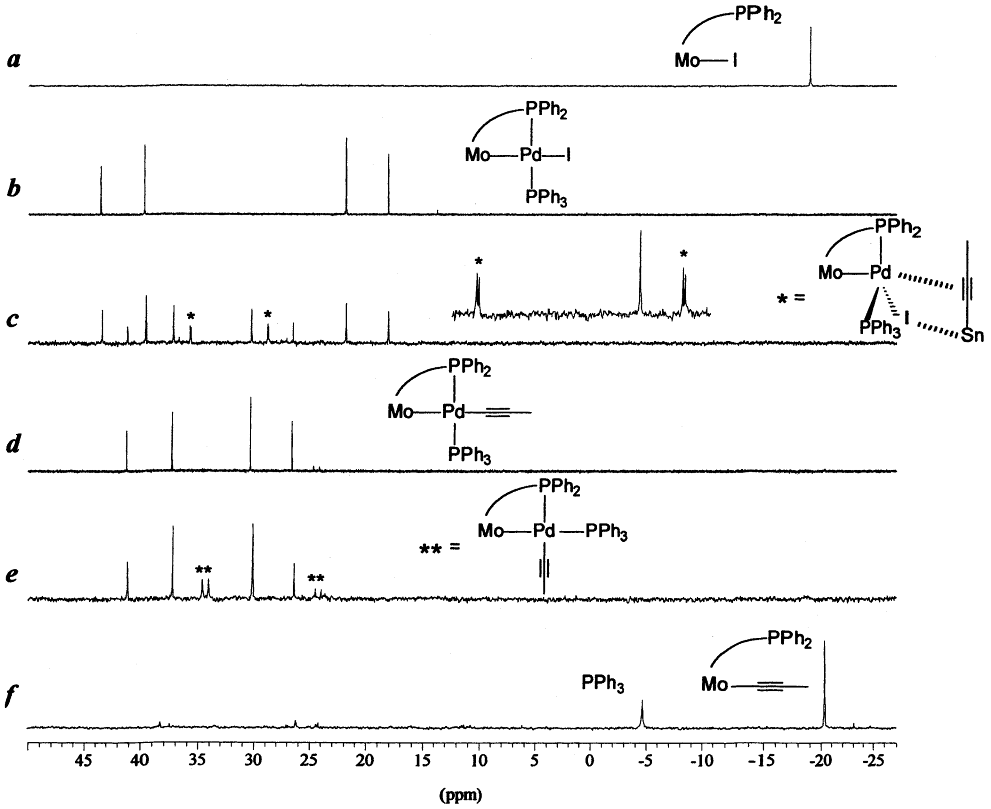
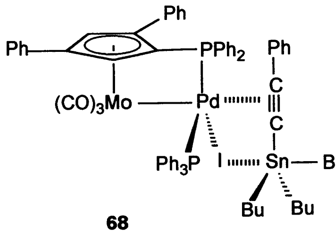


Fig. 7. ^{31}P-NMR study of sequence of transformations occurring in the Pd-catalyzed metal–carbon bond formation in DMF-d_7; (a) pure **62a**, (b) pure **63a**, (c) one equivalent of **63a** + ten equivalents of Bu$_3$Sn–C≡C–Ph (after 10 min at room temperature). Peaks marked with an asterisk (relative to the formation of **68**) are expanded in the inset, (d) complete formation of **64a** (after 30 min at room temperature), (e) *trans*-to-*cis* isomerization (spectrum recorded at 353 K), (f) formation of **66a**. In (f) free triphenilphosphine which is formed during reductive elimination, appears as broad peak at −4.5 ppm.



68

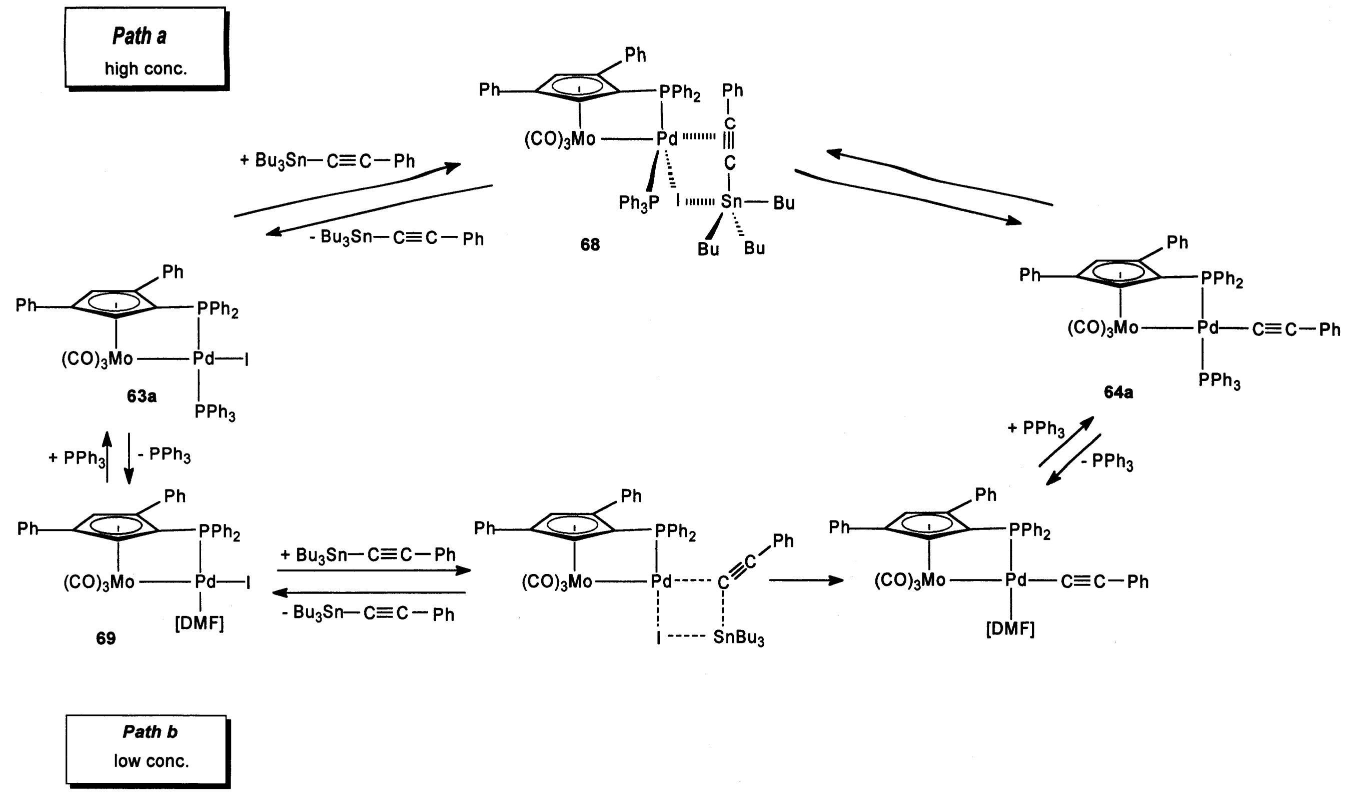
Fig. 8.

tributyltinarylacetylides Bu$_3$Sn–C≡C–(p-XC$_6$H$_4$) (X = H, Cl), in order to work under *pseudo* first-order conditions [32]. Dependence of reaction rate on the concentration of the (p-substituted phenyl)tributyltinacetylide and on the nature of its substituents has been determined. We also found an inverse rate dependence on the concentration of the substrate **63a**.

By this study we have evidenced that the transmetalation reaction of the oxidative addition complex **63a** with tributyltinarylacetylides proceeds by two different pathways (paths a and b), whose occurring is depending on the initial concentration of **63a** (Scheme 14).

In concentrated solutions of complex **63a** ($\cong 10^{-2}$ M), consumption of starting material followed a first-order behavior, and the transmetalation reaction occurred through the formation of the intermediate species **68** (path a). Disappearance of substrate **63a**, formation of the transmetalated product **64a**, as well as of intermediate **68** versus time are shown in Fig. 9. The associative complex **68** accumulates when the transformation carried out in the presence of added PPh$_3$.

When the transmetalation reaction was performed by operating under relatively low concentrations of **63a** ($\cong 10^{-4}$ M) the inverse rate dependence on the initial concentration of the starting complex **63a** was particularly evidenced, suggesting that upon increasing dilution a highly reactive solvent-coordinate species (**69**), in which PPh$_3$ has been substituted by a dimethylformamide (DMF), was formed (path b). The existence of this new species generated by dilution of **63a**, has been evidenced by recording a series of ^{31}P-NMR spectra of increasingly diluted solution of **63a** (Fig. 10). Spectra reported in traces a, b and c of Fig. 10 correspond to different concentrations of **63a** in DMF ($a = 0.029$ M, $b = 0.0019$ M, $c = 0.0010$ M). The clean doublet of doublets of the two non-equivalent phosphorus atoms in a *trans* configuration around palladium is displayed in trace a. In the more dilute sample b, a new peak appears



Scheme 14. Full reaction scheme for the transmetalation of **63a** with $Bu_3Sn-C{\equiv}C-Ph$. Path a: reaction via the metallacycle intermadiate **68**. Path b: reaction via the solvent-coordinate species **69**.

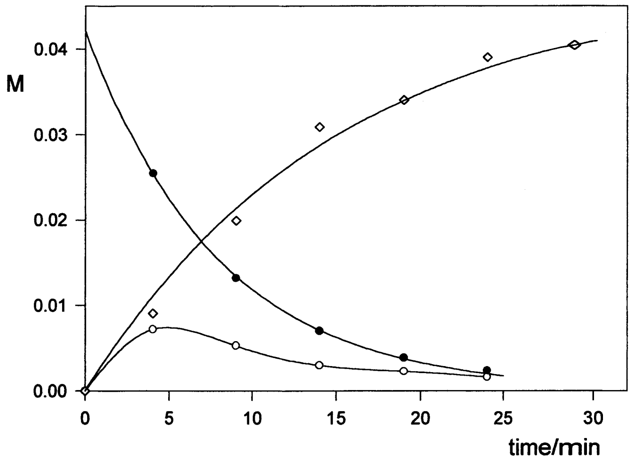


Fig. 9. Reaction profile for the transmetalation step of complex **63a** (0.045 M) with **67** (0.47 M) in DMF-d_7 at 25 °C, obtained from the ^{31}P-NMR signals of **63a** (●, δ 22.0 ppm), **68** (○, δ 29.0 ppm) and **64a** (◇, δ 30.5 ppm). The concentration values of the intermediate species **68** are only an estimate judged from peak intensities.

at δ 51.9 ppm. This becomes the main species in solution c. The change from the doublet of doublets, relative to structure **63a**, into a singlet accounts for the substitution of the PPh_3 by the solvent (DMF) to form species **69**, as represented in Scheme 15. This substitution process is favored by dilution. The signal of free triphenylphosphine is not detectable under these conditions [32].

Trace d is the spectrum obtained upon addition of an excess of triphenylphosphine to the solution of trace c (Fig. 10). Disappearance of the signal at δ 51.9 ppm and formation of the original doublet of doublets of complex **63a** accounts for the reverse reaction of Scheme 15. The formation of **69** accounts for the inverse dependence of k_{obs} on the initial concentration of **63a**. In dilute solutions, the transmetalation reaction proceeds *via* the solvent-coordinate species **69** of Scheme 15. The higher reactivity of complex **69** with respect to the phosphine-substituted complex **63a** may be due to the higher electrophilic character of the palladium center when coordinated by a poor donor ligand such as DMF. As a consequence, since dilution shifts the equilibrium of Chart 29 versus **69**, the transmetalation rate is inversely dependent on the initial concentration of complex **63a**.

In contrast, when the solvent-coordinate species **69** is generated in a PPh_3-free environment, such as the opening by DMF of its dimeric halobridged complex [33], the transmetalation rate is independent of the initial concentration of **69**, due to the absence of PPh_3.

It is remarkable to observe that path a, involving the formation of the metallacycle complex **68**, closely resembles the 'S_E2 cyclic' mechanism proposed by

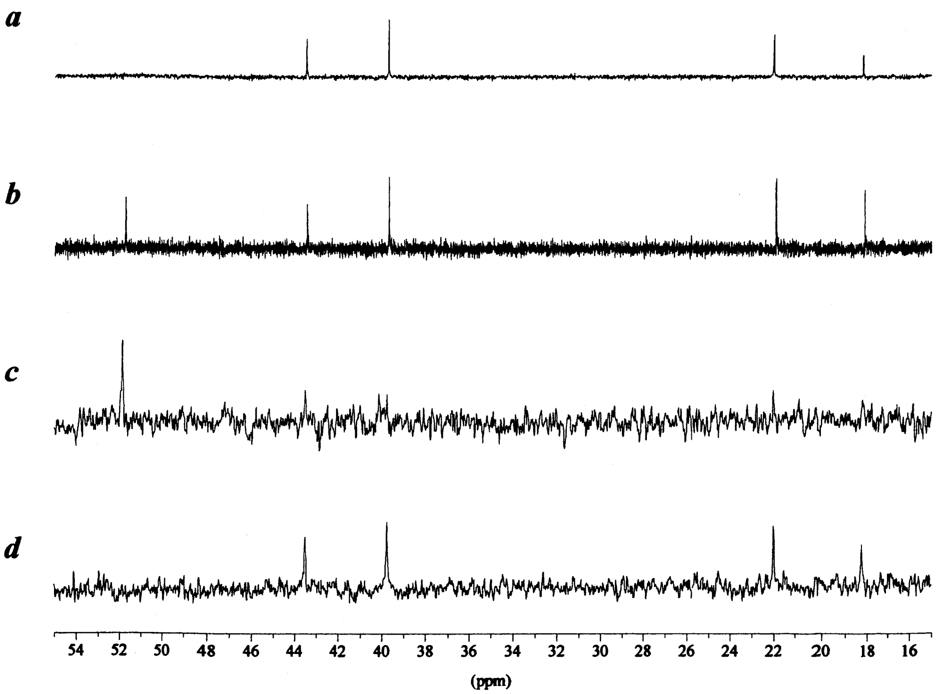


Fig. 10. 31P-NMR spectra of complex 63a at different concentrations, in DMF-d7. Trace a, 30.029 M; trace b, 30.0019 M; trace c, 30.0010 M; trace d, solution of trace c after addition of excess PPh3.

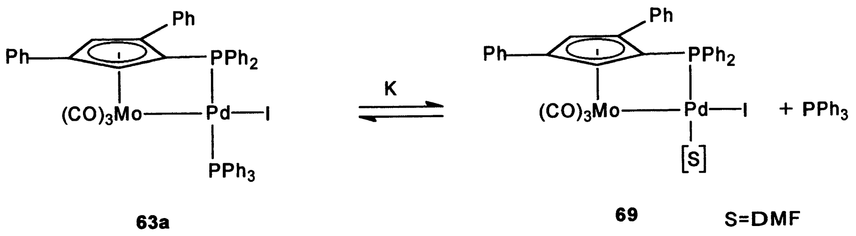
Espinet [26b,34] for the transmetalation step in the coupling of aryl halides with organostannanes (path a of Scheme 16). On the other hand, the transmetalation mechanism of path b in Scheme 14, involving the formation of the highly-reactive solvent-coordinate species **69**, is related to Espinet's 'S_E2 open' mechanism, which occurs when the cyclic mechanism is disfavored by the reaction conditions (paths b and c of Scheme 16). In this respect, it is worth mentioning that the intermediate **69** is a species also analogous to a solvent-coordinate complex proposed by Farina [26c]. Therefore, the results found in this work are characterized by clear analogies with mechanistic studies of the carbon–carbon coupling process and offer a unifying view of previous contradictory interpretations [26b,c,34], with the understanding that different systems have been investigated.

The overall mechanistic picture which comes out of this work is described in Scheme 17.

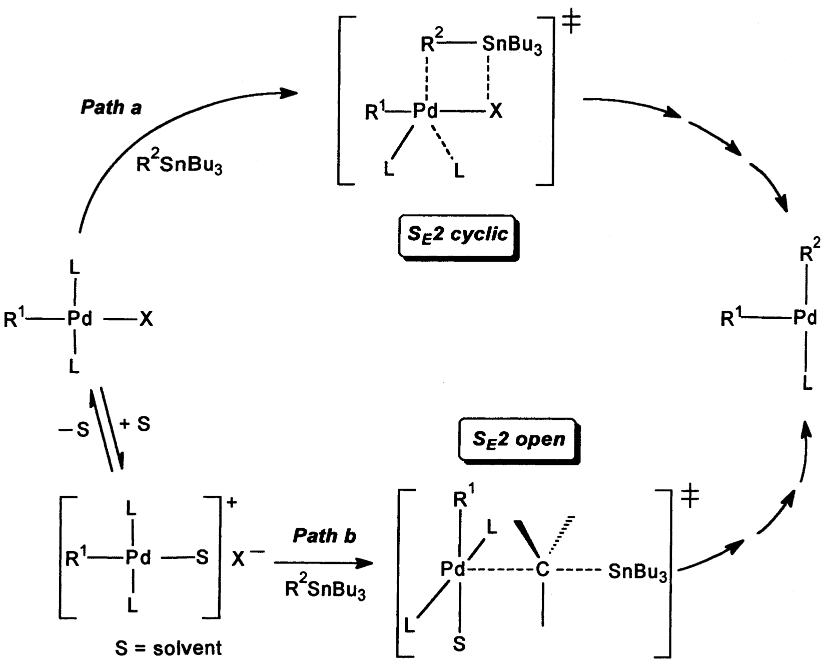
The results obtained in these mechanistic studies have definitely confirmed our early supposition of similar mechanistic features between the palladium-catalyzed metal–carbon (M–C) bond-formation and the carbon–carbon (C–C) bond-formation processes. In this respect, because of the fortunate design of the model substrates **63a** and **63b**, and the easy access to the stable, but still reactive, oxidative addition and transmetalated derivatives **63a**,**b**–**64a**,**b**, further investigations on this palladium-catalyzed process can be foreseen. Such studies may clarify the factors affecting the metal–carbon bond formation reaction, as well as shed light on unclear aspects of the carbon–carbon coupling itself, a phenomenon of paramount importance in synthetic organic chemistry.

4. Conclusions

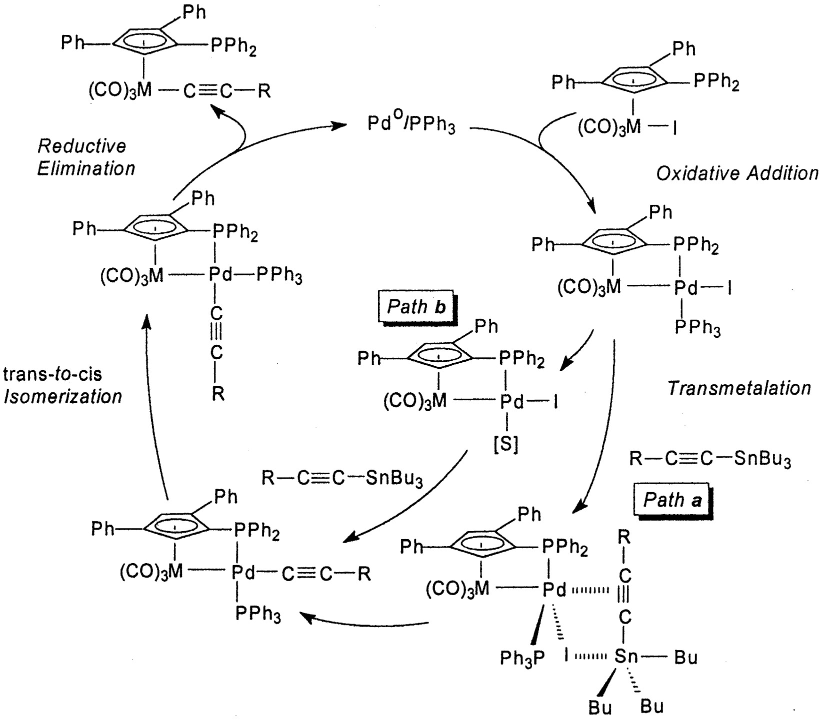
This account summarizes the results we have obtained in the study of the Pd-catalyzed metal–carbon bond-formation process, a phenomenon that following a serendipitous discovery has been for us the focus of



Scheme 15.



Scheme 16.



Scheme 17.

tenacious and intense investigations. These studies have shown both the synthetic potential of this precedently unknown use of palladium and the intimate mechanistic features of the catalytic process. In these respects, the use of the Pd-catalyzed metal–carbon bond-formation process, in combination with the Extended One-Pot (EOP) synthetic protocol, is going to assume a particular relevance toward the preparation of highly ethynylated organometallic polymers, systems of prime interest in the search of innovative materials for future technology. Moreover, with the use of properly engineered organometallic model substrates, accurate studies of the reaction mechanism have been possible, and have shown a close relationship with other important catalytic processes, thus allowing the investigation of fundamental aspects of transition metal catalysis.

Acknowledgements

All work described in this account has been generously and enthusiastically carried out by a number of students to whom we express our gratitude. Their names are listed in the references. We are indebted to Professor Giancarlo Sleiter who kindly revised the manuscript.

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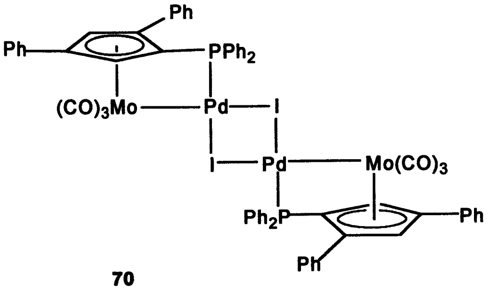
[33] We prepared independently complex **69** by reaction of **62a** with $Pd_2(dba)_3$ in the absence of phosphorus ligands [32]. In spite of the complete formation of **69** observed by ^{31}P-NMR, the work-up of the reaction afforded instead the dimeric halobridged complex **70**:



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