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Title: **Transition metal-mediated metathesis between P–C and M–C bonds: Beyond a side reaction**

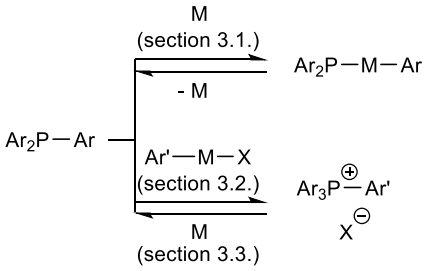
Contents

Abstract

Phosphine ligands often play an important role in controlling reactivity and selectivity in transition metal catalyzed reactions. However, one common drawback of the phosphine ligands is the undesired occurrence of an interchange between P bound aryl and M bound aryl or alkyl groups in the catalytic cycle. This results in the formation of undesirable coupling products as well as changes in catalyst structure through the replacement of the phosphine ligand. This review discusses approaches to

understand this metathesis reaction between P–C and M–C and its productive application in catalytic reactions.

1. Introduction



Scheme 1.

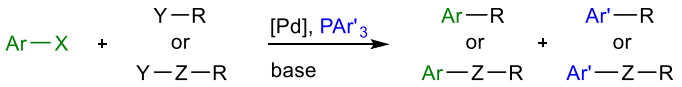
Transition metal-catalyzed cross-coupling is an efficient tool for constructing C–C, C–N and C–O bonds in organic synthesis. Ligands play a crucial role in stabilizing the active metal center and fine tuning the selectivity and reactivity of the transformation. The development of effective ligands that improve catalyst performance has been a longstanding goal of modern chemical research. Of all spectator ligand types, phosphines remain the most significant class of ligands for cross-coupling [1]. Electron density and bulkiness of phosphine ligands usually correlate with the reactivity of their metal complexes [2-6]. Generally, phosphines are widely used as ligands for nickel or palladium catalysts in cross-coupling reactions. They are also effective ligands for rhodium, iridium and gold catalysts and can be used in catalytic reactions such as hydrogenation and cyclization reactions. Furthermore, a number of optically active phosphine ligands have been developed.

Transition metal-catalyzed phosphine decomposition has been observed in several instances. Earlier studies have been thoroughly reviewed in previous literature [7-13]. Among the many known deactivation pathways, Garrou indicated that P–C bond scission is an ubiquitous phenomenon observed with a large number of transition metals and phosphine ligands that often lead to a fatal catalyst deactivation through the irreversible formation of phosphido-bridged di and multi-nuclear complexes [7]. On the one hand, the undesirable aryl/aryl exchanges between the palladium bound aryl (Pd–Ar) and phosphorus bound aryl (P–Ar) groups are frequently observed in palladium-catalyzed cross-coupling reactions leading to the formation of undesired scrambled side products. The replacement of a substituent on a phosphine can indeed have deleterious consequences for its use in metal-mediated synthesis and catalysis, because of the changes in the electronic, steric or even chiral environment on the metal center. Accordingly, early studies were focused on avoiding this side reaction [7,9,11]. Inspired by a better understanding of the mechanism, recently elaborated approaches have shown that useful catalytic reactions can be developed through the strategic utilization of the phosphorus–carbon (P–C) bond/metal–carbon (M–C) bond exchange reactivity. The present review focuses on recent examples using elementary steps derived from well-known mechanistic paths for Ar/Ar exchange. Examples of

direct P–C bond cleavage by a transition metal, formation of a phosphonium salt by reductive elimination, and its reverse reaction by oxidative addition are presented separately in each section (Scheme 1). Finally, recent advances are discussed with regards to the utilization of P–C metathesis in catalytic reactions.

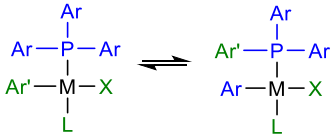
2. Brief overview: early studies

2.1. P–aryl/P–aryl exchange: a side reaction



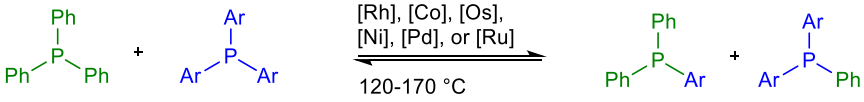
Y= $(R'O)_2B$, R= alkyl or aryl, R'= H or alkyl;
Y= R'_3Sn, R= aryl, R'= alkyl;
Y= H, R= $CH{=}CR^1R^2$ or $C{\equiv}CR^3$;
Y= H, Z= NH, $N(C(O)R^4)$, S or O, R= alkyl or aryl

Scheme 2.



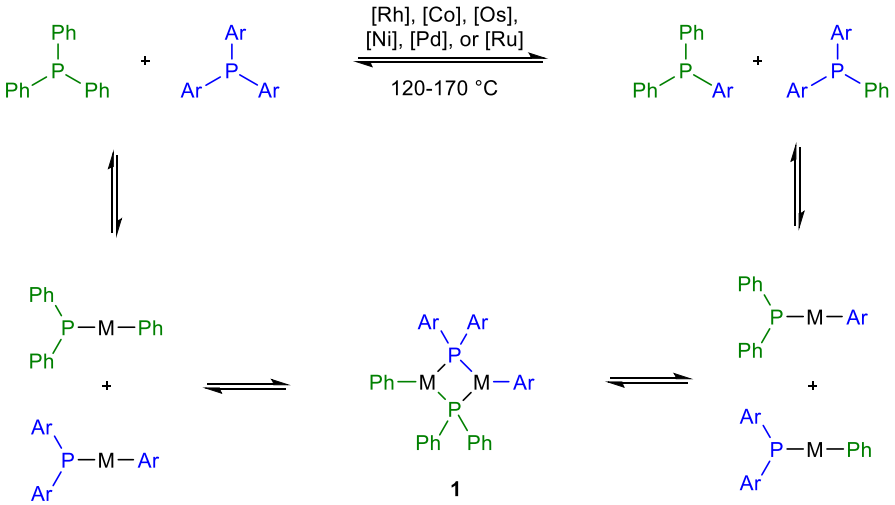
Scheme 3.

P–Ar/Pd–Ar interchange has been observed in numerous Pd-mediated cross coupling reactions such as Heck reactions, Suzuki couplings, Stille couplings, Sonogashira couplings and other C–C, C–N, C–O and C–S coupling reactions, and even in polymer synthesis (Scheme 2) [14-33]. These undesirable side reactions decrease the yield of the reactions and make the purification of products harder. In addition, the variables that control the exchange between P–Ar and Pd–Ar will also affect catalytic activity (Scheme 3). The intermediate complex, *trans*-$[Pd(PAr_3)_2(Ar)X]$ (X= (pseudo)halide) in many Pd-mediated catalysis reactions has been considered to play the critical role in the formation of unwanted side products. Generally, it has been reported that the aryl exchange usually becomes more problematic with electron-rich aryl groups, especially in more polar solvents. The Ar/Ar exchange is not limited to monodentate arylphosphines. When using bidentate diarylphosphine ligands, this type of side reaction was also observed, making this a universal problem of arylated phosphine ligands [19-26]. Thus, early studies have focused on the mechanistic understanding of this phenomenon especially in the context of catalyst deactivation.

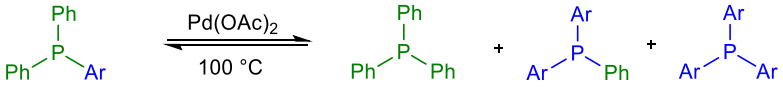


Scheme 4.

In 1984, Bryant et al. discovered the intermolecular aryl scrambling of triarylphosphines when using several transition metals (e.g. Rh, Co, Os, Ni, Pd, and Ru) as catalysts with two different kinds of triarylphosphines (Scheme 4) [34]. The reaction mixture has shown complete equilibration between reactants and products. Depending on metals and Rh complexes, different reaction rates have been observed. One possible mechanism assumes that with the catalyst $[Rh(PPh_3)_3(H)(CO)]$, the initial products of oxidative addition of a P–Ar bond of the phosphine onto the Rh species is able to form P-bridged dimeric intermediates (**1**), which can exchange their Ar and μ-P-bridging groups thereby allowing for scrambling (Scheme 5).

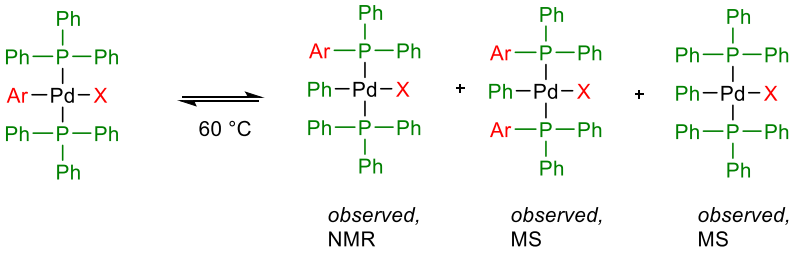


Scheme 5.



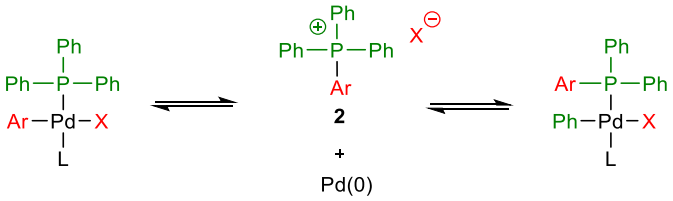
Scheme 6.

Shortly before, Goel also presented a similar process catalyzed by $Pd(OAc)_2$ under even milder conditions. Besides the above-proposed mechanism, they also assumed the possibility of a radical process based on their observation where a spin-trapping agent indicated the formation of radicals in the EPR spectra (Scheme 6) [35].



Scheme 7.

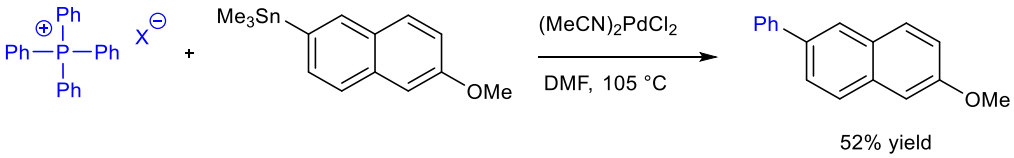
However, in 1991 it became apparent that the aryl scrambling processes from a Ar–Pd(II)–X complex also occurs under much milder conditions [36]. In most Pd-mediated transformation reactions, a Pd complex of the oxidative addition of aryl (pseudo)halides, *trans*-[PdL_2(Ar)X], is involved as an important intermediate. Cheng et al. reported that when the complex was heated at 60 °C in THF or chloroform, a regiospecific exchange between an aryl on the Pd center and a phenyl of the PPh_3 took place and at the same time, rapid intermolecular ligand exchange in the system led to the formation of a statistical mixture (Scheme 7). Similar observations of aryl exchange and ligand exchange were made by Herrmann. The oxidative addition of two different kinds of electron rich aryl chlorides (Ar= 4-MePh and 4-MeOPh) to $Pd(PPh_3)_4$ gave, in almost quantitative yield, mixtures consisting of 90% *trans*-[$Pd(PPh_3)_2$(Ph)Cl] and 10% *trans*-[$Pd(PPh_3)(PPh_2Ar)$(Ph)Cl] [37]. Cheng et al. reported that the addition of one equivalent of PPh_3 to the reaction solution led to a nearly total inhibition of the aryl exchange. Thus, they assumed that the dissociation of a phosphine from the Pd complex to give a three-coordinated intermediate is a necessary step for the exchange reaction. However, it is noteworthy that in the example by Herrmann, the aryl scrambling occurred in the presence of a two fold excess of PPh_3 [37]. The effect of the additional amount of phosphine on the reaction rate is unclear. No inhibition of the reaction by adding free phosphine was indicated from the studies by Norton and Hartwig, respectively [19,38].



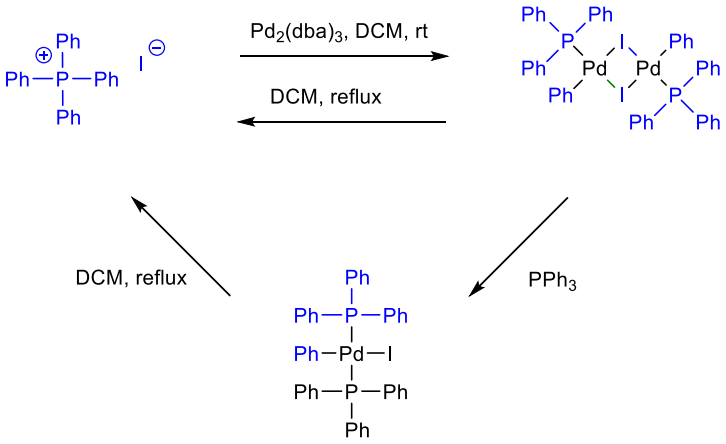
Scheme 8.

In 1995, Chenard et al. proposed that a phosphonium salt intermediate (**2**), first generated through a reductive elimination, undergoes an oxidative addition with a different P–C bond to generate Ph–Pd(II)–X from Ar–Pd(II)–X (Scheme 8) [28]. Actually, the phosphonium salt was already a known side product in the related Heck reaction where it has been noted that with electron-rich aryl halides, the desired Heck reaction competed with the formation of the phosphonium salt [39-40]. The electron-donating group might stabilize the developing positive charge in the formation of the phosphonium salt intermediate. This trend is consistent with Cheng's observation that electron-rich aryl groups facilitate the Pd–Ar/P–Ar interchange reactions [33]. They assumed that Ar/Ar exchange reaction is competing with the Stille

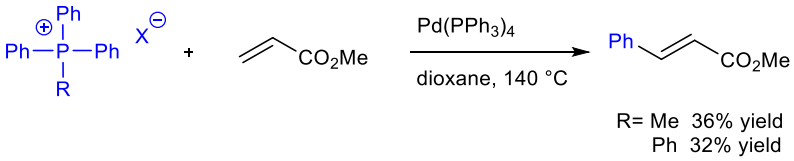
catalytic cycle, in which the intermediate formed via oxidative addition of Pd into the tetraphenylphosphonium ion could be incorporated to generate the undesired product (Scheme 9).



Scheme 9.



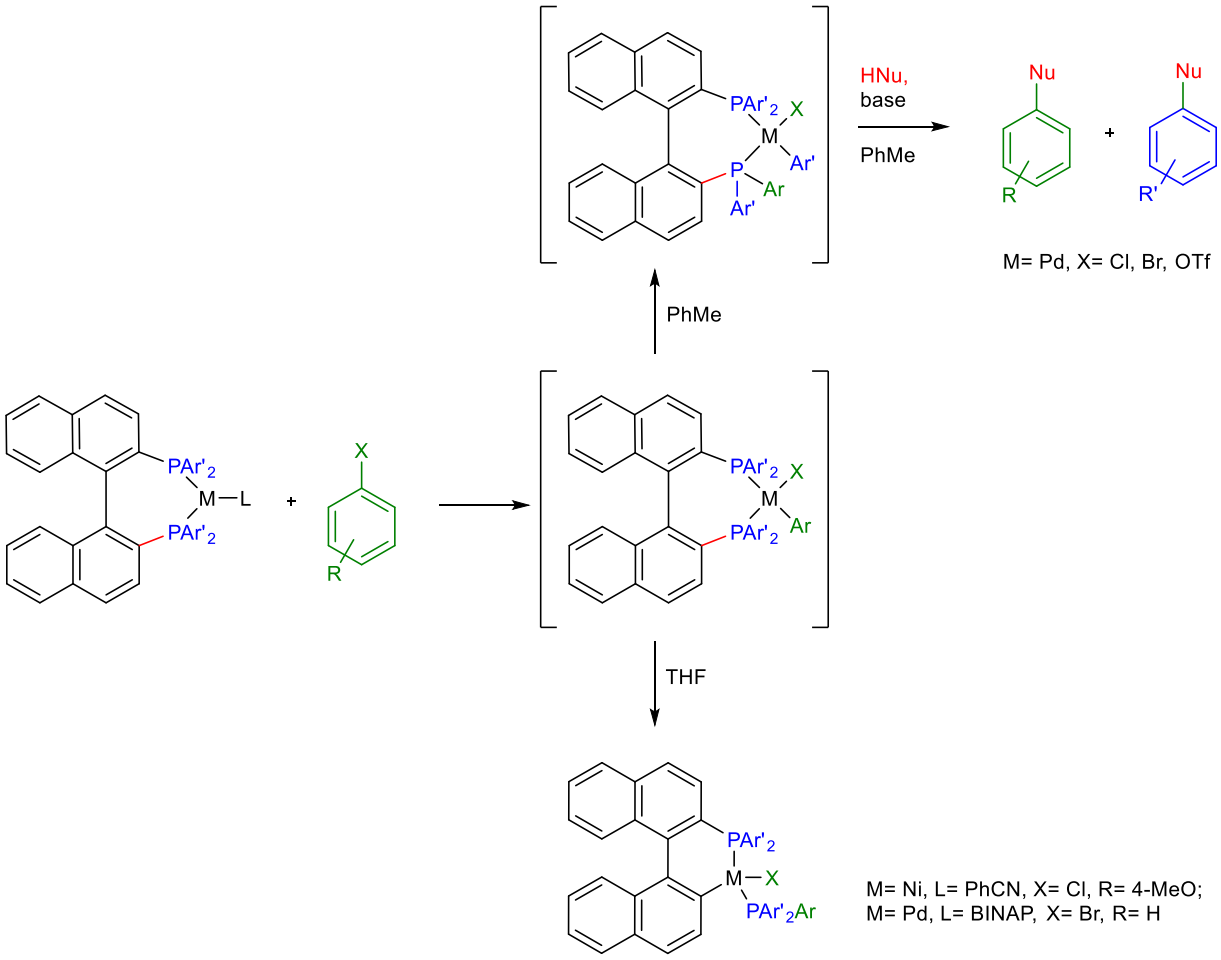
Scheme 10.



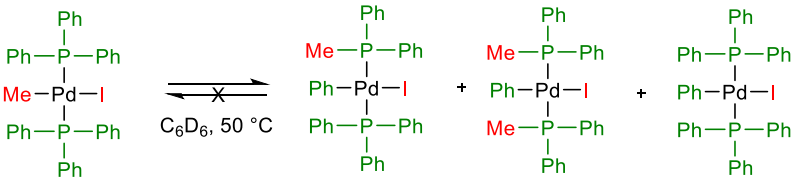
Scheme 11.

Similar observations were reported by Yamamoto and coworkers, who noted a reversible tendency for *trans*-[Pd(PPh_3)$_2$(Ph)I] to produce phosphonium salts in DCM (Scheme 10) [29]. In addition, this paper describes the use of phosphonium salts as an aryl group source for Heck reaction (Scheme 11). Both reports propose a phosphonium salt as the reactive intermediate. P–Ar/Ar exchange is not limited to the reaction with mono arylphosphine. In many Pd-catalyzed coupling reaction using a bidentate arylphosphine as a ligand, the coupling product with an aryl group from the phosphine was reported [19-26,33]. The use of chiral phosphine ligands, which are a dominant ligand class in transition metal-

catalyzed asymmetric reactions, can suffer from an irrevocable damage of the elaborated chiral environment through undesired C–P cleavage. The decomposition of BINAP, a privileged chiral ligand [41-42], has been observed in C–S, C–C, and C–N bonds coupling reactions [20,22,25]. While the phenyl or aryl group exchange of side arms in the BINAP analogues has been reported as a common decomposition path in several coupling reactions employed aryl electrophiles (Scheme 12, top), Hartwig et al. have shown a P–C bond cleavage of the ligand backbone during the reaction of the Ni or Pd complexes bearing BINAP and aryl halides (Scheme 12, bottom) [43-44].



Scheme 12.

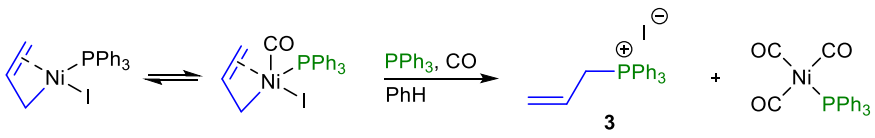


Scheme 13.

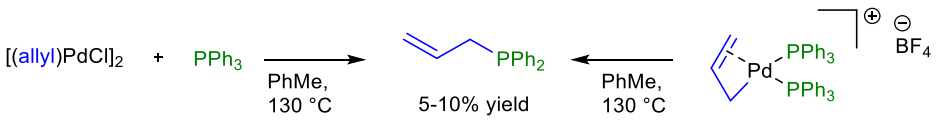
Likewise, in most Pd-catalyzed coupling reactions using both mono and multidentate arylphosphines as ligands, coupling by-products incorporating an aryl group from the phosphine ligand have often been observed. This process likely occurs via a tetraarylphosphonium intermediate involved in the P–C reductive elimination/oxidative addition sequence. Some controlled studies of the exchange reaction from the complex, $[PdL_2(Ar)X]$ (L= arylphosphine, X= I, Br and Cl) have revealed the factors which enhance this side-reactivity [19,21,28,30-31,36-38]: (1) electron donating substituents on both arylphosphines and Pd bound aryl groups increase the Ar/Ar exchange rate. Indeed, the exchange in a strongly electron deficient system using either tris(pentafluorophenyl)phosphine or pentafluorophenyl (pseudo)halides have not yet been reported. Thus, the stabilization of cationic phosphonium intermediates is required to obtain the fast Ar/Ar exchange; (2) Sterically hindered ortho-substituents of Pd bound aryl group inhibit the reaction; (3) The Ar/Ar exchange is more facile under diluted conditions. This is consistent with the lower solubility of the phosphonium intermediates; (4) the presence of excess free phosphine in the system can disturb the exchange by its coordination to Pd(0); (5) the rate of the Ar/Ar exchange in the complex, $[Pd(PPh_3)_2(Ar)X]$ is dependent on the nature of halides, decreasing in the order I > Br > Cl; (6) more polar solvent (e.g. DMF, THF and PhCN) promote the exchange rate.

However, little has been reported on the factors influencing the preference between the reductive elimination and the oxidative addition to drive the reaction to one direction. For the Pd-catalyzed phosphonium halides formation [40,45,46], electron donating substituents of aryl (pseudo)halides are generally favoring the reductive elimination to the phosphonium whereas the electron withdrawing groups are likely to prefer its oxidative addition. Additionally, sterically hindered aryl electrophiles generally seem to favor the oxidative addition product over the phosphonium.

While P–Ar/Ar exchange is mostly an equilibrium process, Norton et al. conducted a series of mechanistic experiments of the P–Ar/alkyl exchange reaction of *trans*-$[Pd(PPh_3)_2(Me)I]$ to show that Ph/Me exchange is irreversible, indicating a significant preference for the formation of P–Me and Pd–Ph bonds over P–Ph and Pd–Me bonds (Scheme 13) [38,47]. Unlike P–Ar/Ar exchange, when $MePh_3POTf$ was incorporated in the reaction, no changes in products distribution were observed. On the basis of these differences, Norton et al. demonstrated that P–Ph/Me exchange does not involve the formation of a free phosphonium salt. However, it is interesting that allyl migration was observed to form an allyltriphenylphosphonium iodide (**3**) from a Ni complex in the presence of CO which is critical to mediate the reaction (Scheme 14) [48]. A similar type of migration shown in Scheme 14, Pd–allyl/P–Ar exchange was reported by Goel (Scheme 15) [49]. An allyldiarylphosphine was observed when $[(allyl)PdCl]_2$ is reacted with PAr_3 at 130 °C in toluene without the detection of any phosphonium intermediate. Although allyl exchanged phosphonium and phosphine from M–allyl bonds were reported previously with Ni and Pd [48-49], repectively, the reversibility of this allyl/aryl exchange remains unclear.



Scheme 14.



Scheme 15.

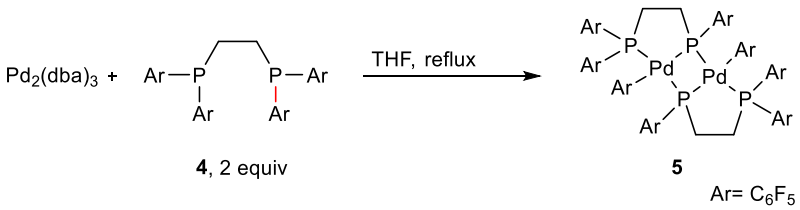
3. Elementary steps for a phosphine activation

As shown from the previous examples, two pathways can be envisioned for the P–C bond metathesis. A first possibility is the direct oxidative addition of neutral P–C bonds followed by transmetallation (Scheme 5) [34-35,50]. A second option proceeds through initial reductive elimination of an M–Ar species with a coordinated phosphine ligand to generate a phosphonium intermediate that can subsequently undergo oxidative addition to form a new M–Ar bond and a new phosphine product (Scheme 8) [28-31]. Recent examples of both modes of activation are covered below.

3.1. Direct oxidative addition of neutral P–C bonds

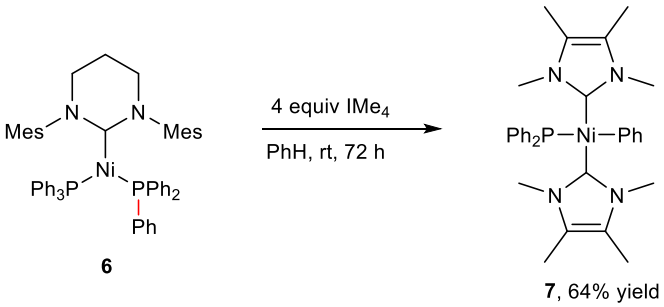
In recent years, cleavage of a P–C bond with transition metals has been an active research topic in organometallic chemistry. Several reactions involving P–C bond fission have appeared in the literature. Among them, the processes through direct oxidative addition of P–C bond to transition metal are fairly scarce. Herein, a range of P–C/M–C exchange processes proceeding through direct oxidative addition are presented.

A rare example of P–C_6F_5 cleavage was reported by Heyn and coworkers in which a Pd-mediated P–C_6F_5 cleavage occurs in a tertiary phosphine (**4**), which leads to an uncommon Pd dimer (**5**) with a chelating and P-bridging ligand (Scheme 16) [51]. The reaction of $Pd_2(dba)_3$ and two equivalents of **4** gave nearly quantitative conversion after 66 hours. The authors suggest that strong electron-withdrawing groups enhance the rate of P–C_6F_5 oxidative addition to low-valent transition metals. The reaction using other analogous ligand scaffolds ($R_2PCH_2CH_2PR_2$) bearing alkyl substituents instead of C_6F_5 groups with Pd(0) did not undergo an oxidative addition of the P–C bond. These results are consistent with the observation that P–C(sp^3) bonds are more difficult to cleave than P–C(sp^2) bonds [38,47]. The facile cleavage of P–C_6F_5 bond has already been reported by Fahey and Mahan [50]. While the reaction between $Ni(PEt_3)_4$ and $C_6F_5PPh_2$ led the formation of $[Ni_2(\mu\text{-}PPh_2)_2(PEt_3)_3]$, the bimetallic complex with μ-PR_2 ligands, a similar experiment using $Pd(PEt_3)_3$ and $C_6F_5PPh_2$ at 60 °C for 1 hour resulted in the formation of *trans*-$[Pd(PEt_3)_2(C_6F_5)(PPh_2)]$, which is an example of formal P–C oxidative addition at a single metal center.



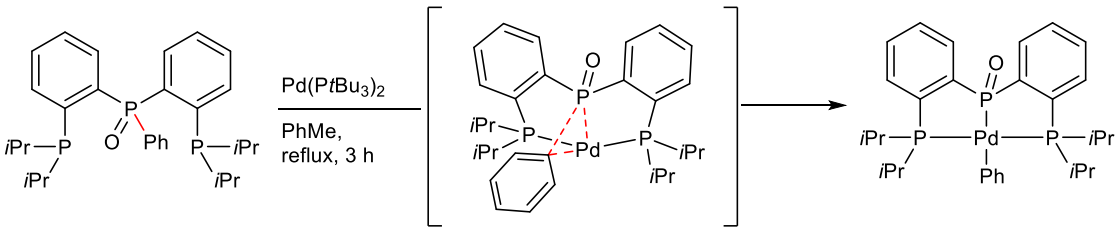
Scheme 16.

Unlike the facile cleavages of P–C_6F_5 bond, the attempts to obtain [$M(PEt_3)_2(PPh_2)Ph$] (M= Pd, Ni) were unsuccessful, leading instead to the formation of $Ni_2(\mu\text{-}PPh_2)_2(PEt_3)_3$ and biphenyl during the thermolysis of [$Ni(PEt_3)_3(PPh_3)$] [50]. Fahey and Mahan noted the lability of the putative intermediate, [$Ni(PEt_3)_2(PPh_2)Ph$], from the occurrence of other competing processes that make the isolation difficult. Later, the generation of [Pt(dppe)(PHAr)(Ar)] (Ar= Mesityl) was observed as a thermodynamic product during the reaction of Pt(dppe)(*trans*-stilbene) with $PHAr_2$ (Ar= Mesityl), in which a reversible P–H oxidative addition to Pt(0) proceeded [52]. Recently, Whittlesey and coworkers have shown the isolation of the analogous Ni–phosphine complex of [$Ni(PEt_3)_2(PPh_2)Ph$] [53]. The three-coordinate Ni(0) N-heterocyclic carbene (NHC) complex, [$Ni(6\text{-}Mes)(PPh_3)_2$] (**6**, 6-Mes = 1,3-bis(2,4,6-trimethylphenyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene) was formed in the reaction of $Ni(cod)_2$ with a 1:2 mixture of 6-Mes and PPh_3. Surprisingly, the Ni complex underwent oxidative addition with the small 5-membered ring NHC, IMe_4 to give the complex [$Ni(IMe_4)_2(PPh_2)Ph$] (**7**) (Scheme 17).



Scheme 17.

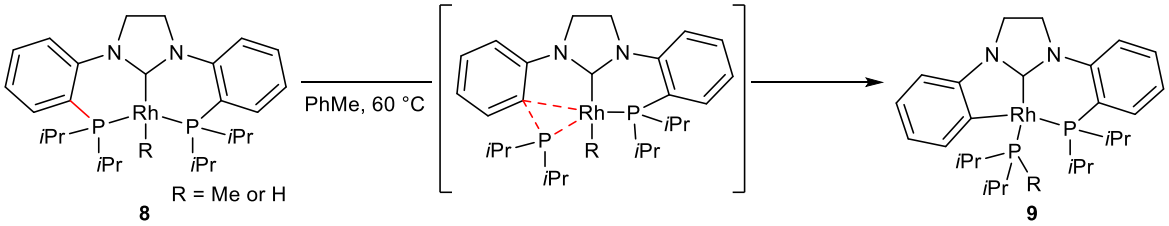
The coordination of the diphosphine-phosphine oxide to Pd(0) was found to proceed with cleavage of the Ph–P(O) bond. This represents a rare example of C–P(O) bond activation by a transition metal and affords an original κ^3-(P,P(O),P)-pincer complex (Scheme 18). DFT calculations indicate that the oxidative addition of the Ph–P(O) bond occurs via a three-centered (P,Pd,C) transition state, analogous to that encountered in related Ar–C and Ar–H bond activations. The process is likely to be chelation-assisted [54].



Scheme 18.

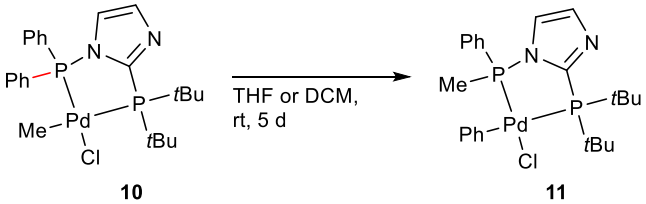
The synthesis of a series of Rh complexes, [PCP]RhR (**8**, R= Cl, H and Me, PCP= a tridentate ligand that contains a central, saturated NHC donor flanked by two *o*-phenylenediisopropylphosphino groups), was reported by Fryzuk et al. [55]. During investigation of the thermal reactivity of these complexes, the authors uncovered an unexpected ligand rearrangement process (for R= H, Me) resulting from intramolecular P–C bond cleavage between one of the phosphine donors and the aryl linker of the ligand

backbone (Scheme 19). The facile thermal P–C bond breaking process for these neutral Rh(I)PCP derivatives is surprising, in view of the inertness of the isovalent Pd(II) cationic hydride ([PCP]PdH)PF_6 to this rearrangement. The authors assumed that this observation may be due to the fact that the cationic palladium complex is more electrophilic than its neutral counterpart and therefore less electron rich, which would impede the oxidative addition step. Later, the optimal mechanistic pathway of the rearrangement of **8** (R= H) to a [CCP]Rh-phosphane pincer (**9**) was suggested to occur by P–C oxidative addition (rate-determining) followed by P–H reductive elimination from DFT calculations [56]. The oxidative addition step proceeds via a three-centered transition state and is accelerated by electron-withdrawing substituents located at the para position relative to the P–C bond being cleaved. When replacing the Rh bound H with other anions (Me, Ph, *t*Bu, OH, F, Cl and CN), only the Me group has shown a decrease in the oxidative addition barrier, which is consistent with the former experimental observations.



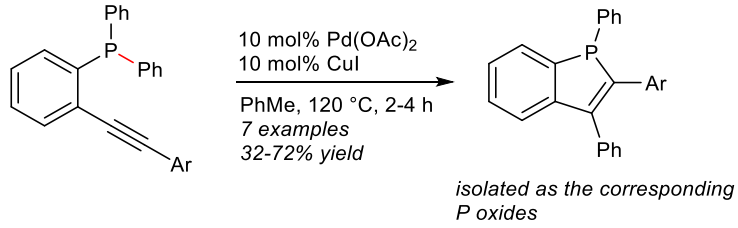
Scheme 19.

In a related rearrangement with the Rh–Me phosphine complex (**10**), Braunstein and coworkers have shown facile P–Ar/Pd–Me exchange at room temperature (Scheme 20) [57]. It is noteworthy that this exchange reaction occurred smoothly under mild conditions, which was impossible with the analogous ([PCP]PdH)PF_6 system reported previously [55]. Although the electronic characteristics of the N bound P and C bound P are not precisely known, the authors reasoned that the C bound P(*t*Bu)$_2$ is the strongest donor in the systems studied, and therefore should weaken the Pd–Me bond placed trans to it. In addition, the rearrangement results in positioning the Ph (with stronger Pd–Ph bond) trans to the C bound P(*t*Bu)$_2$. It also places the electron releasing Me group on the electron deficient (and therefore electrophilic) N bound P center (see **11**).

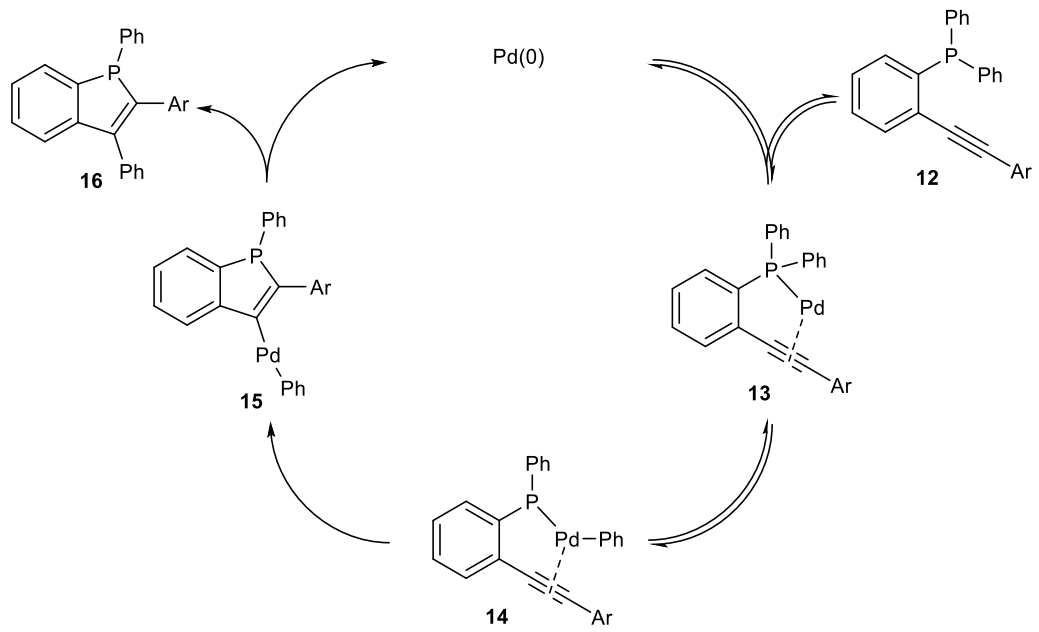


Scheme 20.

Likewise, after finding that transition metals can directly break the strong P–C bonds of tertiary phosphines, some remarkable examples [50-57] have shown more facile stoichiometric reactions between transition metals and phosphines to give stable phosphido complexes through oxidative addition. Unfortunately, the utilization of these processes in catalytic reactions has still been limited. Recently Duan and coworkers reported a protocol that provides an unprecedented intramolecular catalytic aryl phosphination of the internal alkyne with a $Pd(OAc)_2$/CuI bimetallic catalyst system via P–C bond activation of stable tertiaryphosphines (Scheme 21) [58]. The authors indicated that both the lone pair on the phosphine and the alkynyl group tethered to aryl group of the phosphine are crucial for this reaction, and coordination of Pd species with 2-(arylethynyl)phenylphosphine (**12**) gives a bidentate palladium complex (**13**). When they tried the intermolecular reaction as a control reaction, no reaction between PPh_3 and diphenylacetylene was observed under same reaction conditions. Chelation-assistance from the vicinal alkynyl group facilitates the intramolecular activation of the P−Ar bond (Scheme 22). The insertion of Pd into the P−Ar bond gives a phosphido complex by oxidative addition (**14**). Consecutive phosphopalladation of a vicinal alkyne gives a vinylic palladium intermediate (**15**). Eventually, a reductive elimination affords a benzophosphole (**16**) with regeneration of the Pd catalyst. Low yields were obtained with electron donating methoxy-substituted and amino-substituted substrates and no reaction was observed with 1-naphthyl-substituted substrate, which may be due to the steric hindrance. The electronic dependence of this reaction stands in contrast to the trend observed with processes proceeding through phosphonium intermediates. Thus, this discrepancy seems to support that this reaction follows the initial oxidative addition. Meanwhile, the critical role of the copper additive was not rationalized but it could be involved in the challenging oxidative addition step.

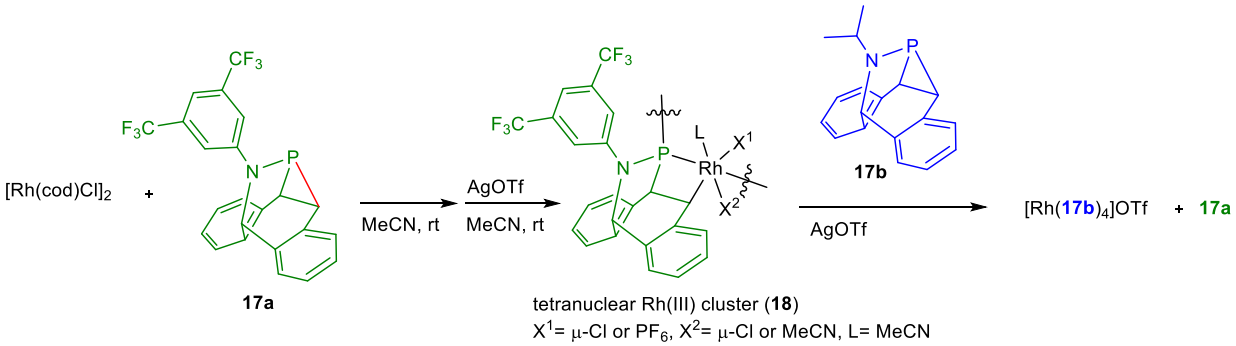


Scheme 21.



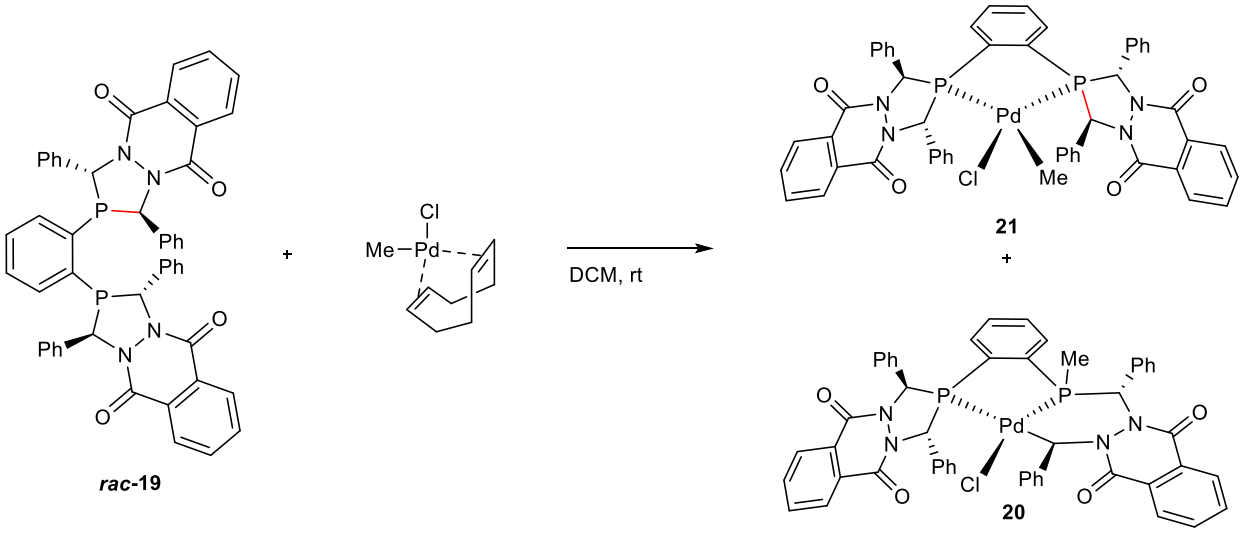
Scheme 22.

While the processes involving direct oxidative addition of P–C(especially sp^3) bonds to transition metals seem uncommon, the P–C(sp^2 and sp^3) cleavages in carbon-phosphorus heterocyclic strained ring system have been considered as more facile [59-65]. The reversible P–C bond cleavage from three-membered carbon-phosphorus heterocycles has also reported by Grützmacher [59-60]. The reaction of air stable phosphiranes (**17a**) embedded in a polycyclic framework with $[Rh(cod)Cl]_2$ formed the tetranuclear rhodium cluster (**18**) wherein each rhodium center has inserted oxidatively into a P–C bond of the phosphirane ring (Scheme 23). Surprisingly, when **18** was treated with an eight-fold excess of **17b** in presence of AgOTf, the intact **17a** was regenerated by reductive P–C bond coupling. Instead of **17b**, the treatment of **17a** did not proceed to form the analogous [Rh(**17a**)$_4$]OTf complex. Because the oxidative addition of some transition metal such as Pt(0) and Rh(I) to P–C bonds of phosphiranes [61], phosphirenes [62-64], and a naphtho[1,8-*b*,*c*]phosphate [65] have mostly resulted in the irreversible formation of metallacylic complexes, it would be valuable to understand the origin of the reversibility of the P–C cleavage in the N-fused polyheterocyclic P-ligated transition metal system.



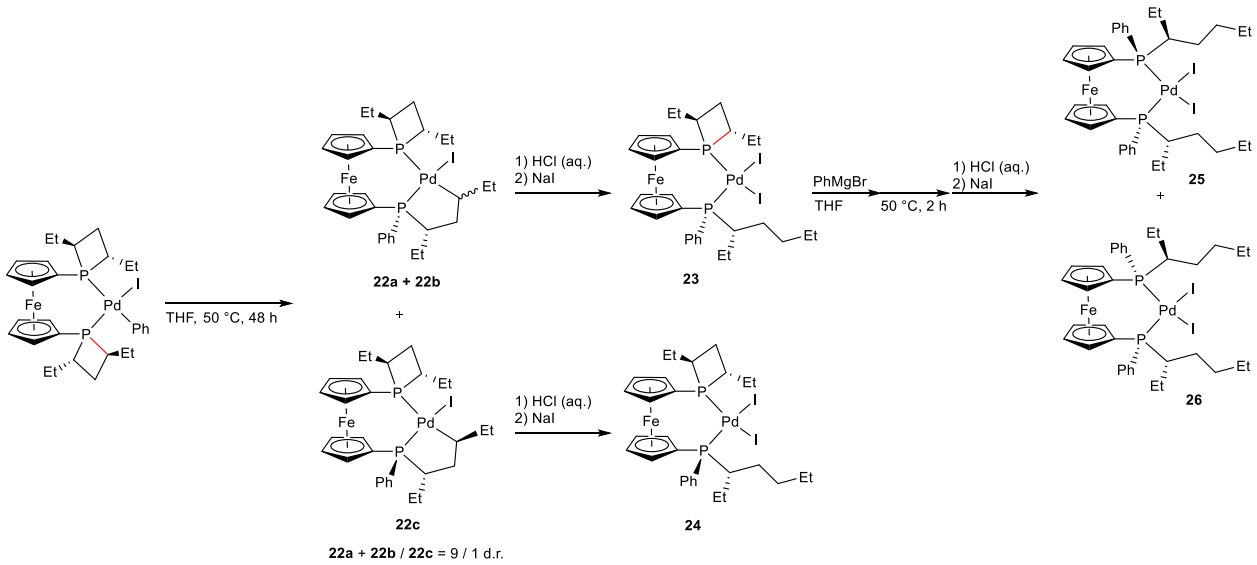
Scheme 23.

Landis and coworkers have witnessed a challenging P–alkyl/M–alkyl exchange during the development of 3,4-diazaphospholanes [66], a new, modular class of chiral phosphine [67] which proved to be effective for many metal-catalyzed asymmetric transformations. While the complexation of $[Rh(cod)Cl]_2$ with bis(3,4-diazaphospholane) (***rac*-19**) afforded the chloride-bridged dimer, the reaction of [(cod)Pd(Me)Cl] and ***rac*-19** yielded the unexpected product of a methyl migration to the phosphine along with a ring opening of the diazaphospholane ring (**20**), accompanied by the formation of the desired complex, [(***rac*-19**)Pd(Me)Cl] (**21**) (Scheme 24). Although the mechanism is unclear, it could be assumed that the mechanistic path involves a cationic iminium [67]. Notably, none of the phospholane methines did epimerize during the process and the transfer of the methyl group occured in a stereoselective manner. In this context, the P–C/M–C exchange process might not just be a decomposition path but could potentially be used as a strategy to access new chiral catalyst precursors.



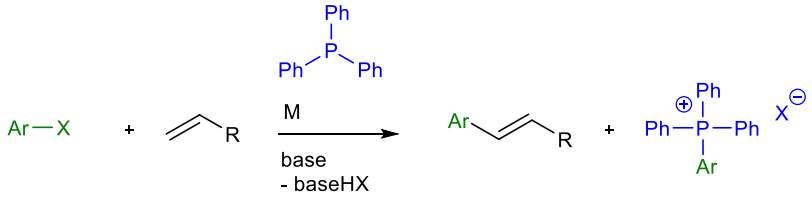
Scheme 24.

Indeed, Glueck and coworkers reported the synthesis of new chiral phosphine ligands, which are otherwise hard to access, through Pd-mediated P–alkyl/Pd–phenyl exchange from phosphetane rings [68]. In a similar manner to the above-mentioned examples of the P–C bond cleavage from three and five-membered carbon–phosphorus heterocycles, four-membered carbon–phosphorus heterocycles [69] can also undergo facile P–C cleavage to give P–alkyl/Pd–phenyl exchanged palladacycles which can easily be transformed into complexes bearing novel bidentate ligands with both P and C stereogenic centers (Scheme 25). Surprisingly, Pd-mediated phosphetane ring opening and simultaneous phenyl migration from Pd to P occurred under mild conditions. Norton et al. noted that the Pd−Ph and P−Me bonds are collectively stronger than the Pd–Me and P–Ph bonds from their observation of the irreversibility of P–Me/Pd–Ph exchange [38,47]. Notably P–C cleavage is highly diastereoselective at phosphorus (**22a** + **22b**/**22c** = 9/1 d.r.).



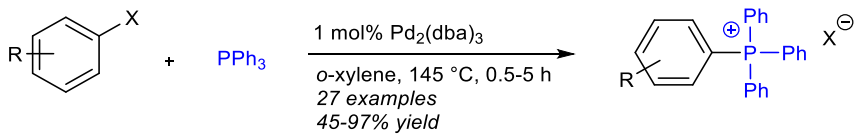
Scheme 25.

3.2. P–C bond formation through formation of phosphonium intermediates via reductive elimination



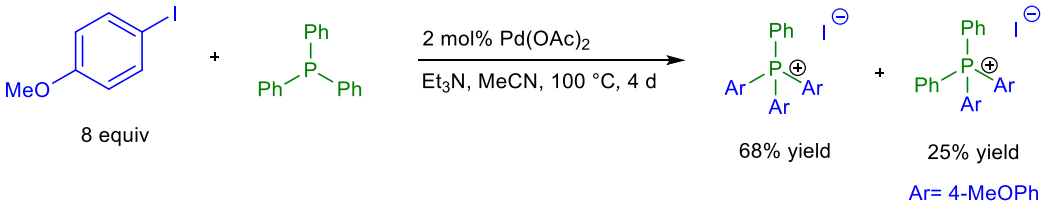
Scheme 26.

The tetraarylphosphonium salt, which results from reductive elimination of [M(PAr_3)(Ar)X], is commonly encountered as a side product in cross coupling reactions. While Ni-mediated phosphonium salt formation reaction from tertiary phosphine are known since the 1950s [70-74], Heck and coworkers first reported the Pd-catalyzed generation of phosphonium iodide and bromide as side products in olefination reactions (Scheme 26) [39]. Subsequent systematic studies with different aryl substituents revealed that the formation of phosphonium side products was facilitated by electron rich substituent on the aryl group on either the aryl halide or triarylphosphine, while the reaction with a triarylphosphine having sterically hindered ortho substituents is comparatively slow [40].

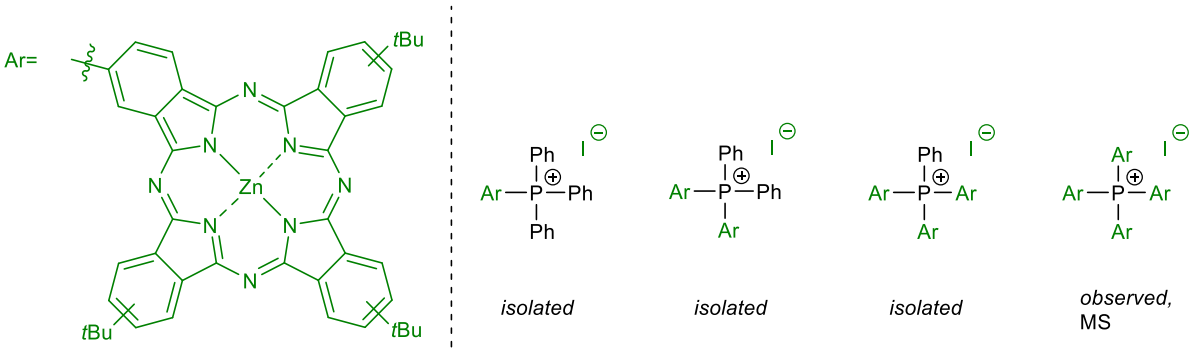


Scheme 27.

Later, Migita and coworkers realized a practical method to prepare these compounds through Pd-catalyzed reaction between aryl halides and triarylphosphines. Similar tendencies with regards to the aryl substituent effect appeared as well [45]. Later, this protocol was improved by Charette et al. with subtle tuning of the reaction conditions (Scheme 27) [46]. In addition to aryl iodides, aryl bromide and triflates were transformed efficiently [46,75-76]. The authors assumed that the heterogeneous nature of the concentrated reaction conditions in *o*-xylene makes the phosphonium salt less available to undergo further reversible oxidative addition with Pd(0), thus driving the reaction forward.



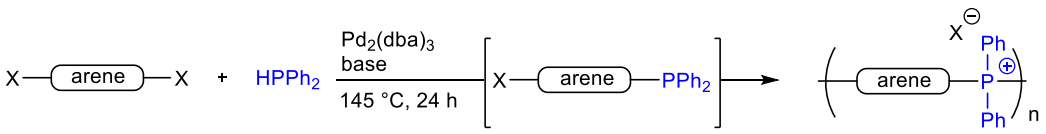
Scheme 28.



Scheme 29.

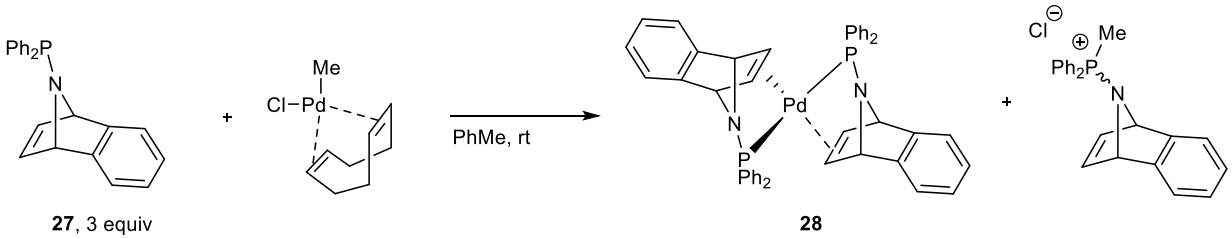
As mentioned above, this type of aryl quaternization reaction of PAr_3 is known to be reversible [28-29], The phosphonium salt can participate iteratively in an oxidative addition/reductive elimination sequence until the equilibration point is reached. Accordingly, upon exposure of an excess aryl iodide substrate, aryl enriched phosphonium salts are obtained in very good yield (Scheme 28) [77]. Torres et al. employed this strategy for functionalization of highly complex molecules. The efficient preparation of the multi-phthalocyanine containing phosphonium salts was enabled. This compound has potential applications in materials science due to their nonlinear optical behaviors (Scheme 29) [78].

As shown in prior examples, phosphonium salts are themselves useful compounds that have been used as phase transfer agents, synthetic reagents, ionic liquids, conducting agents, flame retardants and even anticancer agents and drug carriers. A variety of applications of phosphonium salts prepared by subtle modification of the above described method have been recently reported [79-85]. A polymeric material such as tetraarylphosphonium polyelectrolyte was prepared from aryl (pseudo)halide and diphenylphosphine through the strategical combination of conventional phosphination and phosphonium synthesis (Scheme 30) [86-88].



Scheme 30.

The migration behaviors between M–R (R= alkyl [38, 55-57,59,61, 66, 68], allyl [48-49] and vinyl [89-95]) and P–Ar have also been studied for a long time. However, during P–Ar/Pd–Me exchange, there has been no evidence for the participation of the phosphonium intermediate [38]. As rare examples of a reductively formed phosphonium from R–M–X, two studies published in 2012 have shown that the Me-migrated phosphonium compound was produced under specific circumstances [96-97].

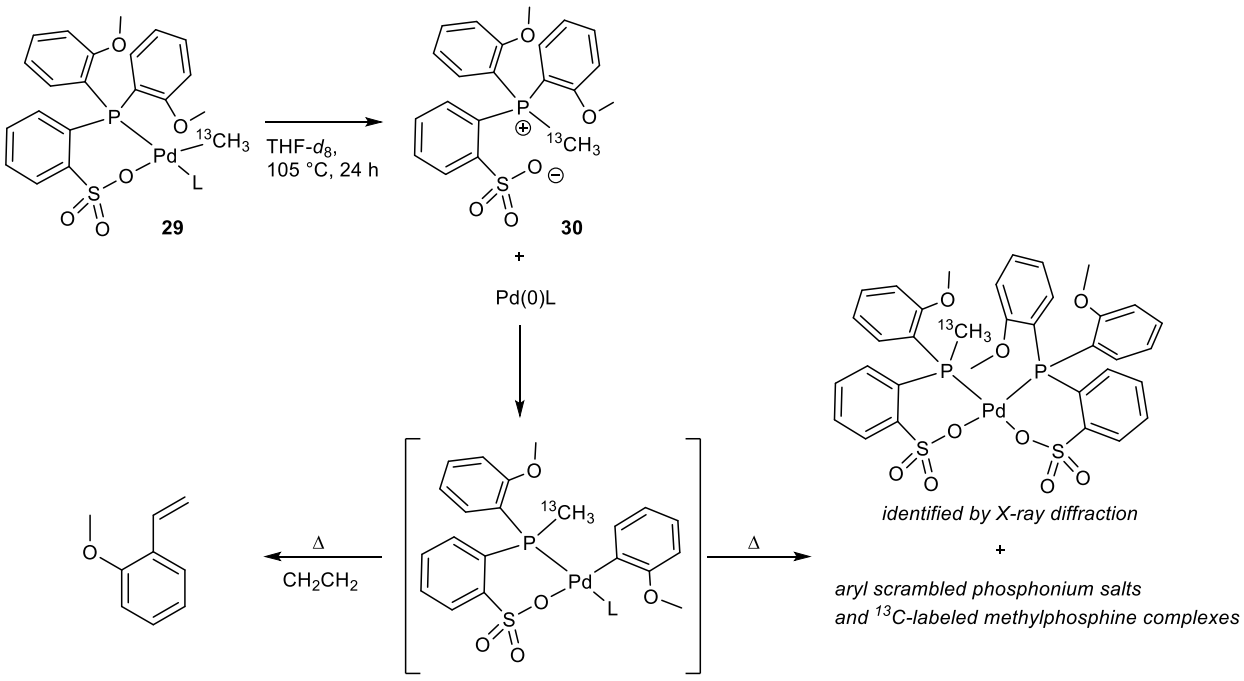


27, 3 equiv

28

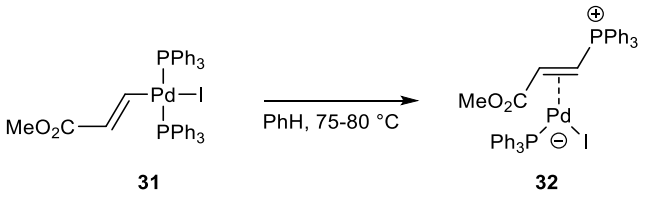
Scheme 31.

In Scheme 31, the bidentate ligand bearing both a poorly donating phosphine component and a strongly π accepting olefin moiety (**27**) seems to efficiently promote reductive elimination from Pd(II) complex. Dyer et al. indicated that this preference seemed to be due to the stability of bis(phosphine-alkene)Pd complex (**28**) which has a distorted-tetrahedral geometry [96].



Scheme 32.

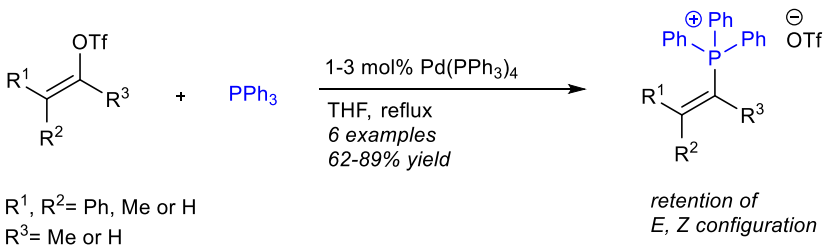
In their analysis of Pd-catalyzed ethylene polymerization reactions, Mecking and coworkers reported several catalyst decomposition pathways [97]. Thermolysis of **29** (L= pyridine or DMSO) in dioxane at 122 °C yielded a range of phosphonium salts as observed by ESI-MS. In addition, the ^{13}C-labeled analogues obtained by thermolysis of **29** (L= DMSO) in THF-d_8 for the same conditions also contained substantial amounts of the ^{13}C-labeled side phosphonium product (**30**) observed under NMR-tube polymerization conditions (Scheme 32). The authors indicated that their observations support the exchange of Ar group of phosphine with Me group on Pd. Through observations of phosphonium species, such exchange of substituents in transition metal complexes can be explained by reductive eliminations and consecutive oxidative additions of comparatively weak P–C bond of phosphonium salts followed, specifically, by Ar/Me exchange reactions. It also was supported by the formation of 2-vinylanisole after ethylene insertion into a [Pd]–(2-MeOPh) bond.



Scheme 33.

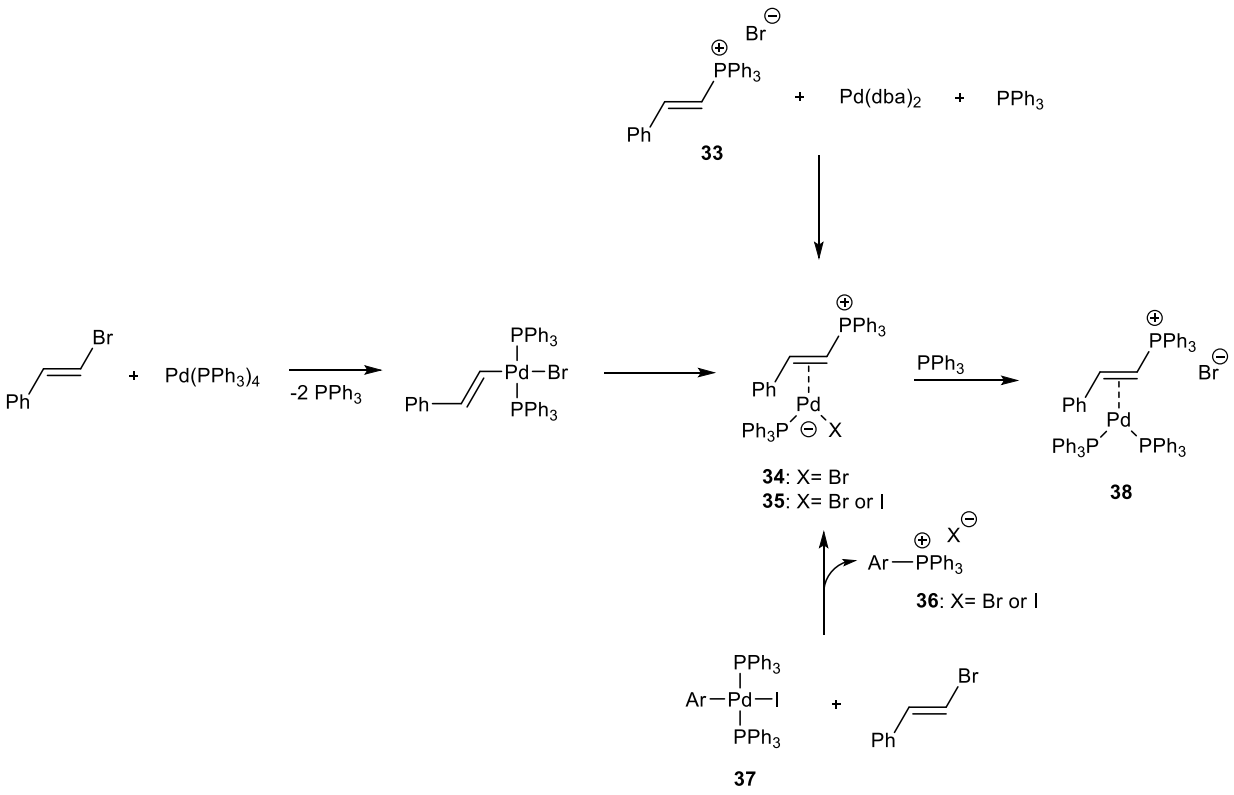
In 1985, Rubinskaya et al. discovered an unusual vinyl group migration. Upon heating to 75–80 °C, the Pd(II) complex resulting from vinyl iodide addition (**31**) was converted to η^2-olefin complex with bearing a vinyl phosphonium ligand (**32**) (Scheme 33) [89]. Shortly thereafter, the process was accomplished in catalytic fashion using vinyl triflate instead of vinyl iodide. One of the most notable features of this

method is the predominant retention of stereochemistry (the Z isomer; >99% to >99%, the E isomer; >99% to ca. 95:5) (Scheme 34) [90-91].

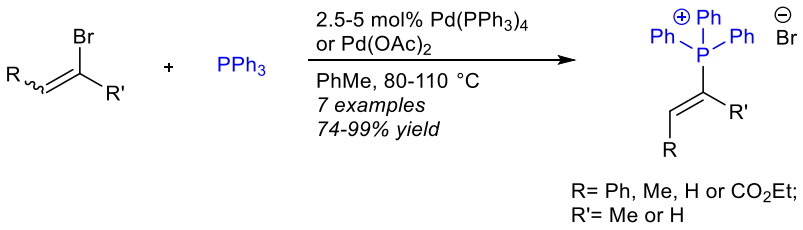


Scheme 34.

More than a decade after the first discovery, Cheng and coworkers conducted a range of mechanistic experiments through stoichiometric reactions [92]. As the extension of Rubinskaya's work, [(*trans*-PhCH=CHPPh$_3$)Pd(PPh$_3$)Br] (**34**) was prepared by treating *trans*-PhCH=CH(PPh$_3$)Br (**33**) with Pd(dba)$_2$ and PPh$_3$ in DCM (Scheme 35). Also, interestingly, treating *trans*-(2-bromovinyl)benzene with *trans*-[Pd(PPh$_3$)$_2$(Ar)I] (**37**, Ar= 4-MeOPh) in THF at room temperature led to the formation of the complex **35** and aryltriphenylphosphonium salt (**36**). [(*trans*-PhCH=CHPPh$_3$)Pd(PPh$_3$)$_2$]Br (**38**) resulted from the reaction of trans-(2-bromovinyl)benzene and Pd(PPh$_3$)$_4$, and was rapidly converted to complex **34**. The authors demonstrated that the reaction with vinyltryphenylphosphonium halides can be catalytic under forcing conditions. Unlike the previous work using vinyl triflates, by using this method, they obtained exclusively the trans isomer products from the corresponding bromides (Scheme 36).



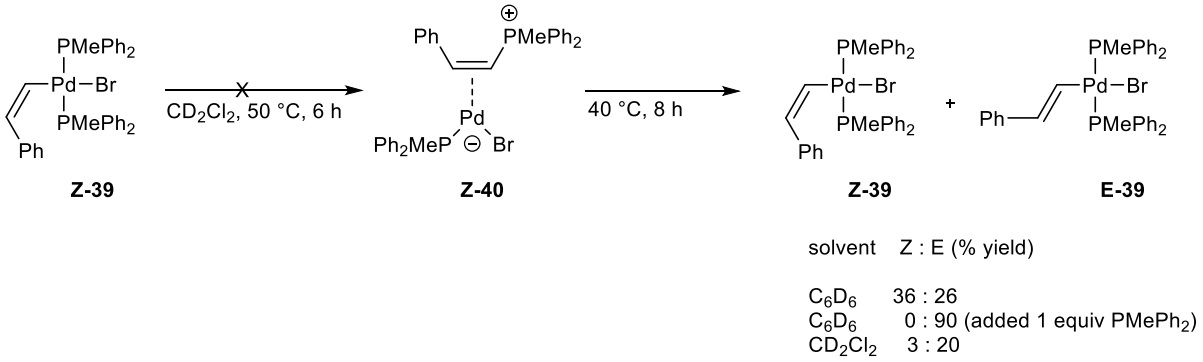
Scheme 35.



Scheme 36.

In 2009, Ozawa and coworkers examined the forward and reverse reactions between [(PhCH=CH)Pd(PMePh$_2$)$_2$Br] (**39**) and [(η^2-PhCH=CHPMePh$_2$)Pd(PMePh$_2$)Br] (**40**) to investigate P–C reductive elimination (**39** to **40**) and P–C oxidative addition (**40** to **39**) behaviors, depending on the configuration of the vinyl group [93]. The (E)-styryl complex (**E-39**) was smoothly converted to **E-40** in CD_2Cl_2. The conversion rate of **E-39** was strongly affected by solvent polarity. For example, in THF and benzene, the reaction decelerated significantly. Unlike **E-39**, the (Z)-styryl complexes (**Z-39**) was stable toward P–C reductive elimination at 50 °C for 6 hours. On the contrary, **Z-40** was found to undergo oxidative addition of styrylphosphonium ligand. Heating of **Z-40** in C_6D_6 at 40 °C for 8 hours resulted in the mixture of **E-39** and **Z-39** whereby the formation of **Z-39** was entirely suppressed by added PMePh$_2$ (Scheme 37). This work might give some explanation for the Z to E isomerization previously observed

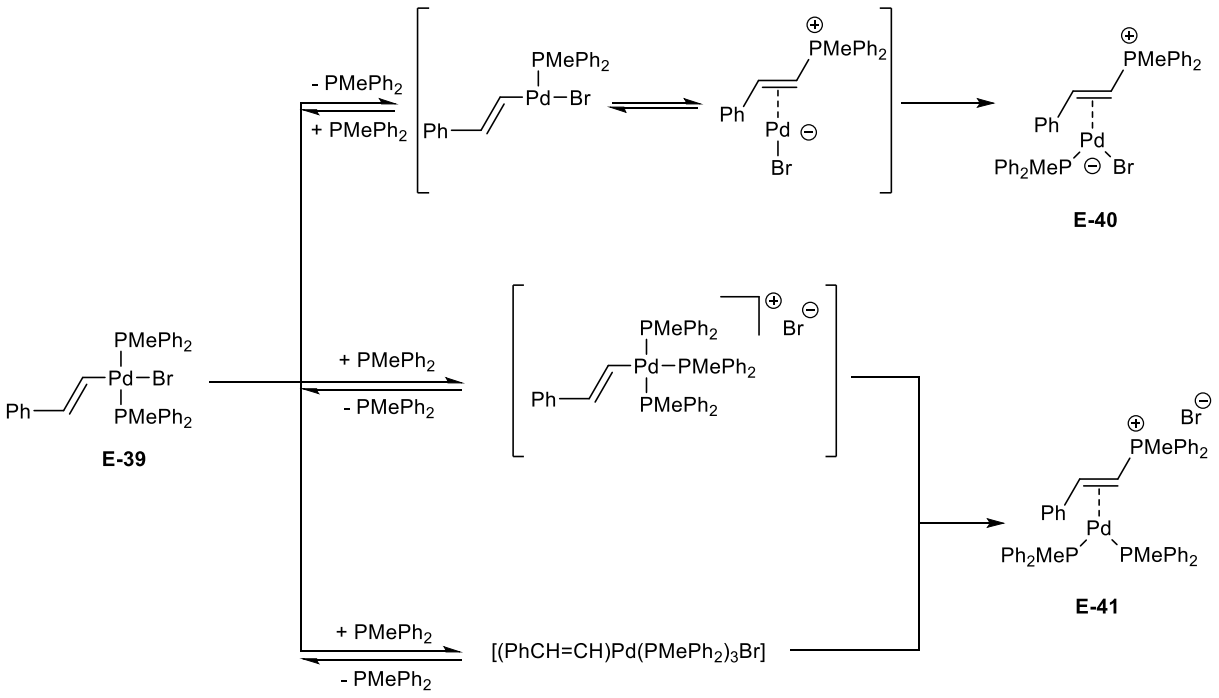
during the quaternization of phosphines under the harsher conditions used by Cheng (Scheme 36) [92]. These results imply that reversible vinylation of phosphines might be feasible under certain conditions.



Scheme 37.

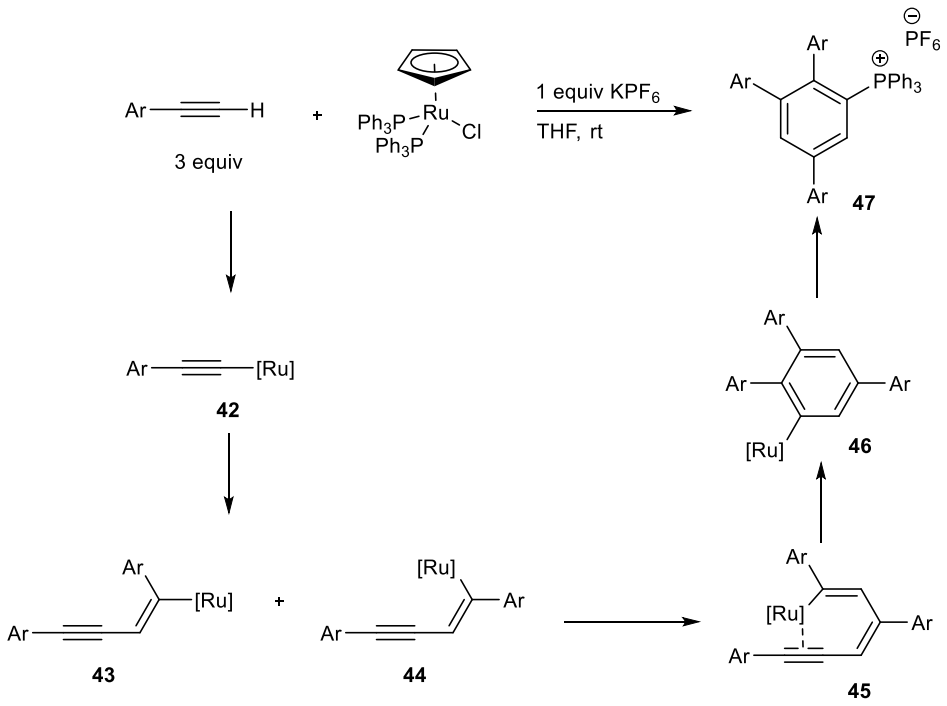
Generally, the reductive elimination from *trans*-[$PdL_2R(R')$]-type complexes has been known to proceed via three possible reaction processes: (1) dissociative path via a three-coordinate intermediate, (2) direct elimination path from the four-coordinate complex, and (3) associative path with precoordination of an external L to give a five-coordinate intermediate, [$PdL_3R(R')$] [93-94,98-101]. Based on kinetic studies depending on the amount of free $PMePh_2$ present in the system, the authors proposed either associative path or dissociative path. In the absence of free $PMePh_2$, initial predissociation of a $PMePh_2$ ligand from **E-39** would result in a three-coordinate [(PhCH=CH)Pd($PMePh_2$)Br] intermediate, which could undergo P–C reductive elimination. They observed that this process was effectively suppressed by addition of $PMePh_2$ to the system, and proposed that an alternative process involving prior association of **E-39** with $PMePh_2$ (> 1 equiv) would take place (Scheme 38).

The associative path also could be divided according to the formation of an ion pair species or a five-coordinate species. To clarify the more plausible reaction path, the author compared the reaction kinetics of [(PhCH=CH)Pd($PMePh_2$)$_3$]OTf as a ion pair model system [95] with the one of **E-39** with $PMePh_2$. The authors suggested that the intermediacy of a five-coordinate species could be more plausible (Scheme 38) [93-94]. The observations of substituent effects of the vinyl compound and the phosphine ligand on the P–C reductive elimination supported that the overall process is facilitated by electron-donating substituents [94]. Based on previous results, the formation of vinyl phosphonium–Pd(0) complex by vinyl migration does not seem to be reversible. However, the prior work of Cheng et al. showed that (Z)-vinyl halide can be converted to corresponding (E)-vinyl phosphonium by Pd catalysis using higher temperatures and non-polar aromatic solvent [92]. This feature might reflect potential reversibility under more forcing conditions.



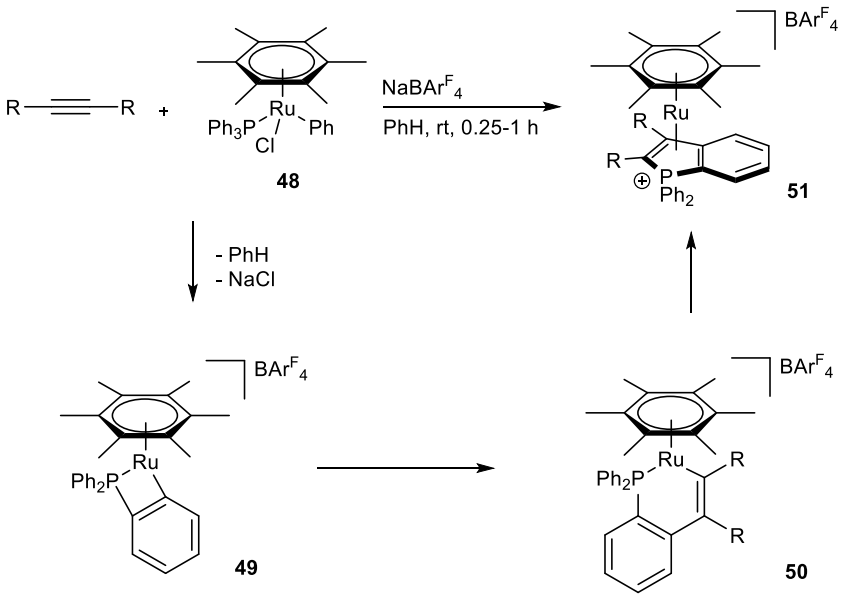
Scheme 38.

A large part of research on the P–C reductive elimination of phosphonium salts has been done on palladium complexes, and only a few examples have been reported with other metals. While investigating the catalytic dimerization reactivity of Ru–cyclopentadienyl complexes with alkynes, an unidentified brown powder was observed by Kirss in 2007, which was produced as a side product during the reaction but has not been fully characterized [102]. Later, Lin and coworkers noted the formation of the brown-colored polyaryl phosphonium salt resulting from the reductive elimination of the alkyne trimerization product with PPh_3 (Scheme 39) [103]. A plausible reaction pathway was proposed to start with metal activation of the terminal alkynyl C−H bond, leading to formation of the acetylide complex (**42**). Subsequent dissociation of a phosphine ligand would generate a vacant site for coordination and subsequent insertion of the alkyne into the Ru−C(sp) bond, giving the two isomeric complexes, **43** and **44**, which contain alkynyl-substituted alkenyl groups. For conventional catalytic dimerization, a subsequent formal σ-bond metathesis of the Ru−alkenyl bonds of **43** and **44** with a terminal alkyne would form (Z)- and (E)-enyne products, respectively, accompanying the regeneration of the acetylide complex (**42**). However, in the presence of KPF_6 in a stoichiometric quantity, a second insertion of an alkyne into the Ru−C(sp^2) bond of **44** generates **45**. Coordination of the alkyne triple bond to the Ru metal center would be not able to occur for **43**. This alkyne coordination was demonstrated to reduce the basicity of the chelating ligand, thus preventing protonation of the ligand to give the linear dienyne product and the acetylide complex (**42**). Subsequent intramolecular insertion of the coordinated alkyne in **45** would be favored to produce the new Ru−C bond, and this would lead to the formation of the polyaryl–Ru species after phosphine coordination (see **46**). Finally, reductive elimination of the polyaryl moiety with PPh_3 from the Ru center would generate the phosphonium salt (**47**) and cause decomposition of the Ru complex instead of a conventional cyclotrimerization product (Scheme 34).



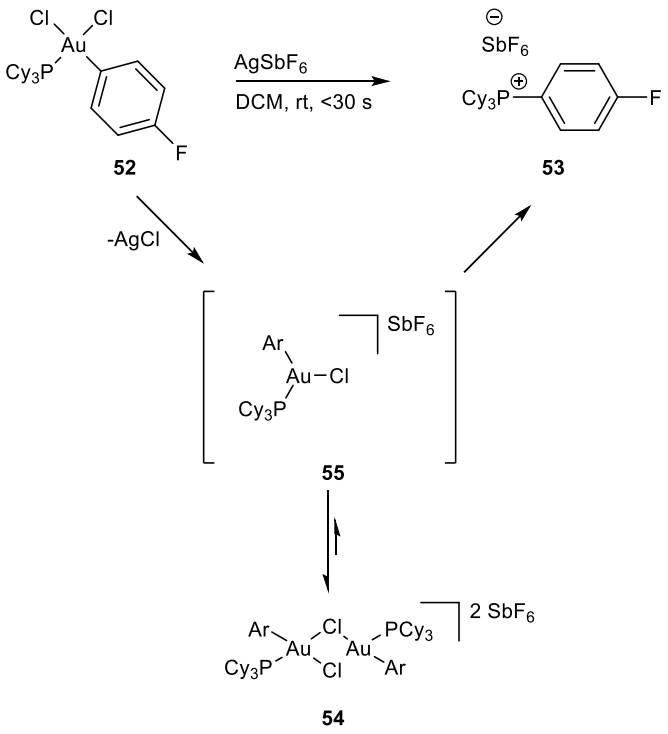
Scheme 39.

In a similar example of P–C reductive elimination, Ishii and coworkers reported the formation of five- and six-membered phosphacycles fused with aromatic systems [104]. On the basis of the results obtained through NMR and X-ray diffraction, the authors uncovered the mechanism for the formation of the phosphacycles involving initial cyclometallation and alkyne 1,2-insertion followed by P–C reductive elimination. After treatment of **48** with $NaBAr^{F}_{4}$, cyclometalation took place to form the ruthenaphosphacyclobutene (**49**) along with the release of a benzene molecule (Scheme 40). An alkyne would then insert into the strained Ru–C bond in the four-membered metallacycle of **49**. In the resulting vinyl complex **50**, which was assigned as the unstable intermediate (its CO adduct structure was determined by X-ray diffraction analysis), P–C reductive elimination would proceed to generate the phosphindolium skeleton (see **51**). Notably, this P–C reductive elimination was completed within 1 hour at room temperature. The major driving force for the facile P–C reductive elimination could be the formation of the 18e Ru(0) complex from the 16e Ru(II) species.



Scheme 40.

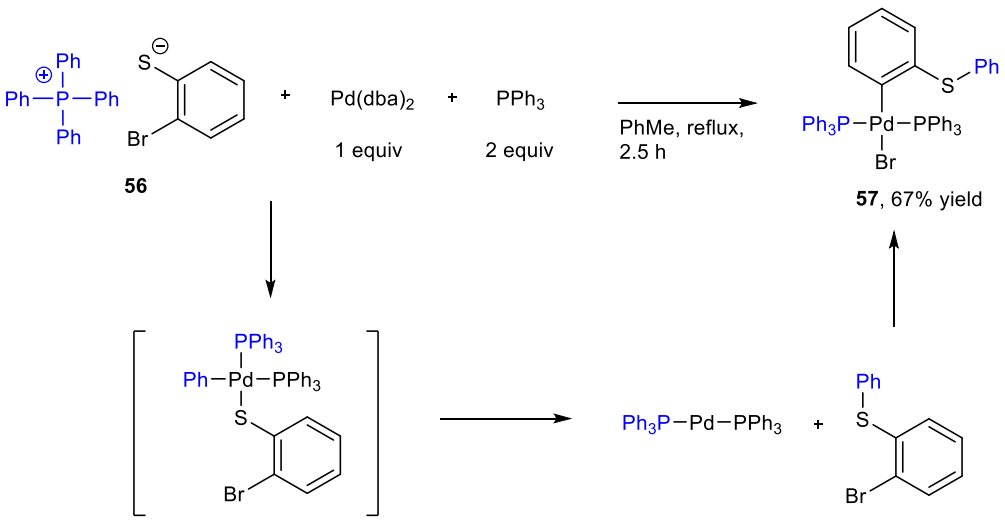
While developing a ring expansion-oxidative arylation reaction of small sized ring-substituted alkenes and allenes that was promoted by dual visible light photoredox catalysis and gold catalysis, Toste and coworkers noted the formation of a phosphonium salt during the reaction [105]. The authors reasoned that Au(III)−Ar intermedite which is formed by formal oxidative addition of Au(I) to aryldiazonium salts could precede the reaction with the alkene. Either after consumption of alkenes or in absence of alkenes, the Au(III) intermediate would undergo a reductive elimination to give a phosphonium salt. Later, the same group reported *cis*-[(Cy_3P)Au(4-FC_6H_4)Cl_2] (**52**), which was prepared by oxidizing (Cy_3P)Au(4-FC_6H_4) with $PhICl_2$, to quickly convert to the phosphonium salt (**53**) by treating $AgSbF_6$ in DCM (Scheme 41) [106]. During their investigations of the extremely fast reductive elimination, they observed new dimeric species (**54**) as the resting state at –78 °C, which dissociated to the three coordinated Au(III) complex (**55**) and consequently generated the phosphonium salt (**53**) at –20 °C. They also demonstrated that the reaction was accelerated by the presence of nucleophiles, such as acetonitrile and phosphines, via a five-coordinate intermediate. As in the former examples, irreversible P–C reductive elimination would be a possible deactivation pathway for Au(III) catalysis in the presence of a phosphine ligand.



Scheme 41.

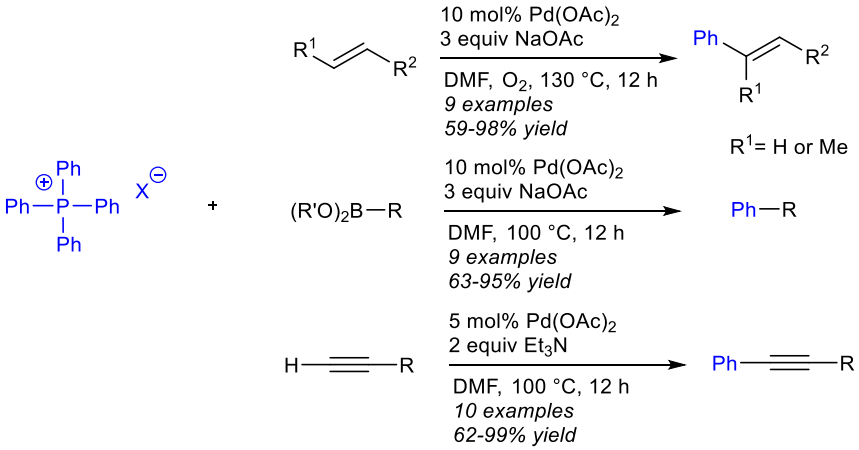
3.3. P–C bond cleavage through oxidative addition of phosphonium intermediates

As mentioned above, early studies suggested that a quaternary phosphonium halide can oxidatively add to Pd(0) complexes through P–Ar bond cleavage. Chenard and Yamamoto showed independently that one phenyl group of the phosphonium could be transferred to react with organotin nucleophiles and activated olefins, respectively [28-29]. Reetz and coworkers reported that the efficiency of the Pd-catalyzed Heck reaction with normally unreactive aryl halides was significantly improved by the presence of phosphonium halides under phosphine ligand free condition [107]. In this context, a tetraarylphosphonium salt can be utilized as an alternative to (pseudo)halides and can be employed as a coupling reagent in transition metal-catalyzed reaction.



Scheme 42.

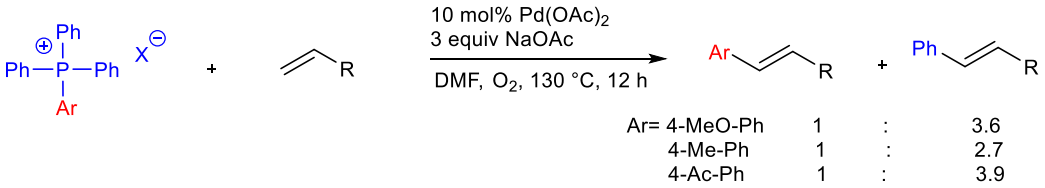
As one of the few examples of arylation using phosphonium salt, Vicente et al. reported that the reaction of [Ph_4P][2-BrPhS] (**56**) with Pd(0) in the presence of PPh_3 surprisingly produced the *trans*-[$Pd(PPh_3)_2$(2-PhSPh)Br] (**57**) instead of *trans*-[PPh_4][$Pd(PPh_3)_2$(2-PhS)Br] (Scheme 42) [108]. The authors proposed a pathway for the formation of the final palladium complex (**57**) through a sequence of reactions consisting of oxidative addition of the tetraphenylphosphonium cation to Pd(0), reductive C–S coupling to give 2-BrC_6H_4SPh, and an oxidative addition of the C–Br bond to Pd(0).



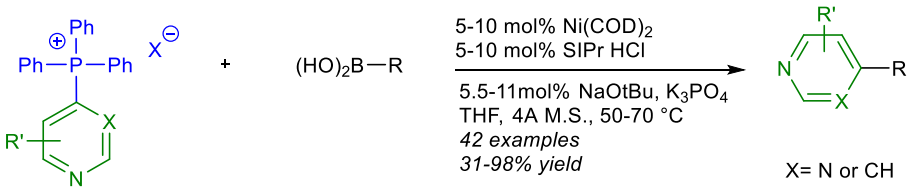
Scheme 43.

In 2005, a practical way to employ tetraarylphosphonium halides as arylating reagents in well-known cross-coupling reactions was reported by Chang et al. [109]. Several Pd catalyzed coupling reactions sharing the Ar–Pd(II)–X complex as a reaction intermediate were applied and optimized. Under given conditions, tetraarylphosphonium halides were readily employed as efficient arylating reagents in the Heck olefination, Suzuki and Sonogashira reactions (Scheme 43). When an electronically differentiated aryl substituted tetraarylphosphonium halide was used in olefinations, a selective aryl transfer was not observed. Independently of the electronic nature of the aryl substituents, a mixture of unsubstituted and

substituted cinnamates were produced with near statistical population (Scheme 44). These tendencies were also observed in the Suzuki and Sonogashira reactions. The authors assumed that the Ar/Ar interchange processes between P–Ar of phosphonium and Pd–Ar that are generated upon cleavage of the P–Ar bond of the phosphonium species are too fast to be sensitive to the electronic nature of the aryl substituents. This could be a limitation of this method for broader applications.

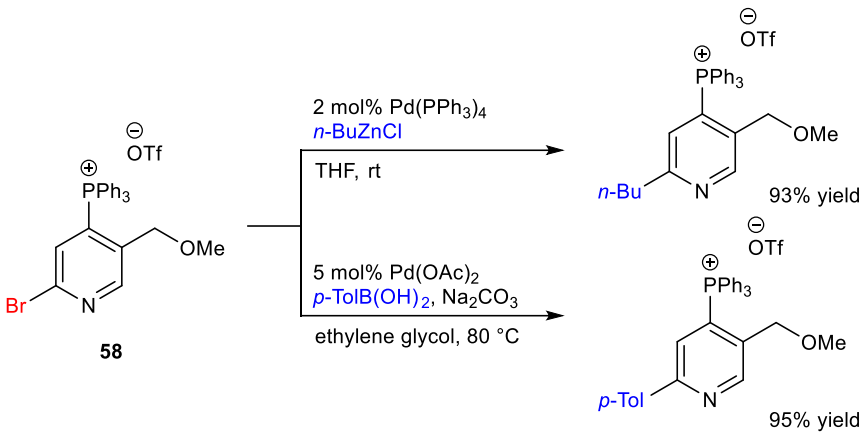


Scheme 44.



Scheme 45.

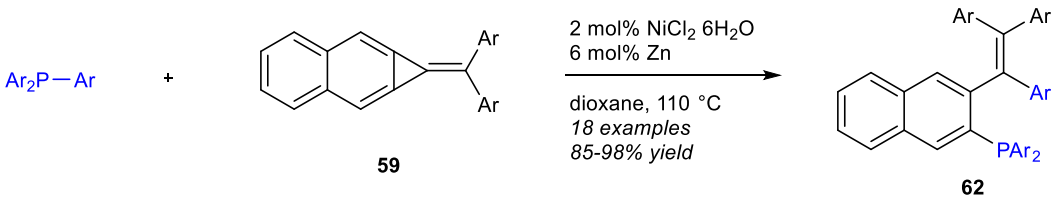
As a successful example to realize a challenging selective aryl transfer, McNally and coworkers recently discovered a Ni-catalyzed heteroarylation reaction, which is uniquely suited for selective heteroarene transfer when heterocyclic phosphonium salts are combined with arylboronic acids or boroxines (Scheme 45) [110]. A broad range of pyridines and diazines such as complex azaarenes and pharmaceuticals were tolerated. Actually, the lack of methods, which can selectively install a halide, or a halide equivalent, onto complex azaarenes, and on the 4-position of pyridines, has made the preparation of some heterobiaryls, a class of important pharmacophores by traditional cross-coupling method, difficult. In this respect, heterocyclic phosphonium salts could be used as alternative heteroaryl electrophiles in Ni-catalyzed Suzuki reactions. They also questioned whether this protocol could be orthogonally reactive to halides and enable iterative coupling sequences. **58** as a difunctional model compound was tested and its C–Br bond reacted exclusively by Pd catalyst to give Negishi and Suzuki coupling products, leaving the phosphonium ion intact for further transformation (Scheme 46). A conceptually similar attempt was conducted between an arylphosphonium thiolate and an aryl bromide [108]. In this context, understanding the difference of relative reactivity between phosphoniums and aryl (pseudo)halide electrophiles in diverse transition metal-catalyzed coupling reactions would be interesting.



Scheme 46.

4. Current research trends

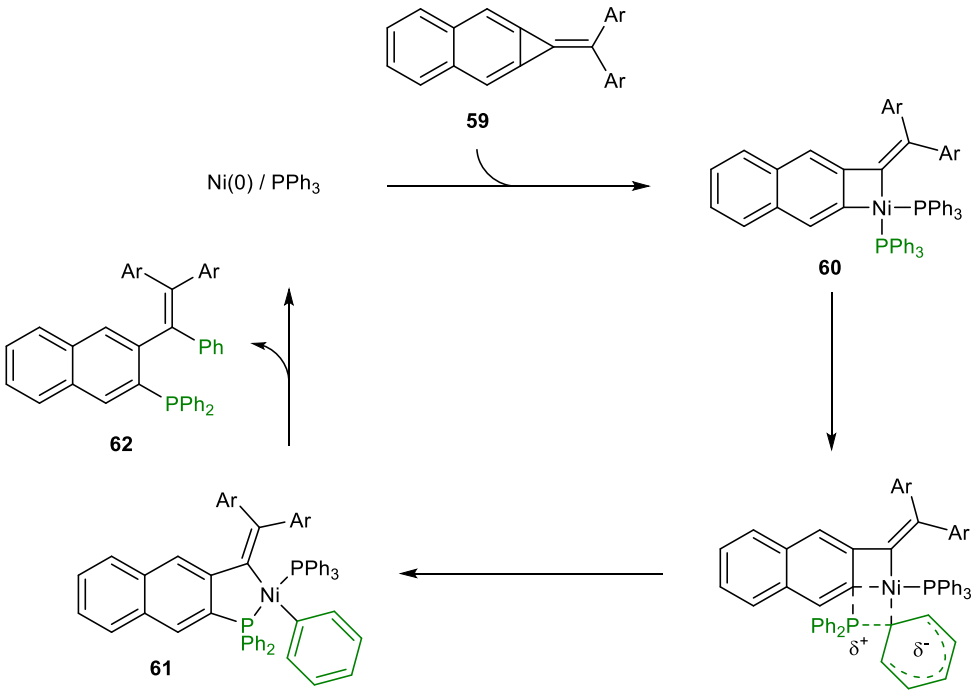
4.1. P–Ar/P–Ar exchange: beyond a side reaction



Scheme 47.

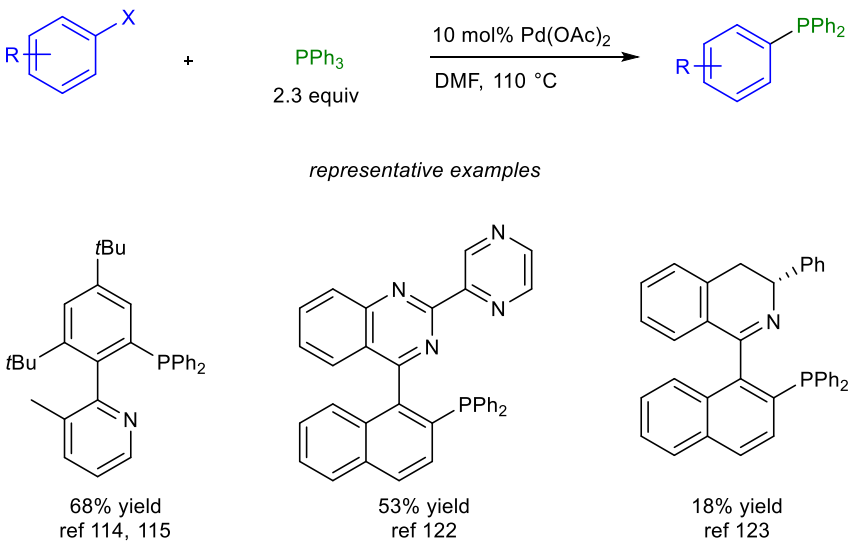
During studies on the synthetic utility of diarylmethylenecyclopropa[*b*]naphthalenes (**59**), Wu and coworkers discovered an unprecedented Ni-catalyzed P–C bond cleavage of phosphines coupled with a ring-opening reaction of **59** (Scheme 47) [111]. In order to isolate the nickelacyclobutene **60**, they envisaged that the reaction of 1-(diphenylmethylene)-1*H*-cyclopropa[*b*]naphthalene (**59**, Ar= Ph) with $Ni(PPh_3)_2$ generated in situ from $Ni(PPh_3)_2Cl_2$ and Zn would give **60** (Ar= Ph) via oxidative addition. Instead, a new product was obtained and identified as **62** (Ar= Ph). When (diarylmethylene) cyclopropa[*b*]-naphthalenes bearing different aryl substituents with varying electronic and steric variation were employed, the reactions all gave the corresponding products (**62**) in good yields. While a range of triarylphosphines bearing meta- or para-substituted aryl group were also tolerated, the reaction with $P(2\text{-}MePh)_3$ showed no reaction. It is not surprising that the reaction of phosphines bearing only one phenyl group, such as dibutyl(phenyl)phosphine and dicyclohexyl(phenyl)phosphine, resulted in the corresponding products arising from exclusive aryl group migration. In a plausible mechanism proposed by the authors, **60** forms via formal oxidative addition of **59**, P–Ar and Ni–Ar exchange might then result in **61** via a four-membered transition structure and is then further reductively eliminated to afford the

product (**62**), regenerating Ni(0) (Scheme 48). Unfortunately, the reaction with unsymmetrical substrates such as (diarylmethylene)cyclopropa[*b*]-naphthalenes has shown poor regioselectivity.



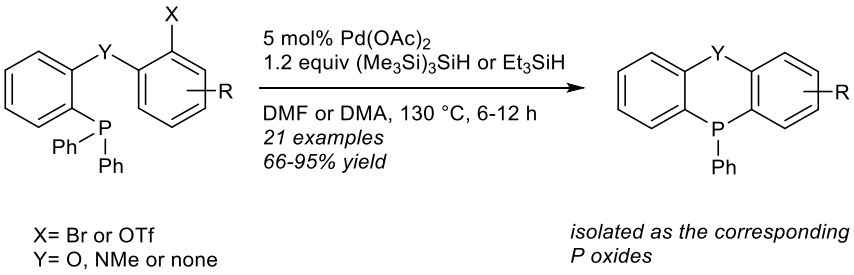
Scheme 48.

Chan and coworkers developed a Pd-catalyzed synthesis of mono-aryl substituted phosphines from PPh_3 by taking advantage of the Ar/Ar exchange. The mono-aryl exchanged phosphine was obtained through the Pd-catalyzed reaction of PPh_3 with aryl bromides [112,116,118,120-121], and aryl triflates [113-119,121] (Scheme 49). Less reactive aryl chlorides also could be utilized as substrates upon addition of an excess amount of sodium iodide (5 equiv) [121]. In the initial reaction stage, the phosphonium salt was produced by reductive elimination. It could then further participate in oxidative addition to give mono-aryl exchanged phosphine as major products. This method has advantages such as broad functional group tolerance and cost efficiency. However, limited yields of desired products due to the innate equilibration nature of the process remain to be addressed. A lower tolerance to ortho-substituted aryl moieties is consistent with previous aryl scrambling results. However, this method operated well with aryl triflates bearing 2-pyridyl group (Scheme 49). The authors assumed that the reaction is likely facilitated by the coordinating pyridine-N atom [114-115,117,122-123].



Scheme 49.

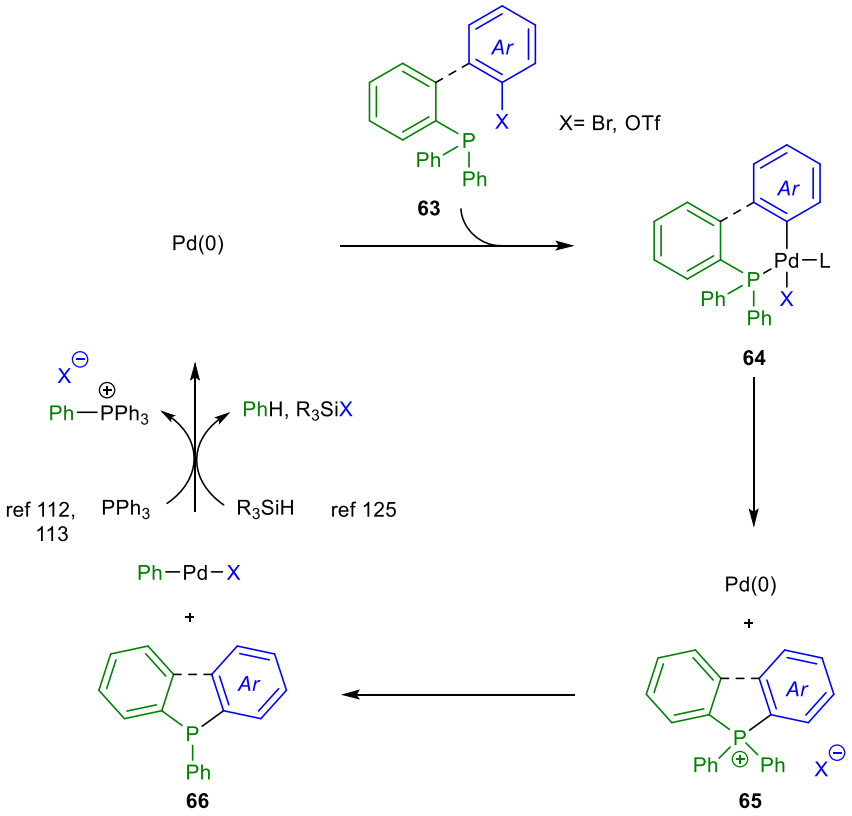
Inspired by the strategy used in the synthetic method to access mono-aryl substituted phosphines, Chatani and coworkers modified and adapted this reaction to produce dibenzofused six and five-membered phosphacycles (Scheme 50). This is a class of phospholes which has rapidly found applications in material science due to their unique optical and electronic properties [124-125]. Conventional synthetic methods using highly reactive ragents for their preparation have been limited by low functional group compatibility. The authors highlighted the compatibility of their method with several functional groups including esters, amides, and carbamates. However they indicated that the extension of this method to the synthesis of seven-membered phosphacycles was unsuccessful [125].



Scheme 50.

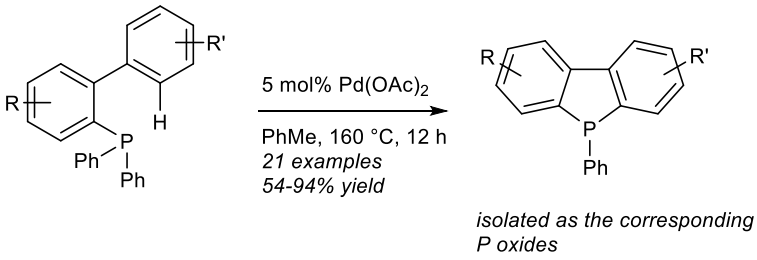
The proposed mechanism involves an oxidative addition of an aryl bromide (**63**) to the Pd(0) species to form a six or seven-membered palladacycle (**64**). Subsequent P–C bond forming reductive elimination from the palladacycle generates a cyclic phosphonium salt (**65**), along with a Pd(0) species. The P–Ph bond in the phosphonium can be cleaved through an oxidative addition onto the Pd(0) species, releasing a desired phosphacycle product (**66**) and Ph–Pd(II)–X (X= Br or OTf). If the Ph–Pd(II)–X intermediate then undergoes reductive elimination to form PhX, an active Pd(0) species can be regenerated. However, such a C–Br bond and C–OTf bond forming reductive elimination is known to be thermodynamically challenging. Thus, a key step in the mechanism is the regeneration of Pd(0) to make the reaction be catalytic. The addition of a proper reductant such as hydrosilanes is required to reduce the complex back

to Pd(0). It is worth comparing the different approaches to regenerate Pd(0) in the construction of a catalytic cycle. In Chan's method, Ph–Pd–X was converted to a phosphonium (pseudo)halide by using excess PPh_3 (Scheme 51) [112-113]. On the other hand, Chatani, inspired by the process involved in the catalytic reductive dehalogenation of aryl halides, employed silane reductants in their reaction to reductively cleave Ph–Pd–X to benzene and silyl bromide (Scheme 51) [125].

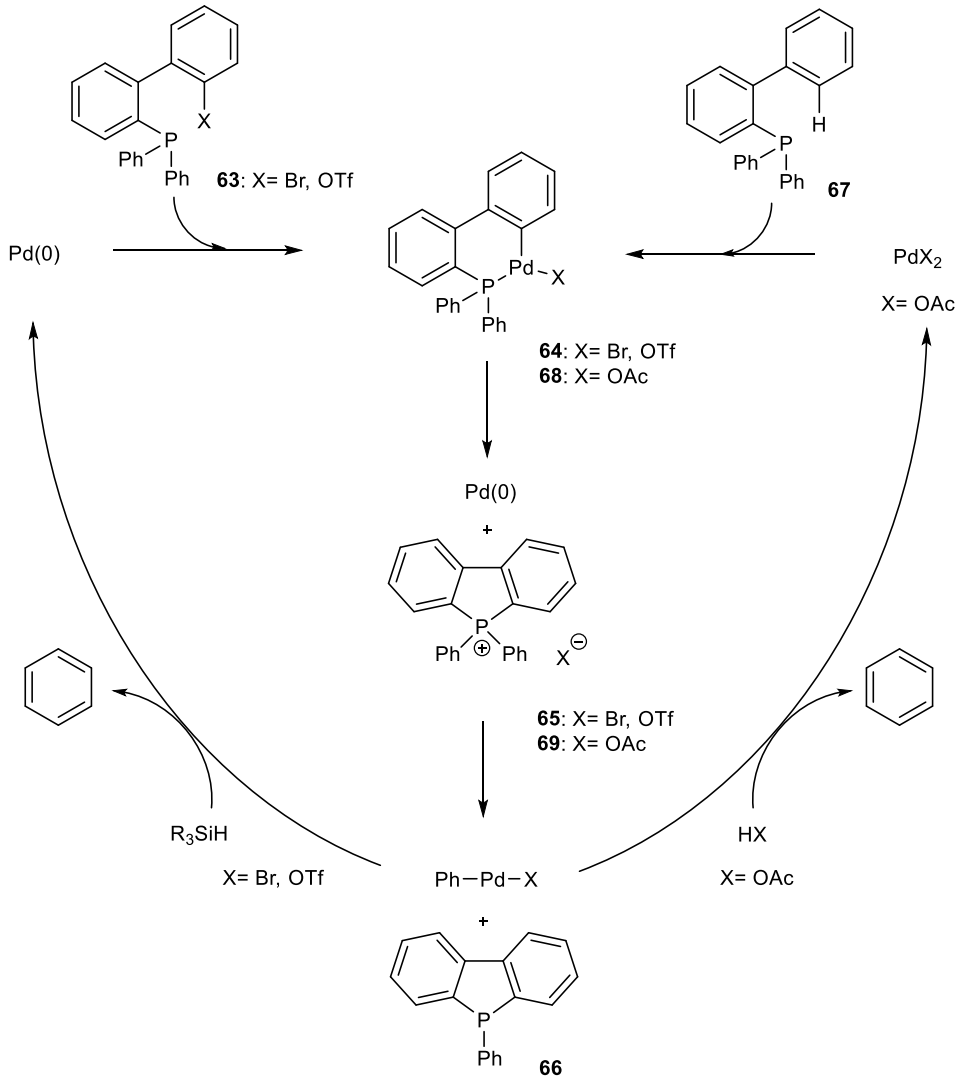


Scheme 51.

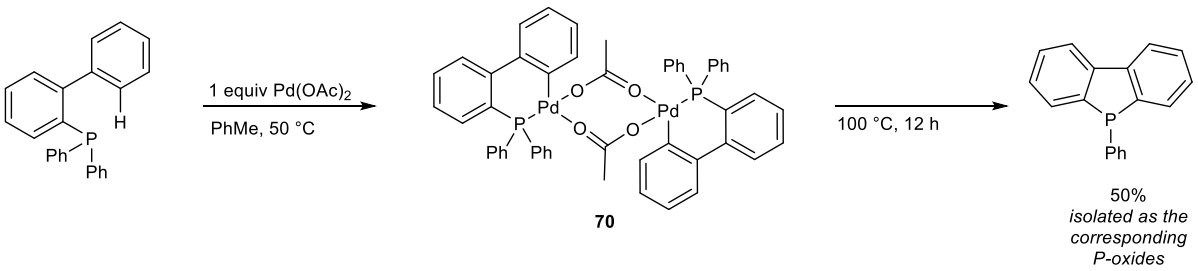
The same group reported a slightly different approach for the synthesis of phospholes through the reaction of simple biphenylphosphine with catalytic $Pd(OAc)_2$ (Scheme 52) [124]. They reasoned that the reaction of a biphenylphosphine (**67**) with $Pd(OAc)_2$ would afford a palladacycle (**68**) through concerted metalation-deprotonation mechanism [126]. Subsequent reductive elimination from the palladacycle leads to the formation of a phosphonium (**69**) along with Pd(0). The phosphonium then undergoes oxidative addition to Pd(0) to provide the desired phosphole product (**66**) and Ph–Pd–OAc. Finally, the Pd(II) complex is protonated by AcOH, which is released in the initial cyclometallation stage, to regenerate $Pd(OAc)_2$ and benzene (Scheme 53, right). To support their proposed mechanism, the synthesis of a cyclopalladated complex was demonstrated under stoichiometric conditions (Scheme 54). The complex was isolated as a dimer (**70**). Upon heating of its solution, a desired phosphole product was produced, thus suggesting that the palladacycle could be a plausible intermediate in the catalytic cycle. The reaction also tolerated a range of electronically different phospholes bearing amines, ketones and O, N-heteroaryl moieties. The compatibility with chlorides and bromides is particularly interesting in light of the occurrence of Pd(0) intermediates.



Scheme 52.



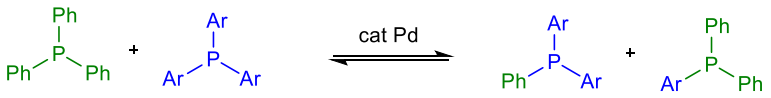
Scheme 53.



70

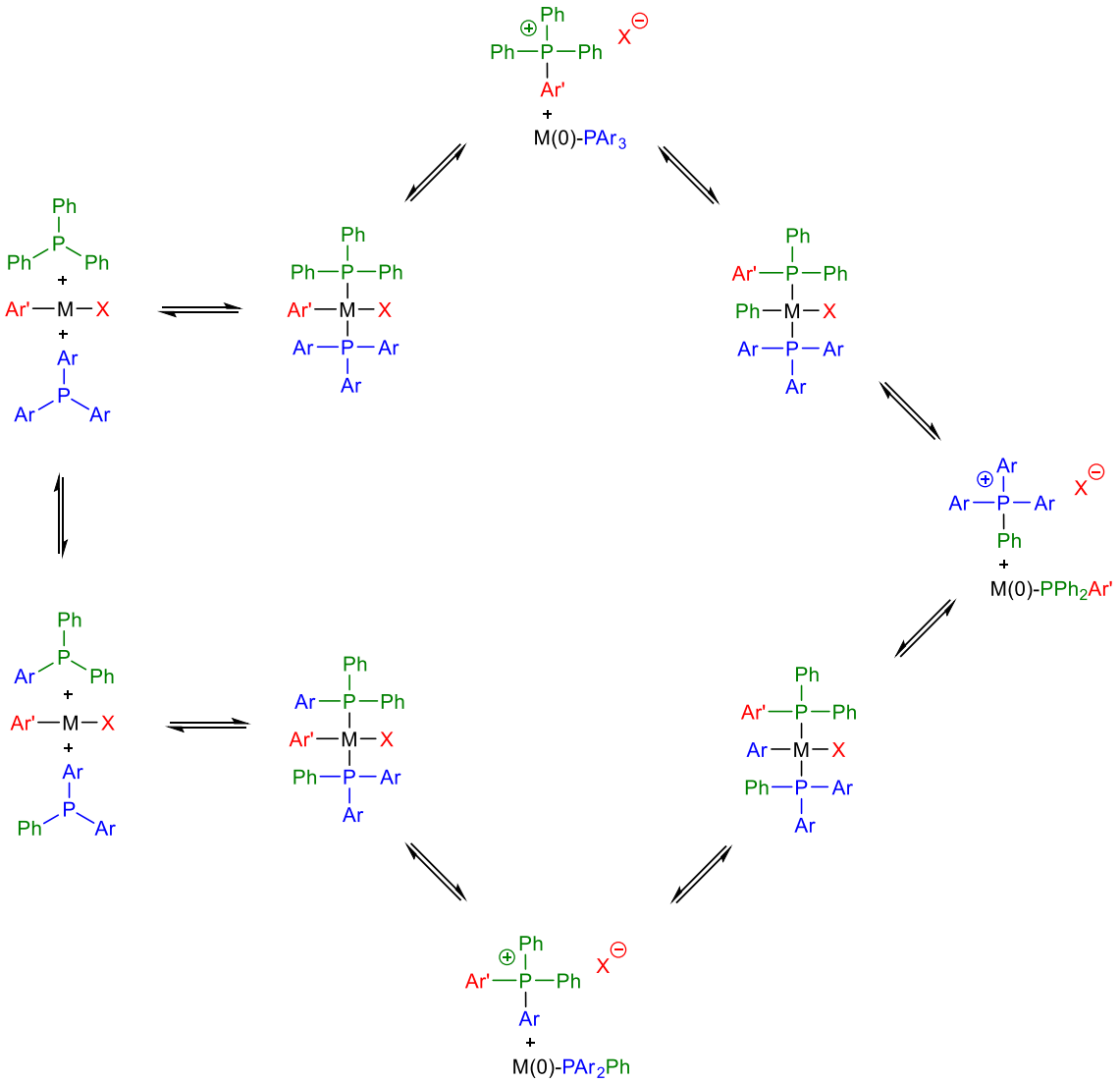
Scheme 54.

One remarkable feature of these reactions from the Chan group and Chatani group is that, while they have different catalytic cycles and substrates, they nevertheless share almost all the same intermediate steps, resulting in the same or analogous products (Scheme 51 and 53).



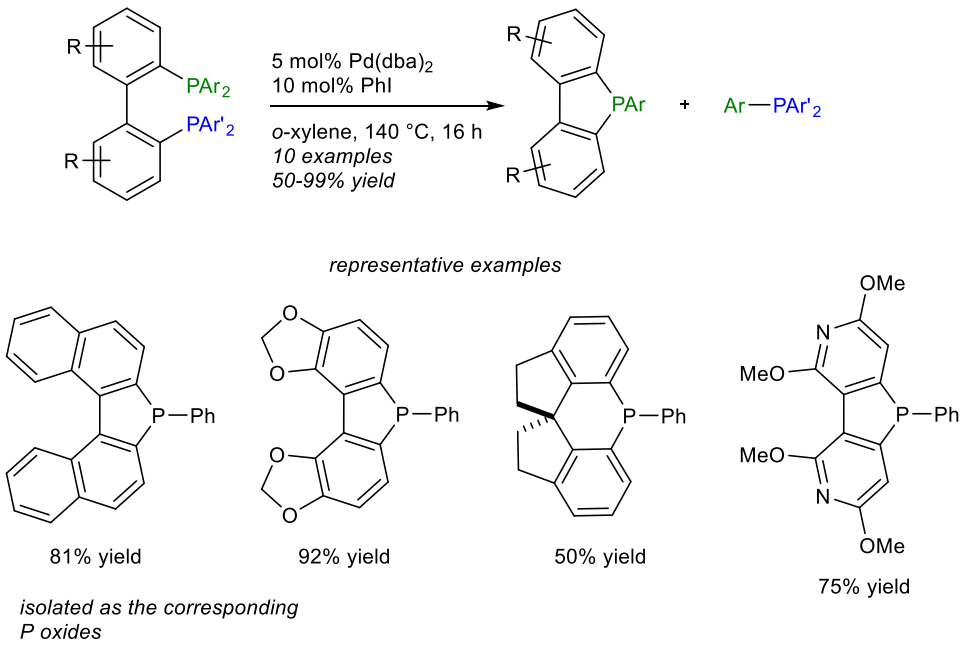
Scheme 55.

Morandi and coworkers recently developed a Pd-catalyzed reversible arylation of P–C bonds which can be coined as P–C bond metathesis [127-128]. Actually, literature precedent has often shown the reversible nature of this P–C bond cleavage and forming. As mentioned above, in 1984, two independent works reported that a P–C/P–C cross-metathesis reaction is a reversible process which seems to proceed through oxidative addition and consecutive reductive elimination by Pd(0) in both cases [34-35]. Inspired by these works, Morandi and coworkers systematically studied both the forward and the reverse reaction of a range of meta- and para-substituted triarylphosphines with PPh_3 using both catalytic amount of Pd(0) and PhI. Pd(0) is converted in situ to Ph–Pd(II)–I, which is proposed to be the actual catalyst in this reaction (Scheme 55). In most instances, thermodynamic equilibrium was reached with negligible loss of mass balance, except when using furan- and naphthyl-substituted phosphines. The reversible arylation mechanism proceeding through phosphonium intermediates is depicted in Scheme 56.



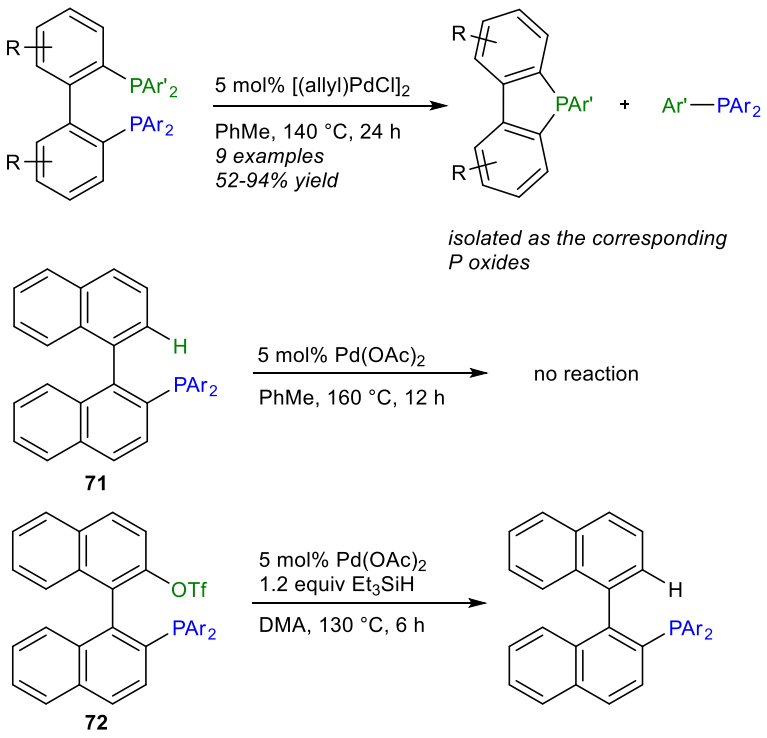
Scheme 56.

The reaction was also applied to the preparation of phosphorus heterocycles including phospholes. From bisphosphines, a cyclic phosphine product and a triarylphosphine by-product were generated in good yield (Scheme 57).

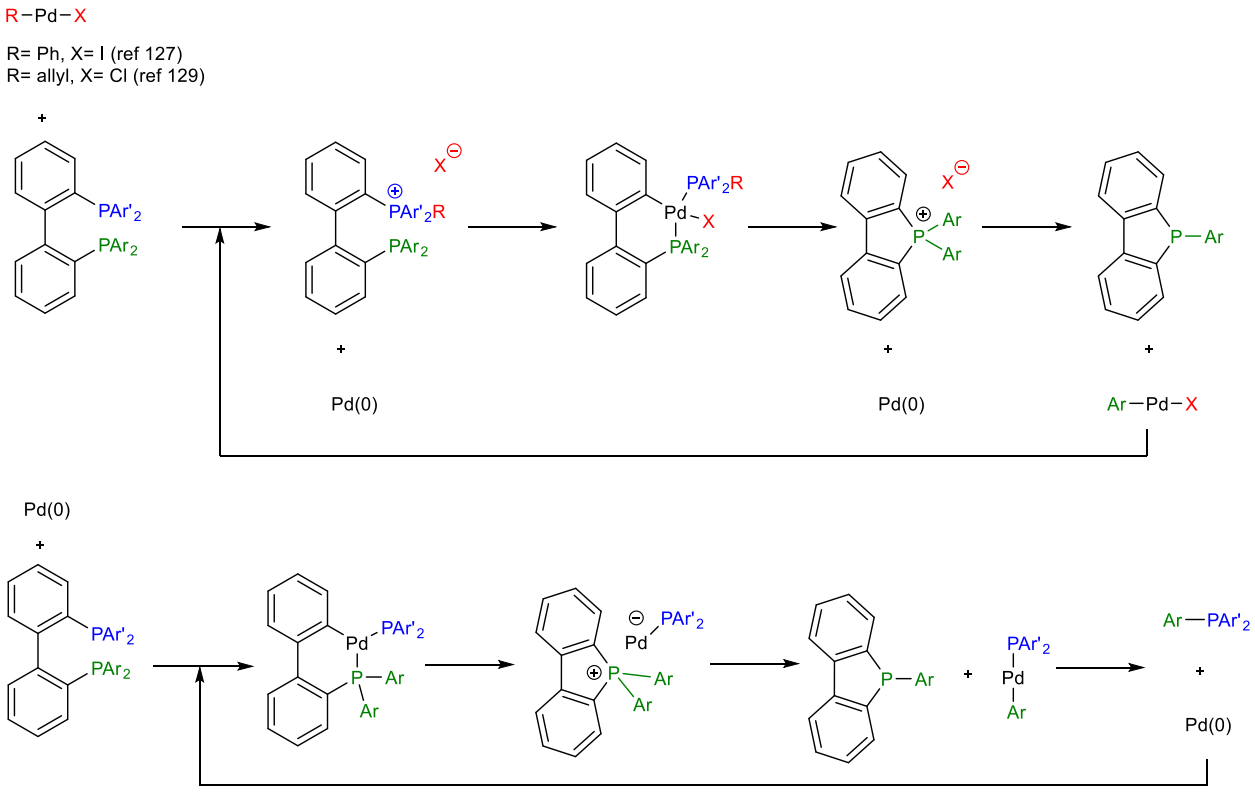


Scheme 57.

Shortly thereafter, Tobisu and Chatani et al. independently reported similar reactivity (Scheme 58, top) [129]. While the Morandi group used $Pd_2(dba)_3$ and PhI as a catalyst system, Tobisu and Chatani used $[(allyl)PdCl]_2$ as a catalyst. In view of related early works, both groups proposed a possible mechanism which involves the initial formation of monophosphonium salts of bisphosphine (Scheme 59, top). In the reaction of the latter group, it is noteworthy that the exchange between Pd–allyl and P–Ph would be feasible based on literature precedent, effectively making allyl–Pd(II)–Cl an equivalent for Ar–Pd(II)–I under the reaction conditions [49]. Additionally, a mechanism involving initial oxidative addition of neutral P–C bond was also proposed on the basis of their observation that the desired cyclized product was obtained from $Pd(BINAP)_2$ complex in good yield (Scheme 59, bottom). The fact that $Pd(PPh_3)_4$ exhibited significant catalytic activity (49% yield vs. 93% yield when applied $[(allyl)PdCl]_2$) indicates that the latter mechanism cannot be excluded [34-35]. Interestingly, the authors reported the cyclization of binaphthyl-type bisphosphines that cannot be accessed through previously reported methods from binaphthyl monophosphine (**71**) and (pseudo)halide substituted binaphthyl monophosphine (**72**), respectively (Scheme 58) [124-125]. the Morandi and Tobisu/Chatani processes enabled the conversion of widely available (chiral) biaryl and binaphthyl-type bisphosphines into cyclic monophosphine compounds, which are species of growing attention in catalysis and electronic materials. On a final note, it is important to realize that the selective cross-metathesis of two different P–C bonds still remains a stimulating challenge for future studies.

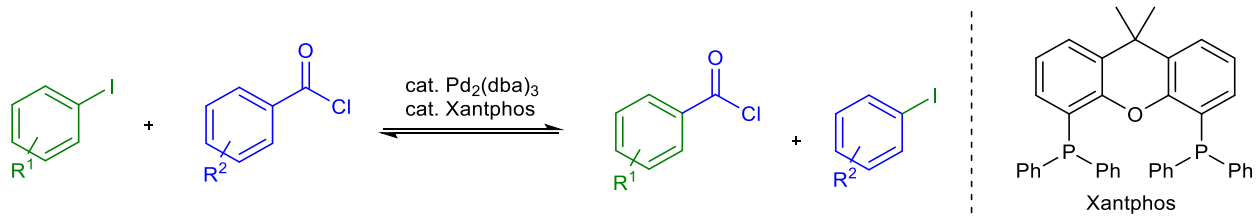


Scheme 58.

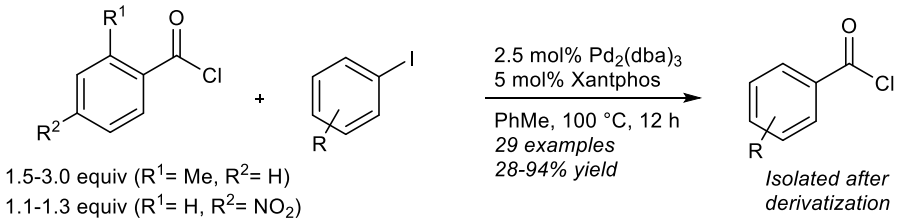


Scheme 59.

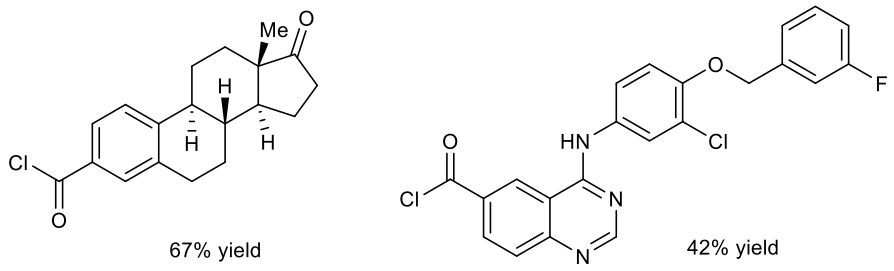
While the recent progresses were mostly focused to the preparation of synthetically useful P containing compounds using P–Ar/P–Ar exchange, a novel approach taking advantage of P–Ar/P–Ar exchange in a catalytic manifold has been recently disclosed. Morandi and coworkers presented a catalytic functional group metathesis between aroyl chlorides and aryl iodides which is enabled by P–Ar/P–Ar metathesis (Scheme 60) [130-131]. The authors pointed out that a limitation of conventional functional group interconversions is the utilization of strong kinetic and thermodynamic forces that prevent the possibility to perform the reverse reaction. Morandi's work provides a simple protocol for both aroyl chloride and aryl iodide synthesis, in which chlorocarbonylation (forward) and iodination (reverse) reaction can be performed under a single set of reaction conditions by controlling the equilibrium with either Le Chatelier's principle or weak thermodynamic driving forces (Scheme 61 and 62) [130]. Both forward and reverse reactions tolerate a broad range of functional groups such as ketones, aldehydes, some heterocycles and (pseudo)halides, and either electron rich and poor substituents, as well. While a wide range of ortho-substituted aroyl chlorides were converted to the desired aryl iodide products in good yields, the forward reaction was not successful with ortho substituents. The use of α-substituted heterocycles was problematic in both directions.



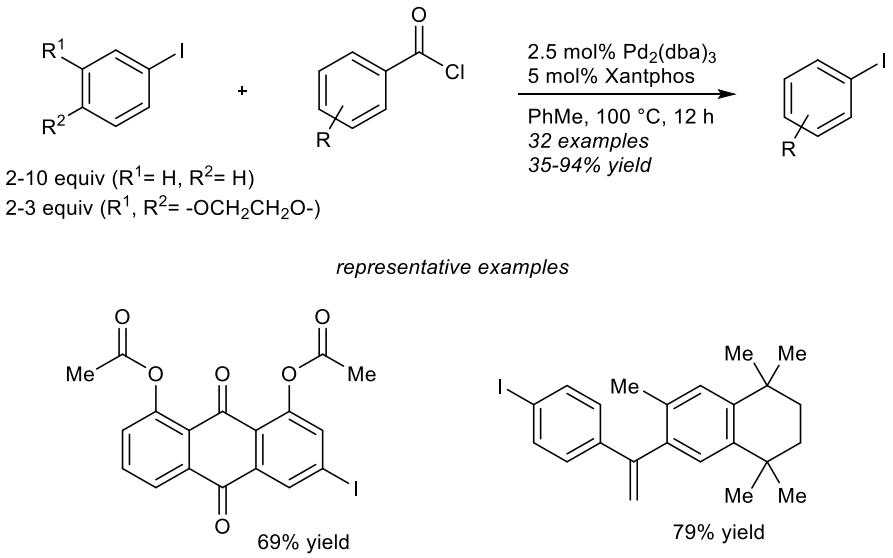
Scheme 60.



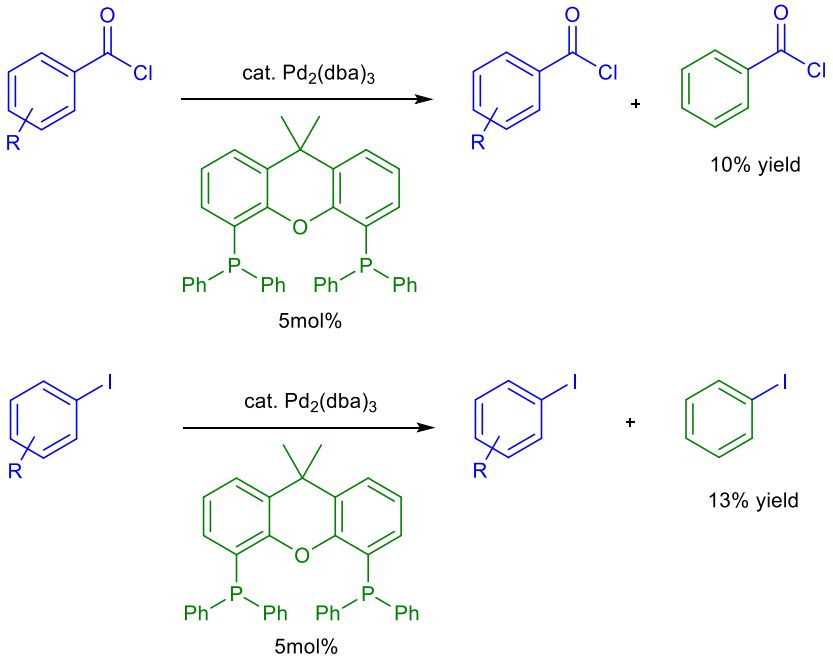
representative examples



Scheme 61.



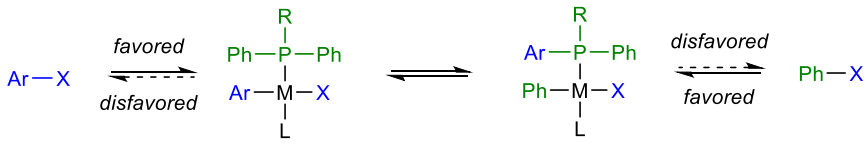
Scheme 62.



Scheme 63.

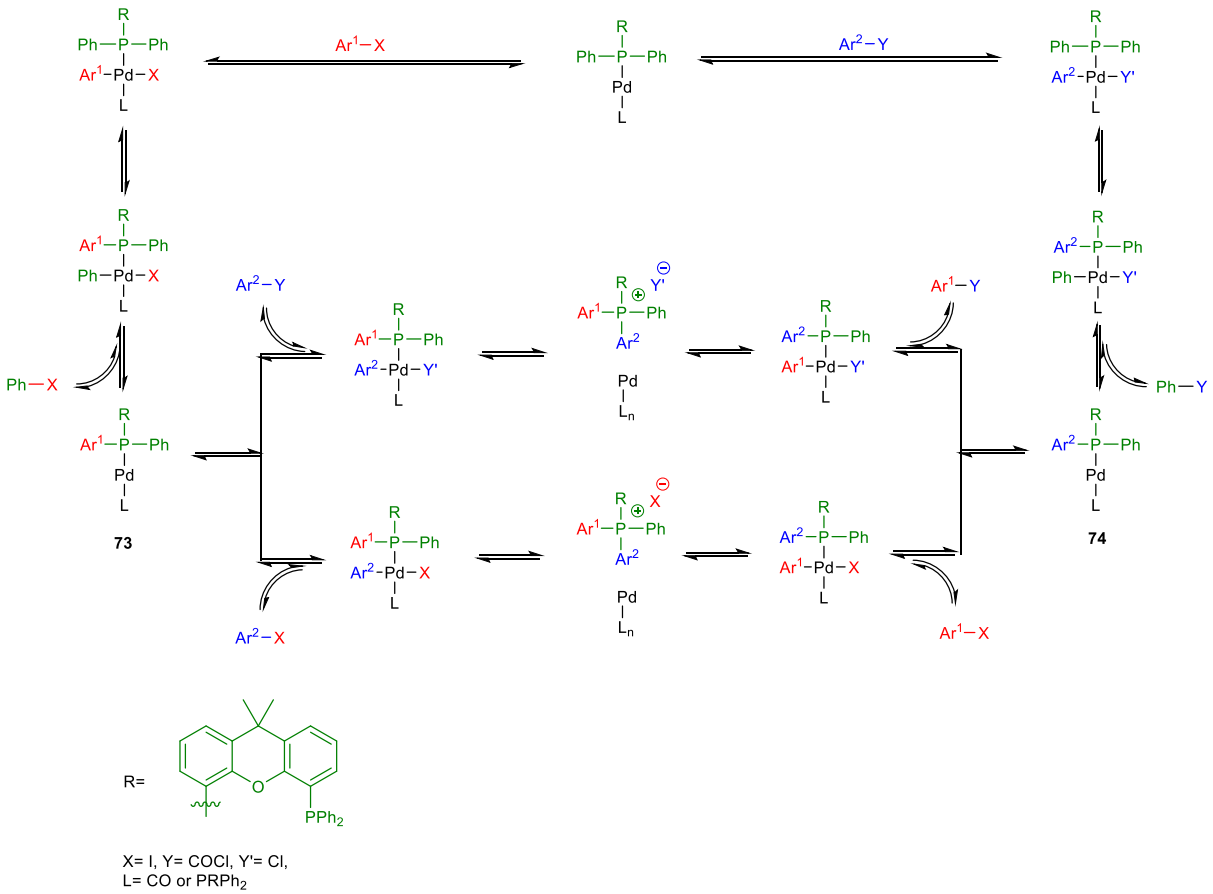
In the preliminary studies, the authors discovered that a significant amount of the aryl groups are exchanged with Ph groups from a Xantphos when reacted with the catalytic amount of Pd under 100 °C in toluene (Scheme 63). It is noteworthy that a simple Pd(0)/Xantphos system enables the reductive elimination of both aryl iodides and aroyl chlorides from its oxidized complex, reversibly. Commonly, reductive elimination toward reactive compounds such as aryl halides and aroyl chloride, is rare because reverse addition is favored thermodynamically (Scheme 64). A few successful examples in achieving this challenging transformation showed that sterically hindered monotrialkylphosphine ligands can drive the reductive elimination through strain release at the Pd center [132]. Thus, the use of privileged bulky and

electron-rich P(*t*Bu)$_3$ is normally essential for C–X bond-forming reductive elimination to proceed [133-135]. Similarly, other sterically hindered monophosphines, Pd-catalyzed systems have been shown to enable C–X bond-forming reductive eliminations by Buchwald et al. (C(sp^2)–Br and Cl) [136-137], Lautens et al. (C(sp^2)–Br and C(sp^3)–I) [138-139] and Sanford et al. (C(sp^2)–Cl) [140]. Recently, Arndtsen and coworkers reported a unique transformation of aryl iodides into extremely reactive aroyl triflates using CO, AgOTf, and a quite simple palladium catalyst under phosphine ligand free condition [141-142].



Scheme 64.

Morandi and coworkers have postulated that the aryl exchange between aryl iodide and aroyl chloride, in which the Xantphos serves as a temporary aryl storage unit, could be feasible if two independent elementary C–P/C–X metathesis reactions could be combined together (Scheme 63). A plausible mechanism is depicted in Scheme 65. The Pd complex bearing an aryl exchanged Xantphos (**73** and **74**) ligand could participate in the oxidative addition to either aroyl chloride (Scheme 65, top) or aryl iodide (Scheme 65, bottom). Then a phosphonium intermediate forms through reductive elimination, and then regenerates a different Pd–Ar species through the oxidative addition of another P–C bond. Reductive elimination then simultaneously generates an aryl electrophile and a new Pd(0) species that have swapped their aryl substituents in the overall process. Iterative processes with the new Pd(0) species would result in rapid equilibration of the mixture to its thermodynamically most stable state. To support the proposed mechanism based on metathesis-active ligands, as a new type of ligand non-innocence, qualitative kinetic experiments have been conducted with a wide range of different substrates. The relative rate of P–C bond metathesis for different aryl substrates correlated well with the overall rate of the catalytic reaction using the same substrates, a result which supports the proposed mechanism. Also, a fast aryl exchange rate for electron-rich substituents was consistent with previous reports [36]. As an additional control experiment, the reaction in an open system with continuous argon purging resulted in the same yield as in the normal reaction. Although this result suggests that free CO is not generated in the reaction media, the authors indicated that mechanistic paths through a CO/halide exchange could not be fully excluded. In particular, ortho substituted aryl electrophiles did not follow the above-mentioned electronic trend, suggesting that an alternative mechanism might be operative in this case.



Scheme 65.

5. Summary and outlook

For a long time, the exchange of Ar groups between Pd–Ar species and the Ar groups of phosphine ligands has been considered as an undesirable side reaction often observed in many Pd-catalyzed cross-coupling processes. However, the accumulation of mechanistic understanding has now opened new avenues for the discovery of unexplored fruitful reactivity utilizing the metathesis of P–C and M–C bonds. We have discussed novel examples of the P–C/ M–C exchange reactivity and recent progress for its strategic utilization in catalysis. The now broad diversity of transition metals and exchanging groups, from aryl to vinyl, allyl, and alkyl groups, demonstrates the wide ranging relevance of these processes. In this context, it is noticeable that Co(III) dimethyl halide species also undergoes reversible Co–Me/P–Me exchange with PMe_3 [143]. Finally, the application of the P–C/P–C metathesis in catalysis is also broadening from the synthesis of useful phosphine derivatives to selective arylation protocols [110] and metathesis reactions between two different single bonds by a metathesis-active ligand [130].

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