DOI: 10.1002/ejoc.200700312

Recent Developments in Catalytic Aryl Coupling Reactions

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Keywords: Aryl coupling / Homogeneous catalysis / Metallacycles / Palladium / Transition metals

The present microreview is aimed at describing the evolution of the methodology used in aryl coupling reactions towards catalytically efficient and highly selective procedures, which have been achieved through the use of assisted and metallacycle-directed reactions.

1. Introduction

Biaryl-containing organic structures are ubiquitous in chemistry and biology and offer a wide range of applications spanning from liquid crystals to pharmaceuticals.[1] Research on the synthesis of biaryls dates back to the well-known Ullmann reaction,[2] which has stoichiometric character. Symmetrical biaryls can be formed by the coupling of aryl halides in the presence of equimolar amounts of copper powder, copper bronze, copper(I) salts, or copper oxides according to Equation (1). These reactions usually require long reaction times and high temperatures and are therefore carried out in solvents such as pyridine, quinoline, DMF, and tetramethylurea, the latter at temperatures above 200 °C.

$$\mathrm{Ar{-}X} \xrightarrow{\mathrm{Cu}} \mathrm{Ar{-}Ar}$$

$\mathrm{X = Cl, Br, I}$ (1)

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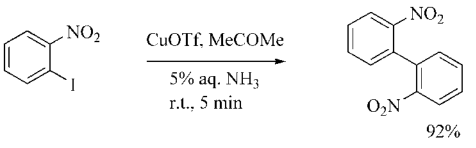
Marta Catellani (center) obtained her Italian Laurea in 1971 under the supervision of Prof. G. Casnati at the University of Parma where she now acts as a full professor. After a period at the Ecological Department, she joined the group of Prof. G.P. Chiusoli in 1977 when she started to work on homogeneous catalysis with group VIII metals. She spent one year as postdoctoral fellow in the group of Prof. J. Halpern at the University of Chicago (1978–79), short periods in Sheffield (Prof. B. Mann, 1989), in Tsukuba (Prof. M. Tanaka, 1990), and as a visiting professor in Russia and China. Her fields of scientific interest include transition-metal-catalyzed organic synthesis of complex molecules through sequential processes, synthesis and reactivity of palladacycles in oxidation states II and IV, monitoring the reaction course by NMR, and catalyst design for selective control.

Elena Motti (right) graduated in Industrial Chemistry in 1997 from the University of Parma, and in 2001 she obtained her Ph.D. in Chemical Sciences working under the supervision of Prof. M. Catellani. Part of her doctoral studies was carried out at the Swiss Federal Institute of Technology (ETH), Zurich, in the group of Prof. P.S. Pregosin. Currently, she is a researcher at the University of Parma, and her major research interests are in the field of catalysis of multistep multicomponent organic reactions by means of palladium complexes.

Nicola Della Ca' (left) graduated in Industrial Chemistry in 2000 from the University of Parma. In 2001, he joined the group of Prof. R. Ungaro to work on a European Community project for one year. He obtained his Ph.D. in Chemical Sciences working under the supervision of Prof. M. Costa. During this period he spent six months as a visiting scholar at Iowa State University with Prof. R. C. Larock. He is presently a researcher at the University of Parma in the group of Prof. M. Catellani, and his main interests are in transition-metal-catalyzed carbon–carbon bond formation reactions.

Raffaella Ferraccioli was born in Avezzano, Italy. She studied at the University "La Sapienza" of Rome, where she obtained a degree in Pharmaceutical Chemistry and Technology in 1982. In 1984, she became a researcher at the Institute of Molecular Science and Technology (CNR) in Milan, where she is still working. Her research activity concerned 1,3-dipolar cycloadditions, synthesis of serine proteinase inhibitors, and carbon acids activation. In 1996, she joined the group of Prof. L. F. Tietze (University of Goettingen) to work on palladium-catalyzed synthesis of anticancer agents. Her current research interests focus on the development of new synthetic methods based on palladium-catalyzed sequential reactions, multicomponent reactions, and their application to the synthesis of interesting heterocycles.

During the last century, substantial improvements were made and nowadays many variants are available that allow the Ullmann coupling reaction to be carried out under mild conditions. For example, 2-iodonitrobenzene in acetone gives the corresponding biaryl at 20 °C in 5 min by using copper(I) triflate and 5% aqueous ammonia [Equation (2)].[3]



(2)

The reactivity of aryl halides follows the order $I^- > Br^- > Cl^-$ and is strongly enhanced by the presence of electron-withdrawing substituents, such as nitro- and alkoxycarbonyl groups, and particularly when these groups are in *ortho* position to the halogen atom. The reaction tolerates many functional groups, but it is inhibited or greatly limited by free OH, NH_2, and CO_2H groups, which need to be protected.

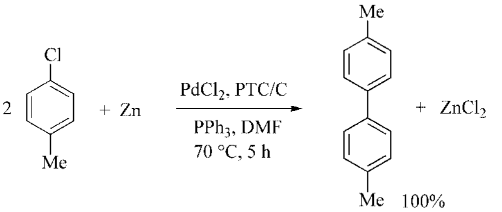
Although the reaction is best suited for the synthesis of symmetrical biaryls, unsymmetrical biaryls can be obtained by coupling aryl halides of different reactivity (Ar^1X and Ar^2X) so that the crossed product (Ar^1–Ar^2) is formed preferentially over the two homocoupled species (Ar^1–Ar^1 and Ar^2–Ar^2). Usually, electronic factors are the most effective to this aim, and the crossed product can be achieved by using a significant excess of the less reactive halide.

Intense effort was dedicated over the years to devise catalytic systems that are able to effect aryl coupling.[4] This was not limited to Ullmann-type reductive coupling but was extended to oxidative and substitutive coupling as well. We shall briefly review the results obtained, eventually concentrating on the direct arylation of unactivated arenes.[5] Other ways to form aryl–aryl bonds such as by aryne reactions will not be discussed here.

2. Catalytic Reductive Coupling

The Ullmann reaction, and in general any reductive coupling of aryl halides and their congeners, can be performed catalytically by using a coreductant that is able to rereduce the oxidized metal species. The latter can be a nickel,[6] iron,[7] rhodium,[8] or ruthenium species.[9]

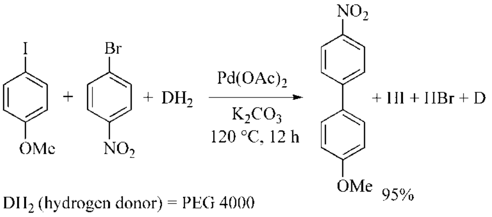
An example of a highly selective reductive homocoupling of substituted haloarenes with the use of $PdCl_2/PPh_3$, Zn as the reductant, and a carbon-supported phase-transfer catalyst (PTC) in DMF at 70 °C was recently reported [Equation (3)].[10] An even simpler procedure that involved the use of ammonium formate as reducing agent[11] was proven to be effective. The use of ultrasound and microwave irradiation was shown to be advantageous.[12]



(3)

Cross-coupling reactions usually are not selective unless they are conducted in two steps, the first one consuming one of the two partners.[13]

It is interesting that in some cases it was possible to perform the cross-coupling in one step under reductive conditions. Thus, the reaction of iodo- or bromoarenes, activated by electron-withdrawing substituents, in the presence of palladium acetate as the catalyst and poly(ethylene glycol) (PEG), both as the solvent and the hydrogen donor DH_2 (possibly through oxidation of the primary hydroxy to aldehyde), provided the expected biphenyls in high yield,[14] as reported for the example in Equation (4).



(4)

The course of the reductive coupling with palladium was traditionally interpreted to involve ArX oxidative addition to palladium(0) followed by disproportionation (Scheme 1).[15]

$$\begin{aligned}
&Pd^0L_2 + ArX \longrightarrow ArL_2PdX\\
&2\,ArL_2PdX \longrightarrow Ar_2L_2Pd + L_2PdX_2\\
&Ar_2L_2Pd \longrightarrow Ar\text{–}Ar + L_2Pd^0\\
&L_2PdX_2 + Zn \longrightarrow ZnX_2 + L_2Pd^0
\end{aligned}$$

Scheme 1. The conventional pathway proposed for reductive coupling.

This scheme is, however, rather simplistic. It was shown by Amatore and Jutand[16] that the true Pd^0 species undergoing oxidative addition is the anionic L_2PdX^- ($X^- = Cl^-$, AcO^-; L = ligand, usually a tertiary phosphane), formed from Pd^0 and the Cl^- or AcO^- ions present in solution when the starting complexes are L_2PdCl_2 or $L_2Pd(OAc)_2$, respectively (Scheme 2).

$$L_2PdX_2 \xrightarrow[-X^-]{\text{red.}} L_2PdX^- \xrightarrow{ArX} ArL_2PdX_2^- \xrightarrow[-2X^-]{\text{red.}}$$
$$\longrightarrow ArL_2Pd^- \xrightarrow{ArX} Ar_2L_2PdX^- \longrightarrow Ar\text{–}Ar + L_2PdX^-$$

Scheme 2. The reaction course proposed by Amatore and Jutand.[16]

ArX oxidative addition gives an anionic pentacoordinate palladium complex, which after reduction with loss of $2X^-$ leads to an ArL_2Pd^- anion. Addition of a new molecule of ArX places another Ar group near the former one and Ar–Ar elimination reforms the initial L_2PdX^- anion. The mechanism is actually more complex and the ion pairing of the anion with its counterion also must play an important role.

The nickel-catalyzed homocoupling reaction of two ArX molecules with Zn (or an electrochemical source) as the reducing agent proceeds by a different mechanism from the palladium-catalyzed reaction owing to the one-electron nature of the nickel reduction.[17] A similar difference exists in other palladium- and nickel-catalyzed homocoupling reactions such as the coupling of aryl triflates.[18]

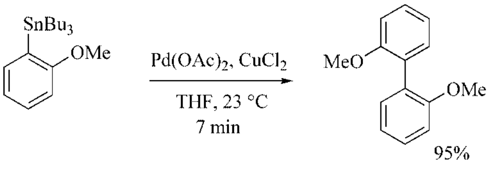
3. Oxidative Coupling

Analogously to reductive coupling, oxidative coupling is effected by a metal catalyst, which is reduced and must be reoxidized by an appropriate oxidant, such as dioxygen. The oxidative coupling of arene species can be performed with ArX species, where X is a certain functional group, in particular $B(OH)_2$, or X is simply a hydrogen atom.

3.1. Catalytic Oxidative Coupling of ArX

This class of oxidative coupling includes substrates such as aryllithium,[19] arylzinc,[20] arylmagnesium,[21] aryltin,[22] arylcopper,[23] and arylboron[24] compounds. The oxidative agent can be oxygen, hydrogen peroxide, copper(II) salts, oxovanadium(V), and high-valent metal salts.

We shall consider two examples. The first example involves the use of aryltributyltin as the substrate with palladium acetate as the catalyst and copper chloride as the oxidant ([Equation (5)] and Scheme 3).[23a]



(5)

$$Pd(OAc)_2 + Ar\text{–}SnBu_3 \longrightarrow Ar\text{–}Pd\text{–}OAc + AcO\text{–}SnBu_3$$

$$Ar\text{–}Pd\text{–}OAc + Ar\text{–}SnBu_3 \longrightarrow Ar\text{–}Pd\text{–}Ar + AcO\text{–}SnBu_3$$

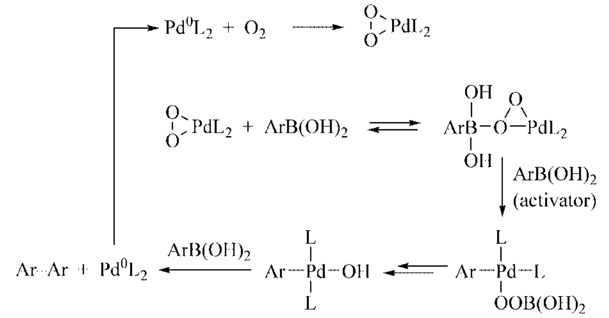
$$Ar\text{–}Pd\text{–}Ar \longrightarrow Ar\text{–}Ar + Pd^0$$

$$Pd^0 + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl$$

Scheme 3. Aryl–aryl coupling of aryltributyltin by using $CuCl_2$ as the oxidant.

The other example refers to the coupling of arylboronic acids in toluene at room temperature in the presence of a Pd^0 catalyst such as $Pd(PPh_3)_4$ under an atmosphere of air [Equation (6)].[24g] Its mechanism is, however, much more complex. Amatore provided evidence that a peroxido complex of palladium plays a key role in the catalytic homocoupling of arylboronic acids. Scheme 4 reports the steps involved in the reaction.[25]

$$2\,ArB(OH)_2 + O_2 \xrightarrow{Pd^0} Ar\text{–}Ar \qquad (6)$$

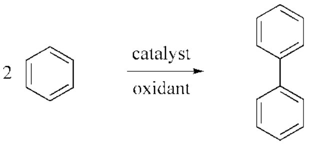


Scheme 4. Palladium-catalyzed cross-coupling of aryl boronic acid in the presence of oxygen.

The homocoupling of arylboronic acids was carried out successfully with Pd/C especially under ultrasound and microwave irradiation.[12]

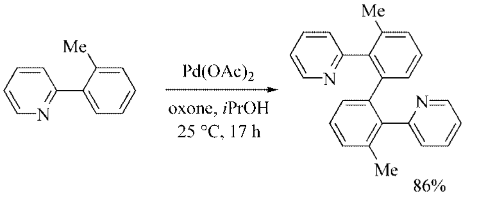
3.2. Catalytic Oxidative Coupling of ArH

We saw in the preceding section that oxidative C–C coupling can be successfully performed with arenes that are functionalized with the appropriate substituents. The simplest direct arene C–H oxidation, which has been known for many years, is the coupling of benzene to biphenyl.[26] The reaction becomes much more interesting if it is achieved catalytically with a suitable oxidant [Equation (7)]. Many metals in a high oxidation state have been used over the years together with oxidants (mostly oxygen) that are able to reoxidize the reduced metal. The intramolecular homocoupling turns out to be the most successful reaction.[26]



(7)

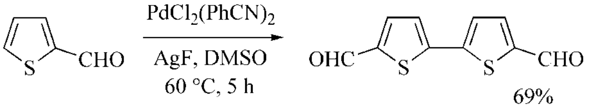
Dehydrogenative coupling reactions of pyridones was performed successfully in the heterogeneous phase,[27] and more recently, a step forward towards selective intermolecular cross coupling reactions was taken. The oxidative coupling step was shown to be selective in the presence of directing groups in the substituent (*o*-arylpyridines) in the presence of $Pd(OAc)_2$ as the catalyst and oxone (potassium peroxymonosulfate) as the oxidant [Equation (8)].[28]



(8)

Interestingly, a coupling pathway that differs from the traditional one, based on disproportionation of arylpalladium species, was proposed. It consists of a two-stage process involving $Pd^0 \rightarrow Pd^{II}$ and $Pd^{II} \rightarrow Pd^{IV}$ complexes. Pd^{IV} would play the role of activating electrophilically the C–H bond of the second phenylpyridine molecule.

The presence of a heteroatom such as sulfur in thiophenes orients C–C coupling selectively. An example is reported in Equation (9).[29] The heteroatom effect was also observed in arylation reactions of heterocycles with aryl halides, which will be described in Section 5.2.4.

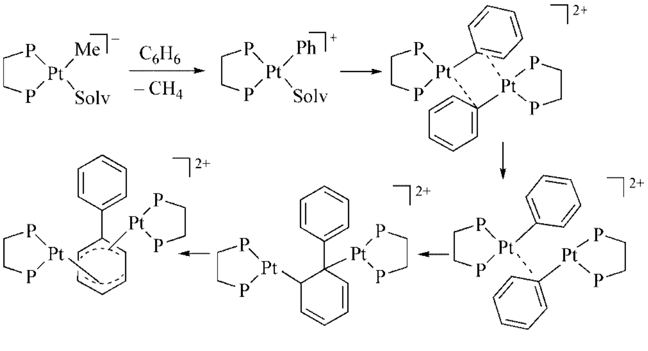


(9)

Heterogeneous catalysis with palladium in zeolites is also a useful technique.[26] Other metals were used stoichiometrically.[30] Thus, $MoCl_5$ was used as a stoichiometric reagent for the coupling of alkylated anisole derivatives at 0 °C in CH_2Cl_2.[30a]

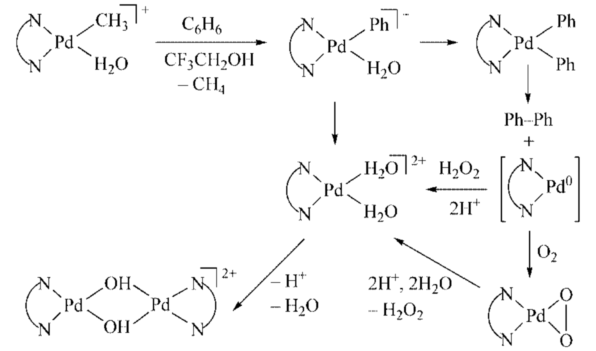
Phenol derivatives have also been shown to direct oxidative C–C coupling at the *ortho* position. Electrophilic attacks at this position have long been known.[31] In particular, new BINOL [1,1′-bis(2-naphthol)] compounds were obtained through enantioselective syntheses. Copper catalysts are best suited owing to their ability to favor one-electron phenol oxidation under oxygen, which leads to a quinone form with one unpaired electron at the *ortho* carbon where coupling occurs. 1,5-Diazadecalin was shown to be a very efficient ligand for copper.[32]

Cooxidants of various types have been used over the years. A more recent development consists of the use of palladium chloride/AcONa with oxygen in AcOH at 105 °C in the presence of $Mn(OAc)_2$, $Co(OAc)_2$, $Zr(OAc)_4$, and acetylacetone. Under these conditions, the rate of reoxidation of palladium(0) is higher than its rate of aggregation to palladium black and the reaction proceeds with high conversion and selectivity.[33] Significant advancements have been made in understanding the coupling pathway with palladium and platinum complexes. Arene coupling by cationic Pt^{II} complexes of the type $[(R_2PC_2H_4PR_2)\text{–Pt–Me}(OEt_2)]\text{-}BAr_F$ (R = Cy, Et) was found to proceed at room temperature through intermolecular C–H activation with benzene or arenes as substrates, giving rise to complexes of the type $[\{Pt(R_2PC_2H_4PR_2)\}_2(\mu\text{-}\eta^3\text{: }\eta^3\text{-biaryl})][BAr_F]_2$.[34] Migration of an η^1-bonded aryl group onto an η^2-coordinated arene molecule was proposed to take place. The process was explained as depicted in Scheme 5. It is worth noting that η^6,η^6-bridged biaryl ligands were also obtained by Fryzuk et al.[35] by the reaction of Cl-bridged dimeric complexes of Y^{III} or other lanthanides with ArLi.



Scheme 5.

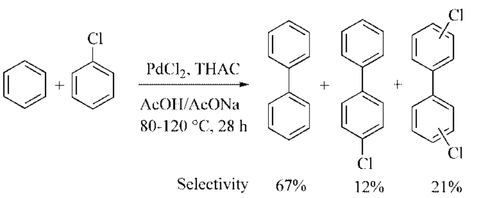
Bercaw et al. carried out research on oxidative coupling with cationic palladium complexes.[36] They found that methylpalladium(II) complexes with $ArN{=}C(CH_3)\text{–}C(CH_3){=}NAr$ [Ar = 3,5-di-*tert*-butylphenol; 3,5-bis(trifluoromethyl)phenyl] ligands undergo protonolysis with HBF_4(aq) in trifluoroethanol to form cationic complexes $[(\alpha\text{-diimine})Pd(CH_3)(H_2O)][BF_4]$ that are able to activate benzene C–H bonds at room temperature. Disproportionation leads to a palladium complex containing two *cis* phenyl groups, which couple to biphenyl and a palladium(0) complex, and to a diaqua complex, which gives rise to a dimeric μ-hydroxido complex. The latter is ultimately formed by the oxidation of the Pd^0 complex. This mechanism is depicted in Scheme 6. According to the authors, it is not excluded that Kubas intermediates[34] are present and oxidized by palladium(II).



Scheme 6.

4. Catalytic Redox Coupling

Reductive and oxidative coupling can also be associated to obtain a true catalytic reaction without the need of cooxidants and coreductants. A mixture of reductive and oxidative coupling products is obtained, however, as shown by the palladium-catalyzed reductive and oxidative coupling of benzene and chlorobenzene ([Equation (10)]; THAC = tetrahexylammonium chloride).[37]



(10)

5. Catalytic Substitutive Coupling

The most important area of aryl–aryl coupling is that of substitutive coupling, which proceeds catalytically. Two main ways have to be considered: the first consists of the replacement of an X group in an arene Ar^1X with an anionic Ar^2 group generated from an appropriate metallic complex Ar^2m (m = group containing a nontransition metal) [Equation (11)]; the second is based on the direct replacement of H in an arene with an aryl group from ArX [Equation (12)].

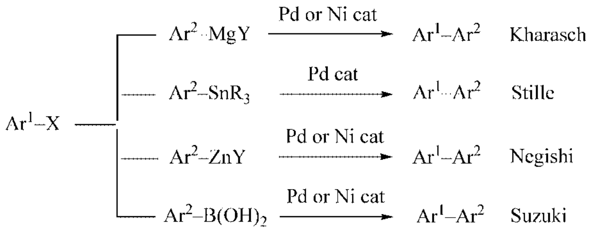
$$Ar^1X + Ar^2m \xrightarrow{\text{cat.}} Ar^1\text{–}Ar^2 + X\text{–}m \quad (11)$$

$$Ar^1X + Ar^2H \xrightarrow{\text{cat.}} Ar^1\text{–}Ar^2 + X\text{–}H \quad (12)$$

5.1. Substitutive Coupling of ArX

5.1.1 Kharasch, Stille, Negishi, and Suzuki Reactions

As shown in Scheme 7, the Kharasch reaction[38] involves the coupling of an aryl Grignard reagent (Ar^2MgY, Y = halogen) with an aryl halide (Ar^1X) to give the biaryl derivative (Ar^1–Ar^2). The reaction usually occurs under mild conditions in the presence of a nickel or palladium species as the catalyst and leads to the formation of the product in good yields. One drawback of the Kharasch reaction is that it precludes the use of aromatic compounds containing functional groups that are able to react with the Grignard reagent, such as aldehydes, ketones, esters, and nitro groups.



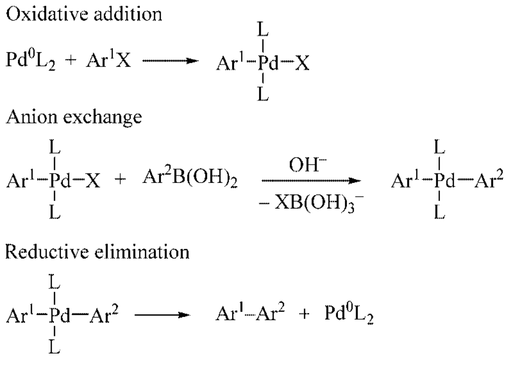
Scheme 7. Kharasch, Stille, Negishi, and Suzuki reactions.

The coupling of an arylstannane (Ar^2SnR_3, R = alkyl group) with an aryl halide or triflate (Ar^1X, X = halogen or OTf) is known as the Stille reaction.[39] The reaction requires mild conditions, proceeds under the catalytic action of palladium(0), and is compatible with the presence of several functional groups in the aromatic ring. The major disadvantage of Stille coupling is that the tin reagents used and the byproducts generated are usually toxic and not easily removed from the reaction product.

In the Negishi reaction,[40] the biaryl product is formed by coupling an arylzinc derivative (Ar^2ZnY, Y = halogen) with an aryl halide or triflate (Ar^1X, X = halogen, OTf) in the presence of catalytic amount of a palladium or nickel species. The reaction proceeds under mild conditions and tolerates various functional groups, such as aldehydes, ketones, and esters, and amino and nitro groups.

Nowadays the most widely used method in biaryl synthesis is the Suzuki reaction,[41] where an arylboronic acid [$Ar^2B(OH)_2$] is the coupling partner of an aryl halide or triflate (Ar^1X, X = halogen, OTf). Palladium or nickel species catalyze the formation of the coupling product, usually in high yield under mild conditions. The success of this methodology is essentially due to the fact that it is not affected by the drawbacks encountered in the previously reported reactions. In fact, arylboronic acids are: (1) compatible with the presence of many functional groups in the coupling partners, (2) stable in the presence of air and humidity, and (3) innocuous and easily removed from the organic product because of their solubility in water.

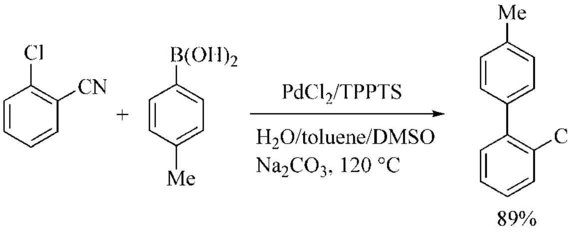
All the reactions shown in Scheme 7 proceed through a common pathway involving three steps, namely: (1) oxidative addition of the Ar^1–X species (aryl halide, -triflate, or -tosylate) to the metal in its low oxidation state [palladium(0) or nickel(0)] with the formation of the aryl–metal bond, (2) anion exchange (or transmetalation) to yield a diarylated species, (3) reductive elimination from the diarylated metal to form the biaryl derivative and to regenerate the metal in its low oxidation state. Scheme 8 shows a largely accepted reaction pathway for the formation of biaryl by palladium-catalyzed Suzuki coupling.



Scheme 8. Possible pathway for the formation of biaryl by the palladium-catalyzed Suzuki reaction.

As previously mentioned, the Suzuki reaction[41] has found widespread use in organic synthesis, and it has become extremely important in fine chemical synthesis[42] particularly in the search and discovery of bioactive compounds and new pharmaceutical products. Because protection and deprotection of the functional groups that are present in the coupling partners are not required, the synthesis of biaryls becomes straightforward in a one-step reaction.

Aside from its wide use in the small-scale synthesis of screening compounds, the Suzuki reaction has also found industrial applications for the production of active intermediates. An example of commercial production is the manufacture of 2-cyano-4′-methylbiphenyl, an intermediate in the synthesis of the antihypertensive drug Valsartan (Novartis).[43] 2-Cyano-4′-methylbiphenyl is prepared from 2-chlorobenzonitrile and *p*-tolueneboronic acid as reported in Equation (13).[44]



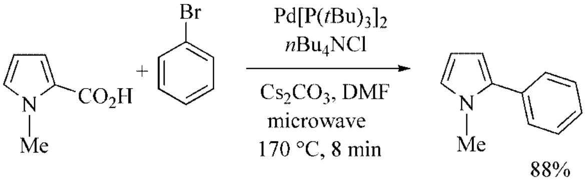
(13)

Catalysts for Suzuki reactions have been improved very much. Sterically demanding tertiary phosphanes were shown to be very efficient ligands in the coupling of both bromides and chlorides at very low catalyst loadings at room temperature.[45] Besides the well-known bulky phosphanes, N-heterocyclic carbenes mixed with triarylphosphane were used as ligands for palladium (TONs up to 2.6×10^6).[46] Suzuki and aryl coupling reactions in general have been carried out successfully in heterogeneous phase.[12,27]

In spite of the wide use of the Suzuki reaction for the synthesis of biaryls, there are still many drawbacks owing to the presence of palladium and phosphorus compounds as product contaminants and to the need for recovering them. These problems limit its industrial application. For these reasons, industrial companies have considered Grignard chemistry as a possible alternative to the Suzuki procedure.[42c] Thus, Sanofi-Chimie at Sisteron in South France has worked out an efficient procedure to prepare the intermediate for Valsartan compound 2-cyano-4′-methylbiphenyl starting from *p*-tolylmagnesium chloride and *o*-bromobenzonitrile.[47]

5.1.2 Other Coupling Procedures

Another interesting alternative to Suzuki coupling is offered by the use of silicon-based organic reagents.[48] More recent developments in aryl cross-coupling reactions should also be highlighted, and they involve the use of decarboxylation pathways. In the first case a heterocycle 2-carboxylic acid reacts at 170 °C with an aryl bromide in the presence of palladium(0) bis(tertiary phosphane) and cesium carbonate in DMF to give the corresponding 2-arylheterocycle, as shown in Equation (14).[49] In the second case an aromatic carboxylic acid reacts with an aryl bromide in the presence of palladium(0) and CuI/phenanthroline at 160 °C in NMP to give a biaryl.[50] Equation (15) reports the synthesis of 4-chloro-2′-nitrobiphenyl, an important intermediate for the synthesis of the agrochemical Boscalid (BASF).[43]



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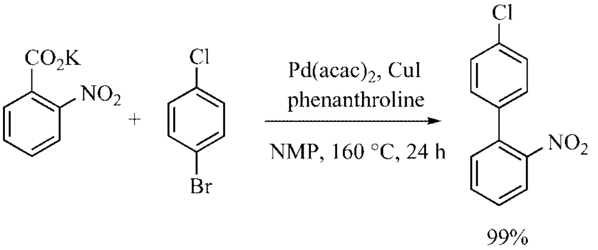


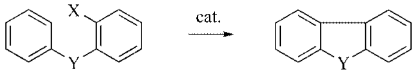
(15)

5.2. Catalytic Substitutive Coupling by Direct Arylation of ArH

The substitutive coupling of ArH represents the most recent area of research. Such a substitution occurs directly, usually by activation of an arene C–H bond; thus, it should be the most advantageous among the catalytic reactions. An important problem must be solved, however, which lies in the lack of selectivity of the C–C coupling in the absence of a suitable orienting effect. The need for selectivity control has progressively led research to devise appropriate means to achieve this goal. Intramolecular, polarity-driven intermolecular, heteroatom-directed, chelation-directed, and metallacycle-directed reactions have been the object of recent studies, which will be reviewed as follows: intramolecular or polarity-driven intermolecular selective attack of Ar^1X on Ar^2H, chelation-directed attack, heteroatom-directed attack, and metallacycle-directed attack.

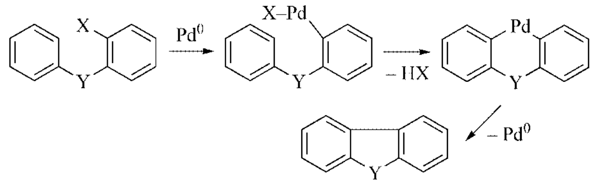
5.2.1. Intramolecular Reactions

This type of cyclization was reported as far back as 1982 for the synthesis of bromocinnolines and subsequently applied to many cases according to Equation (16) where Y can be a carbon, nitrogen, sulfur, or oxygen unit including one or two atoms.[51] The methodology was recently enriched by the discovery of efficient catalytic systems such as those based on $Pd(OAc)_2$/tricyclohexylphosphane·HBF_4 or biphenyldiphenylphosphanes.[52] In most cases, an electrophilic mechanism is generally accepted for the intramolecular attack, according to Scheme 9 where palladium(0) is the catalyst.



(16)

The driving force that allows this arylation to occur selectively is the formation of a five- or six-membered cyclic product. Precoordination of an η^2 bond of the arene to palladium is likely to occur in view of several cases where η^2-



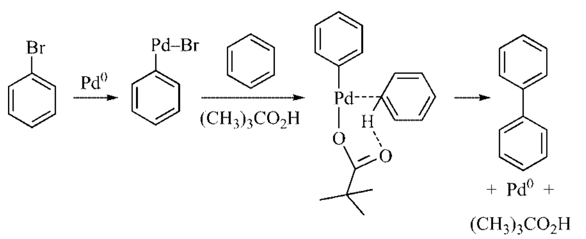
Scheme 9.

arene coordination to palladium was observed.[53] This being the case, we should conclude that the intramolecular arylation of arenes also pertains to the category of reactions assisted by chelation, which will be treated in Section 5.2.3.

5.2.2. Intermolecular Reactions

Intermolecular coupling requires some activation effect that favors electrophilic attack. So far the polar hydrocarbon azulene was reported to react at 140 °C in the presence of palladium acetate.[54]

An interesting advancement was achieved for the arylation of benzene with the use of a bulky organic acid (10% in excess on palladium) in conjunction with K_2CO_3 and catalyzed by palladium acetate coordinated by 2-(2′-dimethylamino)phenyldicyclohexylphosphane at 120 °C. An 81% yield was attributed to the assistance of the carboxylic group of pivalate, which abstracted the benzene proton and transferred it to K_2CO_3 (Scheme 10).[55]

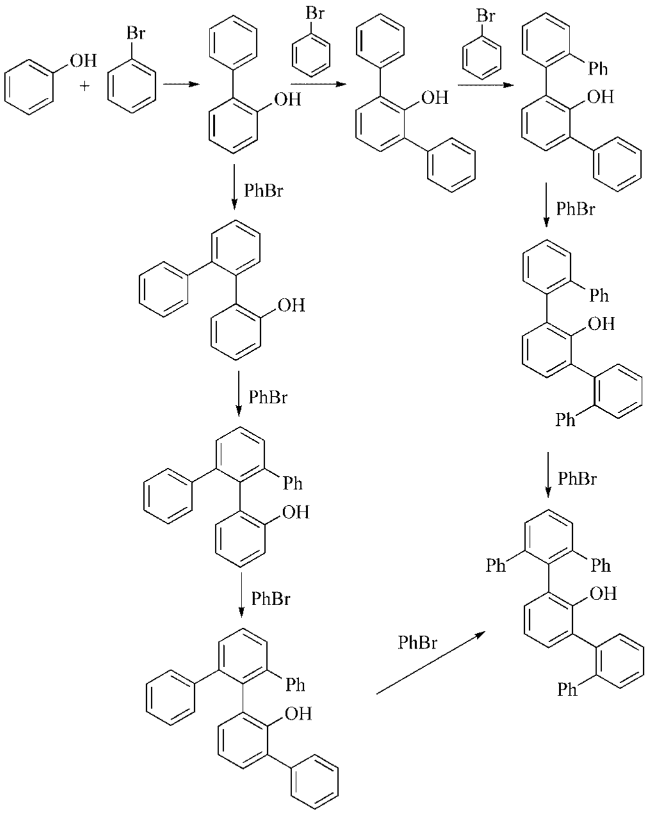


Scheme 10.

Direct, nonselective arylation of an unactivated arene was reported by using iridium(III) as the catalyst in the presence of KO*t*Bu. The reaction was proposed to involve the reduction to iridium(II) with the formation of radicals.[56]

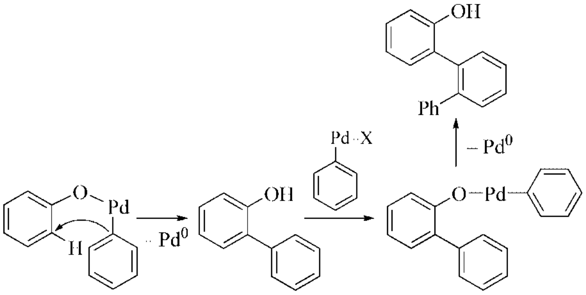
5.2.3. Chelation-Directed Arylation of Arenes

The formation of an oxygen– or nitrogen–palladium bond from Ar–Pd–X and phenols, amides, or imines in the presence of a base, in particular Cs_2CO_3, triggers aryl coupling reactions with the *ortho* carbon. As reported by Miura et al.[57] phenol is *o*-arylated by bromobenzene to *o*-arylphenol, which, in turn, reacts again with bromobenzene to give an *o*-arylated product (Scheme 11). The reaction takes place in refluxing *o*-xylene in the presence of $Pd(OAc)_2$/PPh_3 as the catalyst and Cs_2CO_3 as the base and leads to 2-biphenylyl-6-terphenylylphenol in 58% yield.



Scheme 11.

Benzyl alcohols, acetophenones, and benzyl phenyl ketones behave similarly by coordination of the alcoholic or enolic oxygen. Also, the aliphatic carbons are arylated. Anilides are arylated in the *ortho* position with aryl bromides or -triflates.[5c] These reactions seem to be reminiscent of the *o*-electrophilic attack to phenols for which a cyclic transition state was proposed.[58] A similar situation may occur through chelation (Scheme 12).

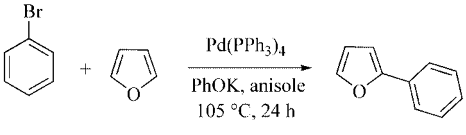


Scheme 12.

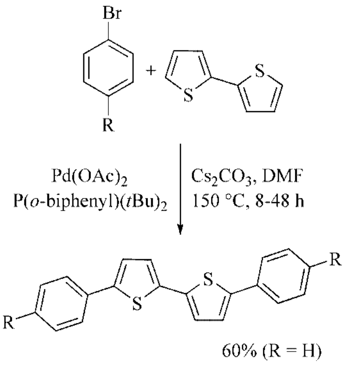
The technique originally reported by Tremont[59] for the assisted alkylation of anilides was recently extended by Daugulis and Zaitsev to arylation.[60] They found that the combination of aryl iodides and silver acetate was effective in catalytic arylation with palladium acetate in acetic acid at 90–130 °C. Up to 1000 turnovers were reached. Other assisted reactions were obtained with Ru[61] and Rh,[62] and a number of examples are reported in a recent review by Lautens.[5a]

5.2.4. Heteroatom-Directed Arylation

Arylation of furan at the 2-position by bromobenzene under palladium(0) catalysis was described as far back as 1985 [Equation (17)].[63] It was not until the 1990s, however, that several reactions involving N, O, and S-heterocycles were reported. These reactions generally occur under mild conditions ($T \approx 100$ °C or lower), are catalyzed by palladium(0), and are regarded as electrophilic attacks.[5c] Thiophenes are also readily arylated at the 2-position under mild conditions ($T \approx 60$ °C) by using AgF and DMSO.[64] 2,2′-Bithiophene gives the biarylation product at the 5- and 5′-positions. A bulky phosphane is used with $Pd(OAc)_2$ [Equation (18)].[65]



(17)



(18)

Under similar conditions, a thiophene-2-carboxamide is arylated at the 2-, 5-, and 3-positions. Arylation at the 2-position occurs with concomitant decarbamoylation (see for comparison refs.[49,50]). Arylation at the 3-position probably occurs through a chelation-assisted process as proposed by Miura.[66]

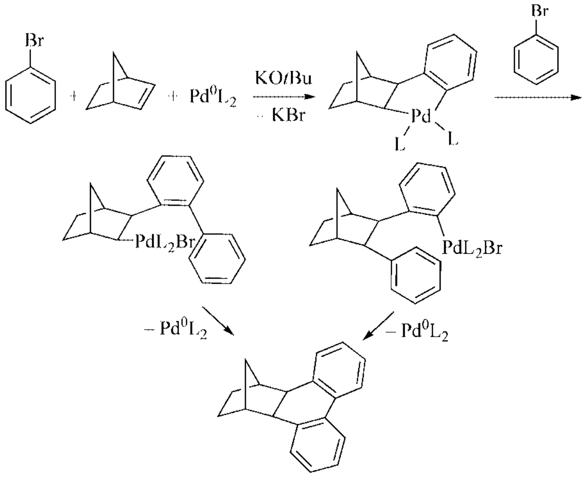
A ruthenium(II)/PPh_3 catalyst selectively arylates the *ortho* position of the aromatic ring in 2-aryloxazolines and 2-arylimidazolines.[67] Ruthenium complexes are also active in the arylation of heteroarenes such as pyridine.[68] $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ allows the coupling of aryl iodides to heterocyclic aromatics including thiophenes, furans, and pyrroles at the carbon adjacent to the heteroatom.[69]

Bergman et al.[70] recently proposed the formation of a heterocyclic carbene as an intermediate in the C–H activation process. For more examples, see a recent review by Fagnou.[71]

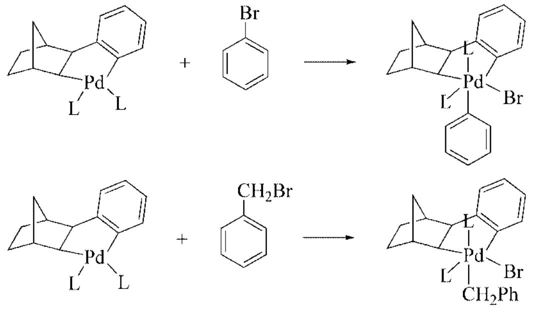
5.2.5. Metallacycle-Directed Arylation of Arenes

5.2.5.1 Biaryls

The first observation that C–C aryl to aryl coupling can occur in the absence of directing heteroatoms through the formation of metallacycles goes back to 1985[72] when a palladium-catalyzed multistep sequential reaction was shown to give rise to an aryl–aryl coupling product together with an aryl–alkyl one via a palladacycle. The latter was formed by norbornene insertion into a palladium–aryl bond, followed by electrophilic attack[73] at the *ortho* position of the original arene substrate (aryl bromide) (Scheme 13). The two pathways were proved by using appropriately substituted aryl iodides which led to different isomers, as expected.[72] The intermediacy of a palladium(IV) complex was postulated as a possible interpretation of the reaction course. It is to be noted that the corresponding alkyl or benzyl palladium(IV) complexes had actually been isolated and characterized.[74] Scheme 14 shows the reaction pathway proposed for the arylation process and proved for the alkylation one.

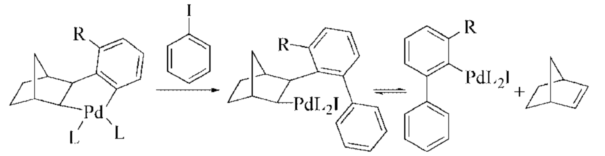


Scheme 13.



Scheme 14.

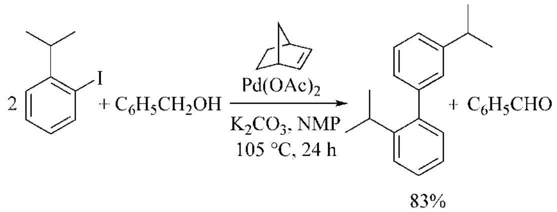
As noticed above, the originally reported aryl coupling reaction was not selective because part of the aryl group migrated onto the alkyl rather than the aryl moiety. Only some years later was it discovered that a sufficiently bulky substituent in the *ortho* position of the aryl halide caused the aryl group of the second aryl halide to migrate exclusively to the arene moiety.[75] A stoichiometric reaction (Scheme 15) threw light on the course of the process, which led to the dismantling of the initially formed metallacycle by norbornene expulsion.



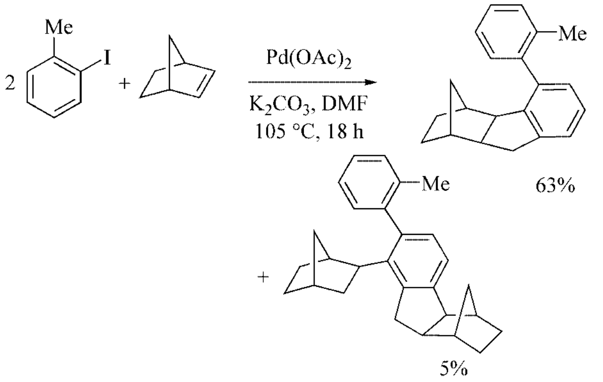
Scheme 15.

This result had important consequences for catalytic synthesis. Because palladacycle formation requires the oxidative addition of an aryl halide to palladium(0) followed by norbornene insertion, it is sufficient to close the catalytic cycle by adding a final step that would convert the palladium(II) complex into palladium(0) again. This concept had already been applied to arene alkylation reactions involving palladium(IV) complexes of the type shown in Scheme 14.[76] These reactions will not be treated here because they are outside the scope of the present review, which is dedicated only to arylation reactions.

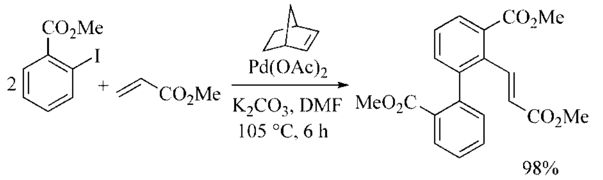
Some catalytic arylation reactions involving metallacycles formed with palladium and norbornene are shown in Equations (19), (20), and (21).[77]



(19)

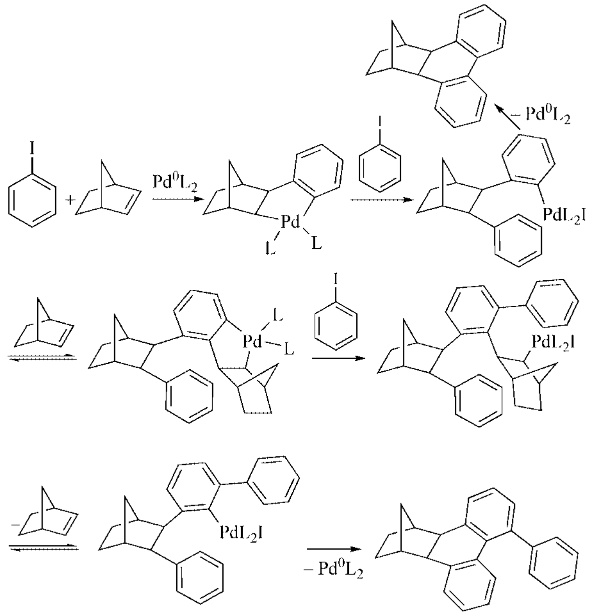


(20)



(21)

The biphenyl-forming reactions represent valid alternatives to Suzuki-type reactions, which require the preparation of arylboronic acids. The *ortho* effect could also explain other reactions which appeared in the literature. Besides tetrahydromethanotriphenylene, de Meijere et al.[78] described the synthesis of a phenylhexahydromethanotriphenylene, the formation of which appeared rather obscure unless viewed in the framework of the *ortho* effect (Scheme 16).[75]



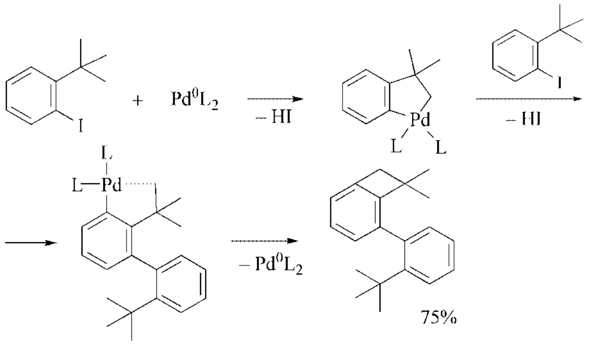
Scheme 16.

As a matter of fact the first-formed palladacycle reacts with iodobenzene to form methanotriphenylene; however, if an excess of norbornene is present, a second palladacycle can be formed, which has the peculiarity of bearing a bulky substituent (the phenylnorbornyl group) *ortho* to the palladacycle. This circumstance favors the selective attack of a new molecule of iodobenzene on the aryl moiety of the same palladacycle. The presence of two *ortho* substituents causes norbornene expulsion and the resulting complex undergoes ring closure to phenylmethanotriphenylene.[75,78]

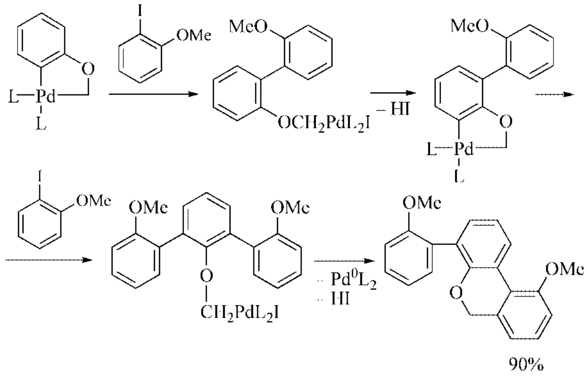
An analogous interpretation applies to the coupling reactions reported by Dyker (Scheme 17).[79] *o*-Iodo-*tert*-butylbenzene reacts with palladium to form a palladacycle that behaves similarly to the one with norbornene. A second molecule of *o*-iodo-*tert*-butylbenzene reacts selectively with the aromatic carbon–palladium bond, thus forming a biaryl unit. Unlike norbornene, an isobutene unit cannot be expelled in this case and a condensed cyclobutene ring is formed instead in 75% yield. The reaction occurs in DMF at 100 °C for 3 d. Isobutene, however, could be expelled in a stoichiometric reaction.[80]

Analogous considerations can be made for the reaction of *o*-iodoanisole where the partner for palladacycle formation would be formaldehyde if it could be reversibly inserted (Scheme 18).[81]

Other unsaturated substrates can replace norbornene or strained olefins in the arylation reactions but they usually are not able to deinsert. Thus, α,β-unsaturated phenyl sulfones give rise to phenanthrenes through double bond aryl-

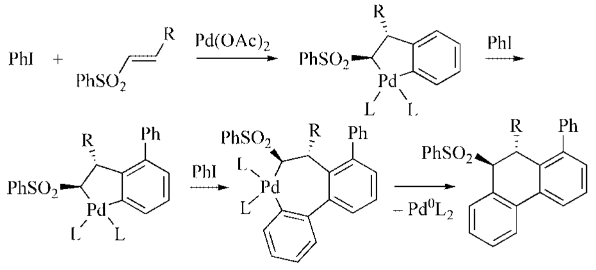


Scheme 17.



Scheme 18.

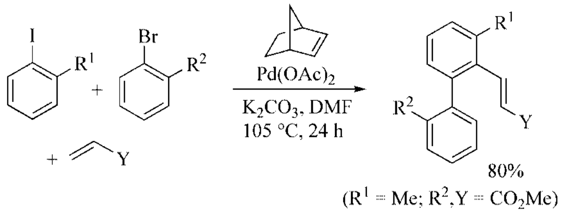
ation, palladacycle formation, double phenylation with iodobenzene, and ring closure (in place of the elimination of the unsaturated sulfone, which is not favored) (Scheme 19).[82]



Scheme 19.

Dyker[83] and Larock[84] utilized the palladium-catalyzed reaction of diphenylacetylene with iodobenzene to obtain different products (9,10-diphenylphenanthrene, 9-benzylidenefluorene) from the initially formed triphenylvinylpalladium iodide depending on the action of the base used (Na_2CO_3 in the former case and NaOAc in the latter).

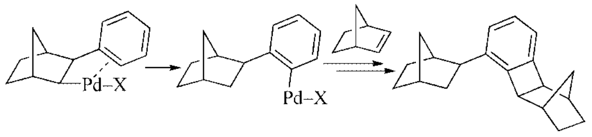
So far we have seen C–C coupling reactions between two equal (aromatic) molecules (homocoupling). An important step forward was taken when two different molecules could be coupled selectively. The reaction between two different iodides was indeed not selective and only the utilization of aryl halides exhibiting different reactivity towards palladium(0) and palladium(II) complexes led to resolution of the problem. It was found[85] that aryl iodides *o*-substituted by electron-donating groups cross-coupled with bromoarene-bearing electron-withdrawing substituents or, in some cases, *o*-OH substituents [Equation (22)].



(22)

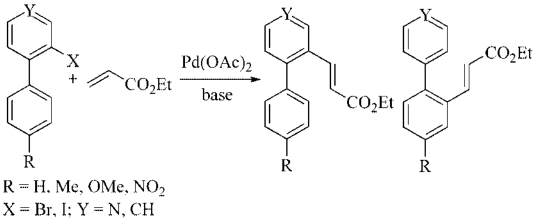
o-Alkyliodobenzenes reacted readily with palladium(0) but rather slowly with the pallada(II)cycle formed by norbornene insertion. Alternatively, bromobenzenes containing electron-withdrawing substituents reacted slowly with palladium(0) but readily attacked the palladacycle. The origin of these preferences is not yet clear, but it may well be related to steric problems in the reaction with the palladacycle. Whether the latter reaction implies oxidative addition or transmetallation still is a matter of debate.[86]

In this context an interesting aspect of the chemistry of aryl coupling has to be considered: the coupling can take place at an arene position different from that of the original C–Pd bond. The fact that palladium could move from one side to the other of a palladacycle was previously shown in the case of norbornene (Scheme 20).[87]



Scheme 20.

Palladium has also been shown to migrate along arene or heteroarene nuclei; for example as in Equation (23).[88] This possibly involves an intermediate palladacycle and is relevant to the aryl coupling process.



(23)

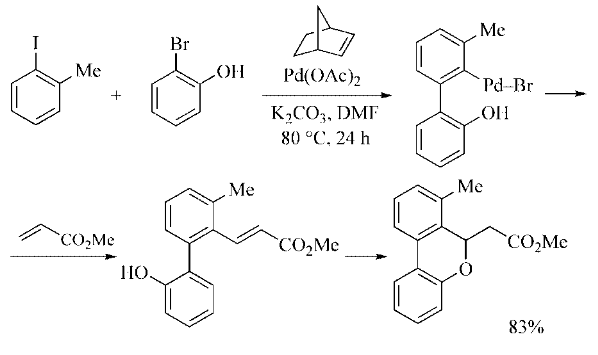
Larock provided several examples where he took advantage of the migration process; for example, the synthesis of vinylcarbazoles[89] from *N*-(3-iodophenyl)anilines and that of 4-phenylfluorene[90] from 2-(3′-benzyl)phenyliodobenzene.

Mechanistic details of catalytic C–H arylation are still scarce, although most authors agree that it has to be considered an electrophilic attack.[91] We have already mentioned interesting hypotheses.[34–36] Other papers are also relevant to a better understanding of the processes that may be involved.[92]

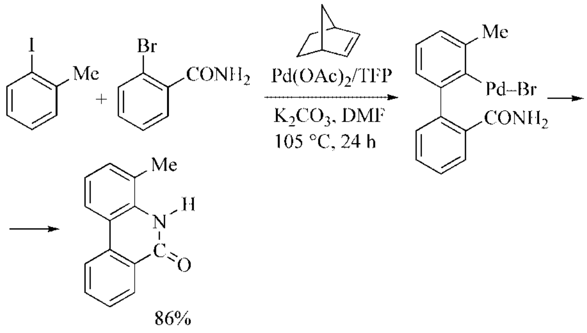
Mechanistic pathways based on electrophilic attack of the metal on the arene C–H, possibly occurring through an arenonium ion[93] or through a variant of a base-catalyzed SE3 process or a σ-bond metathesis,[52] have been proposed. Then again, the alternative exists of oxidative addition of aryl halides or parent species to the metal to give a palladium(IV) intermediate followed by reductive elimination and C–C coupling. The conclusions that can be drawn from these studies do not allow a clear-cut distinction between mechanisms. A recent theoretical analysis favors transmetallation.[86] Another study shows that the intermediacy of palladium(IV) is favored in the case of reactions occurring through palladium 1,3-migration and disfavored in the case of 1,6- or 1,7-migrations, where a binuclear mechanism involving palladium(II) is more likely. In the intermediate cases (1,4; 1,5) both mechanisms can be operating.[94] As suggested in the paper, slight changes in the geometry of the transition state caused by steric hindrance (ligand and solvent effects should also be added) may favor one or the other mechanism.

5.2.5.2 Condensed Heterocycles Containing the Biaryl Unit

The metallacycle-based technique lends itself to the synthesis of a variety of heterocycles containing the biaryl unit. A very simple way consists of utilizing appropriate O, N, or S-containing functional groups for an intramolecular ring closure. Examples are offered by the syntheses of dibenzopyran and phenanthridinone derivatives (Schemes 21 and 22).[95,96] In the former case, a hydroxy function attacks an acrylic double bond according to a Michael-type reaction; in the latter, the $CONH_2$ group attacks the C–PdBr bond intramolecularly to form a six-membered ring.

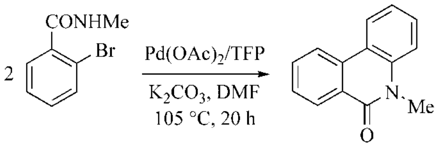


Scheme 21.



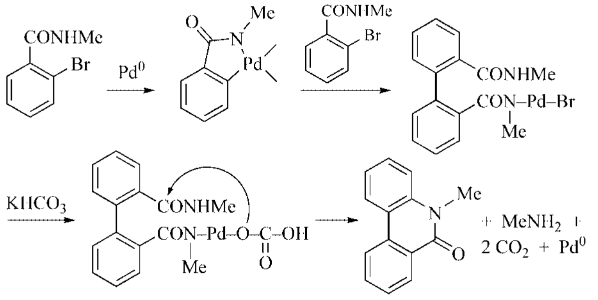
Scheme 22.

Interestingly, whereas the reaction in the presence of norbornene (Scheme 22) gave the cross-coupled product, a homocoupled product was obtained in the absence of norbornene from *o*-bromoamide [Equation (24)].[97]



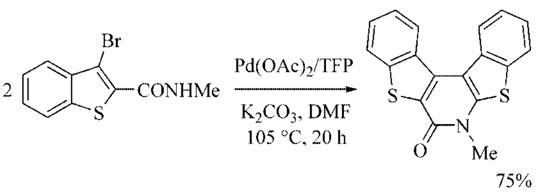
(24)

A concomitant splitting of the MeNHCO-group by *ipso* substitution occurs (see also ref.[66]). The reaction was interpreted to involve a palladacycle formed with the help of the CONHMe group. The latter is split as amine and carbon dioxide, likely as a consequence of nucleophilic attack by hydrogencarbonate OC(O)OH (Scheme 23). This interpretation nicely explains previous results.[98] A similar process with a different catalytic system [$Pd(OAc)_2$/2-(8-methoxy-1-naphthyl)phenyldiphenylphosphane/Cs_2CO_3] gives the same products with expulsion of MeNCO.[99]



Scheme 23.

Heterocyclic rings can also be introduced in the aryl coupling process; for example, *N*-methyl 3-bromobenzothiophene-2-carboxamide gives the pentacyclic pyridone derivative shown in Equation (25).[97]



(25)

6. Conclusions

C–C coupling reactions of arene compounds cover a variety of processes that are becoming more and more efficient and selective. Whereas reductive and oxidative coupling require the use of additional reductants or oxidants to become catalytic, the methods based on direct arylation of arene compounds by selective substitution assisted by heteroatoms, chelation, or metallacycle formation offer wide perspectives of practical applications. Biphenyl-based products are currently manufactured in the area of fine chemicals in general and of pharmaceutical compounds in particular. Further achievements can be expected in the near future.

Acknowledgments

We thank Ministero dell'Università e della Ricerca (MIUR) (grant no. 2006031888), Consiglio Nazionale delle Ricerche (CNR) and the University of Parma for financial support.

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Received: April 6, 2007