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Catalytic Sequential Reactions Involving Palladacycle-Directed Aryl Coupling Steps

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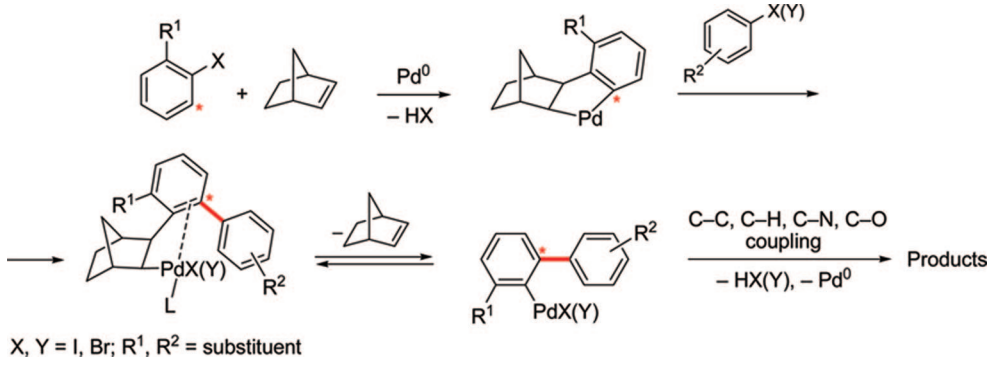
CONSPECTUS



Catalytic methods are important tools for the synthesis of C—C bonds under mild and ambient conditions. Palladium chemistry predominates in this area because it offers the opportunity to form several different types of bonds in one pot. Palladium can also tolerate a variety of functional groups.

Among the many investigations of catalytic aryl—aryl couplings, the most successful technique has been the Suzuki reaction, which uses an arylboronic acid to attack an aryl—Pd bond. This Account reports our methodology, based on the cooperative action of Pd and norbornene, that achieves selective aryl—aryl coupling through C—halide and C—H activation.

We are primarily interested in Pd-catalyzed sequential reactions. These reactions combine palladium as an inorganic catalyst and a strained olefin such as norbornene as an organic catalyst and can lead to biphenyl derivatives. While the palladium facilitates C—C bond formation through C—halide and C—H activation, the norbornene contributes to the construction of a palladacycle, an intermediate structure that controls and directs the subsequent reaction steps selectively. To achieve regioselective arylation at the carbon *ortho* to the original C—halide bond, palladacycles require an additional *ortho* substituent (R^1). The palladacycle opens, giving rise to a biphenylylnorbornylpalladium complex. Because of the steric hindrance exerted by the two *ortho* groups, norbornene deinsertion readily occurs to form a biphenylylpalladium complex. Thus, norbornene acts as a removable scaffold. We used this biphenylylpalladium species to form C—C (with olefins, alkynes, or arylboronic acids) or C—H bonds (by hydrogenolysis).

Using nonidentical aryl or heteroaryl halides, we also formed a biaryl-bonded Pd species able to undergo the final termination reaction (C—C, C—N, or C—O bond formation) either inter- or intramolecularly. We used this method to synthesize a variety of aromatic and heteroaromatic compounds. We also obtained the key metallacycle able to selectively direct the reactions by replacing norbornene with an aryl-bonded aminocarbonyl group. This method provided a diverse series of condensed heterocycles.

Introduction

Catalytic methods represent important tools for the synthesis of C—C bonds under mild and environmentally friendly conditions. Palladium chemistry dominates the area because it offers the opportunity to form several bonds of different types in one-pot reactions that tolerate a wide number of functional groups.[1] Many efforts have been made to synthesize the ubiquitous class of biaryls.[2] Since the discovery of the Ullmann reac-

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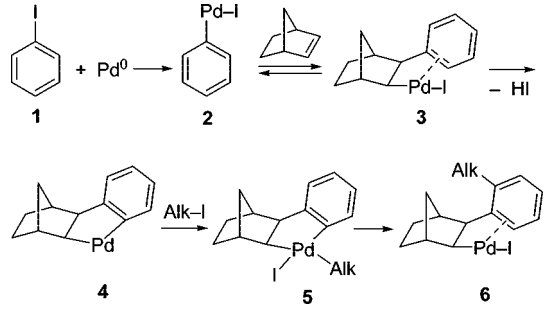
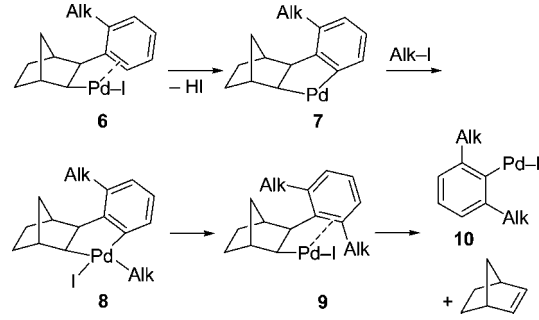
SCHEME 1. Palladacycle Formation and *o*-Alkylation



SCHEME 2. *o*-Dialkylation and Norbornene Deinsertion



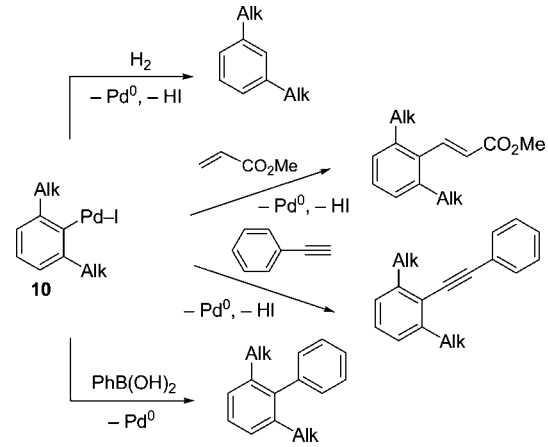
tion, the achievement of a catalytic aryl−aryl coupling has been pursued by many research groups. The most successful technique has been provided by the Suzuki reaction, which is based on the use of an arylboronic acid to attack an aryl−Pd bond. More recently the direct selective attack on an aromatic C−H bond has been reported.[3]

We approached the aryl−aryl coupling problem in the framework of our research on Pd-catalyzed sequential reaction. This Account reports our methodology, based on the cooperative action of Pd and norbornene, to achieve selective aryl−aryl coupling through C−halide and C−H activation.[4] The alkyl−aryl coupling is briefly summarized as a useful introduction to the aryl−aryl coupling. As shown in Scheme 1, the metal-catalyzed reaction sequence is initiated by oxidative addition of an aryl halide such as iodobenzene (**1**) to Pd(0) to form the phenylpalladium species **2**.[5] This first step is followed by norbornene insertion into the phenyl−Pd bond of **2** leading to complex **3** where the phenyl and the Pd groups are bonded to the norbornyl structure in a *cis*,*exo* mode, that is, both pointing to the same side of the methylene bridge.[6] Complexes of this type are rather stable toward β-H elimination,[7] which is the favored termination step in Pd−alkyl species. This path being precluded under the usual reaction conditions, further steps may occur in a relatively easy way. Indeed our studies let us achieve metallacycle formation (complex **4**) through electrophilic activation of a usually inert C−H bond, *ortho* to the original C−halide one.[8]

Thus the use of norbornene as cocatalyst opened the way to working out processes involving selective C−H activation.[4]

The resulting palladacycle **4** offered interesting possibilities for reactions with other organic partners: either the aryl−Pd or the norbornyl−Pd bonds or both could be broken. When alkyl halides (methyl, allyl, and benzyl halides) were used, only the aryl−Pd bond was affected and selective alkylation of the arene moiety occurred leading to complex **6** through the intermediacy of a Pd(IV) species **5** (Scheme 1).[9] At this point, the reaction spontaneously proceeded further (Scheme 2), with formation of a new palladacycle **7**,

SCHEME 3. Termination Steps



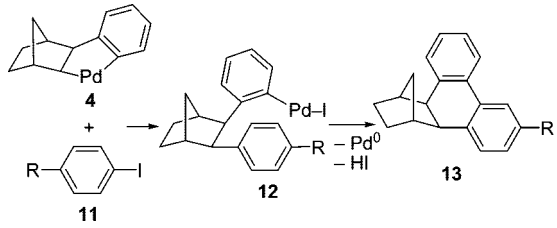
which behaved similarly to the previous species **4** and underwent oxidative addition of Alk−I to form the Pd(IV) metallacycle **8**. Alkyl attack on the aryl−Pd bond gave the *o*-dialkylated complex **9**, which did not remain as such, however, but underwent norbornene deinsertion, the reverse of the metal insertion reaction,[10] because of the steric hindrance exerted by the two alkyl groups.[9]

This meant that norbornene behaved as an organic catalyst cooperating with Pd to provide a scaffold that could be removed through further reaction.[4] In its turn, Pd could be freed again, thus acting as catalyst, by means of well-known reactions of the aryl−Pd bond such as hydrogenolysis, Heck, Suzuki, or Cassar−Sonogashira reactions. C−C bond formation was thus selectively achieved through a multistep catalytic reaction (Scheme 3).[4,11] The described methodology has been largely extended to ring-forming reactions by Lautens and co-workers.[3a,12]

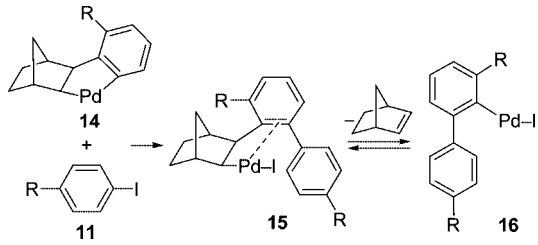
The reaction course and in particular the role of norbornene was established in our previous work by isolating most of the relevant intermediates involved and by studying the single steps through stoichiometric reactions.[9,13]

Aromatic Arylation. As shown above, Pd can activate usually inert aromatic C−H bonds toward catalytic alkylation. We wondered whether the alkylation procedure could be

SCHEME 4. Selective Alkyl−Aryl Coupling



SCHEME 5. Aryl−Aryl Coupling Followed by Norbornene Deinsertion



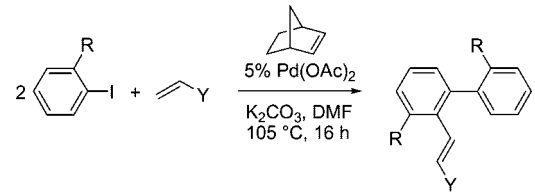
extended to arylation, in other words, whether an alkyl halide could be replaced by an aryl halide in the reaction sequence previously described. This turned out to be a very difficult task, however, because aryl groups preferentially attacked the norbornyl carbon of palladacycle **4**[14] (Scheme 1).

To gain insight into the reaction pathway, we carried out stoichiometric reactions of palladacycle **4** with aryl iodides (Scheme 4). Working in DMF at room temperature and using *para*-substituted aryl iodides **11**, we observed the exclusive formation of methanotriphenylene derivatives **13**. The position of the R substituent in the aromatic ring of the final product **13** clearly indicates that the aryl iodide **11** attacked the aliphatic site of palladacycle **4** with formation of **12** and subsequent intramolecular ring closure to **13**.[15]

As observed for alkylation reactions, the system thus shows a preference to form an sp^2-sp^3 C−C bond. In view of this preference, we were very surprised on finding that palladacycles of type **4**, containing an *ortho* substituent in the aromatic ring (**14**; Scheme 5), directed the attack of an aryl halide toward the aryl site selectively with formation of species **15**. Due to the presence of two *ortho* substituents, conditions are now favorable for norbornene deinsertion to yield the biphenylylpalladium complex **16**, as previously observed in the case of the alkylation reaction.

It should be noted that this new type of aryl−aryl coupling differs from the conventional one in that the positions of the affected carbon atoms are different from each other, one corresponding to the halide-bonded and the other to the *ortho* carbon atom of the arene molecules. Thus this *ortho*-selective homocoupling can be regarded as a cross-coupling reaction.

TABLE 1. Vinylbiphenyls



R	Y	yield (%)
Me	CO_2Me	79
Et	CO_2Me	79
i-Pr	CO_2Me	84
OMe	CO_2Me	88
CO_2Me	CO_2Me	98
Me	SOPh	81
Et	COMe	79
Et	Ph	87

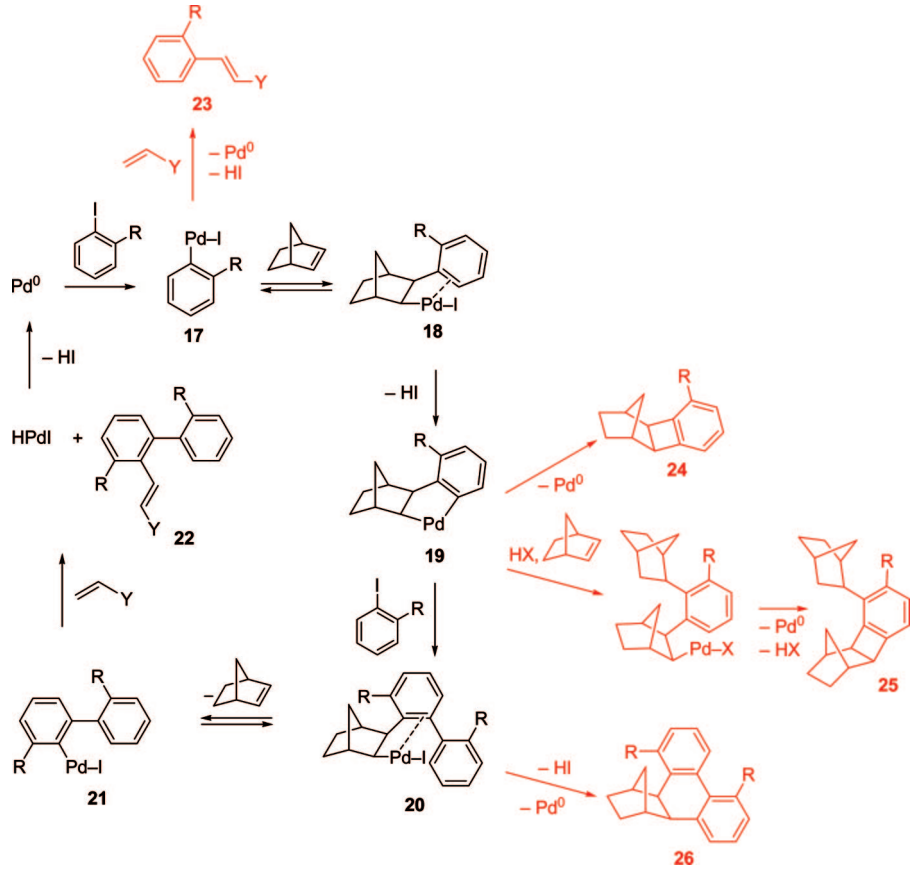
The discovery of the "*ortho* effect" was exploited to work out new catalytic syntheses involving selective arylation of arenes.

Catalytic *ortho*-Selective Aryl Coupling to Biphenyls. To derive a catalytic reaction from Scheme 5, we followed the criterion of trapping the biphenylylpalladium complex **16** with suitable species able to react with formation of an organic product and concomitant liberation of Pd(0), which in its turn could start a new cycle by oxidative addition of an aryl halide to the metal. The choice of a trapping agent is not trivial because it must react selectively with complex **16** and not with the other species involved in the sequence. We shall consider in some detail the overall process terminated by a Heck-type reaction with olefins. The main features, until the formation of complex **16**, are common to the other methods to achieve catalysis by different termination types, which are treated in the following pages.

Trapping Complex 16 with Olefins: Vinylbiphenyls. The reaction of an *ortho*-substituted aryl iodide with a terminal olefin, carried out in DMF under the conditions reported in Table 1, gave 3,2′-disubstituted vinylbiphenyls with good results.[16]

Several aryl iodides containing an *ortho* substituent such as methyl, ethyl, isopropyl, methoxy, or methoxycarbonyl could be coupled with both electron-poor and electron-rich olefins. The former proved to be the best partners, leading to linear *E* products exclusively (as shown in Table 1), while the latter gave rise to a mixture of linear and branched isomers (not reported in Table 1) resulting from olefin arylation at the terminal and internal vinylic carbons in agreement with the regioselectivity usually observed in Heck reaction.[17] Substituents such as the mono- and dimethylamino, hydroxy, and acetoxy ones inhibited the reaction, likely due to interference with Pd. Owing to its

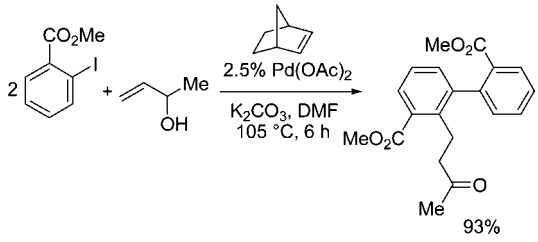
SCHEME 6. Proposed Reaction Pathway for the Formation of 3,2′-Disubstituted Vinylbiphenyls (Black) and Frequently Found Byproducts (Red)



bulkiness, the *t*-Bu group favored reductive elimination from complex **19** (R = *t*-Bu) to the corresponding methanobiphenylene **24** exclusively,[18] as shown in Scheme 6, which reports the proposed reaction course.

Achieving the sequence shown requires that no elimination of the metal occurs from the metal−carbon bonds in the intermediate stages; otherwise the process would stop with formation of undesired byproducts. Oxidative addition of the aryl iodide to Pd(0) leads to the arylpalladium(II) iodide complex **17**,[5] which readily coordinates and stereoselctively inserts norbornene to give the *cis*,*exo* arylnorbornylpalladium species **18**.[6] Although both norbornene and the terminal olefin are able to insert into the aryl−Pd bond of complex **17**, under appropriate conditions norbornene insertion occurs selectively even in the presence of an excess (usually twice) of terminal olefin (black pathway). This is favored by steric strain relief of norbornene. The arylated olefin **23** (red pathway), which should readily form from the arylpalladium species **17** according to Heck reaction,[17] was not detected. It is noteworthy that, as ascertained by X-ray diffraction,[6b,d] a double bond of the aromatic ring of complex **18** binds to Pd. This is a sort of preorganization, which facilitates reaction with the aromatic ring to give the five-membered palladacycle **19** through activation of an aromatic C−H bond. At this point, because of the presence of a substituent *ortho* to the aryl−norbornyl bond, the aryl−Pd bond of **19** becomes susceptible to the selective attack by another molecule of the aryl iodide leading to complex **20**. The reaction pathway is proposed to involve a Pd(IV) species, as suggested by the isolation of Pd(IV) complexes from the reaction with alkyl halides (Scheme 1).[11] Alternatively it may be that the aryl iodide addition proceeds through a transmetalation process involving Pd(II) complexes.[19] Due to the steric hindrance generated by the two *ortho* substituents, complex **20** undergoes norbornene deinsertion to the biphenylylpalladium species **21**, which inserts the terminal olefin according to Heck reaction. Thus norbornene, which was inserted at the beginning of the cycle (from **17** to **18**), is deinserted toward the end of the same cycle (from **20** to **21**) after making possible the selective arylation of the aromatic ring. Although norbornene formally acts as a catalyst, it must be used at a sufficient concentration (usually of the order of 1:1 with respect to the aryl halide) to allow an efficient insertion

SCHEME 7. 3,2′-Dimethoxycarbonyl-2-(3-oxobutyl)-1,1′-biphenyl



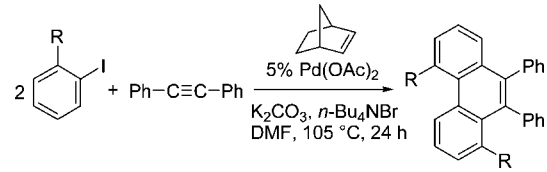
step. On the other side, if norbornene concentration is too high, its elimination (from **20** to **21**) becomes more difficult, because the insertion equilibrium is shifted toward **20** and the entire process slows down. As a consequence another pathway leading to methanotriphenylene derivative **26**[14,15] becomes possible (red pathway).

Other readily formed byproducts, usually found in small amounts, are compounds **24**[18] and **25**,[20] both resulting from palladacycle **19**. As previously shown, compound **24** is the main product with R = *t*-Bu. Its formation appears to be due to the steric effect exerted by the bulky substituent, which favors ring closure (red pathway) and by the difficulty for *t*-BuC_6H_4I to react with palladacycle **19** (black pathway). Compound **25** originates from protonation[21] at the norbornyl site of the palladacycle with ring opening, followed by insertion of another norbornene molecule and ring closure.

Trapping with Allyl Alcohols: Biphenyls with Alkyl Chains Containing Carbonyl Groups. We found that allylic alcohols are satisfactory terminating agents.[22] The reaction of methyl *o*-iodobenzoate and 3-buten-2-ol led to the selectively substituted biphenyl reported in Scheme 7. The aliphatic ketonic chain forms according to a pathway previously described for the insertion of allylic alcohols into an arylpalladium bond.[23] With substituents different from the methoxycarbonyl one, the expected products were obtained in moderate yield (54−75%).

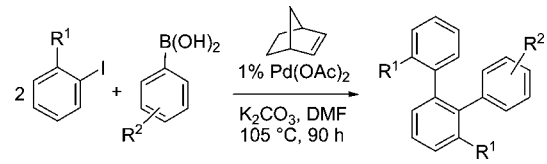
Trapping with Alkynes: Phenanthrenes. Another type of termination was offered by diarylalkynes.[24] Their insertion into the arylpalladium bond of complex **21** in place of olefins led to vinylpalladium bonds, which readily cyclized to give 9,10-diarylphenanthrenes. Table 2 shows the results obtained using *o*-substituted iodobenzenes as reagents and diphenylacetylene as the terminating agent. The *i*-Pr group gave the best results probably because it has the appropriate steric hindrance to favor norbornene deinsertion, which is the step that benefits from the presence of a bulky group. Dialkylalkynes mainly underwent HX elimination giving allenes.

TABLE 2. Phenanthrenes



R	yield (%)
Me	82
Et	85
n-Pr	83
i-Pr	93
n-Bu	84
OMe	64

TABLE 3. *o*-Terphenyls



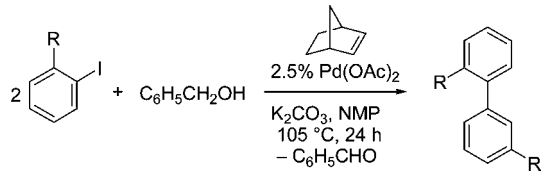
R^1	R^2	yield (%)
Me	H	88
Et	H	77
i-Pr	H	93
n-Bu	H	73
OMe	H	82
CO_2Me	H	89
n-Bu	4-Me	72
n-Bu	4-F	71
n-Pr	2-Me	73

Trapping with Aryls from Arylboronic Acids: *o*-Terphenyls. Also arylboronic acids could be used to terminate the sequence leading to biphenylylpalladium species **21**.[20] *o*-Terphenyl derivatives were obtained with good results (71−93% yield) with a variety of R^1 substituents (Table 3). The reaction is compatible with different R^2 groups in the arylboronic acid, even in the *ortho* position and occurs with a better catalytic efficiency than that using olefins in the final step. Also in this case, the *i*-Pr group acts positively, affording the highest yield.

Trapping by Hydrogen Transfer: Biphenyls. Even the simplest trapping procedure consisting of hydrogenolysis with hydrogen or hydrogen transfer agents such as benzyl alcohol was achieved successfully,[25] despite the fact that this termination process tended to occur earlier at any stage in the sequence, in particular at the level of the norbornyl−Pd bond, which is well-known to undergo an easy hydrogenolysis process (Table 4).

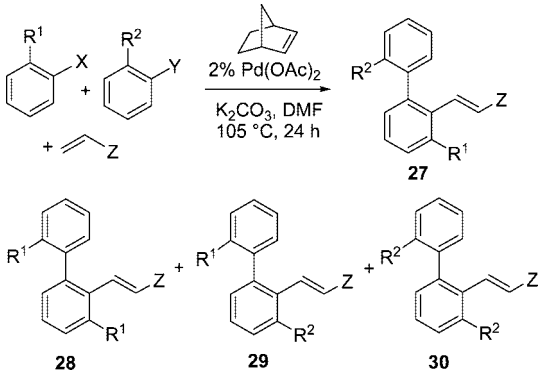
Catalytic *ortho*-Selective Aryl−Aryl Cross-Coupling. All the reactions previously described, leading to the synthesis of selectively substituted biphenyl derivatives, were performed using two molecules of the same aryl iodide. According to the

TABLE 4. Biphenyls



R	yield (%)
Me	72
Et	84
i-Pr	83
n-Bu	79
OMe	48
CO_2Me	87
$(-CH-)_4$	78

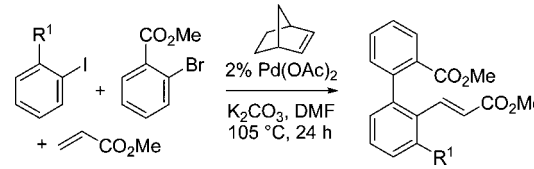
SCHEME 8. Aryl−Aryl Cross-Coupling and Olefin Insertion in Sequence



general reaction pathway depicted in Scheme 6, one molecule oxidatively adds to Pd(0) while the other reacts with Pd(II). Since these Pd(0) and Pd(II) species have different steric and electronic properties, we wondered whether they would be able to discriminate between two aryl halides thus leading to a biphenylylpalladium structure containing two differently substituted aromatic rings. To trap this species, we first resorted to methyl acrylate. The reaction of two different molecules of aryl halides with methyl acrylate implies the selective formation of only one compound (R^1-R^2) out of the possible coupling products (*E*-isomers only) shown in Scheme 8.

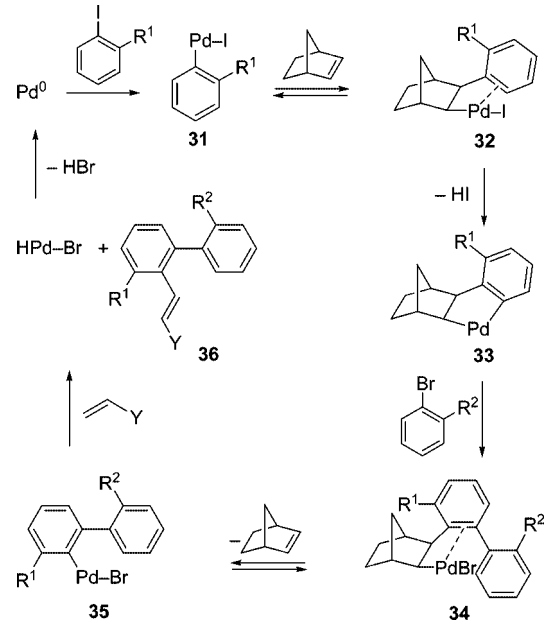
The task turned out to be quite difficult: several attempts to achieve aryl−aryl cross-coupling, taking advantage of the different steric hindrance of the *ortho*-substituent in the aryl iodides, failed, and a mixture of the four possible products (**27**−**30**) was obtained. After several unsuccessful experiments, we were pleased to observe that the reaction of *o*-iodotoluene, methyl *o*-bromobenzoate, and methyl acrylate allowed us to isolate the desired product **27** (R^1 = Me; R^2, Z = CO_2Me) in 80% yield (Table 5).[26] Replacing *o*-iodotoluene with aryl iodides containing other *o*-electron-donating groups led to similar results, which prompted us to follow this criterion to achieve aryl−aryl cross-coupling.

TABLE 5. Vinylbiphenyls from Different Iodobenzenes



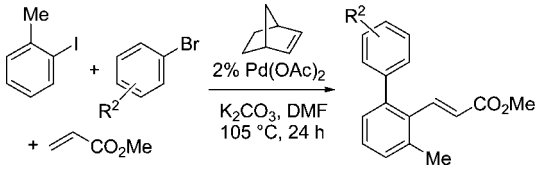
R^1	yield (%)
Me	80
i-Pr	74
t-Bu	37
Ph	73
OMe	83
OCH_2Ph	80
NMe_2	82
CF_3	77

SCHEME 9. Proposed Reaction Pathway for Aryl−Aryl Cross-Coupling



Trapping Aryl−Aryl Cross-Coupling Intermediates with Methyl Acrylate. The results of the reaction of *o*-substituted iodobenzenes with methyl *o*-bromobenzoate and acrylate are reported in Table 5. Results are satisfactory except for the *t*-Bu group, which gave a 37% yield of the expected product, in contrast with the completely negative result of the homocoupling reaction (Scheme 6). Functional groups such as methoxy, dimethylamino, and the bulkier phenylmethoxy are well tolerated and give good yields, but substituents that interfere with Pd, such as monomethylamino, hydroxy, and amino groups inhibit the reaction. A somewhat anomalous behavior was observed in the case of the trifluoromethyl group. *o*-Trifluoromethyl iodobenzene reacted with Pd(0), but it was unable to react with palladacycle **33** (Scheme 9), which

TABLE 6. Vinylbiphenyls from Different Bromobenzenes



R^2	yield (%)
o-NO_2	72
m-NO_2	76
p-NO_2	83
o-CF_3	
m-CF_3	71
p-CF_3	80
o-CN	13
m-CN	62
p-CN	79
o-CO_2Me	80
m-CO_2Me	37
p-CO_2Me	71

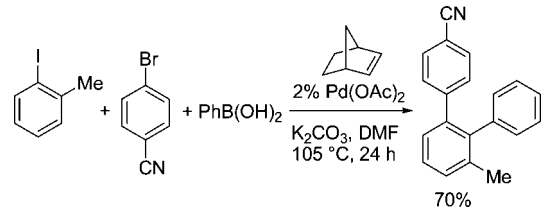
instead was attacked by bromides containing electron-withdrawing substituents.

The catalytic cycle begins, as shown earlier in this paper, to give the alkylaromatic palladacycle **33** (Scheme 9). At this stage, contrary to what was observed at the level of Pd(0), methyl *o*-bromobenzoate ($R^2 = CO_2$Me) reacts faster than the aryl iodide with the Pd(II) metallacycle to give the aryl coupling. The selective attack of methyl *o*-bromobenzoate on the aromatic site of palladacycle **33** results in the formation of intermediate **34**. This species undergoes C−C bond cleavage with norbornene expulsion to afford the biphenylylpalladium complex **35**, which terminates the catalytic cycle by methyl acrylate insertion.

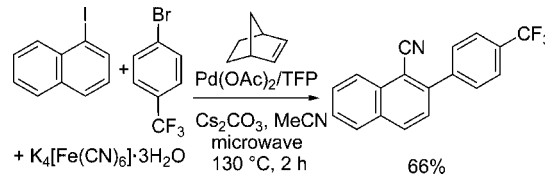
Since the selective aryl−aryl coupling is promoted by the presence of an *ortho* R^1 substituent in palladacycle **33**, the aryl iodide, which is responsible for the formation of palladacycle **33**, must be *ortho* substituted. By contrast the aryl bromide does not need to bear a substituent in the *ortho* position since it does not take part in the formation of palladacycle **33**. We thus carried out the reaction of an aryl iodide containing an *ortho* electron-releasing group such as *o*-iodotoluene with an aryl bromide containing an electron-withdrawing substituent in *ortho*, *meta*, or *para* position, and the results are reported in Table 6.

Satisfactory results were obtained with a variety of substituents on the aryl bromide with the exception of the *o*-CF_3 and *o*-CN groups, which although able to attack Pd(0) are not reactive toward the palladacycle **33**. Both electron-poor and electron-rich terminal olefins could be used albeit linear and branched isomers (from terminal and internal olefin arylation) were obtained in the presence of electron-donating groups.

SCHEME 10. 4-Cyano-3′-methyl-1,1′:2′-1″-terphenyl



SCHEME 11. 2-(4-Trifluoromethylphenyl)-1-naphthonitrile



Regioisomers were observed in the presence of alkyl chains, which offered a different β-H for elimination.

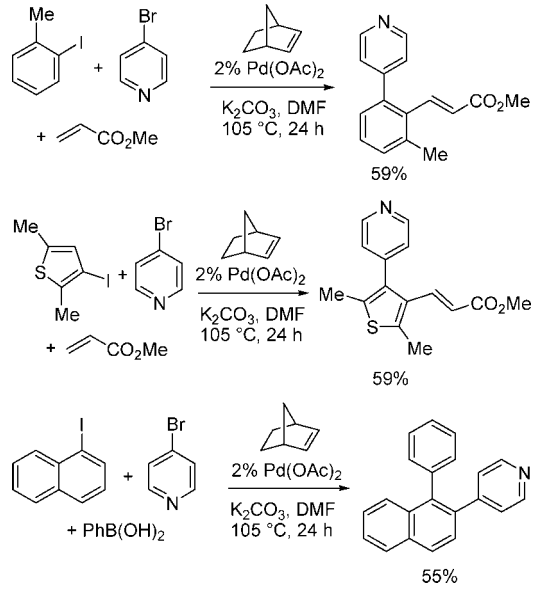
Trapping with Arylboronic Acids: Mixed Terphenyls. Also in this case another way to achieve Pd- and norbornene-catalyzed aryl−aryl cross-coupling takes advantage of the Suzuki reaction to effect a second and terminal cross-coupling by reaction of the biphenylylpalladium complex **35** with arylboronic acids. The reaction reported in Scheme 10 led to 4-cyano-3′-methyl-1,1′:2′-1″-terphenyl in acceptable yield. Interestingly the classical Suzuki reaction with either aromatic halide did not occur, complex **35** only being attacked.[27]

Most of the considerations made for the reactions with olefinic substrates also hold for the sequence terminated by the Suzuki reaction.

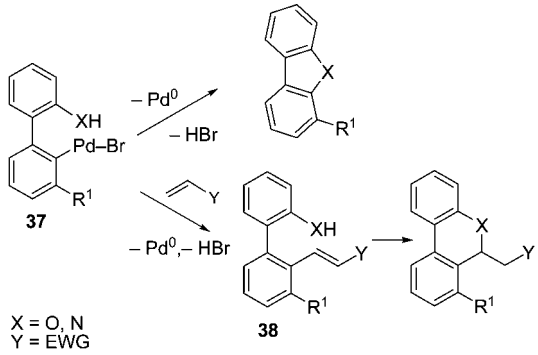
Trapping with CN: Aromatic Nitriles. A further development of the coupling technique involving palladacycles has been described recently by Lautens and co-workers who use the CN anion for the termination step under microwave irradiation (Scheme 11). The yield of the reported example could be increased to 94% by using a 3-fold excess of the aryl bromide.[28]

Synthesis of Biaryl-Containing Heteroatoms in Rings. The aryl cross-coupling methodology can also be applied to heterocyclic halides.[29] The heterocycle can be utilized as iodide as well as bromide provided that the heteroatom is present in a position not leading to an easy interaction with Pd in any of the species involved in the catalytic cycle. Thus 2-bromopyridine completely inhibited the cross-coupling, while 4- or 3-bromopyridine readily reacted with *o*-iodotoluene and methyl acrylate to give the expected compounds in 59% and 52% yield, respectively. 3-Iodo-2,5-dimethylthiophene, methyl *o*-bromobenzoate, and methyl acrylate gave the corresponding vinylbiphenyl derivative in 78% yield. Combining 3-iodo-2,5-dimethylthiophene and 4-bromopyri-

SCHEME 12. Heteroatom-Containing Coupling Products



SCHEME 13. C–C and C–O or C–N Sequential Coupling



dine led to the heteroaryl–heteroaryl coupling with formation of the expected product in 59% yield. In the case of 1-iodonaphthalene and 4-bromopyridine, the final coupling could be achieved using a Suzuki-type reaction.[27] Some examples are shown in Scheme 12.

Condensed Heterocyclic Compounds. The aryl cross-coupling method was also exploited to achieve the synthesis of condensed heterocyclic compounds. The criterion we followed (Scheme 13) is based on the use of aryl bromides bearing an appropriately functionalized *ortho* substituent able to undergo a termination step intramolecularly, either in a biphenylylpalladium complex of type **37** or, after olefin insertion, with the double bond of the resulting vinylbiphenyl derivative **38**. Efficient C–O and C–N couplings have been reported.[30]

Dibenzofurans and Dibenzopyrans. The synthesis of condensed heterocycles containing oxygen was achieved, to our surprise, using *o*-bromophenols as the cross-coupling partner. Although the presence of an electron-donating group in the aryl iodide and of an electron-withdrawing one in the aryl bromide usually appears to be crucial to control the reactivity of these species, *o*-bromophenol could be successfully employed as the aryl bromide despite the presence of the *ortho* hydroxyl group. Thus, as exemplified in Scheme 14, the reaction of *o*-trifluoromethyliodobenzene with *o*-bromophenol under the conditions reported led to 2-trifluoromethyldibenzofuran, although with limited yield.[29]

SCHEME 14. 4-Trifluoromethyldibenzofuran

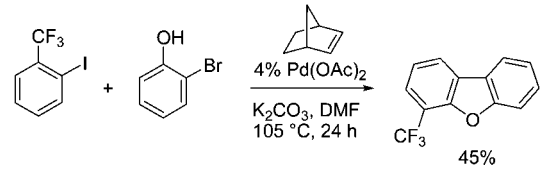
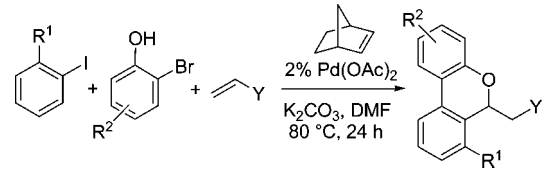


TABLE 7. 6*H*-Dibenzopyrans



R^1	R^2	Y	yield (%)
Me	H	CO_2Me	83
Et	H	CO_2Me	64
CF_3	H	CO_2Me	92
2,4-Me	H	CO_2Me	88
Me	5-Me	CO_2Me	52
Me	5-CO_2Me	CO_2Me	72
Me	5-NO_2	CO_2Me	83
Me	H	CO_2Me	93
Me	H	COMe	73

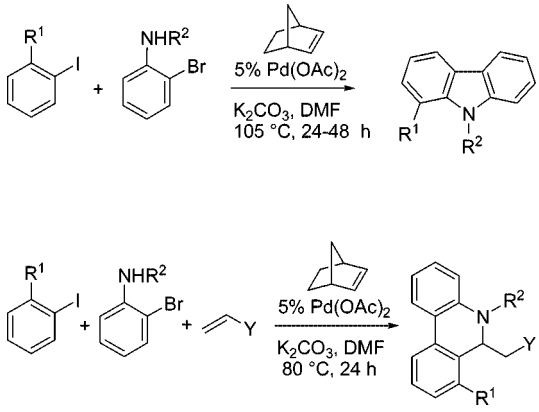
A satisfactory reaction leading to 6*H*-dibenzopyrans was obtained using *o*-substituted aryl iodides and *o*-bromophenols in the presence of an electron-poor olefin. The *ortho* phenolic OH group in the resulting vinylbiaryl derivative favors the intramolecular Michael-type reaction on the double bond to form a dibenzopyran derivative (Table 7). The final cyclization step must take place quite easily since the open precursor has been isolated only in one case.[31]

The replacement of *o*-bromophenol with *p*-bromophenol led only to compound **28** (Scheme 8; R^1 = Me) formed by homocoupling of *o*-iodotoluene followed by reaction with methyl acrylate.[16] This points to the chelation ability of *o*-bromophenol, which favors its own reaction with palladacycle.

The basic structure of the products is found in cannabinols, a well-known class of biologically active compounds.

Carbazoles and Phenanthridines. We also achieved a palladium-catalyzed sequential aryl–aryl and N–aryl coupling leading to the synthesis of carbazoles and phenanthridines. To this end, we reacted *ortho*-substituted aryl iodides with *ortho*-

SCHEME 15. Carbazoles and Phenanthridines



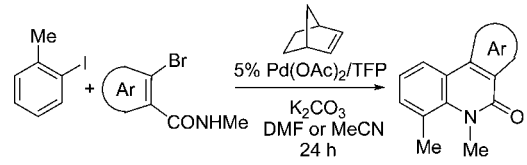
bromoanilines, N-monosubstituted by electron-withdrawing groups, in the absence and in the presence of electron-poor olefins under the conditions reported in Scheme 15.[32] The syntheses of carbazoles and phenanthridines parallel those of dibenzofuran and dibenzopyrans, the oxygen being replaced by the nitrogen function.

Phenanthridinones. Phenanthridinones and their heterocyclic analogues were obtained through Pd-catalyzed sequential aryl−aryl and N−aryl coupling.[33] While all reactions reported up to now take place in the absence of any phosphorus or nitrogen ligand, a triarylphosphine ligand such as tris(furyl)phosphine[34] was found to be necessary in this case to obtain satisfactory yields. The reaction has been successfully applied to *o*-bromobenzamides and several heterocyclic *o*-bromocarboxamides as reported in Table 8.

As shown in Table 8, yields widely differ depending on substrates and solvents, as expected in view of the different reactivity of the C−halide bond and stability of the resulting Pd complex. It can be observed, for example, that in the case of the 3-C−Br bond of the 2-furylcarboxamide in acetonitrile, the reaction gave only 24% yield because of Pd precipitation, while in DMF, where the Pd complex was more stable, a satisfactory yield was obtained, analogously to what observed with the thiophene compound. With the 2-bromofuran isomer the reactivity of the C−Br bond was too high and the yield decreased owing to formation of byproduct. 2-Bromopyridinecarboxamide again was too reactive, and the desired product was not formed. With Cl in place of Br, an acceptable yield was obtained, however.

Condensed Polycyclic Pyridones. An interesting development was achieved when we discovered that a sequential coupling occurred using an aryl-bonded aminocarbonyl group to form a palladacycle (**39**) (Table 9) in place of norbornene.[35] *N*-Monoalkyl-substituted *o*-arylcarboxamides coupled in acceptable yield to **40**, and one CONHR group formed a condensed ring with concomitant elimination of the other (*ipso* substitution) formally as RNCO ($RNH_2 + CO_2$ in the presence of K_2CO_3). The most interesting aspect of this reaction, however, is the formation of a palladacycle from the aryl-bonded CONHR group in place of norbornene. C−N palladacycles have been shown by Buchwald to be transient intermediates in intramolecular Pd-catalyzed arylation of amides.[36] At variance with norbornene, the CONHR group does not act catalytically and is incorporated into the final condensed pyridone. In this way, a variety of condensed pyridones become accessible under mild conditions as shown in Table 9. Yields vary depending on the nature of aromatic/heterocyclic rings: condensed rings performed better than the single ones owing to the higher reactivity of the latter, which led to more complex pyridone derivatives.

TABLE 8. Sequential C−C and C−N Aryl Coupling



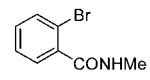
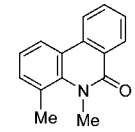
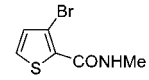
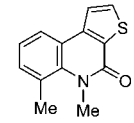
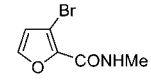
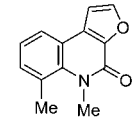
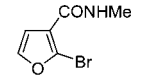
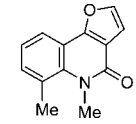
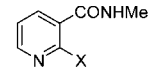
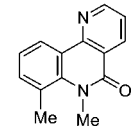
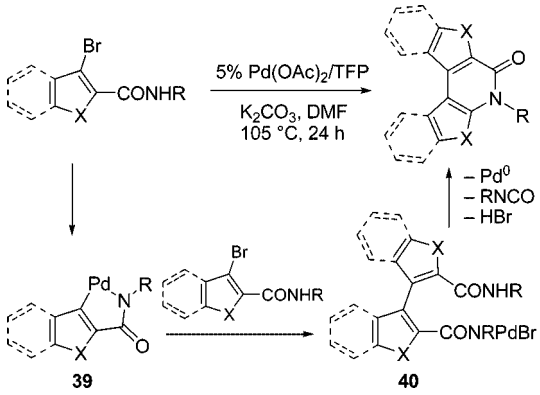
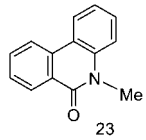
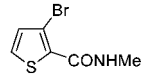
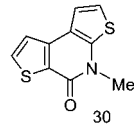
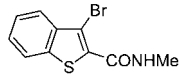
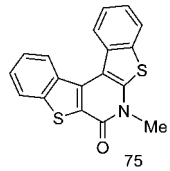
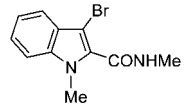
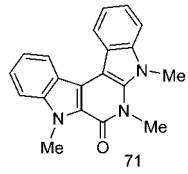
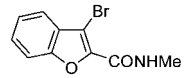
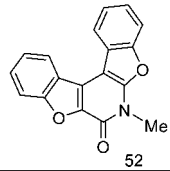
Substrate	Solvent, T (°C)	Product, yield (%)
	MeCN, 85	 87
	MeCN, 85 DMF, 105	 80 70
	MeCN, 85 DMF, 85	 24 82
	DMF, 85	 48
	X = Br X = Cl; DMF, 105	 – 55

TABLE 9. Coupling of N-Containing Palladacycles: Condensed Pyridones



Substrate	Product, yield (%)
	 23
	 30
	 75
	 71
	 52

Conclusions

The Pd-catalyzed sequential reactions we have been studying show a considerable potential for the achievement of highly selective reactions directed by palladacycle formation. They occur in one pot under mild conditions starting from a pool of simple molecules. A proper choice of the reaction parameters allows one to overcome the competitive reactions and to direct the sequence of steps toward a final irreversible step. In this way, a variety of reactions involving palladacycle-directed aryl coupling reactions have been achieved.

From the mechanistic point of view, the course of this reaction appears to be complex and thorough investigations are needed, in particular, to ascertain the nature of the coupling steps occurring on Pd.

We are deeply indebted to all students and colleagues mentioned in the references but in particular to Raffaella Ferraccioli (CNR-ISTM, Milano) for her contributions in the development of condensed heterocyclic syntheses. We thank MIUR, Rome (Grant 2006031888) and the University of Parma for support of our programs.

BIOGRAPHICAL INFORMATION

Marta Catellani graduated in 1971 with Prof. G. Casnati at the University of Parma where she is now professor. After a period working on Ecological Chemistry, she joined Prof. G. P. Chiusoli's group in 1977 when she started to work on new synthetic methodologies catalyzed by group VIII metals. She spent one year as a postdoctoral associate in Prof. J. Halpern's group at the University of Chicago and short periods in Sheffield (Prof. B. Mann) and in Tsukuba (Prof. M. Tanaka). Her scientific interests mainly refer to palladium-catalyzed organic synthesis of complex molecules through sequential processes starting from molecular pools, synthesis and reactivity of palladacycles in oxidation state II and IV, monitoring the reaction course by physical methods, and catalyst design for selectivity control.

Elena Motti (Reggio Emilia, Italy, 1972) obtained her degree in Industrial Chemistry in 1997 and completed her Ph.D. in Chemical Sciences in 2001 under the direction of Prof. M. Catellani (University of Parma). She spent part of her doctoral studies at the Swiss Federal Institute of Technology (ETH), Zurich, working in the group of Prof. P. S. Pregosin. She is a researcher at the University of Parma, and her work is focused on the development of multistep multicomponent reactions by palladium and norbornene catalysis.

Nicola Della Ca' was born in Mantova, Italy, in 1974. He graduated in Industrial Chemistry in 2000 and received his Ph.D. in 2004 under the supervision of Prof. M. Costa at the University of Parma. He worked at Iowa State University (2003) with Prof. R. C. Larock and he joined Catellani's group as a researcher in 2005. His scientific interests are in the field of palladium-catalyzed sequential reactions involving aryl−aryl coupling.

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