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The Palladium/norbornene catalytic system: novel synthetic applications and mechanistic insights

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Catalytic C–C coupling through C–H arylation of arenes or heteroarenes

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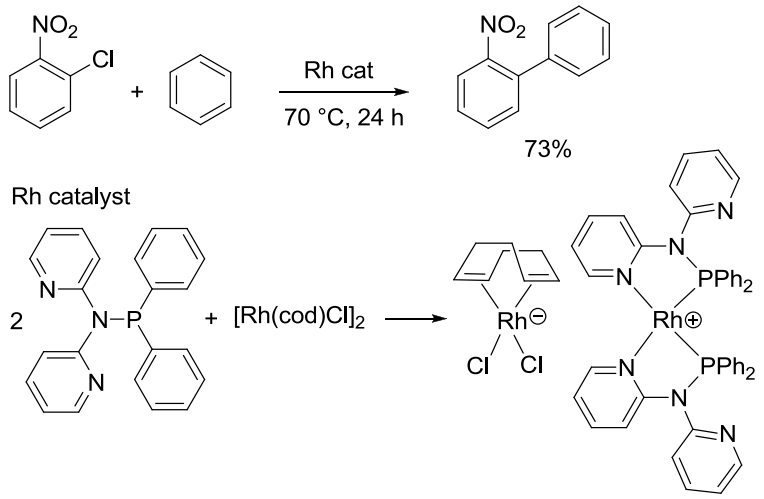
1. Introduction

Catalytic formation of biaryl compounds has been the object of a variety of methods which successfully compete with the more laborious conventional ones. It is essentially based on the replacement of an aryl-bonded leaving group such as a halide with a suitable nucleophile under the catalytic action of a transition metal. The latter must be able to undergo oxidative addition of the aryl halide to afford an arylmetal halide (or other leaving group) complex, where substitution with an aryl group can take place. This latter group generally is another organometallic species such as Grignard, Stille and Negishi reagents or an arylboronic acid.[1–4] Direct C–H arylation of arene compounds overcomes the need for a functional group in one of the aryl moieties undergoing C–C coupling.[5] As we shall see, however, to obtain a selective reaction some type of assistance is usually necessary. For recent reviews on aryl–aryl coupling by metal catalyzed direct arylation see references.[6–12] For the use of oxygen or stoichiometric oxidants, which are not considered here, see ref. [13,14]. We shall deal with catalytic non-oxidative: i) Intermolecular C–H arylation of unactivated arenes; ii) Intramolecular arylation; iii) Assisted intermolecular arene C–H activation.

2. Intermolecular C–H Arylation of Unactivated Arenes

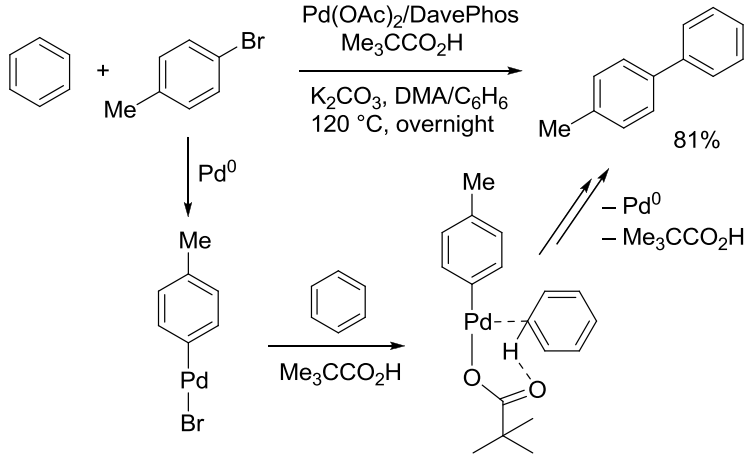
Unactivated arenes such as benzene can be caused to react efficiently with aryl iodides,[15] in general according to an arene electrophilic substitution operated by an arylmetal complex formed by oxidative addition of an aryl halide to a low valent metal. Using [Cp*Ir(H)Cl]2 (Cp*

= C5Me5) in the presence of *t*-BuOK as a base at 80 °C the cross-coupling reaction of 4-iodoanisole and benzene led to a 66% yield of 4-methoxybiphenyl. A new bimetallic rhodium catalyst which tolerates functional groups was used to couple aryl bromides and chlorides with benzene at 70 °C with satisfactory yields and high turn-over numbers. As shown in Scheme 1 the catalyst is formed in situ by reaction of [bis(2-pyridyl)amino]diphenylphosphine with half an equivalent of [Rh(cod)Cl]2 (cod = cyclooctadiene). Both the anionic and cationic rhodium species are needed for catalysis.[16]



Scheme 1.

Radical mechanisms have been proposed both for Ir- [15] and Rh- [16] catalyzed reactions. Palladium catalysis has been successfully used to arylate the polar hydrocarbon azulene regioselectively at the electron-rich 1-position.[17] A recent achievement consists of the use of pivalic acid in the reaction of palladium(0) (from $Pd(OAc)_2$) with bromoarenes and benzene in the presence of K_2CO_3 at 120 °C (Scheme 2). 2- Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (DavePhos) was the ligand of choice for palladium.[18] The addition of 30 mol% Me_3CCO_2H led to 4-methylbiphenyl in 81% yield from *p*bromotoluene and benzene.

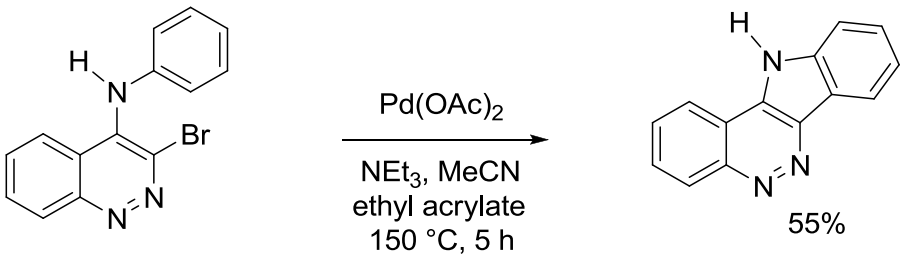


Scheme 2.

An intermediate in which the pivalate anion helps to abstract hydrogen from benzene has been postulated as first proposed by Echavarren.[19] Selectivity in the arene position to be arylated is a problem in these reactions and orienting groups or bridges between the aryl coupling moieties [20] can help to obtain acceptable results. It is noteworthy that pentafluorobenzene and other electron-poor perfluoroaromatics can be crosscoupled with aryl halides using as catalyst precursor $Pd(OAc)_2$ and 2-dicyclohexylphosphino-2',6'- dimethoxybiphenyl (S-Phos) in isopropyl acetate.[21] As in the pivalate case a C–H substitution mechanism involving proton-abstraction as the rate-determining step has been postulated.[22]

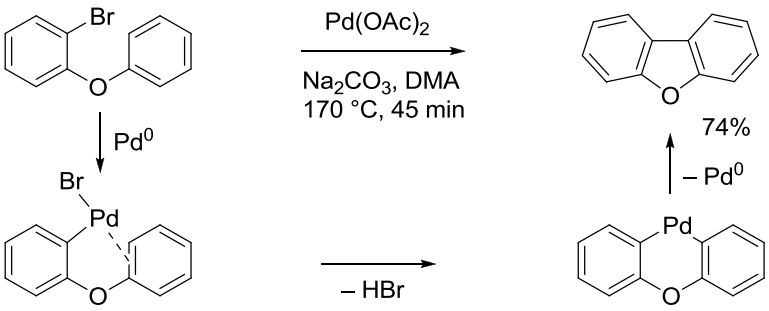
3. Intramolecular Arene C–H Arylation

In contrast with the intermolecular arene C–H arylation we have seen above the intramolecular arylation readily occurs selectively. The field is dominated by palladium catalysis. Intramolecular cyclization between two aryl units was first reported in 1982 when 3-bromo-4-phenylaminocinnoline was converted to indolo[3,2-c]cinnoline in 55% yield by heating in MeCN with triethylamine and ethyl acrylate at 150 °C under the catalytic action of $Pd(OAc)_2$ (Scheme 3).[23] The reaction takes place only in the presence of an olefin such as ethyl acrylate probably because coordination of the latter facilitates reductive elimination from the metal.[24]



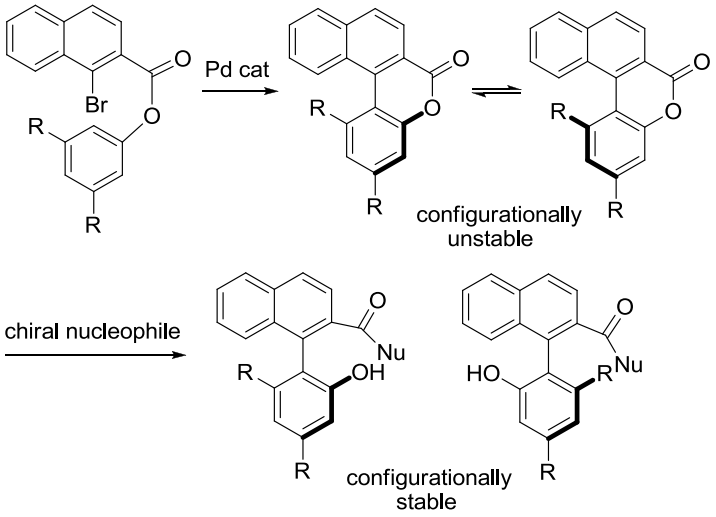
Scheme 3.

This type of cyclization was applied to several aryl halides *ortho*-bonded to an aryl group not only through an NH bridge but also through other bridges containing one or two heteroatoms.[25] Ames reported the palladium-catalyzed synthesis of dibenzofuran from *o*-bromophenyl phenyl ether in 74% yield by heating at 170 °C in DMA (*N*,*N*-dimethylacetamide) in the presence of Na_2CO_3 as a base (Scheme 4). The reaction is likely to proceed through an η^2- or η^1-arene coordinated species favoring C–H activation.[26,27]



Scheme 4.

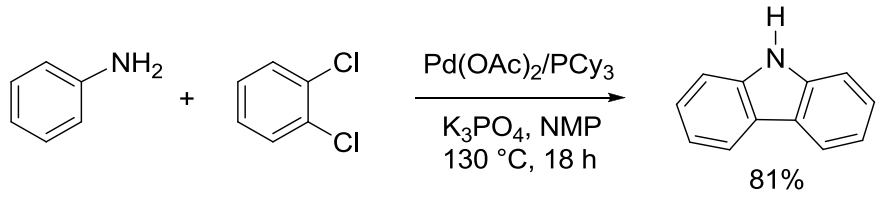
The procedure has been utilized for the synthesis of several natural products containing the biphenyl unit.[28–34] The direct palladium-catalyzed arylation has proved to be quite useful in the synthesis of configurationally unstable lactones (Scheme 5) which allow the atroposelective construction of axially chiral biaryl systems through nucleophilic attack on the lactone. The appropriate choice of the palladium catalyst precursor and the ligand depends on the steric hindrance of the substituents present in the aromatic rings.[35]



Scheme 5.

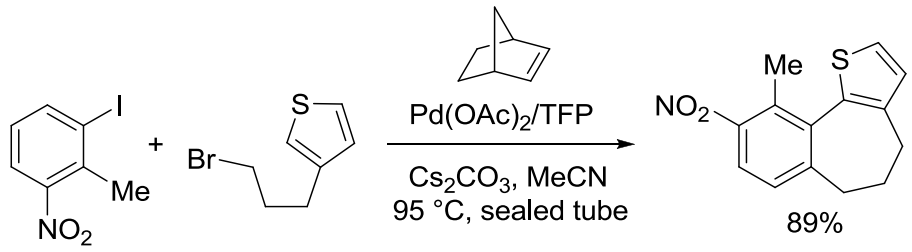
Analogous intramolecular coupling reactions led to condensed dihydroazaphenanthrenes,[36] naphthobenzazepines,[37] pyrrolophenanthridine (alkaloids precursors),[38] and a porphyrin, containing a five-membered condensed ring, from bromotetraphenyl porphyrin.[39] Sequential Pd/P*t*-Bu3 catalyzed amination of *o*-chloroanilines with bromoarenes and intramolecular coupling on the *ortho* C–H of the bromoderivative led to carbazoles. The natural alkaloid Clausine P (1,7-dimethoxy-6-methyl-9*H*-carbazole) was obtained in a one-pot reaction in 80% yield from 2-chloro-5-methoxy-4-methylaniline and 2-bromoanisole under microwave irradiation at 160 °C in toluene using Pd(OAc)2, P*t*-Bu3 and *t*-BuONa.[40] Recently another palladium-catalyzed domino reaction involving amination and direct C–H bond arylation to

generate carbazoles from anilines and 1,2-dihaloarenes was reported by Ackermann (Scheme 6).[41]



Scheme 6.

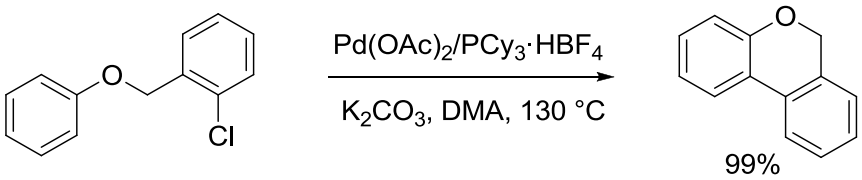
Palladium-catalyzed domino reactions involving *ortho* alkylation of aryl iodides and direct arylation of indoles,[42] pyrroles,[43] thiophenes and furans[44] to produce polycyclic heterocycles have been reported by Lautens' group. For example the seven-membered annulated ring product of Scheme 7 has been obtained in 89% yield. The intramolecular heteroarylation is the last step of a sequence involving alkylation of palladacycles. Arylation via metallacycles is dealt with in Section 4.3.



Scheme 7.

An analogous strategy has been adopted to form annulated 2*H*-indazoles and 1,2,3 or 1,2,4 triazoles.[45]

Recently Fagnou and coworkers have extensively studied the direct intramolecular C–H arylation of arenes to generate a variety of five- and six-membered carbo- or heterocyclic biaryl compounds. They reported that the ligand 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl gave with palladium an efficient catalyst for intramolecular ring closure of aryl bromides *o*-linked 5 to an arene through an ether or an amide group.[46] Using $Pd(OAc)_2/PCy_3 \cdot HBF_4$ they achieved direct arylation of aromatic C–H bonds with chlorides, bromides and iodides (Scheme 8). Iodides were less reactive because of catalyst poisoning due to the accumulation of the iodide salts formed. This could be prevented by the addition of silver additives.[20,47] Aryl chlorides could be cyclized in high yields using electron-rich *N*-heterocyclic carbene ligands.[48,49]



Scheme 8.

The same group also reported that $Pd(OH)_2/C$ (Pearlman's catalyst) is an excellent catalyst for arene direct intramolecular arylation reactions of aryl iodides and bromides. Moreover they provided evidence indicating that an active homogeneous palladium species is formed under the reaction conditions.[50] The significant kinetic isotope effect observed in many direct arylations points to the involvement of processes in which proton abstraction by a base (S_E3 process) or σ-bond metathesis are at work.[20,46,47] Progress in palladium-catalyzed direct C–H intramolecular activation in synthesis of biaryl derivatives has been reviewed.[10] As mentioned before these intramolecular cyclizations are likely to imply pre-coordination of the arene to be arylated to palladium through an η^2- or η^1-bond.[26,27] From this standpoint intramolecular reactions may be regarded as chelation assisted. In this context it is appropriate to mention the recent finding that intramolecular arylation of phenols to benzochromenes can be achieved in dioxane at 140 °C in the presence of 25 eq. of *t*- BuOH and without transition metals. Starting from a derivative of the substrate shown in Scheme 8, containing a hydroxyl group *meta* to the aryl C–O bond, the 1-hydroxy derivative of 6*H*benzo[*c*]chromene was obtained (73% yield) along with its 3-hydroxy isomer. A benzyne intermediate appears to be involved.[51]

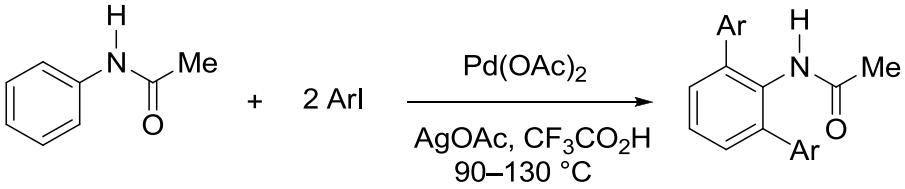
4. Assisted Intermolecular Arene C–H Arylation

This leads us to selective attacks on arene C–H bonds through intermolecular reactions. The need for the assistance of a chelating group,[52] a heteroatom[53] or a metallacycle[54] has been recognized as far back as the eighties.

4.1. Arene C–H Arylation Assisted by Chelation

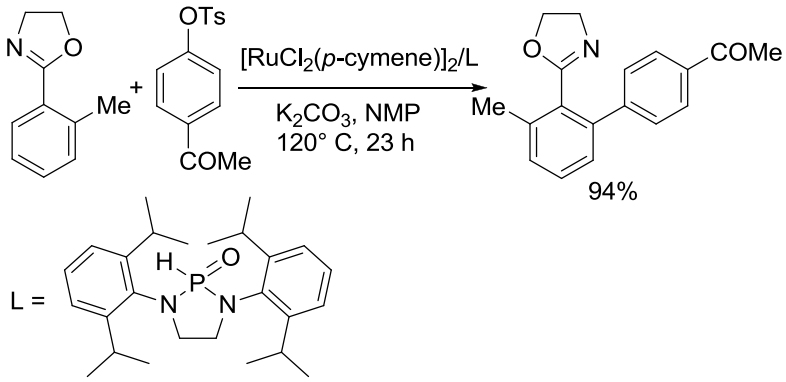
Beginning from chelation-assisted direct arylation of arenes we notice that the original work by Tremont, who reported the alkylation with alkyl iodide at the *ortho* position of acetanilide,[55] has been extended to arylation.[56] A number of anilides as pivaloyl or acetyl derivatives have been arylated with aryl iodides to the corresponding 2,6-diarylanilides using palladium acetate as catalyst and stoichiometric silver acetate in trifluoroacetic acid at 90–130 °C (Scheme 9).

High yields and turnovers up to 1000 have been reported. Benzamides[57] and benzylamines[58] have also been arylated analogously.



Scheme 9.

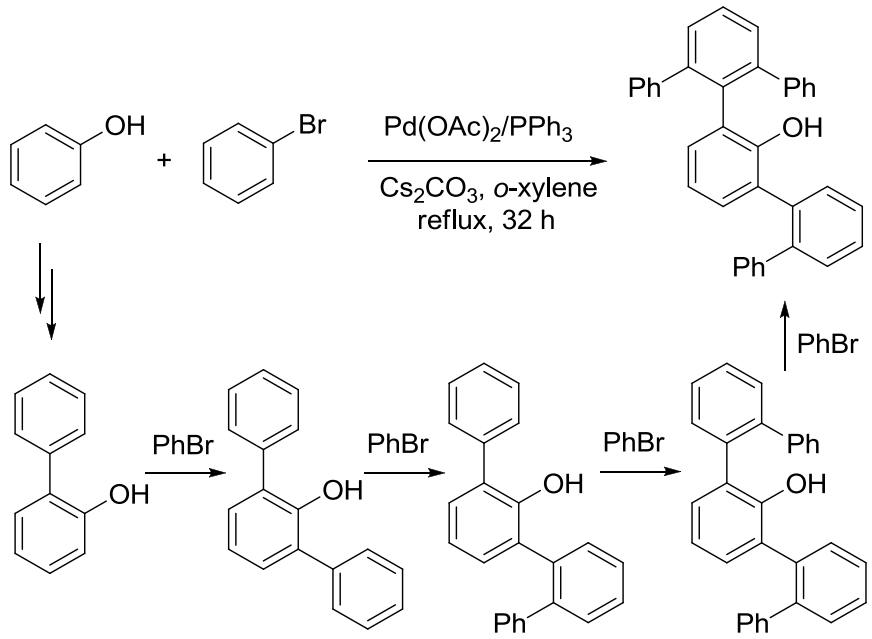
In the same category of reactions can be placed the arylation of benzodioxoles, which have been treated directly using aryl bromides with $Pd(OAc)_2$/P*t*-$Bu_2Me{\cdot}HBF_4$ in the presence of K_2CO_3 and Ag trifluoroacetate at 150 °C in DMA [10,20,47]. 2-Arylpyridines[59], benzaldimines and aryloxazolines were readily arylated with good to excellent yields by both electron-rich and electron-poor aryl chlorides in NMP in the presence of $RuCl_3(H_2O)_n$ as catalyst. The double arylation of arylpyridine derivatives observed with aryl chlorides was prevented by using the less reactive aryl tosylates.[10] Aryl tosylates[60] have also been used[59,61] in ruthenium-catalyzed coupling assisted by an oxazoline group, phosphine oxides being the ligand of choice (Scheme 10). Phenols have been used directly adding a stoichiometric amount of *p*-tosyl chloride to effect tosylation.[62] Previous work by Oi and Inoue reported on the ability of oxazolinyl or imidazolinyl substituents in the aromatic ring to direct ruthenium-catalyzed arylation towards the *ortho* position of the arene.[63] The use of mesitylcarboxylic acid as co-catalyst in assisted ruthenium-catalyzed arene arylations in apolar solvents has also been reported. A deprotonation mechanism[64] analogous to the one mentioned above[18,19] appears to be at work. It is worth noting that aryloxazolynyl ligands have been used to direct *o*-arylation in stoichiometric Grignard reactions with arylmagnesium halides.[65] The oxazolinyl group can be easily converted into a carboxylic function.



Scheme 10.

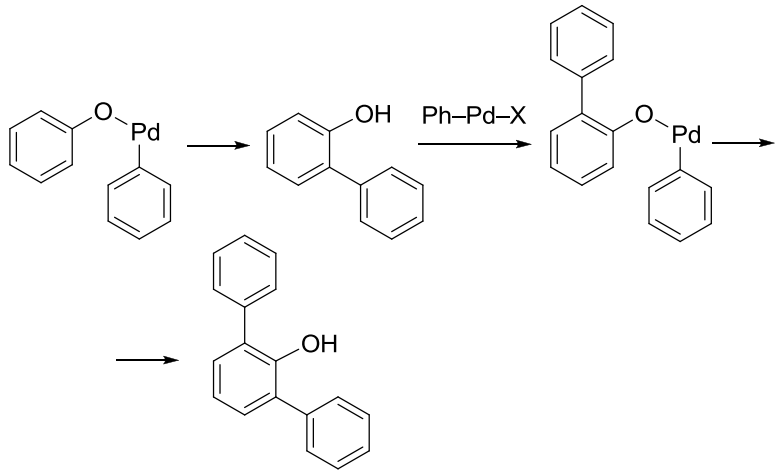
An important development has been reported by Miura and coworkers[9,52] who used phenols to direct palladium-catalyzed arylation at the *ortho* position. For example the reaction of phenol

with bromobenzene in the presence of $Pd(OAc)_2/PPh_3$ as catalyst with Cs_2CO_3 as a base in refluxing *o*-xylene for 32 h gave 2-biphenyl-6-terphenylphenol in 58% yield. One of the possible pathways is shown below in Scheme 11. Benzyl alcohols, acetophenones, benzyl phenyl ketones, anilides[9] and benzaldehydes[66] could be arylated analogously in *ortho* positions. Aliphatic carbons of acetophenones and benzyl phenyl ketones were also arylated.[9]



Scheme 11.

The mechanism seems to correspond to an electrophilic substitution assisted by chelation (Scheme 12). This is in accord with the transition state proposed for electrophilic attack on phenols.[67]



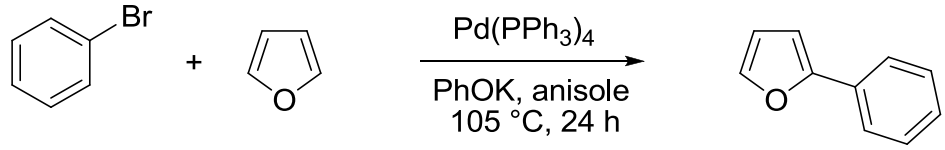
Scheme 12.

Two methods for direct *o*-arylation of benzoic acids with aryl iodides or bromides have been proposed by Daugulis: the first employs stoichiometric amounts of silver acetate for iodide

removal from aryl iodide in acetic acid at 130 °C; the second, suitable for aryl chlorides, uses *n*-butyl-di-1-adamantylphosphine ligand in DMF at 145 °C.[68]

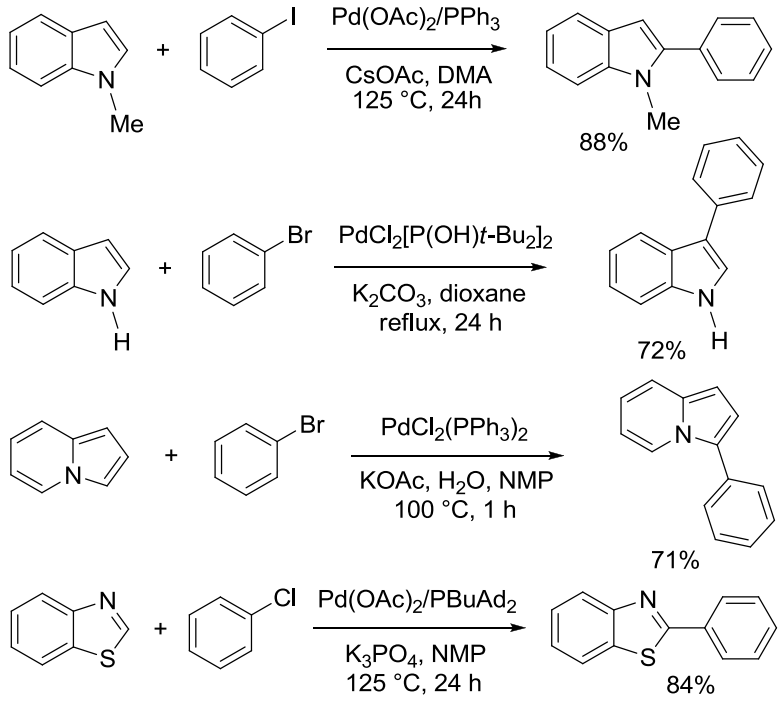
4.2 Arene C–H Arylation Directed by Heteroatoms

The attack of bromobenzene on the 2-position of furan has been recognized since 1985[53] (Scheme 13) but only more recently a methodology of broader scope has been worked out.



Scheme 13.

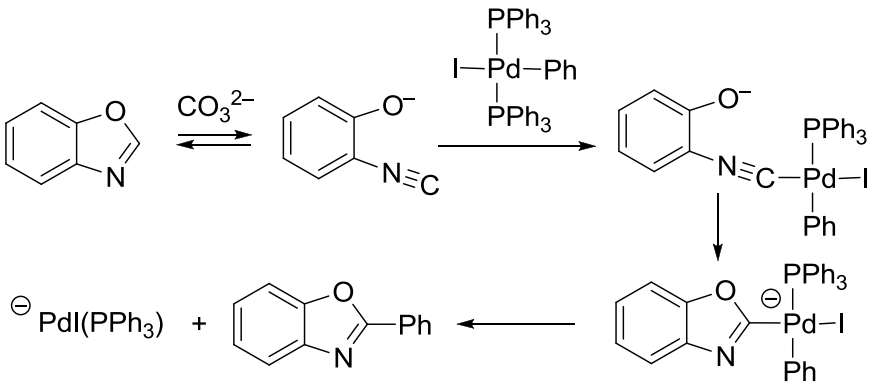
A number of heterocycles can now be arylated selectively using palladium and rhodium catalysts. Beside furans,[69] several types of heterocycles such as pyrroles,[70] indoles, [70,71] thiophenes,[9] oxazoles,[72] thiazoles,[50] imidazoles,[73] indolizines[74] have been reported to undergo selective arylation.[9] Scheme 14 shows some examples using different heterocyclic substrates, aryl halides (iodides, bromides, chlorides), catalysts, bases and additives.



Scheme 14.

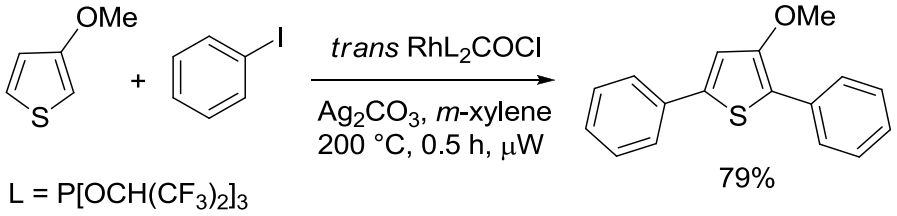
Indoles offer an interesting example of reactivity at two positions (C-2 and C-3). See for examples the first and second equation of Scheme 14. Reactivity at C-3 was obtained in the presence of phosphinous acids as ligands for palladium[71] while phenylation at the C-2 position occurred in the presence of $Pd(OAc)_2/PPh_3$.[75] Sames et al. rationalized this behavior

in the framework of the electrophilic substitution mechanism. Position C-3 is the preferred one, but if proton removal from the initial palladium complex is slow, there is time for a metal migration from C-3 to C-2 and arylation of the latter may occur exclusively.[75] Indole research has been reviewed.[76] In the presence of $PdCl_2(PPh_3)_2$ and under the conditions reported in the third equation indolizine readily reacts with bromobenzene to afford the C-3 phenylated derivative in 71% yield. The reaction is compatible with a variety of substituents both on the indolizine and aryl halide.[74] The use of $AgNO_3$/KF at 150°C allowed Pd-catalyzed arylation of 2-bromothiophenes with aryl iodides without affecting the Br–C bond.[74c] Aryl chlorides can arylate benzothiazole (fourth equation of Scheme 14) under the catalytic action of palladium in the presence of bulky, electron-rich phosphine ligands such as *n*-$BuAd_2P$ (Ad = adamantyl), which gives the best results. The methodology is applicable to a variety of electron-rich heterocycles and aryl chlorides.[72b] Selectivities in cross-coupling of azoles with two or more heteroatoms is discussed in a review.[77] Direct arylation of 1,2,3-triazole can be performed under palladium[78,79] and copper[80] catalysis. Selective arylations at the 2- and 5-positions of azoles were achieved by varying the palladium-based catalytic system. For example CuI addition directed arylation towards position 2 of both *N*-methylimidazole and thiazole, while in the absence of CuI the 5-position was preferred.[81] Sames and coworkers found that some SEM-protected pyrazoles (SEM = 2-(trimethylsilyl)ethoxymethyl) could be arylated selectively at the 5- position and sequentially in the 3- position after SEM shift to the other nitrogen in the presence of palladium acetate, P(*n*-Bu)Ad_2 and potassium pivalate at 140 °C in DMA. The deprotonation mechanism proposed by Fagnou[18,19,82] may be here at work to explain the preferential reactivity of the more acidic 5-position.[83] In some cases it has been shown that a deprotonation with ring opening is involved. Benzoxazoles open up the oxazole ring forming a palladium-coordinated isocyanophenolate.[84] The reaction occurs at 120 °C using $Pd(OAc)_2$/PPh_3, Cs_2CO_3 in DMF for 1 h. A proton abstraction mechanism has been suggested to be at work as shown in Scheme 15. A similar mechanism has been shown to be operative for 2-metalated thiazoles and imidazoles.[85]



Scheme 15.

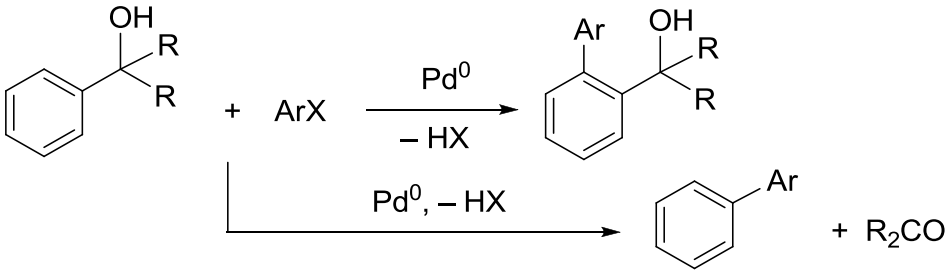
Thiophenes, furans, pyrroles and indoles could be arylated with a rhodium catalyst containing $P[OCH(CF_3)_2]_3$ as ligand. 3-Methoxythiophene was diarylated by iodobenzene selectively at carbons adjacent to sulfur to afford 2,5-diphenyl-3-methoxythiophene in 79% yield (Scheme 16). The reaction was over in 30 min when carried out in *m*-xylene at 200 °C under microwave irradiation.[86] The reaction was also extended to arene derivatives. Experimental data are consistent with an electrophilic mechanism.[87]



Scheme 16.

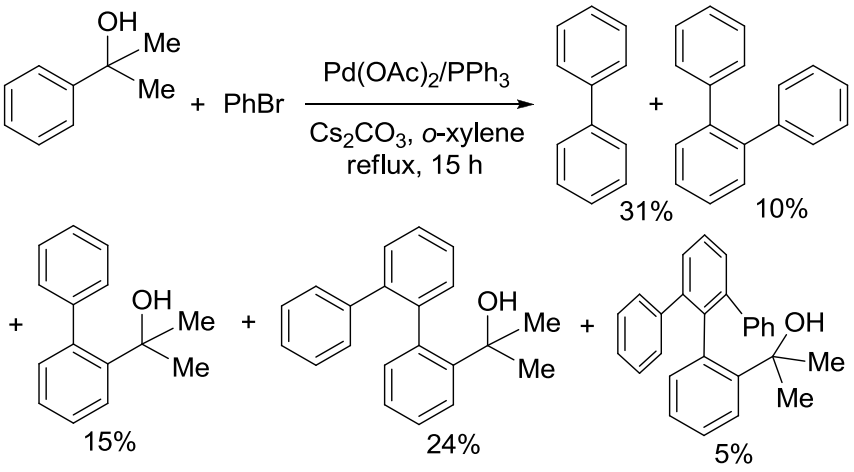
Rhodium-catalyzed arylation of benzimidazole in the presence of 9-cyclohexylbicyclo[4.2.1]-9-phosphanonane (cyclohexylphobane) was achieved by direct coupling of benzimidazole with aryl iodides and bromides bearing a wide variety of functional groups in good yields under microwave conditions (250 °C).[88]

Miura and coworkers described several procedures in which arene and heteroarene C–H[6] and C–C[9] activation are intertwined. We deem it useful to deal first with the general process of arene arylation reported in Scheme 17 for α,α-disubstituted arylmethanols, which can be traced to both type of activation, the former product coming from OH assisted C–H arylation and the latter from C–C bond cleavage with concomitant ketone formation (involving hydroxyl palladation).[89]



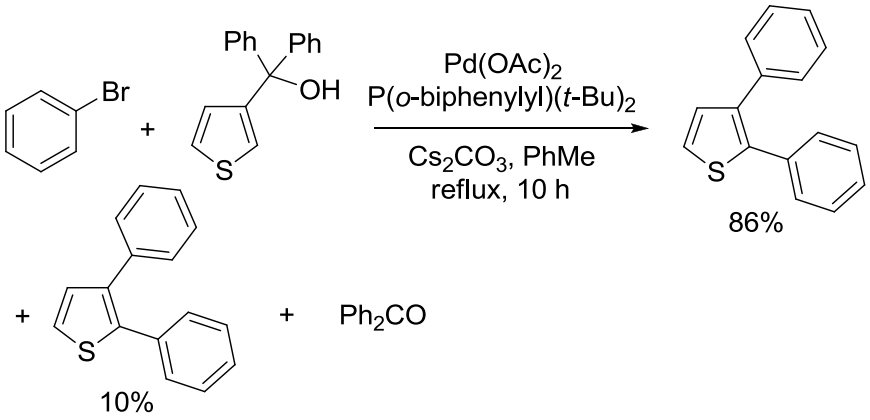
Scheme 17.

The reaction of 2-phenyl-2-propanol with bromobenzene gave rise to mono-, di- and tri-phenylated products as shown in Scheme 18. The first two products result from arylation via C–C bond cleavage, while the others from OH assisted C–H arylation. Selectivation towards the former products (essentially the monoarylated one) can be achieved using triphenylmethanol in place of 2-phenylpropanol and a bulky phosphine such as PCy_3. This also enables aryl chlorides to react efficiently.[89]



Scheme 18.

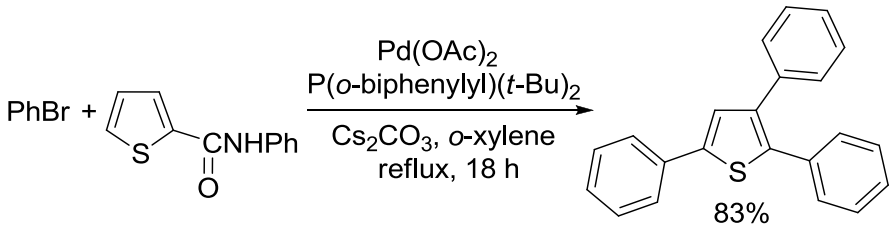
Passing to a heterocyclic substrate such as thiophene, the CR_2OH group was readily removed from the 3-position and replaced by a phenyl group after aryl attack on position 2. A third phenyl group attacked position 5 more slowly. Thus, as reported in Scheme 19, α,α-diphenyl-3-thiophenemethanol and bromobenzene were converted into 2,3-diphenylthiophene in 86% yield. Only a minor amount (10%) of 2,3,5-triphenylthiophene was formed.[90]



Scheme 19.

The first initial attack on the 2-position has been attributed to the assistance of the 3-methanol group while the second attack, replacing the methanol group itself, has been proposed to imply the formation of an –O–Pd–Ar group on the methanol substituent which assisted the electrophilic arene C–H activation. Another electrophilic attack involved position 5.

When a CONHR substituent was present in position 2 of thiophene position 3 was first phenylated likely through the assistance of the amide group. The resulting compound was either phenylated at position 5 or decarbamoylated. Decarbamoylation also occurred in the 3,5-diphenylated compound. Both products were further phenylated or diphenylated to give 2,3,5-triphenylthiophene in good yield (Scheme 20).[91]



Scheme 20.

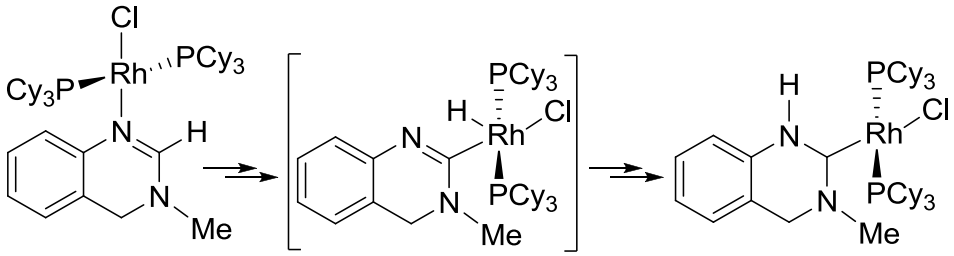
If an appropriate substituent such as CN was present at thiophene C-3 even the 4-position could be phenylated through C–H activation. Thus the reaction of 3-cyanothiophene, carried out under the conditions reported in Scheme 73 for a period of 70 h, gave 3-cyano-2,4,5-triphenylthiophene in 65% yield. The presence of substituents in the bromobenzene significantly affected the amount of product formed (78% yield with 3-$CF_3C_6H_4Br$; 48% with 4-$MeOC_6H_4Br$).[91]

The selectivity problem was addressed by Steglich[92] and by Forgione, Bilodeau et al..[69] The latter authors found that 2-heteroarylcarboxylic acids could direct arylation towards replacement of the COOH group. This process occurred selectively in the presence of an R

substituent in 3 position. If 3 was not substituted arylation in 3 occurred in part by assistance of the COOH group and the resulting 3-aryl-2-carboxylic derivative underwent a new arylation with replacement of the carboxylic group.

Perarylation of 3-thiophene and 3-furanecarboxylic acids has been reported by Miura and coworkers.[93]

Arylation of electron-deficient aromatics of azine type appears more difficult. Bergman, Ellman et al. have recently reported the catalytic arylation of quinolines and pyridines[94a] and azoles[94b,c] *ortho* to nitrogen rhodium(chloro)carbonyl dimer and a rhodium tetrahydrophosphepine complex have been used as catalysts at 175–190 °C. Using 3-methyl-3,4-dihydroquinazoline as model they gathered evidence that Rh first coordinates to nitrogen before C–H activation leading to a carbene species (Scheme 21).[94d]



Scheme 21.

Carmona[95] and Esteruelas[96] groups have proposed analogous C–H activation mechanisms for Ir, Os and Ru complexes. Rh(I) also catalyzes arylation via decarbonylation of benzoic anhydride.[97] A copper-catalyzed procedure which is valid both for electron-poor and electron-rich heterocycles has been developed by Daugulis and his group.[98] Further extension to sp^2 C–H including those of arenes, substituted by electron-withdrawing groups, uses K_3PO_4 or lithium alkoxide as a base and DMF or DMF/xylenes as solvent.[99] 5-Aryl benzotriazepines have also been obtained by direct arylation.[100] Coupling of heteroarenes and aryl halides or triflates to biaryls has been achieved with nickel acetate complexed with bipyridine or diphenylphosphinoferrocene.[101] Nickel also catalyzes arylation of azoles with aryl bromides.[102] In the attempt to address the problem of arylation of azine-type heterocycles Sames et al. have found that $Ru_3(CO)_{12}$ in the presence of PPh_3 and Cs_2CO_3 catalyzed the arylation of pyridine with iodobenzene to give a mixture of 2-, 3-, and 4-phenylpyridines (7:2:1) in 62% yield working in pyridine as solvent. Research to identify the catalyst resting state under reaction conditions led to discover a mixture of two dimers. As shown in Figure 1 these species activate pyridine through bridging the two ruthenium atoms, but unfortunately are not active as catalysts.[103]

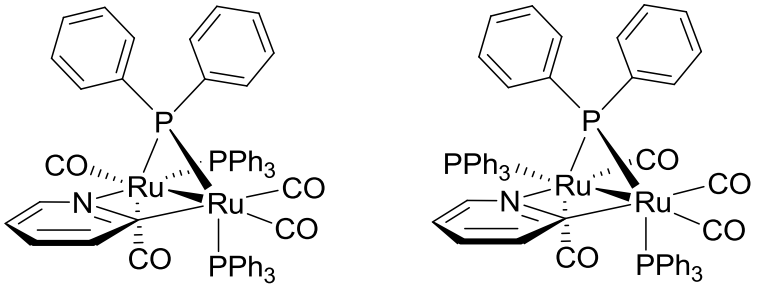
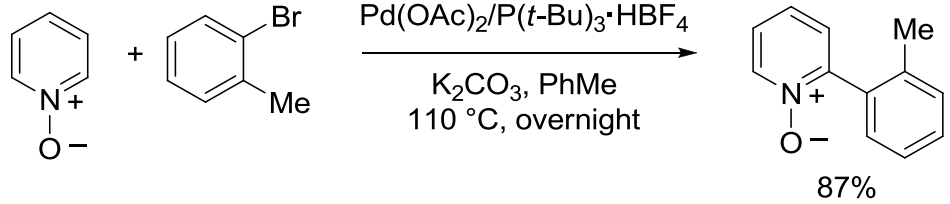


Figure 1. Pyridine C–H activation by coordination to a binuclear complex.

A clever way to cause difficult to arylate heteroarenes to react with aryl bromides to form the 2-arylated products has been reported by Fagnou.[104] It consists of using *N*-oxides such as those of pyridine, pyrazine, pyridazine, pyrimidine and quinoxaline as substrates. The products can be deoxygenated to generate the arylated azines by palladium-catalyzed hydrogenolysis. Pyrimidine *N*-oxide exhibited an inhibiting action which could be overcome by adding stoichiometric amounts of CuCN or CuBr. Diazines reacted faster than pyridines. The reactivity of thiazoles and imidazoles is remarkably enhanced in the order C-2> C-5 > C-4. A concerted palladation-deprotonation has been postulated for C–H activation[22a] in view of the sensitivity of the reaction to C–H acidity (Scheme 22). This mechanism has been shown by theoretical calculations to account also for reactions of electron-rich arenes.[22b]



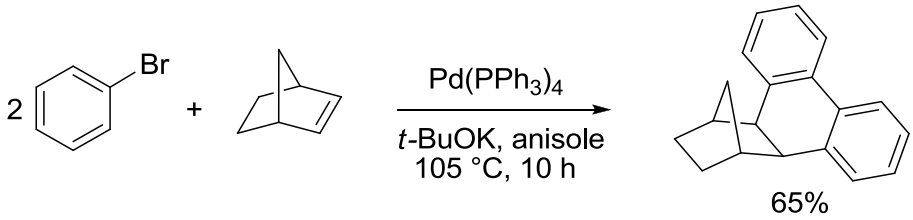
Scheme 22.

If an azole and an azine ring are fused as in 6- and 7-azaindoles the azine ring can be induced to react preferentially by previously forming its *N*-oxide.[105] A comprehensive outlook on the subject of *N*-oxide arylation has recently appeared.[104b] It may be useful to recall in this context that uranium(IV) and thorium(IV) alkyl complexes have been recently reported to activate an *ortho* C–H bond in pyridine *N*-oxide by cyclometalation.[106]

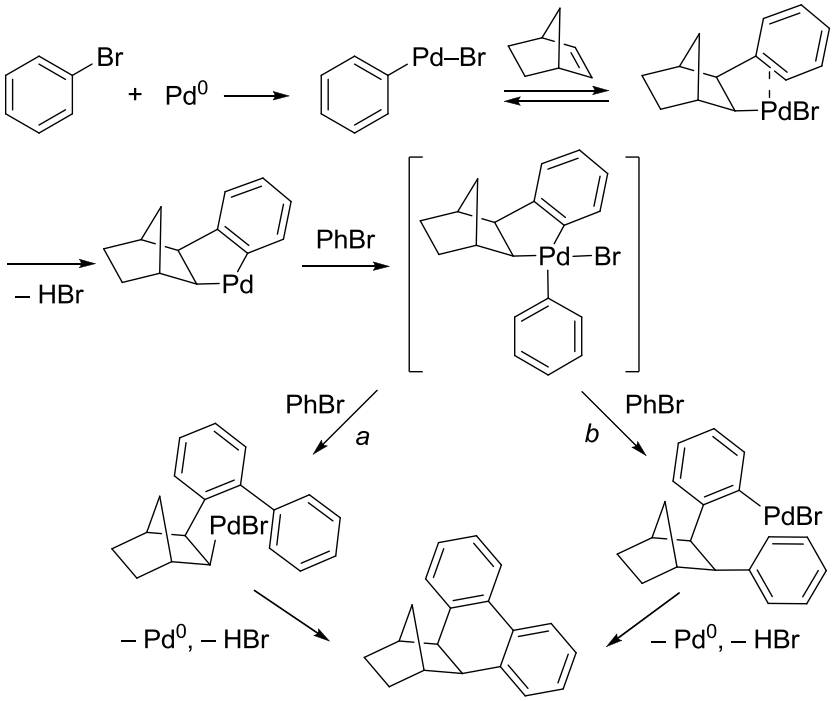
4.3. Metallacycle-Assisted Arene C–H Arylation

A complex reaction leading to a methanotriphenylene (Scheme 23) was described in 1985.[54] Bromobenzene and norbornene reacted in anisole at 105 °C under the catalytic action of $Pd(PPh_3)_4$ and in the presence of *t*-BuOK giving a 65% yield of *cis,exo*-hexahydromethanotriphenylene. The reaction consists of a series of steps starting from the

oxidative addition of bromobenzene to palladium(0) to form the phenylpalladium complex, which undergoes stereoselective norbornene insertion to *cis,exo* phenylnorbornylpalladium bromide with the metal center weakly bound to the aromatic ring through an η^2 coordination as shown by X-ray analysis.[26,27d] This complex is rather stable towards β-H elimination due to the lack of β-hydrogen *syn* to palladium. This circumstance prevents the occurrence of a Heck-type reaction under the conditions used and favors an alternative pathway leading to arene C–H activation to afford the five-membered alkylaromatic palladacycle. The latter directs the attack of a molecule of bromobenzene either on the phenyl (way a) or the norbornyl moiety (way b) possibly through the intermediacy of a palladium(IV) species (isolated with benzyl bromide [107]) in place of bromobenzene. Final ring closure by C–C coupling then occurs both on the norbornyl and the aryl moiety (Scheme 24).



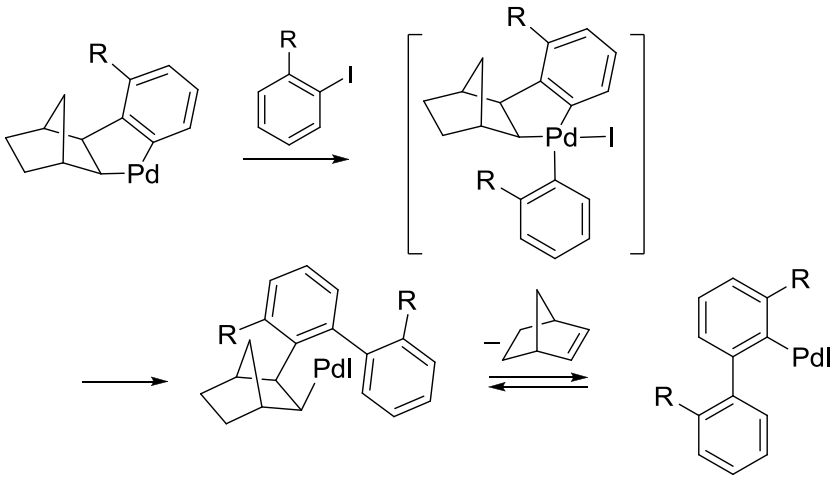
Scheme 23.



Scheme 24.

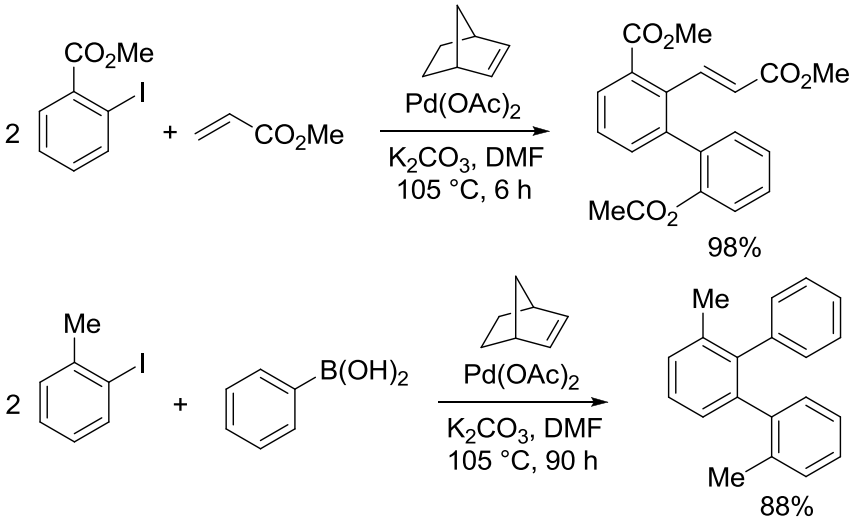
That two pathways (*a* and *b*) are at work was proved by introducing a *para* substituent in the starting bromobenzene, which gave two differently substituted methanotriphenylenes. Thus the aryl–aryl coupling was not selective.

Further study of the metallacycle-assisted reaction led to the discovery that in the presence of an *ortho* substituent in the aryl halide the reaction proceeds selectively according to path *a*, only the aryl–aryl bond and not the aryl–norbornyl bond being formed.[108] This is likely due to the steric effect exerted by the *ortho* substituent which favors the attack at the aryl site of the alkylaromatic palladacycle. Owing to the sterically hindered situation created by the two *ortho* substituents, the resulting complex readily deinserts norbornene thus giving rise to a biphenylylpalladium complex which can be caused to react with different partner molecules according to the known reactivity of arylpalladium species. It is worth noting that norbornene expulsion implies a β-C–C bond cleavage and that norbornene is not incorporated in the final product (Scheme 25).



Scheme 25.

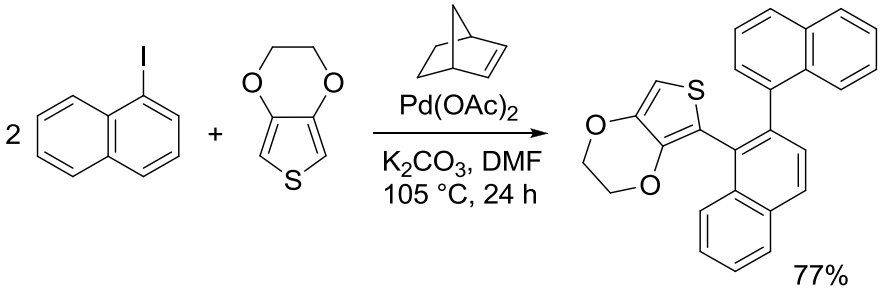
Causing the biphenylylpalladium complex to undergo a reaction able to liberate the organic product and palladium(0) makes the process catalytic. In this way the synthesis of a variety of interesting classes of organic compounds such as selectively substituted biphenyls by reaction with a hydrogen donor such as benzyl alcohol,[109] biphenyl derivatives containing a vinyl[110] or an oxoalkyl chain by reaction with an acrylic ester or an oxoalkyl chain, respectively,[111] phenanthrenes by reaction with diarylalkynes[112] and terphenyls by reaction with arylboronic acids[113] has been achieved. Scheme 26 reports two examples.



Scheme 26.

The problem of delaying the termination step until the end of the stoichiometric sequence to prevent competitive reactions in earlier steps is common to all these reactions but it is particularly critical for hydrogenolysis.[109]

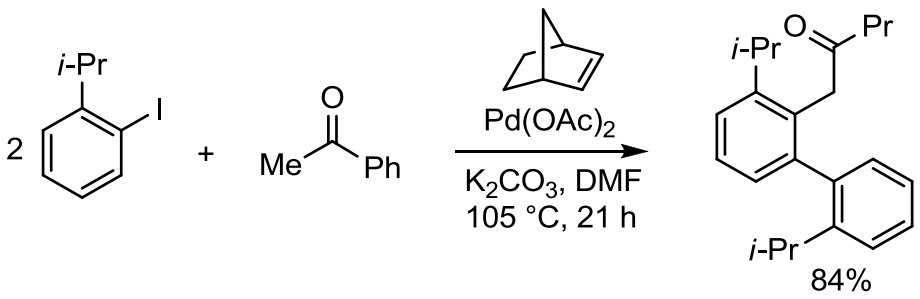
More recently termination of the reaction sequence has been achieved by C–H arylation of a heteroarene (Scheme 27 or the third chapter of this thesis).[114]



Scheme 27.

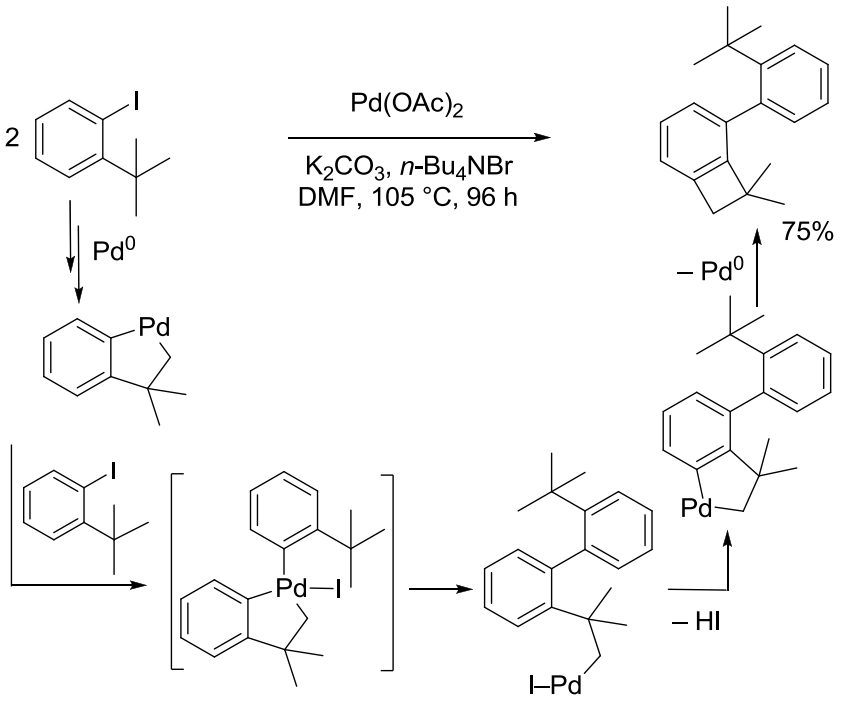
The presence of norbornene thus deviates the direct attack of the iodoarene on the C–H adjacent to the heteroatom shown in Scheme 67 towards the formation of the biphenyl unit before final C–H arylation.

C–H activation of aliphatic species such as ketones has also been achieved (Scheme 28 or the first chapter of this thesis).[115]



Scheme 28.

Neglecting for the moment further considerations on the mechanism of this type of aryl–aryl bond formation which will be treated later in this section, we can place in the general framework of metallacycle-assisted aryl coupling Dyker's findings that *o*-*t*-butyliodobenzene[116] and *o*-iodoanisole[117] undergo aryl coupling through palladacycle formation. As shown in Scheme 29 *o*-iodo-*t*-butylbenzene reacted with palladium to give an alkylaromatic palladacycle through initial oxidative addition followed by cyclometallation of an unactivated sp^3 carbon. A second molecule of *o*-iodo-*t*-butylbenzene reacted selectively with the metallacycle thus formed, possibly through the intermediacy of a palladium(IV) species, to afford a palladium complex containing a biaryl structure. The latter underwent a second cyclometallation followed, this time, by reductive elimination to the organic product.

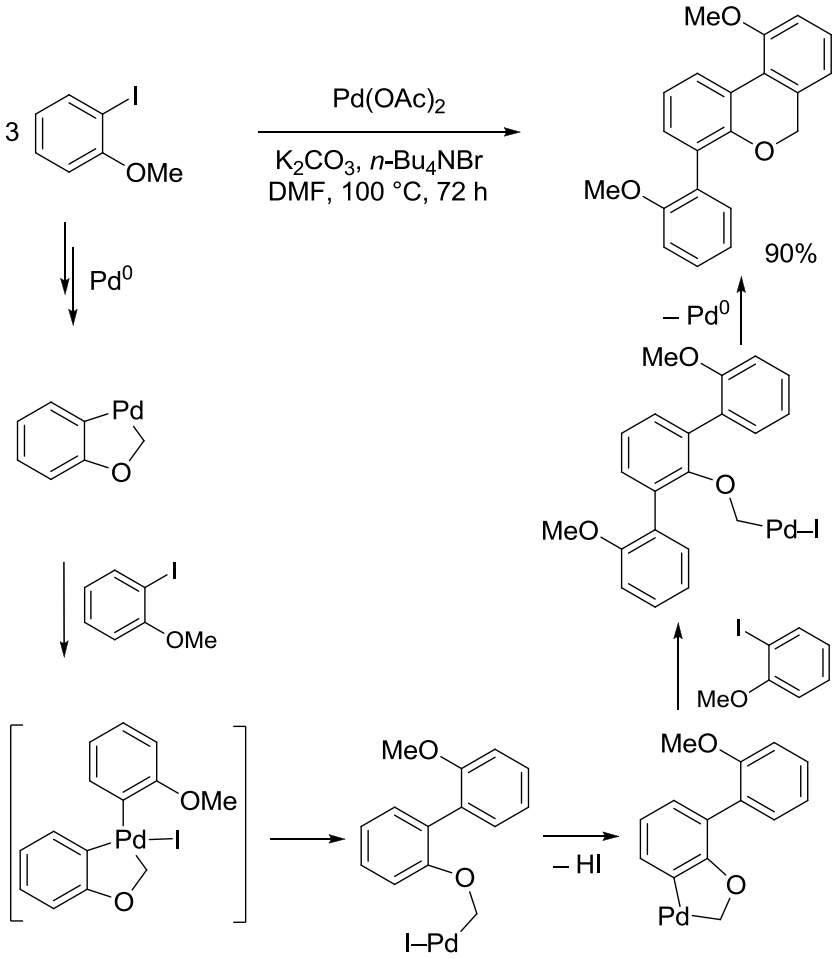


Scheme 29.

o-Iodoanisole behaved in a similar way combining three aromatic units to generate the selectively substituted dibenzopyran derivative reported in Scheme 30 in 90% yield. The

described reaction pathway is similar to the previous one up to the formation of the second metallacycle which, in place of undergoing reductive elimination to a four-membered-ring, repeats the reaction with a new molecule of *o*-iodoanisole to give a new metallacycle which finally reductively eliminates the dibenzopyran derivative. Interestingly, the palladacycles initially involved in these reactions have been isolated with stabilizing ligands.[27a,118] That the main product results from the reaction of three molecules of iodoanisole instead of the two involved in the case of *o*-iodo-*t*-butylbenzene can be attributed to the different tendency to close a 4-membered ring in the two cases. In fact the geminal substituent effect favors competitive ring closure in the former, thus interrupting the sequence.

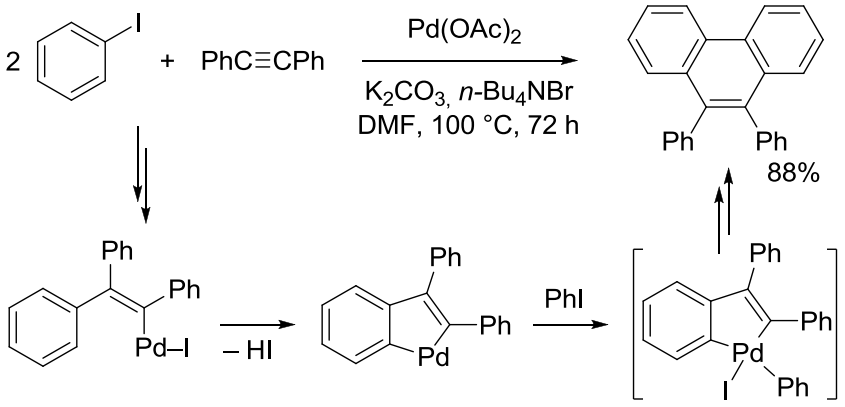
The palladacycles involved in Dyker's reactions behave similarly to the ones containing the norbornyl unit, readily reacting with aryl halides at the aromatic carbon-palladium bond. However in contrast with norbornene the isobutene or the formaldehyde molecules are not expelled in the presence of two *ortho* substituents. It is noteworthy that isobutene could be removed in a stoichiometric reaction.[27b]



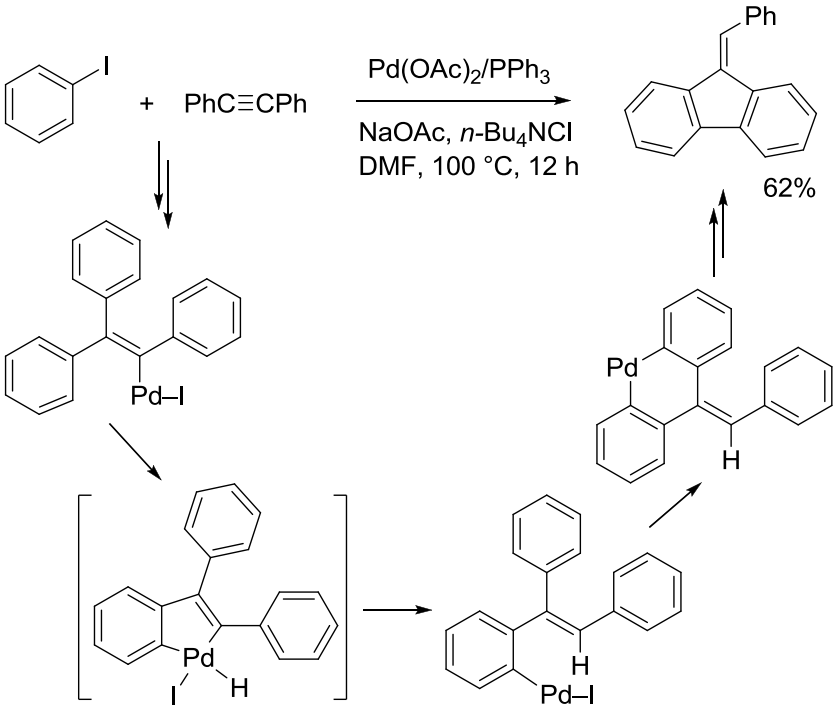
Scheme 30.

An intermediate palladacycle formation could also be obtained using iodobenzene with diphenylacetylene. It was shown that the outcome of the reaction was strongly dependent on

the base used. Dyker obtained 9,10-diphenylphenanthrenes using K_2CO_3 as a base in a 2:1 annulation reaction (Scheme 31)[119] while Larock synthesized 9-benzylidenefluorenes by performing a 1:1 reaction in the presence NaOAc (Scheme 32).[120]



Scheme 31.

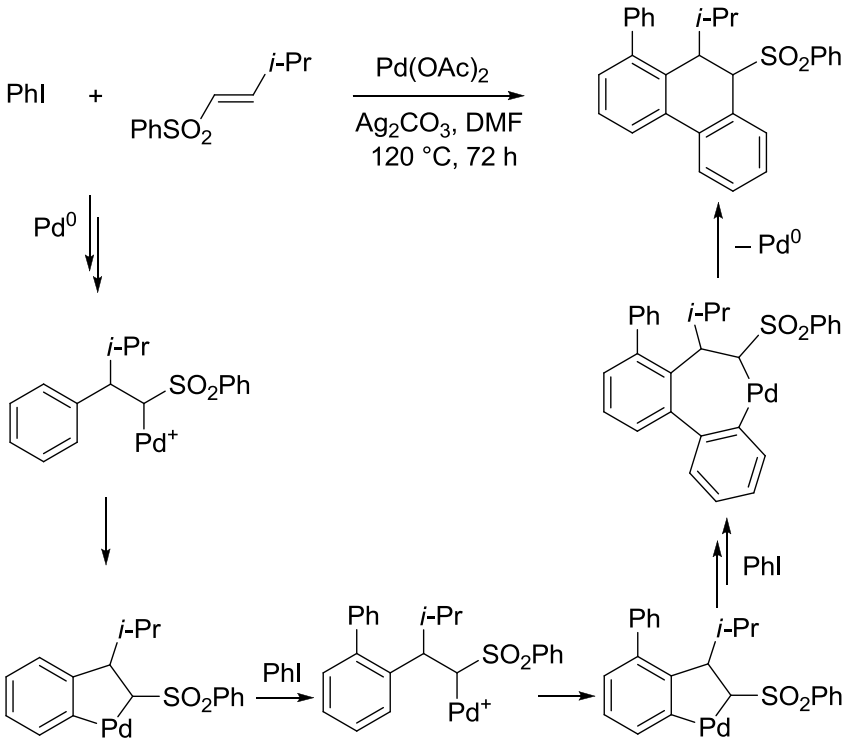


Scheme 32.

An interesting effect has to be noted in Larock's synthesis: the cyclopalladated precursor of benzylidenefluorene originates from the palladium migration from one site to another. This aspect will be considered later in the context of palladium migrations.

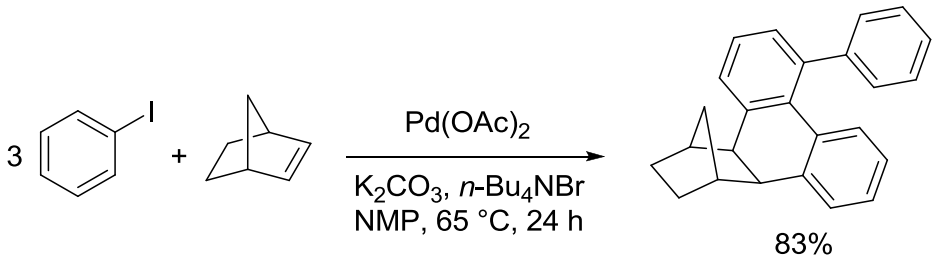
Other unsaturated substrates have been reported to undergo similar palladium-catalyzed arylation reactions. α,β-Unsaturated phenylsulfones reacted with aryl iodides in the presence of $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as a base to give 9-phenylsulfonyl-9,10-dihydrophenanthrenes. The proposed reaction pathway implies double bond arylation, palladacycle formation, double phenylation with iodobenzene and final ring closure to give the observed dihydrophenanthrene derivative. The presence of the sulfone group in the σ-

alkylpalladium intermediates is likely to disfavor β-H elimination thus making possible the intramolecular aromatic C–H activation process with formation of the five-membered palladacycle (Scheme 33).[121]



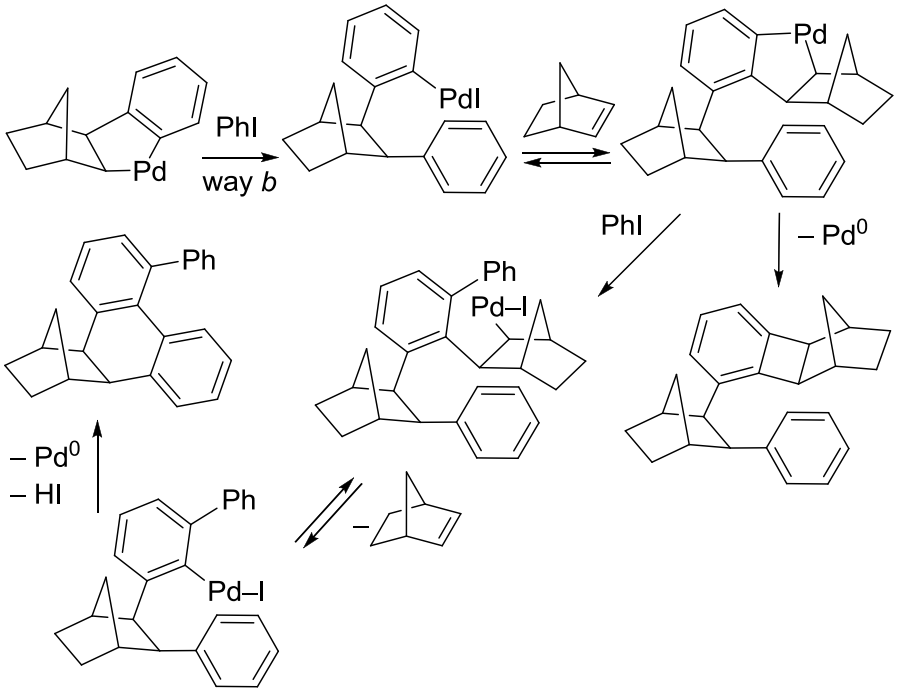
Scheme 33.

The reaction with norbornene and other strained cycloolefins has been further studied by de Meijere.[122] Interestingly he found that the reaction of iodobenzene and norbornene shown in Schemes 79–80 could take a different course leading to the formation of a 3:1 coupling product (Scheme 34).



Scheme 34.

This helps to through light on palladacycle behavior. The initial palladacyle reacting according to way *b* of the same Scheme leads to a species which is not particularly prone to cyclization in the presence of norbornene and prefer to undergo another norbornene insertion. This has been proved[123] by the isolation of the corresponding benzocyclobutene product (Scheme 35).

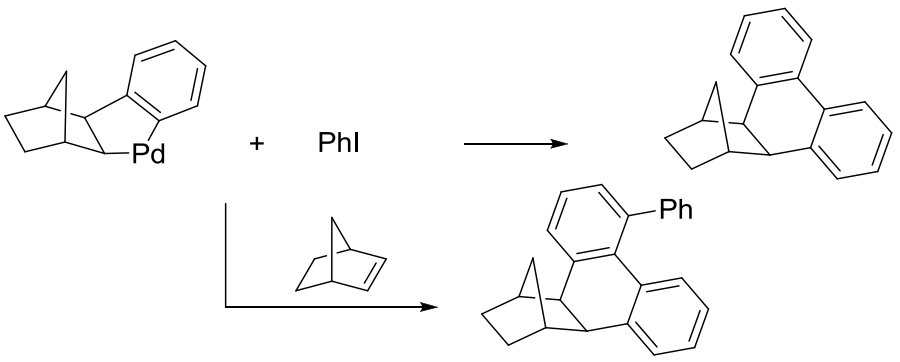


Scheme 35.

If now the first and the second palladacycle of Scheme 35 are compared it can be observed that the situation is quite similar with the only difference that an alkyl (2-phenylnorbornyl) group in *ortho* to the aromatic to aliphatic C–C bond of the palladacycle is present in the latter.

In the presence of iodobenzene the palladacycle does not give rise to reductive elimination to a benzocyclobutene[123] but undergoes functionalisation at the aryl site, the *ortho* substituent clearly causing preferential palladacycle opening according to Scheme 35.

Further evidence was gained by comparing conditions for the formation of hexahydromethanotriphenylene and phenylhexahydromethanotriphenylene. The former was obtained selectively by causing the initial palladacycle to react with iodobenzenze in the absence of norbornene while the latter could be obtained only in the presence of norbornene, in agreement with the proposed mechanism (Scheme 36).[108]



Scheme 36.

It is worth noting that the palladium intermediate formed by norbornene expulsion in a catalytic reaction involving iodobenzene and norbornene (KOAc as a base in DMF at 105 °C) has been trapped by adding olefins such as methyl acrylate or styrene.[124]

This is another instance of the extremely versatile behavior of the reactions via metallacycles with more than two components.

The reaction of Scheme 23 was extended by de Meijere to other norbornene-type strained olefins such as deltacyclene, norbornenol, norbornenone and dicyclopentadiene:[122b] he demonstrated that also indene could give 1:3 coupling products analogous to the ones from norbornene but with different regiochemistry.[125] The use of heterocyclic aryl iodides such as iodothiophenes and iodopyridines led to the synthesis of interesting products although in moderate yields. The reaction of norbornene and *m*-iodopyridine gives the corresponding bipyridine derivative. The reaction required higher temperature and the addition of triphenylphosphine.[122b]

It should be noted that in the reactions depicted in Schemes 33–36 the unsaturated compound needed for metallacycle formation is retained in the final product whereas with norbornene, norbornadiene and similar rigid olefins it is liberated again when aryl to aryl coupling occurs. Even if usually present in substantial concentration to favor their insertion, these olefins act catalytically jointly with palladium catalyst. This is a remarkable feature in catalysis in that an organic and an inorganic catalyst work in cooperation.

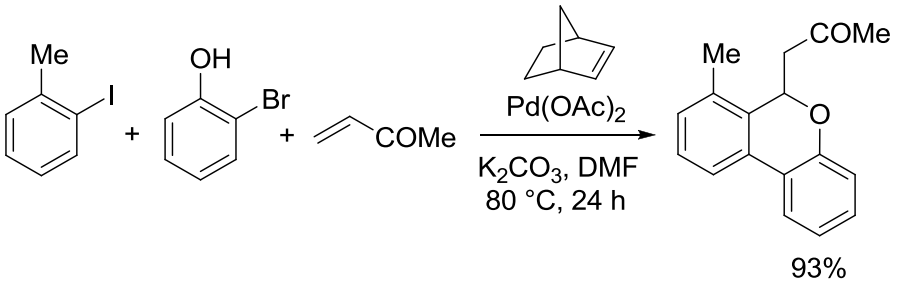
All these reactions involve C–C coupling to biaryls starting from the same aryl halide. Recently it has been found that different aryl halides can be coupled selectively provided that *o*-alkyl-substituted aryl iodides are reacted with aryl bromides and in certain cases also chlorides, containing electron-withdrawing substituents. The syntheses are carried out in one-pot under mild conditions starting from easily available reagents (Scheme 37).[126]

Scheme 37.

The reaction pathway is analogous to the one shown in Scheme 24, way a, but it implies the selective formation of the initial palladacycle at the expenses of the more reactive aryl iodide.

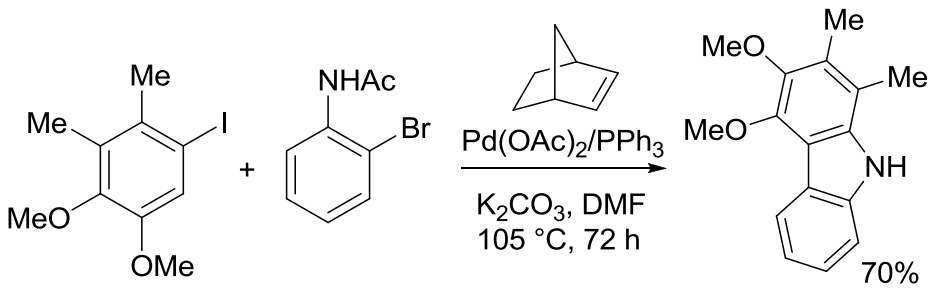
At this point further attack on the palladacycle only occurs by the bromide. The highly preferred reaction of this compound is not easy to explain but it is likely to be due to steric effects. Further study is required to clarify this point, which is also associated with the possible formation of a palladium(IV) complex. Reductive elimination from the latter gives a biphenylylpalladium complex from which a Heck-type reaction liberates the palladium(0) catalyst and the organic product shown in Scheme 37.

The reaction is tolerant of several functional groups which can be further exploited for ring formation. As shown in Scheme 38 the reaction of *o*-bromophenol with *o*-iodotoluene and methyl vinyl ketone led to the formation of the corresponding dibenzopyran derivative in high yield (93%). The cyclization step is triggered by the *o*-hydroxyl group appropriately positioned for an easy attack on the activated double bond through Michael reaction. In spite of the fact that the most effective substituents on the aryl bromide are the electron-withdrawing ones *o*-bromophenols react satisfactorily likely because of the positive chelating effect of the *o*-hydroxyl group.[127]



Scheme 38.

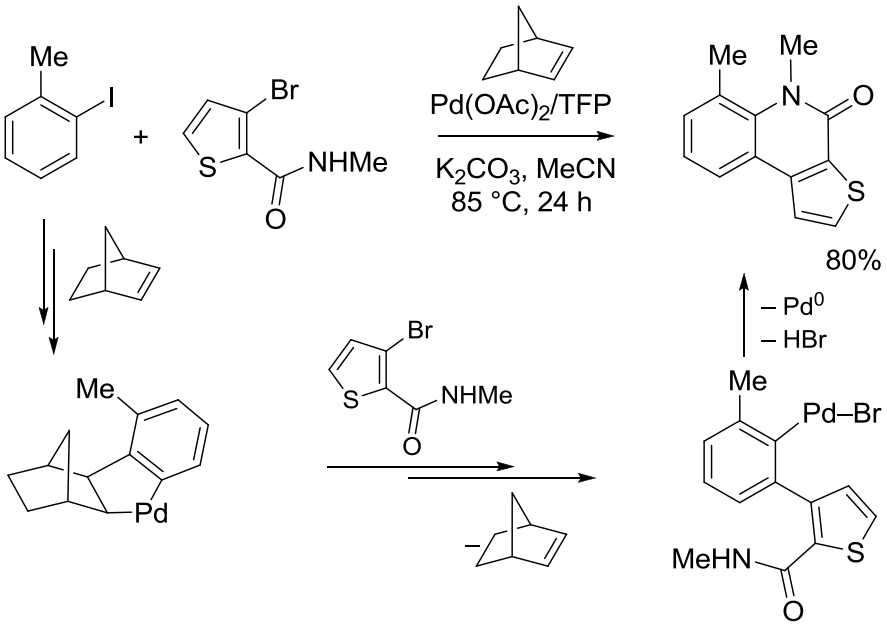
N-Sulfonylated 5,6-dihydrophenanthridines have been prepared analogously but under different conditions also involving the use of sulfonamides.[128] Working in the absence of Michael acceptors carbazoles have been obtained, for example 2- ethylcarbazole in a 98% yield. The antibiotic carbazomycin A has been synthesized from the pertinent iodide and *N*-acetylated *o*-bromoaniline (Scheme 39) in a 70% yield.[129]



Scheme 39.

6-Phenanthridinones and their heterocyclic analogues were synthesized through sequential aryl–aryl and *N*-aryl coupling. Using 3-bromothiophene-2-carboxylic acid methylamide in the

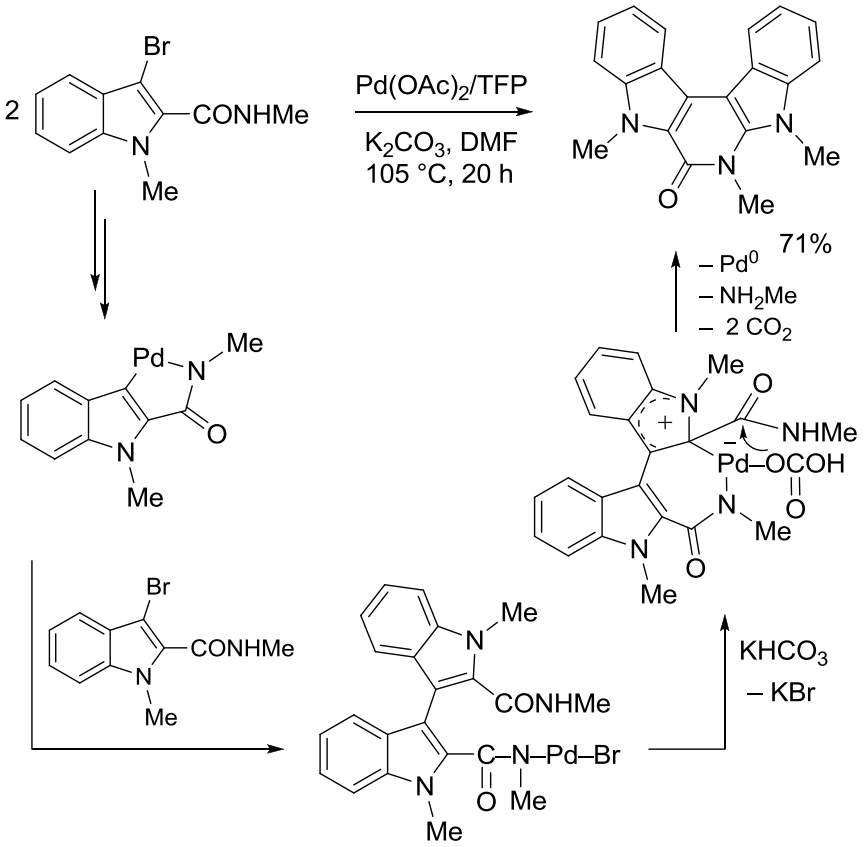
reaction with *o*-iodotoluene in the presence of $Pd(OAc)_2$/TFP, and norbornene as catalyst, K_2CO_3 as a base in MeCN at 85 °C, the corresponding quinolinone derivative was isolated in 80% yield (Scheme 40).[130]



Scheme 40.

A comprehensive report on reactions involving the Pd/norbornene dual catalysts has recently appeared.[131]

Under similar conditions in the absence of norbornene *o*-bromoaromatic carboxamides undergo homocoupling reaction with concomitant decarbamoylation to afford condensed pyridones. As depicted in Scheme 41 3-bromo-1-metil-1*H*-indole-2-carboxylic acid methylamide reacted in the presence of $Pd(OAc)_2$/TFP as catalyst, K_2CO_3 as a base in DMF at 105 °C to give the corresponding pyridine in 71% yield.[132] The reaction has been proposed to proceed through palladacycle-catalyzed homocoupling of the bromoamide followed by splitting of the aminocarbonyl group by intramolecular *ipso* aromatic substitution. The MeNHCO-group is removed as amine and carbon dioxide possibly by attack of a palladium coordinated bicarbonate anion O(CO)OH. The *o*-CONHMe group cooperates in the construction of the palladacycle responsible for the homocoupling step.

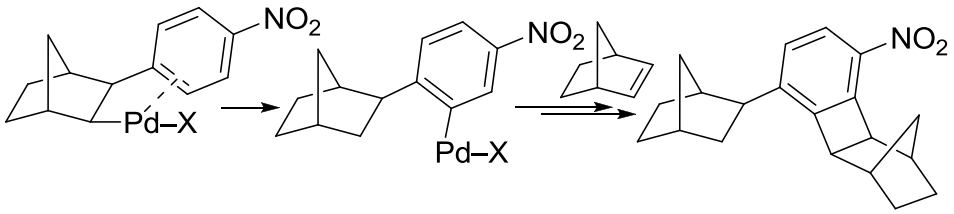


Scheme 41.

The palladium-catalyzed reaction of *o*-bromobenzamides to phenanthridinones with concomitant decarbamoylation was first reported by Caddick.[133] A similar reaction using a catalytic system based on $Pd(OAc)_2$/2-(8-methoxy-1-naphthyl)phenyldiphenylphosphine and Cs_2CO_3 as a base has been recently reported to give the same products with expulsion of isocyanate derivatives.[134]

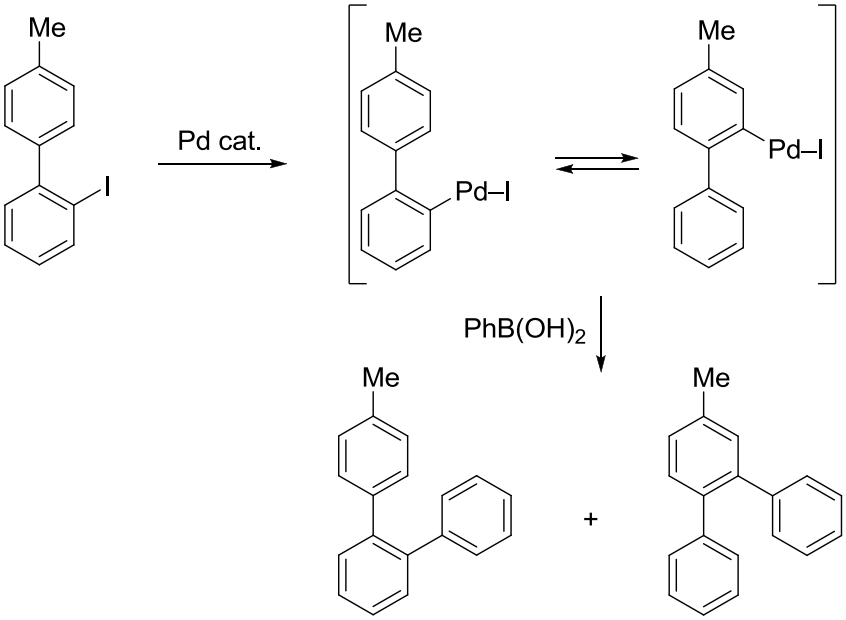
5. Palladium Migration in Arenes

An interesting aspect of the chemistry of aryl coupling is that the aryl coupling can take place at an arene position different from that of the original C–Pd bond. That palladium could move from one side to the other of a palladacycle (from sp^3 to sp^2) had been previously shown in the case of norbornene.[135] The methanobiphenylene derivative reported in Scheme 42 was obtained by reaction of 4-nitrobromobenzene with norbornene in anisole at 105 °C under the catalytic action of $Pd(PPh_3)_4$ and in the presence of KOAc. Other examples of sp^3-sp^2 migrations have been recently reviewed.[136]



Scheme 42.

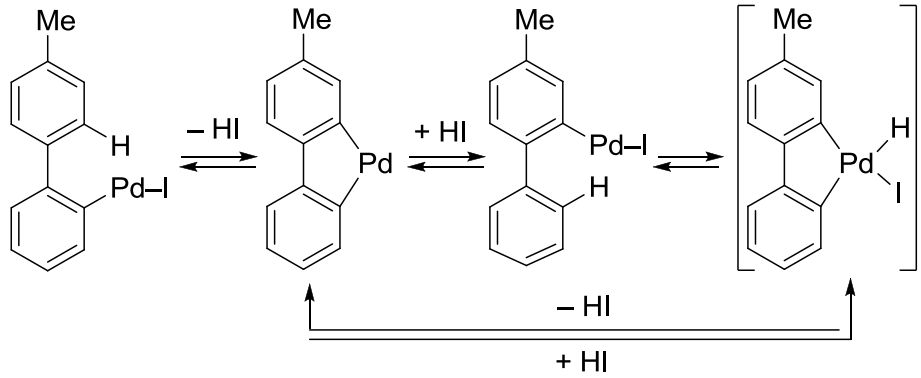
Palladium has been reported by Gallagher[137] and Larock[138] to migrate along arene or heteroarene nuclei and the corresponding complexes have been caused to react with ethyl acrylate to obtain the respective isomers. Recently Larock has trapped the isomer palladium intermediates by Suzuki cross-coupling using arylboronic acids (Scheme 43).[139]



Scheme 43.

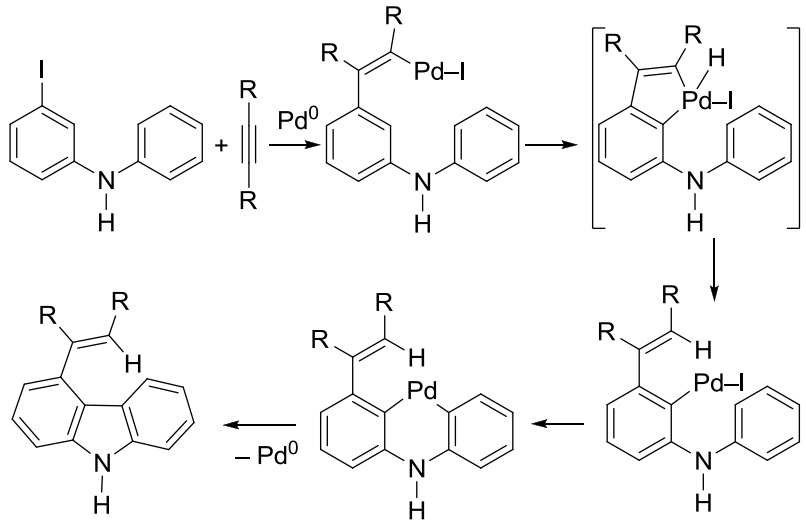
This possibly involves an intermediate palladacycle and is relevant to the aryl coupling process. Palladium migration can be made selective using aromatic C–H bonds of sufficiently different acidity in the two rings. Migration occurs towards the more acidic C–H, if there is time to equilibrate the biphenylyl-bonded palladium intermediate before reaction with a suitable C–C bond forming partner as in the cases of Heck and Suzuki reactions. Appropriate conditions to favor partial or total equilibration of the biphenylyl-bonded palladium intermediates have therefore to be chosen. For example if 2-iodo-4'-methylbiphenyl (Scheme 43) is subjected to a Suzuki reaction with phenylboronic acid the main product derives from the unrearranged intermediate. If however, the base needed for the activation of the phenyboronic acid is buffered using for example cesium pivalate and pivalic acid in equimolecular amount and phenylboronic acid is replaced by its *p*-carbomethoxy derivative a 51:49 mixture of the two products (78% overall yield) is obtained. According to the authors the

preferred pathway implies a palladium(II) rather than a palladium(IV) intermediate (Scheme 44). As previously mentioned an electrophilic attack on the arene is not consistent with the acidity-dependent selectivity.



Scheme 44.

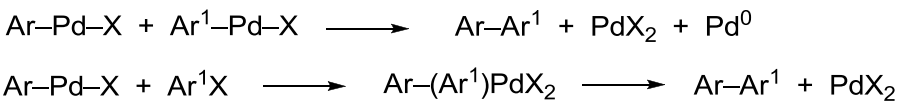
Larock has reported several reactions where he takes advantage of the migration process, for example the synthesis of 4-phenylfluorene[140] from 2-(3'-benzyl)phenyl iodobenzene and that of vinylcarbazoles[141] from *N*-(3-iodophenyl)anilines and alkynes. Vinylcarbazole formation has been proposed to proceed according to the pathway shown in Scheme 45. The vinylpalladium intermediate forms by oxidative addition of the aryl iodide and subsequent alkyne insertion. Cyclopalladation via selective *ortho* C–H bond activation, is then followed by cleavage of the vinyl-metal bond to afford the arylpalladium species. The result is a 1,4 migration of palladium which is now in an appropriate position for an intramolecular ring closure through activation of a second aromatic C–H bond leading to carbazole and palladium(0). A possible involvement of a palladium(IV) species in the hydrogen transfer from the aromatic to the vinyl moiety has been proposed.



Scheme 45.

6. General Considerations on the Mechanism of Arene C–H Arylation

We have seen specific mechanistic aspects of the various types of arene C–H arylation. Common problems refer to the mechanisms of C–H activation and C–C coupling. A study by Milstein on arene C–H activation has pointed out the importance of arene-bonded heteroatoms (Cl, OMe) in directing C–H activation towards the *o*-position.[142] Theoretical studies by Echavarren's group on aryl–aryl intramolecular coupling have shown that in many cases of intramolecular arene arylation substituent effects and kinetic isotopic effect are not compatible with the traditional electrophilic substitution mechanism and are best interpreted by a mechanism involving hydrogen abstraction by a base or by an appropriate ligand.[19] Experiments and theoretical calculations by Fagnou and coworkers have lent support to this interpretation.[22b] As to the aryl–aryl coupling process following arene C–H activation both transmetallation[143] and oxidative addition to give palladium(IV) have been postulated (Scheme 46).[131]



Scheme 46.

Theoretical calculations on a simplified model conducted by Cárdenas and Echavarren suggested that the latter process is not likely to occur.[144] Another recent paper by Grushin and Marshall also points to the inability of palladium(II) to undergo oxidative addition of unactivated aryl halides.[145] In fact under the reaction conditions palladium(II) is often reduced to palladium(0), which can undergo oxidative addition of an aryl halide to form an arylpalladium halide complex able to transmetallate. This specific point, however, has been considered more in detail in the next chapter of this thesis.

In this connection a recent study by Dedieu should be considered.[146] It has been shown that palladium migration from aryl to aryl, likely involving palladacycle formation,[138,139] may be favored by oxidative addition of an acid to the palladacycle, thus forming palladium(IV), if migration is 1,3 and through palladium(II)-catalyzed C–H activation-assisted by proton abstraction, if migration is 1,5 or 1,6; however, these pathways can compete in the case of 1,4 migration. The results indicate that very subtle effects can influence the energy of the transition state. In particular in the reaction of aryl halides in the presence of palladium and norbornene, initially involving the formation of a palladacycle by electrophilic activation of an unactivated

arene C–H, the final coupling could well involve a palladium(IV) intermediate particularly under the multistep catalytic conditions adopted.

As to the state of the "true palladium" catalyst undergoing oxidative addition and insertion, it has been shown that in most cases nanoparticles are formed, that may be in equilibrium with momeric or dimeric form of ligandless palladium complexes.[147–150] Evidence for low ligated Pd–L as the most active species undergoing oxidative addition has been provided by Amatore and Jutand.[151]

7. Conclusions

Research in the area of aryl–aryl coupling reactions continues to grow exponentially, spurred by the importance of practical applications particularly in the pharmaceutical field, and the synthetic and mechanistic challenges. Arene and heteroarene substrates have been arylated selectively through C–H activation reactions directed by chelation or by heteroatoms or by metallacycle formation. Research on catalytic systems hinges on design of homogeneous species on the one hand and of nanoparticles on the other as catalysts. This is a typical interdisciplinary area which will prove to become more and more fertile.

References

[1] F. Diederich, A. de Meijere (Eds.), Metal-Catalyzed Cross-Coupling Reactions, 2nd ed., Wiley-VCH, Weinheim, **2004**.
[2] E.-I. Negishi, A. de Meijere (Eds.), Handbook of Organopalladium Chemistry for Organic Synthesis, Wiley-Interscience, New York, **2002**. Vols. 1, 2.
[3] J.-P. Corbet, G. Mignani *Chem. Rev.* **2006**, *106*,2651.
[4] a) B. Cornils, W.A. Herrmann (Eds.), Applied Homogeneous Catalysis with Organometallic Compounds, 2nd ed., Wiley-VCH, Weinheim, **2002**; b) J. Tsuji (Ed.), Palladium Reagents and Catalysts: New Perspectives for the 21th Century, 2nd ed., Wiley, New York, **2004**; c) M. Beller, C. Bolm (Eds.), Transition Metals for Organic Synthesis; Building Block and Fine Chemicals, 2nd ed., Wiley-VCH, Weinheim, **2004**; d) L.F. Tietze, G. Brasche, K.M. Gericke, Domino Reactions in Organic Synthesis, Wiley- VCH, Weinheim, **2006**; e) K.C. Nicolau, P.G. Bulger, D. Sarlah *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[5] K. Godula, D. Sames *Science* **2006**, *312*, 67.
[6] G. Dyker (Ed.), Handbook of C–H Transformations, Wiley-VCH Verlag, Weinheim, Germany, **2005**.
[7] D. Alberico, M.E. Scott, M. Lautens *Chem. Rev.* **2007**, *107*, 174.
[8] F. Kakiuchi, N. Chatani *Adv. Synth. Catal.* **2003**, *345*, 1077.
[9] M. Miura, T. Satoh *Top. Organomet. Chem.* **2005**, *14*, 55.
[10] L.-C. Campeau, K. Fagnou *Chem. Commun.* **2006**, 1253.
[11] F. Kakiuchi, T. Kochi *Synthesis* **2008**, 3013.
[12] L. Ackermann, Modern Arylation Methods, Wiley-VCH, Weinheim **2009**.
[13] B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi *Angew. Chem. Int. Ed.* **2008**, *47*, 1115.

[14] D. Kalyani, M.S. Sanford *Top. Organometal. Chem.* **2008**, *24*, 85.
[15] K.I. Fujita, M. Nonogawa, R. Yamaguchi *Chem. Commun.* **2004**, 1926.
[16] S. Proch, R. Kempe *Angew. Chem. Int. Ed.* **2007**, *46*, 3135.
[17] G. Dyker, S. Borowski, J. Heiermann, J. Körning, K. Opwis, G. Henkel, M.J. Köckerling *J. Organomet. Chem.* **2000**, *606*, 108.
[18] M. Lafrance, K. Fagnou *J. Am. Chem. Soc.* **2006**, *128*, 16496.
[19] a) D. García-Cuadrado, A.A.C. Braga, F. Maseras, A.M. Echavarren *J. Am. Chem. Soc.* **2006**, *128*, 1066; b) D. García-Cuadrado, P. de Mendoza, A.A.C. Braga, F. Maseras, A.M. Echavarren *J. Am. Chem. Soc.* **2007**, *12*, 6880; c) S. Pascual, P. de Mendoza A.A.C. Braga, F. Maseras, A. Echavarren *Tetrahedron* **2008**, *64*, 6021.
[20] M. Lafrance, D. Lapointe, K. Fagnou *Tetrahedron* **2008**, *64*, 6015.
[21] M. Lafrance, D. Shore, K. Fagnou *Org. Lett.* **2006**, *8*, 5097.
[22] a) M. Lafrance, C.N. Rowley, T.K. Woo, K. Fagnou *J. Am. Chem. Soc.* **2006**, *128*, 8754; b) S.I. Gorelski, D. Lapointe, K. Fagnou *J. Am. Chem. Soc.* **2008**, *130*, 10848.; c) J. Oxgaard, W.J. Tenn III, R.J. Nielsen, R.A. Periana, W.A. Goddard, III *Organometallics* **2006**, *25*, 1565.
[23] D.E. Ames, D. Bull *Tetrahedron* **1982**, *38*, 383.
[24] a) A.E. Jensen, P. Knochel *J. Org. Chem.* **2002**, *67*, 79; b) M. Pérez-Rodríguez, A.A.C. Braga, M. Garcia-Melchor, M.H. Pérez-Temprano, J.A. Casares, G. Ujaque, A.R. de Lera, R. Álvarez, F. Maseras, P. Espinet *J. Am. Chem. Soc.* **2009**, *131*, 3650.
[25] a) D.E. Ames, A. Opalko *Synthesis* **1983**, 234;
(b) D.E. Ames, A. Opalko *Tetrahedron* **1984**, *40*, 1919.
[26] W.V. Konze, B.L. Scott, G.J. Kubas *J. Am. Chem. Soc.* **2002**, *124*, 12550.
[27] a) J. Cámpora, J.A. López, P. Palma, P. Valga, E. Spillner, E. Carmona *Angew. Chem. Int. Ed.* **2005**, *44*, 2142; b) J. Cámpora, E. Gutiérrez-Puebla, J.A. López, A. Monge, P. Palma, D. del Rio, E. Carmona *Angew. Chem. Int. Ed.* **2001**, *40*, 3641; c) C.-S. Li, C.-H. Cheng, F.-L. Liao, S.-L. Wang *Chem. Comm.* **1991**, 710; d) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P.S. Pregosin *J. Am. Chem. Soc.* **2002**, *124*, 4336.
[28] a) T. Harayama, H. Akamatsu, K. Okamura, T. Miyagoe, T. Akiyama, H. Abe, Y. Takeuchi *J. Chem. Soc. Perkin Trans. 1* **2001**, 523; b) T. Harayama, T. Akiyama, H. Akamatsu, K. Kawano, H. Abe, Y. Takeuchi *Synthesis* **2001**, 444.
[29] S. Hernandez, R. SanMartin, I. Tellitu, E. Dominguez *Org. Lett.* **2003**, *5*, 1095.
[30] J.C. Torres, A.C. Pinto, S.J. Garden *Tetrahedron* **2004**, *60*, 9889.
[31] T. Harayama, A. Hori, G. Serban, Y. Morikami, T. Matsumoto, H. Abe, Y. Takeuchi *Tetrahedron* **2004**, *60*, 10645.
[32] T. Harayama, Y. Morikami, A. Hori, H. Nishioka, H. Abe, Y. Takeuchi *Heterocycles* **2002**, *62*, 803.
[33] a) H. Nishioka, Y. Shoujiguchi, H. Abe, Y. Takeuchi, T. Harayama *Heterocycles* **2004**, *64*, 463; b) T. Harayama *Heterocycles* **2005**, *65*, 697.
[34] A.L. Bowie Jr., C.C. Hughes, D. Trauner *Org. Lett.* **2005**, *7*, 5207.
[35] G. Bringmann, T. Gulder, T.A.M. Gulder *Asymmetric Synthesis* **2007**, 246.
[36] G. Cuny, M. Bois-Choussy, J. Zhu *J. Am. Chem. Soc.* **2004**, *126*, 14475.
[37] T. Harayama, T. Sato, A. Hori, H. Abe, Y. Takeuchi *Synlett* **2003**, 1141.
[38] T. Harayama, A. Hori, H. Abe, Y. Takeuchi *Tetrahedron* **2004**, *60*, 1611.
[39] D.-M. Shen, C. Liu, Q.-Y. Chen *J. Org. Chem.* **2006**, *71*, 6508.
[40] R.B. Bedford, M. Betham, J.P.H. Charmant, A.L. Weeks *Tetrahedron* **2008**, *64*, 6038.
[41] L. Ackermann, A. Althammer *Angew. Chem. Int. Ed.* **2007**, *46*, 1627.
[42] C. Bressy, D. Alberico, M. Lautens *J. Am. Chem. Soc.* **2005**, *127*, 13148.
[43] C. Blaszykowski, E. Aktoudianakis, C. Bressy, D. Alberico, M. Lautens *Org. Lett.* **2006**, *8*, 2043.
[44] A. Martins, D. Alberico, M. Lautens *Org. Lett.* **2006**, *8*, 4827.
[45] B. Laleu, M. Lautens *J. Org. Chem.* **2008**, *73*, 9164.

[46] L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou *J. Am. Chem. Soc.* **2004**, *126*, 9186.
[47] L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou *J. Am. Chem. Soc.* **2006**, *128*, 581.
[48] L.-C. Campeau, P. Thansandote, K. Fagnou *Org. Lett.* **2005**, *7*, 1857.
[49] W. A. Herrmann *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.
[50] M. Parisien, D. Valette, K. Fagnou *J. Org. Chem.* **2005**, *70*, 7578.
[51] G.B. Bajracharya, O. Daugulis *Org. Lett.* **2008**, *10*, 4625.
[52] Y. Kawamura, T. Satoh, M. Miura, M. Nomura *Chem. Lett.* **1999**, *28*, 961.
[53] M. Catellani, G.P. Chiusoli, S. Ricotti *J. Organomet. Chem.* **1985**, *296*, C11.
[54] M. Catellani, G.P. Chiusoli *J. Organomet. Chem.* **1985**, *286*, C13.
[55] S.J. Tremont, H.U. Rahman *J. Am. Chem. Soc.* **1984**, *106*, 5759.
[56] O. Daugulis, V.G. Zaitsev *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.
[57] D. Shabashov, O. Daugulis *Org. Lett.* **2006**, *8*, 4947.
[58] A. Lazareva, O. Daugulis *Org. Lett.* **2006**, *8*, 5211.
[59] a) L. Ackermann, A. Althammer, R. Born *Tetrahedron* **2008**, *64*, 6115; b) L. Ackermann *Org. Lett.* **2005**, *7*, 3123.
[60] a) L. Ackermann, A. Althammer, R. Born *Angew. Chem. Int. Ed.* **2006**, *45*, 2619; b) L. Ackermann, A. Althammer, S. Fenner *Angew. Chem. Int. Ed.* **2009**, *48*, 201.
[61] L. Ackermann *Top. Organomet. Chem.* **2008**, *24*, 35.
[62] L. Ackermann, M. Mulzer *Org. Lett.* **2008**, *10*, 5043.
[63] a) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue *J. Org. Chem.* **2005**, *70*, 3113; b) S. Oi, R. Funayama, T. Hattori, Y. Inoue *Tetrahedron* **2008**, *64*, 6051.
[64] L. Ackermann, R. Vicente, A. Althammer *Org. Lett.* **2008**, *10*, 2299.
[65] A.I. Meyers, E.D. Mihelich *J. Am. Chem. Soc.* **1975**, *97*, 7383.
[66] N. Guerbuez, I. Oezdemir, B. Cetinkaya *Tetrahedron Lett.* **2005**, *46*, 2273.
[67] G. Casnati, G. Casiraghi, A. Pochini, G. Sartori, R. Ungaro *Pure Appl. Chem.* **1983**, *55*, 1677.
[68] H.A. Chiong, Q.-N. Pham, O. Daugulis *J. Am. Chem. Soc.* **2007**, *129*, 9879.
[69] a) P. Forgione, M.-C. Brochu, M. St-Onge, K.H. Thesen, M.D. Bailey, F. Bilodeau *J. Am. Chem. Soc.* **2006**, *128*, 11350; b) For decarboxylative coupling see J.-M. Becht, C. Catala, C. Le Drian, A. Wagner *Org. Lett.* **2007**, *9*, 1781.
[70] X.Wang, D.V. Gribkov, D. Sames *J. Org. Chem.* **2007**, *72*, 1476.
[71] Z. Zhang, Z. Hu, Z. Yu, P. Lei, H. Chi, Y. Wang, R. He *Tetrahedron Lett.* **2007**, *48*, 2415.
[72] a) C. Hoarau, A. Du Fou de Kerdaniel, N. Bracq, P. Grandclaudon, A. Couture, F. Marsais *Tetrahedron Lett.* **2005**, *46*, 8573; b) H.A. Chiong, O. Daugulis *Org. Lett.* **2007**, *9*, 1449.
[73] a) F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi, S. Viel *J. Org. Chem.* **2005**, *70*, 3997; b) F. Bellina, S. Cauteruccio, A. Di Fiore, C. Marchetti, R. Rossi *Tetrahedron* **2008**, *64*, 6060; c) D.R. Gauthier, Jr., J. Limanto, P.N. Devine, R.A. Desmond, R.H. Szumigala, Jr., B.S. Foster, R.P. Volante *J. Org. Chem.* **2005**, *70*, 5938.
[74] a) C.-H. Park, V. Ryabova, I.V. Seregin, A.W. Sromek, V. Gevorgyan *Org. Lett.* **2004**, *6*, 1159; b) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui, A. Mori *Org. Lett.* **2005**, *7*, 5083.
[75] B.S. Lane, M.A. Brown, D. Sames *J. Am. Chem. Soc.* **2005**, *127*, 8050.
[76] L. Joucla, L. Djakovitch *Adv. Synth. Catal.* **2009**, *351*, 673.
[77] M. Schnurch, R. Flasik, A.F. Khan, M. Spina, M.D. Mihovilovic, P. Stanetty *Eur. J. Org. Chem.* **2006**, 3283;
[78] L. Ackermann, R. Vicente, R. Born *Adv. Synth. Catal.* **2008**, *350*, 741.
[79] S. Chuprakov, N. Chernyak, A.S. Dudnik, V. Gevorgyan *Org. Lett.* **2007**, *9*, 2333.
[80] L. Ackermann, H.K. Potukuchi, D. Landsberg, R. Vicente *Org. Lett.* **2008**, *10*, 3081.
[81] Y. Kondo, T. Komine, T. Sakamoto *Org. Lett.* **2000**, *2*, 3111.
[82] B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou *J. Org. Chem.* **2009**, *74*, 1826.
[83] R. Goikhman, T.L. Jacques, D. Sames *J. Am. Chem. Soc.* **2009**, *131*, 3042.
[84] R.S. Sánchez, F.A. Zhuravlev *J. Am. Chem. Soc.* **2007**, *129*, 5824.

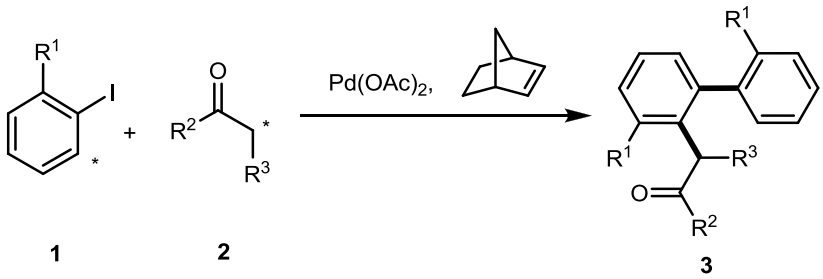
[85] C. Hilf, F. Bosold, K. Harms, M. Marsch, G. Boche *Chem. Ber./Recueil* **1997**, *130*, 1213.
[86] S. Yanagisawa, T. Sudo, R. Noyori, K. Itami *J. Am. Chem. Soc.* **2006**, *128*, 11748.
[87] S. Yanagisawa, T. Sudo, R. Noyori, K. Itami *Tetrahedron* **2008**, *64*, 6073.
[88] J.C. Lewis, J.Y. Wu, R.G. Bergman, J.A. Ellman *Angew. Chem. Int. Ed.* **2006**, *45*, 1589.
[89] Y. Terao, H. Wakui, M. Nomoto, T. Satoh, M. Miura, M. Nomura *J. Org. Chem.* **2003**, *68*, 5236.
[90] M. Nakano, T. Satoh, M. Miura *J. Org. Chem.* **2006**, *71*, 8309.
[91] T. Okazawa, T. Satoh, M. Miura, M. Nomura *J. Am. Chem. Soc.* **2002**, *124*, 5286.
[92] C. Peschko, C. Winklhofer, W. Steglich *Chem. Eur. J.* **2000**, *6*, 1147.
[93] M. Nakano, H. Tsurugi,T. Satoh, M. Miura *Org. Lett.* **2008**, *10*, 1851.
[94] a) A.M. Berman, J.C. Lewis, R.G. Bergman, J.A. Ellman *J. Am. Chem. Soc.* **2008**, *130*, 14926; b) J.C. Lewis, A.M. Berman, R.G. Bergman, J.A. Ellman *J. Am. Chem. Soc.* **2008**, *130*, 2493; c) J.C. Lewis, R.G. Bergman, J.A. Ellman *Acc. Chem. Res.* **2008**, *41*, 1013. d) J.C. Lewis, R.G. Bergman, J.A. Ellman *J. Am. Chem. Soc.* **2007**, *129*, 5332 and references therein.
[95] E. Alvarez, S. Conejero, M. Paneque, A. Petronilho, M.L. Poveda, O. Serrano, E. Carmona *J. Am. Chem. Soc.* **2006**, *128*, 13060.
[96] M.A. Esteruelas, F.J. Fernández-Alvarez, E. Oñate *J. Am. Chem. Soc.* **2006**, *128*, 13044.
[97] W. Jin, Z.Yu, W. He, W.Ye, W.-J. Xiao *Org. Lett.* **2009**, *11*, 1317.
[98] H.-Q. Do, O. Daugulis *J. Am. Chem. Soc.* **2007**, *129*, 12404.
[99] H.-Q. Do, R.M.K. Khan, O. Daugulis *J. Am. Chem. Soc.* **2008**, *130*, 15185.
[100] S. Yotphan, R.C. Bergman, J.A. Ellman *Org. Lett.* **2009**, *11*, 1511.
[101] J. Canivet, J. Yamaguchi, I. Ban, K. Itami *Org. Lett.* **2009**, *11*, 1733.
[102] H. Hachiya, K. Hirano, T. Satoh, M. Miura *Org. Lett.* **2009**, *11*, 1737.
[103] K. Godula, B. Sezen, D. Sames *J. Am. Chem. Soc.* **2005**, *127*, 3648.
[104] a) L.-C. Campeau, S. Rousseaux, K. Fagnou *J. Am. Chem. Soc.* **2005**, *127*, 18020; b) L.-C. Campeau, D.R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou *J. Am. Chem. Soc.* **2009**, *131*, 3291.
[105] M.P. Huestis, K. Fagnou *Org. Lett.* **2009**, *11*, 1357.
[106] J.A. Pool, B.L. Scott, J.L. Kiplinger *J. Am. Chem. Soc.* **2005**, *127*, 1338.
[107] a) G. Bocelli, M. Catellani, S. Ghelli *J. Organomet. Chem.* **1993**, *458*, C12; b) C. Amatore, M. Catellani, S. Deledda, A. Jutand, E. Motti *Organometallics* **2008**, *27*, 4549.
[108] M. Catellani, E. Motti *New J. Chem.* **1998**, *22*, 759.
[109] S. Deledda, E. Motti, M. Catellani *Can. J. Chem.* **2005**, *83*, 741.
[110] E. Motti, G. Ippomei, S. Deledda, M. Catellani *Synthesis* **2003**, 2671.
[111] M. Catellani, S. Deledda, B. Ganchegui, F. Hénin, E. Motti, J. Muzart *J. Organomet. Chem.* **2003**, *687*, 473.
[112] M. Catellani, E. Motti, S. Baratta *Org. Lett.* **2001**, *3*, 3611.
[113] E. Motti, A. Mignozzi, M. Catellani *J. Mol. Catal. A: Chemical* **2003**, *204–205*, 115.
[114] N. Della Ca', G. Maestri, M. Catellani *Chem. Eur. J.* **2009**, *15*, 7850.
[115] G. Maestri, N. Della Ca', M. Catellani *Chem. Comm.* **2009**, *45*, 4892.
[116] G. Dyker *Angew. Chem. Int. Ed.* **1994**, *33*, 103.
[117] G. Dyker *Angew. Chem. Int. Ed.* **1992**, *31*, 1023.
[118] D.J. Cárdenas, C. Mateo, A.M. Echavarren *Angew. Chem. Int. Ed.* **1994**, *33*, 2445.
[119] a) G. Dyker, A. Kellner *Tetrahedron Lett.* **1994**, *35*, 7633; b) G. Dyker, A. Kellner *J. Organomet. Chem.* **1998**, *555*, 141.
[120] R.C. Larock, Q. Tian *J. Org. Chem.* **2001**, *66*, 7372.
[121] P. Mauleón, A.A. Núñez, I. Alonso, J.C. Carretero *Chem. Eur. J.* **2003**, *9*, 1511.
[122] a) O. Reiser, M. Weber, A. de Meijere *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1037; b) K. Albrecht, O. Reiser, M. Weber, B. Knieriem, A. de Meijere *Tetrahedron* **1994**, *50*, 383.
[123] M. Catellani, G.P. Chiusoli, C. Castagnoli *J. Organomet. Chem.* **1991**, *407*, C30.
[124] M. Catellani, E. Motti, L. Paterlini *J. Organomet. Chem.* **2000**, *594*, 240.

[125] A. de Meijere, S. Bräse *J. Organomet. Chem.* **1999**, *576*, 88.
[126] F. Faccini, E. Motti, M. Catellani *J. Am. Chem. Soc.* **2004**, *126*, 78.
[127] E. Motti, F. Faccini, I. Ferrari, M. Catellani, R. Ferraccioli *Org. Lett.* **2006**, *8*, 3967.
[128] N. Della Ca', E. Motti, M. Catellani *Adv. Synth. Catal.* **2008**, *350*, 2513.
[129] N. Della Ca', G. Sassi, M. Catellani *Adv. Synth. Catal.* **2008**, *350*, 2179.
[130] R. Ferraccioli, D. Carenzi, O. Rombola, M. Catellani *Org. Lett.* **2004**, *6*, 4759.
[131] M. Catellani, E. Motti, N. Della Ca' *Acc. Chem. Res.* **2008**, *41*, 1512.
[132] R. Ferraccioli, D. Carenzi, E. Motti, M. Catellani *J. Am. Chem. Soc.* **2006**, *128*, 722.
[133] S. Caddick. W. Kofie *Tetrahedron Lett.* **2002**, *43*, 9347.
[134] T. Furuta, Y. Kitamura, A. Hashimoto, S. Fujii, K. Tanaka, T. Kan *Org. Lett.* **2007**, *9*, 183.
[135] G. Bocelli, M. Catellani, G.P. Chiusoli, S. Larocca *J. Organomet. Chem.* **1984**, *265*, C9.
[136] S. Ma, Z. Gu *Angew. Chem. Int. Ed.* **2005**, *44*, 7512.
[137] G. Karig, M.-T. Moon, N. Thasana, T. Gallagher *Org. Lett.* **2002**, *4*, 3115.
[138] M.A. Campo, R.C. Larock *J. Am. Chem. Soc.* **2002**, *124*, 14326.
[139] M.A. Campo, H. Zhang, T. Yao, A. Ibdah, R.D. McCulla, Q. Huang, J. Zhao, W.S. Jenks, R.C. Larock *J. Am. Chem. Soc.* **2007**, *129*, 6298.
[140] M.A. Campo, Q. Huang, T. Yao, Q. Tian, R.C. Larock *J. Am. Chem. Soc.* **2003**, *125*, 11506.
[141] J. Zhao, R.C. Larock *Org. Lett.* **2005**, *7*, 701.
[142] E. Ben-Ari, R. Cohen, M. Gandelman, L.J.W. Shimon, J.M.L. Martin, D. Milstein, *Organometallics* **2006**, *25*, 3190.
[143] a) F. Ozawa, T. Hidaka, T. Yamamoto, A. Yamamoto *J. Organomet. Chem.* **1987**, *330*, 253; b) F. Ozawa, M. Fujimori, T. Yamamoto, A. Yamamoto *Organometallics* **1986**, *5*, 2144.
[144] D.J. Cárdenas, B. Martín-Matute, A.M. Echavarren *J. Am. Chem. Soc.* **2006**, *128*, 5033.
[145] V.V. Grushin, W.J. Marshall *J. Am. Chem. Soc.* **2006**, *128*, 4632.
[146] A.J. Mota, A. Dedieu *Organometallics* **2006**, *25*, 3130.
[147] a) A.H.M. de Vries, J.M.C.A. Mulders, J.H.M. Mommers, H.J.W. Henderickx, J.G. de Vries *Org. Lett.* **2003**, *5*, 3285; b) J.G. de Vries *Dalton Trans.* **2006**, 421.
[148] N.T.S. Phan, M. Van Der Sluys, C.W. Jones *Adv. Synth. Catal.* **2006**, *348*, 609.
[149] a) M.T. Reetz, E. Westermann *Angew. Chem. Int. Ed.* **2000**, *39*, 165; b) A. Alimardanov, L. Schmieder-van de Vondervoort, A.H.M. de Vries, J.G. de Vries *Adv. Synth. Catal.* **2004**, *346*, 1812.
[150] D. Astruc *Inorg. Chem.* **2007**, *46*, 1884.
[151] C. Amatore, A. Jutand *Acc. Chem. Res.* **2000**, *33*, 314.

A catalytic synthesis of selectively substituted biaryls through activation of an aromatic and an aliphatic C–H bond in sequence

Palladium possesses a remarkable ability in providing easy routes to intermolecular coupling through direct activation of aromatic and aliphatic C–H bonds.[1] Direct C–H functionalization has the great advantage, over the conventional methods, of avoiding the use of functionalized starting materials.

Herein we wish to report the direct α-arylation of ketones by a biarylylpalladium species formed *in situ* under the control of palladium and norbornene.[2] The reaction depicted in Scheme 1 offers a very simple access to α-arylated ketones by attack of selectively substituted biaryl moieties. Palladium-catalyzed α-arylation of ketones by direct cross-coupling of aryl halides with ketones is an important topic which has received much attention and successful methods have been reported.[3] The synthesis here described, however, allows the construction of a biarylylpalladium species before the reaction with ketones. The resulting products **3** contain the biaryl and the α-aryl carbonyl units, both present in many organic compounds with interesting pharmacological and biological properties.[3j]

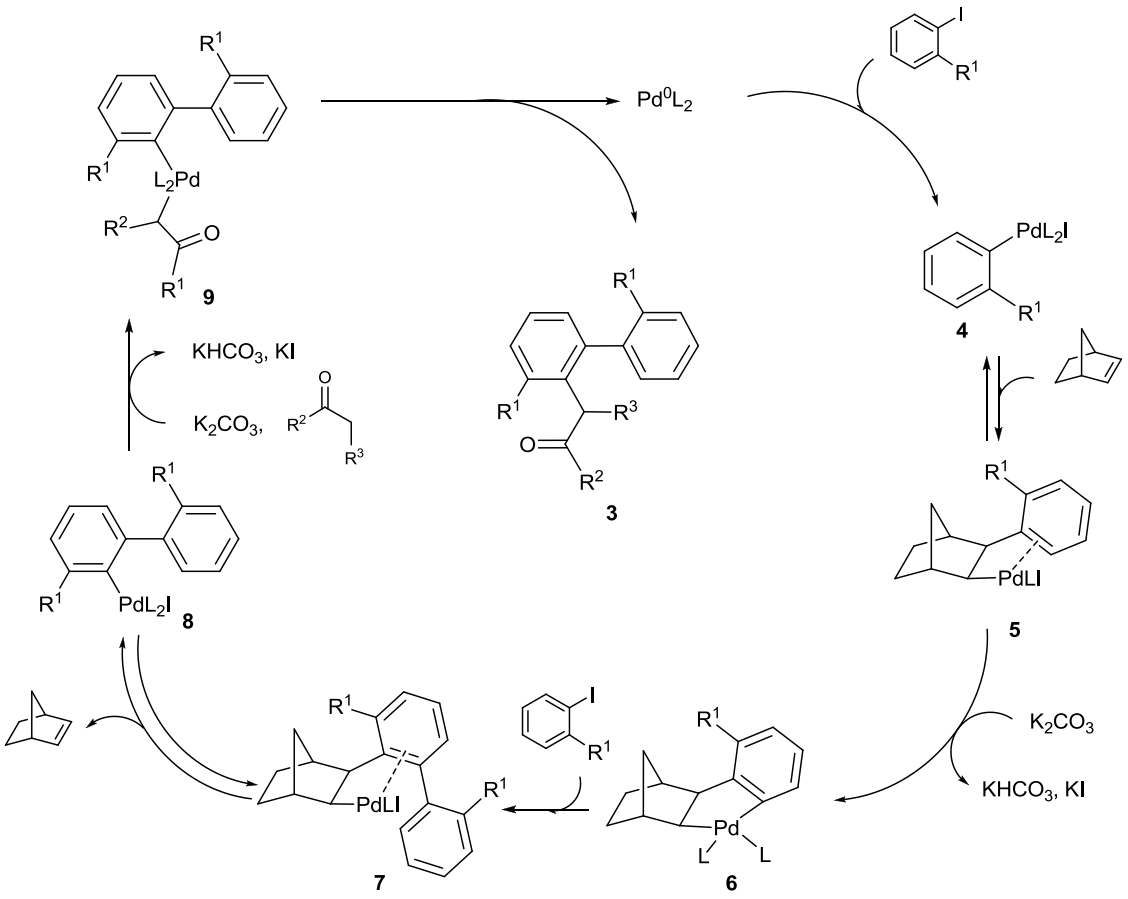


Scheme 1. α-Arylation of ketones by coupling with a biphenylyl group formed *in situ*

Thus, the reaction of an *ortho*-substituted aryl iodide (1.0 equiv) and a ketone (1.25 equiv) in the presence of $Pd(OAc)_2$ (0.025 equiv), norbornene (0.25 equiv), K_2CO_3 (1.1 equiv) and KOPh (0.1 equiv) as bases in DMF at 105 °C under nitrogen leads to formation of compound **3** (Scheme 1). Selected results and reaction conditions are reported in Table 1.

The reaction course, shown in Scheme 2, is explained by the initial formation of the arylpalladium iodide **4** by oxidative addition of one molecule of the iodoarene to palladium(0),[4] formed *in situ* from $Pd(OAc)_2$. Stereoselective norbornene insertion into the arylpalladium bond of **4** leads to the *cis,exo*-arylnorbornylpalladium species **5**[5], from which palladacycle **6**[6] is formed through aromatic C–H activation[7]. Reaction of a second molecule

of iodoarene takes place selectively at the aromatic site of palladacycle **6** giving rise to an intermolecular aryl-aryl coupling, which leaves palladium bonded to the norbornyl ring (complex **7**). At this stage, likely due to the steric hindrance created by the two *ortho* substituents present in the aromatic ring, norbornene deinsertion occurs with formation of a biphenylylpalladium complex **8**,[2] which finally reacts with the ketone through complex **9**. For the selective intermolecular aryl-aryl coupling the presence of an *ortho* substituent in the aryl iodide, or a condensed ring as in 1-iodonaphthalene, is required since the absence of such a substituent leads to a different reaction pathway involving attack of the aryl iodide on the norbornyl site of palladacycle **6**.[8]



Scheme 2 Proposed reaction pathway for the sequential aromatic and aliphatic couplings. L indicates any (weakly) coordinating species present in the reaction mixture.

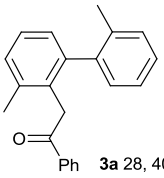
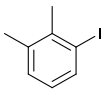
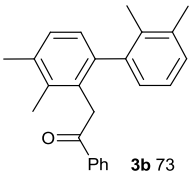
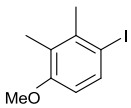
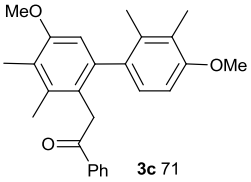
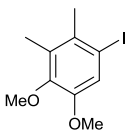
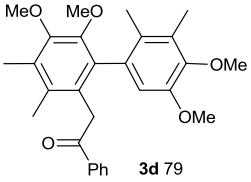
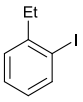
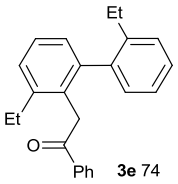
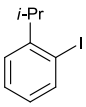
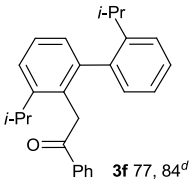
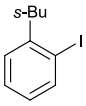
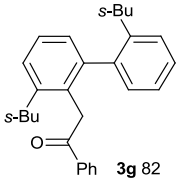
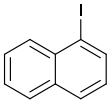
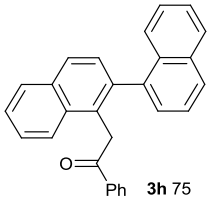
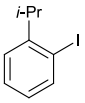
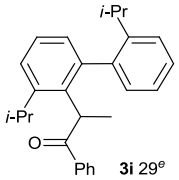
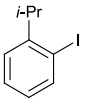
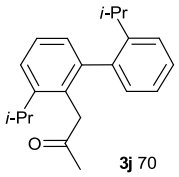
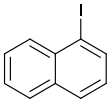
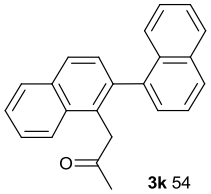
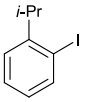
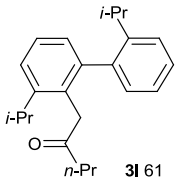
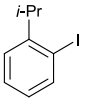
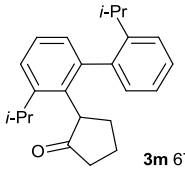
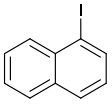
Entry[a]	Aryl iodide **1**	Ketone **2**	*t*/h	Product **3** yield (%)[b]
1			7, 17[c]	 **3a** 28, 40[c]
2			48	 **3b** 73
3			48	 **3c** 71
4			48	 **3d** 79
5			16	 **3e** 74
6			16, 21[d]	 **3f** 77, 84[d]
7			14	 **3g** 82
8			16	 **3h** 75
9			21	 **3i** 29[e]
10			7	 **3j** 70
11			16	 **3k** 54
12			17	 **3l** 61
13			7	 **3m** 67
14			6	**3n** 71

Table 1. Reaction of *o*-substituted aryl iodides with ketones. [a]Reaction conditions: see experimental section. [b] Isolated yield. [c] Yield increased to 40% on dilution (22 mL of DMF). [d] 0.012 mmol $Pd(OAc)_2$ were used. [e] 24% of 2,3'-di-*i*-propyl-1,1'-biphenyl and 30% of (*E*)-3-(2',3-di-*i*-propylbiphenyl-2-yl)-1-phenylprop-2-en-1-one were also present.

It should be added that the key-step leading to palladacycle **6** formation occurs through the catalytic cooperation of norbornene, which is liberated again after the reaction of the second molecule of aryl iodide. This allows the use of half the stoichiometric amount of norbornene. Strong ligands such as tertiary phosphines or carbenes are not used, weakly coordinating ligands such as reagents and solvent, being sufficient to keep the process going.[4c,9]

In view of the many steps involved the substituent effect can only be broadly indicated, detailed mechanistic conclusions awaiting further study. In general the reaction is favored by ortho bulky substituents in the aryl iodide, but also the rate of the final step remarkably influences the outcome. Some comparison are in point: *o*-iodotoluene gives a low yield because of secondary reactions causing palladium precipitation (entry 1), but if more methyl or methoxy groups are present in the arene better yields are obtained (entries 2-4). The higher electron availability, however, causes the formation of by-products deriving from the known reactivity of aryl iodides with ketones[3] in the absence of norbornene (15 and 13% of the corresponding 2-arylated-1-phenylethanone, entries 3 and 4, respectively). The best results were obtained with substituents in *ortho* such as the isopropyl group (only 4% of the main by-product, 84% yield of product **3**, entry 6) or the *sec*-butyl group (82% of **3**, entry 7).[10] Minor amounts of by-products containing the norbornane unit derive from competitive reactions already described in chapter 1 and in our previous works.[2] The basicity conditions reported here (with 10% potassium phenoxide[11] added to potassium carbonate) are essential to keep their percentage at low level (of ca. 3%). The presence in the ketone of substituents affecting its reactivity both sterically and electronically turns out to be very important because a slow final step allows other competitive reactions to predominate. Acetophenone gave the best results (entry 6) while camphor did not react. Also, cyclopentanone gave satisfactory results (entries 13 and 14) while cyclohexanone was not reactive. More activated species such as malonates and acetoacetates inhibited the reaction. The reaction leads to stereoisomers in the presence of stereogenic centers (entry 7) and to atropoisomers in the presence of sufficiently bulky groups (entries 7, 9 and 14), as ascertained by NMR.

The result obtained with propiophenone (entry 9) deserves a brief comment, the expected product **3** being obtained only in 29% yield. Two by-products, 2,3'-di-*i*-propyl-1,1'-biphenyl and (*E*)-3-(2',3-di-*i*-propylbiphenyl-2-yl)-1-phenylprop-2-en-1-one, were isolated in 24% and 30% yield, respectively. They both derive, directly or indirectly, from complex **9** (Scheme 2) which undergoes β-hydrogen elimination of the σ-bonded oxoalkyl group[3g] and hydrogenolysis of the palladium-aryl bond[12] to give phenyl vinyl ketone and 2,3'-di-*i*-propyl-1,1'-biphenyl. The newly formed unsaturated ketone then reacts with complex **8** to afford the second by-product according to a Heck-type reaction previously reported by us.[13]

In conclusion we have achieved a highly selective synthesis of biaryls, containing an oxoalkyl chain, starting from aryl iodides and ketones in one pot reaction. The reaction leads to satisfactory results using palladium and norbornene as catalysts in the absence of sterically

hindered chelating phosphine and carbene ligands, which are usually required for palladium-catalyzed direct α-arylation of ketones.

References and notes

[1] a) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**; b) J. Tsuji, *Palladium in Organic Synthesis*, Springer, Berlin, **2005**; c) G. Dyker, *Handbook of C–H Transformations*, Wiley-VCH Verlag, Weinheim, Germany, **2005**; d) D. Alberico, M. E. Scott, M. Lautens *Chem. Rev*., **2007**, *107*, 174; e) L. Ackerman, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.
[2] a) M. Catellani *Top. Organomet. Chem*., **2005**, *14*, 21; b) M. Catellani, E. Motti, N. Della Ca' *Acc. Chem. Res*., **2008**, *41*, 1512.
[3] a) M. Palucki, S. L. Buchwald *J. Am. Chem. Soc*., **1997**, *119*, 11108; b) B. C. Hamann , J. F. Hartwig *J. Am. Chem. Soc*., **1997**, *119*, 12382; c) T. Satoh, Y. Kawamura, M. Miura, M. Nomura *Angew. Chem. Int. Ed*., **1997**, *36*, 1740; d) D. A. Culkin, J. F. Hartwig *Acc. Chem. Res*., **2003**, *36*, 234; e) M. Miura, T. Satoh *Top. Organomet. Chem*., **2005**, *14*, 55; f) A. Ehrentraut, A. Zapf, M. Beller *Adv. Synth. Catal*., **2002**, *344*, 209; g) M. S. Viciu, R. F. Germaneau, S. P. Nolan *Org. Lett*., **2002**, *4*, 4053; h) F. Churruca, R. SanMartin, M. Carril, I. Tellitu, E. Domínguez *Tetrahedron*, **2004**, *60*, 2393; i) L. Ackermann, J. H. Spatz, C. J. Gschrei, R. Born, A. Althammer *Angew. Chem. Int. Ed*., **2006**, *45*, 7627; j) G. A. Grasa, T. J. Colacot *Org. Process Res. Dev*., **2008**, *12*, 522.
[4] a) P. Fitton, E. A. Rick *J. Organomet. Chem*., **1971**, *28*, 287; b) A. H. Roy, J. F. Hartwig *J. Am. Chem. Soc*., **2003**, *125*, 13944; c) C. Amatore, A. Jutand *Acc. Chem. Res*., **2000**, *33*, 314.
[5] a) H. Horino, M. Arai, N. Inoue *Tetrahedron Lett*., **1974**, 647; b) C.-S. Li, C.-H. Cheng, F.-L. Liao, S.-L. Wang *Chem. Commun*., **1991**, 710; c) M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein *Organometallics*, **1994**, *13*, 3465; d) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin *J. Am. Chem. Soc*., **2002**, *124*, 4336.
[6] a) I. P. Beletskaya, A. V. Cheprakov *J. Organometal. Chem*., **2004**, *689*, 4055; b) M. Catellani, G. P. Chiusoli *J. Organomet. Chem.*, **1992**, *425*, 151; c) M. Catellani, G. P. Chiusoli *J. Organomet. Chem.*, **1988**, *346*, C27; d) C.-H. Liu, C.-S. Li, C.-H. Cheng *Organometallics*, **1994**, *13*, 18.
[7] a) G. Dyker *Angew. Chem. Int. Ed*., **1999**, *38*, 1699; b) F. Kakiuchi, N. Chatani *Adv. Synth. Catal*., **2003**, *345*, 1077; c) A. R. Dick, M. S. Sanford *Tetrahedron*, **2006**, *62*, 2439.
[8] M. Catellani, E. Motti *New J. Chem.*, **1998**, *22*, 759.
[9] a) A. Jutand *Pure Appl. Chem*., **2004**, *76*, 565; b) C. Amatore, E. Carr, A. Jutand, Y. Medjour *Organometallics*, **2002**, *21*, 4540.
[10] O. Navarro, N. Marion, Y. Oonishi, R. A. Kelly, S. P. Nolan *J. Org. Chem*., **2006**, *71*, 685.
[11] Buchwald added phenol to the basic mixture. J. L. Rutherford, M. P. Rainka, S. L. Buchwald *J. Am. Chem. Soc*., **2002**, *124*, 15168.
[12] S. Deledda, E. Motti, M. Catellani *Can. J. Chem*., **2005**, *83*, 741.
[13] E. Motti, G. Ippomei, S. Deledda, M. Catellani *Synthesis*, **2003**, 2671.

Experimental section

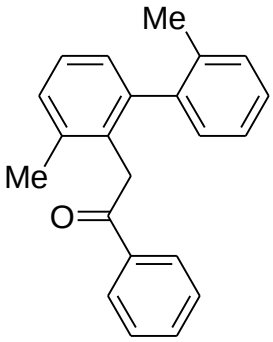
General remarks

Most chemicals were obtained from commercial suppliers and were used without further purification. 2-*i*-Propyliodobenzene and 4-methoxy-2,3-dimethyliodobenzene were prepared by iodination of the corresponding diazonium salt according to the literature.[1] 4,5-Dimethoxy-2,3-dimethyliodobenzene was prepared as previously described.[2] DMF was dried and stored over 4 Å molecular sieves under nitrogen. 2,3'-Di-*i*-propyl-1,1'-biphenyl[3] was identified by comparison with the data reported in the literature. Reactions were carried out under nitrogen by use of conventional standard Schlenk techniques. Flash column chromatography was performed on Merck Kieselgel 60 and thin layer chromatography on Merck $60F_{254}$ silica plates. Gas chromatography analyses were run with a Carlo Erba HRGC 5300 instrument using a 30 m SE-30 capillary column. ^{1}H and ^{13}C NMR spectra were recorded at 293 K, in $CDCl_3$ on a Bruker AC-300 and AVANCE 300 spectrometers at 300.1 and 75.4 MHz, respectively. ^{1}H and ^{13}C chemical shifts are given in ppm using the solvent as internal reference (7.26 and 77.0 ppm respectively for ^{1}H and ^{13}C). The reported assignments are based on decoupling, COSY, NOESY, C–H, HMBC correlation experiments. MS spectra (EI, 70eV) were performed on a Hewlett Packard HP 6890 GC system equipped with a SE-52 capillary column and a HP5973 Mass Selective Detector mass analyzer and are reported as *m/z* (relative intensity). IR spectra were recorded on a Nicolet FT-IR 5700 spectrophotometer (Thermo Electron Corporation) and are reported in wave numbers (cm^{-1}). Melting points were determined with an Electrothermal apparatus and are uncorrected. Elemental analyses were performed with a Carlo Erba EA 1108-Elemental Analyzer.

General procedure for the reaction of ortho-substituted aryl iodides and ketones

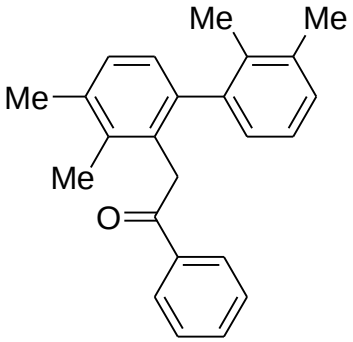
A Schlenk-type flask containing a magnetic stirring bar was charged under nitrogen with the corresponding aryl iodide (1 mmol), palladium acetate (5.6 mg, 0.025 mmol), norbornene (23.5 mg, 0.25 mmol), the desired ketone (1.25 mmol), potassium phenoxide (13.2 mg, 0.10 mmol), potassium carbonate (152 mg, 1.10 mmol) and DMF (11 mL). The resulting mixture was stirred at 105 °C for 6–48 h. At the end of the reaction the mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times with a solution of NaCl (3 × 30 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude reaction mixture was analyzed by GC and ^{1}H NMR spectroscopy. Products were isolated by flash column chromatography on silica gel using a mixture of hexane-EtOAc 95:5 as eluent.

3,2'-Dimethyl-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3a**)



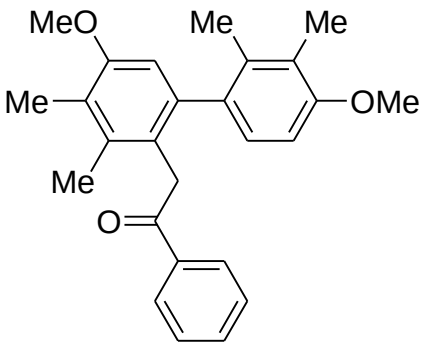
Yield 28% (42 mg); colorless oil. ^{1}H NMR: δ 7.82 (dt, *J* = 7.2, 1.5 Hz, 2H), 7.54 (tt, *J* = 7.2, 1.5 Hz, 1H), 7.41 (tt, *J* = 7.3, 1.5 Hz, 2H), 7.32–7.06 (m, 7H), 4.27 (d, *J* = 17.7 Hz, 1H), 4.04 (d, *J* = 17.7 Hz, 1H), 2.32 (s, 3H), 2.11 (s, 3H); ^{13}C NMR: δ 197.3, 142.3, 141.3, 137.6, 137.0, 135.8, 132.8, 132.0, 129.9, 129.4, 129.1, 128.4, 127.8, 127.2, 127.1, 126.6, 125.4, 40.3, 20.4, 20.0; IR (film, cm^{-1}): 1687; MS (%): M^{+} 300 (20), *m/z* 195 (12), 178 (30), 165 (34), 105 (100), 77 (39), 51 (16). Anal. Calcd. for $C_{22}H_{20}O$: C 87.96; H 6.71. Found: C 87.82; H 6.76.

3,4,2',3'-Tetramethyl-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3b**)



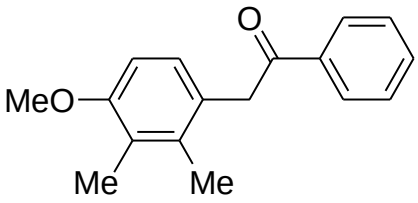
Yield 73% (120 mg); colorless oil. ^{1}H NMR: δ 7.84–7.79 (m, 2H), 7.54 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.44–7.38 (m, 2H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.09 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.97 (br d, *J* = 7.6 Hz, 2H), 4.31 (d, *J* = 17.7 Hz, 1H), 4.06 (d, *J* = 17.7 Hz, 1H), 2.40 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H), 1.98 (s, 3H); ^{13}C NMR: δ 197.5, 141.8, 140.8, 137.0, 136.9, 136.0, 135.5, 134.6, 132.7, 131.9, 128.6, 128.3, 127.8, 127.4, 126.8, 125.0, 40.7, 20.8, 20.4, 16.7, 16.4; IR (film, cm^{-1}): 1689; MS (%): M^{+} 328 (20), *m/z*; 223 (24), 208 (23), 193 (41), 105 (100), 77 (42). Anal. Calcd. for $C_{24}H_{24}O$: C 87.76; H 7.37. Found: C 87.67; H 7.41.

3,4,2',3'-Tetramethyl-5,4'-dimethoxy-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3c**)



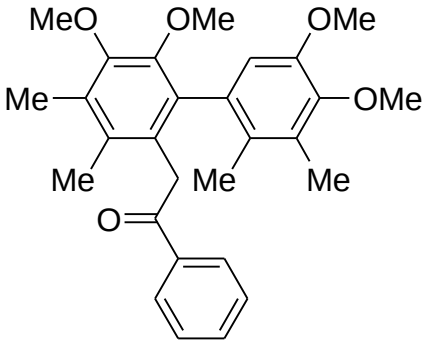
Yield 71% (138 mg); white solid; m.p. (*n*-hexane): 158–159 °C. ^{1}H NMR: δ 7.81–7.76 (m, 2H), 7.50 (t, *J* = 7.3 Hz, further split, 1H), 7.41–7.35 (m, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 4.20 (d, *J* = 17.8 Hz, 1H), 3.95 (d, *J* = 17.8 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.24 (s, 3H), 2.14, 2.13 (2s, 6H), 1.97 (s, 3H); ^{13}C NMR: δ 198.1, 156.5, 155.9, 140.8, 137.1, 137.0, 135.9, 134.7, 132.7, 128.3, 127.9, 127.2, 125.0, 124.6, 124.0, 109.8, 107.3, 55.5, 55.4, 40.5, 17.2, 16.9, 12.2, 12.0; IR (KBr, cm^{-1}): 1688; MS (%): M^{+} 388 (25), *m/z* 283 (100), 268 (53), 253 (40), 237 (21), 105 (59), 77 (54), 51 (19). Anal. Calcd. for $C_{26}H_{28}O_3$: C 80.38; H 7.26. Found: C 80.28; H 7.33.

2-(4-Methoxy-2,3-dimethylphenyl)-1-phenylethanone



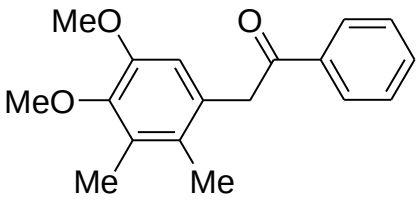
Yield 15% (38 mg); white solid; m.p. (*n*-hexane): 116–117 °C. ^{1}H NMR: δ 7.86 (d, *J* = 7.0 Hz, further split, 2H), 7.59 (t, *J* = 7.3 Hz, further split, 1H), 7.49 (m, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.31 (s, 2H), 3.82 (s, 3H), 2.21 (s, 3H), 2.15 (s, 3H); ^{13}C NMR: δ 197.9, 156.6, 136.8, 136.6, 133.0, 128.6, 128.2, 128.0, 125.5, 125.4, 107.7, 55.4, 43.7, 16.2, 12.1; IR (KBr, cm^{-1}): 1677; MS (%): M^{+} 254 (21), *m/z* 149 (100), 105 (18), 91 (14), 77 (18). Anal. Calcd. for $C_{17}H_{18}O_2$: C 80.28; H 7.13. Found: C 80.14; H 7.19.

3,4,2',3'-Tetramethyl-5,6,4',5'-tetramethoxy-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3d**)



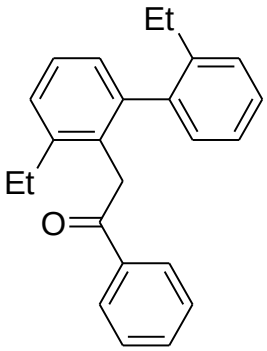
Yield 79% (175 mg); white solid; m.p. (*n*-hexane): 166–167 °C. ^{1}H NMR: δ 7.75–7.71 (m, 2H), 7.51 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.40–7.34 (m, 2H), 6.52 (s, 1H), 4.09 (d, *J* = 17.8 Hz, 1H), 3.86 (d, *J* = 17.8 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.60, 3.59 (2s, 6H), 2.31 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 1.87 (s, 3H); ^{13}C NMR: δ 197.9, 150.0, 149.9, 148.2, 146.1, 136.9, 134.6, 132.9, 132.7, 132.4, 130.6, 130.2, 128.4, 127.7, 111.1, 60.4, 60.2, 60.1, 55.3, 40.5, 16.6 , 12.8, 12.6; IR (KBr, cm^{-1}): 1684; MS (%): M^{+} 448 (31), *m/z*; 343 (50), 328 (19), 312 (64), 297 (26), 281 (21), 105 (100), 77 (71). Anal. Calcd. for $C_{28}H_{32}O_5$: C 74.97; H 7.19. Found: C 75.08; H 7.23.

2-(4,5-Dimethoxy-2,3-dimethylphenyl)-1-phenylethanone



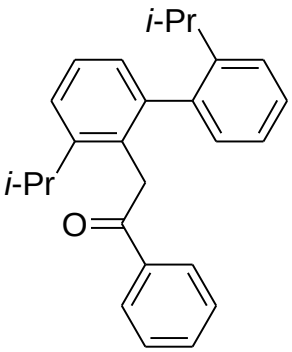
Yield 13% (37 mg); white solid; m.p. (*n*-hexane): 143–144 °C. ^{1}H NMR: δ 8.05 (d, *J* = 7.3 Hz, further split, 2H), 7.59 (t, *J* = 7.3 Hz, further split, 1H), 7.48 (t, *J* = 7.2 Hz, further split, 2H), 6.59 (s, 1H), 4.31 (s, 2H), 3.80, 3.79 (2s, 6H), 2.24 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: δ 197.4, 150.1, 146.0, 136.6, 133.0, 130.9, 128.5, 128.3, 128.2, 128.0, 111.9, 60.1, 55.4, 43.9, 15.5, 12.6; IR (KBr, cm^{-1}): 1683; MS (%): M^{+} 284 (24), *m/z* 179 (100), 105 (19), 91 (10), 77 (22). Anal. Calcd. for $C_{18}H_{20}O_3$: C 76.03; H 7.09. Found: C 75.93; H 7.13.

3,2'-Diethyl-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3e**)



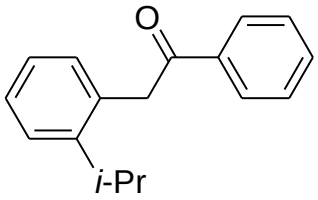
Yield 74% (121 mg); colorless oil. ^{1}H NMR: δ 7.77 (d, *J* = 7.2 Hz, further split, 2H), 7.52 (tt, *J* = 7.2, 1.6 Hz, 1H), 7.39 (tt, *J* = 7.2, 1.6 Hz, 2H), 7.36–7.18 (m, 4H), 7.12–7.06 (m, 3H), 4.28 (d, *J* = 17.7 Hz, 1H), 4.01 (d, *J* = 17.7 Hz, 1H), 2.61 (q, *J* = 7.2 Hz, 2H), 2.41 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: δ 197.6, 143.1, 142.2, 141.8, 140.9, 137.0, 132.8, 131.4, 129.6, 128.4, 128.1, 127.8, 127.4, 127.3, 127.0, 126.6, 125.3, 39.8, 26.3, 26.0, 15.1, 14.6; IR (film, cm^{-1}): 1690; MS (%): M^{+} 328 (16), *m/z*; 178 (18), 165 (20), 105 (100), 77 (33). Anal. Calcd. for $C_{24}H_{24}O$: C 87.76; H 7.37. Found: C 87.64; H 7.43.

3,2'-Di-i-propyl-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3f**)



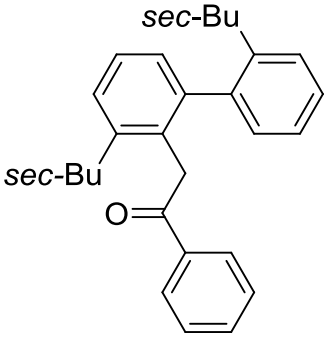
Yield 84% (150 mg); colorless oil. ^{1}H NMR: δ 7.83–7.77 (m, 2H), 7.58–7.50 (m, 1H), 7.46–7.24 (m, 6H), 7.12–7.06 (m, 3H), 4.32 (d, *J* = 18.0 Hz, 1H), 4.11 (d, *J* = 18.0 Hz, 1H), 2.89, 2.82 (2hept, *J* = 6.8 Hz, 2H), 1.31, 129 (2d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ 197.2, 148.1, 146.6, 142.2, 140.5, 137.0, 132.8, 130.5, 129.6, 128.4, 127.8, 127.6, 127.2, 126.6, 125.4, 125.2, 124.3, 39.8, 30.2, 29.7, 24.8, 24.0, 23.9, 23.3; IR (film, cm^{-1}): 1690; MS (%): M^{+} 356 (42), *m/z* 313 (17), 237 (15), 207 (22), 191 (11), 178 (13), 167 (20), 105 (100), 77 (28), 43 (12). Anal. Calcd. for $C_{26}H_{28}O$: C 87.60; H 7.92. Found: C 87.48; H 7.97.

2-(2-i-Propylphenyl)-1-phenylethanone



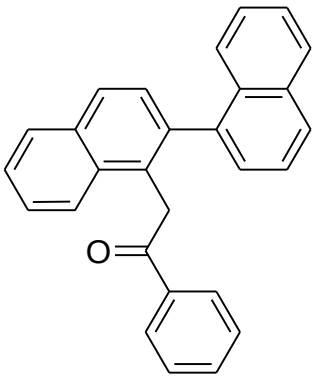
Yield 4% (10 mg); colorless oil. ^{1}H NMR: δ 8.09 (d, *J* = 7.2 Hz, further split, 2H), 7.62 (t, *J* = 7.3 Hz, further split, 1H), 7.58–7.29 (m, 4H), 7.24–7.12 (m, 2H), 4.42 (s, 2H), 3.02 (hept, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR: δ 197.7, 147.3, 136.8, 133.0, 131.7, 130.6, 128.6, 128.2, 127.5, 125.7, 125.4, 42.9, 29.5, 23.6; IR (film, cm^{-1}): 1691; MS (%): M^{+} 238 (15), *m/z* 105 (100), 77 (33). Calcd. for $C_{17}H_{18}O$: C 85.67; H 7.61. Found: C 85.58; H 7.66.

3,2'-Di-sec-butyl-2-(2-oxo-2-phenylethyl)-1,1'-biphenyl (**3g**)



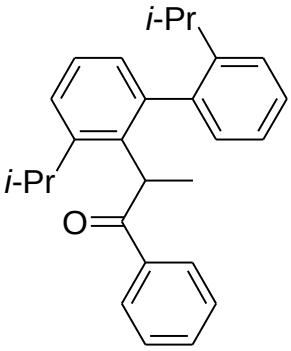
Yield 82% (157 mg); pale yellow oil. A 1:1:1:1 mixture of four stereoisomers. ^{1}H NMR: δ 7.82–7.73 (m, 2H), 7.56–7.48 (m, 1H), 7.43–7.21 (m, 6H), 7.09–6.98 (m, 3H), 4.26, 4.22, 4.21 (3d, *J* = 18.0 Hz, 1H), 4.04, 4.03, 3.99 (3d, *J* = 18.0 Hz, 1H), 2.60–2.42 (m, 2H), 1.78–1.42 (m, 4H), 1.28–1.16 (m, 3H), 1.11, 1.10, 1.08, 0.99 (4d, *J* = 6.9 Hz, 3H), 0.85–0.68 (m, 6H); ^{13}C NMR: δ 197.5, 197.4, 197.3, 197.2, 147.2, 147.0, 146.9, 145.3, 145.1, 145.0, 142.2, 142.1, 141.9, 141.8, 141.4, 141.3, 141.2, 137.1, 137.0, 136.9, 132.7, 131.3, 131.2, 131.1, 130.9, 129.7, 129.5, 128.4, 127.7, 127.6, 127.5, 127.47, 127.44, 127.2, 127.1, 126.6, 126.44, 126.39, 125.62, 125.58, 125.53, 125.50, 125.2, 125.1, 124.6, 124.5, 124.4, 40.4, 40.13, 40.08, 39.9, 37.44, 37.4, 37.22, 37.2, 36.9, 36.8, 36.3, 36.1, 31.9, 31.7, 31.5, 31.3, 30.8, 30.4, 30.3, 30.1, 23.0, 22.8, 22.1, 21.9, 21.7, 21.64, 21.59, 21.57, 12.6, 12.4, 12.37, 12.24, 12.2; IR (film, cm^{-1}): 1691; MS (%): M^{+} 384 (9), *m/z* 265 (7), 221 (8), 193 (13), 178 (20), 167 (20), 105 (100), 77 (39), 57 (17), 43 (19). Anal. Calcd. for $C_{28}H_{32}O$: C 87.45; H 8.39. Found: C 87.37; H 8.45.

1-(2-oxo-2-phenylethyl)-2,1'-binaphthyl (**3h**)



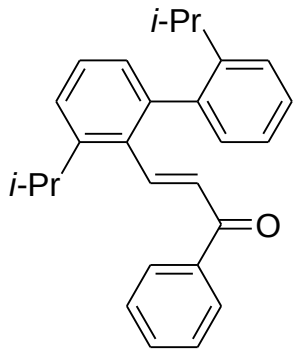
Yield 75% (139 mg); white solid; m.p. (*n*-hexane): 174–174.5 ºC. ^{1}H NMR: δ 8.00–7.66 (m, 7H), 7.59–7.34 (m, 11H), 4.76 (d, *J* = 17.7 Hz, 1H), 4.33 (d, *J* = 17.7 Hz, 1H); ^{13}C NMR: δ 197.5, 139.3, 138.6, 136.6, 133.5, 133.2, 132.9, 132.7, 132.1, 130.0, 128.7, 128.6, 128.4, 128.1, 127.9, 127.7, 127.2, 127.1, 126.6, 126.2, 126.1, 125.8, 125.6, 125.2, 124.4, 40.1; IR (KBr, cm^{-1}): 1684; MS (%): M^{+} 372 (31), *m/z* 265 (73), 252 (26), 105 (100), 77 (43), 51 (12). Anal. Calcd. for $C_{28}H_{20}O$: C 90.29; H 5.41. Found: C 90.14; H 5.44.

3,2'-Di-i-propyl-2-(1-methyl-2-oxo-2-phenylethyl)-1,1'-biphenyl (**3i**)



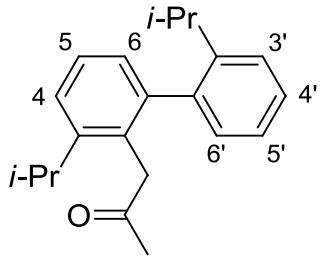
Yield 29% (54 mg); colorless oil. A 1:1 mixture of two stereoisomers. ^{1}H NMR: δ 7.58, 7.53 (2d further split, *J* = 8.3 Hz, 2H), 7.46–7.12 (m, 9H), 7.07-6.99 (m, 1H), 4.27 (br q, *J* = 7.0 Hz, 1H), 2.92, 2.71 (2 hept, *J* = 6.8 Hz, 1H), 2.90, 2.84 (2 hept, *J* = 6.9 Hz, 1H), 1.57, 1.44 (2d, *J* = 7.0 Hz, 3H), 1.24, 1.22 (2d, *J* = 6.7 Hz, 3H), 1.21, 1.18 (2d, *J* = 6.7 Hz, 3H), 1.09, 0.89 (2d, *J* = 6.7 Hz, 3H), 1.01, 0.96 (2d, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ 203.1, 202.7, 148.5, 148.3, 147.3, 146.9, 141.2, 141.0, 140.6, 140.2, 137.7, 137.6, 137.3, 137.0, 132.0, 130.1, 129.3, 128.63, 128.56, 128.3, 128.1, 128.01, 127.96, 127.89, 126.7, 126.6, 126.4, 126.3, 126.1, 125.6, 125.3, 125.0, 47.40, 47.37, 30.2, 29.97, 29.95, 29.7, 25.8, 25.70, 25.67, 25.5, 23.6, 23.5, 23.4, 22.8, 19.2, 17.7; IR (film, cm^{-1}): 1675; MS (%): M^{+} 370 (18), *m/z* 237 (12), 181 (100), 179 (28), 165 (21), 105 (73), 77 (38), 43 (46). Anal. Calcd. for $C_{27}H_{30}O$: C 87.52; H 8.16. Found: C 87.45; H 8.22.

3,2'-Di-i-propyl-2-(3-oxo-3-phenylpropenyl)-1,1'-biphenyl



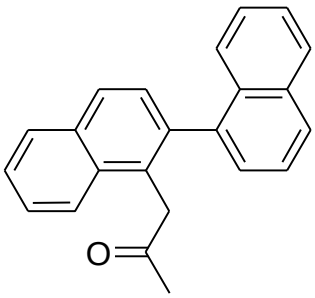
Yield 30% (55 mg); yellow oil. ^{1}H NMR: δ 7.85 (d, *J* = 16.0 Hz, 1H), 7.53–7.25 (m, 10H), 7.19 (d, *J* = 7.4 Hz, further split, 1H), 7.11 (dd, *J* = 5.9, 2.8 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 3.38 (hept, *J* = 6.8 Hz, 1H), 2.74 (hept, *J* = 6.8 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ 190.6, 148.1, 146.2, 142.0, 141.1, 140.7, 137.8, 132.6, 132.5, 130.2, 129.2, 128.44, 128.41, 128.28, 128.26, 127.8, 125.8, 125.6, 124.4, 30.0, 29.9, 25.0, 24.1, 23.7, 22.8; IR (film, cm^{-1}): 1665, 1610; MS (%): M^{+} 368 (5), *m/z* 325 (43), 263 (25), 262 (24), 205 (23), 179 (85), 105 (100), 77 (58). Anal. Calcd. for $C_{27}H_{28}O$: C 88.00; H 7.66. Found: C 88.19; H 7.72.

3,2'-Di-i-propyl-2-(2-oxopropyl)-1,1'-biphenyl (**3j**)



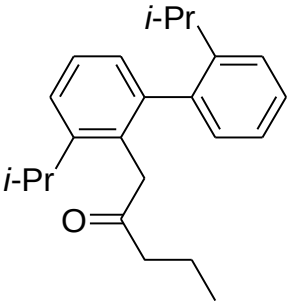
Yield 70% (103 mg) ; white solid; m.p. (*n*-hexane): 91.5–92 ºC. ^{1}H NMR: δ 7.41–7.33 (m, 3H, H3', H4, H4'), 7.30 (t, *J* = 7.8 Hz, 1H, H5), 7.17 (td, *J* = 6.8, 1.8 Hz, 1H, H5'), 7.04–7.01 (m, 2H, H6', H6), 3.72 (d, *J* = 17.7 Hz, 1H, CH(H)), 3.50 (d, *J* = 17.7 Hz, 1H, CH(H)), 2.87 (hept, *J* = 6.8 Hz, 1H, $CH(CH_3)_2$), 2.68 (hept, *J* = 6.8 Hz, 1H, $CH(CH_3)_2$), 1.94 (s, 3H, $COCH_3$), 1.27, 1.26 (2d, *J* = 6.8 Hz, 6H, $2CH_3$), 1.12, 1.10 (2d, *J* = 6.8 Hz, 6H, $2CH_3$); ^{13}C NMR: δ 206.2 (CO), 147.9 (C3), 146.5 (C2'), 141.9 (C1), 140.5 (C1'), 130.3 (C2), 129.6 (C6'), 127.8 (C4'), 127.3 (C6), 126.7 (C5), 125.4 (C3'), 125.2 (C5'), 124.4 (C4), 45.0 (CH_2), 30.0 ($CH(CH_3)_2$), 29.7 ($CH(CH_3)_2$), 29.6 ($COCH_3$), 24.8 (CH_3), 24.1 (CH_3), 23.7 (CH_3), 23.1 (CH_3); IR (KBr, cm^{-1}): 1716; MS (%): M^{+} 294 (18), *m/z* 251 (19), 237 (24), 209 (52), 178 (30), 167 (100), 43 (43). Anal. Calcd. for $C_{21}H_{26}O$: C 85.67; H 8.90. Found: C 85.54; H 9.00.

1-(2-Oxopropyl)-2,1'-binaphthyl (**3k**)



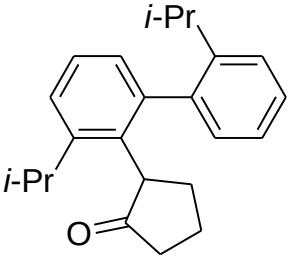
Yield 54% (84 mg); pale yellow oil. ^{1}H NMR: δ 7.99–7.82 (m, 5H), 7.62–7.33 (m, 8H), 4.08 (d, *J* = 17.2 Hz, 1H), 3.77 (d, *J* = 17.2 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR: δ 206.7, 139.3, 138.5, 133.6, 133.2, 132.6, 132.0, 129.7, 128.8, 128.7, 128.3, 128.0, 127.4, 127.2, 126.9, 126.3, 126.1, 126.0, 125.9, 125.3, 124.3, 45.7, 29.4; IR (film, cm^{-1}): 1716; MS (%): M^{+} 310 (30), *m/z*; 265 (100), 252 (35), 43 (79). Anal. Calcd. for $C_{23}H_{18}O$: C 89.00; H 5.85. Found: C 88.87; H 5.89.

3,2'-Di-i-propyl-2-(2-oxo-2-penthyl)-1,1'-biphenyl (**3l**)



Yield 61% (91 mg); colorless oil. ^{1}H NMR: δ 7.41–7.24 (m, 4H), 7.18–7.12 (m, 1H), 7.00 (d, *J* = 7.3 Hz, further split, 2H), 3.68 (d, *J* = 17.6 Hz, 1H), 3.46 (d, *J* = 17.6 Hz, 1H), 2.85 (hept, *J* = 6.8 Hz, 1H), 2.67 (hept, *J* = 6.8 Hz, 1H), 2.18–2.08 (m, 2H), 1.52–1.37 (m, 2H), 1.25, 1.24 (2d, *J* = 6.8 Hz, 6H), 1.11, 1.09 (2d, *J* = 7.0 Hz, 6H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ 208.2, 147.9, 146.5, 141.9, 140.5, 130.4, 129.7, 127.7, 127.2, 126.6, 125.4, 125.2, 124.3, 44.3, 44.2, 30.0, 29.7, 24.8, 24.1, 23.7, 23.1, 17.2, 13.6; IR (film, cm^{-1}): 1719; MS (%): M^{+} 322 (15), *m/z* 237 (30), 209 (42), 195 (22), 178 (28), 167 (100), 71 (74), 43 (88). Anal. Calcd for $C_{23}H_{30}O$: C 85.66; H 9.38. Found: C 85.58;H 9.43.

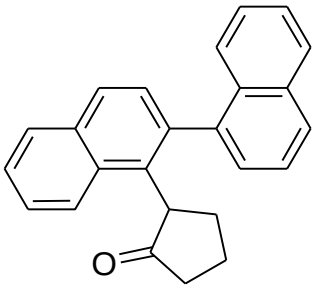
3,2'-Di-i-propyl-2-(2-oxocyclopentyl)-1,1'-biphenyl (**3m**)



Yield 67% (107 mg); colorless oil. ^{1}H NMR: δ 7.40–7.28 (m, 3H), 7.25 (t, *J* = 6.9 Hz, 1H), 7.17 (td, *J* = 6.9, 2.2 Hz, 1H), 7.05 (br d, *J* = 7.5 Hz, 1H), 6.96 (dd, *J* = 7.5, 1.7 Hz, 1H), 3.10 (m, 1H), 2.86 (m, 1H), 2.48–2.17 (m, 4H), 2.15–1.91 (m, 2H), 1.76–1.60 (m, 1H), 1.27 (d, *J* =

6.7 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR: δ 217.5, 147.2, 147.1, 143.2, 140.9, 134.7, 129.3, 127.7, 127.1, 126.5, 125.9, 125.5, 124.9, 54.0, 37.3, 32.1, 31.7, 29.5, 25.0, 24.5, 23.3, 23.0, 20.8; IR (film, cm^{-1}): 1739; MS (%): M^+ 320 (63), *m/z*; 287 (21), 235 (23), 217 (22), 207 (35), 191 (36), 179 (100), 165 (30), 43 (52). Anal. Calcd. for $C_{23}H_{28}O$: C 86.20; H 8.81. Found: C 86.09; H 8.86.

1-(2-Oxocyclopentyl)-2,1'-binaphthyl (**3n**)



Yield 71% (119 mg); white solid; m.p. (*n*-hexane): 129–130.5 °C. A 10:3 mixture of two stereoisomers. ^{1}H NMR: δ 7.98–7.88 (m, 3H), 7.83, 7.82 (2d, *J* = 8.4 Hz, 1H), 7.66 (br d, *J* = 7.8 Hz, 1H), 7.57–7.45 (m, 5H), 7.42–7.32 (m, 3H), 3.68, 3.61–3.42 (dd and m, *J* = 12.0, 9.6 Hz, 1H), 2.69–2.02 (m, 4H), 1.81–1.49 (m, 2H); ^{13}C NMR: δ 218.4, 139.76, 139.72, 134.1, 133.8, 133.6, 133.4, 132.5, 132.3, 129.6, 129.5, 129.4, 128.56, 128.53, 128.2, 127.9, 127.8, 127.5, 127.3, 126.8, 126.6, 126.5, 126.3, 126.2, 126.0, 125.9, 125.49, 125.44, 125.40, 125.1, 54.1, 37.8, 31.3, 29.0; IR (KBr, cm^{-1}): 1737; MS (%): M^+ 336 (83), *m/z* 279 (100), 265 (59), 252 (22), 138 (25), 133 (27). Anal. Calcd. for $C_{25}H_{20}O$: C 89.25; H 5.99. Found: C 89.17; H 6.04.

References

[1] M. S. Lesslie and U. J. H. Mayer *J. Chem. Soc.*, **1961**, 611.
[2] N. Della Ca', G. Sassi and M. Catellani *Adv. Synth. Catal.*, 2008, **350**, 2179.
[3] S. Deledda, E. Motti and M. Catellani *Can. J. Chem.*, 2005, **83**, 741.

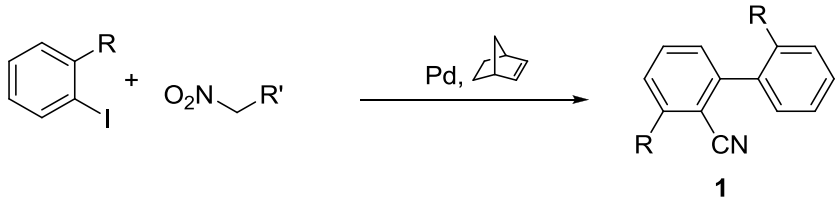
A new palladium catalyzed sequence to aromatic cyanation

Palladium catalysis has emerged as a powerful tool for the synthesis of organic frameworks due to the wide range of chemical transformations that have been successfully developed. Some of these cross coupling sequences represent nowadays the method of choice for otherwise complex reactions and have already found applications in the preparation of fine chemicals, bioactive compounds and material sciences.

In recent years, a deep effort has been directed towards the development of new reactions exploiting the relative easiness of organopalladium(n) complexes to undergo reductive elimination when reacting with nucleophiles. The selective formation of challenging carbon-carbon, -oxygen, -nitrogen or -halides bonds has thus become readily available.

We have recently developed a method to selectively obtain biaryl substituted ketones by merging the nucleophilic behavior of the latter with the versatility offered by the palladium/norbornene catalytic system (highlighted in the first chapter of this thesis), and we have then decided to expand the application of this method towards other masked carbon nucleophiles (palladium catalyzed a-arylation of esters, amides and (non-primary) nitroalkanes have been investigated, mainly, by the groups of Buchwald and Hartwig).[1]

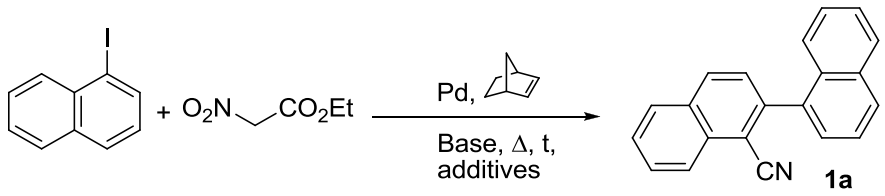
We were surprised that the reaction of an ortho-substituted aryl iodide with ethyl nitroacetate catalyzed by palladium and norbornene did not afford the expected product but traces of the corresponding aryl nitrile **1** (Scheme 1, R' = CO_2Et).



1

Scheme 1. Unexpected formation of the biaryl nitrile 1.

Despite many attempts, products yields were usually low and reactions were affected by serious reproducibility problems (Table 1).



Entry	Time (h)	Conversion (%)	**1a** Yield (%)	Notes/Additives
1	48	100	**30**	
2	72	40	**5**	Temp.: 105 °C
3	24	5	**-**	Cat.: $Pd(dba)CHCl_3$
4	24	20	**-**	Cat.: Pd/C
5	72	5	**-**	Solv.: NMP
6	24	40	**25**	Solv.: DMA
7	24	20	**13**	Solv.: DMA
8	48	20	**12**	
9	40	80	**57**	
10	48	15	**5**	PPh_3 10 mol%
11	60	40	**12**	$INBu_4$ 50 mol%
12	60	20	**10**	*i*-PrOH 1 eq
13	23	100	**10 (45)**	Methyl cinnamate 5 eq
14	36	15	**-**	Dimethyl maleate 5 eq
15	48	10	**4**	Base: 1 eq K_3PO_4
16	72	5	**-**	Base: 1 eq KOAc
17	22	100	**15**	^tBuOK 20 mol%
18	23	100	**30**	Base: 3 eq K_2CO_3
19	48	100	**35**	Base: 3eq, K_2CO_3 PhOK 20 mol %
20	48	100	**56**	As 19 + home-made nitroester

Table 1. Reaction conditions (unless otherwise stated in notes): 5 mol% $Pd(OAc)_2$ (0.04 M), 0.8 eq norbornene, 1 eq Ar-I, 5 eq ethyl nitroacetate, 1 eq K_2CO_3, eq 10 mol % PhOK in 4 mL of DMF under nitrogen at 120 °C for the time needed for visible formation of Pd black.

We tried to improve both halide conversion and product yield by changing the catalyst source (either $Pd(OAc)_2$, $Pd(dba)CHCl_3$ and Pd/C), the solvent (choice in this case was limited to high boiling, non protic, polar ones) and by lowering the reaction temperature. All these attempts were not successful (entries 1–7).

We then turned our attention towards the investigation of effect of the base and other additives (entries 10–17), but without consistent improvement in yields. However we noticed that an excess of a base, 3 eq in respect to the aryl iodide, had a positive effect on the reproducibility of reactions, thus avoiding the discrepancy exerted by results of entries 1, 8 and 9.

Apart from the desired product **1a**, we always noticed the formation of known norbornene containing byproducts, whose formation could easily take place under similar reaction conditions. In most cases, little amount (around 5%) of 1-cyanonaphtalene was observed, with the exception of entry 13, where it was detected in 45 % yield.

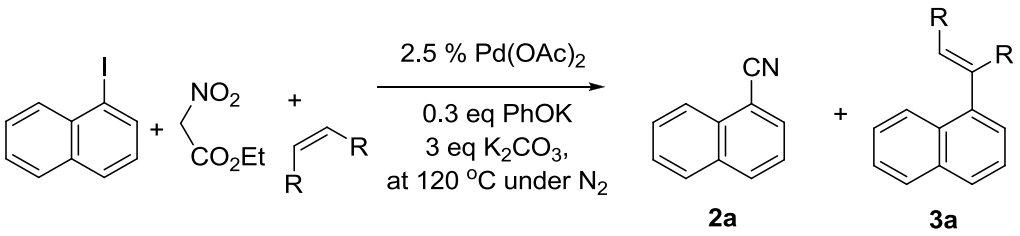
Reactions which gave rise to very low conversion allowed us to identify traces of ethyl cyanoformate in the reaction mixture. Its reactivity with palladium(0) complexes has been

reported,[2] and from control experiments we noticed that even in small amount (10 mol%), it completely inhibits any palladium catalysis in our reaction mixture.

However we were firmly resolute in addressing these issues for both mechanistic and applicative reasons: on the one hand, the straightforward transformation of a nitromethylene group into a nitrile one was, to the very best of our knowledge, not previously observed, while on the other hand, cyanation of an aryl halide by means of Pd catalysis have been for long a challenging goal (recently problems connected with catalyst poisoning and toxicity of reagents were overcome employing poorly-soluble or non-toxic cyanides, although these applications are still limited).[3]

We have then tried to understand this unusual reactivity by simplifying our reaction and excluding the strained olefin to avoid the competitive formation of norbornene-containing byproducts. We always achieved poor conversions and only traces of the product (if any) in the absence of an olefin.

On the contrary, when we added it to the reaction mixture we always found the desired aryl nitrile, although yields were limited when Heck coupling could easily take place. We have then tried to optimize reaction conditions toward the formation of the desired cyanobenzene derivative.



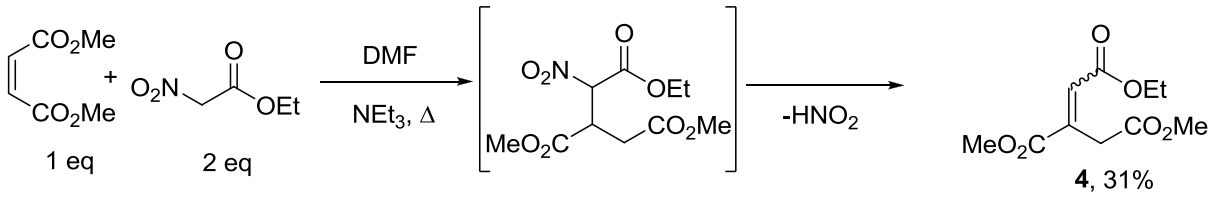
Entry	Olefin	Time (h)	Conversion (%)	**2a** Yield (%)	**3a** Yield (%)	Ligand
1	Diethylmaleate	6	30	**18**	8	-
2	Cyclohexene	20	100	**5**	55	-
3	Methylcinnamate	24	100	**55**	17	-
4	Dimethylmaleate	24	55	**37**	-	-
5	Methylcinnamate	45	100	**61**	15	5% PPh_3
6	Dimethylmaleate	24	90	**74**	-	5% PPh_3
7	Methylcinnamate	42	100	**60**	15	10% PPh_3
8	Dimethylmaleate	22	95	**81**	-	10% PPh_3
9	Dimethylmaleate	24	100	**88**	-	20% PPh_3
10	Stilbene	40	95	**30**	-	20% PPh_3
11	Dimethylfumarate	47	60	**48**	-	20% PPh_3
12	Fumaronitrile	24	5	**-**	-	20% PPh_3
13	Maleic anhydride	24	5	**-**	-	20% PPh_3

Table 2. Reaction conditions: 2.5 mol% Pd(OAc)2 (0.04 M), 1 eq Ar-I, 5 eq ethyl nitroacetate, 2.5 eq of olefin in 4 mL of DMF under nitrogen at 120 °C for the time needed for visible formation of Pd black.

Moderate yields of the desired product **2a** could be obtained emplyoing electron poor olefins (entries 1, 3 and 4), while addition of PPh_3 proved to be beneficial, in particular employing

dimethyl maleate (entries 4 and 6). By further increasing the amount of ligand good to excellent yield could be achieved (entries 8 and 9). For a possible explanation of these results employing an unusually high amount of triphenylphosphine vide infra. Under these conditions, differently substituted double bonds perform much worse (entries 10–13). Naphthalene (due to hydrogenolysis) and Ullmann-type biaryl were observed as aryl halide byproducts, although in minor amounts (around 5% each) in the best cases.

At the end of the reaction we recovered neither the nitroester nor the dimethyl maleate in excess. They give rise to a complex mixture of organic products, probably initiated by Michael attack of the enolate of the nitroester to dimethyl maleate (control experiments supported this hypothesis; a similar complex mixture was obtained by reactions of the same reagents in the absence of a palladium salt and/or an aryl halide).



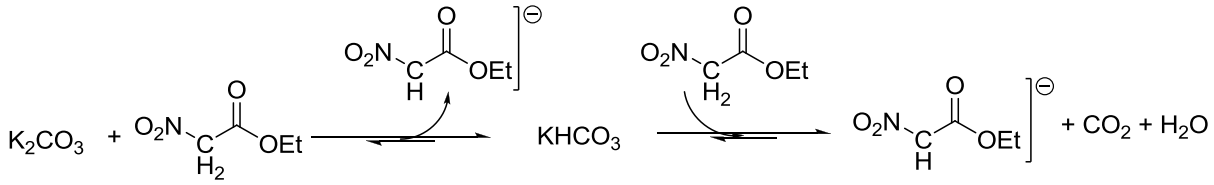
Scheme 2. Formation of Michael-type product 4.

In analogy to similar reactions described in the literature,[4] we were thus able to isolate a 31 % of **4** in a blank experiment employing triethylamine (and recover in this case the excess of both reagents) instead of the K_2CO_3/PhOK mixture used for palladium catalyzed one-pot reactions. We thought that in the latter case **4** is likely to be initially formed but then it subsequently reacts further giving rise to the observed complex mixture of compounds.

The only species we identified at the end of the reaction were diethyl, dimethyl and ethylmethyl succinate resulting from dimethyl maleate in ca. 1:1:1 molar reation (with an overall yield of around 20% in respect to the initial amount of the olefin). These compounds suggested that EtOH is present in the reaction mixture, in agreement with our proposed catalytic cycle (vide infra). Concerning the reduction of the double bond of the olefin, we could not address for sure how it takes place.

Anyway we noticed that dimethyl maleate is not reduced by palladium in DMF at 120 °C for 24 hours in the presence of a base while it could be hydrogenated to dimethyl succinate, in around 20% yield, by adding H_2O (2 eq) to the same reaction mixture.

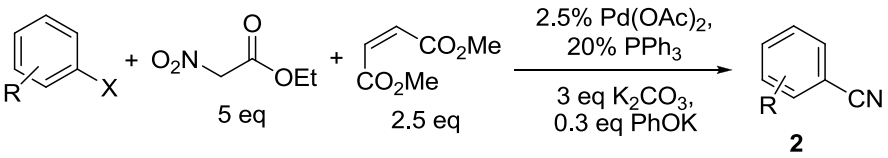
The presence of water in our system could be due to the following reaction (Scheme 3).



Scheme 3. Acid-base neutralization of ethylnitroacetate.

Ethyl nitroacetate is a (relatively) strong organic acid, and its acid-base properties were studied a long time ago.[5] Potassium carbonate is only partially soluble in DMF, and thus, at the very beginning of a reaction, its concentration in solution is surely lower than that of the nitroester. For this reason, neutralization of the latter could be achieved as well by a bicarbonate anion, which forms CO_2 and water. This reactivity is confirmed by the formation of visible bubbles inside the reaction vessel at the beginning of the reaction. The same behavior is moreover observed when adding a DMF solution of the nitro ester to potassium carbonate. Addition of activated 4 Å MS to the reaction mixture did not change the reaction output but this is probably due to the high temperature adopted.

We have then turned our attention towards the scope of the reaction, by employing differently substituted aryl halides together with 5 eq of ethyl nitroacetate and 2.5 eq of dimethyl maleate in the presence of 2.5% $Pd(OAc)_2$, 20% PPh_3 and a mixture of K_2CO_3 and PhOK as bases (3 eq and 0.3 eq respectively).



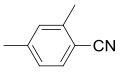
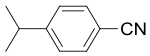
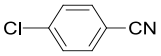
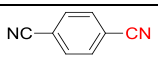
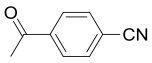
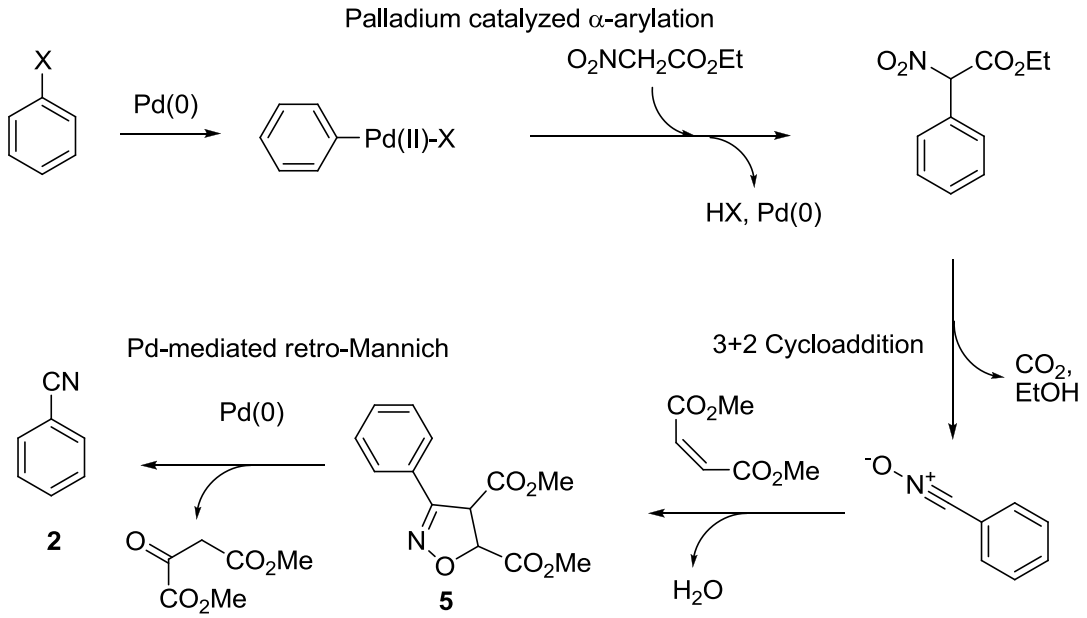
Entry[a]	X	Product	Yield (%)
1	I		**88**
2	Br		**71**
3	I		**81**
4	I		**64**
5	I		**75**
6	I		**71**
7	I		**56**
8	I		**86**
9	Br		**76**
10	I		**94**
11	Br		**78**
12	I		**95**
13	Br		**86**
14	Br		**85**
15	Br		**87**
16	Br		**80**
17	Br		**72**

Table 3. $Pd(OAc)_2$ is 0.04 M. Reactions were carried out at 120 °C, under nitrogen for the time needed for visible formation of Pd black (22-26 hours). Isolated yields based on average of two runs.

Table 3 shows that good results were obtained with alkyl-substituted aryl iodides (entries 3–7), whether ortho, meta or para substituted. The presence of electron withdrawing groups (entries

8,10 and 12) allows to achieve excellent yields with iodides and good results with bromides. Interestingly, the reaction proved to be tolerant to the presence of a chlorine substitutent, which is useful for further functionalizations, and allows the formal cyanation of a bromopyridine. Although the arylation of a ketone could easily take place in similar conditions, we managed to selectively obtain 4-cyanoacetophenone (87% yield, entry 15). The reaction is tolerant towards fluorine substituents, although their relative volatility compared to DMF makes products isolation tedious, and resulting yields are low. The presence of a carboxymethyl substitutent on the aryl halide resulted in a mixture of the corresponding methyl, ethyl esters and free-acid benzonitrile, the latter confirming a significant presence of water in the reaction mixture.

On the basis of our experiments we propose the following mechanism for the palladium catalyzed one-pot synthesis of aryl nitriles from the corresponding halides.



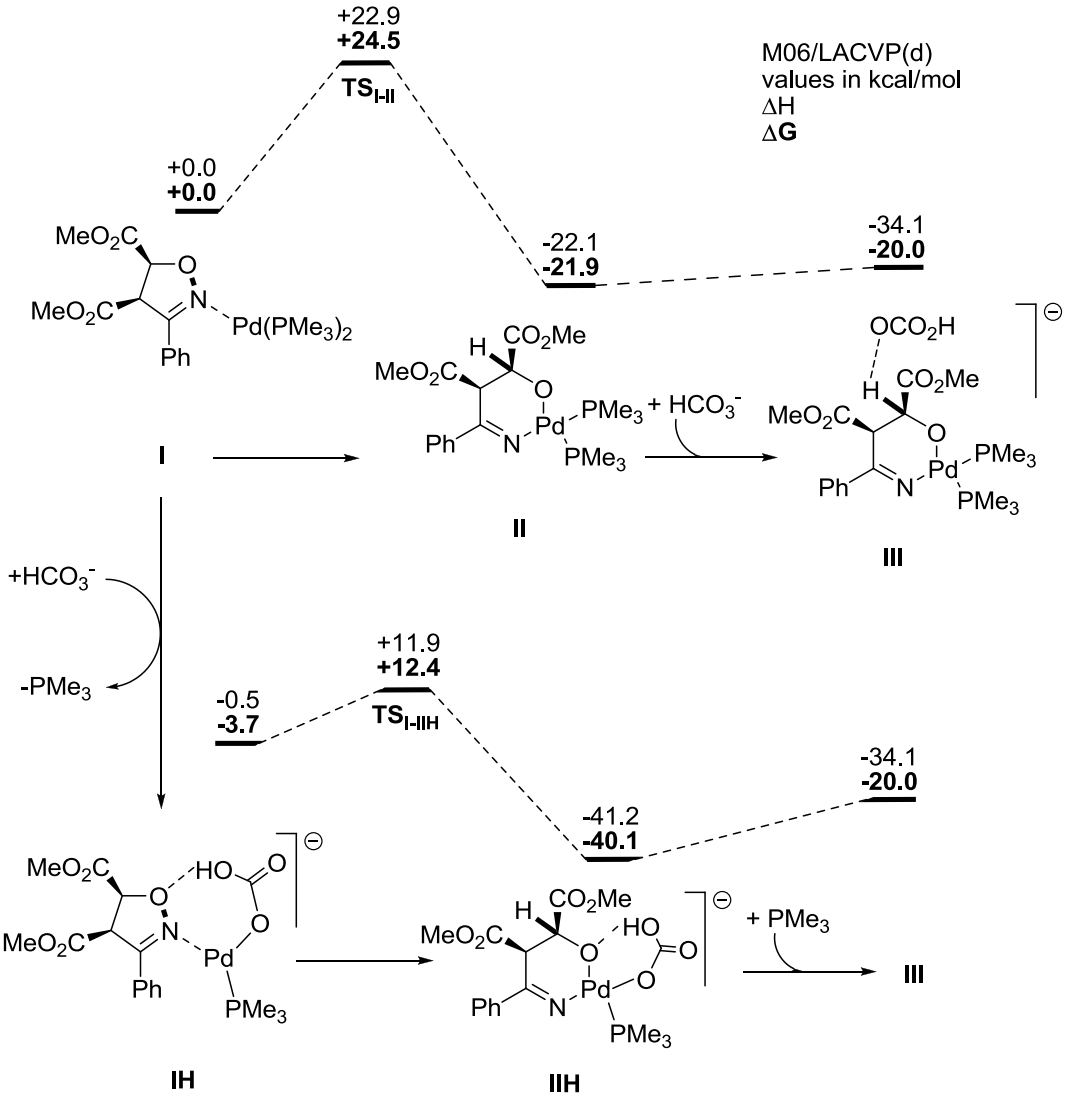
Scheme 4. Proposed reaction mechanism.

The aryl halide could undergo oxidative addition to afford an arylpalladium(II) complex. Reductive elimination, in analogy to the reaction reported by Buchwald for non-primary nitroalkanes, regenerates the metal catalyst and delivers the arylated nitroester. Reasoning that the presence of an olefin is necessary to obtain product **2**, we thought that in our catalytic reaction dimethyl maleate could react with an arylated nitroester to yield the corresponding isoxazoline **5** through a base/thermal catalyzed 3+2 intermolecular cycloaddition.[6] This reactivity is known, and in our reaction conditions this step is likely to take place very easily, since we never observed the starting arylated nitroester. The formation of the nitrile oxide required for the cycloaddition was confirmed employing benzoylnitromethane instead of a nitroester, which afforded benzoic acid and the desired aryl nitrile in an almost equimolar

amount. Thus, by reacting 1-iodonaphtalene, 5 eq of benzoylnitromethane and 2.5 eq of dimethyl maleate in the presence of 2.5% $Pd(OAc)_2$, 20% PPh_3 and a mixture of K_2CO_3 and PhOK as bases (3 eq and 0.3 eq respectively), 1-cyanonapthalene is obtained in 88% yield togheter with benzoic acid (17% yield).

We proposed that the resulting heterocycle could be successfully cleaved by palladium to yield the desired cyanobenzene **2**. To prove this idea, we prepared 3-phenyl-4,5-dicarbomethoxy-4,5-dihydroisoxazole (**5**) and we allowed it to react with 5% $Pd(OAc)_2$ in DMF under nitrogen in the presence of an equimolar amount of K_2CO_3 as base. After 16 hours 76% benzonitrile was determined by GC and GC-MS experiments, thus confirming our proposal. Lowering the temperature of the reaction up to 80 °C did not disfavour this reactivity, in agreement with the observation that we have never recovered 3 in our one pot reactions. No reaction takes place in the absence of $Pd(OAc)_2$ and in the presence of an aryl halide, suggesting that the active catalyst is a zero-valent palladium species. In these reactions it was not possible to identify any (aliphatic) coproduct. Different work-up procedures always resulted in NMR spectra showing only traces of several different products in the aliphatic region. Similarly GC-MS analyses did not provide any results. This could be due to the known instability of ketosuccinates, whether as esters or as free acids.

Metal-catalyzed ring opening of the isoxazoline ring, with the subsequent hydrolysis of the so formed imine function is known, however our observed behavior featuring a sigma C–C bond cleavage has not been reported yet.[7] We have thus decided to investigate this reaction by means of DFT calculation in order to understand its mechanism.



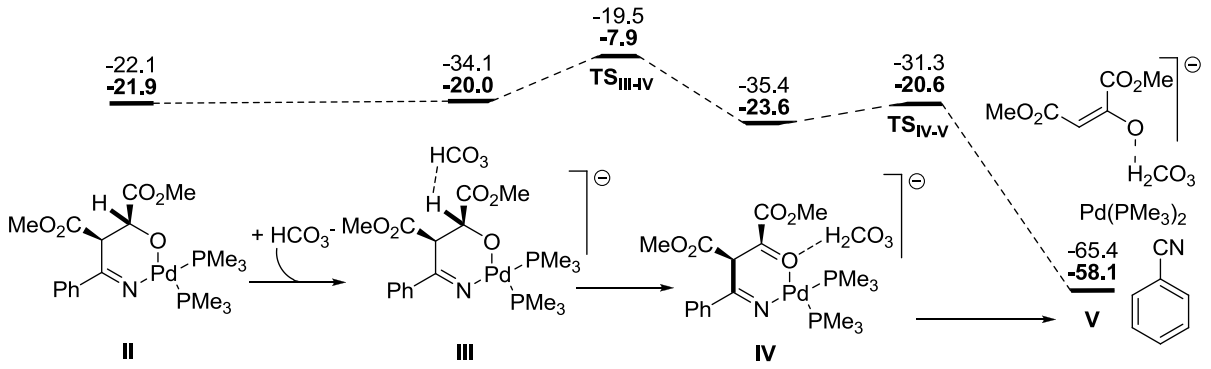
Scheme 5. Modelized pathways for the palladium catalyzed cleavage of the N–O bond.

For sake of simplicity we choose a $Pd(0)L_2$ moiety to start our investigation, employing PMe_3 as ligand. Geometry optimization have been carried out without constraints employing the M06 funtional as implemented in Gaussian09, with the LACVP(d) basis set. Single point energy calculation were made with TZVP basis set, affording similar values to whose of its double-ζ analogue. Introduction of DMF as an implicit solvent trough the CPCM approach did not change our observed trends, and have thus been neglected. Transition states were located through scans of the relative reaction coordinate, and displayed only one imaginary frequency.

The initial cleave of the N–O bond was modelized in two distinct ways, both in the presence and in the absence of an hydrogen-bond donor. Coordination of the nitrogen of the heterocycle afforded complex **I**, (higher energies are obtained with μ^2 coordination of the N–O bond or with exo carboxymethyl groups) from which palladium could insert into the N–O bond with a barrier of +24.5 Kcal in ΔG. Formation of the resulting complex **II** is energetically favored

(ΔG -21.9 Kcal). This complex features a slightly elongated C–H bond (highlighted in red, 1.12 Å) and the relative acidity of this proton is confirmed by the computed ΔH (-12.0 Kcal) shown by complex **III**, in which it interacts with a hydrogencarbonate anion (for the effect of a stronger base, eg a carbonate anion, vide infra).

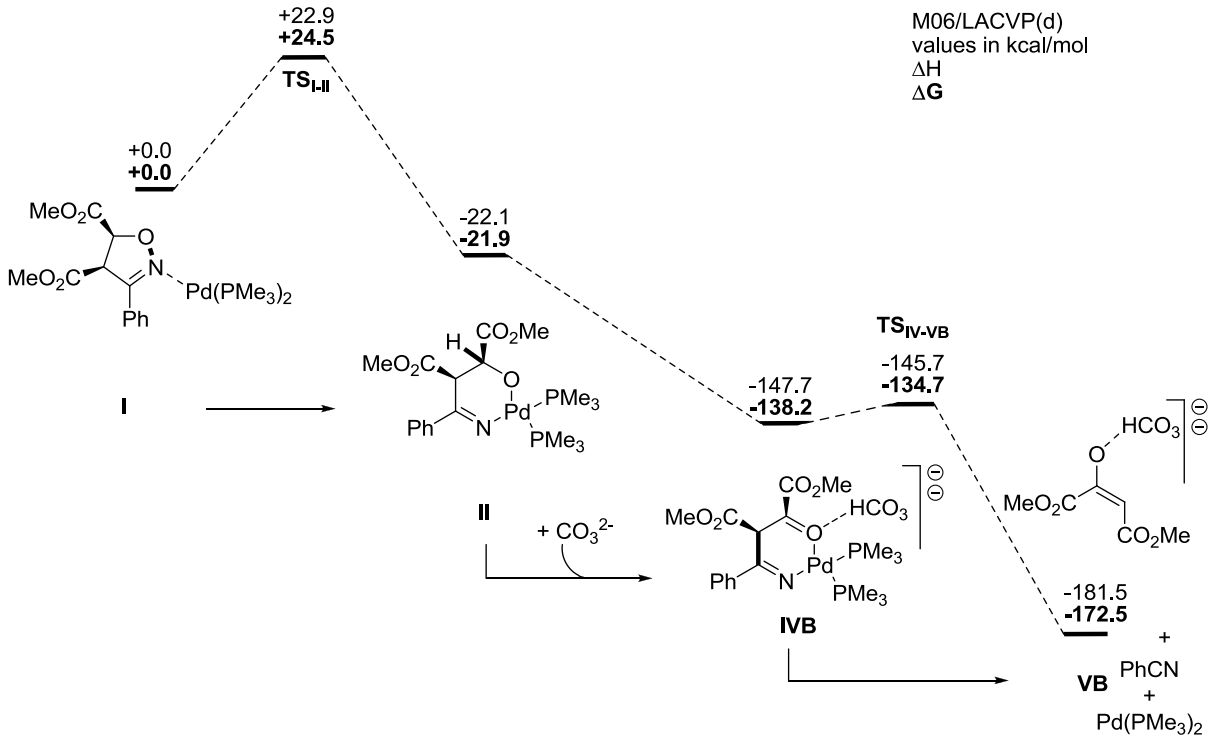
Although the barrier of $\mathbf{TS_{I\text{-}II}}$ could be easily overcome at 120 °C, the temperature of the one pot reaction, we tried to investigate a more feasible route to complex **II**. We thought that the presence of an hydrogen bond with the oxygen of the heterocycle could weaken the strength of the N–O bond, thus lowering the barrier for its cleavage. To introduce this feature, we choose as a model HCO_3^-, which is likely present in the reaction mixture (our experiments suggests also the presence of H_2O, MeOH and EtOH in solution). Scrambling of a phosphine with an hydrogencarbonate anion delivers complex **IH** (ΔG -3.4 Kcal), which features an intramolecular hydrogen bond with the heterocycle. The following barrier $\mathbf{TS_{I\text{-}IIH}}$ is easily accessible (ΔG +12.4 Kcal), and the resulting product, **IIH** lies far below the entry channel (ΔG -40.1 Kcal). For sake of simplicity we neglected cases of intermolecular hydrogen bonds.[8] From these findings, we can conclude that in the presence of a protic species, the palladium mediated N–O cleavage is more easily accessible, and this is in perfect agreement with the experimental finding that the isoxazoline has never been recovered in our one-pot reaction. Coordination of a further molecule of PMe_3 allows to obtain complex **III**, although this step is very energetically demanding (ΔG +20.1 Kcal compared to **IIH**).



Scheme 6. Hydrogen abstraction and sequent C–C bond cleavage.

Hydrogen abstraction from **III** is accessible trough $\mathbf{TS_{III\text{-}IV}}$ (ΔG +12.1 Kcal compared to the reagent), and allows the formation of complex **IV**, in which the resulting carbonic acid makes an hydrogen bond with the oxygen alpha to palladium. Moreover, in **IV** the highlighted C–C bond is unsually elongated (1.66 Å) and the cleavage of this sigma bond is surprisingly easy ($\mathbf{TS_{IV\text{-}V}}$, ΔG +3.0 Kcal compared to **IV**), delivering benzonitrile, the enolate of dimethyl ketosuccinate and $Pd(PMe_3)_2$.

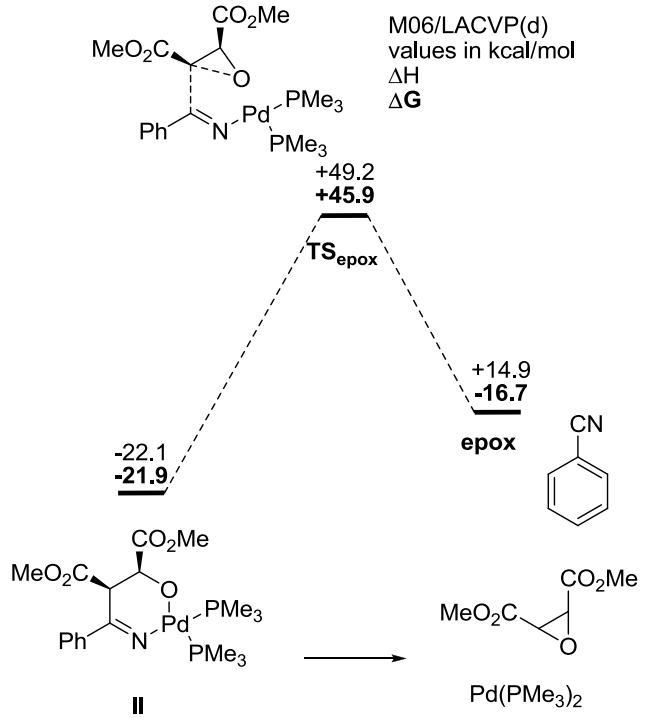
We were unable to find a pathway for hydrogen abstraction (and for the subsequent steps as well) starting from complex **I**, **IH** and **IIH**, probably because of both electrostatic repulsions and less pronounced acidity of the involved proton. Once again this result correlates well with experiments, which showed a beneficial effect exerted by an unsually high amount of PPh_3 (20 mol%, compared to 2.5 mol% of the palladium salt): formation of **IIH** is energetically favored, but in the absence of a ligand that could efficiently scavenge hydrogencarbonate coordination to the metal, any further palladium catalysis in the reaction mixture could be seriously reduced, sinking low the overall TOF.[9]



Scheme 7. Modelized reaction with carbonate anion, confirming the retro-Mannich like mechanism.

This palladium-mediated reaction occurs through a retro-Mannich like mechanism, in which the imine product is replaced by an aryl nitrile. To confirm this behaviour we modelized the same reaction pathway with a carbonate anion. The hydrogen abstraction is, as expected, much easier. It was in fact not possible to determine neither a converged structure nor a transition state for this step in the presence of carbonate, which allows the system to go directly to complex **IVB**. The sequent $\mathbf{TS_{IV\text{-}VB}}$ shows a barrier similar to the previous case (ΔG +3.5 Kcal, thus +0.5 Kcal more than $\mathbf{TS_{IV\text{-}V}}$), and these results correlates well with the proposed retro-Mannich mechanism.[10]

We have recently reported the relative easiness of this reaction in similar condition, and due to its versatility such transformations found large applications in several complex syntheses. However this is the first report of such a reactivity directly mediated by a metal catalyst.



Scheme 8. Comparative pathway for the C-C bond cleavage.

As we were unable to identify ketosuccinate at the end of our one-pot reaction, but only a complex mixture of aliphatic byproducts, we tried to modelize also other pathways for the palladium catalyzed formation of aryl nitriles from isoxazoline **3**. We did not manage to modelize insertion of palladium into the C–C bond that has to be cleaved, but we could find a route to benzonitrile from complex **II** avoiding base catalysis. Formation of an epoxyde together with benzonitrile occurs through $\mathbf{TS_{epox}}$, although this process is much more energy demanding than the previous one (ΔG +67.8 Kcal compared to **II**), and seems thus very unlikely.

In conclusion, we developed a novel method to obtain aryl nitriles from the corresponding halides with a dual palladium catalysis in the absence of a cyanide source. The key step of this new three component cascade is the metal-mediated cleavage of an isoxazoline ring, which delivers the cyanobenzene moiety through a retro-Mannich reaction.

The method allows to obtain desired products in good to excellent yield employing aryl iodides or electron poor aryl bromides.

Further studies are in progress in order to expand this novel reactivity towards other heterocycles.

References and notes

[1] a) E. M. Vogl, S. L. Buchwald *J. Org. Chem.* **2002**, *67*, 106; b) D. A. Culkin, J. F. Hartwig *Acc. Chem. Res.* **2003**, *36*, 234.
[2] Y. Nishihara, M. Miyasaka, Y. Inoue, T. Yamaguchi, M. Kojima, K. Takagi *Organometallics* **2007**, *26*, 4054.
[3] a) T. Schareina, A. Zapf, M. Beller *Chem. Commun.* **2004**, 1388; b) F. G. Buono, R Chidambaram, R. H. Mueller, R. E. Waltermire *Org. Lett.* **2008**, *10*, 5325; c) C. Torborg, M. Beller *Adv. Synth. Catal.* **2009**, *351*, 3027; d) B. Mariampillai, J. Alliot, M. Li, M. Lautens *J. Am. Chem. Soc.* **2007**, *129*, 15372.
[4] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini *Chem. Rev.* **2005**, *105*, 933.
[5] N. Kornblum, R. K. Blackwood, J. W. Powers *J. Am. Chem. Soc.* **1957**, *79*, 2507.
[6] a) E. Trogu, F. De Sarlo, F. Machetti *Chem. Eur. J.* **2009**, *15*, 7940; b) K. V. Gothelf, K. A. Jørgensen *Chem. Rev.* **1998**, *98*, 863.
[7] a) A. P. Kozikowski *Acc. Chem. Res.* **1984**, *17*, 410; because of their relatively easily cleaved N–O bond, Δ^2-isoxazolines were successfully employed as precursors for β-hydroxy ketones, β-amino acids and *γ*-amino alcohols: b) D. Jiang, Y. Chen *J. Org. Chem.* **2008**, *73*, 9181; c) J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira *Angew. Chem., Int. Ed.* **2001**, *40*, 2082; d) D. P. Curran *J. Am. Chem. Soc.* **1983**, *105*, 5826; e) A. R. Minter, A. A. Fuller, A. K. Mapp *J. Am. Chem. Soc.* **2003**, *125*, 6846; f) A. A. Fuller, B. Chen, A. R. Minter, A. K. Mapp *J. Am. Chem. Soc.* **2005**, *127*, 5376; g) E. Marotta, L. M. Micheloni, N. Scardovi, P, Righi *Org. Lett.* **2001**, *3*, 727.
[8] D. Garcìa-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren *J. Am. Chem. Soc.* **2006**, *128*, 1966.
[9] a) S. Kozuch, S. Shaik *J. Am. Chem. Soc.* **2006**, *128*, 3355; b) S. Kozuch, C. Amatore, A. Jutand, S. Shaik *Organometallics* **2005,** *24*, 2319.
[10] a) J. H. Schauble, E. Hertz *J. Org. Chem.* **1970**, *35*, 2529; b) R. J. Sundberg, J. D. Bloom *J. Org. Chem.* **1981**, *46*, 4836; c) F. M. Schell, P. M. Cook *J. Org. Chem.* **1984**, *49*, 4067; d) J. D. Winkler, R. D. Scott, P. G. Williard *J. Am. Chem. Soc.* **1990**, *112*, 8971; e) N. Risch, M. Langhals, T. Hohberg *Tetrahedron Lett.* **1991**, *32*, 4465; f) D. L. Comins, C. A. Brooks, R. S. Al-awar, R. R. Goehring *Org. Lett.* **1999**, *1*, 229; g) Y. Kwak, J. D. Winkler *J. Am. Chem. Soc.* **2001**, *123*, 7429; h) D. J. Aitken, C. Gauzy, E. Pereira *Tetrahedron Lett.* **2004**, *45*, 2359; j) J. D. White, D. C. Ihle *Org. Lett.* **2006**, *8*, 1081; k) P. Chen, P. J. Carroll, S. McN. Sieburth *Org. Lett.* **2009,** *11***,** 4540.

Experimental section and computational details

General remarks

Reagents were obtained from commercial sources and used as received. 2-*i*-Propyliodobenzene and 4-*i*-propyliodobenzene were prepared starting from the corresponding aniline derivative by diazotization procedure.[1] 4,5-Dicarbomethoxy-4,5-dihydro-3-phenylisoxazole was prepared according to the procedure reported in the literature.[2] DMF was dried and stored over 4 Å molecular sieves under nitrogen. Reactions were carried out under nitrogen using standard Schlenk technique. Gas chromatography analyses were performed with a Carlo Erba HRGC 5300 instrument using a 30 m SE-30 capillary column. Flash column chromatography was performed on Merck Kieselgel 60 and thin-layer chromatography on Merck $60F_{254}$ plates. GCMS spectra (EI, 70eV) were performed on a Hewlett Packard HP 6890 GC system equipped with a SE-52 capillary column and a HP5973 Mass Selective Detector mass analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 293 K, in $CDCl_3$ or DMSO-*d6* on Bruker AC-300 and AVANCE 300 spectrometers at 300.1 and 75.4 MHz respectively. ^{1}H and ^{13}C chemical shifts are reported relative to TMS and were determined by reference to residual ^{1}H and ^{13}C solvent resonances. All prepared benzonitriles are known compounds and were identified by comparison with authentic samples (GC-MS and ^{1}H NMR). Analytical data of 2-*i*-propylbenzonitrile, which was not commercially available, were consistent with whose riported in the literature.[3]

Calculations were performed with Gaussian 09 at DFT level.[4] The geometries of all complexes here reported were optimized without any constraints at the generalized gradient approximation using the M06 hybrid functional of Zhao and Truhlar.[5] Optimizations were carried out using LACVP(d) basis set.[6] It consists of the standard 6-31G(d) basis set for lighter atoms (H, C, N, O and P) and the LANL2DZ basis set for Pd. For more accurate energy values, single-point calculations were performed on the optimized geometries using a larger basis set, Def2-TZVP defined by Weigand and Ahlrichs, essentially a valence triple-ζ one.[7] Harmonic frequencies were calculated at the same level of theory with LACVP(d) basis set to characterize stationary points and to determine zero-point energies corrections (ZPC). Energies calculated with both basis sets were corrected with these ZPCs without scaling. The starting approximate geometries for transition states (TS) were obtained through scans of the relative reaction coordinate starting from the corresponding reagents.

General procedure for the reaction of an aryl halide, ethylnitroacetate and dimethylmaleate

To a Schlenk-type flask equipped with a magnetic bar were added under nitrogen K_2CO_3 (300 mg, 2.17 mmol), potassium phenoxide (24 mg, 0.18 mmol), a solution of $Pd(OAc)_2$ (4 mg, 0.0179 mmol in 4 mL of DMF), a solution of the desired aryl halide, ethylnitroacetate and dimethylmaleate (0.72 mmol, 1.78 mmol and 3.57 mmol respectively in 4 mL of DMF) and triphenylphosphine (38 mg, 0.143 mmol). The mixture was placed in an oil bath at 120 ˚C for the time needed for palladium precipitation (22-26 h). At the end of the reaction the mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times (3 × 30 mL) with a 10% aqueous solution of H_2SO_4 (or a saturated $NaHCO_3$ solution employing bromopyridines) and eventually dried over Na_2SO_4. The crude mixture was analyzed by GC and GC-MS. The products were isolated by flash column chromatography on silica gel using a 9:1 mixture of hexane-EtOAc as eluent and analyzed by ^{1}H-NMR.

Comprehensive table in Atomic Units

	H (LACVP(d))	ZPC	S (Cal/K*Mol)	E (TZVP)
Pd(PMe3)2	-1048.501066	0.228564	133.662	-1050.09529479
Pme3	-460.836763	0.112775	77.354	-461.03280201
Isoxazoline	-933.196342	0.248938	134.804	0.00000010
CO3--	-263.459062	0.014480	62.429	-263.64125623
HCO3-	-264.283252	0.027025	63.442	-264.44391096
Benzonitrile	-324.134935	0.099180	78.557	-324.35952144
Epoxyde	-609.050793	0.145293	103.850	-609.44595476
I	-1981.710481	0.479350	210.244	-1983.91203802
TS I-II	-1981.673972	0.477775	205.039	-1983.87140587
II	-1981.745722	0.479245	209.441	-1983.95364940
IH	-1785.157710	0.392100	207.370	-1787.31228034
TS I-IIH	-1785.138069	0.391501	194.586	-1787.28708733
IIH	-1785.222601	0.394072	192.699	-1787.38134868
III	-2246.048043	0.507205	226.636	-2248.40826211
TS III-IV	-2246.024809	0.502390	234.646	-2248.38035679
IV	-2246.050167	0.504579	234.094	-2248.40423460
TS IV-V	-2246.043590	0.503410	238.006	-2248.39663396
V	-2246.098015	0.504549	249.006	-2248.46331787
IVB	-2245.404923	0.490501	240.774	-2247.75558270
TS IV-VB	-2245.401670	0.490171	236.085	-2247.75075835
VB	-2245.458782	0.492995	242.618	-2247.82170304
TS epox	-1981.631993	0.473495	221.545	-1983.83177164

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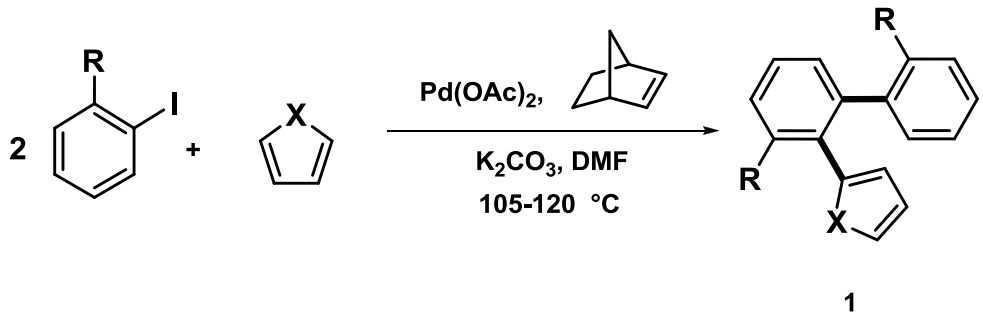
References

[1] M. S. Lesslie, U. J. H. Mayer *J. Chem. Soc.* **1961**, 611.
[2] F. P. Ballistreri, U. Chiacchio, A. Rescifina, G. Tomaselli, M. R. Toscano *Molecules* **2008**, *13*, 1230.
[3] T. Schareina, A. Zapf, W. Magerlein, N. Muller, M. Beller *Chem. Eur. J.* **2007**, *13*, 6249.
[4] Gaussian 09, Revision **A.1**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
[5] Y. Zhao, D. G. Truhlar *Theor. Chem. Account* **2008**, *120*, 215.
[6] a) J. P. Hay, W. R. Wadt *J. Chem. Phys.* **1985**, *82*, 299. b) R. A. Friesner, R. B. Murphy, M. D. Beachy, M. N. Ringlanda, W. T. Pollard, B. D. Dunietz, Y. X. Cao *J. Phys. Chem. A* **1999**, *103*, 1913.
[7] a) F. Weigen, R. Ahlrichs *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297; b) D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss *Theor. Chim. Acta* **1990**, *77*, 123; c) K. A. Peterson, D. Figgen, E. Goll, H. Stoll, M. Dolg *J. Chem. Phys.* **2003**, *119*, 11113.

Palladium/norbornene-catalyzed synthesis of *o*-heteroteraryls from aryl iodides and heteroarenes through sequential double C–H activation

Arylated heterocycles are structures present in many compounds of great importance as their structures are encountered in many compounds of great importance for their biological, pharmaceutical and optical properties.[1] During recent years several novel catalytic processes for direct arylation of heterocycles have been reported.[2] Due to their wide applications, however, the development of new methods for the efficient and selective arylation of heterocycles still remains a challenging goal.

We present herein a new catalytic procedure which allows the synthesis of *o*-heteroteraryls through a sequence of steps occurring under the control of palladium and norbornene, both acting as catalysts.[3] The reaction involves intermolecular aryl-aryl and aryl-heteroaryl bond formation in sequence through direct C–H functionalization (Scheme 1). Direct C–H arylation of arene compounds overcomes the need for a functional group in one of the aryl moieties undergoing C–C coupling.

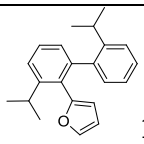
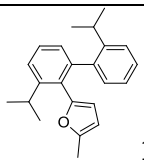
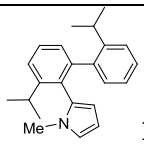
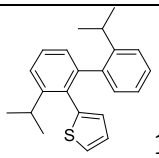
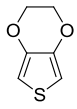
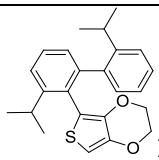
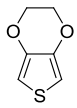
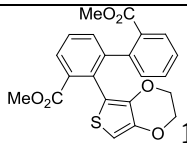
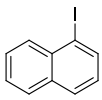
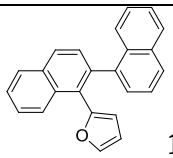
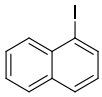
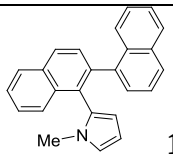
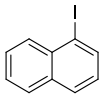
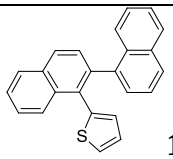
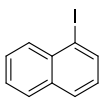
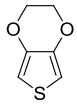
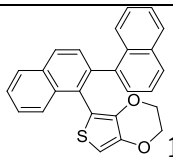


Scheme 1. One pot reaction of an *o*-substituted aryl iodide with a heterocycle.

Product **1** combines the ubiquitous biphenyl structure with heterocyclic nuclei of wide biological and pharmaceutical interest.[2] The reaction depicted in Scheme 1 occurs under mild conditions (105–120 °C) using palladium acetate as precursor of the palladium(0) catalyst, norbornene, the *o*-substituted aryl iodide, a large excess of a heterocycle and potassium carbonate as a base in DMF. 3,4-Ethylenedioxythiophene leads to satisfactory results even in a 25% excess in respect to the aryl iodide.

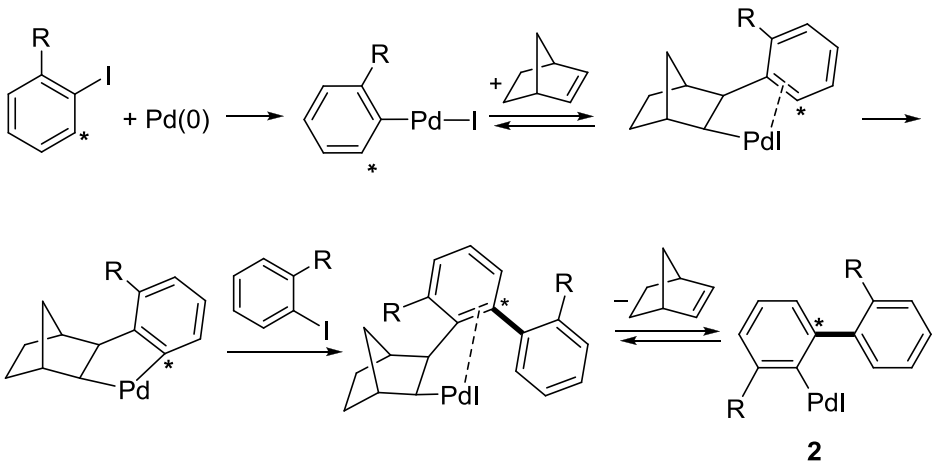
Good results were obtained with 1-naphthyl iodide and 2-isopropylphenyl iodide and are reported in Table 1. An electron-withdrawing substituent such as the methoxycarbonyl group also gave good results. Lower yields were obtained with other linear alkyl substituens (not reported in Table 1).

Table 1. Reaction of *o*-substituted aryl iodides with heterocycles.[a]

Entry	Aryl iodide	Heterocycle	T (°C)	Isolated yield of **1** (%)
1[b]			105	 **1a** 68
2[b]			105	 **1b** 71
3			120	 **1c** 66
4			120	 **1d** 70
5			105	 **1e** 72
6			105	 **1f** 82
7[b]			105	 **1g** 62
8			120	 **1h** 69
9			120	 **1i** 70
10			105	 **1j** 77

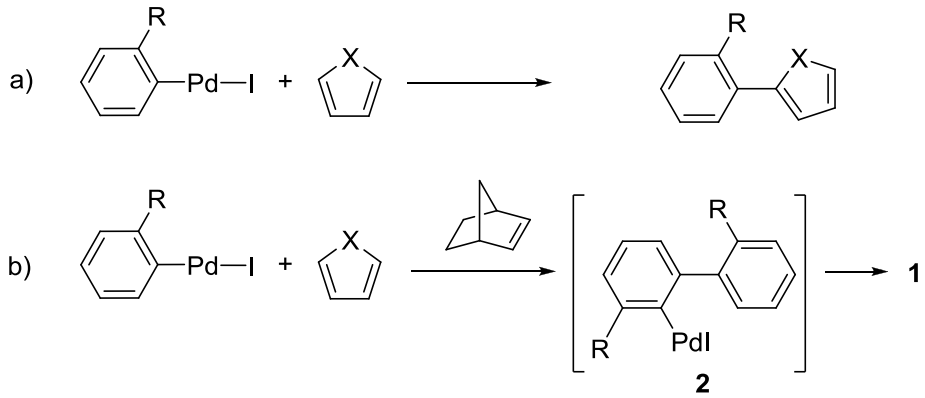
[a] Reactions conditions: see experimental section. Complete conversion of the aryl iodide. [b] Reaction run for 48 h. [c] Unprotected pyrrole does not allow formation of the desired product.

The reaction proceeds according to our protocol for the synthesis of biaryl derivatives[3] until a biarylpalladium iodide complex **2** is formed. An *ortho*-substituted iodobenzene reacts with palladium(0) to give the oxidative addition product,[4] which in its turn inserts norbornene into the arylpalladium bond.[5] This is followed by palladacycle formation[6] through arene C–H activation.[7] A second molecule of aryl iodide then attacks this species forming a C–C bond between the two aryl groups, while palladium remains bonded to the norbornyl moiety. At this point steric hindrance causes norbornene deinsertion with formation of **2**.[3] The *ortho*-substituent in the aryl halide (or a condensed ring, as in 1-iodonaphthalene, not shown in Scheme 1) is necessary to cause the reaction sequence to evolve towards biaryl formation[3] rather than towards other products resulting from ArI attack on the norbornyl site of the palladacycle shown in Scheme 2.



Scheme 2. Simplified course of the reaction leading to a palladium-bonded biaryl **2**.

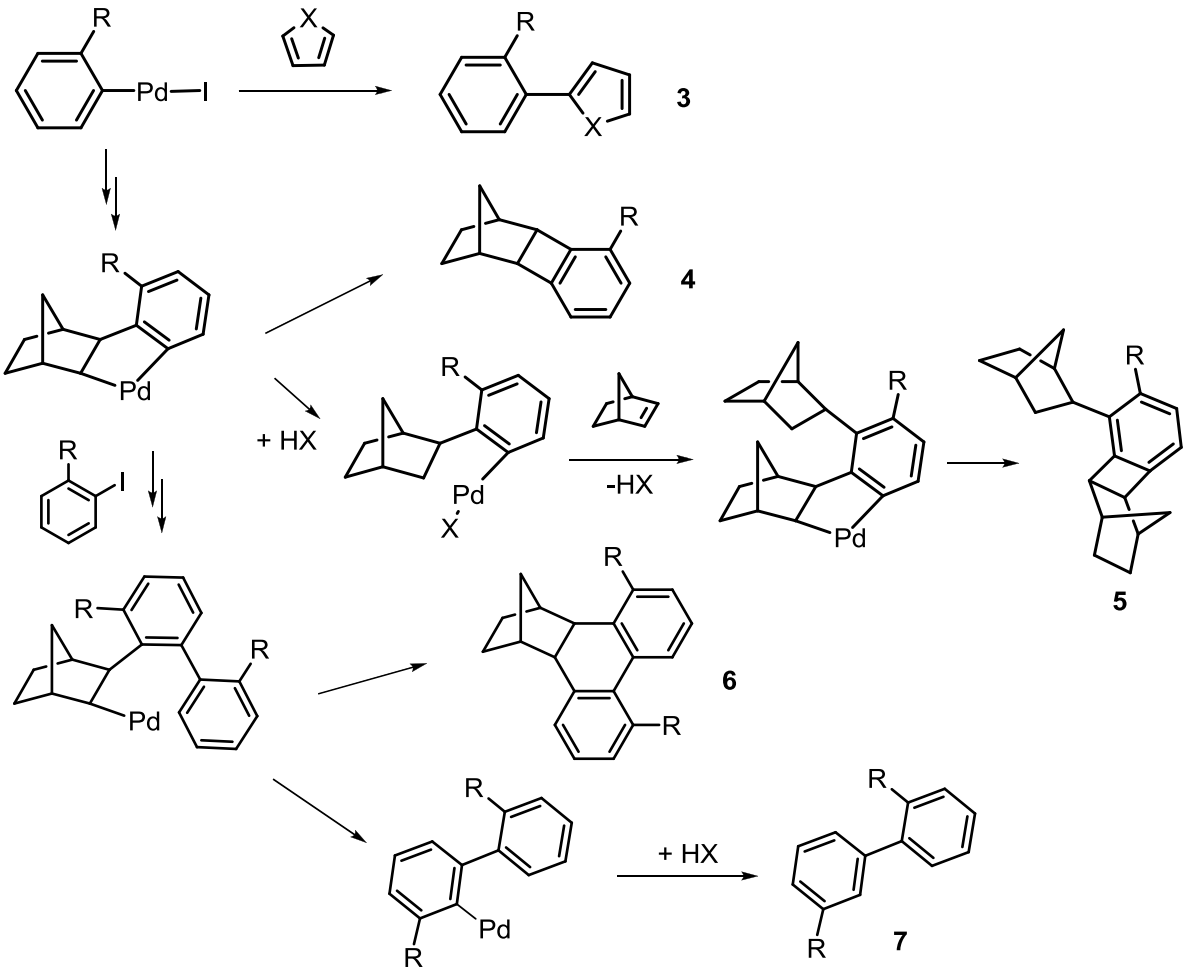
Complex **2** now effects a second C–H activation reacting with a heteroarene belonging to the class of furan, thiophene and pyrrole. Since the heterocycle was present in the reaction mixture from the beginning it is amazing, however, that it reacts mainly at the end of the sequence (way b, Scheme 3) and not with the original aryl halide (way a). This is due to the high reactivity of norbornene which traps the palladium-bonded aryl, forming a palladacycle. Only after the attack of a second molecule of the aryl halide with expulsion of norbornene is the newly formed biaryllpalladium bond of **2** able to react with the heterocycle.



Scheme 3. Different reactivity of arylpalladium bonds in the absence or presence of norbornene.

It is worth noting that reaction b) of Scheme 3 occurs in the best way without the need for adding phosphine ligands. The reason for this behaviour is unclear being related to the effect of the environment of our reaction, including that of the *ortho* substituent. A certain degree of steric hindrance around the metal seems to be necessary. In agreement with this we observe that 1-naphthyl and 2-isopropylphenyl iodides are good substrates. In general we observe that secondary products increase when the steric hindrance of an alkyl group R decreases. The electronic effect shown by an *ortho* CO_2Me also turns out to be positive. Thus the nature of the effect caused by R groups deserves further study.

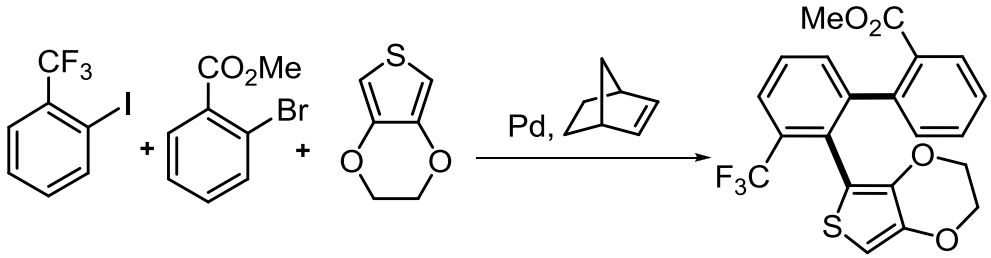
The secondary products derive from competing reactions and show different distribution depending on the *ortho* substituent. Those found with *o*-substituted iodobenzene and an heterocycle are reported in Scheme 4. Analogous norbornene-containing products (**4**–**6**) are observed in the reactions presented in the following chapters of this thesis.



Scheme 4. Secondary products found in the reaction of *o*-substituted iodobenzene and an heterocycle.

Apart from product **3**, resulting from direct attack of the starting aryl iodide on the heterocycle and **7**, from hydrogenolytic aryl coupling, they incorporate norbornene in different ways as we already reported.[8] For example with R = *i*-Pr products **3**–**6** are all formed in 3–5% each. In addition an *ortho* methyl group readily forms condensed cyclopentane structures by cyclization with norbornene[9] and also **3** (R = Me) is present in significant amount (12%), while the yield of **1** is 53% only.

Notably the reaction can be extended to the more complex case of an *ortho* substituted aryl iodide, an aryl bromide,[3c] instead of two molecules of aryl iodide,[3d] and a heterocycle. Yields and selectivities are lower, however, and further study is required to find out the best conditions. Thus the following reaction gives only 49% of product (Scheme 5).



Scheme 5. One pot reaction of an *o*-substituted aryl iodide and an aryl bromide with a heterocycle.

In summary, a simple one-step catalytic process for the synthesis of *o*-heteroteraryl derivatives from readily accessible aryl iodides and heterocycles has been developed taking advantage of the unique opportunities offered by the palladium/norbornene system. Further investigation are in progress to expand the scope of the reaction.

References

[1] L. Ackerman, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.
[2] a) B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou *J. Org. Chem*. **2009**, *74*, 1826; b) M. Lafrance, D. Lapointe, K. Fagnou *Tetrahedron*, **2008**, 64, 6015; c) J. C. Lewis, R. G. Bergman, J. A. Ellman *Acc. Chem. Res*. **2008**, *41*, 1013; d) G. B. Bajracharya, O. Daugulis *Org. Lett*. **2008**, 10, 4625; e) K. Kakiuchi, T. Kochi *Synthesis* **2008**, 3013; f) R. B. Bedford, M. Betham, J. P. H. Charmant, A. L. Weeks *Tetrahedron* **2008**, *64*, 6038; g) F. Bellina, S. Cauteruccio, R. Rossi *Curr. Org. Chem*. **2008**, *12*, 774; h) D. Alberico, M. E. Scott, M. Lautens *Chem. Rev*. **2007**, *107*, 174; i) I. V. Seregin, V. Gevorgian *Chem. Soc. Rev*. **2007**, *36*, 1173; j) I. J. Fairlamb *Chem. Soc. Rev*. **2007**, *36*, 1036; k) K. Godula, D. Sames *Science* **2006**, *312*, 67; l) M. Miura, T. Satoh *Top. Organomet. Chem*. **2005**, *14*, 55; m) G. Dyker, *Handbook of C–H Transformations*, Wiley, Weinheim, **2005**; n) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**; o) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd Ed., Wiley-VCH, Weinheim, **2004**; p) J. Hassan, M. Sevignon, C. Gozzi, E. Schultz, M. Lemaire *Chem. Rev*. **2002**, *102*, 1359.
[3] a) M. Catellani, E. Motti, N. Della Ca' *Acc. Chem. Res*. **2008**, *41*, 1512; b) M. Catellani *Top. Organometal. Chem*. **2005**, *14*, 21; c) F. Faccini, E. Motti, M. Catellani *J. Am. Chem. Soc*. **2004**, *126*, 78; d) E. Motti, G. Ippomei, S. Deledda, M. Catellani *Synthesis* **2003**, 2671; e) E. Motti, F. Faccini, I. Ferrari, M. Catellani, R. Ferraccioli *Org. Lett*. **2006**, *8*, 3967.
[4] a) P. Fitton, E. A. Rick *J. Organomet. Chem*. **1971**, *28*, 287; b) A. H. Roy, J. F. Hartwig *J. Am. Chem. Soc*. **2003**, *125*, 13944; c) C. Amatore, A. Jutand *Acc. Chem. Res*. **2000**, *33*, 314.
[5] a) H. Horino, M. Arai, N. Inoue *Tetrahedron Lett*. **1974**, 647; b) C.-S. Li, C.-H. Cheng, F.-L. Liao, S.-L. Wang *Chem. Commun*. **1991**, 710; c) M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein *Organometallics*, **1994**, *13*, 3465; d) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin *J. Am. Chem. Soc*. **2002**, *124*, 4336.
[6] a) I. P. Beletskaya, A. V. Cheprakov *J. Organometal. Chem*. **2004**, *689*, 4055; b) M. Catellani, G. P. Chiusoli *J. Organomet. Chem.* **1992**, *425*, 151; c) M. Catellani, G. P. Chiusoli *J. Organomet. Chem.* **1988**, *346*, C27; c) C.-H. Liu, C.-S. Li, C.-H. Cheng *Organometallics* **1994**, *13*, 18.

[7] a) G. Dyker *Angew. Chem. Int. Ed*. **1999**, *38*, 1699; b) F. Kakiuchi, N. Chatani *Adv. Synth. Catal*. **2003**, *345*, 1077; c) A. R. Dick, M. S. Sanford *Tetrahedron* **2006**, *62*, 2439.
[8] a) M. Catellani, L. Ferioli *Synthesis* **1996**, 769; b) S. Deledda, E. Motti, M. Catellani *Can. J. Chem*. **2005**, *83*, 741.
[9] M. Catellani, E. Motti, S. Ghelli *Chem. Commun*. **2000**, 2001.

Experimental section

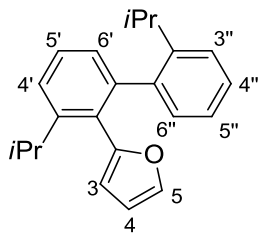
General remarks

Most reagents were obtained from commercial sources and used as received. 2-*i*-Propyliodobenzene was prepared starting from the corresponding aniline derivative by diazotization procedure.[1] DMF was dried and stored over 4 Å molecular sieves under nitrogen. Reactions were carried out under nitrogen using standard Schlenk technique. Gas chromatography analyses were performed with a Carlo Erba HRGC 5300 instrument using a 30 m SE-30 capillary column. Flash column chromatography was performed on Merck Kieselgel 60 and thin-layer chromatography on Merck $60F_{254}$ plates. Melting points were determined with an Electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AC-300 and AVANCE 300 spectrometers at 300.1 and 75.4 MHz respectively, using the solvent as internal standard (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). The reported assignments are based on decoupling, COSY, NOESY, C–H, HMBC correlation experiments. Electron impact mass spectra were performed on a Hewlett Packard instrument working at 70 eV ionization energy (HP 6890 GC system and a HP5973 Mass selective detector). Elemental analyses were carried out with a Carlo Erba EA 1108-Elemental Analyzer.

General procedure for the reaction of an ortho-substituted aryl iodide and a heteroaryl compound

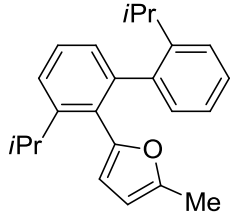
The aryl iodide (1.43 mmol), the heteroarene (1.80 mmol of 3,4-ethylenedioxythiophene; 7.0 mmol of furan, 2-methylfuran, thiophene and *N*-methylpyrrole), norbornene (34 mg, 0.36 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol) and K_2CO_3 (222 mg, 1.61 mmol) in DMF (16 mL) were stirred with a magnetic bar in a closed Schlenk-type flask under nitrogen at 105 °C (in the case of ethylendioxythiophene, furan and 2-methylfuran) or at 120 °C (in the case of thiophene and *N*-methylpyrrole) for 24–48 h. At the end of the reaction the mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times with brine (3 × 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was analyzed by GC and ^{1}H NMR spectroscopy. The products were isolated by flash column chromatography on silica gel using a mixture of hexane-EtOAc as eluent.

2-(3',2''-Di-isopropyl-1',1''-biphenyl-2'-yl)furan (**1a**)



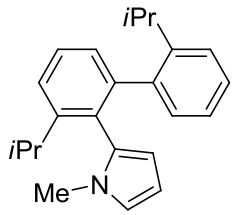
Yield: 65%. M.p.: 74–75 °C. Eluent: hexane-EtOAc 95:5.
^{1}H NMR: δ 7.45–7.41 (2H, m, H4', H5'), 7.30 (1H, dd, *J* = 1.7, 0.7 Hz, H5), 7.27–7.22 (2H, m, H3'', H4''), 7.17–7.11 (1H, m, H6'), 7.11–7.03 (2H, m, H5'', H6''), 6.21 (1H, dd, *J* = 3.2, 1.8 Hz, H4), 5.85 (1H, dd, *J* = 3.2, 0.7 Hz, H3), 2.96 (1H, hept, *J* = 6.8 Hz, CH(C3')), 2.81 (1H, hept, *J* = 6.8 Hz, CH(C2'')), 1.31, 1.24 (6H, 2 d, *J* = 6.8 Hz, CH_3CH(C3')), 1.09, 1.01 (6H, 2 d, *J* = 6.8 Hz, CH_3CH(C2'')). ^{13}C NMR: δ 151.6 (C2), 149.4 (C3'), 146.3 (C2''), 142.9 (C1'), 141.0 (C5), 140.4 (C1''), 129.9 (C6''), 129.7 (C2'), 128.4 (C5'), 127.4 (C6'), 127.2 (C4''), 124.8 (C3''), 124.4 (C5''), 124.2 (C4'), 110.2 (C4), 110.0 (C3), 30.6 (CH(C3')), 29.7 (CH(C2'')), 25.0 (CH_3CH(C2'')), 24.3 (CH_3CH(C3')), 24.2 (CH_3CH(C3')), 22.8 (CH_3CH(C2'')). MS: M^+ 304 (74), *m/z* 261 (31), 243 (29), 233 (51), 231 (50), 229 (37), 219 (100), 217 (33), 215 (50), 203 (64), 202 (91), 191 (47), 178 (38), 165 (36), 152 (17), 43 (57). Anal. Calcd. for $C_{22}H_{24}O$: C, 86.80; H, 7.95; O, 5.26. Found: C, 86.69; H, 7.99.

2-(3,2'-Di-isopropyl-1,1'-biphenyl-2-yl)-5-methylfuran (**1b**)



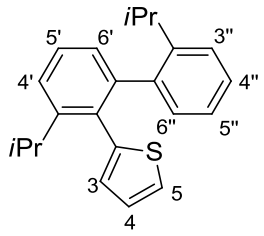
Yield: 71%. M.p.: 58-59 °C. Eluent: hexane-EtOAc 95:5.
^{1}H NMR: δ 7.44–7.36 (2H, m), 7.27–7.22 (2H, m), 7.13–7.02 (3H, m), 5.78 (1H, dq, *J* = 3.1, 0.9 Hz), 5.72 (1H, d, *J* = 3.1 Hz), 3.06 (1H, hept, *J* = 6.9 Hz), 2.80 (1H, hept, *J* = 6.9 Hz), 2.16 (3H, d, *J* = 0.9 Hz), 1.31 (3H, d, *J* = 6.9 Hz), 1.24 (3H, d, *J* = 6.9 Hz), 1.08 (3H, d, *J* = 6.9 Hz), 1.01 (3H, d, *J* = 6.9 Hz). ^{13}C NMR: δ 150.6, 149.6, 149.0, 146.4, 142.7, 140.7, 130.1, 130.0, 128.0, 127.3, 127.1, 124.7, 124.3, 124.2, 110.8, 106.1, 30.4, 29.7, 25.0, 24.3, 22.6, 13.4. MS: M^+ 318 (87), *m/z* 275 (28), 245 (31), 233 (100), 215 (41), 202 (37), 191 (15), 178 (16). Anal. Calcd. for $C_{23}H_{26}O$: C, 86.75; H, 8.23; O, 5.02. Found: C, 86.81; H, 8.26.

2-(3,2'-Di-isopropyl-1,1'-biphenyl-2-yl)-*N*-methylpyrrole (**1c**)



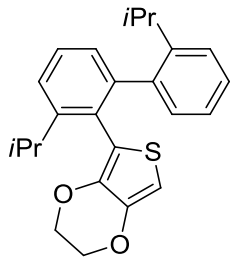
Yield: 66% of a pale yellow oil. Eluent: hexane-EtOAc 95:5. A 2:1 mixture of stereoisomers indicated as A and B.
^{1}H NMR: δ 7.48–7.41 (4H, m), 7.25–7.01 (9H, m), 6.93 (1H, d further split, *J* = 7.9 Hz, A), 6.50–6.46 (2H, m, 1H (A), 1H (B)), 6.03 (1H, dd, *J* = 3.5, 2.5 Hz, B), 5.98 (1H, dd, *J* = 3.5, 2.2 Hz, A), 5.88 (1H, dd, *J* = 3.5, 1.5 Hz, B), 5.78 (1H, br d, *J* = 3.5 Hz, A), 3.31 (3H, s, A), 3.23 (3H, s, B), 2.87, 2.82, 2.77, 2.73 (4H, four overlapping hept, *J* = 6.8 Hz, 2H (A), 2H (B)), 1.28 (3H, d, *J* = 6.8 Hz, B), 1.25–1.17 (12H, four overlapping d, 9H (A), 3H (B)), 1.14 (3H, d, *J* = 6.8 Hz, B), 1.06, 1.05 (6H, two partly overlapping d, *J* = 6.8 Hz, 3H (A), 3H (B)). ^{13}C NMR: δ 150.3, 150.2, 146.5, 145.7, 143.8, 143.0, 140.7, 139.7, 131.3, 131.1, 131.0, 130.5, 130.0, 128.6, 128.0, 127.8, 127.6, 127.4, 127.2, 127.0, 124.9, 124.7, 124.2, 124.03, 123.98, 120.2, 34.1, 33.6, 30.4, 29.8, 29.6, 25.9, 25.5, 25.3, 25.1, 23.31, 23.26, 23.0, 22.4. MS: M^+ 317 (100), *m/z* 302 (40), 274 (71), 245 (39), 232 (36), 217 (23), 215 (18), 202 (17). Anal. Calcd. for $C_{23}H_{27}N$: C, 87.02; H, 8.57; N, 4.41. Found: C, 86.91.17; H, 8.61.

2-(3',2''-Di-isopropyl-1',1''-biphenyl-2'-yl)thiophene (**1d**)



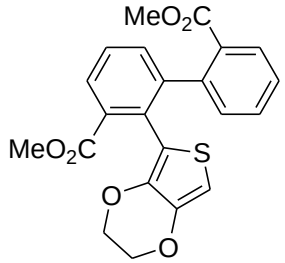
Yield: 70%. M.p.: 64–65 °C. Eluent: hexane-EtOAc 95:5.
^{1}H NMR: δ 7.48–7.38 (2H, m, H4', H5')), 7.27–7.19 (2H, m, H3'', H4''), 7.19–7.12 (2H, m, H5, H6'), 7.09-7.00 (2H, m, H5'', H6''), 6.87 (1H, dd, *J* = 5.1, 3.4 Hz, H4), 6.73 (1H, dd, *J* = 3.4, 1.3 Hz, H3), 3.07 (1H, hept, *J* = 6.9 Hz, CH(C3')), 2.82 (1H, hept, *J* = 6.8 Hz, CH(C2'')), 1.28, 1.25 (6H, 2 d, *J* = 6.9 Hz, CH_3CH(C3')), 1.14, 1.13 (6H, 2 d, *J* = 6.8 Hz, CH_3CH(C2'')). ^{13}C NMR: δ 149.1 (C3'), 146.3 (C2''), 142.8 (C1'), 140.23 (C2), 140.19 (C1''), 132.1 (C2'), 130.5 (C6''), 127.7 (C5'), 127.6 (C3), 127.3 (C6'), 127.2 (C4''), 125.9 (C4), 125.2 (C5), 124.7 (C3''), 124.3 (C4'), 124.2 (C5''), 30.2 (CH(C3')), 29.9 (CH(C2'')), 25.4 ((CH_3CH(C2'')), 24.6 (CH_3CH(C3')), 24.5 (CH_3CH(C3')), 22.6 ((CH_3CH(C2'')). MS: M^+ 320 (100), *m/z* 305 (14), 277 (40), 263 (16), 247 (31), 245 (20), 235 (53), 229 (27), 215 (33), 203 (22), 202 (25). Anal. Calcd. for $C_{22}H_{24}S$: C, 82.45; H, 7.55; S, 10.00. Found: C, 82.37; H, 7.58.

2-(3,2'-Di-isopropyl-1,1'-biphenyl-2-yl)-3,4-ethylenedioxythiophene (**1e**)



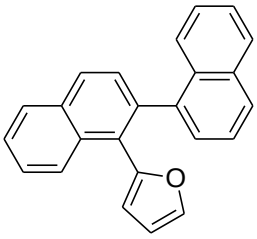
Yield: 70%. M.p.: 130.0–131.5 °C. Eluent: hexane-EtOAc 95:5. A 4:3 mixture of two stereoisomers indicated as A and B.
^{1}H NMR: δ 7.47–7.40 (4H, m, A, B), 7.32–7.12 (9H, m, 4H (A), 5H (B)), 7.05 (1H, ddd, *J* = 7.8, 6.6, 1.9 Hz, A), 6.24, 6.18 (2H, 2 s, 1H (B), 1H (A)), 4.20–3.96 (8H, m, 4H (A), 4H (B)), 3.11, 3.09 (2H, 2 hept, *J* = 6.9 Hz, 1H (A), 1H (B)), 2.90, 2.86 (2H, 2 hept, *J* = 6.9 Hz, 1H (B), 1H (A)), 1.37 (3H, d, *J* = 6.9 Hz, B), 1.30, 1.29 (6H, 2 d, *J* = 6.9 Hz, A), 1.22 (3H, d, *J* = 6.9 Hz, A), 1.21 (3H, d, *J* = 6.9 Hz, B), 1.20 (3H, d, *J* = 6.9 Hz, A), 1.12, 1.09 (6H, 2 d, *J* = 6.9 Hz, B). ^{13}C NMR: δ 150.2, 149.7, 146.7, 146.1, 143.7, 143.4, 140.5, 140.3, 140.21, 140.19, 138.1, 137.7, 130.7, 129.6, 129.2, 129.1, 128.1, 128.0, 127.6, 127.4, 127.23, 127.19, 124.6, 124.5, 124.2, 124.1, 124.0, 123.9, 114.6, 99.0, 98.0, 64.4, 64.22, 64.18, 30.6, 30.4, 29.8, 29.4, 25.6, 25.3, 24.8, 24.3, 24.1, 23.5, 23.0, 22.9. MS: M^+ 378 (100), *m/z* 335 (53), 287 (20), 261 (15), 221 (18), 202 (24), 189 (17), 178 (12), 165 (15). Anal. Calcd. for $C_{24}H_{26}O_2S$: C, 76.15; H, 6.92; O, 8.45; S, 8.47. Found: C, 76.07; H, 6.94.

2-(3,2'-Dicarbomethoxy-1,1'-biphenyl-2-yl)-3,4-ethylenedioxythiophene (**1f**)



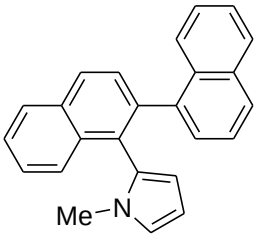
Yield: 82%. M.p.: 88–89 °C. Eluent: hexane-EtOAc 70:30.
^{1}H NMR: δ 7.86–7.81 (2H, m), 7.48–7.39 (3H, m), 7.32 (1H, td, *J* = 7.6, 1.5 Hz), 7.21 (1H, br d, *J* = 7.5 Hz), 6.17 (1H, s), 4.08–3.75 (4H, m), 3.72 (3H, s), 3.59 (3H, s). ^{13}C NMR: δ 168.2, 167.1, 144.5, 141.6, 140.2, 138.0, 133.1, 132.3, 131.3, 130.8, 130.0, 129.8, 129.7, 128.7, 127.5, 127.2, 113.6, 99.5, 64.2, 52.0, 51.6. MS: M^+ 410 (100), *m/z* 351 (29), 59 (10). Anal. Calcd. for $C_{22}H_{18}O_6S$: C, 64.38; H, 4.42; O, 23.39; S, 7.81. Found: C, 64.27; H, 4.46.

2-(2,1'-Binaphthyl-1-yl)furan (**1g**)



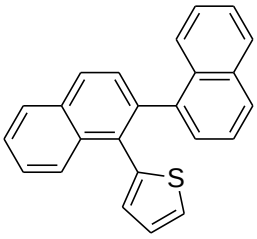
Yield: 62%. M.p.: 139.5–140.5 °C. Eluent: hexane-EtOAc 95:5.
^{1}H NMR: δ 8.02–7.90 (3H, m), 7.86 (1H, d further split, *J* = 8.1 Hz,), 7.81 (1H, d further split, *J* = 8.2 Hz), 7.66–7.52 (4H, m), 7.48–7.39 (2H, m), 7.35 (1H, ddd, *J* = 8.4, 6.9, 1.5 Hz), 7.32–7.26 (2H, m), 6.15 (1H, dd, *J* = 3.2, 1.9 Hz), 5.92 (1H, dd, *J* = 3.2, 0.7 Hz). ^{13}C NMR: δ 150.9, 141.8, 139.6, 139.1, 133.3, 133.1, 133.0, 132.2, 128.8, 128.55, 128.51, 128.04, 128.01, 127.3, 127.1, 126.8, 126.4, 126.2, 126.1, 125.8, 125.5, 124.9, 110.9, 110.4. MS: M^+ 320 (100), *m/z* 303 (36), 289 (70), 276 (23), 265 (28), 145 (15). Anal. Calcd. for $C_{24}H_{16}O$: C, 89.97; H, 5.03; O, 4.99. Found: C, 89.90; H, 5.05.

2-(2,1'-Binaphthyl-1-yl)-*N*-methylpyrrole (**1h**)



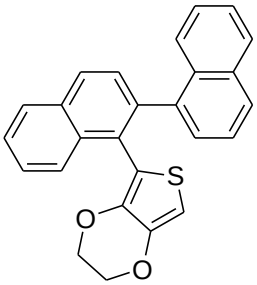
Yield: 69%. M.p.: 141–142 °C. Eluent: hexane-EtOAc 90:10. A 1:1 mixture of two stereoisomers indicated as A and B.
^{1}H NMR: δ 8.01–7.94 (4H, m), 7.89–7.82 (2H, m), 7.78–7.73 (2H, m), 7.72–7.67 (2H, m), 7.66–7.32 (15H, m), 7.10 (1H, *J* = 7.0, 1.2 Hz), 6.57 (1H, dd, *J* = 2.6, 1.7 Hz, B), 6.39 (1H, dd, *J* = 2.6, 1.8 Hz, A), 6.18 (1H, dd, *J* = 3.5, 1.8 Hz, A), 6.08 (1H, dd, *J* = 3.5, 2.6 Hz, A), 5.84 (1H, dd, *J* = 3.6, 2.6 Hz, B), 5.61 (1H, dd, *J* = 3.6, 1.7 Hz, B), 3.35, 2.92 (6H, 2 s, 3H (B), 3H (A)). ^{13}C NMR: δ 140.2, 140.0, 139.2, 138.5, 134.7, 134.4, 133.5, 133.2, 132.8, 132.5, 131.9, 130.6, 130.4, 129.9, 129.2, 129.0, 128.8, 128.6, 128.4, 128.0, 127.8, 127.6, 127.3, 126.9, 126.7, 126.6, 126.5, 126.4, 126.01, 125.94, 125.8, 125.66, 125.60, 125.56, 125.54, 125.3, 124.9, 124.7, 121.3, 121.1, 112.3, 109.6, 107.2, 107.0, 34.3, 34.1. MS: M^+ 333 (100), *m/z* 317 (14), 303 (19), 302 (25), 289 (28). Anal. Calcd. for $C_{25}H_{19}N$: C, 90.06; H, 5.74; N, 4.20. Found: C, 90.13; H, 5.77.

2-(2,1'-Binaphthyl-1-yl)thiophene (**1i**)



Yield: 70%. M.p.: 169–170 °C. Eluent: hexane-EtOAc 95:5.
^{1}H NMR: δ 7.98 (2H, two overlapping d, *J* = 8.2 Hz), 7.92 (1H, d further split, *J* = 8.4 Hz), 7.83 (1H, d further split, *J* = 8.3 Hz), 7.75 (1H, d further split, *J* = 8.2 Hz), 7.62–7.25 (8H, m), 7.13–7.08 (1H, m), 6.83–6.77 (2H, m). ^{13}C NMR: δ 139.3, 139.1, 133.7, 133.2, 132.9, 132.4, 131.5, 128.7, 128.0, 127.9, 127.6, 127.3, 126.6, 126.4, 126.1, 126.0, 125.71, 125.67, 125.5, 124.8. MS: M^+ 336 (100), *m/z* 303 (67), 302 (73), 289 (18), 276 (14), 150 (16). Anal. Calcd. for $C_{24}H_{16}S$: C, 85.68; H, 4.79; S, 9.53. Found: C, 85.57; H, 4.82.

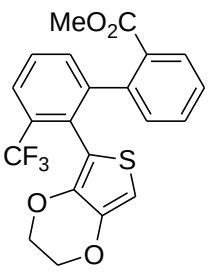
2-(2,1'-Binaphthyl-1-yl)-3,4-ethylenedioxythiophene (**1j**)



Yield: 77%. M.p.: 196–197 °C. Eluent: hexane-EtOAc 95:5. A 3:2 mixture of two stereoisomers indicated as A and B.
^{1}H NMR: δ 8.07–7.25 (26H, m, A, B), 6.18, 6.07 (2H, 2 s, 1H (A), 1H (B)), 4.32–3.89 (5H, m, 4H (B), 1H (A)), 3.74–3.60 (2H, m, A), 3.07–2.93 (1H, m, A). ^{13}C NMR: δ 140.5, 140.42, 140.36, 140.1, 139.6, 139.3, 138.9, 133.6, 133.4, 133.22, 133.17, 133.0, 132.9, 132.3, 132.0, 128.8, 128.7, 128.34, 128.30, 128.1, 128.0, 127.7, 127.4, 127.3, 127.2, 126.9, 126.74, 126.71, 126.5, 126.4, 126.3, 126.0, 125.7, 125.5, 125.3, 124.9, 124.8, 124.7, 99.2, 99.1, 64.5, 64.2, 63.6. MS: M^+ 394 (100), *m/z* 361 (87), 295 (37), 276 (26), 265 (73), 263 (71), 147 (13), 131 (10). Anal. Calcd. for $C_{26}H_{18}O_2S$: C, 79.16; H, 4.60; O, 8.11; S, 8.13. Found: C, 79.01; H, 4.62.

2-(2'-Carbomethoxy-3-trifluoromethyl-1,1'-biphenyl-2-yl)-3,4-ethylenedioxythiophene

(Scheme 5)



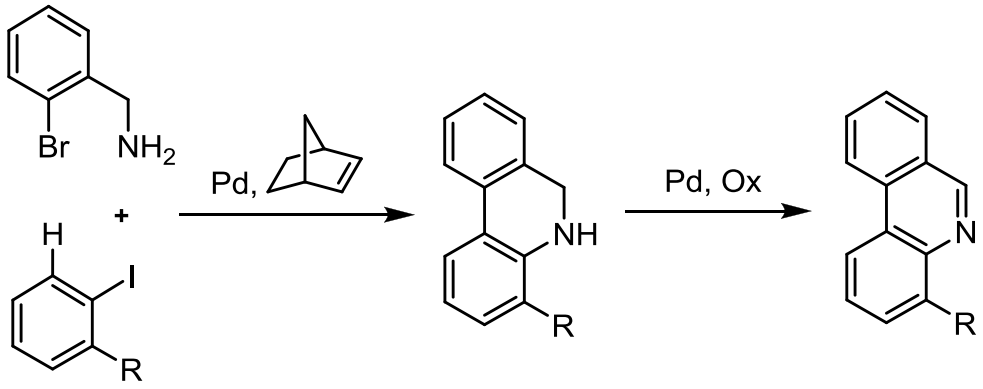
Yield: 49%. M.p.: 113–114 °C. Eluent: hexane-EtOAc 80:20. A 2:1 mixture of stereoisomers indicated as A and B.
^{1}H NMR: δ 7.96–7.87 (2H, m, 1H (A), 1H (B)), 7.83–7.73 (2H, m, 1H (A), 1H (B)), 7.59–7.28 (8H, m, 4H (A), 4H (B)), 7.24 (1H, dd, *J* = 7.5, 1.5 Hz, A), 7.12 (1H, dd, *J* = 7.5, 1.5 Hz, B), 6.17 (2H, s, 1H (A), 1H (B)), 4.13–3.81 (8H, m, 4H (A), 4H (B)), 3.66 (3H, s, A), 3.58 (3H, s, B). ^{13}C NMR: δ 167.2, 167.0, 146.8, 146.4, 141.4, 140.9, 140.1, 139.8, 139.1, 138.9, 133.0, 132.0, 131.42 and 131.38 (two partly overlapping q, $J_{C,F}$ = 29.3 Hz), 131.37, 130.9, 130.8, 130.7, 130.0, 129.8, 129.6, 129.3, 128.65 and 128.61 (two partly overlapping q, $J_{C,F}$ = 1.6 Hz), 128.1, 127.53, 127.51, 127.4, 125.16 and 125.06 (two partly overlapping q, $J_{C,F}$ = 5.4 Hz), 123.9 (q, $J_{C,F}$ = 272.3 Hz), 111.1, 110.9, 99.8, 99.7, 64.33, 64.31, 64.29, 64.1, 51.8, 51.6. MS: M^{+} 420 (100), *m/z* 361 (40), 289 (18), 264 (17), 233 (19), 232 (18), 182 (13), 59 (8). Anal. Calcd. for $C_{21}H_{15}F_3O_4S$: C, 60.00; H, 3.60; F, 13.56; O, 15.22; S, 7.63. Found: C, 59.89; H, 3.65.

References

[1] M. S. Lesslie, U. J. H. Mayer *J. Chem. Soc.* **1961**, 611.

Straightforward synthesis of phenanthridines from aryliodides and bromobenzylamines *via* dual palladium catalysis

Palladium-catalyzed cascades involving direct C–H bond activation have emerged as powerful tools for rapid access to complex polycyclic structures because they bypass the limitations associated to traditional cross coupling methodologies, such as introduction of activating groups.[1] In this context, the addition of norbornene as cocatalyst triggers the formation of Pd(IV) intermediates, which give access to complex catalytic sequences uniquely suited to selective sequential bond forming.[2] New syntheses of polycyclic frameworks from simple substrates are thus easily accessible.[3] Yet, despite the variety of possibilities offered by Pd/norbornene catalysis, the introduction of a *C*-amination step in a cascade has been limited to anilines.[4] Nitrogen containing polycyclic heteroaromatic compounds are ubiquitous in medicinal chemistry, and there is thus a constant need for new strategies for their rapid assembling from simple reagents. Furthermore, a Pd(IV)-manifold has never been associated to another metal-mediated reaction in a dual catalytic process.

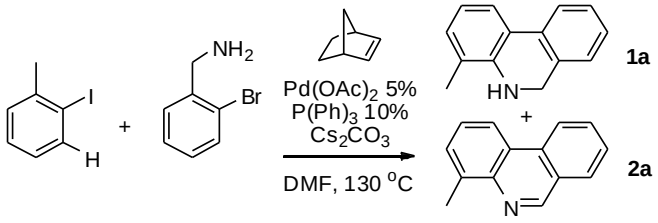


Scheme 1. One-pot strategy to Phenanthridines

Reasoning that some Pd(II) complexes could also catalyze oxidative dehydrogenations to generate alkenes,[5] we felt that a combination of the latter reaction with Pd/norbornene mediated formations of *N*-containing heterocycles could drive the reactivity of *unprotected benzylic amines* toward the formation of phenanthridines *via* a one pot aromatization step.

We report herein the protecting-group free rapid assembly of substituted phenanthridines from bromo-benzylamines and *o*-substituted iodo arenes.

Table 1. Formation of Phenanthridines from benzylamines



Entry	Norbornene	Conv. Ar-I[a]	Conv. Ar-Br[a]	Yield (%) **1a**[b]	Yield (%) **2a**[b]
1[c]	1 eq.	10	7	6	-
2	1 eq.	95	70	53	12
3	0.5 eq.	99	95	58	27
4	0.25 eq.	55	45	20	24
5	0.5 + 3 eq.	99	95	17	65
6[d]	0.5 eq.	99	95	-	85

Reactions conditions: $Pd(OAc)_2$ (0.013 mmol), PPh_3 (0.026 mmol), norbornene, Cs_2CO_3 (0.6 mmol), Ar-I (0.29 mmol), Ar-Br (0.26 mmol) in DMF (6 mL) at 130 °C under argon until palladium black precipitation (24-48h); [a] determined by GC; [b] ^1H NMR yield using $MeNO_2$ as internal standard; [c] without PPh_3; [d] O_2 added after full conversion.

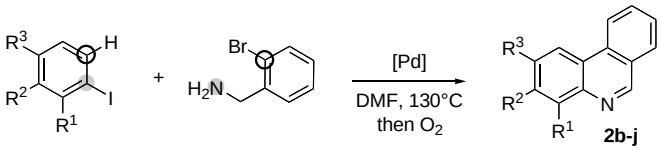
We selected 2-iodotoluene and 2-bromobenzylamine as representative reagents. Those were reacted in the presence of palladium acetate (5 mol%) and norbornene (1 equiv) as co-catalysts in DMF at 130 °C. The conversion was low (10%), and only 4-methyl-5,6-dihydrophenanthrine **1a** — that is the product that underwent only the Pd(IV) cycle — was obtained in 6% yield (Table 1, entry 1). Addition of triphenylphosphine proved beneficial, yielding 53% of **1a** and 12% of the desired phenanthridine **2a** (entry 2). Lowering the norbornene amount to 50 mol% increased the relative ratio of **2a** (entry 3). Further lowering of that amount again increased the ratio of **2a**, albeit at the expense of conversion (entry 4).

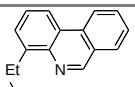
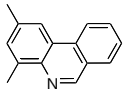
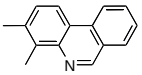
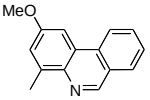
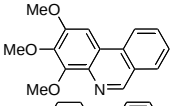
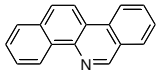
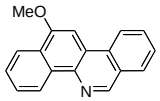
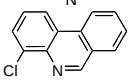
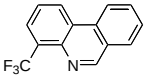
This suggested that in the initial stage of the reaction, too much norbornene and the use of reactive aryl iodide led to norbornyl-containing byproducts.[6] Phenanthrdinine **2a** is formed *via* dehydrogenation of **1a**, which requires a sacrificial olefin to accept the dihydrogen. Thus, part of the norbornene is most probably also consumed for the aromatization of **1a**. If its initial amount drops too low, none is available for further catalysis. We thus decided to add three

equivalents of norbornene at 90 % conversion in order to optimize both conversion and aromatization. This resulted in a increased ratio of **2a** (**1a**/**2a** = 1:4, entry 5).[7]

Addition of more norbornene after full conversion did not change the products ratio. We finally found that simple induction of oxygen *via* a balloon at the end of the reaction (evidenced by precipitation of Pd black) allowed us to get rid of any trace of **1a**. Indeed, in a typical experiment, 1.1 eq. of 2-iodotoluene was reacted with 2-bromobenzylamine in the presence of 5 mol% palladium, 10 mol% triphenylphosphine and 50 mol% norbornene in DMF at 130 °C under argon for 36 h, then, after addition of O_2,the reaction mixture was kept overnight at the same temperature. Phenanthridine **2a** was obtained in 85% yield (entry 6). With these optimized conditions in hands, we first investigated the scope of the reaction with substituted aryl iodides.

Table 2. Effect of Subsituents on the Aryl Iodide Partner



Entry[a]	R^1, R^2, R^3	Product	Yield (%)
1[b]	Et, H, H		**2b**, 82
2[b]	Me, H, Me		**2c**, 81
3[b]	Me, Me, H		**2d**, 91
4	Me, H, OMe		**2e**, 65
5	Me, OMe, OMe		**2f**, 95
6	$R^1 = R^2 = (CH)_4$ R^3 = OMe		**2g**, 80
7	$R^1 = R^2 = (CH)_4$ R^3 = OMe		**2h**, 77
8	Cl, H, H		**2i**, 31
9	CF_3, H, H		**2j**, 22

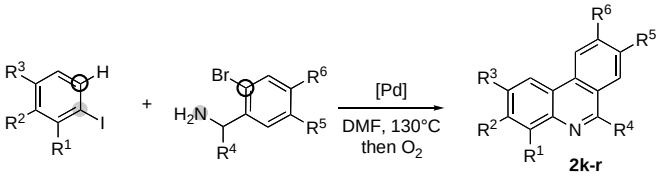
[a] Conditions: see table 1. An O_2 ballon is introduced after apparition of Pd black and the reaction left overnight at 130 °C. [b] without O_2 the phenanthridine/dihydrophenanthridine ratio was 1:2 ratio (same combined yield).

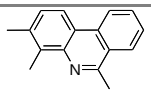
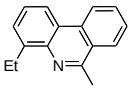
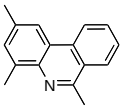
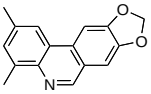
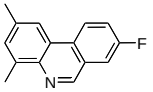
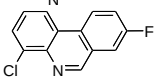
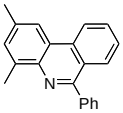
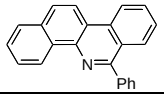
Good results were obtained with electron-donating substituents, whether alkyl (entries 1-3) or alkoxy (entries 4-5). Benzo[c]phenanthridines were also prepared in high yields starting from substituted iodonaphthalenes (entries 5 and 6). On the other hand, iodides bearing electron

withdrawing groups at the *ortho* position led to moderate to poor yields (Table 2, entries 8 and 9). This reflects previous results on similar Pd(IV)-type reactions involving electron poor aryl iodides.[1c,8] As before, omission of the oxygen resulted in phenanthridine/dihydrophenanthridine mixtures.

Variation of the benzyl amine was investigated next (table 3). Diversely 6-substituted phenanthridines were obtained with excellent yields both from secondary α-methylbenzylamine (Table 3, entries 1-3) and dibenzylamine derivatives (entries 8-9). Aromatic substituents of different electronic and steric properties did not disrupt the reaction, which proved much more tolerant of substitution of the benzylamine part (entries 4-7) than it was of substitution of the iodide partner. In particular, electron-donating and electron-withdrawing groups worked equally well, independently of the substitution on the other parner. Again this is in agreement both with previous findings[3a,8] and the proposed reaction mechanism (*vide infra*). Note that our method is thus suitable for the synthesis of fluorinated phenanthridines.

Table 3. Effect of Substituents on the Aryl Bromide Partner



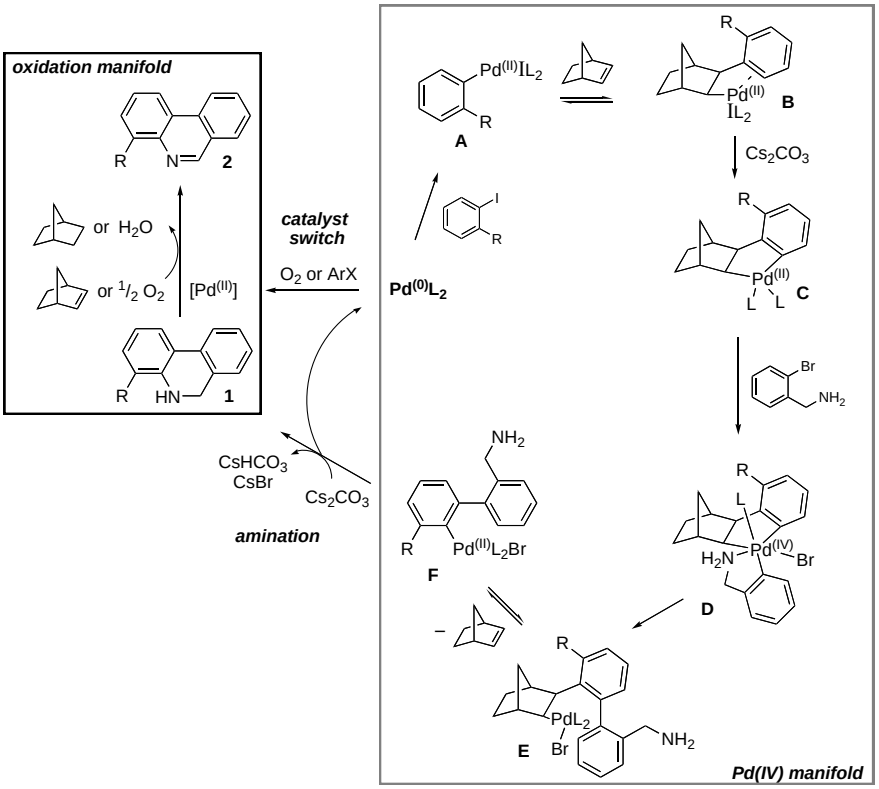
Entry[a]	Substituents	Product	Yield
1	$R^1 = R^2 = Me$ $R^4 = Me$		**2k**, 90
2	$R^1 = Et$ $R^4 = Me$		**2l**, 88
3	$R^1 = R^3 = Me$ $R^4 = Me$		**2m**, 90
4[b]	$R^1 = R^3 = Me$ R^5, R^6 = $–OCH_2O–$		**2n**, 82
6	$R^1 = R^3 = Me$ $R^5 = F$		**2o**, 86
7	$R^1 = Cl$ $R^5 = F$		**2p**, 46
8	$R^1 = R^3 = Me$ $R^4 = Ph$		**2q**, 97
9	$R^1 = R^2 =$ $(CH)_4$ $R^4 = Ph$		**2r**, 92

[a] Conditions: see table 1. [b] without O_2 the phenanthridine/dihydrophenanthridine ratio was 1:2 ratio (same combined yield).

A tentative mechanism is depicted in Scheme 2. The *ortho*-substituted aryl iodide first oxidatively adds to Pd(0) to give intermediate Pd(II) complex **A**,[9] which inserts norbornene into the aryl–Pd bond to generate **B**.[10] Arene C–H activation[11] delivers palladacycle **C**.[12] This latter intermediate reacts with the aryl bromide possibly affording Pd(IV) complex **D**, in analogy to observations made for *ortho* alkylations,[2b] in which the amine moiety likely completes the Pd(IV) coordination sphere. Reductive elimination forms biphenyl derivative **E**. Since the norbornyl moiety remains bonded, the steric hindrance in complex **E** causes norbornene to be eliminated to **F**,[2a,1c] which undergoes the final intramolecular amination from the amine, and generates dihydrophenanthridine **1**. Phenanthridine **2** is formed in the presence of dioxygen (or a sacrificial olefin), which presumably both regenerates a Pd(II) species to switch from one catalytic cycle to the other, and acts as the hydrogen scavenger in the dehydrogenation step.[5c]

When norbornene was omitted, low conversions were achieved, and only traces of Ullmann-type coupled biphenyl derivatives were observed. This rules out the possibility that the reaction proceeds *via* initial amination of the iodide followed by intramolecular ring closure. The *ortho*-substituent on the aryl iodide is necessary to trigger biaryl formation rather than attack of a second aryl halide at the norbornyl site of palladacycle **C**.[13,1c]

Scheme 2. Proposed Reaction Mechanism



As phenanthridines form a well known class of molecules with biological properties,[14] many protocols for the synthesis of this class of compounds have been reported.[15] Even if some of these methodologies are efficient, they usually require prefunctionalization of substrates or presence of protecting groups. which impact their atom economy. From that perspective also our method compares well to the reported methods.

In conclusion we have developed a new methodology for the expeditious synthesis of phenanthridines from benzylamines and aryl iodides, by successfully coupling a palladium/norbornene co-catalyzed domino sequence ending *via* an intramolecular amination with an oxidative dehydrogenation, without interference of the free amine. No protecting group or prefunctionalization of the amine is thus required, and the process uses dioxygen as the terminal oxidant. It should thus be of great use for the preparation of bioactive phenanthridines.

References and notes

[1] a) L. Ackermann, V. Rubén, R. K. Anant *Angew. Chem. Int. Ed.* **2010**, *49*, 9792; b) T.W. Lyons, M.S. Sanford *Chem. Rev.* **2010**, *110*, 1147; c) G. P. Chiusoli, M. Catellani, M. Costa, E. Motti, N. Della Ca, G. Maestri *Coord. Chem. Rev.* **2009**, *254*, 456; d) D. Alberico, M. E. Scott, M. Lautens *Chem. Rev.* **2007**, *107*, 174.

[2] a) M. Catellani, M. C. Fagnola *Angew. Chem.* **1994**, *106*, 2559; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2421. b) C. Amatore, M. Catellani, S. Deledda, A. Jutand, E. Motti *Organometallics* **2008**, *27*, 4549; Other recent representative examples of high oxidation state Pd-reactions: c) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb *Chem. Rev.* **2010**, *110*, 824; d) N. D. Ball, J. W. Kampf, M. S. Sanford *J. Am. Chem. Soc.* **2010**, *132*, 2878; e) D. C. Powers, T. Ritter *Nature Chem.* **2009**, *1*, 302.

[3] Recent examples: a) M. Catellani, E. Motti, N. Della Ca *Acc. Chem. Res.* **2008**, *41*, 1512; b) K. M. Gericke, D. I. Chai, N. Bieler, M. Lautens *Angew. Chem. Int. Ed.* **2009**, *48*, 1447; c) Y.-B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Z. Li, M. Lautens *Angew. Chem. Int. Ed.* **2009**, *48*, 1849.

[4] a) N. Della Ca, G. Sassi, M. Catellani *Adv. Synth. Catal.* **2008**, *350*, 2179; b) P. Thansandote, E. Chong, K.-O. Feldman, M. Lautens *J. Org. Chem.* **2010**, *75*, 3495; c) A. Martins, B. Mariampillai, M. Lautens in *Top. Curr. Chem.*, **2010**, *292*, 1; for reviews on Pd-catalyzed *C*-aminations: d) L. Jiang, S. L. Buchwald, in: *Metal Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), 2nd edn., Wiley-VCH: Weinheim, **2004**; e) J. F. Hartwig *Synlett* **2006**, 1283.

[5] a) B. M. Trost; P. J. Metzner *J. Am. Chem. Soc.* **1980**, *102*, 3572; b) J. E. Bercaw, N. Hazari, J. A. Labinger *J. Org. Chem.* **2008**, *73*, 8654; c) J. Muzart *Chem. Asian J.* **2006**, *1*, 508.

[6] N. Della Ca, G. Maestri, M. Catellani *Chem. Eur. J.* **2009**, *15*, 7850.

[7] Diphenylethane was detected in the reaction mixture when stilbene was added at the start of the reaction. This further proves that a metal-catalyzed transhydrogenation reaction is involved.

[8] a) F. Faccini, E. Motti, M. Catellani *J. Am. Chem. Soc.* **2004**, *126*, 78; b) E. Motti, F. Faccini, I. Ferrari, M. Catellani, R. Ferraccioli *Org. Lett.* **2006**, *8*, 3967.

[9] a) P. Fitton, E. A. Rick *J. Organomet. Chem*. **1971**, *28*, 287; b) A. H. Roy, J. F. Hartwig *J. Am. Chem. Soc*. **2003**, *125*, 13944; c) C. Amatore, A. Jutand *Acc. Chem. Res*. **2000**, *33*, 314.

[10] a) H. Horino, M. Arai, N. Inoue *Tetrahedron Lett*. **1974**, 647; b) C.-S. Li, C.-H. Cheng, F.-L. Liao, S.-L. Wang *Chem. Commun*. **1991**, 710; c) M. Portnoy, Y. Ben-David, I. Rousso, D.

Milstein *Organometallics*, **1994**, *13*, 3465; d) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin *J. Am. Chem. Soc*. **2002**, *124*, 4336.
[11] a) I. P. Beletskaya, A. V. Cheprakov *J. Organomet. Chem.* **2004**, *689*, 4055; b) M. Catellani, G. P. Chiusoli *J. Organomet. Chem.* **1988**, *346*, C27; c) C.-H. Liu, C.-S. Li, C.-H. Cheng *Organometallics* **1994**, *13*, 18.
[12] a) G. Dyker *Angew. Chem. Int. Ed.* **1999**, *38*, 1699; b) F. Kakiuchi, N. Chatani *Adv. Synth. Catal.* **2003**, *345*, 1077; c) A. R. Dick, M. S. Sanford *Tetrahedron* **2006**, *62*, 2439.
[13] M. Catellani, G. P. Chiusoli *J. Organomet. Chem.* **1985**, *286*, C13.
[14] a) S.D. Phillips, R.N. Castle *J. Heterocyclic Chem.* **1981**, *18*, 223; b) D. Makhey, B. Gatto, C. Yu, A. Liu, L. F. Liu, E. J. LaVoie *Bioorg. Med. Chem.* **1996**, *4,* 781; c) T. Ishikawa *Med. Res. Rev.* **2001**, *21*, 61; d) W. A. Denny *Curr. Med. Chem.* **2002**, *9*, 1655.
[15] Pd-catalyzed approaches to Phenanthridines: a) D. A. Candito, M. Lautens *Angew. Chem. Int. Ed.* **2009**, *48*, 6713; b) T. Gerfaud, L. Neuville, J. Zhu *Angew. Chem. Int. Ed.* **2009**, *48*, 572; c) N. Della Ca, E. Motti, A. Mega, M. Catellani *Adv. Synth. Catal.* **2010**, *352*, 1451; d) D. Shabashov, O. Daugulis *J. Org. Chem.*, **2007**, *72*,7720.

Experimental section

General remarks

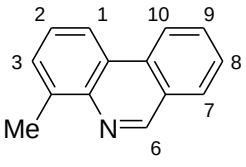
Reagents were obtained from commercial sources and used as received. 4-Methoxy-2-methyliodobenzene, 3,4-dimethoxy-2-methyliodobenzene,[1] 4-methoxyiodonaphthalene,[2] 2-bromo-5-fluorobenzylamine, 1-aminoethylbromobenzene, (2-bromophenyl)-benzylamine and 5-bromo-6-aminomethylbenzo[1,3]dioxole[3] were prepared according to reported procedures. DMF was dried and degassed using an MBraun Solvent Purification System, from which it was collected in a Schlenk-type flask immediately prior to use. Reactions were carried out under argon using standard Schlenk technique. Gas chromatography analyses were performed with a Carlo Erba HRGC 8000Top instrument using a 12 m HSP-5 capillary column. Flash column chromatography was performed on Merck Geduran SI 60 A silica gel (35−70 mm) and thin-layer chromatography on Merck $60F_{254}$ plates. Melting points were determined with a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded with a Bruker Tensor 27 ATR diamant PIKE spectrometer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300 K on Bruker 400 AVANCE spectrometer fitted with a BBFO probehead at 400.1, 100.5 and 376 MHz respectively, using the solvent as internal standard (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR) and $CFCl_3$ (0.00 ppm) for ^{19}F. The reported assignments are based on decoupling, COSY, NOESY, HMBC, HMQC correlation experiments. The terms m, s, d, t, q represent multiplet, singlet, doublet, triplet, quadruplet respectively, and the term br means a broad signal. Exact masses were recorded by Structure et function de molecules bioactives (UMR 7201) of Université Pierre et Marie Curie (electrospray source). CCDC 787343 contains the supplementary crystallographic data for 3,4-dimethylphenanthridine (**2d**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the reaction of ortho-substituted aryl iodide and a bromobenzylamine

To a Schlenk-type flask were added under argon Cs_2CO_3 (185 mg; 0.6 mmol; 2.1 equiv), triphenylphosphine (7 mg; 0.026 mmol; 0.10 equiv), a solution of DMF (3 mL) containing the aryl iodide (0.29 mmol; 1.1 equiv), the (substituted) 2-bromobenzylamine (0.26 mmol; 1 equiv) and norbornene (12 mg, 0.13 mmol; 0.5 equiv), and a solution of $Pd(OAc)_2$ (3 mg, 0.013 mmol; 0.05 equiv) in 3 mL of DMF. The same procedure could be adopted when using 2-bromobenzylamines hydrochloric salts by adding 1 more equiv of base in the reaction vessel.

The resulting suspension was stirred with a magnetic bar at 130 °C until visible formation of palladium black (24-48 h). Oxygen was then added to the reaction mixture *via* balloon, and the suspension was kept at 130°C under stirring until complete oxidation (12 h to overnight), as evidenced by ^{1}H NMR. The mixture was then allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times with a saturated K_2CO_3 solution (3 × 30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was analyzed by GC and ^{1}H NMR spectroscopy. The products were isolated by flash column chromatography on silica gel.

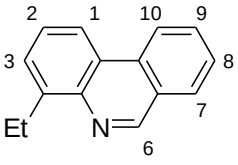
4-Methylphenanthridine **(2a)**



C14H11N M = 193.24 g/mol

Isolated as a white solid. Yield: 85%. M.p.: 73–75 °C. Eluent: Pentane/EtOAc 95:5.
Data correspond to those described in the literature4.
1H NMR: δ 9.34 (1H, s, H6), 8.62 (1H, d, J = 8.4 Hz, H10), 8.46 (1H, dd, J = 8.0, 1.2 Hz, H1), 8.06 (1H, d, J = 8.0 Hz, H7), 7.86 (1H, ddd, J = 8.0, 6.8, 1.2 Hz, H9), 7.73-7.67 (1H, m, H8), 7.64-7.55 (2H, m, H2, H3), 2.92 (3H, s, Me). 13C NMR: δ 152.5 (C6), 143.5 (C4a), 138.0 (C4), 133.2 (C10a), 131.1 (C9), 129.8 (C3), 129.0 (C7), 127.6 (C8), 127.0 (C2), 126.4 (C6a), 124.2 (C10b), 122.4 (C10), 120.4 (C1), 19.0 (Me).

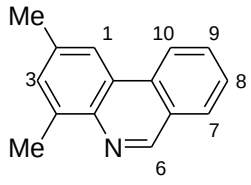
4-Ethylphenanthridine **(2b)**



$C_{15}H_{13}N$ M = 207.27 g/mol

Isolated as a colorless oil. Yield: 82%. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2961, 1616, 1589, 1525, 1462, 1444, 750 cm^{-1}; ^{1}H NMR: δ 9.34 (1H, s, H6), 8.62 (1H, d, *J* = 8.4 Hz, H10), 8.47 (1H, dd, *J* = 8.0, 2.4 Hz, H1), 8.05 (1H, d, *J* = 7.6 Hz, H7), 7.85 (1H, t, *J* = 8.0 Hz, H9), 7.74-7.67 (1H, m, H8), 7.65-7.58 (2H, m, H2, H3), 3.42 (2H, q, *J* = 7.6 Hz, CH_2), 1.46 (3H, t, *J* = 7.6 Hz, Me). ^{13}C NMR: δ 152.1 (C6), 143.6 (C4), 142.6 (C4a), 132.9 (C10a), 130.7 (C9), 128.6 (C7), 128.0 (C3), 127.2 (C8), 126.9 (C2), 126.1 (C6a), 124.0 (C10b), 122.0 (C10), 120.0 (C1), 25.1 (CH_2), 15.5 (Me). HRMS calcd. for $C_{15}H_{14}N$ ($[M + H]^+$) 208.1121, found 208.1120.

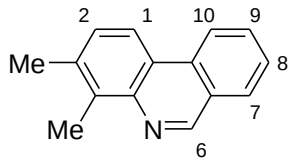
2,4-Dimethylphenanthridine **(2c)**



$C_{15}H_{13}N$ M = 207.27 g/mol

Isolated as a white solid. Yield: 81%. M.p.: 117–118 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2922, 1616, 1588, 1454, 754 cm^{-1}; ^{1}H NMR: δ 9.27 (1H, s, H6), 8.58 (1H, d, *J* = 8.4 Hz, H10), 8.22 (1H, s, H1), 8.03 (1H, d, *J* = 8.0 Hz, H7), 7.82 (1H, td, *J* = 8.0, 1.2 Hz, H9), 7.67 (1H, td, *J* = 8.0, 1.2 Hz, H8), 7.46 (1H, s, H3), 2.91 (3H, s, Me(C2)), 2.64 (3H, s, Me(C4)). ^{13}C NMR: δ 151.2 (C6), 141.0 (C4a), 137.0 (C4), 136.5 (C2), 132.6 (C10a), 131.4 (C3), 130.7 (C9), 128.7 (C7), 127.1 (C8), 126.0 (C6a), 123.8 (C10b), 122.0 (C10), 119.6 (C1), 21.8 (Me(C4)), 18.5 (Me(C2)). HRMS calcd. for $C_{15}H_{14}N$ ($[M + H]^+$) 208.1121, found 208.1118.

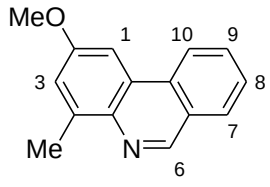
3,4-Dimethylphenanthridine **(2d)**



$C_{15}H_{13}N$ M = 207.27 g/mol

Isolated as a white solid. Yield: 91%. M.p.: 90–91 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2918, 1616, 1589, 1469, 1444, 748 cm^{-1}; ^{1}H NMR: δ 9.31 (1H, s, H6), 8.59 (1H, d, *J* = 8.4 Hz, H10), 8.35 (1H, d, *J* = 8.4 Hz, H1), 8.04 (1H, d, *J* = 7.6 Hz, H7), 7.81 (1H, td, *J* = 8.0, 1.2 Hz, H9), 7.73-7.67 (1H, m, H8), 7.51 (1H, d, *J* = 8.4 Hz, H2), 2.85 (3H, s, Me(C4)), 2.56 (3H, s, Me(C3)). ^{13}C NMR: δ 152.0 (C6), 143.1 (C4a), 136.9 (C3), 135.5 (C4), 133.0 (C10a), 130.7 (C9), 129.2 (C7), 128.6 (C2), 126.8 (C8), 125.7 (C6a), 121.9 (C10b), 121.8 (C10), 119.0 (C1), 20.7 (Me(C4)), 20.6 (Me(C3)). HRMS calcd. for $C_{15}H_{14}N$ ($[M + H]^+$) 208.1121, found 208.1118.

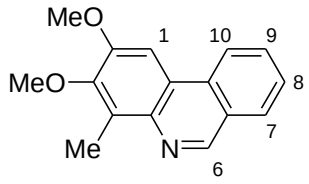
2-Methoxy-4-methylphenanthridine **(2e)**



$C_{15}H_{13}NO$ M = 223.27 g/mol

Isolated as a white solid. Yield: 65%. M.p.: 76–77 °C. Eluent: Pentane/EtOAc 85:15.
IR (neat): ν = 2955, 1611, 1523, 1494, 1456, 1401, 1354, 1206, 1052, 753 cm^{-1}; ^{1}H NMR: δ 9.17 (1H, s, H6), 8.51 (1H, d, *J* = 8.0 Hz, H10), 8.01 (1H, dd, *J* = 8.0, 0.8 Hz, H7), 7.80 (1H, td, *J* = 8.0, 1.2 Hz, H9), 7.75 (1H, d, *J* = 2.4 Hz, H1), 7.67 (1H, td, *J* = 8.0, 1.2 Hz, H8), 7.24 (1H, d, *J* = 2.4 Hz, H3), 3.99 (3H, s, OMe), 2.85 (3H, s, Me). ^{13}C NMR: δ 157.9 (C2), 149.6 (C6), 139.5 (C4), 138.7 (C4a), 132.3 (C10a), 130.2 (C9), 128.6 (C7), 127.2 (C8), 126.4 (C6a), 125.1 (C10b), 122.0 (C10), 119.3 (C3), 100.6 (C1), 55.4 (OMe), 18.7 (Me). HRMS calcd. for $C_{15}H_{14}NO$ ($[M + H]^+$) 224.1070, found 224.1066.

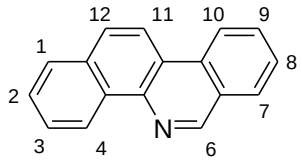
2,3-Dimethoxy-4-methylphenanthridine **(2f)**



$C_{16}H_{15}NO_2$ M = 253.30 g/mol

Isolated as a white solid. Yield: 95%. M.p.: 86–87 °C. Eluent: Pentane/EtOAc 75:25.
IR (neat): ν = 2928, 1606, 1475, 1403, 1272, 1239, 1077, 751 cm^{-1}; ^1H NMR: δ 9.17 (1H, s, H6), 8.45 (1H, d, *J* = 8.4 Hz, H10), 7.99 (1H, dd, *J* = 8.0, 0.8 Hz, H7), 7.78 (1H, td, *J* = 8.4, 1.2 Hz, H9), 7.74 (1H, s, H1), 7.63 (1H, td, *J* = 8.0, 0.8 Hz, H8), 4.07 (3H, s, OMe), 3.93 (3H, s, OMe), 2.80 (3H, s, Me(C4)). ^{13}C NMR: δ 152.5 (C3 or C2), 150.0 (C6), 148.7 (C2 or C3), 139.2 (C4a), 132.1 (C4), 130.4 (C10a), 130.2 (C9), 128.6 (C7), 126.7 (C8), 125.9 (C6a), 121.7 (C10), 121.0 (C10b), 99.9 (C1), 60.6 (OMe), 55.7 (OMe), 10.9 (Me). HRMS calcd. for $C_{16}H_{16}NO_2$ ($[M + H]^+$) 254.1176, found 254.1175.

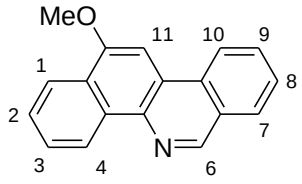
Benzo[*c*]phenanthridine **(2g)**



$C_{17}H_{11}N$ M = 229.28 g/mol

Isolated as a white solid. Yield: 80%. M.p.: 126–129 °C. Eluent: Pentane/EtOAc 95:5.
Data correspond to those described in the literature[4].
^1H NMR: δ 9.48 (1H, s, H6), 9.42 (1H, d, *J* = 8.4 Hz, H4), 8.65 (1H, d, *J* = 8.4 Hz, H10), 8.53 (1H, d, *J* = 8.8 Hz, H1), 8.13 (1H, d, *J* = 8.0 Hz, H12), 8.02 (1H, d, *J* = 8.8 Hz, H2), 7.98 (1H, d, *J* = 8.0 Hz, H11), 7.88 (1H, t, *J* = 7.2 Hz, H9), 7.79 (1H, t, *J* = 7.2 Hz, H8), 7.73-7.67 (2H, m, H7 + H3).
^{13}C NMR: δ 151.9, 141.5, 133.2, 132.8, 132.1, 130.8, 128.6, 127.8, 127.6, 127.3, 127.1, 127.0, 126.9, 124.7, 122.2, 121.0, 119.9.

12-Methoxybenzo[*c*]phenanthridine **(2h)**

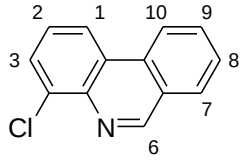


$C_{18}H_{13}NO$ M = 259.30 g/mol

Isolated as a white solid. Yield: 77%. M.p.: 114–115 °C. Eluent: Pentane/EtOAc 85:15.
IR (neat): ν = 2957, 1620, 1598, 1518, 1452, 1408, 1254, 1232, 1215, 1094, 761 cm^{-1}; ^1H NMR: δ 9.36 (1H, d, *J* = 8.3 Hz, H10), 9.31 (1H, s, H6), 8.51 (1H, d, *J* = 8.7 Hz, H4), 8.38 (1H, d, *J* = 8.3 Hz, H1), 8.07 (1H, d, *J* = 8.0 Hz, H7), 7.85-7.76 (2H, m, H3, H9), 7.72-7.65 (2H, m, H2, H8), 7.64 (1H, s, H11), 4.16 (3H, s, OMe). ^{13}C NMR: δ 154.6 (C12), 149.3 (C6), 137.2 (C4b), 132.8 (C4a), 132.2 (C10a), 130.1 (C3), 128.6 (C7), 127.5 (C9), 127.0 (C6a), 127.0 (C2), 126.9 (C8), 126.8 (C10b), 124.5 (C10), 122.0 (C4), 121.84 (C12a), 121.81 (C1), 95.7 (C11), 55.5 (OMe).

HRMS calcd. for $C_{18}H_{14}NO$ ([M + H]$^+$) 260.1070, found 260.1071.

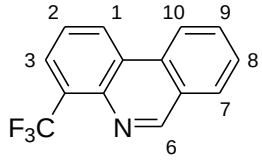
4-Chlorophenanthridine **(2i)**



$C_{13}H_8NCl$ M = 213.66 g/mol

Isolated as a yellow solid. Yield: 31%. M.p.: 98–100 °C. Eluent: pentane-EtOAc 95:5.
Data correspond to those described in the literature[4].
^{1}H NMR: δ 9.40 (1H, s, H6), 8.67 (1H, d, *J* = 8.0 Hz, H10), 8.58 (1H, dd, *J* = 8.0, 0.8 Hz, H1), 8.14 (1H, d, *J* = 8.0, 0.8 Hz, H7), 7.94 (1H, ddd, *J* = 8.0, 7.4, 1.2 Hz, H9), 7.88 (1H, dd, *J* = 7.6, 1.2 Hz, H3), 7.80 (1H, ddd, *J* = 8.0, 7.4, 1.2 Hz, H8), 7.68-7.60 (1H, m, H2). ^{13}C NMR: δ 154.9 (C6), 141.6 (C4a), 134.6 (C4), 133.0 (C10a), 132.0 (C3), 129.9 (C9), 129.7 (C7), 129.0 (C8), 127.8 (C2), 127.3 (C6a), 126.7 (C10b), 123.0 (C10), 122.2 (C1).

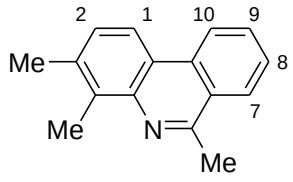
4-Trifluoromethylphenanthridine **(2j)**



$C_{14}H_8F_3N$ M = 247.22 g/mol

Isolated as a pale yellow solid. Yield: 22%. M.p.: 132–134 °C. Eluent: pentane-EtOAc 95:5.
Data correspond to those described in the literature[4].
^{1}H NMR: δ 9.46 (1H, s, H6), 8.81 (1H, d, *J* = 8.4 Hz, H1), 8.65 (1H, d, *J* = 8.4 Hz, H10), 8.13 (1H, d, *J* = 8.0 Hz, H3), 8.11 (1H, d, *J* = 7.6 Hz, H7), 7.94 (1H, *J* = 8.0 Hz, H8), 7.80 (1H, t, *J* = 8.0 Hz, H2), 7.75 (1H, t, *J* = 8.0 Hz, H9). ^{13}C NMR: δ 154.4 (C6), 141.4 (C4a), 132.0 (C10a), 131.6 (C9), 129.0 (C7), 128.6 (q, $^2J_{C\text{-}F}$ = 18.2 Hz, C4), 128.3 (C8), 126.8 (q, $^3J_{C\text{-}F}$ = 5.5 Hz, C3), 126.5 (C2), 126.2 (C6a), 125.9 (C10), 124.9 (C10b), 124.3 (q, $^1J_{C\text{-}F}$ = 273.2 Hz, CF_3), 121.9 (C1). ^{19}F NMR: δ –60.9.

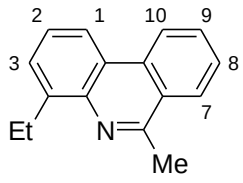
3,4,6-Trimethylphenanthridine **(2k)**



$C_{16}H_{15}N$ M = 221.30 g/mol

Isolated as a white solid. Yield: 90%. M.p.: 120–121 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2920, 1612, 1588, 1482, 1447, 1375, 757 cm^{-1}; ^{1}H NMR: δ 8.57 (1H, d, *J* = 8.4 Hz, H10), 8.28 (1H, d, *J* = 8.4 Hz, H1), 8.16 (1H, d, *J* = 8.4 Hz, H7), 7.77 (1H, td, *J* = 8.4, 1.2 Hz, H9), 7.63 (1H, td, *J* = 8.0, 1.2 Hz, H8), 7.42 (1H, d, *J* = 8.4 Hz, H2), 3.05 (3H, s, Me(C6)), 2.85 (3H, s, Me(C4)), 2.53 (3H, s, Me(C2)). ^{13}C NMR: δ 157.1 (C6), 142.2 (C4a), 136.7 (C4), 134.8 (C3), 133.0 (C10a), 129.9 (C9), 128.2 (C2), 126.5 (C8), 126.2 (C7), 125.1 (C6a), 122.2 (C10), 121.5 (C10b), 118.7 (C1), 23.7 (Me(C6)), 20.7 (Me(C3)), 13.5 (Me(C4)). HRMS calcd. for $C_{16}H_{16}N$ ([M + H]$^+$) 222.1277, found 222.1274.

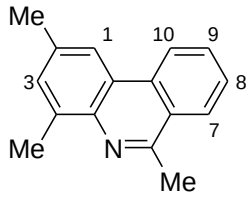
4-Ethyl-6-methylphenanthridine **(2l)**



$C_{16}H_{15}N$ M = 221.30 g/mol

Isolated as a white solid. Yield: 88%. M.p.: 75–76 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2962, 1585,1527, 1446, 1375, 1319, 752 cm^{-1}; ^{1}H NMR: δ 8.61 (1H, d, *J* = 8.3 Hz, H10), 8.40 (1H, dd, *J* = 8.0, 1.6 Hz, H1), 8.19 (1H, dd, *J* = 8.3, 0.8 Hz, H7), 7.79 (1H, t, *J* = 8.3 Hz, H9), 7.66 (1H, t, *J* = 8.3 Hz, H8), 7.62–7.52 (2H, m, H2, H3), 3.40 (2H, q, *J* = 7.6 Hz, CH_2(C4)), 3.05 (3H, s, Me(C6)), 1.44 (3H, t, *J* = 7.6 Hz, Me). ^{13}C NMR: δ 157.1 (C6), 143.1 (C4), 141.8 (C4a), 132.9 (C10a), 129.9 (C9), 127.6 (C2), 126.9 (C8), 126.3 (C7), 125.9 (C3), 125.6 (C6a), 123.5 (C10b), 122.5 (C10), 119.6 (C1), 24.7 CH_2(C4), 23.6 Me(C6), 15.4 (Me). HRMS calcd. for $C_{16}H_{16}N$ ($[M + H]^+$) 222.1277, found 222.1278.

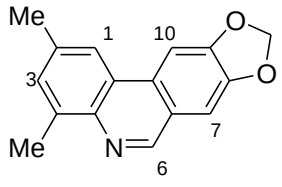
2,4,6-Trimethylphenanthridine **(2m)**



$C_{16}H_{15}N$ M = 221.30 g/mol

Isolated as a white solid. Yield: 90%. M.p.: 87–88 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2920, 1612, 1585, 1451, 1374, 755 cm^{-1}; ^{1}H NMR: δ 8.57 (1H, d, *J* = 8.0 Hz, H10), 8.16 (1H, d, *J* = 8.0 Hz, H7), 8.15 (1H, s, H1), 7.77 (1H, t, *J* = 8.0 Hz, H9), 7.63 (1H, t, *J* = 7.6 Hz, H8), 7.40 (1H, s, H3), 3.03 (3H, s, Me(C6)), 2.85 (3H, s, Me(C4)), 2.56 (3H, s, Me(C2)). ^{13}C NMR: δ 156.2 (C6), 140.7 (C4a), 136.7 (C4), 135.2 (C2), 132.5 (C10a), 131.0 (C3), 129.8 (C9), 126.7 (C8), 126.2 (C7), 125.6 (C6a), 123.3 (C10b), 122.4 (C10), 119.3 (C1), 23.5 (Me(C6)), 21.8 (Me(C2)), 18.1 (Me(C4)). HRMS calcd. for $C_{16}H_{16}N$ ($[M + H]^+$) 222.1277, found 222.1277.

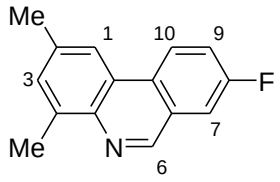
2,4-Dimethyl-8,9-methylenedioxyphenanthridine **(2n)**



$C_{16}H_{13}NO_2$ M = 251.28 g/mol

Isolated as a white solid. Yield: 82%. M.p.: 98–99 °C. Eluent: Pentane/EtOAc 80:20.
IR (neat): ν = 2912, 1619, 1488, 1461, 1252, 1217, 1239, 1037, 940, 835 cm^{-1}; ^{1}H NMR: δ 9.04 (1H, s, H6), 7.99 (1H, s, H1), 7.87 (1H, s, H10), 7.38 (1H, s, H3), 7.30 (1H, s, H7), 6.14 (2H, s, CH_2), 2.82 (3H, s, Me(C4)), 2.56 (3H, s, Me(C2)). ^{13}C NMR: δ 151.1 (C8), 149.6 (C6), 147.9 (C9), 141.3 (C4a), 137.2 (C4), 135.9 (C2), 130.6 (C3), 130.1 (C10a), 124.0 (C6a), 122.9 (C10b), 119.4 (C1), 105.2 (C7), 101.7 (CH_2), 100.0 (C10), 21.8 (Me(C2)), 18.6 (Me(C4)). HRMS calcd. for $C_{16}H_{14}NO_2$ ($[M + H]^+$) 252.1019, found 252.1016.

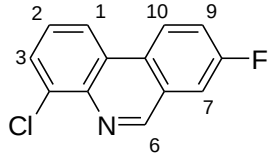
2,4-Dimethyl-8-fluorophenanthridine **(2o)**



$C_{15}H_{12}NF$ M = 225.26 g/mol

Isolated as a white solid. Yield: 86%. M.p.: 112–113 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2920, 1620, 1525, 1264, 1198, 1153, 958, 825 cm^{-1}; ^{1}H NMR: δ 9.17 (1H, s, H6), 8.55 (1H, dd, *J* = 9.0, 5.1 Hz, H10), 8.13 (1H, s, H1), 7.63 (1H, dd, *J* = 8.4, 2.6 Hz, H7), 7.57-7.52 (1H, m, H9), 7.43 (1H, s, H3), 2.83 (3H, s, Me(C4)), 2.57 (3H, s, Me(C2)). ^{13}C NMR: δ 161.2 (d, $^{1}J_{C\text{-}F}$ = 248.2 Hz, C8), 150.1 (C6), 141.2 (C4a), 137.5 (C4), 136.9 (C2), 131.1 (C3), 129.2 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, C10a), 127.3 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz, C6a), 124.7 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, C10), 123.5 (C10b), 119.8 (d, $^{2}J_{C\text{-}F}$ = 23.9 Hz, C9), 119.4 (C1), 112.4 (d, $^{2}J_{C\text{-}F}$ = 20.5 Hz, C7), 21.9 (Me(C2)), 18.5 (Me(C4)). ^{19}F NMR: δ -113.71. HRMS calcd. for $C_{15}H_{13}NF$ ($[M + H]^{+}$) 226.1026, found 226.1025.

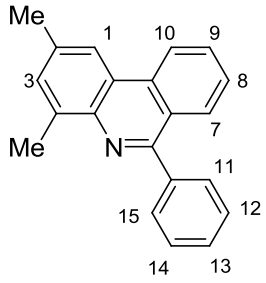
4-Chloro-8-fluorophenanthridine **(2p)**



$C_{13}H_{7}NClF$ M = 231.65 g/mol

Isolated as a white solid. Yield: 46%. M.p.: 73–74 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2922, 2852, 1597, 1495, 1455, 1366, 806 cm^{-1}; ^{1}H NMR (CD_2Cl_2): δ 9.36 (1H, s, H6), 8.67 (1H, dd, *J* = 9.2, 5.2 Hz, H10), 8.52 (1H, dd, *J* = 8.4, 0.9 Hz, H1), 7.88 (1H, dd, *J* = 7.6, 1.2 Hz, H3), 7.75 (1H, dd, *J* = 8.4, 2.4 Hz, H7), 7.68-7.60 (2H, m, H9, H2). ^{13}C NMR (CD_2Cl_2): δ 162.7 (d, $^{1}J_{C\text{-}F}$ = 248.2 Hz, C8), 153.8 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz, C6), 141.3 (C4a), 135.4 (C4), 129.84 (d, $^{4}J_{C\text{-}F}$ = 1.1 Hz, C10a), 129.80 (C3), 128.6 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, C6a), 128.3 (C2), 126.4 (C10b), 125.9 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz, C10), 121.9 (C1), 121.5 (d, $^{2}J_{C\text{-}F}$ = 24.4 Hz, C7), 113.6 (d, $^{2}J_{C\text{-}F}$ = 20.8 Hz, C9). ^{19}F NMR: δ -111.63. HRMS calcd. for $C_{13}H_{8}NClF$ ($[M + H]^{+}$) 232.0324, found 232.0322.

2,4-Dimethyl-6-phenylphenanthridine **(2q)**

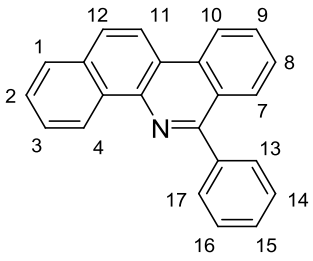


$C_{21}H_{17}N$ M = 283.37 g/mol

Isolated as a pale yellow solid. Yield: 97%. M.p.: 132–133 °C. Eluent: Pentane/EtOAc 95:5.
IR (neat): ν = 2920, 2849, 1599, 1488, 1445, 1362, 816 cm^{-1}; ^{1}H NMR: δ 8.68 (1H, d, *J* = 8.4 Hz, H10), 8.26 (1H, s, H1), 8.19 (1H, dd, *J* = 8.4, 0.8 Hz, H7), 7.87–7.83 (2H, m, H11, H15),

7.80 (1H, td, *J* = 8.0, 1.2 Hz, H9), 7.61–7.50 (4H, m, H8, H12, H13, H14), 7.48 (1H, s, H3), 2.89 (3H, s, Me(C4), 2.62 (3H, s, Me(C2)). ^{13}C NMR: δ 158.2 (C6), 140.9 (C4a), 140.4 (C11a), 137.8 (C4), 136.1 (C2), 133.5 (C10a), 131.2 (C13), 130.2 (C11, C15), 129.8 (C3), 128.5 (C8), 128.4 (C7),128.1 (C12, C14), 126.6 (C9), 124.7 (C6a), 123.3 (C10b), 122.4 (C10), 119.2 (C1), 21.9 (Me(C2)), 18.2 (Me(C4)). HRMS calcd. for $C_{21}H_{18}N$ ($[M + H]^+$) 284.1434, found 284.1437.

6-Phenylbenzo[*c*]phenanthridine **(2r)**

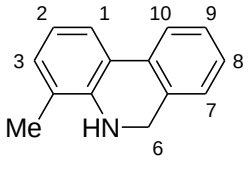


$C_{23}H_{15}N$ M = 305.37 g/mol

Isolated as a pale yellow solid. Yield: 92%. M.p.: 189–190 °C. Eluent: Pentane/EtOAc 95:5. IR (neat): ν = 2921, 2853, 1564, 1493, 1445, 1372, 799 cm^{-1}; ^{1}H NMR: δ 9.50 (1H, dd, *J* = 8.4, 0.8 Hz, H4), 8.76 (1H, d, *J* = 8.4 Hz, H10), 8.59 (1H, d, *J* = 9.0 Hz, H11), 8.31 (1H, d, *J* = 8.0 Hz, H1), 8.04 (1H, d, *J* = 9.0 Hz, H12), 7.99 (1H, d, *J* = 8.0 Hz, H), 7.96–7.92 (2H, m, H13, H17), 7.88 (1H, ddd, *J* = 8.4, 8.0, 1.2 Hz, H), 7.77–7.56 (6H, m, H). ^{13}C NMR: δ 159.4 (C6), 140.7 (C4b), 140.3 (C13a), 133.8 (C10a), 133.4 (C12a), 132.2 (C4a), 130.4 (C13, C17), 130.2 (C9), 128.6 (C14, C16), 128.3 (C7, C15), 127.6 (C1), 127.5 (C2), 127.3 (C8), 126.8 (C3), 126.7 (C12), 125.3 (C6a), 125.2 (C4), 122.6 (C10), 120.4 (C10b), 119.7 (C11). HRMS calcd. for $C_{23}H_{16}N$ ($[M + H]^+$) 306.1277, found 306.1278.

5,6-Dihydrophenanthridines were isolated as a mixture with the corresponding phenanthridines. After purification, probably because of traces of palladium, they slowly tend to aromatize (few days to 4 weeks).

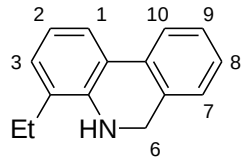
5,6-Dihydro-4-methylphenanthridine **(1a)**



$C_{14}H_{13}N$ M = 195.26 g/mol

^{1}H NMR: δ 7.69 (1H, d, *J* = 8.0 Hz, H10), 7.60 (1H, d, *J* = 8.0 Hz, H1), 7.31 (1H, td, *J* = 8.0, 1.6 Hz, H9), 7.22 (1H, td, *J* = 7.6, 1.2 Hz, H8), 7.13 (1H, dd, *J* = 7.6, 0.8 Hz, H7), 7.03 (1H, dd, *J* = 7.6, 0.8 Hz, H3), 6.78 (1H, t, *J* = 7.6 Hz, H2), 4.43 (2H, s, CH_2), 4.05 (1H, br s, NH), 2.19 (3H, s, Me). ^{13}C NMR: δ 144.1 (C4a), 132.8 (C6a), 132.7 (C10a), 130.4 (C3), 127.9 (C9), 127.2 (C8), 126.0 (C7), 122.9 (C10), 122.4 (C10b), 121.9 (C1), 121.7 (C4), 118.7 (C2), 46.6 (C6), 17.3 (Me).

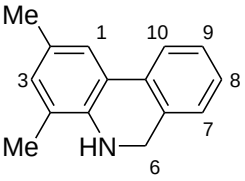
5,6-Dihydro-4-ethylphenanthridine **(1b)**



$C_{15}H_{15}N$ M = 209.29 g/mol

^{1}H NMR: δ 7.71 (1H, d, *J* = 7.6 Hz, H10), 7.64 (1H, d, *J* = 7.2 Hz, H1), 7.32 (1H, t, *J* = 7.6 Hz, H9), 7.23 (1H, td, *J* = 7.6, 1.2 Hz, H8), 7.14 (1H, d, *J* = 7.6, H7), 7.06 (1H, d, *J* = 7.2 Hz, H3), 6.84 (1H, t, *J* = 7.2 Hz, H2), 4.40 (2H, s, C*H*$_2$NH), 4.09 (1H, br s, NH), 2.55 (2H, q, *J* = 7.6 Hz, CH_2), 1.28 (3H, t, *J* = 7.6 Hz, Me). ^{13}C NMR: δ 143.3 (C4a), 132.6 (C6a), 132.5 (C10a), 128.0 (C4), 127.8 (C3), 127.6 (C9), 126.8 (C8), 125.7 (C7), 122.7 (C10), 121.8 (C10b), 121.6 (C1), 118.6 (C2), 46.3 (C6), 23.8 (CH_2), 13.1 (Me).

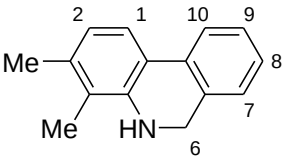
5,6-Dihydro-2,4-dimethylphenanthridine **(1c)**



$C_{15}H_{15}N$ M = 209.29 g/mol

^{1}H NMR: δ 7.70 (1H, d, *J* = 8.0 Hz, H10), 7.43 (1H, s, H1), 7.31 (1H, t, *J* = 7.6 Hz, H8), 7.22 (1H, td, *J* = 7.6, 0.8 Hz, H9), 7.13 (1H, d, *J* = 7.6 Hz, H7), 6.90 (1H, s, H3), 4.41 (2H, s, CH_2), 3.90 (1H, br s, NH), 2.35 (3H, s, Me(C4)), 2.20 (3H, s, Me(C2)). ^{13}C NMR: δ 141.4 (C4a), 132.7 (C2), 132.5 (C10a), 130.9 (C3), 127.5 (C8), 127.4 (C4), 126.8 (C9), 125.7 (C7), 122.5 (C10), 122.1 (C6a), 121.9 (C1), 121.5 (C10b), 46.5 (C6), 20.7 (Me(C4)), 16.9 (Me(C2)).

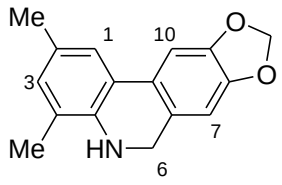
5,6-Dihydro-3,4-dimethylphenanthridine **(1d)**



$C_{15}H_{15}N$ M = 209.29 g/mol

^{1}H NMR: δ 7.66 (1H, d, *J* = 7.6 Hz, H10), 7.49 (1H, d, *J* = 7.6 Hz, H1), 7.30 (1H, t, *J* = 7.6 Hz, H9), 7.19 (1H, t, *J* = 7.6 Hz, H8), 7.12 (1H, d, *J* = 7.6 Hz, H7), 6.78 (1H, d, *J* = 7.6 Hz, H2), 4.40 (2H, s, CH_2), 4.07 (1H, br s, NH), 2.31 (3H, s, Me(C4)), 2.10 (3H, s, Me(C3)). ^{13}C NMR: δ 143.8 (C4a), 136.8 (C3), 132.7 (C10a), 132.2 (C6a), 127.5 (C9), 126.6 (C8), 125.6 (C7), 122.4 (C10), 120.8 (C1), 120.7 (C2), 120.3 (C10b), 119.6 (C4), 46.5, (C6), 13.9 (Me(C3)), 12.4 (Me(C4)).

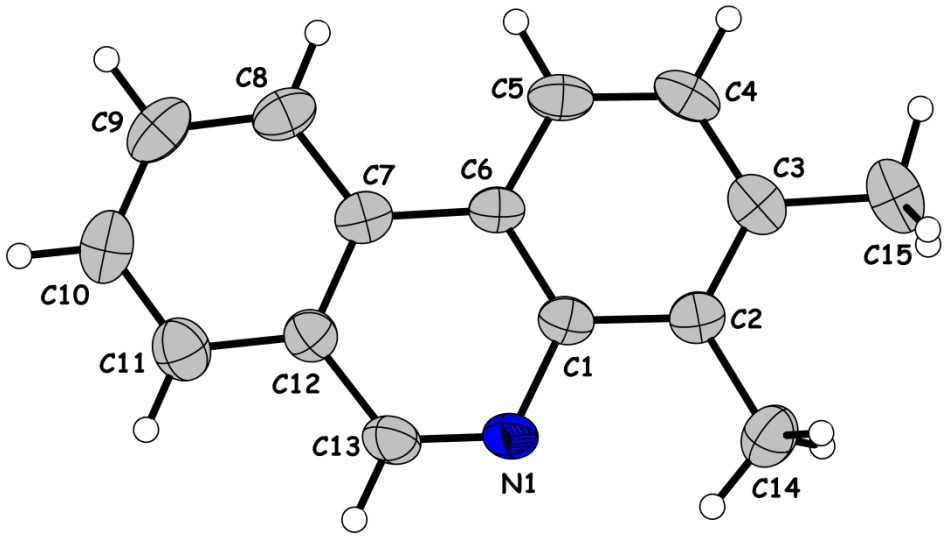
5,6-Dihydro-2,4-dimethyl[1,3]dioxolo[4,5-*j*]phenanthridine **(1n)**



$C_{16}H_{15}NO_2$ M = 253.30 g/mol

^{1}H NMR: δ 7.23 (1H, s, H1), 7.16 (1H, s, H10), 6.81 (1H, s, H3), 6.61 (1H, s, H7), 5.95 (2H, s, CH_2), 4.26 (2H, s, H6), 3.90 (1H, br s, NH), 2.28 (3H, s, Me(C2)), 2.15 (3H, s, Me(C4)). ^{13}C NMR: δ 147.4 (C8), 146.5 (C9), 140.7 (C4a), 130.3 (C3), 127.6 (C2), 126.7 (C4), 127.6 (C10a), 122.0 (C6a), 121.9 (C10b), 121.5 (C1), 106.2 (C7), 103.4 (C10), 100.9 (CH_2), 46.6 (C6), 20.7 (Me(C2)), 16.7 (Me(C4)).

Crystal Stucture of 3,4-dimethylphenanthridine (**2d**)



References

[1] N, Della Ca, E. Motti, A. Mega, M. Catellani *Adv. Synth. Catal.* **2010**, *352*, 1451.
[2] A.-S. Castanet, F. Colobert, P.-E. Broutin *Tetrahedron Lett.* **2002**, *43*, 5047.
[3] a) B. D. Chapsal, I. Ojima *Org. Lett.* **2006**, *8*, 1395; b) R. Beugelmans, J. Chastanet, H. Ginsburg, L. Quintero-Cortes, G. Roussi *J. Org. Chem.* **1985**, *50*, 4933.
[4] D. A. Candito, M. Lautens *Ang. Chem. Int. Ed.* **2009**, *48*, 6713.

A theoretical investigation of the ortho effect in palladium/norbornene-catalyzed reactions

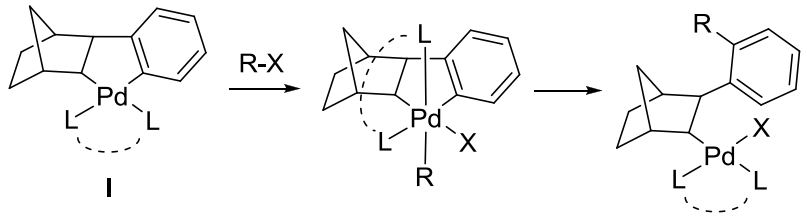
Contents

1. Introduction

Palladium-catalyzed C–C bond forming reactions of synthetic interest usually involve Pd(0) and Pd(II) complexes.[1] Working in this area, in 2010 Heck, Negishi and Sukuzi have been awarded the Nobel prize.[2] In catalytic C-C coupling reactions Stille initially proposed the intermediacy of Pd(IV) complexes.[3] In the last few years an increasing number of reactions based on Pd(II)/Pd(IV) catalysis were presented.[4] Pd(IV) complexes resulting from oxidative addition of alkyl halides to Pd(II) are known.[5] Activation of C(sp2)-X electrophiles, such as aryl halides, by oxidative addition has been reported in the case of Ir(I) and Pt(II) complexes, but such a process has not been observed yet for Pd(II) derivatives. Although reaction of Ph_2IOTf with Pd(II) and Pt(II) has recently been reported to give metal(IV) species by formal transfer of Ph^+,[6] there is no clear-cut experimental evidence for the oxidative addition of aryl (*pseudo*)halide electrophiles to Pd(II) complexes. C–C bond formation through palladium chemistry has been the topic of several reviews highlighting advantages over conventional chemistry, which include high yields and selectivities, one-pot multistep reactions, mild and ambientally friendly conditions.[7]

At the beginning of the 90s, selectively alkyl-substituted aromatics have been obtained catalytically by reaction of alkyl halides RX with a palladium complex, formed in situ from an aryl halide, a palladium salt and norbornene. This complex was shown to be metallacycle **I** (Scheme 1). Reactions of metallacycles **I** with $C(sp^3)$–X electrophiles yield indeed the

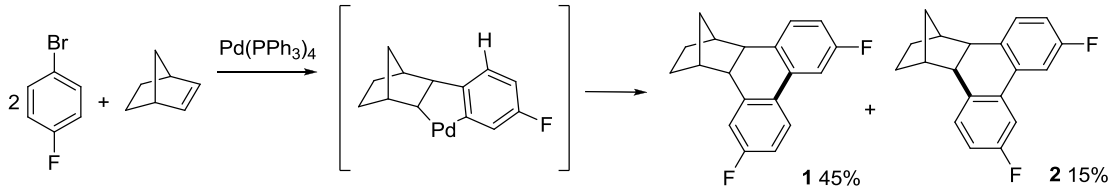
corresponding Pd(IV) octahedral complexes *via* oxidative addition.[8] Using rigid ligands, such as 1,10-phenanthroline, some structures have been characterized.[5e,8c,9]



Scheme 1. Palladacycle **I** and its reported reactivity with C(sp^3)-X electrophiles.

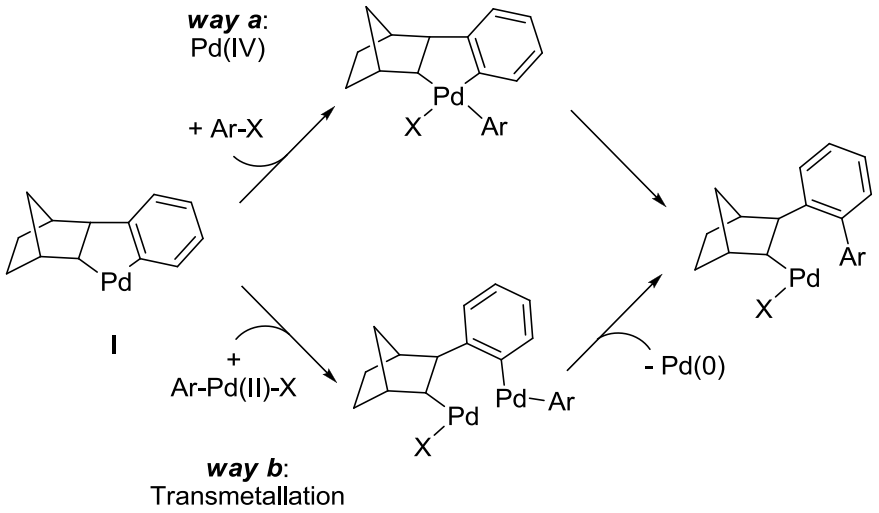
Reductive elimination from them, although formally possible to occur on both the aromatic and the aliphatic site of the planar metallacycle, has been observed only with selective formation of sp^2-sp^3 C–C bond.[10] Taking advantage of the reactivity of the letter Pd(II) complex, many application have been reported so far,[11] and little doubts exist on this mechanism.

On the other hand, the situation considering the reactivity of **I** with aryl (*pseudo*)halides is more complicated. A mixture of two products is obtained, which derive from aryl attack on the norbornyl or the aryl sites of the metallacycle followed by ring closure. In the presence of a para substituent two positional isomers of hexahydromethanotriphenylene are formed. For example 4-bromofluorobenzene gives a mixture of 45 and 15% of the two products (Scheme 2, X = F). The former comes from initial sp^2-sp^2 bond formation the latter from sp^2-sp^3.[12]



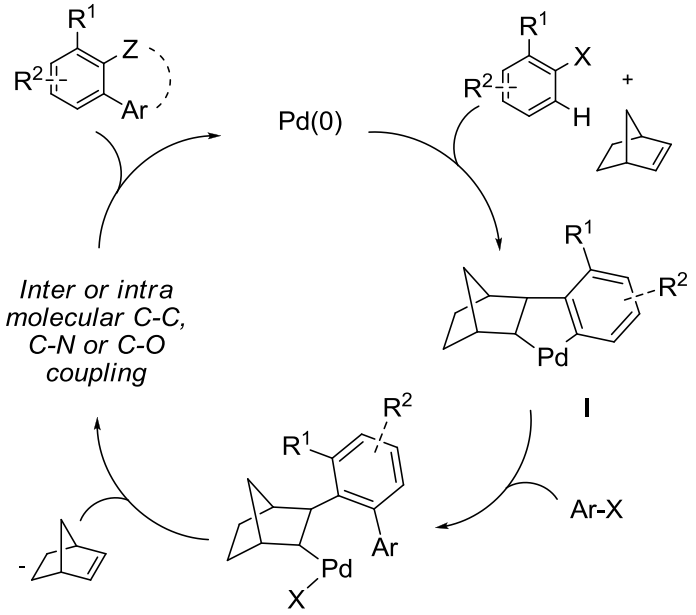
Scheme 2. Unselective sp^2-sp^2 and sp^2-sp^3 coupling by reaction of 4-fluorobormobezene and norbornene.

For the aryl-aryl coupling two mechanisms have been so far suggested. One postulates the generation of a Pd(IV) species in analogy to the known reactivity observed with alkyl halides (Scheme 3, *way a*),[11] while an alternative mechanism, put forward by Cardenas and Echavarren, involves a transmetalation[13] between two Pd(II) centers (*way b*, herein after simply called TM in tables).[14] Their DFT calculations on simplified systems, where the norbornene unit is modelized with an ethylene bridge, suggests the latter being favored over the former.[15]



Scheme 3. Proposed pathways for reaction of **I** with C(sp^2)-X electrophiles; ancillary ligands omitted for clarity.

The second relevant open question in these sp^2-sp^2 bond forming catalytic sequences is related to the so-called "*ortho* effect": a substituent *ortho* to the aryl-norbornyl bond of **I** (hereinafter simply called ortho substituent) is required to achieve the selective transfer of the second aryl unit to the *ortho'* position of the first aromatic ring. Among the reported methodologies featuring construction of a biaryl unit with the joint catalysis of palladium and norbornene is in fact always stated that low conversion and poor selectivity are otherwise obtained (Scheme 4, R^1 on **I**).[16] On contrary, the reactivity of **I** when R^1 = H is reported to afford sequences in which norbornene is no longer a catalyst, being usually trapped in products.



Scheme 4. Simplified scheme of reported application of the Pd/norbornene catalytic system.

These methodologies have been applied to various types of palladium catalyzed reactions, thus changing reagents, halides, solvents, additives and ligands, but the requirement that R^1 has to be different from H is always mandatory. However, although the ortho effect has been refered to as "a key finding in the development of ortho arylation chemistry",[16e] it is worthnoting to underline that this has been so far an empirical observation for which no rational explanation has been yet proposed.

We have thus decided to investigate the reactivity of **I** by means of DFT calculation trying to enlighten the still unclear aspects of the palladium and norbornene catalytic system, regarding both the mechanism involved in the reaction with aryl halides and the key role exerted by the *ortho* (R^1) substituent. To this end we examined the energy profile of the reactions of unsubstituted (R = H) or ortho-substituted (R = Me) complexes of type **I**, involving either oxidative addition to Pd(IV) or transmetalation (TM).

2. Computational Methods

Calculations were performed with Gaussian 09 at DFT level.[17] The geometries of all complexes here reported were optimized at the generalized gradient approximation using the M06 functional of Zhao and Truhlar.[18] This functional has been shown to accurately describe Pd complexes.[19] Moreover description of high-oxidation-state metal centers (*way a*) and of a possible metal-metal bond (together with its coupling to electronegative halide ligands, *way b*) demand for exchange-correlation hybrid DFT functionals rather than orthodox hybrid ones.[20] Optimizations were carried out using LACVP(d) basis set.[21] It consists of the standard 6-31G(d) basis set for lighter atoms (H, C, N, O and P) and the LANL2DZ basis set, which includes the relativistic effective core potential (ECP) of Hay and Wadt and employs a split-valence (double-ζ) basis set for Pd, Br and I. For more accurate energy values, single-point calculations were performed on the optimized geometries using a larger basis set, Def2-TZVP defined by Weigand and Ahlrichs, essentially a valence triple-ζ one.[22] *The corresponding energies are labeled in italic in the Schemes.* Harmonic frequencies were calculated at the same level of theory with LACVP(d) basis set to characterize stationary points and to determine zero-point energies corrections (ZPC). Energies calculated with both basis sets were corrected with these ZPCs without scaling. The starting approximate geometries for transition states (TS) were obtained through scans of the relative reaction coordinate starting from the

corresponding reagents. Intrinsic reaction coordinate (IRC) studies were performed to confirm the relation of the transition states with the corresponding minima.

In the following discussion computed structures will be designated by numbers, with letters referring to the various systems analyzed by varying ligands, aryl rings and halides.

3. Results and Discussion

3.1 Reaction of Palladacycle I without an ortho substituent (R^1 = H)

Palladacycles of type **I** were chosen as the common reagents for our investigations, being the proposed key intermediates in the abovementioned domino reactions (Scheme **4**). In these complexes the Pd atom is coordinated to one aliphatic carbon of the norbornene unit and an aromatic one of the aryl ring in a cis arrangement. The square planar environment around the metal is ensured by two ancillary ligands, in agreement with isolated complexes of **I**.[23] Two ligands have been modelized, $P(Me)_3$ and DMF. The phosphine has been chosen to represent the tertiary phosphines employed in these domino sequences, mainly triphenylphospine and trifurylphosphine, without a severe increase of the computational cost. DMF was tested as phospine-free conditions have been reported in the presence of this highly coordinating solvent.[24] Three different aryl halides as been tested: iodobenzene, 4-iodotoluene and 4-bromobenzaldehyde, as reaction on **I** are usually reported for aryl iodides and electron poor aryl bromides. Although the so constructed systems were quite costly from a computational point of view, we thought necessary to minimize the simplification on them as from experimental evidences the "*ortho* effect" seems to be mainly due to steric factors (rather than electronic ones). We have than investigated the two proposed reaction profiles for the reaction of **I** with aryl halides: an oxidative addition to yield a Pd(IV) species versus a transmetallation between two Pd(II) centers as proposed by Echavarren.[14] The calculated free energy profiles for these two pathways in the presence of $P(Me)_3$ as ligand is shown in Figure 1. The scheme presents the reaction of **Ia** with either iodobenzene (Pd(IV) manifold) and its relative Pd(II) complex aroused by its oxidative addition on a $Pd(0)L_2$[25] species (transmetallation pathway).

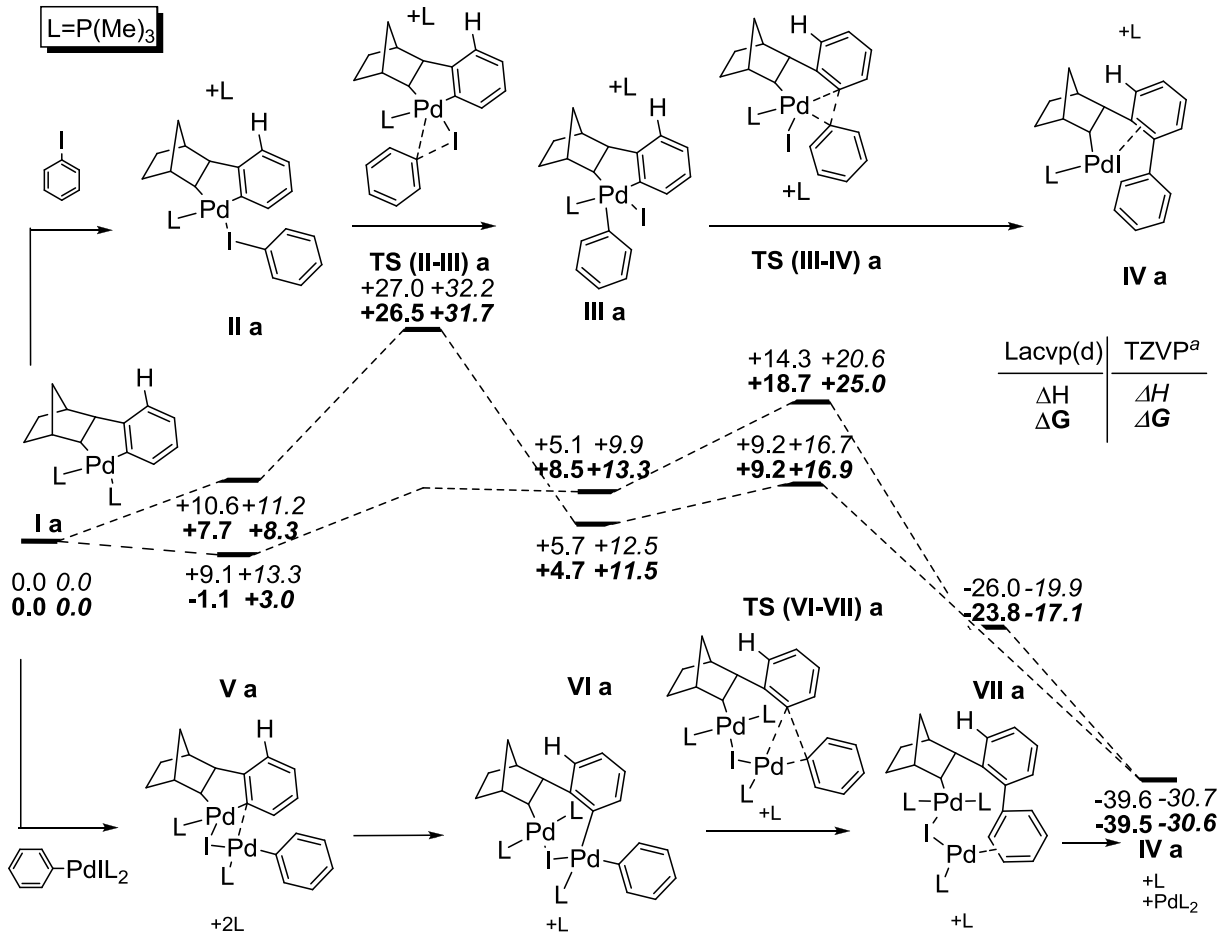


Figure 1. Reaction pathway and energies in kcal/mol for the reaction of **Ia**; *a*: using ZPC and entropy calculated with lacvp(d) basis set.

The Pd(IV) pathway will be considered first. Complex **Ia** could exchange one of his ancillary ligand with iodobenzene, affording **IIa**. The replacement of the phosphorus atom in the coordination of the metal with iodine is endotermic (ΔH +10.6 kcal/mol), but is accompanied by a posivite entropic variation. Transition state **TS(II-III)a** is reached from complexes **IIa**. Activation energies from **IIa** are lower than 20 kcal/mol, and similar for both ΔH and ΔG. However, since ligand exchange from **Ia** is endothermic, this transition state lies far above the entry channel (ΔG +26.5 kcal/mol). The reaction led to the pentacoordinated Pd(IV) complex **IIIa**. This complex features a Y-distorted trigonal bipyramidal geometry, in which the aromatic carbon of the metallacycle and the phosphine occupy the axial positions in respect to the Y plane.[26] The **TS(III-IV)a** for reductive elimination is easily accessible (ΔG +4.5 kcal/mol in respect to **IIIa**) and takes place between the C(sp^2) of the metallacycle and the C(sp^2) of the lone aryl ring. The product **IVa**, which features the biaryl unit, lies far below the entry channel (ΔG -39.5 kcal/mol), as expected with the formation of the C–C bond. **IVa** has a square planar coordination ensured by a ligand, the iodide, the C(sp^3) of norbornene and a slipped η^2

coordination of the aryl ring, in agreement with literature data on similar complexes.[27] We found an octahedral transition state for the direct reaction between complexes **Ia** and iodobenzene, however its activation energy is higher than that of **TS(II-III)a**. Similarly reductive elimination from an octahedrical Pd(IV) complex resulted in higher energies than that of **TS(III-IV)a**.[28] These data are in accord with the reductive elimination from pentacoordinated Pd(IV) complexes previously reported and in agreement with the usual lower reactivity of 18-electrons complexes compared to their relative 16-electrons counterparts.

Examining the transmetallation pathway, reaction of **Ia** with a second Pd(II) center delivers **Va**. The displacement of two molecules of ligands ensured a negative ΔG of -1.1 kcal/mol. In **Va** both palladium atoms present a slightly distorted square planar coordination and the two planes forms an angle of around 60°. The metal centre of the palladacycle completes its coordination with one ligand and the iodide, while the second, as reported by Echavarren, is interacting with the halide, both the aryl rings and a phosphine. The bimetallic complex thus assumes a clamshell conformation in which the calculated distance between metal nuclei is lower (2.78 Å) than the sum of their Van der Waals radii (3.26 Å). Several X-ray structures of complexes featuring Pd-Pd distances ranging from 2.55 to 3.05 Å have been reported.[29]

The aryl ring of the metallacycle could now be transferred to the second metal center, delivering **VIa**. Here, encorporation of a ligand results in a positive ΔG of +9.6 kcal compared to **Va**. We could not find a transition state for this process, however relative scans shows a very flat potential energy surface around the product **VIa**.[30] The transfer of the aryl ring from the initial 5-membered palladacycle to the second metal atom is ensured by a formal rotation of the aromatic moiety in respect to the plane of the metallacycle itself: while the dihedral angle formed by its 4 carbon atoms in both **Ia** and **Va** is lower than 5°, in **VIa** it goes up to 65°. Reductive elimination from **VIa** allows to form the biaryl unit present in **VIIa**, through a **TS(VI-VII)a**. Even if this process is more energy costly (ΔG +10.2 kcal from **VIa**) than in the Pd(IV) pathway, the highest transition state of this mechanism is still lower to **TS(II-III)a** by 7.8 kcal in ΔG. The same trend (ΔΔG -6.7 kcal) is obtained with TZVP single points, and even if the entropic factor is negative in the case of transmetallation pathway, the gap between the two mechanism is always above 5 kcal in the temperature range in which these reactions usually take place (80-130 °C). We have then modelized the reaction with other aryl halides, and we obtained closely related results. Relevant data of the two important transition states are summarized in table 1 (the complete pathways are available in the computationl details section).

System	Aryl halide	ΔG TS(II-III) [Pd(IV)]	ΔG TS(VI-VII) [TM]
a	iodobenzene	+26.5	+18.7
b	4-iodotoluene	+26.4	+17.5
c	4-bromobenzaldehyde	+26.2	+15.8

Table 1. Relevant free Gibbs energies for the reaction of **Ia** with aryl halides; values in kcal/mol at the M06/LACVP(d) level.

Among the three substrates we have decided to modelize to represent those adopted in these domino sequences, we noticed that limited differences arouse among them, and the transmetallation course is always favoured over the Pd(IV) manifold by 8-10 kcal in ΔG. Beside the previously shown transfer of the aryl ring of metallacycle **Va** onto the Ph-Pd center leading to VIa (Figure 1), we also considered the norbornyl transfer onto the same Ph-Pd unit (Figure 2). The pathway of Figure 2, referring to the aryl transfer, is reported once more, to allow a direct comparison of the two reaction modes. Migration of the C(sp^3) atom from one to the other palladium center results in complex **VIIIa**. Although this intermediate is higher in energy compared to **VIa**, its barrier for reductive elimination (**TS(VIII-IX)a**, ΔG +8.4 kcal on **VIIIa**) with formation of the sp^2-sp^3 C–C bond requires a lower activation energy. Furthermore, the entropy loss from reagents is lower than in the case of **TS(VI-VII)a**, and as a result the ΔΔG between them is reduced increasing the temperature. This narrow gap could thus explain the lack of selectivity experimentally observed in the absence of an ortho substituent in palladacycle **I** (see for example Scheme 2).

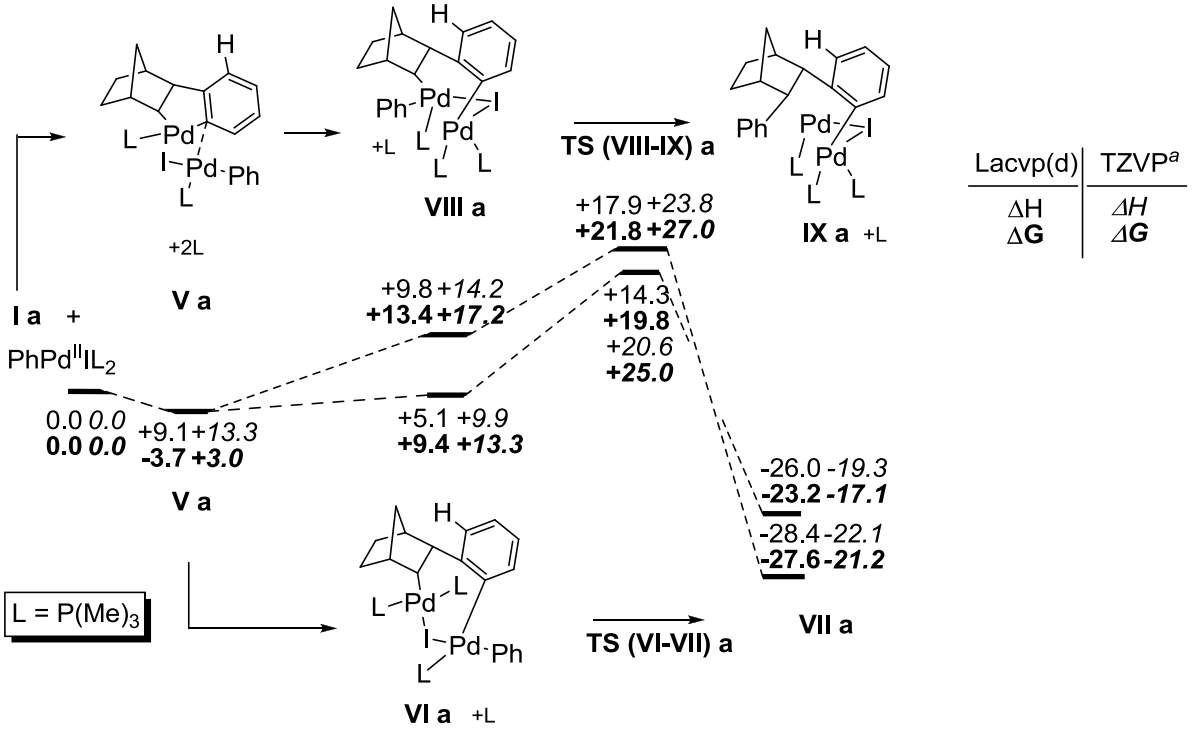


Figure 2. Reaction pathway and energies in kcal/mol comparing the formation of sp^2-sp^3 and the sp^2-sp^2 C–C bond from **Ia**; *a*: using ZPC and entropy calculated with lacvp(d) basis set.

To support this hypothesis we modelized the reaction of Figure 2 also with other arylpalladium(II) complexes, and found that the same trend could be observed (Table 2). In all the three modelized systems the gap is quite narrow, between 1.5 and 2 kcal/mol.

System	Aryl halide	ΔG TS(VI-VII)	ΔG TS(VIII-IX)
a	Iodobenzene	+19.8	+21.8
b	4-Iodotoluene	+20.0	+21.5
c	4-Bromobenzaldehyde	+16.8	+18.7

Table 2. Relevant activation barrier comparing sp2-sp2 and sp2-sp3 C-C bond formation in the transmetallation pathway; values in kcal/mol at 373 K, calculated at the M06/LACVP(d) level.

We have then investigated the system when DMF is present as ancillary ligand around palladium (Figure 3). Energetic trends and geometrical considerations made for the phosphine system are very similar in this case, although energy barriers are lower for both mechanisms.

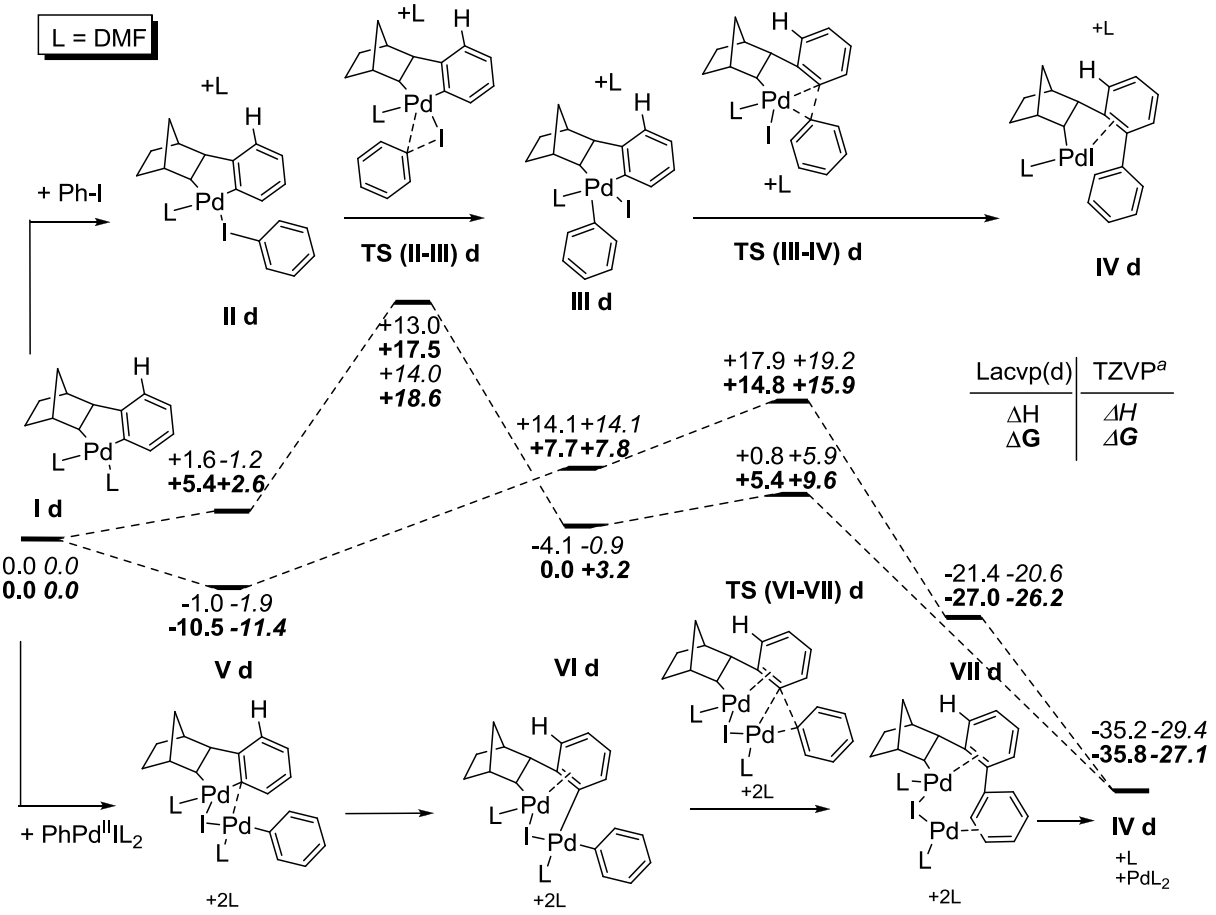


Figure 3. Reaction pathway and energies in kcal/mol for the reaction of **Id**; *a*: using ZPC and entropy calculated with lacvp(d) basis set.

Replacing a DMF molecule of **Id** with iodobenzene affords **IId** intermediate. The process is less enthalpy demanding compared to the phosphine case as expected (ΔH +1.6 kcal), although, as the solvent molecule is smaller, the resulting ΔG is similar (+5.4 kcal). The oxidative addition leading to Pd(IV) complex **IIId** proceeds trough **TS(II-III)d** (ΔG +12.1 kcal relative to **IId**). Reductive elimination has a very low barrier as above (**TS(III-IV)d**, ΔG +5.4 kcal) leading to product **IVd**.

The transmetallation pathways begins with the association intermediate **Vd**, which is below the entry level in both ΔH (-1.0 kcal) and ΔG (-10.5 kcal) in this case. In contrast to the case of the phosphinic ligand, transfer of the C(sp^2) of the metallacycle to the second palladium atom to obtain **VId** does not require insertion of another L molecule.[31] As in the above mentioned case, reductive elimination from the bimetallic intermediate **VId** is more energy costing than from Pd(IV) (ΔG +7.1 kcal relative to **VId**). Even in this case however, **TS(VI-VII)d** is substantially lower than **TS(II-III)d**, by 2.7 kcal in ΔG (same value obtained using TZVP single points).

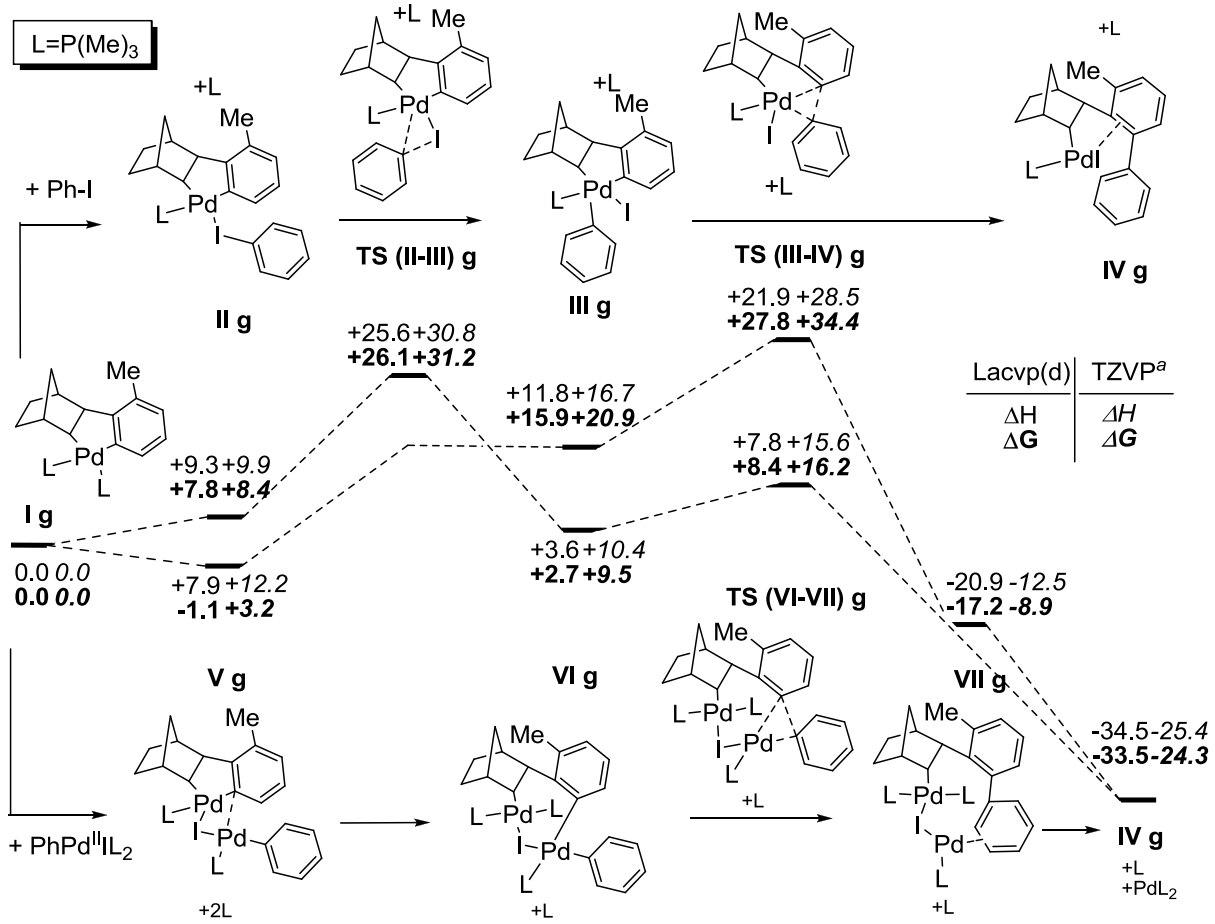
System	Aryl halide	ΔG TS(II-III) [Pd(IV)]	ΔG TS(VI-VII) [TM]
d	Iodobenzene	+17.5	+14.8
e	4-Iodotoluene	+17.6	+14.8
f	4-Bromobenzaldehyde	+17.4	+11.3

Table 3. Relevant free Gibbs energies for the reaction of Id with aryl halides; values in kcal/mol at the M06/LACVP(d) level.

By considering other coupling partner for **Id** results are very similar. A transmetallation pathway among two Pd atoms is always favored over the mechanism involving oxidative addition from Pd(II). Differences are in the range of 3-6 kcal/mol in these representative systems.

We have shown that a transmetallation pathway is favored, as in the case of L = $P(Me)_3$ even in "ligand-free" conditions, when DMF is bound to the metal. The mechanism firstly proposed by Echavarren and Cardenas is probably at work in the palladium catalyzed domino sequences involving palladacycles **Ia**-**If**, in which norbornene acts as a reagent. A further prove of the feasibility of this mechanism is that it can explain the experimental evidence of unselective aryl-aryl and aryl-alkyl coupling (Scheme 2) observed in the absence of *ortho* substituent on **I**.

3.2 Reaction of Palladacycle I with an ortho substituent (R^1 = Me)



Scheme 8. Reaction pathway and energies in kcal/mol for the reaction of **Ig**; *a*: using ZPC and entropy calculated with lacvp(d) basis set.

As mentioned in the introduction, to achieve selective aryl-aryl coupling and thus develop new catalytic methodologies in which both palladium and norbornene acts as catalysts, an ortho substituent on **I** is always required.[11,16] The smallest group possible is a Me group, and thus we modelized the reaction systems starting from complex **Ig** containing the methyl group in the ortho position to the C(sp^2)-C(sp^3) bond of the palladacycle (I, R = Me).

The Pd(IV) pathway closely resemble values obtained without substituents on the metallacycle (see Figure 1). Coordination of iodobenzene is slightly less energy costing (**IIg**, ΔG +7.6 kcal), and the following **TS(II-III)g** is 26.1 kcal above the entry channel (thus, only 0.4 kcal less than the **TS(II-III)a** of Scheme 4). Pd(IV) intermediate **IIIg** shares the same Y-distorted trigonal bipyramidal geometry of **IIIa**, and could allow the formation of the biaryl unit present in **IVg** trough **TS(III-IV)g** (ΔG +5.7 kcal relative to **IIIg**).

In strict contrast to the Pd(IV) pathway, values obtained analyzing the transmetallation pathway are very different. Formation of the association complex **Vg** accounts for a negative

ΔG of -1.1 kcal (thus exactly the same value obtained for **Va**, Scheme 4). However, transfer of the aryl ring from the metallacycle to the second palladium atom to obtain **VIg** is much more energy costing in this case (ΔG of +17 kcal relative to **Vg**).[32]

Reductive elimination from **VIg** proceeds through **TS(VI-VII)g**, which lies 27.8 kcal above the entry channel, and thus 1.7 kcal above **TS(II-III)g**, the highest energy transition state of the Pd(IV) manifold. Analyzing the reaction course in the presence of a substituent on complex **I** resulted in a significant increase in the energy of the transmetallation pathway (ΔΔG between **VIa-g** and **TS(VI-VII)a-g** being +7.4 and +9.1 kcal respectively).

Moreover, as the entropy loss in this pathway is more severe, the gap between the two mechanism increase with the temperature, as shown in Table 4 for the different aryl halides considered here.

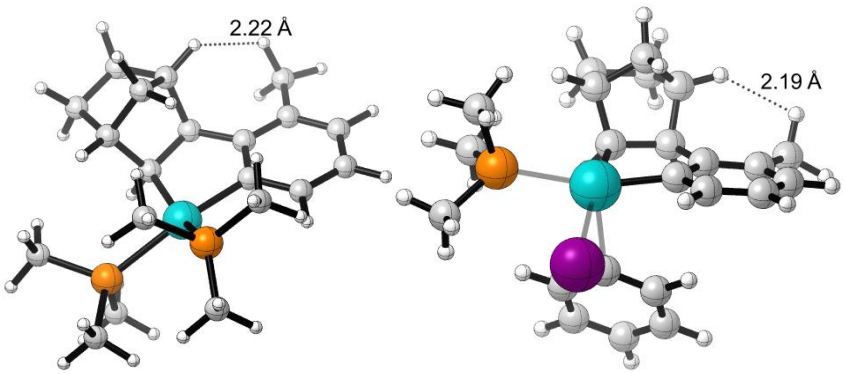
System	Aryl halide	ΔG TS(II-III) [Pd(IV)]	ΔG TS(VI-VII) [TM]
g	Iodobenzene	+26.2	+29.3
h	4-Iodotoluene	+25.9	+28.1
i	2-Iodotoluene	+28.7	+35.9
j	4-Bromobenzaldehyde	+25.4	+26.5
k	2-Bromobenzaldehyde	+28.8	+33.9

Table 4. Relevant activation barrier comparing Pd(IV) and Transmetallation pathways on **Ig** calculated at the M06/LACVP(d) level; values in kcal/mol at 373 K, the average reported reaction temperature in the presence of phosphinic ligands.

In sharp contrast to the data shown in Table 1, the values obtained shows how the Pd(IV) pathway lies below the transmetallation one in the presence of an ortho substituent on complex I (1-7 kcal less in the five representative system analyzed).

While the presence of an ortho substituent on the aryl ring that reacts with **Ig** is not reported as necessary, we decided to test also these kind of reagents (systems i and k) to check their influence.[33] As expected, in these cases barriers are higher to those of the corresponding para-substituted aryl halides (systems h and j), in particular for the transmetalation mechanism.

Analysis of the geometry of relevant reaction species (Figure 5) shows clearly why the Pd(IV) course reveals similar values between reaction of **Ia** and **Ig** while the transmetallation manifold suffers a severe penalty in the presence of substituent on the starting metallacycle.



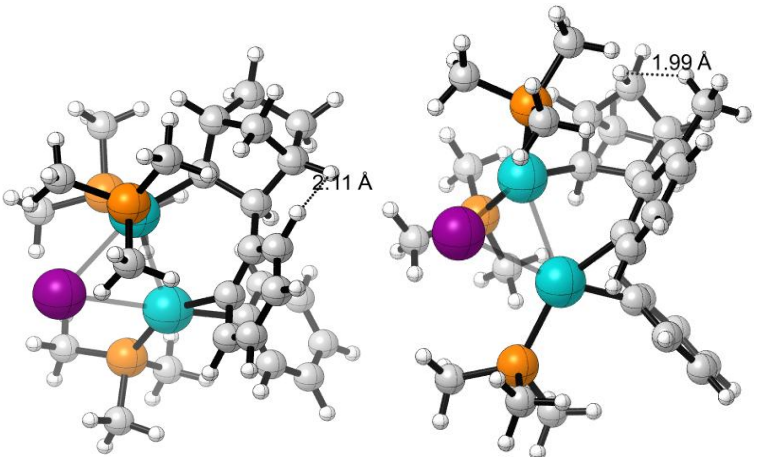
Ig **TS (II-III) g**

Figure 5. Modelized structere of **Ig** and **TS(II-III)g** highlighting shortest H-H distance.

Analysis of the geometry of relevant reaction species (Figure 5) clearly shows the reason why the Pd(IV) course reveals similar values for the reactions of Ia and Ig while the transmetalation pathway suffers a severe penalty in the presence of a methyl substituent in the starting metallacycle. Figure 5 shows the modelized structures of the relevant species involved in the Pd(IV) pathway, namely the starting metallacycle Ig and the TS (II-III)g, the latter reaching the highest energy of the entire profile. In complex Ig the norbornyl moiety, the aromatic ring and the palladium atom are coplanar and the methyl group points to a direction of the space not occupied by the bulky norbornyl ring. The geometry of Ig does not change significantly in the TS(II-III)g, as shown by the shortest H–H distances between the methyl group and the norbornyl unit observed in Ig and TS(II-III)g. A difference of 0.03 Å between the shortest H-H distances in the two modelized structures clearly indicates that no significant change takes place on going from Ig to the highest energy TS of the Pd(IV) pathway.[34]

Thus, in catalytic reactions, even when employing more sterically demanding substituents, if matallacycle **I** is formed (and its formation, being the reagent for both Pd(IV) and TM reaction pathways, is mandatory to obtain catalysis), an oxidative addition transition state did not suffer from steric clashes related to the bulkyness of these substituent *more* than the starting metallacycle itself.[35]

By contrast, Figure 6 presents the geometry of intermediates **TS(VI-VII)a** and **g**. As transfer of the aromatic ring to the second palladium atom occurs with a formal rotation of the aryl-norbornyl C-C bond in respect to the plane of palladacycle **I**, when a substituent is present (**g**, on the letf), it points in the region of space occupied by the bridging CH_2 group of norbornene. A steric clash appears already in intermediate **VIg** (where the shortest H-H distance is 2.07 Å) but is more severe in sequent transition state (shortest H-H distance is lower in the reaction of **Ig** of 0.12 Å compared to **Ia**, and the trend is likely to be even more severe when more sterically demanding groups are at work).



TS (VI-VII) a **TS (VI-VII) g**

Figure 6. Caption of **TS(VI-VII)a** and **TS(VI-VII)g** highlighting shortest H-H distance.

The presence of an ortho substituent also in the reacting aryl halide, as in the case of 2-iodotoluene and 2-bromobenzaldehyde (Table 4, systems i and k) enhances this steric effect in the transmetalation pathway, due to a closer proximity of their 6-hydrogens with the endo protons of the metallacycle.[34]

Analizying the system with DMF as ancillary ligand for palladium (Figure 7) confirms the effect found in the phosphine system and reveals similar trends.

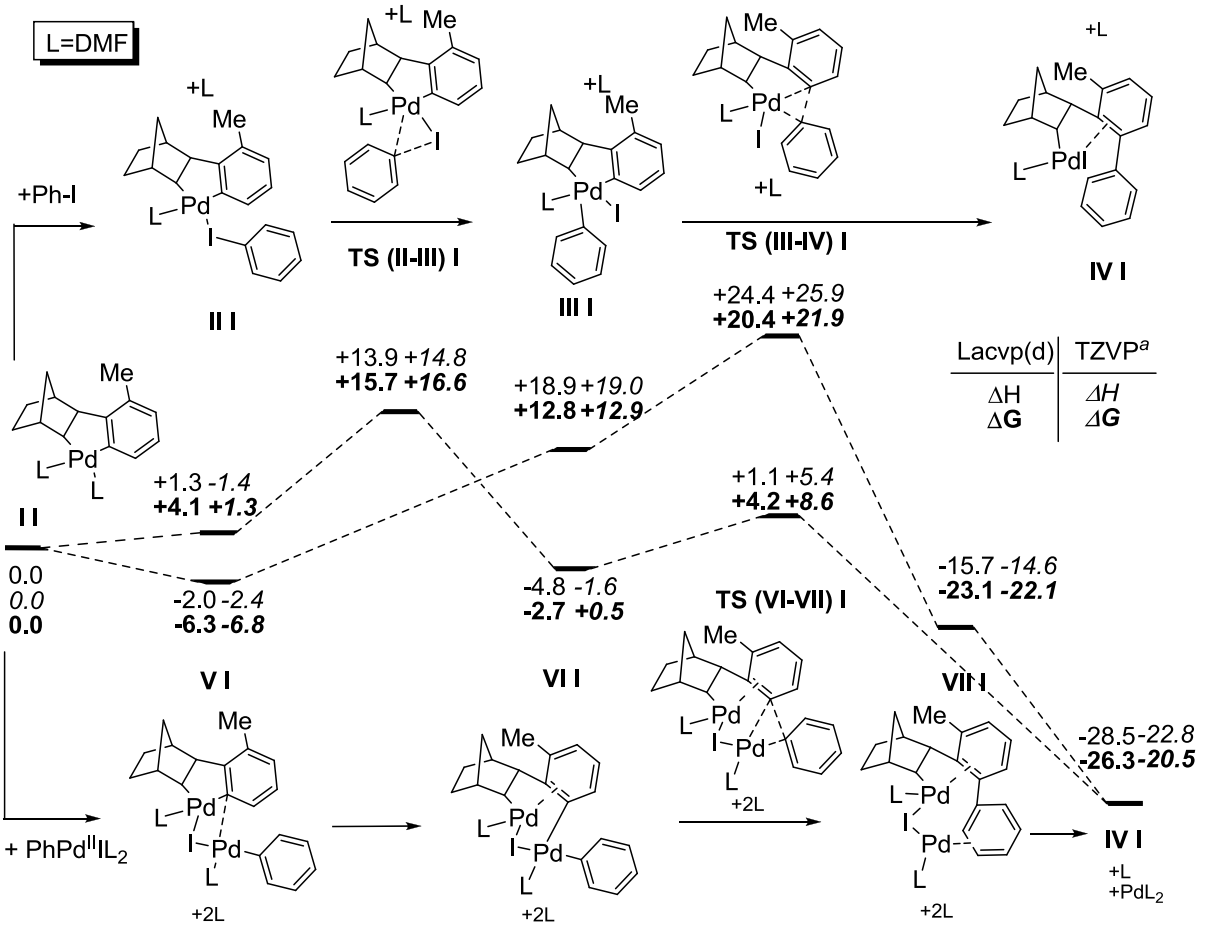


Figure 7. Reaction pathway and energies in kcal/mol for the reaction of **Ij**; *a*: using ZPC and entropy calculated with lacvp(d) basis set.

The Pd(IV) reaction course in the presence of a substituent on the reagent (**Il**) has slightly lower energy values compared to the **Id** system of Scheme 7. Scrambling a DMF molecule with iodobenzene is slightly less energy costing (**IIl**, ΔG +4.1 kcal compared to **IId**, +5.4 kcal), and the oxidative addition **TS(II-III)l** is 15.7 kcal above the entry channel (thus, 1.8 kcal less than the **TS(II-III)d**, see Scheme 7). Pd(IV) intermediate **IIIl** is now even below (-2.7 kcal) the entry channel of the Pd(II) complex **Il**. It features the same Y-distrorted trigonal bipyramidal geometry discussed above, and could allow the formation of the C-C bond present in **IVl** trough the easily accessible **TS(III-IV)l** (ΔG +4.2 kcal).

As in the case of the phosphine, values obtained analyzing the transmetallation pathway are very different from the **Id** system (without ortho substituent on the reagent) of Figure 3. Formation of the association complex **Vl** accounts for a negative ΔG of -6.3 kcal (thus 4.2 kcal above the value obtained for **Vd**, Figure 3). Transfer of the tolyl ring from the palladacycle to the second metal atom to obtain **VIl** is energy costing even in this case (ΔG of +19.1 kcal relative to **Vl**). The reductive elimination from **VIl** proceeds through **TS(VI-VII)l**, which lies

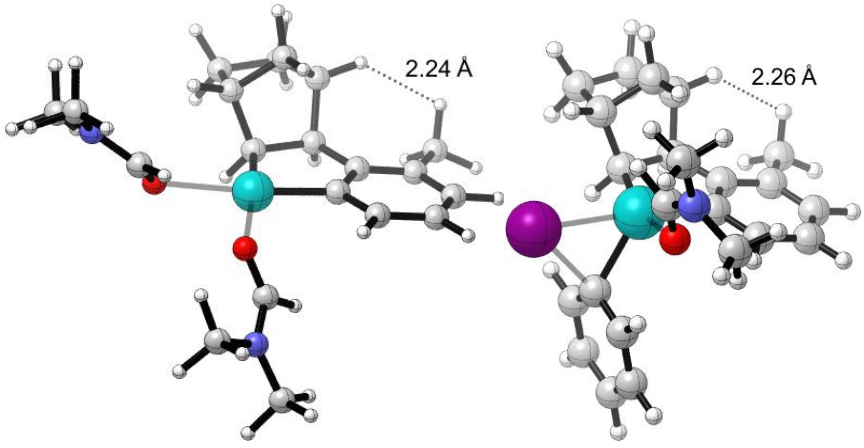
20.4 kcal above the entry channel, and, moreover, 4.7 kcal above the oxidative addition transition state of the Pd(IV) manifold **TS(II-III)l**. As in the posphine case this transition state of the transmetallation pathway shows a significant increase in the energy comparing reaction of **Id** and **Il** (ΔΔG between **TS(VI-VII)d-l** is +5.6 kcal). Even if now the entropy term favours the transmetallation pathway, the gap between the oxidative addition to Pd(IV) and the reductive elimination of transmetallation still let the former being favored over the latter even at high temperature.

Table 5 sumarize the data of the relevant TSs for the different aryl halides considered in this paper.

System	Aryl halide	ΔG TS(II-III) [Pd(IV)]	ΔG TS(VI-VII) [TM]
l	Iodobenzene	+15.7	+20.4
m	4-Iodotoluene	+15.4	+22.4
n	2-Iodotoluene	+19.2	+27.4
o	4-Bromobenzaldehyde	+14.6	+16.6
p	2-Bromobenzaldehyde	+15.2	+23.1

Table 5. Relevant free Gibbs energies comparing Pd(IV) and TM pathways on **Il**; values in kcal/mol, calculated at the M06/LACVP(d) level.

In strict contrast to the data shown in Table 3, the values obtained reacting **Il** metallacycle shows how the Pd(IV) manifold always lies below the transmetallation one in all the analyzed systems (2-8 kcal less in these five representative ones).

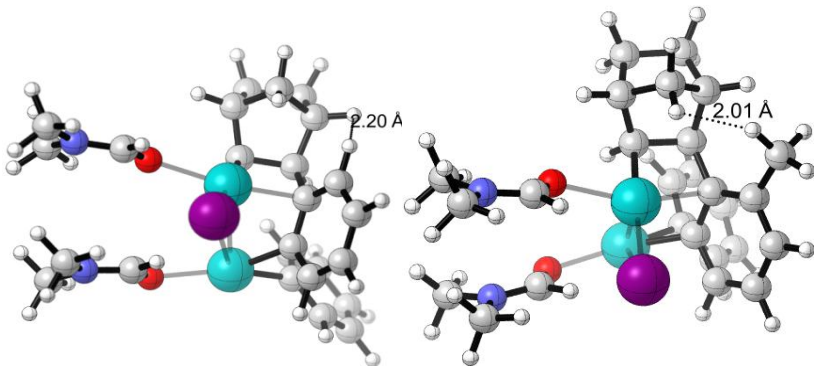


Ij **TS(II-III)j**

Figure 8. Calculated structures of **Il** and **TS(II-III)l** highlighting the shortest H-H distance.

Analysis of the geometry of relevant reaction species (Figure 8) confirms the observed feature described above in the case of the phosphinic ligand: while the Pd(IV) course reveals similar values between **Id** and **Il**, the transmetallation pathway suffers a penalty due to the steric clash between the substituent and the bridging CH_2 group of norbornene. In fact, in agreement with

the above mentioned trend, in **Ig**, the shortest H-H distance is 2.24 Å and in the related **TS(II-III)l** there is even a slight increase to 2.26 A (similarly for the hydrogen substituent in **Id** the increment in the ts is 0.04 Å). As a result, oxidative addition from Pd(II) is not affected by the presence of (bulky) substituent on the starting metallacycle, as the steric environment in the resulting transition state closely resemble the situation of the reagent itself.

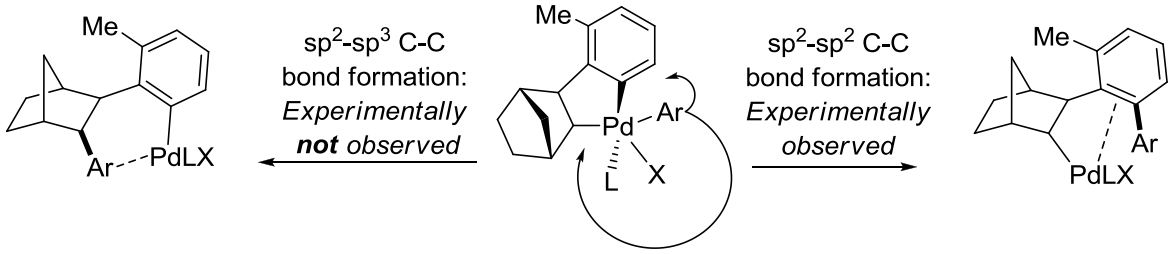


TS (VI-VII) d **TS (VI-VII) l**

Figure 9. Modelized structures of **TS(VI-VII)d** and **TS(VI-VII)l** highlighting the shortest H-H distance.

Figure 9 shows on the other hand how the shortest H-H distance in **TS(VI-VII)d** (H substituent on the initial palladacycle) of 2.20 Å, sinks low to 2.01 Å when a (relatively) small methyl group is places on the reagent. In other words, the rotation of the aryl ring of the starting palladacycle, required for the reductive elimination in the transmetallation mechanism, generates a steric clash when an ortho substituent is present on **I**, among the lone CH_2 of norbornene and the substituent itself. This steric clash, by increasing the energy required for the transmetallation reaction pathway, allows the Pd(IV) mechanism to become a more feasible reaction route for the aryl-aryl coupling also with DMF as ligand.

As mentioned in the introduction, the presence of a substituent on the starting palladacycle is necessary to achieve the selective formation of the sp^2-sp^2 C-C bond. Analysis of the reductive elimination from Pd(IV) complexes **III** could properly explain this experimental observation. Table 6 compares the barriers of reductive elimination from **III** to form either the sp^2-sp^2 and the sp^2-sp^3 C-C bond.



System	Ligand	Aryl halide	ΔG TS(III-IV) [Ary]	ΔG TS(III-X) [Alk]
g	$P(Me)_3$	Iodobenzene	+5.7	+17.5
h	$P(Me)_3$	4-Iodotoluene	+6.2	+17.4
i	$P(Me)_3$	2-Iodotoluene	+10.4	+22.4
j	$P(Me)_3$	4-Bromobenzaldehyde	+4.8	+15.1
k	$P(Me)_3$	2-Bromobenzaldehyde	+9.2	+22.5
l	DMF	Iodobenzene	+6.9	+11.0
m	DMF	4-Iodotoluene	+7.6	+11.0
n	DMF	2-Iodotoluene	+4.7	+9.8
o	DMF	4-Bromobenzaldehyde	+4.6	+10.7
p	DMF	2-Bromobenzaldehyde	+3.0	+9.9

Table 6. Comparison of the two possible reductive eliminations from Pd(IV) complexes **IIIg-p**; values in kcal/mol, referred to their relative intermediate **III** and calculated at the M06/LACVP(d) level.

Among these representative systems, formation of the sp^2-sp^2 C-C bond is always favored over the sp^2-sp^3 one (by 4-12 kcal/mol in ΔG). Reductive elimination from **III** takes place between the electrophilic sp^2 carbon atom previously belonging to the aryl halide and the aryl site of the metallacycle which, according to both APT and Mulliken formal charges, is more nucleophilic than its aliphatic counterpart. Moreover, the *endo* hydrogen atom of the latter is responsible of a steric clash in each TS(III-X) with the incoming electrophilic carbon of the aryl ring (C-H distances are around 2.1 Å in these analyzed systems, thus 0.1 A less than the distance between the reacting carbon atoms).

The proposed Pd(IV) model is thus in agreement with experimental evidences: aryl-alkyl coupling is not observed when an ortho substituent is present on the starting metallacycle as this pathway is always more energy costing than sp^2-sp^2 bond forming.

4. Conclusions

We have attempted to answer the mechanistic questions concerning palladium and norbornene catalyzed reactions: what is the rational explanation of the "ortho effect" and how aryl halides react with palladacycles. We have considered two possible pathways, one involving oxidative

addition of an aryl halide to a palladacycle, the other passing through a palladium (II) transmetalation.

We have shown that the palladium catalyzed reaction of ortho unsubstituted aryl halides and norbornene has a good probability to occur through a transmetalation mechanism, energetically favored over the Pd(IV) one. The reported unselective sp^2-sp^2 and sp^2-sp^3 coupling can be explained in the framework of the transmetalation pathway since the energetic difference between aryl attack onto the aryl or norbornyl carbon is quite small (Scheme 2 and Figure 2). On the other hand, the experimentally observed "ortho effect" stipulates that in palladium *and norbornene* catalyzed domino reactions involving *ortho*-substituted aryl halides, selective aryl-aryl coupling only occurs. The present work offers the first possible rationalization of this statement. When *in-situ* formed metallacycles, containing an ortho substituent, undergo oxidative addition of an aryl halide the process becomes less energy costly than the one involving reductive elimination from the transmetalation intermediate, which would be subject to steric clash in the transition state. The now accessible Pd(IV) intermediate features a Y-distorted trigonal bipyramidal structure from which an easy reductive elimination can account for the reported selective aryl-aryl coupling. Thus the steric effect represents the main factor that dictates the energetic convenience of the system to follow the Pd(IV) or the transmetalation pathway. Ortho substituents cause a higher energy transition state for reductive elimination from the transmetalation intermediate than for oxidative addition from the metallacyclic palladium (II) and the pathway based on the latter predominates.

In conclusion, we tried to answer the two open mechanicistic questions of palladium and norbornene catalytic sequences: how aryl halides react with palladacycles and what is the rational explanation of the "ortho effect". Our investigations suggests that the two points are closely related, as the favored reaction mechanism, and thus the outcome of these domino reactions, depends mainly on the presence or the absence of a substituent on the reagent.

Referencesand notes

[1] a) J. Tsuji, *Palladium Reagents and Catalysts – New Perspectives for the 21st Century*, John Wiley & Sons, Chichester, **2004**, pp 409–415. b) F. Diederich, A. de Meijere, Eds., *Metal-Catalyzed Cross–Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**. c) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[2] a) R. F. Heck *Acc. Chem. Res*. **1979**, *12*, 146. b) E.-I. Negishi Ed., *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**. c) A. Suzuki *Pure Appl. Chem*. **1994**, *66*, 213. d) A. Suzuki *Chem. Commun*. **2005**, 4759.

[3] a) J. K. Stille, K. S. Y. Lau *J. Am. Chem. Soc.* **1976**, *98*, 5841. b) D. Milstein, J. K. Stille *J. Am. Chem. Soc.* **1979**, *101*, 4981.

[4] For recent reviews on Pd(IV) chemistry: a) K. Muñiz *Angew. Chem., Int. Ed*. **2009**, *48*, 9412. b) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb *Chem. Rev*. **2010**, *110*, 824. (c) L. M. Xu, B. J. Li, Z. Yang, Z. J. Shi *Chem. Soc. Rev*. **2010**, *39*, 712.
[5] a) P. K. Byers, A. J. Canty, B. W. Skelton, A. H. White *J. Chem. Soc., Chem. Commun.* **1986**, 1722. (b) A. J. Canty *Acc. Chem. Res*. **1992**, *25*, 83. (c) W. De Graaf, J. Boersma, G. van Koten *Organometallics* **1990**, *9*, 1479. d) R. Vanasselt, E. Rijnberg, C. J. Elsevier *Organometallics* **1994**, *13*, 706. e) M. Catellani, B. E. Mann *J. Organomet. Chem.* **1990**, *390*, 251. (f) J. Campora, J. A. Lopez, P. Palma, P. Valerga, E. Spillner, E. Carmona *Angew. Chem. Int. Ed.* **1999**, *38*, 147.
[6] a) A. Bayler, A. J. Canty, J. H. Ryan, B. W. Skelton, A. H. White *Inorg. Chem. Commun.* **2000**, *3*, 575. b) A. J. Canty, T. Rodemann *Inorg. Chem. Commun.* **2003**, *6*, 1382. c) A. J. Canty, J. Patel, T. Rodeman, J. H. Ryan, B. W. Skelton, A. H. White *Organometallics* **2004**, *23*, 3466. d) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford *J. Am. Chem. Soc*. **2005**, *127*, 7330. e) A. R. Dick, J. W. Kampf, M. S. Sanford *J. Am. Chem. Soc.* **2005**, *127*, 12790.
[7] a) J. Tsuji Ed. *Palladium in Organic Synthesis*, Springer-Verlag, Berlin, **2005**. b) D. Alberico, M. E. Scott, M. Lautens *Chem. Rev.* **2007**, *107*, 174. c) I. P. Beletskaya, A. V. Cheprakov *J. Organometal. Chem.* **2004**, 689, 4055. d) L. Ackerman *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**. e) P. Espinet, A. M. Echavarren *Angew. Chem. Int. Ed.* **2004**, *43*, 4704. f) J. Dupont, M. Pfeffer Eds. *Palladacycles: Synthesis, Characterization and Applications*, Wiley-VCH, Weinheim, **2008**. g) G. Dyker *Angew. Chem. Int. Ed.* **1999**, *38*, 1699. h) A. R. Dick, M. S. Sanford *Tetrahedron* **2006**, *62*, 2439. (i) J. Campora, P. Palma, E. Carmona *Coord. Chem. Rev*. **1999**, *193–195*, 207. j) G. Zeni, R. C. Larock *Chem. Rev.* **2006**, *106*, 4644. k) A. de Meijere, P. von Zezschwitz, S. Braese *Acc. Chem. Res*. **2005**, *38*, 413. l) P. Mauleón, A. A. Núñez, I. Alonso, J. C. Carretero *Chem. Eur. J*. **2003**, *9*, 1511.
[8] a) M. Catellani, G. P. Chiusoli *J. Organomet. Chem.* **1988**, *346*, C27. b) M. Catellani, M. C. Fagnola *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2421. c) C. Amatore, M. Catellani, S. Deledda, A. Jutand, E. Motti *Organometallics* **2008**, *27*, 4549. (d) A. Dedieu, A. J. Mota *Can. J. Chem.* **2009**, 87, 838.
[9] G. Bocelli, M. Catellani, S.Ghelli *J. Organomet. Chem.* **1993**, *458*, C12.
[10] M. Catellani, M. C. Fagnola *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2421.
[11] a) M. Catellani, F. Frignani, A. Rangoni *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119. b) M. Catellani *Top. Organomet. Chem*. **2005**, *14*, 21. c) J. Tsuji *Palladium Reagents and Catalysts – New Perspectives for the 21st Century*, John Wiley & Sons, Chichester, **2004**, 409. (d) M. Catellani in E.-I. Negishi (Ed.), *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, New York, **2002**, pp 1479. e) A. Martins, B. Mariampillai, M. Lautens *Top. Curr. Chem*. **2010**, *292*, 1. f) M. Lautens, D. Alberico, C. Bressy, Y.-Q. Fang, B. Mariampillai, T. Wilhelm *Pure Appl. Chem.* **2006**, *78*, 351. g) C. Bressy, D. Alberico, M. Lautens *J. Am. Chem. Soc.* **2005**, *127*, 13148. h) A. Rudolph, N. Rackelmann, M. Lautens *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. j) K. M. Gericke, D. I. Chai, N. Bieler, M. Lautens *Angew. Chem. Int. Ed.* **2009**, *48*, 1447.
[12] M. Catellani, G. P. Chiusoli *J. Organomet. Chem.* **1985**, *286*, C13.
[13] a) F. Ozawa, T. Hidaka, T. Yamamoto, A. Yamamoto *J. Organomet. Chem.* **1987**, *330*, 253. b) F. Ozawa, M. Fujimori, T. Yamamoto, A. Yamamoto *Organometallics* **1986**, *5*, 2144. c) Y. Suzaki, T. Yagyu, Y. Yamamura, A. Mori, K. Osakada *Organometallics* **2003**, 5254.
[14] a) D. J. Cárdenas, B. Martín-Matute, A. M. Echavarren *J. Am. Chem. Soc*. **2006**, *128*, 5033. b) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren *J. Am. Chem. Soc.* **2006**, *128*, 1966.
[15] Relevance of steric factors in a transmetalation step have been already reported for Negishi coupling: Q. Liu, Y. Lan, J. Liu, G. Li, Y.-D. Wu A. Lei *J. Am. Chem. Soc*. **2009**, *131*, 10201.

[16] a) M. Catellani, E. Motti *New J. Chem.* **1998**, *22*, 759. b) M. Catellani, E. Motti, S. Baratta *Org. Lett*. **2001**, *23*, 3611. Selected recent applications: c) M. Catellani, E. Motti, N. Della Ca' *Acc. Chem. Res*. **2008**, *41*, 1512. d) M. Catellani, E. Motti, N. Della Ca', R. Ferraccioli *Eur. J. Org. Chem*. **2007**, 4153. e) Y.-B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Z. Li, M. Lautens *Angew. Chem. Int. Ed.* **2009**, *48*, 1849. f) B. Mariampillai, J. Alliot, M. Li, M. Lautens *J. Am. Chem. Soc.* **2007**, *129*, 15372. g) D. A. Candito, M. Lautens *Angew. Chem. Int. Ed.* **2009**, *48*, 6713. h) G. Maestri, N. Della Ca', M. Catellani *Chem. Comm.* **2009**, *45*, 4892.
[17] Gaussian09 rev A.01. Complete citation in Computational details section.
[18] Y. Zhao, D. G. Truhlar *Theor. Chem. Account* **2008**, *120*, 215.
[19] D. Benitez, E. Tkatchouk, W. A. Goddard, III *Organometallics* **2009**, *28*, 2643.
[20] a) S. Petrie, R. Stranger *Inorg. Chem.* **2004**, *43*, 2597. b) C. J. Cramer, D. G. Truhlar *Phys. Chem. Chem. Phys.* **2009**, *11*, 10757.
[21] a) J. P. Hay, W. R. Wadt *J. Chem. Phys.* **1985**, *82*, 299. b) R. A. Friesner, R. B. Murphy, M. D. Beachy, M. N. Ringlanda, W. T. Pollard, B. D. Dunietz, Y. X. Cao *J. Phys. Chem. A* **1999**, *103*, 1913.
[22] a) F. Weigen, R. Ahlrichs *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297. b) D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss *Theor. Chim. Acta* **1990**, *77*, 123. c) K. A. Peterson, D. Figgen, E. Goll, H. Stoll, M. Dolg *J. Chem. Phys.* **2003**, *119*, 11113.
[23] a) C.-H. Liu, C.-S. Li, C.-H Cheng *Organometallics* **1994**, 13, 18. b) M. Catellani, G. P. Chiusoli *J. Organomet. Chem*. **1992**, *425*, 151.
[24] a) F. Faccini, E. Motti, M. Catellani *J. Am. Chem. Soc.* **2004**, *126*, 78. b) E. Motti, G. Ippomei, S. Deledda, M. Catellani *Synthesis* **2003**, 2671. c) E. Motti, F. Faccini, I. Ferrari, M. Catellani, R. Ferraccioli *Org. Lett*. **2006**, *8*, 3967. d) E. Motti, N. Della Ca', S. Deledda, E. Fava, F. Panciroli M. Catellani *Chem. Commun*. **2010**, *46*, 4291.
[25] This Pd(II) complex is likely present in solution, as it is required as well to form **I**.
[26] For other studies on reductive elimination from Pd(IV) complexes: a) P. K. Byers, A. J. Canty, M. Crespo, R. J. Puddephatt, J. D. Scott *Organometallics* **1988**, *7*, 1363. b) A. J. Canty *Acc. Chem. Res.* **1992**, *25*, 83. c) V. P. Ananikov, D. G. Musaev, K. Morokuma *J. Am. Chem. Soc.* **2002**, *124*, 2839. d) A. R. Dick, J. Kampf, M. S. Sanford *J. Am. Chem. Soc.* **2005**, *127*, 12790. e) A. J. Mota, A. Dedieu *Organometallics* **2006**, *25*, 3130. f) S. R. Whitfield, M. S. Sanford *J. Am. Chem. Soc.* **2007**, *129*, 15142. g) Y. Fu, Z. Li, S. Liang, Q.-X. Guo, L. Liu *Organometallics* **2008**, *27*, 3736. h) J. M. Racowski, A. R. Dick, M. S. Sanford *J. Am. Chem. Soc.* **2009**, *131*, 10974. j) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard, III, T. Ritter *J. Am. Chem. Soc.* **2010**, *132*, 3793. k) O. Blacque, C. M. Frech *Chem. Eur. J.* **2010**, *16*, 1521.
[27] a) C.-S. Li, C.-H Cheng, F.-L. Liao, S.-L. Wang *Chem. Commun*. **1991**, 710. b) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreño, P. S. Pregosin *J. Am. Chem. Soc*. **2002**, *124*, 4336.
[28] **TS(II-III)a** and **TS(III-IV)a** lie 5.5 and 4.5 kcal in ΔG below their octahedrical counterparts respectively.
[29] Our theoretical approach has been successfully adopted to describe dipalladium complexes: D. C. Powers, D. Benitez, E. Tkatchouk, W. A. Goddard, III, T. Ritter *J. Am. Chem. Soc.* **2010**, *132*, 14092. Recently, investigations establishing an attractive d^8-d^8 interaction in certain Pd(II) dimers have been carried out: J. E. Bercaw, A. C. Durrell, H. B. Gray, J. C. Green, N. Hazari, J. A. Labinger, J. R. Winkler *Inorg. Chem.* **2010**, *49*, 1801.
[30] **TS(V-VI)a** could be found employing B3LYP and PBE0 functionals. They lye only +0.3 and +0.8 kcal/mol above **VIa**, respectively.
[31] We modelized also this system, as proposed by Cardenas and Echavarren in their model, but the resulting energies are higher than those reported in Figure 3. This is probably related to the simplified model they employed, where steric congestion was much lower.

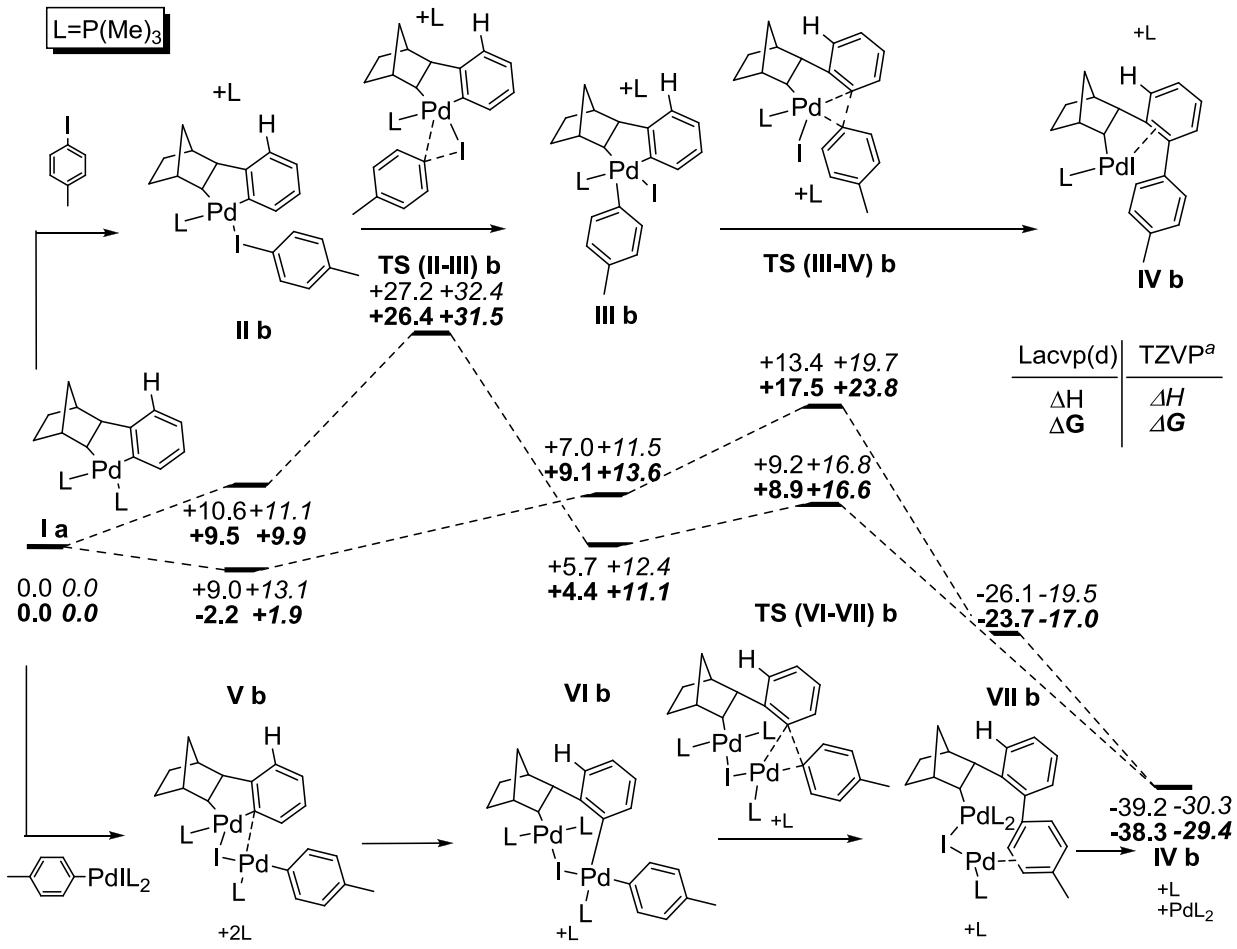
[32] Using B3LYP and PBE0 functionals didn't allow to determine either the TS or intermediate **VIg**, and led to a direct connection, although very energetically disfavored, between **Vg** and **TS(VI-VII)g**.
[33] 2-substituted aryl halides have been tested as simplified model substrates for catalytic methods featuring a final intramolecular ring closure, as those of reference XIV c–e.
[34] The distance is reduced by 0.03 Å only, while this contraction is greater (0.23 Å) when the Me group is replaced by a H atom, as found for Ia and its corresponding **TS(II-III)a**.
[35] The methyl group in our model, or even much more sterically demanding groups such as the *i*-Pr, *s*-Bu and Ph were experimentally employed in successful way.
[36] Modelized relevant structures evidencing these further H-H close proximity (less than 2 Å) for i,k,n and p systems could be found in the Computational details section.
[37] Relevant data for these three reacting carbon atoms and relevant calculated charges for palladium nuclei of both formal Pd(IV) and transmetalation (TM) mechanisms is available in the Computational details section.

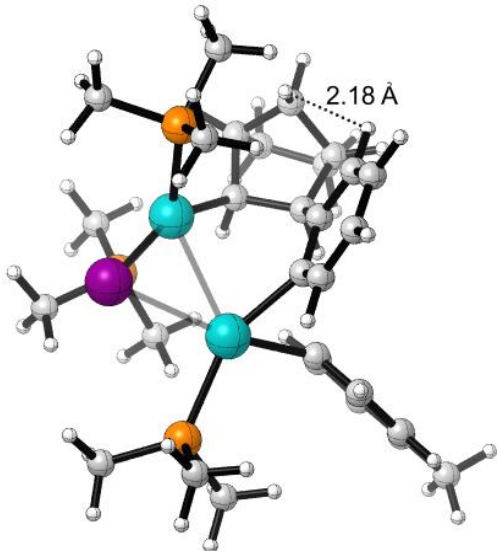
Computational details

1. General Remarks

All calculations were performed at the DFT level using the M06[1] functional as implemented in Gaussian09.[2] Geometry optimization were carried out employing LACVP(d)[3] basis set. The structures of the reactants, intermediates, transition states, and products were fully optimized without any restriction. Transition states were identified by having one imaginary frequency in the Hessian matrix. Single point calculations were made on optimized structures using Def2-TZVP[4] basis set, and show no significant differences with the trends obtained with the double-ζ basis set. Reaction schemes from which relevant transition states have been presented in the article on form of table for sake of space, are presented herein with captions of the relevant species thereby involved.

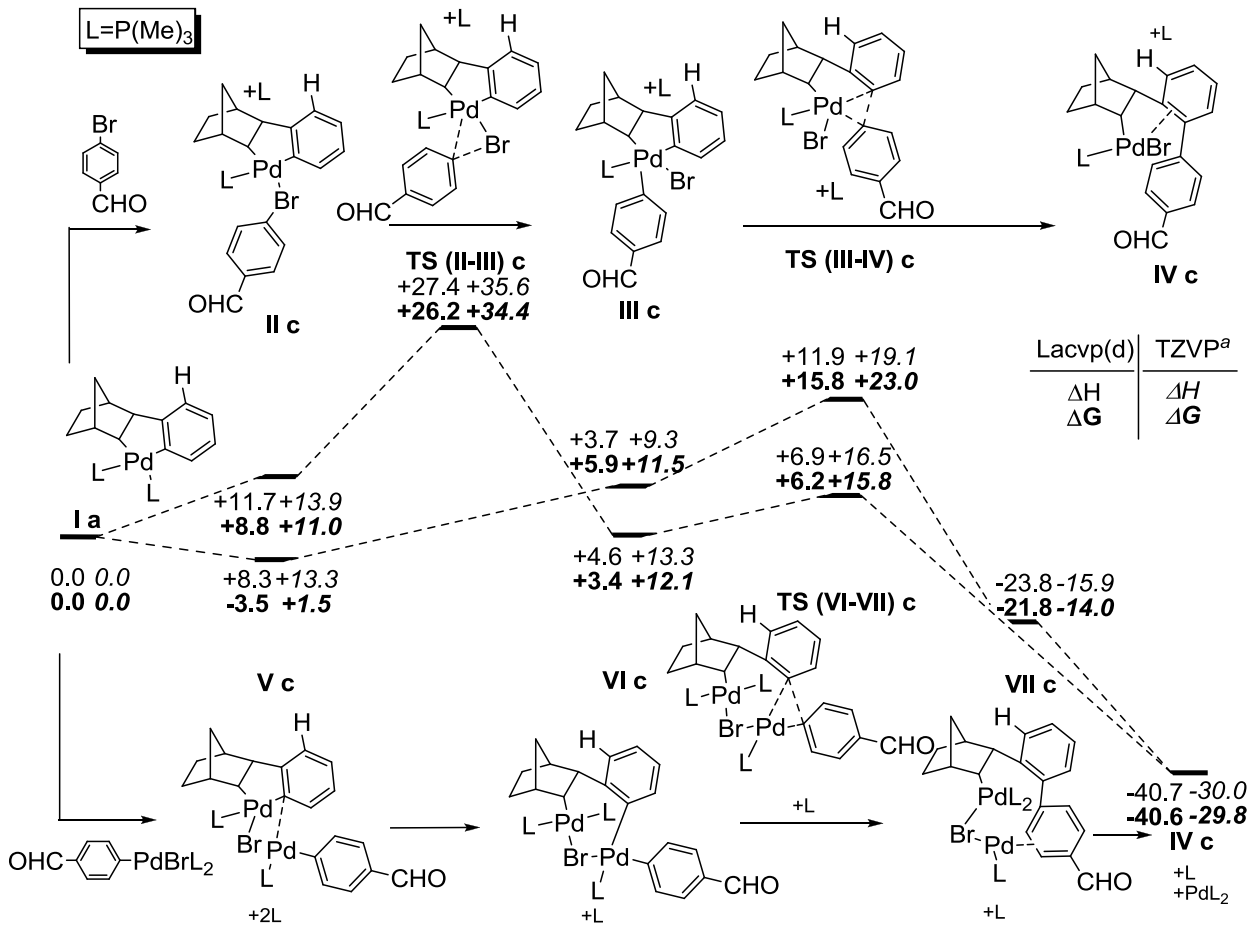
2. Reaction scheme (b)

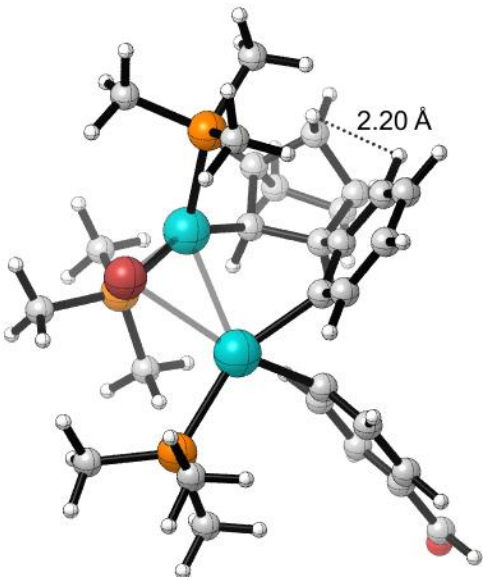




TS (VI-VII) b

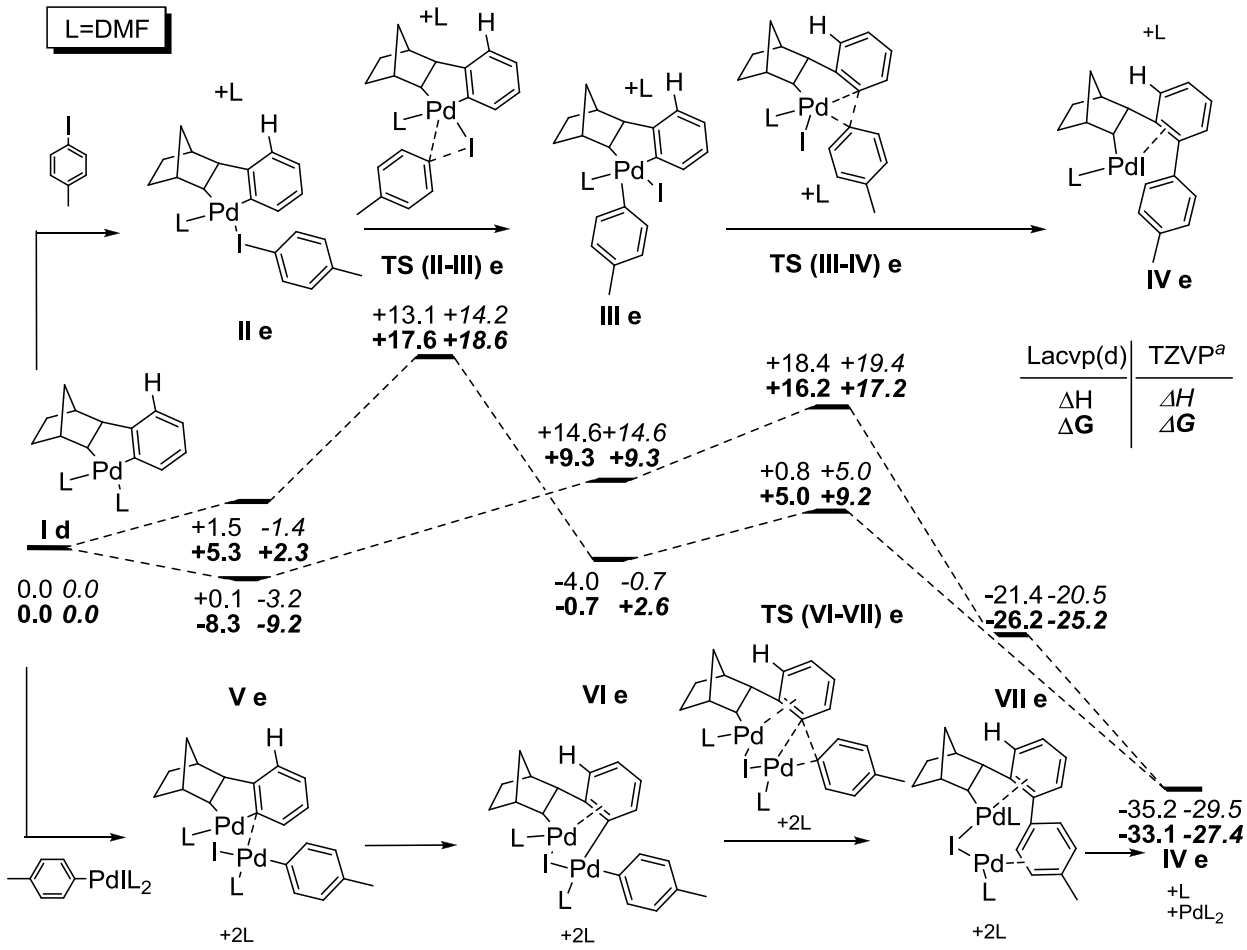
Reaction scheme (c)

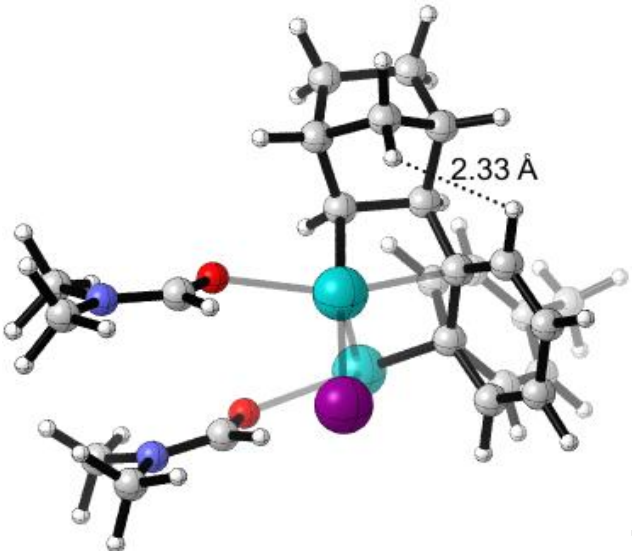




TS (VI-VII) c

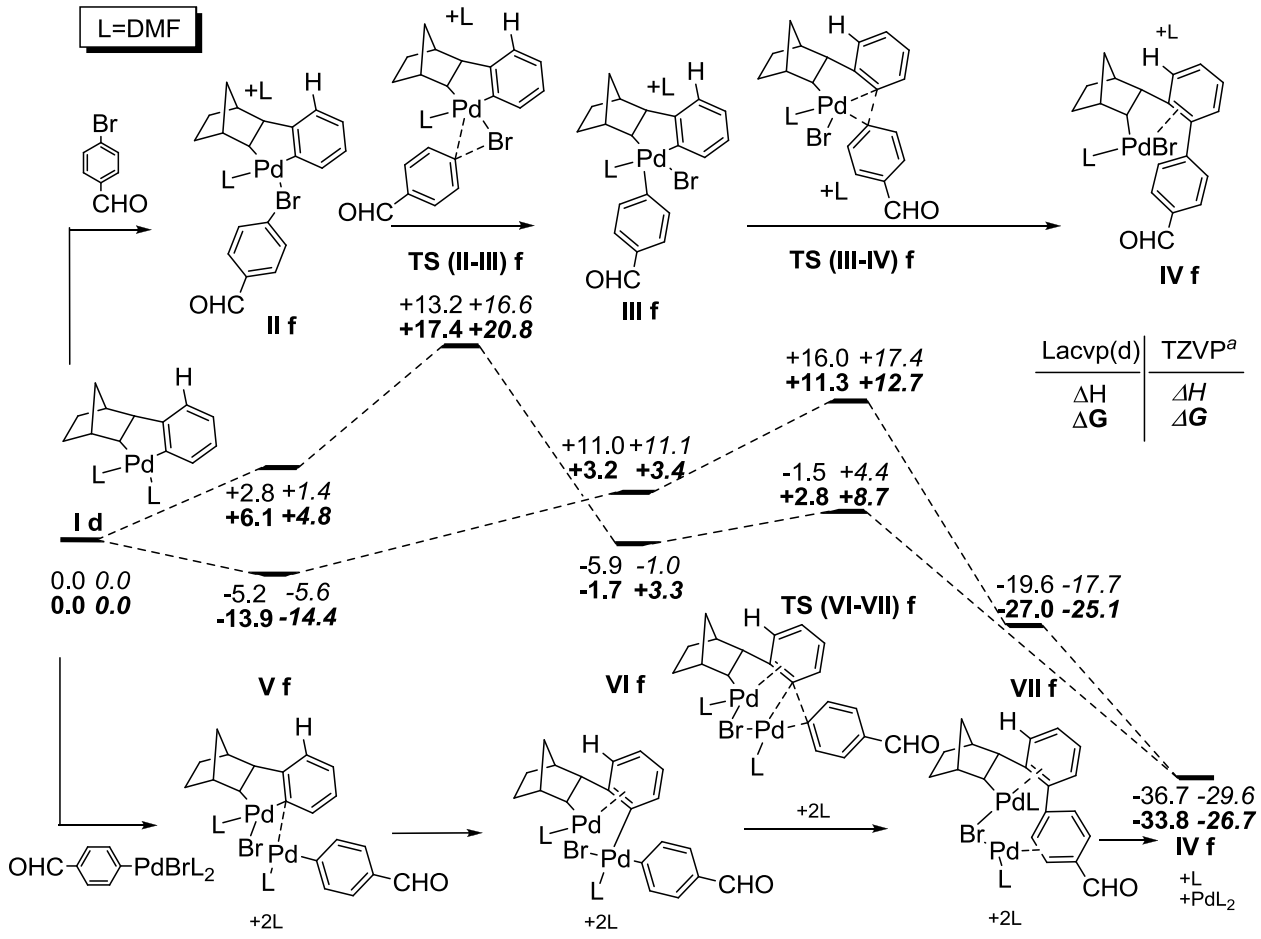
Reaction scheme (e)

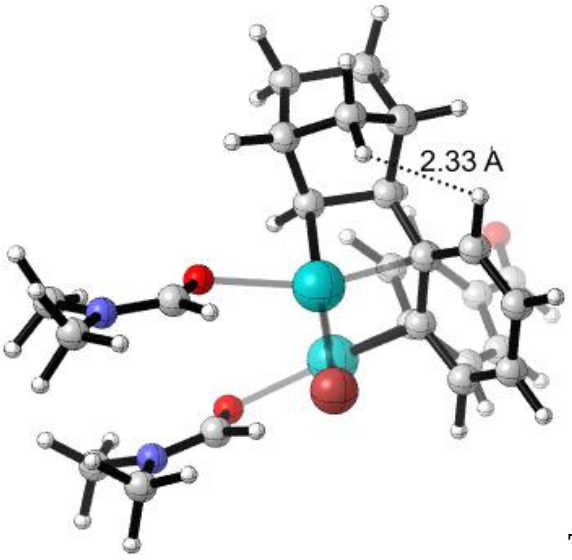




TS (VI-VII) e

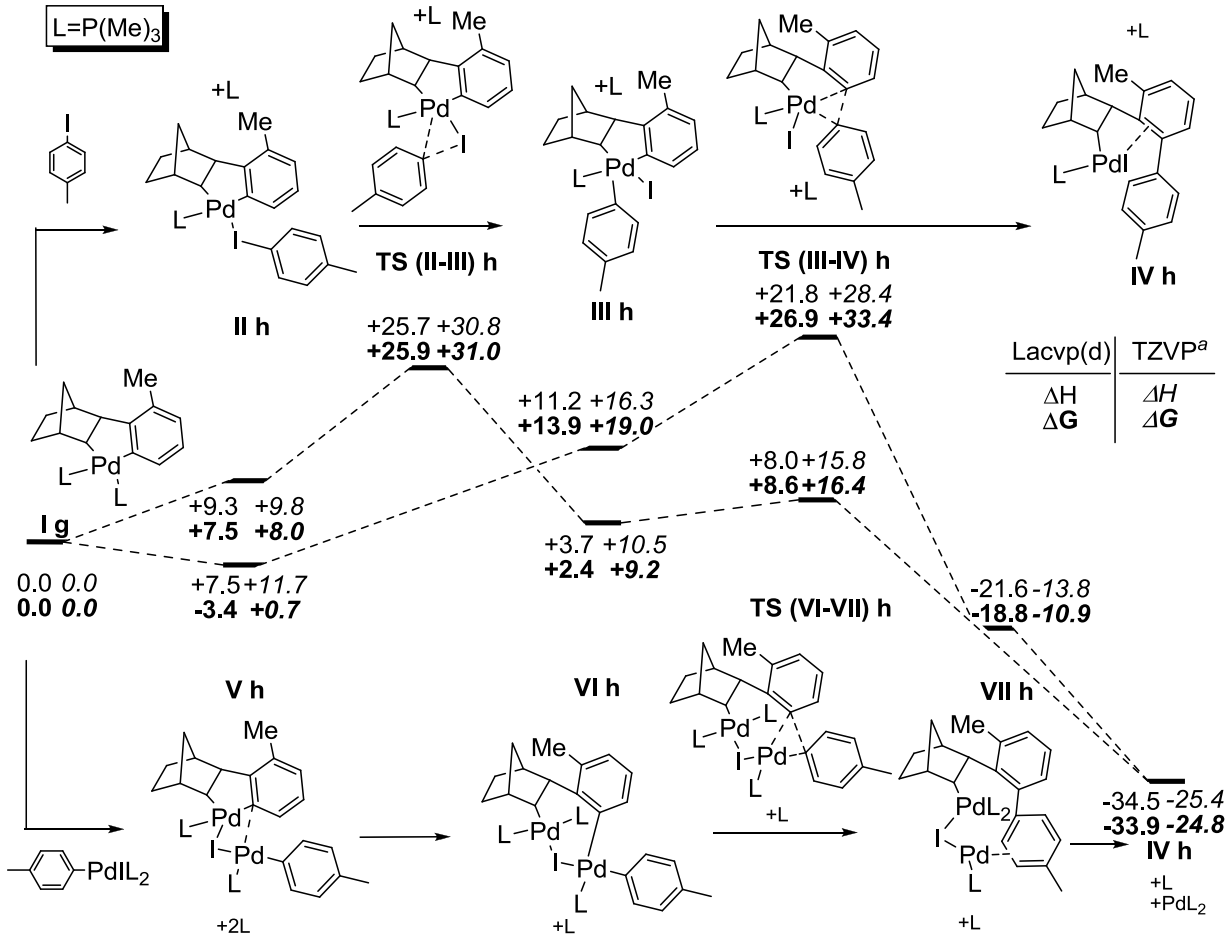
Reaction scheme (f)

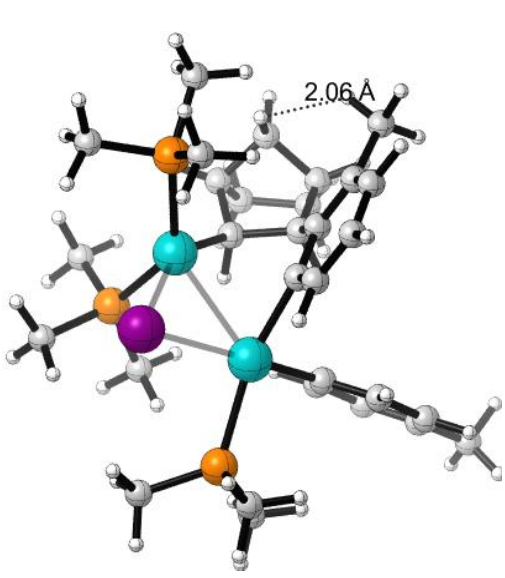




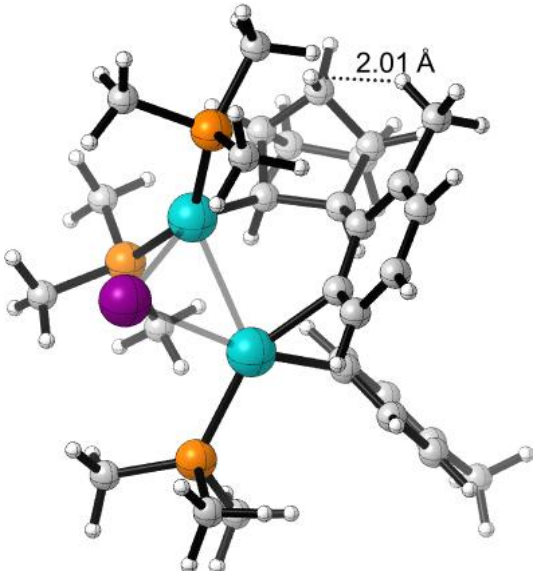
TS (VI-VII) f

Reaction scheme (h)



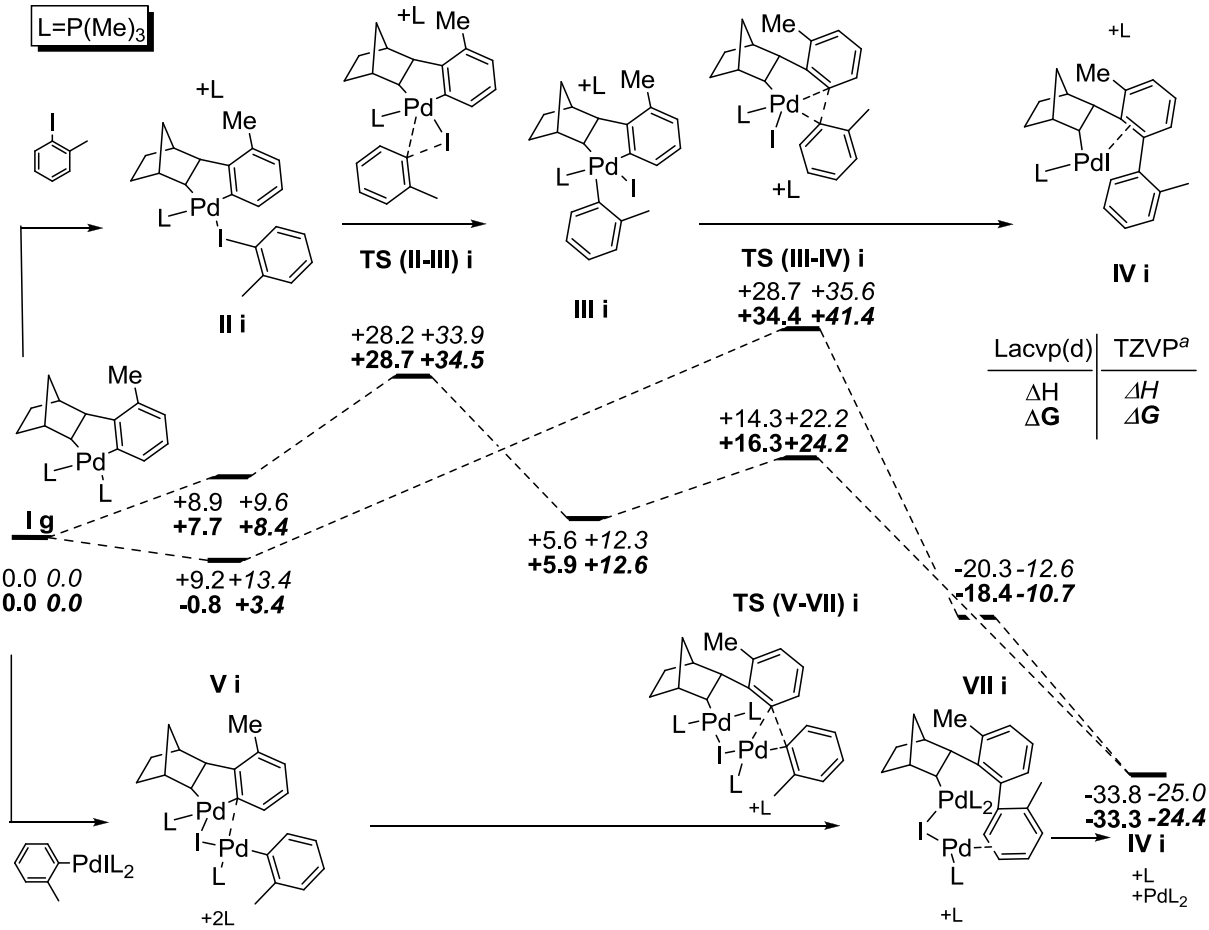


VI h

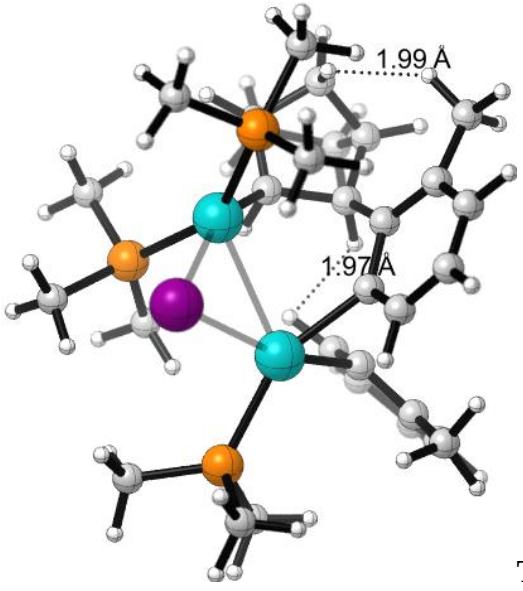


TS (VI-VII) h

Reaction scheme (i)

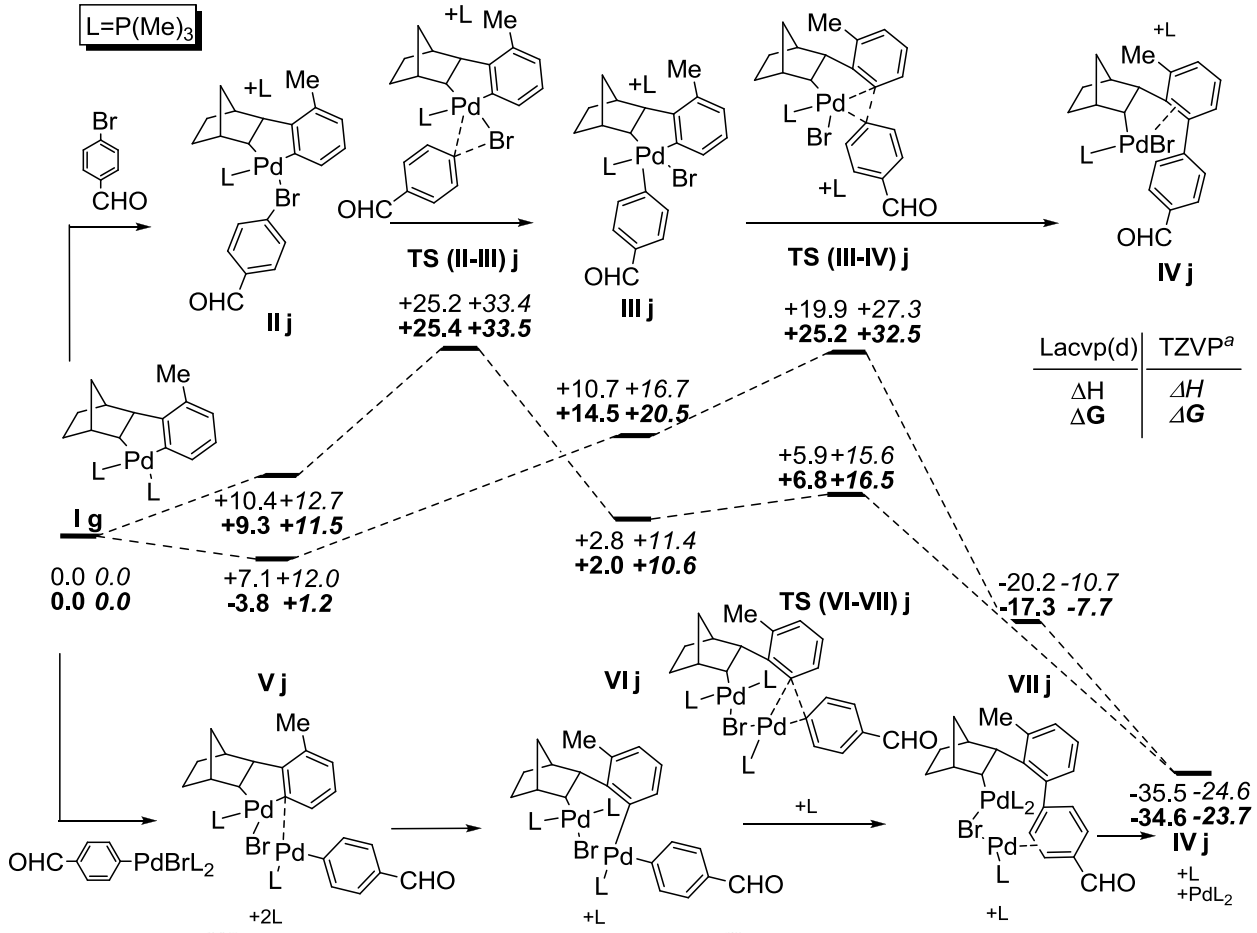


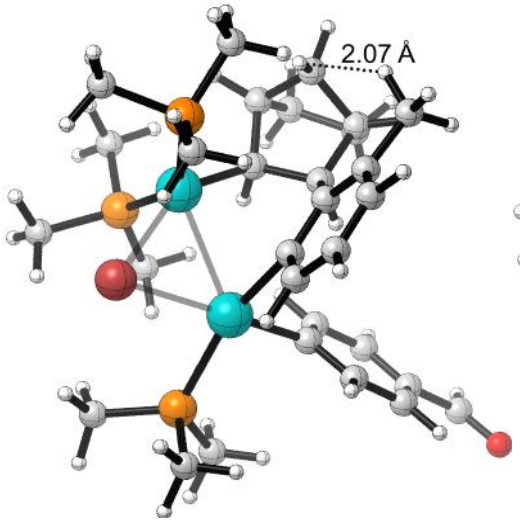
The presence of an *o*-methyl group on the aryl halide increases the steric hinderance of complexes in the transmetalation pathway. It was not possible to obtain a converged structure for intermediate **VIi**, resulting in a direct connection between **Vi** and and **VIIi** trough **TS(V-VII)i**.



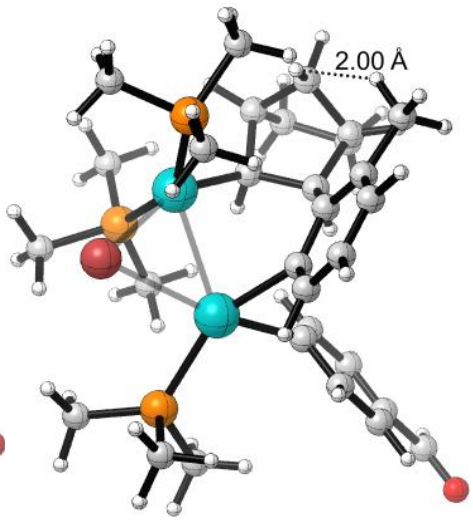
TS(V-VII)i

Reaction scheme (j)



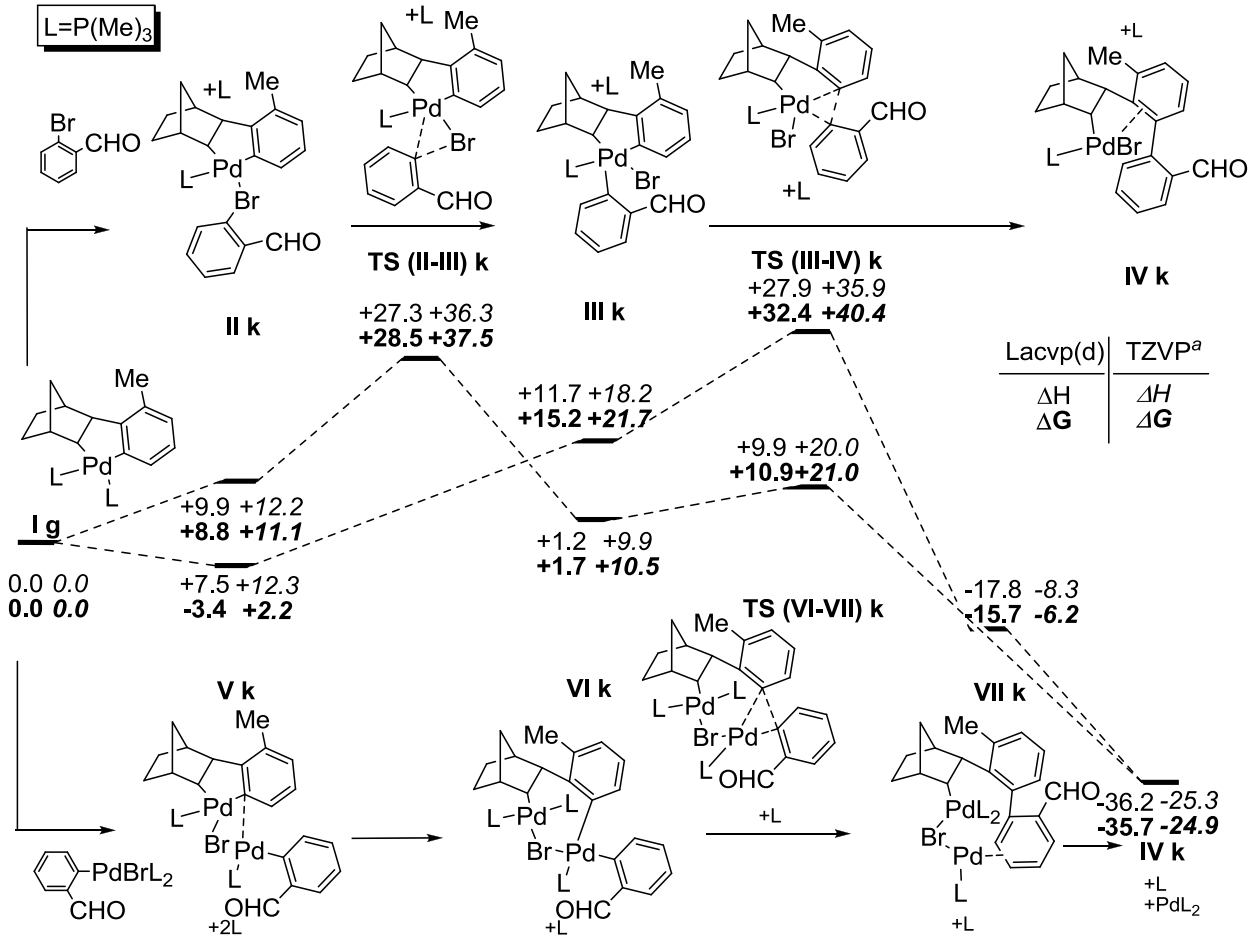


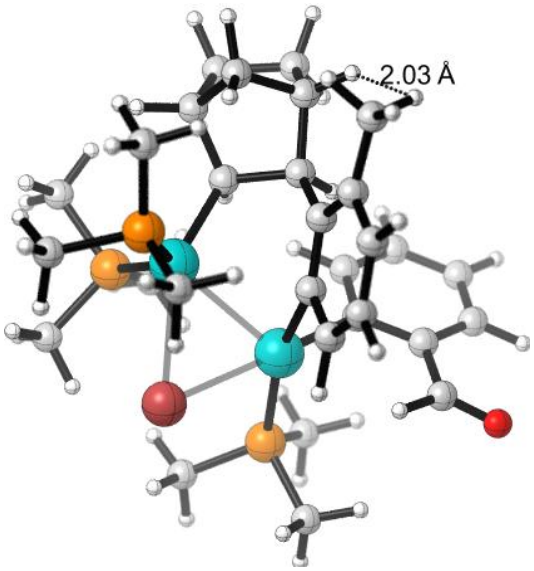
VI j



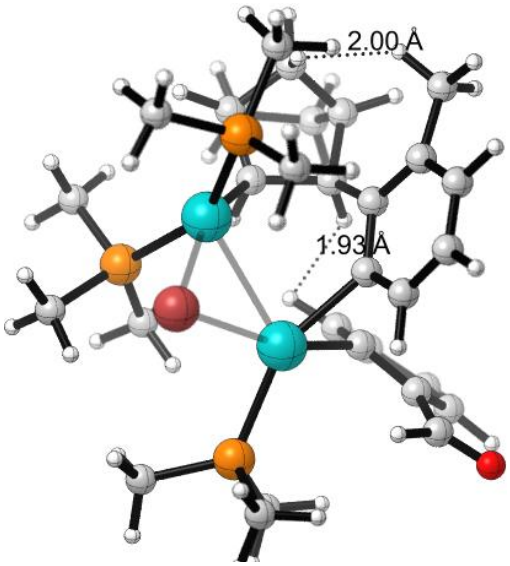
TS(VI-VII) j

Reaction scheme (k)



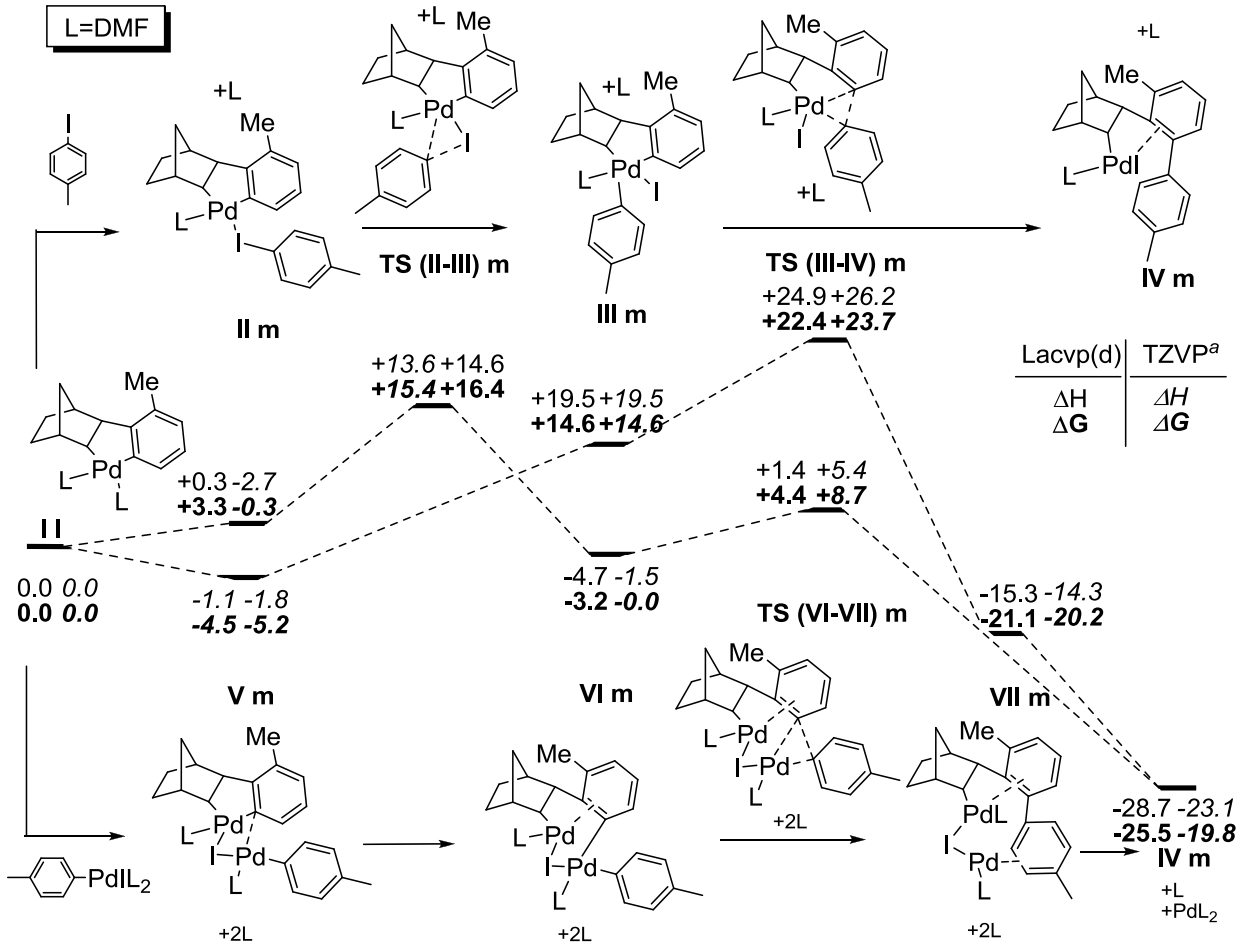


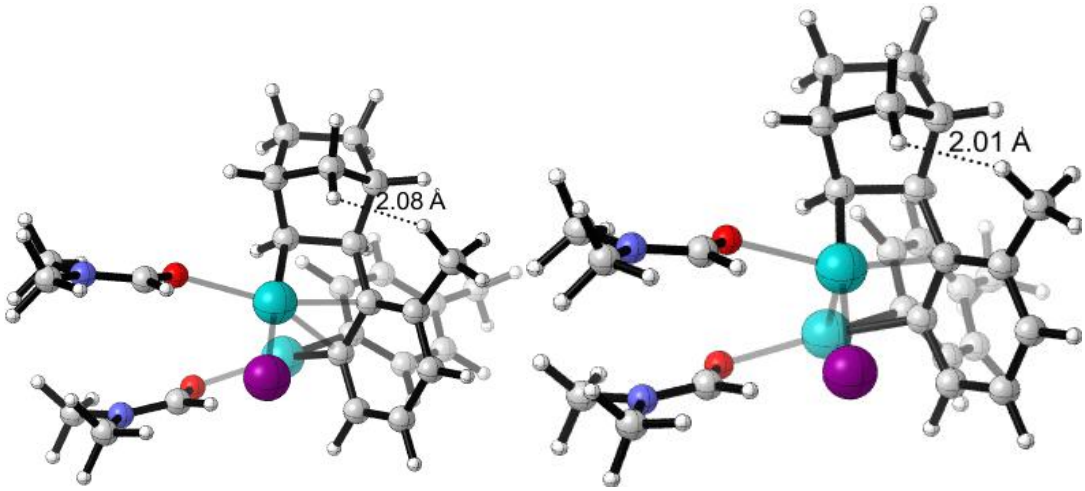
VI k



TS (VI-VII) k

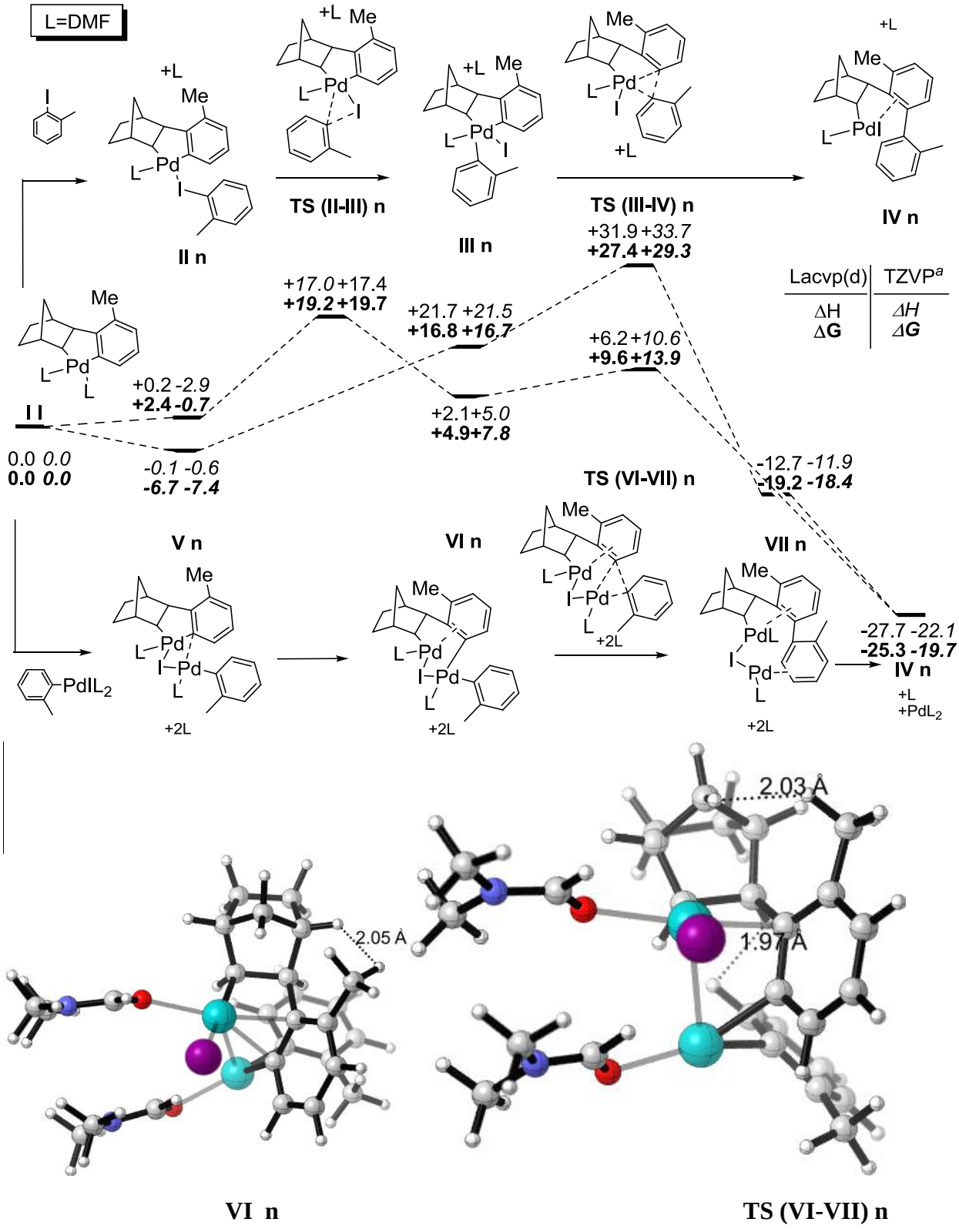
Reaction scheme (m)





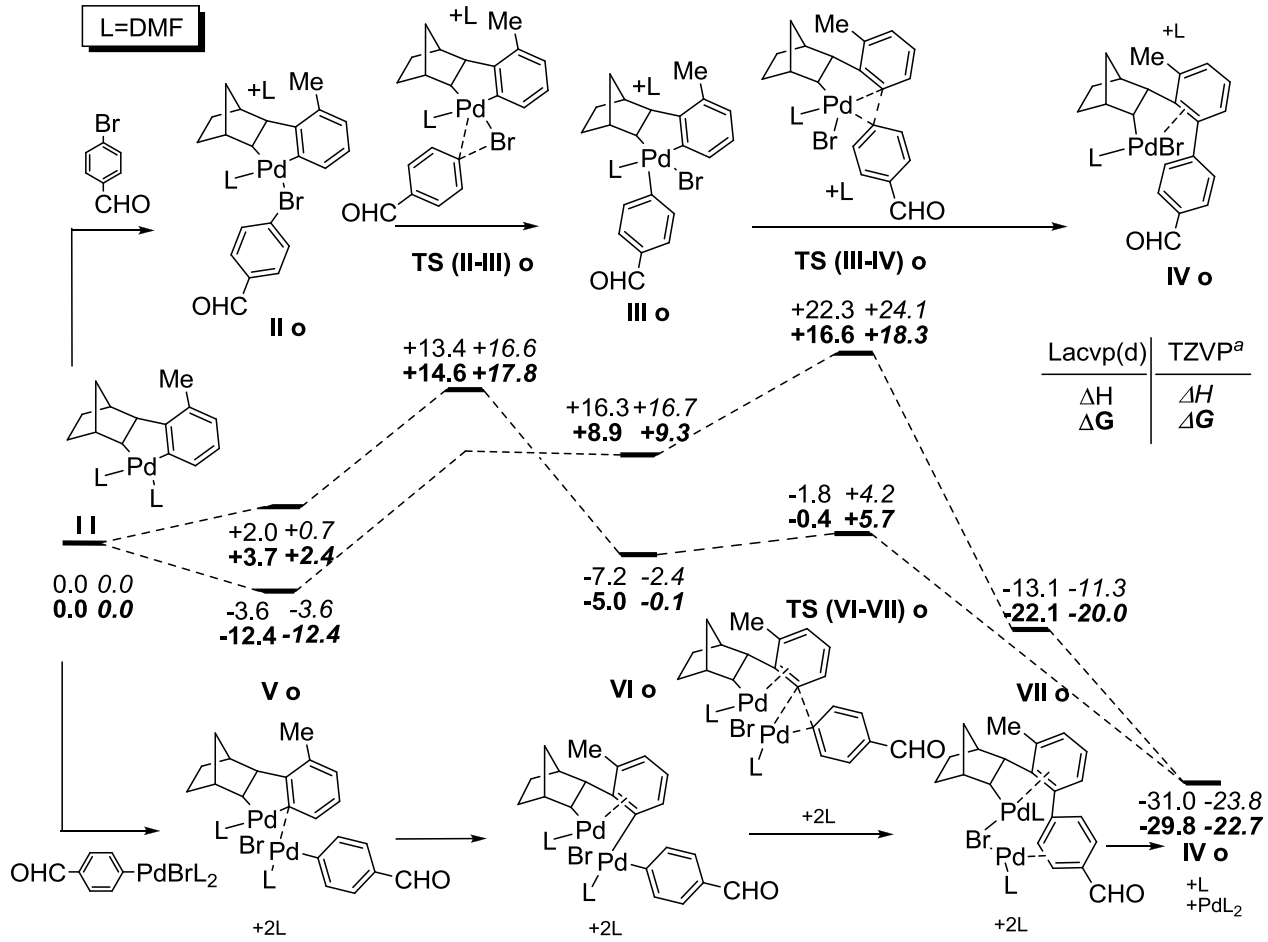
VI m **TS (VI-VII) m**

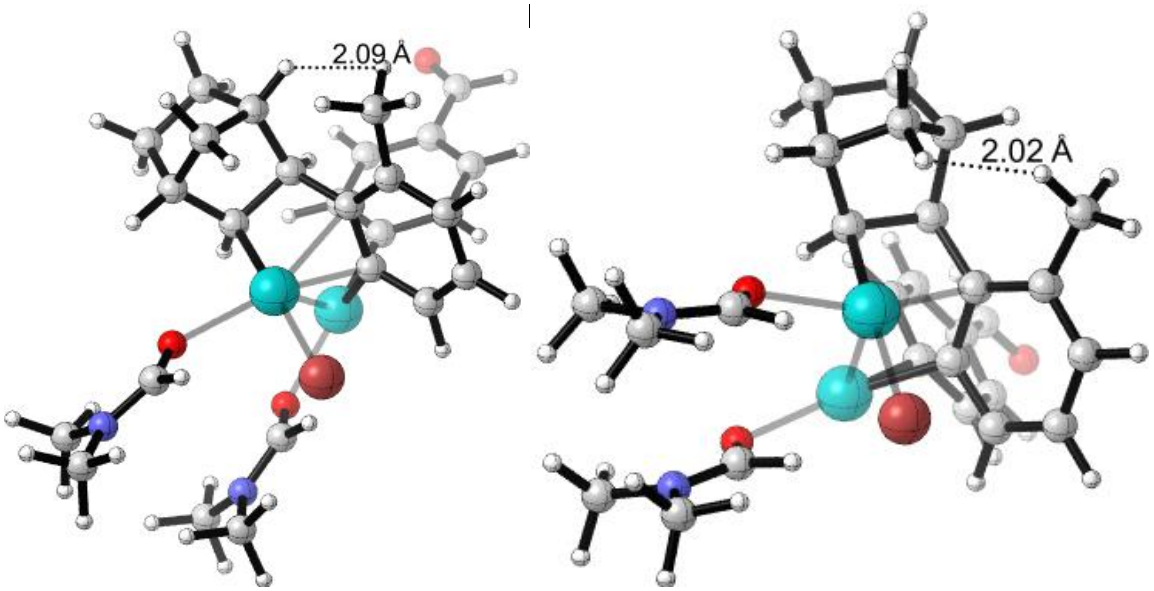
Reaction scheme (n)



VI n **TS (VI-VII) n**

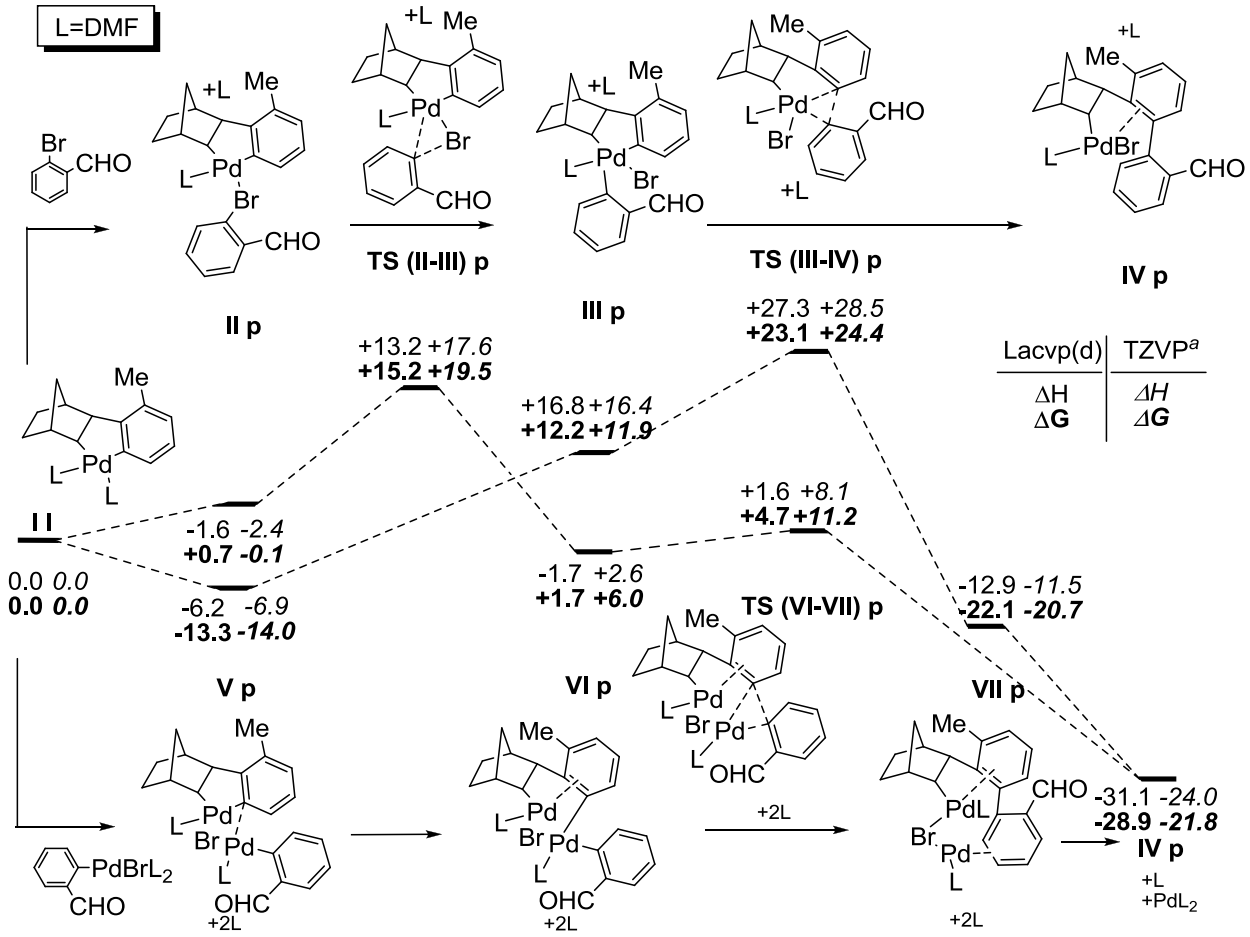
Reaction scheme (o)

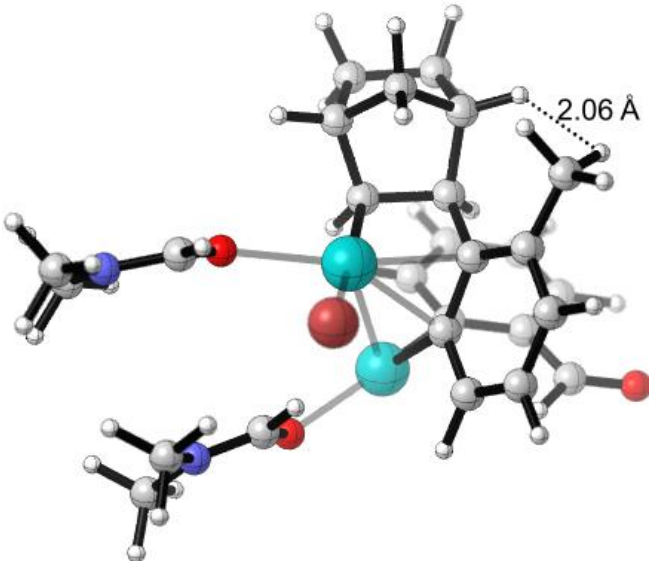




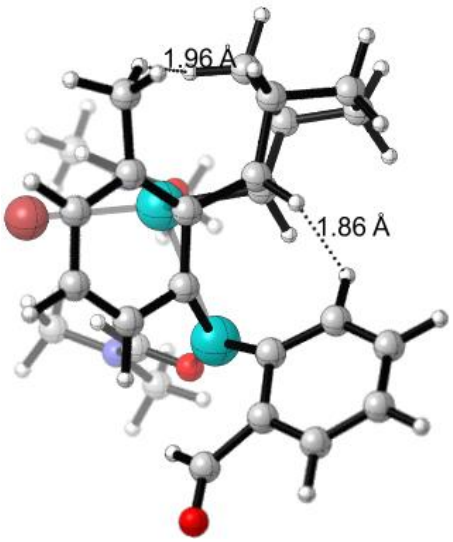
V o **TS (VI-VII) o**

Reaction scheme (p)



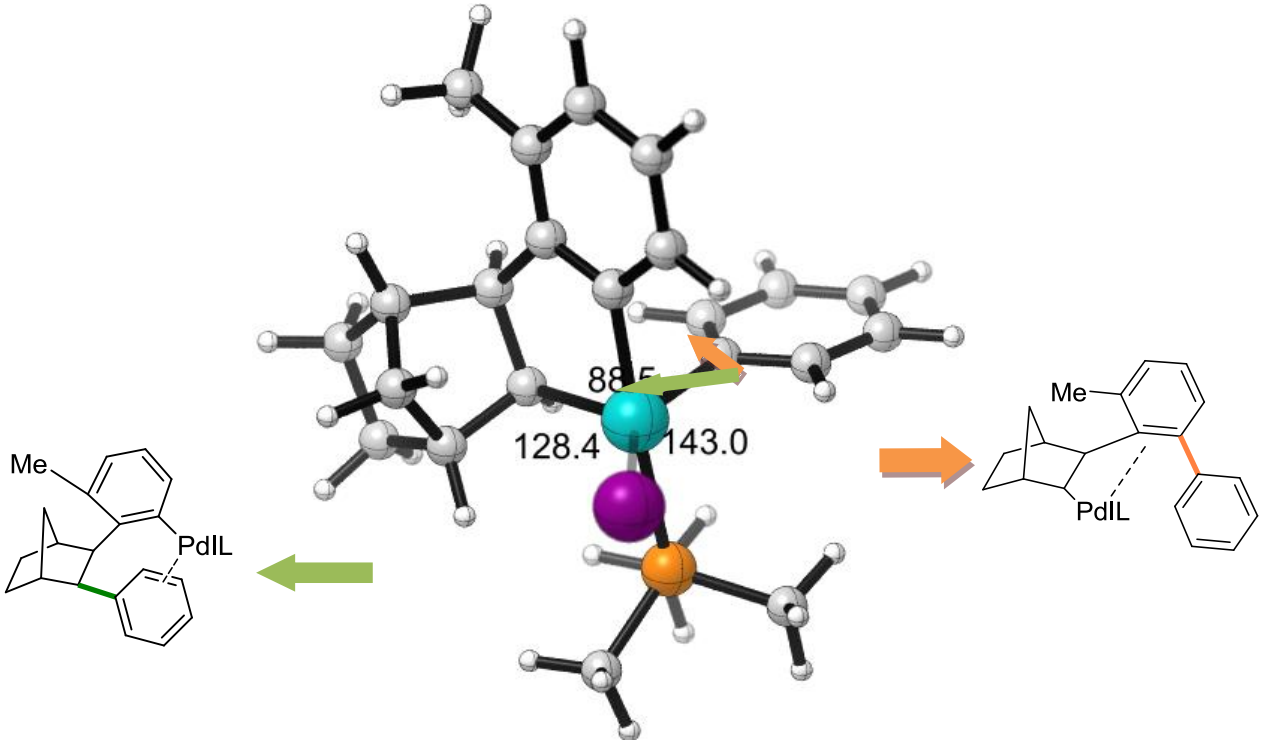


VI p

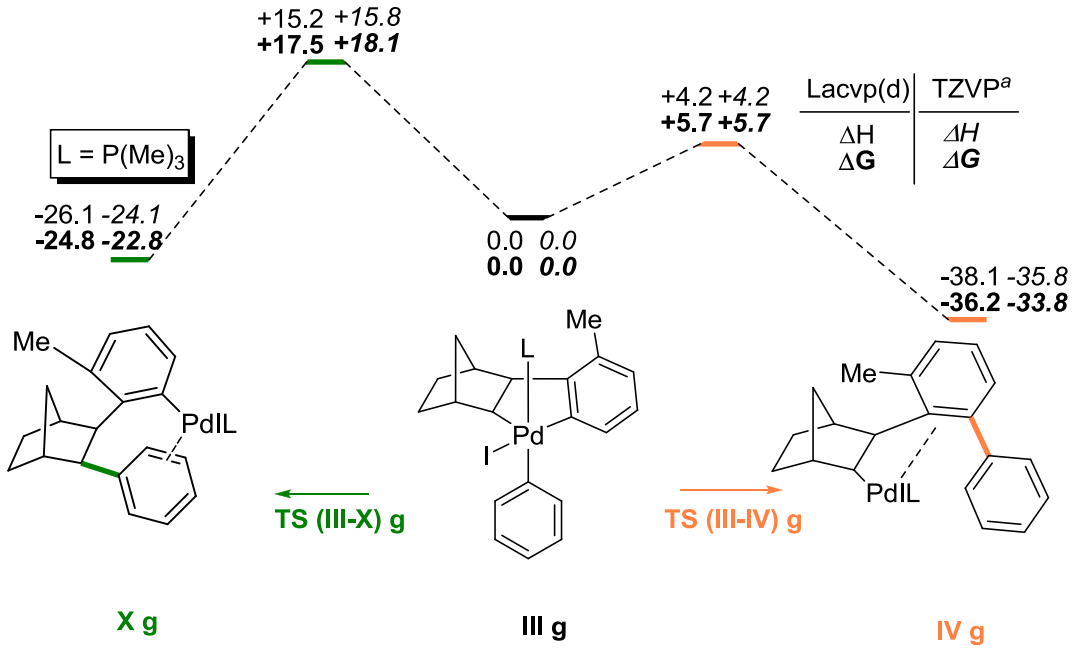


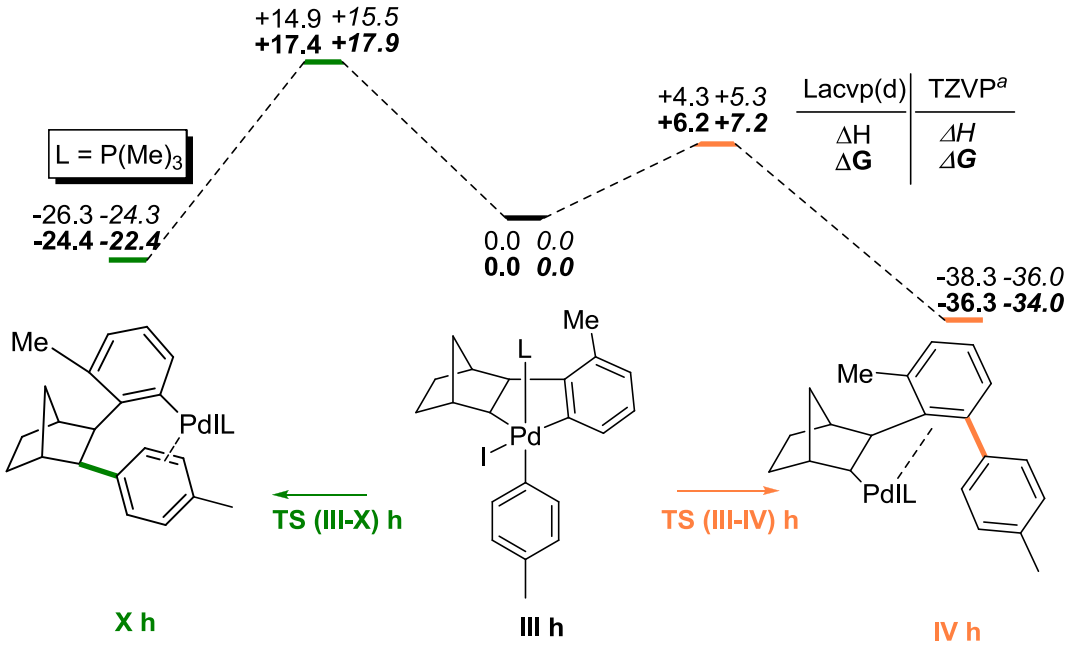
TS (VI-VII) p

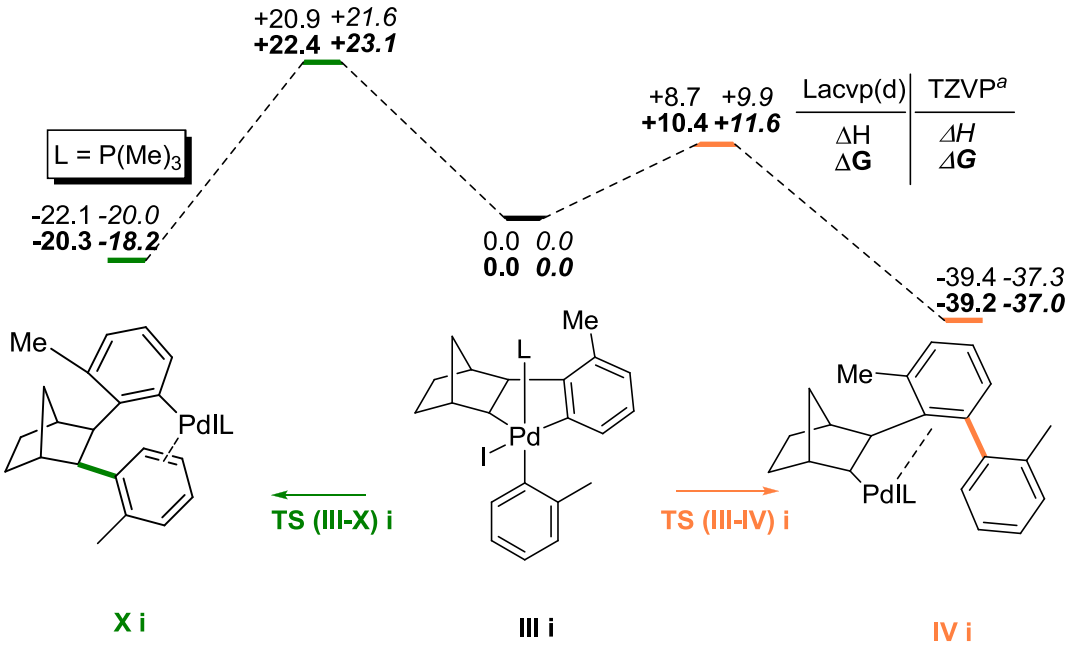
3. Reductive eliminations from complexes III g-p

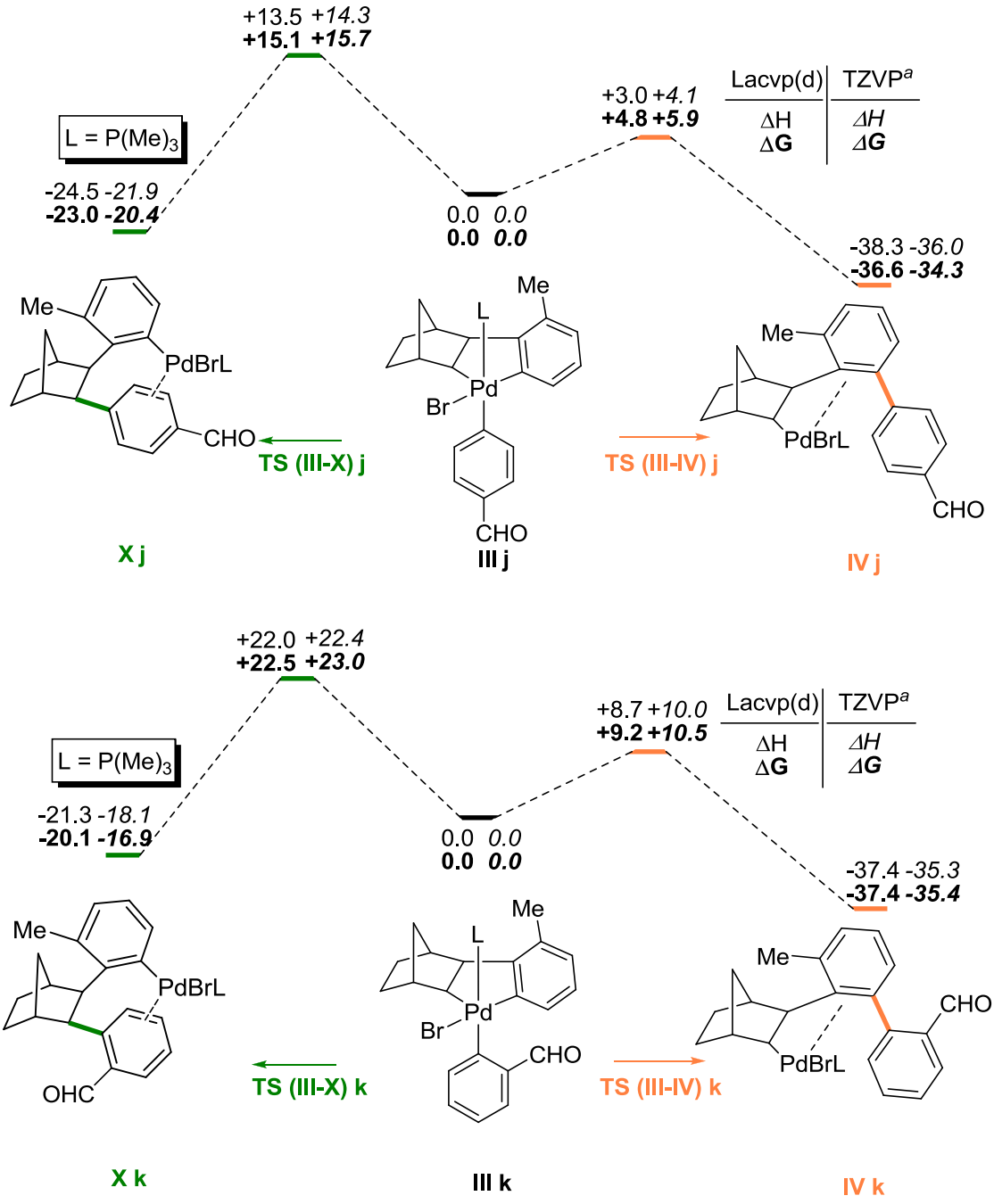


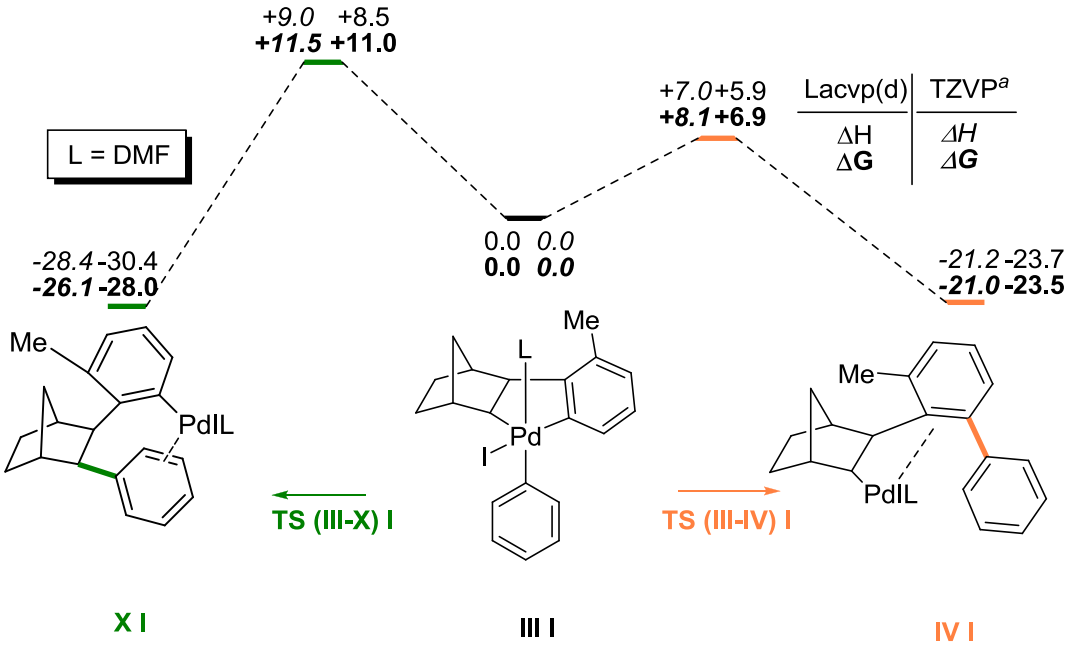
III g (highlighting angles of the Y plane)

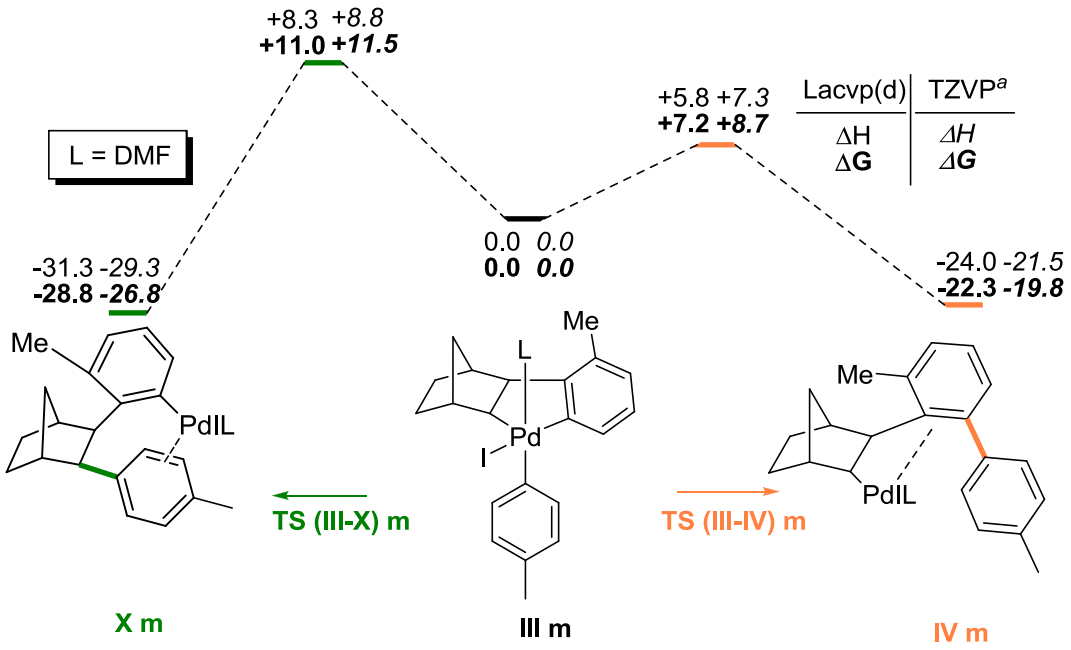


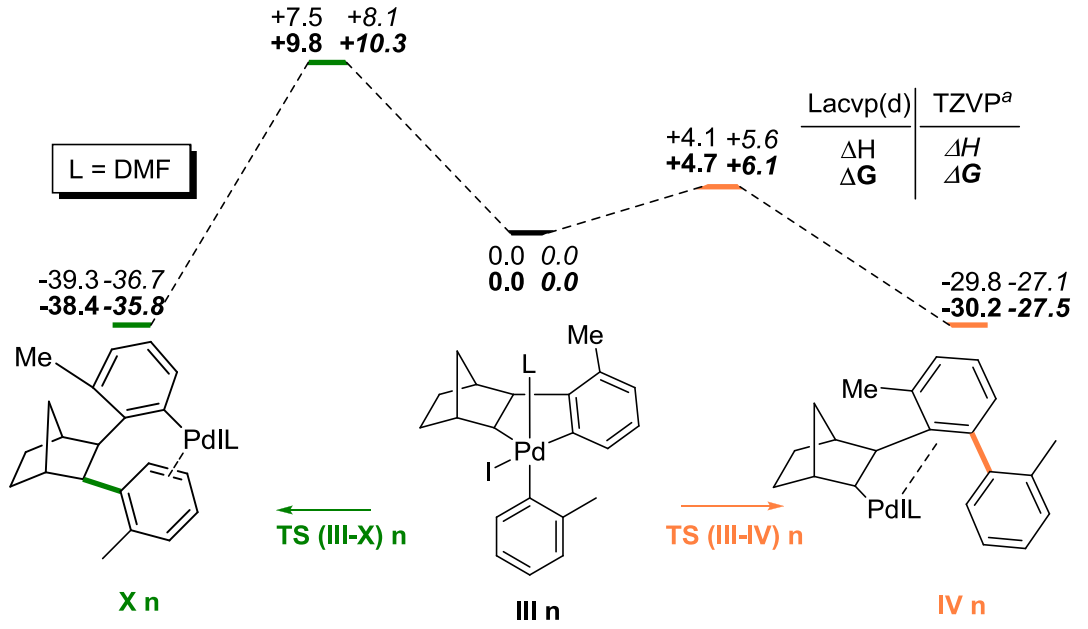

+14.9 +15.5
+17.4 +17.9
L = P(Me)3
-26.3 -24.3
-24.4 -22.4
0.0 0.0
0.0 0.0
+4.3 +5.3
+6.2 +7.2
Lacvp(d)
TZVP[a]
ΔH
ΔG
ΔH
ΔG
-38.3 -36.0
-36.3 -34.0
Me
PdIL
TS (III-X) h
Me
L
Pd
I
TS (III-IV) h
Me
PdIL
X h
III h
IV h

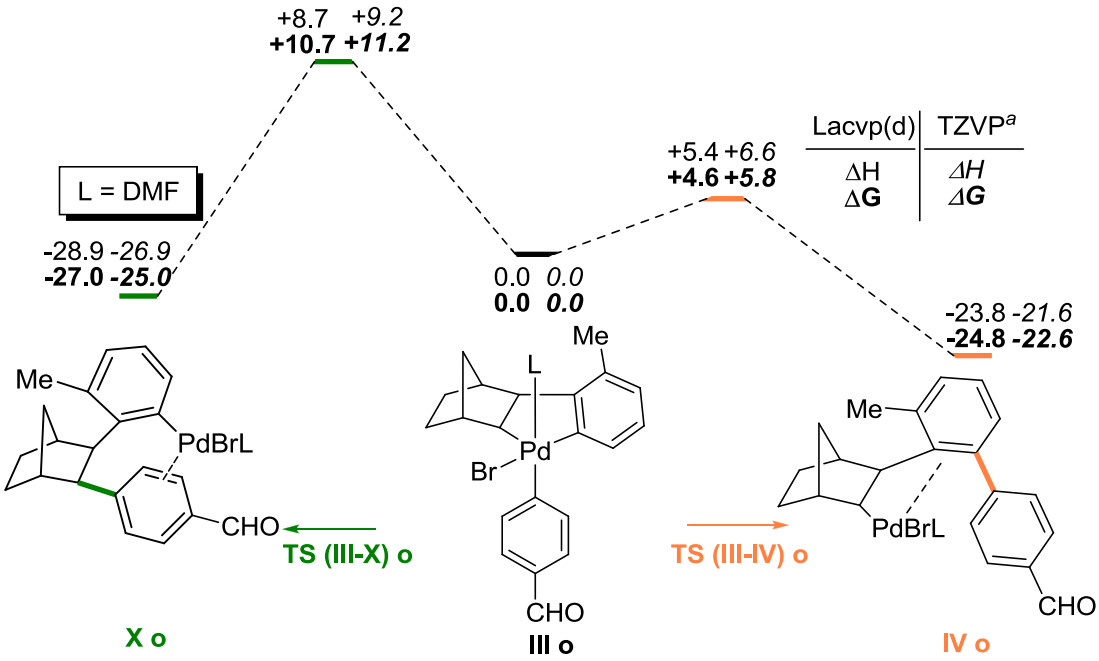

+20.9 +21.6
+22.4 +23.1
L = P(Me)3
-22.1 -20.0
-20.3 -18.2
0.0 0.0
0.0 0.0
+8.7 +9.9
+10.4 +11.6
Lacvp(d)
TZVP[a]
ΔH
ΔG
ΔH
ΔG
-39.4 -37.3
-39.2 -37.0
Me
PdIL
TS (III-X) i
Me
L
Pd
I
TS (III-IV) i
Me
PdIL
X i
III i
IV i

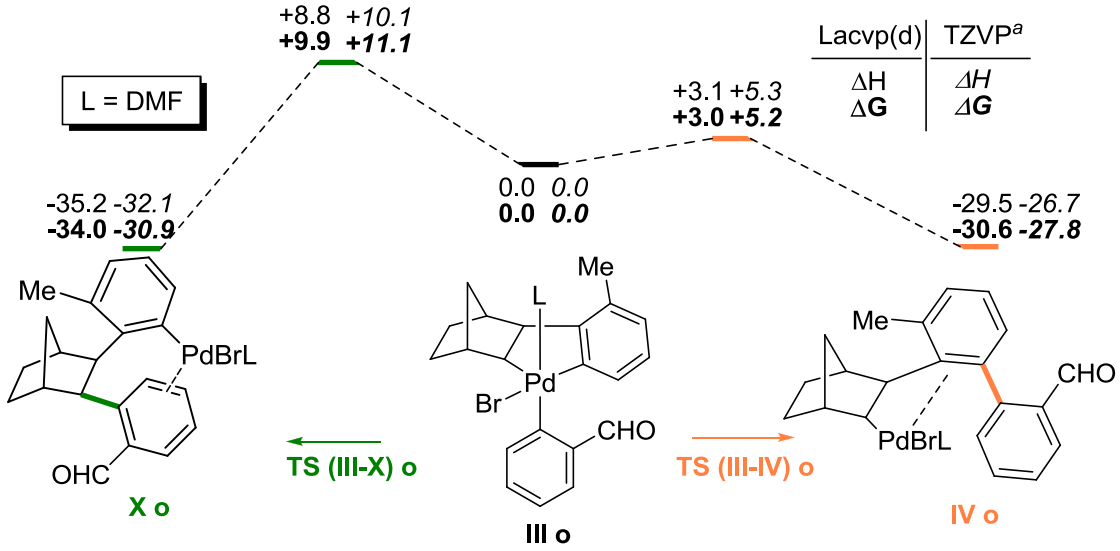

+13.5 +14.3
+15.1 +15.7
L = P(Me)3
-24.5 -21.9
-23.0 -20.4
0.0 0.0
0.0 0.0
+3.0 +4.1
+4.8 +5.9
Lacvp(d)
TZVPa
ΔH
ΔG
ΔH
ΔG
-38.3 -36.0
-36.6 -34.3
Me
PdBrL
CHO
TS (III-X) j
Me
L
Pd
Br
CHO
Me
PdBrL
CHO
TS (III-IV) j
X j
III j
IV j
+22.0 +22.4
+22.5 +23.0
L = P(Me)3
-21.3 -18.1
-20.1 -16.9
0.0 0.0
0.0 0.0
+8.7 +10.0
+9.2 +10.5
Lacvp(d)
TZVPa
ΔH
ΔG
ΔH
ΔG
-37.4 -35.3
-37.4 -35.4
Me
PdBrL
OHC
TS (III-X) k
Me
L
Pd
Br
CHO
Me
PdBrL
CHO
TS (III-IV) k
X k
III k
IV k


+9.0 +8.5
+11.5 +11.0
L = DMF
+7.0+5.9
+8.1+6.9
Lacvp(d)
TZVP[a]
ΔH
ΔG
ΔH
ΔG
-28.4 -30.4
-26.1 -28.0
0.0 0.0
0.0 0.0
-21.2 -23.7
-21.0 -23.5
Me
PdIL
L
Pd
I
Me
Me
PdIL
TS (III-X) I
TS (III-IV) I
X I
III I
IV I


+8.3 +8.8
+11.0 +11.5
L = DMF
+5.8 +7.3
+7.2 +8.7
Lacvp(d)
TZVP[a]
ΔH
ΔG
ΔH
ΔG
-31.3 -29.3
-28.8 -26.8
0.0 0.0
0.0 0.0
-24.0 -21.5
-22.3 -19.8
Me
PdIL
L
Pd
I
Me
Me
PdIL
TS (III-X) m
TS (III-IV) m
X m
III m
IV m


+7.5 +8.1
+9.8 +10.3
L = DMF
Lacvp(d) TZVP[a]
ΔH ΔH
ΔG ΔG
+4.1 +5.6
+4.7 +6.1
0.0 0.0
0.0 0.0
-39.3 -36.7
-38.4 -35.8
-29.8 -27.1
-30.2 -27.5
Me
PdIL
L
Pd
I
Me
Me
PdIL
TS (III-X) n
TS (III-IV) n
X n
III n
IV n

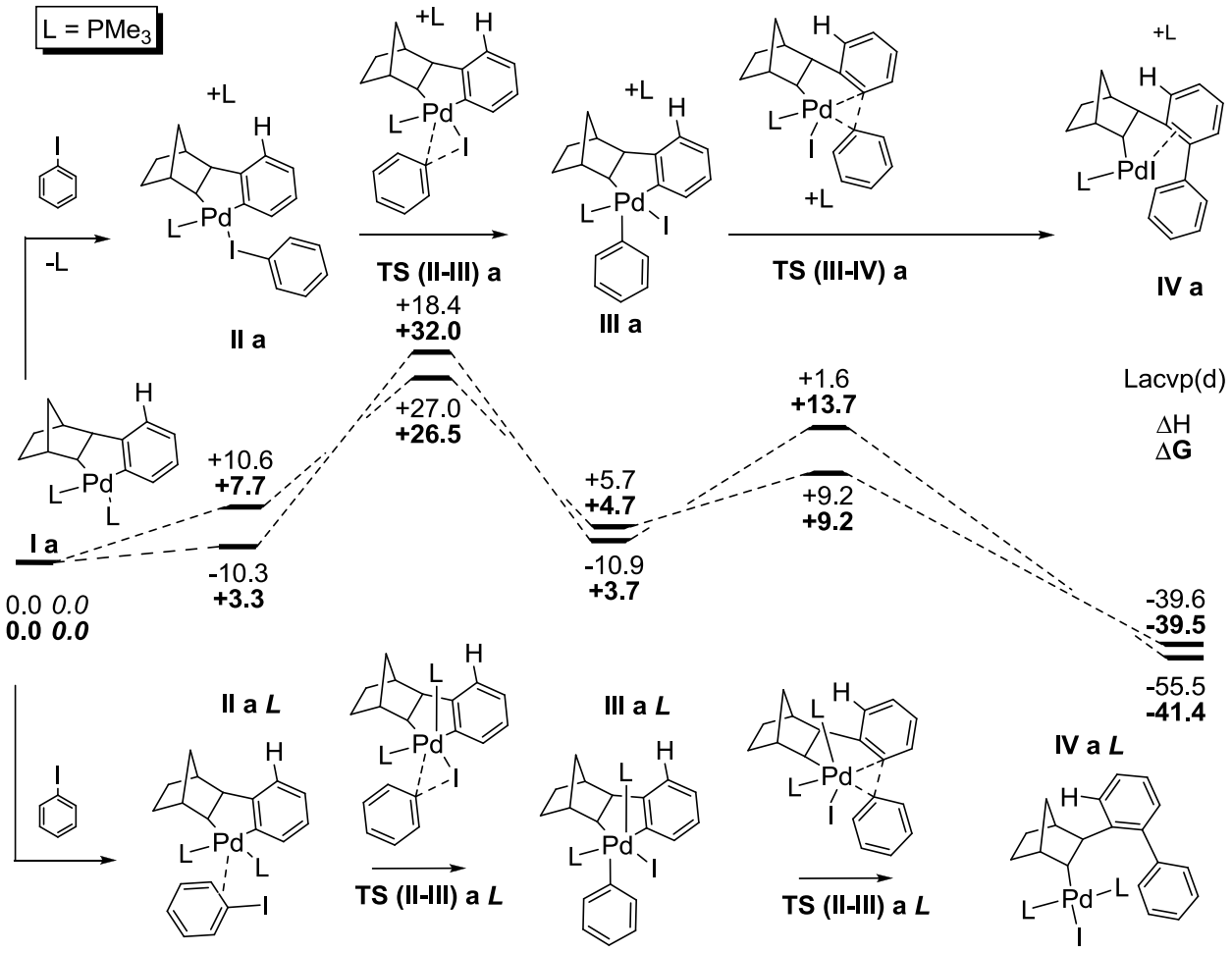

+8.7 +9.2
+10.7 +11.2
L = DMF
Lacvp(d) TZVP[a]
ΔH ΔH
ΔG ΔG
+5.4 +6.6
+4.6 +5.8
-28.9 -26.9
-27.0 -25.0
0.0 0.0
0.0 0.0
-23.8 -21.6
-24.8 -22.6
Me
PdBrL
CHO
L
Pd
Br
CHO
Me
Me
PdBrL
CHO
TS (III-X) o
TS (III-IV) o
X o
III o
IV o



4. Atomic charges of reacting carbon atoms in Pd(IV) complexes III g-p

		C(sp2)	C(sp3)	C electrophile
III g	Mulliken	-0.011069	0.017381	0.071492
	APT	0.232250	0.374999	0.360504
III h	Mulliken	-0.010132	0.017679	0.067265
	APT	0.231922	0.376882	0.343705
III I	Mulliken	0.002832	0.037153	0.042540
	APT	0.247154	0.432490	0.279129
III j	Mulliken	-0.024656	0.028013	0.080475
	APT	0.219619	0.412601	0.457968
III k	Mulliken	-0.004601	0.056818	0.056302
	APT	0.242055	0.490761	0.294159
III l	Mulliken	-0.054092	0.030906	0.017574
	APT	0.358586	0.392164	0.242542
III m	Mulliken	-0.053002	0.030762	0.013144
	APT	0.359349	0.392209	0.216655
III n	Mulliken	-0.033246	0.021625	-0.014809
	APT	0.349217	0.401520	0.249722
III o	Mulliken	-0.063282	0.039343	0.018637
	APT	0.353253	0.428645	0.326686
III p	Mulliken	-0.063754	0.030617	-0.000229
	APT	0.289172	0.443021	0.256007

5. Comparison of trigonal bypiramidal vs octahedrical Pd(IV) (a)



An octahedral transition state for the oxidative addition of an aryl halide on I lies above its intramolecular counterpart. Similarly, reductive elimination from an hexacohordinated palladium(IV) complex is more energy costly. These results are in agreement with the usually poor catalytic properties exerted by bidentate ligands in Pd/norbornene catalyzed domino sequences.

6. Relevant atomic charges of Palladium atoms

We present atomic charges of starting palladacycles **I** and of Pd(IV) complexes **III**. The calculated charge for these latter complexes are usually below zero (Mulliken) or slightly above (APT, between +0.2 and +0.25). For easy comparison we show also intermediates **V** and **VI** of the transmetalation pathway. For these intermediates the first values refers to the palladium atom of the reacting metallacycle. In phosphinic complexes these metal atoms always display computed charges above their formally +4 counterparts (intermediates **V**). When DMF is present, on the other hand, the palladium atom engaged in reductive elimination always give rise to calculated charges above values of formal Pd(IV) complexes **III**.

L = PMe3	**Mulliken**	**APT**	L = DMF	**Mulliken**	**APT**
I a	-0.214652	-0.224972	**I d**	-0.018266	0.400909
III a	-0.361109	0.211837	**III d**	-0.070148	0.454711
V a	-0.108267	0.061930	**V d**	0.051778	0.603679
	-0.407895	0.251033		-0.114432	0.417929
VI a	-0.501054	0.199842	**VI d**	-0.134494	0.364977
	-0.293894	0.056589		0.107690	0.407111
III b	-0.362522	0.211444	**III e**	-0.078417	0.454775
V b	-0.110250	0.252517	**V e**	0.058438	0.420958
	-0.408903	0.061064		-0.122774	0.606939
VI b	-0.504331	0.202100	**VI e**	-0.134168	0.366138
	-0.306798	0.062422		0.104116	0.410970
III c	-0.304245	0.201569	**III f**	-0.016124	0.469190
V c	-0.081984	0.076951	**V f**	0.082762	0.437460
	-0.368112	0.251946		-0.084344	0.616374
VI c	-0.443202	0.188228	**VI f**	-0.100600	0.364145
	-0.263641	0.034152		0.131704	0.421759
I g	-0.229548	-0.197807	**I l**	-0.029922	0.394097
III g	-0.358239	0.221841	**III l**	-0.071334	0.460122
V g	-0.119942	0.044189	**V l**	0.055908	0.394003
	-0.401825	0.251713		-0.130027	0.621920
VI g	-0.518892	0.204264	**VI l**	-0.149915	0.355793
	-0.303196	0.064566		0.116632	0.438116
III h	-0.358512	0.220681	**III m**	-0.072665	0.467719
V h	-0.121652	0.043150	**V m**	0.064208	0.402229
	-0.403867	0.253018		-0.136096	0.627717
VI h	-0.515437	0.215424	**VI m**	-0.149483	0.356344
	-0.298496	0.067881		0.113462	0.444870
III I	-0.401316	0.251177	**III n**	-0.061285	0.472722
V I	-0.134358	0.047883	**V n**	0.045018	0.387372
	-0.392797	0.263848		-0.112854	0.622232
III j	-0.300966	0.212500	**VI n**	-0.152953	0.342021
V j	-0.091411	0.055459		0.126331	0.487168
	-0.366502	0.257021	**III o**	-0.025448	0.464576
VI j	-0.472890	0.223239	**V o**	0.075398	0.002978

	-0.262455	0.037639		-0.075966	0.201158
III k	-0.329168	0.270350	**VI o**	-0.092912	0.437361
V k	-0.085375	0.048530		0.130646	0.437361
	-0.371028	0.282762	**III p**	-0.000660	0.493877
VI k	-0.473296	0.248333	**V p**	0.073346	0.402539
	-0.274980	0.102559		-0.074157	0.657433
			VI p	-0.105279	0.355263
				0.145991	0.490648

7. Comprehensive Table of reagents, complexes and transition states

Reagents	E(lacvp(d))	E(tzvp)	zpc	S
$P(Me)_3$	-460.94953800	-461.03280201	0.112775	77.354
Iodobenzene	-242.80465000	-529.30784051	0.089730	81.268
4-Iodotoluene	-282.08916300	-568.60658388	0.117318	89.165
2-Iodotoluene	-282.09049000	-568.60761982	0.117841	87.736
4-Br-benzaldehyde	-357.85280200	-2918.91771160	0.099402	89.555
2-Br-benzaldehyde	-357.85032700	-2918.91437145	0.099748	89.249
DMF	-248.34199000	-248.44547809	0.102703	74.955
$(P(Me)_3)_2$PhPd(II)I	-1291.58107600	-1579.44299596	0.319888	168.855
$(P(Me)_3)_2$(4-Me)PhPd(II)I	-1330.86492000	-1618.74098419	0.347894	174.484
$(P(Me)_3)_2$(2-Me)PhPd(II)I	-1330.86889500	-1618.74502684	0.347930	171.723
$(P(Me)_3)_2$(4-CHO)PhPd(II)Br	-1406.63246800	-3969.05315672	0.330093	173.934
$(P(Me)_3)_2$(2-CHO)PhPd(II)Br	-1406.63561300	-3969.05573945	0.330460	172.081
$(DMF)_2$PhPd(II)I	-866.31884000	-1154.21113458	0.298103	172.719
$(DMF)_2$(4-CHO)PhPd(II)Br	-981.36954900	-3543.82076549	0.308348	176.624
$(DMF)_2$(2-CHO)PhPd(II)Br	-981.36862200	-3543.81784686	0.308762	179.990
$(DMF)_2$(4-Me)PhPd(II)I	-905.60391700	-1193.51033230	0.325838	186.017
$(DMF)_2$(2-Me)PhPd(II)I	-905.60720400	-1193.51362038	0.326375	180.875
Intermediates & Tss				
I a	-1552.10266400	-1553.65122089	0.465118	172.086
II a	-1333.93854200	-1621.90615296	0.439817	185.851
TS(II-III) a	-1333.91166500	-1621.87193818	0.439051	177.773
III a	-1333.94772100	-1621.90536367	0.441059	179.401
TS(III-IV) a	-1333.94140500	-1621.89764980	0.440375	175.944
IV a	-1334.02219100	-1621.97640823	0.443334	175.680
V a	-1921.76762900	-2211.00494020	0.557002	220.811
VI a	-2382.72605600	-2672.04563415	0.672277	252.200
TS(VI-VII) a	-2382.71123300	-2672.02838070	0.672041	248.917
VII a	-2382.77729500	-2672.09380841	0.673830	256.043
VIII a	-2382.71850400	-2672.03888285	0.672277	253.417
TS(VIII-IX) a	-2382.70493800	-2672.02274665	0.671431	252.788
IX a	-2382.78095900	-2672.09812351	0.673687	260.656
II b	-1373.22308600	-1661.20504922	0.467366	187.744
TS(II-III) b	-1373.19585100	-1661.17030312	0.466632	186.844
III b	-1373.23174400	-1661.20370207	0.468197	188.402
TS(III-IV) b	-1373.22572600	-1661.19613355	0.467643	184.754
IV b	-1373.30681800	-1661.27531391	0.471745	181.058
V b	-1961.05145100	-2250.30292725	0.584681	229.384
VI b	-2422.00664500	-2711.34089608	0.699998	262.133
TS(VI-VII) b	-2421.99519300	-2711.32647603	0.698713	255.449
VII b	-2422.06166700	-2711.39244325	0.702273	261.030
VIII b	-2422.00212400	-2711.33674213	0.699736	261.350
TS(VIII-IX) b	-2421.98890700	-2711.32153691	0.699314	262.816

IX b	-2422.06578000	-2711.39748603	0.701277	267.846
II c	-1448.98501600	-4011.51163927	0.449450	194.010
TS(II-III) c	-1448.95919500	-4011.47627126	0.448615	188.296
III c	-1448.99721000	-4011.51356482	0.450444	188.523
TS(III-IV) c	-1448.99294100	-4011.50781359	0.449724	186.552
IV c	-1449.07238600	-4011.58541253	0.453276	183.672
V c	-2036.81954900	-4600.61433833	0.566416	230.989
VI c	-2497.77916100	-5061.65623338	0.681929	261.441
TS(VI-VII) c	-2497.76666500	-5061.64116766	0.682452	255.453
VII c	-2497.82520200	-5061.69872766	0.684183	262.054
VIII c	-2497.77234400	-5061.64983146	0.681469	261.455
TS(VIII-IX) c	-2497.75856000	-5061.63435775	0.681071	261.714
IX c	-2497.83413800	-5061.70957357	0.684285	264.850
I d	-1126.85308800	-1128.43030966	0.442654	185.875
II d	-1121.31414700	-1409.29563498	0.430645	179.301
TS(II-III) d	-1121.29473600	-1409.26998416	0.429338	176.894
III d	-1121.32399700	-1409.29582236	0.431397	178.513
TS(III-IV) d	-1121.31470600	-1409.28500442	0.429974	176.726
IV d	-1121.37363200	-1409.34143588	0.431534	184.373
V d	-1496.49107100	-1785.75498661	0.533792	234.235
VI d	-1496.46505400	-1785.72753219	0.534925	230.080
TS(VI-VII) d	-1496.45921600	-1785.72003982	0.535561	219.921
VII d	-1496.52451000	-1785.78564737	0.537701	227.362
II e	-1160.59874200	-1448.59463172	0.458209	187.469
TS(II-III) e	-1160.57891200	-1448.56833674	0.456813	185.157
III e	-1160.60803600	-1448.59401178	0.458679	188.956
TS(III-IV) e	-1160.59907300	-1448.58363489	0.457389	185.931
IV e	-1160.65798700	-1448.64009987	0.458949	193.185
V e	-1535.77472000	-1825.05285373	0.561146	242.194
VI e	-1535.74900700	-1825.02564452	0.562369	239.961
TS(VI-VII) e	-1535.74354700	-1825.01862561	0.562899	229.423
VII e	-1535.80881800	-1825.08393436	0.564694	237.913
II f	-1236.36014400	-3798.90091853	0.440078	189.345
TS(II-III) f	-1236.34233600	-3798.87557433	0.438806	186.380
III f	-1236.37532500	-3798.90610455	0.441358	186.257
TS(III-IV) f	-1236.36653600	-3798.89577416	0.439576	186.130
IV f	-1236.42481400	-3798.95208967	0.441701	190.544
V f	-1611.54485600	-4175.36689172	0.543441	241.679
VI f	-1611.52026300	-4175.34144039	0.544672	238.574
TS(VI-VII) f	-1611.51286800	-4175.33215536	0.545378	228.400
VII f	-1611.57128700	-4175.38971185	0.546935	237.222
I g	-1591.38239400	-1592.94532145	0.492120	181.581
II g	-1373.22194400	-1661.20387381	0.468407	190.581
TS(II-III) g	-1373.19479800	-1661.16942802	0.467202	184.007
III g	-1373.23111600	-1661.20315185	0.468407	188.327
TS(III-IV) g	-1373.22406800	-1661.19445410	0.468012	183.298
IV g	-1373.29512300	-1661.26343806	0.471666	181.912

V g	-1961.05054800	-2250.30202806	0.585261	226.162
VI g	-2421.99601900	-2711.32976431	0.700063	259.023
TS(VI-VII) g	-2421.98016800	-2711.31125660	0.700310	253.128
VII g	-2422.05080600	-2711.37912623	0.702861	260.722
TS(III-X) g	-1373.20811600	-1661.17919646	0.469695	180.863
X g	-1373.27619600	-1661.24493772	0.471829	183.913
II h	-1412.50648200	-1700.50277405	0.495909	199.322
TS(II-III) h	-1412.47901600	-1700.46788692	0.494550	192.655
III h	-1412.51525400	-1700.50152855	0.495862	194.468
TS(III-IV) h	-1412.50823200	-1700.49283710	0.495622	191.312
IV h	-1412.57944300	-1700.56205465	0.499070	191.241
V h	-2000.33426400	-2289.60007345	0.612520	238.206
VI h	-2461.27964300	-2750.62727999	0.727018	269.665
TS(VI-VII) h	-2461.26405200	-2750.60933478	0.728327	261.923
VII h	-2461.33491700	-2750.67807553	0.729874	269.171
TS(III-X) h	-1412.49268300	-1700.47803091	0.497059	189.618
X h	-1412.56077300	-1700.54387182	0.499457	191.292
II i	-1412.50817800	-1700.50393843	0.496236	196.001
TS(II-III) i	-1412.47641800	-1700.46410274	0.495133	189.993
III i	-1412.51449500	-1700.50063833	0.497282	190.992
TS(III-IV) i	-1412.50042900	-1700.48463636	0.497071	185.289
IV i	-1412.57901200	-1700.56171769	0.498992	190.186
V i	-2000.33582000	-2289.60162169	0.612714	232.215
TS(V-VII) i	-2461.25805400	-2750.60281150	0.729289	256.649
VII i	-2461.33696200	-2750.68043544	0.730057	269.591
TS(III-X) i	-1412.48130600	-1700.46635254	0.497419	185.913
X i	-1412.55287400	-1700.53565765	0.500465	184.921
II j	-1488.26872300	-4050.80966819	0.478411	197.674
TS(II-III) j	-1488.24331700	-4050.77485850	0.476579	193.283
III j	-1488.28059300	-4050.81149150	0.478193	196.460
TS(III-IV) j	-1488.27578700	-4050.80492771	0.478234	190.511
IV j	-1488.34468300	-4050.87183383	0.481126	190.733
V j	-2076.10253300	-4639.91169431	0.594682	237.226
VI j	-2537.04913400	-5100.93994697	0.710275	265.235
TS(VI-VII) j	-2537.03483000	-5100.92342848	0.710621	260.543
VII j	-2537.10056900	-5100.98560588	0.712288	268.133
TS(III-X) j	-1488.25980600	-4050.78984016	0.478903	190.996
X j	-1488.32248800	-4050.84919300	0.481001	191.447
II k	-1488.26689800	-4050.80695662	0.478562	197.119
TS(II-III) k	-1488.23809600	-4050.76739377	0.477489	189.487
III k	-1488.28121800	-4050.81094911	0.478986	191.697
TS(III-IV) k	-1488.26676800	-4050.79445294	0.478458	189.968
IV k	-1488.34280600	-4050.86921771	0.481019	191.908
V k	-2076.10622800	-4639.91384330	0.595032	232.964
VI k	-2537.05034600	-5100.93982246	0.710355	264.496
TS(VI-VII) k	-2537.02473200	-5100.91184429	0.710595	261.328

VII k	-2537.09917800	-5100.98394830	0.712544	269.931
TS(III-X) k	-1488.24598700	-4050.77491660	0.478728	189.723
X k	-1488.31814000	-4050.84282523	0.481972	187.624
I l	-1166.13664700	-1167.72833328	0.471205	188.589
II l	-1160.59782700	-1448.59362132	0.458853	185.607
TS(II-III) l	-1160.57566000	-1448.56569116	0.456824	188.985
III l	-1160.60775900	-1448.59401514	0.459045	187.867
TS(III-IV) l	-1160.59697100	-1448.58147253	0.457700	184.453
IV l	-1160.64704400	-1448.62926033	0.460493	187.417
V l	-1535.77375500	-1825.05162796	0.563134	226.290
VI l	-1535.74080700	-1825.01774236	0.563371	231.907
TS(VI-VII) l	-1535.73219500	-1825.00691133	0.563610	224.965
VII l	-1535.79761600	-1825.07296254	0.565056	236.439
TS(III-X) l	-1160.59426900	-1448.57973200	0.459165	179.458
X l	-1160.65851100	-1448.64164624	0.461387	180.043
II m	-1199.88299500	-1487.89343371	0.485518	192.799
TS(II-III) m	-1199.86068300	-1487.86465063	0.484320	196.809
III m	-1199.89198200	-1487.89247858	0.486447	197.604
TS(III-IV) m	-1199.88130500	-1487.88009458	0.485137	191.835
IV m	-1199.93128600	-1487.92788541	0.487497	191.886
V m	-1575.05738400	-1864.34953670	0.590658	236.082
VI m	-1575.02470900	-1864.31584350	0.590850	241.251
TS(VI-VII) m	-1575.01649000	-1864.30546242	0.591149	232.960
VII m	-1575.08184000	-1864.37148583	0.592539	244.259
TS(III-X) m	-1199.87879100	-1487.87859387	0.486559	188.564
X m	-1199.94435000	-1487.94167947	0.488870	189.050
II n	-1199.88488300	-1487.89518980	0.486419	193.987
TS(II-III) n	-1199.85682800	-1487.86136337	0.485044	193.879
III n	-1199.88248300	-1487.88316900	0.486996	191.913
TS(III-IV) n	-1199.87462600	-1487.87300426	0.485726	190.150
IV n	-1199.93128300	-1487.92776477	0.488330	193.254
V n	-1575.05817400	-1864.35052671	0.590649	242.289
VI n	-1575.02481200	-1864.31612172	0.591629	235.903
TS(VI-VII) n	-1575.00825400	-1864.29650311	0.591360	234.412
VII n	-1575.08107800	-1864.37088245	0.593130	241.409
TS(III-X) n	-1199.87083200	-1487.87059738	0.487314	184.364
X n	-1199.94723600	-1487.94379859	0.489162	189.116
II o	-1275.64391500	-3838.19904949	0.467617	197.630
TS(II-III) o	-1275.62429600	-3838.17230876	0.466176	199.299
III o	-1275.65952900	-3838.20494050	0.468427	195.553
TS(III-IV) o	-1275.64922700	-3838.19266666	0.466772	198.358
IV o	-1275.69849300	-3838.24024120	0.469599	199.287
V o	-1650.82675700	-4214.66263038	0.572877	244.641
VI o	-1650.79584200	-4214.63105434	0.573800	240.285
TS(VI-VII) o	-1650.78548700	-4214.61869257	0.573019	234.585
VII o	-1650.84343800	-4214.67604289	0.574468	245.494

TS(III-X) o	-1275.64573900	-3838.19027637	0.468480	188.804
X o	-1275.70805700	-3838.25026213	0.470915	189.354
II p	-1275.64833000	-3838.20172398	0.468970	195.162
TS(II-III) p	-1275.62243700	-3838.16771778	0.466806	196.436
III p	-1275.64834200	-3838.19363706	0.468872	191.470
TS(III-IV) p	-1275.64119200	-3838.18313957	0.467002	192.481
IV p	-1275.69633200	-3838.23725353	0.469971	195.493
V p	-1650.82946200	-4214.66443411	0.572844	242.612
VI p	-1650.79453800	-4214.62903785	0.574593	234.040
TS(VI-VII) p	-1650.77676200	-4214.60871833	0.573531	232.648
VII p	-1650.84096600	-4214.67281271	0.573749	249.536
TS(III-X) p	-1275.63428200	-3838.17767518	0.468981	188.042
X p	-1275.70743600	-3838.24771471	0.471866	187.507

8. References

[1] Y. Zhao, D. G. Truhlar *Theor. Chem. Account* **2008**, *120*, 215.
[2] Gaussian 09, Revision **A.1**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
[3] a) J. P. Hay, W. R. Wadt *J. Chem. Phys.* **1985**, *82*, 299. b) R. A. Friesner, R. B. Murphy, M. D. Beachy, M. N. Ringlanda, W. T. Pollard, B. D. Dunietz, Y. X. Cao *J. Phys. Chem. A* **1999**, *103*, 1913.
[4] a) F. Weigen, R. Ahlrichs *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297; b) D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss *Theor. Chim. Acta* **1990**, *77*, 123; c) K. A. Peterson, D. Figgen, E. Goll, H. Stoll, M. Dolg *J. Chem. Phys.* **2003**, *119*, 11113.

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About the author

Giovanni Maestri was born in Mantova, the 14th of June, 1984. In July 2002 he obtained his diploma at Liceo Classico "Virgilio" in Mantova. In July 2005 he got his bachelor degree, *magna cum laude*, at University of Parma in Packaging Technologies. Two years later, in November 2007 he received his advanced degree, *magna cum laude*, in Industrial Chemistry at the University of Parma, discussing an experimental thesis realized under the supervision of Prof. Marta Catellani. During his thesis he spent a period of three months in the group of Prof. Cornelis Elsevier at University of Amsterdam. In January 2008 he started his PhD in Chemical Sciences under the supervision of Professor Marta Catellani to work out a research project focused on the synthesis of complex organic molecules through sequential intramolecular and intermolecular activation of C–H bonds catalyzed by palladium and norbornene. In 2010 he spent a period of eight months in the group of Prof. Max Malacria at Université Pierre et Marie Curie in Paris where he investigated, under the supervision of Dr. Etienne Derat, organopalladium catalysis by means of DFT calculations. The main scientific results he achieved during the years 2008–2010 are presented herein.