PALLADIUM-CATALYZED SYNTHESES OF FUSED TRICYCLIC HETEROCYCLES: A PERSONAL ACCOUNT

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Abstract. *Fused tricyclic heterocycles are frequently found in pharmaceuticals, bioactive natural products and materials with unique molecular properties. The synthesis of these complex molecular scaffolds usually requires several reaction steps and harsh reaction conditions that may compromise the overall process yield. Therefore, the development of catalytic sequential reactions that enable the easy and efficient preparation of condensed tricyclic systems in a single reaction step is in high demand. In this account, we present recent advances in this direction based on the use of palladium-catalyzed cascade reactions developed in our laboratories.*

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1. Introduction

Palladium-catalyzed sequential reactions have been widely exploited for the synthesis of fine as well as commodity chemicals. The versatility of palladium has allowed the environmentally friendly construction of extremely sophisticated molecules in a step- and atom-economical manner.[1-4] In most cases, condensed heterocycles can be easily accessed by palladium catalysis in an efficient way that can hardly be achieved through the conventional organic synthesis. Some challenging examples of this kind are presented in this account (Figure 1). They are based on two main strategies: 1) the palladium/norbornene cooperative catalysis (Catellani reactions) and 2) the PdI$_2$/KI-catalyzed oxidative carbonilation process.

The Catellani reaction, discovered by Marta Catellani and co-workers in 1997,[5] consists in the sequential and selective functionalization of both *ortho* and *ipso* positions of an aryl halide, through the cooperative action of palladium and norbornene.[6-11] This catalytic methodology has been exploited for the synthesis of a wide variety of richly decorated aromatic rings, biaryl-containing molecules, condensed heterocycles and natural compounds as well. An aryl-norbornyl palladacycle, generated typically from an aryl iodide, palladium(0) and norbornene, is the key intermediate that starts an ordered reaction sequence involving different organic reagents (*i.e.* alkyl/aryl iodides and bromides, activated olefins, arylboronic acids, *etc.*) to give a large number of aromatic products (Scheme 1a). An *ortho*-substituted aryl iodide and an *ortho*-functionalized aryl bromide are suitable partners able to directly deliver fused tricyclic systems under palladium and norbornene catalysis, as we will detail in the next sections.

An alternative strategy that enabled the efficient construction of fused tricyclic systems is represented by the oxidative carbonylation reaction catalyzed by PdI$_2$ in the presence of KI.[12] This powerful

methodology, discovered by Gabriele and co-workers in 1992,[13] has allowed us to prepare a long series of high value-added compounds, including heterocyclic ones, and more recently has also enabled the easy access to several tricyclic systems, such as furoindolones and furobenzofuranones (Figure 1). One or two cyclization steps with the concomitant incorporation of one or two molecules of carbon monoxide can lead to a high level of molecular complexity in a one-pot fashion (Scheme 1b).
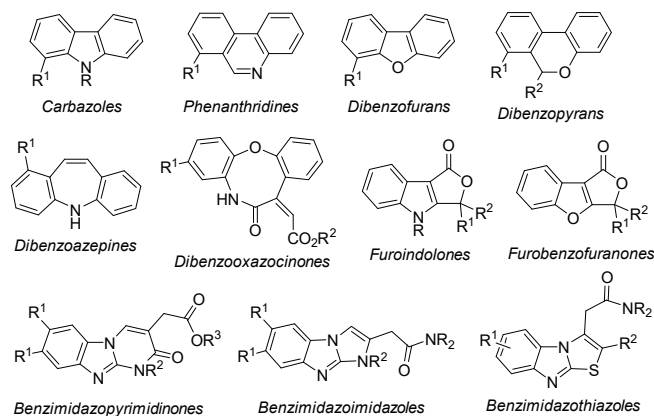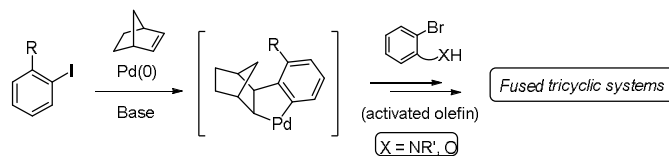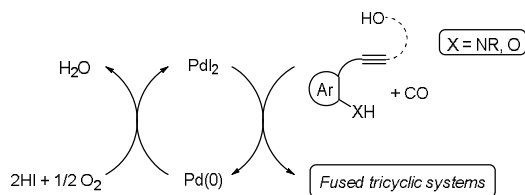

Figure 1. Fused tricyclic systems obtained from palladium-catalyzed cascade reactions.

Scheme 1. a) Pd/norbornene and b) PdI$_2$/KI-based catalysis to fused tricyclic systems.

2. Palladium/norbornene cooperative catalysis (Catellani reactions)
2.1. Synthesis of carbazoles and phenanthridines

Catellani reactions continue to demonstrate their huge potential in the field of organic chemistry.[6] In 2008, we firstly applied the Catellani-based methodology to the synthesis of carbazole derivatives.[14] This class of tricyclic compounds displays a very broad variety of biological activities[15] as well as electronic properties[16]. The protocol is based on the cooperative catalysis of palladium and norbornene and starts from *ortho*-substituted iodoarenes and *N*-sulfonylated or *N*-acetylated *ortho*-bromoanilines (Scheme 2).

Under these conditions, aryl iodides bearing electron donating groups (EDGs) at the *ortho* position with additional substituents in *meta* and *para* reacted with *o*-bromo-*N*-tosylaniline to deliver carbazole derivatives in excellent yields (Figure 2). Methyl and chloro groups were also tolerated on the aniline partner. An aryl iodide substituted with the CF$_3$ group in *ortho*, afforded the corresponding carbazole in 65% yield at 120 °C and the presence of PPh$_3$ was required. Similar conditions were essential when the

p-NO$_2$-o-bromo-N-tosylaniline was employed, leading in this case to the deprotected carbazole in 58% yield. We have also demonstrated that o-bromoacetamides can be used in place of o-bromosulfonamides (Scheme 3a), even though the acetyl group was removed under the reaction conditions. Following this procedure, Carbazomycin A was successfully obtained in 70% yield (Scheme 3b).
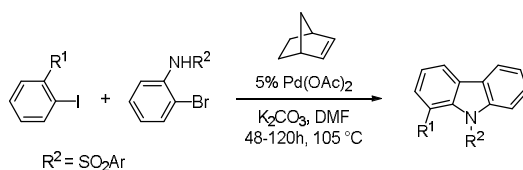
Scheme 2. Catellani-type synthesis of carbazoles from o-substituted iodoarenes and N-sulfonylated o-bromoanilines.
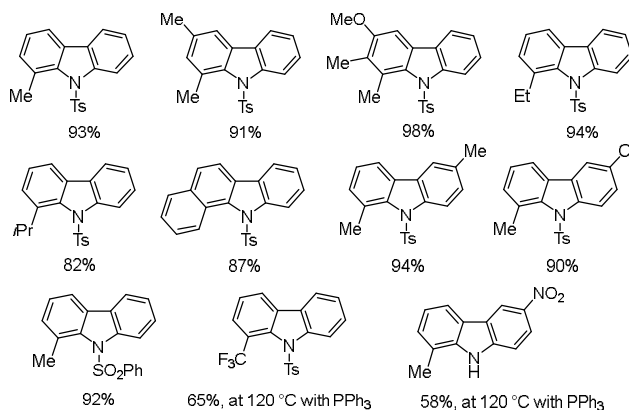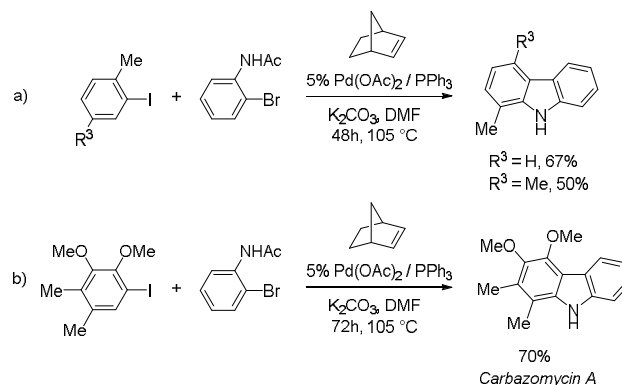

93%   91%   98%   94%

82%   87%   94%   90%

92%   65%, at 120 °C with PPh$_3$ 58%, at 120 °C with PPh$_3$

Figure 2. Carbazole derivatives from a Catellani-type reaction.

R^3 = H, 67%
R^3 = Me, 50%

70%
Carbazomycin A

Scheme 3. Catellani-type synthesis of carbazoles from o-substituted iodoarenes and N-acetylated o-bromoanilines.

Mechanistically, the *ortho* substituted aryl iodide gives oxidative addition on palladium(0) species, affording the aryl palladium iodide complex **I**, which inserts norbornene to give the palladium(II) intermediate **II** in a stereoselective manner (Scheme 4, ligand are omitted for clarity). A subsequent *ortho* C-H activation process affords the aryl norbornyl palladacycle **III**. The o-bromo-N-tosylaniline reacts with palladacycle **III** delivering the Pd(IV) species **IV**, which evolves to intermediate **V** by selective attack of the

aryl group of the *o*-bromo-*N*-tosylaniline onto the aromatic site of palladacycle, with formation of a biaryl moiety (Csp^2-Csp^2 coupling). At this point, owing to the steric effect exerted by the two *ortho* substituents, norbornene deinserts and intermediate **VI** is generated. The latter easily undergoes, under the reaction conditions, an intramolecular C-N coupling with formation of a 5-membered ring and Pd(0), which can restart a new catalytic cycle (Scheme 4).
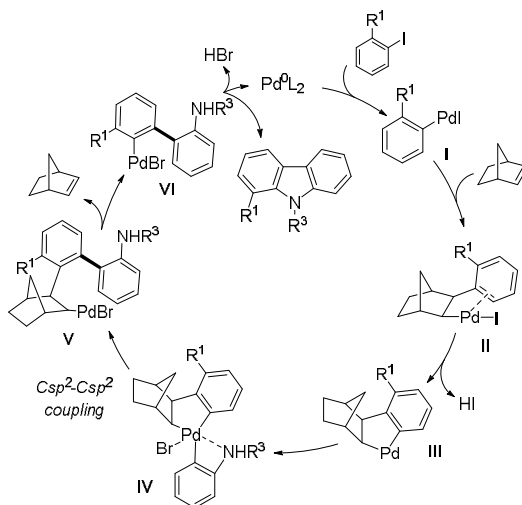
Scheme 4. Reaction pathway towards carbazole derivatives.

In the same year, we reported a different reactivity using the same reagents. In particular, an *o*-substituted aryl iodide and a sulfonylated *o*-bromo aniline were caused to react with an activated olefin in presence of the palladium and norbornene catalytic system, potassium carbonate and *n*Bu$_4$N, in acetonitrile at 80 °C. Under these conditions, phenanthridine derivatives were obtained in high yields (Scheme 5).[17]
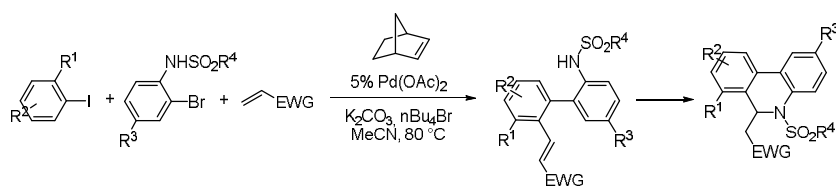
Scheme 5. Synthesis of 5,6-dihydrophenanthridines from *o*-substituted aryl iodides, *o*-bromo *N*-sulfonyl anilines and activated olefins.

The phenanthridine motif is ubiquitous in biological active compounds and pharmaceuticals,[18,19] therefore, synthetic efforts have been devoted to the construction of this scaffold.[20-25] Our approach implies the use of readily available precursors in a multicomponent one-pot reaction under mild conditions.

The pathway leading to phenanthridines of Scheme 5 starts with the formation of palladacycle **III** as reported above in Scheme 4. The oxidative addition of the *o*-bromo sulfonyl aniline leads to a palladium(IV) species **IV** that undergoes sequential Csp^2-Csp^2 coupling and norbornene deinsertion leading to intermediate **VI**. Then, thanks to the presence of an activated olefin in the reaction medium, the Heck reaction takes place to afford the acyclic vinyl intermediate (Scheme 5), which, in ist turn, undergoes an aza-Michael cyclization to give the phenanthridine compound. A consistent issue connected with this synthesis was to avoid an initial Heck reaction between complex **I** and the olefin, which would lead to a cynnamate-type byproduct. To address this problem and consequently improving the selectivity of the reaction, several changes were necessary. The less coordinating acetonitrile was used as the solvent in place of DMF. Secondly, Bu$_4$Br

proved to be essential in order to slow down the cyclization step from **VI** (Scheme 4) to carbazole. Finally, to disfavor the Heck product in favor of intermediate **III**, a consistent excess of norbornene (10 equiv.) was employed. Under the optimized conditions, several substituted 5,6-dihydrophenanthridines were synthesized (Figure 3).
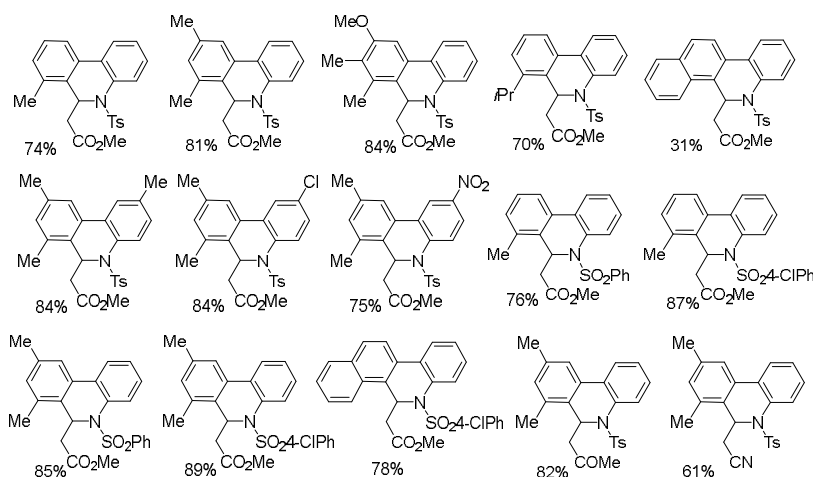

Figure 3. 5,6-Dihydrophenanthidine derivatives from a Catellani-type reaction.

The use of a sulfonyl containing protecting group on the nitrogen proved to be essential for the accomplishment of the reaction. Under the same conditions, trifluoroacetylated *o*-bromo aniline provided only 10% of the unprotected 5,6-dihydrophenanthridine together with a small amount of phenanthridine. To achieve synthetically useful yields of phenanthridines from trifluoroacetylated *o*-bromo aniline, the use of methyl vinyl ketone turned out to be essential (Scheme 6).[26] The optimized reaction conditions involve the use of potassium carbonate as the base in DMF at 105 °C. The amount of norbornene was reduced to 1 equiv. with respect to the bromo aniline, while 4 equiv. of methyl vinyl ketone turned out to be the best compromise.[26]
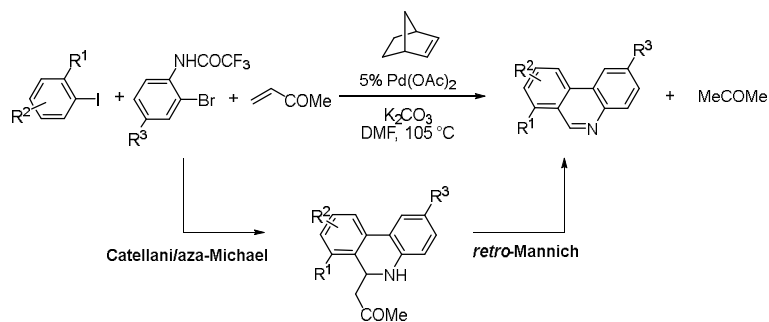
Scheme 6. Synthesis of phenanthridines from *o*-substituted aryl iodides, *N*-trifluoroacetylated *o*-bromo anilines and methyl vinyl ketone *via* Catellani reaction.

Different substituted aryl iodides behaved nicely under these reaction conditions, leading to the desired product in moderate to good yields (Figure 4). EW and ED groups on the aniline ring were also well tolerated.
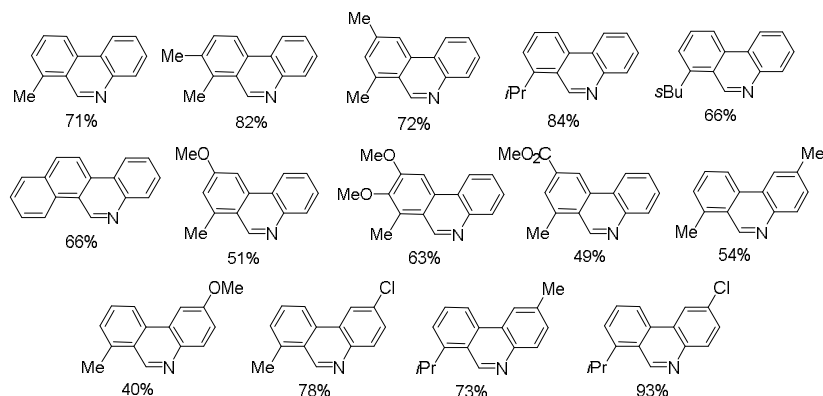
Figure 4. Phenanthridine derivatives from a Catellani-type reaction

The mechanism is similar to the one described above for 5,6-dihydrophenanthridines. However, the *N*-trifluoroacetyl group is easily removed under these conditions and a subsequent *retro*-Mannich-type reaction occurs to form the desired phenanthridine and acetone as coproduct (Scheme 6).

2.2. Synthesis of dibenzofurans and dibenzopyrans

In 2006, we became interested in the reaction of *o*-bromophenol derivatives and aryl iodides in order to obtain condensed tricyclic compounds, such as dibenzopyrans and dibenzofurans. These classes of heterocyclic products, which display interesting pharmaceutical properties,[27-29] are tipically obtained with multi-step procedures[30,31]. Causing to react an *o*-substituted aryl halide, an *o*-bromophenol and a terminal olefin, in the presence of palladium acetate, norbornene and potassium carbonate, a dibenzopyran derivative was obtained with good yield and selectivity (Scheme 7).[32]
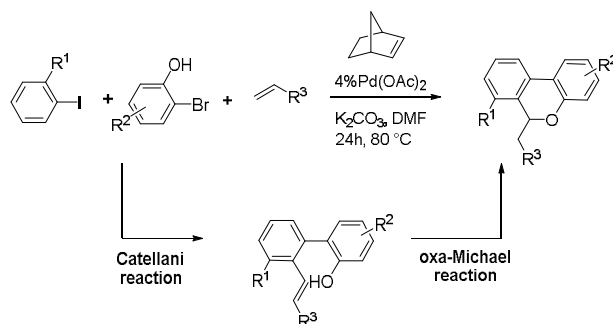
Scheme 7. Synthesis of dibenzopyrans from *o*-substituted aryl iodides, *o*-bromophenols and activated olefins *via* Catellani reaction.

Similarly to the formation of phenanthridines, the reaction proceeds with the "unsymmetrical" aryl-aryl coupling between the aryl iodide and the bromophenol, expulsion of norbornene and formation of the vinyl intermediate (Scheme 7) *via* Heck reaction owing to the presence of the activated olefin. The latter undergoes an intramolecular oxa-Michael reaction between the OH group and the activated double bond to afford the six-membered condensed heterocycle. A wide variety of dibenzopyran derivatives have been efficiently synthesized through this methodology (Figure 5).

The same reaction was later carried out in the presence of a cinchona alkaloid base as organocatalyst (Scheme 8).[33] A number of dibenzopyrans with good yields and interesting ees has been obtained (Figure 6).
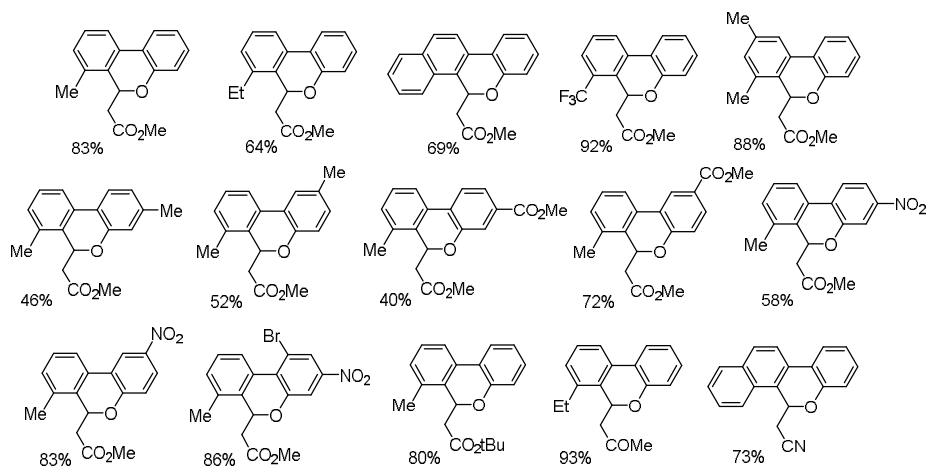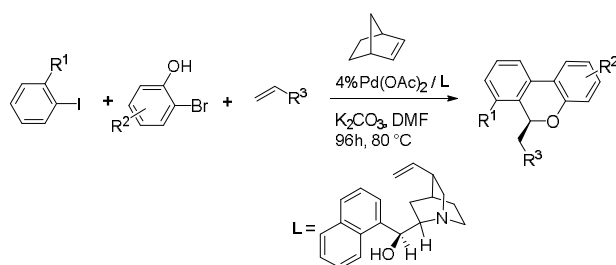
Figure 5. Dibenzopyran derivatives from a Catellani-type reaction.

Scheme 8. Enantioselective Catellani-type synthesis of dibenzopyrans from *o*-substituted aryl iodides, *o*-bromophenols and activated olefins.
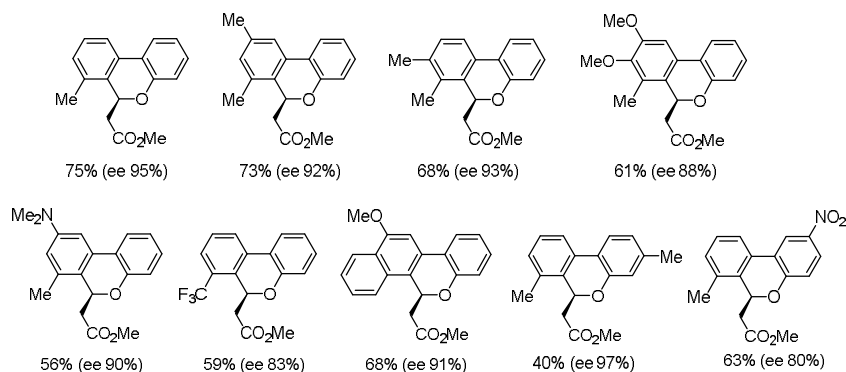

**Figure 6.** Catellani-type enantioselective synthesis of dibenzopyrans.

Operating under similar conditions but in the absence of the olefin, *o*-substituted iodo arenes and *o*-bromophenols can lead to dibenzofuran derivatives in satisfactory yields (Scheme 9).[34] The formation pathway for dibenzofuran compounds is very similar to that of carbazoles (Scheme 4). However, the absence of an activated olefin (which tipically acts both as ligand and reactant as well) results in a more difficult deinsertion of norbornene, which is retained in the structure of some byproducts. In order to obtain

satisfactory yields, it is crucial to decrease the amount of norbornene and increase the temperature to 120 °C to favor its expulsion. The reaction scope was, however, quite limited.
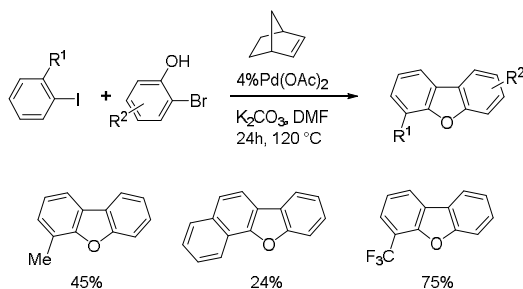
Scheme 9. Catellani-type synthesis of dibenzofurans from *o*-substituted aryl iodides and *o*-bromophenols.

Dibenzopyran derivatives can be also obtained starting from *o*-bromobenzyl alcohols in place of *o*-bromophenols and in the absence of the olefin as terminating agent. Either primary, secondary or tertiary bromobenzyl alcohols may be used, under slightly different conditions. With a disubstituted bromobenzyl derivative (tertiary alcohol), eccellent yields may be achieved using potassium carbonate as a base, DMF as a solvent, at 105 °C for 24 h (Scheme 10).[35]
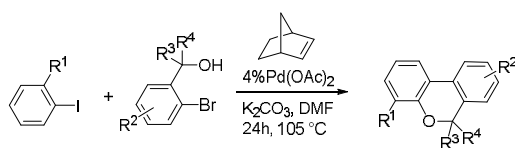
Scheme 10. General Catellani-type synthesis of dibenzopyrans from *o*-substituted iodoarenes and *o*-bromobenzyl alcohol derivatives (primary, secondary or tertiary).

The reaction mechanism is very similar to the above described pathway for the formation of carbazoles (Scheme 4). The sequential steps reported in Scheme 11, are: a) oxidative addition of the aryl iodide to Pd(0), b) insertion of norbornene, c) formation of a five-membered palladacycle **III**, d) oxidative addition of the aryl bromide to Pd(II) to give **VII**, e) reductive elimination to **VIII**, f) deinsertion of norbornene and formation of a seven-membered oxapalladacycle **IX**, g) reductive elimination of **IX** to dibenzopyran derivative and Pd(0). A variety of dibenzopyrans bearing EW or ED groups and having different hindrance on the benzylic carbon can be efficiently prepared by this protocol (Figure 7). When a primary benzyl alcohol is used as aryl bromide in place of a tertiary one, biaryl aldehydes result as the main products. The oxapalladacycle intermediate **IX**, gives rise to reductive elimination with formation of the carbonyl moiety instead of the formation of the cycle.[35] The use of cesium pivalate as a base was crucial to direct the sequence towards aldehyde-containing compounds. Nevertheless, primary benzyl alcohol led preferentially to dibenzopyran derivatives using trifurylphosphine (TFP) as ligand and potassium carbonate as base (Figure 8).[36]

In a similar manner, the use of TFP had positive effects when secondary *o*-bromobenzyl alcohols were employed as partners in this sequence, avoiding the formation of ketone derivatives. Noteworthy, the reactivity of secondary 2-bromobenzyl alcohols can be shifted to fluorenol derivative under different reaction conditions, using cesium carbonate as a base in the presence of PPh$_3$ and using toluene as a solvent.[37]

2.3. Synthesis of dibenzoazepines

In 2011, a new strategy to dibenzoazepine derivatives was reported.[38] The described palladium and norbornene methodology features the formation of 'unsymmetrical' biaryl units resulting from the combination of an *ortho* substituted aryl iodide and an aryl bromide (Schemes 4 and 11). The presence of the

ortho substituent causes the formation of a Csp^2-Csp^2 bond rather than promoting the Csp^2-Csp^3 coupling (so called "*ortho effect*"). However, the presence of certain chelating groups on the aryl bromide is responsible for the Csp^2-Csp^3 bond construction (*vide infra*). When we caused to react an *ortho* substituted aryl iodide and an *o*-bromo aniline in presence of a stoichiometric amount of norbornene and palladium acetate as catalyst, we observed the formation of a seven-membered nitrogen heterocycle (Scheme 12).
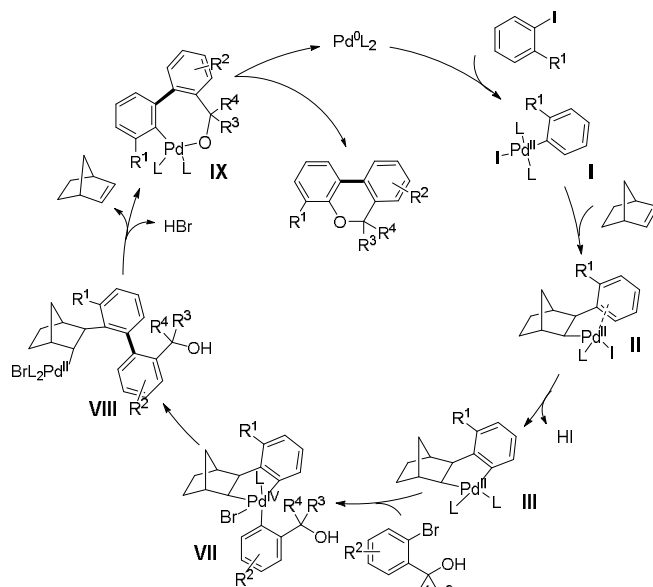
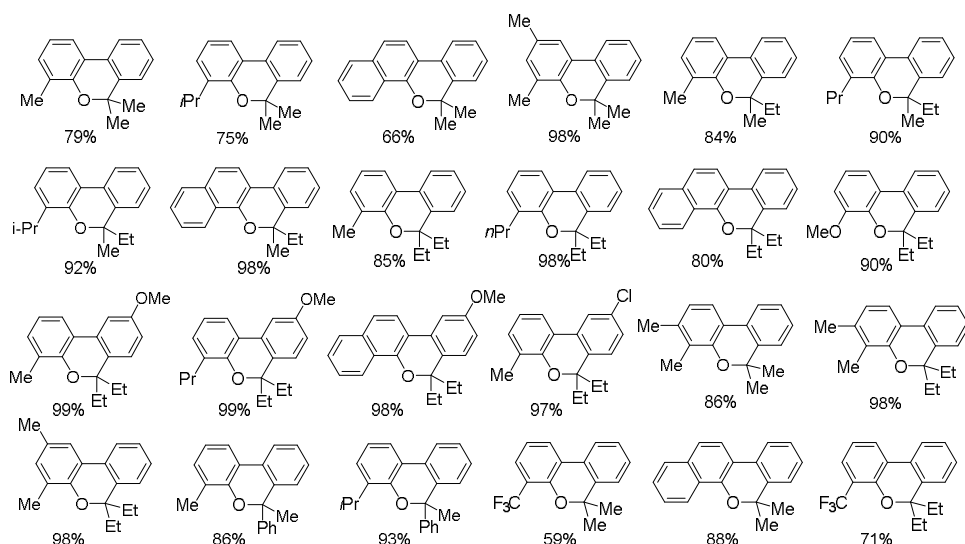**Scheme 11.** Mechanism for the forrmation of dibenzopyrans from *o*-bromo benzylic alcohols.

Figure 7. Dibenzopyrans *via* Catellani-type synthesis from tertiary *o*-bromobenzyl alcohols.

When norbornadiene was used in place of norbornene, a subsequent *retro*-Diels-Alder step occurred with the formation of an internal C-C double bond in the final product and cyclopentadiene as co-product. Dibenzoazepines as well as dihydrodibenzoazepines are found in a wide number of pharmaceutically important structures,[39-45] such as carbamazepine, oxcarbazepine and clomipramine, which are well-known antiepileptic and anti-anxiety drugs. Various methods to access these compounds have been reported in literature.[46-49] Our straightforward strategy involves the use of easily available reagents and an inexpensive ligand such as triphenylphosphine.
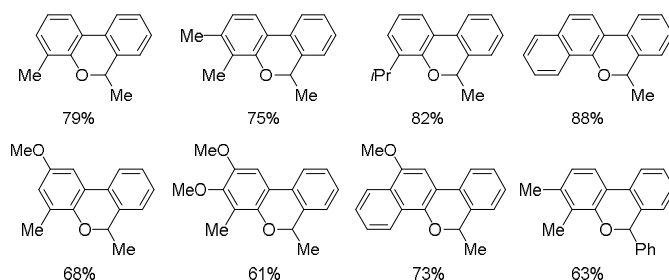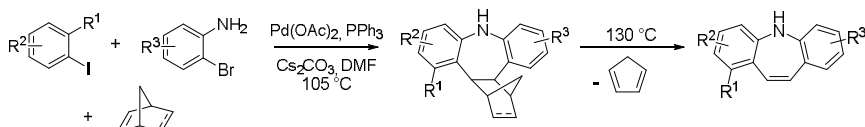
Figure 8. Dibenzopyrans *via* Catellani-type synthesis from secondary *o*-bromobenzyl alcohol derivatives in the presence of TFP as ligand.

Scheme 12. Palladium-catalyzed reaction of *ortho* substituted aryl iodides, *o*-bromo anilines and norbornene/norbornadiene to dibenzo[b,f]azepine derivatives.

Under these conditions, it was possible to obtain differently decorated azepine derivatives (Figure 9). As anticipated, unsubstituted aryl iodides provided the target compound albeit in lower yields.
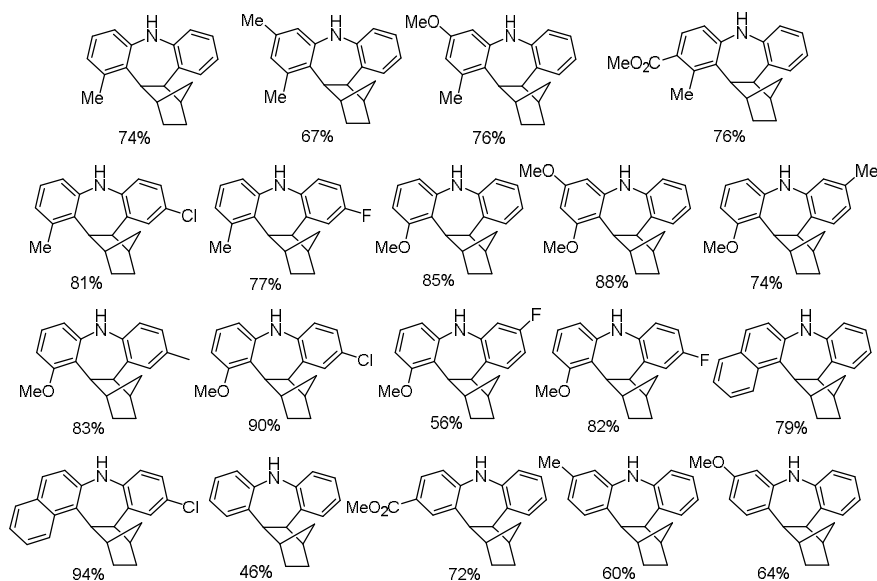
Figure 9. Dihydrodibenzo[b,f]azepines from aryl iodides, *o*-bromo anilines and norbornene.

Figure 10 shows the results obtained using norbornadiene in place of norbornene. A higher amount of norbornadiene (2 equiv.) was essential in order to obtain satisfactory yields.
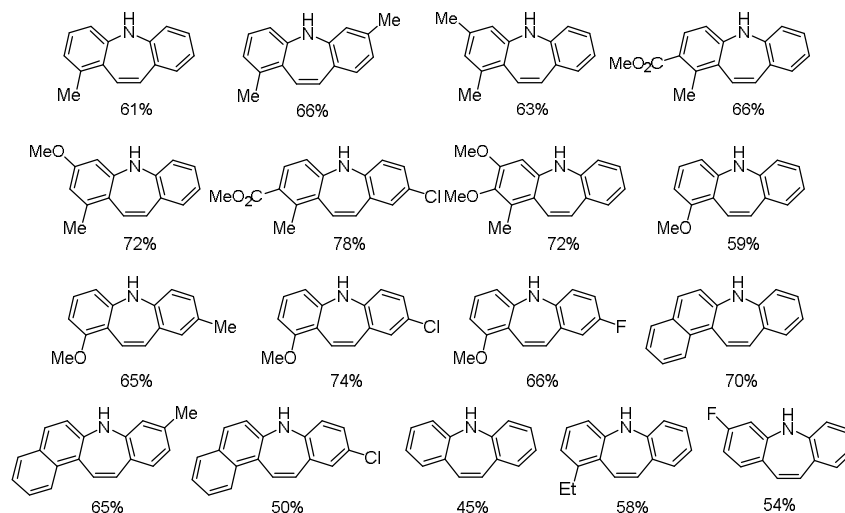

Figure 10. Dibenzo[b,f]azepines from aryl iodides, *o*-bromo anilines and norbornadiene.

The mechanism involves the oxidative addition of the aryl iodide to a palladium(0) species resulting in complex **I** (Scheme 13). The stereoselective insertion of norbornene leads to the formation of a *cis,exo* arylnorbornyl palladium intermediate **II**, that undergoes C-H activation in presence of a base affording the palladacycle **III**. A second oxidative addition involving the *ortho*-bromo aniline provides a palladium(IV) complex **X**. In agreement with DFT calculations, the assistance of the NH_2 chelating group favors the subsequent formation of a Csp^2-Csp^3 bond *via* reductive elimination. The seven-membered ring is then generated through an intramolecular Buchwald-Hartwig reductive elimination.
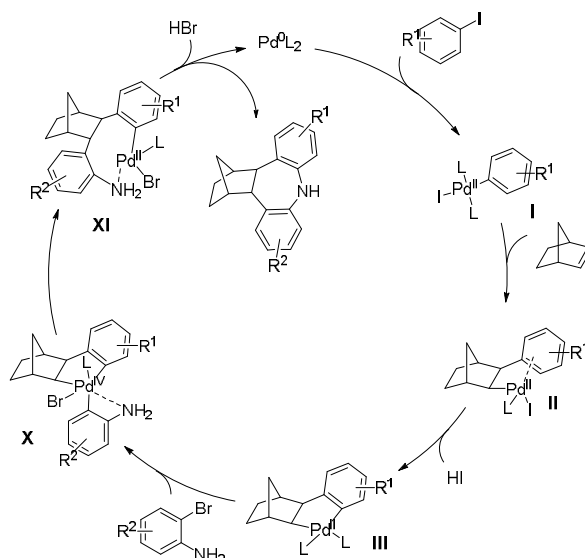
Scheme 13. Proposed reaction pathway for the synthesis of dibenzo[b,f]azepines.

We have recently developed a complementary protocol that allows the synthesis of dibenzo[b,f]azepine derivatives bearing EW groups from aryl bromides only (Scheme 14).[50]
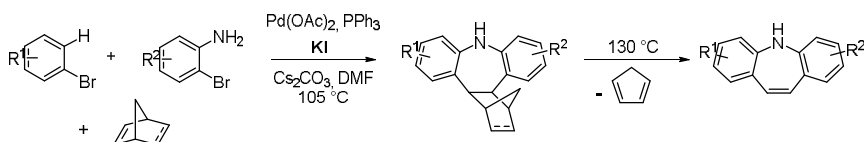
Scheme 14. Our complementary protocol for the synthesis of dibenzo[b,f]azepines using aryl bromides, *o*-bromo anilines and norbornene/norbornadiene.

After a careful screening of the reaction conditions we identified the potassium iodide as an important additive in order to achieve high reactivity and selectivity. The increased reactivity due to the presence of iodide anions can be explained with the *in situ* formation of nucleophilic palladium species, which are known to be able to increase the rate of the oxidative addition of aryl bromides.[51-55] Properly designed experiments suggested that iodide anions play the role of active ligand in this transformation, enhancing the reactivity of both aryl iodides and aryl bromides.

Richly decorated dihydrodibenzoazepines were synthesized starting from *o*-, *m*-, *p*-substituted aryl bromides. This protocol was particularly suitable for electron poor aromatic rings, even though electron rich ones were also tolerated as starting materials (Figure 11).
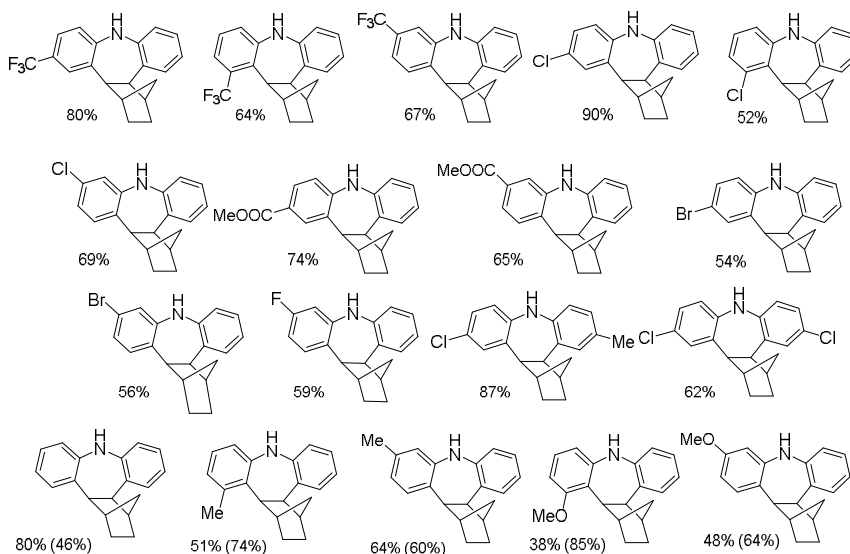

Figure 11. Pd-catalyzed synthesis of dihydrodibenzoazepines from aryl bromides, 2-bromoanilines and norbornene, in brackets the yields using aryl iodides.

Similarly, 5*H*-dibenzoazepines bearing mainly electron withdrawing groups were successfully prepared employing norbornadiene instead of norbornene (Figure 12). We further demonstrated the synthetic utility of this protocol with the formal synthesis of Clomipramine®, which was prepared in three steps starting from commercial reagents.[50]

From a mechanistic point of view, the reaction pathway is similar to the one described above (Scheme 13). However, in this case, both the aryl bromides may engage the oxidative addition to palladium(0) species. The most probable reaction sequence, involving the initial oxidative addition of the aryl bromide on

palladium(0), was proposed on the base of isolated organic compounds, which were generated by trapping key organometallic intermediates through the Suzuki-Miyaura coupling.
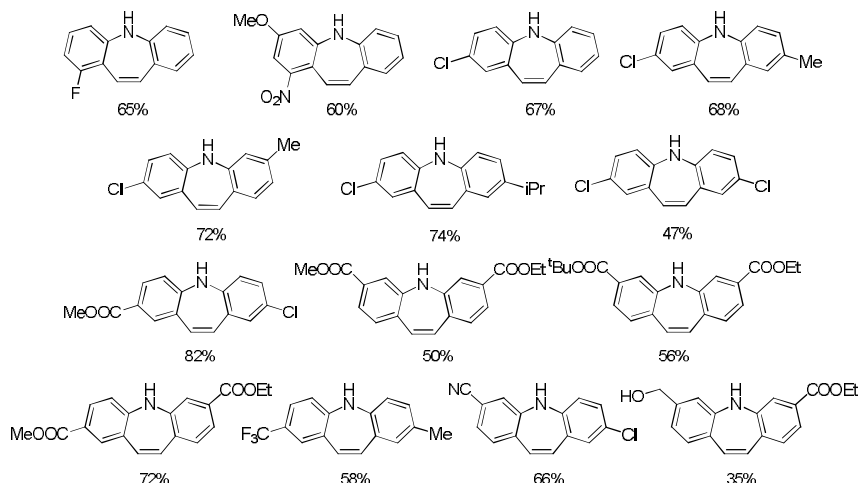

Figure 12. Pd-catalyzed synthesis of 5H-dibenzoazepines from aryl bromides, 2-bromoanilines and norbornadiene.

2.3.1. DFT studies

The presence of a substituent *ortho* to the aryl-norbornyl bond of palladacycle **III** (Scheme 15) is crucial to direct the selective formation of a Csp^2-Csp^2, hence promoting the selective transfer of the second aryl coupling partner to the aromatic site of the palladacycle. The "*ortho effect*" has been extensively studied by means of DFT calculations and a rational explanation has been proposed.[56] Two possible pathways may be at work: the first (*pathway a*, Scheme 15) involves the formation of a palladium(IV) species, resulting from the oxidative addition of an aryl halide to palladacycle **III**, while the second (*pathway b*, Scheme 15) features a transmetallation between two palladium(II) complexes. The detailed calculations showed that for *ortho* naked aryl halides the reaction likely evolve through a bimetallic mechanism. The transmetallation mechanism is energetically favored over the formation of a palladium(IV) intermediate. The experimental lack of selectivity observed when R^1=H on the palladacycle, can be explained according to the trasmetallation pathway, since the energetic difference between the two couplings (Csp^2-Csp^2 *vs* Csp^2-Csp^3) is rather small.
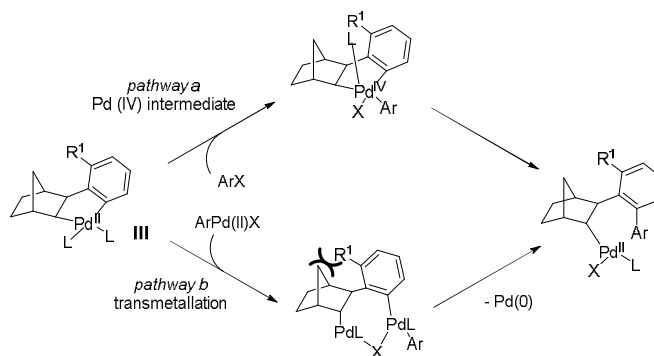
Scheme 15. Possible reaction pathways for the formation of the Csp^2-Csp^2 bond from palladacycle **III**.

On the contrary, when a substituent is present in *ortho* position, the formation of a palladium(IV) species after oxidative addition is energetically more favored than the other featuring the transmetallation. The latter displays a steric hindrance between the CH_2 of the norbornene bridge and the *ortho* group in the transition state.

Some exceptions to the "*ortho effect*" have been disclosed. The presence of certain chelating substituents is crucial to promote the Csp^2-Csp^3 coupling rather than the biaryl formation. As reported above, the synthesis of dibenzoazepines derivatives falls in this trend.[38,50] The presence of the NH_2 group of the *ortho*-bromo aniline ensures a chelating effect that favors the reductive elimination step from palladium(IV) complexes towards Csp^2-Csp^3 coupling. The Malacria group's reported another deviation from the *ortho* effect. Using 2-bromo-phenylacetamide in combination with aryl iodides, the selective formation of norbornene-containing dihydrophenantrene derivatives *via* Csp^2-Csp^3 coupling was observed (Scheme 16).[57]
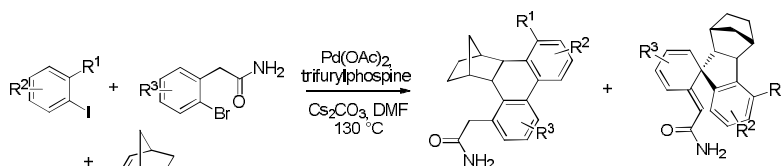
Scheme 16. Synthesis of dihydrophenantrenes from *o*-substituted aryl iodides, *o*-bromo phenylacetamides and norbornene. Spiro compounds were the main products in the presence of water.

They also noticed that in precence of water the classical effect exerted by the *ortho* group was restored, affording norbornene-containing spiro derivatives. DFT calculations showed that the formation of a palladium(IV) intermediate is favored upon bimetallic species and, moreover, the apical ligand is surprisingly important to direct the regioselectivity of the subsequent reductive elimination. In the presence of a phosphine ligand, the Csp^2-Csp^3 coupling is energetically favored. On the contrary, water in place of a phosphine stabilizes the transition state, leading to the Csp^2-Csp^2 bond formation, likely for steric reasons. The calculations also included the evaluation of the energy barriers for both Csp^2-Csp^3 and Csp^2-Csp^2 couplings from a palladium(IV) species, generated from the oxidative addition of the *o*-bromo benzylamine. In this case, the chelating *ortho* group is not able to hamper the *ortho* effect leading selectively to the Csp^2-Csp^2 coupling route. Taking advantage from this finding, in 2014 Malacria and co-workers reported the diastereoselective synthesis of dibenzo[*c,e*]azepines using the palladium/norbornene catalytic system.[58] *o*-Substituted aryl iodides, *o*-bromo benzylamines and activated olefins were caused to react at 130 °C in DMF, using K_2CO_3 as a base, triisopropyl phosphine as ligand and palladium acetate as catalytic precursor (Scheme 17).
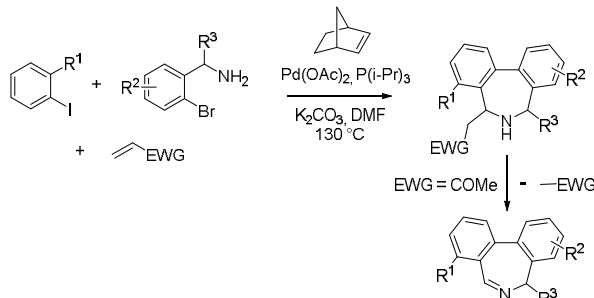
Scheme 17. Synthesis of dibenzo[*c,e*]azepines from *o*-substituted aryl iodides, 2-bromo benzylamines and activated olefins in the presence of the palladium/norbornene catalytic system.

The reaction of racemic bromides afforded the target azepine as a single diastereomer out of the four possible. Moreover, using an enolizable olefin, such as methyl vinyl ketone, a *retro*-Mannich reaction

smoothly occured under the reaction conditions, delivering the corresponding imine derivative. The mechanism of this reaction is consistent with the above-mentioned "*ortho effect*". The aryl iodide, norbornene and palladium(0) species give rise to palladacycle **III**, which reacts with *o*-bromo benzilamine producing a chelated Pd(IV) complex (Scheme 18). A reductive elimination step ensures the formation of a Csp^2-Csp^2 bond, retaining the N chelation and thus preventing rotation around the biaryl axis. After norbornene expulsion, the biaryl conformation is preserved. At this point, the a Heck-type reaction provides the acyclic styrene derivative, which undergoes an *aza*-Michael intramolecular reaction delivering the seven-membered heterocycle as a single diastereoisomer. A *retro*-Mannich reaction occurs when methyl vinyl ketone was employed.
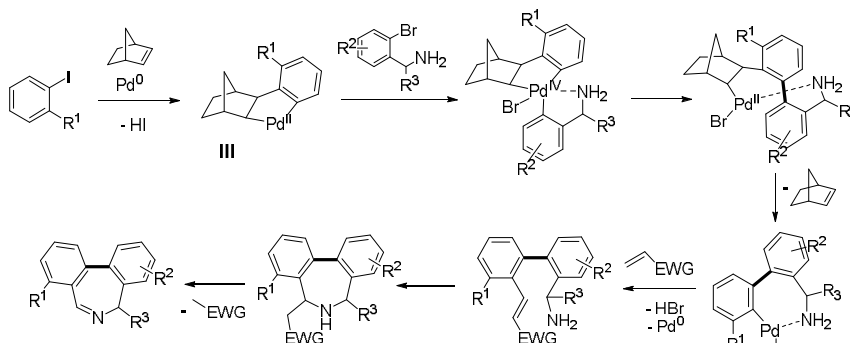

Scheme 18. Proposed pathway for the formation of dibenzo[*c,e*]azepines.

3. PdI$_2$/KI-catalyzed oxidative carbonylation processes
3.1. Synthesis of dibenzooxazocinones

Over the years, the methodology based on the use of PdI$_2$ and KI as catalytic system, proved to be very useful for the construction of tricyclic system dysplaing high molecular complexity and interesting biological activities. For instance, the reactivity of 2-(2-alkynylphenoxy)anilines in the presence of the PdI$_2$/KI catalytic system under oxidative carbonylation conditions, such as a mixture of carbon monoxide and air (4:1) in an alcohol as solvent/reagent (Scheme 19), has been recently investigated.[59] Under the optimized conditions, ξ-lactam derivatives were successfully synthesized in good yields (Figure 13). A promising antitumor activity against breast cancer cell lines was also demonstrated.[59]
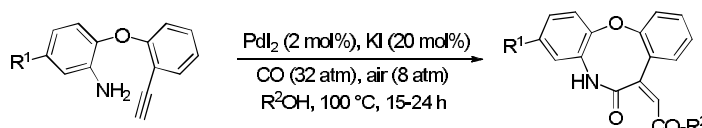
Scheme 19. Synthesis of ξ-lactams by PdI$_2$/KI-catalyzed oxidative carbonylation
of 2-(2-ethynylphenoxy)anilines.

From a mechanicistic point of view, this reaction starts with a N-palladation followed by the formation of a carbamoylpalladium iodide. A remarkable intramolecular *syn* 8-*exo-dig* triple bond insertion is the key step for the formation of these useful derivatives. The nucleophilic displacement by the alcohol ends the reaction sequence, affording the final product (Scheme 20).

3.2. Synthesis of furoindolones and furobenzofuranones

More recently, acetylenic substrates bearing two suitably placed nucleophilic groups were employed under oxidative carbonylation conditions (Scheme 21). In particular, 2-(hydroxypropyn-1-yl)anilines led to dihydrofuro[3,4-*b*]indolones in good to excellent yields *via* a double cyclization process.[60]
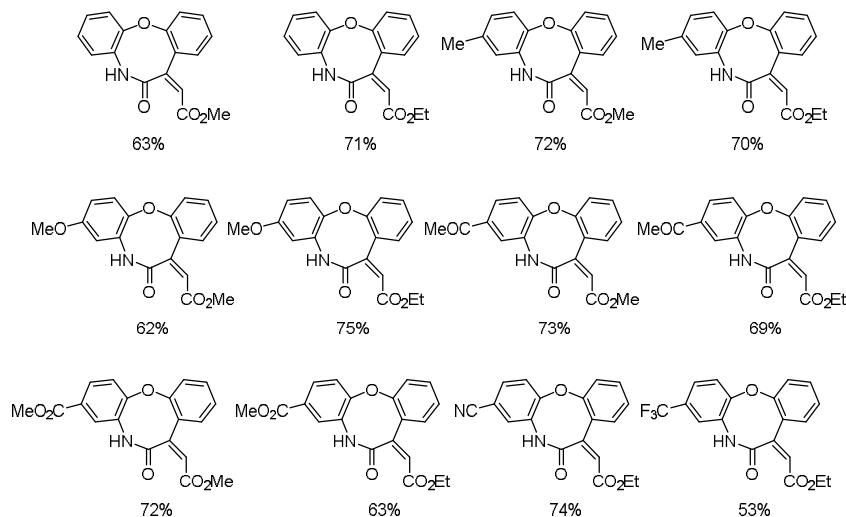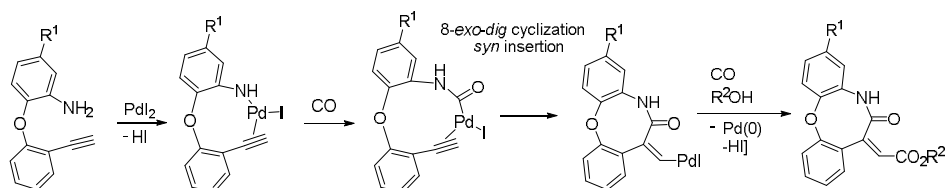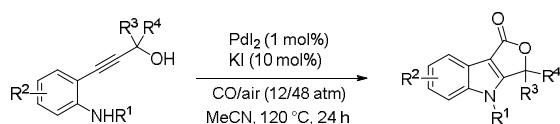
Figure 13. Scope of the PdI$_2$/KI-catalyzed oxidative carbonylation of 2-(2-ethynylphenoxy)anilines.

Scheme 20. Possible pathway for the construction of ξ-lactam derivatives.

Scheme 21. PdI$_2$/KI-catalyzed oxidative carbonylation of 2-(hydroxypropyn-1-yl)anilines to dihydrofuro[3,4-*b*]indolones.

After a careful optimization of the reaction conditions, we applied the developed protocol for the synthesis of variously substituted dihydrofuro[3,4-*b*]indolones (Figure 14). The unprotected aniline derivative (R^1=H) led to the corresponding furoindolone in a lower yield. Electron donating substituents on the aromatic ring gave better results compared to electron withdrawing ones. Moreover, the starting reagent was completely unreactive in the presence of EWGs on the nitrogen (R^1=Ts, Ac).

In a similar way, furobenzofuranone derivatives were synthesized in 74-86% yields starting from 2-(3-hydroxy-1-yn-1-yl)phenols, in BmimBF$_4$ as unconventional solvent (Scheme 22).[61] Interestingly, the same reaction performed in conventional solvents resulted in poor selectivity, as a not negligible amount of the compound resulting from cyclization to the benzofuran ring with the OH function untouched was formed. Moreover, the presence of a base was essential to ensure a successful reaction outcome, owing to the low nucleophilicity of the phenolic moiety, which needs to be deprotonated to generate the phenoxide function able to attack the triple bond.

Several functional groups were tolerated under these reaction conditions (Figure 15). In addition, the catalytic system was efficiently recycled up to six times without appreciable loss of reactivity.
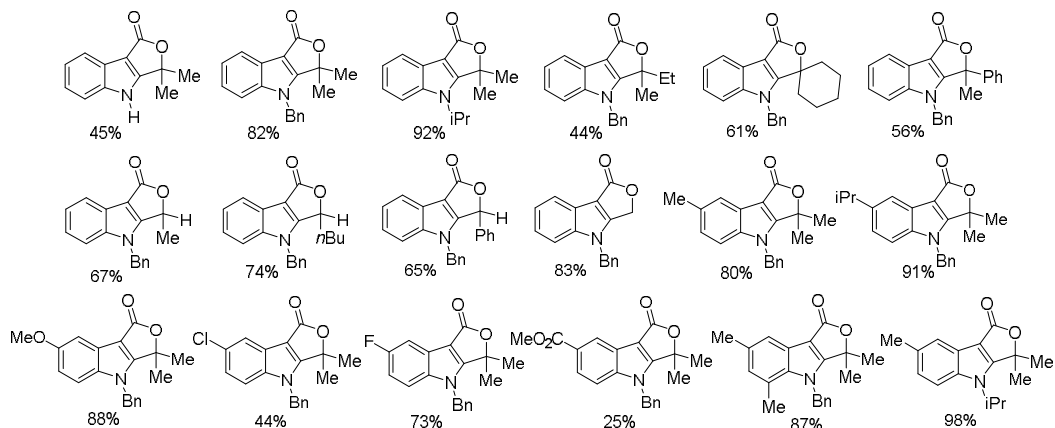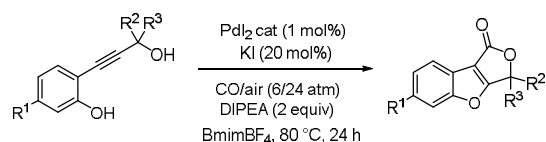
Figure 14. Scope of the synthesis of 3,4-dihydrofuro[3,4-*b*]indol-1-ones.

Scheme 22. PdI$_2$/KI-catalyzed oxidative carbonylation of 2-(3-hydroxy-1-yn-1-yl)phenols to furo[3,4-*b*]benzofuran-1(3*H*)-ones in BmimBF$_4$.
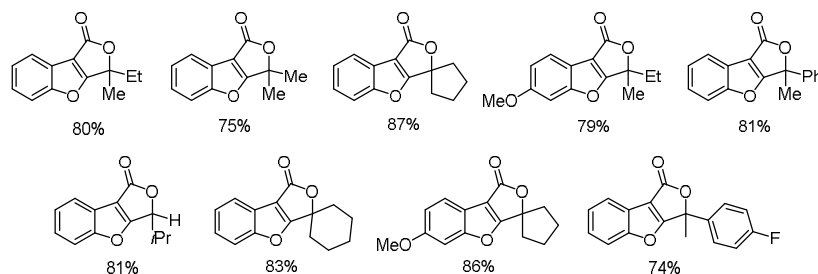

**Figure 15.** Scope of the synthesis of furo[3,4-*b*]benzofuran-1(3H)-ones.

The mechanism proposed for furoindolones and furobenzofuranones is described in Scheme 23. The coordination of Pd(II) species to triple bond affords the palladium π-complex **XII**. This species undergoes an intramolecular nucleophilic attack of the XH group to the activated acetylenic moiety following a 5-*endo-dig* cyclization mode, leading to intermediate **XIII**. The CO insertion likely delivers palladacycle **XIV**, which might be in equilibrium with its isomer **XIV'**. Then, a reductive elimination step provides the desired tricyclic compound and a palladium(0) species, which is reoxidized *in situ* by molecular oxygen in the presence of HI.[62]

3.3. Synthesis of benzimidazopyrimidinones, benzimidazoimidazoles and benzimidazothiazoles

Using the above mentioned cyclocarbonylation-alkoxycarbonylation sequence (see Scheme 19 for the formation of ξ-lactam derivatives), condensed tricyclic heterocycles, such as benzimidazopyrimidinones, were obtained (Scheme 24).[63] Benzimidazopyrimidinones were efficiently synthesized through a two-step procedure, involving a) the palladium-catalyzed oxidative carbonylation and b) the base-mediated isomerization to recover the target compound, featuring an endocyclic double bond.
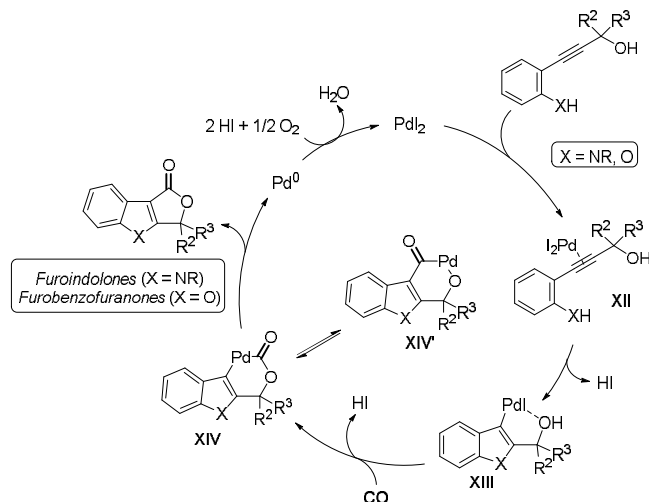
Scheme 23. Proposed reaction pathways for the PdI$_2$-catalyzed oxidative carbonylation to furoindolones and furobenzofuranones.
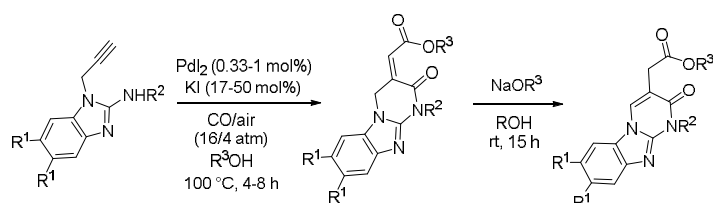
Scheme 24. Synthesis of benzimidazopyrimidinones by PdI$_2$/KI-catalyzed oxidative carbonylation of propynylbenzimidazolamines.

To test the generality of the methodology, variously substituted substrates and alcohols were evaluated (Figure 16).

67% 71% (64%) 67% (55%) 61% (60%)

66% (45%) 61% 65% (60%) 69% (58%) 81% (80%)
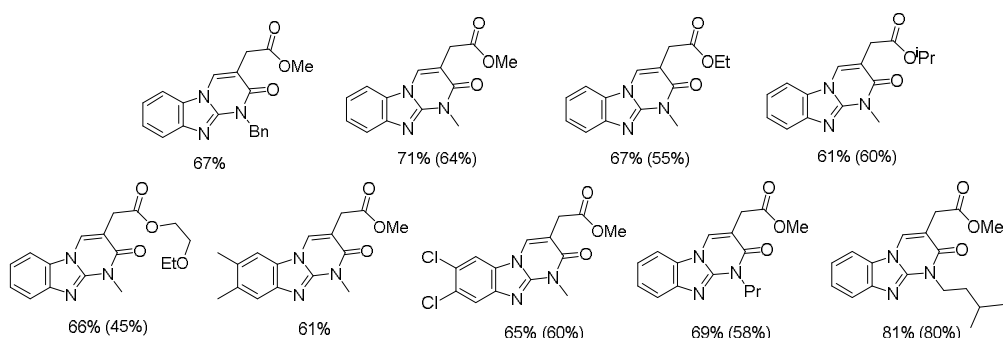
Figure 16. Scope of the PdI$_2$/KI-catalyzed synthesis of benzo[4,5]imidazo[1,2a]pyrimidin-2(1H)-ones. In brackets the yield obtained using 0.33% of PdI$_2$ instead of 1%.

Propynylbenzimidazolamines were also employed as substrates under oxidative aminocarbonylation conditions, to obtain benzimidazoimidazoles after an additional isomerization process (Scheme 25).[64] The intermediate **XV** is generated after CO insertion into an alkynylpalladium species followed by nucleophilic

displacement by the amine. Then an intramolecular conjugate addition leads to compound **XVI**, which undergoes double bond isomerization to the desired benzimidazoimidazoles.
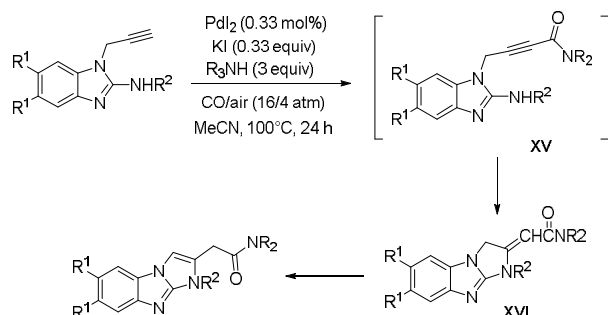
Scheme 25. Synthesis of benzimidazoimidazoles by sequential oxidative PdI$_2$/KI-catalyzed aminocarbonylation-*N*-cyclization-isomerization of propynylbenzimidazolamines.

The described methodology was successfully applied to different substituted starting reagents obtaining the target compounds in good to excellent yields, in many cases with TON higher than 250 (Figure 17).
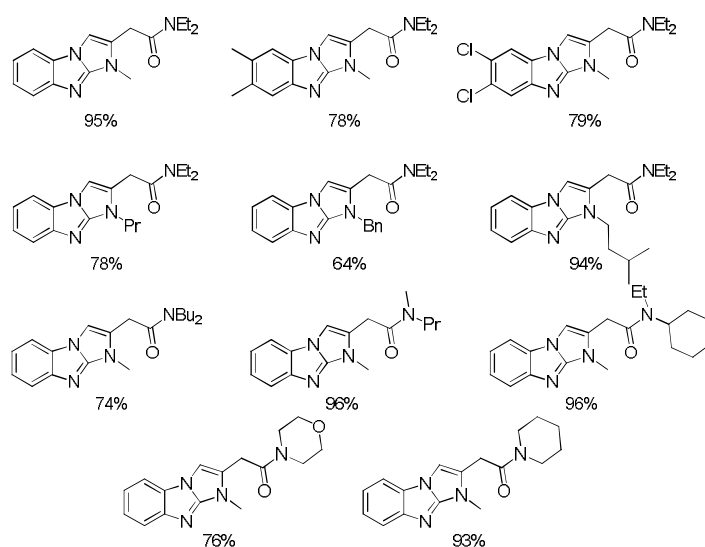

Figure 17. Scope of the synthesis of benzimidazoimidazoles by PdI$_2$/KI-catalyzed aminocarbonylation-*N*-cyclization-isomerization of propynylbenzimidazolamines.

In a similar way, benzimidazothiazoles were synthesized from propynylsulfanylbenzimidazoles, obtained *in situ* from the corresponding benzimidazolium bromide salts (Scheme 26).[65] In this case, the initial aminocarbonylation of the triple bond was followed by the intramolecular nucleophilic attack of the nitrogen of the imidazole ring to the acetylenic moiety and subsequent double bond isomerization under the same reaction conditions.

The reaction was applied to differently substituted benzimidazolium bromide salts and various secondary amines. A mixture of regioisomers was obtained starting from a non-symmetric reagent (Figure 18).
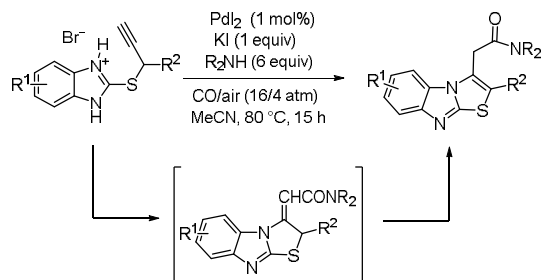
Scheme 26. Synthesis of benzimidazothiazoles by sequential PdI$_2$-catalyzed oxidative aminocarbonylation-*N*-cyclization-isomerization of benzimidazolium bromide salts.
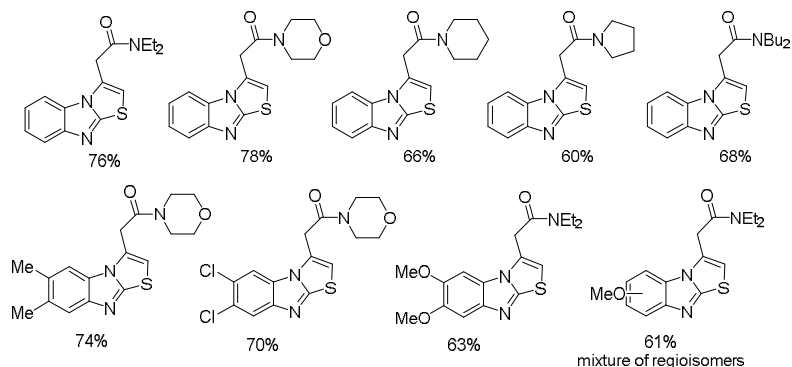

Figure 18. Scope of the synthesis of functionalized benzimidazothiazoles.

4. Conclusion

In summary, we have described several synthetic approaches to condensed tricyclic systems that are difficult to prepare by the conventional organic synthesis. Both the presented methodologies are based on the use of palladium (palladium and norbornene catalysis and palladium iodide/potassium iodide-catalyzed oxidative carbonylation), and have demonstrated a remarkable potentiality to achieve high molecular complexity starting from easily available reagents. We believe that the area of sequential reactions still reserves plenty of space for exciting new discoveries, considering the possibility a) to combine the action of different metals, b) to employ alternative solvents, and c) to start from multifunctional reagents.

Acknowledgements

References

1. Hagui, W.; Doucet, H.; Soule, J.-F. *Chem* **2019**, *5*, 2006-2078.
2. Gabriele, B.; Mancuso, R.; Veltri, L.; Ziccarelli, I.; Della Ca', N. *Eur. J. Org. Chem.* **2019**, *2019*, 5073-5092.
3. Perrone, S.; Troisi, L.; Salomone, A. *Eur. J. Org. Chem.* **2019**, *2019*, 4626-4643.
4. Dondas, H. A.; Retamosa, M. G.; Sansano, J. M. *Organometallics* **2019**, *38*, 1828-1867.
5. Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem. Int. Ed.* **1997**, *36*, 119-122.
6. Wang, J.; Dong, G. *Chem. Rev.* **2019**, *119*, 7478-7528.
7. Cheng, H.-G.; Chen, S.; Chen, R.; Zhou, Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 5832-5844.
8. Liu, Z.-S.; Gao, Q.; Cheng, H.-G.; Zhou, Q. *Chem. Eur. J.* **2018**, *24*, 15461-15476.
9. Cheng, H.-G.; Zhou, Q. *Chem* **2018**, *4*, 1775-1777.

10. Della Ca', N; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389-1400.
11. Ye, J.; Lautens, M. *Nature Chem.* **2015**, *7*, 863-870.
12. Mancuso, M.; Della Ca', N.; Veltri, L.; Ziccarelli, I.; Gabriele B. *Catalysts* **2019**, *9*, 610.
13. Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G.P. *J. Chem. Soc., Chem. Commun.* **1992**, 1007-1008.
14. Della Ca', N.; Sassi, G.; Catellani, M. *Adv. Synth. Catal.* **2008**, *350*, 2179-2182.
15. Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 6, 3193-3328.
16. Sigwalt, P.; Wegner, G.; Morin, J.-F.; Leclerc, M.; Adès, D.; Siove, A. *Macromol. Rapid Commun.* **2005**, *26*, 761-778.
17. Della Ca', N.; Motti, E.; Catellani, M. *Adv. Synth. Catal.* **2008**, *350*, 2513-2516.
18. Katritzky, A. R.; Rees, C. W.; Scriven, E. F., Eds., Comprehensive Heterocyclic Chemistry II, Pergamon, Oxford, 1996.
19. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, *2002*, 2671-2681.
20. Candito, D. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6713-6716.
21. Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.
22. Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720-7725.
23. Xiao, T.; Li, L.; Lin, G.; Wang, Q.; Zhang, P.; Mao, Z. W.; Zhou, L. *Green Chem.* **2014**, *16*, 2418-2421.
24. Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846-4849.
25. Intrieri, D.; Mariani, M.; Caselli, A.; Ragaini, F.; Gallo, E. *Chem. Eur. J.* **2012**, *18*, 10487-10490.
26. Della Ca', N.; Motti, E.; Mega, A.; Catellani, M. *Adv. Synth. Catal.* **2010**, *352*, 1451-1454.
27. Garazd, Y. L.; Garazd, M. M. *Chem. Nat. Comp.* **2016**, *52*, 1-18.
28. Ahmed, A.; Dhara, S.; Ray, J.K *Tetrahedron Lett.* **2013**, *54*, 1673-1676.
29. Ahmed, M.G.; Slade, D.; Gul, W.; Alfy, T. E. A; Ferreira, D.; Elsohly, M. A *Recent Pat. CNS Drug Discov.* **2009**, *4*, 118-136.
30. Pratap, R.; Ram, V. J. *Tetrahedron* **2017**, *73*, 2529-2590.
31. Minami, Y.; Hiyama, T. *Acc. Chem. Res.* **2016**, *49*, 67-77.
32. Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. *Org. Lett.* **2006**, *8*, 3967-3970.
33. Xu, D; Catellani, M.; Motti, E.; Della Ca', N.; Zhou, Z.-M. *Org Biomol. Chem.* **2015**, *13*, 2260-2263.
34. Motti, E.; Della Ca', N.; Xu, D.; Armani, S.; Aresta, B.M.; Catellani, M. *Tetrahedron* **2013**, *69*, 4421-4428.
35. Motti, E.; Della Ca', N.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z.-M.; Catellani, M. *Org. Lett.* **2012**, *14*, 5792-5795.
36. Della Ca', N.; Fontana, M.; Xu, D.; Cremaschi, M.; Lucentini, R.; Zhou, Z.-M.; Catellani, M.; Motti, E. *Tetrahedron* **2015**, *71*, 6389-6401.
37. Casnati, A.; Fontana, M.; Motti, E.; Della Ca', N. *Org. Biomol. Chem.* **2019**, *17*, 6165-6173.
38. Della Ca', N.; Maestri, G.; Malacria, M.; Derat, E.; Catellani, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12257-12261.
39. Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101-123.
40. Hirschfeld, R. M. A.; Kasper, S. *Int J Neuropsychopharmacol* **2004**, *7*, 507-522.
41. Gomez-Arguelles, J. M.; Dorado, R.; Sepulveda, J. M.; Herrera, A.; Gilo Arrojo, F.; Aragòn, E.; Ruiz Huete, C.; Terròn, C.; Anciones, B. *J. Clin. Neurosci.* **2008**, *15*, 516-519.
42. Kumar, V. H.; Naik, N. *Eur. J. Med. Chem.* **2010**, *45*, 2-10.
43. Priya, B. S.; Swamy, S. N.; Tejesvi, M. V.; Sarala, G.; Gaonkar, S. L.; Naveen, S.; Prasad, J. S.; Rangappa, K. S. *Eur. J. Med. Chem.* **2006**, *41*, 1262-1270.
44. Taleli, L.; de Kock, C.; Smith, P. J.; Pelly, S. C.; Blackie, M. A. L.; van Otterlo, W. A. L. *Bioorg. Med. Chem.* **2015**, *23*, 4163-4171.
45. Boykin, D. W.; Das, B. P. *J. Med. Chem.* **1971**, *14*, 56-58
46. Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048-14051.
47. Lam, H.; Tsoung, J.; Lautens, M. *J. Org. Chem.* **2017**, *82*, 6089-6099.
48. Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255-5258.
49. Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2005**, *7*, 4787-4789.
50. Casnati, A.; Fontana, M.; Coruzzi, G.; Aresta, B. M.; Corriero, N.; Maggi, R.; Maestri, G.; Motti, E.; Della Ca', N. *ChemCatChem* **2018**, *10*, 4346-4352.

51. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314-321.
52. Amatore, C.; Jutand, A.; Lemaître, F.; Ricard, J. L.; Kozuch, S.; Shaik, S. *J. Organomet. Chem.* **2004**, *689*, 3728-3734.
53. Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531-9541.
54. Maitlis, P. M.; Haynes, A.; James, B. R.; Catellani, M.; Chiusoli, G. P. *Dalton Trans* **2004**, 3409-3419.
55. Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26-47.
56. Maestri, G.; Motti, E.; Della Ca', N.; Malacria, M.; Derat, E.; Catellani, M. *J. Am. Chem. Soc.* **2011**, *133*, 8574-8585.
57. Larraufie, M. H.; Maestri, G.; Beaume, A.; Derat, E.; Ollivier, C.; Fensterbank, L.; Courillon, C.; Lacôte, E.; Catellani, M.; Malacria, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 12253-12256.
58. Narbonne, V.; Retailleau, P.; Maestri, G.; Malacria, M. *Org. Lett.* **2014**, *16*, 628-631.
59. Mancuso, R.; Raut, D.S.; Marino, N.; De Luca, G.; Giordano, C.; Catalano, S.; Barone, I.; Andò, S.; Gabriele, B. *Chem. Eur. J.* **2016**, *22*, 3053-3064.
60. Acerbi, A.; Carfagna, C.; Costa, M.; Mancuso, R.; Gabriele, B.; Della Ca', N. *Chem. Eur. J.* **2018**, *24*, 4835-4840.
61. Mancuso, R.; Miliè, R.; Palumbo Piccionello, A.; Olivieri, D.; Della Ca', N.; Carfagna, C.; Gabriele, B. *J. Org. Chem.* **2019**, *84*, 7303-7311.
62. Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc. Perkin Trans. 1* **1994**, 83-87.
63. Mancuso, R.; Veltri, L.; Russo, P.; Grasso, G.; Cuocci, C.; Romeo, R.; Gabriele, B. *Synthesis* **2018**, *50*, 267-277.
64. Veltri, L.; Giofrè, S.V.; Devo, P.; Romeo, R.; Dobbs, A.P.; Gabriele, B. *J. Org. Chem.* **2018**, *83*, 1680-1685.
65. Veltri, L.; Grasso, G.; Rizzi, R.; Mancuso, R.; Gabriele, B. *Asian J. Org. Chem.* **2016**, *5*, 560-567.