Pd-catalyzed Auto-tandem Cascades Based on *N*-Sulfonylhydrazones: Hetero- and Carbocyclization processes.

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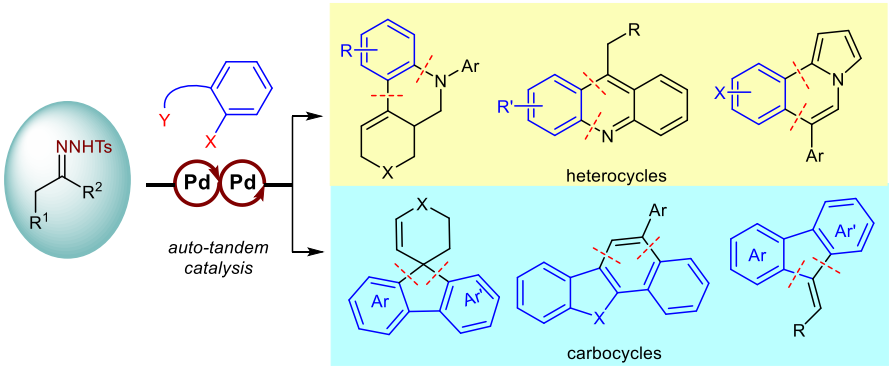

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Abstract The Pd-catalyzed cross-coupling between *N*-tosylhydrazones and organic halides is a powerful method for the creation of C-C bonds. This transformation has been included recently in cascade processes in which the same catalyst promotes various independent catalytic steps, auto-tandem catalysis. This strategy has proved to be very useful for the construction of relatively complex carbo- and heterocyclic structures, as well as for the generation of molecular diversity. The minireview will cover the different Pd-catalyzed auto-tandem reactions involving *N*-tosylhydrazones organized by the bond forming sequence: C-C/C-N and C-C/C-C. Some examples of related tandem reactions leading to acyclic compounds will be also highlighted.

Key words *N*-tosylhydrazones, cross-coupling, auto-tandem catalysis, Palladium, cascade reactions

1. Introduction

Cascade reactions are highly desirable transformations in organic synthesis.[1] In a typical cascade reaction, several bonds are created in one single synthetic operation, allowing for the generation of structural complexity from relatively simple starting materials. Indeed, cascade processes that lead to the formation of carbo- or heterocyclic structures are particularly powerful methodologies.[2] In the context of metal-catalyzed cascade reactions, Pd-catalyzed processes stand as the most versatile and widely studied transformations.[3] A variety of different types of metal-catalyzed cascade processes can be distinguished depending on the role of the catalyst in the different steps of the reaction sequence, and several clasifications have appeared in the literature in the recent years.[4] A quite interesting mode of catalysis in cascade reactions is auto-tandem catalysis.[5] In this type of processes, the same catalyst promotes various independent reactions with separated catalytic cycles. Consequently, an intermediate, formed in the first catalytic step is the substrate of the next catalytic step, and so on (figure 1).

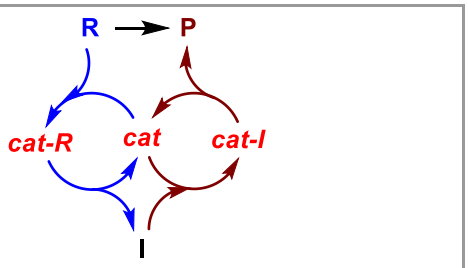


Figure 1 Cartoon representing a two-steps auto-tandem reaction through the formation of the intermediate **I**.

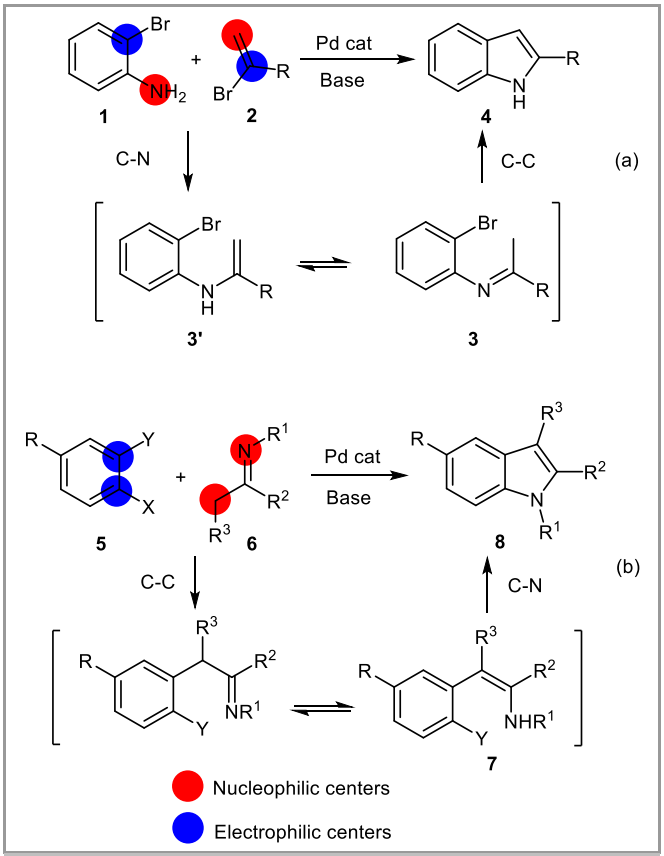
Taking advantage of the high versatility and robustness of Pd-catalysts,[6] many examples have been developed of Pd-catalyzed auto-tandem processes combining different independent C-C and C-N bond forming reactions.[7-9] Some of the obvious advantages of auto-tandem processes are catalyst, solvent and time economy, as well as the avoidance of purification of intermediate products. Additionally, unstable intermediates, that might be difficult to isolate can be engaged in this class of stepwise cascade processes.

Considering Pd-catalyzed cross-couplings as the combination of an electrophilic reagent (the organic halide) with a nucleophile (the organometallic compound, or the alkene in Heck type reactions), two main strategies can be applied for the construction of cyclic molecules through auto-tandem catalyzed cascades: a) Reaction between two molecules featuring one nucleophilic and one electrophilic center each. b) Reaction of a molecule featuring two electrophilic centers (ambidentate

electrophile) with a molecule with two nucleophilic centers (ambidentate nucleophile). Nevertheless, in order to achieve the desired transformation, a careful selection of coupling partners is necessary, so that the proper sequence of events takes place.

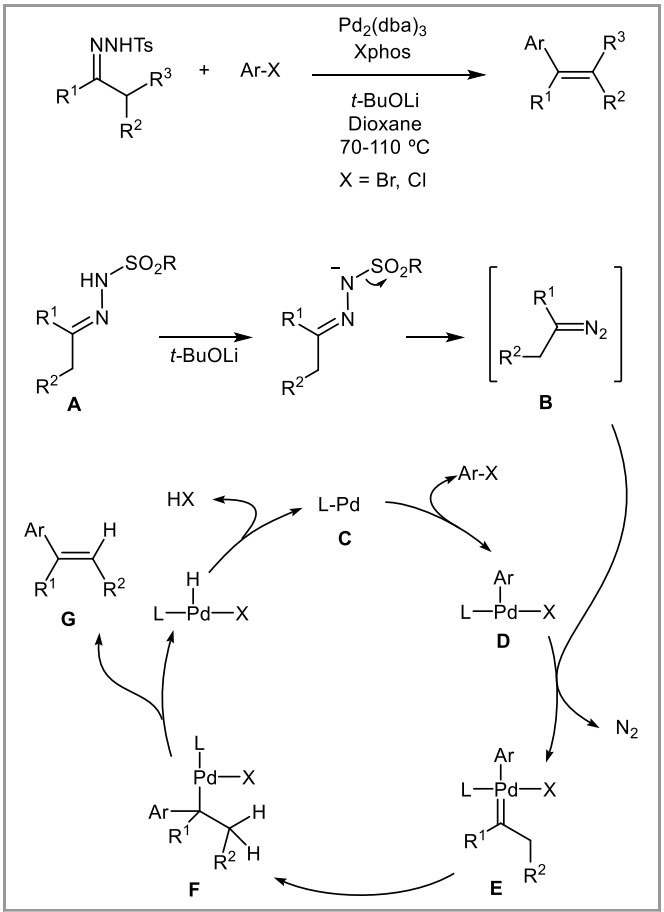
In our research group, we have been interested in the development of Pd-catalyzed auto-tandem sequences oriented to the synthesis of heterocycles. In scheme 1 are presented two different reactions for the synthesis of indoles that illustrate both strategies mentioned above. In equation (a) the indole **4** is constructed by a sequence that implies the Pd-catalyzed *N*-alkenylation of a *o*-haloaniline **1** with an haloalkene **2**, followed by a Pd-catalyzed intramolecular α-arylation of the intermediate imine **3**.[10] Therefore, two reactants both featuring an electrophilic and a nucleophilic center are combined.

The reaction presented in equation (b) constitutes an example of the second approach. This time the construction of the indole **8** is achieved by reaction of 1,2-dihalobenzene derivatives **5** (ambidentate electrophile) and ketimines **6** (ambidentate nucleophiles).[11] Again, two Pd-catalyzed processes occur consecutively promoted by the same catalytic system: the intermolecular α-arylation of the imine and the intramolecular C-N bond forming reaction on the intermediate enamine **7**.



Scheme 1 Examples of Pd-catalyzed auto-tandem reactions leading to the synthesis of indoles.

One type of Pd-catalyzed C-C bond forming reaction that resembles classical cross-couplings are the Pd-catalyzed reactions between *N*-sulfonylhydrazones and organic halides (Scheme 2). This transformation, which was initially reported by our group in 2007,[12] leads to the obtention of alkenes, with formation of a Csp^2-Csp^2 bond. The mechanism accepted for this cross-coupling is initiated by the oxidative addition of the aryl halide to the Pd(0) complex **C**. The arylpalladium complex **D** reacts with the diazo compound **B** generated by the base-promoted thermal decomposition of the tosylhydrazone **A**, leading to a Pd-carbene complex **E**. The migratory insertion of the carbene ligand into the Pd-Ar bond generates a benzylpalladium complex **F**, which upon β-hydride elimination releases the coupling product **G** and regenerates the Pd(0) catalyst.[13] Interestingly, this catalytic cycle features a differential step, when compared with Heck reactions and organometallic-based cross couplings: the formation of the Pd-carbene and the migratory insertion of the carbene ligand. Moreover, by comparison to conventional cross-coupling reactions, the *N*-tosylhydrazone could be identified as the nucleophilic component that reacts with the electrophilic partner, the aryl halide.



Scheme 2 Pd-catalyzed cross-coupling reaction of *N*-tosylhydrazones with aryl halides and mechanism proposed.

Some key features, that have been fundamental in the remarkable development of the new chemistry of *N*-sulfonylhydrazones were already present in this seminal publication.[12a] On one side the wide scope and synthetic potential of this transformation was clearly highlighted. On the other, this paper demonstrated that *N*-sulfonylhydrazones could be employed as diazo compound sources without any structural restriction, as the typical decomposition via the Bamford-Stevens reaction, was much slower than the Pd-catalyzed cross-coupling.

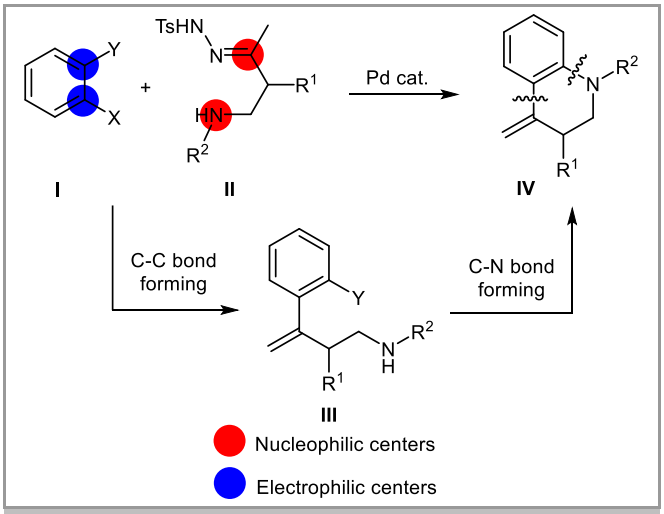
Indeed, since the appearance of the initial publications, this new cross-coupling has found remarkable applications in organic synthesis, and has stimulated considerable research by many groups. As a result, an ample variety of Pd-catalyzed reactions

based on the Pd-carbene formation/carbene migratory insertion sequence have been uncovered in the last years. Several reviews have appeared that deal with the applications of the Pd-catalyzed cross-coupling reactions employing *N*-sulfonylhydrazones, which are strongly recommended to the interested reader.[14] This minireview will be restricted to the application of this reaction in Pd-catalyzed auto-tandem cascades, with special attention on carbo- and heterocyclization processes. Some related examples of assisted tandem catalysis will be also discussed. The presentation of the different processes has been organized attending to the bonds that are formed in the cascade processes: (1) C-C/C-N; (2) C-C/C-C; then some examples of tandem reactions which do not involve cyclization processes (3) will be shown.

2. Auto-tandem C-C/C-N Bond-Forming Reactions.

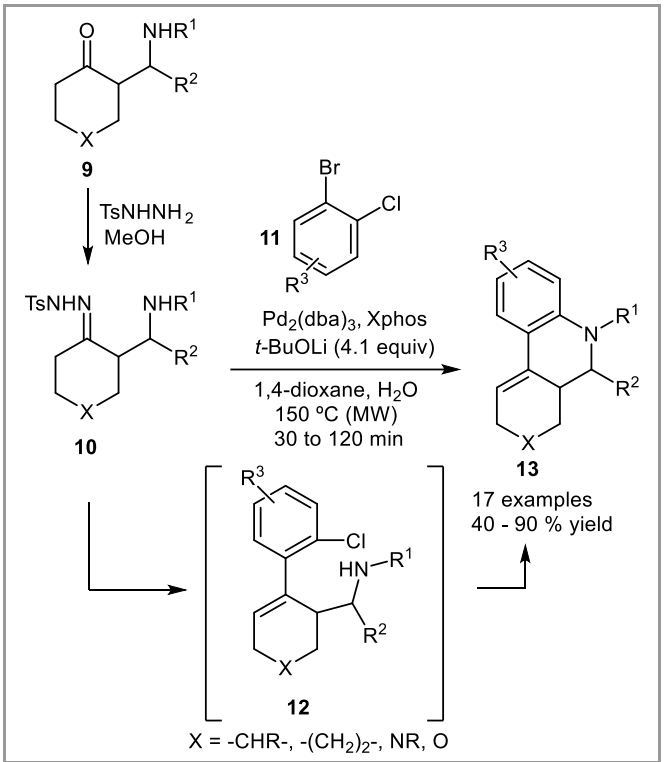
2.1 Synthesis of tetrahydrophenanthridines or tetrahydroquinolines by N-tosylhydrazone arylation followed by intramolecular amination.

The first example of a Pd-catalyzed auto-tandem reaction employing *N*-tosylhydrazones was reported by our research group in 2011 and involved the sequencial formation of a C-C and a C-N bond promoted by the same Pd-catalyst.[15] In a similar way as the synthesis of indoles described in equation b of Scheme 1, a possible cascade reaction was envisioned by combining 1,2-dihalobenzene derivatives **I** with a *N*-tosylhydrazone **II** featuring an additional nucleophilic position. Thus, the *N*-tosylhydrazones **II** derived from β-aminoketones were identified as potential ambidentate nucleophiles for a sequential C-C/C-N cyclization (Scheme 3). Following this idea, a new Pd-catalyzed cascade was developed, which consisted in the C-C cross-coupling reaction of the *N*-tosylhydrazone **II** with the 1,2-dihalogenated aromatic system **I** (arylation), followed by an intramolecular C-N bond-forming reaction on the intermediate **III** (amination). This approach would lead to quinoline derivatives **IV**.



Scheme 3 Initial proposal for a Pd-catalyzed C-C/C-N auto-tandem cascade with *N*-tosylhydrazones.

The *N*-tosylhydrazones **10** obtained from Mannich adducts **9** were selected as very convenient substrates for the process. The reaction with *o*-bromochlorobenzene derivatives **11** turned out to be quite challenging, and an exhaustive experimentation was required to find proper reaction conditions for the auto-tandem process. The optimal conditions found included the employment of a Pd/Xphos catalytic system (Figure 2), with *t*-BuOLi as base and under microwave irradiation at 150 °C. The presence of a small amount of water was also important to drive the reaction to completion. This process afforded tetrahydrophenanthridine derivatives **13** in one single synthetic step (Scheme 4). The process could be conducted from the isolated *N*-tosylhydrazone **10** or directly from the aminoketone **9** in a *one-pot* process that comprises the formation of the tosylhydrazone by condensation of the ketone with the *N*-tosylhydrazide followed by the Pd-catalyzed cascade.



Scheme 4 Synthesis of tetrahydrophenanthridines **13** by Pd-catalyzed auto-tandem reaction of β-amino-*N*-tosylhydrazones **10** and *o*-bromochlorobenzene derivatives **11**.

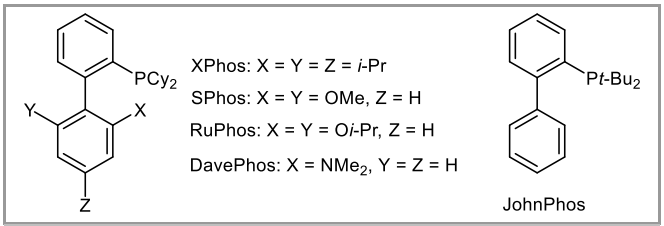
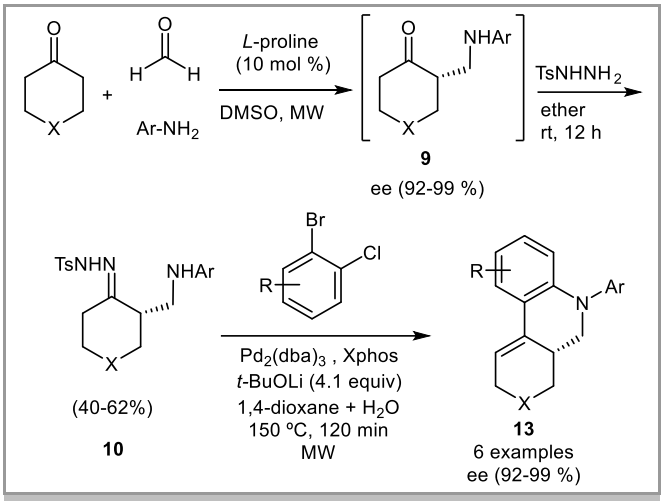


Figure 2 Structures of the biphenyl phosphine ligands employed in most of the auto-tandem catalyzed reactions described along the review.

Some aspects are noteworthy in this reaction. First, it is established that the cross-coupling with the *N*-tosylhydrazone takes place preferentially than the Pd-catalyzed amination reaction. Second, when the reaction is conducted with substituted 1-bromo-2-chlorobenzenes, the reaction takes place in a regioselective manner to furnish the product in which the C-C bond is formed on the C-Br more reactive position.

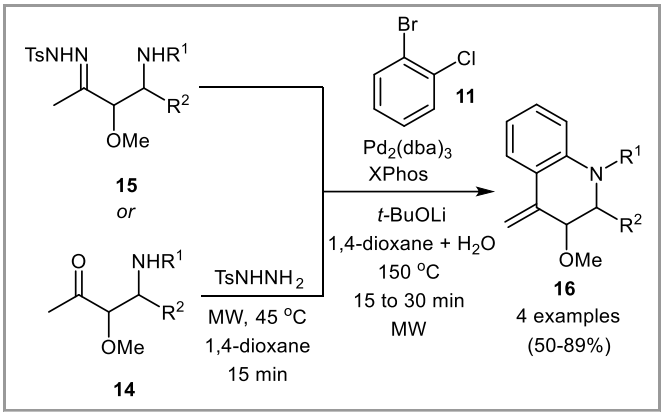
Moreover, the β-aminoketones **9** can be prepared in enantiomerically enriched form through asymmetric organocatalyzed Mannich reaction.[16] Thus, an

organocatalysis/Pd-catalysis sequence was successfully designed to prepare enantiomerically enriched phenanthridines **13** with high ee (92-99%) (Scheme 5). It is important to point out that no erosion of the enantiomeric purity was observed during the whole sequence, that comprises formation of the *N*-tosylhydrazone **10** and the Pd-catalyzed cascade.



Scheme 5 Synthesis of enantiomerically enriched tetrahydrophenanthridines **13** by a combination of organocatalysis and a Pd-catalyzed auto-tandem C-C/C-N coupling reaction .

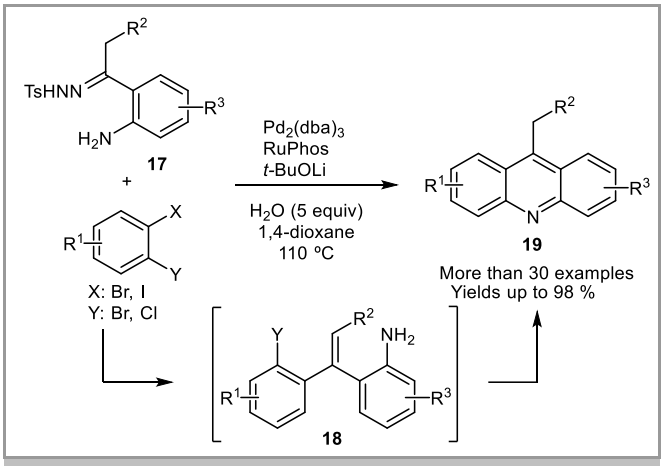
Furthermore, the reaction was extended to β-aminoketones derived from acyclic ketones **14** affording the corresponding tetrahydroquinoline derivatives **16** with retention of the diastereomeric ratio. It is important to point out that in this case the reactions require shorter times to reach complete conversion, and tolerate the presence of electron-withdrawing substituents on the nitrogen atom (Scheme 6).



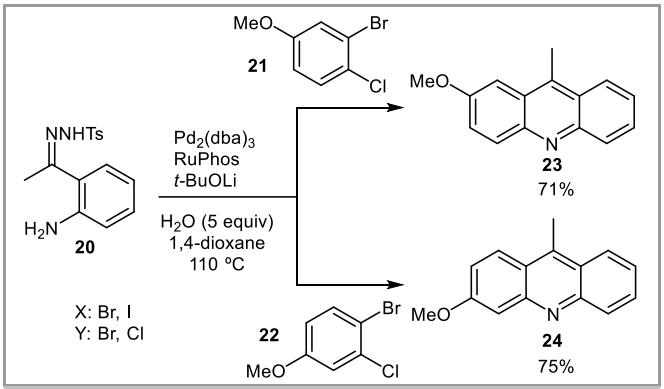
Scheme 6 Synthesis of substituted quinoline derivatives **16** by reaction of β-aminoketones **14** with *o*-bromochlorobenzene.

2.2. Synthesis of acridines by N-tosylhydrazone arylation followed by intramolecular amination.

This first example of auto-tandem Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones, opened the door to the development of other appealing cascade transformations based on the same principle. In this way, in 2012, Wang and co-workers reported a facile and convergent Pd-catalyzed synthesis of acridines **19** from *o*-dihalobenzenes and *N*-tosylhydrazones derived of *o*-acylanilines **17.** A single Pd-catalyst formed from $Pd_2(dba)_3$ and the biaryl ligand RuPhos promoted the two independent reaction steps (Scheme 7).[17] This methodology proved to be very general regarding the substitution of both coupling partners. Like in the examples above, the C-C bond forming reaction with the *N*-tosylhydrazone is formed preferentially than the aryl amination of the primary amines to give the intermediate 1,1-diarylalkene **18**, which then undergoes the intramolecular amination. Thus, employing appropriate *o*-dihalobenzene derivatives the regiochemistry of the cyclization can be controlled. An illustration of this concept is shown in Scheme 8, by the synthesis of the isomeric **23** and **24** by reaction of the tosylhydrazone **20** with the regioisomeric dihaloarenes **21** and **22**.



Scheme 7 Synthesis of acridines **19** by reaction of *o*-acylaniline tosylhydrazones **17** and *o*-dihalobenzene derivatives.



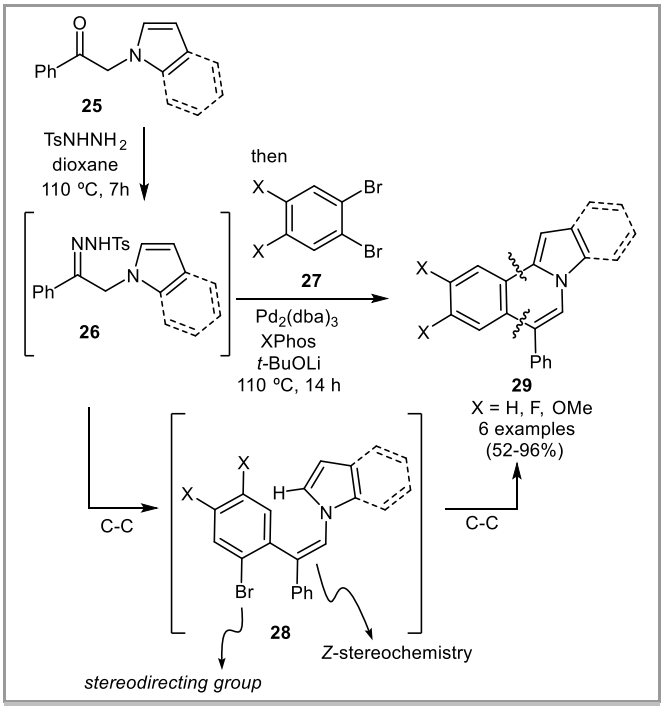
Scheme 8 Regioselectivity in the synthesis of substituted acridines **23** and **24**.

3. Auto-tandem C-C/C-C Bond-Forming Reactions.

3.1 Synthesis of indolo- and pyrrolo[2,1-a]isoquinolines by N-tosylhydrazone arylation followed by intramolecular C-H arylation

In 2013, the first C-C/C-C bond forming auto-tandem Pd-catalyzed processes involving *N*-tosylhydrazones was uncovered.[18] The cascade cyclization consisted in the reaction between α-*N*-indoleacetophenone **25** as carbonyl compound, *N*-tosylhydrazide, and 1,2-dibromobenzene derivatives **27** (Scheme 9). The elemental processes involved in the cascade are the following. In first place, the tosylhydrazone **26** is formed by condensation of the carbonyl compound and *N*-tosylhydrazide. Then, the *o*-dihalogenated aromatic compound **27**, the Pd-source, the ligand, and the base are added to the reaction mixture, promoting the arylation of the *N*-tosylhydrazone to give the intermediate trisubstituted alkene **28**. Subsequently, and

promoted by the same Pd-catalyst, the C-H arylation occurs to give the final polyheterocycles **29** through a process that would likely involve oxidative addition, carbopalladation of the double bond of the azole, and *β*-hydride elimination. For the C-H arylation to occur is essential that the two substituents that are going to be connected are in a *cis* relationship in the intermediate **28**. Importantly, it had been previously observed the stereodirecting effect exerted by *o*-substituted aromatic rings in the synthesis of trisubstituted alkenes.[19] Indeed, due to the presence of the halogen in the *o*-position, the *o*-substituted aromatic rings and the azole are in a *cis* arrangement in **28**, and therefore properly preorganized for the Pd-catalyzed C-H functionalization. This methodology was employed for the preparation of a variety of indolo- and pyrrolo[2,1-*a*]isoquinolines **29** by starting from *N*-indolyl- or *N*-pyrrolylacetophenones **25** respectively.

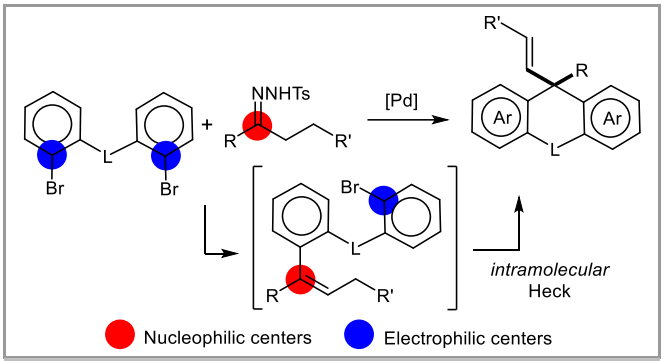


Scheme 9 First C-C/C-C Pd-catalyzed auto-tandem cascade employing *N*-tosylhydrazones. Preparation of indolo- and pyrrolo[2,1-*a*]isoquinolines **29**.

3.2. Synthesis π-extended conjugated polycarbo- and heterocycles by N-tosylhydrazone arylation followed by intramolecular Heck-type reaction.

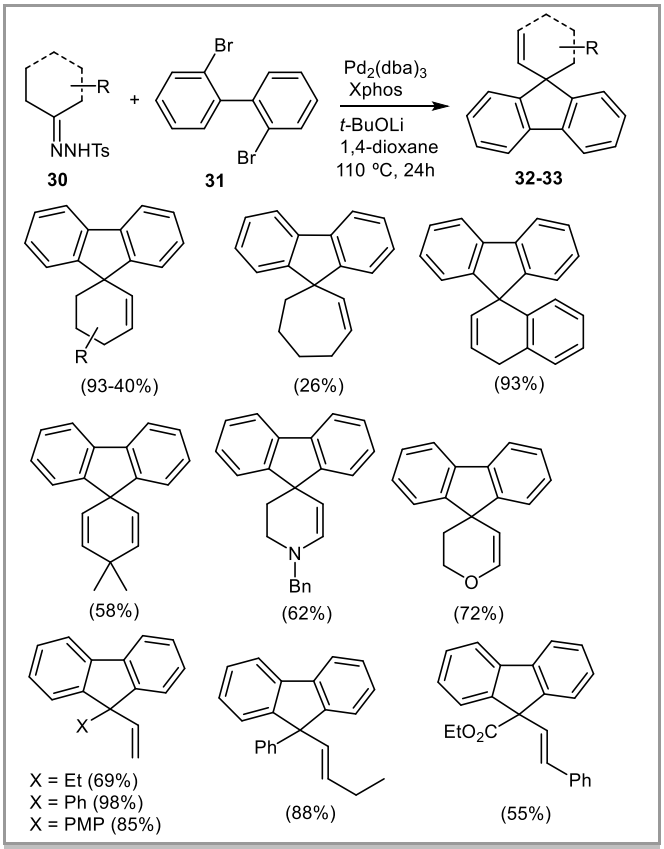
All the auto-tandem processes presented so far follow the pattern introduced in scheme 3, meaning that all reacting functional groups are already present in the starting coupling partners. In particular, for cascade reactions leading to cyclic compounds, two bifunctional reactive partners are required. Continuing with our interest in the Pd-catalyzed cross-coupling reactions employing *N*-tosylhydrazones, in 2014 our research group envisioned a new auto-tandem C-C/C-C process with a different approach.[20] Therefore, the new double bond formed in the first Pd-catalyzed cross-coupling reaction would participate in the second Pd-catalyzed process, an intramolecular Heck-type reaction, to provide carbocyclic systems (Scheme 10). In this manner, *N*-tosylhydrazones with no additional functionalization could be employed as partners for the carbocyclization process.

This strategy was initially explored employing 2,2'-dibromobiphenyl **31** and *N*-tosylhydrazones **30** derived from cyclic ketones (scheme 11). Under the appropriate reaction conditions, the cascade process proceeded as expected leading to the spirofluorenes **32**.



Scheme 10 New approach for Pd-catalyzed auto-tandem carbocyclizations employing *N*-tosylhydrazones without additional functionalization.

The reaction featured wide scope regarding the structure of the *N*-tosylhydrazone. A variety of cyclic tosylhydrazones were compatible with the reaction, including those derived from substituted cyclohexanones, cycloheptanone, 4-piperidone and 4-oxanone, and leading to the corresponding spirofluorenes **32**. Moreover, tosylhydrazones derived from acyclic ketones could be also used under the same reaction conditions providing a new synthesis of functionalized 9,9-disubstituted fluorenes **33**.



Scheme 11 Synthesis of spirofluorenes **32** and 9,9-disubstituted fluorenes **33** by Pd-catalyzed auto-tandem reaction of 2,2'-dibromobiphenyl and *N*-tosylhydrazones.

Furthermore, this methodology can be applied to the synthesis of structurally diverse fluorene derivatives using substituted dibrominated scaffolds. It is important to notice that the auto-tandem reaction affords the desired substituted spirofluorenes either if halogen or amino groups are present in the starting material, which allows the synthesis of further elaborated structures with interesting photophysical properties (Figure 3).

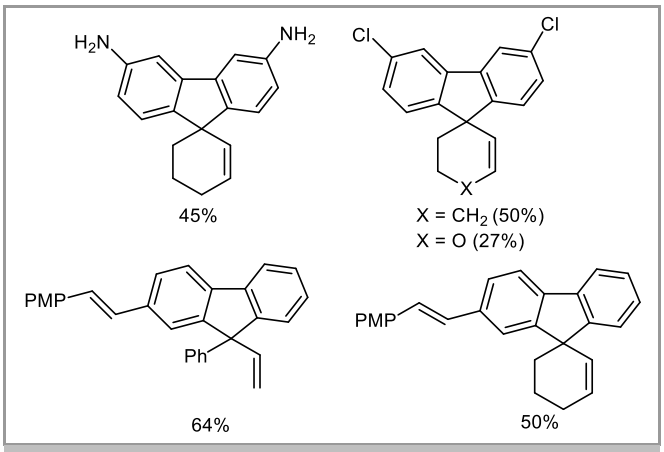
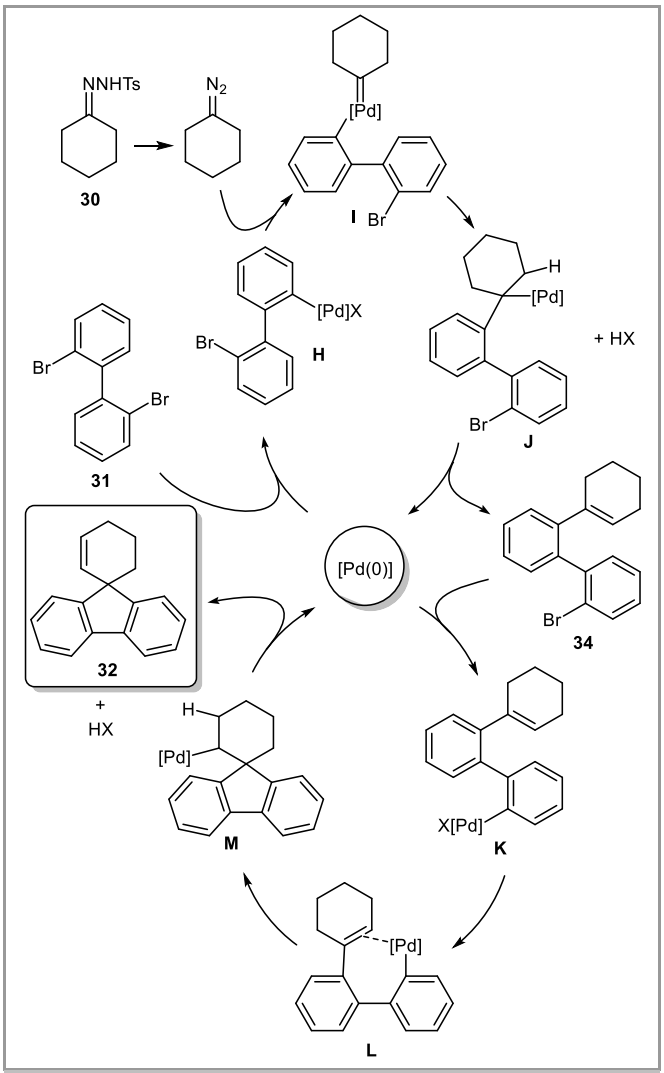


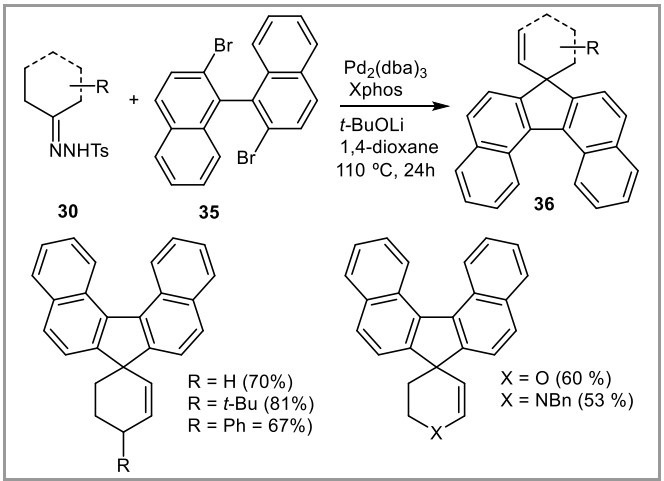
Figure 3. Selected examples of symmetrically- and unsymmetrically substituted fluorenes synthesized

The formation of the spirofluorenes **32** can be explained by considering two independent processes catalyzed by the same Pd species (Scheme 12). The first catalytic cycle involves the formation of the alkene intermediate **34** through oxidative addition of the Pd(0) species to one of the C-Br bonds on the 2,2'-dibromobiphenyl **31**, to form arylpalladium complex **H**, generation of the Pd-carbene intermediate **I**, migratory insertion to give the benzylpalladium complex **J** and β-hydride elimination to release the intermediate **34**. Then, **34** enters the second catalytic cycle that consists on an intramolecular Heck reaction, which leads to the spirocycle **32** after the second β-hydride elimination from the alkylpalladium complex **M**. It is clear that the intramolecular cyclization must be favored against the incorporation of a second molecule of tosylhydrazone from the intermediate **34**. This is the case observed for 5-*exo*-trig and for 6-*exo*-trig cyclizations, but it failed for reactions involving the formation of seven-membered rings by a 7-*exo*-trig cyclization. It is important to point out that for these auto-tandem processes to be successful, the *N*-tosylhydrazone should feature hydrogen atoms that could be eliminated at both the α and the β positions.

The versatility of this auto-tandem process was explored by considering a variety of dibrominated scaffolds.[21] Interestingly, the process is very efficient for the preparation of spirodibenzofluorenes **36** from 2,2'-dibromobinaphthyl **35** (Scheme 13). Again, both carbo- and heterocyclic tosylhydrazones were compatible with the cascade reaction. These new structures are interesting because of their extended π-conjugation. The presence of the five-membered ring enforces a very rigid structure that enables extended conjugation between the two naphthalene moieties. A study of their UV/Vis absorption and fluorescence spectra in CH_2Cl_2 showed a π–π* transitions about λ_{max} = 353-370 nm, showing a large bathochromic shift when compared with the 1,1'-binaphthyl (λ_{max} = 280 nm), and emission band at about 403 nm with high quantum yields.



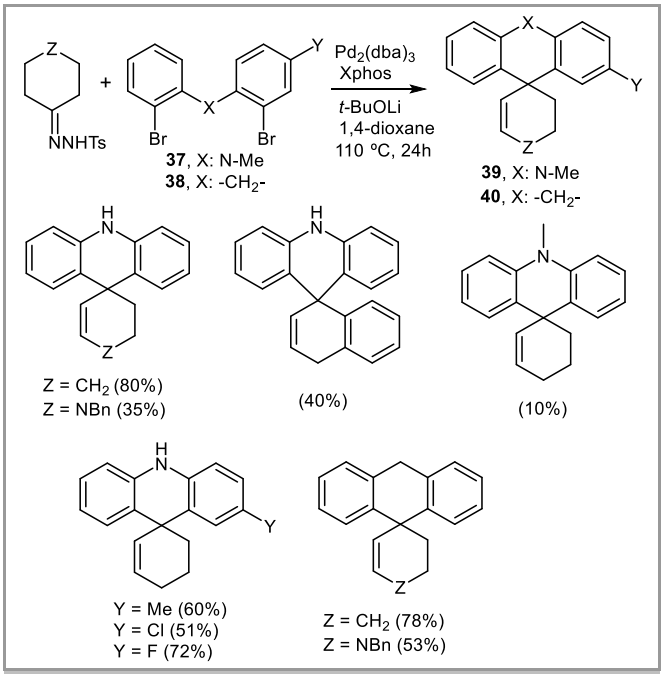
Scheme 12. Mechanism proposed for the C-C/C-C Pd-catalyzed auto-tandem synthesis of spirofluorenes.



Scheme 13 Synthesis of spirobenzofluorenes **36** by Pd-catalyzed auto-tandem reaction of 2,2'-dibromobinaphthyl and cyclic *N*-tosylhydrazones.

The auto-tandem Pd-catalyzed cascade was also examined employing bis(2-bromophenyl)amines **37**, and bis(2-bromophenyl)methane **38**. These reactions were expected to afford the corresponding spiro compounds featuring a central six-membered ring through a 6-*exo*-trig cyclization. (Scheme 14). The auto-tandem reaction under these conditions proceeded successfully with the N-H free anilines, leading

to the expected spirodihydroacridines **39**, however, the *N*-methylated analogue, showed a higher tendency to cyclize to the carbazole. Additionally, the reaction with bis(2-bromophenyl)methane provided the spirodihydroanthracenes **40** in good yields.

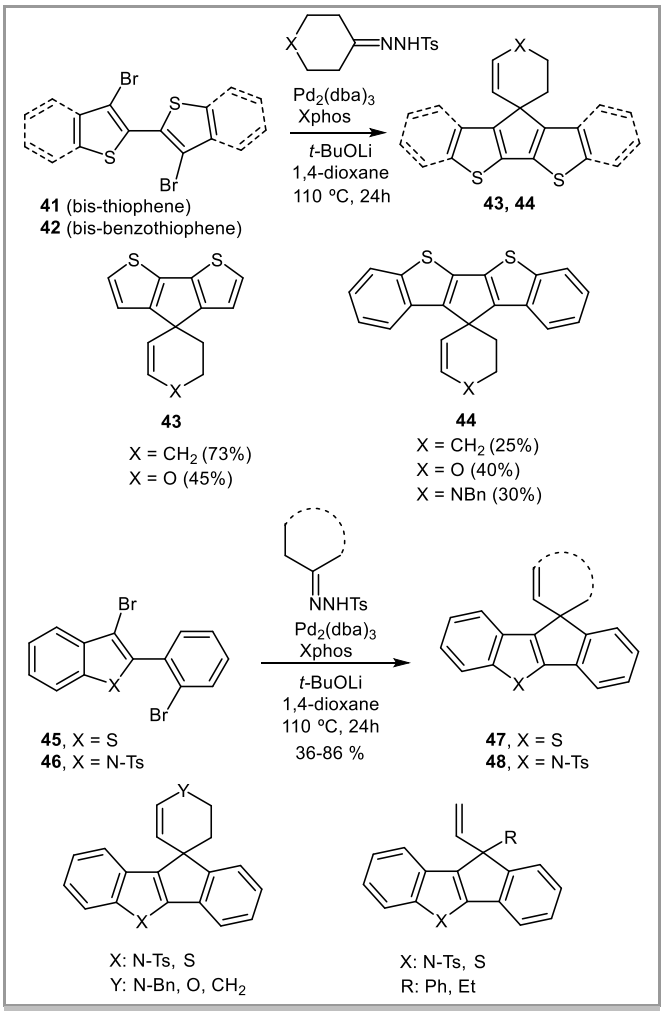


Scheme 14 Synthesis of spirodihydroacridines **39** and spirodihydroanthracenes **40**

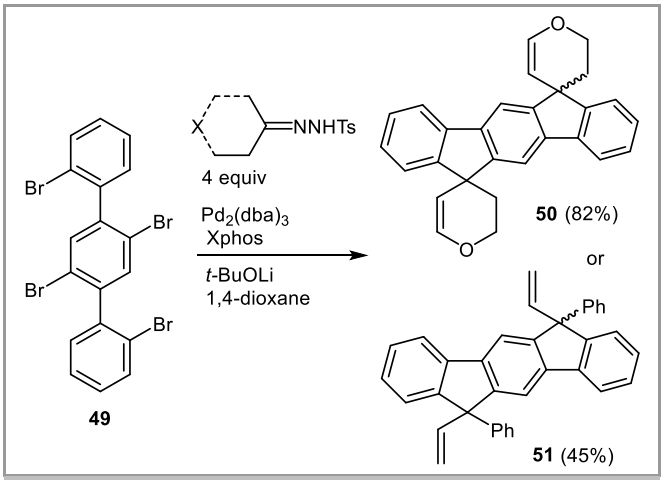
Furthermore, the robustness of this cascade transformation was demonstrated with the employment of more elaborated heterocyclic scaffolds that led to heterocyclic structures of interest in medicinal chemistry as well as in the development of molecules with optoelectronic properties. Thus, thiophene and benzothiophene derivatives **41** and **42,** led to symmetrical polycyclic structures of spirodithiophenes **43** and **44** respectively, which are interesting structures with potential applications as monomers in conductive polymers (Scheme 15). Moreover, 3-bromo-2-(2-bromophenyl)-benzothiophene **45** and 3-bromo-2-(2-bromophenyl)indole **46** led to unsymmetrical previously unknown polycyclic structures **47** and **48** respectively (scheme 15).

The Pd-catalyzed auto-tandem cyclization was also applied for the construction of other fluorene-based structures with more π-extended conjugation, employing appropriately designed tetrabrominated precursors. In these cases, two independent auto-tandem reactions took place on the same molecule, giving rise to new flat polyaromatic structures. Thus, the reaction of tetrabromide **49** with both cyclic or acyclic *N*-tosylhydrazones proceeded successfully, affording 6,12-dihydroindeno[1,2-*b*]fluorenes **50** and **51** featuring an all-carbon ladderane structure (Scheme 16).

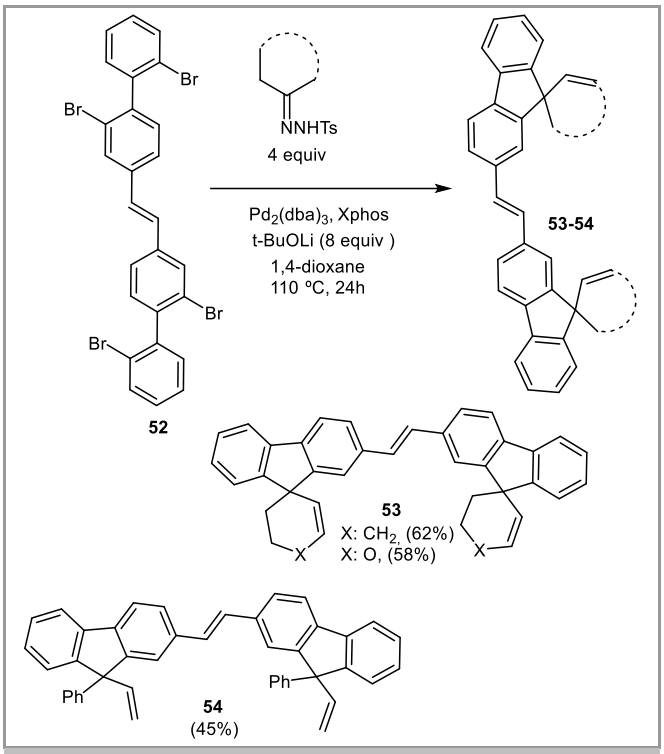
Similarly, the cascade reaction of the tetrabromide derivative **52** with an excess of the appropiate *N*-tosylhydrazones led to the new π-extended structures **53** and **54**, which include the fluorene and vinylphenylene fragments, common moieties in functional organic materials (Scheme 17). Again, both cyclic and acyclic tosylhydrazones can be employed in the coupling reaction. These molecules, which feature a very long conjugated structure, are strong fluorescence blue-emitters in CH_2Cl_2 solution, with sharp emission bands at 399-423 nm and very high quantum yields (ϕ = 68-100), showing the potential of this methodology in the development of molecules with interesting optoelectronic properties.



Scheme 15 Pd-catalyzed auto-tandem cyclizations for the synthesis of structurally diverse polyheterocyclic and spirocyclic structures .



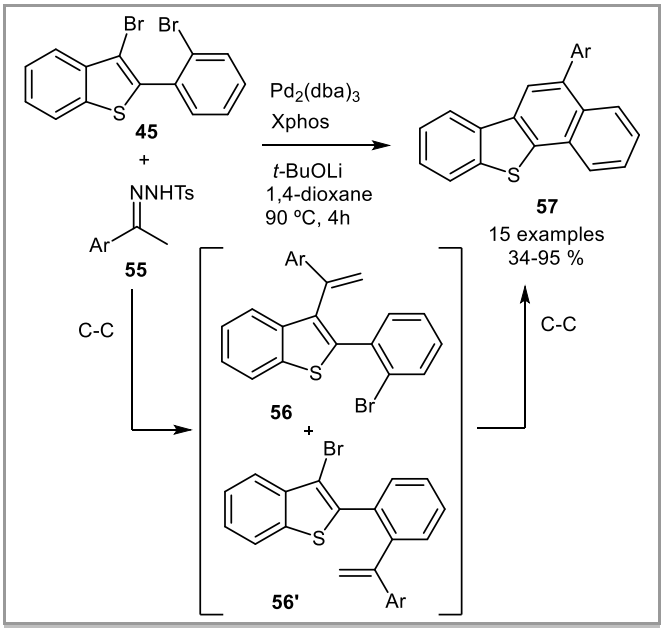
Scheme 16 Pd-catalyzed auto-tandem cyclizations for the synthesis of all-carbon ladderane structures.



Scheme 17 Double auto-tandem cyclizations for the synthesis of fluorene-vinylphenylene hybrids **53** and **54**.

3.3. Synthesis naphtho-fused heterocycles by N-tosylhydrazone arylation followed by a "formal" 6-endo-trig cyclization.

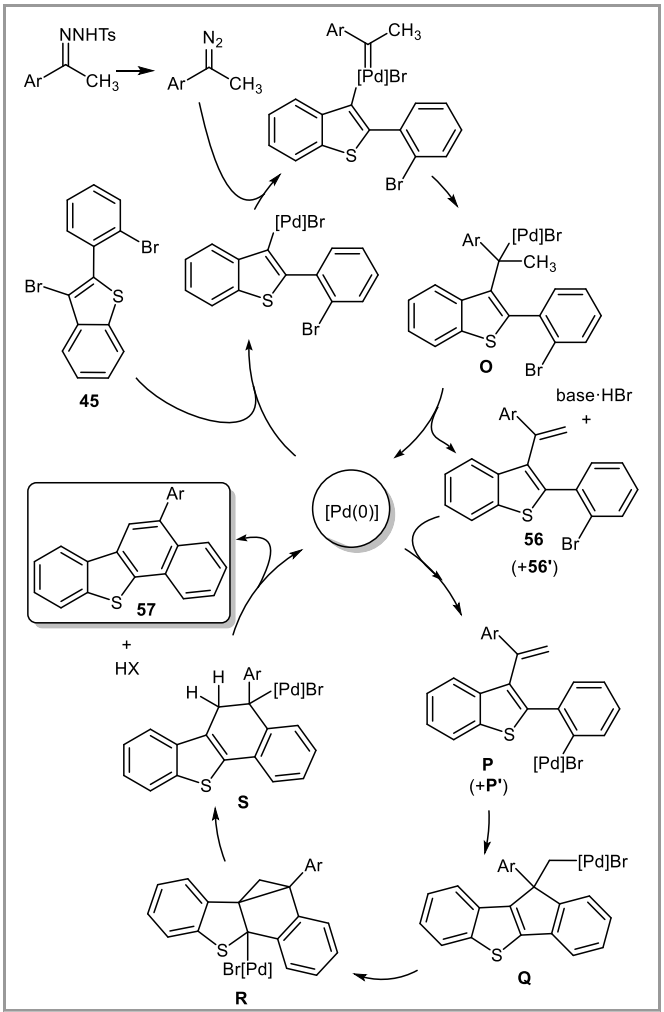
One year later, and closely related with the chemistry described above, Langer and co-workers reported a novel Pd-catalyzed auto-tandem process which involves the cross-coupling reaction of the the dibromide **45** with *N*-tosylhydrazones **55** derived from acetophenones to afford benzo[*b*]naphtho[2,1-*d*]thiophenes **57** (Scheme 18).[22] In this case, and unlike the reactions described in scheme 15, benzonaphthothiophenes **57** were obtained, instead of the benzoindenothiophenes **47,** due to lack of a hydrogen atom on the β-position in the starting hydrazone.



Scheme 18 Pd-catalyzed auto-tandem synthesis of benzo[*b*]naphtho[2,1-*d*]thiophenes **57**.

Interestingly, the two intermediates **56** and **56'** could be detected, since the first coupling of *N*-tosylhydrazone with **45** could take place at either C-Br bond. However, both intermediates give rise to a single regioisomer of the final compound **57**, excluding the possibility of a direct 6-*endo*-trig cyclization.

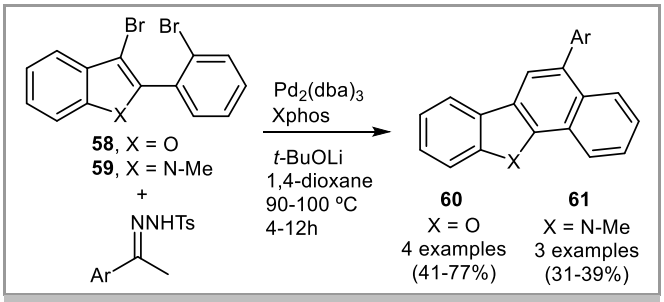
Accordingly, the authors propose the following mechanism to explain the formation of the benzo[*b*]naphtho[2,1-*d*]thiophenes (Scheme 19). First, the typical catalytic cycle of the arylation of *N*-tosylhydrazones takes place to give alkenes **56** and **56'** (not shown). Then, a second oxidative addition results in the formation of a new active palladium complexes **P** and **P'**. The intramolecular carbopalladation of **P**, via 5-*exo*-trig cyclization affords the fluorene intermediate **Q**. However, in this case, and due to the absence of β-hydrogens, no β-hydride elimination is possible. Therefore, this system evolves through a 3-*exo*-trig cyclization to give cyclopropane intermediate **R**. Then, ring opening of cyclopropane leads to the more stable palladium complex **S**, that now can experiment the second β-hydride elimination, to release the cyclization product **57**. Noteworthy, **56** and **56'** give rise to the same intermediate **Q** upon carbopalladation via **P** and **P'**. Additionally, the 3-*exo*-trig cyclization takes place only by carbopalladation of the more reactive double bond of the heterocycle in **Q**, and therefore one single regioisomer **57** is obtained.



Scheme 19 Mechanism proposes for the Pd-catalyzed cascade reaction leading to benzo[*b*]naphtho[2,1-*d*]thiophenes **57**

The cascade process could also be applied to the analogous benzofuran **58** and indole **59** derivatives to give the corresponding naphtho[1,2-*b*]benzofurans **60** and

benzo[*a*]carbazoles **61** respectively (scheme 20). Higher reaction times and temperatures were required and lower yields were obtained in some cases, probably due to the more difficult 3-*exo*-trig cyclization on these systems. Moreover, the reactions employing monocyclic aromatic derivatives, such as 2,2'dibromobiphenyl, 3-bromo-2-(2-bromophenylpyridine) and 3-bromo-2-(2-bromophenyl)-thiophene did not afford the cyclized products, but the alkenes derived from the coupling reaction with the *N*-tosylhydrazone were isolated, as the 3-*exo*-trig cyclization was highly disfavoured.

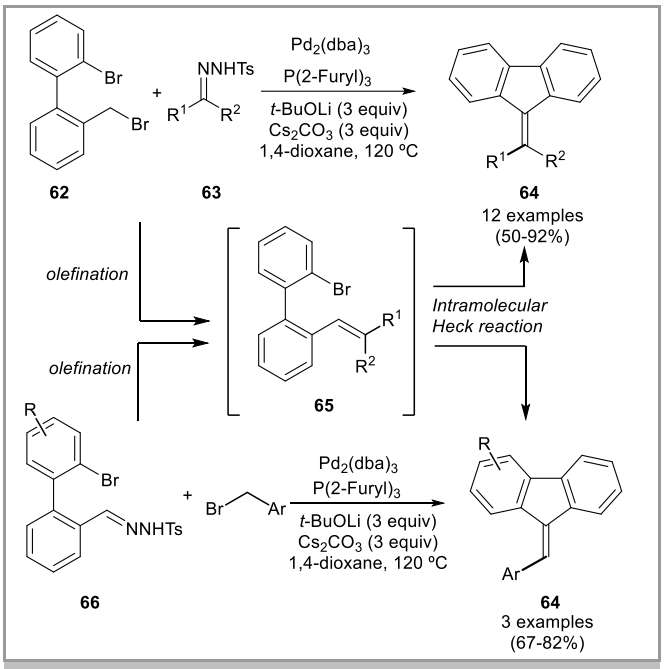


Scheme 20 Synthesis of naphtha[1,2-*b*]benzofurans **60** and benzo[*a*]carbazoles **61** by a Pd-catalyzed C-C/C-C auto-tandem cascade

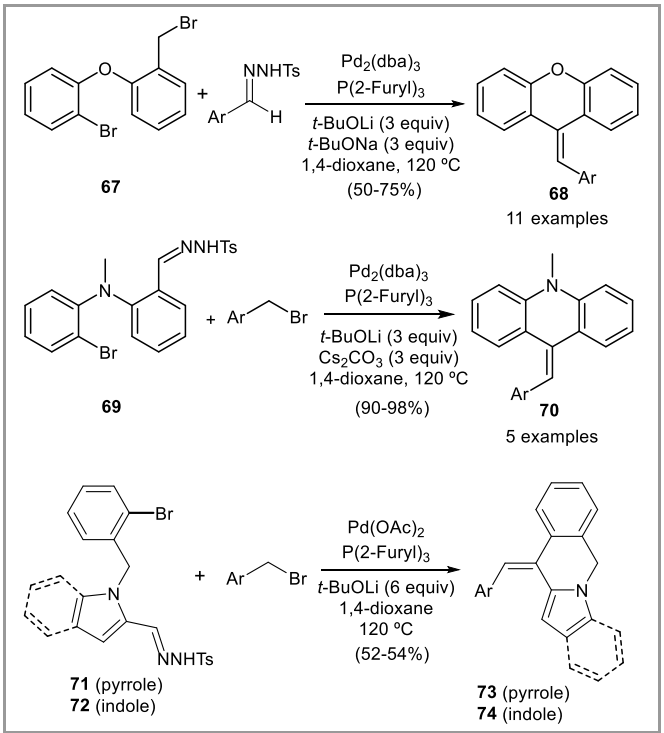
3.4. Pd-catalyzed auto-tandem reactions by N-tosylhydrazone olefinations with benzyl bromides followed by intramolecular Heck reactions.

Very recently, and as a continuation of the work described above, a different C-C/C-C auto-tandem cascade was developed taking advantage of the Pd-catalyzed olefination of *N*-tosylhydrazones with benzyl bromides.[23] Thus, the Pd-catalyzed reaction between aromatic tosylhydrazones **63** and 2-bromo-2'-(bromomethyl)-1,1'-biphenyl **62** led to 9-methylene-9-fluorenes **64** through the cross-coupling/intramolecular Heck reaction sequence (scheme 21).[24] Employing the Pd(0)/P(2-Furyl)$_3$ catalytic system, the reaction is started by the benzylic bromide, leading to the intermediate stilbene derivative **65**, that undergoes the 5-*exo*-trig cyclization. Thus, in this cascade reaction a C-C single bond and a C=C double bond are formed on the same carbon atom. Interestingly, the same cascade reaction can be achieved by exchanging the arrangement of the functional groups, employing the *N*-tosylhydrazone **66** of 2'-bromo-[1,1'-biphenyl]-2-carbaldehyde and benzylbromides. The initial cross-coupling arrives at same intermediate stilbene **65**, which evolves again to the cyclization product **64**.

Similar Pd-catalyzed cascades were developed, employing both possible arrangements of functionalities, for the synthesis of 9-benzylidene-9*H*-xantenes **68** and 9-methylene-9,10-dihydroacridines **70** through olefination/6-*exo*-trig cyclization sequences from appropriate acyclic diaryl ether **67** or *N*-arylaniline **69** precursors respectively (scheme 22). Additionally, and taking advantage of the very simple preparation of the starting materials **71** and **72**, the same approach was applied for the synthesis of pyrroloisoquinoline **73** and indoloisoquinoline **74** derivatives (scheme 22). It should be pointed that although the nature of the catalytic system is essentially the same for the reactions of the different scaffolds, the nature of the base has great importance, and in most cases combination of two bases had to be employed.



Scheme 21 Synthesis of 9-methylene-9*H*-fluorenes **64** by Pd-catalyzed auto-tandem C-C/C-C bond forming cascades.



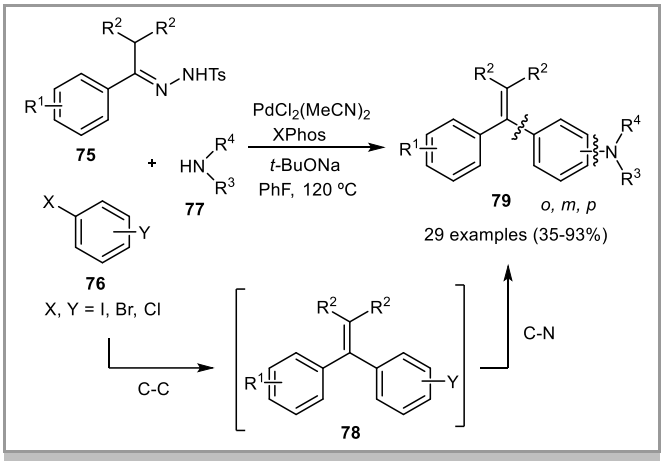
Scheme 22 Synthesis of polyheterocyclic condensed systems by Pd-catalyzed auto-tandem cascades with formation of two bonds on the same carbon atom.

4. Tandem reactions for the synthesis of linear molecules

The Pd-catalyzed cross-coupling with *N*-sulfonylhydrazones has been also included in various tandem and multicomponents reactions oriented to the synthesis of linear molecules, and therefore not involving cyclization processes. Due to their mechanistic similarities and synthetic interest, we have included these cascade processes in this last section.

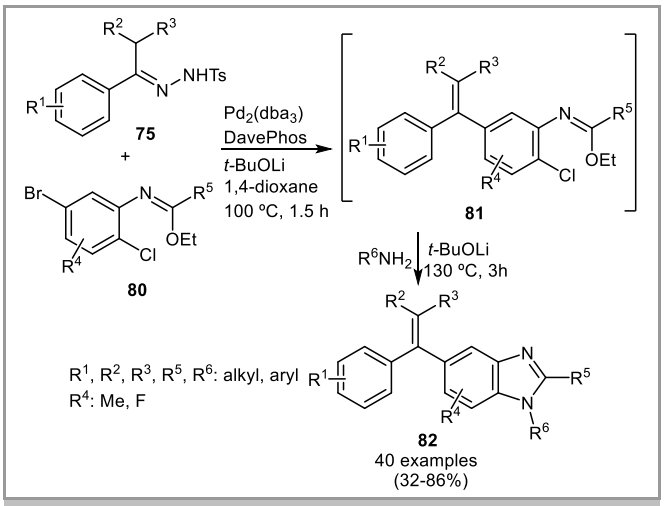
4.1. Autotandem C-C/C-N bond forming reactions.

The efficient construction of complex molecules from simple precursors in a single step without isolation of intermediates is an ongoing challenge in organic synthesis, and one efficient strategy are multicomponents reactions (MCRs). In this context, the possibility of combining the palladium-catalyzed auto-tandem strategy with MCRs is particularly attractive. In 2013, Alami and co-workers reported a novel Pd-catalyzed auto-tandem three-components assembly between *N*-tosylhydrazones **75**, dihaloarenes **76** and primary or secondary amines **77**, involving consecutive C-C and C-N bond forming reactions.[25] This cascade reaction produces amino-substituted 1,1'-diarylethylenes **79** (Scheme 23). Moreover, the reaction can be conducted one-pot directly from the carbonyl compound, avoiding the tosylhydrazone isolation. The multicomponents reaction takes place through the initial formation of 1,1-diarylethylene **78**, followed by the intermolecular Buchwald-Hartwig amination. Once again, the success of the cascade process relies on the ability of the *N*-tosylhydrazone to undergo arylation in the presence of an amine, and on the capacity of the same Pd-catalyst to promote the two different transformations. From a synthetic perspective, the availability of amines and dihaloarenes makes this MCR approach a practical methodology for the generation of large combinatorial chemical libraries for the synthesis and development of new medicinal agents.



Scheme 23 Three-components synthesis of aminosubstituted-1,1-diarylethylenes **79**.

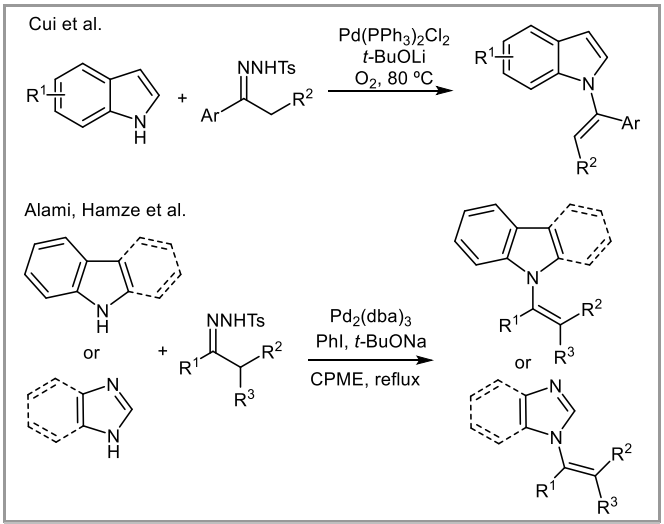
More recently, the same group disclosed a related one-pot reaction oriented to the synthesis of 5-(1-arylvinyl)-1*H*-benzimidazoles (Scheme 24).[26] In this process, a *N*-tosylhydrazone **75** is coupled with 3-bromo-6-chlorophenyl imidates **80** to give the intermediate imidates **81** in the presence of the Pd/Davephos catalytic system. Then, addition of an amine and an additional load of base leads to the formation of the benzimidazole **82** through the Pd-catalyzed amination/heterocyclization process. This reaction cannot be strictly considered an auto-tandem cascade, but a one-pot process, because the amine is added once the first coupling reaction has already taken place. Anyway, just like in the typical auto-tandem reactions, the same Pd catalyst promotes both different steps, and therefore, retains most of the advantages of cascade reactions. This methodology turned out to be fairly general and allowed for the synthesis of a remarkable structural variety of substituted benzimidazoles **82**. Some of the molecules synthesized exhibited very promising activity against cell lines of various human carcinomas.



Scheme 24 Pd-catalyzed one-pot synthesis of alkenyl-substituted benzimidazoles **80** through a C-C/C-N/heterocyclization sequence.

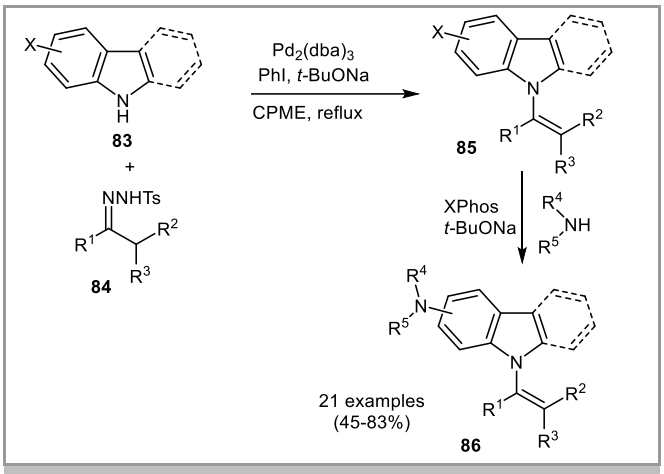
4.2 Assisted tandem C-N/C-N Bond-Forming Reactions.

In 2013, the groups of Cui,[27] and Alami and Hamze[28] reported independently different methodologies for the Pd-catalyzed oxidative *N*-alkenylation of azoles with *N*-tosylhydrazones (Scheme 25). While in Cui's method O_2 was employed as oxidant, Alami and Hamze employed an excess of PhI as a sacrifice oxidant.

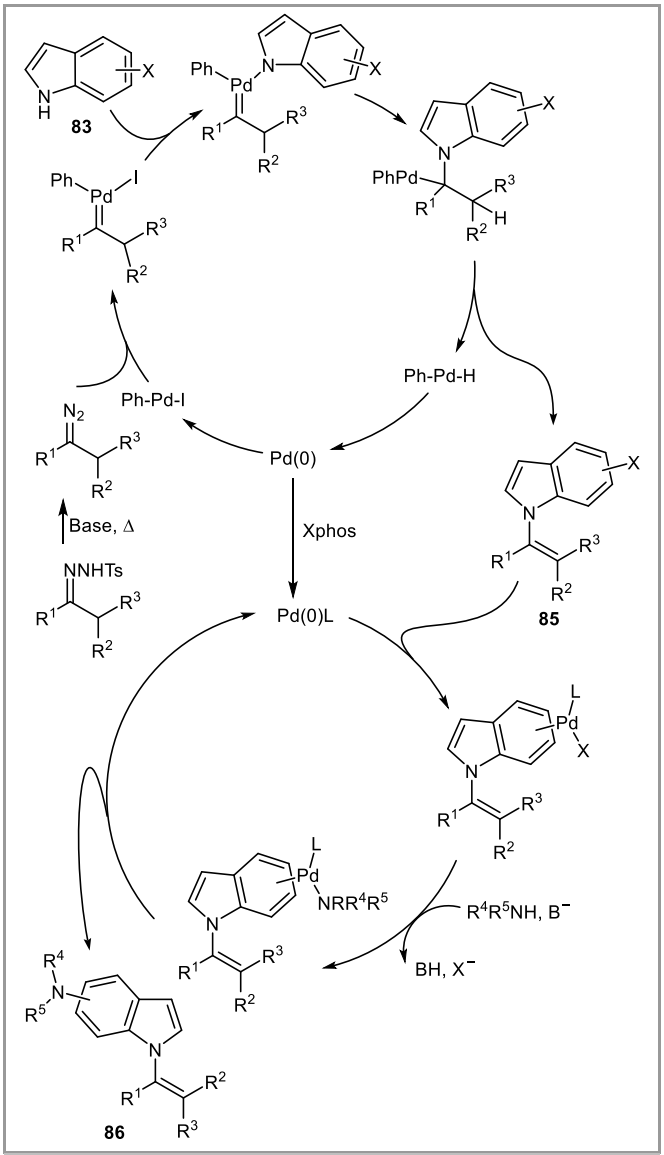


Scheme 25 Pd-catalyzed oxidative alkenylation of azoles.

Subsequently, Alami and Hamze applied this methodology for the generation of a diversity of aminosubstituted-*N*-alkenylazoles **86** combining the *N*-alkenylation reaction discussed above with an intermolecular Pd-catalyzed aryl amination (Scheme 26).[29] This is indeed a one-pot process and not an auto-tandem reaction. Thus, in this case, after the *N*-alkenylation has finished to give *N*-alkenylazole **85**, the amine, an additional load of base and the ligand Xphos are added to the mixture. Interestingly, no additional Pd is needed. Thus, the same metal participates in two different catalytic cycles, although the modification of the catalytic species by the addition of the ligand is necessary for the amination reaction.



Scheme 26 Assisted tandem Pd-catalyzed C-N/C-N reaction based on *N*-tosylhydrazones for the synthesis of N-alkenylazoles **86**.

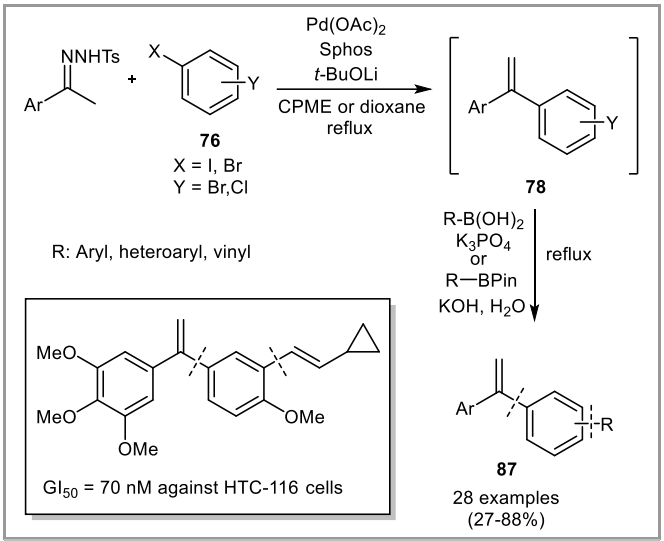


Scheme 27 Mechanism proposed for the assisted tandem Pd-catalyzed C-N/C-N reaction based on *N*-tosylhydrazones.

In scheme 27 are presented the two different Pd-catalyzed processes. In the first cycle, the Pd(0) undergoes oxidative addition by the action of PhI, to promote the *N*-alkenylation of indole **83** to give **85**. Interestingly, no ligand is necessary in this step. The second process occurs upon addition of the Xphos ligand, that modifies the nature of the catalyst, and corresponds to a typical Buchwald-Hartwig aryl amination that furnishes **86**. Of note, the scope of the reaction was very general and good to high yields of amino-substituted *N*-vinylindoles **86** were obtained using a wide range of amine partners, including anilines, heterocyclic amines, as well as secondary aliphatic amines. The process is also very general with regard to the *N*-tosylhydrazones **84** and the halo-substituted azoles **83**. This methodology allowed the identification of molecules active against human colon carcinoma cells, validating this procedure as a tool in diversity oriented synthesis for drug discovery.

4.3. One-pot C-C/C-C bond forming reactions

The multicomponents strategy applied by Alami and Hamze consisting on the combination of the *N*-tosylhydrazone arylation with other Pd-catalyzed cross-coupling reaction for the straightforward generation of molecular diversity (scheme 23), was also applied to the Suzuki reaction.[30] The challenge of the work was to devise a catalytic system that could promote efficiently both C-C bond forming reactions. Thus, a one-pot three-components reaction was reported in which a diversity of substituted 1,1-diarylethylenes **87** were synthesized by Pd-catalyzed arylation of *N*-tosylhydrazones of substituted acetophenones with dihalobenzene derivatives **76** followed by cross-coupling with boronic acids or pinacolboronic esters (Scheme 28). The Pd/Sphos catalytic combination was found to be optimal to promote the independent steps, and once the cross-coupling with the *N*-tosylhydrazone had been completed to give **78**, only the addition of the boronic reagent, the appropriate base and a certain amount of water were required for the Suzuki coupling to take place.



Scheme 28 One-pot three-components synthesis of substituted 1,1,-diarylethylenes **87** by a *N*-tosylhydrazone arylation/Suzuki cross-coupling sequence

Again, this is not an auto-tandem cascade reaction but a one-pot process that employs the same catalysts for both steps. Nevertheless, the methodology is a very powerful method for the generation of molecular diversity oriented to drug discovery. Indeed, through this methodology new analogs of

isocombrestatin-A4 were identified that featured in vitro cytotoxicity against HCT116 cell lines (human colon tumor).

5. Summary and outlook.

The Pd-catalyzed cross-coupling with *N*-tosylhydrazones has reached a considerable degree of maturity, that makes it a very useful transformation in organic synthesis. In this minireview it has been shown the ability of this reaction to be inserted in auto-tandem cascade processes that combine various C-C and C-N bond forming reactions, by selecting appropriate substrates and adequately programing the sequence of events. In this way, it has been possible to access to a variety of relatively complex structures from simple starting materials in one single step and explore new areas of the chemical space. These methodologies have led to the synthesis of molecules of interest in the areas of materials and medicinal chemistry. Moreover, the modular nature of these class of cascade reactions makes them a powerful tool for the generation of molecular diversity.

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Biosketches

Raquel Barroso (center) obtained the bachelor and master degrees in Chemistry at the University of Oviedo. She then started PhD work under the supervision of Profs. Cabal and Valdés dedicated to Pd-catalyzed and metal-free cascade reactions based on sulfonylhydrazones. She plans to obtain her PhD by September 2017.

María P. Cabal (right) conducted PhD studies at the University of Oviedo under the supervision of Profs. Barluenga and Aznar obtaining the degree at 1986. Subsequently, she pursued postdoctoral studies with Prof. Danishefsky at Yale University, developing methods for the synthesis of complex natural products (calicheamicin and prostaglandins). In 1991 she returned to the University of Oviedo as a tenured professor. She has had several stays at University of Buffalo, NY and University of South Florida at Tampa. Her current research focuses on organic synthesis, organometallic chemistry, heterocyclic chemistry, and organocatalysis.

Carlos Valdés (left) received his PhD in 1992, from the University of Oviedo working under the guidance of Profs. Barluenga and Aznar. He then carried out a postdoctoral stay at the group of Prof. Rebek at MIT working on the self-assembly of molecular *tennis balls*. He has occupied various academic positions at the University of Oviedo, and has recently been promoted to full professor. His current research interests are focused on the development of new efficient synthetic methodologies for metal catalyzed and metal-free C-C bond formation, and on the design of cascade reactions oriented to the synthesis of carbo- and heterocycles.

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