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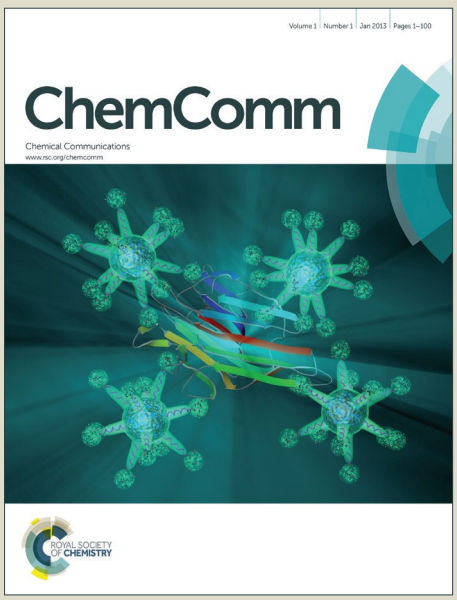

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Pd-catalyzed cascade reactions between *o*-iodo-*N*-alkenylanilines and tosylhydrazones. Novel approaches to the synthesis of polysubstituted indoles and 1,4-dihydroquinolines.

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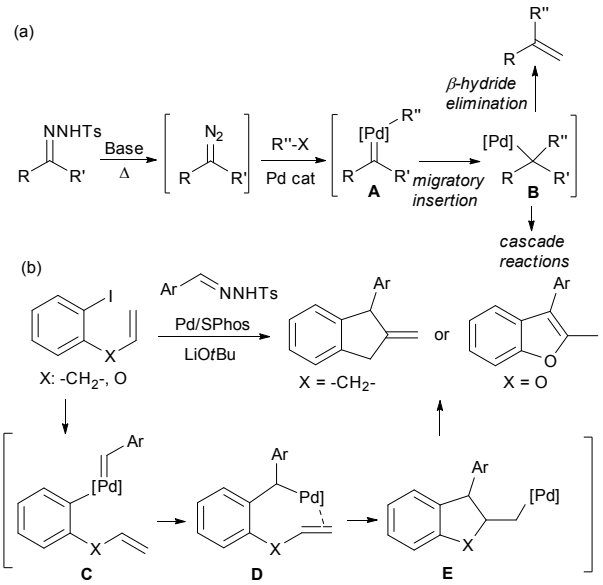
Two different Pd-catalyzed cascade reactions between o-iodo-*N*-alkenylanilines and tosylhydrazones are described. The outcome of the cascade process is determined by the substitution on the *N*-alkenyl fragment. The reactions with *N*-tosyl-*N*-ethylene-*o*-iodoanilines lead to indoles through a sequence that involves the sequential migratory insertions of a carbene ligand and a C-C double bond, featuring a 5-*exo*-trig cyclization. The reactions with *N*-alkyl-*N*-alkenyl-*o*-iodoanilines provide 1,4-dihydroquinolines through a cascade reaction that includes a formal 6-*endo*-trig cyclization. In both cases the benzofused heterocycles are built through the formation of two C-C bonds on the hydrazonic carbon atom.

Diazo compounds have established over that last years as a new type of nucleophilic partners for Pd-catalyzed cross-coupling reactions. Among the different sources of diazo compounds, sulfonylhydrazones represent the most versatile intermediates.[1] Indeed, since the introduction of tosylhydrazones in Pd-catalyzed C-C-bond forming reactions,[2] this field has experimented a remarkable development, and a large number of different applications have been uncovered.[3-5] The differential steps in the catalytic cycle of Pd-catalyzed reactions with diazo compounds are the formation of a Pd-carbene **A** and the migratory insertion of the carbene ligand into a Pd-C bond (scheme 1, a). The Csp^3-Pd containing intermediate **B** generated may evolve in a number of ways, depending on the particular structure. If the organopalladium intermediate features β-hydrogens, the typical β-hydride elimination takes place giving rise to alkenes. Interestingly, when the β-hydride elimination is not possible, the intermediate palladium complex can be engaged in different types of cascade reactions. Over the last years, several examples have been described that take advantage of this approach, which involve the generation of allyl-Pd or benzyl-Pd complexes that can react with nucleophiles through intra- or intermolecular processes or participate in a subsequent cross-coupling reaction.[6-9]

In the context of our interest in the Pd-catalyzed reactions with sulfonylhydrazones, we reported recently set of cascade reactions based on the employment of aromatic tosylhydrazones and *o*-halobenzenes featuring a double bond in a proper position (scheme1, b). [10,11] Thus, after the oxidative addition/carbene migratory insertion, the benzylpalladium complex **C** undergoes the migratory insertion of the double bond, through a 5-*exo*-trig pathway, and finally a β-hydride elimination. In this manner, starting from 1-allyl-2-halobenzenes, the process leads to indenes, while employing 1-iodo-2-vinyloxybenzenes, 2,3-disubstituted furans are obtained.



Scheme 1: (a) Key steps in Pd-catalyzed reactions with tosylhydrazones. (b) Synthesis of indenes and benzofurans through a cascade process that involves the sequential migratory insertions of a carbene and a C-C double bond into Pd-Csp^3 bonds.

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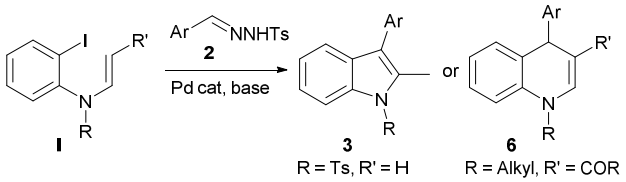
Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data and copies of the ^{1}H and ^{13}C NMR spectra].

Continuing with our interest on these cascade processes as a method for the synthesis of benzofused five-membered heterocycles, and taking into consideration the high interest of the indole scaffold, we decided to apply a similar strategy to access to indole derivatives from *o*-iodo-*N*-alkenylanilines **I**. We observed that under the proper reaction conditions, compounds **I** were appropriate substrates for Pd-catalyzed cascade reactions with tosylhydrazones. However, depending on the nature of substituents R and R', indoles **3** or dihydroquinolines **6** were obtained, through cascade processes which involve the migratory insertion reaction followed by formal 5-*exo*-trig or 6-*endo*-trig carbopalladations respectively (scheme 2).



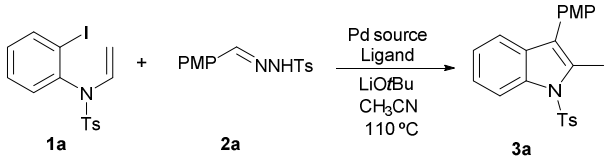
Scheme 2: General outline of the Pd-catalyzed cascade synthesis of trisubstituted indoles and dihydroquinolines described in this work.

Herein we wish to report our progress in this research, that has led to the development of new methods for the synthesis of indoles and dihydroquinolines through novel [4+1] and [5+1] approximations respectively, in which two C-C bonds are created on the same carbon atom.

We initiated our research with the model reaction between *o*-iodo-*N*-tosyl-*N*-vinylaniline **1** and the tosylhydrazone of *p*-anisaldehyde **2a**. Firstly, the reaction was attempted employing the standard reaction conditions that had been applied for the cascade reactions that led to indenes and benzofurans, and which employed a Pd(0)/Sphos catalytic system.[10a] Quite disappointingly, in this case the cascade reaction did not take place and the iodoaniline **1a** was recovered untouched (table 1, entry 1). Thus, an array of different catalytic conditions, involving changes in Pd source, ligand and base were examined (table 1). Formation of the indole **3a** derived from expected cascade reaction was detected by GC/MS only when PPh_3 was employed as ligand and in the presence of different Pd sources. Both Li*O*t*Bu* and LiOH promoted the reaction, however, when LiOH was employed (entry 7), and also when the cascade reaction was carried out in the presence of 5 equiv of H_2O (entry 6), substantial amounts of the detosylated indole were obtained. Finally, the slow syringe-pump addition of the tosylhydrazone to the reaction mixture led to an enhancement of the yield (entry 12).

The optimized reaction conditions were then applied to the preparation of a collection of *N*-tosyl-2,3-trisubstituted indoles, by variation of both coupling partners (table 2). It must be noted that in some examples, substantial amounts of the indoline **3'** were detected in the reaction crude together with the indole **3**, leading to a drop in the isolated yield after chromatography. To drive the reactions to the complete formation of the final indole, the reaction mixtures were treated with aqueous 1M HCl prior to the chromatographic purification.

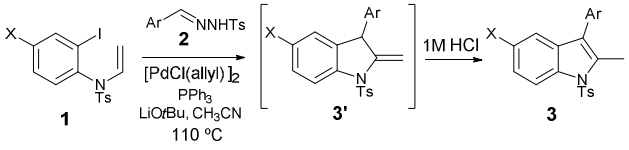
Table 1: Selected optimization data for the synthesis of indole **3a**.[a]



Entry	Pd source	Ligand	Yield[b] %
1[c,d]	Pd_2dba_3	Sphos	0
2[c,d]	Pd_2dba_3	Xphos	0
3[c,d]	Pd_2dba_3	$P(2\text{-Furyl})_3$	0
4[d]	$PdOAc_2$	PPh_3	20
5[d]	$PdCl_2(MeCN)_2$	PPh_3	20
6[d]	$[PdCl(allyl)]_2$	PPh_3	45
7[e]	$[PdCl(allyl)]_2$	PPh_3	46
8[d]	$[PdCl(allyl)]_2$	$P(o\text{-Tol})_3$	0
9[d]	$[PdCl(allyl)]_2$	$P(o\text{-MeO-}C_6H_4)_3$	0
10	$[PdCl(allyl)]_2$	PPh_3	50
11[f]	$[PdCl(allyl)]_2$	PPh_3	18
12[g]	$[PdCl(allyl)]_2$	PPh_3	60 (53)[h]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), Li*O*t*Bu* (6 equiv), Pd source (6 mol % in Pd), Ligand, CH_3CN (1 mL), 110 °C. [b]Determined by GC/MS with internal patron. [c]Identical result was obtained employing $PdOAc_2$. [d]Carried out in the presence of 5 equiv of H_2O. [e]LiOH was used as base. [f]Carried out employing 3 mol % of Pd. [g]Conducted with syringe pump slow addition of **2a**. [h]Isolated yield after column chromatography.

Table 2: Synthesis of indoles **3** by reaction of o-iodo-N-ethenylanilines **1** and tosylhydrazones **2** .[a]



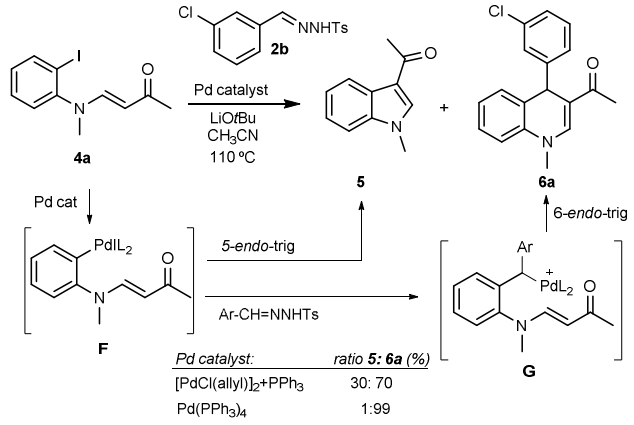
Compound	Ar	X	Yield[b] %
3a	4-MeO-C_6H_4	H	53
3b	4-F-C_6H_4	H	58
3c	4-Cl-C_6H_4	H	84
3d	Ph	H	72
3e	4-Tol	H	80
3f	4-F_3C-C_6H_4	H	62
3g	4-AcO-C_6H_4	H	55
3h	4-NC-C_6H_4	H	47
3i	2-Naphthyl	H	55
3j	3-Cl-C_6H_4	H	66
3k	3-NC-C_6H_4	H	53
3l	3-Cl-C_6H_4	F	60
3m	4-Tol	F	58
3n	3-Cl-C_6H_4	Cl	62
3o	4-Tol	Cl	50
3p	Ph	Cl	52
3q	3-Cl-C_6H_4	CF_3	50

[a]Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), Li*O*t*Bu* (6 equiv), $[PdCl(allyl)]_2$ (3 % mol), PPh_3 (12 % mol), CH_3CN (1 mL), 110 °C. [b]Isolated yield after column chromatography.

As presented in table 2, the reaction tolerates the employment of all types of aromatic tosylhydrazones, featuring either electrondonating or electronwithdrawing susbtituents. Moreover, substitution on the benzene ring of the *o*-iodoaniline is also tolerated. Noteworthy, this methodology features a quite unusual [4+1] disconnection in the synthesis of indoles,[12,13] in which the five-membered ring is built by formation of two C-C bonds on the hydrazonic carbon. Thus it might enable the synthesis of indoles not easily available through conventional methodologies.

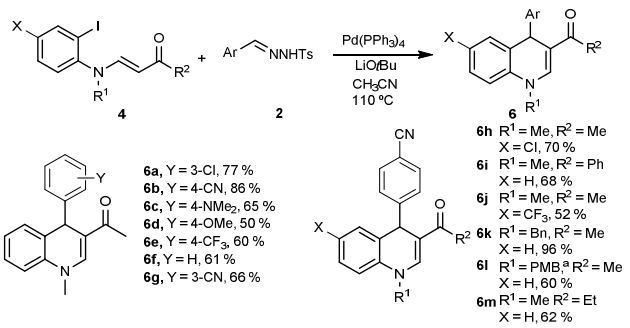
Continuing with the study of the scope of the reaction, the cascade process was attempted with the readily available *o*-iodo-*N*-alkenylaniline **4a**. Interestingly, the initial experiments conducted employing **4a** and 3-chlorophenyltosylhydrazone **2b**, under the optimized reaction conditions of table 1, did not afford the expected trisubstituted indole through a cascade reaction similar to that described above. In contrast, a mixture of indole **5** and the dihydroquinoline **6a** was detected in the reaction crude (scheme 3). Indole **5** derives from an intramolecular Heck reaction on **4a** through a 5-*endo*-trig cyclization from arylpalladium complex **F**. This type of cyclization, although not very common, has been previously employed in the synthesis of indoles.[14] More surprising was the formation of **6a**, which could be envisioned as a formal 6-*endo*-trig cyclization from the intermediate benzylpalladium complex **G**.

In an attempt to avoid the formation of the indole **5** and drive the reaction to the exclusive formation of the dihydroquinoline **6a**, a new optimization study was conducted. A decrease of the reaction temperature below 100 °C reduced dramatically the conversion, and the starting enaminone **4a** was recovered. After some experimentation, it was found that employing $Pd(PPh_3)_4$ as Pd source, with no additional ligand added, the dihydroquinoline **6a** could be obtained in good yield, with almost complete disappearance of the indole **5** (scheme 5).



Scheme 3: Pd catalysed reactions of enaminone **4a** with tosylhydrazone **2b**: Influence of the Pd-catalyst.

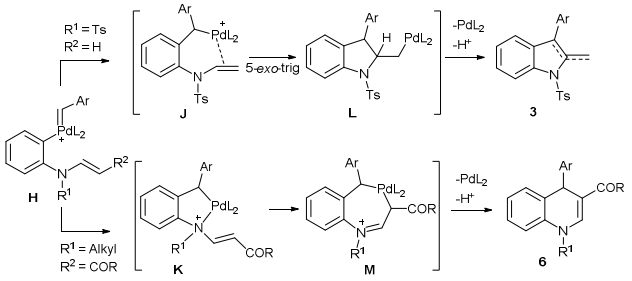
A preliminary study of the scope of the reaction revealed that the cascade process was suitable for the synthesis of structurally diverse dihydroquinolines **6** with several different points for diversification (Scheme 4). First, the reaction is compatible with aromatic tosylhydrazones featuring a variety of substitutions at the aromatic ring (**6a-g**). Regarding the structure of the enaminone **4**, different alkyl substitution can be present at the nitrogen (**6k,l**), at the acyl substituent (**6i,m**), as well as in the aromatic ring of the starting iodoaniline (**6h**, **6j**). Considering the simple access into the starting enaminones **4** through a highly efficient modular approach (see ESI for details), this methodology offers a very powerful alternative for the generation structurally diverse dihydroquinolines, a valuable heterocycle substructure for medicinal chemistry.[15,16]



Scheme 4: Polysubstituted dihydroquinolines **6** prepared by Pd-catalyzed reaction between enaminones **4** and tosylhydrazones **2**. [a]PMB: *p*-methoxybenzyl

Mechanistic considerations

The mechanisms proposed for the formation of both the indoles **3** and the dihydroquinolines **6**, depicted in scheme 5, are initiated following the typical pathway of Pd-catalyzed cross-couplings based on diazo compounds: oxidative addition and formation of the Pd-carbene **H**. Then, the migratory insertion of the carbene ligand, would lead to the benzylpalladium intermediates **J** and **K** respectively. Intermediate **J** (R^1 = Ts, R^2 = H), undergoes an 5-*exo*-trig intramolecular carbopalladation, leading to **L**, and after the β-hydride elimination/aromatization sequence to the corresponding indoles **3**. This was certainly the expected pathway, as 5-*exo*-trig Heck type reactions are usually favored towards the alternative 6-*endo*-trig reactions.[17] Additionally, this behavior have been previously observed in analogous reactions leading to indenes and benzofurans.[10]



Scheme 5: Mechanistic proposal for the formation of indoles **3** and dihydroquinolines **6**.

The evolution of intermediate **K** (R^1 = alkyl, R^2 = COR) is quite intriguing because 6-*endo*-trig intramolecular carbopalladations are rather unusual.[17] A plausible explanation

might involve the participation of the more nucleophilic nitrogen atom of the *N*-alkylated enaminone, that might favour the formation of the transient five-membered ring palladacycle in **K** instead of the Pd-alkene complex necessary for the typical carbopalladation reaction. Then, a 1,3-palladatropic rearrangement would lead to intermediate **M**, and reductive elimination followed by tautomerization, to the observed dihydroquinoline **6**.

As summary, herein we report two different and unprecedented Pd-catalyzed cascade processes triggered by reaction of tosylhydrazones and *o*-iodo-*N*-alkenylanilines. First, a new synthesis of 1,2,3-trisubstituted indoles **3** is presented, through Pd-catalyzed cascade reactions that involve the migratory insertion of a Pd-carbene followed by a Heck-type 5-*exo*-trig cyclization. Second, a highly versatile synthesis of 1,3,5-trisubstituted dihydroquinolines **6** is reported through a similar process, but this time finished by a formal 6-*endo*-trig cyclization. Interestingly, the formation of the different type of heterocycle is determined by the substitution of the *N*-alkenylaniline. It is worth noting that novel [4+1] and [5+1] approaches respectively are presented for the synthesis of these benzofused heterocycles, in which two C-C bonds are formed on the same carbon during the cascade process.

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