Pd-catalyzed Auto-tandem C-C/C-C Bond-forming Reactions with Tosylhydrazones. Synthesis of Spirocycles with Extended π–Conjugation.

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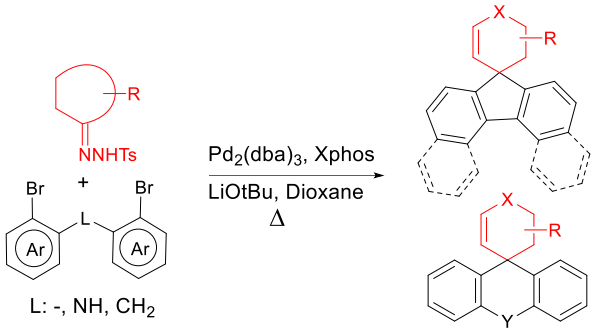
Supporting Information Placeholder



ABSTRACT: A new Pd-catalyzed auto-tandem process is presented by the reaction of tosylhydrazones of cyclic ketones and 2,2'-dibromobiphenyls and related systems. The process involves cross-coupling with tosylhydrazone followed by an intramolecular Heck reaction and gives rise to spirocyclic structures. Noteworthy, two C-C_{Ar} bonds are formed on the hydrazonic carbon during the process. Depending on the starting dibromide, an array of spiro fluorenes, spiro dibenzofluorenes, spiro acridines. and spiro anthracenes have been prepared. Thus, this methodology may be applied for the preparation of interesting structures useful in the development of optoelectronic materials.

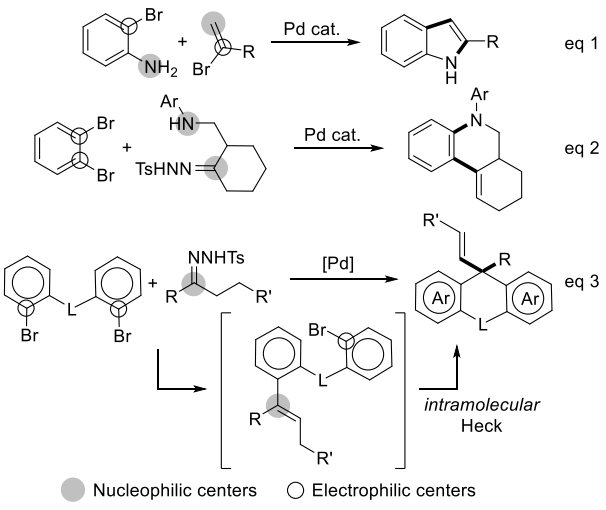
Cascade reactions are amongst the most attractive methods for the construction of molecular complexity. A particular type of transition metal catalyzed cascade processes are the so called "auto-tandem" processes.[1] In these transformations, the same catalyst is able to promote various independent bond-forming reactions, which proceed through distinct catalytic cycles. Over the last decade, a considerable number of examples of Pd-catalyzed "auto-tandem" processes have been developed, mainly oriented to the synthesis of heterocycles. These reactions generally rely on the concatenation of sequential C-heteroatom and C-C bond forming cross-couplings.[2-4] An advantage of these approaches is that the adequate selection of the coupling partners permits the construction of relatively complex cyclic structures from properly functionalized simple materials in one single operation. The vast majority of these reactions are based on the employment of complementary bifunctionalyzed reagents, either a species with two electrophilic positions towards an ambidentate nucleophile or two coupling partners, both featuring an electrophilic and a nucleophilic reacting point (Scheme 1, eq 1, 2).

In the context of our interest on the Pd-catalyzed cross-coupling reactions employing tosylhydrazones,[5,6] we reported recently the first auto-tandem process through a C-C/C-N sequence,[7a] and more recently, the first auto-tandem C-C/C-C process with participation of tosylhydrazones as coupling partner.[8] Nevertheless, all these examples follow the usual pattern presented in eq 1 of scheme 1: all the reacting functional groups are already present in the starting coupling partners.

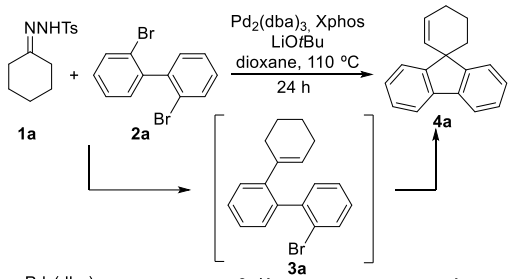
We envisioned a different approach by designing a reaction sequence in which the functionality generated in the first step would react in the second step of the auto-tandem process. In particular, considering the cross-coupling of tosylhydrazones, the double bond formed in the first Pd-catalyzed cross-coupling might participate in an intramolecular Heck reaction, to render cyclic systems through a C-C/C-C auto-tandem sequence (Scheme 1, eq 3).

With this initial idea, we considered first the reaction between an appropriate tosylhydrazone and 2,2'-dibromobiphenyl **2a**. We expected that, after the initial cross-coupling reaction, a 5-*exo*-trig Heck type cyclization[9] might occur to provide the corresponding spiro fluorene derivatives (Scheme 2).[10,11] To avoid regioselectivity problems, we chose the reaction between cyclohexanone tosylhydrazone **1a** and 2,2'-dibromobiphenyl **2a** as a model to investigate the feasibility of the process and develop proper experimental conditions (Scheme 2).

Scheme 1. Examples of typical Pd-catalyzed auto-tandem reactions of ambidentate nucleophiles (eq 1,2).[3b,7a] This work's approach (eq 3). The new bonds are represented in bold.



Scheme 2. Initial C-C/C-C Pd-catalyzed auto-tandem reaction considered and some optimization results.

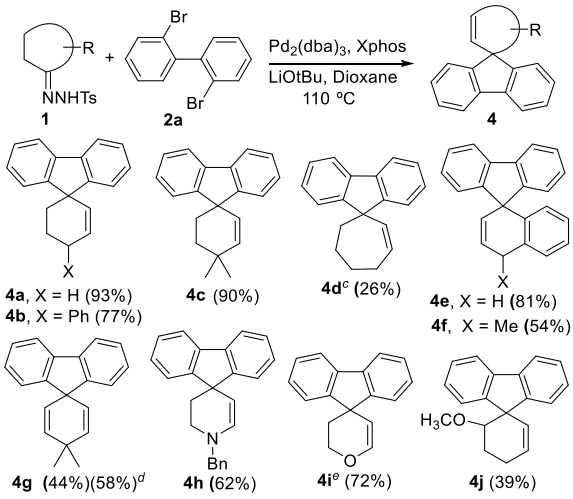


$Pd_2(dba)_3$	1a/2a	3a/4a	Isolated Yield 4a
2 mol %	1: 1	70: 30	24%
2 mol %	2: 1	55: 45	43%
4 mol %	2: 1	0: 100	93%

As a starting point for the optimization we employed the standard reaction conditions developed for the cross-coupling reactions with tosylhydrazones: the $Pd_2(dba)_3$•Xphos catalytic system and LiO*t*Bu as base.[5] The initial experiments employing a 1: 1 ratio of both coupling partners and 2 mol % $Pd_2(dba)_3$ led to the obtention of a mixture of the cross-coupling product **3a** and the desired spirocycle **4a**. Delightfully, upon increasing of the catalyst loading and the **1a**: **2a** ratio, the spirocyclic derivative **4a** could be obtained as the only reaction product with an excellent isolated yield of 93%. The structure **4a** could be assigned based on the ^{13}C, ^{1}H NMR and MS spectra. In particular, the presence of two dt at 5.35 (^{3}J = 9.9 Hz, ^{4}J = 2.1 Hz) and 6.12 ppm (^{3}J = 9.9 Hz, ^{3}J = 3.8 Hz) respectively in the ^{1}H NMR spectrum was a clear indication of the presence of the endocyclic double bond. Moreover, the spirocyclic structure was later confirmed by x-ray crystallographic analysis in another member of this family of spiro compounds (Figure 1). Interestingly, during the auto-tandem reaction the unusual formation of two C-C_{Ar} bonds on the same carbon atom has taken place.[4b,11,12]

This result prompted us to study the scope of this novel process regarding both coupling partners, the tosylhydrazone and the dibromide derivative. First, the scope of the reaction regarding the structure of the tosylhydrazone was examined. As presented in Scheme 3, the reaction could be carried out with an array of tosylhydrazones derived from cyclic ketones to provide a collection of spiro fluorene derivatives **4** with unprecedented structures. The reaction proceeded with the tosylhydrazone of cyclohexanone, 4-substituted cyclohexanones, and also cycloheptanone. Moreover, tetralone tosylhydrazone was also an appropriate substrate for the reaction leading to the interesting spiro derivatives **4e** and **4f** which feature and additional aromatic ring. Similarly, the reaction with the hydrazone of 4,4,-dimethylcyclohexenone led to the symmetric spirofluorene **4g** featuring two unconjugated double bonds. Interestingly, the cascade reaction could be achieved also with the tosylhydrazones of *N*-benzyl-4-piperidone and 4-piranone, which led to the corresponding spiro derivatives **4h** and **4i** featuring enamine and enol ether functionalities respectively. In particular the structure of **4i** was confirmed by x-ray crystallographic analysis (Figure 1).[13] Finally, the reaction with the hydrazone of 2-methoxycyclohexanone furnished spiro compound **4j** in a complete regioselective manner.[5d]

Scheme 3. Synthesis of spiro fluorenes 4 by reaction between cyclic N-tosylhydrazones 1 and 1,1'-dibromobiphenyl 2a.[a,b]



[a]Reaction conditions: Dibromide **2** (0.2 mmol, 1 equiv), tosylhydrazone **1** (0.4 mmol, 2 equiv), $Pd_2(dba)_3$ (4 mol %), Xphos (8 mol %), LiO*t*Bu (4 equiv), dioxane (2 mL), 110 ºC, 24 h. [b]Isolated yields after column chromatography. [c]Reaction

time 48 h. [d]Yield determined by ^{1}H NMR employing triphenylmethane as internal reference. [e]Structure confirmed by x-ray diffraction.

It is worth noting the interest of spiro fluorene structures, which are currently employed in the development of electroluminescent and optoelectronic materials.[13] This approach may offer the opportunity to build structurally diverse and functionalized derivatives of this family of compounds.

Encouraged by these results, the auto-tandem reaction was then examined employing other dibrominated scaffolds, to explore the versatility of this approach in the synthesis of structurally diverse spiro compounds. Thus, we selected a series of dibrominated scaffolds, binaphtyl **2b**, diarylanilines **2c-2g**, diarylmethane **2h** and arylbenzylether **2i** (Figure 2).

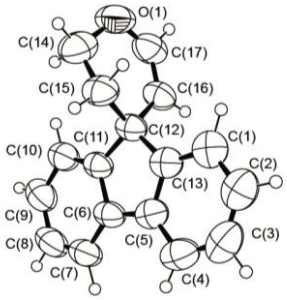


Figure 1. ORTEP representation of the molecular structure of **4i** determined by x-ray crystallographic analysis (see Supporting Information).

In an initial approximation, the reactions were carried out under similar reaction conditions to those employed for biphenyl **2a**. However, in some cases, further tuning of the reaction conditions was required. The results are summarized in Scheme 4.

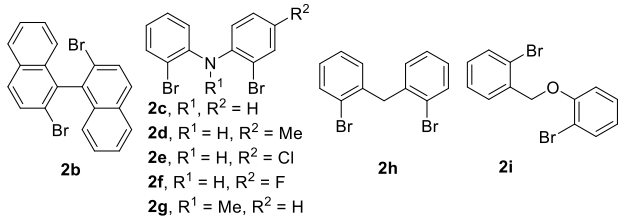
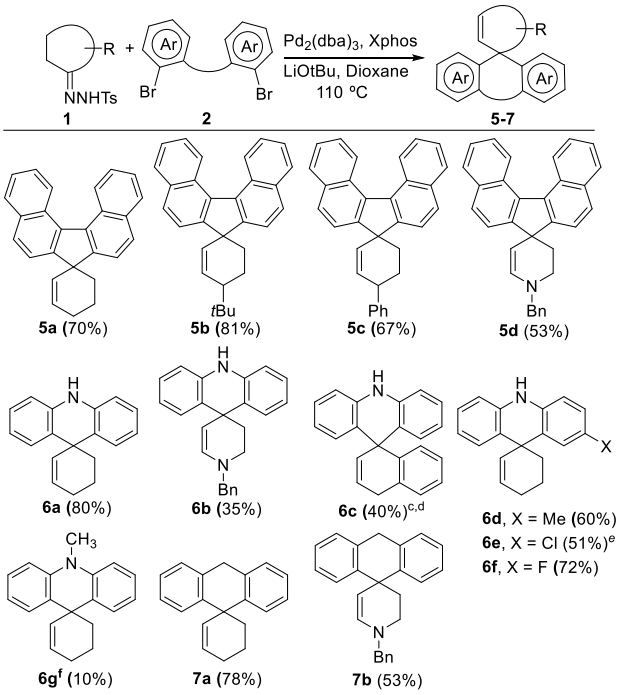


Figure 2. Bis(bromoaryl) compounds **2** employed in the Pd-catalyzed auto-tandem reaction

The process is also very efficient for the preparation of spiro dibenzofluorenes **5**,[14] interesting structures which feature a more extended π-conjugation, with yields similar to the reactions with the biphenyl system (Scheme 4). The reactions of bis(bromoaryl) compounds **2c-h** were expected to afford the corresponding spiro compounds **6** and **7**, which feature a central six-membered ring through a 6-*exo*-trig cyclization. However, these reactions turned out to be more challenging. In our initial experiments, under the typical reaction conditions described above, the diarylanilines **2c** and **2g** showed some tendency to cyclize form carbazoles.[4b] After some experimentation it was found that the employ of a higher excess of *N*-tosylhydrazone was necessary to achieve the synthesis of the spiroacridines **6** with preparatively interesting yields. Noteworthy, under the proper conditions, the auto-tandem reaction proceeded successfully with the N-H-free anilines leading to the corresponding spiroacridines **6**, also valuable structures for the development of molecules with electronic properties,[15] and amenable for further derivatization through the N-H position. However, in the case of the *N*-methylated system **2g** formation of *N*-methylcarbazole resulted in the major reaction product[4b] even in the presence of excess of the *N*-tosylhydrazone. Finally, the reaction with bis(2-bromophenyl)methane **2h** allowed for the synthesis of the spiro dihidroantracenes **7**.

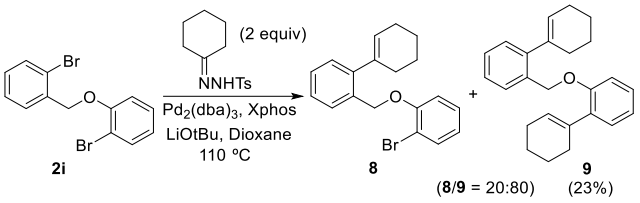
In contrast, when the reaction with tosylhydrazone **1a** was carried out under the same conditions employing dibromide **2i**, formation of the spiro compound was not detected. Instead, a mixture of the products **8** and **9**, derived from mono- and dialkenylation respectively (Scheme 5) were obtained in different ratios depending on the reaction conditions, indicating that the 7-*exo*-trig cyclization is not a favoured reaction pathway.

Scheme 4. Synthesis of spiro compounds 5-7 by reaction between cyclic *N*-tosylhydrazones 1 and dibromides 2b-g.[a,b]



[a]Reaction conditions: dibromide **2** (0.2 mmol, 1 equiv), tosylhydrazone **1** (0.4 mmol, 2 equiv), $Pd_2(dba)_3$ (4 mol %), Xphos (8 mol %), LiO*t*Bu (4 equiv), dioxane (2 mL), 110 ºC, 24 h. [b]Isolated yield after column chromatography. [c]4 equiv of tosylhydrazone were employed. [d]Reaction time 48 h. [e]3 equiv of tosylhydrazone and 5 equiv of LiO*t*Bu were employed. [f] *N*-Methyl carbazole was obtained as major product.

Scheme 5. Reaction with dibromide 2i which do not afford the spiro cyclic structure.



In summary, we reported herein a new Pd-catalyzed auto-tandem C-C/C-C bond forming sequence that involves a tosylhydrazone cross-coupling followed by an intramolecular Heck reaction. Interestingly, during the process, two C-C_{Ar} bonds were formed on the same carbon atom. Moreover, these processes led to the obtainment of rigid spirocyclic structures featuring extended π-conjugation in one single step from readily available starting materials. These novel scaffolds may find application in the development of optoelectronic materials, and also in ligand design and diversity oriented synthesis. The examples presented herein already show the versatility of this approach for the preparation of structurally diverse and functionalized spirocyclic systems. The development of more sophisticated structures based on this approach and the study of their properties are currently in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data and copies of the ^{1}H and ^{13}C NMR spectra for the compounds **4-7** and **9**. X-ray crystallographic data of **4i**.

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