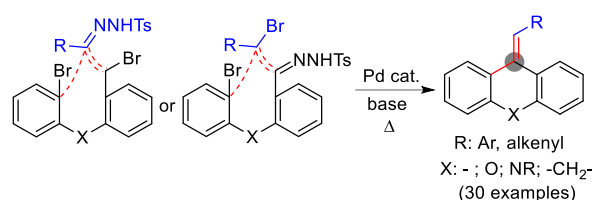# Pd-catalyzed autotandem reactions with *N*-tosylhydrazones. Synthesis of condensed carbo- and heterocycles by formation of a C-C single bond and a C=C double bond on the same carbon atom

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Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica "Enrique Moles". Universidad de Oviedo. c/ Julián Clavería 8. Oviedo 33006. Spain.

Supporting Information Placeholder

R: Ar, alkenyl
X: - ; O; NR; -CH₂-
(30 examples)

ABSTRACT: A new Pd-catalyzed autotandem reaction is introduced that consists of the cross-coupling of a benzylbromide with a *N*-tosylhydrazone followed by an intramolecular Heck reaction with an aryl bromide. During the process, a single and a double C-C bonds are formed on the same carbon atom. Two different arrangements for the reactive functional groups are possible, rendering great flexibility to the transformation. The same strategy led to 9-methylene-9*H*-fluorenes, 9-methylene-9*H*-xanthenes, 9-methylene-9,10-dihydroacridines, and also dihydropyrroloisoquinoline and dihydroindoloisoquinoline derivatives.

Cascade reactions are very powerful methodologies for the synthesis of complex carbocyclic structures.[1] In cascade processes, two or more bonds are formed in one single synthetic operation, enabling cyclization processes from two independent subunits, and therefore the development of highly convergent synthetic methodologies. Within the widely studied field of metal catalyzed cascade reactions, Pd-catalyzed processes can be regarded as some of the most versatile methodologies.[2]

In the context of our interest in Pd-catalyzed C-C bond forming reactions based on *N*-sulfonylhydrazones,[3,4] we have recently focused on the development of new cascade reactions oriented to the synthesis of carbo- and heterocycles.[5-7] Within this research program, we described a new method for the synthesis of spirofluorenes through a Pd-catalyzed cascade between *N*-tosylhydrazones and 2,2'-dibromobiphenyls (Scheme 1, eq 1).[8] In this process, two different C-C bonds are formed on the hydrazonic carbon atom. First, the cross-coupling reaction between the *N*-tosylhydrazone and one of the bromides leads to an intermediate D that experiments an intramolecular Heck reaction, that provides the final spirofluorene structure C. Interestingly, the process involves two separate catalytic cycles which are promoted by the same Pd-catalyst – so called autotandem catalysis.[9,10] We envisioned that this approach, that combines the formation of an alkene by the cross-coupling reaction with a *N*-tosylhydrazone followed by the cyclization by carbopalladation of the newly formed double bond features considerable potential for the synthesis of polycyclic

aromatic hydrocarbons, upon the selection of the proper coupling partners. Thus, we decided to explore a similar cascade, employing dibromobiphenyls with the general structure E, which feature a benzylic bromide and an aryl bromide in the proper positions to undergo an autotandem cascade sequence (Scheme 1, eq 2).

Scheme 1. (1) Synthesis of spirofluorenes by Pd-catalyzed autotandem reaction; (2) This work.
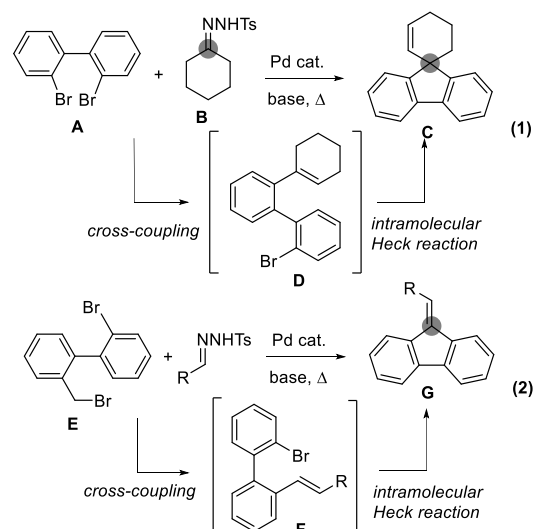
Taking advantage of the higher reactivity of benzyl bromides than aryl bromides in the oxidative addition step, we expected the initial formation of stilbene F by reaction with the *N*-tosylhydrazone,[11] followed by the 5-*exo*-trig intramolecular Heck reaction, that would provide the final 9-fluorenylidene G[12] (Scheme 1, eq 2). If this approach were successful, it might represent a novel and convergent route to an important class of fluorenyl derivatives.[13] Moreover, it would consist on a rare example of the formation of a C-C single bond a C=C double bond on the same carbon atom in a single reaction.

In this manuscript, we wish to describe our progress towards this goal, that have led to the development of new cascade reactions that take place with formation of two consecutive C-C bonds, and enable the straightforward synthesis of a variety of carbo- and heterocyclic structures.

Table 1. Selected optimization experiments for the C-C/C-C Pd-catalyzed autotandem reaction.[a]
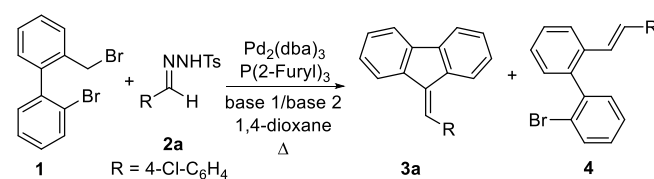
entry	base 1/base 2 (6 equiv)	$t(^{\circ}C)^f$	$3/4^b$
1	*t*-BuOLi/-	80	$0:1^c$
2	*t*-BuOLi/-	100	$1:4^e$
3	*t*-BuOLi/-	100	1:1
4	*t*-BuOLi/-	100	$2:3^d$
5	*t*-BuOLi/K_2CO_3	100	2:1
6	K_2CO_3/-	100	0:1
7	*t*-BuOLi/Na_2CO_3	100	1:4
8	*t*-BuOLi/Li_2CO_3	100	7:3
9	*t*-BuOLi/Cs_2CO_3	100	4:1
10	*t*-BuOLi/Cs_2CO_3	120	$1:0\ (79\%)^g$

[a]Reaction conditions: Dibromide 1, (0.1 mmol), *N*-tosylhydrazone 2a, (1 equiv), Pd$_2$(dba)$_3$ (5 mol %), P(2-Furyl)$_3$ (30 mol %), base 1 (6 equiv) or base1 (3 equiv)/base 2 (3 equiv), 1,4-dioxane (2 mL), 12 h. [b]Calculated by GS/MS. [c]Carried out in toluene as solvent. [d]Carried out in CH$_3$CN as solvent. [e]Pd$_2$(dba)$_3$ (3 mol %) was used. [f]Temperature of the bath in the sealed tube reaction. [g]Isolated yield of 3a after column chromatography

We initiated our study with the reaction between 2-bromo-2'-(bromomethyl)-1,1'-biphenyl 1 and the *N*-tosylhydrazone of 4-chlorobenzaldehyde 2a. In an initial experiment we chose a set of catalytic conditions similar to that described by Wang for the Pd-catalyzed cross-couplings between *N*-tosylhydrazones and benzyl bromides,[11] that should be the first step of the autotandem process: Pd$_2$dba$_3$ (5 mol %)/P(2-Furyl)$_3$ (20 mol %), in toluene at 80 °C, but employing 6 equiv of *t*-BuOLi as base, as an additional load of base would be necessary for the second step of the cascade process. Under these conditions, the cross-coupling proceeded with excellent conversion leading to stilbene 4, but formation of the desired benzylidenefluorene 3a was not detected (Table 1, entry 1).

Nevertheless, formation of 3a occurred to a considerable extent when the reactions were conducted under reflux of 1,4-dioxane or CH$_3$CN (Table 1, entries 2-4). In particular, the reaction in 1,4-dioxane provided a 1:1 mixture of 3a and 4 (Table 1, entry 3). After some experimentation, it was found that the employment of a combination of two bases, *t*-BuOLi (3 equiv) and an alkaline carbonate (3 equiv) led to an increment on the formation of 3a (Table 1, entries 5, 7-9). The presence of both bases in the reaction has a beneficial effect in the conversion, as the reaction carried out only with the participation of K$_2$CO$_3$ led again to the exclusive formation of stilbene 4. It was finally determined that the combination *t*-BuOLi (3 equiv)/Cs$_2$CO$_3$ (3 equiv) afforded the best 3a: 4 ratio. Finally, running the reaction in a sealed tube with a bath temperature of 120 °C brought a complete conversion into the fluorene 3a with an isolated yield of 79% (Table 1, entry 10). In a separate experiment, 4 was subjected to the same reaction conditions of entry 10, giving rise to 3a with complete conversion, indicating that 4 is indeed an intermediate in the autotandem catalyzed cascade.

The optimized reaction conditions were applied to the coupling of dibromide 1 with a set of different *N*-tosylhydrazones 2 to establish the scope of the reaction (Table 2). Thus, a wide number of fluorenes 3 were obtained with excellent to moderate yields through the reactions with *N*-tosylhydrazones derived from aromatic aldehydes bearing both electron-donating (3c, 3d, 3j) or electron-withdrawing (3b, 3h) functional groups, as well as heterocycles 3g. Moreover, *ortho*-substitution is also tolerated, as represented by the highly sterically hindered 3j. The *N*-tosylhydrazone of *trans-p*-methoxycinnamaldehyde provided the 2-propenyl-1-ylidene-9*H*-fluorene 3k in excellent yield. Finally, the reaction was also attempted with the *N*-tosylhydrazone derived from 4-methoxyacetophenone leading to the fluorene featuring a tetrasubstituted double bond 3l.

Table 2. Pd-catalyzed synthesis of 9-methylene-9*H*-fluorenes 3 by reaction of dibromide 1 with *N*-tosylhydrazones 2.[a]

| 3	R^1	R^2	yield %[b]
3a	4-Cl-C$_6$H$_4$	H	79
3b	4-NC-C$_6$H$_4$	H	88
3c	4-MeO-C$_6$H$_4$	H	92
3d	4-Me$_2$N-C$_6$H$_4$	H	85
3e	Ph	H	76
3f	4-Tol	H	90
3g	2-Furyl	H	52
3h	4-MeO$_2$C-C$_6$H$_4$	H	50
3i	3-Cl-C$_6$H$_4$	H	87
3j	(see structure)	H	90

3k	MeO-C₆H₄-CH=CH (structure)	H	88
3l	4-MeO-C₆H₄	Me	78

Next, the cascade reaction was applied to diphenyl ether 5, which should provide xanthenes 6, after the cross-coupling/6-exo-trig Heck cyclization. However, under the experimental conditions described above, the reaction furnished the intermediate stilbene in which the cross-coupling reaction with the N-tosylhydrazone, but not the Heck reaction, had taken place. After some experimentation, we observed that the employment of a mixture of t-BuOLi (3 equiv) and t-BuONa (3 equiv) as base combination allowed for the complete transformation into the desired xanthenes 6. Under these conditions the reaction showed a similar scope than the synthesis of fluorenes 3, including N-tosylhydrazones derived from aromatic aldehydes featuring a variety of functional groups (Table 3).

Table 3. Pd-catalyzed synthesis of 9-benzylidene-9H-xantenes 6 by reaction of dibromide 5 with N-tosylhydrazones 2.[a]
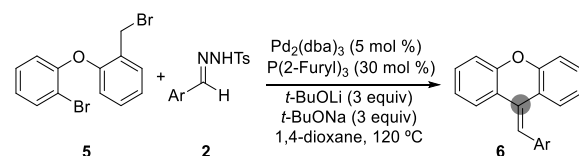
6	Ar	yield %[b]
6a	4-MeO-C₆H₄	50
6b	Ph	56
6c	4-NC-C₆H₄	63
6d	4-Me₂N-C₆H₄	67
6e	4-Tol	64
6f	3-Cl-C₆H₄	62
6g	4-F₃C-C₆H₄	74
6h	4-Cl-C₆H₄	55
6i	2-MeO-C₆H₄	57
6j	4-F-C₆H₄	62
6k	2-Naphthyl	59

The mechanism proposed for the Pd-catalyzed autotandem reactions involve the formation of an intermediate stilbene F (Scheme 1, eq 2) by cross-coupling of the N-tosylhydrazone with the dibromide at the benzylic position, followed by the intramolecular Heck reaction. Interestingly, the same intermediate stilbene could be reached by exchanging the positions of the reactive functional groups. Indeed, when the reaction of N-tosylhydrazone 7a and benzylbromide 8 was conducted under the conditions described in Table 2, the 9-methylene-9H-fluorene 3e was obtained in nearly identical yield than the original reaction employing

dibromide 1 and the N-tosylhydrazone of benzaldehyde (Scheme 2).

The possibility of synthesizing the same products through the same reaction but from different starting materials is very interesting, since it may enable the access to wider variety of structures depending on the availability of the coupling partners. In particular, N-tosylhydrazones 7 featuring additional substitution on the aromatic rings are readily available, and have been previously employed by Hamze et al. in the Cu-catalyzed synthesis of 9H-fluorene-9-amines.[14] Thus, we turned our attention to N-tosylhydrazone 7b as a platform to check the stereoselectivity of the cascade reaction. As presented in Scheme 3, the reaction between 7b and benzyl bromides 8 provided the non-symmetrically substituted 9-methylene-9H-fluorenes 3m and 3n, as a 6:1 mixture of Z/E-diastereoisomers.

Scheme 2. Synthesis of 9-methylene-9H-fluorene 3e through the same reaction from different starting materials
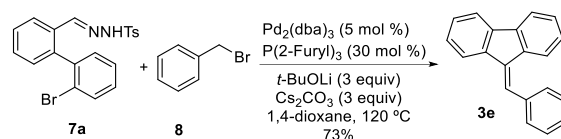
The major isomer corresponds to the one expected considering a syn-carbopalladation followed by a syn-β-hydrogen elimination (Scheme 3). It must be noted that 9-methylene-9H-fluorenes 3 have been reported to undergo slow Z/E isomerization upon heating in the presence of Pd-catalysts,[13d,e] thus, the presence of a minor amount of the E isomer can be explained considering partial isomerization under the reaction conditions.

Scheme 3. Stereoselective synthesis of non-symmetrically substituted 9-methylene-9H-fluorenes 3.
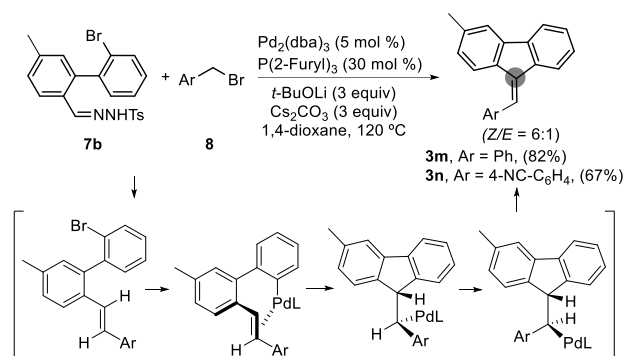
This approach was then applied for the preparation of 9-benzylidene-9,10-dihydroacridines 10 from easily available N,N-diarylaniline 9 and benzyl bromides 8. The reaction conditions established for the synthesis of 9-methylene-9H-fluorenes 3, involving the t-BuOLi/Cs₂CO₃ combination, were the most appropriate for these transformations. Again, the examples selected include benzyl bromides bearing both electron-donating or electro-withdrawing functional groups (Table 4) and led to the obtention of this important class of condensed heterocycles[15] in nearly quantitative yields.

Finally, to further illustrate the versatility of the autotandem process, we chose the heterocyclic N-tosylhydrazones 11 and 13 as substrates for the C-C/C=C cascade reaction with benzyl bromides,

that would lead to pyrroloisoquinoline and indoloisoquinoline derivatives respectively. In these cases the employment of Pd(OAc)$_2$ as Pd source provided better results. Additionally, the participation of two different bases did not result in any reaction improvement. In this manner dihydropyrrolo[1,2-*b*]isoquinoline 12 and dihydropyrrolo[1,2-*b*]isoquinoline 14 were obtained with moderate stereoselectivity (Scheme 4). In both cases the major isomer corresponded to that expected considering the *syn*-β-hydride elimination on the last step of the cascade process. These results demonstrate the wide versatility of this approach for the preparation of polyaromatic carbo- and heterocyclic structures, by combining in the proper way the three reactive elements required for the Pd-catalyzed cascade: the aromatic bromide, the benzyl bromide and the *N*-tosylhydrazone.

Table 4. Synthesis of 9-methylene-9,10-dihydroacridines 10 by reaction of benzylbromides 8 with *N*-tosylhydrazones 9.[a]
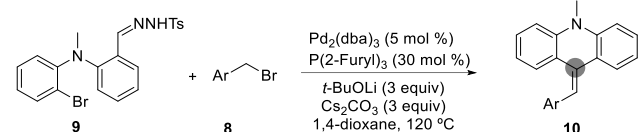
10	Ar	yield %[b]
10a	Ph	90
10b	4-Tol	93
10c	4-F-C$_6$H$_4$	91
10d	4-NC-C$_6$H$_4$	98
10e	4-Cl-C$_6$H$_4$	95

[a]See Table 2 for reaction conditions. [b]Isolated yield after column chromatography.

Scheme 4. Synthesis of pyrroloisoquinoline 12 and indoloisoquinoline derivatives 14
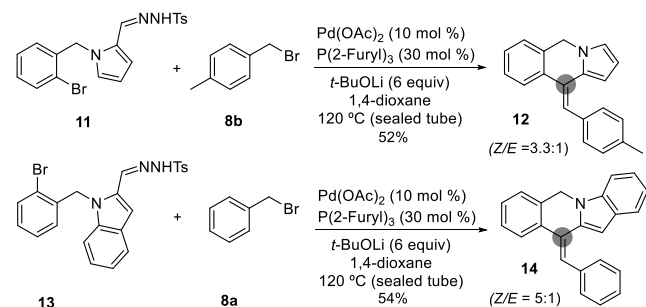
As summary, we report herein a new type of Pd-catalyzed autotandem cyclization that proceeds by formation of a C-C single bond and a C-C double bond on the same carbon atom. The cascade process includes the cross-coupling reaction between *N*-tosylhydrazones and benzyl bromides followed by an intramolecular Heck reaction. The cyclization occurs by reaction of a bifunctional coupling partner with a monofunctionalized system. Interestingly, two different arrangements for the reactive groups are possible, greatly enhancing the synthetic possibilities of the reaction. The versatility has been illustrated with the synthesis of a variety of carbo- and heterocyclic structures employing the same synthetic strategy including, fluorene, xanthene, acridine, pyrroloisoquinoline and indoloisoquinoline derivatives.

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