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Pd-catalyzed Synthesis of Benzofused Carbo- and Heterocycles through Carbene Migratory Insertion/Carbopalladation Cascades with Tosylhydrazones

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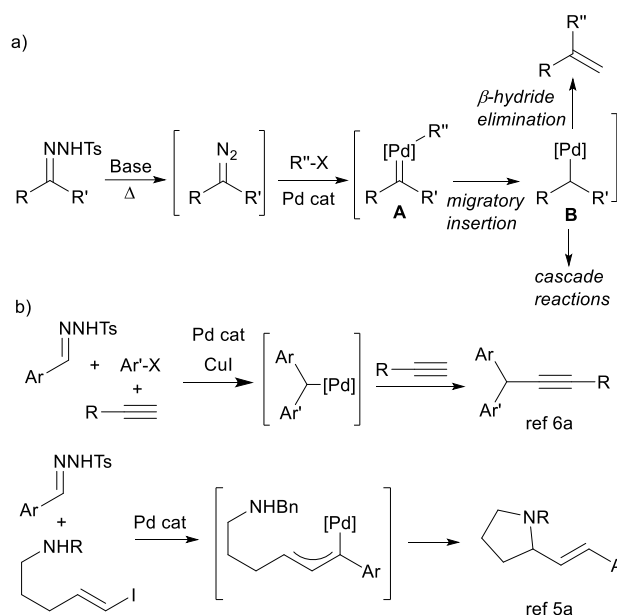
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The Pd-catalyzed reaction between *o*-iodoallylbenzene and tosylhydrazones gives rise to indene derivatives through a process that involves a carbene migratory insertion followed by an intramolecular carbopalladation, with formation of two C-C bonds on the same carbon atom. The same strategy has been also applied for the synthesis of 2,3-disubstituted benzofurans and indenones by selecting the proper *o*-substituted iodoarene.

The Pd-catalyzed cross-coupling between tosylhydrazones and organic halides, first introduced by our research group in 2007,¹ have established since then as a very reliable C-C bond forming reaction, and has been successfully applied in the synthesis of substituted alkenes.² The accepted catalytic cycle of these transformations^{1a} (scheme 1, a), involves as characteristic steps the formation of a Pd-carbene complex **A** by reaction of a Pd(II) complex with the diazo compound generated from the tosylhydrazone, and the migratory insertion of the carbene ligand into the Pd-C bond to give alkylpalladium complex **B**. Then, β -hydride elimination releases the coupling product and regenerates the Pd(0) catalyst. If the reaction is carried out with substrates that cannot undergo the β -hydride elimination step, alternative cascade transformations could be designed taking advantage of the reactivity of the alkylpalladium complex.^{3,4} In this context, several cascade processes have been devised making use of this concept, involving the formation of intermediate allylpalladium⁵ or benzylpalladium⁶ complexes in the migratory insertion reaction followed by a subsequent evolution (scheme 1, b).

Continuing with our interest on Pd-catalyzed reactions with tosylhydrazones and their application in cascade processes,⁷ we decided to combine the C-C bond forming reaction based on the migratory insertion step with an intramolecular carbopalladation reaction.

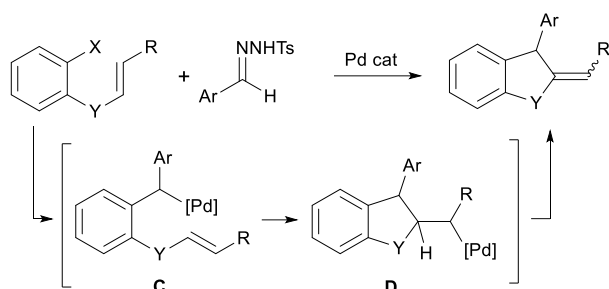


Scheme 1: a) General mechanisms of Pd-catalyzed cross-coupling reactions with tosylhydrazones. b) Selected examples of cascade reactions.

In our design (scheme 2), the benzylpalladium complex **C** would experiment the migratory insertion of the alkene, to give the new alkylpalladium intermediate **D**, and after the final β -hydride elimination, the corresponding cyclic compound would be formed. Interestingly, in the overall transformation, two C-C bonds would have been formed on the former hydrazonic carbon atom. It must be noted that this approach had been previously studied by Van Vranken employing trimethylsilyldiazomethane as carbene precursor,⁸ however, those reactions showed limited applicability and synthetic interest due to the formation of subproducts derived from the incorporation of more than one molecule of carbene during the cascade process. For these reasons, we found interesting to investigate whether the same approach could be carried out with tosylhydrazones instead of stabilized diazo compounds and if it would be possible to find the reaction conditions to overcome the limitations reported in those reactions.

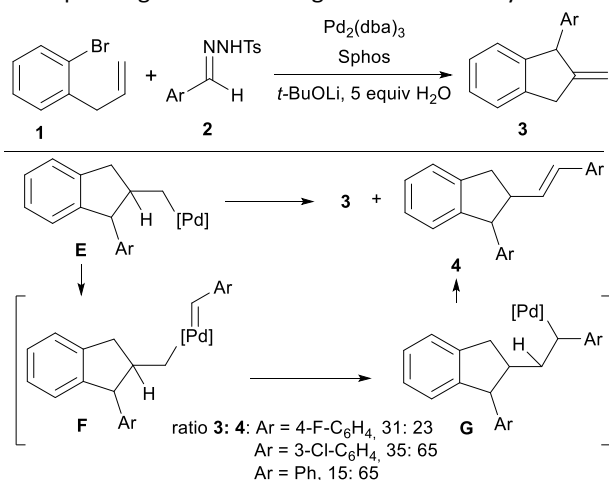
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Scheme 2: This work's proposed cascade reaction.

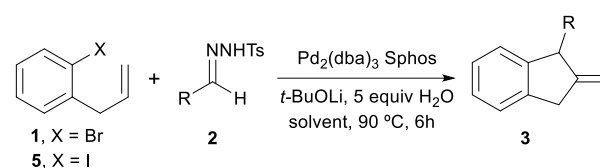
We started our research employing 1-allyl-2-bromobenzene **1** and the hydrazone derived from 4-dimethylaminobenzaldehyde **2a** as a model to develop proper reaction conditions. We expected that upon the oxidative addition, the incorporation of the diazo compound to the catalytic cycle might be favoured towards the intramolecular 5-*endo-trig* Heck reaction.⁹ Indeed, preliminary experiments under the standard reaction conditions for cross-coupling reactions with tosylhydrazones revealed the formation of the expected indane **3a** with moderate yield. After some experimentation that included the variation of several reaction parameters as well as the ligand and the base, the best reaction conditions found involved the employment of Sphos a ligand and LiOtBu as base, as well as the addition of 5 equiv of water.^{1d} Under these conditions (scheme 3, table 1, method A), the scope of the reaction was examined leading to the corresponding indanes although with moderate yields.

Scheme 3: Preliminary results on the synthesis of methyleneindanes **3** from 1-allyl-2-bromobenzene and tosylhydrazones.

The relative low yield obtained in most examples was due to the formation of compound **4**, which incorporates two diazo compound fragments. The generation of **4** can be justified (scheme 3) considering that the alkylpalladium complex **E** can react with a second diazo compound at a faster rate than the β -hydride elimination step to give intermediate Pd-carbene complex **F**. Then, the migratory insertion/ β -hydride elimination sequence furnishes compound **4**. Unfortunately, after extensive experimentation, it was not possible to shut down completely this reaction pathway. Indeed, at 70 °C the formation of **4** could be minimized, but at expenses of a lower conversion. For this

reason we decided to examine the reaction with the analogous iodides, in the expectation that the higher reactivity of the aromatic iodides might allow more flexibility in the composition of the catalyst, and thus, tune the activity towards the desired indanes.

Thus, a reoptimization was conducted with 1-allyl-2-iodobenzene **5**. In spite of the examination of a large array of structurally diverse phosphines as ligands, Sphos turned out to be again the best for the transformation. Additionally, better yields were obtained by conducting the reactions in acetonitrile as solvent, but also in the presence of 5 equiv of water. The scope of the process turned out to be wider than in the case of the reaction with the bromide (table 1 method B) providing, generally much higher yields. Moreover, the formation of the undesired subproduct **4** was never detected, in these cases.

Table 1: Synthesis of indanes **3** from 1-allyl-2-bromobenzene and 1-allyl-2-iodobenzene **5** and tosylhydrazones.

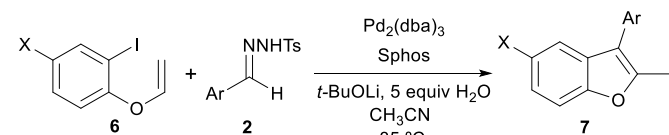
Compound	X/Method ^a	R	Yield ^b %
3a	Br/Method A	4-Me ₂ N-C ₆ H ₄	76
	I/Method B		96
3b	Br/Method A	4-MeO-C ₆ H ₄	40
	I/Method B		96
3c	Br/Method A	Ph	56
	I/Method B		77
3d	Br/Method A	4-F-C ₆ H ₄	47
	I/Method B		80
3e	Br/Method A	4-Me-C ₆ H ₄	35
	I/Method B		90
3f	I/Method B	3-Cl-C ₆ H ₄	82
3g	Br/Method A	3-Pyridyl	87
3h	I/Method B	<i>t</i> -Butyl	48
3i	I/Method B	4-HO-C ₆ H ₄ ^c	63
3j	I/Method B	4-NC-C ₆ H ₄	50
3k	I/Method B	2,4,6-(MeO) ₃ -C ₆ H ₂	71

^a **Method A**: Aryl bromide, 1 equiv; tosylhydrazone, 1.1 equiv; Pd₂(dba)₃ (2 mol %); Sphos, (8 mol %); *t*-BuOLi 2.5 equiv; H₂O, 5 equiv, 1,4-dioxane, 90 °C, 6 h. **Method B**: Aryl iodide, 1 equiv; tosylhydrazone, 2 equiv; Pd₂(dba)₃ (3 mol %); Sphos, (8 mol %); *t*-BuOLi, 6 equiv; H₂O, 5 equiv; CH₃CN, 1 h. ^b Isolated yields after column chromatography. ^c Prepared employing the tosylhydrazone of acetoxybenzaldehyde.

As illustrated by the examples presented in table 1, the reaction can be applied to tosylhydrazones derived from aromatic and heteroaromatic aldehydes with a variety of different substitutions, including a highly hindered diortho-substituted system (**3k**). Additionally, the hydrazone of pivalaldehyde was also an appropriate substrate (**3h**).[‡] It is worth noting that the indene scaffold is present in a variety of molecules with bioactive and pharmaceutical activity,¹⁰ therefore, this methodology represents a versatile synthetic alternative for the preparation of this important building block.

With these results in hand we turned our attention to allyl ethers **6** (table 2), that would hopefully lead to benzofuran derivatives through a similar cascade reaction. In some preliminary experiments, the benzofurans **7** were obtained with moderate yields, but in many cases, the undesired compound derived from the incorporation of a second unit of tosylhydrazone was again detected. Nevertheless, the formation of these subproducts could be avoided by carrying out the reactions with slow syringe-pump addition of the tosylhydrazone. In this way, the concentration of the diazo compound is kept low, and therefore the β -hydride elimination on the alkylpalladium intermediate **D** (scheme 2) occurs at a faster rate than the reaction with the transient diazo compound. Thus, under the proper reaction conditions, a set of 2,3-disubstituted benzofurans **7** were obtained in a very straightforward manner from readily available starting materials (Table 2). Interestingly, this method represents an original approach to substituted benzofurans,¹¹ which are constructed by formation of two C-C bonds on the same carbon atom.

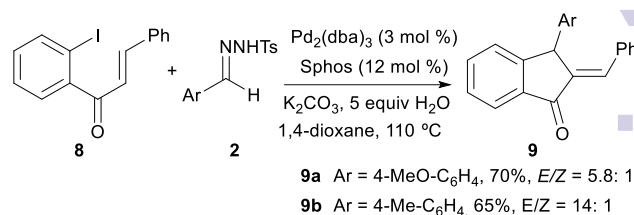
Table 2: Indanes **7** prepared from iodoenolethers **6** and tosylhydrazones.



Compound	X	Ar	Yield ^b %
7a	H	4-Me ₂ N-C ₆ H ₄	50
7b	H	4-MeO-C ₆ H ₄	77
7c	H	Ph	60
7d	H	4-F-C ₆ H ₄	57
7e	H	2,4,6-(MeO) ₃ -C ₆ H ₂	59
7f	H	4-Me-C ₆ H ₄	58
7g	H	3-Cl-C ₆ H ₄	57
7h	H	4-CF ₃ -C ₆ H ₄	68
7i	H	4-CN-C ₆ H ₄	73
7j	H	2-Furyl	40
7k	MeO	Ph	68
7l	MeO	4-CN-C ₆ H ₄	53

^a Reaction conditions: Aryl iodide, 1 equiv; tosylhydrazone, 2 equiv; Pd₂(dba)₃ (3 mol %); Sphos, (12 mol %); *t*-BuOLi, 6 equiv; H₂O, 5 equiv; CH₃CN, 85 °C, 1 h. The tosylhydrazone is added via syringe pump over a period of 1 h. ^bIsolated yields after column chromatography.

To further illustrate the versatility of this cascade reaction as a method for the synthesis of benzofused five membered rings, we studied also the reaction with iodoalkene **8**, a quite challenging substrate due to the presence of additional functionality as well as substitution on the double bond. Delightfully, the reaction led to the obtention of the benzylideneindenones **9** derived from the cyclization reaction (scheme 4). Noteworthy, the final β -hydride elimination took place with high stereoselectivity leading to the *E* stereoisomer as major product.



Scheme 4: Synthesis of benzylideneindenones **9** from tosylhydrazones and iodoalkene **8**

As summary, we have reported a new cascade reaction that leads to the obtention of benzofused five-membered rings through a catalytic cycle that involves a migratory insertion of a Pd-carbene generated from a tosylhydrazone, followed by an intramolecular Heck reaction. This process constitutes a novel approach to substituted indene and benzofuran derivatives, in which two C-C bonds are formed on the same carbon atom. Moreover, these preliminary results show great promise for the synthesis of different benzofused carbo- and heterocycles through the same methodology. We are currently investigating the expansion of the scope and the synthetic usefulness of this reaction.

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† With regard to the substitution of the double bond, the reactions with the 1,2-disubstituted alkene 1-(but-2-en-1-yl)-2-iodobenzene took place successfully, but gave rise to a mixture of three isomeric indanes arising from an unselective β -hydride elimination. However, ethoxycarbonyl substitution on the terminal position of the double bond or substitution at both the internal and terminal positions were not tolerated, as the formation of the indenes were not detected (see ESI for details).

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