Synthesis of Highly Substituted Polyenes by Palladium-Catalyzed Cross–Couplings of Sterically Encumbered Alkenyl Bromides and *N*-Tosylhydrazones

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To the memory of Prof. José Barluenga (deceased September 7, 2016)

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Abstract: A new method for the synthesis of polysubstituted conjugated dienes is described, through the palladium-catalyzed cross-coupling between *N*-tosylhydrazones and alkenyl bromides. The reaction proceeds efficiently when a combination of a highly substituted bromoalkene and a hydrazone derived from a ketone are employed, pointing to the convenience of a sterically encumbered environment. This unprecedented process allows for the stereocontrolled preparation of highly substituted dienes and polyenes.

Keywords: Palladium catalysis; diene; polyene; *N*-tosylhydrazone; alkenyl bromide

Introduction

The Palladium-catalyzed cross-couplings between sulfonylhydrazones and aryl halides[1] has been established over the last decade as a highly robust method for the synthesis of substituted alkenes,[2] which has found wide application in organic synthesis, such as the preparation of biologically active molecules,[3] fluorinated alkenes,[4] and also participate in a variety of cascade and auto-tandem catalyzed reactions.[5]

The reaction features an almost total compatibility with all types of *N*-sulfonylhydrazones, including those derived from functionalized,[6] and also α,β-unsaturated ketones.[7] Regarding the structure of the organic electrophile, the coupling reaction has been applied not only to aryl halides and sulfonates, but also to benzyl[8] and allyl derivatives.[9] The mechanism cur-rently accepted for this cross-coupling reaction (Scheme 1, a) involves formation of a palladium carbene **II**, that undergoes migratory insertion to give benzylpalladium complex **III**, followed by a fast β-hydride elimination that releases the coupling product and regenerates the Pd (0) species.
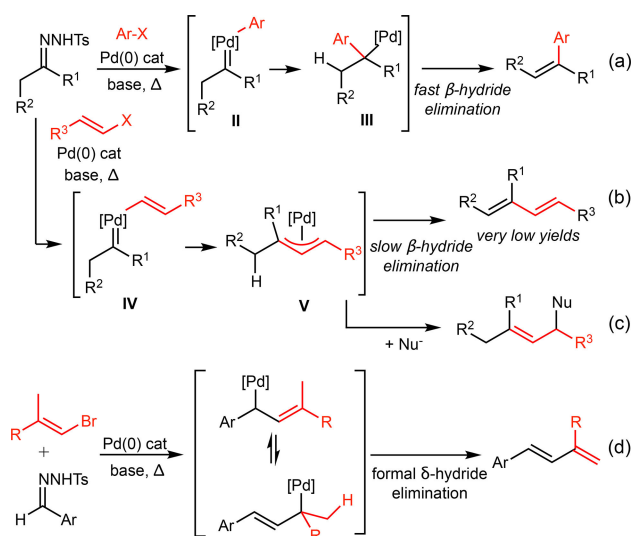
Scheme 1. Different reaction pathways of Pd-catalyzed reactions involving migratory insertion reactions on Pd-carbenes. Influence of the hydride elimination on the reaction outcome.

Notably, the application of this methodology to the coupling reaction with alkenyl halides *remains almost unexplored*. We reported several years ago some limited examples on the couplings of certain alkenyl

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halides with arylaldehyde tosylhydrazones, which led to 1,3-dienes through a non-conventional catalytic cycle that involved a formal δ-hydride elimination step (Scheme 1, d).[7] On the other hand, Van Vranken, in the context of the study of the elegant three-components carbenylative aminations of alkenyl iodides,[5g,10] showed that the η[3]-allylpalladium intermediates **V** (Scheme 1) generated upon migratory insertion of the carbene ligand on the palladium-alkenyl bond on intermediate **IV**, do not undergo fast β-hydride elimination (Scheme 1, b).

Instead, nucleophilic attack at the less hindered site of the η[3]-allylpalladium complex **V** takes place, giving rise to the product of the three-components reaction (Scheme 1, c). However, in the absence of an external nucleophile, the catalytic cycle is slowed down and uncatalyzed decomposition of the *N*-tosylhydrazone takes place, leading to very low yields of the coupling products (Scheme 1, b). Noteworthy, the cross-couplings of certain alkenyl tosylates, leading to dienes have been reported in processes that required the employment of an extremely bulky ligand.[11]
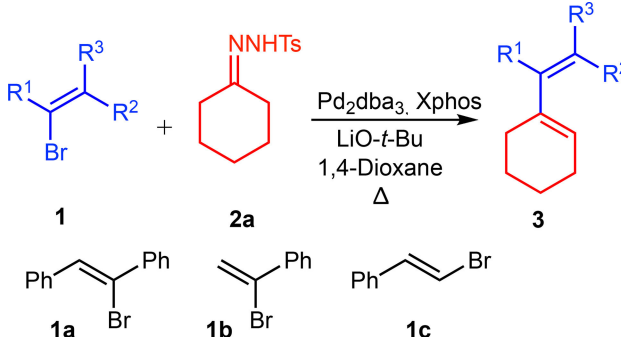
In the context of an ongoing project in our lab, we were interested on exploring the cross-couplings of *N*-tosylhydrazones with sterically encumbered alkenyl halides. In the course of this work, we discovered that, unlike the previous observations with less hindered alkenyl bromides, the coupling reaction proceeded successfully for the synthesis of highly substituted conjugated dienes. However, under the same reaction conditions, monosubstituted alkenyl halides, such as α- and β-bromostyrene failed to provide the coupling products in synthetically useful yields. Herein we wish to report our results.

Results and Discussion

Thus, we initiated our study with the reaction between (*Z*)(1-bromoethene-1,2-diyl)dibenzene **1a** and cyclohexanone tosylhydrazone **2a**. Several reaction conditions and catalytic systems were examined (Table 1) to discover that the diene **3a** could be best obtained employing a combination of Pd₂(dba)₃ (4 mol%) and Xphos (16 mol%) with LiO-*t*-Bu as the base in 1,4-dioxane as solvent at 130°C (Table 1, entry 3). Lower catalyst loading (entry 7) led to the recovery of substantial amounts of the starting bromide **1a** while almost no reaction product was obtained at lower temperature (entry 9). In contrast, when the same reaction was conducted employing α-bromostyrene **1b**, the expected diene was obtained in a quite poor 33% isolated yield (Table 1, entry 12). Moreover, in the reaction with β-bromostyrene **1c**, although the expected diene could be detected by GC/MS of the reaction crude, very low isolated yield was finally obtained (Table 1 entry 13). Of note, the employment

of bulkier ligands such as *t*-BuXphos did not provide any improvement in the outcome of the coupling reactions (Table 1, entry 14).

Table 1. Optimization of the reaction conditions for the cross-coupling between bromoalkenes **1** and *N*-tosylhydrazone **2a**.[a]

Entry	1	Base	Ligand	Yield (%)
1	1a	LiO-*t*-Bu	P(2-furyl)₃[b]	50
2	1a	LiO-*t*-Bu	PPh₃[b]	70
3	1a	LiO-*t*-Bu	Xphos	79
4	1a	LiO-*t*-Bu	P(*o*-Tol)₃[b]	0
5	1a	LiO-*t*-Bu	BINAP	0
6	1a	LiO-*t*-Bu	Xantphos	0
7[c]	1a	LiO-*t*-Bu	Xphos	35
8[d]	1a	LiO-*t*-Bu	Xphos	46
9[e]	1a	LiO-*t*-Bu	Xphos	<10
10	1a	Cs₂CO₃	Xphos	<10
11	1a	K₂CO₃	Xphos	36
12	1b	LiO-*t*-Bu	Xphos	33
13	1c	LiO-*t*-Bu	Xphos	<10
14	1b	LiO-*t*-Bu	*t*-BuXphos	<10

[a] Reaction conditions: Bromide **1**, (0.1 mmol), hydrazone **2**, (2 equiv.), Pd₂(dba)₃ (4 mol%), Ligand (16 mol%), base (4 equiv.), 1,4-dioxane (2 mL), 130°C, 12 h.
[b] A 3:1 Ligand/Pd ratio was used.
[c] Pd₂(dba)₃ (2 mol%) and Xphos (8 mol%).
[d] *N*-tosylhydrazone **2a** (1.2 equiv.) and LiO-*t*-Bu (3.2 equiv.).
[e] Carried out at 110°C.

The optimized reaction conditions were applied to the coupling of alkenyl bromide **1a** with a set of different *N*-tosylhydrazones **2** to establish the scope of the reaction (Scheme 2). Thus, the substituted 1,3-dienes **3** were obtained with excellent to moderate yields for the reactions with cyclic *N*-tosylhydrazones derived from cyclohexanones, cyclopentanones, cycloheptanone and tetralones. Also the *N*-tosylhydrazone of 3-pentanone provided the coupling product in excellent yield (**3f**). The employment of unsymmetrically substituted *N*-tosylhydrazones led to a mixture of regioisomers derived from a non-selective β-hydride elimination step (**3g**, **3l**). Finally, hydrazones derived

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from acetophenone or aliphatic aldehydes failed to provide the expected dienes in a synthetically useful yield, although small amounts of the dienes, together with several unidentified products were detected by GC/MS. These results point to the necessity of a sterically congested environment to enable the efficient coupling reaction.
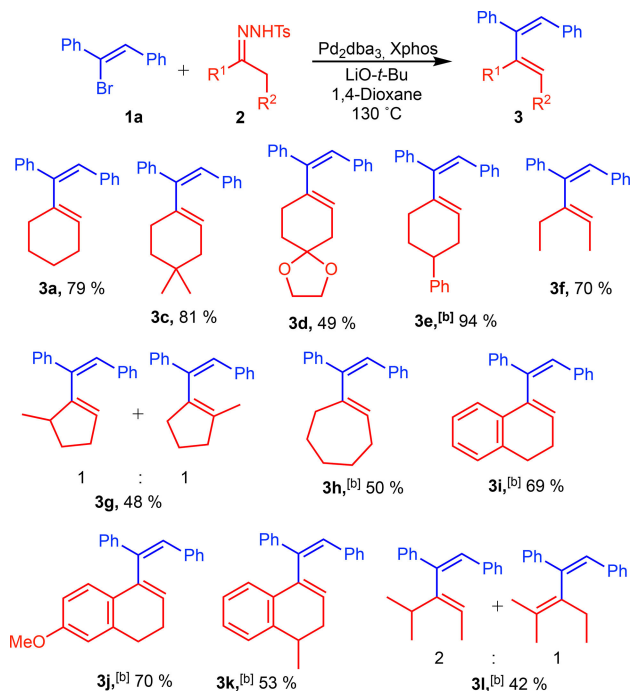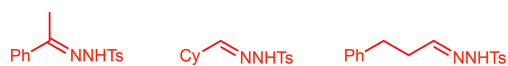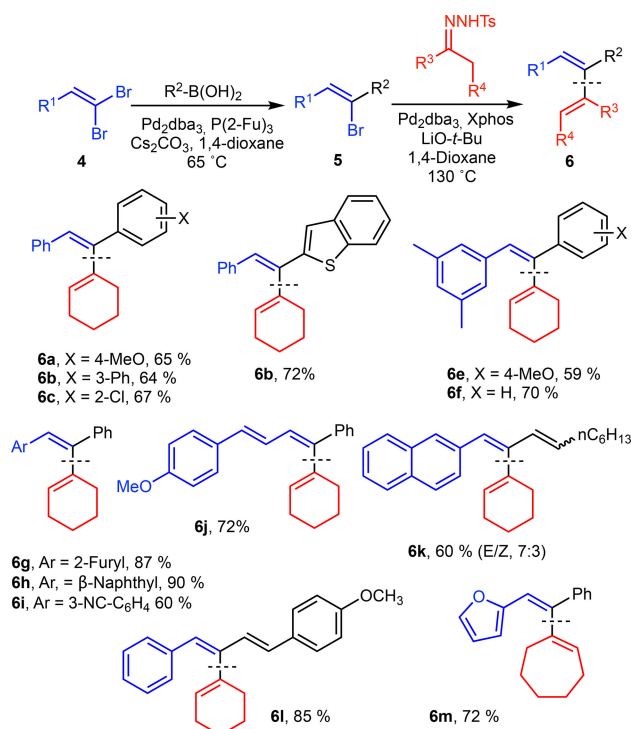

Scheme 2. [a] 1,3-Dienes prepared by Pd-catalyzed cross-coupling between bromoalkene **1a** and different tosylhydrazones **2**.

[a] Reaction conditions: Bromide **1a**, (0.1–0.3 mmol), hydrazone **2**, (1–2 equiv.), Pd$_2$(dba)$_3$ (4 mol %), Xphos (16 mol %), LiO-t-Bu (4 equiv.), 1,4-dioxane (2 mL), 130 °C, 12 h.

[b] N-tosylhydrazone **2a** (1.2 equiv.) and LiO-t-Bu (3.2 equiv.).

Next, we decided to apply the coupling reaction to different trisubstituted bromoalkenes. Sterodefined trisubstituted bromoalkenes **5** can be efficiently prepared by the stereoselective cross-coupling of 1,1-dibromoolefins with boronic acids.[12] Following the Suzuki coupling, a set of trisubstituted bromoalkenes **5** was prepared, and the cross coupling reactions with N-tosylhydrazones **2** were examined (Scheme 3).

The results presented in Scheme 3 show that the scope of the reaction is very broad allowing for the preparation of a diversity of sterically encumbered dienes **6**, and also the synthesis of linear-conjugated (**6j**) and cross-conjugated (**6k**, **6l**) trienes.


Scheme 3. [a] Structurally diverse and stereodefined dienes **6** prepared by sequential Pd-catalyzed Suzuki and N-tosylhydrazone cross-couplings.

[a] Reaction conditions for the Pd-catalyzed cross-coupling: Bromide **5**, (0.1–0.3 mmol), hydrazone **2**, (2 equiv.), Pd$_2$(dba)$_3$ (4 mol%), Xphos (16 mol%), LiOtBu (4 equiv.), 1,4-dioxane (2 mL), 130 °C, 12 h.

The reactions presented in Schemes 2 and 3 were restricted to the employment (Z)-alkenyl bromides. To continue the study of the scope of the cross-coupling, we tested the reaction with bromides **7**, as representatives of trisubstituted (E)-alkenyl bromides. Bromides **7** could be efficiently prepared also from the corresponding N-tosylhydrazones following a procedure recently reported by Prabhu et al.[13] However, the reaction of **7a** with N-tosylhydrazone **2a** proceeded sluggishly, leading to a mixture of various isomeric coupling products differing in the position of the double bonds, that could not be separated.

Gratifyingly, when the coupling reaction was conducted with the tetralone derived N-tosylhydrazones **2b–d**, the expected 3,3′,4,4′-tetrahydro-1,1′-binaphthalenes **8** were obtained in good yields (Scheme 4). It is worth noting the synthetic interest of dienes **8**, that have been previously used as precursors of substituted binaphthyls, as well as dienes in [4+2] cycloadditions, oriented to the preparation of polycyclic aromatic hydrocarbons, phtalocyanines and helicenes with applications in materials chemistry,[14] and even in graphene functionalization.[15] Noteworthy, the methods available for their synthesis are based on the

dimerization of the corresponding tetralone, and thus, restricted to symmetric systems. However, our methodology enables the selective synthesis of the non-symmetrically substituted systems in a straightforward manner from two different tetralones through their tosylhydrazones. As an example of the usefulness of these dienes, reaction of **8b** with *N*-phenylmaileimide[14e] led to the unprecedented nonsymmetrically substituted pentahelicene precursor **9** (Scheme 4).
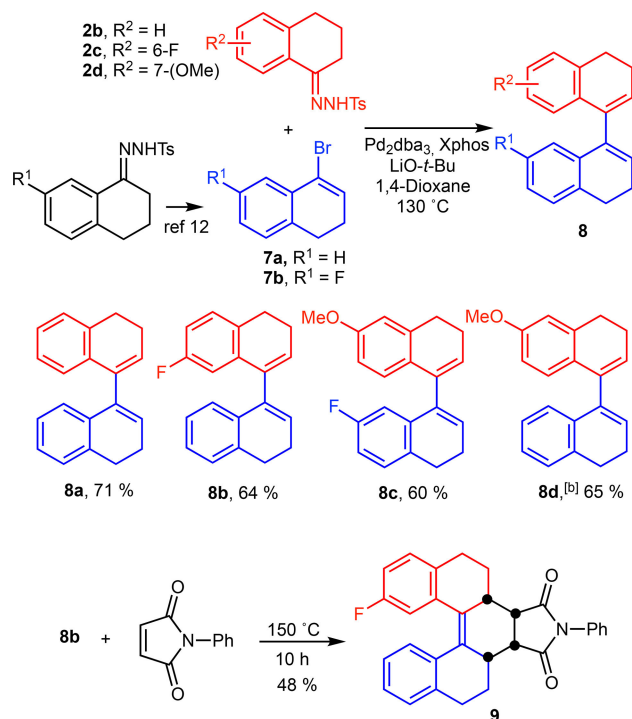
Scheme 4. [a] Synthesis of 3,3′,4,4′-tetrahydro-1,1′-binaphthalenes **8** starting from two *N*-tosylhydrazones and application in the synthesis of the non-symmetric pentahelicene precursor **9**.
[a] Reaction conditions for the Pd-catalyzed cross-coupling: Bromide **7**, (0.1–0.3 mmol), hydrazone **2**, (2 equiv.), Pd$_2$(dba)$_3$ (4 mol%), Xphos (16 mol %), LiO-*t*-Bu (4 equiv.), 1,4-dioxane (2 mL), 130 °C, 12 h.
[b] Obtained as a 3: 1 inseparable mixture with a partially aromatized dihydrobinaphthyl.

Conclusion

As summary, we have described herein the Pd-catalyzed cross-coupling of alkenyl bromides and *N*-tosylhydrazones as an efficient method for the preparation of a wide structural variety of conjugated dienes and polyenes. These results contribute to highlight the versatility of the already well developed Pd-catalyzed cross-couplings with *N*-sulfonylhydrazones by the incorporation of sterically congested alkenyl bromides as coupling partners. Moreover, the methodology

presented allows for the straightforward preparation of these class of poorly described polienic systems.

Experimental Section

General Experimental Procedure for the Cross–Coupling Reaction Between Alkenyl Bromides 1, 5 or 7 and *N*-Tosylhydrazones 2:

A carousel reaction tube under nitrogen atmosphere was charged with the corresponding alkenyl bromide (0.15 mmol), *N*-tosylhydrazone (1 to 2 equiv.), tris(dibenzylideneacetone)dipalladium(0) (4 mol%), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (16 mol%), lithium *tert*-butoxide (3-4 equiv. for 1–2 equiv. of hydrazone respectively), and 1,4-dioxane (2.4 mL). The reaction mixture was stirred at 130 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ethyl acetate.

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