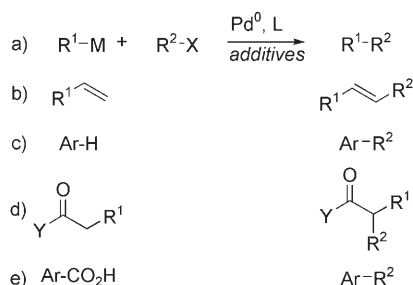


N-Tosylhydrazones as Reagents for Cross-Coupling Reactions: A Route to Polysubstituted Olefins**

José Barluenga,* Patricia Moriel, Carlos Valdés, and Fernando Aznar

Pd-catalyzed cross-coupling reactions can be considered nowadays to be the most reliable methodology for the formation of C(sp²)-C(sp²) bonds.^[1] These types of reactions find increasing application in the synthesis of complex organic molecules.^[2] In a cross-coupling reaction, an electrophile is combined with a nucleophile to provide the corresponding coupling product (Scheme 1 a). Organometallic reagents such



Scheme 1. General strategies for Pd-catalyzed C-C bond-forming reactions.

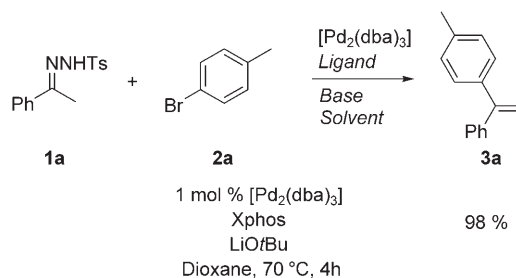
as organomagnesium,^[3] -zinc,^[4] -tin,^[5] -silicon,^[6] and -boron^[7] compounds among others, are generally employed as the nucleophilic component. In spite of the wide applicability of these methodologies, a limitation of the general approach is the requirement of a stoichiometric amount of the organometallic reagent, which in many cases has to be prepared through expensive, moisture-sensitive, and multistep procedures.

The Heck reaction (Scheme 1 b) can be considered as the earliest example of a C-C bond-forming reaction that does not require stoichiometric amounts of the organometallic coupling partner.^[8] In recent years, some other examples have been discovered which differ from cross-coupling: the direct activation of C-H bonds^[9] (Scheme 1 c), the α -arylation of ketones,^[10] esters,^[11] and amides^[12] (Scheme 1 d), and the

employment of arene carboxylic acids in decarboxylative Pd-catalyzed synthesis of biaryls (Scheme 1 e).^[13] The common feature of all these methodologies is that no stoichiometric organometallic reagent is employed in the reaction.

During recent years we have been studying the employment of different types of nitrogenated reagents in Pd-catalyzed cross-coupling reactions.^[14] In this context, we discovered that *N*-tosylhydrazones behave as a nucleophilic component in a new type organometallic-free Pd-catalyzed C-C-bond-forming reaction.^[15,16] Herein we present our preliminary results, which have led to the development of a new methodology for the synthesis of polysubstituted olefins.

We started our study with the model reaction between the acetophenone *N*-tosylhydrazone (**1a**) and *p*-bromotoluene (**2a**; Scheme 2). In initial experiments employing different



Scheme 2. Formation of diaryl olefin **3a** by coupling between aryl halide **2a** and acetophenone hydrazone **1a**.

reaction conditions, ligands, and bases we never observed formation of either *C*- or *N*-arylation products. Instead, we obtained variable amounts of the disubstituted olefin **3a**. After some experimentation, we concluded that [Pd₂(dba)₃] (dba = *trans,trans*-dibenzylideneacetone), Xphos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) as ligand, and LiOtBu as base in dioxane at 70 °C provided the coupling product **3a** in quantitative yield. Having these efficient experimental conditions in hand, we studied the scope of the reaction regarding both coupling partners, the hydrazone and the aryl halide. Representative examples are presented in Table 1.

The reaction can be carried out with *N*-tosylhydrazones derived from both ketones and aldehydes, giving rise to the corresponding di- or trisubstituted olefins. Hydrazones derived from cyclohexanone (Table 1, entries 5–7) and cyclohexane carboxaldehyde (Table 1, entries 13–15) required more-demanding experimental conditions. Thus, an increase in the temperature or the catalyst loading was required to achieve high conversions.

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Table 1: Synthesis of di- and trisubstituted olefins by cross-coupling of tosylhydrazones with aryl halides.^[a]

$ \begin{array}{c} \text{NNHTs} \\ \\ \text{R}^1\text{C}=\text{C}(\text{R}^2)\text{R}^3 + \text{Ar-X} \\ \text{1} \qquad \qquad \text{2} \end{array} \xrightarrow[\text{LiOtBu, Dioxane}]{[\text{Pd}_2(\text{dba})_3], \text{Xphos}} \begin{array}{c} \text{Ar} \\ \\ \text{R}^1\text{C}=\text{C}(\text{R}^2)\text{R}^3 \\ \text{3} \end{array} $						
Entry	Hydrazone 1	Halide 2	<i>T</i> [°C]	<i>t</i> [h]	Olefin 3	Yield [%] ^[b]
1			70	4		98
2			90	6		96
3			90	4		98
4			70	3		82 ^[c]
5			110	15		74
6			110	16		90
7			110	16		95
8			90	15		78 ^[d]
9			110	5		80
10			90	16		80 ^[e]
11			90	4		75
12			90	10		68
13			90	16		99 ^[f]
14			110	17		62 ^[f,g]
15			90	17		52 ^[h]
16			90	10		67 ^[i]

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), [Pd₂(dba)₃] (1 mol%), Xphos (2 mol%), LiOtBu (2.2 mmol), dioxane (6 mL). [b] Yields of isolated product. [c] Yield of the combined mixture of esters. [d] A 92:8 *E*:*Z* mixture of isomers was obtained. [e] A 1:1 *E*:*Z* mixture of isomers was obtained. [f] 2 mol% [Pd₂(dba)₃] and 4 mol% Xphos were employed. [g] 88% conversion. [h] 84% conversion. [i] The major regioisomer was obtained as a 78:4 *E*:*Z* mixture of isomers.

Stereochemistry is a very important issue in the synthesis of polysubstituted olefins. In this context, a hydrazone derived from a linear aldehyde provided exclusively the *trans* olefins (Table 1, entries 11 and 12). In the case of trisubstituted olefins, the stereochemical outcome of the reaction seems to be directed by the size of the substituents (Table 1, entries 8–10).

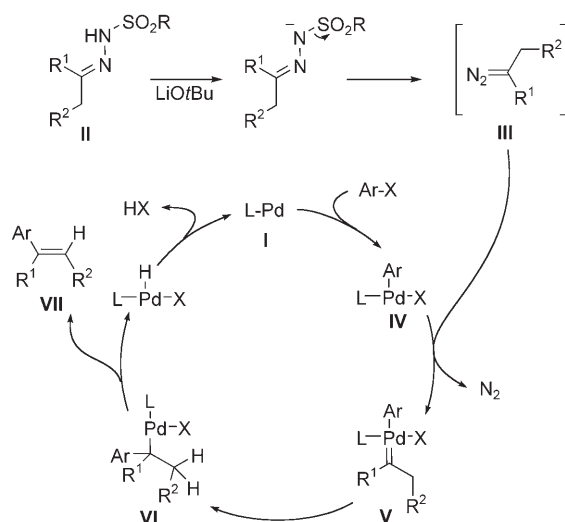
The reaction is general with respect to the structure of the aryl halide. Bromides and chlorides can be employed with similar results (Table 1, entries 1 and 2). Electron-donating (Table 1, entries 7, 10, 12, and 14) and electron-withdrawing groups (Table 1, entries 3, 4, and 8) in benzene rings are tolerated in the reaction. Moreover, both π -rich (Table 1, entry 6) and π -deficient (Table 1, entry 15) heterocycles

participate efficiently in the coupling. Nitrile (Table 1, entry 3) and carbonyl groups (Table 1, entry 8) are also compatible with the transformation. Furthermore, when the reaction was performed in the presence of a methyl ester, the coupling reaction proceeded with very high yield, although a mixture of the expected product and the transesterified *tert*-butyl ester was obtained (Table 1, entry 4).

Finally, the reaction with the hydrazone prepared from 4-phenyl-2-butanone showed a promising regioselectivity (Table 1, entry 16): an 82:18 mixture of the trisubstituted olefin (as a 78:4 mixture of the *E* and *Z* isomers) and the terminal disubstituted olefin was obtained. Further tuning of the reaction conditions might lead to higher regioselectivities.

It is well known that *N*-tosylhydrazones in the presence of alkoxides undergo base-mediated decomposition through the Bamford–Stevens^[17] reaction to generate diazo compounds, which evolve to produce metal carbenes in the presence of a transition metal.^[18] Thus, it seems reasonable that the transformation presented herein should proceed through the formation of a transient palladium carbene complex, generated from the tosylhydrazone.

A plausible catalytic cycle for this coupling reaction might start with the oxidative addition of the aryl halide to the Pd⁰ catalyst **I** to give aryl palladium complex **IV** (Scheme 3).

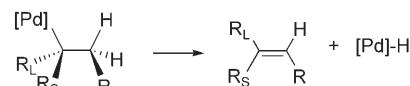


Scheme 3. Proposed mechanism for the Pd-catalyzed cross-coupling of *N*-tosylhydrazones.

Then, reaction of the diazo compound **III** (generated by the base-mediated decomposition of the tosylhydrazone **II**) with aryl palladium complex **IV** would produce Pd carbene complex **V**.^[19] The unstable aryl palladium carbene complex **V** may evolve through a migratory insertion of the aryl group to give the alkyl palladium complex **VI**. Finally, β -hydrogen elimination would provide the arylated olefin **VII** and regenerate the Pd⁰ catalyst.

Migratory insertion reactions have been previously proposed for *N*-heterocyclic-,^[20] amino-, and methoxycarbene palladium complexes.^[21,22] Moreover, Van Vranken et al. have reported the Pd-catalyzed insertion of diazo compounds into benzyl and vinyl halides, in processes that most likely proceed

through a Pd–carbene complex.^[23] In this reaction pathway, the stereochemistry of the final olefin would be determined by the *syn* β -hydrogen elimination step of complex **VI**. Thus, in the transition state for the formation of 1,2-disubstituted olefins and trisubstituted olefins, the R group would be eclipsed with the smaller substituent of the vicinal carbon atom to minimize the steric interactions (Scheme 4). This is



Scheme 4. The *syn* β -hydrogen elimination that determines the stereochemistry of the olefins.

indeed the general trend, as hydrazones derived from non-branched aldehydes provide *trans* olefins (Table 1, entries 11 and 12), and trisubstituted olefins feature the bulky groups also in a *trans* arrangement (Table 1, entries 8 and 9). As shown by the example in entry 10, when the substituents R_S and R_L have similar sizes, a 1:1 mixture of isomers is obtained.

In summary, we have reported a new type of Pd-catalyzed cross-coupling reaction that employs *N*-tosylhydrazones as nucleophilic coupling partners. The main features of this new methodology are: 1) stoichiometric organometallic reagents are not required for the coupling reaction; 2) di- and trisubstituted olefins can be prepared with high stereoselectivity in most cases and with very high functional-group tolerance; 3) in view of the simple transformation of carbonyl compounds into tosylhydrazones, this methodology represents a very simple way to convert aldehydes and ketones into reagents for Pd-catalyzed cross-coupling reactions; 4) from a mechanistic point of view, the reaction most likely proceeds through a Pd–carbene complex in a process that has not yet been widely exploited, but has great promise, in Pd-catalyzed cross-coupling reactions. For these reasons, we think that this reaction will find wide application in target-oriented organic synthesis. Future work will include detailed mechanistic investigations, extension of this concept to other transition metals, optimization of the reaction conditions to achieve high regio- and stereoselectivities, and extension of the coupling reaction to other types of halides (vinyl, alkyl) and pseudohalides.

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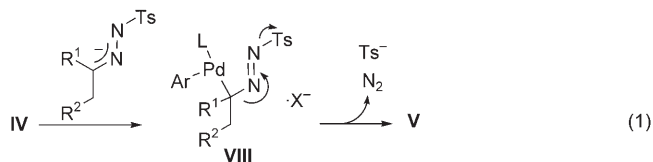
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