Palladium Catalysis

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Developments in Pd Catalysis: Synthesis of 1*H*-1,2,3-Triazoles from Sodium Azide and Alkenyl Bromides**

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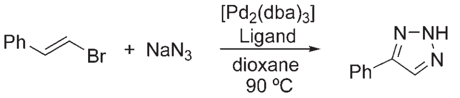
1,2,3-Triazoles are an important class of heterocycles which display an ample spectrum of biological activities and are widely employed as pharmaceuticals and agrochemicals. Moreover, compounds containing 1,2,3-triazoles have found industrial applications as dyes, corrosion inhibitors, and photostabilizers.[1] The conventional route to triazoles is the Huisgen dipolar cycloaddition of alkynes with organic azides. The development of the copper(I)-catalyzed reaction between organic azides and terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles[2] has represented a definitive advance in triazole chemistry, and has become a paradigm of a "click chemistry" reaction.[3] The reaction is effective in the preparation of a wide variety of triazole-containing molecules.[4] However, the reaction has a limitation in that inorganic azides are not good substrates. Consequently 1*H*-1,2,3-triazoles, which also have a wide range of uses,[5] cannot be prepared directly by using the click chemistry strategy, but instead require sequences involving deprotection steps and the employment of more elaborated azides.[6] Other routes to 1*H*-1,2,3-triazoles include dipolar cycloadditions between sodium azide and alkynes with an electron-withdrawing substituent,[7] the reaction of sodium azide with nitroalkenes,[8] and the rearrangement of propargyl azides.[9]

Over the last few years, we have been interested in Pd-catalyzed reactions between alkenyl halides and nitrogenated species for the formation of C–N bonds.[10] During our search for new coupling partners for such processes, we decided to explore the potential ability of the azide anion to participate in a Pd-catalyzed cross-coupling reaction.[11] We expected that the coupling of an azide with alkenyl halides would lead to vinyl azides. However, vinyl azides were never detected and instead 1*H*-1,2,3-triazoles were obtained under the standard reaction conditions. This unexpected result represents a novel method for the preparation of 1*H*-1,2,3-triazoles and a new

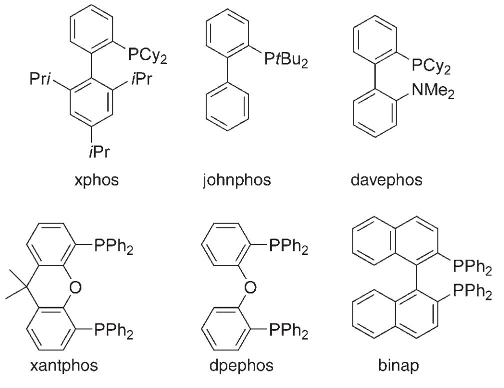
Table 1: Influence of the ligand in the reaction of β-bromostyrene with sodium azide.[a]



1a **2a**

Entry	Ligand	Pd [%]	Conv. [%]
1	PPh$_3$	2	15
2	davephos	2	0
3	johnphos	2	0
4	xphos	2	0
5	binap	2	0
6	dpephos	2	100
7	xantphos	2	100
8	no ligand	2	0
9	no ligand	0	0

[a] Reaction conditions: Alkenyl bromide **1** (1 mmol), sodium azide (3 mmol), 2:1 ligand/Pd, solvent (3 mL), 90 °C, 12 h. dba = *trans,trans*-dibenzylideneacetone, Cy = cyclohexyl.



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reactivity for Pd^0 catalysts. Herein, we report our findings regarding this new and intriguing reaction.

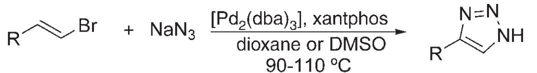
In a preliminary set of experiments we studied the reaction of β-bromostyrene (**1a**) with sodium azide in dioxane in the presence of [Pd$_2$(dba)$_3$] and a range of supporting ligands. In most cases, **1a** was recovered with no trace of any reaction product (Table 1). However, when the bidentate ligand xantphos was employed, no **1a** was recovered and instead the 1*H*-1,2,3-triazole **2a** was obtained in near quantitative yield.

The ligand specificity of the reaction is remarkable indeed. Only the chelating diphosphines xantphos and dpephos, in which the bite angle is large, promoted the reaction to a considerable extent.[12] Very low conversion was achieved with triphenylphosphine and no conversion at all was observed for binap, a bidentate phosphine with a smaller bite angle, nor for the bulky electron-rich monophosphines, johnphos, davephos, and xphos, which are usually very active. Moreover, no conversion at all was observed for control experiments in the absence of ligand (Table 1, entry 8) and in the absence of metal and ligand (Table 1, entry 9), thereby indicating the important role of the catalytic system.

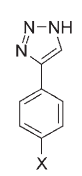
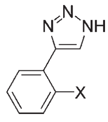
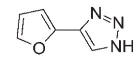
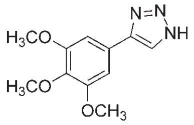
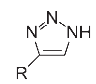
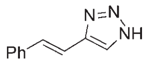
The scope of the reaction was examined using the optimized experimental conditions (Table 2). The formation of triazoles **2** occurred in very high yields for substituted β-bromostyrenes. The substitution on the aromatic ring had no influence on the outcome of the reaction, as systems substituted with neutral (Table 2, entry 1), electron-withdrawing (entries 3 and 4), or electron-releasing groups (entries 2 and 9) provided similar results. The reaction tolerates sensitive functional groups such as methyl esters or nitriles, *ortho* substitution in the aromatic ring (Table 2, entries 5–7), and heteroaromatic rings such as the 2-furan group (entry 8). The chemoselectivity of the reaction is noteworthy, as the presence of a halide (bromide or chloride) on the aromatic ring furnishes the triazole **2** as the sole reaction product.

Formation of the triazoles derived from alkyl-substituted bromoethylenes required a different set of reaction conditions. Thus, when the reaction of 1-bromodecene was carried out under the same conditions as previously used, we observed no conversion. By changing the solvent to DMSO, which enhances the solubility of the inorganic azide, we observed formation of the triazole with 55 % conversion after 24 h. After some experimentation, we determined that the optimal conditions for this transformation required an increase in the catalyst loading and reaction temperature (to 110 °C) (Table 2, entries 10 and 11). Finally, reaction of 1-bromo-4-phenyl-1,3-butadiene, as a representative bromodiene, proceeded in a very short time under the standard reaction conditions (dioxane, 90 °C). However, the alkenyl-substituted triazole suffered partial dimerization,[13] which reduced the overall yield of the triazole (Table 2, entry 13). Nevertheless, when the reaction was conducted in DMSO, the dimerization was inhibited, and gave rise to the corresponding triazole as the sole reaction product (Table 2, entry 12).

Table 2: Triazoles prepared by the Pd-catalyzed reaction of alkenyl bromides and sodium azide.[a]



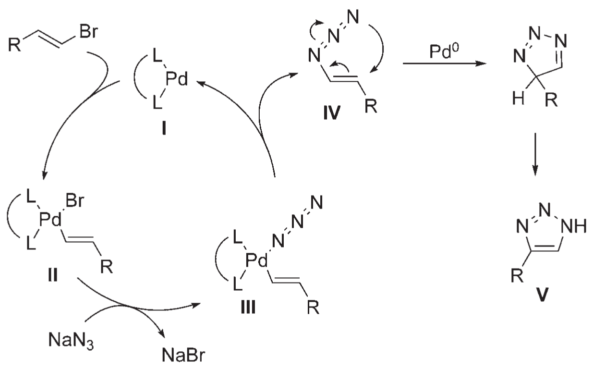
1 2

Entry	Triazole		Pd [%]	Method[b]	t[c] [h]	Yield[d] [%]
1		X=H **2a**	2	A	14	93
2		X=OMe **2b**	2	A	14	92
3		X=CN **2c**	2	A	14	89
4		X=CO$_2$Me **2d**	2	A	14	74
5		X=Cl **2e**	2	A	14	72
6		X=Br **2f**	2	A	14	70
7		X=Me **2g**	2	A	14	73
8		**2h**	2	A	14	94
9		**2i**	2	A	14	76
10		R=*n*-C$_8$H$_{17}$ **2j**	8	B	24	62
11		R=CH$_2$OBn **2k**	10	B	20	80
12		**2l**	4	B	20	84
13			2	A	10	45[e]

[a] Reaction conditions: Alkenyl bromide 1 (1 mmol), sodium azide (3 mmol), [Pd$_2$(dba)$_3$] (see Table), xantphos (2:1, xantphos/Pd), solvent (3 mL). [b] Method A: Dioxane, 90 °C; Method B: DMSO, 110 °C. [c] Reaction times are not optimized. [d] Yields after column chromatography. [e] Complete conversion of the starting material.

This novel transformation represents an unprecedented Pd-catalyzed reaction, which adds to the already enormous repertoire of processes promoted by this transition metal.[14] It is also worth noting the differential behavior of Pd and Cu catalysts in their reactions with sodium azide and alkenyl halides. While the Cu-catalyzed reaction furnishes alkenyl azides,[11] these compounds are not even detected in the reaction with Pd, which provides only 1*H*-1,2,3-triazoles.

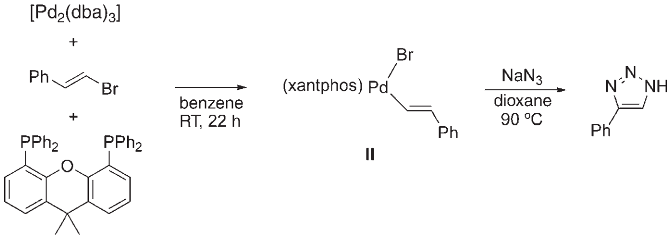
A tentative reaction pathway (Scheme 1) might involve oxidative addition of the bromoalkene to the Pd^0 complex **I** to form alkenylpalladium complex **II**, followed by substitution of the bromine by the azide to provide complex **III**. Reductive elimination would furnish the alkenyl azide **IV** and release the Pd^0 catalyst.[15] Finally, a Pd-promoted 1,5-electrocyclization followed by tautomerization would furnish the 1*H*-1,2,3-triazole **V**.



Scheme 1. Tentative mechanism for the Pd-catalyzed formation of triazoles from alkenyl bromides and sodium azide.

It must be noted that vinyl azides do not undergo cyclization to 1,2,3-triazoles upon heating; instead 2*H*-azirines and nitriles are formed with evolution of nitrogen.[16] For this reason, if this mechanistic manifold were operative, the Pd catalyst should play a role in promoting the electrocyclization of the intermediate vinyl azide. In an attempt to validate this mechanistic hypothesis we carried out several experimental and computational studies.

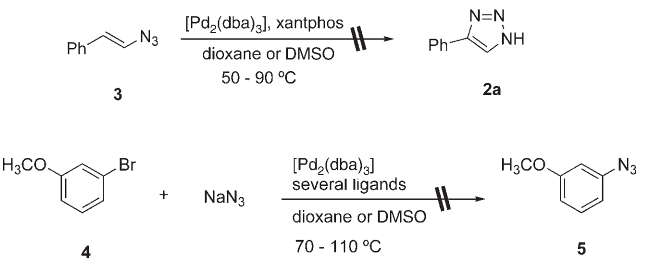
First of all, we have found evidence that the oxidative addition step is indeed occurring. The alkenylpalladium bromide complex **II** ligated with xantphos was generated following a procedure reported by Buchwald and co-workers for the analogous aryl bromides,[12d,e] in which a mixture of $[Pd_2(dba)_3]$, xantphos, and β-bromostyrene were stirred in benzene at room temperature for 22 h. Treatment of the resulting solid crude material with sodium azide in dioxane at 90°C led to the formation of the triazole (Scheme 2). This observation clearly indicates that **II** is an intermediate in the catalytic process and therefore that the oxidative addition step takes place.



Scheme 2. Evidence for the oxidative addition step.

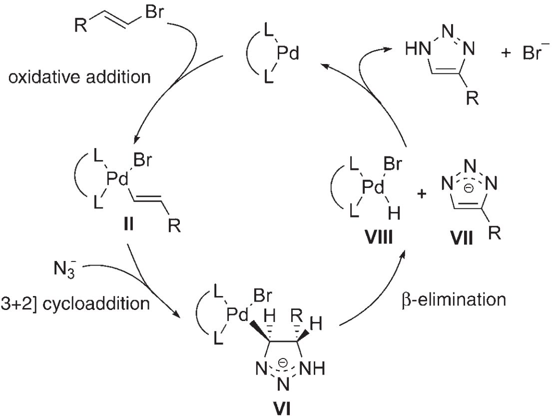
However, we have not found any experimental support for the reductive elimination/electrocyclization sequence (Scheme 3).[17] We attempted to transform the preformed styryl azide (**3**)[16a,b,18] into triazole **2a** by treatment with the Pd–xantphos catalytic system. Despite extensive experimentation involving different temperatures and reaction conditions, we never detected formation of the triazole, only decomposition of the vinyl azide.

On the other hand, when 3-bromoanisole (**4**), a typical aryl bromide, was subjected to the array of reaction conditions described during the optimization of the synthesis of the triazoles, no reaction ever occurred and the aryl bromide was always recovered unaltered. From these observations, we conclude that formation of the vinyl azide through a reductive elimination process might not be occurring and therefore discount the mechanism proposed in Scheme 1.



Scheme 3. Reactions that are not consistent with the mechanism depicted in Scheme 1.

After excluding a reaction pathway involving a reductive elimination step and taking into account that the vinylpalladium complex **II** is in fact an intermediate of the reaction, the formation of the triazole can be only explained by a [3+2] cycloaddition (either concerted or stepwise) of the azide anion with a vinylpalladium complex (Scheme 4). The dihydrotriazolylpalladium complex **VI** would then undergo β elimination to release the triazolide **VII** and the hydridopalladium complex **VIII**. Finally, reductive elimination releases HBr which protonates the triazolyl anion and regenerates the Pd^0 complex.



Scheme 4. Proposed mechanism for the Pd-catalyzed formation of triazoles from alkenyl bromides and sodium azide.

In summary, we have reported a new methodology for the Pd-catalyzed synthesis of 1*H*-triazoles from alkenyl halides and sodium azide. Importantly, the process represents a completely new reactivity pattern in the context of Pd chemistry. Detailed investigations to clarify the mechanism of this intriguing reaction and further synthetic applications are underway.

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