Efficient synthesis of allylic azides and one-pot regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles from homoallyl alcohols

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ABSTRACT

This protocol is for an expedient and operationally simple synthesis of allylic azides and one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from homoallyl alcohols. Synthesis of allylic azides involves the palladium-catalyzed hydroazidation of unactivated olefins with migration of double bond. This hydroazidation can be coupled to Cu(I) promoted 1,3-dipolar cycloaddition to afford the corresponding 1,4-disubstituted 1,2,3-triazoles.

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Amines and related functional groups are ubiquitous in natural products as well as in pharmaceutical substances. Consequently, the development of methods for the introduction of nitrogen into simple organic compounds is an intense focus of research.[1] While the enormous interest in the chemistry of azides and azido-related compounds[2] dates from the 19th century, only recently have the synthesis and reactivity of multifunctional allylic azides become an area of active research.[3] Allylic azides are versatile building blocks for the synthesis of natural products and nitrogen-containing heterocycles of pharmacological relevance.[4] Copper(I)-catalyzed cycloaddition with terminal alkynes, which results in 1,4-disubstituted 1,2,3-triazoles, is among the recent advances in the chemistry of organic azides.[5] The rare chemical orthogonality of the azide and alkyne functionalities (that is, inertness to acidic and mildly basic conditions) has enabled unique applications of this process in chemical biology, organic synthesis, and materials science.[6] However, the propensity of allylic azides to undergo dynamic [3,3]-sigmatropic rearrangement[7] at an ambient temperature must be taken into account, because the thermodynamic ratio of the two equilibrating regioisomeric azides is normally substrate-dependent.[8] Therefore, the development of simple and efficient methods to selectively access allylic azides of structural complexity is highly desirable.

The most common access route to alkyl/allyl azides involves the substitution reaction of primary or secondary alkyl/allyl halides or tosylates with inorganic azides.[9] The direct reaction of alkenes with hydrazoic acid sources is limited to alkenes that give rise to stabilized carbocations and require excess HN_3, $TMSN_3$, or zeolite-supported NaN_3, unactivated monosubstituted olefins being described as unreactive in these processes.[10] Recently, Wang and co-workers reported palladium-catalyzed hydroalkoxydation of unactivated alkenes for the synthesis of a variety of allylic ethers.[11] Herein, we report the hydroazidation of homoallyl alcohols to the corresponding allylic azides with migration of the double bond using $PdCl_2$ as a catalyst and $TMSN_3$ as an azide source. Moreover, as it is a part of our research program directed toward the synthesis of triazoles under various reaction conditions,[12] the formed allylic azides were subsequently converted to 1,4-disubstituted 1,2,3-triazoles through CuI-catalyzed 1,3-dipolar cycloaddition with terminal alkynes without isolation and purification of azides (Scheme 1).

In our initial studies, various palladium catalysts in combination with different solvents were investigated using 1-phenylbut-3-en-1-ol **1** as a model substrate for the synthesis of allylic azides (Table 1). The conditions were optimized and the best condition was found to be 2 mol % of $PdCl_2$, 1.2 equiv of $TMSN_3$ with dichloromethane as the solvent and the results are summarized in Table 1, entry 1. By virtue of these optimized conditions, the reaction afforded the desired product in 92% yield. Reactions with other palladium catalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, and Pd/C did not generate the desired product (Table 1, entries 2–4). However, the reaction with Pd $(CH_3CN)_2Cl_2$ gave the product in a moderate yield (Table 1, entry 5). As can be seen from Table 1, the nature of the counter ion as well as the oxidation state of the palladium plays a significant role in this reaction. Subsequently, the reaction conditions were optimized by

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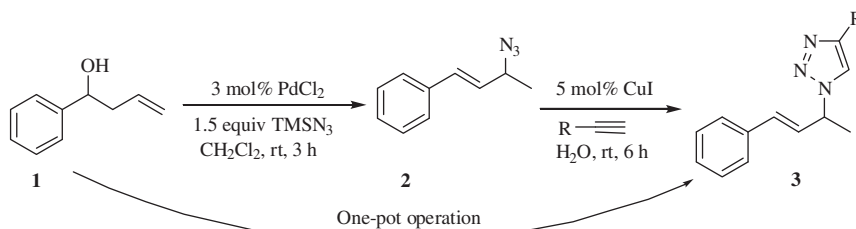
Scheme 1.

Table 1
Catalyst and solvent screening for the synthesis of allyl azides from homoallylic alcohols[a]
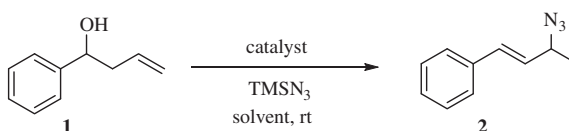

Entry	Solvent	Catalyst	Time (h)	Yield (%)
1	CH$_2$Cl$_2$	PdCl$_2$	3	92
2	CH$_2$Cl$_2$	Pd(OAc)$_2$	12	0
3	CH$_2$Cl$_2$	Pd(PPh$_3$)$_4$	12	0
4	CH$_2$Cl$_2$	Pd/C	12	0
5	CH$_2$Cl$_2$	Pd(CH$_3$CN)$_2$Cl$_2$	12	53
6	CH$_2$Cl$_2$	PdCl$_2$	3	90
7	Toluene	PdCl$_2$	12	60
8	DMF, H$_2$O ACN 1,4-dioxane CH$_3$NO$_2$	PdCl$_2$	12	0

[a] Reaction conditions: homoallyl alcohol (1 mmol), trimethylsilyl azide (1.5 mmol), catalyst (3 mol %), solvent (3 mL).

employing different solvents. Thus, various polar and non-polar solvents were examined and it was found that the product was obtained in a moderate yield with toluene and all other solvents had negative influence on the reaction and no product was formed (Table 1, entry 8). Instead of TMSN$_3$ as azide source when sodium azide was used, no reaction was observed.

On the basis of these results, together with the literature reports,[13] we propose a plausible mechanism as shown in Scheme
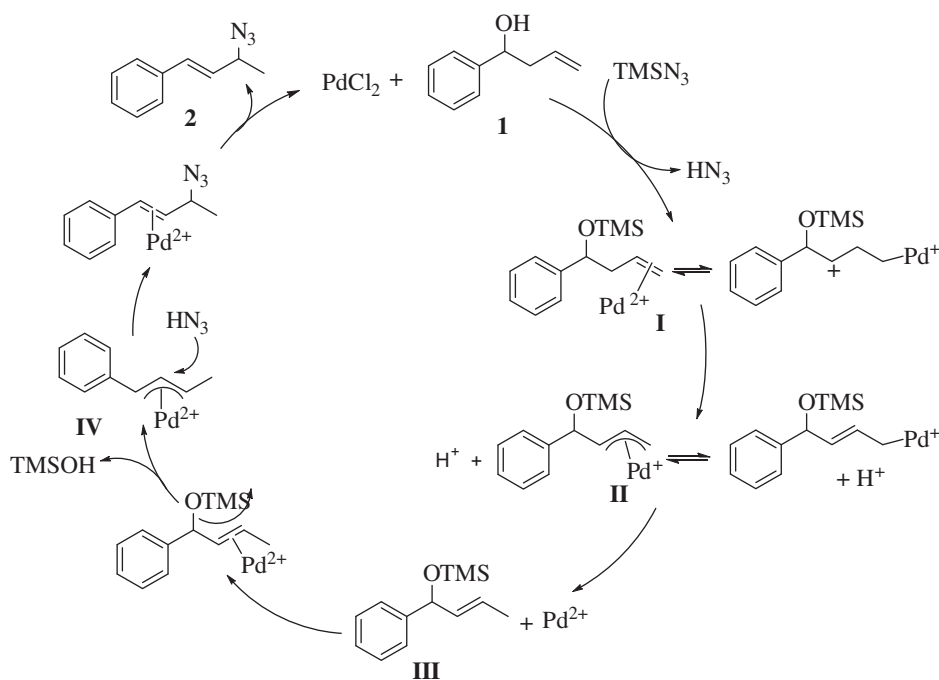
Scheme 2.

Table 2
Synthesis of allylic azides from different homoallylic alcohols[a]

Entry	Homoallyl alcohol	Allylic azide	Yield (%)
1			92
2			82
3			85
4			84
5			90
6			90
7			80
8			67

[a] Reaction conditions: homoallylic alcohol (1 mmol), TMSN$_3$ (1.5 mmol), PdCl$_2$ (3 mol %), dichloromethane (3 mL) stirred at room temperature for 3 h.[20]

2. The silylation of **1** with TMSN$_3$ takes place at the first step and gives the intermediate trimethylsilylether and hydrazoic acid (HN$_3$). The observations made in the optimization of reaction conditions such as low yield of the product obtained with the Pd(CH$_3$CN)$_2$Cl$_2$ and no product was formed with Pd (PPh$_3$)$_4$, would rule out a mechanism involving the oxidative addition of an allylic CH bond to the metal, since the propensity to undergo oxidative addition should increase with increasing electron density on the metal.[14] The key intermediate in the proposed mechanism is incipient carbocation **I** generated through the interaction of the alkene with Pd(II) center, loss of H$^+$ from **I** would yield the cationic allyl compound, **II**.[15] The proton then cleaved the Pd–C bond in a well precedented step[16] to produce the isomerized alkene **III** and regenerating the catalyst. The formation of **II** and H$^+$ from alkene and

Pd(II) may be visualized as a heterolytic cleavage of CH bond by Pd(II). Then, the structure of π-allyl-palladium **IV**[17] is built up through the departure of the TMS-protected hydroxyl group. The cationic π-allylpalladium intermediate **IV** generated should be electrophilic enough to be attacked by the nucleophile hydrazoic acid which results in the stable product, allylic azide **2** without any [3,3]-sigmatropic rearrangement.

With reliable procedure in hand, we proceeded to examine the scope of the hydroazidation reaction with different homoallyl alcohols, and the generality of this methodology and the results are summarized in Table 2. As can be seen from the table, various homoallyl alcohols were converted into the corresponding allylic azides in good to excellent yield (Table 2, entries 1–7) as single regioisomer exclusively without any [3,3]-sigmatropic rearrangement. It is presumably because of its increased stability due to conjugation of the double bond with the phenyl ring. Such compatibility is further demonstrated by homoallyl alcohol derived from terephthalaldehyde, where the product bis-allylic azide is formed predominantly (Scheme 3). However, the allylic azide derived from homoallyl alcohols having aliphatic substituent, engaged in [3,3]-sigmatropy, and product obtained as regioisomers in the ratio of 9:1 (Table 2, entry 8).[18]

The mild conditions of the hydroazidation reaction permitted us to examine various processes that effect the conversion of the product to other useful compounds without the need of isolation and purification of azides themselves. Recently, Lee et al. reported CH$_2$Cl$_2$/H$_2$O as an effective solvent for Cu(I)-catalyzed azide and alkyne cycloaddition.[19] The formed allylic azide from the homoallyl alcohol through palladium-catalyzed hydroazidation was treated with terminal alkyne, CuI, and water to furnish 1,4-disubstituted 1,2,3-triazoles in a one-pot operation. Water plays an important role in the formation of copper acetylide from copper iodide and acetylene, without using any amine base and accelerates the reaction.

As exemplified in Table 3, the reaction proceeds smoothly to completion and the products were obtained in good yields with excellent purity without isolating the intermediate allylic azide. Various allylic alcohols were subjected to reaction with TMSN$_3$ followed by terminal alkynes and it was found that the reaction was fairly general and tolerated a variety of substituted secondary alcohols (Table 3, entries 1–7). To extend the general applicability of this reaction, several terminal alkynes were reacted with allylic azides that are generated in situ from alcohol **1** and TMSN$_3$ under optimized reaction conditions and the results are presented in Table 4. Structurally and electronically diverse terminal alkynes were used in this study. 4-Methyl, 2,4,5-trimethyl and 3-F phenylacetylenes reacted smoothly to give the desired products in good yields (Table 4, entries 1–4). Whereas, the reaction with 2-nitrophenylacetylene was observed to be slow and product obtained was in a low yield. The reaction with heterocyclic alkynes such as 2-ethynyl pyridine gave the product in a moderate yield. In addition, aliphatic alkynes underwent the reaction smoothly to give the corresponding products in excellent yield under these optimized reaction conditions.

To show the convenience of our approach for the synthesis of multivalent structures, compound **1** and 1,3-diethynyl benzene
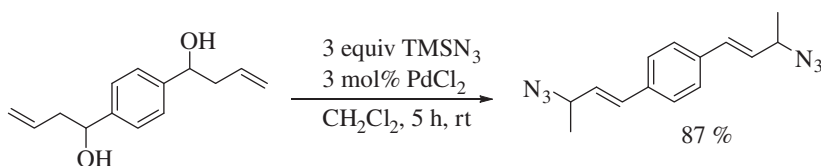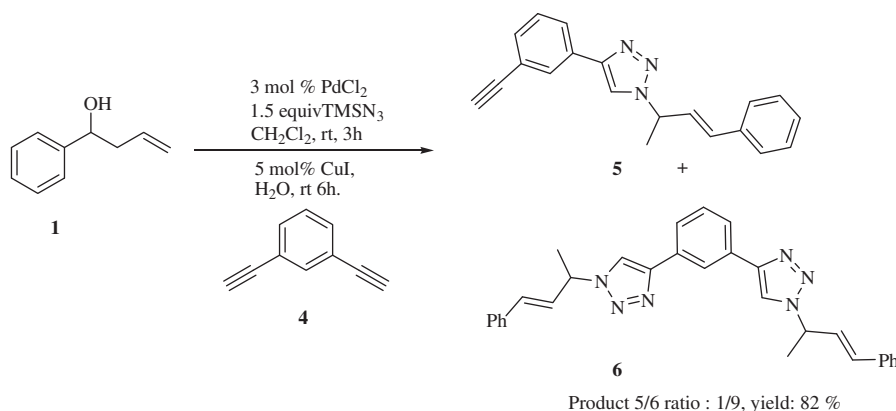
Scheme 3.

Table 3
One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from homoallyl alcohols using PdCl$_2$ and Cu(I) catalysts[a]

Entry	Homoallyl alcohol	Allyl triazoles	Yield (%)
1			85
2			75
3			80
4			80
5			82
6			80
7			68

[a] Reaction conditions as exemplified in typical experimental procedure.[21]

Scheme 4.

were reacted under the optimized reaction conditions to afford high yields of bistriazoles showing the versatility of the catalytic system for generating multivalent structures (Scheme 4).

In conclusion, we have developed an efficient route for the synthesis of allylic azides from homoallyl alcohols through palladium-catalyzed hydroazidation with double bond migration. This conceptually new approach provides a straightforward and efficient access to allylic azides. In addition, the reaction can be coupled to copper-catalyzed 1,3-dipolar cycloaddition to generate 1,4-disubstituted 1,2,3-triazoles in one-pot without isolating the azide intermediate and should prove to be useful for generating multivalent structures

Table 4
One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from different terminal alkynes and homoallylic alcohol (**1**) using PdCl$_2$ and Cu(I) catalysts[a]

Entry	Alkyne	Product	Yield
1			85
2			87
3			85
4			80
5			56
6			75
7			80
8			70
9			75

[a] Reaction conditions as exemplified in typical experimental procedure.[21]

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.097.

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21. *Typical procedure for the one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from homoallyl alcohols*: a mixture of homoallyl alcohol (1 mmol), TMSN$_3$ (1.5 mmol), and palladium chloride (3 mol %) in dichloromethane (3 mL) was stirred at room temperature for 3 h, and the reaction was monitored by TLC. Phenylacetylene (1.2 mmol), CuI (5 mol %) and water (2 mL) were added and the reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (as monitored by TLC), the reaction mixture was filtered through Celite and the product was extracted with dichloromethane (2 × 10 mL). After removing the solvent under vacuum, the crude product was purified by column chromatography on silica gel using (hexane–ethyl acetate) to afford pure product. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. Please see Supplementary data for spectral data of all compounds.