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$PdCl_2$-catalyzed hydrosulfonamidation of homo allylic alcohols: an efficient synthesis of allylic sulfonamides

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ABSTRACT

A new protocol for the palladium chloride-catalyzed direct hydrosulfonamidation of homoallylic alcohols with migration of the double bond is described. This method requires no preactivation of alcohols and the reaction is environmentally benign with water as the only by-product. Various homoallylic alcohols on hydrosulfonamidation with sulfonamides gave the corresponding products in good yields.

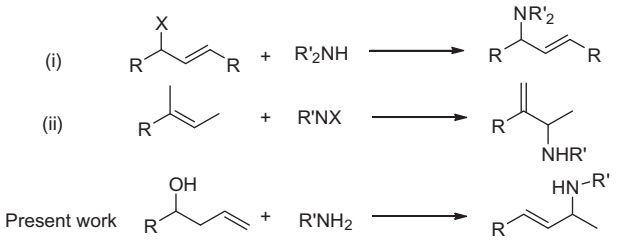
Amines and their derivatives are of fundamental importance as natural products, pharmacological agents, fine chemicals, and dyes.[1] Furthermore, a plethora of naturally bioactive compounds such as, alkaloids, amino acids, and nucleotides contain amine groups. Despite numerous known procedures, the development of improved methods for the synthesis of amines continues to be a highly challenging and active area of research.[2] In this respect hydroamination,[3] the addition of an N–H bond across carbon–carbon unsaturation, offers an efficient, atom-economical route to nitrogen-containing molecules that are important for fine chemicals, pharmaceuticals, or useful chiral building blocks. Although several efficient catalysts for the hydroamination of alkynes,[4] vinylarenes,[5] dienes,[6] and electron-deficient alkenes[7] have recently been discovered, general systems for intermolecular hydroaminations of unactivated olefins remain elusive.[8]

Allylamines are ubiquitous in various biologically active compounds and their synthesis is an important industrial and synthetic goal. The allylamine fragment can be encountered in natural products, but often the allylamine is transformed to a range of products by reduction, oxidation, or other functionalization of the double bond. Thus allylamines have been used as starting materials for the synthesis of numerous compounds such as, α- and β-amino acids,[9] different alkaloids[10], and carbohydrate derivatives.[11]

The synthesis of allylic amines can, in principle, be divided into two groups of reactions, which are outlined in Scheme 1. The first type (i) constitutes allylic amines synthesized by nucleophilic allylic substitution and the second (ii) is the direct allylic amination of simple alkenes.[12]

A transition metal-catalyzed substitution reaction of activated allylic alcohol derivatives with nitrogen nucleophiles is one of the most powerful and reliable methods for the synthesis of allylic amines.[13] However, they usually require preactivation of the parent allylic alcohol to the corresponding allylic halides, carboxylates, carbonates, phosphates, and related compounds. The reaction proceeds through π-allyl metal intermediates, generated by the oxidative addition of allylic substrates to a low-valence metal center, and the following nucleophilic addition gives allylic amines as a consequence of new C–N bond formation. In terms of atom-economy[14] and environmental concerns, however, these catalyses still have much room for improvement.

The current study was motivated by our recent finding that hydroazidation of homoallyl alcohols to the corresponding allylic azides using $PdCl_2$ as a catalyst and $TMSN_3$ as an azide source, which appears to involve the nucleophilic attack of an azide onto



Scheme 1. Protocols for the synthesis of allylic amines.

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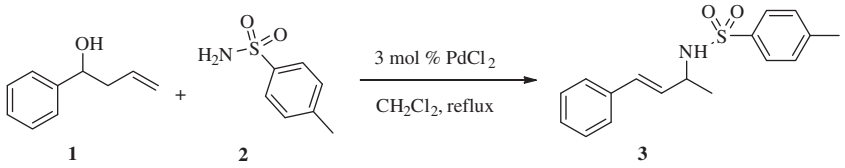
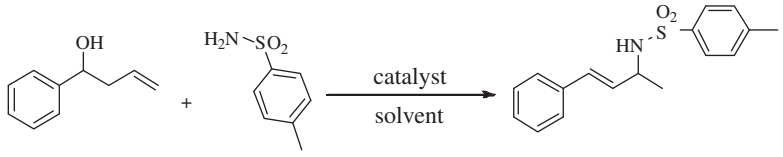


Scheme 2.

Table 1
Screening of various solvents and catalysts for reaction of allylic amines from homoallylic alcohols[a]



Entry	Catalyst	Solvent	Temp (°C)/time (h)	Yield (%)
1	$PdCl_2$	CH_2Cl_2	40/8	90
2	$Pd(OAc)_2$	CH_2Cl_2	40/8	0
3	$Pd(PPh_3)_4$	CH_2Cl_2	40/8	0
4	Pd/C	CH_2Cl_2	40/8	0
5	$Pd(dba)_2$	CH_2Cl_2	40/8	0
6	$Pd(dppf)Cl_2$	CH_2Cl_2	40/8	0
7	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	40/8	27
8	$Pd(CH_3CN)_2Cl_2$	CH_2Cl_2	40/8	42
9	$PdCl_2$	THF	60/12	30
10	$PdCl_2$	1,4-Dioxane	100/12	40
11	$PdCl_2$	DCE	80/12	Trace
12	$PdCl_2$	DMF, DMSO, CH_3NO_2, H_2O	100/12	0
13	$PdCl_2$	Toluene, xylene	100/12	0

[a] Reaction conditions: homoallylic alcohol (1 mmol), tosylamide (1.2 mmol), catalyst (3 mol %) solvent (3 mL).

Table 2
Direct hydrosulfonamidation of different homoallylic alcohols with *p*-toluenesulfonamide using $PdCl_2$ for the synthesis of allylic amines[a]

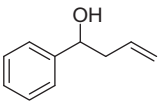
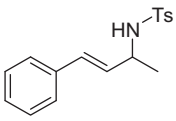
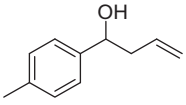
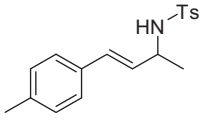
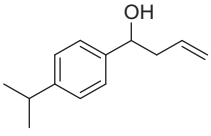
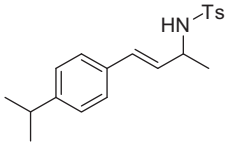
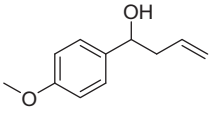
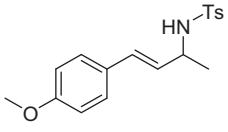
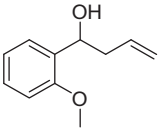
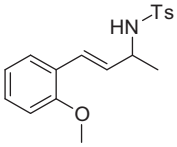
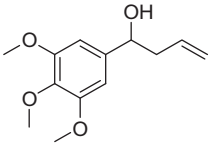
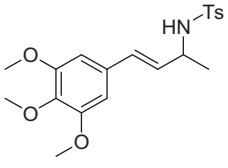
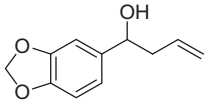
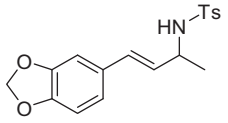
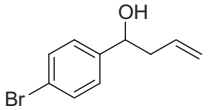
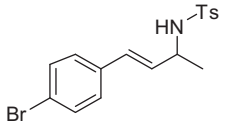
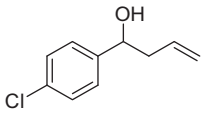
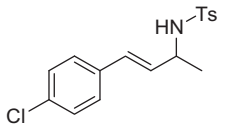
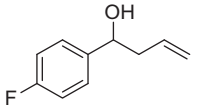
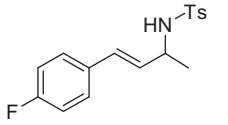
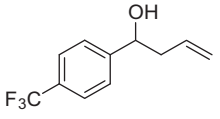
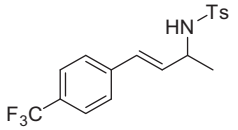
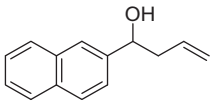
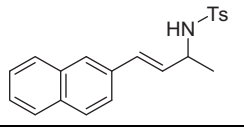
Entry	Homoallyl alcohol	Product	Yield (%)
1			90
2			91
3			90
4			84
5			79[b]
6			84

Table 2 (*continued*)

Entry	Homoallyl alcohol	Product	Yield (%)
7			87
8			75
9			75
10			70
11			70
12			82

[a] Reaction conditions as exemplified in typical experimental procedure.[22]
[b] Yield of the *E* isomer.

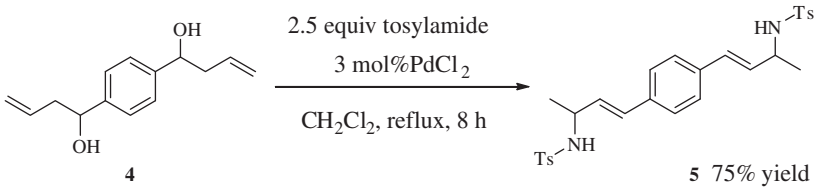
a π-allyl–palladium complex.[15] This prompted an investigation of analogous reactions involving the addition of N–H bonds to olefins, since amines seemed to be potential candidates as analogous nucleophiles in a related process. In this Letter, we describe an efficient system for the hydrosulfonamidation of homoallylic alcohols to the corresponding allylic sulfonamides with migration of the double bond using $PdCl_2$ as a catalyst and sulfonamides as an amine source (Scheme 2).

For initial optimization of the reaction conditions and the identification of the best palladium source and solvent, 1-phenylbut-3-en-1-ol **1** and *p*-toluenesulfonamide **2** were chosen as model substrates for the synthesis of allylic sulfonamides and the results are presented in Table 1. The conditions were optimized and the best conditions were found to be 3 mol % of $PdCl_2$, 1.2 equiv of **2** with dichloromethane as the solvent (Table 1, entry 1). By virtue of these optimized conditions, the reaction afforded the desired product in 90% yield. Reactions with other palladium catalysts such as, $Pd(OAc)_2$, $Pd(PPh_3)_4$, Pd/C, $Pd(dba)_2$, and $Pd(dppf)_2Cl_2$ did not generate the desired product (Table 1, entries 2–6). However, the reaction with $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$ gave the product in low yield (Table 1, entries 7 and 8). As can be seen from the table, the nature of the counter ion as well as the oxidation state of palladium plays a significant role in this reaction. Subsequently, the reaction conditions were optimized by employing different solvents. Thus, various polar and non polar solvents were examined and it was found that the product was obtained in low yield with THF and 1,4-dioxane and only a trace amount of the product was formed in dichloroethane, whereas no product was formed in DMF, DMSO, ACN, nitromethane, water, toluene, and xylene as the solvents (Table 1, entries 9–13).

Under the optimized reaction conditions, various homoallylic alcohols were subjected to amination with *p*-toluenesulfonamide **2** and the results are presented in Table 2. The reaction of electronically and structurally diverse homoallylic alcohols such as, 4-methyl, 4-methoxy, 4-isopropyl, 3,4,5-trimethoxyphenyl substituted homoallylic alcohols with **2** gave the desired products in good yields, whereas the 2-methoxyphenyl substituted homoallylic alcohol gave the product in mixture as *E*/*Z*- isomers in the ratio of 90:10 (entries 1–7) with moderate yield. The presence of electron-withdrawing substituents on the phenyl ring such as, chloro, bromo and fluoro, the products were formed in moderate yields (Table 2, entries 8–11). On the other hand, 1-(naphthalen-2-yl)but-3-en-1-ol reacted smoothly with **2** to furnish the desired product in good yield (Table 2, entry 12).

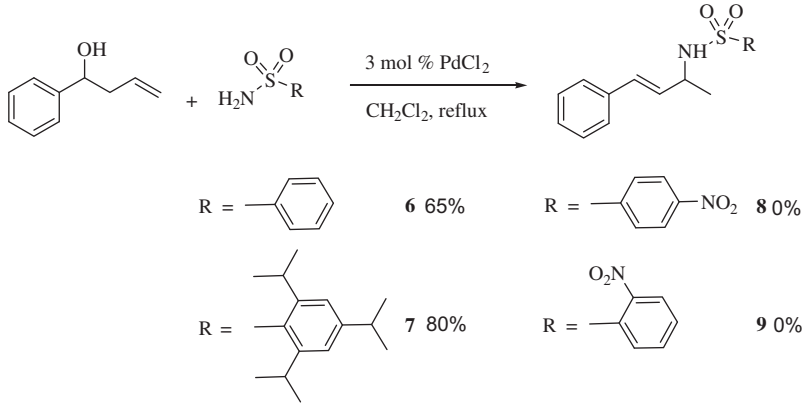
To show the convenience of our approach for the synthesis of multivalent structures, the homoallylic alcohol derived from terephthalaldehyde was reacted with **2** under the optimized reaction conditions to afford the bis-allylic sulfonamide product in good yield (Scheme 3).

Furthermore, the scope of the reaction with respect to sulfonamide substrate was also examined and the results are given in Scheme 4. Both benzenesulfonamide and 2,4,6-triisopropylben-

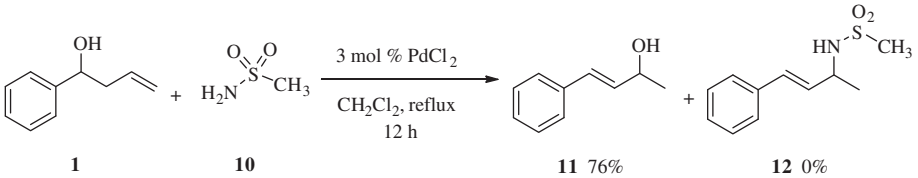


4 **5** 75% yield

Scheme 3.

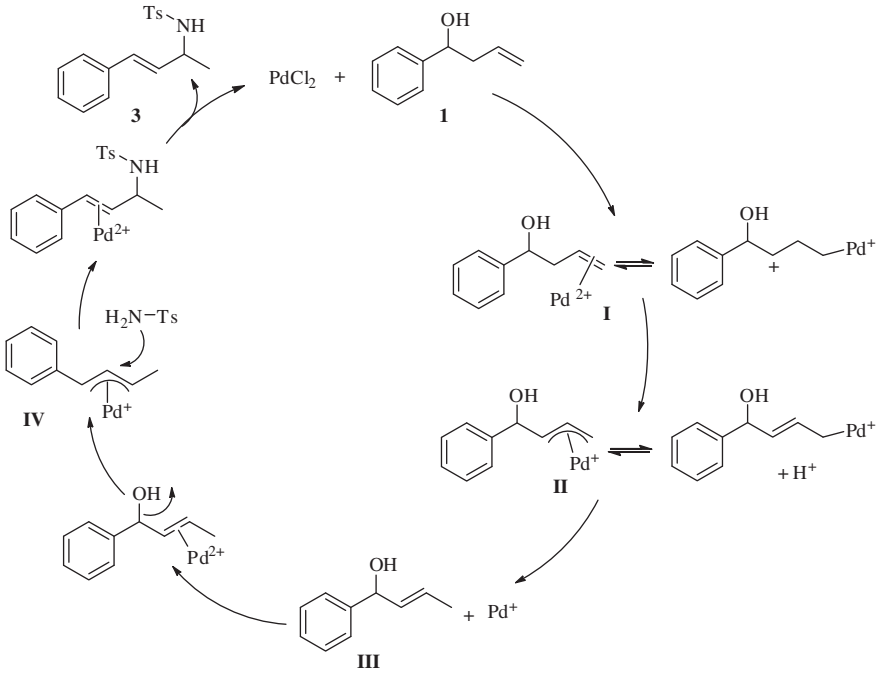


Scheme 4.



1 **10** **11** 76% **12** 0%

Scheme 5.



Scheme 6.

zene sulfonamides were equally effective for this reaction and gave the corresponding allylic sulfonamides in good yield. However, no product was formed with 4-nitrobenzenesulfonamide and 2-nitrobenzenesulfonamides, having an electron-withdrawing nitro group, under the optimized reaction conditions. Interestingly, with methanesulfonamide, which contains a relatively electron-donating methyl group, we observed the formation of allylic alcohol **11** instead of allylic amine **12** (Scheme 5). This may be attributed to higher nitrogen basicity leading to lower reactivity in this catalysis.[16]

On the basis of these results, together with the literature reports,[17] a plausible reaction course is proposed as shown in Scheme 6. The catalytic isomerization of alkenes by Pd(II) compounds, has been studied.[15,18] The commonly postulated mechanism involves the oxidative addition of an allylic CH bond to the Pd(II) catalyst to produce a Pd(IV) allyl hydride species. The observations made in the optimization of reaction conditions, such as low yield of the product obtained with the $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ and no product being formed with $Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$, would rule out a mechanism involving the oxidative addition of an allylic C–H bond to the metal, since the propensity to undergo oxidative addition should increase with increasing electron density on the metal.[19] The key intermediate in the proposed mechanism is the incipient carbocation **I** generated through the interaction of the alkene with the Pd(II) center, with loss of H^+ from **I** to yield the cationic allyl compound, **II**. The proton then cleaves the Pd–C bond in a well precedented step[20] to produce the isomerized alkene **III** and regenerates the catalyst. The formation of **II** and H^+ from the alkene and Pd(II) may be visualized as a heterolytic cleavage of the C–H bond by Pd(II). Then, the structure of π-allyl–palladium **IV**[21] is built up through the departure of the hydroxyl group and the following sulfonamide attack on this allyl–palladium complex which results in the stable product, allylic amine **3**.

In summary, we have developed an efficient route for the synthesis of allylic sulfonamides from homoallylic alcohols through palladium-catalyzed hydrosulfonamidation of unactivated double bonds. The new catalytic reaction presented in this Letter could be a meaningful addition to the existing methods for hydrosulfonamidation and this conceptually new approach provides a straightforward and efficient access to the allylic amines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.024.

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22. *Typical procedure for the hydrosulfonamidation of homoallyl alcohols*: A mixture of homoallyl alcohol (1 mmol), sulfonamide (1.2 mmol) and palladium chloride (3 mol %) in dichloromethane (3 mL) was stirred under reflux for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel to afford the 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.