ORGANIC LETTERS

2012
Vol. 14, No. 3
768–771

Direct Catalytic Azidation of Allylic Alcohols

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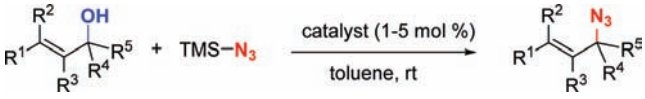
Received December 11, 2011

ABSTRACT



A direct catalytic azidation of primary, secondary, and tertiary allylic alcohols has been developed. This new azidation reaction affords the corresponding allylic azides in high to excellent yields and regioselectivities. The reaction provides straightforward access to allylic azides that are valuable intermediates in organic synthesis, including the preparation of primary amines or 1,2,3-triazole derivatives.

The interest in the synthesis of allylic amines has grown significantly due to the importance of these compounds as building blocks for the synthesis of various therapeutic agents,[1] amino acids[2] and natural products.[3] Due to their readily availability, allylic alcohols are preferred substrates for the synthesis of allylic amines. Substitution of the alcohol moiety by a nitrogen nucleophile requires normally preactivation of the alcohol in the form of a better leaving group such as halide, carboxylate, phosphate, carbonate or related compounds.[4] Thus, direct catalytic substitution of allylic alcohols is of great interest for organic synthesis in terms of atom-economy and environmental concerns.[5]

In this context, several methods have been reported for the direct allylic amination using Brønsted acids,[6] iodine,[7] and various metal based catalysts.[8] Despite a large number of reported methodologies for the direct amination of allylic alcohols,[6–8] the related direct azidation remains still underexplored.[9] To date, only

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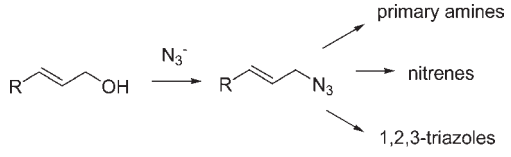
10.1021/ol203310h
Published on Web 01/18/2012

a few examples of catalytic allylic azidations with use of preactivated allylic esters have been reported.[10]

The catalytic allylic azidation of free alcohols has not been achieved although allylic azides are useful precursors for primary amines and nitrenes[11] and versatile synthetic intermediates, e.g. 1,3-dipoles in the Huisgen 1,3-dipolar cycloaddition[12] providing 1,2,3-triazolo-heterocyclic compounds which recently attracted much attention in medicinal and pharmaceutical chemistry[13] as well as material science (Scheme 1).[14]

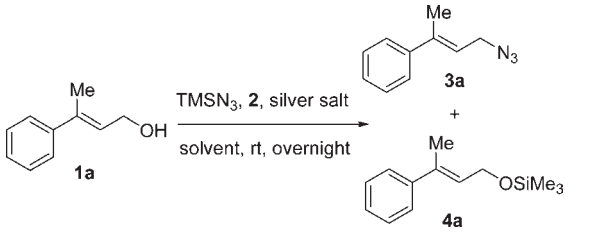
Hence, the development of a practical procedure for the catalytic synthesis of allylic azides is highly desirable. Herein, we present the first direct azidation of allylic alcohols using silver salts as useful catalysts.

Scheme 1. Versatility of Allylic Azides



The reaction between (*E*)-3-phenylbut-2-en-1-ol (**1a**) and $TMSN_3$ (**2**) was chosen as a model reaction for the optimization study (Table 1). Among various metal salts as well as different silver salts evaluated in the direct azidation of allylic alcohol **1a**, AgOTf showed the best chemoselectivity, affording the desired allylic azide **3a** as single product in 88% yield (entry 2). $AgNTf_2$ also provided the desired product **3a**, along with traces of the silylated alcohol **4a** (entry 4). With other silver salts, the silylated alcohol **4a** was obtained either in a considerable amount (entry 3) or as the major product (entries 5–11). Subsequently, different solvents were tested in the allylic azidation reaction using AgOTf as the catalyst (entries 12–16). The highest yield was obtained when toluene was used as the solvent. A decrease of the catalyst loading to 2 respectively 1 mol % (entries 17 and 18) had a negative effect on the selectivity of the reaction, resulting in an increase of the undesired silylated alcohol **4a**. Finally, other azides were tested including NaN_3, $TosN_3$, and $(PhO)_2PON_3$. However, in all of these cases, the formation of the desired product **3a** was not observed. The use of triflic acid resulted in product formation with reduced yields, indicating Brønsted acid catalysis.[15] Interestingly, if 2,6-lutidine was added, only formation of **4a** was observed. With the optimized conditions in hand, we explored the scope of the reaction with different primary allylic alcohols **1a**–**g** (Table 2).

Table 1. Optimization of the Azidation of Allylic Alcohols[a]



entry	silver salt (mol %)	solvent	**3a** (%)[b]	**4a** (%)	*E*:*Z*[c]
1		toluene		30	
2	AgOTf (5)	toluene	88		7:1
3	$AgSbF_6$ (5)	toluene	65	25	7:1
4	$AgNTf_2$ (5)	toluene	83	4	7:1
5	$AgCF_3CO_2$ (5)	toluene	3	76	
6	$AgPhCO_2$ (5)	toluene	3	92	
7	AgF (5)	toluene	4	79	
8	Ag_3PO_4 (5)	toluene	3	73	
9	$AgBF_4$ (5)	toluene	2	56	
10	$AgPF_6$ (5)	toluene	6	44	
11	$AgCO_3$ (5)	toluene	2	44	
12	AgOTf (5)	THF	35		7:1
13	AgOTf (5)	m-xylene	68		7:1
14	AgOTf (5)	ether	69		7:1
15	AgOTf (5)	CH_2Cl_2	72		7:1
16	AgOTf (5)	CH_3CN		54	
17	AgOTf (2)	toluene	74	15	7:1
18	AgOTf (1)	toluene	45	30	7:1
19[d]		toluene	69		5:1
20[e]	AgOTf (5)	toluene		68	

[a] Reactions were performed with allylic alcohol **1a** (0.175 mmol), **2** (3 equiv), and 5 mol % of catalyst in 0.5 mL of solvent for 14 h at room temperature. [b] Yield after column chromatography. [c] *E*:*Z* ratio of the product determined by NMR analysis. [d] 5 mol % of HOTf was used as catalyst. [e] 5 mol % of 2,6-lutidine was added.

In general, different substituted primary allylic alcohols could be employed, and the corresponding azides **3a**–**g** were isolated in good yields. Notably, in all cases almost complete regioselectivity to the terminal azide **3** was observed.

After studying the azidation of primary alcohols, we focused our attention on the reaction with secondary

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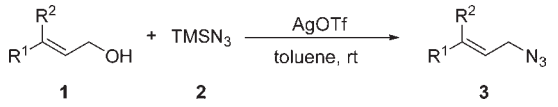
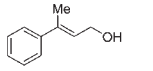
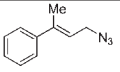
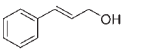
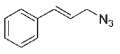
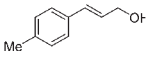
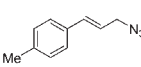
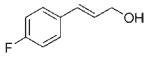
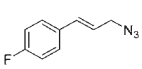
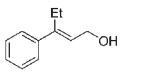
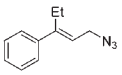
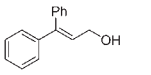
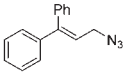
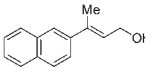
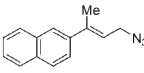
Table 2. Substrate Scope for the Direct Azidation of Primary Allylic Alcohols[a]



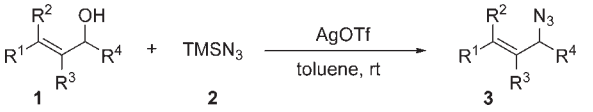
1 2 3

entry	allylic alcohol	azide	yield[b]	(*E*:*Z*)[c]	(α:γ)[c]
1	 **1a**	 **3a**	88	7:1	>20:1
2	 **1b**	 **3b**	69	>20:1	>20:1
3	 **1c**	 **3c**	70	>20:1	>20:1
4	 **1d**	 **3d**	57	>20:1	>20:1
5	 **1e**	 **3e**	77	4:1	>20:1
6	 **1f**	 **3f**	97	-	>20:1
7	 **1g**	 **3g**	48	10:1	>20:1

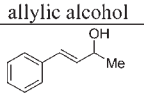
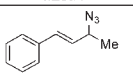
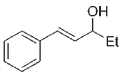
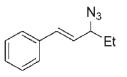
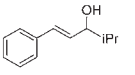
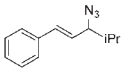
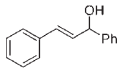
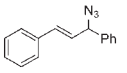
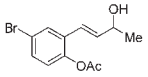
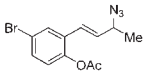
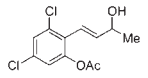
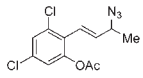
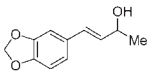
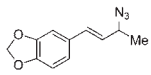
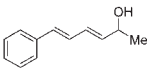
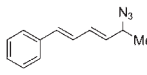
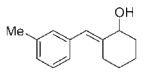
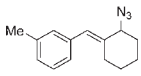
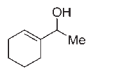
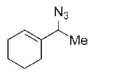
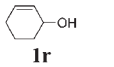
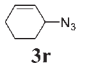
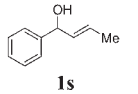
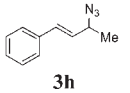
[a] Reactions were performed with allylic alcohol **1** (0.35 mmol), **2** (3 equiv), and 5 mol % of AgOTf in 1.0 mL of toluene for 4–16 h at rt. [b] Yield (%) after column chromatography. [c] *E*:*Z* ratio of the product determined by NMR analysis.

allylic alcohols **1h**–**s** (Table 3). First, the influence of the substitution pattern at the α-position to the alcohol (Me, Et, iPr, Ph, Table 3, entries 1–4) was studied. In all cases we obtained excellent regioselectivity and high yields. In the case of secondary alcohols the catalyst loading could be decreased to 2 or even 1 mol %, without loss of reactivity (entry 2, Table 3). The reaction of secondary allylic alcohols bearing electron-donating and electron-withdrawing aryl substituents **1l**–**n** proceeded smoothly and provided the desired allylic azides **3l**–**n** in good yields (62–96% Table 3, entries 5–7). The α,*β*,*γ*,*δ*-unsaturated allylic alcohol (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-ol (**1o**) gave the azide **3o** with good yield and high regioselectivity. Different secondary alcohols **1p**–**q** with a trisubstituted double bond were also tested (Table 3, entries 9 and 10), and the corresponding azides **3p**–**q** were obtained in high yields, though with a decrease in the regioselectivity. The cyclohexenol **1r** (Table 3, entry 11) showed good reactivity, and the allylic azide **3r** was isolated in an excellent yield of 95%. Finally, the azidation with the (*E*)-1-phenylbut-2-en-1-ol **1s** (Table 3, entry 12) proceeded regioselectively to the *γ* product (**3h**) in a very good yield of 96%.

Table 3. Substrate Scope for the Direct Azidation of Secondary Allylic Alcohols[a]

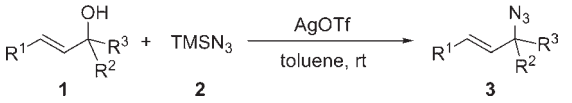


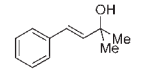
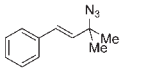
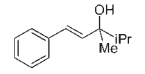
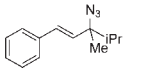
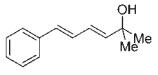
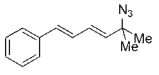
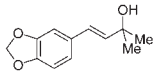
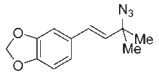
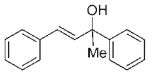
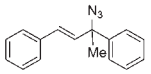
1 2 3

entry	allylic alcohol	azide	yield[b]	(*E*:*Z*)[c]	(α:γ)[c]
1	 **1h**	 **3h**	84	>20:1	>20:1
2	 **1i**	 **3i**	83 78[d] 81[e]	>20:1 >20:1[d] >20:1[e]	>20:1 >20:1[d] >20:1[e]
3	 **1j**	 **3j**	90	>20:1	>20:1
4	 **1k**	 **3k**	89	>20:1	-
5	 **1l**	 **3l**	90	>20:1	>20:1
6	 **1m**	 **3m**	62	>20:1	>20:1
7	 **1n**	 **3n**	96	>20:1	>20:1
8	 **1o**	 **3o**	79	9:1	>20:1
9	 **1p**	 **3p**	81	6:1	6:1
10	 **1q**	 **3q**	91	-	3:1[f]
11	 **1r**	 **3r**	95	-	-
12	 **1s**	 **3h**	96	>20:1	>1:20[g]

[a] Reactions were performed with allylic alcohol **1** (0.35 mmol), **2** (3 equiv), and 5 mol % of AgOTf in 1.0 mL of toluene for 2–16 h at rt. [b] Yield (%) after column chromatography. [c] *E*:*Z* ratio of the product determined by NMR analysis. [d] 2 mol % of AgOTf was used. [e] 1 mol % of AgOTf was used. [f] *γ* product had a 3:1 (*E*:*Z*) relation as determined by NMR analysis (see Supporting Information).

Table 4. Substrate Scope for the Direct Azidation of Tertiary Allylic Alcohols[a]



entry	allylic alcohol	azide	yield[b]	(*E*:*Z*)[c]	(α:γ)[c]
1	 **1t**	 **3t**	81	>20:1	>20:1
2	 **1u**	 **3u**	95	>20:1	>20:1
3	 **1v**	 **3v**	92	>20:1	>20:1
4	 **1w**	 **3w**	93	>20:1	>20:1
5	 **1x**	 **3x**	89	>20:1	1.7:1[d]

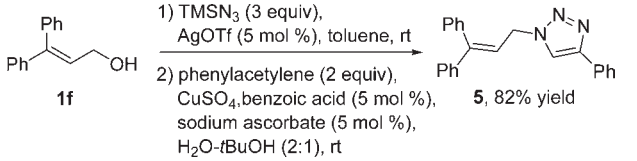
[a] Reactions were performed with allylic alcohol **1** (0.35 mmol), **2** (3 equiv), and 5 mol % of AgOTf in 1.0 mL of toluene for 1−4 h at rt. [b] Yield (%) after column chromatography. [c] *E*:*Z* ratio of the product determined by NMR analysis. [d] γ product had a relation 1.9:1 (*E*:*Z*) determined by NMR analysis.

Following the successful azidation of primary and secondary allylic alcohols, we decided to examine different tertiary allylic alcohols in order to expand the scope of this methodology (Table 4). In general very good yields and excellent regioselectivities were obtained for various tertiary alcohols. In the case of (*E*)-2,4-diphenylbut-3-en-2-ol **1x** (Table 4, entry 5) a decrease in the regioselectively was observed, and azide **3x** was obtained as a mixture of the α and γ products in a 1.7 to 1 ratio.

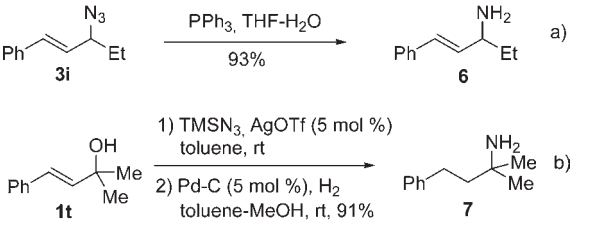
Once the scope of the azidation with different allylic alcohols was assessed, we decided to study the applicability of this methodology for the synthesis of different types of interesting compounds. The one-pot synthesis of 1,2,3-triazole **5** was achieved using click chemistry (Scheme 2). The 1,2,3-triazole **5** was obtained in 82% yield from the corresponding 3,3-diphenylprop-2-en-1-ol (**1f**) through azidation and subsequent 1,3-cycloaddition with phenylacetylene.

The reduction of (*E*)-(3-azidopent-1-enyl)benzene **3i** by treatment with Ph_3P led to the primary allylic amine **6** in a very good yield (Scheme 3, equation a). Moreover, the primary amine **7** was obtained in 91% yield from alcohol **1t** by a simple one-pot procedure consisting of azidation and subsequent reduction with Pd−C/H_2 (Scheme 3, equation b).

Scheme 2. One-Pot Synthesis of 1,2,3-Triazoles



Scheme 3. Reduction of the Azides to Primary Amines



Regarding the reaction mechanism, we propose a reaction pathway in which a carbocation intermediate is formed.[16] Taking into consideration that Ag salts are reported to interact with C−C multiple bonds,[8h,17] coordination of the Ag(I) to the double bond cannot be ruled out.

In summary, we have developed an efficient and practical direct azidation of primary, secondary, and tertiary allylic alcohols. The reaction proceeds in general with excellent regioselectivities and yields, affording valuable allylic azides, which can in a one-pot procedure be converted into interesting products, including primary amines or 1,2,3-triazole derivatives.

Acknowledgment. The authors acknowledge financial support by the European Research Council. U.U. thanks "Eusko Jaurlaritza-Gobierno Vasco" for a postdoctoral fellowship.

Supporting Information Available. Experimental procedures and full characterization (^1H and ^{13}C NMR data and spectra, MS and IR analyses) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) When the azidation was performed with enantiomerically pure alcohol **1h**, racemic allylic azide **3h** was obtained. Furthermore, in the case of enantiomerically pure allylic alcohol **1s**, azide **3h** was obtained as a racemic mixture.

(17) Alvarez-Corral, M.; Muñoz-Dorado, M.; Rodriguez-Garcia, I. *Chem. Rev.* **2006**, *108*, 3174.