Direct Catalytic Azidation of Allylic Alcohols

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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 acids² 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

(4) (a) Tsuji, J. *Transition Metal reagents and Catalysis*; Wiley-VCH: Weinheim, 2000. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2000.

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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 ⁽a) Petranyi, G.; Ryder, N. S.; Stütz, A. Science 1984, 224, 1239.
 (b) Stütz, A. Angew. Chem., Int. Ed. 1987, 26, 320. (c) Nanavati, S. M.; Silverman, R. B. J. Am. Chem. Soc. 1991, 113, 9341. (d) Jakobsche, C. E.; Peris, G.; Miller, S. J. Angew. Chem., Int. Ed. 2008, 47, 6707. (e) Blacker, A. J.; Roy, M.; Hariharan, S.; Upare, A.; Jagtap, A.; Wankhede, K.; Mishra, S. K.; Dube, D.; Bhise, S.; Vishwasrao, S.; Kadam, N. Org. Proc. Res. Dev. 2010, 14, 1364.

^{(2) (}a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301. (b) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758. (c) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225.

⁽³⁾ For a review, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. For selected examples, see: (b) Kondo, H.; Nakai, H.; Goto, T. *Tetrahedron* **1973**, *29*, 1801. (c) Brosius, A. D.; Overman, L. E.; Schwink, L. J. Am. Chem. Soc. **1999**, *121*, 700. (d) Nakanishi, M.; Mori, M. Angew. Chem., Int. Ed. **2002**, *41*, 1934.

⁽⁵⁾ For reviews, see: (a) Muzart, J. Tetrahedron 2005, 61, 4179. (b) Tamaru, Y. Eur. J. Org. Chem. 2005, 2647.

⁽⁶⁾ Sanz, R.; Martinez, A.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841.

⁽⁷⁾ Wu, W.; Rao, W.; Er, Y. Q.; Loh, J. K.; Poh, C. Y.; Chan, P. W. H. Tetrahedron Lett. **2008**, 49, 2620.

⁽⁸⁾ For a review on Pd-catalyzed allylic amination: (a) Muzart, J. Eur. J. Org. Chem. 2007, 3077. For bismuth-catalyzed reactions:
(b) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. Angew. Chem., Int. Ed. 2007, 46, 409. For molybdenium-catalyzed reactions:
(c) Yang, H.; Fang, L.; Zhang, M.; Zhu, C. Eur. J. Org. Chem. 2009, 666. For platinum-catalyzed reactions: (e) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. Org. Lett. 2007, 9, 3371. (f) Mora, G.; Piechaczyck, O.; Houdard, R.; Mezailles, N.; Le Goff, X.-F.; le Floch, P. Chem.—Eur. J. 2008, 14, 10047. (g) Das, K.; Shibuya, R.; Nakahara, Y.; Germain, N.; Oshima, T.; Mashima, K. Angew. Chem., Int. Ed. 2011, 51, 150–154. For silver-catalyzed reactions: (h) Giner, X.; Trillo, P.; Najera, C. J. Organomet. Chem. 2011, 696, 357. For iridium-catalyzed reactions: (i) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. Angew. Chem., Int. Ed. 2007, 46, 3139. (j) Roggen, M.; Carreira, E. M. J. Am. Chem. Soc. 2010, 132, 11917. For gold-catalyzed reactions: (k) Guo, S.; Song, F.; Liu, Y. Synlett 2007, 964. (l) K othandaraman, P.; Foo, S. J.; Hong Chan, P. W. J. Org. Chem. 2009, 74, 5947. (m) Mukherjee, P.; Widenhoefer, R. A. Org. Lett. 2010, 12, 1184. (n) Mukherjee, P.; Widenhoefer, R. A. Org. Lett. 2011, 13, 1334. For calcium-catalyzed reactions: (o) Haubenreisser, S.; Niggemann, M. Adv. Synth. Catal. 2011, 354, 469.

^{(9) (}a) Organic Azides Syntheses and Applications; Bräse, S., Banert, K., Eds.; John Wiley & Sons Ltd.: Chichester, 2010. For the direct azidation of allylic alcohols with NaN₃ and stoichiometric amounts of BF₃·Et₂O, see: (b) Sampath Kumar, H. M.; Subba Reddy, B. V.; Anjaneyulu, S.; Yadav, J. S. *Tetrahedron Lett.* **1998**, *39*, 7385. Mo-catalysis: (c) Malkov, A. V.; Spoor, P.; Vinader, V.; Kocovsky, P. J. Org. Chem. **1999**, *64*, 5308. Acidic ionic liquid mediated azidations: (d) Hajipour, A. R.; Rajaei, A.; Ruoho, A. E. *Tetrahedron Lett.* **2009**, *50*, 708.

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 nitrenes¹¹ and versatile synthetic intermediates, e.g. 1,3-dipoles in the Huisgen 1,3-dipolar cycloaddition¹² providing 1,2,3-triazolo-heterocyclic compounds which recently attracted much attention in medicinal and pharmaceutical chemistry¹³ 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.



The reaction between (*E*)-3-phenylbut-2-en-1-ol (1a) and TMSN₃ (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). AgNTf₂ 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

(12) (a) Huisgen, R. In 1,3-Dipolar Cycloaddition Chemistry; Padwa,
A., Ed.; Wiley: New York, 1984; pp 1–176. (b) Rostovtsev, V. V.; Green,
L. G.; Fokin, V. V.; Sharpless, K. B. Angew. Chem., Int. Ed. 2002, 41, 2596.

(13) (a) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B. J. Am. Chem. Soc. 2003, 125, 3192. (b) Speers, A. E.; Cravatt, B. F. Chem. Biol. 2004, 11, 535. (c) Speers, A. E.; Adam, G. C.; Cravatt, B. F. J. Am. Chem. Soc. 2003, 125, 4686. (d) Link, A. J.; Tirrell, D. A. J. Am. Chem. Soc. 2003, 125, 1164. (e) Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. J. Am. Chem. Soc. 2003, 125, 11782. (f) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. J. Am. Chem. Soc. 2003, 125, 9588.

(14) (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Sheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (b) Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A* **2004**, *42*, 4392.

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 NaN₃, TosN₃, and (PhO)₂PON₃. 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).

			Me	N ₃	
	Me TMSN ₃	, 2 , silver salt	· ·	+	
Í	OH	t rt overnight	► Me		
<	la la	i, ii, oronigiii			0.
				-	63
			~ 4	а	
entry	silver salt (mol %)	solvent	$\mathbf{3a}(\%)^b$	4a (%)	$E:Z^c$
1		toluene		30	
2	$\operatorname{AgOTf}(5)$	toluene	88		7:1
3	$AgSbF_{6}(5)$	toluene	65	25	7:1
4	$AgNTf_{2}(5)$	toluene	83	4	7:1
5	$AgCF_{3}CO_{2}(5)$	toluene	3	76	
6	$AgPhCO_{2}(5)$	toluene	3	92	
7	$\mathrm{AgF}\left(5 ight)$	toluene	4	79	
8	$Ag_{3}PO_{4}(5)$	toluene	3	73	
9	$AgBF_{4}(5)$	toluene	2	56	
10	$\operatorname{AgPF}_{6}(5)$	toluene	6	44	
11	$AgCO_{3}(5)$	toluene	2	44	
12	$\operatorname{AgOTf}(5)$	THF	35		7:1
13	$\operatorname{AgOTf}(5)$	m-xylene	68		7:1
14	$\operatorname{AgOTf}(5)$	ether	69		7:1
15	$\operatorname{AgOTf}(5)$	CH_2Cl_2	72		7:1
16	AgOTf (5)	CH_3CN		54	
17	$\operatorname{AgOTf}(2)$	toluene	74	15	7:1
18	$\operatorname{AgOTf}(1)$	toluene	45	30	7:1
19^d		toluene	69		5:1
20^e	AgOTf (5)	toluene		68	

Table 1. Optimization of the Azidation of Allylic Alcohols^a

^{*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

^{(10) (}a) Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. Tetrahedron Lett. **1986**, 27, 227. (b) Murahashi, S.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. J. Org. Chem. **1989**, 54, 3292. (c) Aufranc, P.; Ollivier, J.; Stolle, A.; Bremer, C.; Es-sayed, M.; de Meijere, A.; Salaün, J. Tetrahedron Lett. **1993**, 34, 4193. (d) Trost, B. M.; Pulley, S. R. J. Am. Chem. Soc. **1995**, 117, 10143. (e) Trost, B. M.; Cook, G. C. Tetrahedron Lett. **1996**, 37, 7485.

⁽¹¹⁾ Labbé, G. Chem. Rev. 1969, 69, 345.

⁽¹⁵⁾ Dang, T. T.; Boeck, F.; Hintermann, L. J. Org. Chem. 2011, 76, 9353 and references therein.

Table 2. Substrate Scope for the Direct Azidation of Primary

 Allylic Alcohols^a



^{*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 electronwithdrawing aryl substituents 11-n proceeded smoothly and provided the desired allylic azides 31-n in good yields (62–96% Table 3, entries 5–7). The $\alpha,\beta,\gamma,\delta$ unsaturated allylic alcohol (3E,5E)-6-phenylhexa-3,5dien-2-ol (10) gave the azide 30 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-qwere 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%.





^{*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. ^{*f*} 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 TertiaryAllylic Alcohols a





^{*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 Ph₃P 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 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.

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Supporting Information Available. Experimental procedures and full characterization (¹H and ¹³C 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.