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Brønsted acid mediated nitrogenation of propargylic alcohols: an efficient approach to alkenyl nitriles†

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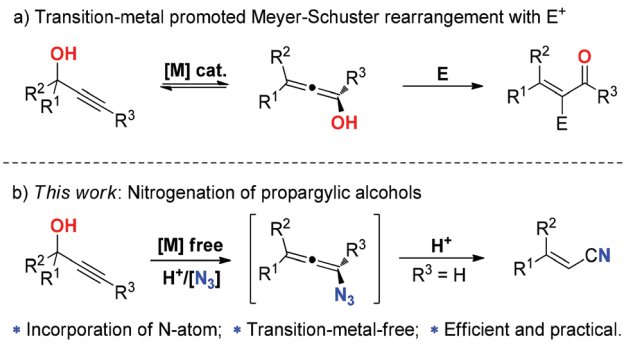
A novel and efficient approach to alkenyl nitriles from readily available propargylic alcohols has been developed. This nitrogenation reaction is transition-metal-free and could be conducted under air at ambient temperature, which makes this protocol promising and practical. Moreover, NH_4Br is disclosed as an efficient additive to promote the stereoselectivity of this reaction.

Propargylic alcohols, which are readily available by practical and vigorous strategic bond-forming reactions, are very useful building blocks and have been widely used in organic synthesis.[1] The Meyer–Schuster rearrangement represents a significant transformation of propargylic alcohols and provides an efficient, highly selective and atom-economic protocol to enones,[2] which are definitely one of the most versatile bifunctional building blocks as well as core components of many bioactive natural products, pharmaceuticals and materials.[3] The exploration of novel transformations of propargylic alcohols and the broadening of the utility of the Meyer–Schuster rearrangement have attracted considerable attention.[4] Enlightened by the mechanism, the capture of allenol, which is the key intermediate in this named reaction, opens up a fertile world for chemists to develop new reactions. Recently, some elegant studies for the synthesis of complex enones from propargylic alcohols directly have been carried out by the groups of Zhang,[5a] Trost,[5b,c] Gaunt,[5d] Tan and Liu[5e] respectively (Scheme 1, a). In these cases, the electrophilic interception of the allenoate type intermediate has been designed to replace the protonation step and represents a fascinating strategy for modification of the Meyer–Schuster rearrangement. To enable these novel processes, transition-metal catalyst systems were employed to promote the desired rearrangement over many side reactions of propargylic alcohols.[2a]



Scheme 1 Nitrogenation of propargylic alcohols.

Inspired by the above work and in the course of our studies on using azides as the nitrogen source to construct nitrogen-containing compounds,[6] we hypothesized that if a highly reactive allenyl azide[7] could be generated *in situ* during the rearrangement of propargylic alcohols in the presence of an azido nucleophile, a new type of reaction with N-containing products would be discovered. Herein, we report a novel Brønsted acid mediated nitrogenation of propargylic alcohols for the efficient synthesis of alkenyl nitriles (Scheme 1, b).

The significance and advantages of the present protocol can be summarized as follows: (1) this is a novel metal-free transformation of simple propargylic alcohols to alkenyl nitriles which is an important class of α,β-unsaturated carbonyl compounds due to their significance in chemistry and biology,[8] through a direct N-incorporation strategy. Although various methods have been developed,[9] the preparation of alkenyl nitriles from a wide range of readily available substrates *via* an efficient and practical way is still extremely attractive. (2) This process is transition-metal-free and could be conducted under air at ambient temperature, which makes this protocol promising and practical.

Commercially available propargylic alcohol 1-phenylprop-2-yn-1-ol (**1a**) was chosen to evaluate our hypothesis of inter-

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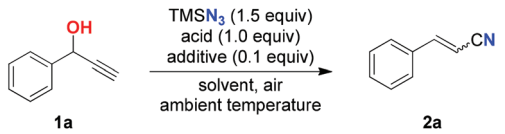
Table 1 Optimization of the nitrogenation reaction[a]



Entry	Acid (1 equiv.)	Additive	Solvent	Yield[b] (%)	*E*/*Z*[c]
1	*conc.* H_2SO_4	—	MeCN	71	66 : 34
2	*conc.* HCl	—	MeCN	0	—
3	$TsOH{\cdot}H_2O$	—	MeCN	35	71 : 29
4	$Cu(OTf)_2$	—	MeCN	0	—
5	$FeCl_3$	—	MeCN	0	—
6	***conc.* H_2SO_4**	**NH_4Br**	**MeCN**	**82 (79)[d]**	***E* only**
7	*conc.* H_2SO_4	NH_4Cl	MeCN	81	93 : 7
8	*conc.* H_2SO_4	TBAB	MeCN	73	95 : 5
9[e]	*conc.* H_2SO_4	NH_4Br	MeCN	82	*E* only
10[f]	*conc.* H_2SO_4	NH_4Br	MeCN	0	—
11	*conc.* H_2SO_4	NH_4Br	THF	0	—
12	*conc.* H_2SO_4	NH_4Br	Toluene	65	96 : 4
13	*conc.* H_2SO_4	NH_4Br	DMF	0	—

[a] Reaction conditions: **1a** (0.5 mmol), $TMSN_3$ (1.5 equiv.), acid (1.0 equiv.), additive (0.1 equiv.) and solvent (2.0 mL), stirred at ambient temperature under air for 12 hours. [b] Determined by ^1H NMR yield using 1,1,2,2-tetrachloroethane as the internal standard. [c] Determined by ^1H NMR measurement of the crude mixture. [d] The number in parenthesis is the isolated yield. [e] The reaction was run under Ar. [f] NaN_3 (1.5 equiv.) instead of $TMSN_3$ was employed. TBAB = tetrabutylammonium bromide.

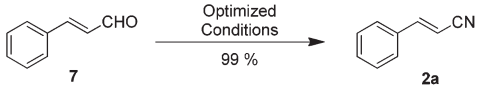
ception of allenyl azides using proton as an electrophile. To our delight, the expected product cinnamonitrile (**2a**) was obtained in 71% yield although in low stereoselectivity, when **1a** was treated with azido trimethylsilane ($TMSN_3$) and 1.0 equiv. of concentrated sulfuric acid (*conc.* H_2SO_4)[10] under air at ambient temperature (Table 1, entry 1). After failing in using a catalytic amount of acid (see ESI†), other stoichiometric Lewis acids and Brønsted acids were tested for this transformation (entries 2–5). The results indicate that *conc.* H_2SO_4 is the best choice in this present ionization of propargylic alcohols. Then we turned our attention to improve the stereoselectivity by screening a wide range of additives (entries 6–8, also see ESI†).[11] Gratifyingly, the *E*-selectivity was dramatically achieved in the presence of only 0.1 equiv. of NH_4Br as an additive with also a slight improvement in yield (entry 6). No product was obtained when NaN_3 was employed instead of $TMSN_3$ (entry 10). Further screening of the solvent showed that MeCN was the best one (entries 11–13).

With the optimized conditions in hand, we next investigated the substrate scope of this transformation. Secondary propargylic alcohols were proved to be efficient to afford the corresponding alkenyl nitriles in moderate to excellent yields with high stereoselectivity (Table 2, entries 1–10). Generally, substrates bearing an electron donating group performed better than that containing an electron withdrawing group. However, as to strong electron donating groups, alkenyl nitriles (**2c**, **2n** and **2o**) were obtained in lower yields mainly because of the unknown side reactions.[2a] The substituting position of the methyl group did not affect the efficiency (Table 2, entries 2, 8 and 9). It is noteworthy that the cinnamonitriles (**2a–2g**, **2i–2j**) were obtained with high stereoselectivity regardless of the substituents at the phenyl ring of the corresponding propargylic alcohols. Moreover, naphthyl and thienyl groups were tolerated under these conditions, though in lower yields (Table 2, entries 12 and 13). Intriguingly, 1-(ferrocenyl)prop-2-yn-1-ol performed well, generating *E*-**2n** in 23% yield (Table 2, entry 14).

Meanwhile, the effects of additives, electronic nature and steric hindrance on the stereoselectivity of products were studied. Therefore, a series of tertiary propargylic alcohols were investigated under optimized conditions. The reactions of tertiary propargylic alcohols worked well affording the desired alkenyl nitriles in moderate to good yields (Table 2, entries 15–23). Interestingly, NH_4Br played a dual role in both improving the yield and affecting the stereoselectivity dramatically (compare entries 1 and 6 of Table 1, entries 16 and 17 of Table 2). In contrast, the electronic nature of propargylic alcohols did not affect the stereoselectivity remarkably (entries 16, 18–21 of Table 2). Notably, the selectivity decreased with the increase of the steric hindrance of substrates (compare entries 1, 16, 22, 23 of Table 2; compare entries 1, 11 of Table 2; and compare entries 2, 8, 9 of Table 2). It is interesting that *Z*-4-methyl-3-phenylpent-2-enenitrile (**2v**) was mainly obtained. In other words, the cyano group preferred to be *trans* to the larger substituent in the presence of NH_4Br as an additive. In conclusion, bromide ion and the steric hindrance played an important role in the control of stereoselectivity.

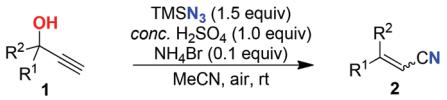
As mentioned above, alkenyl nitriles are among the most versatile building blocks in organic synthesis due to their bifunctional and dipolar nature. The product **2a** could be easily converted into diverse building blocks for further applications such as the primary allylic amine **3** (90%, a, Scheme 2),[12] a diphenylphosphine oxide addition product provided **4** (96%, b, Scheme 2),[13] α,β-unsaturated amide **5** (99%, c, Scheme 2),[14] and tri-substituted alkenyl nitrile **6** (94%, d, Scheme 2).[15] Moreover, **2a** could undergo some other interesting reactions, creating a compound library including many bioactive natural products, pharmaceuticals and materials according to the literature.[16]

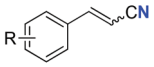
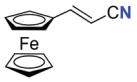
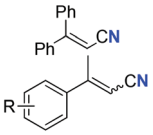
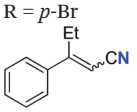
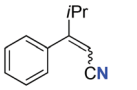
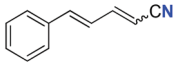
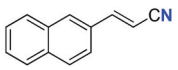
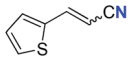
To demonstrate the mechanism of this transformation, some control experiments were investigated. Although cinnamaldehyde **7** was converted into **2a** under the optimal conditions *via* a Schmidt reaction[17] (eqn (1)), **1a** was unable to produce **7** through the Meyer–Schuster reaction (eqn (2)). These results may exclude the possibility of a tandem process involving the Meyer–Schuster reaction of propargylic alcohols into α,β-unsaturated aldehydes and a subsequent Schmidt reaction giving alkenyl nitriles.



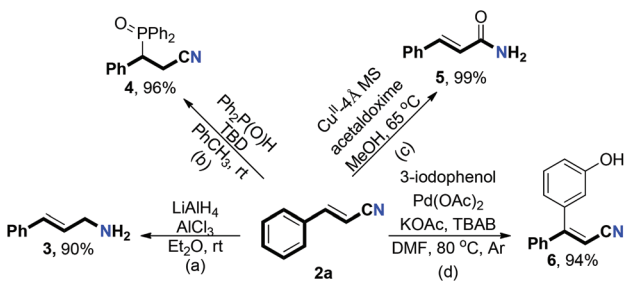
(1)

Table 2 The scope of the propargylic alcohols[a]

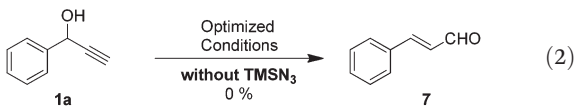


Entry	Product	(Yield[b], *E*/*Z*[c])	Entry	Product	(Yield[b], *E*/*Z*[c])
			14		**2n** (24%, *E* only)
1	R = H	**2a** (79%, *E* only)	15		**2o** (39%, —)
2	R = *p*-Me	**2b** (98%, *E* only)	16	R = H	**2p** (92%, 78 : 22)
3	R = *p*-OMe	**2c** (58%, *E* only)	17[e]	R = H	**2p** (58%, 32 : 68)
4	R = *p*-*t*Bu	**2d** (93%, *E* only)	18	R = *p*-Me	**2q** (65%, 76 : 24)
5	R = *p*-F	**2e** (75%, *E* only)	19	R = *p*-F	**2r** (87%, 84 : 16)
6	R = *p*-Cl	**2f** (69%, *E* only)	20	R = *p*-Cl	**2s** (82%, 77 : 23)
7[d]	R = *p*-Br	**2g** (70%, *E* only)	21	R = *p*-Br	**2t** (85%, 78 : 22)
8	R = *o*-Me	**2h** (87%, 96 : 4)	22		**2u** (66%, 54 : 46)
9	R = *m*-Me	**2i** (84%, *E* only)	23		**2v** (41%, 21 : 79)
10	R = 3,4-dimethyl	**2j** (83%, *E* only)			
11		**2k** (44%, 93 : 7)			
12		**2l** (51%, *E* only)			
13		**2m** (42%, 98 : 2)			

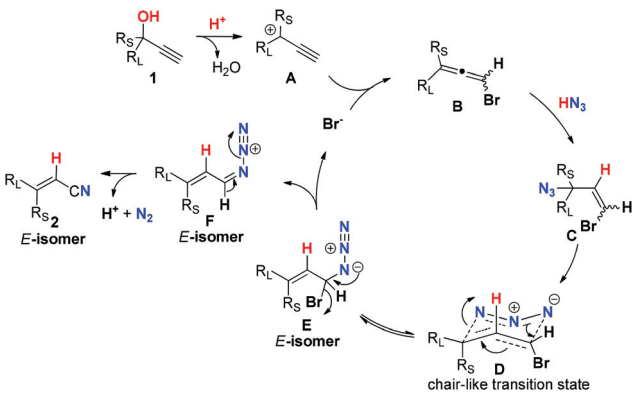
[a] Reaction conditions: see entry 6, Table 1. [b] Isolated yields. [c] Determined by ^{1}H NMR measurement of the mixture. [d] The reaction was carried out at 30 °C. [e] Without NH_4Br.



Scheme 2 Further applications of the product.



(2)



Scheme 3 Proposed mechanism.

On the basis of the above results and previous work, a plausible mechanism is illustrated in Scheme 3. First of all, the ionization of propargylic alcohol **1** forms the carbocationic intermediate **A**.[2] When the reaction was executed in the presence of a catalytic amount of NH_4Br as an additive, N_3^- shows a weaker nucleophilicity than Br^-,[18] which preferentially attacks the carbocationic intermediate **A** to generate the

allenic bromide intermediate **B**.[19] Subsequently, regioselective hydroazidation to the styryl double bond of the allene takes place to form the intermediate **C**,[20] which undergoes [3,3]-sigmatropic rearrangement to produce *E*-terminal allylic azide (*E*)-**E** *via* the chair-like transition state **D**.[21] The elimination of intermediate (*E*)-**E** generates species (*E*)-**F** and Br^- to recycle this process. Finally, the Schmidt type rearrangement of the carbocation (*E*)-**F** occurs leading to (*E*)-**2** and H^+ to complete this transformation[6,17] (Scheme 3). Alternatively, when NH_4Br was not employed in this reaction, the reaction will undergo the allenyl azide[7] pathway (b, Scheme 1) followed by H^+ electrophilic addition leading to carbocations **F** for the subsequent Schmidt type rearrangement.

Conclusions

In summary, we developed a novel transformation to alkenyl nitriles under mild and transition-metal-free conditions *via* the direct incorporation of a nitrogen atom into readily assembled propargylic alcohols. Moreover, NH_4Br is disclosed as an efficient additive to promote the stereoselectivity of this reaction. This transformation would broaden the toolbox of chemical reactions and provide a facile entry to alkenyl nitriles. Further studies on the mechanism and the applications of this transformation are ongoing in our group.

Acknowledgements

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