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Visible Light Promoted Metal-Free Aerobic Hydroxyazidation of Alkenes

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Visible Light Promoted Metal-Free Aerobic Hydroxyazidation of Alkenes

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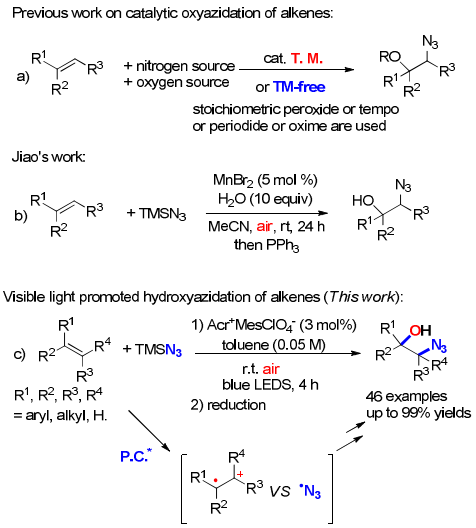
Supporting Information Placeholder

ABSTRACT: A highly efficient visible light promoted metal-free aerobic hydroxyazidation of alkenes has been developed. This protocol was operationally simple with broad substrate scope using relatively simple and readily available starting materials, such as alkenes and air, to construct valuable ß-azido alcohols which are significant building blocks to build *N*-containing compounds. The distinct possible mechanisms were proposed via the generation of azido radical and alkene radical cation.
KEYWORDS: *metal-free, hydroxyazidation, alkenes, visible light*

The direct and regioselective olefin difunctionalization is one of the most efficient strategies for the synthesis of 1,2-difunctionalized products[1] which have been widely used for constructing complex natural products or diversified chemical libraries. The ß-azido alcohols are a significant class of compounds in synthetic chemistry, which have emerged tremendous utilities in chemistry, medicine, biology as well as materials science.[2] The ß-azido alcohols exist in biologically active molecules,[3] and also serve as synthetic precursors of ß-amino alcohols[4] and *N*-containing heterocycles.[5] Conventionally, the ß-azido alcohols are prepared through the ring opening of corresponding epoxides or substitution of ß-haloalcohols.[6] However, these methods suffer from the prefunctionalization of the corresponding starting materials and limited the substrate scope. The direct olefin difunctionalization offers a great chance for the construction of ß-azido alcohols from readily available starting materials.

Shibasaki and co-workers[7] developed a directly $(Cl_2SnO)_n$-catalyzed hydroxyazidation of alkenes to provide ß-azido alcohols in moderate yields using the superstoichiometric peroxy reagent. Despite several achievements (**Scheme 1a**)[8] have been made by these methods, there are still some issues to be addressed: 1) stoichiometric or excess oxidants, such as high valent iodine salts or peroxy reagent, are used; 2) the tolerance of functional group is not so well; 3) the specified *O*-sources, such as hydroxylamine or TEMPO limit their further utilities. Recently, Jiao[9] developed a facile Mn-catalyzed highly efficient aerobic hydroxyazidation of alkenes using $TMSN_3$ as N_3 source and dioxygen as oxygen source (**Scheme 1b**). The azido radical was proposed as an initial activated intermediate. Although it is a great stride in this field, the development of highly efficient and metal-free aerobic methods is still remain a challenge and highly desirable. Visible light, as a safe, abundant and clean energy source, has emerged as a powerful tool to construct organic molecules under mild conditions.[10] Dioxygen is generally considered as an ideal and green oxidant, and also a clean and cheap oxygen source.[11]

To the best of our knowledge, visible light promoted hydroxyamination of alkenes using molecular oxygen as an oxygen source has not been previously reported. Prior to this work, we have developed a visible light-promoted neutral intramolecular oxyamination of alkenes with highly controllable



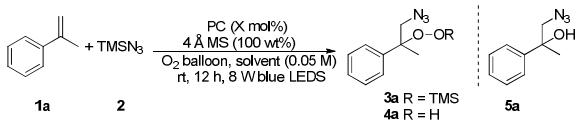
Scheme 1. Catalytic oxyazidation of alkenes.

diastereoselectivity.[12] We consequently aimed at extending more general, efficient and powerful methodology to furnish valuable amino alcohol derivatives. Herein, we report a visible light promoted metal-free aerobic hydroxyazidation of alkenes. The olefin radical cation or azido radical were proposed (**Scheme 1c**).

In an initial investigation to optimize the reaction, we employed α-methyl styrene **1a** as a model substrate, $TMSN_3$ as a nitrogen source, dioxygen gas as an oxygen source, 4Å MS as a desiccant and $Acr^+MesClO_4^-$ (9-mesityl-10-methylacridinium perchlorate) as a visible light photocatalyst at room temperature under the irradiation of 8W blue LEDs (**Table 1**). To our delight, the reaction in a solution of acetonitrile afforded the ((1-azido-2-phenylpropan-2-yl)peroxy)trimethylsilane **3a** in 41% yield (entry 1). Various solvents, such as dichloromethane, tetrahydrofuran and toluene were used instead of acetonitrile. Toluene was more suitable for this transformation, yielding **3a** in 87% yield (entry 4). When the catalyst loading was reduced to 3 mol%, the reaction afforded **3a** in 95% yield (entry 5). Further reducing the catalyst loading, the yields were decreased (entries 6 and 7). The reaction could be completed in 4 h (entry 8). The ruthenium or iridium photocatalysts did not work for this transformation (entries 9 and 10). Control experiments were performed either without photocatalyst or light (entries 11 and 12), reactions did not occur at all. The amount of $TMSN_3$ could be reduced to 2 equiv., however, using 3 equiv. of $TMSN_3$ afforded **3a** in a better yield (entries 13 and 14). Air could be used instead of O_2 balloon (entry 15). The reaction without 4Å MS underwent smoothly to afford **5a** in 94% yield after reduction of **3a** (entry 16). When heated at 80 ^oC in the absence of light, the model reaction did not work.

With the optimal reaction conditions in hand, we next investigated the scope of a variety of 1,1-disubstituted alkenes summarized in **Table 2**. The methyl group on *ortho*-, *meta*- and *para*-positions on styrene could be tolerated (**5b-d**). A number of

Table 1. Optimization of the reaction conditions.

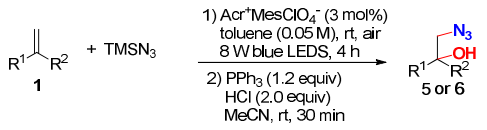


Entry	$TMSN_3$(equiv.)	PC (mol%)	Solvent	Yield (%)[a]
1	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (5)	MeCN	41
2	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (5)	DCM	40
3	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (5)	THF	43[b]
4	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (5)	Toluene	87
5	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (3)	Toluene	95
6	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (2)	Toluene	86
7	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (1)	Toluene	20
8[c]	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (3)	Toluene	97
9[c]	$TMSN_3$ (5)	$Ru(bpy)_3(PF_6)_2$ (3)	Toluene	0
10[c]	$TMSN_3$ (5)	$Ir(ppy)_2(dtbbpy)PF_6$(3)	Toluene	0
11[c]	$TMSN_3$ (5)	-	Toluene	0
12[c,d]	$TMSN_3$ (5)	$Acr^+MesClO_4^-$ (3)	Toluene	0
13[c]	$TMSN_3$ (3)	$Acr^+MesClO_4^-$ (3)	Toluene	90
14[c]	$TMSN_3$ (2)	$Acr^+MesClO_4^-$ (3)	Toluene	86
15[c,e]	$TMSN_3$ (3)	$Acr^+MesClO_4^-$ (3)	Toluene	95
16[c,e,f]	$TMSN_3$ (3)	$Acr^+MesClO_4^-$ (3)	Toluene	94[g]
17[d,h]	$TMSN_3$ (3)	$Acr^+MesClO_4^-$ (3)	Toluene	0

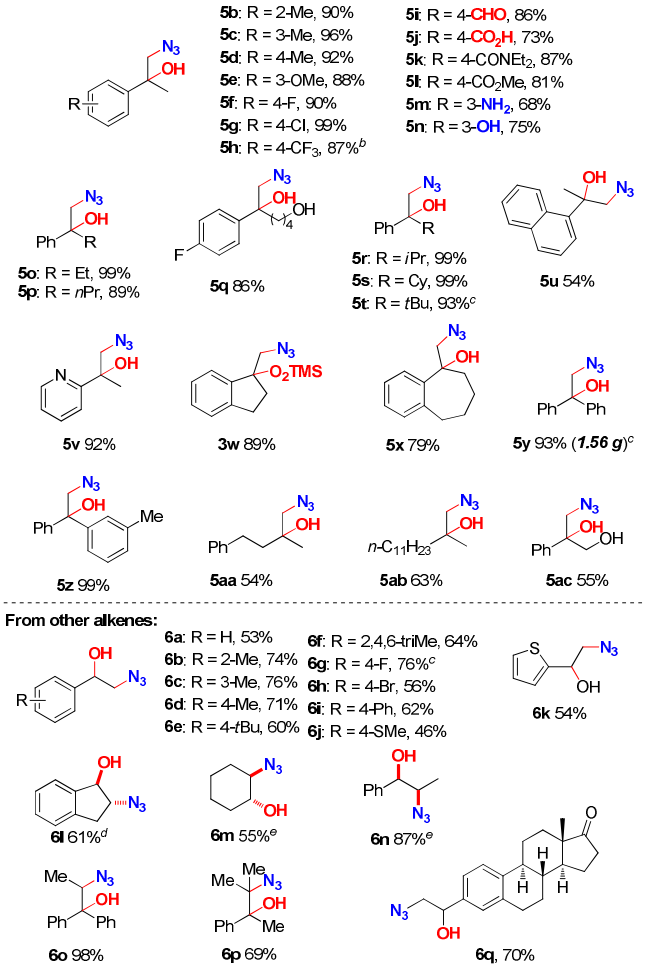
[a]**1a** (0.3 mmol). Yields of **3a** were determined by ^1H NMR with mesitylene as an internal standard. [b]39% yield of **4a** was observed. [c]The reaction was run for 4 h. [d]Without light. [e]Air was used instead of O_2 balloon. [f]No 4Å MS. [g]The crude product was stirred in MeCN (2 mL) with PPh_3 (1equiv.) and HCl (Conc.) (2 equiv.) at r.t. for 30 min to obtain the final product. The isolated yield of **5a**. [h]80 °C

styrenes bearing both the electron-donating and electron-withdrawing groups, such as ether, halides, trifluoromethyl, phenol, aldehyde, acid, ester, amide, free amine and alcohols could be converted to the corresponding desired ß-azido alcohols in good to excellent yields (**5e-n**). The α-substituents on styrenes could be not only 1°-alkyl group but also more sterically hindered 2°- and 3°-alkyl groups (**5o-t**). The 1-naphthyl and 2-pyridyl substrates could be transformed into the ß-azido alcohols **5u-v** in 54 and 92% yield, respectively. Notably, the 1-methyleneindane and 5-methylene-6,7,8,9-tetrahydro-5H-benzo[7]annulene could be delivered into **3w** and **5x** in good yields, respectively. The 1,1-diaryl terminal alkenes were allowed for the transformations providing **5y** and **5z** with up to 99% yields. It is noteworthy that the reaction of 1,1-diphenylethylene could be conducted in a gram-scale under air to afford the **5y** in 93% yield. Importantly, the reactions of 1,1-dialkyl terminal alkenes proceeded smoothly to provide the ß-azido alcohols **5aa-ab** in good yields. It was worthy to note that the allylic alcohol was also feasible for this transformation to access **5ac** in 55% yield. Further interrogation of the substrate scopes of this transformation was illustrated. Due to potential over oxidation of products, the reactions of the monosubstituted styrenes afforded the corresponding hydroxyazidation products **6a-i** with a slightly low yield (46-76%). Moreover, easily oxidized *S*-containing substrates such as thiol ether and thiophene were tolerated to be convert to the desired products **6j-k** in moderate yields. The 1,2-disubstituted internal alkenes were also suitable partners with $TMSN_3$ to deliver the corresponding products **6l-m**. Gratifyingly, the cyclic alkenes, such as indene and cyclohexene, could be reacted smoothly under the standard conditions to access the desired products in 61% yield with 3/1 *dr* and 55% yield with 2/1 *dr*, respectively. The ß-methyl styrene could also be transformed into the product **6n** in 87% yield with 2/1 *dr*. To our

Table 2. Substrate scope[a]



From 1,1-disubstituted alkenes:

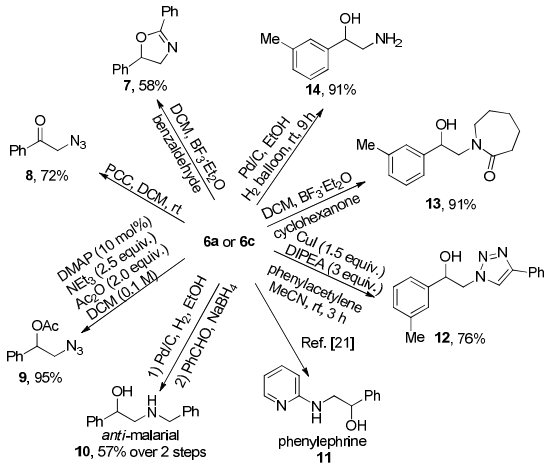


From other alkenes:

[a]Standard conditions: alkenes (0.3 mmol), $Acr^+MesClO_4^-$ (0.03 equiv.), $TMSN_3$ (3 equiv.) in a solution of toluene (0.05 M) under the irradiation of 8 W blue LEDS under air for 4 h at room temperature. Isolated yield of products after treated with HCl (Conc.) (2 equiv.) and PPh_3 (1.0 equiv.) in MeCN (2 mL). [b]6 h. [c]12 h. [d]3/1 *dr*. [e]2/1 *dr*.

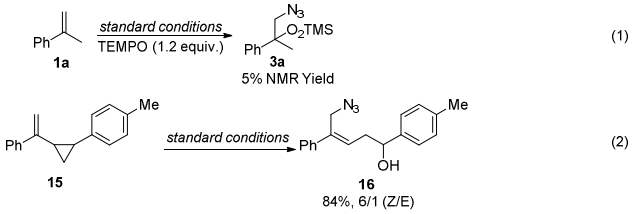
delight, the trisubstituted and fully substituted alkenes bearing relatively bulkier hindrance could also participate to deliver **6o** and **6p** in 98% and 69% yields, respectively. To explore its utility for late-stage functionalization of complex molecules, estrone-derived styrene was converted to hydroxyazidation product **6q** in 70% yield. This result shows great potential for the structure modification of an array of complex biological molecules in medicinal chemistry.[13]

There are great utilities for ß-azido alcohols which could be transformed to a variety of useful molecules (Scheme 2).[14] Oxazoline **7**, ß-azide ketone **8** and ß-azide ester **9** could be obtained via the cyclization with benzaldehyde or oxidation or esterification reactions of **6a**, respectively. The ß-azido alcohol **6a** could be easily transformed to anti-malarial product **15** in 57% yields over two steps and phenylephrine **16**, a approved drug.[14f] Additionally, triazole **12** and lactam **13** could be obtained through "click" reaction with phenylacetylene or Schmidt reaction. Amino alcohol **14** was also obtained through hydrogenation.



Scheme 2. Transformations of ß-azido alcohols and synthesis of bioactive compounds.

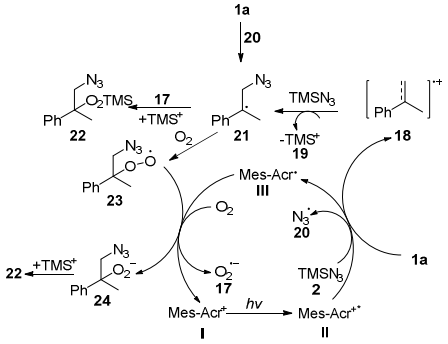
To gain mechanistic insights, control experiments were performed in **Scheme 3**. In the presence of radical trap TEMPO, the reaction almost shut down (eq. 1), indicating that a radical intermediate might be involved in this transformation. The radical clock reaction of vinylcyclopropane **15** was performed to afford the radical ring-opening product **16** in 84% yield, suggesting that this protocol undergoes via a radical pathway (eq. 2).



Scheme 3. Mechanistic studies

Based on the previously reported literature result,[15] the alkene could be directly oxidized to be the radical cation by excited state of 9-mesityl-10-methylacridinium perchlorate.

The plausible mechanisms for this transformation are proposed in **Scheme 4**. The photosensitizer (Mes-Acr$^+$) absorbs visible light under the irradiation of 8 w blue LEDs to generate its excited state (Ered* = 2.06 V vs SCE)[16] which could oxidize the styrene **1a** (Eox = 1.91 V vs SCE)[17] to afford corresponding radical cation **18** and the reduced species **III** (Mes-Acr•). The Mes-Acr• could be oxidized by dioxygen to provide superoxide **17** and regenerate photocatalyts. The high regioselective reaction of radical cation **18** is attributed to the fact that the charge of the resonance hybrid is usually found at the less substituted position.[18] Moreover, Arnold[19] found that the radical with more substituents resulting from nucleophilic attack on the alkene radical cation was more favored on the basis of computational studies. The radical cation **18** is then captured by $TMSN_3$ to afford the benzylic radical **21**. The benzylic radical **21** is consequently reacted with superoxide **17** and TMS^+ to afford the peroxyazidation product **22**, exclusively. Alternatively, it should be noted that the oxidation potential of free azide anion is found to be +1.32 V (NHE).[20] The fact that the oxidation potential of the azide anion is quite a bit lower than that of alkene demonstrates the possibility that the excited state **II** could oxidize azide anion to the azido radical **20** following trapping by alkenes to form **21**. Importantly, **III** could also react directly with peroxy radicals **23** resulting from the trapping of oxygen by **21** to generate **24** which react with TMS^+



Scheme 4. A Plausible Mechanism.

to from **22**. During the investigation of substrate scope, the longer time of reaction of the α-methyl styrene bearing electron-withdrawing groups with $TMSN_3$ was needed and the yields of reaction of monosubstituted styrenes were relative lower compared to the reaction of the α-methyl styrene. These results suggested that the reactions were provided with the choice of two alternative pathways, alkene oxidation pathway and azido radical pathway.

In summary, we have developed a highly efficient metal-free visible light promoted hydroxyazidation of alkenes using air as the terminal oxidant to afford ß-azido alcohols. This protocol features metal-free and mild conditions with excellent functional-group toleration and air serving as both the oxygen source and electron acceptor. The resulting ß-azido alcohols can be used as direct precursors to construct an array of important molecules. The alternative possible mechanisms were proposed via the generation of azido radical or alkene radical cation. Current efforts in our laboratory are underway to explore asymmetric transformations.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data for all compounds (PDF).

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