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Mn-Catalyzed Highly Efficient Aerobic Oxidative Hydroxyazidation of Olefins: A Direct Approach to β-Azido Alcohols

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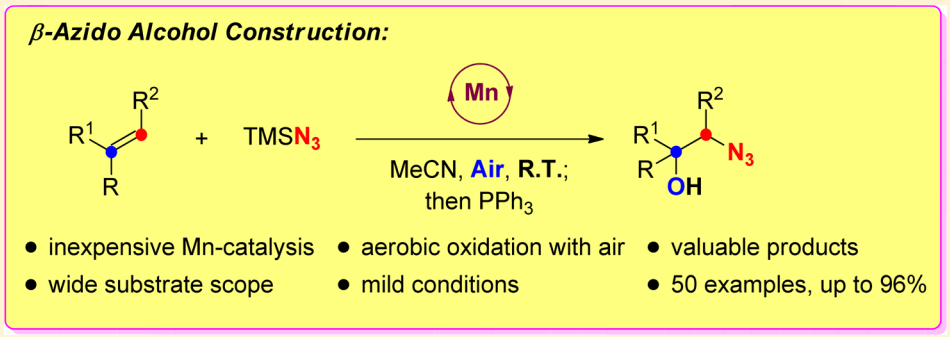
Supporting Information



ABSTRACT: An efficient Mn-catalyzed aerobic oxidative hydroxyazidation of olefins for synthesis of β-azido alcohols has been developed. The aerobic oxidative generation of azido radical employing air as the terminal oxidant is disclosed as the key process for this transformation. The reaction is appreciated by its broad substrate scope, inexpensive Mn-catalyst, high efficiency, easy operation under air, and mild conditions at room temperature. This chemistry provides a novel approach to high value-added β-azido alcohols, which are useful precursors of aziridines, β-amino alcohols, and other important N- and O-containing heterocyclic compounds. This chemistry also provides an unexpected approach to azido substituted cyclic peroxy alcohol esters. A DFT calculation indicates that Mn catalyst plays key dual roles as an efficient catalyst for the generation of azido radical and a stabilizer for peroxyl radical intermediate. Further calculation reasonably explains the proposed mechanism for the control of C−C bond cleavage or for the formation of β-azido alcohols.

INTRODUCTION

The synthesis of organic azides always attracts considerable attention,[1,2] because organoazides are highly valuable and interesting compounds, and have been widely employed in organic synthesis as precursors of a great number of N-containing molecules.[3] Moreover, the practical click chemistry further promotes their use in bioconjugation.[4] Additionally, owing to their remarkable biological activities, the azido moieties have been applied to design lead compounds for drug discovery.[5a] During the past decades, organic azides have achieved a significant position at the interface between chemistry, medicine, biology, and material science.[5] Particularly, β-azido alcohols are ubiquitous structural motifs in organic molecules.[6−8] Featuring of high potential chemical reactivity, these compounds are of particular synthetic utility.[6] In addition, the high value-added β-azido alcohol can serve as direct precursors of aziridines[7a,b] and β-amino alcohols,[7c,d] both of which are important building blocks[7a−d] and widely exist in biologically active compounds, e.g., β-adrenergic receptor blockers and immune stimulants.[7e−g] β-Azido alcohols also show significant importance in the chemistry of carbohydrates and nucleosides.[8]

Traditionally, β-azido alcohols are prepared through ring-opening of corresponding epoxides[9a,b] or their variants.[9c] Reduction and subsequent substitution of α-bromo ketones provide a complementary way to β-azido alcohols.[9d,e] However, these methodologies suffer from multistep synthesis and limited substrate scope. To develop simple and efficient approach to β-azido alcohols from readily available substrates is still highly desired.

In recent years, the alkene difunctionalization has become an extremely powerful strategy in organic synthesis as evidenced by many elegant works.[2,10,11] Despite the significances, there are still some challenging issues: (1) The alkene difunctionalization dominantly focuses on relatively active olefins such as styrenes, as well as less sterically hindered terminal alkenes. In contrast, the widely existing unactivated or internal alkenes are usually hard to undergo the difunctionalization; (2) Although the regioselective intramolecular alkene difunctionalizations have been developed well, regioselective control of intermolecular alkene difunctionlization still desires more attention; (3) Stoichiometric organic or transition-metal salt oxidants, such as

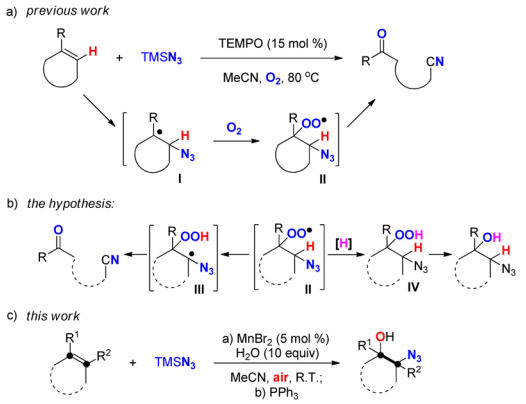
Received: March 5, 2015
Published: April 20, 2015

DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059−6066

$PhI(OAc)_2$, benzoquinone, Cu^{II}, or Ag^{I}, are generally required in previous alkene difunctionalization reactions. Dioxygen has been thought as an ideal oxidant in terms of green and sustainable chemistry.[12,13] Furthermore, the air, a mixture containing about 20% (v/v) oxygen gas, shows more advantages over pure oxygen in aspect of accessibility, safety, and cost. Replacement of these oxidants with molecular oxygen or air represents a significant fundamental challenge.

Under this strategy, many elegant aerobic alkene difunctionalization methods have been developed tolerating unactivated or internal alkenes.[14,15] Inspired by these significant works, we hypothesized that the privileged motifs, β-azido alcohols, could be obtained by the alkene difunctionalization strategy. Recently, we developed a TEMPO-catalyzed oxygenation and nitrogenation of alkenes for the synthesis of oxo nitriles via C=C double bond cleavage (a, Scheme 1).[16] However, the mechanism was unclear. After the azido radical addition and the generation of peroxide radical **II**, how does the C−C bond cleavage occur? How can we control the C−C bond cleavage process? If the peroxide radical **II** is stabilized, probably we can achieve the β-azido alcohol synthesis through the simple aerobic alkene difunctionalization. According to these questions, we hypothesized that if the intramolecular H abstraction of the peroxide radical **II** occurred leading to the carbon radical intermediate **III**, then the C−C bond cleavage rearrangement was triggered to afford oxo nitriles (b, Scheme 1). Alternatively, when the peroxide radical **II** could abstract a H atom from other intermolecular H-source, the corresponding β-azido peroxy alcohols **IV** should be produced. Azido peroxy alcohols **IV** can be easily transformed into β-azido alcohols (b, Scheme 1). Therefore, the high value-added β-azido alcohols could be simply prepared by the alkene difunctionalization strategy through the aerobic generation of azido radicals process participated by molecular oxygen or air.

Scheme 1. Strategy Design to Construct β-Azido Alcohols

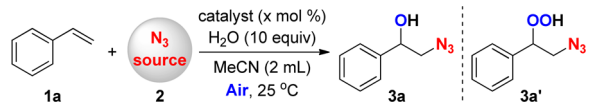


Herein, we report a novel and efficient Mn-catalyzed aerobic oxidative hydroxyazidation of alkenes by using ambient air as oxidant (c, Scheme 1). The mechanistic studies and DFT calculation reasonably explain the proposed the mechanism for the control of C−C bond cleavage or for the formation of β-azido alcohols (b, Scheme 1). This protocol consequently provides a mild and efficient method for the synthesis of high value-added β-azido alcohols, which are usually prepared through a multistep transformation from alkenes or ketones.[9] This transformation is also appreciated by its high regioselectivity and wide substrate scope ranging from styrenes to unactivated olefins and internal alkenes. Additionally, unexpected cyclic peroxy alcohol esters can be obtained, which makes the reaction more interesting and valuable.

RESULTS AND DISCUSSION

Initially, styrene **1a** was chosen as model substrate for the designed aerobic oxidative azidation approach under ambient air. According to the above hypothesis, these reactions were investigated in the presence of H_2O. However, when the reaction was catalyzed by TEMPO,[16] no desired product was detected with most of styrene **1a** remained (entry 1, Table 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	N_3 source	catalyst (mol %)	atmosphere	yield[b] (%)
1	$TMSN_3$ (**2a**)	TEMPO (15)	air	–
2	$TMSN_3$ (**2a**)	$CuBr_2$ (5)	air	–
3	$TMSN_3$ (**2a**)	$FeBr_2$ (5)	air	–
4	$TMSN_3$ (**2a**)	$MnBr_2$ (5)	air	**3a**′ + **3a** (71[d], 9:1)
5[c]	**$TMSN_3$ (2a)**	**$MnBr_2$ (5)**	**air**	**87**
6	NaN_3 (**2b**)	$MnBr_2$ (5)	air	–
7	$N(^nBu)_4N_3$ (**2c**)	$MnBr_2$ (5)	air	–
8[c]	$TMSN_3$ (**2a**)	$Mn(OAc)_2$ (5)	air	45
9[c]	$TMSN_3$ (**2a**)	$Mn(OAc)_3{\cdot}2H_2O$ (5)	air	50
10[c]	$TMSN_3$ (**2a**)	MnO_2 (5)	air	80
11[c]	$TMSN_3$ (**2a**)	$MnBr_2$ (5)	O_2	88
12	$TMSN_3$ (**2a**)	$MnBr_2$ (5)	Ar	trace
13[c,e]	$TMSN_3$ (**2a**)	$MnBr_2$(1)	air	72

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), H_2O (10 equiv), catalyst (5 mol %) in MeCN (2 mL) at room temperature for 24 h under air. [b]Isolated yields of **3a**. [c]PPh_3 (1.0 equiv) was added after 24 h and the mixture was stirred for another 10 min. [d]Determined by ^1H NMR. [e]**1a** (3 mmol) was used.

We then envisioned that if an appropriate metal catalyst was added, the transition metal might donate an electron to the peroxide radical **II** to form a peroxo-metal complex which probably could promote the generation of β-azido peroxy alcohols **IV** (b, Scheme 1). Therefore, various single-electron catalysts such as $CuBr_2$, $FeBr_2$, and $MnBr_2$ were examined (entries 2−4, Table 1, also see the Supporting Information (SI)). We were glad to find that styrene **1a** was converted into a mixture of **3a** and **3a**′ (see SI) when $MnBr_2$ (5 mol %) was employed (entry 4). This intriguing result reveals that $MnBr_2$ is suitable for both azido radical generation and peroxyl radical intermediate stabilization. With the further addition of PPh_3 (1.0 equiv) to reduce the generated peroxy alcohols, β-azido alcohol **3a** was obtained in 87% yield (entry 5). Further screening of other azide sources showed that only $TMSN_3$ could enable this hydroxyazidation transformation (entries 6 and 7). Other Mn salts such as $Mn(OAc)_2$, $Mn(OAc)_3{\cdot}2H_2O$, and MnO_2 could also execute this reaction but with lower efficiencies (entries 8−10). Moreover, when the reaction was carried out under pure O_2, a similar result was obtained (cf. entries 5 and 11). As expected, the reaction under Ar atmosphere did not work (entry 12), which indicates the vital participation of molecular oxygen in this reaction. During the

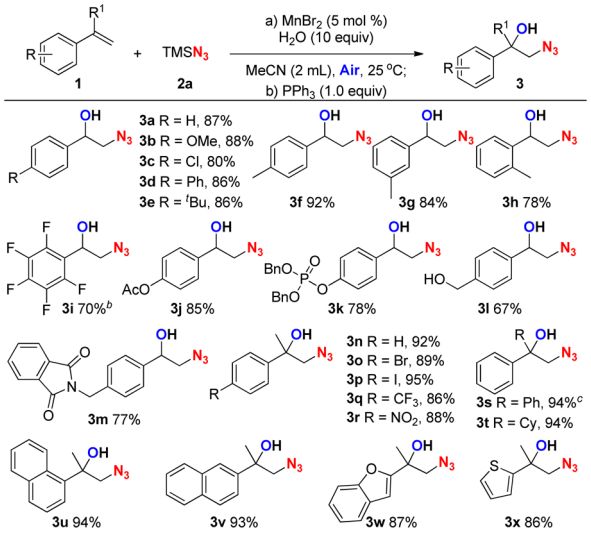
DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059−6066

screening of this reaction, trace amount of diazidation product was detected as byproduct (see SI).

Notably, even when the loading of $MnBr_2$ was reduced to 1 mol %, the reaction afforded **3a** in 72% yield (entry 13), which demonstrates high catalytic efficiency of this $MnBr_2$-air oxidative system for generation of azido radical. In the past decades, reactions with the generated azido radicals showed significant availability in synthesis of organic azides.[1,2,3c] However, despite the significance of these reactions, the conventional initiations of azido radicals limited their further applications, because of the following: (1) Oxidation of the azide anion has been well explored by employing stoichiometric oxidants[3c,17] such as peroxides,[3c] transition-metal salts,[17a,b] and hypervalent iodine compounds.[17c−f] However, these strong oxidants may cause limited functional groups compatibility, low atom economy, and equivalent reduction wastes. (2) Certain azide compounds can be employed as an alternative azido radical precursor, such as halo-azides[18a,b] and azide-iodine(III) reagents.[18c] However, these reagents need to be pre-prepared and are usually unstable. (3) Electro- and photochemistry have been applied in the single electron transfer (SET) process of the azide anion to the azido radical,[19] yet limitation also exists, such as limited substrate scope and low efficiency. Therefore, the present chemistry provides a simple, mild, and efficient protocol to generate azido radicals.

With the optimum conditions in hand, we next explored the scope of terminal styrenes in the presence of $TMSN_3$ **2a** (2.0 equiv), $MnBr_2$ (5 mol %), and H_2O (10 equiv) in MeCN under air at room temperature. The results were summarized in Scheme 2. As expected, a series of styrenes bearing both

Scheme 2. Substrate Scope of Terminal Styrenes[a]

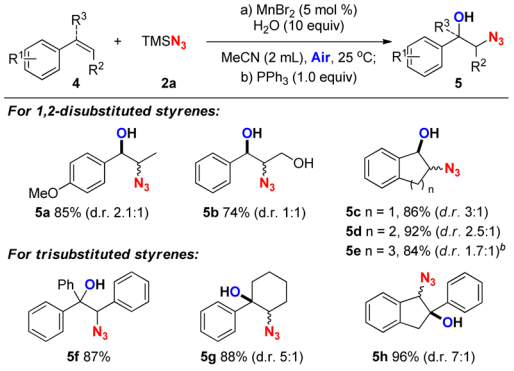


[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $MnBr_2$ (5 mol %), H_2O (10 equiv) in MeCN (2 mL) under air at room temperature. Yield of isolated product after PPh_3 (1.0 equiv) workup. [b]**2a** (0.9 mmol) was used at 40 °C. [c]This reaction was carried out at 15 °C.

electron-donating groups (R = OMe, ^{t}Bu, Me) or electron-withdrawing groups (R = Cl, Br, I, CF_3, NO_2) furnished the transformation producing the desired β-azido alcohols in high efficiencies (Scheme 2). Halo substituents on the phenyl ring were well tolerated (**3c**, **3o**, and **3p**). *p*-, *m*-, and *o*-Methylstyrenes in which the methyl showed different steric hindrance resulted in 92, 84, and 78% yields, respectively (**3f**–**h**). It is noteworthy that α-methyl, phenyl, and cyclohexyl styrenes performed well under the standard conditions giving the corresponding β-azido alcohol products in excellent yields (**3n**–**x**). Both of α- and β-vinyl substituted naphthalene were tolerated in this reaction and showed almost the same efficiency (**3u**,**v**). In addition, heteroaromatic alkenes bearing benzofuryl and thienyl were also compatible under these reaction conditions, giving the expected products (**3w**,**x**) in 87 and 86% yields, respectively. Moreover, pentafluorostyrene which performs a potential bioactivity was a good candidate for this transformation in 70% yield (**3i**). Notably, the vinyl phenylmethanol bearing a hydroxyl group which is sensitive to the oxidative environment delivered the product (**3l**) in 67% yield.

Inspired by the above results, we turned our attention to internal styrenes which show bulky steric hindrance. As shown in Scheme 3, 1,2-disubstituted styrenes were first surveyed

Scheme 3. Substrate Scope of Internal Styrenes[a]



[a]Reaction conditions: **4** (0.3 mmol), **2a** (0.6 mmol), $MnBr_2$ (5 mol %), H_2O (10 equiv) in MeCN (2 mL) under air at room temperature. Yield of isolated product after PPh_3 (1.0 equiv) workup. [b]At 10 °C.

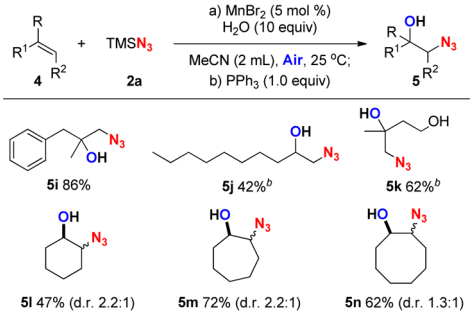
under the standard reaction conditions. *trans*-Anethole (**4a**), a natural bioactive molecule, was transformed into the corresponding product in high yield. Besides, cinnamyl alcohol was also tolerated affording **5b** in 74% yield. Moreover, the reactions of benzo cyclic substrates from five- to seven-membered rings proceeded smoothly to produce the cyclic β-azido alcohols in good yields (**5c**–**e**). To our delight, trisubstituted styrenes, which display bulkier hindrance, provided β-azido substituted tertiary alcohols in excellent yields (**5f**–**h**).

Gratifyingly, the unactivated alkenes which were of chemical inertness in previously reported olefin difunctionalizations, performed well under the standard conditions (Scheme 4). (2-Methylallyl)benzene (**4i**) bearing a sensitive benzyl position delivered the product **5i** in 86% yield. It is noteworthy that the reaction of 1-decene afforded **5j** in 42% yield. Additionally, trisubstituted **4k** containing a hydroxyl group produced a diol product **5k** in 62% yield. Moreover, the reaction was applicable to simple *cis*-cyclo-hexene, octylene, and dodec-1-ene, as demonstrated by the formation of **5l**–**n** in 47, 72, and 62% yields, respectively. These results demonstrate that the efficient protocol could be applied to the hydroxyazidation of various aliphatic alkenes.

Interestingly, when conjugated diene **4o** was employed as substrate (Scheme 5), 1,2-addition product **5o** was obtained in 86% yield without any 1,4-addition result.[20] In this transformation, 1.2 equiv of $TMSN_3$ was used to avoid a further

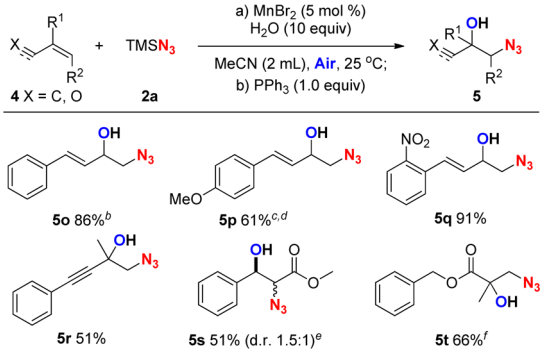
DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059−6066

Scheme 4. Substrate Scope of Unactivated Aliphatic Alkenes[a]



[a]Reaction conditions: **4** (0.3 mmol), **2a** (0.6 mmol), $MnBr_2$ (5 mol %), H_2O (10 equiv) in MeCN (2 mL) under air at room temperature. Yield of isolated product after PPh_3 (1.0 equiv) workup. [b]At 40 °C.

Scheme 5. Substrate Scope of Other Kinds of Alkenes[a]



[a]Reaction conditions: **4** (0.3 mmol), **2a** (0.6 mmol), $MnBr_2$ (5 mol %), H_2O (10 equiv) in MeCN (2 mL) under air at room temperature. Yield of isolated product after PPh_3 (1.0 equiv) workup. [b]1.2 equiv of $TMSN_3$ was used. [c]At 10 °C. [d]1.5 equiv of $TMSN_3$ was used. [e]At 40 °C. [f]3.0 equiv of $TMSN_3$ was used.

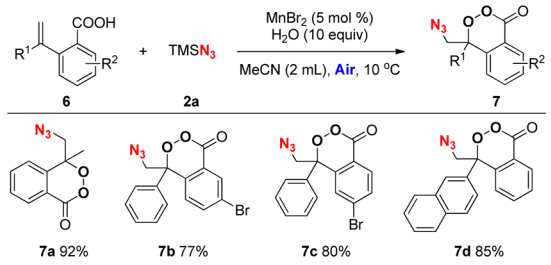
difunctionalization of **5o**. Besides, changing electronic effect of the phenyl ring showed no effect on the regioselectivity, merely offering 1,2-addition products **5p** and **5q** in yields of 61 and 91%, respectively. The conjugate enyne **4r** produced the desired product **5r** in 51% yield, without the detection of the azide/alkyne cycloaddition product[4] or the alkyne addition product.[21]

Furthermore, *trans*-methyl cinnamate was transformed to **5s** in 51% yield with 1.5:1 diastereoselectivity. This kind of product could be easily converted into the corresponding important β-hydroxy-α-amino acid. Finally, α,β-unsaturated ester **4t** was tested, affording **5t** in 66% yield.

To our surprise, when we used 2-vinylbenzoic acids as substrates, which usually underwent lactonization to construct kinds of substituted lactons,[22] unexpected cyclic peroxy alcohol esters were produced (Scheme 6). When **6a** was tested as substrate, product **7a** was offered in excellent yield (92%). Besides, bromo substituent on the phenyl ring was well tolerated, producing **7b** and **7c** in 77 and 80% yields, respectively. **6d** containing a naphthyl group also reacted smoothly, giving **7d** in 85% yield. This transformation should undergo a facile intramolecular nucleophilic substitution of −OOH to carboxyl group.

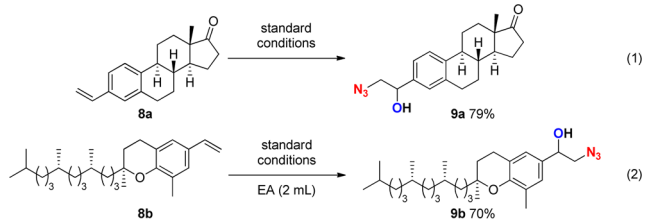
After having been proven a wide substrate scope tolerance, this reaction was applied to complex bioactive molecules containing alkenyl group. To be specific, **8a** bearing a steroid

Scheme 6. Substrate Scope of 2-Vinylbenzoic Acids[a]



[a]Reaction conditions: **6** (0.3 mmol), **2a** (0.6 mmol), $MnBr_2$ (5 mol %), H_2O (10 equiv) in MeCN (2 mL) under air at 10 °C. Yield of isolated product.

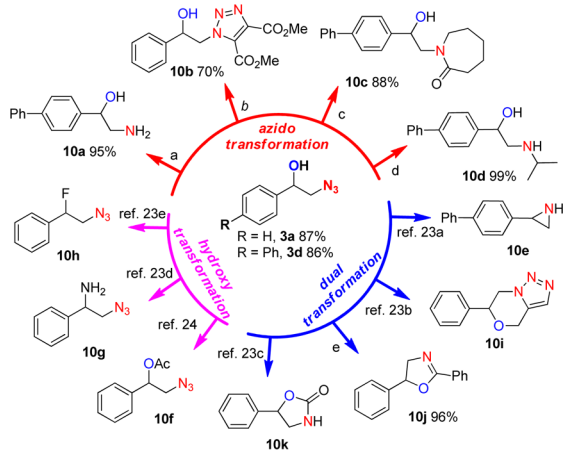
scaffold furnished the transformation, giving **9a** in 79% yield (eq 1). Additionally, **8b** derived from (+)-δ-tocopherol was



suitable for the reaction by switching the solvent from MeCN to EA to enhance its solubility, affording the desired **9b** in 70% yield (eq 2). These two products may have potential utilities in medicinal chemistry.

It is noteworthy that the β-azido alcohol products could be widely applied in direct and efficient synthesis of many bioactive molecules as useful building blocks (Scheme 7). For instance, β-amino alcohol **10a** and aziridine **10e** can be easily

Scheme 7. Further Transformations of β-Azido Alcohols

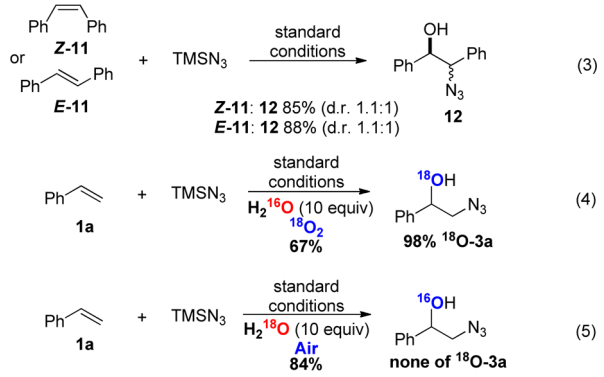


[a]Reaction conditions: **3d** (0.3 mmol), 10% Pd/C (10 mg) in EtOH (2 mL) under H_2 (1 atm) at 25 °C. [b]Reaction conditions: **3a** (1 mmol), DMAD (1.1 equiv) in water (8 mL) at 70 °C. DMAD = dimethyl acetylenedicarboxylate. [c]Reaction conditions: **3d** (0.3 mmol), cyclohexanone (1.5 equiv), $BF_3{\cdot}OEt_2$ (4.0 equiv) in DCM (3 mL) at −84 °C, then 50% KOH (1 mL). [d]Reaction conditions: **3d** (0.2 mmol), acetone (1.1 equiv), PtO_2 (5 mol %), 4 Å MS (90 mg) in MeOH (2 mL) under H_2 (1 atm) at 35 °C. [e]Reaction conditions: benzaldehyde (0.5 mmol), **3a** (1.1 equiv), $BF_3{\cdot}OEt_2$ (2.0 equiv) in DCM (1 mL) at 0 °C, then saturated $NaHCO_3$ (30 mL).

DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059−6066

prepared from **3d** through a simple reduction reaction and a Staudinger reaction.[23a] Furthermore, **10d**, an analogue to many pharmaceutically active β-adrenergic receptor blockers such as (*R*)-pronethalol and (*R*)-nifenalol,[24] was afforded quantitatively via the reduction of the azide and subsequent reductive alkylation process with acetone. Additionally, lactam **10c** and oxazoline **10j** were directly synthesized in excellent yields from **3d** and **3a** respectively through hydroxyl-group-assisted Schmidt reaction. Undoubtedly, click reaction was employed to yield β-hydroxy triazole **10b** which was regarded as a "drug-like" molecule.[7g] Moreover, a more complex heterocyclic scaffold **10i** can be synthesized through a reported two-steps transformation.[23b] Oxazolidinone **10k** can also be achieved by the reaction of **3a** with CO_2/PMe_3.[23c] Besides, maintaining the azido group intact, the hydroxyl group could be converted into other useful functional groups, such as ester,[24] amino,[23d] and fluoro[23e] groups (**10f**–**10h**, Scheme 7). These representative transformations clearly demonstrate the versatilities of β-azido alcohols in organic chemistry.

To get insight into the mechanism, (*Z*) and (*E*)-1,2-diphenylethenes ***Z*-11** and ***E*-11** were tested under the standard conditions, resulting the same diastereoselectivity (1.1:1) and almost the same yield (85 and 88%, respectively) (eq 3). Besides, $^{18}O_2$ and $H_2{}^{18}O$ isotopic labeling experiments were investigated. As expected, the oxygen atom of **3a** originated from molecular oxygen rather than water (eqs 4 and 5).



To further unravel the mechanism, the density functional theory (DFT) calculation investigation into the $MnBr_2$-catalyzed hydroxyazidation of olefins to β-azido alcohols was first conducted (Figure 1).[25] Initially, Mn^{II} is easily oxidized to Mn^{III}, which oxidizes $TMSN_3$ to deliver azido radical feasibly, requiring free energy of only 2.0 kcal/mol. When azido radical is formed, its addition to indene **4c** is facile, with an activation free energy of only 6.9 kcal/mol to give the intermediate **INT1** that is further trapped by dioxygen to furnish **INT2** barrierlessly. Consequently, complex **INT3** is produced by the reaction of **INT2** with Mn^{II} catalyst. Then, complex **INT3** is further hydrolyzed to provide **13** with the formation of Mn^{III} catalyst to complete the catalytic circle. Therefore, $MnBr_2$ plays dual roles as an efficient catalyst for the generation of azido radical and a stabilizer for peroxyl radical intermediate. When **INT2** oxidizes $TMSN_3$ through homolytic substitution process to initiate azido radical and offer **INT4**, it is endergonic by 7.9 kcal/mol, indicating a disfavored pathway in comparison with Mn-catalytic pathway.

The DFT calculation on our previous TEMPO-catalyzed oxo nitriles synthesis through C=C double bond cleavage[16] was also conducted (Figure 2). TEMPO reacts with $TMSN_3$ to give

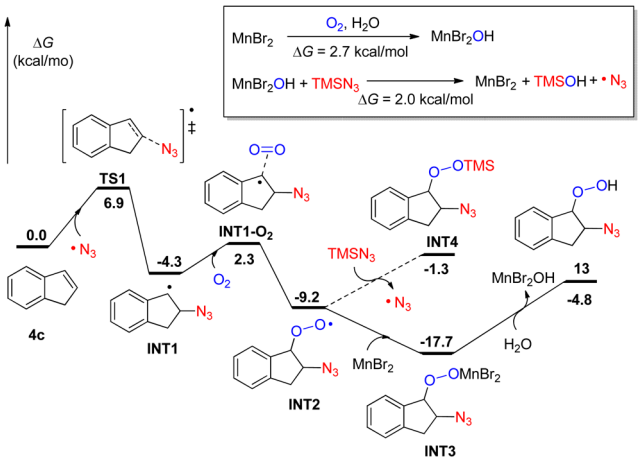


Figure 1. DFT-computed energy profiles for $MnBr_2$-catalyzed hydroxyazidation of **4c** to β-azido alcohol.

TEMPOTMS and azido radical, which is endergonic by 32.2 kcal/mol. This indicates that TEMPO is not an efficient oxidant for the generation of azido radical, in accord with the heat condition and long reaction time. After the generation of **INT2** through the same radical addition and oxygenation processes, the intramolecular H-abstraction through transition state **TS2** requires an activation free energy of 26.4 kcal/mol to afford **INT5**. The following fragmentation is a stepwise process. First, the α-azido radical induces the thermal azido N–N bond cleavage with the release of N_2 through **TS3**, which only requires an activation free energy of 1.5 kcal/mol. This is a highly exergonic process by 56.8 kcal/mol to afford **INT6**. The next C–C bond cleavage and OH radical release occur through **TS4** in a significantly asynchronous fashion, but really undergo a concerted process, as further determined by intrinsic reaction coordinate (IRC) analysis of the transition state structure (see Figure S4 and S5 in SI for details). This pyrolysis process is also feasible with an activation free energy of only 12.7 kcal/mol and highly exergonic by 40.8 kcal/mol to deliver oxo nitrile **14**. Another stepwise fragmentation including O–O bond cleavage followed by C–C bond cleavage and N_2 release is unfavorable (see Figure S2 in SI for details). The formed OH radical can react with $TMSN_3$ via a homolytic substitution reaction at silicon through **TS5** with an activation free energy of 15.4 kcal/mol to regenerate azido radical to complete the catalytic circle.

Alternatively, **INT2** could oxidize $TMSN_3$ through **TS6** to give azido radical and **INT4** with an activation free energy of 30.7 kcal/mol, which is unfavored over **TS2** by 4.3 kcal/mol. The intermolecular H-abstraction of **INT4** by in situ formed azido radical provides **INT7** feasibly with a free energy barrier of 11.8 kcal/mol. The consequent fragmentation is an analogical stepwise process as above-mentioned that thermal azido N–N bond cleavage removes N_2 almost barrierlessly, followed by C–C bond cleavage and TMSO radical release feasibly to give rise to oxo nitrile **14**. Another stepwise fragmentation including O–O bond cleavage followed by C–C bond cleavage and N_2 release is unfavorable (see Figure S3 in SI for details). The formed TMSO radical can react with HN_3 or $TMSN_3$ to generate azido radical to complete the catalytic circle. The comitant TMSOH or TMS_2O can be further detected by GC–MS.[16]

Reviewing the whole energy profiles, we found that the pathway through **TS2** is the prominent process and the intramolecular H-abstraction is the rate-determining step, in

DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059–6066

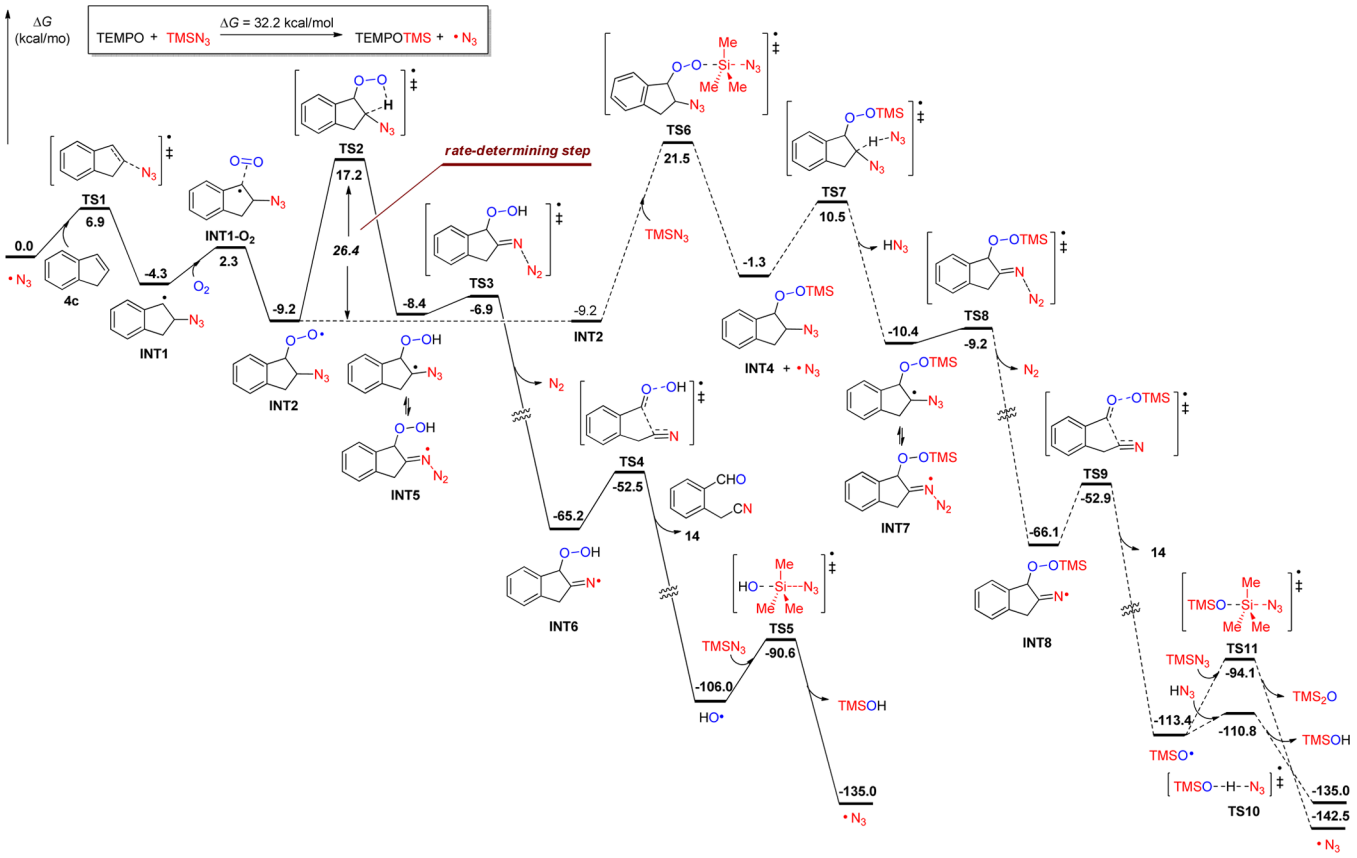
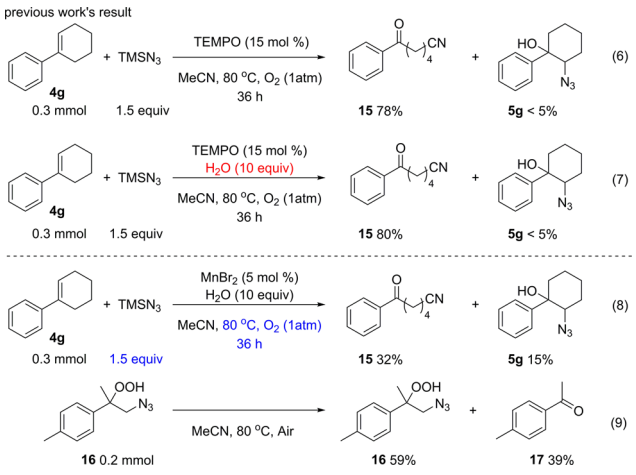


Figure 2. DFT-computed energy profiles for TEMPO-catalyzed oxygenation and nitrogenation of **4c** to afford oxo nitrile **14** through C═C double bond cleavage.

accord with the heat conditions.[16] The alternative pathway through **TS6** is the minor process.

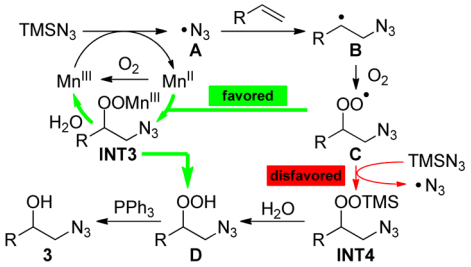
Additional experiments were conducted to further understand the differences between the two catalytic systems. First, H_2O (10 equiv) was added in the former reaction, resulting in no difference (cf. eqs 6 and 7). Then, using $MnBr_2$ as catalyst



under 80 °C in oxygen, the oxo nitrile **15** (32% yield) and *β*-azido alcohol **5g** (15% yield) were obtained. The results support the DFT calculation: (1) By using $MnBr_2$, a more stable complex **INT3** can formed easily, which contributed to the formation of **5g** (eq 8); (2) Under the heating conditions, the generation of **INT5** is possible to produce oxo nitrile **15**. Besides, when **16** was employed under 80 °C in open air, it cannot be efficiently transformed to ketone **17** through C−C bond cleavage with the recovery of **16** in 59% yield (eq 9), which demonstrates that once **16** is formed, it cannot easily undergo C−C bond cleavage.

On the basis of the above results, a plausible mechanism was proposed (Scheme 8). Initially, under the standard conditions,

Scheme 8. Proposed Mechanism



$MnBr_2$ catalyst[26] is oxidized to Mn^{III} or Mn^{IV} by dioxygen.[27] Subsequently, Mn^{III} oxidizes $TMSN_3$ to azido radical **A**. Mn^{IV} can also participate in the oxidation of $TMSN_3$ to form azido radical **A** with the generation of Mn^{III} catalyst.[17b,27,28] The generated azido radical **A** then attacks alkene at sterically less hindered position, producing carbon radical **B** which is trapped by molecular oxygen to form peroxyl radical **C**. According to the DFT calculation, it is favored for the peroxyl radical **C** to undergo Mn-participated SET and protonation processes to afford *β*-azido peroxy alcohols **D**. In comparison, the pathway through **INT4** is disfavored. Finally, *β*-azido peroxy alcohol **D** is reduced by PPh_3 to form *β*-azido alcohol **3**.

DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059−6066

CONCLUSION

In conclusion, we have developed a highly efficient Mn-catalyzed aerobic oxidative hydroxyazidation of olefins for the direct synthesis of β-azido alcohols, which are important and useful building blocks in various organic synthesis. This chemistry discloses a novel $MnBr_2$ catalyzed azido radical generation under ambient air. The inexpensive Mn-catalyst, neutral conditions, using air as oxidant, broad substrate scope, and high value-added products make this protocol very practical and attractive. The mechanistic studies and DFT calculation reasonably explain the proposed mechanism for the control of C−C bond cleavage or for the formation of β-azido alcohols. Further applications and mechanistic study of this transformation are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR spectra, and computational details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02347.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from National Basic Research Program of China (973 Program) (Grant No. 2015CB856600) and National Natural Science Foundation of China (Nos. 21325206, 21172006), and National Young Top-notch Talent Support Program are greatly appreciated. We thank Yujie Liang in this group for reproducing the results of **3v** and **5k**.

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DOI: 10.1021/jacs.5b02347
J. Am. Chem. Soc. 2015, 137, 6059−6066