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Direct hydroxyazidation of alkenes: A viable strategy for the synthesis of β-azido alcohols

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ABSTRACT

The aim of this review is to summarize the available literature on the direct hydroxyazidation of alkenes, with particular emphasize on the mechanistic features of the reactions. The metal-catalyzed reactions are discussed first. This is followed by iodine- and enzyme-catalyzed reactions. Finally, the available examples on light-mediated reactions will be covered at the end of this review.

1.Introduction

Organic azides play a tremendously important role in the field of organic chemistry [1], medicinal chemistry [2], and material sciences [3]. Among them, β-azido alcohols are a particularly attractive subclass. Because they often encountered in some drugs and bioactive compounds, as exemplified by antiretroviral 2′-deoxy-2′-β-fluoro-4′-azidocytidine [4], hepatitis C virus (HCV) NS5B inhibitor R-1479 [5], and antibiotic drug azidocillin [6]. In addition, β-azido alcohols play a significant role as synthetic precursors toward a variety of value-added chemicals [7-11], such as β-amino alcohols, β-fluoroamines, aziridines, β-hydroxy triazoles, 6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazines, oxazolidin-2-ones, and 4,5-dihydrooxazoles. Traditionally, the main synthetic approaches used for the formation of β-azido alcohols are ring-opening of corresponding epoxides [12] and reduction of α-azidoketones [13]. However, these methodologies suffer from multistep synthesis and limited substrate scope. Therefore, the development of simple and efficient approach to the titled compounds from readily available substrates is still highly desired.

In recent years, the direct vicinal difunctionalization of alkenes has become an extremely powerful strategy for rapid increasing molecular complexity *via* concomitant incorporation of two functional groups onto an unsaturated carbon–carbon double bond within a single click [14-20]. Along this line, in continuation our previous works [21-27], various methodologies have recently been developed for the direct hydroxyazidation of alkenes to the corresponding β-azido alcohol derivatives with high regio- and stereo-selectivities (Fig. 1).

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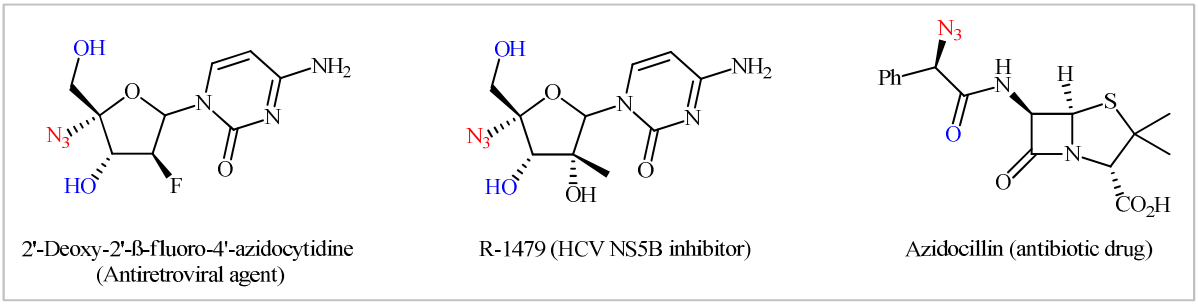


Scheme 1. Selected examples of biologically active β-azido alcohols.

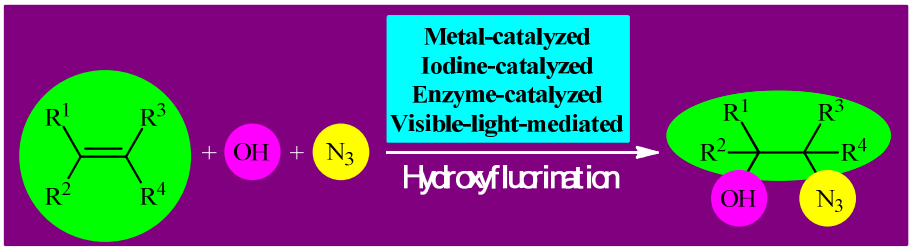
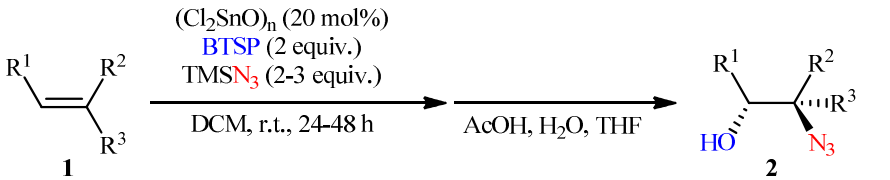


Fig. 1. Direct hydroxyazidation of alkenes.

Despite the remarkable advancements in this hot research field over the past few years, no comprehensive review has yet appeared in the literature. Therefore, it is an appropriate time to summarize these achievements. With the aim of stimulating further research in the field of difunctionalization of alkenes, follow up on previous published reviews in organic synthesis [28-30], herein, we will summarize the latest discoveries and advances in the arena of direct hydroxyazidation of C-C double bonds with an emphasize on the mechanistic features of the reactions.

2. Metal-catalyzed reactions

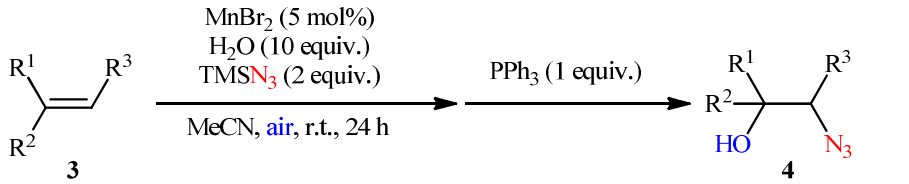
After pioneering work with Draper and co-workers on the direct conversion of a small library of steroidal olefins into the corresponding vicinal azidohydrins [31] using chromium trioxide (CrO_3)/sodium azide (NaN_3) system in acetic acid, the first general report on the direct synthesis of β-azidohydrins in a single step form the respective alkenes was published by Shibasaki's research group in 2000 [32]. In this investigation, six *trans* β-azido alcohols **2** were obtained in reasonable yields through the reaction of various internal (cyclic and acyclic) alkenes **1** with bis(trimethylsilyl) peroxide (BTSP) and trimethylsilyl azide ($TMSN_3$) in DCM through the action of $(Cl_2SnO)_n$ at ambient conditions (Scheme 2). Notably, in all cases, besides the desired β-azidohydrins, small amounts of β-chlorohydrines were obtained as side-products. Intriguingly, when $TMSN_3$ was replaced with trimethylsilyl acetate (TMSOAc), the corresponding trans β-acetoxy alcohol products were obtained in moderate yields along with small but noticeable amounts of undesired chlorohydrine side products, isolated in 6-19% yield. Unfortunately, applicability of terminal alkenes as starting materials was not investigated in this seminal study.



R^1= ^{n}Bu
R^2= ^{n}Bu
R^3= H, Me
$R^1 + R^2$= -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-

Scheme 2. Shibasaki's synthesis of *trans* β-azido alcohols **2**.

In 2015, Jiao and co-workers described that simple and inexpensive $MnBr_2$ can be used as an effective catalyst for aerobic oxidative hydroxyazidation of olefins employing $TMSN_3$ as the azide source and air as the terminal oxidant [33]. Thus, a diverse array of β-azido alcohols **4** were synthesized in moderate to almost quantitative yields by treatment of the corresponding alkenes **3** with over stoichiometric amounts of $TMSN_3$ in the presence of 5% $MnBr_2$ under open air in $MeCN/H_2O$ (Scheme 3). The reaction is noteworthy in that both aromatic and aliphatic (terminal and internal) alkenes were well tolerated. Interestingly, the reaction has demonstrated a high degree of regioselectivity, in which azide group predominantly added to the less hindered carbon atom of the C=C bond. Notably, other azide sources such as NaN_3 and $N(^nBu)_4N_3$ could not enable this hydroxyazidation transformation. On the other hand, replacing $MnBr_2$ with some other single-electron catalysts such as $CuBr_2$, $FeBr_2$, $Mn(OAc)_2$, and MnO_2 led to much lower yields or even no desired product at all. Based on a series of control experiments such as isotopic labeling experiments and the density functional theory (DFT) calculation, the author proposed a mechanistic course for this hydroxyazidation, which is outlined in Scheme 4. Initially, oxidation of $MnBr_2$ catalyst by dioxygen under the standard conditions generates Mn^{III} or Mn^{IV} which participate in the oxidation of $TMSN_3$ to azido radical ($N_3^{\cdot}$). Subsequently, this radical selectively attacks to the less hindered end of alkene **3** to furnish carbon radical **A** that, after reaction with molecular oxygen affords peroxyl radical **B**. Next, the newly formed radical **B** undergoes Mn-participated the single electron transfer (SET) and protonation processes to produce β-azido peroxy alcohol **C**. Finally, reduction of β-azido peroxy alcohol **C** by PPh_3 leads to the generation of β-azido alcohol **4**.

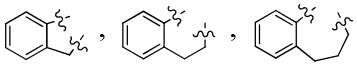


44 examples (42-96%)

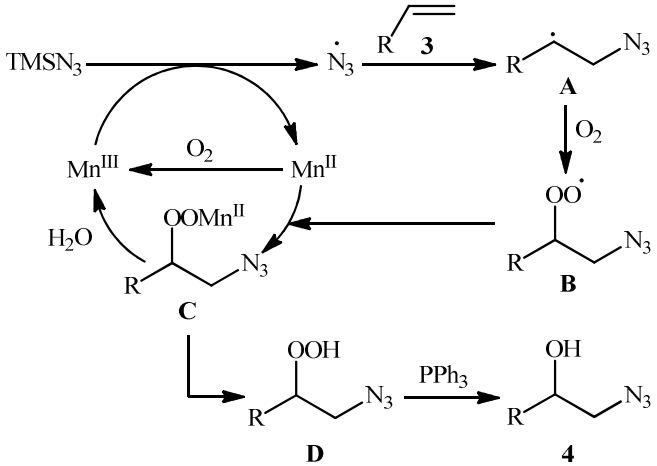
R^1= Me, ^{n}Oct, Bn, Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-CH_2OH-C_6H_4, 4-OMe-C_6H_4, 4-OP(O)$(OBn)_2$-C_6H_4, 4-OAc-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 4-CH_2-NPhth-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, C_6F_6, 2-thienyl, 1-naphthyl, 2-naphthyl, 2-benzofuryl, CH=CHPh, CH=CH-(4-OMe-C_6H_4), CH=CH-(2-NO_2-C_6H_4), phenylacetylenyl

R^2= H, Me, ^{c}Hex, CH_2OH, CH_2CH_2OH, Ph, CO_2Me, CO_2Bn

R^3= H, Ph

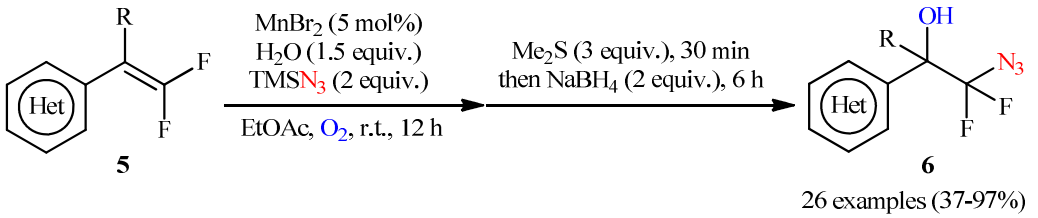
$R^1 + R^3$= -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, 

Scheme 3. Mn-catalyzed aerobic oxidative hydroxyazidation of alkene **3**.



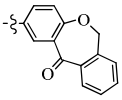
Scheme 4. Proposed mechanism for the reaction in Scheme 3.

Along this line, very recently, Cai, Jiang, and Zhu reported a practical and selective $MnBr_2$-catalyzed aerobic hydroxyazidation of fluoroalkenes with $TMSN_3$ and molecular oxygen under mild conditions [34]. Here, various (2,2-difluorovinyl)arenes **5** were compatible with the reaction condition and afforded the target 2-azido-2,2-difluoro-1-arylethanols **6** in modest to excellent yields and outstanding regioselectivity (Scheme 5). The reaction is noteworthy in that various sensitive functional groups such as CN, NO_2, SO_2, CO_2Me, Br, Cl, and NHAc were well tolerated. In addition, the reaction could be scaled up to produce the target β-azido alcohols in high yield without difficulty. The system was also applied for the highly selective hydroxyazidation of (trifluoromethyl)alkenes into the corresponding β-trifluoromethyl-β-hydroxy alkyl azides. However, 1-(4,4-difluoro-2-methylbut-3-en-1-yl)-4-isopropylbenzene did not take part in this difunctionalization reaction and therefore no other aliphatic alkenes were examined in the protocol. The authors proposed a SET pathway based mechanism analogous to that of Jiao and co-workers.



(Het)Ar= Ph, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-NHAc-C_6H_4, 4-CO_2Me-C_6H_4, 4-SO_2Me-C_6H_4, 4-Br-C_6H_4, 4-morpholinyl-C_6H_4, 4-O-propargyl-C_6H_4, 3-Me-C_6H_4, 3-CN-C_6H_4, 3-NO_2-C_6H_4, 3-Cl-C_6H_4, 2-Me-C_6H_4, 2-Cl-C_6H_4, 3,4-$(OMe)_2$-C_6H_3, 2-F-5-Br-C_6H_3, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-benzothienyl, 5-(2-OMe)-pyridyl,

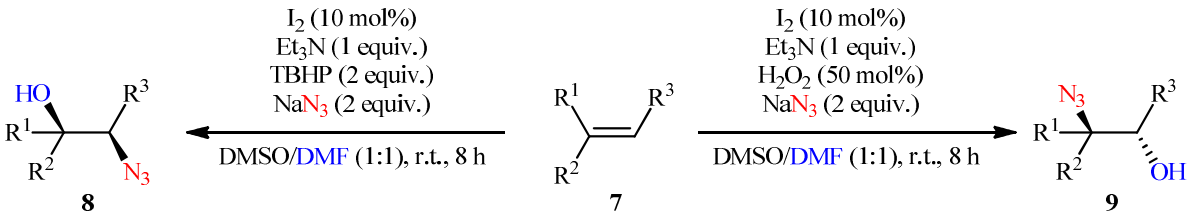
R= H, ^{n}Pent, 4-Br-C_6H_4



Scheme 5. Mn-catalyzed aerobic hydroxyazidation of (2,2-difluorovinyl)arenes **5** with $TMSN_3$ and molecular oxygen.

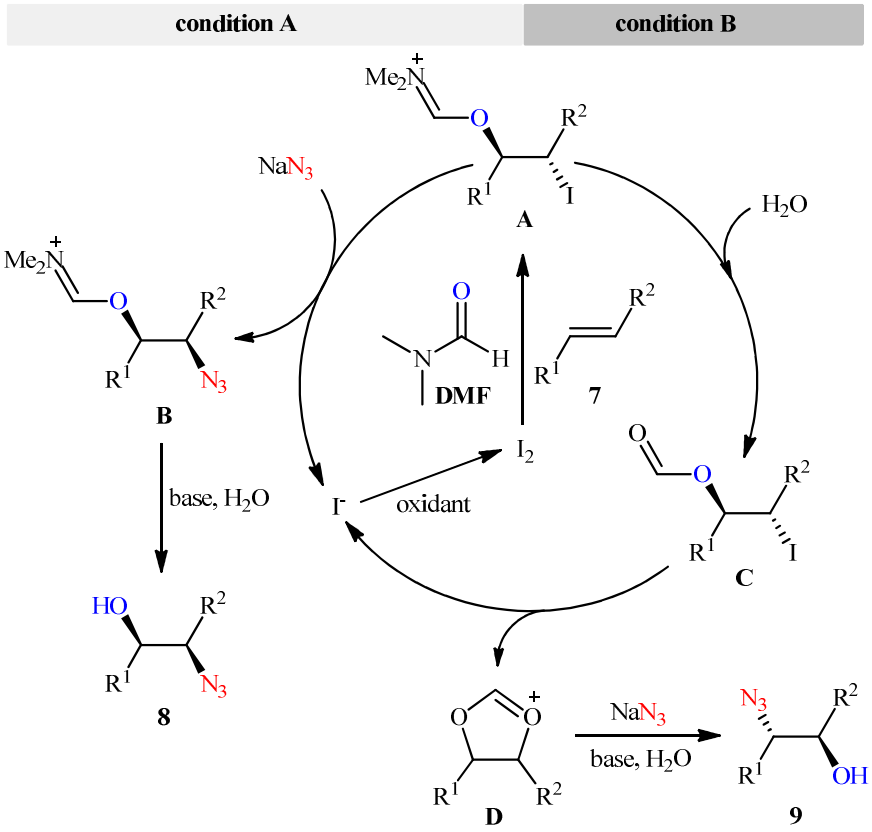
3. Iodine-catalyzed/mediated reactions

In 2015, Sudalai and co-workers informed for the first time the usefulness of molecular iodine as catalyst for the direct hydroxyazidation of alkenes **7** using NaN_3, and DMF as N- and O-nucleophiles, respectively [35]. They found that the oxidant could be able to play a key role in controlling the regioselectivity, thus leading to the generation of the 1,2-azidoalcohols **8** and **9** in a selective manner. When the TBHP was employed, secondary alcohols **8** were yielded as the exclusive regioisomers with *syn*-stereochemistry (Scheme 6). On the contrary, when 50% aq. H_2O_2 was used as oxidant instead of TBHP, a complete reversal in product regioselectivity was observed affording tertiary alcohols **9** with *anti*-stereochemistry. Both open chain internal alkenes and cyclic alkenes worked well under both conditions indicating the general applicability of these methods. Applying this methodology, the authors also successfully synthesized an antibiotic drug, chloramphenicol, and a cytokine modulator, (+)-cytoxazone. Notably, ^{18}O labelling studies proved that DMF served as the O-nucleophile. A plausible reaction mechanism was proposed and shown in Scheme 7. Initially, an iodonium ion is formed by the reaction of alkene with molecular iodine, which undergoes subsequent regioselective ring opening with DMF to give the corresponding iodo intermediate **A**, followed by subsequent stereoselective displacement with azide ion to form species **B**. This intermediate **B** on hydrolysis affords *syn* 1,2-azidoalcohols **8**. On the other hand, under aq. H_2O_2 conditions, the iodo intermediate **A** is hydrolyzed *in situ* to yield iodoformate **C**. Next, the species **D** is formed from iodoformate **C** by the anchimeric assistance from the formate group, which in then reacts with the azide anion in a regioselective manner to give *anti* azido alcohols **9** with the liberation of the iodide ion. Finally, iodide ion reoxidized with $TBHP/H_2O_2$ to regenerate I_2 in the catalytic cycle.



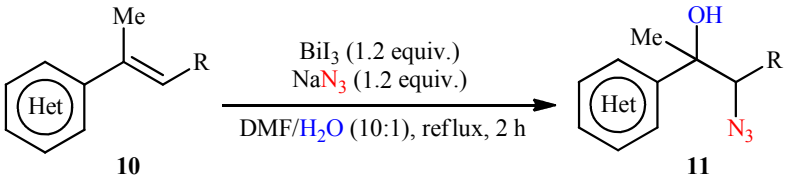
R^1= Me, ^{n}Hex, CH_2CH_2OBn, Ph, 4-Me-C_6H_4, 4-OH-C_6H_4, 3-NO_2-C_6H_4, 2-Br-C_6H_4
R^2= H, Me
R^3= H, Me, CH_2OMe, CH_2OBn
$R^1 + R^3$= -$(CH_2)_4$-,

Scheme 6. I_2-catalyzed oxidant controlled regio- and stereodivergent hydroxyazidation of alkenes **7** developed by Sudalai.



Scheme 7. A proposed mechanism for the hydroxyazidation of alkenes **7** reported in Scheme 6.

Three years later, Chang's research team reported a similar vicinal hydroxyazidation of styrene derivatives with NaN_3 and water in the presence of bismuth iodide (BiI_3) as a mediator [36]. In this report, 10 1-azido-2-arylpropan-2-ols **11** were synthesized in moderate to high yields from the corresponding α-methylstyrenes **10** by means of 1.2 equiv. of BiI_3 in wet DMF without consuming any additional base or oxidant (Scheme 8). Interestingly, when the reaction was carried out in dry DMF condition, 1,2-azidoiodides were exclusively generated without any β-azidoalcohol formation. Based on a series of control experiments, the authors proposed a five-step reaction mechanism for this transformation (Scheme 9): (i) coordination of BiI_3 to the double bond of alkene **10** to form complex **A**; (ii) generation of intermediate **B** from intermediate **A** through the removal of an iodide ion; and (iii) intermolecular substitution of **B** with the water to afford intermediate **C**; (iv) insertion of iodide ion into **C** to give intermediate **D**; and (v) coordination of **D** with *in situ* generated HN_3 to yield the expected product **11** *via* the five-membered ring transition state.

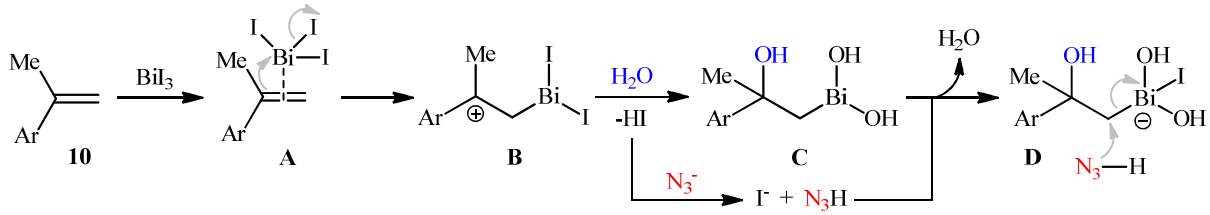


(Het)Ar= Ph, 4-Ph-C_6H_4, 4-F-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 3-F-C_6H_4, 3,4-Cl_2-C_6H_4, 3,4-$(CH{=}CH)_2$-, 4-pyridyl

R= H

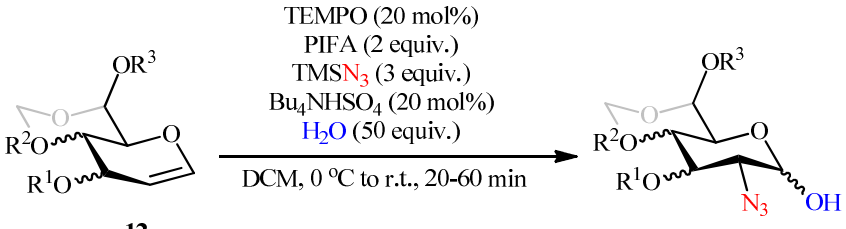
Ar + R= 

Scheme 8. BiI_3-mediated hydroxyazidation of styrene derivatives with NaN_3 and water.



Scheme 9. Possible mechanism for the formation of 1-azido-2-arylpropan-2-ols **11**.

In 2018, Chennaiah and Vankar developed a one-step procedure for the 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO)-catalyzed regiospecific and stereoselective azidohydroxylation of glycals **12** into 2-azido-2-deoxysugars **13** with $TMSN_3$ and H_2O as N- and O-nucleophiles respectively, using a (bis(trifluoroacetoxy)iodo)benzene (PIFA)–Me_3SiN_3 reagent system in the presence of Bu_4NHSO_4 as a phase-transfer catalyst (Scheme 10) [37]. The reactions were carried out under mild conditions, tolerated a variety of protecting groups, and generally afforded the desired 2-azido-2-deoxysugar products in good yields within minutes. Applying this method, the authors also successfully synthesized an important trisaccharide unit bound by the monoclonal anti-I Ma antibody. Mechanistically, the reaction started with the formation of $PhI(N_3)_2$ **A** from PIFA and $TMSN_3$. The treatment of this intermediate **A** with TEMPO results a radical intermediate **B**, which then reacts with glycals **12** to form an oxonium ion intermediate **D** *via* π-complex **C**. Addition of H_2O into the intermediate **D** affords the observed 2-azido-2-deoxysugars **13** (Scheme 11).

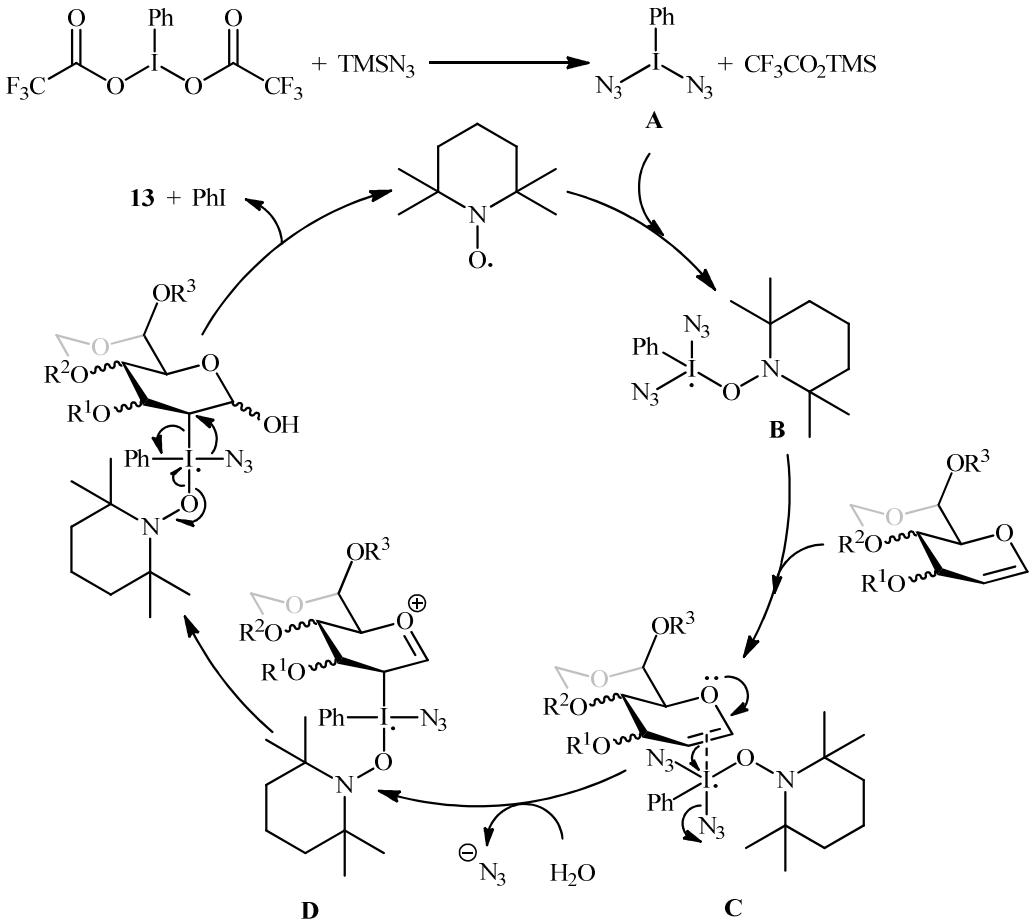


R^1= OMe, OAc, OBn, OTBS

R^2= OMe, OAc, OBn, OTBS

R^3= OMe, OAc, OBn, OTBS

Scheme 10. TEMPO-catalyzed azidohydroxylation of glycals **12** into 2-azido-2-deoxysugars **13** with a PIFA–Me_3SiN_3-Bu_4NHSO_4 reagent system.

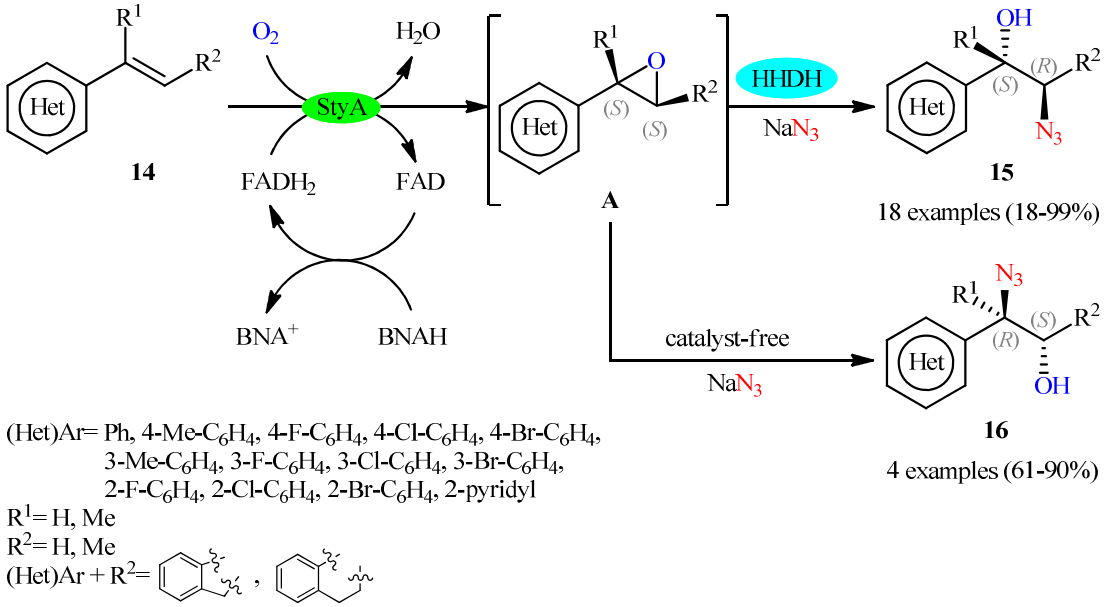


Scheme 11. Proposed mechanism for the formation of 2-azido-2-deoxysugars **13**.

Very recently, in a closely related study, Juhász and co-workers investigated behavior of a small series of 1-C-acceptor-substituted glycals under azidohydroxylation conditions [38]. After careful evaluation of reaction variables such as azide source, hypervalent iodine reagent, catalyst, and solvent, they found that treatment of 1-carbamoyl and 1-methoxycarbonyl substituted $_D$-*lyxo* and $_D$-*arabino* configured *O*-peracylated glycals with NaN_3 in the present of 30 mol% PIFA and 50 mol% TEMPO in H_2O/dry DCM at 0 ˚C, afforded the desired 3-azido-3-deoxy ulopyranosonic acid derivatives in good yield with α-$_D$-*galacto* configuration exclusively, while the transformation of the 1-cyano derivative under the identical conditions gave a 2,3-vicinal diazide in low yield. The application of an azidohydroxylated derivative in a glycosylation reaction with 4-nitrophenol using Mitsunobu condition was also successfully demonstrated.

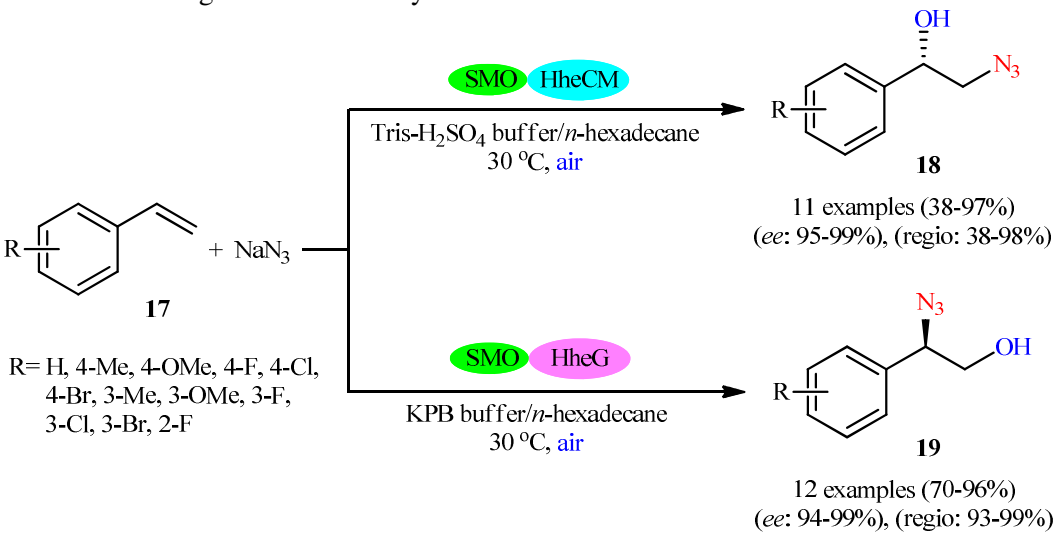
4. Enzyme-catalyzed reactions

In 2021, Paul and co-workers reported an attractive example of *in vitro* one-pot preparation of enantioenriched 2-azido-1-phenylethanols **15** from the corresponding styrene derivatives **14** through enzymatic asymmetric epoxidation using a flavin-dependent styrene monooxygenase (StyA), the oxygenase component of SMO, as a biocatalyst and 1-benzyl-1,4-dihydronicotinamide (BNAH) as a practical reductant, followed by a halohydrin dehalogenase (HHDH)-catalyzed regioselective azidolysis using NaN_3 as a source of azide anion (Scheme 12) [39]. On the other hand, the SMO was coupled with a chemical step by the addition of NaN_3 as a nucleophile to produce 1-azido-2-phenylethanols **16** with high regio- and stereo-selectivity (up to 99% diastereomeric excess). It should be mentioned that among the various HHDHs (HheA3, HheA5, HheB5, HheD3, HheD5, HheD6, HheE5) examined; HheE5 from *Gammaproteobacterium* strain IMCC3088 gave the best ratio of α:β. On the other hand, similar to uncatalyzed reaction, the enzymatic reactions with HheA3, HheD6, and HheD3 afforded 1-azido-2-phenylethanols as the major products. The other HHDHs (*i.e.*, HheA5, HheB5, HheD5) also showed mixed ratios.



Scheme 12. Bi-enzymatic azidohydroxylation of styrene derivatives **14** developed by Paul and co-workers.

Concurrently, Wu *et al*. [40] presented two related dual-enzyme cascade strategies for regiodivergent and stereoselective hydroxyazidation of alkenes. Thus, a variety of styrenes **17** were selectively converted to the enantiopure 2-azido-1-phenylethanols **18** through SMO-catalyzed asymmetric epoxidation, using air as oxidant, followed by HheCM-catalyzed regioselective ring opening of epoxides with NaN_3 (Scheme 13). Intriguingly, when HheCM was replaced with HheG, the respective 1-azido-2-phenylethanol products **19** were obtained in in good to excellent yields and outstanding optical purities. Notably, this innovative research group successfully synthesized a library of chiral β-hydroxytriazoles from the corresponding alkenes by combining their biocatalytic cascades with Cu(I)-catalyzed click reaction. In addition, they also demonstrated two examples of chiral 1,2-amino alcohols synthesis by simple reduction reaction of azidoalcohols using catalytic Pd/C under H_2-balloon pressure at room temperature.

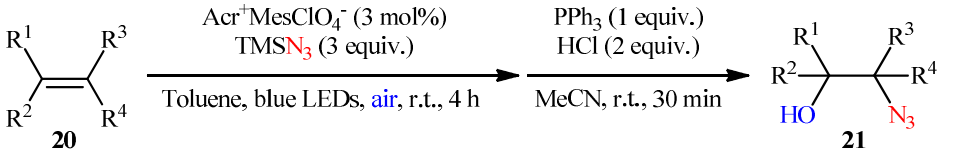


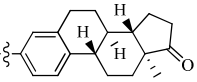
Scheme 13. Dual-enzyme cascade strategy for regio- and stereoselective hydroxyazidation of alkenes **17**.

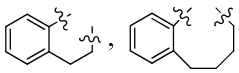
5. Visible-Light-mediated reactions

In 2017, Lu and co-workers demonstrated the first visible-light-mediated metal-free hydroxylazidation of alkenes **20** using $TMSN_3$ as the N_3 source, dioxygen as both the green oxidant and oxygen source [41]. The reaction took place using low loading (3 mol %) of 9-mesityl-10-methylacridinium perchlorate ($Acr^+MesClO_4^-$) as the organic photocatalyst under

irradiation of 8 w blue LEDs at room temperature and provided the target β-azido alcohols **21** in moderate to quantitative yields after hydrolysis under acidic condition. As shown in Scheme 14, in all examples, N_3 insertion preferred to occurred at the least-hindered carbon atom and OH insertion at the carbon atom bearing the bulkiest group. It should be mentioned that the presence of the organic photocatalyst is crucial for the success of this difunctinalization reaction. In the absence of the photocatalyst, or by replacing $Acr^+MesClO_4^-$ with $Ru(bpy)_3(PF_6)_2$ and $Ir(ppy)_2(dtbbpy)PF_6$, no desired product was detected at all. In Scheme 15 a plausible mechanism for this hydroxylazidation is illustrated. Initially, the ground state photosensitizer (Mes-Acr^+) undergoes photoexcitation under the irradiation of blue LEDs to produce the excited state Mes-Acr^+*, which could oxidize the alkene **20** to afford radical cation **A** and the reduced species (Mes-$Acr^•$). Subsequently, Mes-$Acr^•$ undergoes oxidization by dioxygen to regenerate photocatalyts and form superoxide $O_2^{•-}$. The radical cation **A** is then captured by $TMSN_3$ to afford the radical **B** that, after reaction with superoxide and TMS^+ produces the peroxyazidation product **C**. In another possibility, direct reaction of Mes-$Acr^•$ with peroxy radical **D** (resulting from the trapping of oxygen by **B**) leads to the formation of peroxide anion **E**, which after reaction with TMS+ affords the peroxyazidation product **C**.

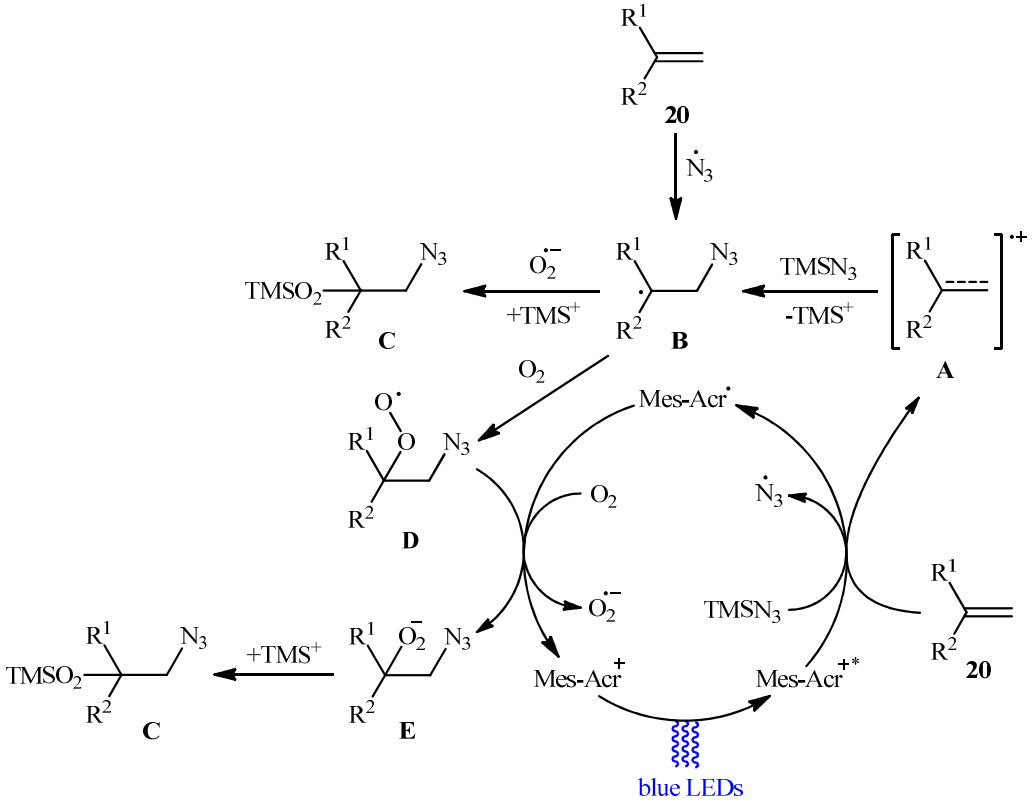


R^1= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-SMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-CF_3-C_6H_4, 4-CHO-C_6H_4, 4-CO_2H-C_6H_4, 4-$CONEt_2$-C_6H_4, 4-CO_2Me-C_6H_4, 3-Me-C_6H_4, 3-OMe-C_6H_4, 3-NH_2-C_6H_4, 3-OH-C_6H_4, 2-Me-C_6H_4, 2,4,6-Me_3-C_6H_2, 1-naphthyl, 2-pyridyl, 2-thienyl, CH_2Bn, ^{n}$C_{11}H_{23}$, 

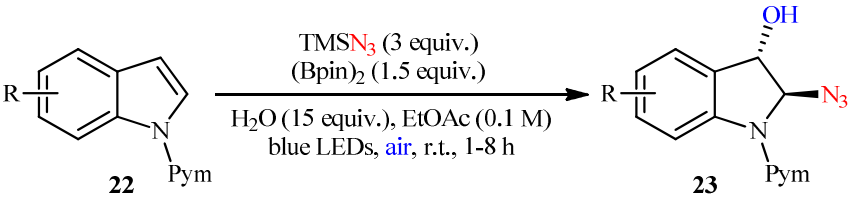
R^2= H, Me, Et, ^{n}Pr, ^{i}Pr, ^{t}Bu, ^{c}Hex, CH_2OH, $(CH_2)_4OH$, Ph, 3-Me-C_6H_4
R^3= H, Me
R^4= H, Me
$R^1 + R^3$= -$(CH_2)_4$-, 

Scheme 14. Visible-light-promoted aerobic hydroxyazidation of alkenes **20**.

Recently, Lu and Wang along with their co-workers extended the above hydroxyazidation to indoles [42]. They showed that *N*-pyrimidin-2-yl indoles **22** can undergo visible-light-promoted regio- and stereo-selective hydroxyazidation with $TMSN_3$ to give corresponding *trans*-2-azidoindolin-3-ols **23** in moderate to high yields under catalyst-free conditions (Scheme 16). The protocol tolerated a series of sensitive functional groups (*e.g.*, F, Cl, Br, OMe); however, it was not compatible with strong electron-withdrawing groups such as trifluoromethyl, cyano, and nitro functionalities. It is noteworthy that the presence of pyrimidinyl moiety is crucial to the success of this reaction. Replacing pyrimidine with some other nitrogen heterocycles (e.g., triazine, pyridine) led to much lower yields or even no desired product at all. On the other hand, NH-free indoles failed to produce any product under the optimized conditions.



Scheme 15. Proposed reaction mechanism for the formation of β-azido alcohols **21**.



R= H, 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 5-Me, 5-OMe, 5-F, 5-Cl, 5-Br, 6-Me, 6-OMe, 6-F, 6-Cl, 6-Br, 7-Me

Scheme 16. Lu-Wang's synthesis of *trans*-2-azidoindolin-3-ols **23**.

6. Conclusions

In conclusion, this review provides concise overview on the synthesis of β-azido alcohols though the direct hydroxyazidation of corresponding alkenes. Without slight doubt, this page of β-azido alcohol synthesis provides milder conditions and simpler procedures than previously reported methodologies. This research area is at its infancy and has still further possibilities for growth and we believed that more research and further improvements will be attainable in this field in the near future.

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