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Direct vicinal cyano- and nitro-hydroxylation of alkenes: A review to construction of the biologically and synthetically β-functionalized alcohols

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ABSTRACT

Direct vicinal hydroxy-functionalization of alkenes allows the atom- and step-economical and original construction of biologically and synthetically important β-functionalized alcohols from inexpensive and abundant feedstock chemicals. In this context, synthesis of versatile β-hydroxy nitriles and β-nitro alcohols through the direct vicinal cyano- and nitro-hydroxylation of alkenes has recently attracted considerable attention from organic and bioorganic synthetic communities due to their straightforward manner as well as easily accessible starting materials. This review highlights up-to-date developments in this exciting research field with special emphasis on the mechanistic aspects of the reactions.The resulting β-functionalized alcohols frequently exhibit potent biological activity and serve as key intermediates in the synthesis of pharmaceuticals and other bioactive molecules.

1. Introduction

A significant number of organic compounds exhibit diverse biological and pharmaceutical properties, and their broad applicability has garnered considerable attention from both organic chemists and biologists [1-3]. Among these, β-hydroxy nitriles and β-nitro alcohols are particularly noteworthy and will be the focus of further examination in this study. The nitrile group is an important functional moiety frequently found in many drug molecules and biologically active compounds. Currently, more than 30 nitrile-containing medications are available on the market, and over 20 potential drug candidates bearing this unique functionality are undergoing clinical trials [4]. Within this family, β-hydroxy nitriles represent a privileged subclass in a wide array of natural products, bioactive compounds, and clinically approved drugs. For instance, Remdesivir (brand name Veklury) is a synthetic β-hydroxy nitrile used globally for the treatment of SARS-CoV-2 infection, while Dienogest (Visanne) is a synthetic progestin prescribed for alleviating endometriosis symptoms and lesions. Beyond their biological activities, β-hydroxy nitriles exhibit versatile reactivity, enabling their transformation into value-added compounds such as β-hydroxy acids, γ-hydroxy amines, and lactones [5].

In a similar manner, the β-nitro alcohol moiety is found in several therapeutic agents, such as Entacapone (an anti-Parkinson drug), and natural products [6]. Notably, the cyclic peptide antibiotics Ilamycin, Ilamycin B_1, and Ilamycin B2, produced by Streptomyces islandicus-each incorporate a β-nitro alcohol motif (Scheme 2). Biologically active β-nitro alcohols are also recognized as powerful synthetic intermediates capable of undergoing various transformations en route to fine chemicals and active pharmaceutical ingredients [7]. In particular, they serve

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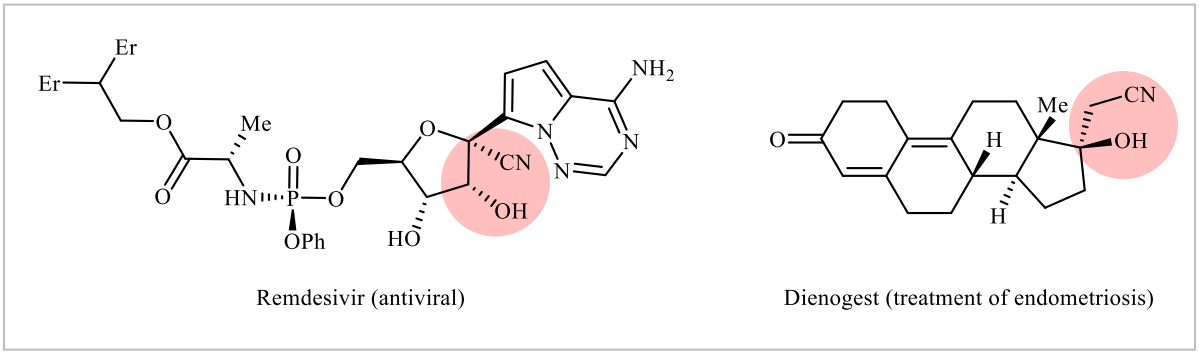
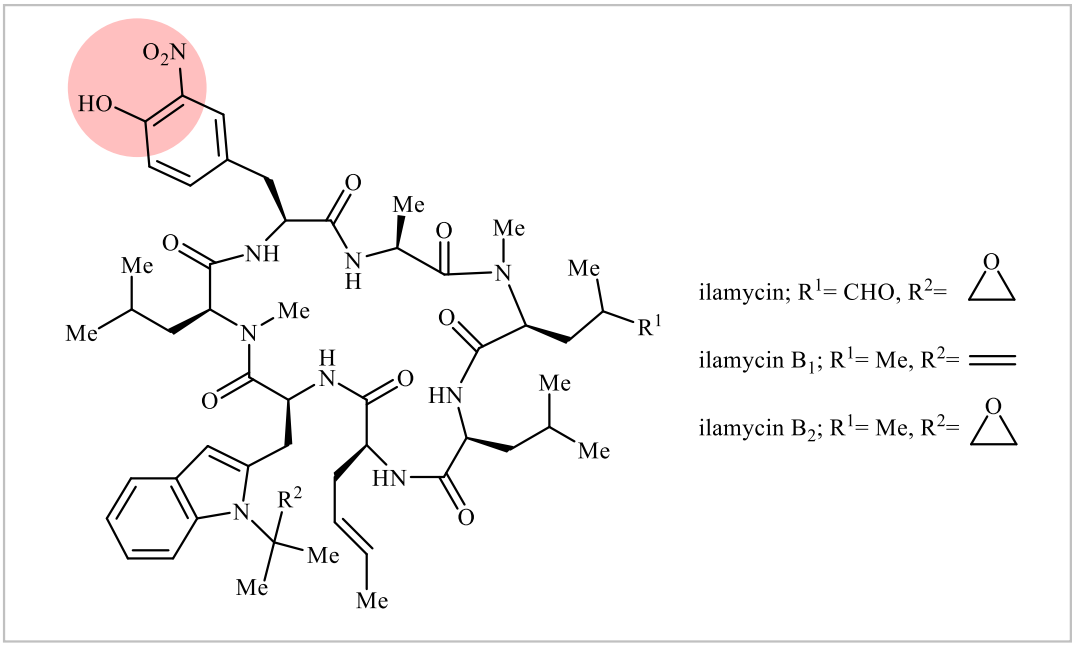


Scheme 1. Selected examples of FDA-approved drugs possessing β-hydroxy nitrile units, which are core motifs in bioactive pharmaceutical compounds.



Scheme 2. Chemical structures of ilamycin, ilamycin B_1, and ilamycin B_2.

as precursors to β-hydroxy amines, which are essential structural elements in a wide range of pharmaceuticals and bioactive natural products [8].

The major approaches used for the synthesis of β-hydroxy nitriles include conversion of alkenes to epoxides or 2-isoxazolines, followed by ring-opening functionalizations [9, 10]. However, these methods suffer from certain drawbacks such as the use of highly toxic reagents and harsh reaction conditions. On the other hand, β-nitro alcohols are conventionally synthesized by Henry (nitroaldol) reaction which relies upon condensation of an aldehyde or ketone with a nitroalkane [11]. Aside from the reversibility of the reaction which could prevent the reaction from proceeding, long reaction times, requirement for strong bases, and formation of secondary products are the main drawbacks on this reaction [12]. Therefore, there is a clear need to develop alternative, safer, efficient, and less toxic routes towards the titled compounds from readily available starting materials.

Recently, the direct vicinal hydroxy-functionalization of easily accessible alkene feedstocks, in which a hydroxy moiety and a functional group are simultaneously introduced at the vicinal position, has arisen as a straightforward and versatile tool for direct construction of β-functionalized alcohol scaffolds [13-20]. While the past few years have witnessed the development of vicinal hydroxy-functionalization of alkenes [21], only limited examples of the use of method for cyano- and nitro-hydroxylations are known (Figure 1). In this review, we summarize the data available from the literature on the direct synthesis of β-cyano and β-nitro alcohols through the vicinal cyano- and nitro-hydroxylation of respective alkenes, by hoping it will inspire and stimulate further research on the topic.

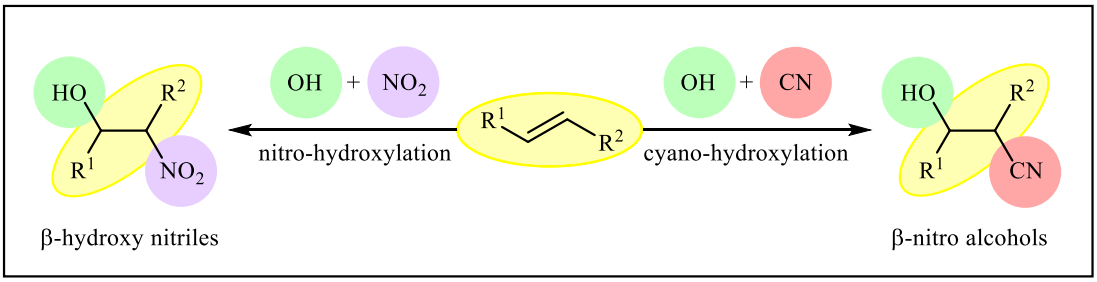
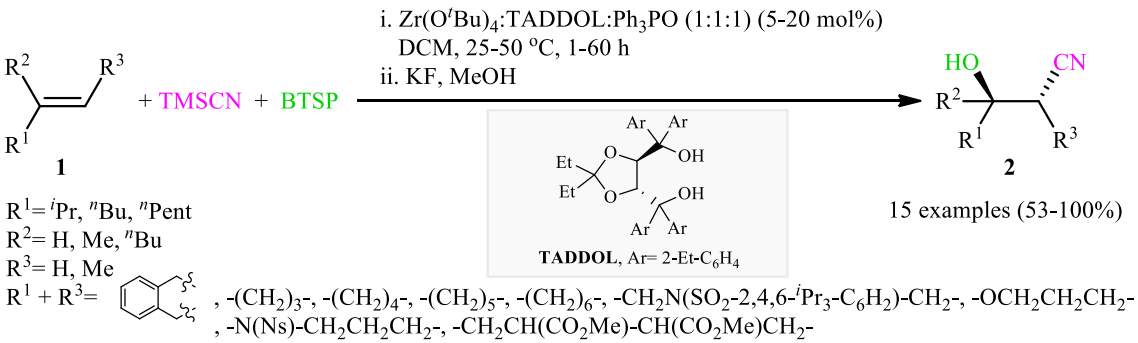


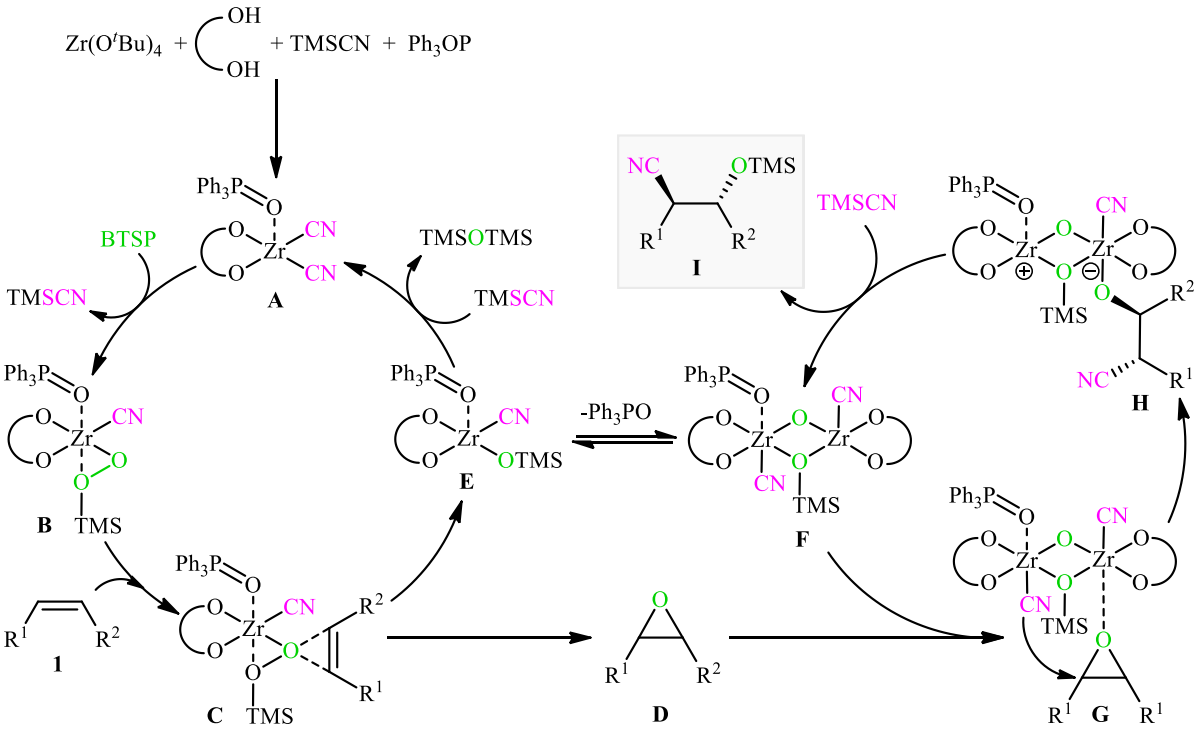
Fig. 1. Representative examples of biologically and synthetically relevant β-functionalized alcohols formed via vicinal hydroxylation.

2. Cyano-hydroxylation of alkenes

In 2001, Shibasaki and co-workers reported the first one-pot vicinal cyano-hydroxylation of alkenes, using trimethylsilyl cyanide (TMSCN) and bis(trimethylsilyl) peroxide (BTSP) as the cyanide and oxygen sources, respectively [22]. In the presence of Zr(OtBu)4/TADDOL/Ph3PO combination as a catalytic system in DCM, a relatively broad range of terminal (aliphatic and aromatic) and internal (cyclic and acyclic) alkenes 1 successfully underwent the reaction to generate corresponding β-hydroxy nitriles 2 in moderate to quantitative yields after hydrolysis (Scheme 3). The reaction displayed high degree of stereoselectivity in which both (Z)- and (E)-alkenes predominantly provided trans-products. Notably, when sterically unsymmetrical substrates were used under the optimized condition, the major isomers were derived from the attack of cyanide at the less sterically hindered end of the double bond. It is worth mentioning that the conversion and selectivity of the target difunctionalized products heavily depended on all catalytic components. Thus, no target product was detected in the absence of the Zr catalyst and the chiral ligand (TADDOL). Similarly, the lack of Ph3PO resulted in the formation of many side products. According to the authors, in this reaction the Zr catalyst played multiple roles; an oxidant, a Lewis acid, and a nucleophile. Based on a series of control experiments, the authors suggested that this reaction proceeds through two intertwined catalytic cycles as shown in Scheme 4. At first, the precatalyst A undergoes ligand exchange with BTSP to produce complex B. Afterwards, coordination of alkene 1 to the peroxide center of B provides intermediate C, which subsequently delivers the epoxide as the initial product D and E. Next, the latter E undergoes ligand exchange by TMSCN to regenerate the precatalyst A. Meanwhile, E can undergo partial dissociation of Ph3PO to form a binuclear catalyst F possessing a vacant site on Zr. Later, coordination the epoxide D, generated by the first catalytic cycle, to the Zr center of F provides intermediate G, which after intramolecular cyanide transfer process affords intermediate H. Finally, silylation of H by TMSCN results in the formation of the silylated β-cyanohydrin I.

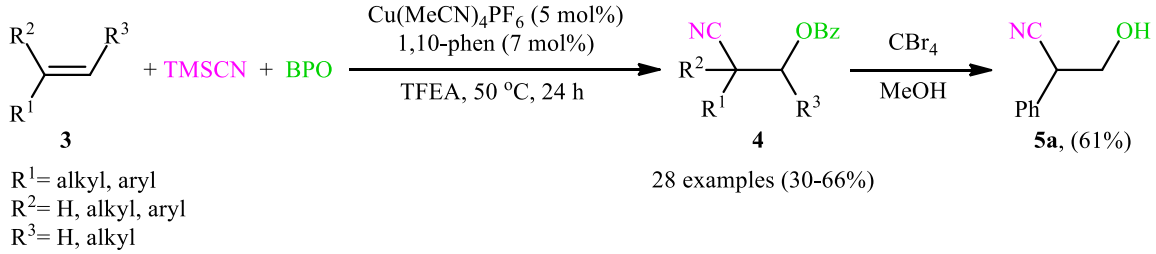


Scheme 3. Shibasaki's synthesis of β-hydroxy nitriles 2.



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

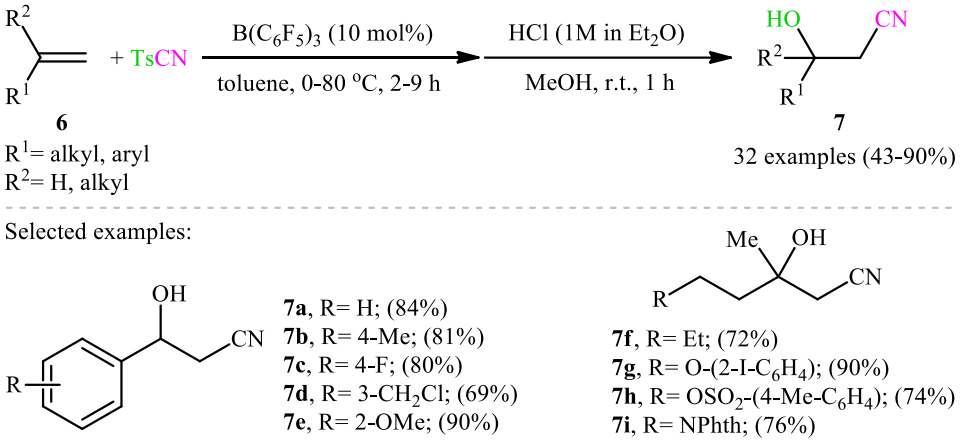
Two decades later, Bao's research group developed an efficient method for the synthesis of β-hydroxy nitriles 5 through the Cu-catalyzed three-component reaction between alkenes 3, TMSCN, and benzoyl peroxide (BPO), followed by treatment of the resulting 2-cyano-ethyl benzoates 4 with CBr4 in MeOH (Scheme 5) [23]. In this study commercially available Cu(CH3CN)4PF6 was used as the catalyst and 1,10-phenanthroline (1,10-phen) as a chelating bidentate ligand. Interestingly, an opposite regioselectivity pattern to that reported by Shibasaki was observed under this reaction condition, in which the addition of CN to unsymmetrical alkenes predominantly occurred at the more hindered site. Unfortunately, the authors did not investigate the applicability of their methodology to the one-pot synthesis of β-hydroxy nitriles from the respective alkenes. It is worth noting that prior to this work, Liu's research group had reported a relatively similar oxycyanation by reaction of vinyl ethers with 2,2,6,6-tetramethyl-N-oxopiperidinium and TMSCN employing K3PO4 as an additive [24].



Scheme 5. Bao's synthesis of β-hydroxy nitriles 5.

Very recently, Kiyokawa et al revealed that when terminal alkenes 6, p-toluenesulfonyl cyanide (TsCN) and a catalytic amount of tris(pentafluorophenyl)borane (B(C6F5)3) are mixed in one pot, and then hydrolyzed under acidic conditions, the corresponding β-hydroxy nitriles 7 can be afforded in modest to excellent yields and outstanding regioselectivity (Scheme 6) [25]. The examples displayed that various terminal (aliphatic, aromatic) and 1,1-disubstituted alkenes were compatible with this methodology. Moreover, a diverse range of useful functional groups (e.g., F, Cl, Br, CF3, CN, Bpin, SiMe3, CO2Me, OMe) were tolerated under these reaction conditions, thus promising further manipulation of products. Under similar conditions, the reaction of internal alkenes proceeded sluggishly, even at higher temperatures. The authors nicely solved this

limitation by performing the process in the presence of stoichiometric amounts of B(C6F5)3. Thus, twenty α,β-disubstituted β-hydroxy nitriles were synthesized in fair to high yields (48-82%) from the corresponding internal alkenes (cyclic and acyclic) with this scenario. It is interesting to note that when a trans-β-methylstyrene was used, the corresponding cis-β-hydroxy nitrile was obtained as a single regio- and diastereoisomer. Meanwhile, the use of the cis isomer of the same substrate selectively afforded trans-product. These results clearly indicated that the oxycyanation proceeds through a stereospecific syn-addition. Mechanistic investigations by experimental studies and density functional theory (DFT) calculations revealed that B(C6F5)3 efficiently activates TsCN through the coordination of the cyano group to the boron center (Figure 2). Notably, Replacing B(C6F5)3 with some other Lewis acids (e.g., BF3·OEt2, BCl3, BBr3, BPh3, AlCl3, GaCl3, GaBr3, InCl3, In(NTf2)3, Zn(OTf)2, Cu(OTf)2, Sc(OTf)3, Me3SiOTf, TsOH, TfOH) led to much lower yields or even no desired product at all.



Scheme 6. Kiyokawa's synthesis of β-hydroxy nitriles 7.

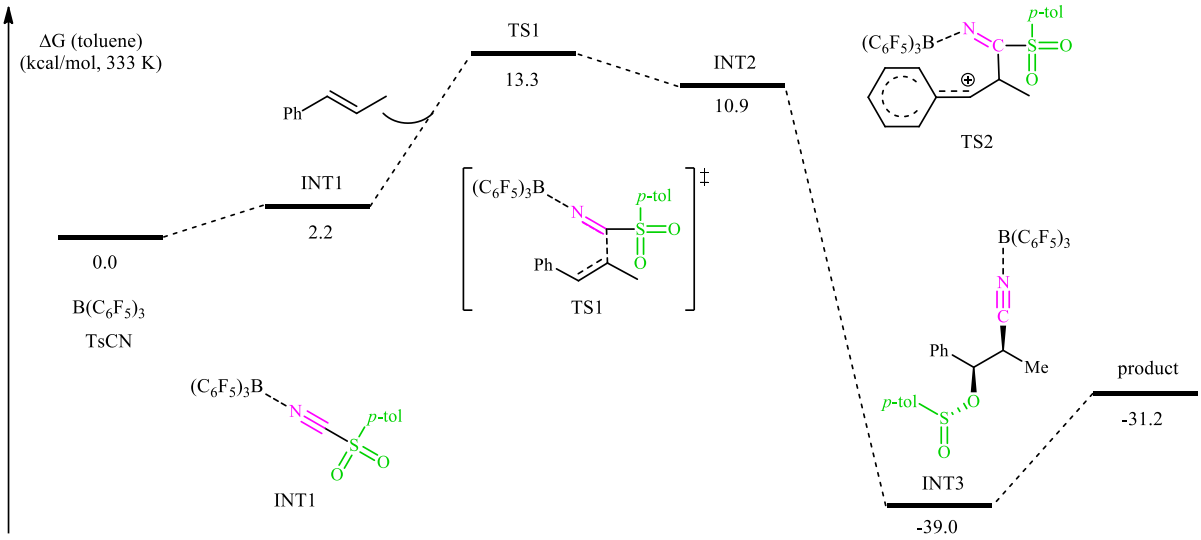
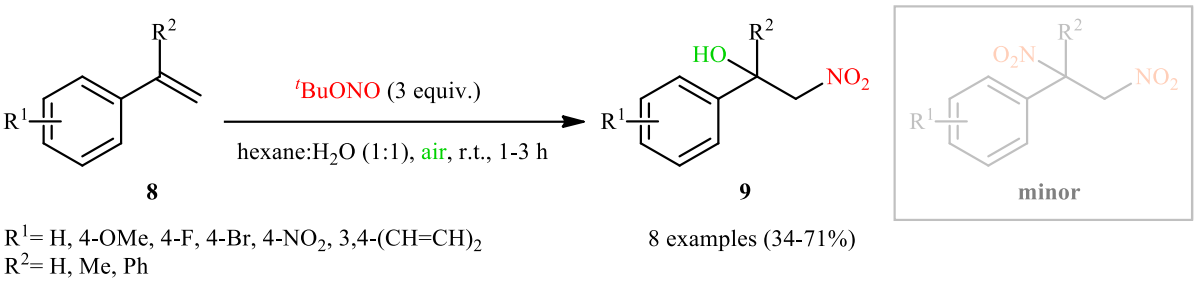


Fig. 2. Calculated free energy profile for the oxycyanation of trans-β-methyl styrene.

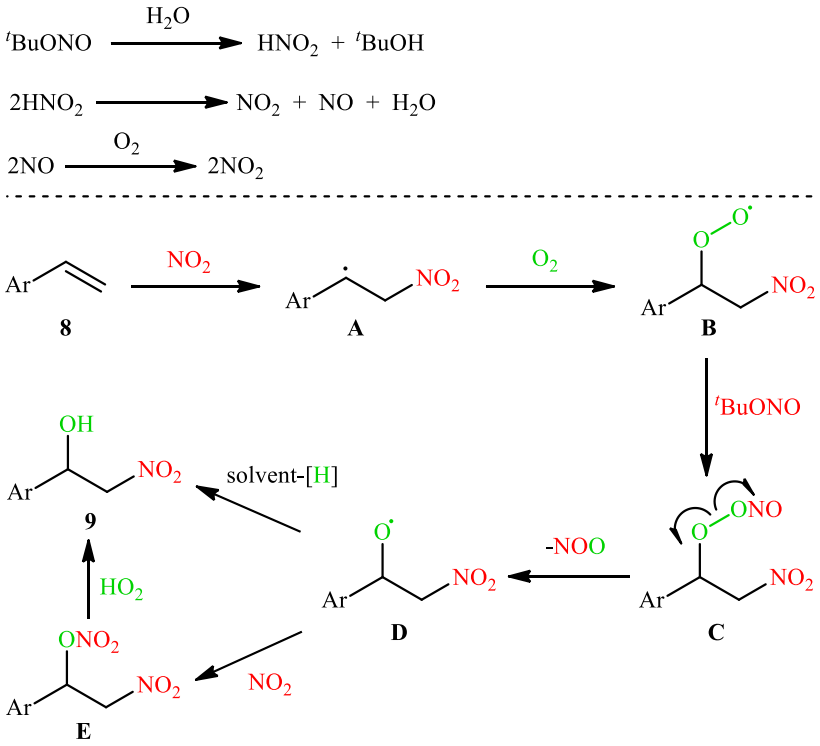
3. Nitro-hydroxylation of alkenes

The possibility of direct vicinal nitro-hydroxylation of alkenes to β-nitro alcohols was first realized by Taniguchi and co-workers, who showed that treatment of styrene derivatives 8 with tert-butyl nitrite (tBuONO) in the binary solvent hexane/water (1:1) under an air atmosphere afforded the corresponding β-nitro alcohols 9 in synthetically useful yields along with some amounts of unwanted nitro nitrate side products (Scheme 7) [26]. The reaction was highly regioselective, and a single regioisomer was obtained in all cases. Notably, water played a key role to improve the selectivity of this reaction. In the absence of water, the yield of nitro-hydroxylated products is significantly decreased in favor of nitrated products. Unfortunately,

aliphatic alkenes (either activated or unactivated) were not effective in this system and unsatisfactory results for the yields of nitro-hydroxylation products were obtained. The prominent features of this innovative reaction are its mild reaction conditions with metal-free reagents, and without the use of external oxidants. The mechanism of this oxidative nitration is believed to involve (Scheme 8): (i) generation of nitrous acid (HNO2) by hydrolysis of tBuONO; (ii) decomposition of unstable HNO2 to produce NO2 and nitrogen monoxide (NO); (iii) oxidization of NO with air oxygen to give NO2; (iv) addition of NO2 to alkene 8 to form radical intermediate A; (v) trapping of radical A by dioxygen to produce peroxy radical intermediate B; (vi) reaction of radical B with tBuONO to give peroxynitrite C; (vii) cleavage of the O-O bond of peroxynitrite C to yield alkoxy radical intermediate D; and (viii) hydrogen abstraction of radical D from the solvent to afford the observed β-nitro alcohol 9. In another possibility, alkoxy radical D undergoes coupling with NO2 to provide nitrate E, which after hydrolysis produces the observed nitro-hydroxylated product 9.



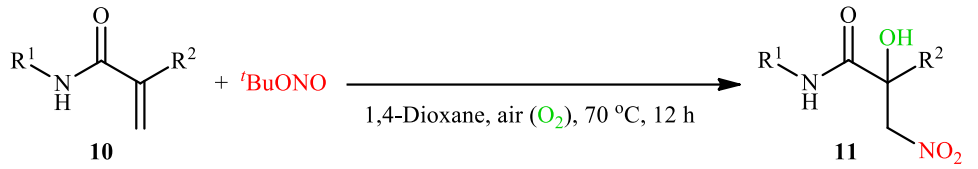
Scheme 7. Taniguchi's synthesis of β-nitro alcohols 9.



Scheme 8. Proposed mechanism for the formation of β-nitro alcohols 9.

Later on, an extension of the substrate scope to include α,β-unsaturated carbonyl compounds was investigated by Gao et al [27]. Upon treatment with 3.0 equiv. of tBuONO in 1,4-dioxane under the open air, a panel of fourteen N-substituted acrylamide derivatives 10 underwent regioselective nitro-hydroxylation to give corresponding 2-hydroxy-3-nitro-propanamide derivatives 11 in moderate to high yields, ranging from 56% to 84% (Scheme 9). Both N-alkyl and N-aryl substituted acrylamides were compatible substrates in this difunctionalization reaction. However, N-heteroaryl-substituted failed to participate in this nitro-hydroxylation and no examples were given with NH2-free substrates. Surprisingly, when N,N-disubstituted acrylamides were employed as reaction partners for this nitro-hydroxylation under optimal reaction conditions,

nitro-carbocyclization products were obtained as the sole products without any nitro-hydroxylated derivatives. The influence of substituents on the α- and β-positions of carbonyls for this nitro-hydroxylation were also examined, the presence of either alkyl or aryl groups on the α-position were well. However, the reaction was completely shut down with presence of a substituent on β-position. Interestingly, when a model reaction was performed in anhydrous 1,4-dioxane, a poor yield of the desired compound was obtained. Moreover, when the model reaction was implemented in the presence of radical scavengers such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl)), BHT (butylated hydroxytoluene) and hydroquinone, the nitro-hydroxylation was obviously inhibited, and majority of starting acrylamide (>90%) was recovered. These results clearly indicated the involvement of the radical processes in this reaction. Thus, the authors proposed a radical-based mechanism similar to the report described by Taniguchi group and suggested that water may act as the proton source in this transformation.



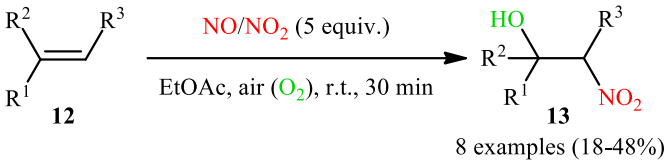
R^1= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-CL-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 2-Me-C_6H_4, CH_2CH_2-(3,4-OMe_2-C_6H_3), Bn, CH_2Bn

R^2= H, Me, Ph

14 examples (56-84%)

Scheme 9. Gao's synthesis of 2-hydroxy-3-nitro-propanamide derivatives 11.

In 2015, Heinrich's research group reported an interesting method for the synthesis of β-nitro alcohols 2 from the corresponding activated and non-activated alkenes 12 using NO/NO2 radicals with EtOAc as the solvent under an air atmosphere at room temperature for 30 minutes (Scheme 10) [28]. Although this protocol exhibits some novelties, poor yield due to the formation several unwanted by-products such as nitroketones, nitro nitrates, nitroso nitrates as well as a number of related decomposition products can be considered as a major drawback. The plausible mechanistic pathway suggested by the authors for this transformation is similar to the one described in Scheme 8.

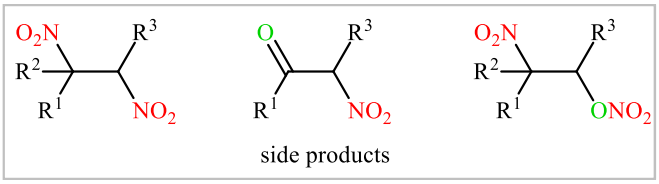


8 examples (18-48%)

R^1= ^{n}Hex, CH_2CH_2OAc, CO_2Et, Ph, 4-Cl-C_6H_4

R^2= H, Me

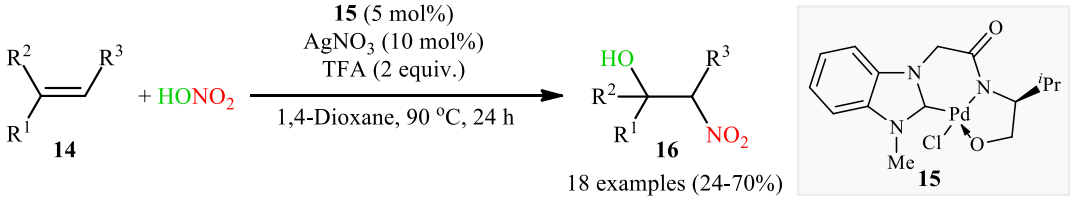
R^3= H, Me, CH_2OH



Scheme 10. Heinrich's synthesis of β-nitro alcohols 12.

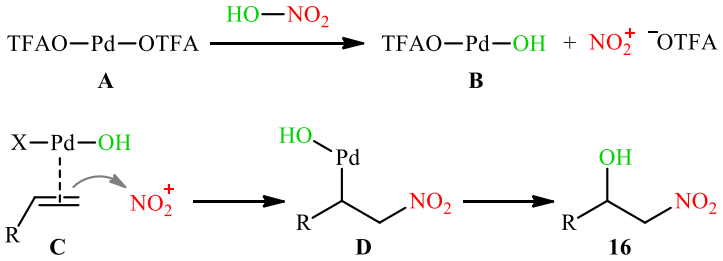
With the objective of designing a more efficient and practical protocol to β-nitro alcohols through the direct nitro-hydroxylation of corresponding alkenes, Jung and co-workers unveiled a robust Pd-catalyzed methodology to synthesize a broad array of β-nitro alcohols 16 by reaction of respective alkenes 14 with nitric acid (as the source for both NO2 and OH) in near refluxing dioxane in presence of 5 mol% tridentate NHC–amidate–alkoxide containing palladium catalyst 15, 10 mol% AgNO3 as a co-catalyst, and 2 equiv. of trifluoroacetic acid (TFA) as additive under air atmosphere (Scheme 11) [29]. The results demonstrated that the reaction was equally efficient for both aliphatic and aromatic alkenes and provided the desired β-nitro

alcohols 16 in moderate to good yields. Howbeit, methoxy-group bearing styrenes and sterically hindered acrylates reacted poorly under the standard reaction condition. From the viewpoint of stereochemistry, all tested internal alkenes resulted in the formation of both the syn- and anti-addition products, thus indicating a lack of stereospecificity of this reaction. It should be mentioned that apart from catalyst 15, other transition-metal catalysts such as NiCl2·6H2O, (Ni(acac)2)3, PdCl2, Pd(PPh3)2Cl2, Pd(CH3CN)2Cl2, and Pd(OAc)2 were also found to promote this nitro-hydroxylation reaction; albeit, in lower yields. Unfortunately, no comment was made by the authors regarding scalability of the reaction as well as regarding the recovery and reusability of the catalyst. While the detailed mechanistic picture remains unclear, a preliminary mechanistic proposal was provided by the authors (Scheme 12), which consists of an initial ligand exchange between the Pd(II) catalyst A and HNO3 to generate the complex B and a nitronium ion (NO2+). The coordination of alkene 14 with Pd-center of complex B gave the Pd–π complex C, which undergoes nitration with the external nitronium ion to afford nitration intermediate D. Finally, reductive elimination of this intermediate D delivers the observed β-nitro alcohols 16.



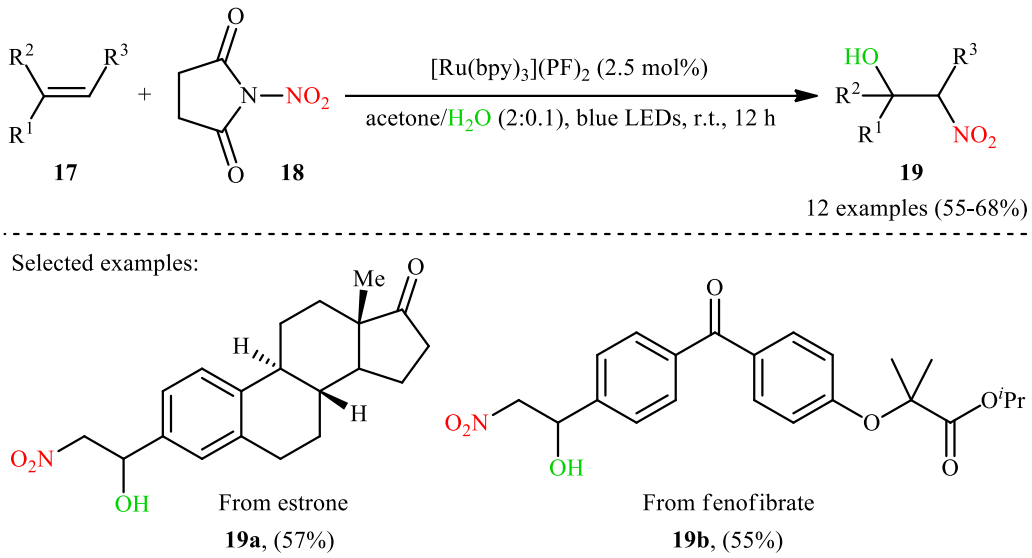
R^1= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 2-Cl-C_6H_4, 2,4-$(Me)_2$-C_6H_3, 2-naphthyl, Et, CH_2Bn, CH_2OBn, CO_2Et, $CO_2{}^tBu$
R^2= H, Me, Et
R^3= H, Me
$R^1 + R^3$= 

Scheme 11. Jung's synthesis of β-nitro alcohols 16.

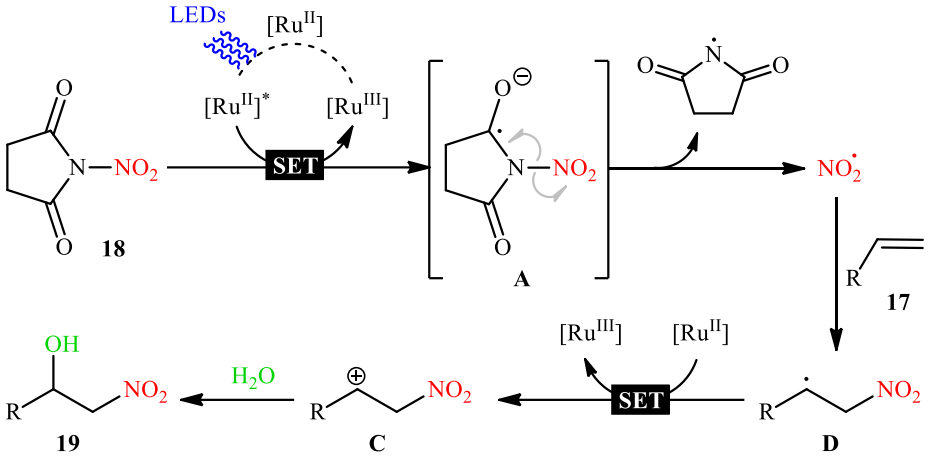


Scheme 12. Mechanistic proposal for the formation of β-nitro alcohols 16.

In 2019, the group of Katayev developed an efficient photo-induced protocol for direct nitro-hydroxylation of various terminal and internal alkenes 17 by using inexpensive and bench-stable N-nitrosuccinimide 18 and water as the NO2 and OH sources, respectively [30]. The reaction setup for this nitro-hydroxylation methodology involves irradiation of 2.0 equivalents of N-nitrosuccinimide 18 and 2.5 mol% of commercially available [Ru(bpy)3](PF6)2 in acetone/water (2:0.1) with 350 W blue light under ambient conditions for 12 h. under the optimized conditions, the reaction tolerated various terminal, 1,1-disubstituted, 1,2disubstituted, and 1,1,2-trisubstituted alkenes 17, and generally provided the desired β-nitro alcohols 19 in moderate to good yields with complete regioselectivity for unsymmetrical alkenes (Scheme 13). Notably, the reaction was also successfully applied to the "late-stage nitro-hydroxylation" of complex, biorelevant substrates such as estrone and fenofibrate. Interestingly, when the mixed solvent was replaced by MeCN, the corresponding nitroalkene products were exclusively obtained (through the direct nitration of the sp2 C–H bond of alkenes), without any of nitro-hydroxylated product. According to the authors proposed mechanism, the generation of the nitro radical through photoinduced mesolytic N-N bond fragmentation of the reagent was the key to promote this reaction (Scheme 14). Along this line, recently, Cong and co-workers disclosed that cytochrome P450BM3 enzymes can be used as effective biocatalysts for direct nitro-hydroxylation of aryl alkenes using NaNO2 as the nitrating agent [31]. This biocompatible, light-driven methodology also offers exciting opportunities for the late-stage functionalization of complex, biologically relevant molecules.



Scheme 13. Katayev's synthesis of β-nitro alcohols 19**.**



Scheme 14. A proposed pathway for the formation of β-nitro alcohols 19.

4. Conclusion

The direct vicinal hydroxy-functionalization of alkenes is a remarkable strategy which simultaneously incorporates a hydroxy moiety and a functional group into the C-C double bond, forming versatile β-functionalized alcohols. The cyano and nitro groups are very unique functionalities in medicinal chemistry due to their strong electron-withdrawing properties and high polarity. Alcohols possessing a cyano or nitro groups are not only prevalent in various important classes of natural products and synthetic pharmaceuticals but also used as valuable building blocks in organic synthesis and in the preparation of biologically active agents. The direct vicinal cyano- and nitro-hydroxylation of alkenes into biologically and synthetically important β-hydroxy nitriles and β-nitro alcohols, respectively, have recently attracted considerable attention from organic synthetic communities, not only because alkenes are cheap and widely abundant feedstock chemicals, but also due to high atom-, step, and pot-economy of these reactions. Despite notable advances over the past few years, this chemistry is still in infancy and further developments and improvements will be needed to reach maturity. Given the biomedical importance of β-hydroxy nitriles and β-nitro alcohols, further exploration of their synthesis will continue to bridge the gap between methodology development and drug discovery.

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