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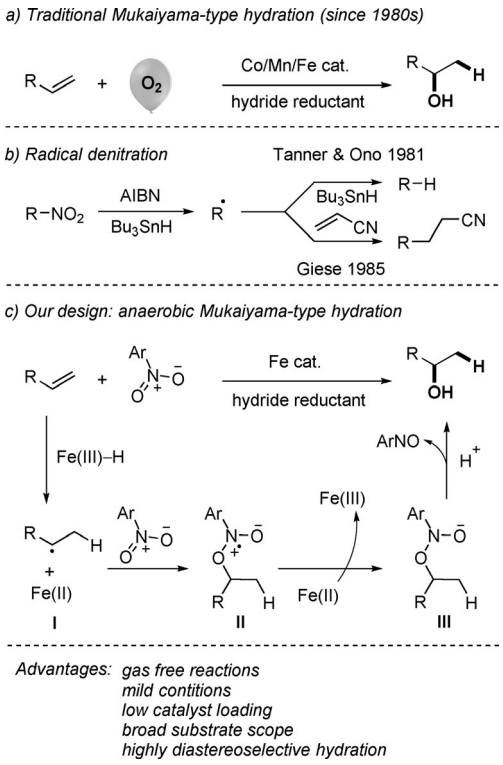
Fe-Catalyzed Anaerobic Mukaiyama-Type Hydration of Alkenes using Nitroarenes

*Anup Bhunia, Klaus Bergander, Constantin Gabriel Daniliuc, and Armido Studer**

Abstract: *Hydration of alkenes using first row transition metals (Fe, Co, Mn) under oxygen atmosphere (Mukaiyama-type hydration) is highly practical for alkene functionalization in complex synthesis. Different hydration protocols have been developed, however, control of the stereoselectivity remains a challenge. Herein, highly diastereoselective Fe-catalyzed anaerobic Markovnikov-selective hydration of alkenes using nitroarenes as oxygenation reagents is reported. The nitro moiety is not well explored in radical chemistry and nitroarenes are known to suppress free radical processes. Our findings show the potential of cheap nitroarenes as oxygen donors in radical transformations. Secondary and tertiary alcohols were prepared with excellent Markovnikov-selectivity. The method features large functional group tolerance and is also applicable for late-stage chemical functionalization. The anaerobic protocol outperforms existing hydration methodology in terms of reaction efficiency and selectivity.*

Introduction

Due to the high abundance of the alcohol functionality in drugs and natural products, the transformation of an alkene to an alcohol is a highly important process in synthesis. Although the most obvious approach is the acid catalyzed addition of water, it is often not practical leading to side products (ether formation, cationic rearrangements etc.). Therefore, radical Markovnikov hydration using Mukaiyama-type protocols and anti-Markovnikov hydration using hydroboration-oxidation are the commonly applied methods in laboratory scale.[1] The hydration of alkenes in the presence of a transition metal catalyst, oxygen and a reductant has been intensively investigated in the past with the first studies being published already in the 1980s (Scheme 1 a).[2–14] In these cascades, mainly first row transition metals (Fe/Co/Mn) have been applied.[15] Moreover, O_2 is generally used as the C-radical oxygenation reagent in a reaction that proceeds either near the diffusion limit or diffusion-controlled and accordingly is difficult to run with high stereoselectivity in non-rigid systems.[16–18] We regarded that critical issue as a fundamental problem and sought to explore the possibility of using an alternative bulky less reactive oxygen source in Mukaiyama-type hydrations. Notably, since oxygen in organic solvents might lead to explosive mixtures, an anaerobic variant should also be beneficial in that regard.[19a] Moreover, the O_2-mediated hydrations are often mass transport limited due to the need of gaseous O_2 to diffusion into the solution.[19b]



Scheme 1. Literature background and suggested process.

In the early-twenty century, organic nitro compounds were mainly used as ingredients for explosives and propellants.[20] Later, synthetic chemists utilized the activating effect of the nitro group in a number of valuable ionic transformations (Henry reaction, Michael addition, cycloaddition, Nef reaction, and amine synthesis).[21] In radical chemistry, the nitro functionality often shows detrimental effects to chain reactions (chain termination). However, Kornblum and co-workers demonstrated C–C bond formation by replacement of a nitro group via a one electron-transfer process in 1970.[22] Later, Tanner and Ono developed the radical hydrodenitration of secondary and tertiary nitro compounds using tributyltin hydride[23,24] and Giese applied that strategy to

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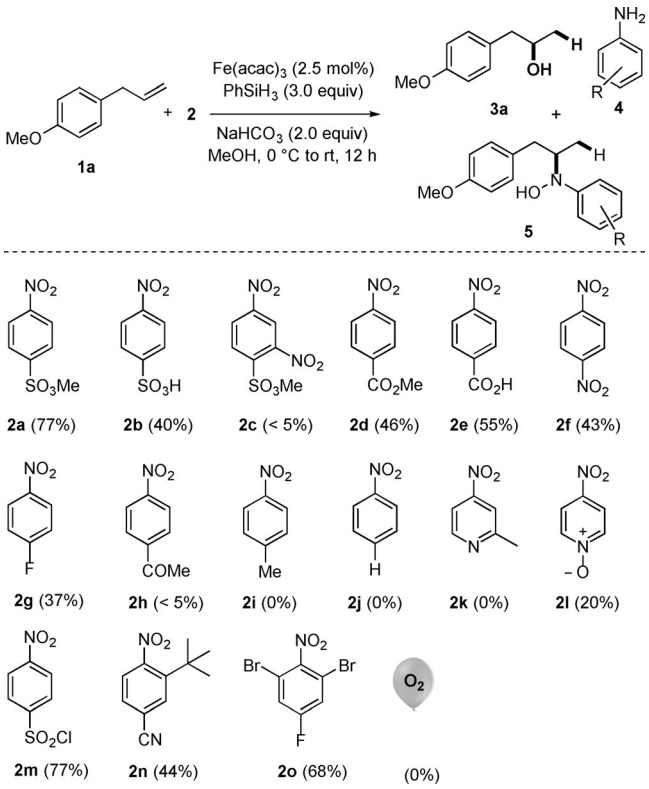
reductive alkylations (Scheme 1b).[25] These denitrations are limited to nitroalkanes and nitroarene radical chemistry is even less well explored.[26] Notably, nitroarene radical anions have been suggested as alkyl radical trapping reagents.[27,28]

Aromatic nitro compounds are electrophilic in nature and frequently used as inhibitors in free radical polymerization.[29,30] Hammond and Bartlett proposed the inhibition mechanism based on kinetic studies[31] and C-radicals were found to react with the nitro group at the O-atom to form ethers and N,O-alkylated adducts. Drawing inspiration from these works, we speculated that appropriately functionalized nitroarenes could serve as non-gaseous O-sources in free radical oxygenations under catalytic conditions and disclose our results on the anaerobic Mukaiyama-type alkene hydration for the preparation of secondary and tertiary alcohols with excellent regio- and diastereoselectivity (Scheme 1c).

Mechanistically, in situ generated Fe^{III}–H first reacts chemoselectively with the alkene via hydrogen atom transfer (HAT) to give the corresponding adduct radical **I**.[18] C-radical **I** in turn gets trapped by a nitroarene to provide the heteroatom centered radical **II** along with a Fe^{II}-species. The intermediate **II** is then reduced by the Fe^{II}-species to give the intermediate **III** which undergoes ionic fragmentation followed by protonation to form the desired hydration product, a nitroso arene and an Fe^{III}-species which should react with a stoichiometric hydride reductant to regenerate the Fe^{III}–H species. Importantly, the intermediately formed nitroso arene, known as a highly efficient C-radical trapping reagent, must be immediately reduced under the applied conditions prior to engage in radical chemistry. Along these lines, the Baran laboratory developed an elegant Fe-catalyzed HAT process for hydroamination of alkenes using nitroarenes as formal radical amination reagents.[32,33] Cheung and Hu reported an amine synthesis using Fe-catalyzed reductive coupling of alkyl halides with nitroarenes.[34] These Fe-catalyzed amine syntheses were suggested to proceed through initial reduction of the nitroarene to the corresponding nitroso arene,[35] which then acts as in situ generated radical amination reagent. Hence, our suggested process that uses the nitroarene in a chemodivergent manner as an oxygenation reagent would complement these known transformations.

Results and Discussion

Reaction optimization was conducted using 1-allyl-4-methoxybenzene (**1a**) and the nitroarene **2** (1.3 equiv) was systematically varied with $Fe(acac)_3$ as the precatalyst in combination with $PhSiH_3$ as the stoichiometric reductant in MeOH under basic conditions (Scheme 2). Pleasingly, we found that nitroarenes bearing electron withdrawing substituents at the para position are capable of effecting the targeted hydration (**2a**–**2g**) and the readily available cheap methyl 4-nitrobenzenesulfonate **2a** provided the best result. The secondary alcohol **3a** was isolated in 77% yield with complete regioselectivity. Formation of the reduced alkene (hydrogenation) was fully suppressed.[36,37] Hydroxylamine **5a** arising from in situ generated nitroso intermediate was



Scheme 2. Fe-catalyzed anaerobic Mukaiyama-type hydration of **1a**.

obtained as a side product in traces only (< 5% yield, see the Supporting Information for more details) and methyl 4-amino-(methyl benzenesulfonate) (**4a**) was formed as the byproduct. Electron rich or neutral nitroarenes (**2i** and **2j**) as well as the pyridine-based nitro compound **2k** did not provide the targeted **3a** under the same conditions. Sulfonyl chloride **2m** can be used in place of **2a** without compromising reaction efficiency. It is obvious that the chloride **2m** gets converted to the ester **2a** under the reaction conditions. This may be of practical importance, since the chloride is commercially available and very cheap, whereas ester **2a** has to be prepared in one step. The sterically bulky 2- and 2,6-substituted nitroarenes **2n** and **2o** proved to be efficient reagents for the hydration reaction.

The commercially available $Fe(acac)_3$ can be replaced by $Fe(dpm)_3$, $Fe(dibm)_3$ without diminishing the yield, but $Fe_2(ox)_3$ (ferric oxalate) or Fe(II)phthalocyanine provided worse results (see Supporting Information). Co-based and Mn-based catalysts also led to inferior results. Reaction in the absence of the nitroarene **2a** under oxygen atmosphere (balloon) did not provide **3a** (for the detailed optimization study, see Supporting Information). Hirobe,[38] Kano,[39] Setsune,[40] Takeuchi[41] and Boger[42] previously demonstrated the aerobic hydration of alkenes by using a porphyrin-based Fe-catalyst and Boger also developed an $Fe_2(ox)_3$-mediated process.[42] However, Fe-catalysts with 1,3-diketone-type ligands were not used for alkene hydration to date due to their incompatibility with aerobic conditions. Notably, TEMPO was used as a radical trap under anaerobic conditions to access the corresponding oxygenated product.[42,43] However,

to get the free alcohol an additional reduction step is required and reactions are not catalytic.

We next addressed the scope and limitations of the new hydration method. Various alkenes were reacted with methyl 4-nitrobenzenesulfonate **2a** under the optimized conditions and the scope of the reaction was found to be remarkably broad (Table 1). Aliphatic terminal alkenes equipped with various functional groups, for example, aromatic phenol (**3b**), amine (**3c**) amide (**3d**), silane (**3e**), bromo substituent (**3f**), and free amine (**3g**) worked well to provide the secondary alcohols **3a**–**3g** in moderate to good yields. Ketones, peroxides and dimerized compounds, that are usually observed as side products in oxygen mediated hydration processes[15] were not formed. Our anaerobic hydration is also effective for β-substituted terminal alkenes (**3i**–**3o**) and tolerates a wide range of functional groups including O-benzyl, O-silyl, ester, aliphatic alcohol, ketone, and heterocycles. Of note, sulfonyl chloride **2m** was used for the hydration reaction to form the alcohols **3g**, **3i**, and **3j** (for details, see Supporting Information). Late stage functionalization of more complex alkenes derived from (−)-isopulegol (**3l**), rotenone (**3m**), betulin (**3n**) and pentoxifylline (**3o**) could be achieved to provide the corresponding tertiary alcohols in good yields. Hydration also proceeds with internal alkenes (**3p**–**3t**) including natural products such as β-citronellol (**3q**), phytol (**3r**, dr = 1:1) and osthole (**3s**). Regioselective hydration of (−)-perillyl alcohol afforded **3u** (70%) as major compound along with 5% of the doubly hydrated product. Notably, the same reaction with a large excess of reagent **2a** (4.0 equivalents) gave a 4:1 mixture of **3u** and the corresponding double hydrated product as an inseparable mixture. Styrene derivatives worked to provide the benzylic alcohols **3v**–**3ad** with moderate to good yields. However, conjugated dienes did not engage in this hydration process (not shown).

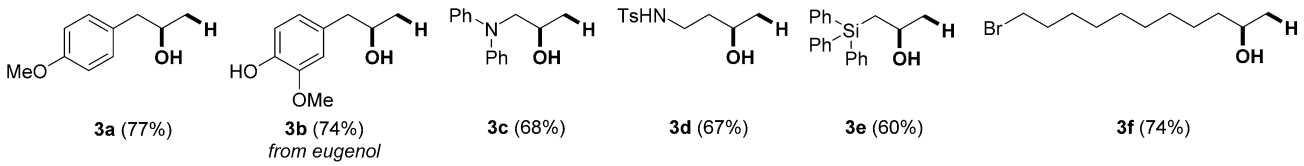
Next, we focused on diastereoselective hydrations (Table 2). In order to document the potential of our process, we additionally conducted some of these hydrations using existing aerobic protocols for comparison (methods **A**–**E**). Method E, that we considered as the most general process, was used in all cases where comparisons have been made. Hydration applying our protocol proceeds smoothly on (4-methylenecyclohexyl)benzene to afford **3ae** in 74% yield with a high diastereoselectivity (10:1). Selectivity could be further improved upon running the radical hydration with the bulkier nitroarene **2o** to afford **3ae** with a 14:1 diastereoselectivity (67%). Aerobic hydration using Mn- or Co-catalysis provided **3ae** with similar or significantly lower yield (30–70%) albeit with poor stereoselectivity (dr = 1.5:1 to 1.7:1). **2a**-mediated hydration of α-terpineol and (−)-terpinen-4-ol worked well to afford **3af** and **3ag** with excellent diastereoselectivity (dr > 20:1) without the need of protection of the free alcohol group. For **3af** and **3ag**, traces of the other diastereoisomer were identified by GC but the minor isomer could not be isolated. Again, only a low diastereoselectivity (1.7:1 to 2:1) was achieved for hydration of these two terpenes with existing aerobic hydration methodology. Our reaction tolerates the phenolic group of (−)-Δ^8-THC to form the hydrated product **3ah** with perfect selectivity (dr > 20:1). For this phenolic substrate, the traditional Mukaiyama-type hydration methods tested were found to be ineffective. (+)-3-Carene worked well to provide the alcohol **3ai** albeit with moderate selectivity (dr = 3:1). For (+)-3-carene, established methodology (superstoichiometric Fe or Co-catalysis) again provided a poorer selectivity (dr = 1.5:1).

Investigations were continued by studying the chemical modification of bicyclic monoterpene derivatives. Alkene hydration worked smoothly on (−)-α-pinene (**3aj**), (−)-*trans*-pinocarveol (**3ak**), (*S*)-*cis*-verbenol (**3al**), the benzoate ester of (*R*)-(−)-nopol (**3am**) and (−)-myrtenyl acetate (**3an**) to afford the targeted tertiary alcohols in moderate to good yields with excellent diastereoselectivities (> 20:1). For **3aj**–**3an**, nitroarene-mediated oxygenation occurred anti to the bulky dimethylmethylene bridge, as expected. For all alkenes of this bicyclic series, significantly lower diastereoselectivity was noted upon running the radical hydration using known aerobic protocols (1.3:1 to 5:1). Nitroarene-mediated hydration of more complex (+)-aromadendrene gave the tertiary alcohol **3ao** with high diastereoselectivity (dr = 9:1) and high yield. Selectivity could be further improved upon switching from **2a** to the more bulky ortho,ortho′-disubstituted nitroarene **2o** providing **3ao** with a 14:1 diastereoselectivity. A similar selectivity was also achieved with the ortho-*tert*-butylnitroarene **2n** (see Supporting Information). Again, existing methodology did not perform well in particular considering the diastereoselectivity issue. Epoxides are tolerated, as documented by the successful hydration of natural (−)-caryophyllene oxide to **3ap**, which was isolated in good yield and excellent diastereoselectivity (> 20:1). In line with all other transformations, poor diastereoselectivity was achieved by using aerobic hydration methodology (1.2:1). Steroids were found to be eligible substrates and hydration of cholesterol (**3aq**) as well as cholesteryl chloride (**3ar**) occurred in good yields and excellent diastereoselectivity (> 20:1). The relative configuration of **3aq** and **3ar** was unambiguously assigned by X-ray structure analysis.

The efficiency of the novel protocol was further demonstrated for the hydration of acyclic systems, where the control of the diastereoselectivity is even more challenging (Scheme 3). We were pleased to find that good to excellent selectivities can be achieved for the hydration of various β-disubstituted styrene derivatives. Reaction of α-methyl, β-phenyl-substituted vinyl pinacolatoborane afforded the targeted benzylic alcohol **3as** in 78% yield with 9:1 diastereoselectivity and complete regioselectivity. The diastereoselectivity can be understood considering the allylic A[1,3] strain model where the bulky R_L moiety steers the nitroarene to react from the opposite site.[44–46] For the α-ethyl substituted congener, a 5:1 diastereoselectivity was obtained. 2-Naphthyl vinyl pinacolatoboranes reacted with nitroarene **2a** to **3au** with good yield, excellent regioselectivity and good diastereoselectivity. It is worth noting that the tested aerobic hydration protocols did not provide the targeted benzylic alcohols, while the starting materials fully decomposed. The vinyl boron entity turned out to be incompatible with these protocols. β-Silyl-substituted styrenes afforded the hydrated products **3av** and **3aw** in high yields, with excellent diastereoselectivity besides 15–16% of regioisomeric α-hydrated product (see Supporting Information). Again, the established

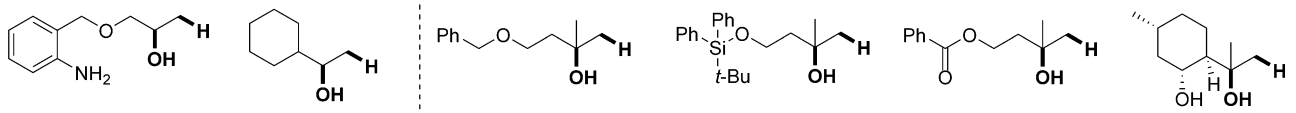
Table 1: Anaerobic radical hydration of various alkenes.

From 2° radicals



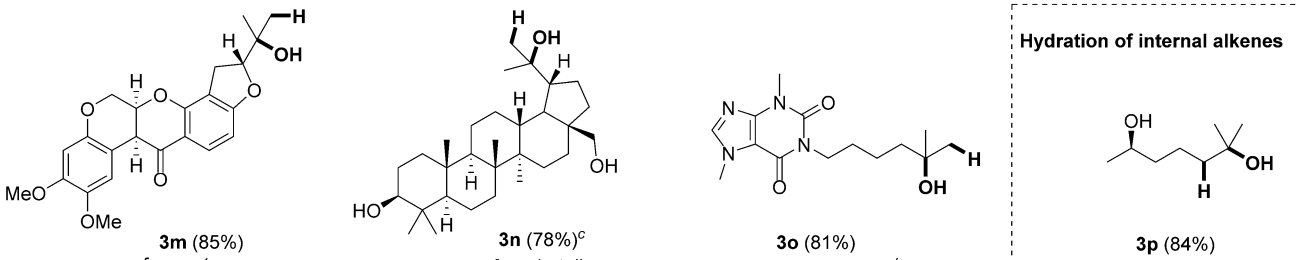
3a (77%) **3b** (74%) *from eugenol* **3c** (68%) **3d** (67%) **3e** (60%) **3f** (74%)

From 3° radicals



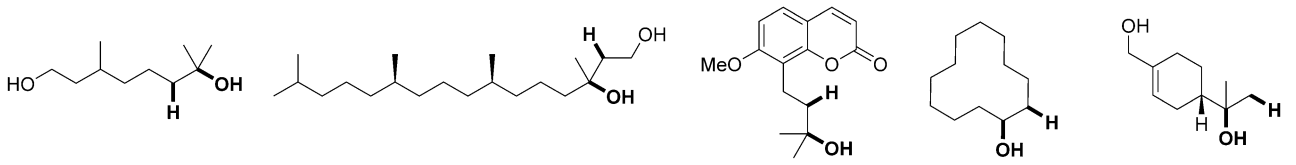
3g (64%)[b] **3h** (57%) **3i** (79%)[b] **3j** (69%)[b] **3k** (77%) **3l** (80%) *from (-)-isopulegol*

Hydration of internal alkenes



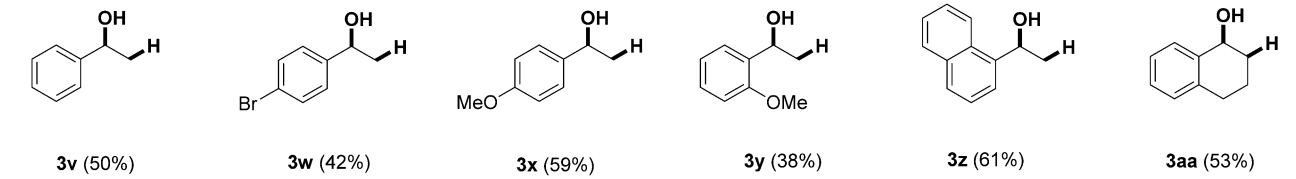
3m (85%) *from rotenone* **3n** (78%)[c] *from betulin* **3o** (81%) *from pentoxifylline*[d] **3p** (84%)

Regioelective hydration



3q (75%) *from β-citronellol* **3r** (81%, *dr* = 1:1) *from phytol* **3s** (71%) *from osthole* **3t** (48%) **3u** (70%)[e] *from (-)-perillyl alcohol*

Hydration of styrenes



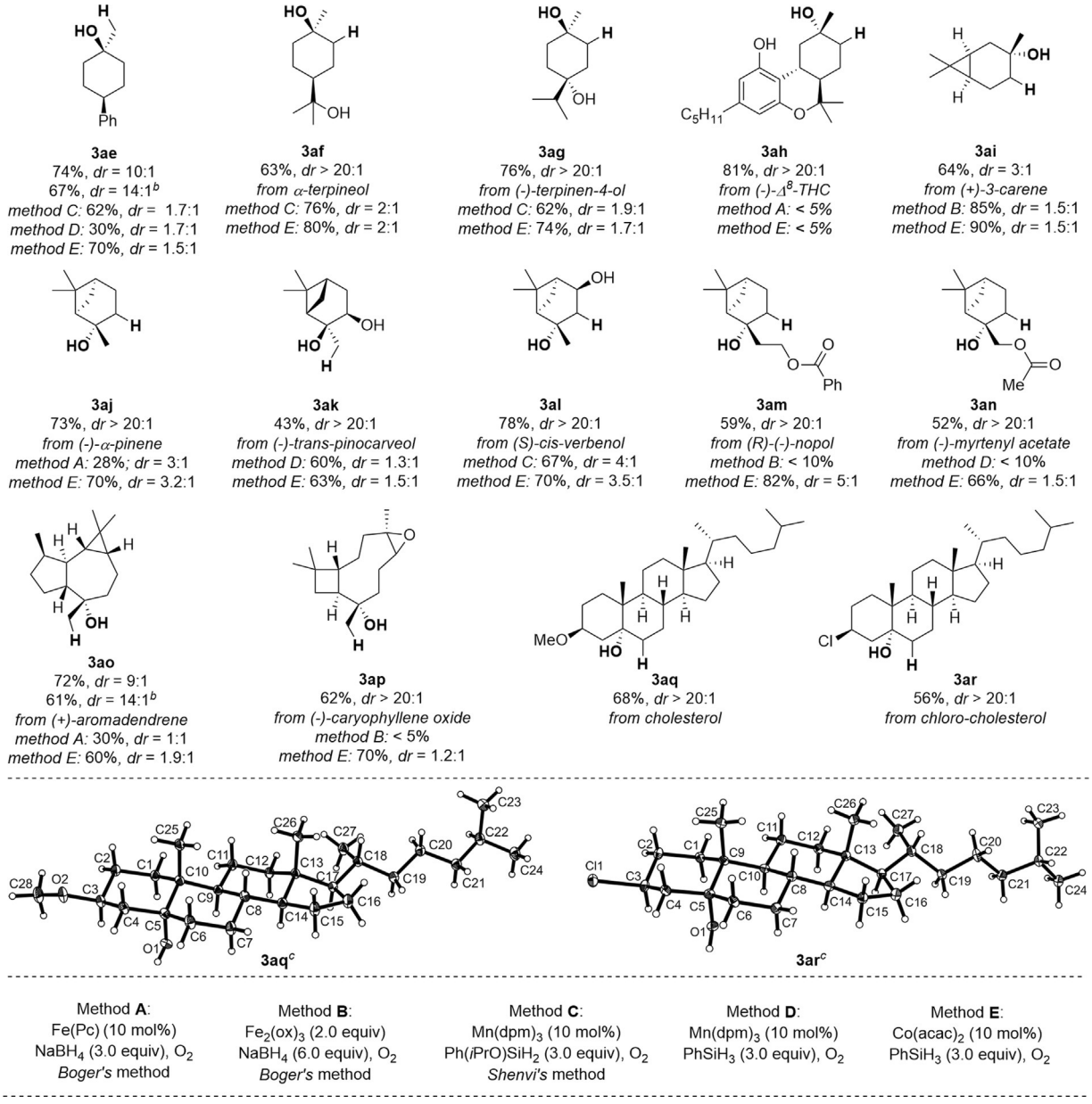
3v (50%) **3w** (42%) **3x** (59%) **3y** (38%) **3z** (61%) **3aa** (53%)

3ab (47%) **3ac** (55%, *dr* = 3.5:1)[f] **3ad** (59%)

[a] Standard conditions: $Fe(acac)_3$ (2.5 mol%), $PhSiH_3$ (3.0 equiv), **2a** (1.3 equiv) and $NaHCO_3$ (2.0 equiv), MeOH (4.0 mL), 0 °C to rt, 12 h, isolated yield on a 0.5 mmol scale. [b] Reaction performed with 2 m (1.5 equiv). [c] For product isolation and characterization, primary and secondary alcohols were protected with the acetyl group. [d] Reaction performed at 0.25 mmol scale. [e] Reaction performed with 1.2 equiv of alkene and 1.0 equiv of nitroarene. The doubly hydrated triol was formed as a side product in 5% yield. [f] Inseparable, dr was determined by ^1H NMR spectroscopy, *trans*-product formed as major isomer.

aerobic hydration protocols did not perform well for this substrate class (yield $< 10\%$, dr = 1:1). The mildness of the method was further documented by the successful transformation of an α-silylated vinyl pinacolatoborane. Complete regioselectivity was achieved for the sterically crowded geminal borylsilyl-substituted styrene which afforded the

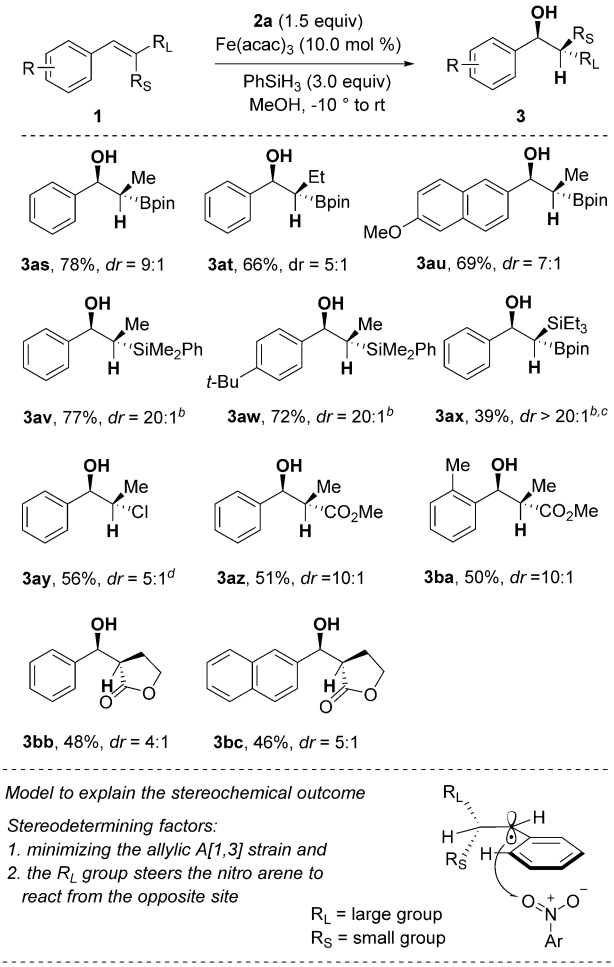
Table 2: Diastereoselective anaerobic hydration in cyclic.



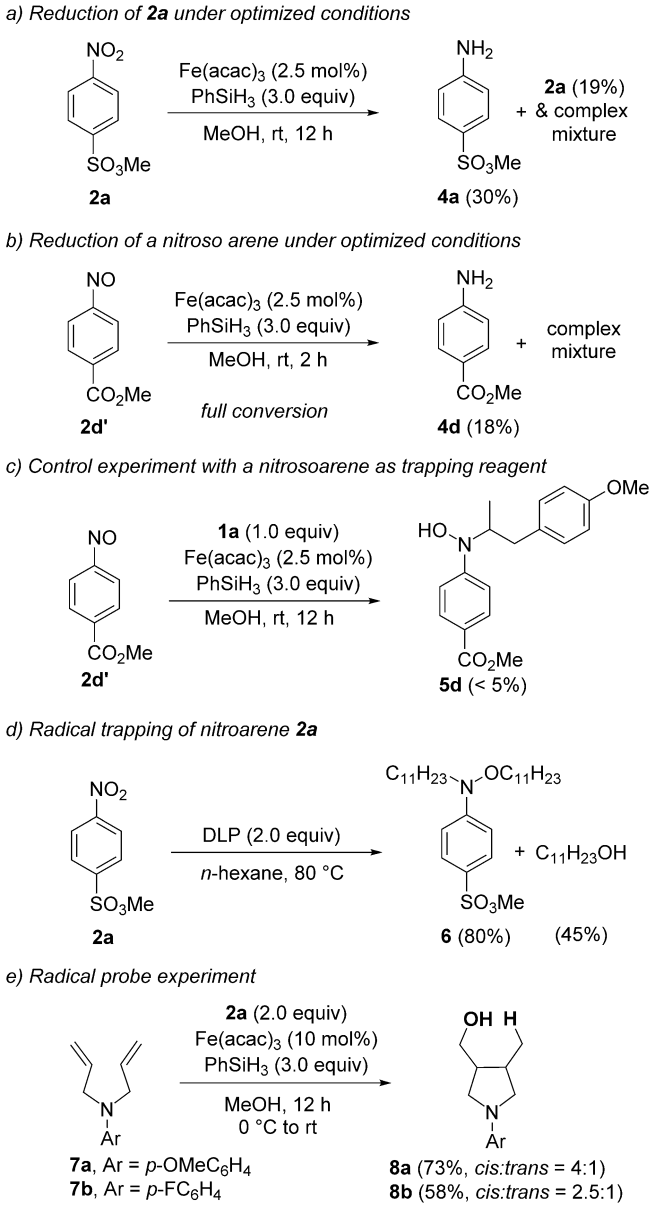
[a] Standard conditions: $Fe(acac)_3$ (2.5 mol%), $PhSiH_3$ (3.0 equiv), **2a** (1.3 equiv) and $NaHCO_3$ (2.0 equiv), MeOH (4.0 mL), 0 °C to rt, 12 h, isolated yield on a 0.5 mmol scale. [b] Reaction conducted with the bulky nitroarene **2°**. [c] Thermal ellipsoids are set at 50% probability.[52]

benzylic alcohol **3ax** with excellent diastereoselectivity in 39% yield (brsm 95%). Moreover, α-chloro-β-methyl-styrene afforded the chlorohydrin **3ay** in 56% yield with complete regioselectivity and a 5:1 diastereoselectivity. Considering the allylic A[1,3] strain model, the nitroarene reacts opposite to the Cl-substituent likely due to electronic repulsion. No selectivity was obtained for this transformation using an oxygen-mediated hydration process (dr = 1:1, see Supporting Information). For the assignment of the relative configuration of all these benzylic alcohols, we refer to the Supporting Information (in Table 3 only the major diastereoisomer is drawn). The β-selective hydration of polar alkenes e.g., α,β-unsaturated esters (**3az** and **3ba**) and α,β-lactones (**3bb** and **3bc**) afforded the desired products in moderate yields and moderate to good diastereoselectivity with a detectable amount of hydrogenated side product. $Co(acac)_2$ catalyzed oxygen mediated hydration failed to deliver the desired β-hydroxy product. Of note, Rizzacasa and co-workers previously demonstrated aerobic hydration of α,β-unsaturated esters by using a designed Mn-catalyst.[47] However, the sterically more hindered even more challenging α,α-disubstituted systems as studied herein were not included in these investigations.

To shed light on the mechanism of the nitroarene-mediated hydration, additional experiments were conducted. Reduction of 4-nitrobenzenesulfonate **2a** under the opti-



Scheme 3. Diastereoselective anaerobic hydration in open-chain systems: [a] Standard conditions: $Fe(acac)_3$ (10.0 mol%), $PhSiH_3$ (3.0 equiv), **2a** (1.5 equiv), reaction run at −10° to rt. [b] Reaction was performed in THF:MeOH (9:1) solvent mixture. [c] Yield is 95% based on recovered starting material (brsm). [d] Starting chloro-styrene derivative was used as an *E*/*Z*-mixture of isomers.



Scheme 4. Mechanistic studies.

mized conditions provided 30% aniline **4a** and 19% unreacted **2a** besides unidentified material (Scheme 4a).[48] This result shows that the reduction of the nitro group in **2a** under the applied conditions is a slow process, indicating that the nitroarene under optimized conditions in the presence of an alkene likely reacts exclusively as a radical oxygenating reagent. Furthermore, under the standard conditions, the nitroso arene **2d′** was fully consumed within 12 hours to give aniline **4d** (18%) along with other unidentified compounds (Scheme 4b). A similar result was noted after 2 hours reaction time. This outcome reveals that a nitroso arene decomposes fast under these conditions, in line with our reaction design (see Scheme 1). Treatment of nitroso arene **2d′** in the presence of the alkene **1a** provided <5% of the hydroxyl amine **5d** (Scheme 4c). The lower efficiency of formation of hydroxylamine **5d** is due to uncompetitive trapping of alkyl radical generated from Fe-mediated HAT by nitroso arene **2d′** and/or uncompetitive HAT compared with the nitroso reduction. To document that the nitroarene **2a** can act as an alkyl radical acceptor, dodecanoyl peroxide was thermally decomposed in the presence of **2a** to give alkoxyamine **6** (80%)[29,49] and undecanol (45%) (Scheme 4d). The presence of undecanol indicates that the nitro functionality in such electron-poor nitroarenes can react at the O-atom with a C-radical, since it is unlikely that under such oxidizing conditions the alcohol derives from a hydroxyl amine or alkoxyamine intermediate. To further prove that radical intermediates are involved, we conducted radical probe experiments (Scheme 4e) with the 1,6-dienes **7a** and **7b**. Products **8a** and **8b** formed via radical 5-*exo* cyclization were isolated in good yields and moderate *cis*/*trans* selectivity.[50] All these findings support the mechanism suggested in Scheme 1. Moreover, hepta-1,6-diene was used as a radical clock to estimate the rate constant for the reaction of nitroarene **2a** with a secondary alkyl radical. Trapping occurs

with a second order rate constant of $1.9 \times 10^5\ M^{-1} s^{-1}$ at room temperature (see Supporting Information), clearly showing this reaction to be rather fast. For comparison, Bu_3SnH as the most popular C-radical reducing reagent reacts with a secondary alkyl radical with a rate constant of $2.3 \times 10^6\ M^{-1} s^{-1}$.[51]

Conclusion

In summary, we have developed a highly efficient anaerobic Markovnikov selective alkene hydration process with electron deficient nitroarenes as efficient C-radical oxygenation reagents. As compared to known Mukaiyama-type hydration protocols, the nitroarene mediated process delivers the product alcohols with significantly higher diastereoselectivity. Considering all facets of the novel radical hydration process, we are confident that this method will find broad application for stereoselective alkene hydration in natural product synthesis and for late stage chemical modification of complex alkenes.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anaerobic hydration · hydrogen-atom transfer · iron catalysis · late-stage modifications · nitroarenes · radical chemistry

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