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Sequential Oxidative α-Cyanation/Anti-Markovnikov Hydroalkoxylation of Allylamines

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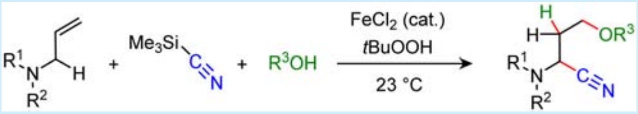
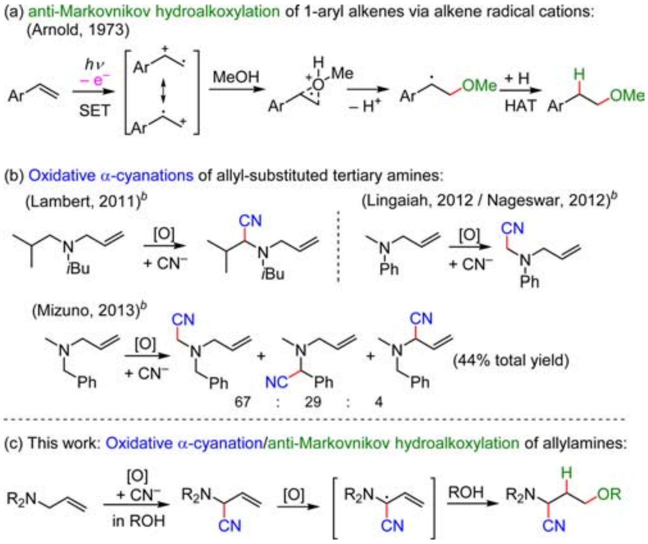
S Supporting Information

ABSTRACT: Iron-catalyzed oxidative α-cyanations at tertiary allylamines in the allylic position are followed by anti-Markovnikov additions of alcohols across the vinylic CC double bonds of the initially generated α-amino nitriles. These consecutive reactions generate 2-amino-4-alkoxybutanenitriles from three reactants (allylamines, trimethylsilyl cyanide, and alcohols) in one reaction vessel at ambient temperature.



Additions to alkenes are atom-economic reactions that are used by synthetic chemists in academia and industry to introduce a broad variety of functional groups into hydrocarbons.[1] However, only a limited number of methods exist so far for anti-Markovnikov additions of alcohols to simple aliphatic olefins. Arnold studied the photosensitized generation of alkene radical cations,[2] which were trapped with alcohols to provide anti-Markovnikov adducts.[3] Since then, only a few related examples for photochemically induced anti-Markovnikov alcohol additions have been reported, all of which use 1-aryl- or 1,1-diarylalkenes as reaction partners (Scheme 1a).[4−6] General methods for intermolecular anti-Markovnikov hydroalkoxylations under mild and practical conditions are still lacking because of a shortage of applicable catalytic processes,[7] in particular with catalysts based on earth-abundant elements such as iron.[8−10]

Scheme 1. Direct Anti-Markovnikov Additions of Alcohols to Alkenes[a] and Oxidative α-Cyanations of Allylamines



[a]SET, single electron transfer; HAT, hydrogen atom transfer. [b]For reaction conditions, see notes in ref 17.

According to the methylenology principle,[11] Michael additions of alcohols at intrinsically nucleophilic C=C double bonds could be mediated by linking the electron-rich π-system with an electron-accepting group through a radical center. As C-centered radicals are efficiently stabilized by captodative effects,[12] vinyl-substituted α-amino nitriles would be ideal substrates for testing this approach.

The introduction of nitrile groups at C−H bonds adjacent to the nitrogen of tertiary amines has recently been achieved with several catalyst-oxidant combinations and various cyanide sources.[13−15] Hence, allylamines may serve as potential precursors for vinyl-substituted α-amino nitriles. Indeed, it has been reported that allylamines can be used in oxidative α-cyanations under various conditions[16,17] (Scheme 1b). The few examples show, however, that oxidation occurs preferentially at aliphatic or benzylic α-positions of the amines,[17a−c] and only Mizuno and co-workers detected small amounts of α-cyanated products that originated from reaction at the allyl group.[17d,18]

In recent years, we have developed iron-catalyzed oxidative α-cyanations of a variety of tertiary amines.[19,20] Here, we report that $FeCl_2$-catalyzed direct α-cyanations at tertiary allylamines in the allylic position are followed by anti-Markovnikov additions of alcohols across the vinylic CC double bonds of the initially generated α-amino nitriles (Scheme 1c).

Monitoring the oxidative cyanation of *N*,*N*-diallylaniline **1a** under our standard conditions in methanol [10 mol % $FeCl_2$, 2 equiv of Me_3SiCN, 2.5 equiv of *t*BuOOH (5.5 M in decane), dry N_2 atmosphere, ambient temperature][19c,21] by GC−MS indicated that significant amounts of the α-cyanation product **2a** accumulated in the reaction mixture only during the initial phase of the reaction. The cyanation product **2a** was accompanied by the generation of compounds with a molecular mass of **2a**·MeOH. While **2a** was isolated in low yield (21%) when the reaction was worked-up after 4 h reaction time, the

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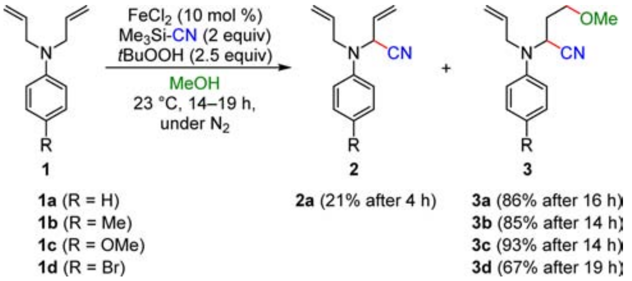
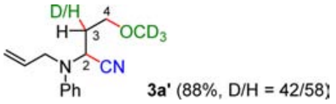
product of the addition of methanol to **2a** was obtained in 86% yield after 16 h (Scheme 2). 2D-NMR spectroscopic characterization of **2a**·MeOH showed the presence of a terminal methoxy group, in agreement with structure **3a**. *N*,*N*-Diallylanilines **1b**,**c** with electron donating *p*-methyl ($\sigma_p = -0.17$)[22] or *p*-methoxy substituents ($\sigma_p^- = -0.27$)[22] at the phenyl rings analogously gave 2-anilino-4-methoxybutanenitriles **3b**,**c** in yields of 85% and 93%, respectively. The electron-withdrawing *p*-bromo-substituted aniline **1d** (σ_p^-(Br) = 0.25)[22] gave **3d** in a moderate yield of 67%.

Scheme 2. Sequential Oxidative Cyanation/Hydroalkoxylation of *N*,*N*-Diallylanilines 1a−d[a]



[a]Yields refer to isolated products after chromatographic purification.

Changing the solvent from CH_3OH to CD_3OD for the reaction of **1a** under otherwise identical conditions of Scheme 2 yielded the d_3-methyl ether **3a′** in 88% yield.

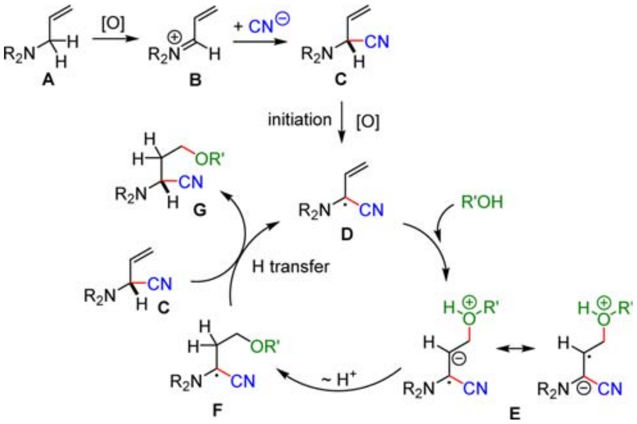


3a′ (88%, D/H = 42/58)

While the ^{1}H and ^{13}C NMR spectra of **3a′** indicate a quantitative OCD_3 incorporation, the methylene group at C3 of the 4-methoxybutanenitrile branch shows a ca. 42% uptake of D (see Supporting Information). Because of fast H/D exchange between CD_3OD and *t*BuOOH under the conditions applied, it is presently not possible to unequivocally assign the source of the H or D that adds to the C3 position.

To rationalize the selective anti-Markovnikov addition of methanol, we suggest that iron-catalyzed oxidation converts the allyl-substituted amines **A** into *α*,*β*-unsaturated iminium ions **B**, which are then trapped by kinetically controlled attack of cyanide ions at the iminium carbon (Scheme 3).[23] Further oxidation of the intermediate *α*-amino nitriles **C** generates the donor/acceptor-substituted radicals **D**, which enter a radical chain reaction. In accord with the methylenology principle,[11] radicals **D** show reactivity comparable to the *π*-electron-deficient acrylonitriles. Therefore, Michael-type addition of alcohols to the terminal C-4 may generate intermediates **E**, in which the negative charge is delocalized and efficiently stabilized by the electron-withdrawing cyano group. Fast proton transfer converts **E** to radicals **F**, which benefit from captodative stabilization.[12] Deuteration at C2 in product **3a′** was not observed (see above). Therefore, we conclude that O−H of *t*BuOOH or C−H of methanol do not act as hydrogen atom donors toward radicals **F**. The catalytic cycle may be closed, however, by direct or indirect hydrogen atom transfer[24] from *α*-amino nitriles **C** to radicals **F** to generate the final products **G** as well as the radicals **D** that take part in the next cycle of the radical chain reaction. On the basis of the quantum-chemically calculated radical stabilization energies (RSEs),[25] transfer of a hydrogen atom from **C** to radical **F** is thermodynamically feasible and exothermic by 38 kJ mol^{-1} (in the gas phase, for details see Supporting Information).

Scheme 3. Suggested Mechanism for the Oxidative C1-Cyanation of the *N*-Allyl Group with Subsequent Anti-Markovnikov Hydroalkoxylation



Both radicals **D** and **F** involved in the proposed catalytic cycle are unusually stable in absolute terms, which implies weak C−H bonds in the closed shell parent systems **C** and **G**. On the basis of bond dissociation energies (BDEs), the relevant C−H bond of **2a** (+310 kJ/mol) is slightly weaker than that of 2-phenylmalononitrile (+322 ± 4 kJ/mol, from ref 26), which was successfully used as the H atom donor in intramolecular anti-Markovnikov hydroetherifications.[5g,6a] The relevant C−H bond of **2a** is also weaker than in reaction product **3a** (+348 kJ/mol) and much weaker than the allylic C−H bond in propene (+369 kJ/mol)[27] or the *α*−C-H bond in the glycine-derivative (+364 kJ/mol) depicted in Figure 1.[25,28] Interestingly, the *α*−C-H bond in **3a** is of comparable strength as the O−H bond in *t*BuOOH (BDE = +353 ± 9 kJ/mol, from ref 29).

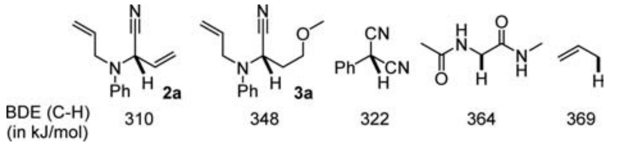
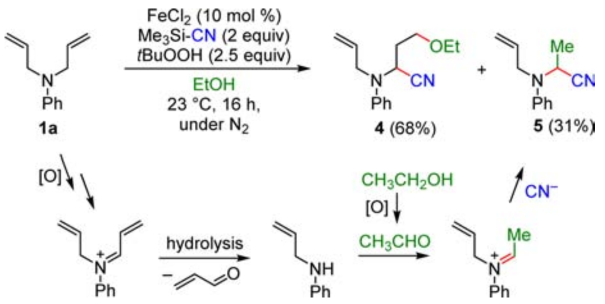


Figure 1. Comparison of C−H bond dissociation energies (BDEs) in *α*-amino nitriles **2a** and **3a** with those in structurally analogous compounds and in 2-phenylmalononitrile.

When ethanol was used as the solvent instead of methanol, the 4-ethoxy-substituted 2-aminobutanenitrile **4** (68%) was obtained from **1a** by the cyanation/hydroalkoxylation sequence (Scheme 4). Ethyl ether **4** was accompanied by the 2-aminopropanenitrile **5** (31% isolated yield), whose formation is rationalized in analogy to the previously described oxidative dealkylation/cyanomethylation of *N*,*N*-dialkylanilines in methanol.[19c] Oxidative degradation of **1a** via hydrolysis of the intermediate *α*,*β*-unsaturated iminium ions forms *N*-allylaniline, which condenses with acetaldehyde, generated by oxidation of the solvent ethanol,[30] to yield iminium ions, which are finally trapped by cyanide to yield **5** (Scheme 4).

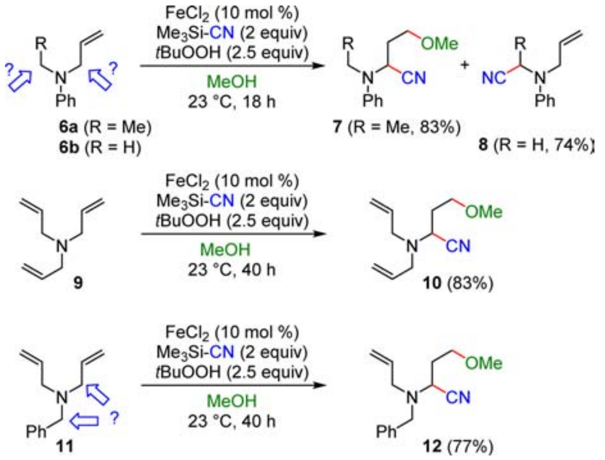
Reactions with *N*-allyl-*N*-ethylaniline (**6a**) and triallylamine (**9**) showed that the scope of the oxidative *α*-cyanation/-hydroalkoxylation can be extended to mono- and triallyl-

Scheme 4. Oxidative Cyanation of *N*,*N*-Diallylaniline (1a) in Ethanol[a]



[a]Yields refer to isolated products after separation and purification by column chromatography.

Scheme 5. Oxidative Cyanation/Hydroalkoxylation of the Monoallylamines 6a,b, Triallylamine (8) and *N*,*N*-Diallylbenzylamine (11)[a]



[a]All reactions under dry N_2 atmosphere. Yields refer to isolated products after chromatographic purification.

substituted amines (Scheme 5). Preferred cyanation of the NMe group of *N*-allyl-*N*-methylaniline (**6b**) to yield the α-amino nitrile **8** is in agreement with previous reports[17b−d] and allows one to derive the reactivity order NMe > *N*-allyl > NEt for the regioselectivity of these oxidative α-functionalizations of *N*,*N*-disubstituted anilines. This reactivity order differs from Lambert's observation of a preferred hydride transfer from the aliphatic group of allyl-diisobutylamine to tropylium ions.[17a] Our reactivity order also differs from that for relative rates for the deprotonation of laser-flash photolytically generated amine radical cations by acetate, $k_{\mathrm{rel}} = 2.7$ (*N*-allyl) > 1 (NMe) > 0.24 (NEt), which were explained by stereoelectronic effects in the preferred transition state conformation.[31] One consequence of the chemoselectivity NMe > *N*-allyl of the oxidative functionalization step is that this preference makes NMe groups in tertiary amines incompatible with the α-cyanation/anti-Markovnikov hydroalkoxylation sequence because the α-cyanation is directed to the *N*-methyl group. Whereas a 7-fold preference for *N*-benzyl over *N*-allyl reactivity was found by Mizuno,[17d] we succeeded in preparing methyl ether **12** from *N*,*N*-diallylbenzylamine **11** under our reaction conditions.

In conclusion, an iron-catalyzed α-cyanation of tertiary allylamines has been developed that is coupled with a subsequent chemo- and regioselective addition of alcohols to the π-system of the vinyl-substituted α-amino nitrile intermediate. Thus, this reaction combines three components[32] in one pot to yield 2-amino-4-alkoxybutanenitriles under mild conditions. Such ether-functionalized α-amino nitriles may further extend the rich synthetic versatility of α-amino nitriles.[33] Detailed studies of the mechanism including further characterization of highly stabilized radicals of structural type **D**, as well as broadening the scope of this novel type of anti-Markovnikov hydroalkoxylation are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02319.

> Experimental details, discussion of the quantum-chemically calculated RSEs, and spectroscopic characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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