

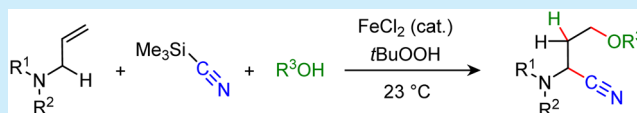
Sequential Oxidative α -Cyanation/Anti-Markovnikov Hydroalkoxylation of Allylamines

Alexander Wagner, Nathalie Hampel, Hendrik Zipse, and Armin R. Ofial*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, 81377 München, Germany

S Supporting Information

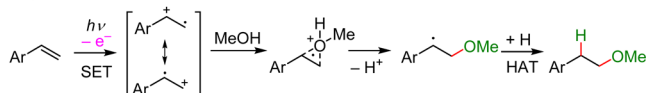
ABSTRACT: Iron-catalyzed oxidative α -cyanations at tertiary allyl amines in the allylic position are followed by anti-Markovnikov additions of alcohols across the vinylic CC double bonds of the initially generated α -amino nitriles. These consecutive reactions generate 2-amino-4-alkoxybutanenitriles from three reactants (allyl amines, 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-diarylethenes as reaction partners (Scheme 1a).^{4–6} General methods for intermolecular anti-Markovnikov hydroalkoxylation under mild and practical conditions are still lacking because of a shortage of applicable catalytic processes,⁷

Scheme 1. Direct Anti-Markovnikov Additions of Alcohols to Alkenes^a and Oxidative α -Cyanations of Allyl Amines

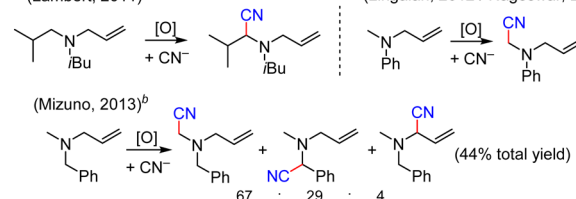
(a) anti-Markovnikov hydroalkoxylation of 1-aryl alkenes via alkene radical cations: (Arnold, 1973)



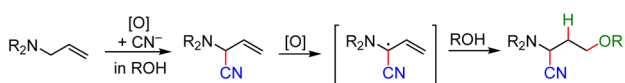
(b) Oxidative α -cyanations of allyl-substituted tertiary amines:

(Lambert, 2011)^b

(Lingaiah, 2012 / Nageswar, 2012)^b



(c) This work: Oxidative α -cyanation/anti-Markovnikov hydroalkoxylation of allyl amines:



^aSET, single electron transfer; HAT, hydrogen atom transfer. ^bFor reaction conditions, see notes in ref 17.

in particular with catalysts based on earth-abundant elements such as iron.^{8–10}

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, allyl amines may serve as potential precursors for vinyl-substituted α -amino nitriles. Indeed, it has been reported that allyl amines 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}

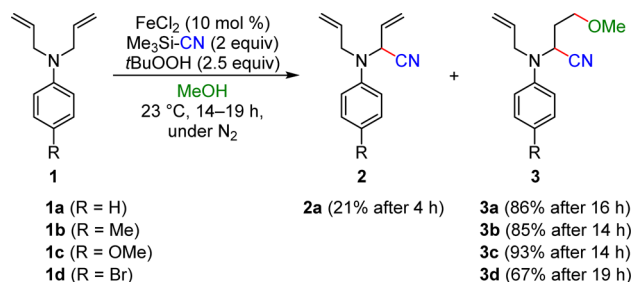
In recent years, we have developed iron-catalyzed oxidative α -cyanations of a variety of tertiary amines.^{19,20} Here, we report that FeCl₂-catalyzed direct α -cyanations at tertiary allyl amines in the allylic position are followed by anti-Markovnikov additions of alcohols across the vinylic CC double 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 % FeCl₂, 2 equiv of Me₃SiCN, 2.5 equiv of *t*BuOOH (5.5 M in decane), dry N₂ 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 character-

Scheme 2. Sequential Oxidative Cyanation/Hydroalkoxylation of *N,N*-Diallylanilines **1a–d^a**



^aYields refer to isolated products after chromatographic purification.

ization 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** ($\sigma_p(\text{Br}) = 0.25$)²² gave **3d** in a moderate yield of 67%.

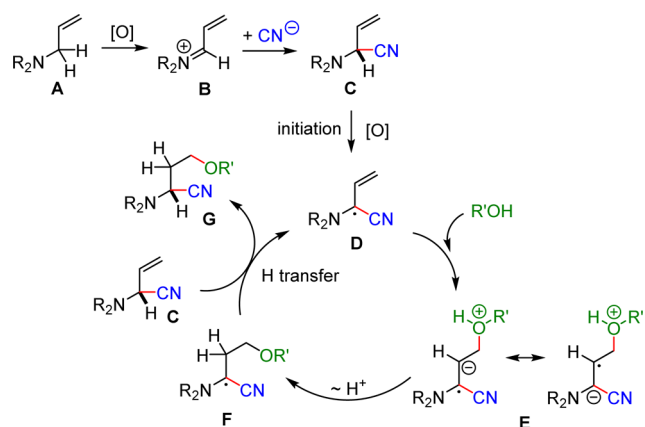
Changing the solvent from CH₃OH to CD₃OD for the reaction of **1a** under otherwise identical conditions of Scheme 2 yielded the *d*₃-methyl ether **3a'** in 88% yield.



While the ¹H and ¹³C NMR spectra of **3a'** indicate a quantitative OCD₃ 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 CD₃OD 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 transfer²⁴ 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-

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



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).

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).

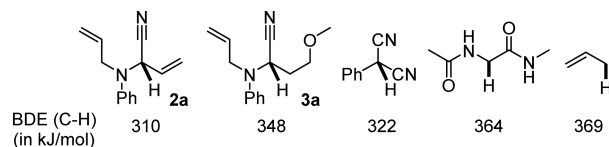
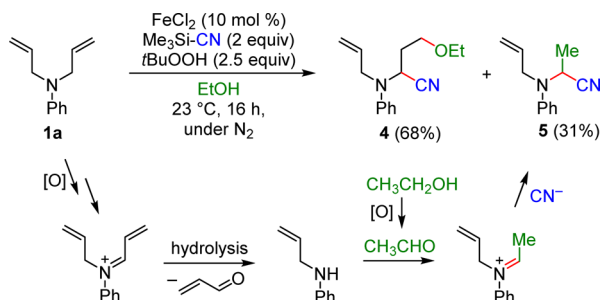


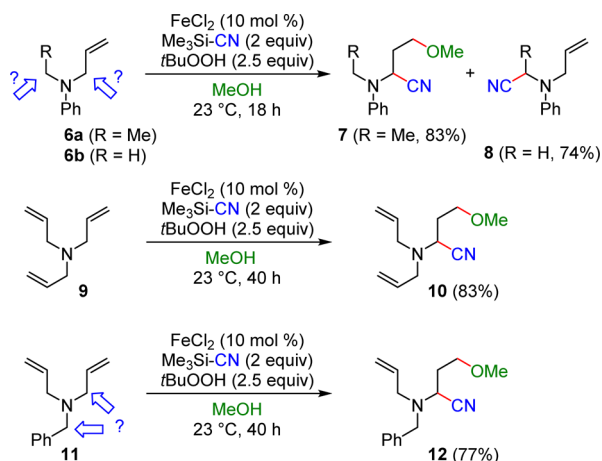
Figure 1. Comparison of C–H bond dissociation energies (BDEs) in α -amino nitriles **2a** and **3a** with those in structurally analogous compounds and in 2-phenylmalononitrile.

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

^aYields 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

^aAll reactions under dry N₂ 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, $k_{\text{rel}} = 2.7$ (*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 components³² 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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ofial@lmu.de.

Notes

The authors declare no competing financial interest.

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