Aminohydroxylation

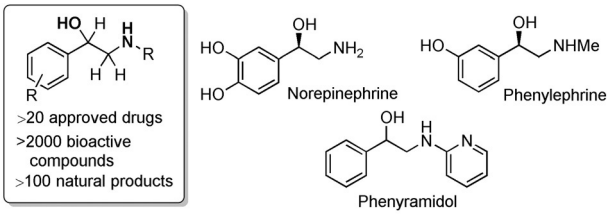
International Edition: DOI: 10.1002/anie.201507630
German Edition: DOI: 10.1002/ange.201507630

Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phthalocyanine

*Luca Legnani and Bill Morandi**

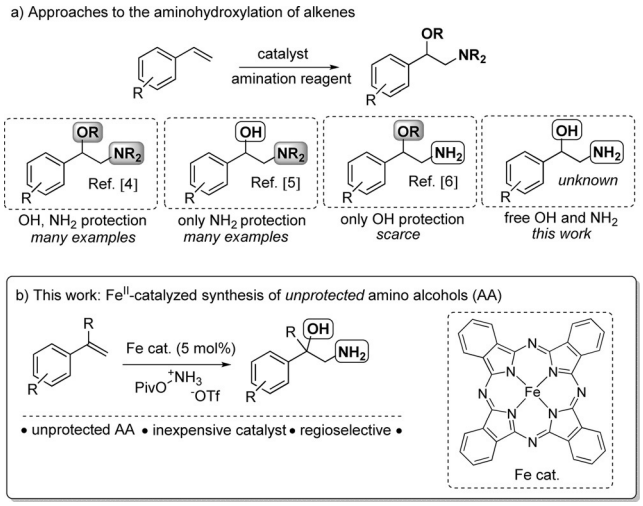
Abstract: *Aryl-substituted amino alcohols are privileged scaffolds in medicinal chemistry and natural products. Herein, we report that an exceptionally simple and inexpensive Fe^{II} complex efficiently catalyzes the direct transformation of simple alkenes into unprotected amino alcohols in good yield and perfect regioselectivity. This new catalytic method was applied in the expedient synthesis of bioactive molecules and could be extended to aminoetherification.*

The direct catalytic synthesis of amine-containing molecules from simple alkenes is a critical challenge in the synthesis of bioactive molecules.[1] 2-Amino-1-phenylethanol derivatives are a particularly important subclass of amino alcohols (Scheme 1) that is widely represented in marketed drugs and bioactive compounds.[2,3] The rapid synthesis of this structural motif is thus of outmost important to the drug discovery process.



Scheme 1. Medicinal importance of 2-amino-1-phenylethanols.[3]

Several catalytic approaches have been developed to access 2-amino-1-phenylethanols from alkenes by using different protecting-group strategies (Scheme 2a).[4–8] Many transformations provide the amino alcohol bearing protecting groups on both the N and O atoms,[4] including Fe- and Cu-catalyzed reactions using alkenes and hydroxylamine-derived reagents. Alternatively, methods have been developed to introduce a protected form of the N atom only.[5] Among them, Os-catalyzed aminohydroxylation is still the most commonly employed method to access amino alcohol derivatives from alkenes. More recently, a Mn-catalyzed two-step process was reported that enables the preparation of azido alcohols.[5a] Finally, a few scarce examples of the synthesis of primary aminoethers bearing poorly cleavable O-atom substituents (Me and Ar) have been documented.[6] No catalytic reactions have been reported to date that are capable of directly introducing the ideal unprotected amino alcohol motif, despite the potential for such a reaction to dramatically increase the step and atom economy of the aminohydroxylation reaction and streamline the synthesis of bioactive compounds.[6a,9] Herein, we report a novel and efficient iron-catalyzed aminohydroxylation of alkenes that enables the direct synthesis of unprotected amino alcohols (Scheme 2b).



Scheme 2. Context of the work.

The direct catalytic synthesis of unprotected amino alcohols has remained challenging in part because the products can strongly chelate the metal catalyst and inhibit the catalytic cycle.[10] In our design, we reasoned that the use of a protonated amino source should prevent any undesired chelation of the catalyst and would likely favor the formation of highly electrophilic nitrogen intermediates that can readily react with alkenes. We therefore investigated a series of various transition-metal catalysts with $PivONH_3OTf$ as an easily accessible, shelf-stable aminating[11] reagent (Table 1 and Table S1 in the Supporting Information). Neither Mn nor Cu complexes known to catalyze amination reactions initiated by SET[5a,7b] afforded the desired product in more than 10% yield (Entries 1–2) and most of the styrene starting material was left unreacted. Simple Fe^{II} salts proved more effective (Entries 3–4), giving up to 42% yield of desired product **2**. However, in contrast to the Mn and Cu catalysts, the styrene was completely consumed under Fe catalysis.[12] The addition of bipyridine and phenanthroline to $FeSO_4$ revealed a significant ligand effect (Entries 5–6).

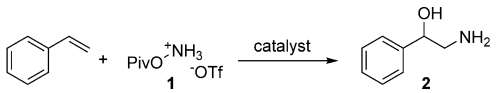
Ultimately, inexpensive and widely available Fe^{II} Phthalocyanine ($Fe^{II}Pc$) gave full conversion to a single regioisomer

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Table 1: Evaluation of reaction conditions.[a]



Entry	Catalyst (5 mol%)	Ligand (10 mol%)	Yield[b]
1	$MnSO_4$	–	< 5%
2	$[Cu(CH_3CN)_4]PF_6$	–	9%
3	$Fe(OAc)_2$	–	27%
4	$FeSO_4$	–	42%
5	$FeSO_4$	Phenanthroline	52%
6	$FeSO_4$	Bipyridine	63%
7	$Fe^{II}Pc$	–	78%
8	Pc	–	< 5%

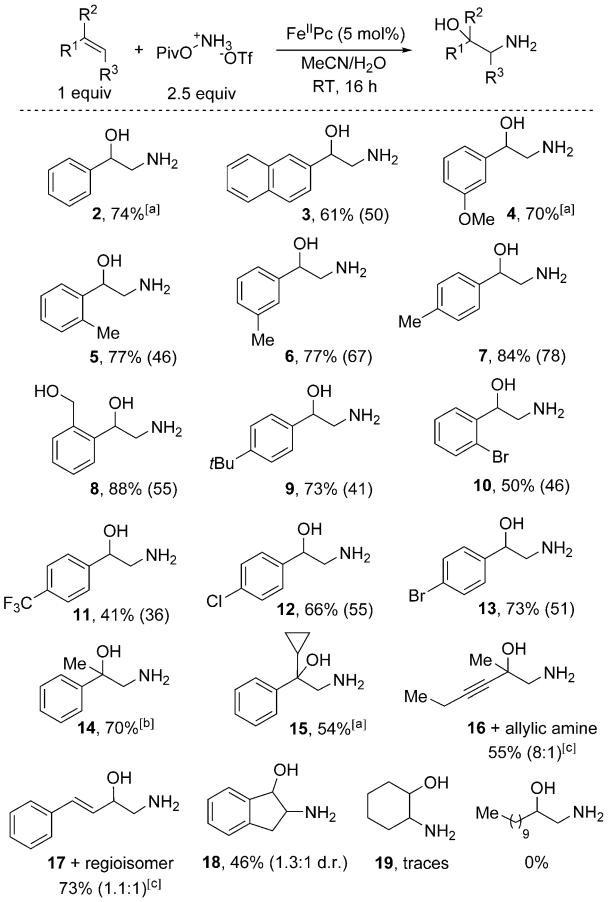
[a] 5 mol% catalyst, $MeCN/H_2O$, 16 h, RT, 2.5 equiv of **1**. [b] NMR yield.

of the desired product in 78% yield (Entry 7). Importantly, the alkene can be used as the limiting reagent, which bodes well for the application of this new method to more elaborate alkene substrates.

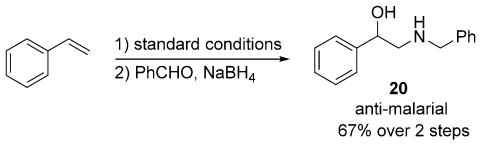
A wide range of styrene derivatives afforded the unprotected amino alcohols in good yields and perfect regioselectivity (Scheme 3). Electron-rich substituents (MeO, *t*Bu, Me, CH_2OH) were tolerated and products **2**–**9** could be efficiently prepared. Mildly electron-withdrawing groups, such as halogens, also provided the products in good yields. A substrate bearing a more strongly electron-withdrawing group, CF_3, did not lead to full conversion and gave a reduced yield of the product **11**, a result consistent with a possible electrophilic addition pathway. A larger Br substituent at the *ortho* position led to a reduced yield of **10** when compared to the *para* isomer **13**, however *o*-Me substitution in **5** was well tolerated. α-Me styrene and a cyclopropyl styrene also provided the corresponding products **14** and **15** in good yields. Finally, we evaluated a few additional non-styrenyl substrates to expand the scope beyond the synthesis of bioactive 2-amino-1-phenylethanols. A simple, non-conjugated enyne afforded the propargylic amino alcohol derivative **16** in good yield. Allylic amino alcohol **17** can also been obtained from the corresponding diene. Cyclohexene and dodecene failed to react under the normal reaction conditions.

The crude, unpurified amino alcohol **2** can be directly transformed into a range of derivatives (see Scheme S1 in the Supporting Information). In particular, a simple two-step procedure for direct reductive amination without intermediate purification was developed, giving a 67% yield of antimalarial product **20** over two steps (Scheme 4).[13] This practical procedure avoids any additional protecting-group manipulations that are usually necessary when traditional aminohydroxylation methods are applied and provides a powerful entry to the synthesis of diverse bioactive secondary amines.

We then explored the use of additional oxygen nucleophiles to access aminoethers that are difficult to prepare by using other methods (Scheme 5). Both a primary alcohol, MeOH, and a secondary alcohol, *i*PrOH, afforded the trapping products **21** and **22** in high yields (Scheme 5, 96% and 81%). As little as 10 equiv of *i*PrOH in CH_3CN was



Scheme 3. Substrate Scope. NMR yields of the corresponding $RNH_2{\cdot}HX$ salt in D_2O. Yields in parentheses are yields of isolated product after Boc derivatization. [a] Yield of isolated pure amino alcohol. [b] Yield of isolated product after Boc protection. [c] Ratio of products.

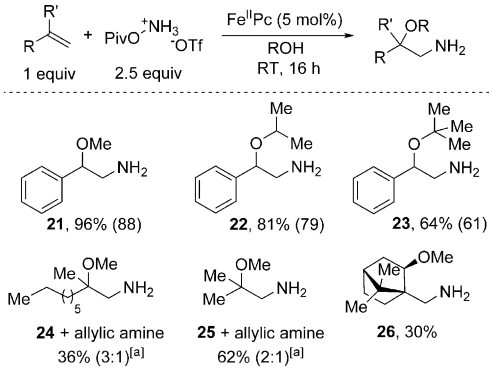


Scheme 4. Practical sequential aminohydroxylation and reductive amination.

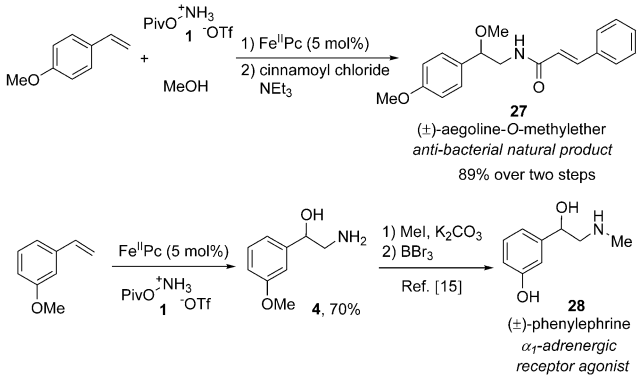
sufficient to afford the product in synthetically useful yield (61%). Remarkably, even *t*BuOH, a relatively poor nucleophile, gave the *t*Bu ether **23** in good yield. In preliminary experiments, we could also show that a range of simple disubstituted aliphatic alkenes were transformed into aminated products (**24**, **25**, and **26**), albeit in moderate yields (30–62%). Product **26** was obtained through a tandem aminohydroxylation–rearrangement of camphene. Overall, these results suggest that the reaction could support the use of more elaborate alcohol nucleophiles and tolerate a broad range of useful substrates.

Next, we applied our transformation in the rapid synthesis of aegoline-*O*-methylether (**27**, Scheme 6),[14] a natural product isolated from *Aegle marmelos* that exhibits antibacterial

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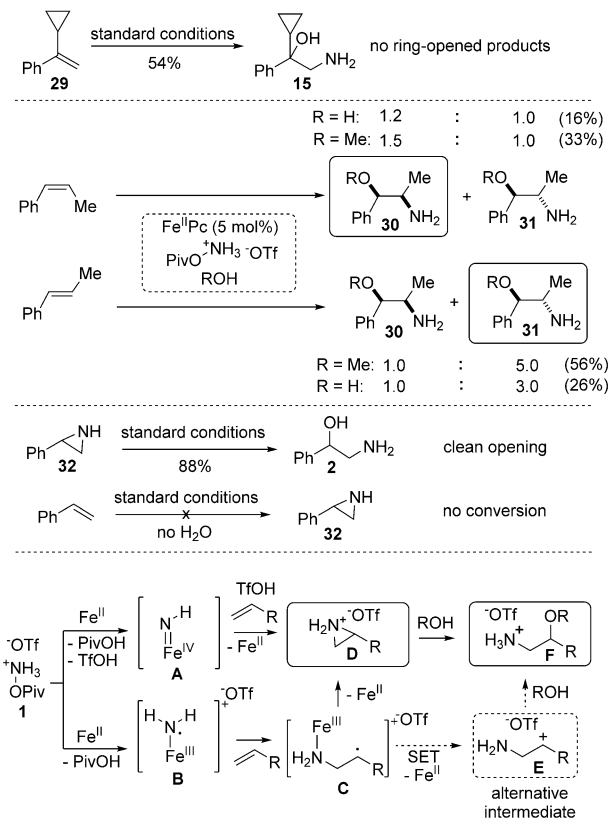
Scheme 5. Use of different alcohol nucleophiles. NMR yields of the corresponding $RNH_2{\cdot}HX$ salt in D_2O. Yields in parentheses are yields of isolated product after Boc derivatization. **25** was obtained from (2-methyl-propenyl)trimethylsilane and **26** from camphene. [a] Ratio of products.



Scheme 6. Synthesis of bioactive compounds.

activity. Submitting *p*-MeO styrene to our normal conditions for aminomethoxylation followed by acylation of the crude material provided the product in excellent yield (89%). A formal synthesis of phenylephrine (**28**) from isolated amino alcohol **4** is also depicted to illustrate the versatility of unprotected amino alcohols in the preparation of marketed drugs.[15]

Intrigued by several aspects of our new transformation, including the competency of several nucleophiles, the lower reactivity exhibited by electron-deficient substrates, and the steric effects, we performed preliminary mechanistic experiments (Scheme 7). Initially, a dramatic decrease in the yield (18%) of the reaction was observed in the presence of TEMPO as a potent radical inhibitor. Furthermore, no asymmetric induction was obtained when chiral, enantiopure ligands were used in the transformation.[16] Although these initial experiments were consistent with the involvement of free-radical intermediates, an experiment using a cyclopropyl alkene substrate known as a radical clock[17] suggests that any substrate-based radical intermediates must be short-lived because no ring-opened products were observed. Further insight into the reactive intermediates can be obtained by comparing the diastereoselectivity of the reaction when using two stereochemically pure alkene isomers.[18] Interestingly, when we performed the aminomethoxylation and hydroxylation of *cis*- and *trans*-β-Me styrene, we obtained drastically different ratios of isomers (**30** and **31**), with the major product arising from an overall *anti* addition onto the alkene in each case. The partial transfer of alkene stereochemical information provides additional support against the formation of a discrete, long-lived carbon-centered radical or carbocationic intermediate. Interestingly, the stepwise Fe(porphyrin)-catalyzed aziridination of β-methyl styrenes is known to provide similar selectivity.[19] Given these data, an alternative mechanism proceeding through the stereospecific ring-opening of a protonated aziridine intermediate could be envisioned, and an aziridine substrate was indeed opened under normal reactions conditions.[6a] The putative aziridine intermediate could not be observed by performing the amination of styrene under strictly anhydrous conditions and the substrate was recovered unreacted. ROH is thus likely a critical component in the initial C–N bond forming step and possibly acts as a proton shuttle. Overall, the results of the mechanistic experiments are consistent with the following mechanism: protonated aziridine **D**, formed through the poorly stereospecific, stepwise attack of an Fe intermediate (**A** or **B**) on the alkene, is rapidly opened by the nucleophilic ROH to release the product **F**. However, a pathway involving fast solvolysis of alternative intermediate **E** cannot be ruled out. The exact nature of the Fe species that mediates the C–N bond forming step remains unclear but could possibly involve an iron nitrene complex (**A**) or an iron aminyl complex (**B**).[20]



Scheme 7. Mechanistic studies.

In conclusion, we have described the first direct catalytic synthesis of unprotected amino alcohols from simple alkenes.

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The process works under mild conditions with an inexpensive and commercially available iron catalyst and can be extended to aminoetherification reactions. The products are all versatile intermediates for the synthesis of an essential class of bioactive compounds.

Acknowledgments

Generous funding from the Max-Planck-Society and the Max-Planck-Institut für Kohlenforschung is acknowledged. We kindly thank Prof. B. List for sharing analytical equipment, and our technical departments for assistance.

Keywords: alkenes · amino alcohols · bioactive compounds · homogeneous catalysis · iron

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2248–2251
Angew. Chem. **2016**, *128*, 2288–2292

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Received: August 17, 2015
Revised: October 19, 2015
Published online: January 14, 2016

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