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Highlights

Iron Catalysis

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Hydroaminations of Alkenes: A Radical, Revised, and Expanded Version

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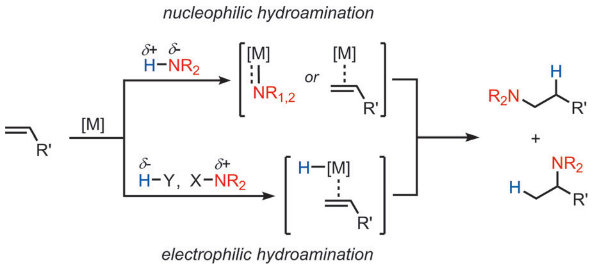
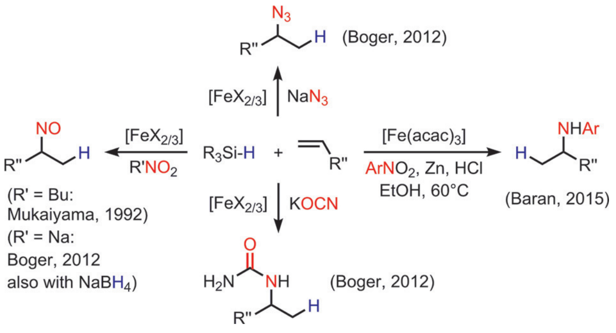
The preparation of nitrogen-containing molecules is of utmost importance to all fields of organic chemistry, and the prevalence of C–N motifs in natural products, drugs, fine chemicals, agrochemicals, and materials is a constant driver for innovation of synthetic methods.[1] Among the numerous concepts for forging a C–N bond, the hydroamination of olefins constitutes an especially attractive strategy, which relies upon olefins and amines as most basic, widely available, yet diverse families of starting materials.[2] Today, a vast arsenal of metal-catalyzed hydroamination methods are available (Scheme 1). Depending on the nature of the employed metal catalyst and substrates, the reaction mechanism can be based on one of two general activation modes: The formation of active amido or imido complexes is mostly observed with Lewis acidic catalysts (alkaline earth, rare earth, early transition metals).[2] Late transition metals and Group 11 and 12 metals mostly undergo coordinative π-activation of the alkene.[2] Contrary to this, electrophilic aminations have been reported with hydroxylamine derivatives.[3] These strategies require the employment of a hydride reagent (hydrosilane, alkyl magnesium halide). The low price and the low toxicity of iron have recently stimulated great interest in the development of iron-catalyzed hydroamination procedures based on either mechanistic scenario.[4] However, the substrate scope is still very limited (styrenes with weakly nucleophilic tosylamines,[4a] intramolecular reactions of *gem*-dialkyl-substituted aminoalkenes,[4b–d] low functional-group tolerance because of the Grignard reagent).[4e]



Scheme 1. Common modes of substrate activation in metal-catalyzed nucleophilic (top) and electrophilic (bottom) hydroaminations.[2–4]

A conceptually different radical addition with nitroarenes was very recently added to the manifold of net hydroamination processes.[5] Baran et al. reported the sequential combination of an Fe-catalyzed hydrogen atom transfer (HAT)[6] and an Fe-catalyzed reductive deoxygenation in a one-pot operation that allows the facile preparation of *tert*- and *sec*-alkyl aryl amines. Based on some literature precedents,[7,8] a highly practical procedure was developed, which uses various alkenes, aromatic nitro compounds as N electrophiles, phenylsilane as the HAT reagent, and iron(III) acetylacetonate as the pre-catalyst under thermal conditions (ethanol, 60 °C; Scheme 2). Isolated examples of Fe-catalyzed HAT to alkenes and subsequent reactions of the alkyl radicals with 1-butylnitrite to give nitrosoalkanes under similar conditions were reported by Mukaiyama and Kato in 1992.[7a] Boger and co-workers extended this formal hydroamination method to include other N-based radical traps (NaN_3, KOCN, $NaNO_2$).[7b] Cobalt-catalyzed oxidative hydroaminations were reported by Carreira et al. and Shigehisa and co-workers.[8]

The new Fe-catalyzed hydroamination is believed to proceed by dual substrate activation through initial HAT from an in situ prepared hydrido iron complex[9] to both the alkene and the nitroarene (Scheme 3). The resultant alkyl radical and the nitrosoarene combine to an aminyloxyl radical,[10] which engages in sequential re-oxidation of two equivalents of iron catalyst upon generation of a hydroxylamine intermediate, which ultimately leads to the amine product. It is especially noteworthy that the reduction of the



Scheme 2. Evolution of iron-mediated radical hydroaminations.[5,7] acac = acetylacetonate.

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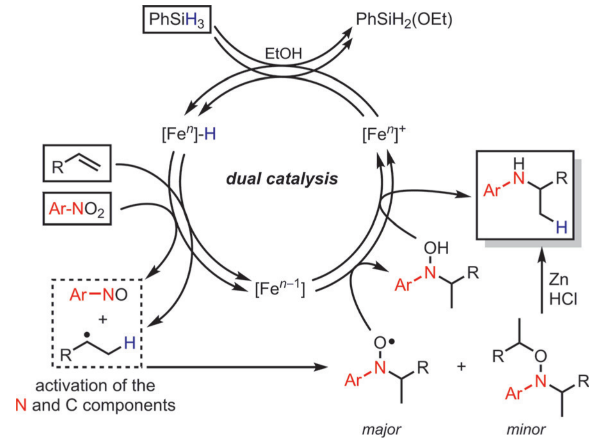


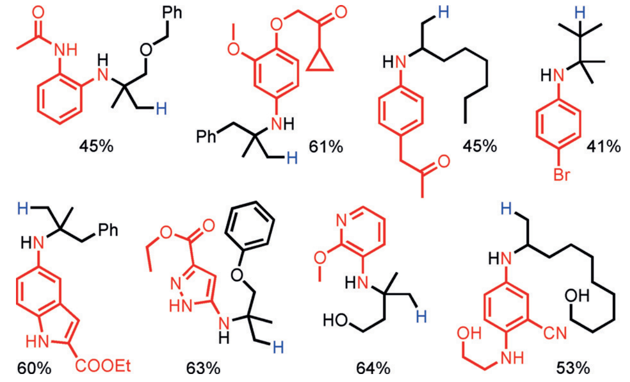
Scheme 3. Proposed mechanism involving dual catalytic activation.

N electrophile (nitroarene) is embedded within the overall catalytic cycle, which obviates the need for a separate reductive operation. The mechanistic design of Baran and co-workers elegantly draws on two closed catalytic one-electron redox cycles. These effect two H atom transfers to the alkene and the nitroarene, which are both formal one-electron reductions of Fe^{III} to Fe^{II}, and two sequential one-electron oxidations of Fe^{II} to Fe^{III} by the intermediate alkyl aminyloxyl species. This mechanistic layout in combination with the use of simple starting materials renders the method utmost industrial relevance. The double alkylation of the nitrosoarene to give the *N*,*O*-dialkyl hydroxylamine as a side product could be suppressed by addition of Zn/HCl to the reaction mixture. Some of the nitrosoarene undergoes further reduction to give the corresponding aniline, which is unreactive under these reaction conditions (Scheme 3, bottom right).

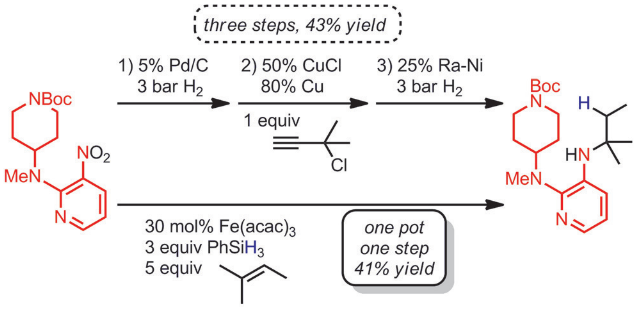
The reaction tolerates various functional groups, including thioethers, amides, ketones, amines, halides, triflates, alcohols, nitriles, heterocycles, and boronic acids. The covered chemical space is much wider and diverse than that achieved with common hydroamination reactions, and includes the synthesis of many highly substituted and functionalized amines for the first time. Sterically congested amines can easily be obtained from the tri- and tetrasubstituted olefins in a single catalytic operation (Scheme 4). However, the general procedure is limited to aromatic nitro compounds and cannot be applied to the synthesis of tertiary amines.

This strategy bears great potential to significantly shorten and streamline the synthesis of bioactive molecules, as exemplarily shown by vinblastine functionalizations[7b] and the preparation of an HIV-1 reverse transcriptase inhibitor, which had required three synthetic steps with noble-metal catalysts thus far (Scheme 5).[11]

A key challenge of common hydroamination endeavors is the strict control of regioselectivity. Significant efforts have been devoted to the development of anti-Markovnikov reactions owing to the immediate relevance of linear alkyl amines as biologically active building blocks. On the contrary, the radical nature of the underlying mechanism stipulates that the reaction developed by Baran et al. will proceed with Markovnikov selectivity. Technical applications will certainly benefit from the inexpensive, stable, easy-to-handle, and "ligand-free" pre-catalyst [Fe(acac)$_3$] in comparison with common rare-earth or transition-metal catalyst systems. However, the addition of 2–3 equiv phenylsilane (830 €/mol) as the H atom donor and excess amounts of Zn (20 equiv) as a reductant of the undesired double alkylation product diminish the overall efficiency. Altogether, this Fe-catalyzed reductive hydroamination of alkenes with nitroarenes is an important addition to the arsenal of available amine syntheses, which is based on a different mechanistic paradigm than the common hydroamination reactions of rare-earth, alkaline-earth, and transition-metal catalysts. Highly functionalized, sterically encumbered alkyl aryl amines could thus be prepared, and the method exhibits an orthogonal scope to Buchwald–Hartwig and reductive amination reactions. Its incipient exploitation in syntheses of important bioactive molecules by Baran and co-workers is surely only the beginning of an era to come during which such strategies will be gaining a strong foothold among modern amination methods.



Scheme 4. Selected substrate scope.



Scheme 5. Exemplary synthesis of an HIV-1 reverse transcriptase inhibitor by conventional noble-metal and new iron catalysis.

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[1] a) *Science of Synthesis*, *Vol. 40* (Eds.: D. Enders, E. Schaumann), Thieme, Stuttgart, **2009**; b) *Amino Group Chemistry* (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2008**; c) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.

[2] a) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795–3892; b) L. Huang, M. Arndt, K. Goossen, H. Heydt, L. J. Goossen, *Chem. Rev.* **2015**, *115*, 2596–2697; radical transfer hydroaminations based on the single-electron redox activation of either reagent were also achieved under metal-free conditions; see: c) E. Bernoud, C. Lepori, M. Mellah, E. Schulz, J. Hannedouche, *Catal. Sci. Technol.* **2015**, *5*, 2017–2037.

[3] X. Yan, X. Yang, C. Xi, *Catal. Sci. Technol.* **2014**, *4*, 4169–4177.

[4] a) J. Michaux, V. Terrasson, S. Marque, J. Wehbe, D. Prim, J.-M. Campagne, *Eur. J. Org. Chem.* **2007**, 2601–2603; b) K. Komeyama, T. Morimoto, K. Takaki, *Angew. Chem. Int. Ed.* **2006**, *45*, 2938–2941; *Angew. Chem.* **2006**, *118*, 3004–3007; c) M. S. Jung, W. S. Kim, Y. H. Shin, H. J. Jin, Y. S. Kim, E. J. Kang, *Org. Lett.* **2012**, *14*, 6262–6265; d) E. Bernoud, P. Oulie, R. Guillot, M. Mellah, J. Hannedouche, *Angew. Chem. Int. Ed.* **2014**, *53*, 4930–4934; *Angew. Chem.* **2014**, *126*, 5030–5034; e) B. Huehls, A. Lin, J. Yang, *Org. Lett.* **2014**, *16*, 3620–3623.

[5] J. Gui, C.-M. Pan, Y. Jin, T. Qin, J. C. Lo, B. J. Lee, S. H. Spergel, M. E. Mertzman, W. J. Pitts, T. E. La Cruz, M. A. Schmidt, N. Darvatkar, S. R. Natarajan, P. S. Baran, *Science* **2015**, *348*, 886–891.

[6] For related hydrofunctionalization reactions of alkenes initiated by HAT, see: a) M. D. Greenhalgh, A. S. Jones, S. P. Thomas, *ChemCatChem* **2015**, *7*, 190–222; b) J. C. Lo, J. Gui, Y. Yabe, C.-M. Pan, P. S. Baran, *Nature* **2014**, *516*, 343–348; c) J. C. Lo, Y. Yabe, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307.

[7] a) K. Kato, T. Mukaiyama, *Chem. Lett.* **1992**, 1137–1140; b) E. K. Leggans, T. J. Barker, K. K. Duncan, D. L. Boger, *Org. Lett.* **2012**, *14*, 1428–1431.

[8] a) J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712; b) H. Shigehisa, N. Koseki, N. Shimizu, M. Fujisawa, M. Niitsu, K. Hiroya, *J. Am. Chem. Soc.* **2014**, *136*, 13534–13537.

[9] H. Nakazawa, M. Itazaki, *Top. Organomet. Chem.* **2011**, *33*, 27–81.

[10] G. A. Russell, C. F. Yao, *Heteroat. Chem.* **1993**, *4*, 433–434.

[11] D. L. Romero, R. A. Olmsted, T. J. Poel, R. A. Morge, C. Biles, B. J. Keiser, L. A. Kopta, J. M. Friis, J. D. Hosley, K. J. Stefanski, D. G. Wishka, D. B. Evans, J. Morris, R. G. Stehle, S. K. Sharma, Y. Yagi, R. L. Voorman, W. J. Adams, W. G. Tarpley, R. C. Thomas, *J. Med. Chem.* **1996**, *39*, 3769–3789.

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