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Hydroamination

Amine-bis(phenolate) Iron(III)-Catalyzed Formal Hydroamination of Olefins

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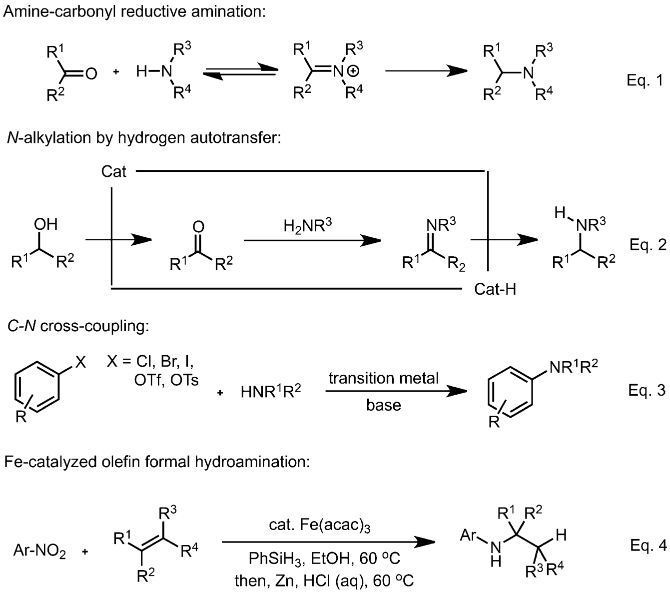
Abstract: A practical synthesis of highly functionalized amines by the formal hydroamination reaction of alkenes with nitroarenes catalyzed by an air stable amine-bis(phenolate) iron(III) complex is reported. The reaction uses an easily handled silane, low catalyst loadings, and mild reaction conditions. A wide range of substrates are transformed with synthetically useful yields (21 examples).

The efficient synthesis of functionalized amines is of great importance as these substrates are key components of natural products, pharmaceuticals, fine chemicals, materials, and agrochemicals.[1] Conventional methods for amine synthesis include amine-carbonyl reductive amination,[2] amine *N*-alkylation by hydrogen autotransfer,[3] and transition-metal-catalyzed C–N cross-coupling [Eq. (1)–(3), Scheme 1].[4] Given the limitations of these methods, including their low functional group tolerance, new methods with a wide substrate scope and mild reaction conditions are still required. Very recently, Baran and coworkers reported a practical formal hydroamination of alkenes with nitroarenes catalyzed by $Fe(acac)_3$ using phenylsilane as the stoichiometric reducing agent [Eq. (4), Scheme 1].[5] Based on experimental observations and previous mechanistic studies on related systems,[6] a radical reaction pathway was proposed: an in situ generated hydrido–iron complex transfers a hydrogen atom to the alkene to give an alkyl radical, which undergoes *N*-alkylation of a nitrosoarene, generated in situ by hydrido–iron-mediated nitroarene reduction. The reaction showed good functional group tolerance including substrates bearing an amide, ketone, halide, and alcohol functionalities, showcasing this as a potent tool for the construction of highly functionalized amines. Excellent regioselectivity for amination at the most substituted carbon center was observed for this radical reaction, in contrast to transition-metal-catalyzed hydroamination reactions, in which strict control of regioselectivity remains challenging. However, the high catalyst loading (30 mol %) and reaction temperature (60 °C) diminish the overall reaction efficiency. Our success with amine-bis(phenolate) iron(III) catalyzed hydrosilylation[7] and mediation of radical reactions such as atom transfer radical polymerization[8] suggested these could be ideal catalysts for this formal hydroamination process. In addition, the synthesis of amine-bis(phenolate) iron(III) complexes is straightforward and they are highly stable towards air and moisture.[9]



Scheme 1. Methods for the construction of heavily functionalized amines.

In our most recent work, we demonstrated that amine-bis(phenolate) iron(III) complexes showed excellent catalytic activity for the chemoselective reduction of nitroarenes to the corresponding anilines using triethoxysilane as the reducing agent.[10] Excellent functional group tolerance (22 examples) and high isolated yields of amine (up to 98 %) were obtained under mild conditions (Scheme 2). Here we extend the application of this catalyst system to the formal hydroamination of alkenes with nitroarenes.

The reaction of 4-nitrothioanisole **1** and 2-methyl-2-butene **A** using phenylsilane as the reducing agent was chosen as the model reaction to establish optimal reaction conditions (Table 1). When the reaction was carried out in EtOH at 60 °C with two equivalents of $PhSiH_3$ and three equivalents of alkene, the nitroarene was completely consumed in 1 h, and a mixture of *N*,*O*-dialkylated adduct **2**, aniline **5a** and a small

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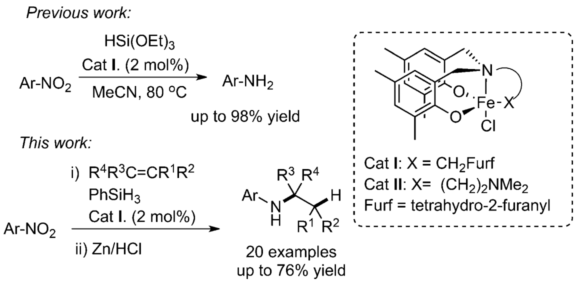
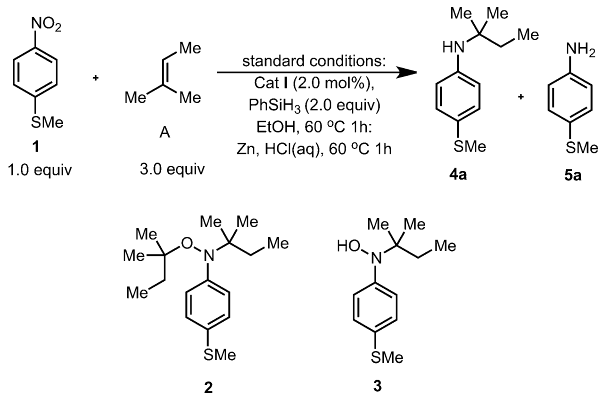


Scheme 2. Amine-bis(phenolate) iron(III) complexes as efficient catalysts for: a) nitroarene reduction and b) olefin formal hydroamination.

Table 1. Optimization of Hydroamination Conditions.[a]



Entry	Variation from standard condition	**4a** [%][b]	**5a** [%][b]
1	none	40	30
2	r.t. instead of 60 °C	45	25
3	r.t. 1.0 equiv of $PhSiH_3$	51	22
4	Toluene instead of EtOH	low conversion	
5	MeCN instead of EtOH	low conversion	
6	Cat **II**, rt, 1.0 equiv of $PhSiH_3$	35	40
7	$Fe(acac)_3$, rt, 1.0 equiv of $PhSiH_3$	15	65
8	PMHS (6.0 equiv), 2 h	20	30

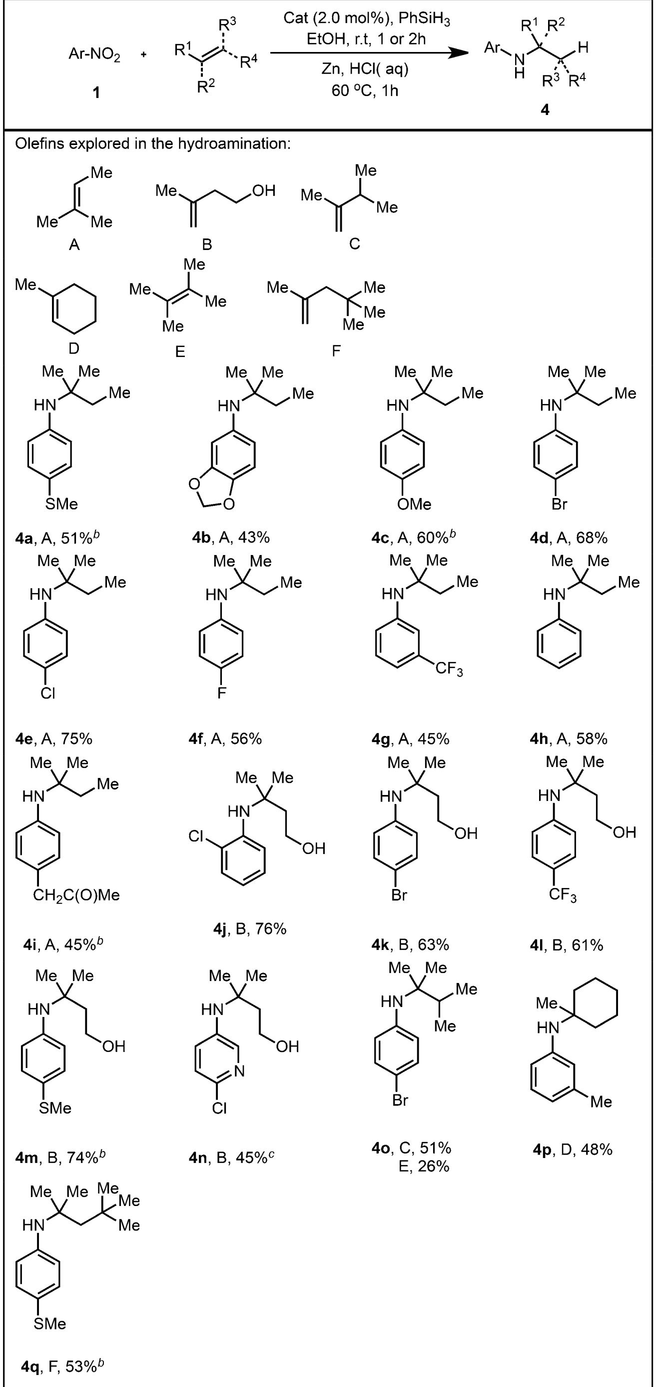
[a] All reactions were carried out using 0.3 mmol of 4-nitrothioanisole. [b] Yield of isolated product. rt = room temperature.

amount of the hydroamination product **4a** was produced. Zinc and aqueous hydrochloric acid were subsequently added, converting intermediate **2** into the hydroamination product **4a** in 40% isolated yield after the Zn/HCl work up (Table 1, entry 1). As expected, aniline **5a** was also isolated in 30% yield from the direct reduction reaction of the nitroarene (Table 1, entry 1). The reaction temperature was then lowered to room temperature in a bid to reduce the amount of direct nitroarene reduction, a reaction that generally requires elevated temperatures. Indeed, a slightly higher yield of the hydroamination product **4a** was obtained at room temperature and the relative amount of aniline **5a** was reduced (Table 1, entry 2). Interestingly, under these reaction conditions hydroxylamine **3** was observed as the major intermediate, presumably as a product of the addition of alkyl radical to the nitrosoarene, but without any *O*-alkylation. Reducing the amount of silane from two equivalents to one equivalent gave an even higher yield of the hydroamination product **4a** (Table 1, entry 3). Other solvents such as toluene and acetonitrile gave low conversions (Table 1, entries 4 and 5). Replacing the furanyl donor with an amine moiety, Cat **II**, gave 35% of the hydroamination product **4a** along with 40% of aniline **5a** using one equivalent of silane at room temperature (Table 1, entry 6). Under the same reaction conditions, $Fe(acac)_3$ produced just 15% of the hydroamination product (Table 1, entry 7), thus showing the benefit imparted by the amine-bis(phenolate) ligand. The nature of the silane was important as polymethylhydrosiloxane (PMHS) was less reactive, giving the hydroamination product **4a** in only 20% yield along with 30% of aniline **5a** (Table 1, entry 8). These optimized conditions give similar or improved isolated yields to those previously reported using 30 mol% $Fe(acac)_3$ while offering an improvement in catalyst loading and reaction temperature.

With optimized reaction conditions developed, the substrate scope of this iron-catalyzed olefin formal hydroamination was investigated. Seven different olefins were tested with an array of nitroarenes bearing different arene substituents. Using trisubstituted alkene **A**, a range of nitroarenes were explored as reaction partners. Nitroarenes bearing electron-donating groups (**4a–4c**), halide substituents (**4d–4f**), and electron-withdrawing groups (**4g**) were all tolerated under the developed reaction conditions to give the corresponding amines in synthetically useful isolated yields (Table 2). In all cases, the reaction was chemoselective for hydroamination without any deleterious side-reactions, such as protodehalogenation[11] or reductive amination, observed. Nitrobenzene was also a suitable substrate, giving the hydroamination product **4h** in 58% isolated yield. It was noteworthy that a nitroarene bearing a carbonyl group was also tolerated without any reduction at the ketone (**4i**), suggesting good chemoselectivity for the catalyst. Olefin **B**, bearing a free alcohol was also investigated, successfully reacting with nitroarenes bearing a halide (**4j**, **4k**), electron-withdrawing (**4l**), and electron-donating substituents (**4m**). In these cases, significantly higher isolated yields were obtained than those using olefin **A**. By using 2-chloro-5-nitropyridine, a moderate yield of formal hydroamination was obtained with alkene **B** (**4n**). Amine **4o** can be prepared using either alkene **C** or **E**. When terminal alkene **C** was used, the hydroamination product **4n** was isolated in 51% yield. However, when the sterically hindered alkene **E** was used, the same product **4o** was isolated in just 26% yield. Cyclic olefin **D** gave the corresponding product in 48% yield (**4p**). When olefin **F** was used, the highly hindered amine **4q** was prepared in 53% yield, a product challenging to make using other methods. It should be noted that in all cases, the reaction takes place on the more hindered site of the olefin, thus supporting the previously hypothesized radical pathway.

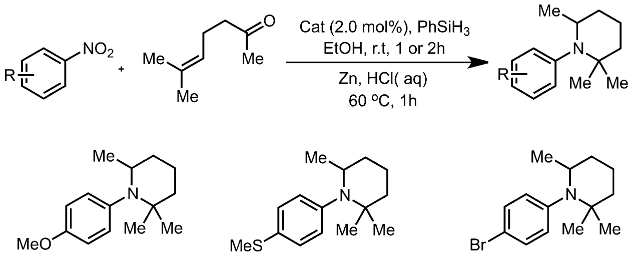
Using olefin **G**, which bears a distal carbonyl functionality, *N*-arylpiperidines were formed by a formal hydroamination/reductive amination cascade process (**6a–6c**). In these cases, nitroarenes with an electron-donating group gave the *N*-arylpiperidine products **6a** and **6b** in 45% and 51% yield, respectively, while a nitroarene with an electron-withdrawing substituent gave a reduced amount of hydroamination product **6c** (Scheme 3).

Table 2. Substrate Scope.[a]



4a, A, 51%[b]
4b, A, 43%
4c, A, 60%[b]
4d, A, 68%
4e, A, 75%
4f, A, 56%
4g, A, 45%
4h, A, 58%
4i, A, 45%[b]
4j, B, 76%
4k, B, 63%
4l, B, 61%
4m, B, 74%[b]
4n, B, 45%[c]
4o, C, 51%
E, 26%
4p, D, 48%
4q, F, 53%[b]

[a] Unless otherwise noted, all reactions were carried out using three equivalents of olefin (0.9 mmol), two equivalents of $PhSiH_3$ (0.6 mmol), one equivalent of nitroarene (0.3 mmol), 0.02 equiv of catalyst (0.006 mmol) in EtOH (1.5 mL) at room temperature for 2 h. Zn (20.0 equiv) and HCl (2N, 3.0 mL) were then added and the mixture stirred for another 1 h at 60 °C. Yields are those of the isolated product. [b] 1.0 equiv of $PhSiH_3$, 1 h. [c] 60 °C, 1 h.



6a, G, 45%[b]
6b, G, 51%[b]
6c, G, 30%

Scheme 3. Synthesis of *N*-arylpiperidine with nitroarene and olefin G.[a]
[a] Unless otherwise noted, all reactions were carried out using three equivalents of olefin (0.9 mmol), two equivalents of $PhSiH_3$ (0.6 mmol), one equivalent of nitroarene (0.3 mmol), 0.02 equivalents of catalyst (0.006 mmol) in 1.5 mL EtOH at room temperature for 2 h. Zn (20.0 equiv) and HCl (2N, 3.0 mL) were then added and the mixture was stirred for another 1 h at 60 °C. Yields are those of the isolated product. [b] One equivalent of $PhSiH_3$, 1 h.

In conclusion, we have reported that an amine-bis(phenolate) iron(III) complex can be used as an efficient catalyst for olefin formal hydroamination with nitroarenes using phenylsilane as the reducing agent. The reaction requires just 2.0 mol% catalyst, as low as one equivalent of silane, and operates at room temperature. A wide range of substrates were tolerated with synthetically useful yields (21 examples, up to 76% yield). We continue to explore catalyst design in this formal hydroamination reaction and the application of these exceptional catalysts in other such radical reactions.

Experimental Section

General Hydroamination Procedure: Alkene (0.9 mmol, 3.0 equiv) and $PhSiH_3$ (1.0 or 2.0 equiv) were added to a solution of the nitro compound (0.3 mmol, 1.0 equiv) and catalyst (2.8 mg, 0.006 mmol, 2.0 mol%) in EtOH (1.5 mL). The resulting mixture was stirred at room temperature until full consumption of the staring nitro compound was observed as indicated by TLC. Zinc (390 mg, 6.0 mmol, 20 equiv) and aqueous HCl (2N, 3.0 mL) were added to the reaction mixture. After stirring at 60 °C for another 1 h, the reaction mixture was cooled to room temperature and filtered through Celite and the filter cake washed with EtOAc. The filtrate was collected and saturated aqueous $NaHCO_3$ solution added until strongly basic and then extracted with EtOAc three times. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product purified by flash column chromatography using petroleum spirit/ethyl acetate.

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Keywords: amine-bis(phenolate) · hydroamination · iron · radicals · silanes

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