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Iron-Catalyzed Intermolecular Hydroamination of Styrenes

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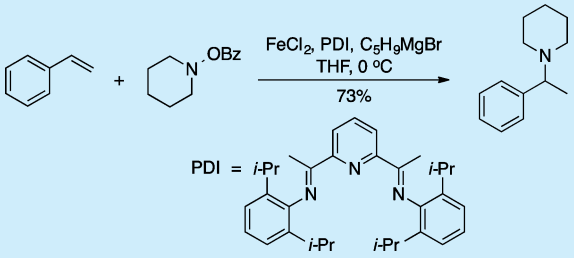
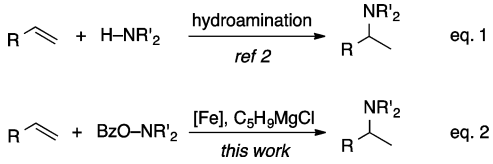
Supporting Information

ABSTRACT: An iron-catalyzed formal hydroamination of alkenes has been developed. It features *O*-benzoyl-*N*,*N*-dialkylhydroxylamines as the electrophilic nitrogen source and cyclopentylmagnesium bromide as the reducing agent for intermolecular hydroamination of styrene and derivatives with good yield and excellent Markovnikov regioselectivity. The reaction presumably proceeds through the iron-catalyzed hydrometalation of styrene followed by electrophilic amination with the electrophilic *O*-benzoylhydroxylamine.



Amines are an important class of organic compounds because of their ubiquity in bulk chemicals, materials, and bioactive compounds.[1] Among the numerous methods for synthesis of amines, addition of H-NR_2 across unactivated double bonds, i.e., the so-called hydroamination of alkenes (Scheme 1, eq 1), represents a particularly effective approach as it allows efficient preparation of alkylamines from readily available substrates. A number of catalytic systems have been developed over the decades for this transformation.[2] However, despite all the advances, significant challenges remain as many of these catalytic systems are hampered by the limited substrate scope, the reliance on precious and/or toxic transition metals, or elevated reaction temperatures. Thus, new approaches for the hydroamination of alkenes, particularly those through alternative reaction pathways, are attractive because of their potential of complementary reactivities, selectivities, and efficiencies compared with the existing methods.

Scheme 1. Hydroamination of Alkenes



Electrophilic amination reagents such as *N*-chloroamines and hydroxylamine *O*-esters have emerged as versatile tools for synthesis of substituted amines using nucleophilic substrates.[3] Recently, we became interested in iron-catalyzed transformations in general and low-valent iron-catalyzed functionalization of unactivated alkenes in particular because of the unique reactivity of iron compared with other transition metals[4] and the high abundance and low toxicity of many iron salts.[5] We envisioned that the umpolung reactivity of these electrophilic amination reagents might be exploited in low-valent iron-catalyzed hydrometalation of double bonds for electrophilic amination of unactivated alkenes.[6] Unknown at the outset of our research was whether these electrophilic amination reagents would be compatible with the low-valent iron species presumably formed during the functionalization of unactivated alkenes. We were also not aware of precedents of iron-catalyzed hydroamination reactions using electrophilic amination reagents.[7,8] Herein we report the results of our study, which led to an approach for iron-catalyzed formal hydroamination of unactivated alkenes using the electrophilic *O*-benzoyl-*N*-hydroxylamines as the nitrogen source and cyclopentylmagnesium bromide as the reducing agent (Scheme 1, eq 2).

Our research commenced with screening iron−ligand systems for the formal electrophilic hydroamination of styrene (**1a**) using *O*-benzoyl-*N*-hydroxypiperidine (**2a**) (Table 1). The initial results were disappointing as only a small amount of the desired product (**3a**) was formed when a solution of **1a** and **2a** in THF was treated with $FeCl_2$, the iminopyridine ligand **L1** or **L2**, and cyclopentylmagnesium bromide (not shown). Speculating that the reducing reaction conditions might be detrimental to **2a**, we hypothesized that the yield of the reaction might be improved by the slow addition of **2a**. Indeed, under otherwise identical reaction conditions, **3a** was obtained in 34% and 55% yields with the iminopyridine ligand **L1** and **L2**, respectively, when *O*-benzoyl-*N*-hydroxylpiperidine was slowly added via a syringe pump (Table 1, entries 1 and 2). The regioselectivity of the reaction was excellent as none of the isomeric anti-Markovnikov hydroamination product was observed. A number of common bidentate and tridentate ligands were screened under similar conditions (**L3**−**L8**, entries 3−10) with the bis(imino)pyridine (PDI) **L8** being found to be superior to the others giving **3a** in 71% yield. The hydroamination reaction could be reproduced when $FeCl_2$ of high purity (99.99%) was used (entry 9).[9] The desired product **3a** could also be formed, but with minimal enantiomeric excess when the chiral tridentate ligands **L9** and **L10** were employed (entries 10 and 11).[10] Other Grignard reagents were also tested in the reaction, and each of them gave **3a** as the product, but with varying efficiency. The lowest yield

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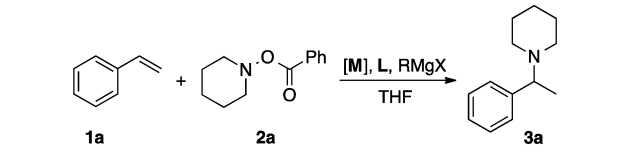
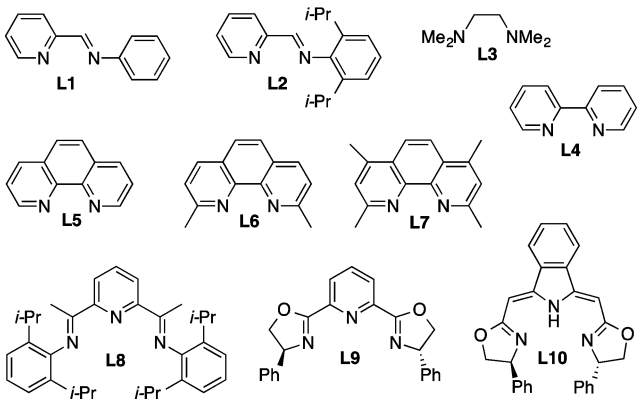
Table 1. Screening of Reaction Conditions[a]





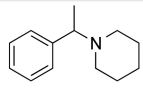
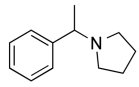
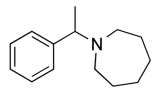
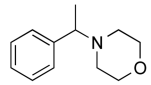
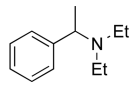
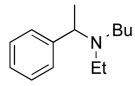
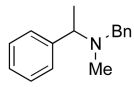
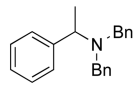
entry	[M]	L	RMgX	yield of **3a**[b] (%)
1	$FeCl_2$	**L1**	C_5H_9MgBr	34
2	$FeCl_2$	**L2**	C_5H_9MgBr	55
3	$FeCl_2$	**L3**	C_5H_9MgBr	60
4	$FeCl_2$	**L4**	C_5H_9MgBr	49
5	$FeCl_2$	**L5**	C_5H_9MgBr	48
6	$FeCl_2$	**L6**	C_5H_9MgBr	55
7	$FeCl_2$	**L7**	C_5H_9MgBr	<55
8	$FeCl_2$	**L8**	C_5H_9MgBr	71
9[c]	$FeCl_2$	**L8**	C_5H_9MgBr	73
10	$FeCl_2$	**L9**	C_5H_9MgBr	27
11	$FeCl_2$	**L10**	C_5H_9MgBr	47
12	$FeCl_2$	**L8**	EtMgBr	51
13	$FeCl_2$	**L8**	*i*-PrMgBr	64
14	$FeCl_2$	**L8**	*t*-BuMgBr	11
15	$FeCl_3$	**L8**	C_5H_9MgBr	40
16	$Fe(OAc)_2$	**L8**	C_5H_9MgBr	26
17	$Fe(acac)_3$	**L8**	C_5H_9MgBr	42
18	$CoCl_2$	**L5**	C_5H_9MgBr	25
19	$NiCl_2$	**L5**	C_5H_9MgBr	53

[a]Unless noted otherwise, the reactions were carried out with 10 mol % of [M], 10 mol % of **L**, 2.0 equiv of styrene, 4 equiv of RMgBr, and 1.0 equiv of *O*-benzoyl-*N*-hydroxylpiperidine in THF at 0 °C. [b]Isolated yield. [c]$FeCl_2$ of 99.99% purity was used.

(11%, entry 14) was observed with *tert*-butylmagnesium chloride. It was followed by ethylmagnesium bromide (51%, entry 12) and isopropylmagnesium bromide (64%, entry 13). Thus, cylopentylmagnesium bromide remained the reagent of choice. The desired product was also formed when other ferrous and ferric salts were used even though none of them were as effective (entries 15−17). Interestingly, $NiCl_2$ was found to give **3a** in a yield comparable to that of $FeCl_2$ (entry 19), but $CoCl_2$ was significantly less effective for the reaction (entry 18).

We explored the scope of the reaction using *O*-benzoyl-*N,N*-dialkylhydroxylamines prepared from various secondary amines for the hydroamination of styrene under the optimized conditions (Table 2). The reaction appeared to be general and gave the products in good to moderate yields and excellent Markovnikov selectivity (Table 2). For example, the reaction of styrene with *O*-benzoyl-*N*-hydroxylpyrrolidine gave **3b** in 70%

Table 2. Scope of *O*-Benzoyl-*N,N*-dialkylhydroxylamines[a]

entry	product		yield (%)[b]
1	**3a**		73
2	**3b**		70
3	**3c**		61
4	**3d**		52
5	**3e**		80
6	**3f**		65
7	**3g**		58
8	**3h**		trace

[a]The reactions were carried out using 1.4 mmol of the styrene, 0.07 mmol of $FeCl_2$, 0.07 mmol of **L8**, 2.8 mmol of cyclopentylmagnesium bromide, and 0.7 mmol of the *O*-benzoyl-*N*-hydroxylamines in 3 mL of THF at 0 °C. [b]Isolated yield.

yield, while the corresponding *O*-benzoyl-*N*-hydroxylamines of azepane and morpholine gave **3c** and **3d** in 61% and 52% yield, respectively. The *O*-benzoyl-*N,N*-dialkylhydroxylamines prepared from acyclic secondary amines proved to be equally effective in the reaction. Thus, good yields were obtained upon reaction of styrene with the *O*-benzoyl-*N,N*-dialkylhydroxylamines prepared from diethylamine, *N*-ethylbutylamine, and *N*-benzylmethylamine to give the products in good yields (i.e., **3e** in 80% yield, **3f** in 65% yield, and **3g** in 58% yield). To our surprise, only a trace amount of **3h** was formed when *O*-benzoyl-*N,N*-dibenzylhydroxylamine was used, likely due to rapid decomposition of the electrophilic amination reagent under the reducing reaction conditions.

Further examination of the reaction showed that it is compatible with substituted styrenes as well (Table 3). For example, *o*-, *m*-, and *p*-methylstyrene all participated in the hydroamination reactions. The yield of the reaction with the *ortho*-substituted substrate (**3k** in 49% yield) was lower than those of the other two isomers (**3i** in 66% yield and **3j** in 62% yield), possibly due to steric reasons. *Para*-substitution of styrene with the *tert*-butyl group gave the hydroamination product **3l** in 75% yield. Styrenes substituted with the electron-donating methoxy group are also compatible with the reaction and showed a trend similar to that of the methyl-substituted styrenes. The hydroamination of *m*- and *p*-methoxy-substituted styrenes gave **3m** and **3n** in 55% and 55% yield, respectively. On the other hand, a significantly reduced yield was observed when the methoxy group was at the *ortho*-position (**3o** in 24% yield), possibility because of the ability of the methoxy group to interfere through coordination with the metal center of the intermediates.

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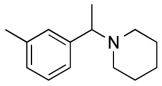
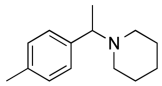
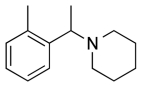
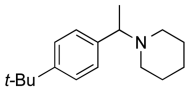
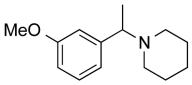
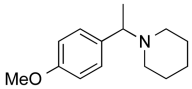
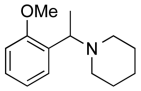
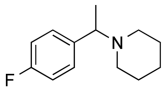
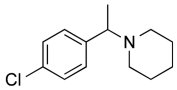
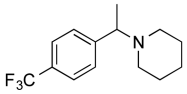
Table 3. Scope of the Styrene Derivatives[a]

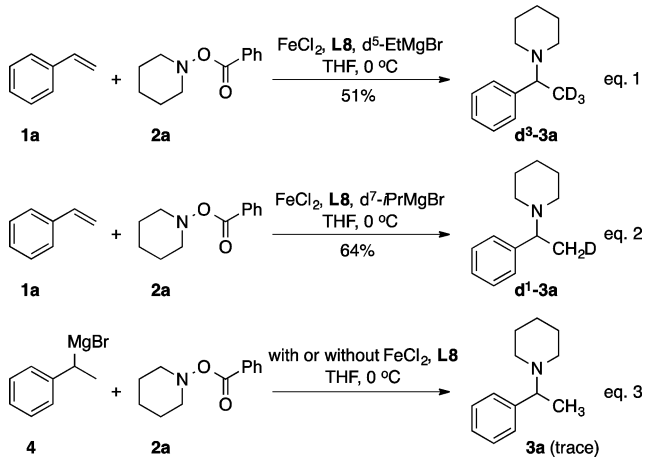
entry	product		yield (%)[b]
1	**3i**		66
2	**3j**		62
3	**3k**		49
4	**3l**		75
5	**3m**		55
6	**3n**		55
7	**3o**		24
8	**3p**		46
9	**3q**		n.d.[c]
10	**3r**		n.d.

[a]The reactions were carried out using 1.4 mmol of the styrene, 0.07 mmol of $FeCl_2$, 0.07 mmol of **L8**, 2.8 mmol of cyclopentylmagnesium bromide, and 0.7 mmol of the *O*-benzoyl-*N*-hydroxylamines in 3 mL of THF at 0 °C. [b]Isolated yield. [c]Only **3a** was isolated, likely due to reductive dechlorination. The yield was not determined.

The reaction proved to be compatible with the electron-withdrawing fluorine substituent as **3p** was obtained in moderate yield (46%) when 4-fluorostyrene was used. 4-Chlorostyrene also underwent the hydroamination reaction, but with **3a** as the only isolated product due to dechlorination under the reducing reaction conditions.[11] Attempts for the hydroamination of 4-trifluoromethylstyrene to form **3r** gave an untraceable reaction mixture. The hydroamination of α- and β-methylstyrene afforded the products in low yield only (<5%). No hydroamination product was formed when aliphatic terminal alkenes were used (not shown).

To better understand the mechanism of the reaction, the hydroamination of styrene with **2a** was also carried out using excess d^5-ethylmagnesium bromide. Such a combination of reagents led to formation of d^3-**3a** (Scheme 2, eq 1), which was consistent with the report by Greenhalgh and Thomas that the iron-catalyzed hydrometalation of styrene using ethylmagnesium bromide is rapid and reversible.[6] However, only one deuterium was incorporated (i.e., d^1-**3a**) when d^7-isopropylmagnesium bromide was used as the hydride source (eq 2), suggesting that the hydrometalation of styrene with isopropylmagnesium

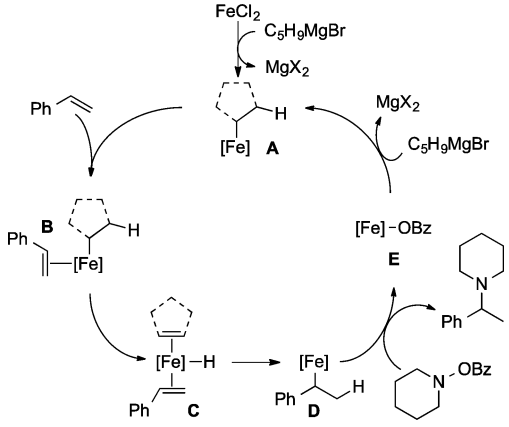
Scheme 2. Some Mechanistic Studies



bromide (and likely cyclopentylmagnesium bromide as well) is irreversible under the reaction conditions. Interestingly, only a trace amount of **3a** was formed upon reaction of the independently prepared Grignard reagent **4** and **2a** with and without $FeCl_2$-**L8** (eq 3), suggesting that the Grignard reagent itself is not the reactive intermediate of the reaction.

On the basis of these experimental findings, a proposed mechanism of the reaction is shown in Scheme 3. Alkylation of

Scheme 3. Proposed Reaction Mechanism



$FeCl_2$ with the Grignard reagent forms organoferrate **A**. Coordination of this intermediate with styrene followed by β-hydride elimination of the Grignard alkyl group gives iron hydride complex **C**, which undergoes hydrometalation with styrene to form **D**.[12] The tertiary amine product is formed upon reaction of **D** with *O*-benzoyl-*N*-hydroxyamine leaving the iron benzoate **E**.[13] Further reaction of **E** with the Grignard reagent regenerates **A** and completes the catalytic cycle.

In summary, we report an operationally simple iron-catalyzed umpolung hydroamination reaction. This transformation employs the electrophilic *O*-benzoyl-*N*-hydroxylamine as the source of nitrogen and cyclopentylmagnesium bromide as the reducing agent for the hydroamination of styrenes to give tertiary amines in good yield and excellent Markovnikov regioselectivity. To the best of our knowledge, this transformation represents the first example of iron-catalyzed hydroamination of alkenes using electrophilic nitrogen sources.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Another mechanistic scenario would be that the low-valent iron-mediated N-O bond cleavage *precedes* the iron-mediated hydrometalation of styrene. However, since the yield of the reaction was improved by the slow addition of *O*-benzoyl-*N*-hydroxylamine, the possibility of such a reaction pathway appears to be low even though the nonproductive reduction of *O*-benzoyl-*N*-hydroxylpiperidine to give piperidine appears to be partially responsible for the low yield of the reaction when the *O*-benzoyl-*N*-hydroxylamine was added in one portion at the beginning of the reaction.

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