

**Conversion of Aldimines to Secondary Amines Using Iron-Catalysed Hydrosilylation**

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Conversion of Aldimines to Secondary Amines Using Iron-Catalysed Hydrosilylation

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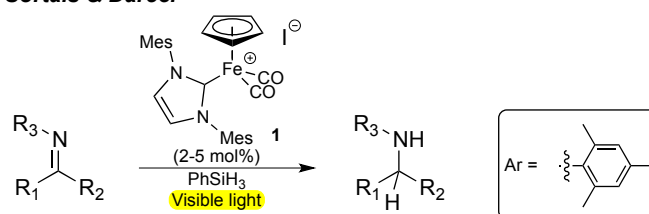
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Iron-Catalyzed hydrosilylation of imines to amines using a well-defined iron complex is reported. This method employs relatively mild conditions, by reaction of imine, (EtO)₃SiH in a 1:2 ratio in the presence of 1 mol % precatalyst ([BIAN]Fe(η⁶-Toluene), **3, BIAN = bis(2,6-diisopropylaniline)acenaphthene)) at 70 °C. A broad scope of imines was readily converted into the corresponding secondary amines without the need for precatalyst activators.**

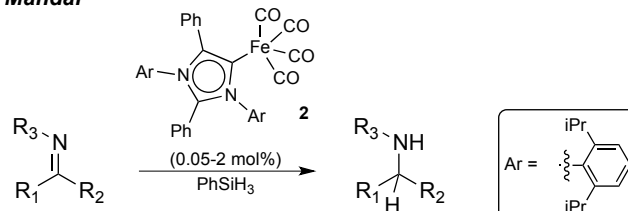
The amine functional group represents an important component of a variety of biologically relevant compounds: amino acids, vitamins, and commonly used analgesics such as morphine and demerol.¹ The reductive amination of carbonyl derivatives employing primary amines remains one of the most commonly utilized methods to synthesize amines; this is now a well-established and practical approach.² The direct reduction of amides is another common route found in amine synthesis, generally using metal catalyzed processes, but its use is still limited owing to the lower electrophilicity of the carbonyl group in amides.^{3a-c} The generic metal catalyzed reduction of imines (encompassing hydrogenation,⁴ hydrogen transfer⁵ and hydrosilylation⁶) is a direct and efficient method for accessing amines. Among these catalytic methods, hydrosilylation has emerged as a convenient route as it employs readily available silanes as the source of hydrogen, which are easy to handle, activated under mild conditions, and provide excellent chemoselectivity in functional group-rich molecular settings. Many groups have now used this strategy, yet the most efficient catalysts developed to date are usually based on precious metal elements such as ruthenium, iridium and rhodium.⁷ The high cost and toxicity of precious metals imposes limits on their potential industrial use, i.e., in the synthesis of amine based compounds with pharmacological relevance. These limitations provide just some of the driving

force behind the development of non-toxic and abundant replacements; iron has emerged as a leading candidate in the context of first-row metal catalysis.⁸

Sortais & Darcel¹⁰



Mandal¹¹



This Work

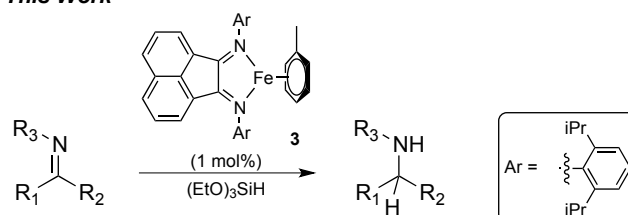


Figure 1. Recent examples of iron-based complexes capable of the catalytic hydrosilylation of imines.

The iron-catalysed hydrosilylation of alkenes, aldehydes, and ketones has been studied extensively; surprisingly, only a handful of reports exist detailing the iron-catalyzed hydrosilylation of imines.⁹ Thus, in 2012, Darcel and coworkers¹⁰ reported the first general and efficient catalytic system for the hydrosilylation of imines using a well-defined iron complex (Figure 1). Recently Mandal and coauthors have employed a closely related iron catalyst (Figure 1).¹¹ A low

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catalyst loading of 0.05 mol % afforded turnovers of 17000, demonstrating remarkable efficiency when compared to previous catalyst systems in imine hydrosilylation.

Common to both structures is the presence of a carbene ancillary ligand, and although such moieties have been extensively used in designing base-metal catalysts, recent interest has shifted more toward the use of redox active ligands in iron catalysis; such iron complexes have been shown to mimic some of the catalytic properties of noble metals.¹² Among the most prominent classes of redox-active ligands are the diimines. Specifically, the late transition metal complexes of the bis(arylimino)acenaphthene (BIAN) have been extensively studied by many research groups.¹³ Moreover, BIAN ligands are known to undergo multiple, successive electron-accepting redox events, making them an attractive ligand to deploy in redox non-innocent applications in catalysis.¹⁴ Surprisingly, iron-based BIAN complexes are relatively scarce. Most reports on BIAN-Fe complexes comprise an 'extra' donor arm in addition to the two nitrogen atoms of the diimine.¹⁵

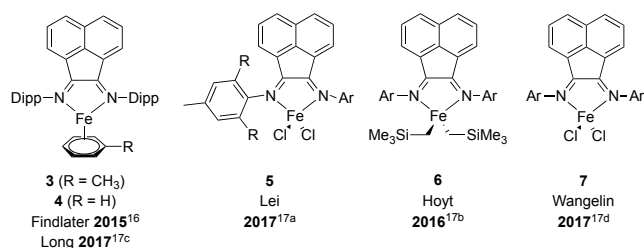
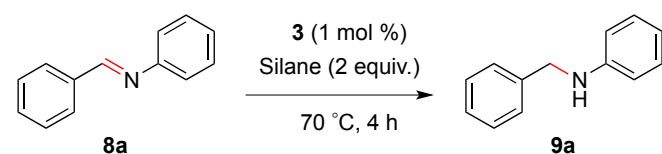


Figure 2. Examples of BIAN-based iron complexes capable of catalytic hydrosilylation and ring-opening polymerization chemistry.

This virtual absence from the literature of BIAN-Fe complexes motivated us to study their preparation and potential applications in catalysis.¹⁶ In our initial report we disclosed the synthesis, molecular structure and catalytic application of complex **3** in the hydrosilylation of aldehydes and ketones.¹⁶ Notable progress has been made in this area since then, as several studies have been reported investigating similar catalytic systems in the last two years (Figure 2). Recently, Lei and co-workers^{17a} demonstrated sterically hindered BIAN-FeCl₂ (**5**) complexes as precatalysts for hydrosilylation of carbonyl compounds and olefins. Further, Hoyt and coworkers^{17b} have investigated closely related analogues (**6**) using Mossbauer spectroscopy, solution state magnetic measurements and DFT quantum-chemical calculations. These studies were also applied to complex **3** and strongly suggest a 1-electron transfer has occurred from metal to the BIAN ligand; an oxidation state of +1 would thus seem to be a more appropriate description of the electronic state of the iron center in **3**. In collaboration with our group, Long and co-authors^{17c} successfully employed **4** as precatalyst in the ring opening polymerization of L-lactide. Finally, Wangelin and co-workers^{17d} reported the synthesis and electrochemical properties of several (R-BIAN)FeCl₂ (**7**) complexes using cyclic voltammetry. Building upon our previous work and in an effort to enhance the knowledge of well-defined Fe complexes of the BIAN ligands, herein we

describe the hydrosilylation of imines using iron complex **3** as the pre-catalyst.

Table 1. Optimization of reaction conditions using model substrate N-benzylideneaniline (**8a**)^a



Entry	Silane	Yield (%) ^b
1	PhSiH ₃	100
2	Ph ₂ SiH ₂	100
3	Et ₃ SiH	0
4	(iPr) ₃ SiH	0
5	(EtO) ₂ MeSiH	0
6	(EtO) ₃ SiH	100
7 ^c	(EtO) ₃ SiH	100
8 ^d	(EtO) ₃ SiH	0

a. Reaction conditions: **8a** (0.5 mmol), **3** (3 mg, 1 mol %), silane (1 mmol), methylene chloride (1 mL), 70°C. b. As determined by GC-MS analysis. c. Neat conditions, no solvent. d. No added **3**.

We examined the catalytic hydrosilylation of imines using N-benzylideneaniline (**8a**) as our model substrate using 1 mol % of precatalyst **3**. Precatalyst **3** is readily prepared following the literature procedure.¹⁶ A range of silane reagents were explored, and we observed that Ph₃SiH, Ph₂SiH₂ and (EtO)₃SiH were effective in the hydrosilylation of the imine moiety. Neither of the trialkylsilanes explored, triethyl- or triisopropylsilane, were competent reagents for hydrosilylative reduction of the imine bond. Triethoxysilane is a more electron-rich and sterically less congested silane source, which may have an impact on its success relative to trialkylsilanes. The progress of the hydrosilylation reaction was monitored using GCMS analysis. At 1 mol % catalyst loading and within 4 hours (70 °C), our model substrate was converted quantitatively to the corresponding secondary amine. Subsequently, we decided to explore the scope of imine substrates amenable to our reaction conditions using the inexpensive triethoxysilane as our preferred silane reductant (Table 2).

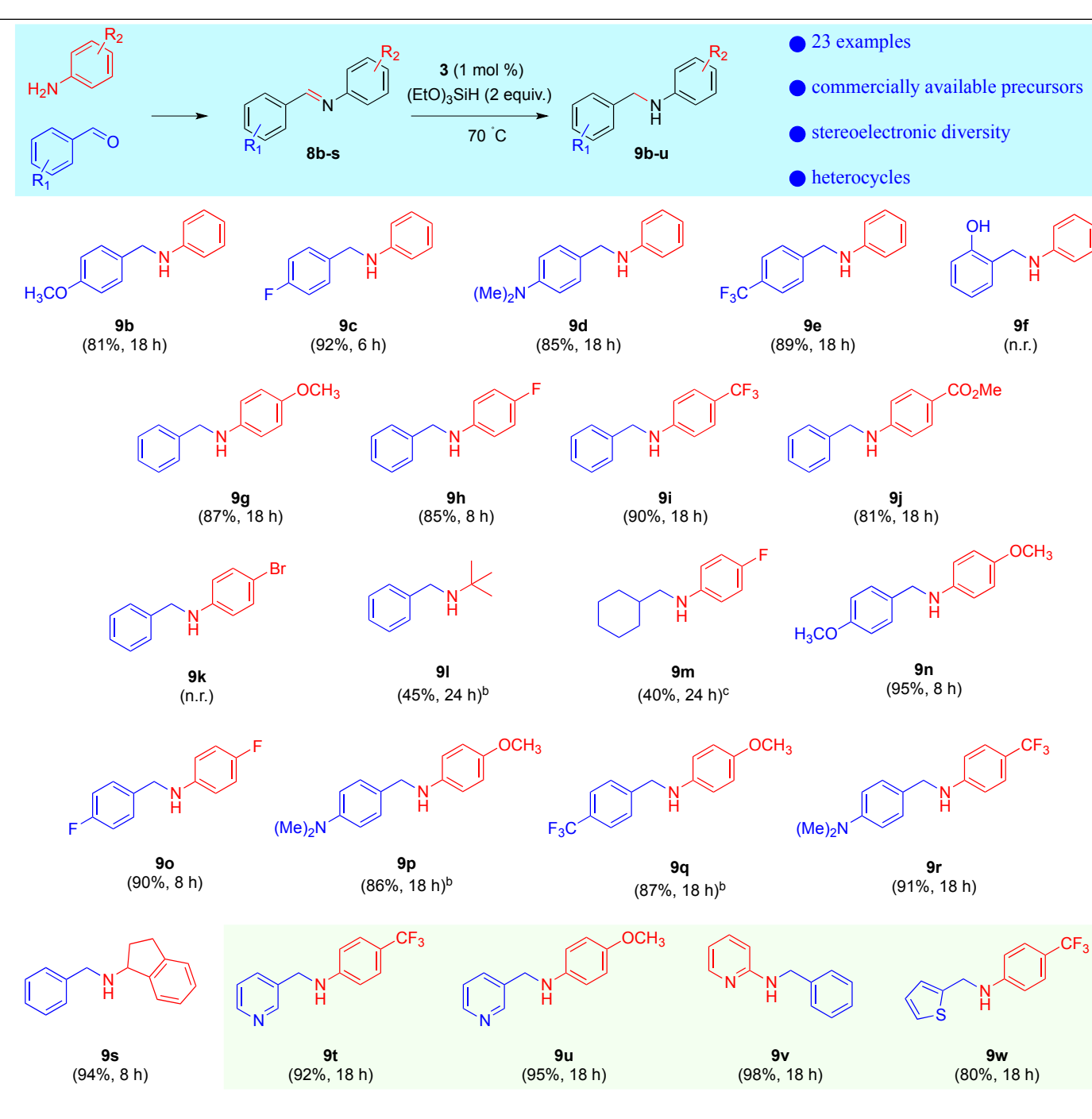
A broad substrate scope was observed; a diverse set of imines is readily accessible from commercially available aldehydes and (aryl)amines. Imines that are derived from combinations of (aryl)aldehydes and (aryl)amines typically underwent hydrosilylation in high yield. Introduction of either electron-releasing (**8b** and **8d**) or electron-withdrawing (**8c** and **8e**) substituents in the para-position of the aldehyde-derived aromatic ring did not result in diminished yields (81 – 92%). Similarly, no erosion in product yield was observed upon introduction of electronically diverse substituents to the para-position of the (aryl)amine-derived ring (**8g-8j**; 81 – 90%). Combinations of mixed electronic effects, "push-push", "push-pull", and "pull-pull", via use of appropriately substituted pairs of (aryl)aldehyde / (aryl)amine precursors, were also explored.

In all cases (**8n-8r**), good to excellent yields of reduced products were obtained (86 – 95%). Taken together, there appears to be no clear-cut electronic influence on the performance of imine substrates in hydrosilylative reduction chemistry.

In contrast to the aryl-derivatives, imines derived from either aliphatic amines (**8i**) or aliphatic aldehydes (**8m**) give lower yields, even after extended reaction times (24 h). Ester (**8j**), amine (**8d**, **8p** and **8r**) and ether (**8b**, **8g**, **8n**, **8p** and **8q**) groups were also tolerated as substituents on imine substrates in

either the (aryl)aldehyde or (aryl)amine rings. Disappointingly, the presence of hydroxyl- or bromo-substituents (**8f** and **8k**, respectively) on imine substrates was not tolerated. We have previously shown that alcohols react with complex **3** to afford (as yet) unidentified paramagnetic species.^{17c} In an extension from aldimines **8a-8r**, we attempted reduction of more hindered indanone-derived imine, **8s**. Secondary amine, **9s** was obtained in excellent yield (94%). Moreover, **9s**, is a precursor to the monoamine oxidase inhibitor rasagiline.¹⁸

Table 2. Scope of the Fe-Catalyzed Hydrosilylative Reduction of Aldimines^a

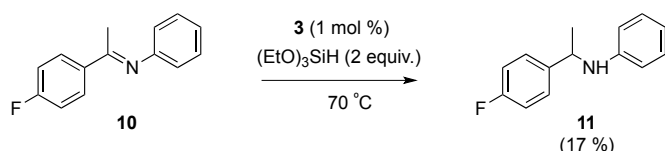


^aYield. ^bCalculated using GCMS analysis by adding mesitylene as internal standard; response factors were not determined. ^cCatalyst loading 5 mol %. ^dCalculated using ¹H NMR analysis by adding mesitylene as internal standard.

Finally, imine substrates comprising heterocycles were also studied (**8t-8w**). Gratifyingly, both pyridine- and thiophene-based imines were amenable to our optimized hydrosilylation conditions and were converted to corresponding amine products in good to excellent yields (80 – 98%); in the case of thiophene-derived imine **8w**, slightly extended reaction times were necessary to afford good yields of the amine product.

To extend our methodology to ketimines, we attempted the hydrosilylation of substrate **10** (Scheme 1). Disappointingly, the ketimine proved to be a poor substrate for hydrosilylation using catalyst **3**. Moderate yield (42 %) was only obtained after increasing catalyst loading to 5 mol %.¹⁹

In summary, we have isolated a well-defined BIAN-based iron complex (**3**) and shown it to be an efficient precatalyst system for hydrosilylation of imines to secondary amines. Further derivatization of the ligand and their use in reducing more challenging substrates such as amides are in progress. Details of the hydrosilylation mechanism are currently being explored in our group.



Scheme 1. Hydrosilylation of ketone-derived ketimine **10**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 19 Complete separation of amine product from imine starting material could not be achieved, see Supporting Information for spectra.