Reductive Amination

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Knölker's Iron Complex: An Efficient In Situ Generated Catalyst for Reductive Amination of Alkyl Aldehydes and Amines**

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During the past two decades, procedures for the highly selective catalytic reduction of imines have been developed, but unfortunately in these procedures the imines, which have limited stability, have to be synthesized and isolated in an additional step. Thus, the reductive amination of aldehydes and ketones constitutes a more efficient and direct route for their syntheses.[1] Such advantage allows its application into pharmaceutical and agrochemical processes, as well as materials science.[2]

The two commonly protocols for reductive amination are based on either the use of a stoichiometric amount of borohydrides reagents[3] or heterogeneous hydrogenation.[4] The former method suffers from severe drawbacks such as high toxicity and wastes generation. Taking into account the ecological point of view, the latter is more promising, as the reducing agent is molecular hydrogen and has found several applications in industry. However, heterogeneous hydrogenation is poorly chemoselective, and the reaction conditions are not compatible with some other unsaturated functional groups (namely, reduction of alkenes, alkynes, and nitro functions can occur with the same catalyst). Homogeneous reductive amination in the presence of a catalyst and a reducing agent was also developed. Various reducing agents[5–8] were previously employed. However, again, the most appealing reducing agent is molecular hydrogen.[1] In such reaction conditions, water is the only side-product in the overall transformation. In homogeneous catalysis, many catalysts rely on precious metals.[9–12] However, the limited availability, toxicity, and high price diminish their attractiveness. Thus, their replacement by more easily available metals is of great interest. Iron salts are usually nontoxic and very abundant, and accordingly among the most inexpensive and environmentally friendly metal derivatives. Iron-catalyzed reduction is a recent intensive research area.[13] Although impressive progress has been made in iron-catalyzed transfer hydrogenation[14] and hydrosilylation,[15] still little is known about hydrogenation of alkenes, alkynes,[16] and C=X bonds.[17] Iron has consequently been scarcely investigated in reductive amination.[18] Enthaler demonstrated that iron chloride catalyzed reductive amination through Lewis acid activation in the presence of silyl hydride derivatives.[19] Finally, Beller and co-workers recently showed that iron–carbonyl complexes are active in the reductive amination of carbonyl compounds with aromatic amines.[20]

To the best of our knowledge, there are no reports on iron-catalyzed challenging reductive amination of aliphatic amines and aliphatic aldehydes under smooth reaction conditions with a well-defined catalyst and using molecular hydrogen as reducing agent. As a result, we report our work on reductive amination catalyzed by iron complexes under low hydrogen pressure and mild reaction conditions. To define the best reaction conditions, the reductive amination at 85 °C under 5 bar of hydrogen in ethanol between citronellal and piperidine was used as a model reaction (see Table in the Supporting Information).

Iron(II) and $FeCl_3$ salts did not provide any alkylated amine. With these salts, only the corresponding enamine was detected by ^{1}H NMR spectroscopic analysis. As shown in Figure 1, some iron complexes were also evaluated. As observed previously by Beller and co-workers, iron dodecacarbonyl did not give any amino derivative.[20] Iron(II) complexes **1**[16a–c] and **2**[15c] were inactive as well. We turned then our attention to Morris iron complexes (**3a**, **3d**)[14b–e,17b] or related complexes (**3b**, **3c**). Whereas **3a** and **3d** were known to be active either in hydrogenation or hydride transfer reduction of acetophenone,[14c] they proved to be poorly active or inactive in the reductive amination. Complex **3a** led to a 68:32 ratio of alcohol/amine, and **3d** provides a mixture of aldehyde and enamine. Related complexes **3b** and **3c** did not give any improvement, and only aldehyde and enamine were observed by ^{1}H NMR spectroscopic analysis. However, to our delight, the Knölker's complex **4a** led to the alkylated amine with a total conversion.[21] While complex **4a** is an active catalyst, it is air-sensitive and decomposes quickly after exposure to air.[22] By contrast, compound **4b** is air- and moisture-stable, but is not active in this reaction. However, treatment of the tricarbonyl precursor **4b** with trimethylamine *N*-oxide oxidatively removed a CO ligand and generated the 16-electron species.[23] The latter can react with hydrogen and then generate **4a** in situ. Application of this in situ generated complex **4a** in the reductive amination

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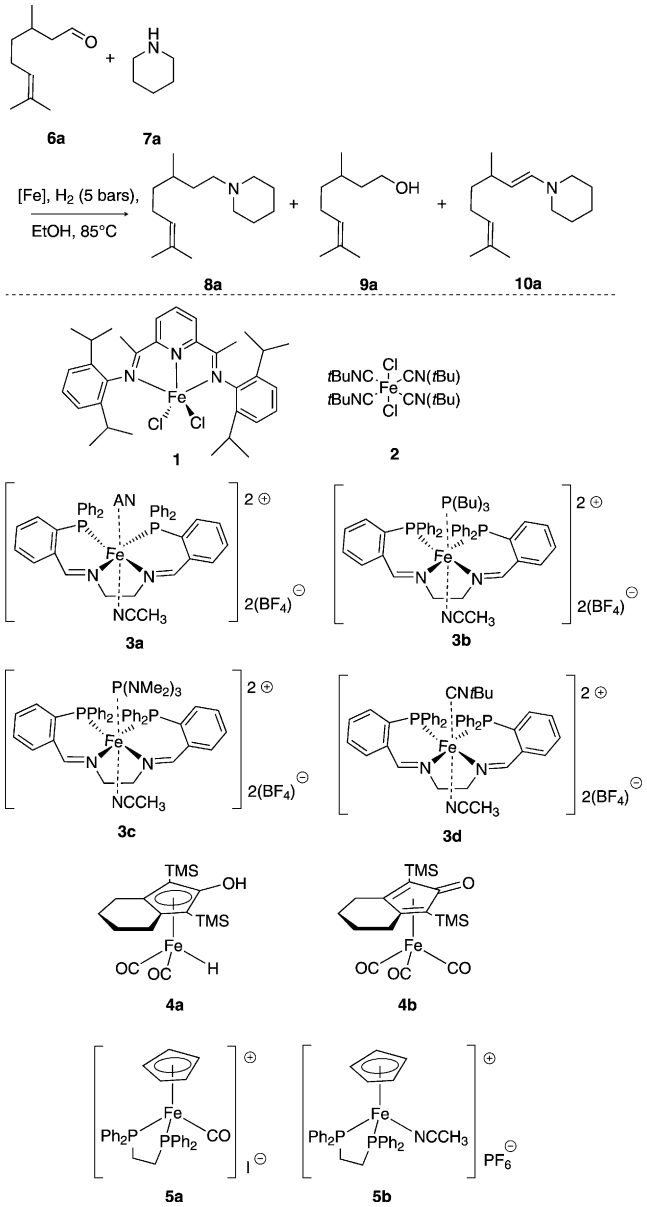


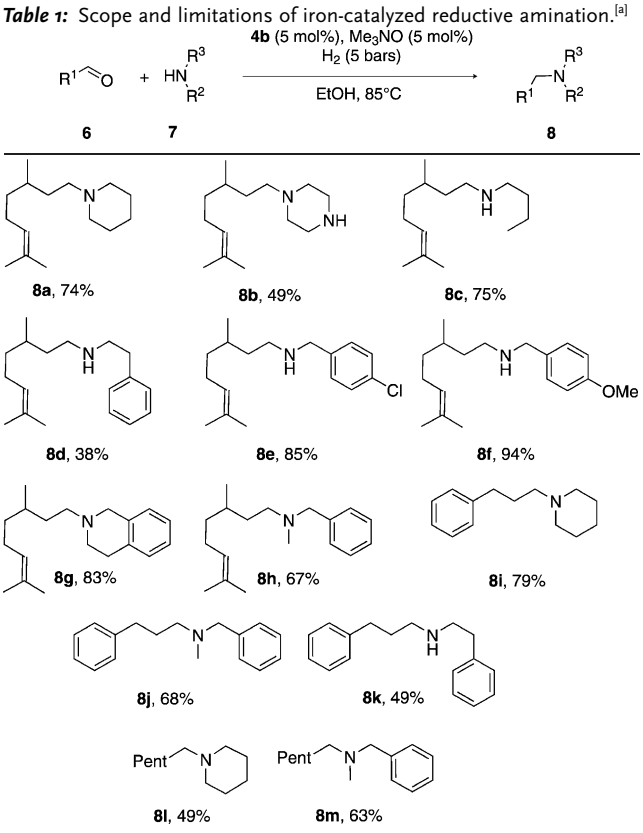
Figure 1. Screening of iron salts or complexes.

reaction provided the alkylated amine with total conversion. Remarkably, this result suggested also that trimethylamine oxide reacted faster with the iron complex than with the solvent. Noteworthy, other piano-stool iron complexes, such as $[CpFe(CO)_2I]$, $[Cp^*Fe(CO)_2I]$, **5a**, and **5b** did not catalyze the reductive amination. As also shown by Casey and Guan during their work on carbonyl reduction,[17a,b] one explanation for the different behavior of the Cp–iron complexes may arise from the non-innocent ancillary cyclopentadienyl ligand.[17a–b,d,24]

Various catalyst loading and temperature conditions were also tested, but no improvement was observed. A threshold temperature (85 °C) and catalyst loading (5 mol %) appeared necessary to ensure efficient reductive amination and to avoid side-product formation. Next, variation of the solvent was examined. In dichloromethane and dioxane, the reaction was not complete; **9a** was the main compound, accompanied by some enamine **10a** intermediate as detected by ^{1}H NMR spectroscopic analysis. In THF, ethyl acetate, and toluene, the reduction took place but, again, the alcohol was present as a side-product (the ratio alcohol/amine was 21:79, 32:68, and 48:52 in these solvents, respectively). Then, only ethanol allowed exclusively the reductive amination. Under the optimized conditions, 1 mmol of citronellal **6a** and 1.2 mmol of piperidine **7a** underwent reductive amination in the presence of 5 mol % of **4b** and 5 mol % of trimethylamine *N*-oxide under 5 bar of hydrogen at 85 °C to give 74 % of the isolated corresponding amine **8a**.

With these conditions in hand, we delineated the scope of this procedure by treating citronellal with various amines (Table 1). As previously observed by Casey and Guan in their seminal work on the C=O reduction,[17a–b] the iron catalyst shows functional group tolerance. Thus, carbon–halide bonds (**8c**) and ether functions (**8f**) were not cleaved during the hydrogenation. Isolated alkenes (**8a**–**h**) and benzyl framework (**8e**–**h**,**j**,**m**) were also not hydrogenated. Then, some variously substituted alkyl amines were engaged in the reductive amination of citronellal. All the corresponding amines were isolated in good to excellent yields (46–99 %, compounds **8a**–**8h**, Table 1). The use of primary or secondary amines is not detrimental for the iron complex and had little impact on its activity. Thus, with butylamine, compound **8c**

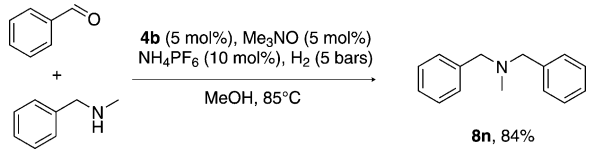
Table 1: Scope and limitations of iron-catalyzed reductive amination.[a]



[a] The hydrogenation reactions were carried out with aldehyde (1 mmol) and amine (1.2 mmol) in the presence of iron precatalyst (5 mol %) and trimethyl-*N*-oxide (5 mol %) in ethanol (2 mL) under 5 bar of hydrogen at 85 °C.

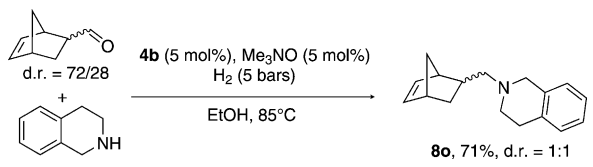
was isolated in 75% yield, and, with benzylamine derivatives, the yields ranged from 83 to 94% (compounds **8e–h**, Table 1). Other aldehydes reacted also quite well under these conditions to give the corresponding amines in good yields (**8i–8m**, Table 1). Again, primary amines and linear or cyclic secondary amines were good partners in this reaction with 3-phenylpropanal and hexanal. The corresponding amines (**8i–m**) were obtained in moderate to gratifying isolated yields (46–79%, Table 1). Worth mentioning is that amine was exclusively obtained under these conditions.

Benzaldehyde may also undergo reductive amination under slightly modified reaction conditions. Indeed, one of the key steps in a reductive amination is the condensation of the amine onto the carbonyl group. Direct reduction was mainly observed when the reaction was carried out at 85°C under the previous conditions. Addition of some Lewis acids, molecular sieves, or sodium sulfate did not improve the selectivity in favor of the amine. However, the addition of a catalytic amount of ammonium hexafluorophosphate led to the desired amine. Thus, in the presence of 10 mol% of this additive and 5 mol% of the iron catalyst at 85°C in methanol under 5 bar of hydrogen, the reductive amination of benzaldehyde and *N*-methylbenzylamine provided the corresponding bis(benzyl)methylamine **8n** in 84% yield (Scheme 1).



Scheme 1. Reductive amination with benzaldehyde.

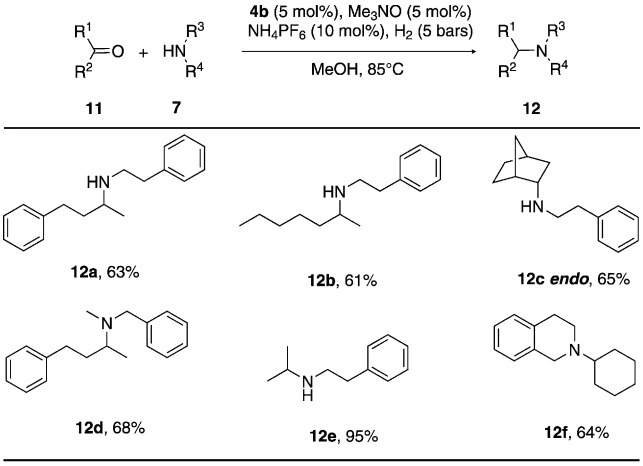
To obtain some mechanistic information, we carried out the reductive amination between the enolisable norbornene carboxaldehyde and tetrahydroisoquinoline under the optimized reaction conditions. The corresponding amine derivative **8o** was isolated in 71% yield and as a 1:1 mixture of diastereoisomers (Scheme 2). So, we assume that imine/enamine equilibrium occurred during this reaction. Indeed, to gain further evidence, we condensed the tetrahydroisoquinoline and the aldehyde in ethanol at 85°C. After 1 hour, ^{1}H NMR spectroscopy of an aliquot revealed complete conversion into a mixture of enamine, which was engaged in the reductive amination process under the optimized conditions. We were pleased to obtain the amine in 82% yield and in a 1:1 diastereomeric ratio. However, we do not yet have any further mechanistic information to delineate whether the imine or the enamine is hydrogenated.



Scheme 2. Reductive amination with norbornene carboxaldehyde and tetrahydroisoquinoline.

Next, the reductive amination of some ketones **11** was examined. Under the reaction conditions used with aliphatic aldehydes, mainly direct reduction of the carbonyl was observed. An increase of the temperature to 100°C improved the selectivity in favor of the amine **12**, although not yet to a satisfactory degree. However, by applying the reaction conditions used with benzaldehyde, the substituted amines **12** were produced in better selectivities and acceptable yields (Table 2). Then, with phenylethylamine, the alkylated amines

Table 2: Reductive amination with ketones.

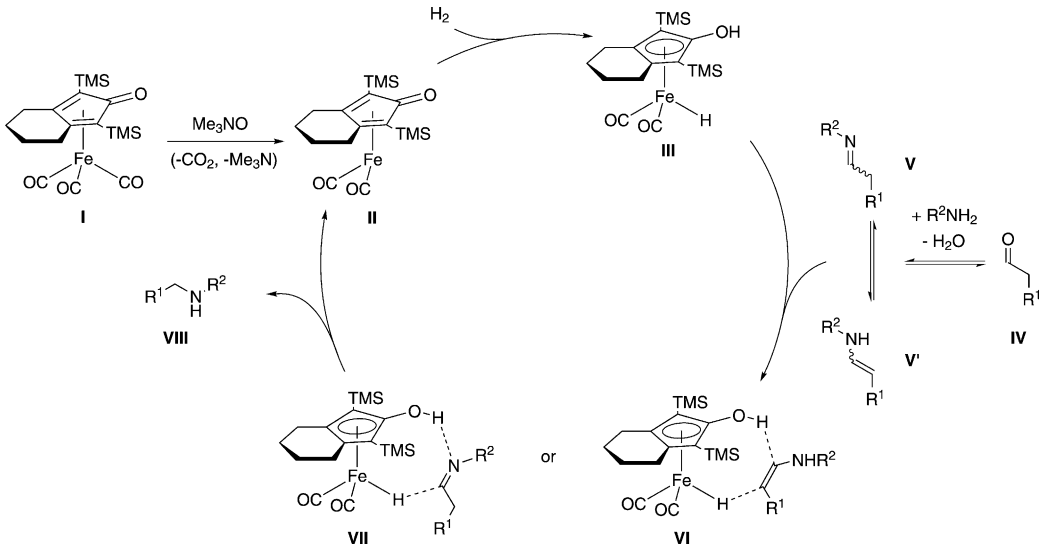


[a] The hydrogenation reactions were carried out with ketone (1 mmol) and amine (1.2 mmol) in the presence of iron precatalyst (5 mol%), trimethyl-*N*-oxide (5 mol%), and NH_4PF_6 (10 mol%) in methanol (2 mL) under 5 bar of hydrogen at 85°C.

12a–c,e were isolated in 61 to 95% yields. Notably, with 4-hydroxy-4-methyl-pentan-2-one, the alkylated amine **12e** was the sole product (95% yield). Reductive amination of acetone under the same reaction conditions led to a mixture of alkylated amine (38% yield) and some imine intermediate, as observed by ^{1}H NMR spectroscopy. Again, the use of primary or secondary amine is not detrimental for the iron complex and had little impact on its activity. Thus, starting from *N*-methylbenzylamine and tetrahydroisoquinoline, the corresponding amines **12d** and **12f** were isolated in 68% and 64% yield, respectively.

On the basis of previous work on polar C=X bond reduction[17a–b,f] and on our results, we propose the following mechanism (Scheme 3). After oxidative removal of one CO ligand with trimethyl-*N*-oxide, the 16-electron iron species (**II**) reacted with hydrogen to generate the iron(II) hydride complex **4a** (**III**). Activation of the imine (**V**) or the enamine (**V′**) with the hydroxy group (intermediate **VI or VI′**) and addition of the hydride liberate the reduced amine and regenerate the unsaturated iron(0) complex (**II**).

In summary, we have reported the first hitherto homogeneous well-defined iron catalyst for the reductive amination of aliphatic aldehydes with aliphatic amines under low pressure of hydrogen. Good to excellent yields were achieved for a range of alkyl aldehydes and ketones with primary or secondary alkylamines. Future work will be dedicated to



Scheme 3. Postulated mechanism.

extend this research to other C=N bonds and to elucidate the mechanism of this reaction.

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