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Mild and Selective Et_2Zn-Catalyzed Reduction of Tertiary Amides under Hydrosilylation Conditions

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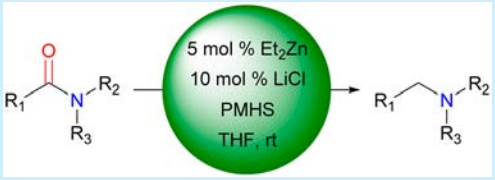
Supporting Information

ABSTRACT: Diethylzinc (Et_2Zn) can be used as an efficient and chemoselective catalyst for the reduction of tertiary amides under mild reaction conditions employing cost-effective polymeric silane (PMHS) as the hydride source. Crucial for the catalytic activity was the addition of a substoichiometric amount of lithium chloride to the reaction mixture. A series of amides containing different additional functional groups were reduced to their corresponding amines, and the products were isolated in good-to-excellent yields.



The development of selective and efficient methods for the production of substituted amines is of great importance, since the final products constitute valuable building blocks for fine and bulk chemicals as well as for polymers and dyes.[1] Substituted amines are common structural features in biologically active compounds, and hence, efficient and selective methods for their formation are especially valuable for the pharmaceutical industry (Figure 1). The synthesis of amines via

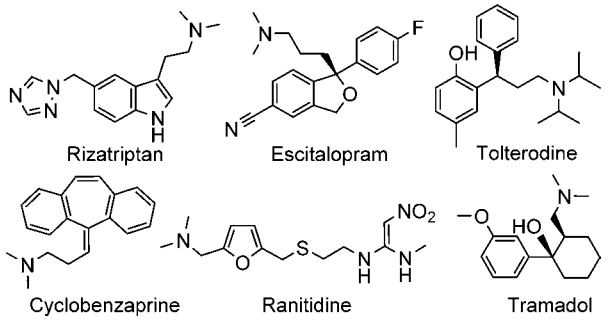


Figure 1. Some examples of the top selling drugs containing tertiary amine groups.

reduction of the amide functionality can provide a controlled substitution pattern in the final amine and, therefore, avoid problems encountered using other methods (e.g., amine alkylation). Taking into account that the amide is a stable and hard to reduce functionality, methods for the mild deoxygenation of amides to amines are highly desired. Despite the increasing number of catalytic protocols available for amide reductions, stoichiometric alkali metals, or aluminum-, and boron hydrides are still the most common reagents used in industrial and academic applications.[2] This is surprising, since these reagents are associated with air and water sensitivity, poor selectivity, and formation of large amounts of waste that complicates the workup procedures and purification of the target compounds.

In contrast, catalytic procedures offer more versatile strategies for the selective reduction and can allow for increased chemo- and regioselectivity.[3] Employing molecular hydrogen as the reducing agent leads to the most atom efficient method; however, current protocols suffer from low selectivity together with relatively harsh reaction conditions.[4] On the other hand, hydrosilanes are a mild and easy to handle hydride source. Most of them tolerate air and moisture and can be activated by Brønsted[5] and Lewis acids,[6] bases,[7] and transition metals[8] and used for the reduction of polarized unsaturated compounds.[9]

Presently, there are a significant number of protocols developed for the catalytic hydrosilylation of amides based on noble metals.[10] Developing cost-efficient methods employing more abundant first-row transition metals such as copper[11] and biocompatible zinc- and iron-based catalysts is a great challenge. Iron, being the most abundant transition metal, is currently employed in a number of different catalytic procedures for the deoxygenation of amides;[12] conversely, there are only two zinc-based systems described for amide reductions. Beller and co-workers reported that $Zn(OAc)_2$ is catalytically active under mild reaction conditions (rt or 40 °C) for the reduction of different tertiary amides to yield the corresponding tertiary amines in high selectivity.[13] However, the trialkoxysilane that was used as the hydride source is known to generate highly pyrophoric gases during the reaction.[14] In an attempt to overcome this issue, the same group developed a catalytic protocol employing $(EtO)_2MeSiH$, but longer reaction times (up to 30 h) and elevated temperatures (65 °C) were required to achieve high conversion of the starting amides.[15]

Herein we report a Zn-based catalytic reduction of tertiary amides to the corresponding amines under mild reaction conditions. The use of polymethylhydrosiloxane (PMHS) as a hydride source, in combination with an ambient reaction temperature, makes the developed protocol highly favorable in

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comparison to previously reported systems. PMHS is an air and moisture stable silane, and the lack of reactivity of the reagent in the absence of a catalyst makes it easy to handle.[16]

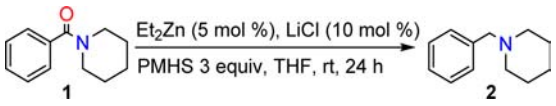
Initial experiments on carbonyl reduction indicated that Et_2Zn together with the polymeric silane PMHS as the hydride source could be applicable for deoxygenation of tertiary amides. Further investigations using *N*-benzoylpiperidine **1** as a model substrate showed that its corresponding amine **2** was efficiently formed, depending on the conditions used (Table 1 and Scheme 1).

Table 1. Screening of the Conditions for the Et_2Zn Catalyzed Reduction of Tertiary Amides to Amines[a]

entry	Et_2Zn (mol %)	LiCl (mol %)	solvent	conversion[b]
1	5	0	THF	9%
2	0	10	THF	0%
3	5	10	THF	>95%
4	5	10	Et_2O	61%
5	5	10	toluene	41%

[a]Reaction conditions: Et_2Zn (*x* mol %), LiCl (*y* mol %) PMHS (3 equiv), solvent (2 mL), amide (1.0 mmol), 24 h, rt. [b]Conversion was determined by ^1H NMR.

Scheme 1. Optimized Reaction Conditions for the Reduction *N*-Benzoylpiperidine Catalyzed by Et_2Zn[a]



[a]Et_2Zn was used as a 1.0 M hexane solution.

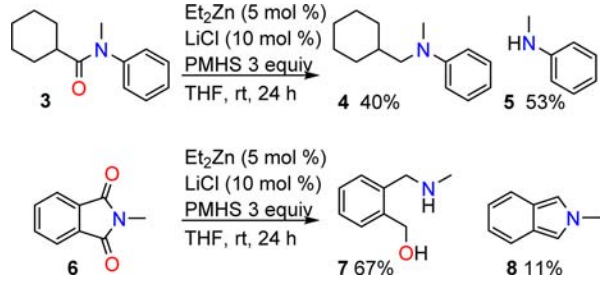
It was found that the addition of LiCl to the reaction mixture significantly enhanced the reaction rate and selectivity of the process (Table 1, entries 1 and 3). Previously, similar effects from LiCl additions were observed in catalytic transfer hydrogenation and hydrosilylation reactions.[12f,17] Omitting diethyl zinc from the reaction mixture resulted in no conversion to the product (Table 1, entry 2). Evaluation of different solvents showed that THF was the solvent of choice, whereas, in toluene and Et_2O, the yields of the amine were significantly lower, probably because of the poor solubility of LiCl in these solvents (Table 1, entries 3–5). The best results were obtained employing 10 mol % of anhydrous LiCl in THF. The use of 5 mol % of Et_2Zn allowed for full conversion of the model substrate within 24 h at rt (Scheme 1). Reducing the amount of catalyst to 2 mol % resulted in a longer reaction time (48 h) to achieve full turnover of the substrate to the product (see Supporting Information). Noteworthy, when the optimized conditions were employed using zinc acetate instead of diethylzinc, we observed no conversion to the desired amine.[18]

The nature of the catalytic species in the diethylzinc–lithium chloride protocol is currently unknown. However, given the fact that both Et_2Zn and LiCl are vital for a successful reaction outcome, it is likely that the process is promoted by a nucleophilic zinc hydride species, in combination with Lewis acid activation of the amide carbonyl by LiCl. Mechanistic studies are currently being pursued.

Using the optimized catalytic protocol it was possible to deoxygenate a wide range of electron-rich and -poor aromatic, heteroaromatic, and aliphatic tertiary amides (Table 2). The described catalytic system displayed high tolerance to a variety of functional groups, providing excellent yields of the formed amines (Table 2). In general aliphatic amides displayed lower reactivity in comparison to aromatic amides, resulting in lower yields; however, this limitation can be overcome by increasing the reaction temperature to 40 °C (Table 2, entries 14 and 15). Pyridine-, furan-, and thiophene-based heteroaromatic amides known to be more difficult to reduce were efficiently transformed to the corresponding amines in good to excellent yields (Table 2, entries 16–18). The catalytic system proved to be rather insensitive toward sterical hindrance, as demonstrated by the results obtained in the reduction of bulky substrates (Table 2, entries 4, 13, and 15). Furthermore, using the Et_2Zn protocol, it was possible to chemoselectively reduce the amide functionality in the presence of other potentially reducible functional groups such as nitro-, cyano-, and multiple bonds (Table 2, entries 19–22). It should be noted that an amide containing a stereogenic center was successfully converted to the amine with a negligible decrease of the product enantiopurity (Table 2, entry 23). The amide bearing an N-Boc protected tertiary amino group was deoxygenated to the target compound without deprotection of the Boc-group (Table 2, entry 24).

Catalytic hydrosilylation of the aniline-based amide *N*-methyl-*N*-phenylcyclohexanecarboxamide **3** resulted in a mixture of two products, where the expected tertiary amine **4** was isolated in 40% yield, along with *N*-methylaniline **5** in 53% yield (Scheme 2). Similarly, reduction of *N*-methylphthalimide

Scheme 2. Catalytic Reductions of Compounds 3 and 6



6 resulted in the mixture of the expected amino alcohol **7** and the aromatic compound 2-methylisoindole **8** in 67% and 11% yields, respectiviely (Scheme 2).

A few limitations with respect to functional group compatibility were encountered during the substrate scope evaluation of the Zn-based catalytic protocol (Figure 2). Unfortunately neither primary **9** nor secondary **10** amides were reduced to their corresponding amines, and in these reactions, the starting materials were fully recovered. Furthermore, the reduction of the tertiary amide **11**, containing a secondary N-Boc protecting group, did not result in the formation of the expected amine; instead starting amide **11** was extracted. All of the above substrates contain labile protons that presumably react with the catalyst in an acid–base reaction and thereafter ligates to the zinc-center, which effectively inhibits the reduction reaction.

In contrast, the substrate containing an *ortho*-phenolic substituent was successfully reduced to the corresponding amine (Table 2, entry 25). In the latter case, it is possible that the substrate acts as a bidentate ligand to Zn after initial phenol deprotonation, forming an active complex for the hydrosilylation of the tertiary amide. The reduction of the benzylic amide **12** resulted in a mixture of the expected tertiary amine,

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Table 2. Substrate Scope for Reduction of Tertiary Amides Catalyzed by Et_2Zn

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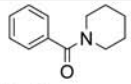
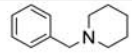
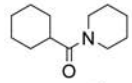
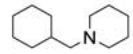
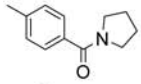
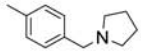
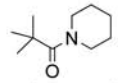
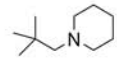
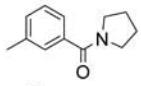
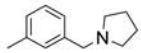
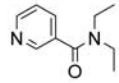
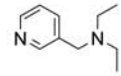
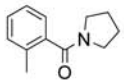
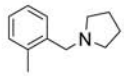
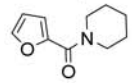
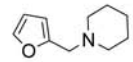
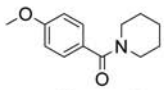
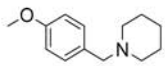
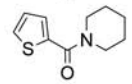
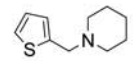
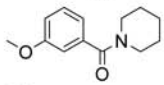
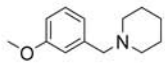
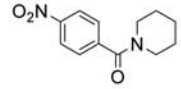
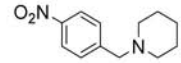
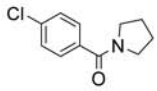
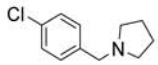
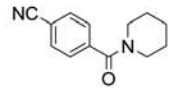
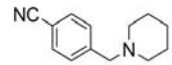
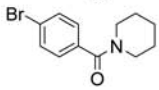
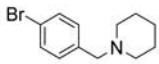
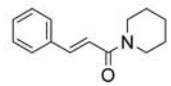
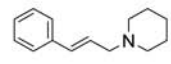
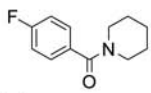
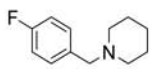
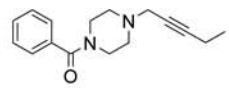
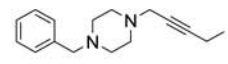
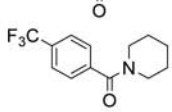
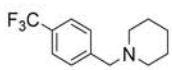
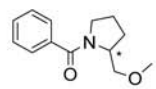
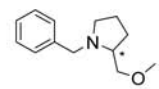
1			98	14			65 (92)[c]
2			98	15			74
3			70 (95)[c]	16			72
4			98	17			75 (88)[c]
5			98	18			98
6			98	19			84
7			98	20			98
8			98	21			77
9			98	22			98
10			98	23			98 (ee 95%)
11			98	24			98
12			98	25			52 (82)[c]
13			98				

[a]Reaction conditions: Et_2Zn (5 mol %), LiCl (10 mol %), PMHS (3 equiv), THF (2 mL), amide (1.0 mmol), 24 h, rt. [b]Isolated yield. [c]Reaction was carried out for 24 h at 40 °C.

along with the enamine and 2-phenylethanol. Amide **13**, containing a conjugated triple bond, proved to be inactive under the developed reaction conditions, whereas the amide bearing an isolated alkyne was efficiently converted to its corresponding amine in high yield (Table 2, entry 22). The reduction of the substrates **14** and **15**, which contain additional, more reactive, carbonyl groups, resulted in mixtures of compounds. Further investigation on the use of the Zn-catalyzed protocol for the reduction of other carbonyl compounds together with mechanistic investigations of the reaction and the role of LiCl are currently being pursued.

To conclude, an efficient catalytic system for the room temperature reduction of tertiary amides to the corresponding tertiary amines has been developed. The protocol takes advantage of commercially available Et_2Zn as the catalyst and the inexpensive, commercially available, and nontoxic silane PMHS as the hydride source. It was found that the addition of catalytic amounts of LiCl to the reaction mixture effectively increases the rate and selectivity of the reduction reaction. The mild reaction conditions used in the catalytic protocol allowed for a variety of tertiary amides, containing a number of different functional groups, including common protecting groups, to efficiently be reduced to their target amines. Furthermore, the majority of the formed amines were obtained in excellent yields. The mild reaction conditions and the high chemoselectivity of the process make the current catalytic protocol a strong competitor to the use of stoichiometric hydride reagents and other catalytic methods for the reduction of tertiary amides.

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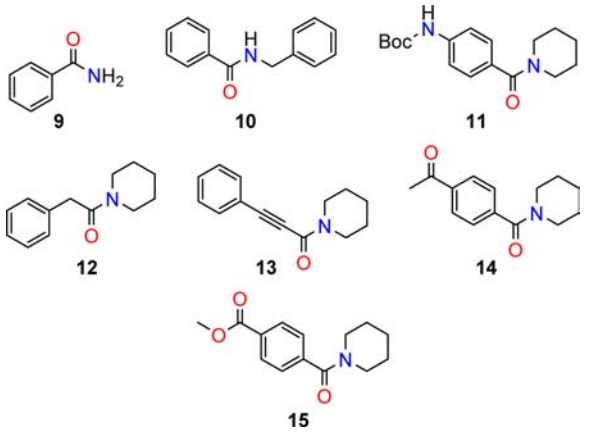

Figure 2. Functional group limitations.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedure and characterization for all products present in the Supporting Information. 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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