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Zinc-Catalyzed Reduction of Amides: Unprecedented Selectivity and Functional Group Tolerance

Shoubhik Das, Daniele Addis, Shaolin Zhou, Kathrin Junge, and Matthias Beller*

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

Received November 30, 2009; E-mail: matthias.beller@catalysis.de

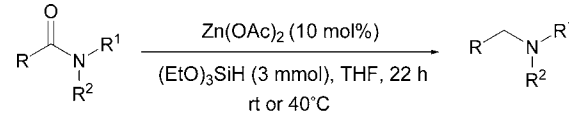
The catalytic reduction of amides to amines under mild conditions constitutes a highly desired transformation for organic synthesis and the pharmaceutical as well as agrochemical industry.[1] In this respect, high selectivity and broad tolerance toward functional groups are key factors for the acceptance and application of a given methodology. Most of the known reductive transformations of amides to amines make use of stoichiometric amounts of traditional aluminum and boron hydrides.[2,3] In spite of their utility, clear drawbacks of these reagents are air and moisture sensitivity as well as the resulting costly purification of the products and concomitant formation of environmentally hazardous waste materials. Due to these problems, the development of catalytic reductions of amides is of high actual interest.[4] Unfortunately, the direct hydrogenation is still in its infancy.[5] On the other hand, the catalytic hydrosilylation of carboxamides applying precious metal catalysts like Rh,[6a−c] Ru,[6c−g] Pt,[6c,h] Pd,[6c] Ir,[6c] and others[6c,i−k] has been more intensively investigated. Most recently, also Fe-based catalysts have been successfully applied for this purpose at higher temperature.[6l,m] Nevertheless, until today a general methodology for the reduction of amides under mild conditions with inexpensive and environmentally friendly catalysts is not available.

Herein, we report for the first time the efficient reduction of tertiary amides using convenient zinc catalysts with excellent chemoselectivity and unique functional group tolerance. Parallel to this work, Nishiyama and co-workers used a similar catalyst system for the hydrosilylation of ketones.[7] At the start of our project, the reaction of *N*,*N*-dimethylbenzamide with $(EtO)_3SiH$[8] was investigated as a model system to identify and optimize potential catalysts and the critical reaction parameters. Summarizing these experiments we observed that in the presence of 10 mol % zinc acetate and 3 equiv of triethoxysilane reduction took place at room temperature leading to the corresponding amine in 97% yield! As expected, the reaction did not occur in the absence of any zinc catalyst. Nevertheless, other zinc salts such as ZnX_2 (X = F, Cl, Br, OTf) and hydrated complexes $ZnX_2 \cdot 6H_2O$ (X = ClO_4, NO_3) showed some activity but gave significantly lower yields, and other sources of metal acetate (Cu, Fe) were completely inactive in this reaction.[9,10]

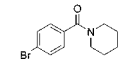
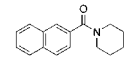
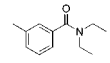
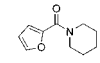
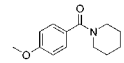
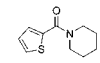
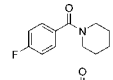
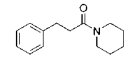
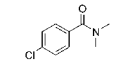
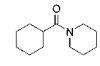
Next, we investigated the influence of different silanes in more detail. Noteworthy, other silanes did not react at room temperature, however $PhSiH_3$, Ph_2SiH_2, and $(EtO)_2MeSiH$ gave excellent yields (>90%) toward *N*,*N*-dimethylbenzylamine at 65 °C. Applying triethoxysilane to the reaction worked also well at room temperature in solvents like dichloromethane, toluene, diglyme, 1,2-dimethoxyethane, 1,4-dioxane, and di-*n*-butylether. To exclude the influence of potential metal contaminants in the catalyst precursor, we used zinc acetate from different suppliers (ABCR, Acros, Sigma Aldrich) giving similar product yields. We were also pleased to find that the reaction is easily performed on a multigram scale without special precautions. After surveying the reaction conditions we started to investigate the scope and limitations of this first zinc-catalyzed reduction of amides. As shown in Table 1 aromatic, aliphatic, alicyclic, and heterocyclic amides are smoothly reduced under the optimized reaction conditions with triethoxysilane. Comparing differently substituted benzamides, we observed that the introduction of electron-withdrawing groups at the *para*-position of the benzene ring (Table 1, entries 6−8) resulted in faster reduction than in the case of those bearing electron-donating groups (Table 1, entry 4). Indeed, when a 1:1 mixture of *N*-(4-methoxy-benzoyl)piperidine (**1f**) and *N*-(4-fluorobenzoyl)piperidine (**1d**) was subjected to the standard hydrosilylation conditions, the mixture contained 23% **2f** and 8% **2d**, respectively, after 10 h. It should be noted that in a few cases a slightly higher temperature (40 °C) was needed to achieve full conversion (Table 1, entries 4, 6, 8−11).

After demonstrating the general applicability of our procedure, we were interested in the functional group tolerance of the catalytic system. Hereby, we studied especially challenging substrates, which might undergo additional reductive transformations. As summarized in Table 2 the amide is reduced in the presence of ester, ether, nitro, cyano, and azo substituents as well as isolated and conjugated double bonds! To our delight none of the functional groups are

Table 1. Zinc Acetate-Catalyzed Reduction of Tertiary Amides



1 **2**

entry	amide		yield (%)	entry	amide		yield (%)
1		**1a**	**2a** 97	8		**1h**	**2h** 97
2		**1b**	**2b** 85	9		**1i**	**2i** 99
3		**1c**	**2c** 75	10		**1j**	**2j** 73
4		**1d**	**2d** 80	11		**1k**	**2k** 82
5		**1e**	**2e** 87	12		**1l**	**2l** 96
6		**1f**	**2f** 92	13		**1m**	**2m** 73
7		**1g**	**2g** 87	14		**1n**	**2n** 86

[a] Reported yields are isolated yields except entries 1 and 12. [b] All reactions were performed with 1 mmol of amide except entries 3 and 10 (3 mmol). [c] Products of entries 4 and 13 were purified by column chromatography, and products of entries 3 and 10 were purified by distillation.

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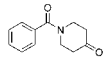
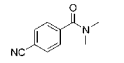
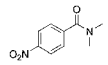
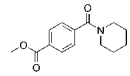
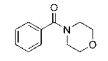
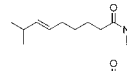
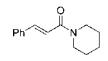
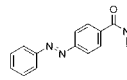
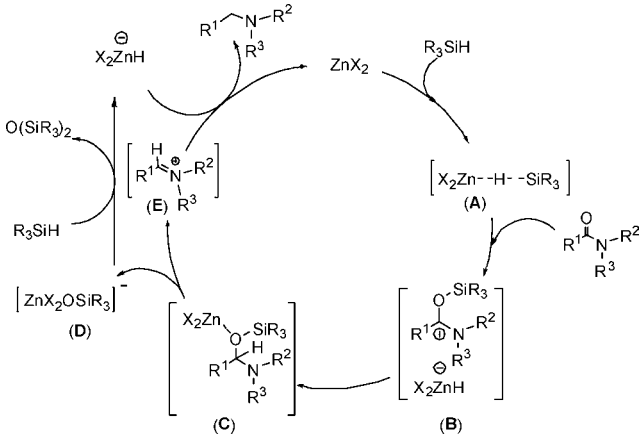
Table 2. Functional Group Tolerance

entry	amide		yield (%)	entry	amide		yield (%)
1		**1o**	**2o** 83	5		**1s**	**2s** 72
2		**1p**	**2p** 85	6		**1t**	**2t** 65
3		**1q**	**2q** 84	7		**1u**	**2u** 87
4		**1r**	**2r** 78	8		**1v**	**2v** 91

[a] All reactions were performed on 1 mmol scale of the respective amide. [b] Entries 4−7 were purified by column chromatography.

Scheme 1. Proposed Mechanism



reduced (>99% selectivity)! *Notably, amide reduction took place chemoselectively even in the presence of a ketone group, which is known to be much more active* (Table 2, entry 1).[1c] To the best of our knowledge there is no other example of this type of selectivity. The unparalleled chemoselectivity of the catalyst system is also verified by exploring 1:1 mixtures of acetophenone, benzonitrile, methyl benzoate, and nitrobenzene with *N*,*N*-dimethylbenzamide under the optimized reaction conditions. Again, we obtained highly selective reduction of the amide and no reduction of the other substrates.

For preliminary mechanistic investigations we stirred a 1:1 mixture of zinc acetate and the model amide **1a** for 2 h in THF, but in contrast to previous studies by Piers and co-workers[10b] no change of the C═O stretching frequency was observed in the IR spectra. Apparently, the role of zinc acetate in this reaction is not to activate the carbonyl group of the substrate rather than to activate the silane. Indeed, in monitoring a 1:1 mixture of zinc acetate and triethoxysilane in THF-d_8 by ^{1}H NMR spectroscopy a perturbation in the integration of the resonances for the silane hydrogen is observed. Applying ^{29}Si NMR spectroscopy for this mixture showed the formation of a single new peak at 82.2 ppm (chemical shift of $HSi(OEt)_3$: 59.24), which indicates an activation of the silane hydrogen.

Based on these observations, we propose the reaction mechanism shown in Scheme 1. Zinc acetate reacts with triethoxysilane at room temperature and forms an activated species **A**. Next, the amide is coordinated to the metal center in **A** and generates the corresponding *N*,*O*-acetal **C** via **B**. Release of the anionic zinc ether **D** led to the iminium species **E**. Finally, another equivalent of the silane converts the iminium ion to the product and the siloxane. This mechanistic proposal is in agreement with the reaction of **1a** with Ph_2SiD_2 where both deuterium atoms are incorporated on the carbonyl carbon.

In conclusion, we have established for the first time a highly chemoselective reduction of amides to the corresponding amines with silanes in the presence of inexpensive zinc catalysts under mild conditions. We expect our system will be useful for organic synthesis allowing amide reduction without using protecting groups and deprotection steps. Further studies on the application of primary and secondary amides as well ester are ongoing in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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