Reduction

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Chemoselective Reduction of Tertiary Amides under Thermal Control: Formation of either Aldehydes or Amines

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Abstract: *The chemoselective reduction of amides in the presence of other more reactive reducible functional groups is a highly challenging transformation, and successful examples thereof are most valuable in synthetic organic chemistry. Only a limited number of systems have demonstrated the chemoselective reduction of amides over ketones. Until now, the aldehyde functionality has not been shown to be compatible in any catalytic reduction protocol. Described herein is a [Mo($CO)_6$]-catalyzed protocol with an unprecedented chemoselectivity and allows for the reduction of amides in the presence of aldehydes and imines. Furthermore, the system proved to be tunable by variation of the temperature, which enabled for either C–O or C–N bond cleavage that ultimately led to the isolation of both amines and aldehydes, respectively, in high chemical yields.*

Although highly efficient reduction of carboxamides can be realized using stoichiometric amounts of either aluminum- or boron-based hydride reagents, these methods lack versatility due to the intolerance towards other reducible functional groups.[1] Several research groups have focused on the development of protocols for hydrosilylation of amides, which have led to a number of catalytic systems based on the platinum-group metals,[2] as well as Fe,[3] Zn,[4] Au,[5] Co,[6] In,[7] Mg,[8] and B.[9] While ester, cyano, and nitro functionalities generally are well tolerated, selective reduction of amides over ketones is significantly less developed and to the best of our knowledge only two catalytic protocols have been able to demonstrate this level of chemoselectivity to date. Nagashima and co-workers were the first to develop an efficient catalytic method in which the amide moiety was selectively reduced in the presence of a ketone.[2b] Recently, the group of Beller demonstrated a highly chemoselective protocol for the hydrosilylation of amides employing catalytic amounts of $Zn(OAc)_2$ in combination with triethoxysilane [$(EtO)_3SiH$].[4] Among other reducible groups, a ketone-containing amide substrate was reduced to afford the corresponding ketone-amine compound. Even though significant progress has been made in the field of chemoselective amide reduction, no system based on either a catalyst or stoichiometric reagents has demonstrated the selective reduction of an amide into an amine in the presence of aldehydes. This highly chemoselective transformation is performed for the first time with the catalytic protocol presented here.

Early procedures for the reduction of amides to the corresponding aldehydes proceeding by C–N bond cleavage were based on lithium aluminum hydride reagents and the reactions were highly substrate dependent and had limited functional-group tolerance.[10] Today, a few non-catalytic protocols have demonstrated high levels of chemoselectivity for this transformation. Recently Charette and co-workers reported a system based on stoichiometric amounts of triflic anhydride, 2-fluoro pyridine, and triethylsilane (Et_3SiH) for the selective reduction of amides into aldehydes via imine hydrolysis.[11] To the best of our knowledge, this protocol constitutes the sole example where an amide was selectively reduced to an imine in the presence of an aldehyde. Georg and co-workers have demonstrated the reduction of amides to aldehydes using an excess of the Schwartz reagent.[12] Some degree of chemoselectivity was observed and nitro, cyano, and ester groups were tolerated. However, ketones and aldehydes were reduced to alcohols. In addition, stoichiometric systems based on $Ti(OiPr)_4$, for the transformation of amides into aldehydes, were reported by Buchwald and co-workers[13] and more recently by the group of Lamaire.[14]

A limited number of chemoselective catalytic systems for the reduction of amides to aldehydes or precursors thereof have been reported. An iridium-catalyzed protocol for the reduction of tertiary amides towards enamines was reported by Nagashima and co-workers.[15] The system displayed high chemoselectivity and was compatible with ketones. Brookhart and Cheng also used an iridium-catalyst for the reduction of secondary amides into imines.[2d] The transformations could be performed selectively in the presence of esters, however, ketone- or aldehyde-containing amides were not included in the scope.

Herein we present a protocol based on catalytic amounts of [$Mo(CO)_6$], in combination with the inexpensive and air-stable hydride source TMDS (1,1,3,3-tetramethyldisiloxane), for the selective reduction of tertiary amides. The catalytic system displays levels of chemoselectivity that previously have been unattainable and allows the reduction of amides in the presence of aldehydes and imines. Moreover, by variation of the reaction temperature it is possible to obtain either amines or aldehydes as the major products (Scheme 1).

Recently, we developed a catalytic protocol based on [$Mo(CO)_6$] for the chemoselective reduction of α,β-unsaturated amides, in which selective reduction of the amide over the olefin moiety was demonstrated.[16] We continued our investigations with [$Mo(CO)_6$] as the catalyst for the reduction of benzamides. Performing the reaction on **1a**

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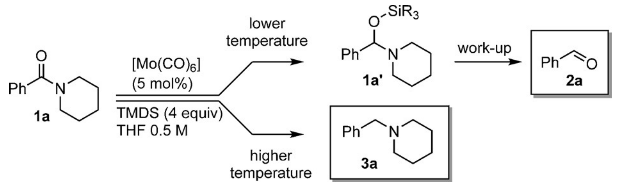
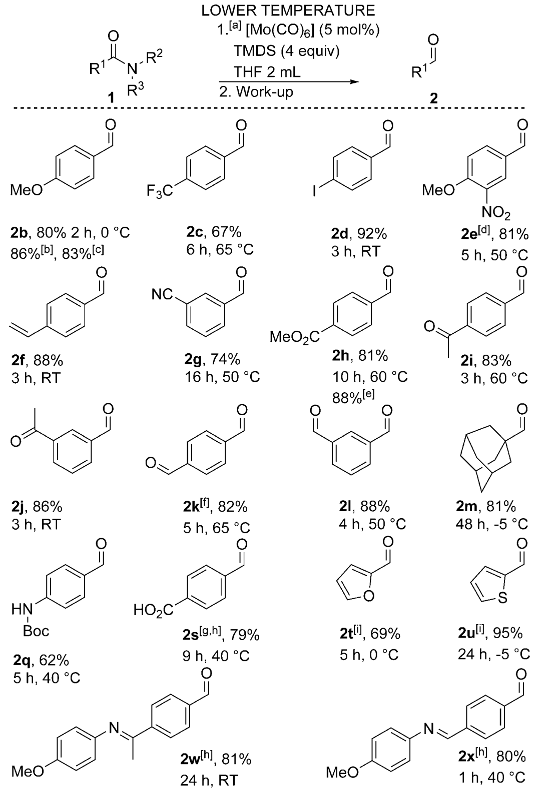


Scheme 1. Catalytic reduction of amides into aldehydes or amines.



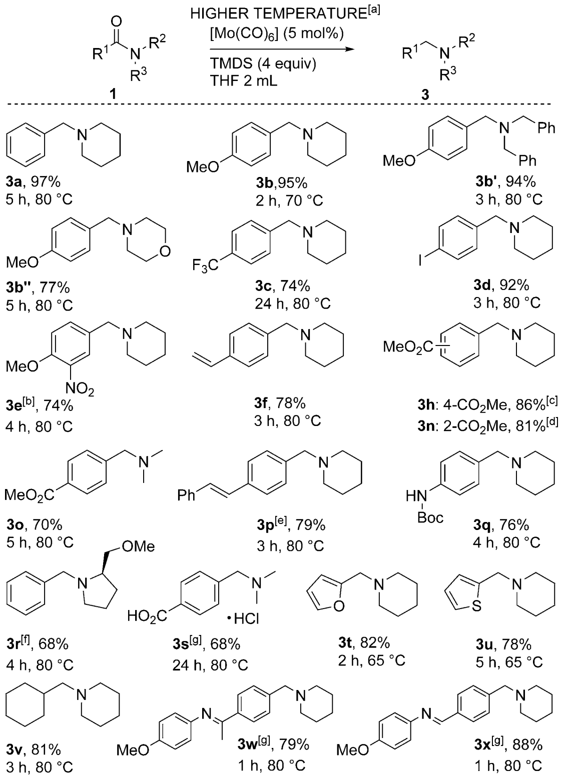
Scheme 2. Chemoselective formation of aldehydes. [a] Piperidine-derived amide (1.0 mmol), $[Mo(CO)_6]$ (5 mol%), TMDS (4.0 mmol), THF (2.0 mL). Yield refers to the isolated product. [b] Dibenzyl-derived amide (**1b′**), 3 h, RT. [c] Morpholine derived amide (**1b″**), 13 h, RT. [d] $[Mo(CO)_6]$ (10 mol%), TMDS (6.0 mmol). [e] *N*,*N*-dimethyl derived amide (**1o**), 2 h, RT. [f] $[Mo(CO)_6]$ (10 mol%). [g] TMDS (8 equiv). [h] 0.5 mmol scale. [i] Yield determined by ^{1}H NMR spectroscopy.

(Scheme 1) in THF using 5 mol% of $[Mo(CO)_6]$ in combination with TMDS afforded the corresponding amine **3a** after 3 hours at 80 °C. During the temperature optimization, the silylhemiaminal **1a′** was identified by ^{1}H NMR spectroscopy as the major product when the reaction was performed at room temperature.[17] Previously it was proposed that the reduction of amides to amines occurs by a two-step process with the silylhemiaminal being an intermediate.[18] Pannell and co-workers recently performed a mechanistic study and showed that this species was formed in the $[Mo(CO)_6]$-catalyzed hydrosilylation of simple amides such as *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylamide.[19] The authors identified the silylhemiaminal as the initial hydrosilylation product of DMF, which is in line with our observations. Simultaneously, the silylhemiaminal species was observed by Brookhart and Park in their investigation of iridium-catalyzed reduction of amides.[20] It is relatively unusual to be able to stop at the silylhemiaminal stage under metal-catalyzed reaction conditions because of the rapid in situ collapse of this species into the iminium ion with the subsequent reduction to amine. We envisioned that the high amount of silylhemiaminal formed in our reactions would allow high yields of the corresponding aldehydes after work-up.

To simplify the aldehyde isolation process *p*-methoxy benzamide (**1b**) was employed as the model substrate in the optimization. Performing the reaction at 0 °C for 2 hours gratifyingly gave the corresponding benzaldehyde **2b** in 80% yield after work-up (Scheme 2). Different N-substituents of the amide were evaluated and **2b** was obtained in 86 and 83% from morpholine and *N*,*N*-dibenzylamine derived amides. During the substrate evaluation it was observed that electronic properties of the aromatic ring influenced the reduction efficiency of the amide functionality and substrates bearing electron-withdrawing groups required higher reaction temperature and/or longer reaction time. As a result only a moderate yield of *p*-(trifluoromethyl) benzaldehyde (**2c**) was obtained, and a *p*-nitro-substituted amide could not be reduced at low temperature. Aryl halides were readily tolerated and *p*-iodobenzaldehyde (**2d**) was obtained in high yield without any detectable dehalogenation. We continued to evaluate substrates with reducible functional groups and the nitro- (**2e**), vinyl- (**2f**), nitrile- (**2g**), and carboxylic-acid-containing (**2s**) compounds, were isolated in 81, 88, 74 and 79% yield, respectively. No overreduction of the ester functionality in the amide **1h** was observed and the ester-aldehyde **2h** was obtained in 81% yield. Ketones were tolerated and the *p*-acetyl-substituted benzaldehyde **2i** and *m*-acetyl benzaldehyde **2j** were obtained in high yields after 3 hours. More importantly, aldehydes and imines were not reduced under these reaction conditions and we were able to isolate the bis(aldehydes) **2k** and **2l** in 82 and 88% yield, respectively, and the imine-aldehydes **2w** and **2x** in 81 and 80% yield, respectively. The protocol was applicable for aliphatic amides as demonstrated by the formation of the adamantyl aldehyde **2m** which was isolated in 81% yield. It was observed that tertiary aliphatic amides need to be branched at the α-carbon atom, and reactions with aliphatic amides such as 2-phenyl-1-(piperidin-1-yl)ethanone generated the corresponding enamine while 1-(piperidin-1-yl)pentan-1-one resulted in a mixture of an enamine and amine.

N,*N*-dimethylamide **1o** underwent reduction at a lower reaction temperature and in shorter reaction time to yield **2h** in 88% yield (Scheme 2). In general only minor formation of the amine could be observed in the reactions to give aldehydes. However, it was difficult to avoid amine formation in the case of the carbamate-substituted amide **1q** and the furanylamide **1t**. The reduction of the thiophene amide **1u** worked well, and gave the corresponding aldehyde **2u** in 95% yield as determined by ^{1}H NMR spectroscopy.

By performing the reaction at higher temperature it was possible to obtain amines as the major product and a variety of different amides were evaluated for this transformation (Scheme 3). Investigation of the substrate scope revealed that the method is applicable for both electron-poor and electron-

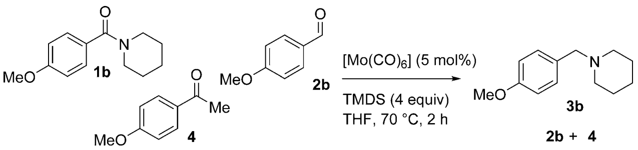


Scheme 3. Chemoselective formation of amines. [a] Amide (1.0 mmol), $[Mo(CO)_6]$ (5 mol%), TMDS (4.0 mmol), THF (2.0 mL). Yield refers to the isolated product. [b] $[Mo(CO)_6]$ (10 mol%), TMDS (2.0 mmol). [c] TMDS (2.0 mmol) 9 h, 80 °C. [d] 24 h, 65 °C. [e] THF (3.0 mL). [f] 99% *ee*. [g] 0.5 mmol scale.

rich amides (**1b**/**1c**). However, the electron-deficient substrate *p*-trifluoromethyl benzamide (**1c**) was more challenging to reduce and required longer reaction time to ensure a good yield of the amine **3c**. Amides with different N-substituents such as piperidine (**1b**), *N*,*N*-dibenzylamine (**1b′**), morpholine (**1b″**), *N*,*N*-dimethylamine (**1o**/**1s**), and pyrrolidine (**1r**) gave the corresponding amines in good to excellent yields. Heteroaryl-containing amides were readily reduced into the corresponding amines **3t** and **3u**, and the *p*-iodo-substituted amide **3d** was deoxygenated without any dehalogenation occurring. The method can be applied for chiral amide substrates without racemization of the stereocenters and the enantiomerically pure amide **1r** underwent reduction to the amine **3r** which was obtained in a good yield with an *ee* value of 99%. Furthermore, several functional groups, such as nitro, olefin, carbamate, ester, and carboxylic acid moieties, were tolerated under the optimized reaction conditions (**3e**–**q** and **3s**). Ketimine and aldimine functionalities were surprisingly stable under the reaction conditions and high yields of the amine-imine compounds **3w** and **3x** were obtained.

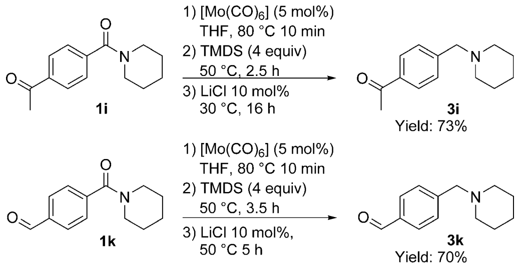
Some limitations of the scope were observed and the nitrile-containing amide **1g** and a *p*-nitro-substituted amide could not be selectively deoxygenated. Furthermore, the attempted reduction of a terminal alkyne substituted amide resulted in a complex mixture of products even when performing the reaction at low temperature.

To further evaluate the chemoselectivity of the catalytic system, a competitive reduction experiment was performed by employing a 1:1:1 ratio of amide, ketone, and aldehyde substrates as shown in Scheme 4. By using the optimized reaction conditions for **1b** we observed full conversion of the amide into the corresponding amine within a 2 hour reaction time, while the ketone **4** and aldehyde **2b** remained unreacted.



Scheme 4. Competitive reduction between amide, ketone, and aldehyde substrates.

After the competitive evaluation of the protocol we investigated benzamides substituted with either a ketone (**1i**) or an aldehyde (**1k**; Scheme 5). These amides constituted the most challenging substrates, taking into account that these groups are highly reducible and that they impose an electron-withdrawing effect which was observed to slow down the reduction. During the extensive screening of the ketone-containing substrate **1i** we observed that the catalyst became more active if the reaction vessel was purged with N_2 after the thermal activation of the catalyst.[17] This observation led us to perform the reduction to the silylhemiaminal at 50 °C, and a yield of 94% of this species was observed after 2 hours, as determined by ^1H NMR analysis. We hypothesized that the addition of an oxophilic Lewis acid would promote the cleavage of the silylhemiaminal into an iminium ion, thus enabling the reduction to the amine to proceed at milder reaction conditions.[3e,4c] An evaluation of Lewis acids showed that catalytic amounts of LiCl indeed promoted the collapse of the tetrahedral intermediate if this Lewis acid was added after the silylhemiaminal formation.



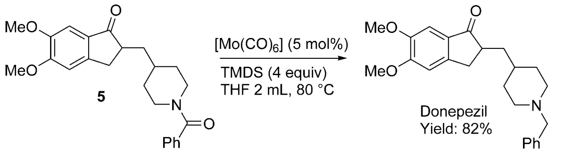
Scheme 5. Chemoselective reduction of amides into amines.

The reduction to the amine was efficient at 50 °C when LiCl was added. However, the Lewis acid also activated the ketone and we were not able to obtain the desired ketone-amine **3i** in high yield under these reaction conditions. Fortunately, by lowering the reaction temperature in the second step to 30 °C and prolonging the reaction time, an increase in chemoselectivity was observed and **3i** was isolated in 73% yield (Scheme 5). Intriguingly, the *p*-aldehyde-substituted benzamide **1k** could be kept at 50 °C in the second step and the aldehyde-amine **3k** was isolated in 70% yield. Such levels of chemoselectivity have not been demonstrated previously by any catalytic or stoichiometric protocols.

Primary and secondary amides are known to be less reactive under hydrosilylation conditions and also proved to be challenging with this protocol.[18] The evaluation of secondary and primary amides yielded silylated amides as the major products according to ^{1}H NMR analysis. These species were previously reported by Nahashima and co-workers.[21]

An important aspect for the academic and industrial community is the possibility to scale-up catalytic protocols. To investigate this feature of the developed catalytic procedure, we evaluated the substrate **1d** on a 10 mmol scale (> 3 g) in 2-methyl THF, which is considered as a more environmentally friendly solvent. The corresponding amine **3d** was obtained in 91% yield after performing the reaction under refluxing conditions for 1.5 hours. The large-scale reaction for the preparation of the corresponding aldehyde was performed at room temperature, and compound **2d** was isolated in 90% yield (2.1 g) after work-up.

To further demonstrate the synthetic utility of the protocol, we targeted the pharmaceutical compound Donepezil, a drug used in the palliative treatment of Alzheimer's disease (Scheme 6).[22] Donepezil contains both a ketone and amine motif and the synthesis of the amide precursor **5** was performed in a similar fashion to the route reported by Charette and Barbe.[11a] The use of the molybdenum-based catalytic protocol allowed facile selective reduction of **5** and Donepezil was isolated in 82% yield. In this case the ketone does not impose an electron-withdrawing effect on the amide and the reaction could be performed without the requirement of the Lewis acid co-catalyst.



Scheme 6. Late stage chemoselective reduction for the preparation of Donepezil.

To conclude, we have developed a mild catalytic hydrosilylation protocol for the reduction of tertiary amides. The reaction is tunable by variation of temperature, thus allowing for either selective C–O or C–N bond cleavage to furnish the corresponding amines or aldehydes in high yields. It was observed that electron-deficient substrates were more challenging and stands in contrast to classic carbonyl reactivity. A mechanistic investigation is currently being pursued to explain this trend along with the high chemoselectivity of the process. Aldehydes were readily tolerated over amides when running the reaction to give the silylhemiaminal species, and upon work-up yielded bis(aldehydes). The system also displayed unprecedented chemoselectivity in the transformation of amides into amines as shown by the competitive reduction set-up with amide, ketone, and aldehyde. It was more challenging to obtain chemoselectivity in case of the ketone- and aldehyde-containing amides because of the electron-withdrawing properties of these groups. Nevertheless, the corresponding amines were obtained in high yields by the use of a co-catalyst to facilitate the silylhemiaminal cleavage. Surprisingly, imines were highly stable and the amide moiety was selectively reduced to give both aldehyde-imine and amine-imine compounds. The attractive properties of this system along with the scalability and low cost/high stability of TMDS should make this method applicable in both academic and industrial settings. Because of the mildness and high level of chemoselectivity it can easily be envisioned that amides could serve as stable protection groups, which upon late-stage removal would afford either the aldehyde or the amine functionality.

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