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Review

Base Metal Catalysts for Deoxygenative Reduction of Amides to Amines

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Received: 24 April 2019; Accepted: date; Published: 28 May 2019

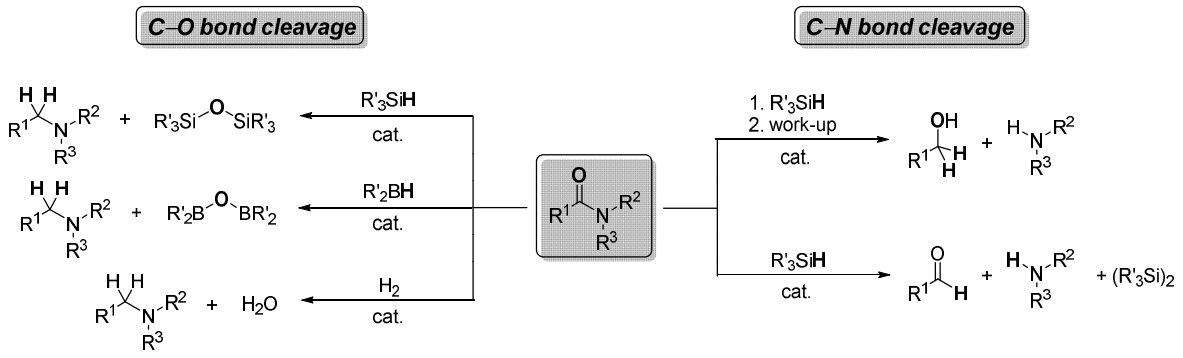
Abstract: The development of efficient methodologies for production of amines attracts significant attention from synthetic chemists, because amines serve as essential building blocks in the synthesis of many pharmaceuticals, natural products, and agrochemicals. In this regard, deoxygenative reduction of amides to amines by means of transition-metal-catalyzed hydrogenation, hydrosilylation, and hydroboration reactions represents an attractive alternative to conventional wasteful techniques based on stoichiometric reductions of the corresponding amides and imines, and reductive amination of aldehydes with metal hydride reagents. The relatively low electrophilicity of the amide carbonyl group makes this transformation more challenging compared to reduction of other carbonyl compounds, and the majority of the reported catalytic systems employ precious metals such as platinum, rhodium, iridium, and ruthenium. Despite the application of more abundant and environmentally benign base metal (Mn, Fe, Co, and Ni) complexes for deoxygenative reduction of amides have been developed to a lesser extent, such catalytic systems are of great importance. This review is focused on the current achievements in the base-metal-catalyzed deoxygenative hydrogenation, hydrosilylation, and hydroboration of amides to amines. Special attention is paid to the design of base metal catalysts and the mechanisms of such catalytic transformations.

Keywords: Base metals; homogeneous catalysis; amides; reduction; hydrogenation; hydroboration; hydrosilylation; amines

1. Introduction

Amines represent one of the most important classes of compounds for the modern synthetic organic chemistry, owing to their indispensable role as structural motifs of many natural products, biologically active molecules, pharmaceutical compounds, and agrochemicals [1–5]. Among a number of conventional synthetic routes developed for the preparation of amines, the most significant approaches include N–H alkylation with alcohols and alkyl halides, stoichiometric reduction of the corresponding amides and imines, and reductive amination of carbonyl compounds with metal hydride reagents [2,4]. Such transformations often suffer from a lack of control [3] and functional group tolerance, and many of them lead to the formation of large amounts of metallic salt byproducts [4,5], as observed in the reactions with traditional stoichiometric reductants, such as aluminum and boron hydrides [6]. In contrast, transition-metal-catalyzed deoxynenative reduction of readily available primary, secondary, and tertiary amide precursors via hydrogenation [7–13], hydrosilylation [14], and hydroboration reactions [15] represents a straightforward methodology for

production of a large variety of amines (Scheme 1), and serves as an attractive alternative to conventional stoichiometric methods.



Scheme 1. Deoxygenative hydrosilylation, hydroboration, and hydrogenation of amides to amines (C–O bond cleavage) and catalytic C–N bond cleavage in amides.

In comparison to aldehydes, ketones, and esters, for reduction of which efficient catalytic systems have been developed [16], the electrophilicity of the amide carbonyl group is considerably lower, which makes the reduction of amides a challenging task. The majority of the reported examples concerning selective deoxygenation of amides to amines have employed catalysts based on precious metals, such as ruthenium [7–11,14,17–23], rhodium [14,24–26], iridium [12,14,27–31], and platinum [32–34]; however, the reactions often require rather harsh conditions, such as elevated temperatures and long reaction times. Due to the skyrocketing prices of heavy late transition metals, the development of more economical catalytic systems for deoxygenative reduction of amides, using non-precious metals and operating under mild conditions, has been an intensive area of research in the last decades, with deoxygenative hydrosilylation being the most studied approach. Thus, a few examples of deoxygenative hydrosilylation of amides to amines have been demonstrated using relatively inexpensive titanium [35,36], molybdenum [37,38], copper [39], and zinc pre-catalysts [40–43], and efforts to develop transition metal free systems have also been undertaken [44,45]. However, the vast majority of these reactions concern hydrosilylation of tertiary amides and generally require rather high catalyst loadings (up to 20 mol%), elevated temperatures (up to 155 °C) and long reaction times (up to 72 h). In addition, many of these reactions have been shown to be unselective in the C–O vs. C–N bond cleavage, and lead to complex mixtures of tertiary and secondary amines along with formation of either aldehyde or alcohol byproducts (Scheme 1) [35,46,47]. The hydrosilative reduction of secondary and primary amides to amines has proven even more arduous [36] due to the competing silane-assisted dehydration of these substrates to imines and nitriles, respectively [14].

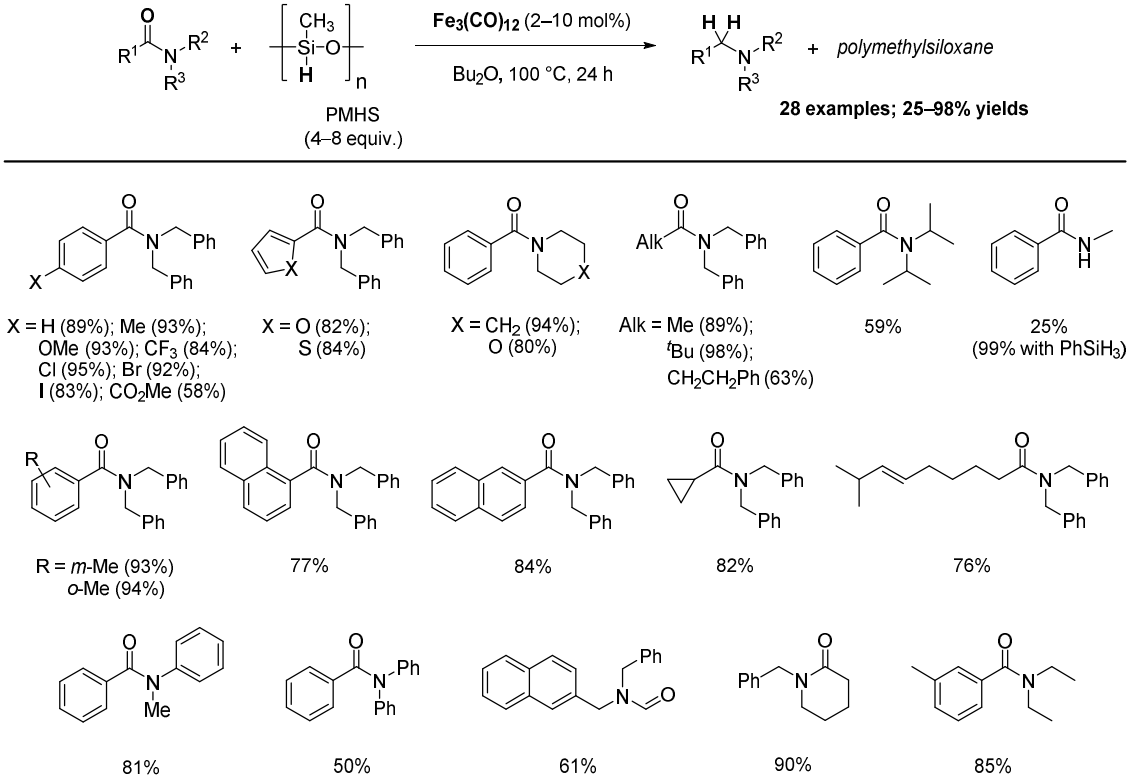
One of the practical approaches for designing more economical surrogates to precious metal catalysts with retention of the precious-metal-like reactivity includes the use of complexes with earth-abundant late transition metals, so called base metals, such as Mn, Fe, Co, and Ni [48]. Indeed, a number of such complexes have been found to efficiently catalyze the deoxygenative reduction of amides to amines under rather mild conditions [15,49–51], including conversion of more challenging secondary and primary amides to the corresponding amines [15,49,51]. This review summarizes the recent developments in the area of base-metal-catalyzed deoxygenative hydrosilylation, hydroboration, and hydrogenation of amides to amines, including a detailed discussion of the mechanisms of these catalytic transformations.

2. Deoxygenative Hydrosilylation of Amides

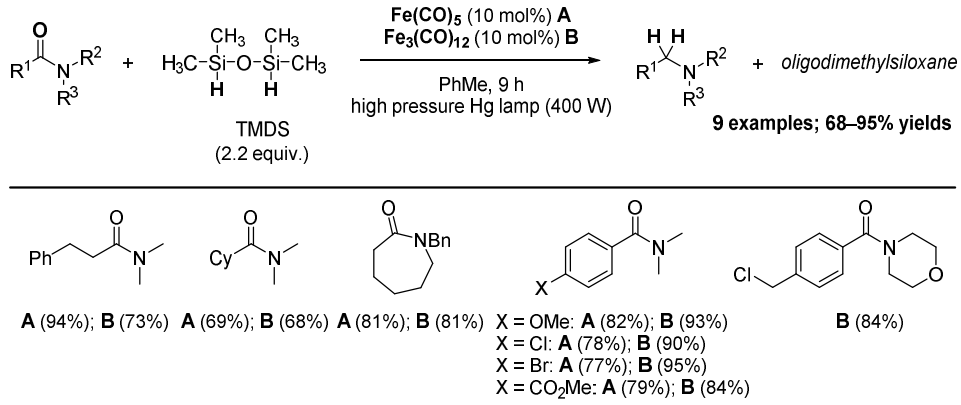
2.1. Iron-catalyzed Reactions

Although probably the first instance of catalytic deoxygenative hydrosilylation of tertiary and secondary amides appeared back in 1962 ($ZnCl_2$-catalyzed reactions) [40,52], and the first

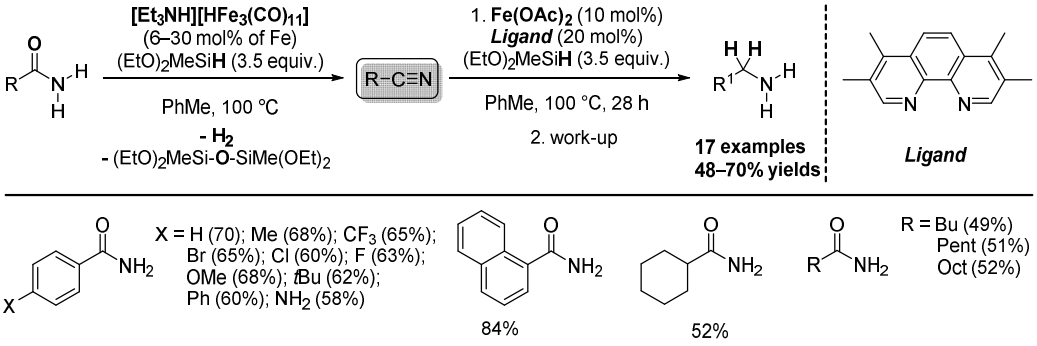
hydrosilylation of tertiary amides to amines using well-defined rhodium catalysts was reported in 1998 [24], the first examples of base-metal-catalyzed deoxygenative hydrosilylation of amides were demonstrated only in 2009 by Beller et al. [53] and Nagashima et al. [54], using iron carbonyl complexes, $Fe(CO)_5$ and $Fe_3(CO)_{12}$. Both systems were found to mediate the reductions of a large variety of tertiary aliphatic, aromatic, and heterocyclic amides using $PhSiH_3$, PMHS (PMHS = polymethylhydrosiloxane), and TMDS (TMDS = tetramethyldisiloxane) (Schemes 2 and 3) [53,54]. The reactions were conducted under either thermal (100 °C, 24 h) [53,54] or photochemical (400 W high pressure mercury lamp, 25 °C, 9 h) [54] activation conditions, and required rather high catalyst loadings (6–30 mol% of Fe). Using $Fe_3(CO)_{12}$, only one example of deoxygenative hydrosilylation of a secondary amide, namely *N*-methylbenzamide, with 2.5 equiv. of $PhSiH_3$ as a reductant was described by Beller et al., whereas the analogous reaction with PMHS (6 equiv.) was shown to be more sluggish, and resulted in only 25% conversion of *N*-methylbenzamide to *N*-benzylmethylamine (Scheme 2) [53]. Reduction of primary amides with either PMHS or $PhSiH_3$ (3 equiv. for both) proved more difficult, and in the presence of either $Fe_3(CO)_{12}$ (6 mol% of Fe) or $[Et_3NH][HFe_3(CO)_{11}]$ (6 mol% of Fe) at 100 °C in toluene, instead of the desired deoxygenation to primary amines, led to the selective dehydration of the amides to the corresponding nitriles, with the most efficient hydrosilane for this transformation being $(EtO)_2MeSiH$ [55]. Later on, this strategy was used by Beller et al. [56] as a detour for the challenging conversion of primary amides to primary amines. The reported approach (Scheme 4) [56] allowed the issues of direct deoxygenative hydrosilylation of primary amides to be overcome and involved consecutive silane-assisted dehydration of the amides to nitriles using $[Et_3NH][HFe_3(CO)_{11}]$ (7.5 mol% of Fe) at 100 °C in toluene, followed by double hydrosilylation of the nitriles to the corresponding amines [14,57–61] using $Fe(OAc)_2$ (10 mol%) ligated with 3,4,7,8-Tetramethyl-1,10-phenanthroline (20 mol%).



Scheme 2. Thermal deoxygenative hydrosilylation of amides to amines catalyzed by $Fe_3(CO)_{12}$.



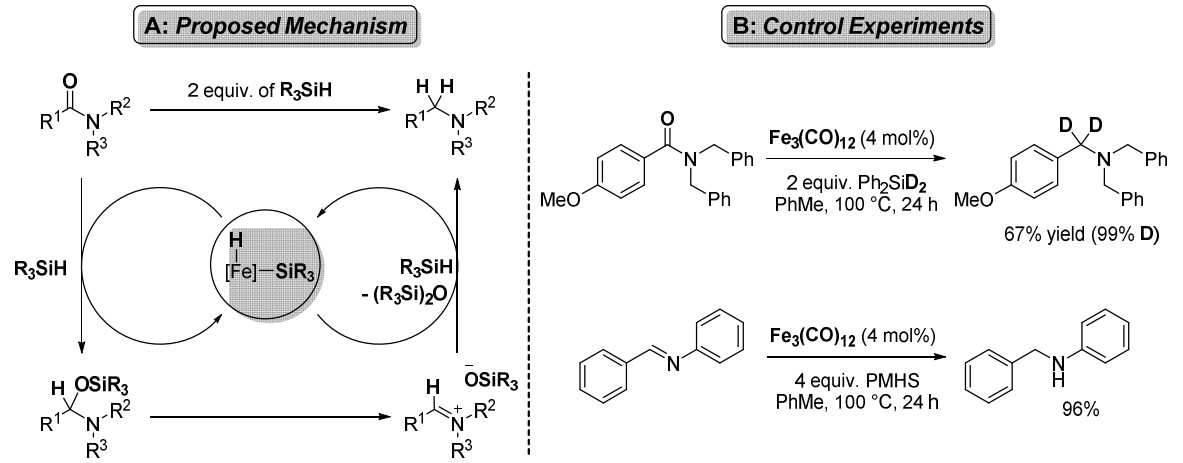
Scheme 3. Photoassisted deoxygenative hydrosilylation of tertiary amides catalyzed by $Fe(CO)_5$ and $Fe_3(CO)_{12}$.



Scheme 4. Fe-catalyzed consecutive dehydration–hydrosilylation approach for conversion of primary amides to primary amines.

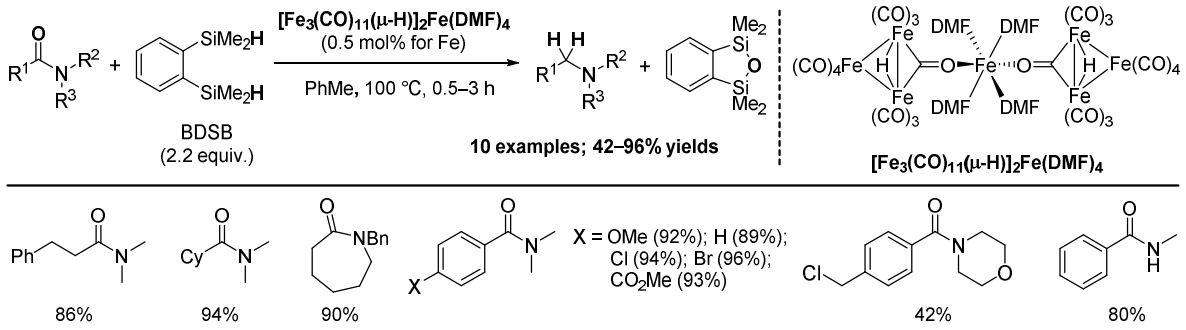
The mechanism of $Fe_3(CO)_{12}$-catalyzed deoxygenative hydrosilylation of tertiary amides was proposed by Beller and co-workers (Scheme 5A) [53], and is somewhat similar to the reaction pathway reported earlier by Nagashima et al. for analogous Ru-catalyzed transformations [21]. It is generally assumed that in the presence of hydrosilanes, either thermal or photochemical activation of the iron carbonyl complex leads to the formation of a catalytically active silyl hydride species [62], which first hydrosilylates the amide carbonyl group to give an *O*-silylated *N,O*-acetal. This latter compound is then transformed to an iminium species, followed by its reduction with the second molecule of hydrosilane. This mechanistic proposal was further supported (i) by selective (99%) incorporation of two deuterium atoms at the benzylic position of *N,N*-dibenzyl-1-(4-methoxyphenyl)methanamine-d_2 upon $Fe_3(CO)_{12}$-catalyzed deoxygenative hydrosilylation of *N,N*-dibenzyl-4-methoxybenzamide with 2 equiv. of Ph_2SiD_2, and (ii) by efficient $Fe_3(CO)_{12}$-catalyzed reduction of *N*-benzylideneaniline to *N*-benzylaniline with 4 equiv. of PMHS (Scheme 5B) [53].

Notably, iron-carbonyl-catalyzed deoxygenative hydrosilylation of tertiary amides reported by Beller et al. and Nagashima et al. tolerates internal alkene and ester functionalities (Scheme 2) [53,54]. However, in contrast to ruthenium and platinum catalysts, which were found to tolerate nitro groups, the $Fe_3(CO)_{12}$-catalyzed reaction of *N,N*-dimethyl-*p*-nitrobenzamide with an excess of TMDS (10 equiv. of Si–H) showed reverse chemoselectivity and instead of the expected *p*-[(dimethylamino)methyl]aniline, selective formation of *N,N*-dimethyl-*p*-aminobenzamide (77% isolated yield) was observed after 24 h at 100 °C [54].

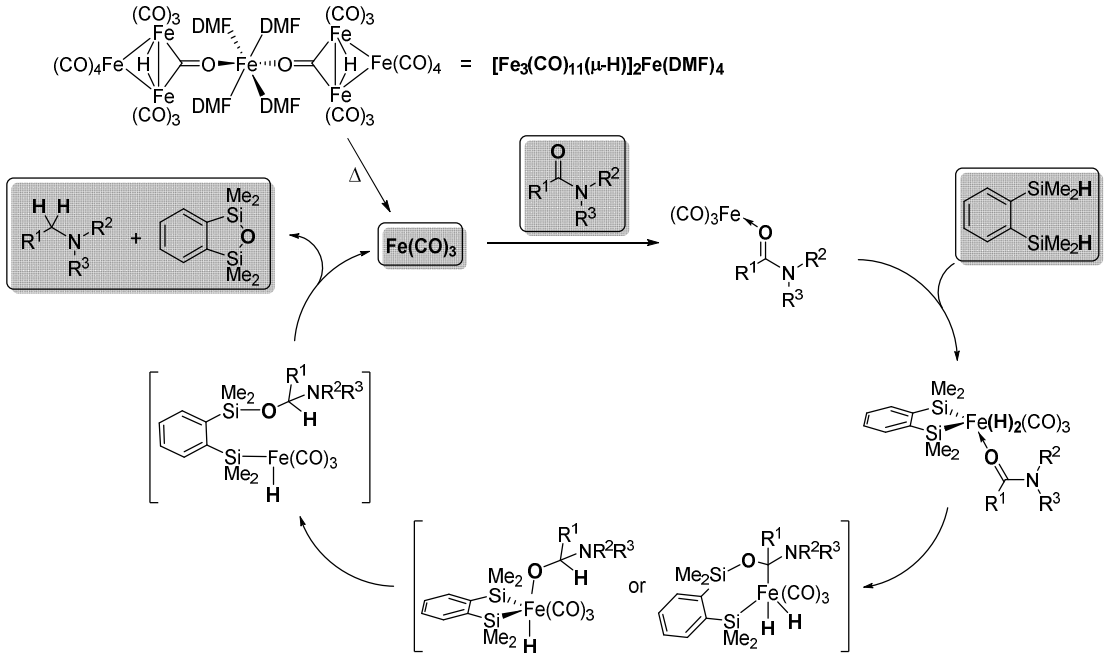


Scheme 5. Proposed mechanism for $Fe_3(CO)_{12}$-catalyzed deoxygenative hydrosilylation of tertiary amides (**A**) and control experiments in favor of this mechanistic proposal (**B**).

In 2011, driven by the intention to improve Fe-catalyzed reduction of amides and to decrease the reaction times and catalyst loading, Nagashima et al. reported a modified iron carbonyl pre-catalyst, $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$, obtained by treatment of $Fe(CO)_5$ with DMF at 65 °C [63]. This Fe_7-cluster was found to efficiently mediate deoxygenative reduction of carboxamides with 1,2-bis(dimethylsilyl)benzene (BDSB) within 0.5–3 h at 100 °C, with significantly reduced loading for Fe of only 0.5 mol% (Scheme 6) [63]. Interestingly, DBSB showed considerably enhanced reactivity compared to Me_2PhSiH, $(EtO)_3SiH$, and TMDS in the reduction of *p*-$MeOC_6H_4C(O)NMe_2$. Superior activity of $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$ to $Fe(CO)_5$ and $Fe_3(CO)_{12}$ in the reduction of *N,N*-dimethyl-*p*-methoxybenzamide with BDSB remained even when the reaction temperature was reduced to 50–80 °C. The proposed mechanism of $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$-catalyzed deoxygenative hydrosilylation of carboxamides with BDSB is depicted in Scheme 7 [63]; it is believed that $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$ behaves as a dormant species, and that under the reaction conditions it is reversibly converted to unsaturated $Fe(CO)_3$, which allows for coordination of the amide substrate to form the $Fe(CO)_3(\kappa^1\text{-amide})$ intermediate, followed by the oxidative addition of the Si–H bonds of BDSB and insertion of the coordinated amide into either the Fe–H bond or Fe–Si bond [63]. Interestingly, addition of PPh_3 inhibits the $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$-catalyzed reactions, and $Fe(CO)_3(PPh_3)_2$ was recovered from the reaction mixture [63]. This suggests that the enhanced reactivity of $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$ (CO/Fe ratio of 3.1) compared to $Fe(CO)_5$ and $Fe_3(CO)_{12}$ (CO/Fe ratio of 5 and 4, respectively) can be explained by the suppression of the catalytic activity of $Fe(CO)_3$ generated from $Fe(CO)_5$ or $Fe_3(CO)_{12}$ by coordination of CO present in the reaction mixture [63].



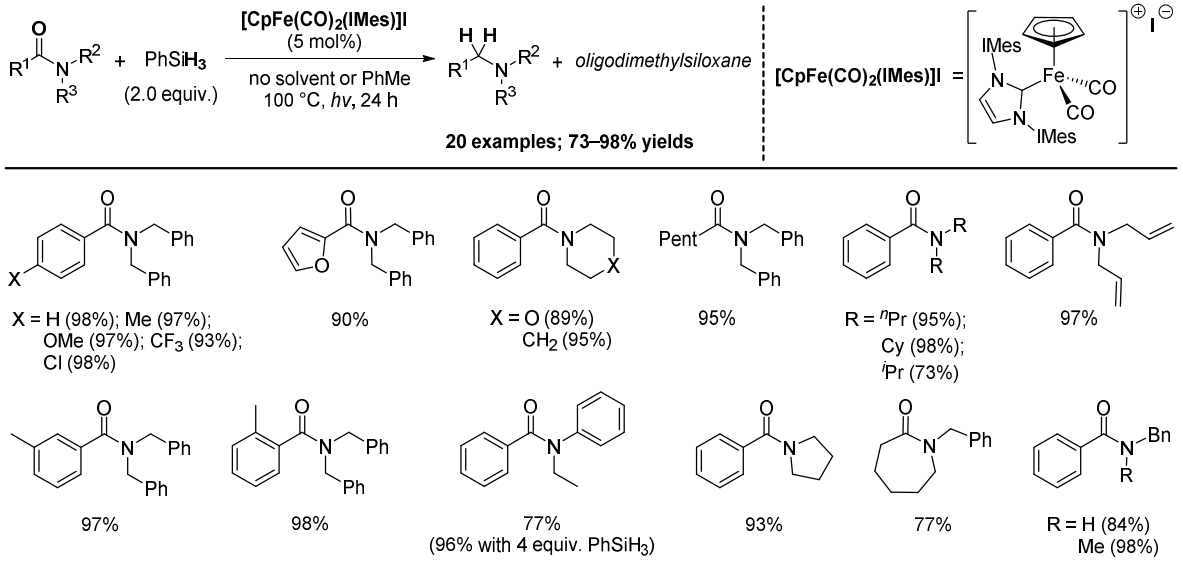
Scheme 6. $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$-catalyzed deoxygenative hydrosilylation of carboxamides.



Scheme 7. Proposed mechanism of $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$-catalyzed deoxygenative hydrosilylation of carboxamides.

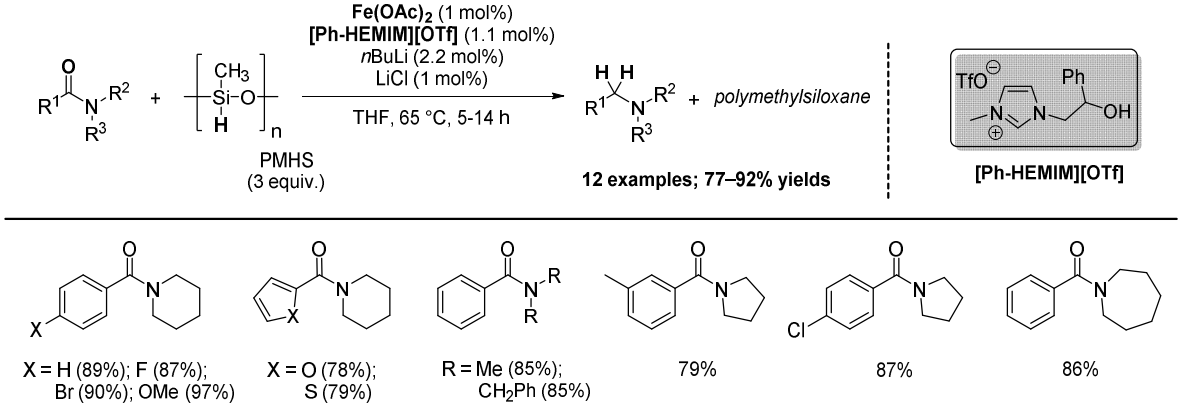
In contrast, $[Fe_3(CO)_{11}(\mu\text{-H})]_2Fe(DMF)_4$ was found to be inactive in deoxygenative reduction of primary amides, and, similarly to $Fe_3(CO)_{12}$ and $[Et_3NH][HFe_3(CO)_{11}]$ [55], treatment of benzamide with BDSB at 100 °C for 3 h resulted in a dehydration reaction and formation of benzonitrile [63].

In the same year, Sortais, Darcel, and co-workers reported photoassisted deoxygenative hydrosilylation of a series of tertiary amides with $PhSiH_3$, catalyzed by a well-defined iron cyclopentadienyl *N*-heterocyclic carbene (NHC) complex, $[CpFe(CO)_2(IMes)]I$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) (Scheme 8) [64]. The reduction of various tertiary amides led to the corresponding amines in good to excellent isolated yields (73–98%), tolerating alkene functionalities at the nitrogen atom. The steric crowding around the amide nitrogen was shown to somewhat affect the reactivity, as the yields of the deoxygenated products decreased in the order $PhC(O)NCy_2$ (98%) > $PhC(O)N^nPr_2$ (95%) > $PhC(O)N^iPr_2$ (73%) (Scheme 8) [64]. For secondary amides, only the reduction of *N*-benzylbenzamide was demonstrated, whereas primary amides, benzamide and *p*-bromobenzamide, were selectively dehydrated to the corresponding nitriles [64], similarly to the iron carbonyl systems discussed above [53,54].

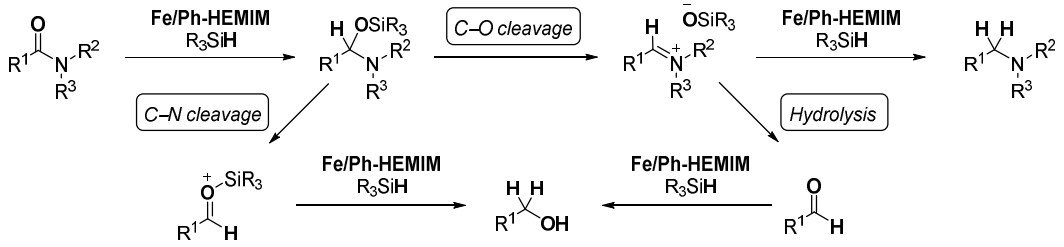


Scheme 8. [CpFe(CO)2(IMes)]I-catalyzed deoxygenative hydrosilylation of amides.

A similar reactivity in hydrosilylation of tertiary amides to amines was observed for the iron-NHC complex generated in situ from iron(II) acetate and 1-(2-hydroxy 2-phenylethyl)-3-methylimidazolium triflate [Ph-HEMIM][OTf] (Scheme 9) [65]. Using the catalytic system composed of $Fe(OAc)_2$ (1 mol%), [Ph-HEMIM][OTf] (1.1 mol%), *n*BuLi (2 mol%) and LiCl (1 mol%) a series of aromatic and heteroaromatic tertiary amides were converted to tertiary amines with PMHS at a significantly reduced (compared with previous examples of Fe-catalyzed reactions) temperature of 65 °C [65]. LiCl seems to play an important role for the selectivity of the reactions, as, in the absence of LiCl, the reduction of *N*,*N*-dimethylbenzamide resulted in the formation of substantial amounts of benzaldehyde (11%) and benzyl alcohol (15%). Using the same reaction conditions, a Fe/[Ph-HEMIM] catalytic system failed to reduce primary or secondary benzamides, as well as aliphatic amides, to their corresponding amines [65]. A proposed schematic mechanism for the Fe/[Ph-HEMIM]-catalyzed deoxygenative hydrosilylation of tertiary amides is depicted in Scheme 10 [65], and is somewhat similar to the mechanism suggested for analogous transformations mediated by $Fe_3(CO)_{12}$ [53]. First, hydrosilylation of the carbonyl group leads to an *O*-silylated *N*,*O*-acetal, which upon C–O bond cleavage gives an iminium ion (Scheme 10) [65], followed by its reduction to the desired amine. Formation of benzaldehyde and benzyl alcohol byproducts was suggested to proceed via two pathways: (i) decomposition of *N*,*O*-acetal to a silylated oxo-carbenium ion, accompanied by elimination of dimethylamine (C–N bond cleavage path; Scheme 10) [65], and (ii) hydrolysis of the iminium intermediate to an aldehyde, followed by its reduction to an alcohol. LiCl (1 mol%) acts as an oxophilic Lewis acid that assists the formation of the iminium intermediate from *O*-silylated *N*,*O*-acetal, therefore increasing the yield of the desired amine and decreasing the probability of the C–N bond cleavage pathway (Scheme 10) [65].

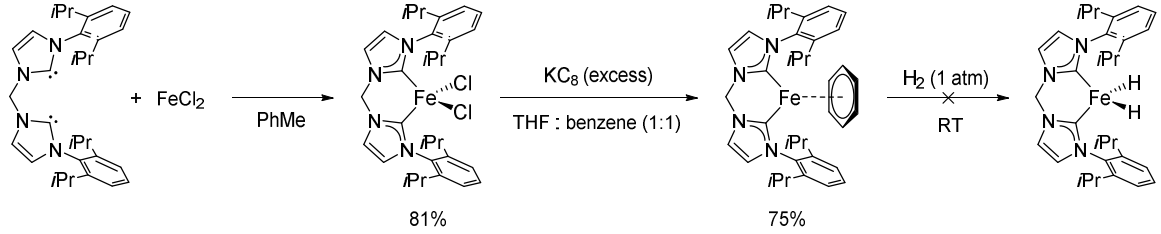


Scheme 9. Fe/[Ph-HEMIM]-catalyzed hydrosilylation of tertiary amides to amines.

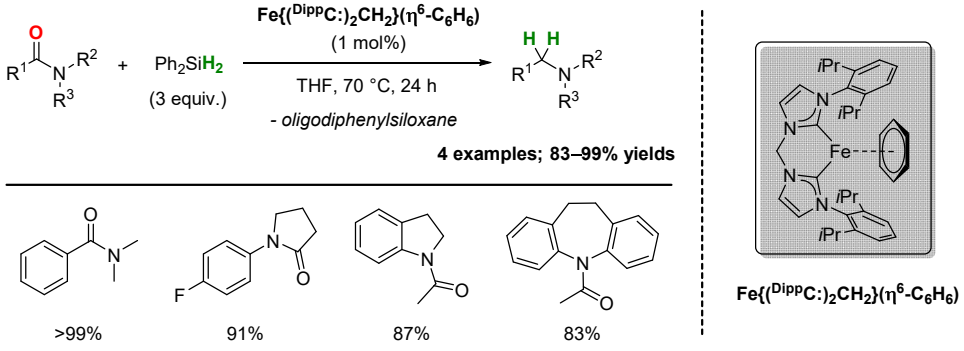


Scheme 10. Proposed schematic mechanism for Fe/Ph-HEMIM-catalyzed hydrosilative reduction of tertiary amides to amines.

An example of a well-defined iron(0) bis-*N*-heterocyclic carbene (bis-NHC) catalyst, Fe{(^{Dipp}C:)$_2$CH$_2$}(η^6-C$_6$H$_6$) for reduction of tertiary amides to amines under hydrosilylation conditions was reported by Driess et al.[66] The catalyst can be easily prepared by coordination of the bis-NHC ligand to FeCl$_2$, followed by reduction of the resulting dichloride complex with KC$_8$ in the presence of benzene (Scheme 11) [66]. Using Ph$_2$SiH$_2$ (3 equiv.) as a reductant and 1 mol% of the iron bis-NHC catalyst, a number of tertiary amides bearing different steric and electronic properties were converted in good to excellent yields to the corresponding amines under rather mild reaction conditions (70 °C, 24 h; Scheme 12) [66]. In some cases, the yields of tertiary amines were superior to other iron-based systems for hydrosilylation of amides [53–55,63–66]. The authors noted [66] that the use of a well-defined Fe(0) bis-NHC pre-catalyst could facilitate mechanistic studies; however, no mechanism was proposed. One could assume that the reactions start with oxidative addition of Ph$_2$SiH$_2$ to the Fe(0) center to form Fe(II) silylhydride species; however, the reactivity of Fe{(^{Dipp}C:)$_2$CH$_2$}-(η^6-C$_6$H$_6$) with hydrosilanes has not been reported. Notably, no oxidative addition of H$_2$ and formation of a dihydride species akin to Fe{(^{Dipp}C:)$_2$CH$_2$}(H)$_2$ was observed when a sample bis-NHC Fe(0) complex was exposed to 1 atm of H$_2$ at room temperature for several days (Scheme 11) [66].



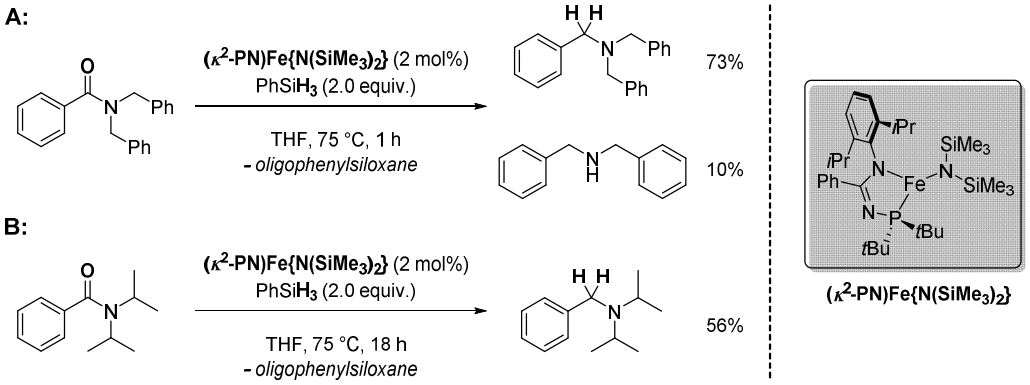
Scheme 11. Preparation of Fe{(^{Dipp}C:)$_2$CH$_2$}(η^6-C$_6$H$_6$) and its reactivity with H$_2$.



Scheme 12. Fe{(^{Dipp}C:)$_2$CH$_2$}(η^6-C$_6$H$_6$)-catalyzed hydrosilylation of tertiary amides to amines.

The most recent example of Fe-catalyzed hydrosilative reduction of amides was demonstrated in 2019 by Sydora, Stradiotto, Turculet, et al., for the reaction of *N*,*N*-dibenzylbenzamide with

$PhSiH_3$ in the presence of a Fe(II) *N*-phosphinoamidinate pre-catalyst, (κ^2-P,N)Fe{$N(SiMe_3)_2$} (Scheme 13) [51]. With 2 mol% of (κ^2-P,N)Fe{$N(SiMe_3)_2$} after only one hour at 75 °C in THF, the reaction showed >95% conversion of *N,N*-dibenzylbenzamide to a mixture of C–O and C–N cleavage products, NBn_3 (73%) and $HNBn_2$ (10%), respectively (Scheme 13,A) [51]. Similar reactivity with 92% overall conversion of the substrate in 18 h was observed in hydrosilylation of *N,N*-diisopropylbenzamide with 2 equiv. of $PhSiH_3$ at 75 °C; however, only 56% formation of diisopropylbenzylamine was observed by GC (Scheme 13,B) [51]. The reductions are believed to proceed via a reactive Fe-hydride intermediate generated by reaction of (κ^2-P,N)Fe{$N(SiMe_3)_2$} with $PhSiH_3$ under catalytic conditions [67]. Bis(hexamethyldisilazide) pre-catalyst Fe{$N(SiMe_3)_2$}$_2$ turned out to be significantly less effective in hydrosilylation of *N,N*-dibenzylbenzamide under analogous reaction conditions, and resulted only in 39% conversion of the amide to give 33% of NBn_3 and <5% of $HNBn_2$ [51], indicating an important role of ancillary ligands. To the best of our knowledge, no examples of Fe(amide)-catalyzed hydrosilylation of secondary or primary amides have been reported.



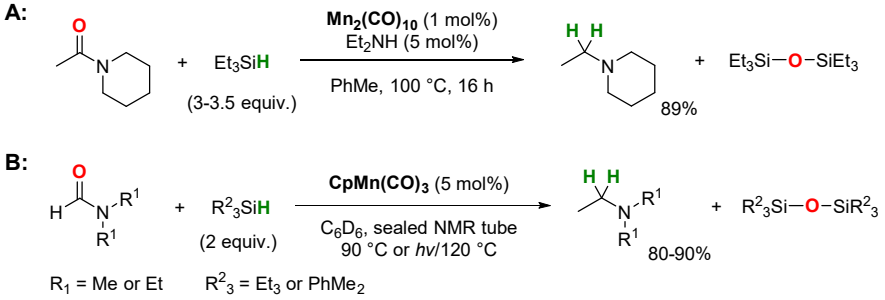
Scheme 13. (κ^2-PN)Fe{$N(SiMe_3)_2$}-catalyzed hydrosilative reduction of *N,N*-dibenzylbenzamide.

Thus, except a few cases of Fe-catalyzed deoxygenative hydrosilylation of secondary amides [53,63,64], most of the reported iron-based systems are limited to conversion of tertiary amides to amines. Catalytic reduction of primary amides still represents a challenging problem, and to date, with an exception of the dimetal-catalyzed sequential dehydration–hydrosilylation route developed by Beller et al. [56], no direct single-metal approach for Fe-catalyzed hydrosilylation of primary amides to primary amines has been reported.

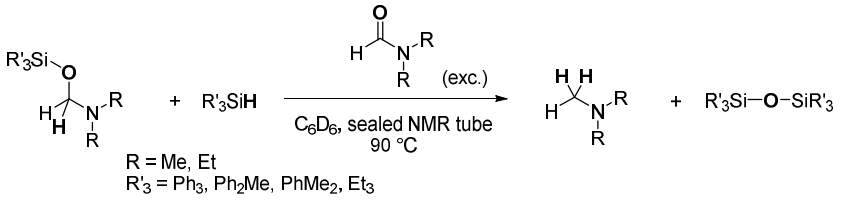
2.2. Manganese-catalyzed Reactions.

Mn-catalyzed deoxygenative hydrosilylations of amides are limited to only a few systems, all of which concern the reductions of tertiary amides. Similarly with iron, the manganese-catalyzed reduction of amides with hydrosilanes was initially attempted with carbonyl complexes under either thermal or photolytic conditions [17,68]. Thus, deoxygenative hydrosilylation of *N*-acetylpiperidine with Et_3SiH (3-3.5 equiv.) at 100 °C to give *N*-ethylpiperidine (89%; Scheme 14,A) was demonstrated by Fuchikami et al. for $Mn_2(CO)_{10}$ (1 mol%) in the presence of 5 mol% of Et_2NH [17]. The second example was shown by Pannell and co-workers for thermal (90 °C, 28 h) and photochemical (120 °C, 12-18 h) addition of Et_3SiH and $PhMe_2SiH$ to DMF and *N,N*-diethylformamide (DEF) in the presence of 5 mol% of $CpMn(CO)_3$ (Scheme 14,B) [68]. The reactions were suggested to proceed through activation of an amide via coordination to the metal complex, followed by formation of siloxymethylamines $R_2NCH_2OSiR'_3$ (R = Me, Et; R'_3 = Et_3, $PhMe_2$), observed in situ by NMR spectroscopy and isolated when the analogous transformations were performed in the presence of $Mo(CO)_6$ pre-catalyst (5 mol%) [68]. Interestingly, further conversion of siloxymethylamines to the corresponding amines and disiloxanes did not require any catalyst. Thus, Pannell et al. found that, in the absence of any metal catalyst, the siloxymethylamines $R_2NCH_2OSiR'_3$ were unreactive towards various silanes; however, at 90 °C, addition of an excess of DMF or DEF (ca. 5 equiv.) to the mixtures of $R_2NCH_2OSiR'_3$ and silanes resulted in >90% conversions of

siloxymethylamines to the corresponding amines and disiloxanes (Scheme 15) [68]. Activation of the Si–H bond in this metal-free transformation may proceed via DMF (or DEF) coordination to the silicon center to form 5- and/or 6-coordinated species significantly increasing polarization of the Si–H bond [69,70].

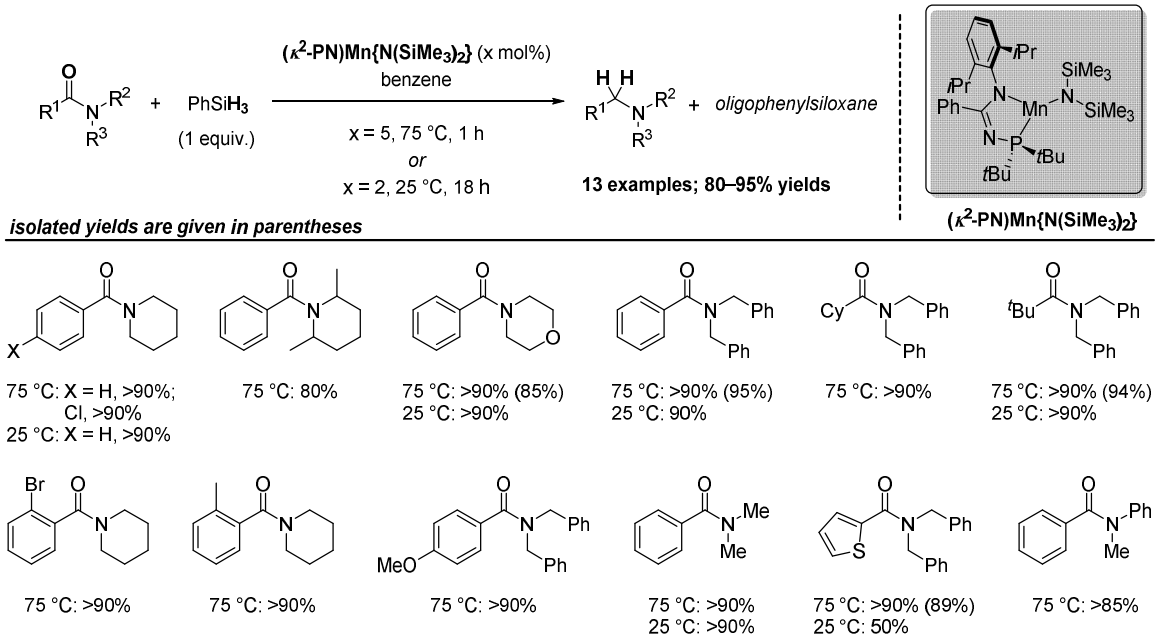


Scheme 14. Deoxygenative hydrosilylation of tertiary amides catalyzed by Mn carbonyl complexes.



Scheme 15. DMF promoted metal-free reaction of $Me_2NCH_2OSiR_3$ with hydrosilanes.

The most recent report on hydrosilative reduction of tertiary amides to amines with $PhSiH_3$ and a manganese amide pre-catalyst supported by a *N*-phosphinoamidinate ligand (κ^2-P,N)Mn{$N(SiMe_3)_2$} (Scheme 13) was released by Sydora, Stradiotto, Turculet, et al. [50,51]. Operating under modest heating and relatively short reaction times [50], this catalytic system presented the first example of mild, efficient, and selective base-metal-catalyzed deoxygenative hydrosilylation of tertiary amides, with reactivity superior relative to (κ^2-P,N)Fe{$N(SiMe_3)_2$} [51]. Thus, with 5 mol% loading of (κ^2-P,N)Mn{$N(SiMe_3)_2$}, a series of aromatic and aliphatic amides were converted to corresponding amines in only 1 hour at 75 °C (Scheme 16) [50]. Moreover, (κ^2-P,N)Mn{$N(SiMe_3)_2$} allowed for conversion of several carboxamides to amines, even at room temperature (2 mol% of Mn, 25 °C, 18 h; Scheme 16) [50], presenting the first example of a 3d transition metal catalyst for reduction of tertiary amides to amines at room temperature without photochemical activation. It should be noted that under the conditions of (κ^2-P,N)Mn{$N(SiMe_3)_2$}-catalyzed reactions (5 mol% pre-catalyst, 75 °C, 1 h), the related bis(hexamethyldisilazide) complex Mn{$N(SiMe_3)_2$}$_2$ was also found to mediate the reduction of *N,N*-dibenzylpivalamide with $PhSiH_3$; however, it showed lower conversion of the amide to the corresponding amine compared to the (κ^2-P,N)Mn{$N(SiMe_3)_2$} pre-catalyst (70% vs. >90%, respectively) [50].



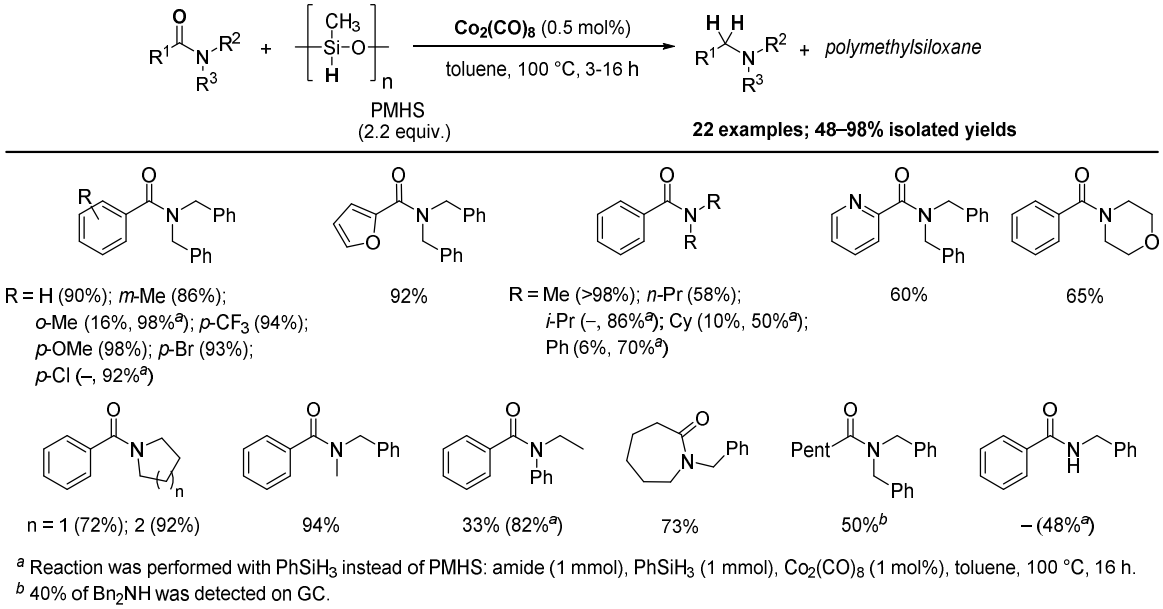
Scheme 16. (κ^2-P,N)Mn{N(SiMe$_3$)$_2$}-catalyzed hydrosilylation of tertiary amides to amines.

2.3. Cobalt-catalyzed Reactions.

Compared to manganese pre-catalysts, cobalt based catalytic systems are even less common in amide hydrosilylation reactions [49,51,71]. The first Co catalyst for hydrosilative reduction of tertiary amides to tertiary amines was reported as recently as 2013 by Darcel, Sortais, et al. for $Co_2(CO)_8$ (0.5 mol%), activated either photochemically (350 nm, 25 °C, 15 h) or thermally (100 °C, 3-16 h; Scheme 17) [71]. Under photolytic conditions, >97% conversion of *N,N*-dimethylbenzamide to dimethylbenzylamine was observed in the presence of 0.5–1 mol% of $Co_2(CO)_8$ and 2.2 equiv. of TMDS. In thermal reactions at 100 °C in toluene, a large variety of aliphatic amides, benzamides, *N,N*-dibenzylamides, *N,N*-dialkylamides, and heterocyclic amides were converted to the corresponding tertiary amines in moderate to good yields, using inexpensive PMHS as a reductant and tolerating ester and alkene functionalities (Scheme 17) [71]. In certain instances, the yields of the amine products were significantly increased when $PhSiH_3$ was used instead of PMHS, which was attributed to the influence of the steric hindrance in the hydrosilane reductant [71]. Steric hindrance of the amide substrate was also shown to affect the reactivity. Thus, deoxygenative hydrosilylation of *N*-methyl-*N*-benzylbenzamide and *N,N*-di-*n*-propylbenzamide resulted in 58% and 94% yields of the corresponding amines, respectively, whereas with more hindered *N,N*-diisopropylbenzamide and *N,N*-dicyclohenylbenzamide, only a 10% conversion was detected [71].

In contrast to tertiary amides, reduction of the secondary amide substrates was proven to be more difficult, and hydrosilylation of *N*-benzylbenzamide with PMHS and 0.5 mol% of $Co_2(CO)_8$ at 100 °C in toluene led to only 10% conversion to dibenzylamine. However, with 1 equiv. of $PhSiH_3$ and prolonged heating up to 16 h, a 68% conversion of *N*-benzylbenzamide and 48% isolated yield of dibenzylamine (Scheme 17) was achieved [71].

In general, the cobalt system reported by Darcel, Sortais, et al. [71] strongly resembles the reactivity of iron carbonyl complexes $Fe(CO)_5$ and $Fe_3(CO)_{12}$ [53,54], however, it requires somewhat shorter reaction times (3–16 h vs. 9–24 h) and significantly lower catalyst loading (1 mol% of Co) compared to iron-catalyzed deoxygenative hydrosilylation reactions (6–30 mol% of Fe).



[a] Reaction was performed with $PhSiH_3$ instead of PMHS: amide (1 mmol), $PhSiH_3$ (1 mmol), $Co_2(CO)_8$ (1 mol%), toluene, 100 °C, 16 h.
[b] 40% of Bn_2NH was detected on GC.

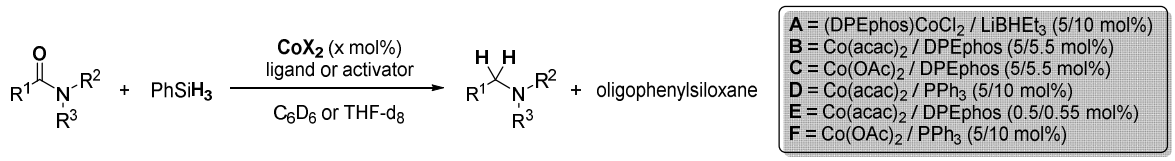
Scheme 17. $Co_2(CO)_8$-catalyzed deoxygenative hydrosilylation of amides to amines.

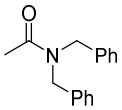
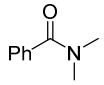
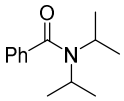
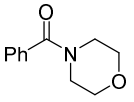
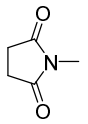
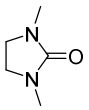
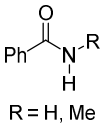
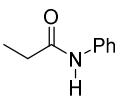
In moving beyond cobalt carbonyl complexes, our group have recently reported the use of bench-stable, commercially available $CoCl_2$, $Co(OAc)_2$, and $Co(acac)_2$ ligated with 1 equiv. of bis[(2-diphenylphosphino)phenyl] ether (DPEphos) as pre-catalysts for mild and efficient deoxygenative hydrosilylation of a diversity of aliphatic, aromatic, and cyclic tertiary amides with $PhSiH_3$ (Table 1) [49]. Reactions with (DPEphos)$CoCl_2$ (5 mol%) were performed in C_6D_6 at 60 °C, and showed excellent conversions of tertiary amides (91–99%, Table 1) [49], however they required external activation with $LiBHEt_3$ (10 mol%) to generate catalytically active Co(I) hydride species. On the other hand, external activator-free systems were developed for $Co(OAc)_2$/DPEphos (5 mol% of Co) and $Co(acac)_2$/DPEphos (0.5–5 mol% of Co), and the catalysts were activated by the reaction with hydrosilanes [49]. Interestingly, the activity of $Co(OAc)_2$ in the reduction of DMF remained high even upon replacement of DPEphos with 2 equiv. of PPh_3 (>99% conversion in 5 h at 60 °C and 25 °C; Table 1, entry 1), whereas $Co(acac)_2$/PPh_3 (5 mol% of Co) showed lower activity compared to $Co(acac)_2$/DPEphos (5 mol% of Co) and 79% conversion of DMF and 80% conversion of *N*,*N*-dibenzylacetamide (vs. >99% conversions of both substrates in 3–5 h at 25 °C for $Co(acac)_2$/DPEphos) were observed at room temperature after 24 h (Table 1, entries 1 and 3) [49]. Overall, the highest hydrosilylation activity among all three pre-catalysts was found for $Co(acac)_2$/DPEphos (5 mol% of Co and 5.5 mol% of DPEphos), which showed excellent conversions of amides to amines (90–99%, 8 examples) with 1.5 equiv. of $PhSiH_3$ at room temperature within 3–24 hours. Moreover, the reactions were found to tolerate molecules bearing alkene, nitrile, and ester functionalities [49]. After the manganese *N*-phosphinoamidinate complex, (κ^2-P,N)Mn{$N(SiMe_3)_2$} reported by Sydora, Stradiotto, Turculet, et al. [50,51], this system represents only the second example of a base metal catalyst for hydrosilative reduction of tertiary amides performed at ambient temperature in the absence of photochemical activation, and the first example of a mild catalytic system based on a combination of commercially available and bench-stable pre-catalyst and a ligand.

Similarly to the $Co_2(CO)_8$-catalyzed reductions reported by Darcel, Sortais, et al. [71], hydrosilylation of tertiary amides with (DPEphos)CoX_2 (X = Cl, OAc, acac) is highly affected by the steric hindrance in the silane reductant, and replacement of $PhSiH_3$ with $PhMeSiH_2$, $PhMe_2SiH$, Et_3SiH and PMHS in the reaction with DMF showed either low or no conversion to the reduced product [49]. Analogous observations were recorded for hydrosilative reduction of *N*-methylsuccinimide with (DPEphos)$CoCl_2$/$LiBHEt_3$ system, which was proven to be more difficult for the $PhMeSiH_2$ reductant (96% conversion in 16 h at 65 °C), compared to $PhSiH_3$ (>99% conversion in 5 h at 60 °C) (Table 1, entry 8) [49]. In contrast, despite a large bite angle of the DPEphos ligand

(102.2°) [72], steric hindrance of the amide substrate had no pronounced effect on hydrosilylation with $PhSiH_3$ and very similar conversions were obtained for *N*,*N*-diisopropylbenzamide and 4-benzoylmorpholine (>99% for both amides in 5 h at 60 °C; Table 1, entries 5 and 6) [49]. Room temperature hydrosilylation of bulky *N*,*N*-diisopropylbenzamide was also achieved with $Co(acac)_2$/DPEphos, affording a 93% isolated yield of the amine product after 17 hours. Interestingly, the reduction of less crowded *N*,*N*-dimethylbenzamide with $PhSiH_3$ appears more challenging than the analogous reaction with *N*,*N*-diisopropylbenzamide, and led to a 91% conversion in 16 hours at 60 °C (Table 1, entry 4) [49].

Table 1. CoX_2/DPEphos-catalyzed (X = Cl, OAc, acac) deoxygenative hydrosilylation of amides[a].

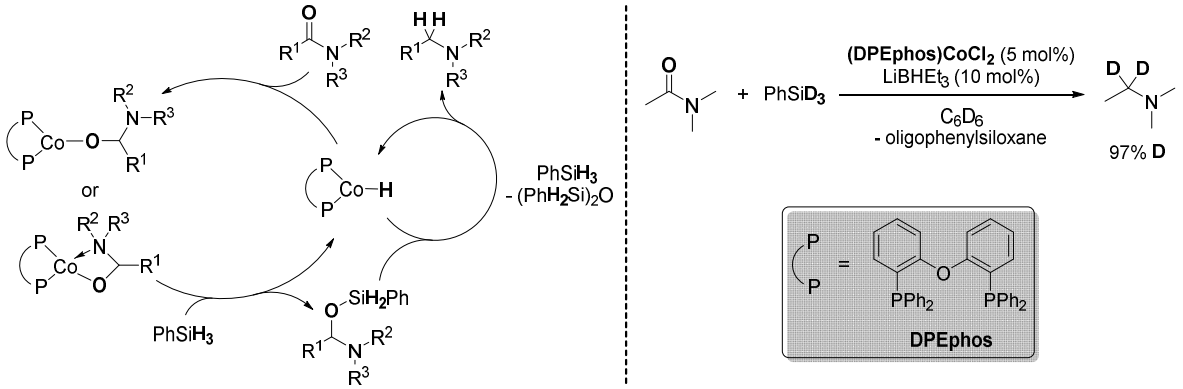


#	Amide	Pre-cat.	T, °C / t, h	Yield, %
1		A–F	60 / 5	>99
		A–C, F	25 / 5	>99
		E	25 / 6.5	>99[b]
		D	25 / 24	79
2		A	60 / 5	>99
		B	25 / 17	>99
		E	60 / 5	82
		E	60 / 24	94
3		A	60 / 5	>99
		B	25 / 3	>99 (95)
		D	25 / 24	80[c]
		E	25 / 32	68
		E	60 / 5	>99
4		A	60 / 16	91[d]
		B	60 / 24	>99[e]
		E	60 / 24	28
		E	60 / 48	37
5		A	60 / 5	>99
		B	25 / 17	>99 (93)
		B	65 / 5	>99
		E	60 / 24	72
6		A	60 / 5	>99
		B	25 / 17	87
		B	60 / 5	85
		E	60 / 24	87[f]
7		A	60 / 5	>99
		B	25 / 17	>99
		E	60 / 24	61[g]
8		A	60 / 5	>99
		A	65 / 16	96[h]
		B	25 / 24	90[i]
		E	60 / 24	43[j]
9		A	60 / 5	28
		A	65 / 16	44[k]
		B	100 / 24	15
10		B	75 / 24	45
		B	75 / 48	73
		B	75 / 72	>99
11	 R = H, Me	R=H: B	100 / 24	83[l]
		R=Me: B	75 / 24	89[m]
		R=Me: B	75 / 48	>99[m]
12		B	60 / 60	>99[n]

[a]Conditions: THF-d_8 (0.48 M) for $Co(acac)_2$ and $Co(OAc)_2$ and C_6D_6 (0.48 M) for (dpephos)$CoCl_2$/$LiBHEt_3$. Yields were determined by ^{1}H-NMR. Yields of isolated products are given with parentheses. [b]92% conversion in 5 h at 25 °C. [c]>99% conversion in 10 h at 60 °C. [d]19% conversion in 24 h at 25 °C and >99% conversion in 24 h at 60 °C. [e]38% conversion in 24 h at 25 °C. [f]83% conversion in 5 h at 60 °C. [g]45% conversion in 5 h at 60 °C. [h]Reaction with $PhMeSiH_2$ (4 equiv.), 71% conversion in 5 h at 65 °C. [i]81% conversion in 17 h at 25 °C. [j]34% conversion in 5 h at 60 °C. [k]Reaction with $PhMeSiH_2$ (3 equiv), 32% conversion in 5 h at 65 °C. [l]Determined by GC-MS after hydrolysis with 20% NaOH (aq). [m]A mixture of the amine and silylamines was produced; overall yield for the mixture. [n]A mixture of the amine and silylamines was produced; overall yield for the mixture.

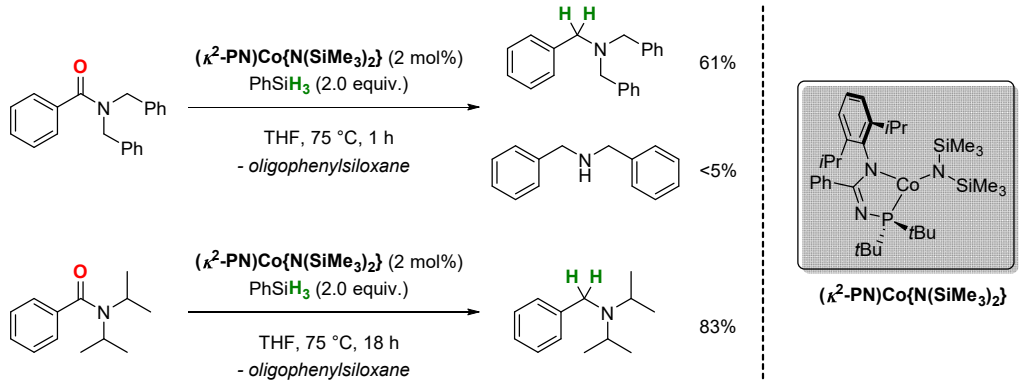
Notably, $Co(acac)_2$/DPEphos was also found to mediate deoxygenative hydrosilylation of secondary amides *N*-methylbenzamide and *N*-phenylpropionamide, and more challenging primary

amides acetamide and benzamide; however, more forcing conditions were required (24–72 h, 60–100 °C; Table 1) [49]. No formation of nitriles was observed during the reactions with primary amides, and $Co(acac)_2$/DPEphos was found to be inactive in hydrosilylation of nitriles, such as CH_3CN and PhCN. Taking this into account, $Co(acac)_2$/DPEphos-catalyzed reduction of primary amides with $PhSiH_3$ was suggested to proceed via a direct deoxygenative hydrosilylation route, similar to hydrosilylation of tertiary amides [49]. This is in contrast to the silane-assisted dehydration of $RC(O)NH_2$ to RC≡N reported for iron catalysts [53–56,63]. Overall, the suggested mechanism of CoX_2/DPEphos-catalyzed (X = Cl, OAc, acac) hydrosilative reduction of amides (Scheme 18) [49] is somewhat similar to those proposed by Nagashima et al. [21] and Beller et al. [53] for the Ru- and Fe-catalyzed reactions, respectively, and includes the intermediacy of the Co(I) hydride species (DPEphos)CoH as an active catalyst, and formation of siloxymethylamines $R_2NCH_2OSiR'_3$. Similarly with the $Fe_3(CO)_{12}$-catalyzed transformations reported by Beller et al. (see Scheme 5) [53], treatment of *N*,*N*-dimethylacetamide with $PhSiD_3$ in the presence of (DPEphos)$CoCl_2$/$LiBHEt_3$ system (5 mol% of Co) resulted in 93% saturation of the methylene moiety of the produced $EtNMe_2$ with deuterium (Scheme 18) [49], suggesting that the two newly added hydrogen atoms in the amine product originated from the hydrosilane reductant and were supporting the proposed mechanism.



Scheme 18. Proposed mechanism of CoX_2/DPEphos-catalyzed (X = Cl, OAc, acac) deoxygenative hydrosilylation of amides to amines (*left*) and D-labeling experiment in favor of this mechanistic proposal (*right*).

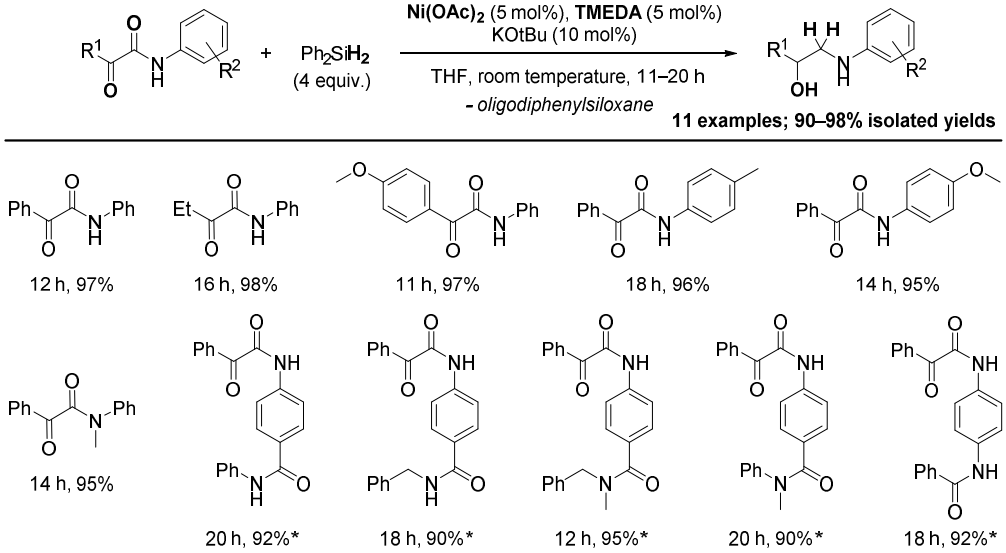
Another non-carbonyl cobalt pre-catalyst for deoxygenative hydrosilylation of tertiary amides, the low coordinate Co(II) *N*-phosphinoamidinate amide complex, (κ^2-P,N)Co{$N(SiMe_3)_2$}, has been recently published by Sydora, Stradiotto, Turculet, et al. [51]. Similarly to the iron analogue discussed above [51], the (κ^2-P,N)Co{$N(SiMe_3)_2$}-catalyzed (2–5 mol% of Co) the reduction of *N*,*N*-dibenzylbenzamide and *N*,*N*-diisopropylbenzamide in the presence of 2 equiv. of $PhSiH_3$ at 75 °C and resulted in a >95% overall conversion of the amide substrates; however, formation of only 61% and 83% of the corresponding amine products, respectively, was detected on the basis of calibrated GC data (Scheme 19) [51]. Under analogous conditions, Co{$N(SiMe_3)_2$}$_2$ proved less reactive compared to its *N*-phosphinoamidinate derivative, (κ^2-P,N)Co{$N(SiMe_3)_2$}, and only 43% of tribenzylamine and 47% of diisopropylbenzylamine were obtained upon reduction of $PhC(O)NBn_2$ and $PhC(O)N^iPr_2$, respectively [51].



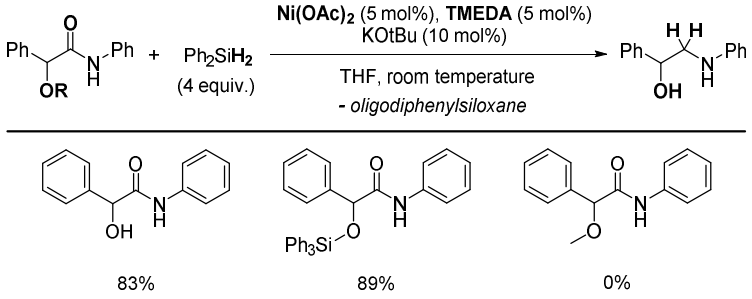
Scheme 19. (κ^2-PN)Co{N(SiMe$_3$)$_2$}-catalyzed hydrosilative reduction of *N*,*N*-dibenzylbenzamide and *N*,*N*-diisopropylbenzamide.

2.4. Nickel-catalyzed reactions.

Prior to 2019, the application of nickel catalysts in deoxygenative hydrosilylation of amides was limited to two reports, from Sekar et al. [73] and Garg et al. [74]. The first example describes complete hydrosilative reduction of both keto and amide groups of α-keto amides with Ph_2SiH_2 (4 equiv.) to produce a series of β-amino alcohols, accomplished with $Ni(OAc)_2$ (5 mol%) in the presence of 10 mol% of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and 10 mol% of KO^{t}Bu at room temperature (Scheme 20) [73]. Notably, the reduction of α-keto amides with Ph_2SiH_2 could be performed chemoselectively, tolerating other amide functional groups, as indicated in Scheme 20 [73]. Moreover, switching from Ph_2SiH_2 to PMHS resulted in highly chemoselective hydrosilylation of keto groups of α-keto amides, producing α-hydroxy amides even in the presence of other simple ketone functionalities in the substrate [73]. Using experimental conditions analogous to the reduction of α-keto amides with Ph_2SiH_2, both α-hydroxy and α-siloxy amides could be converted to β-amino alcohols. In contrast, treatment of an α-methoxy derivative of *N*,2-diphenylacetamide with Ph_2SiH_2 did not give even a trace amount of the reduced product (Scheme 21) [73]. Taking all these observations into consideration, Sekar et al. suggested that complete hydrosilative reduction of α-keto amides proceeds with an intermediacy of α-hydroxy amides, produced via initial chemoselective hydrosilylation of the α-keto amide's keto functional group [73]. In a subsequent reaction, α-hydroxy amides coordinate with the nickel hydride species to reduce the amide group, which is not possible in the case of isolated amides [73]. Unfortunately, no control experiments with isolated secondary and tertiary amides, other than α-methoxy derivative of *N*,2-diphenylacetamide, have been reported.

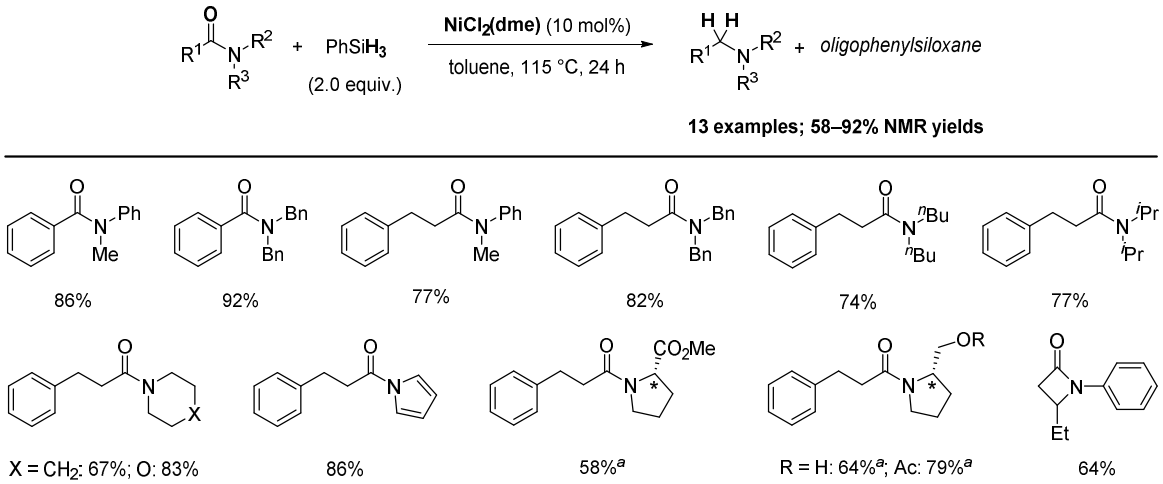


Scheme 20. Reduction of α-keto amides with Ph_2SiH_2 using $Ni(OAc)_2$/TMEDA/KO^{t}Bu.

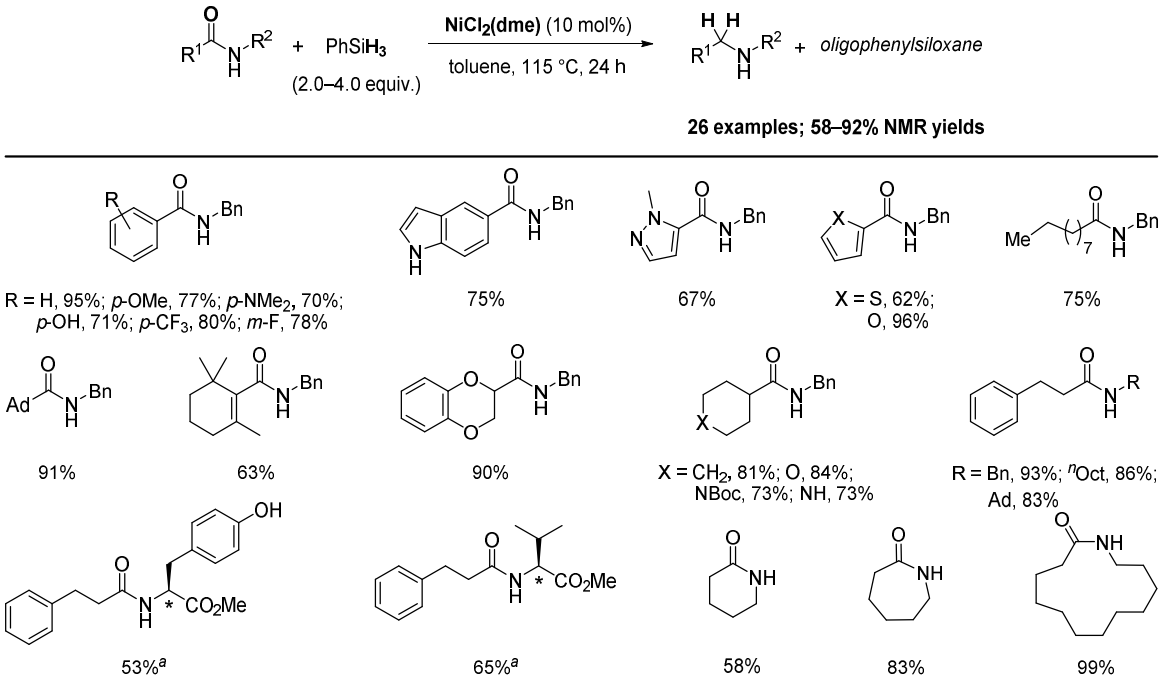


Scheme 21. Ni-TMEDA-catalyzed deoxygenative hydrosilylation of α-hydroxy, α-siloxy and α-methoxy amides with Ph_2SiH_2.

An impressive scope of tertiary and secondary amides in hydrosilylation reactions with $PhSiH_3$ was reported in 2017 by Garg and co-workers for $NiCl_2$(dme) (dme = 1,2-dimethoxyethane) pre-catalyst (Schemes 22 and 23) [74]. The reactions were performed with rather high pre-catalyst loading (10 mol%) and under forcing conditions (115 °C, 24 h), but the system was found to operate in the absence of an external activator, and effected the reduction of amides with a synthetically useful substrate scope, including a series of lactams, *N*-alkyl, and *N*-aryl substituted aliphatic, aromatic, and heterocyclic amides and tolerating ester, NH, and OH functionalities [74]. Moreover, the hydrosilative reduction of optically enriched tertiary and secondary amides with $PhSiD_3$ (2–4 equiv.) was found to proceed without epimerization, giving an access to pharmaceutically relevant chiral α-deutero amines (Schemes 22 and 23) [74]. Such amines are important in drug discovery because they are less prone to undergoing metabolism, compared to their non-deuterated analogues [75]. An ability of $NiCl_2$(dme) to mediate hydrosilative reduction of a large variety of secondary amides to synthetically useful secondary amines makes it unique among all other 3d transition metal catalytic systems for deoxygenative reduction of amides reported to date.



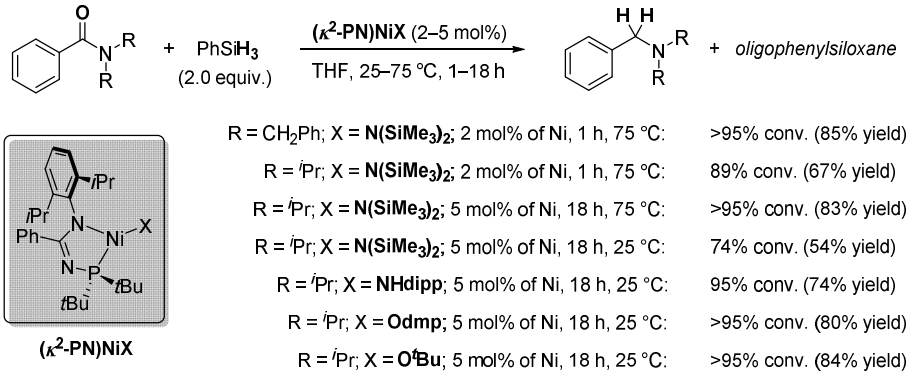
Scheme 22. $NiCl_2$(dme)-catalyzed deoxygenative hydrosilylation of tertiary amides to amines.



Scheme 23. $NiCl_2$(dme)-catalyzed deoxygenative hydrosilylation of secondary amides to amines.

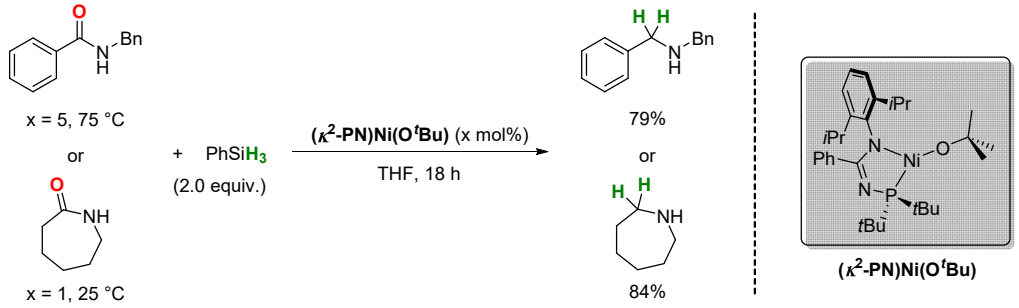
In 2019, Sydora, Stradiotto, Turculet, et al. have reported a few examples of mild (25–75 °C) deoxygenative hydrosilylation of tertiary (Scheme 24) and secondary amides (Scheme 25) using tricoordinate *N*-phosphinoamidinate (κ^2-P,N)NiX pre-catalysts (X = $N(SiMe_3)_2$, NHdipp, O^{t}Bu, and Odmp; dipp = 2,6-^{i}Pr$_2$C$_6$H$_3$, dmp = 2,6-Me$_2$C$_6$H$_3$) [51]. Compared to the aforementioned iron [51], manganese [50,51] and cobalt analogues [51], (κ^2-P,N)Ni{$N(SiMe_3)_2$} showed supreme activity in hydrosilylation of *N,N*-dibenzylbenzamide and sterically demanding *N,N*-diisopropylbenzamide, leading within 18 h at 75 °C to 85% and 83% yields of tribenzylamine and diisopropylbenzylamine, respectively [51]. Even higher catalytic activity in deoxygenative hydrosilylation of *N,N*-diisopropylbenzamide was detected for the NHdipp derivative, which allowed for 95% conversion of the amide in 18 h at room temperature, yielding 74% of diisopropylbenzylamine. However, among all tested (κ^2-P,N)NiX pre-catalysts, the *tert*-butoxide complex (X = ^{t}OBu) turned out to be the most active allowing for >95% conversion of *N,N*-diisopropylbenzamide and 84%

isolated yield of diisopropylbenzylamine after 18 h at 25 °C (Scheme 24) [51]. Assuming that hydrosilylation reactions with (κ^2-P,N)NiX pre-catalysts proceed via silane-assisted formation of a common catalytically active species (κ^2-P,N)NiH, it was suggested that the different activity of (κ^2-P,N)NiX systems could be attributed to the different catalyst activation rates [51]. Indeed, control experiments performed by Sydora, Stradiotto, Turculet, et al. for reactions of (κ^2-P,N)Ni{N(SiMe$_3$)$_2$} and (κ^2-P,N)Ni(O^{t}Bu) with 40 equiv. of PhSiH$_3$ in the absence of amide substrate showed significantly faster consumption of O^{t}Bu vs. N(SiMe$_3$)$_2$ derivative and formation of [(κ^2-P,N)NiH]$_2$ [67] in a mixture with unidentified decomposition products [51].



Scheme 24. (κ^2-P,N)NiX-catalyzed deoxygenative hydrosilylation of *N*,*N*-dibenzylbenzamide and *N*,*N*-diisopropylbenzamide.

Apart from *N*,*N*-dibenzylbenzamide and *N*,*N*-diisopropylbenzamide, (κ^2-P,N)Ni(O^{t}Bu) was also shown to catalyze deoxygenative hydrosilylation of secondary amides, caprolactam, and *N*-benzylbenzamide (Scheme 25) [51]. The reactions were performed for 18 h under rather mild conditions (1 and 5 mol% of Ni, 25 °C and 75 °C, respectively), compared to those reported previously by Garg et al. (10 mol% of Ni, 115 °C, 24 h) for NiCl$_2$(dme)-mediated reduction of secondary amides with PhSiH$_3$ (Schemes 23) [74]. Notably, none of the *N*-phosphinoamidinate Ni(II) pre-catalysts were found to be useful for the hydrosilative reduction of primary amides, such as benzamide or pivalamide, and, despite high conversion of the amide substrates, the reactions with PhSiH$_3$ resulted in complex mixtures of products [51].

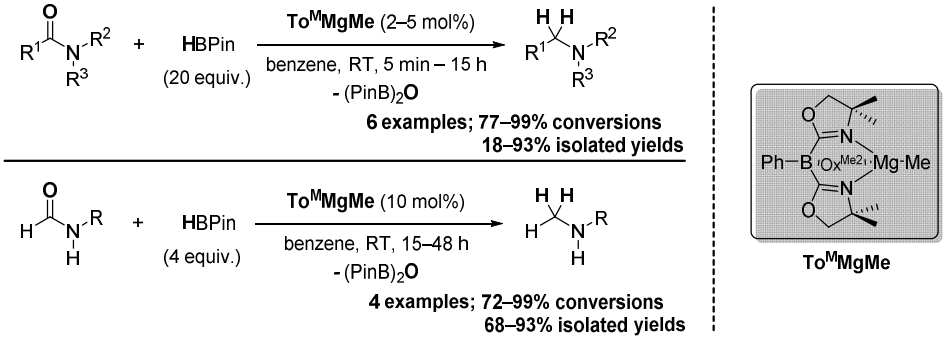


Scheme 25. (κ^2-P,N)Ni(O^{t}Bu)-catalyzed deoxygenative hydrosilylation of *N*-benzylbenzamide and caprolactam.

3. Deoxygenative Hydroboration of Amides

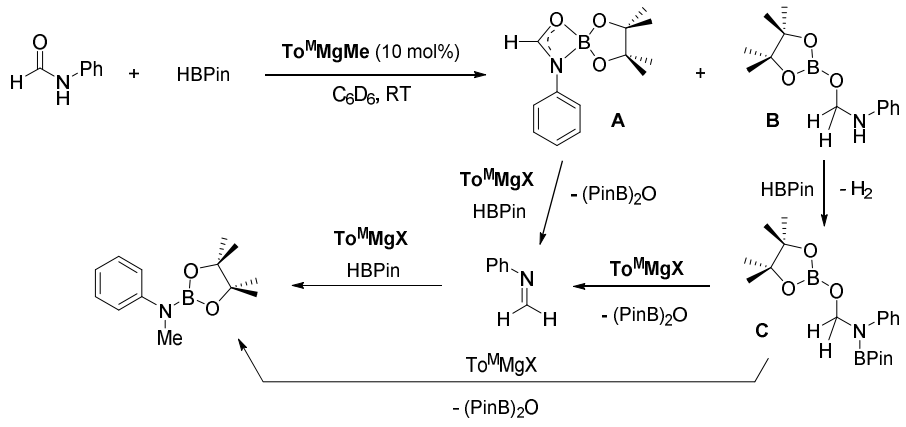
In sharp contrast to hydrosilylation, selective catalytic deoxygenative hydroboration of amides is still in its infancy. Prior to 2019, no transition-metal-mediated additions of hydroboranes, akin to HBPin or HBCat (Pin = pinacol, Cat = catechol), to carboxamides were reported in the literature, and hydroborative reduction of amides to amines was limited to only two examples of Mg-catalyzed transformations [76,77]. Although these systems are beyond the scope of the current review, the discussion of their reactivity and the mechanisms of their operation are of value for further

development of hydroborative reduction of amides using base metal catalysts. Thus, the first report on hydroborative reduction of amides with HBPin, catalyzed by a magnesium complex To^{M}MgMe (To^{M} = tris(4,4-dimethyl-2-oxazolinyl)phenylborate) was published in 2015 by Sadow et al. (Scheme 26) [76]. The reduction of tertiary amides was shown to proceed under mild conditions at room temperature with only 2–5 mol % of To^{M}MgMe; however, a huge excess of HBpin (ca. 20 equiv.) was required. Various *N*,*N*-disubstituted aromatic and aliphatic amides, including functionalized ones bearing nitro- and azo- moieties, were reduced with good yields to the corresponding tertiary amines, isolated in the form of ammonium salts [76]. Deoxygenation of tertiary amides with HBPin and To^{M}MgMe showed a significant dependence on HBPin concentration [76]. Careful control of the C–O vs. C–N bond cleavage in the reactions with tertiary amides was achieved by tuning the amount of excess HBpin. A large excess of the borane reductant was found to be essential to drive the reaction towards the desired tertiary amines produced via the C–O bond cleavage pathway, whereas low concentrations of HBPin resulted in competitive C–N bond cleavage and formation of RCH_2OBPin and R_2NBPin byproducts [76].



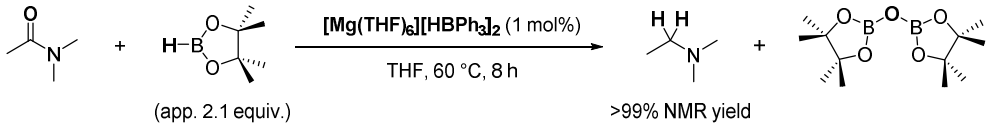
Scheme 26. To^{M}MgMe-catalyzed deoxygenative hydroboration of tertiary and secondary amides.

Not surprisingly, the reduction of secondary amides with HBPin proved more challenging, and only secondary formamides were successfully reduced into corresponding amines, using To^{M}MgMe (10 mol%) and 4 equiv. of HBPin (Scheme 26) [76]. On the basis of spectroscopically (NMR and GC/MS) detected composition of the reaction mixture during hydroboration of *N*-phenylformamide with HBPin, the reduction of secondary amides to amines was proposed to proceed via two concurrent pathways (Scheme 27) [76], which start either with catalytic dehydrogenative borylation of the amide group to give formimidate boronic ester **A**, or proceed through hydroboration of the C=O moiety to give intermediate **B**, followed by nitrogen borylation to species **C**. It is noteworthy that the given oxazolinylborato Mg complex does not affect the hydrosilylation of either amides or esters [76]. Catalytic hydroboration of primary amides and secondary amides beyond formamides is still a challenge.



Scheme 27. Proposed mechanism for To^{M}MgMe-catalyzed hydroboration of *N*-phenylformamide with HBPin.

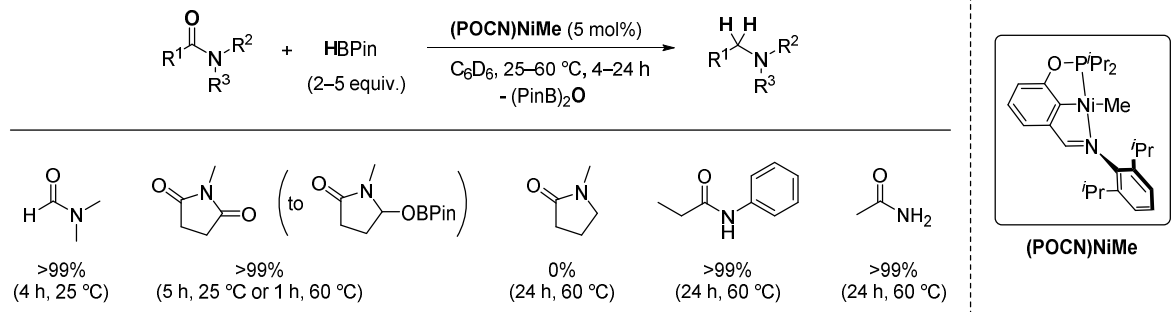
$[Mg(THF)_6][HBPh_3]_2$, reported by Okuda et al., was also found to mediate deoxygenative hydroboration of *N*,*N*-dimethylacetamide with HBPin (app. 2.1 equiv.) in THF-d_8 (1 mol% of Mg; Scheme 28) [77]; however, the system was found to be less active, and full conversion to *N*,*N*-dimethylethylamine was achieved only after 8 h at 60 °C (vs. 6 h at 25 °C for 2 mol% of $To^{M}MgMe$ [76]).



Scheme 28. $[Mg(thf)_6][HBPh_3]_2$-catalyzed deoxygenative hydroboration of *N*,*N*-dimethylacetamide.

The first and only instance of transition-metal-catalyzed hydroborative reduction of tertiary, secondary, and primary amides was recently reported by our group, using iminophosphinite pincer complex of Ni(II), (POCN)NiMe (Scheme 29) [15]. With 5 mol% of the methylnickel pre-catalyst and 2 equiv. of HBPin, DMF was selectively converted to trimethylamine within 4 hours at room temperature. In contrast, hydroboration of *N*-methylsuccinimide with 4.2 equiv. of HBPin did not afford the corresponding amine products, *N*-methyl-2-pyrrolidone or *N*-methylpyrrolidine. Instead, after 5 hours at room temperature, the reaction resulted in selective formation of *O*-borylated aminal as the product of the single addition of HBPin to only one carbonyl moiety of *N*-methylsuccinimide (Scheme 29) [15]. No further HBPin addition products were formed, even at 60 °C. Similarly, *N*-methyl-2-pyrrolidone remained untouched even after 24 h treatment with excess HBPin at 60 °C (Scheme 29) [15].

(POCN)NiMe-catalyzed deoxygenative hydroboration of primary and secondary amides with HBPin was found to compete with the dehydrogenative coupling reactions and the room temperature reactions with acetamide, and *N*-phenylpropanamide produced mixtures of borylated amine and amide products [15]. However, full conversion of both acetamide and *N*-phenylpropanamide to the corresponding borylated amines $EtN(BPin)_2$ and $^{n}PrN(BPin)Ph$ was achieved within 24 h at 60 °C using excess HBPin (ca. 5 equiv.) (Scheme 29) [15], demonstrating the first example of deoxygenative hydroboration of primary and secondary amides beyond formamides [76,77].



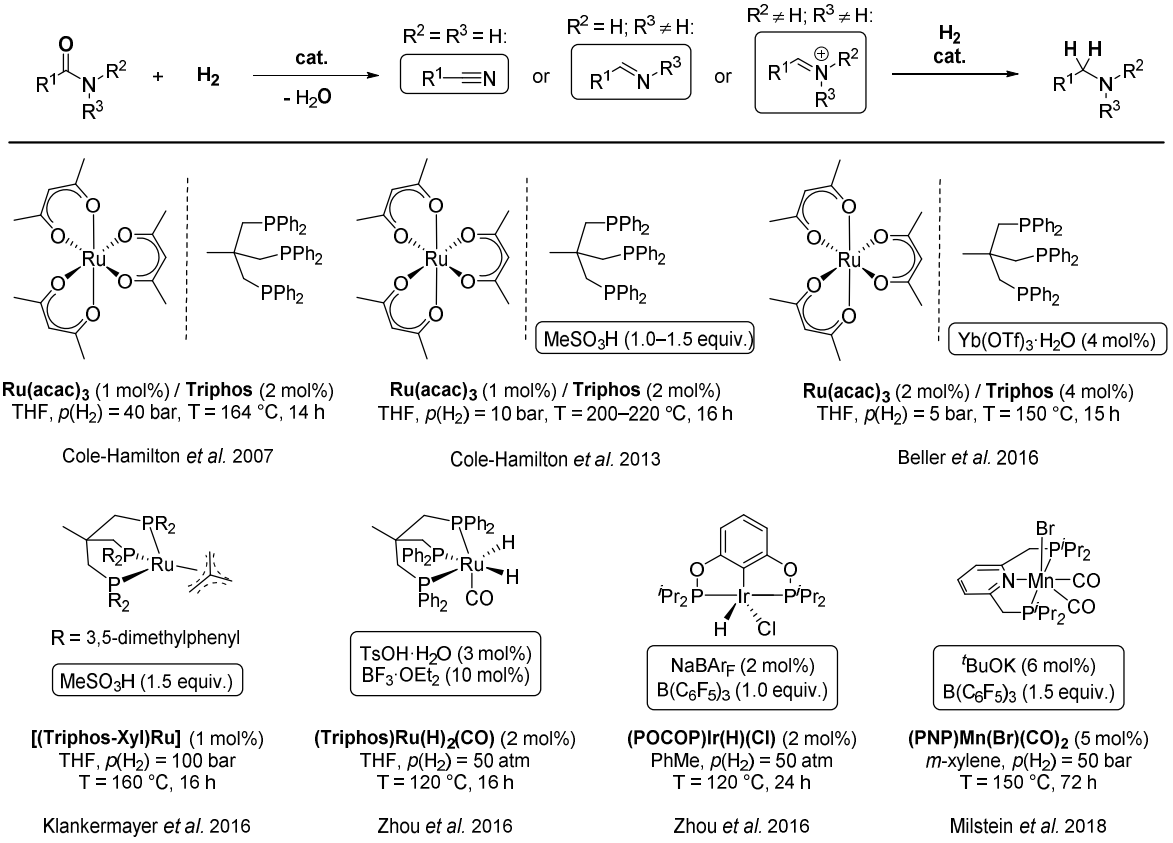
Scheme 29. (POCN)NiMe-catalyzed hydroboration of amides.

4. Deoxygenative Hydrogenation of Amides

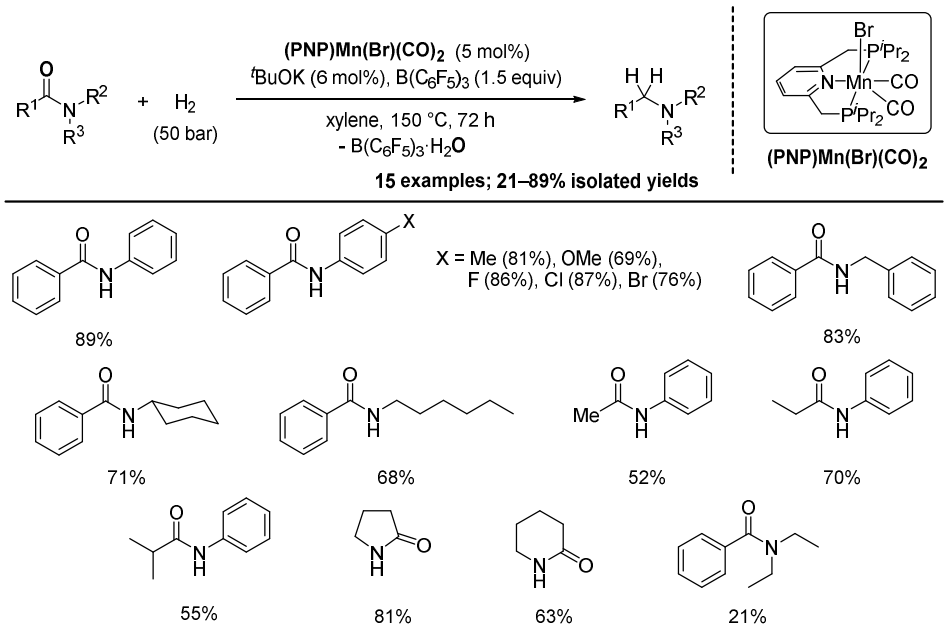
Deoxygenative reduction of amides to amines using hydrogen as a reductant, forming water, is the most atom-economical, and, therefore, the most attractive transformation among all amide reduction approaches. Examples of hydrogenation of amides to amines have been reported for heterogeneous systems [78–84]; however, these reactions usually require high H_2 pressure [78,79] and high temperatures [78,80–82], and suffer from poor selectivity [81,83,84]. In contrast, the examples of homogeneously catalyzed deoxygenative hydrogenation of amides are rare, and the main developments in this area are limited to only a few reports, mostly concerning precious metal

catalysts based on ruthenium [7–11] or iridium [12] (Scheme 30). Compared to deoxygenative hydrosilylation reactions, which work the best for tertiary amide substrates [14], the majority of the reports on hydrogenation of amides to amines concern secondary substrates, whereas primary and tertiary amides have been shown to be significantly less reactive [7–13]. A general strategy for hydrogenation of amides to amines consists of formal reductive dehydration of amides under acidic conditions in the presence of $MeSO_3H$ or strong Lewis acids, such as $Yb(OTf)_3$, BF_3, or $B(C_6F_5)_3$, followed by hydrogenation of the dehydrated products to the corresponding amines (Scheme 30) [7,8,10,12,13]. This pathway accounts for the observed superior applicability of the secondary amides in deoxygenative hydrogenation reactions, as their dehydration leads to the corresponding imines, which are readily hydrogenated to secondary amines [85]. The reported reactions usually require rather harsh conditions, such as a high pressure of hydrogen (up to 100 bar) and high temperatures (up to 220 °C) [7–12].

The use of 3d transition metal systems in homogeneous deoxygenative hydrogenation of amides is restricted to the manganese pincer complex, $(PNP)Mn(Br)(CO)_2$, reported recently by Milstein and co-workers (Scheme 31) [13]. Using 5 mol% of $(PNP)Mn(Br)(CO)_2$, a series of *N*-arylbenzamides with substituents of different electronic natures on the *N*-phenyl ring, as well as *N*-alkylbenzamides, *N*-phenyl aliphatic amides, and cyclic lactams were selectively hydrogenated to the corresponding amines with moderate to good isolated yields (52–89%; Scheme 31) [13]. Similarly to the precious metal systems based on Rh and Ir [7–12], the reactions were conducted under rather forcing conditions during 72 hours in xylene at 150 °C with 50 bar pressure of H_2, and required the presence of an over-stoichiometric amount (1.5 equiv.) of the strong Lewis acid, $B(C_6F_5)_3$ [13]. In contrast to secondary amides, *N*,*N*-diethylbenzamide gave only a scarce yield of the desired reduced product, *N*,*N*-diethylbenzylamine (47% conversion and 21% isolated yield; Scheme 31) [13]; primary amides were beyond the scope of this method. Despite quite harsh reaction conditions, this work is a promising starting point for further developments of homogeneous deoxygenative hydrogenation of amides using earth-abundant transition metal complexes.

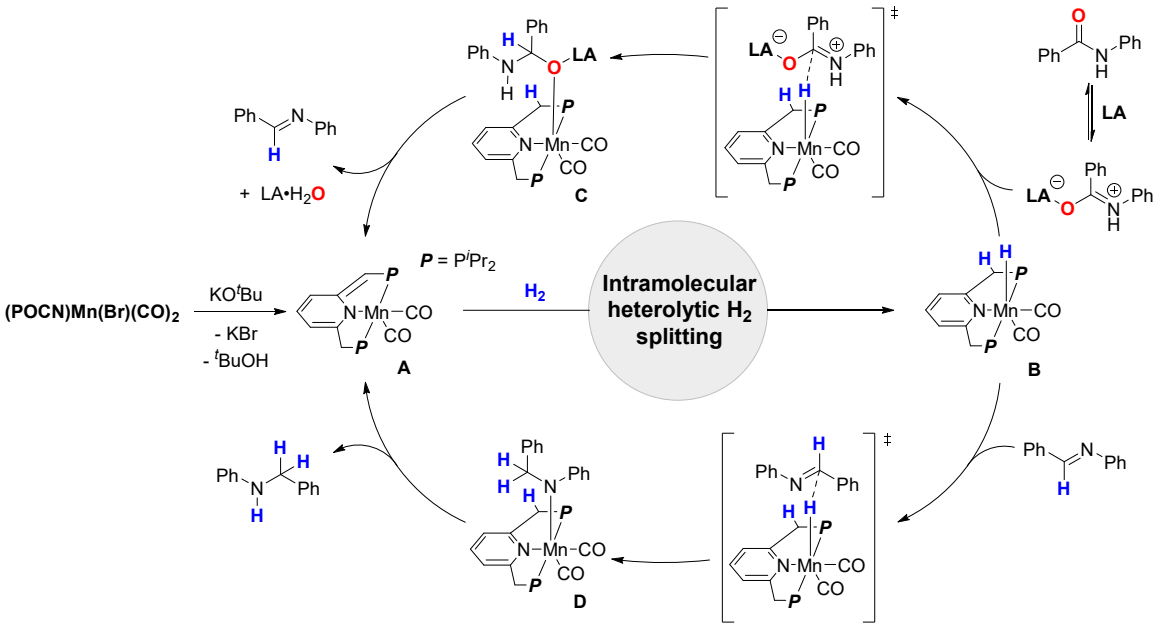


Scheme 30. Homogeneous transition metal catalysts for deoxygenative hydrogenation of amides.



Scheme 31. (PNP)Mn(Br)(CO)2-catalyzed deoxygenative hydrogenation of amides to amines.

With regard to hydrogenation of secondary amides, the reactions were suggested to proceed via metal–ligand cooperation and intermediacy of a dearomatized manganese PNP pincer complex **A**, which is likely the actual catalyst (Scheme 32) [13]. This latter species is capable of intramolecular heterolytic H_2 splitting to produce an aromatized manganese–hydride intermediate **B**. Subsequently, the amide carbonyl group, activated by Lewis acid, electrophilically attacks the coordinatively saturated Mn–H complex through the outer-sphere pathway [13]. The resulting hemiaminal derivative **C** then undergoes Lewis-acid-assisted dehydration to afford the corresponding imine. The imine itself can react with the Mn–H complex **B** through an analogous outer-sphere pathway to produce the amide derivative **D**, and, finally, the elimination of amine regenerates the catalyst [13].



Scheme 32. The proposed mechanism for the (PNP)Mn(Br)(CO)2-catalyzed deoxygenative hydrogenation of secondary amides.

5. Conclusions

Homogeneously catalyzed selective deoxygenative reduction of amides by means of hydrosilylation, hydroboration, and hydrogenation reactions presents an attractive approach towards a variety of synthetically useful amines. During the last two decades, significant progress in such reactions has been made using traditional heavy late transition metal catalysts; however, examples of applications of more environmentally benign and more economical earth-abundant 3d transition metals, so called base metals, such as Mn, Fe, Co, and Ni, are still scarce, and the transformations are still quite challenging owing to the significantly reduced electrophilicity of the amide carbonyl group compared to aldehydes, ketones, and even esters. Nevertheless, great efforts to develop mild base-metal-catalyzed reduction of amides by many research groups have recently resulted in several outstanding findings, albeit that the majority of these findings concern deoxygenative hydrosilylation of tertiary amides. Generally, direct hydrosilylation of secondary and primary amides to the corresponding amines is significantly more challenging: reactions with secondary amides require rather forcing conditions, whereas the problem of direct hydrosilative reduction of primary amides still awaits its solution. Our research group have also contributed to hydrosilylation of amides and found a new bench-stable cobalt pre-catalyst, allowing for selective and efficient room temperature transformations of tertiary amides to tertiary amines, and have demonstrated a few examples of the deoxygenative reduction of more challenging secondary and primary amide substrates.

Compared to hydrosilylation strategies, deoxygenative hydroboration and hydrogenation have been developed to a lesser extent, and only single examples of homogeneous base metal pre-catalysts for each of these transformations have been reported to date. These exciting pioneering results may serve as grounds for further developments in homogeneous base-metal-catalyzed preparation of amines from amides, and the search for novel base-metal-catalytic systems and investigation of the mechanisms of these reactions is expected to be continued.

Author Contributions: Conceptualization, A.Y.K.; writing—original draft preparation, A.Y.K., K.A.G. and D.H.; writing—review and editing, A.Y.K., K.A.G. and D.H.; supervision, A.Y.K.; funding acquisition, A.Y.K.

Funding: This work was supported by Nazarbayev University through the NU Research University Development Program (NU-ORAU grant to A.Y.K. No. 2016023).

Conflicts of Interest: The authors declare no conflict of interest.

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