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# Magnesium-Catalyzed Mild Reduction of Tertiary and Secondary Amides to Amines

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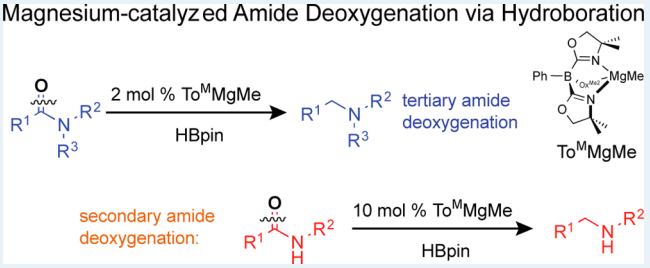
Supporting Information

**ABSTRACT:** The first example of a catalytic hydroboration of amides for their deoxygenation to amines is reported. This transformation employs an earth-abundant magnesium-based catalyst. Tertiary and secondary amides are reduced to amines at room temperature in the presence of pinacolborane (HBpin) and catalytic amounts of $To^{M}MgMe$ ($To^{M}$ = tris(4,4-dimethyl-2-oxazolinyl)phenylborate). Catalyst initiation and speciation is complex in this system, as revealed by the effects of concentration and order of addition of the substrate and HBpin in the catalytic experiments. $To^{M}MgH_2Bpin$, formed from $To^{M}MgMe$ and HBpin, is ruled out as a possible catalytically relevant species by its reaction with *N*,*N*-dimethylbenzamide, which gives $Me_2NBpin$ and PhBpin through C−N and C−C bond cleavage pathways, respectively. In that reaction, the catalytic product benzyldimethylamine is formed in only low yield. Alternatively, the reaction of $To^{M}MgMe$ and *N*,*N*-dimethylbenzamide slowly gives decomposition of $To^{M}MgMe$ over 24 h, and this interaction is also ruled out as a catalytically relevant step. Together, these data suggest that catalytic activation of $To^{M}MgMe$ requires both HBpin and amide, and $To^{M}MgH_2Bpin$ is not a catalytic intermediate. With information on catalyst activation in hand, tertiary amides are selectively reduced to amines in good yield when catalytic amounts of $To^{M}MgMe$ are added to a mixture of amide and excess HBpin. In addition, secondary amides are reduced in the presence of 10 mol % $To^{M}MgMe$ and 4 equiv of HBpin. Functional groups such as cyano, nitro, and azo remain intact under the mild reaction conditions. In addition, kinetic experiments and competition experiments indicate that B−H addition to amide C═O is fast, even faster than addition to ester C═O, and requires participation of the catalyst, whereas the turnover-limiting step of the catalyst is deoxygenation.




**KEYWORDS:** *hydroboration, amide reduction, magnesium, deoxygenation, catalysis*

## INTRODUCTION

The demand for efficient syntheses of amines is ever increasing because of the need to produce chemicals through sustainable processes and amines' continued importance in pharmaceutical, agrochemical, and materials chemistry applications.[1,2] Amides, which are naturally prevalent among biological molecules or are readily synthetically accessed, provide attractive starting materials for amine preparations through reductive transformations.[3−5] However, selective reduction of the amide functional group is challenging for thermodynamic and kinetic reasons and often requires strongly reducing metal hydride reagents, such as $LiAlH_4$, $NaBH_4$, or $B_2H_6$, that also react with a number of functional groups. For example, nitrile and nitro groups are readily reduced by $LiAlH_4$, nitriles are reduced by $B_2H_6$, and olefins are readily hydroborated by $B_2H_6$ or $BH_3$·THF.[6] Amide reductions that avoid $LiAlH_4$ and $BH_3$ were identified as key challenging conversions by the ACS Green Chemistry Institute Pharmaceutical Roundtable,[2] and this need continues, even with remarkable progress in the last five years.

Notably, these stoichiometric reagents contain both reducing hydrides and Lewis acid sites (Li, Na, B, or Al), presumably to activate amides (as well as esters and other carbonyls) for reduction. Thus, pathways involving hydride attack upon a Lewis acid-coordinated C═O intermediate are similarly invoked for ester and amide reductions.[5] Although this idea is accepted for stoichiometric reductions, minimal experimental evidence is available for amide reductions.[3] Well-defined main group reductants, either as stoichiometric reagents or as part of the catalytic systems, may also contribute experimental support for elementary steps in $LiAlH_4$ or $NaBH_4$ reductions.

A number of pathways have been reported for reductive interactions of metal compounds and amides, including deoxygenation to amines,[7−12] deoxygenation and alkylation,[13−15] dehydration to nitriles,[16] and C−N bond cleavage to amines and aldehydes.[17,18] Although catalytic hydrogenations are appealing on the basis of their atom economy, most amide deoxygenations via hydrogenation require forcing conditions, including high pressure and elevated temperature (>150 °C). In addition, hydrodeoxygenation of primary and secondary amines often yields mixtures resulting from alkyl group disproportionation.[3,13,17,18] Although a range of late metal complexes have been reported to efficiently reduce amides through hydrosilylation,[8,9,19] new catalytic processes are

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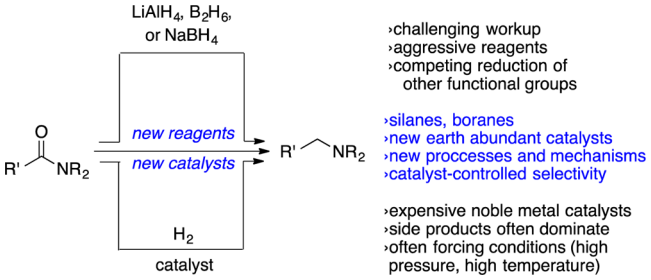
**Scheme 1. Chemical Routes for Amide Reduction**



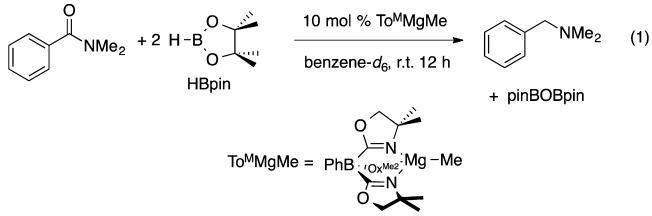

still needed to address the challenges facing amide deoxygenations (Scheme 1). Few catalytic systems are able to effectively reduce primary, secondary, and tertiary amides,[11] and few catalysts are based on metal complexes other than non-oxophilic late metals.[20,21] Moreover, many catalysts require elevated temperatures for effective operation, and disproportionation of primary and secondary amides into a mixture of tertiary, secondary, and primary amines also hinders the application of catalytic hydrosilylation for deoxygenation. An exception is the $[Ir(\eta^2\text{-}C_8H_{14})_2Cl]_2/Et_2SiH_2$ system, which reduces secondary amides at room temperature (but also catalyzes silane redistribution).[8] This catalyst, as well as many of the first-row transition-metal hydrosilylation catalysts such as $Zn(OAc)_2$,[22] are appealing for their simplicity, but the tuning effects of ancillary ligands may be difficult to introduce for conversions in which advanced activity and selectivity is needed. Other mild systems are applicable only for tertiary amides and employ main group metal catalysts.[21−23]

In contrast, the reduction of amides by catalytic hydroboration with HBpin is not reported.[24] Magnesium compounds have been shown to be good catalysts for the hydroboration of a number of carbonyl compounds and unsaturated substrates, such as pyridine.[25−28] Our group has recently found that $To^MMgMe$ ($To^M$ = tris(4,4-dimethyl-2-oxazolinyl)-phenylborate) catalytically reduces and cleaves esters with 2 equiv of pinacolborane (HBpin) to give alkoxyboronic pinacol esters (ROBpin).[29] Amides are slightly stabilized relative to esters, which can be shown by the $\Delta H_{rxn}$ for the metathesis reaction of methyl acetate and dimethylamine to *N*,*N*-dimethylacetamide and methanol, which is −7.5 kcal/mol.[30] On this basis, the reduction of amides might be predicted to be slower than the reduction of esters.

Thus, the feasibility and reaction pathway(s) of a magnesium-catalyzed amide reduction is of interest in relation to the ester reduction. In addition, the classic studies of Brown on hydroboration and deoxygenation of amides with $B_2H_6$ reveal good selectivity, even with this highly reactive reagent,[31,32] which nonetheless is limited by its reactivity toward olefins and alkynes. Herein, we report the catalytic reduction of tertiary and secondary amides to amines using pinacolborane and the precatalyst $To^MMgMe$ under mild, room temperature conditions. Pinacolborane does not react at room temperature with secondary and tertiary amides, which allows for functional group tolerance and potential selectivities not known with $B_2H_6$ or $LiAlH_4$. The isolated magnesium dihydridopinacolborate adduct $To^MMgH_2Bpin$, which is a precatalyst in the aforementioned ester cleavage, is not effective as a catalytic species in the reduction of amides. To the best of our knowledge, this report describes the first example of the catalytic hydroboration of amides.

## RESULTS AND DISCUSSION

*N*,*N*-Dimethylbenzamide reacts with 2 equiv of pinacolborane (HBpin) upon addition of $To^MMgMe$ (10 mol %) to form benzyldimethylamine in 54% yield (eq 1). Control experiments reveal that *N*,*N*-dimethylbenzamide and 2 equiv of pinacolborane are unchanged after 24 h at temperatures up to 120 °C in the absence of $To^MMgMe$.




The $To^MMgMe$-catalyzed amide deoxygenation reaction of eq 1 contrasts the hydroboration/reductive ester cleavage catalyzed by $To^MMgMe$, instead following the typically observed conversion of amides to amines in the presence of strong metal hydrides, such as $LiAlH_4$ or $NaBH_4$.[6] The byproduct of the catalytic hydroboration/deoxygenation is pinBOBpin, which is characterized by $^1H$ and $^{11}B$ NMR signals at 1.02 and 21.7 ppm, respectively (in benzene-$d_6$).[33]

These catalytic experiments were initially performed by dissolving *N*,*N*-dimethylbenzamide and HBpin in benzene, followed by addition of $To^MMgMe$. In contrast, benzyldimethylamine is not efficiently produced (18% yield) in experiments in which *N*,*N*-dimethylbenzamide is added to a solution of $To^MMgMe$ and HBpin. Instead, the magnesium compound and HBpin react instantaneously to give MeBpin and a black, intractable and catalytically inactive precipitate. Although this decomposition may be avoided (in the absence of amide) by adding $To^MMgMe$ to excess HBpin (>10 equiv) to form $To^MMgH_2Bpin$, experiments in which *N*,*N*-dimethylbenzamide is added to a 20:1 mixture of HBpin/$To^MMgMe$ do not afford greater than ∼20% benzyldimethylamine. In those experiments, the characteristic black precipitate is still observed. Furthermore, isolated $To^MMgH_2Bpin$ is less efficient as a catalyst precursor for amide reduction than $To^MMgMe$ (Table 1). Finally, the deoxygenation yield is poorer and C−N cleavage products are higher in reactions performed in methylene chloride (see below and Scheme 2 for discussion of the observed pathways in this catalytic system). That solvent is effective for the formation of $To^MMgH_2Bpin$, and it is also effective as a solvent for the $To^MMgMe$-catalyzed cleavage of esters. Thus, these empirical observations for amide deoxygenation contrast those of the $To^MMg$-catalyzed ester hydroboration,[29] which is proposed to involve $To^MMg\{RO(H)Bpin\}$ as a catalytic intermediate formed from $To^MMgH_2Bpin$ and esters.

Other oxazoline-based magnesium compounds also show catalytic activity for hydroboration and deoxygenation of amides (Table 1), and the catalytic efficacy varies with substrate and ancillary oxazolinylborate-based ligand. The chiral $C_3$-symmetric $To^PMgMe$ ($To^P$ = tris((4*S*)-isopropyl-2-oxazolinyl)-phenylborate) gives slightly greater conversion to benzyldimethylamine (67% NMR yield) than $To^MMgMe$ after 12 h, and it gives 97% yield after 24 h. This product is obtained with 54% yield after 12 h when $To^MMgMe$ is the catalyst, and the same yield is measured after 24 h, indicating that the product does not decompose under the reaction conditions, and the $To^PMg$-derived catalyst is longer-lived than the $To^MMg$-derived species.



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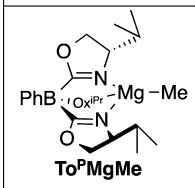
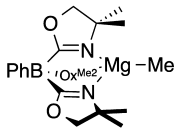
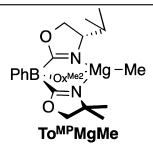
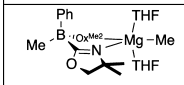
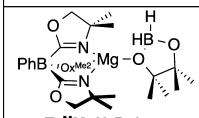
**Table 1. Effects of Ancillary Ligand and Reaction Conditions on Catalytic Deoxygenation of *N,N*-Dimethylbenzamide with Pinacol Borane**

| Catalyst | mol% cat. | Equiv. HBpin | Time (h) | Solvent | NMR Yield (%) |
|---|---|---|---|---|---|
|  To$^{P}$MgMe | 10 | 2 | 12 | benzene-$d_6$ | 67 |
| | 10 | 2 | 24 | benzene-$d_6$ | 97 |
| | 10 | 4 | 24 | benzene-$d_6$ | 78 |
| | 10 | 2 | 24 | $CD_2Cl_2$ | 26 |
|  To$^{M}$MgMe | 10 | 2 | 12 | benzene-$d_6$ | 54 |
| | 10 | 2 | 24 | benzene-$d_6$ | 54 |
| | 10 | 4 | 12 | benzene-$d_6$ | 94 |
| | 10 | 20 | 0.25 | benzene-$d_6$ | 97 |
| | 5 | 20 | 0.5 | benzene-$d_6$ | 97 |
| | 2 | 20 | 3 | benzene-$d_6$ | 99 |
|  To$^{MP}$MgMe | 10 | 2 | 26 | benzene-$d_6$ | 46 |
|  PhMeB(Ox$^{Me2}$)$_2$MgMeTHF$_2$ | 10 | 2 | 6 | benzene-$d_6$ | 44 |
| | 10 | 2 | 12 | benzene-$d_6$ | 44 |
|  To$^{M}$MgH$_2$Bpin | 10 | 2 | 12 | benzene-$d_6$ | 17 |
| | 10 | 4 | 24 | benzene-$d_6$ | 30 |

With To$^{M}$MgMe, yields are improved with even 4 equiv of HBpin, whereas amine yield is decreased with a greater concentration of HBpin when To$^{P}$MgMe is the catalyst. The less efficient $C_1$-symmetric To$^{MP}$MgMe (To$^{MP}$ = bis(4,4-dimethyl-2-oxazolinyl)((4*S*)-isopropyl-2-oxazolinyl)-phenylborate) requires >24 h for <50% yield, and amine yields are not improved with longer reaction times. Similarly, a bis(oxazolinyl)boratomagnesium methyl gives an even lower yield with both short and long reaction times, implying that the catalyst quickly deactivates.

Although To$^{P}$MgMe gives the highest yield in Table 1, most other substrates below in Table 2 are reduced in equal or higher yield with To$^{M}$MgMe than with the $C_3$-symmetric To$^{P}$MgMe complex. In fact, for most tertiary and secondary amides, To$^{M}$MgMe is a superior precatalyst in terms of reaction times, NMR yields, and selectivity. Moreover, 10, 5, or even 2 mol % To$^{M}$MgMe as the catalyst provides benzyldimethylamine in >95% yield under optimized conditions with excess HBpin. There appears to be a trade-off between To$^{M}$MgMe and HBpin loadings: high catalyst loading and low HBpin concentration give >90% yield of the amine, and low catalyst loading requires a larger excess of HBpin. This is undoubtably a kinetic effect and suggests that the intermediate formed from C═O hydroboration is catalytically deoxygenated through reactions that involve both To$^{M}$MgX and HBpin species.

Thus, the interaction of To$^{M}$MgH$_2$Bpin and amides could provide insight into pathways available during catalytic amide reduction to guide further optimizations. To$^{M}$MgH$_2$Bpin and 1 equiv of *N,N*-dimethylbenzamide give complete consumption of the amide and formation of benzyldimethylamine in 11% yield in a process that affords a mixture of species. In Scheme 2, pathways associated with C−O, C−N, and C−C cleavage are identified on the basis of the assigned products. Two sets of new To$^{M}$-containing signals were observed. The major species was assigned to To$^{M}$MgOCH$_2$Ph on the basis of a comparison with an authentic sample generated from To$^{M}$MgMe and HOCH$_2$Ph. In addition, a signal at 2.15 ppm was assigned to HNMe$_2$ on the basis of an identical chemical shift of an authentic dilute sample of dimethylamine in benzene-$d_6$.

The reactant To$^{M}$MgH$_2$Bpin, as well as To$^{M}$MgNMe$_2$, are ruled out as the other To$^{M}$-containing species on the basis of a comparison with authentic samples. PhCH$_2$OBpin and Me$_2$NBpin are formed; PhCH$_2$OBpin was assigned on the basis of $^{1}$H and $^{11}$B NMR spectroscopy and GC/MS ($\delta_H$ 1.04, 4.96, 7.05, 7.10, 7.30; $\delta_B$ 22.7; and *m*/*z* 234.1),[34,35] and Me$_2$NBpin was assigned on the basis of $^{1}$H and $^{11}$B NMR spectroscopy ($\delta_H$ 1.12, 2.64; $\delta_B$ 23.9).[36] A small signal in the GC/MS was assigned to PhBpin on the basis of its identical retention time as an authentic sample, its parent ion peak of 204.1 *m*/*z* in the MS, and the overall similarity of daughter ion



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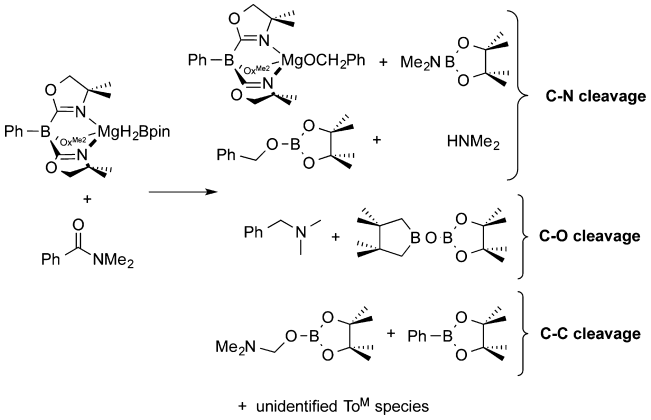
**Scheme 2. Multiple Pathways Observed in Reactions of $To^{M}MgH_2Bpin$ and *N,N*-Dimethylbenzamide**




peaks in the MS. In addition, a signal in the GC/MS was assigned to $Me_2NCH_2OBpin$. Similarly, two equiv of *N,N*-dimethylbenzamide rapidly give benzyldimethylamine in 16% yield (vs $To^{M}MgH_2Bpin$ as the limiting reagent) after 15 min, and no changes are observed after that point. In that experiment, *N,N*-dimethylbenzamide is partly consumed (37% *N,N*-dimethylbenzamide is unreacted), and several unidentified $To^{M}$-containing compounds are observed.

The dominance of the C–N bond cleavage pathway from the reaction of $To^{M}MgH_2Bpin$ contrasts the catalytic deoxygenation pathway observed with $To^{M}MgMe$ and excess HBpin. Amide deoxygenation requires two reducing equivalents, both of which could, in principle, be provided by $To^{M}MgH_2Bpin$. The experiments above, however, indicate that the second reducing equivalent in $To^{M}MgH_2Bpin$ goes to C–N bond cleavage if there is no excess HBpin present. On the basis of this idea, the effect of excess HBpin on deoxygenation yields and reaction times was investigated. Neat HBpin results in nearly quantitative yields and fast reaction rates, and the optimal yield is obtained with excess pinacolborane (20 equiv; see Table 1). Moreover, the C–N cleavage products $Me_2NBpin$ and $PhCH_2OBpin$ are not detected when a high concentration of HBpin is used. Thus, the role of excess HBpin under catalytic conditions is not to give $To^{M}MgH_2Bpin$ in high yield because catalyst activation does not involve that compound as an intermediate. Instead, HBpin plays an important role in controlling selectivity toward deoxygenation vs C–N cleavage.

An alternative pathway for catalyst activation might instead involve the interaction of $To^{M}MgMe$ and an amide. Interestingly, 1:1 or 1:2 mixtures of $To^{M}MgMe$ and *N,N*-dimethylbenzamide are unchanged after 2 h at room temperature in benzene. After 24 h, all $To^{M}MgMe$ signals disappeared, and multiple broad signals associated with unidentified $To^{M}$-containing species appeared. Neither $H[To^{M}]$ nor methane signals were detected, ruling out adventitious hydrolysis. However, ~95% of the initial *N,N*-dimethylbenzamide was unreacted. This process is much slower than the catalytic reaction and likely unrelated to amide deoxygenation. These observations also contrast the reaction of $To^{M}MgMe$ and EtOAc, which react instantaneously at room temperature to give acetone and $To^{M}MgOEt$.[11] The catalytic yields of benzyldimethylamine (51–54%), however, are similar either when 2 equiv of HBpin are added to a mixture of $To^{M}MgMe$ and *N,N*-dimethylbenzamide or when catalyst is added to the mixture of HBpin and *N,N*-dimethylbenzamide. In total, these observations suggest that the formation of the active catalytic species requires all three reaction components ($To^{M}MgMe$, HBpin, and amide) and may involve an unusual dual substrate-catalyst initiation process.

Unfortunately, attempts to determine a quantitative catalytic rate law for tertiary amide hydroboration/reduction were hindered by precipitation that occurs during the reaction. Qualitatively, an increased concentration of HBpin (with all other variables kept constant) results in a faster disappearance of amide and faster appearance of the amine product. A higher catalyst concentration also provides faster conversions.

Valuable, albeit nonquantitative, mechanistic information is provided by in situ UV–vis spectroscopy. A transient absorption at 330 nm, assigned to a reaction intermediate, quickly increases in intensity in the early stages of the reaction and then slowly decays (Figure 1). This signal is attributed to a species that is formed from the combination of $To^{M}MgMe$, HBpin, and $Ph(Me_2N)C{=}O$. Independent experiments indicate that bimolecular combinations ($To^{M}MgMe$ and HBpin or $To^{M}MgMe$ and $Ph(Me_2N)C{=}O$) do not provide this absorbance; the catalytic products pinBOBpin and $PhCH_2NMe_2$ also do not produce this signal.

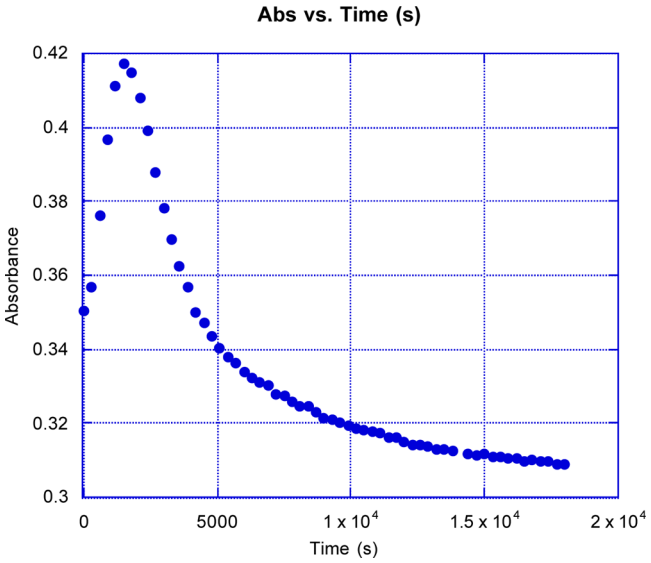



**Figure 1.** Plot of absorbance vs time for the transient signal at 330 nm assigned to the catalytically active species.

To analyze the formation of the intermediate, we independently and systematically varied $[To^{M}MgMe]$, [HBpin], and [*N,N*-dimethylbenzamide] and measured the signal intensity and slope of curves of absorbance at 330 nm vs time for the initial portion of the reaction. Variation in the catalyst concentration from 3.95 to 7.91 mM provided a linear plot of initial rate ($d$(absorbance)/$dt$) vs $[To^{M}MgMe]$ ($k_{obs} \approx 0.02\ s^{-1}$; [HBpin] = 0.791 M and $[Ph(Me_2N)C{=}O]$ = 0.040 M). Moreover, the absorbance increases as $[To^{M}MgMe]$ increases, suggesting that the signal is associated with a magnesium species. Variation of [HBpin] from 0.395 to 1.79 M shows a generally increasing slope of d(absorbance)/d$t$ with increasing [HBpin], although the data are not sufficient for a quantitative linear least-squares analysis. Interestingly, at low concentration of *N,N*-dimethylbenzamide, the initial rate shows little change at low concentration until 40 mM, but shows a sharp increase in rate above ~45 mM. These rate dependences



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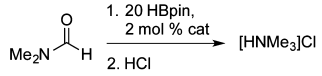
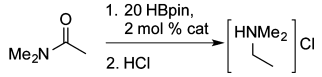
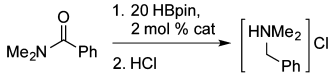
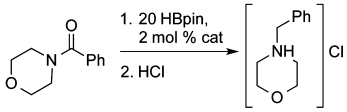
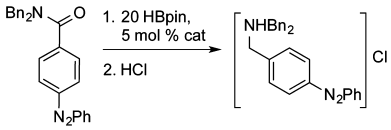
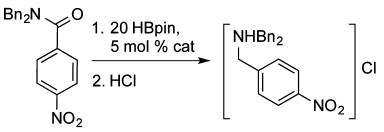
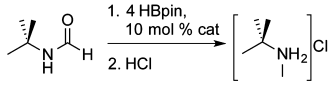
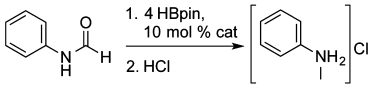
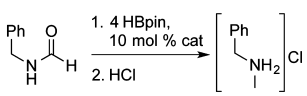
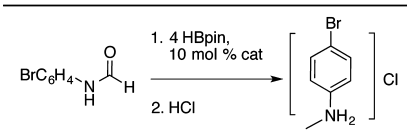
parallel our general observations regarding the effects of catalyst initiation on the catalytic conversion. On the basis of these similarities, we suggest that the 330 nm signal is due to a catalytically relevant species that contains To$^{M}$Mg, amide, and HBpin derived moieties.

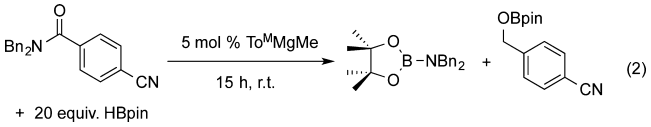
This system gives reduction of amides under mild conditions at room temperature with good yields (Table 2) and advantageously tolerates nitro and azo moieties typically reduced by common stoichiometric metal hydride reagents such as $LiAlH_4$. Aryl bromide is tolerated, and benzyl groups on the amide are not cleaved under reaction conditions, as might be expected under late-metal catalyzed hydrogenations. Notably, the conversion works with both aliphatic, aromatic, and formamide-based substrates. However, *N*,*N*-dimethyl acrylamide reacts instantaneously with To$^{M}$MgMe and HBpin to give an unidentified precipitate.

**Table 2. To$^{M}$MgMe-Catalyzed Hydroboration and Reduction of Tertiary and Secondary Amides**

| Reaction | Time | Yield[a] |
|---|---|---|
|  | 5 min. | 77 (18) |
|  | 6 h | 99 (91) |
|  | 3 h | 99 (93) |
|  | 6 h | 99 (92) |
|  | 15 h | 88 (79) |
|  | 15 h | 83 (78) |
|  | 24 h | 72 (71) |
|  | 48 h | 99 (93) |
|  | 48 h | 86 (85) |
|  | 48 h | 71 (68) |

[a]Isolated yield in parentheses.

Under catalytic hydroboration conditions, *N*,*N*-dibenzyl-4-cyanophenylamide gives the amide C−N cleavage product rather than the deoxygenated product (eq 2); however, the



(2)

cyano moiety is not reduced under the reaction conditions. Although the boronate-protected *p*-cyanobenzyl alcohol was not isolated, its NMR yield is equal to the NMR yield of dibenzylamine (89%), and dibenzylammonium chloride is isolated in 77% yield. The starting material contained $^{13}C\{^{1}H\}$ NMR signals at 114.1 and 118.5 ppm assigned to *ipso*-$C_6H_4C{\equiv}N$ and $C{\equiv}N$ signals, and similar resonances in $pinBOCH_2C_6H_4CN$ were measured at 111.7 and 119.3 ppm. Deoxygenation of the related electron-poor *para*-nitrophenyl amide is straightforward under the standard catalytic conditions, in contrast to $LiAlH_4$ reductions.

Secondary amides are also deoxygenated to secondary amines, although increased catalyst loading (Table 2) is required for high yield. Interestingly, the highest yields are obtained with 4 equiv of HBpin with respect to the amide rather than the larger excess preferred for tertiary amides. The fastest reactions and the highest yields are obtained with substrates containing small groups adjacent to the carbonyl, most notably the formamides. These observations, along with the significant variation of yield with a series of similar oxazoline-based ancillary ligands, suggest that steric effects greatly affect the reaction. Significantly, formation of tertiary amines (e.g., $PhNMe_2$) via imine alkylation is not observed. This amine alkylation is a common pathway under hydrosilylation and hydrogenation conditions.[3]

A closer investigation of the secondary amide hydroboration reaction through in situ NMR spectroscopy is revealing, even though the reaction pathway appears complex. First, *N*-phenylformamide and HBpin are unchanged at room temperature in the absence of catalyst. That is, the amide NH and the pinacolborane BH do not eliminate $H_2$ and form a B−N bond at room temperature. Upon addition of To$^{M}$MgMe as the catalyst, *N*-phenylformamide and HBpin react rapidly to consume all of the formamide starting material within 5 min. Effervescence of hydrogen gas is observed, as is a mixture of species in solution that includes a formimidate boronic ester intermediate (**A**) and reduced hydroboration intermediate **C** (Scheme 3).

A $^{1}H$ NMR spectrum of the reaction mixture contained a new singlet at 8.10 ppm assigned to a formimidate boronic ester (**A** in Scheme 3), and this peak is downfield of the signal at 7.87 ppm for the *N*-phenylformamide starting material. The formimidate signal correlates to a phenyl signal at 6.85 ppm in a NOESY experiment, which allows assignment of the ortho phenyl group. From a COSY experiment, the para and meta phenyl protons are identified at 6.76 and 7.00 ppm. The $^{13}C\{^{1}H\}$ NMR spectrum contained a signal at 168.7 ppm that correlated with the $^{1}H$ NMR signal at 8.10 ppm in a $^{1}H-^{13}C$ HMQC experiment. For comparison, the imine carbon of *N*-phenyl iminoether is 154.2 ppm.[37] The formimidate proton also correlated to a $^{15}N$ NMR signal at −202 ppm in a $^{1}H-^{15}N$ HMBC experiment. This $^{15}N$ NMR chemical shift is similar to the three-coordinate imidate nitrogen in a protonated oxazolinylborate.[38] The $^{1}H$ NMR signal at 8.10 ppm also



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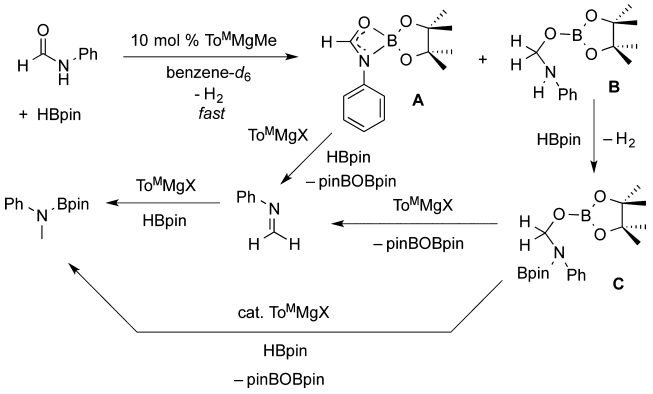
**Scheme 3. Pathways for Catalytic Conversion Based on the Spectroscopically Detected Composition of the Reaction Mixture**




correlated in a $^{1}H-^{11}B$ HMBC experiment to a $^{11}B$ NMR resonance at 5.1 ppm. The intensity of that $^{11}B$ NMR signal is much larger than the To$^{M}$-derived $^{11}B$ NMR signals of the catalyst. In addition, the $^{11}B$ NMR chemical shift appeared in the range consistent with a neutral four-coordinate boron center.[39] Finally, a high resolution mass spectrum contained the parent ion signal at 247.1480 $m/z$, and the isotopic pattern in the mass spectrum indicated that this species contained only one boron atom. These data strongly implicate **A** as a formimidate species, likely formed from catalytic dehydrogenative borylation of the amide proton.

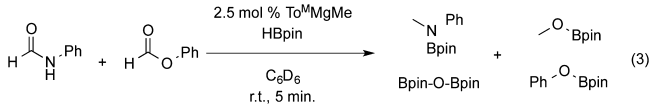
A second intermediate, tentatively assigned as the boronic ester resulting from hydroboration of the C═O and nitrogen borylation (**C**), was characterized by a methylene signal at 5.65 ppm in the $^{1}H$ NMR spectrum. A $^{1}H-^{13}C$ HMQC experiment revealed a correlation between this signal and a $^{13}C$ NMR signal at 55.1 ppm. A DEPT-135 experiment indicated that the signal is from a $CH_2$ group. Unfortunately, crosspeaks to this signal were not detected in $^{1}H-^{11}B$ and $^{1}H-^{15}N$ HMBC experiments. However, two signals in the $^{11}B$ NMR spectrum are assigned to O–Bpin (22.5 ppm) and N–Bpin (24.7 ppm) moieties. The mass spectrum of the reaction mixture did not contain the parent ion peak of 248 or 375 $m/z$ for such a species or its borylated derivative, possibly because of HOBpin or pinBOBpin elimination and hydrolysis during the mass spectrometry experiment. Instead, a signal at 106 $m/z$ assigned to the protonated iminium $[Ph(H)N{=}CH_2]^+$ is detected. This intermediate **C** associated with the methylene $^{1}H$ NMR signal at 5.65 ppm is formed preferentially under reaction conditions with lower amounts of HBpin (2 equiv), whereas the formimidate boronic ester is favored at higher HBpin loading (4 equiv relative to formamide).

Intermediate **C** contains 2 Bpin groups, whereas **A** is only monoborylated; this is the opposite of the selectivity that might be expected on the basis of the reaction conditions. The contrast between the stoichiometry of the intermediates and their apparent kinetic preference can be rationalized as shown in Scheme 3. Intermediates **A** and **C** form concurrently, and study of the reaction timecourse suggests that **A** is not on the pathway to **C**. From this data, we suggest that the rate constants for formation of **A** and **B** have different [HBpin] dependences and a fast uncatalyzed NH/BH dehydrocoupling occurs from intermediate **B**. Even though intermediates **A** and **C** are formally related by a hydroboration event, the hydroboration of **A** is not observed in this catalytic system.

Over 48 h, signals assigned to the product MePhN–Bpin appear in the NMR spectra of the reaction mixture. The signals in the $^{1}H$ NMR spectrum for **A** at 8.10 ppm and **C** at 5.65 ppm disappear as MePhN–Bpin resonances increase in intensity. Thus, the slow steps in the catalysis are the conversion of **A** and **C** to product, and these steps are faster with greater To$^{M}$MgMe loading.

To further probe the catalytic additions, we turned to competition experiments between amides and esters. Previous studies of To$^{M}$Mg-catalyzed ester reductive cleavage showed very fast conversions,[29] with reactions completing in less time than the above amide deoxygenation pathway. Our kinetic studies in that system implicated a catalyst-mediated reversible ester cleavage prior to hydroboration with To$^{M}$Mg{RO(H)-Bpin}. This mechanism is based on a half-order rate dependence on ester concentration and zero-order dependence on HBpin concentration. Likely, the initial ester cleavage involves addition to the carbonyl, whereas the studies of amide hydroboration suggest concurrent catalytic dehydrocoupling and hydroboration reactions. Moreover, studies of secondary and tertiary amides suggest rapid consumption of starting materials and rapid formation of intermediate(s), followed by slow formation of the amine products. Thus, competition experiments probe the relative rates of HBpin addition to amide vs ester.

The initial rates of consumption of phenyl formate and phenylformamide reactants, chosen for their similar steric and structural features, were compared. Phenyl formate and phenylformamide react with HBpin in the presence of 2.5 mol % To$^{M}$MgMe to give phenylmethylamidopinacolborane and the boryl ether products MeOBpin and PhOBpin (eq 3).




(3)

Under the conditions of excess carbonyl vs HBpin (formamide:formate:HBpin =1:1:1), the competition experiment reveals that the rate of amide consumption is faster than the rate of ester consumption. The initial concentrations of phenylformamide and phenyl formate decrease by 0.14 and 0.04 M, respectively, over the first 5 min of the reaction. In contrast, when the concentration of HBpin is increased (formamide:formate:HBpin =1:1:2 with all other variables held constant), the rate of amide consumption is slower than the rate of ester consumption. In this case, the initial concentrations of phenylformamide and phenyl formate decreased by 0.09 and 0.13 M, respectively, over the first 5 min of the reaction. In both cases, these experiments show that the presence of formamide substantially inhibits the rate of catalytic ester cleavage. However, with a larger amount of HBpin (formamide:formate:HBpin =1:1:4), all of the ester substrate is consumed within 5 min, while ca. 50% phenylformamide is unreacted at that time. Because the ester cleavage is zero-order in [HBpin], these observations suggest that the active catalytic species are not the same for amide and ester conversion.

There are no further changes to the NMR spectra of these reaction mixtures after 15 min. In the experiments with 1:1:1 formamide:formate:HBpin, substantially more of the intermediates **A** and **C** are formed (21% and 29% NMR yield) from the catalytic addition of HBpin and *N*-phenylformamide than



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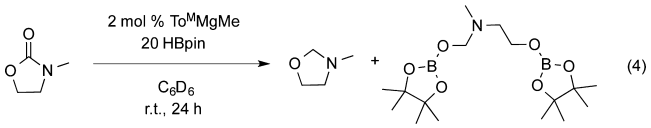
MeOBpin (8%) from ester cleavage. Thus, the formamide reacts approximately 5× faster than the formate, but the addition of HBpin to formate leads directly to the product whereas the catalyzed interaction of HBpin and *N*-phenylformamide provides intermediate species that are further reduced at longer reaction times.

An oxazolidinone substrate provides an alternative competition between ester cleavage and deoxygenation (eq 4). This




(4)

2 : 1

competition experiment compares product formation from either pathway, rather than initial consumption of ester or amide under conditions of low HBpin concentration needed in the above experiments.

Under conditions with a large excess of HBpin (20 equiv), deoxygenation is favored 2:1 over ester cleavage as determined from the ratio of products in the $^{11}$B NMR spectrum. Decreasing the amount of HBpin to 2 equiv. reduces the product ratio to 1.3:1, but deoxygenation is still favored. These reactions require 1 day for full conversion, which is similar to the rate of amide deoxygenation. The change in product ratio with lower [HBpin] in this case likely reflects the direct dependence of the amide deoxygenation reaction on the pinacolborane concentration observed in synthetic experiments.

## CONCLUSION

A number of important general observations are revealed from our study of the first example of catalytic hydroboration for amide deoxygenation. The ancillary ligands, based on the oxazolinylborate motif, show a range of catalytic activity and selectivity, and it is clear that ancillary ligand effects are important in these magnesium-catalyzed amide deoxygenations. To$^{M}$MgMe generally outperforms the other tested oxazolinylborate-based magnesium complexes as an effective precatalyst for the hydroboration of amides, although the sensitivity of the reaction to conditions suggests that other catalysts based on oxophilic early metal centers should be explored in the future. Moreover, comparisons between tertiary and secondary amides reveals that in general, catalytic hydroboration is fast, and reductive deoxygenation is slow. However, the results of this study clearly show that the pathway of tertiary amide reduction is tuned for C−O vs C−N bond cleavage by HBpin concentration. Interestingly, this C−N cleavage pathway occurs at low HBpin concentration, and amide deoxygenation shows a significant HBpin dependence. In contrast, secondary amides undergo reductive deoxygenation in preference to C−N cleavage with only a slight excess of HBpin, which is needed in the case of the reaction with the amide NH in a catalyzed dehydrocoupling reaction. Thus, the apparent turnover-limiting steps in the catalysis involve deoxygenation (C−O bond cleavage), whereas the catalytic addition of HBpin to the amide is apparently fast. This appears to be the case for both secondary and tertiary amides. In contrast, the related ester reductive cleavage pathway is zero-order in HBpin. Overall, the magnesium catalyst activation and speciation for amide deoxygenation and ester cleavage appear to be inequivalent, and the interaction of HBpin with catalytic intermediates are distinct for the two transformations. Further work to clarify the pathway(s) and identify the reactive species for deoxygenation and C−N cleavage in amides is currently underway.

Organosilanes are not effective reductants of amides in this oxazolinylborato magnesium system; neither are silanes effective in the related magnesium-catalyzed reductive cleavage of esters. Although silanes reduce amides to amines in many transition-metal-based catalytic systems, these catalysts are typically less oxophilic (e.g., iron group or later). In the present reduction employing a highly oxophilic magnesium center, the HBpin is likely important because of its ability to act as a hydride donor and as a Lewis acid. This principle may guide future developments of catalytic amide reductions to improve efficiency, yield, and selectivity for mild conversion methods. Our current efforts are directed toward this goal.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01038.

Experimental description of the synthesis and characterization of magnesium catalysts and catalytic products, and representative spectra of isolated products and in situ experiments (PDF)

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### Notes

The authors declare no competing financial interest.

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