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$B(C_6F_5)_3$-Catalyzed Deoxygenative Reduction of Amides to Amines with Ammonia Borane

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Abstract. The first $B(C_6F_5)_3$-catalyzed deoxygenative reduction of amides into the corresponding amines with readily accessible and stable ammonia borane (AB) as a reducing agent under mild reaction conditions is reported. This metal-free protocol provides facile access to a wide range of structurally diverse amine products in good to excellent yields, and various functional groups including those that are reduction-sensitive were well tolerated. This new method is also applicable to chiral amide substrates without erosion of the enantiomeric purity. The role of BF_3•OEt_2 co-catalyst in this reaction is to activate the amide carbonyl group via the in situ formation of an amide–boron adduct.

Keywords: Amide Reduction, Deoxygenative, Ammonia Borane, Boron Lewis Acid, Catalysis

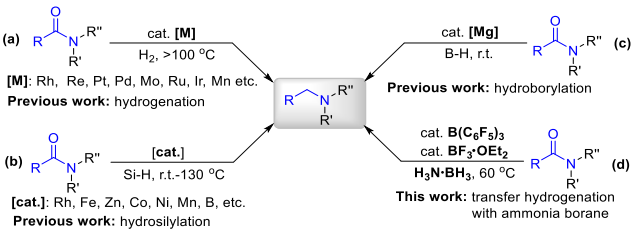
Introduction

The deoxygenative reduction of amides into the corresponding amines constitutes an important methodology in organic synthesis.[1] Although the classic reducing agent such as lithium aluminum hydride and borane is still widely employed to transform amides into amines, these reductions suffer from the necessity of (over)stoichiometric amounts of sensitive and hazardous chemicals, difficult product purification, poor functional group tolerance and the concomitant formation of large amounts of undesired by-products.[2] Clearly catalytic hydrogenation is an ideal alternative because theoretically water is generated as the only by-product. Although impressive advances in heterogeneous and homogeneous catalytic hydrogenation of amides to amines via C-O bond scission have been achieved in the past decade (Scheme 1a),[3,4] major disadvantages such as the required harsh conditions (high pressure and elevated temperatures), limited functional group compatibility and difficulty in the control of C-O bond cleavage selectivity remain to be addressed. Alternatively, catalytic hydrosilylation of amides to amines has been intensively explored due to its convenience and simplicity,[5] and various amides could be smoothly converted into the corresponding amines under the catalysis of precious metals,[6] earth abundant metals[7] and even the simple bases[8] (Scheme 1b). Notably, the boron-based organocatalysts have been successfully applied in this transformation under metal-free conditions.[9] More Recently, Sadow et al. reported the first magnesium-catalyzed deoxygenative reduction of tertiary and secondary amides to amines with pinacolborane (Scheme 1c).[10] Despite these impressive advances, there is still much room for improvement, particularly in terms of substrate scope, catalytic efficiency, reaction conditions and workup procedure.

In recent years considerable effort has been devoted to the exploration of ammonia borane (AB) as a promising H_2 storage material because of its high hydrogen density, remarkable thermal and hydrolytic stability and easy availability and handling.[11] Consequently, it is not surprising that AB has been frequently employed as a reducing agent for the reduction of imines,[12a] olefins,[12b,c] carbonyls[12d-f] and other unsaturated compounds.[12g-i] In particular, with the rapid development of frustrated Lewis pair (FLP) chemistry,[13] catalytic transfer hydrogenation with AB activated by FLP has recently drawn the attention of chemists. Du and co-workers accomplished asymmetric transfer hydrogenation of imines and 2,3-

10.1002/adsc.201801447

disubstituted quinoxalines with AB in the presence of a FLP catalyst consisting of Piers' borane and chiral *tert*-butylsulfnamide.[14a,b] The same group also developed $B(C_6F_5)_3$-catalyzed selective reduction of pyridines to piperidines with AB.[14c] More recently, the group of Shi described the selective reduction of *N*-heteroarenes with AB under the catalysis of $B(C_6F_5)_3$.[14d] The broad substrate scope, high functional group tolerance and mild reaction conditions observed in these studies led us to envisage that AB, if generally applicable, would have the potential to serve as a promising reducing agent for transforming amides into the corresponding amines. On the basis of our experience in catalytic reduction of *N*-heteroarenes and amides,[15] herein we report the first catalytic deoxygenative reduction of amides to the corresponding amines by employing $B(C_6F_5)_3$ as the catalyst and AB as the reductant under mild and metal-free conditions (Scheme 1d).

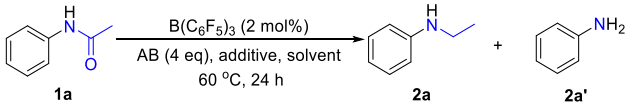


Scheme 1. Catalytic Deoxygenative Reduction of Amides to Amines.

Results and Discussion

In the beginning, we investigated the reduction of *N*-phenylacetamide (**1a**) to *N*-ethylaniline (**2a**) with $B(C_6F_5)_3$ as the catalyst and AB as the reducing agent (Table 1 and Supporting Information (SI)). We first demonstrated the reduction of **1a** at 60 °C in THF to achieve an 89% conversion in 24 h, and the desired product **2a** was obtained in 47% yield together with aniline (**2a'**) in 40% yield (Table 1, entry 1). Switching the solvent to 1,2-dichloroethane (DCE) resulted in a better conversion of 97% and yield of 78% for **2a** (Table 1, entry 2). A change of reaction solvent from DCE to 1,4-dioxane, dibutyl ether or methyl *tert*-butyl ether (MTBE) did not improve the reaction efficiency (Table 1, entries 3-5). With DCE as the reaction medium, the following investigations focused on enhancing the selectivity of **2a**. Inspired by the reports on the use of Lewis acid or Bronsted acid additive to facilitate the deoxygenative hydrogenation of amides,[4] we speculated that the introduction of a catalytic amount of an acid additive might also favor the generation of reduction product resulting from C-O bond cleavage in our case. Delightfully, introducing BF_3•OEt_2 (10 mol %) as the additive led to a nearly full conversion of **1a** with 86% and 12% yield of **2a** and **2a'**, respectively (Table 1, entry 6). The performance of other acid additives were also evaluated, but none of them worked as effectively as BF_3•OEt_2 (Table 1, entries 7-12). Moreover, increasing the loading of BF_3•OEt_2 to 30 mol % improved the yield of **2a** to 96%, and the reduction with C-N bond scission was totally suppressed as no formation of **2a'** was detected (Table 1, entry 13). Varying the amount of BF_3•OEt_2 did not lead to any improvement (see SI). Attempts to decrease the catalyst loading, the temperature or the amount of AB led to diminished yields of **2a** (Table 1, entries 14-16). Some other boron catalysts, such as (5-bromobenzo[*b*]thiophen-2-yl)boronic acid,[9b] BPh_3[9e] and bis(2-chlorophenyl)(hydroxy)borane,[9g] were tested in the reaction as well, but were less efficient than $B(C_6F_5)_3$ (Table 1, entries 17-19). Finally, a control experiment confirmed the indispensability of $B(C_6F_5)_3$ catalyst for this transformation (Table 1, entry 20). It should be stressed that the reaction is operationally simple with easy workup, and neither a dried solvent nor an inert atmosphere is required.

Table 1. Optimization of reaction conditions.[a,b]



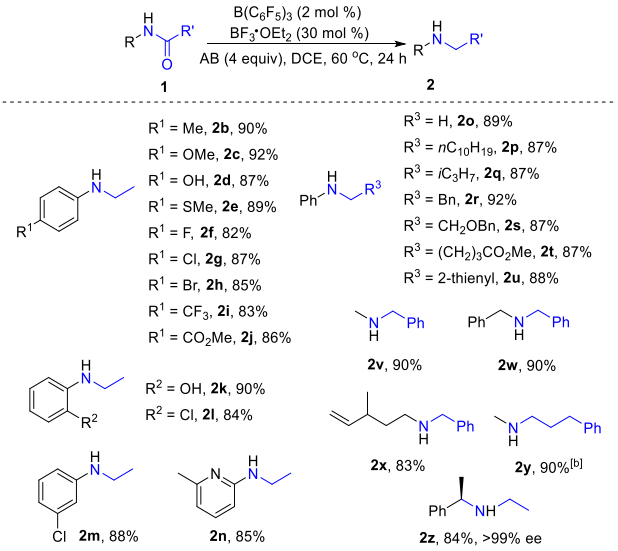
Entry	Solvent	Additive	Conv. (%)[b]	2a (%) [b]	2a' (%) [b]
1	THF	-	89	47	40
2	DCE	-	97	78	16
3	1,4-dioxane	-	88	14	73
4	nBu_2O	-	83	43	38
5	MTBE	-	85	40	42
6	DCE	BF_3•OEt_2	98	86	12
7	DCE	TfOH	93	69	22
8	DCE	$HNTf_2$	92	62	28
9	DCE	MSA	88	44	43
10	DCE	TsOH•H_2O	87	44	40
11	DCE	$Al(OTf)_3$	94	70	22
12	DCE	$Yb(OTf)_3$•H_2O	87	55	31
13[c]	DCE	BF_3•OEt_2	99	96	0
14[c,d]	DCE	BF_3•OEt_2	92	84	5
15[c,e]	DCE	BF_3•OEt_2	87	84	2
16[c,f]	DCE	BF_3•OEt_2	91	85	5
17[c,g]	DCE	BF_3•OEt_2	27	18	8
18[c,h]	DCE	BF_3•OEt_2	66	37	28
19[c,i]	DCE	BF_3•OEt_2	48	33	13
20[c,j]	DCE	BF_3•OEt_2	29	16	12

[a] Reaction conditions: **1a** (0.25 mmol), $B(C_6F_5)_3$ (2 mol %), AB (1 mmol), additive (10 mol %), solvent (1.0 mL) at 60 °C for 24 h. [b] Conversions and yields were determined by GC with Ph_3N as an internal standard. [c] BF_3•OEt_2 (30 mol %) was used. [d] $B(C_6F_5)_3$ (1 mol %) was used. [e] Reaction temperature 50 °C. [f] AB (0.75 mmol) was used. [g] (5-bromobenzo[*b*]thiophen-2-yl)boronic acid (2 mol %) was used as the catalyst. [h] BPh_3 (2 mol %) was used as the catalyst. [i] bis(2-chlorophenyl)(hydroxy)borane (2 mol %) was used as the catalyst. [j] No $B(C_6F_5)_3$.

10.1002/adsc.201801447

With the establishment of the optimized reaction conditions, we then investigated the deoxygenative reduction of a series of differently substituted secondary amides. As shown in Table 2, a series of *N*-arylacetamides (**1b-1n**) bearing various substituents on the aryl ring underwent smooth deoxygenative reduction to provide the expected amine products (**2b-2n**) in good to excellent yields, irrespective of the electronic nature and positions of these substituents. Gratifyingly, the sensitive OH, F, Cl, Br and CO_2Me groups were tolerable. Likewise, *N*-phenyl amides with aliphatic and aryl acyl groups (**1o-1u**) exhibited good reactivity to afford the reduction products (**2o-2u**) in good to excellent yields, and structural variation has a less pronounced effect on the reaction outcome. It is noteworthy that the reaction of methyl 5-oxo-5-(phenylamino)pentanoate (**1t**) proceeded readily to afford **2t** in 87% yield, and the reducible ester group remained intact during the transformation. Moreover, the benzamides **1v-1x** successfully engaged in the reduction to provide the target products **2v-2x** in high yields with the sensitive C=C bond in **1x** kept intact throughout the reaction. However, submitting *N*-methylcinnamamide (**1y**) with a conjugated double bond to the reaction conditions only led to the formation of the product (**2y**) with reduced C=C bond in 70% yield together with the remaining **1y**. Increasing the amount of AB to 6 equiv improved the yield of **2y** to 90%. Importantly, optically active amide **1z** (>99% ee) could afford an 84% yield of the desired product **2z** with no erosion of enantiomeric purity.

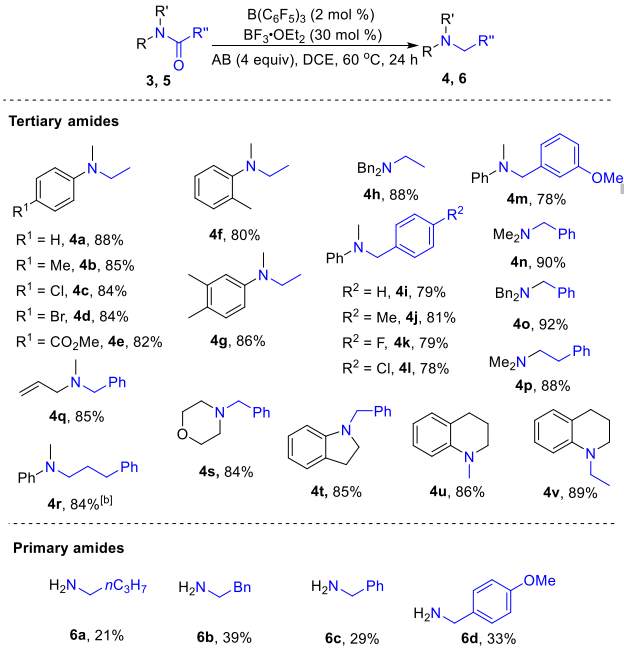
Table 2. Reduction of Secondary Amides with AB.[a]



[a] Reaction conditions: **1** (0.25 mmol), $B(C_6F_5)_3$ (2 mol %), AB (1 mmol), BF_3•OEt_2 (30 mol %), DCE (1 mL) at 60 °C for 24 h, isolated yields. [b] AB (1.5 mmol) were employed.

The metal-free deoxygenative reduction was readily extended to tertiary amides (**3a-3q**) to afford the target products (**4a-4q**) in high yields, and the halides (F, Cl, Br), ester, methoxy and C=C groups can also be accommodated (Table 3). However, when the conjugating enamide **3r** was employed as the substrate, the reduction of both the amide and C=C moieties took place to give the product **4r** in 84% yield. Furthermore, reactions conducted with substrates **3s-3v** produced N-substituted heterocycles (**4s-4v**) in good yields. In addition to secondary and tertiary amides, the primary amides (**5a-5d**) were amenable to the reaction, delivering the target products (**6a-6d**) albeit in lower yields together with recovered starting materials.

Table 3. Reduction of Tertiary and Primary Amides with AB.[a]



[a] Reaction conditions: **3, 5** (0.25 mmol), $B(C_6F_5)_3$ (2 mol %), AB (1 mmol), BF_3•OEt_2 (30 mol %), DCE (1 mL) at 60 °C for 24 h, isolated yields. [b] AB (1.5 mmol) were employed.

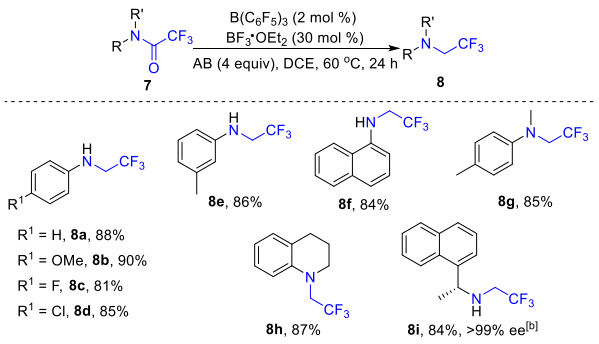
In order to further explore the utility of our catalytic system, we next examined the deoxygenative reduction of trifluoroacetyl amides into the corresponding trifluoromethyl-containing amines, which are useful building blocks in the pharmaceutical industry.[16] As depicted in Table 4, differently substituted trifluoroacetyl amides (**7a-7h**) were smoothly reduced with good to excellent yields. The chiral substrate **7i** was also suitable, giving the corresponding product **8i** in 84% yield with retained enantioselectivity.

After the successful deoxygenative reduction of normal amides, we became interested in the application of our novel catalytic protocol for the synthesis of cyclic amines from lactams (Table 5). As expected, the reduction of 3,4-dihydroquinolin-2(*1H*)-one (**9a**) proceeded well, giving the target product **10a** in 90% isolated yield. Notably, when using $B(C_6F_5)_3$ alone as the catalyst in the absence of any co-catalyst, almost the same yield was obtained, indicating that the addition of BF_3•OEt_2 co-catalyst is not necessary for the easier-to-reduce lactams. Similarly, a variety of benzo-fused lactams (**9b-9m**) were efficiently

10.1002/adsc.201801447

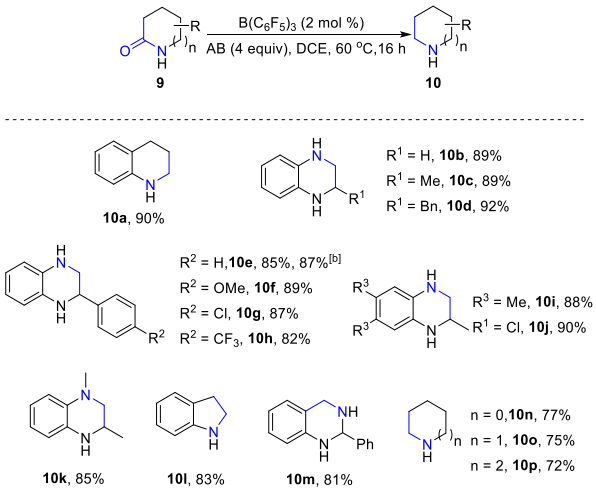
converted into the corresponding cyclic amines (**10b-10m**), and the ring size and the presence of amine group did not impact on the reaction efficiency. The aliphatic lactams (**9n-9p**) with different ring size were also reactive albeit in slightly diminished yields. Interestingly, reduction of 3-phenylquinoxalin-2(*1H*)-one (**9e'**) under the standard conditions resulted in the formation of 3-phenyl-1,2,3,4-tetrahydroquinoxalines (**10e**, 41%) and 3-phenyl-3,4-dihydroquinoxalin-2(*1H*)-one (**9e**, 57%), indicating the involvement of sequential reduction of imine and amide moieties in the process. When the amount of AB was increased to 6 equiv, **9e'** could be totally transformed into **10e** in 87% yield.

Table 4. Reduction of Trifluoroacetyl Amides with AB.[a]



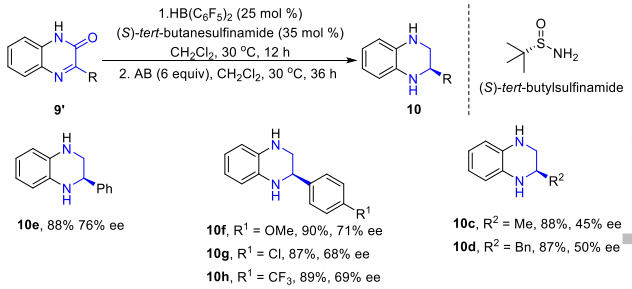
[a] Reaction conditions: **7** (0.25 mmol), $B(C_6F_5)_3$ (2 mol %), AB (1 mmol), BF_3•OEt_2 (30 mol %), DCE (1 mL) at 60 °C for 24 h, isolated yields. [b] **7i** (>99% ee) was used.

Table 5. Reduction of Lactams with AB.[a]



[a] Reaction conditions: **9** (0.25 mmol), $B(C_6F_5)_3$ (2 mol %), AB (1mmol), DCE (1 mL) at 60 °C for 16 h, isolated yields. [b] **9e'** (0.25 mmol) and AB (1.5 mmol) were employed.

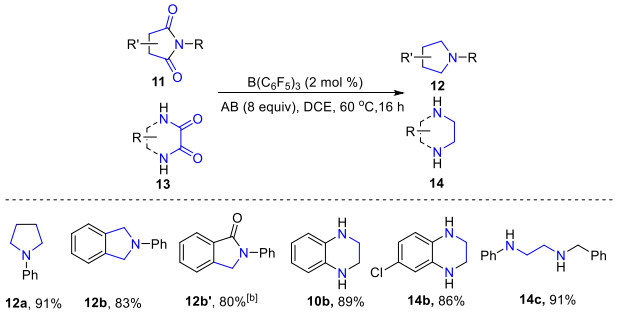
Inspired by the above results and recent reports from the group of Du on the asymmetric transfer hydrogenation of imines and quinoxalines using chiral *tert*-butanesulfinamide and Piers' borane as a FLP catalyst with AB as the reductant,[14a,b] we then envisioned that chiral 1,2,3,4-tetrahydroquinoxalines could be directly produced from quinoxalin-2(1*H*)-ones via sequential reduction of imine and amide moieties under similar catalysis. After a systematic evaluation of the reaction parameters with **9e'** as the model substrate, we found that **10e** could be obtained in 88% yield with 76% ee under the optimal reaction conditions (Scheme 2). Similarly, quinoxalin-2(1*H*)-ones **9c'**, **9d'** and **9f'-9h'** also successfully participated in the reduction to give the target products in 88-90 yields with 45-71% ee values.



Scheme 2. Synthesis of Chiral 1,2,3,4-Tetrahydro-quinoxalines

Notably, cyclic imides and oxalamides with two carbonyl moieties, such as 1-phenylpyrrolidine-2,5-dione (**11a**), 2-phenylisoindoline-1,3-dione (**11b**), 1,4-dihydroquinoxaline-2,3-dione (**13a**), 6-chloro-1,4-dihydroquinoxaline-2,3-dione (**13b**) and oxanilide (**13c**) were also suitable for this reduction to give the corresponding cyclic amine products in high yields (Table 6). Moreover, reducing the amount of AB to 4 equiv enabled the removal of only one carbonyl moiety in substrate **11b** to provide product **12b'**.

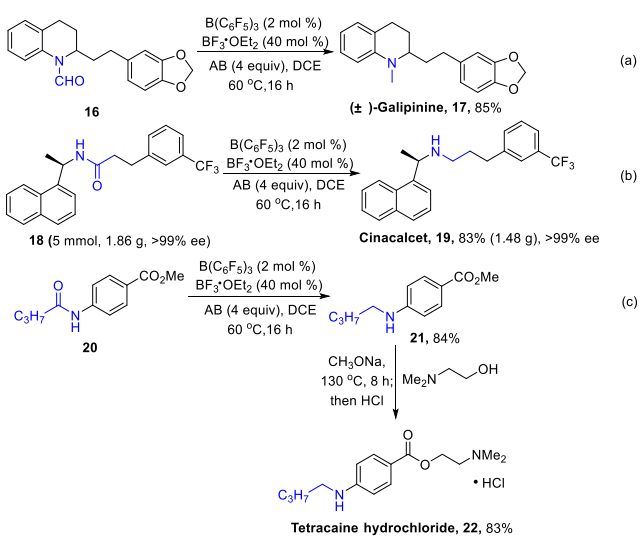
Table 6. Reduction of Cyclic Imides and Oxalamides with AB.[a]



[a] Reaction conditions: **11, 13** (0.25 mmol), $B(C_6F_5)_3$ (2 mol %), AB (2 mmol), DCE (1 mL) at 60 °C for 16 h, isolated yields. [b] AB (1.0 mmol) was employed.

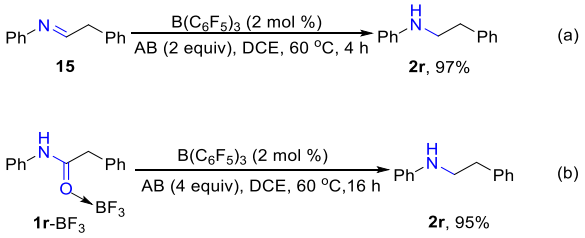
To showcase the practical utility of this transformation, we then evaluated the application of this boron-catalyzed method for the synthesis of natural product (±)-galipinine (**17**)[17a] and two drug molecules, cinacalcet (**19**)[17b] and tetracaine hydrochloride (**22**)[17c]. As shown in Scheme 3, our reaction proved to be a powerful tool for the preparation of these useful compounds. It is

noteworthy that cinacalcet (**19**) could be readily synthesized on a gram scale, demonstrating the scalability of this transformation.



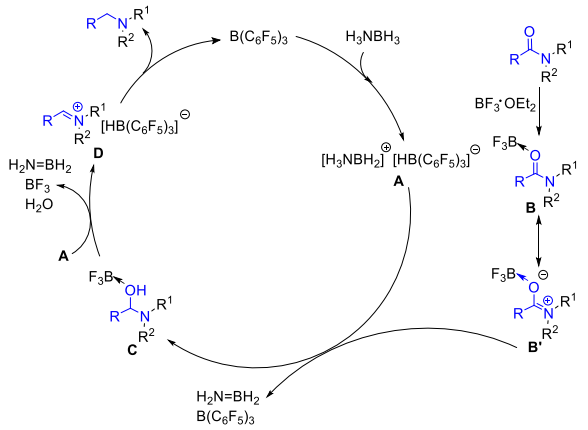
Scheme 3. Synthesis of Drug Molecules

In order to get insights into the reaction mechanism, we first examined the reduction of imine **15** in the absence of BF_3•OEt_2, and the target product was obtained in 97% yield (Scheme 4a), indicating the involvement of an imine intermediate in the reaction. On the basis of Zhou's report,[4g] it appears that the role of BF_3•OEt_2 co-catalyst in this reaction is to activate the amide carbonyl group via the in situ formation of amide-boron adduct. This was confirmed by the fact that treatment of the separately prepared adduct **1r**-BF_3 with AB under $B(C_6F_5)_3$ catalysis resulted in the generation of the desired product in 95% yield (Scheme 4b).



Scheme 4. Control Experiments

Based on the above observations and previous reports,[14] a plausible reaction mechanism is proposed (Scheme 5). The present reaction proceeds with the generation of a zwitterion species **A** from $B(C_6F_5)_3$ and AB. Meanwhile, BF_3•OEt_2 activates the amide substrate to give rise to the amide-boron adduct **B** or **B'**, which is subsequently attacked by **A** to provide the intermediate **C**. The following dehydration of **C** with **A** generates the highly electrophilic iminium species **D**, which is then reduced into the amine product with the release of $B(C_6F_5)_3$ catalyst.



Scheme 5. Proposed Reaction Mechanism.

Conclusion

In conclusion, we have described the first examples of $B(C_6F_5)_3$-catalyzed metal-free deoxygenative reduction of structurally diverse amides into the corresponding amines in the presence of bench-stable and easily accessible ammonia borane as a hydrogen source. The catalytic system consists of the $B(C_6F_5)_3$ catalyst and BF_3•OEt_2 co-catalyst and operates under mild conditions, allowing for highly selective C-O bond cleavage to afford to a variety of synthetically valuable amine products in high yields with good functional group compatibility. This method offers a powerful alternative to the currently known methods for deoxygenative reduction of amides.

Experimental Section

For details of instruments used and the general experimental procedures, see the Supporting Information.

General procedure for deoxygenative reduction of amides

To a pressure tube were sequentially added amide **1** (0.25 mmol), $B(C_6F_5)_3$ (2.56 mg, 2.0 mol %), NH_3•BH_3 (30.87 mg, 1.0 mmol), BF_3•OEt_2 (10.64 mg, 30 mol%) and DCE (1.5 mL). Then the reaction mixture was stirred at 60 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with EtOAc (5.0 mL). Then aqueous NaOH (5.0 mL, 4.0 M) was added to the reaction mixture, which was extracted with EtOAc three times (5.0 mL each). The combined organic phases were dried over Na_2SO_4, then filtered and evaporated under reduced pressure. After the removal of volatile materials by rotary evaporation, the resultant mixture was purified by silica gel column chromatography using a mixture of EtOAc and hexane to give the corresponding pure product.

Gram-scale synthesis of cinacalcet (19)

To a pressure tube were sequentially added amide **18** (1.88 g, 5 mmol), $B(C_6F_5)_3$ (51.2 mg, 2.0 mol %), NH_3•BH_3 (617.4 mg, 20.0 mmol), BF_3•OEt_2 (212.9 mg, 30 mol%) and DCE

(30 mL). Then the reaction mixture was stirred at 60 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with EtOAc (100.0 mL). Then aqueous NaOH (100.0 mL, 4.0 M) was added to the reaction mixture, which was extracted with EtOAc three times (100.0 mL each). The combined organic phases were dried over Na_2SO_4, then filtered and evaporated under reduced pressure. After the removal of volatile materials by rotary evaporation, the resultant mixture was purified by silica gel column chromatography using a mixture of EtOAc and hexane to give the corresponding pure product **19** (1.48g, 83%).

General procedure for synthesis of chiral 2-substituted tetrahydroquinoxalines

To a pressure tube were added $HB(C_6F_5)_2$ (43.2 mg, 25 mmol %), (*S*)-*tert*-butylsulfinamide (21.2 mg, 35 mmol %), quinoxalin-2(*1H*)-one **9'** (0.5 mmol), and CH_2Cl_2 (2 mL) in a glovebox under nitrogen atmosphere. After being sealed, the resulting mixture was stirred for 12 h at 30 °C followed by addition of ammonia borane (61.74 mg, 2 mmol) and CH_2Cl_2 (1 mL). The mixture was stirred for another 36 h at 30 °C. After cooling to ambient temperature, the mixture was diluted with EtOAc (5.0 mL). Then NaOH aqueous (5.0 mL, 4.0 M) was added to the reaction mixture, which was extracted with EtOAc three times (5.0 mL each). The combined organic phases were dried over Na_2SO_4, then filtered and evaporated under reduced pressure. After the removal of volatile materials by rotary evaporation, the resultant mixture was purified by silica gel column chromatography using a mixture of EtOAc and hexane to give the corresponding pure product.

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FULL PAPER

$B(C_6F_5)_3$-Catalyzed Deoxygenative Reduction of Amides to Amines with Ammonia Borane

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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