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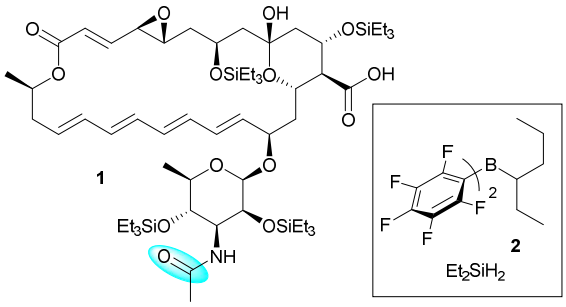
Heteroleptic borane catalyst $(C_6F_5)_2B(CH_2CH_2CH_2)BPin$ is found to hydrosilylatively reduce amides under mild conditions. Simple tertiary amides can be reduced using Me_2EtSiH, whereas tertiary benzamides required a more reactive secondary silane, Et_2SiH_2, for efficient reduction. The catalytic system described exhibits exceptional chemoselectivity in the reduction of oligoamides and tolerates functionalities which are prone to reduction under similar conditions

The reduction of amides to amines is a fundamental transformation that has traditionally been accomplished with main-group metal hydrides (LAH, DIBAL-H, etc.). However, the aggressive nature of these reagents can lead to poor selectivity and functional group tolerance. Catalytic methods[1,2] employing transition metal catalysts in combination with hydrogen as the stoichiometric reductant have been developed, however in most cases elevated temperatures and pressures of hydrogen must be employed.[3–6] Alternatively, the catalytic, reductive hydrosilylation of amides using transition metals (Ni,[7] Rh,[8,9] Ir,[10] Pt,[11] Zn[12]) can occur under milder conditions and thus exhibit good functional group tolerance and selectivity. In addition to transition metal catalysts is the recent emergence of main-group Lewis acids[13–16], such as $B(C_6F_5)_3$ (BCF), however, many of these systems require elevated temperature,[17,18] stoichiometric activation of the amide,[19] or activated amides.[20]

While investigating the chemoselective reduction of complex bioactive molecules,[21] we were struck by the unprecedented selectivity of catalyst **2** to chemoselectively and hydrosilylatively reduce the acetamide moiety of **1** (57% yield, Scheme 1). Homoleptic $B(Ar_F)_3$ as catalysts, by contrast, do not reduce the amide and instead carry out reductions at the enoate, lactol, or combinations thereof. In each case, other reactive sites were not affected (epoxide, tetraene, anomeric center, etc.). One alluring facet of the heteroleptic borane catalyst **2** is its high modularity. By virtue of its *in situ* formation from readily available starting materials ($(C_6F_5)_2BH$ and the corresponding olefin[22–28]), catalyst variations can quickly be assessed, akin to the variation of ligands in transition metal catalysed reactions. To this end, we sought to utilize this platform to develop a second generation catalyst that might offer increased efficiency and selectivity for amide reductions.



Scheme 1 Chemoselective amide reduction of natamycin derivative by heteroleptic borane catalyst **2**

We began by monitoring (^{1}H-NMR) the initial rate of reducing tertiary alkyl amide (**3**) with 2.5 equiv. Me_2EtSiH and several novel borane catalysts (Table 1). From this short screen, we identified a catalyst (**5**), which performed the reduction at a rate x13 of catalyst **2**. Since boryl migration at elevated temperatures is possible in certain cases,[23] and sterics should inhibit this in catalyst **7**, we focused on the allyl Bpin derived catalyst. It performed at a rate x8 faster than **2** and existed as a single major species by ^{19}F-NMR (see supplemental information). Notably, all catalysts in this study out performed **2** in terms of initial rates.

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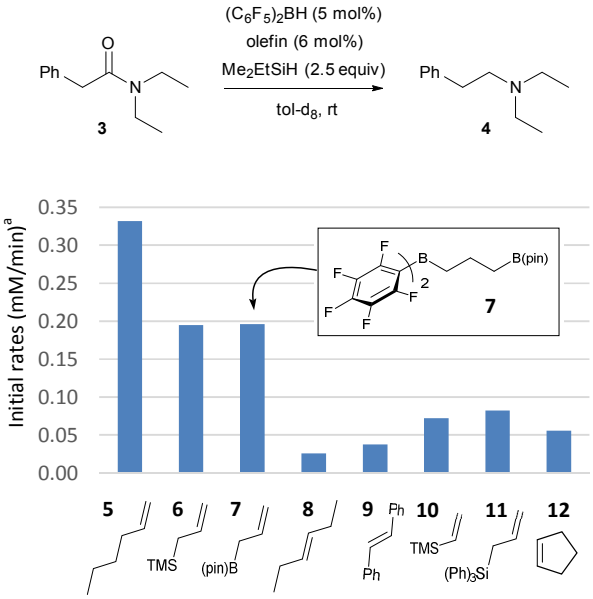
Table 1: Initial rates for the reduction of 3° amide, **3,** by various boron catalysts



[a]Conversion was assessed by ^{1}H-NMR spectroscopy. Initial rates reflect the first 6 hours of reaction time.

Despite these rapid initial rates, incomplete conversion of starting material was observed after 24 h. Preliminary studies on the reduction of dipeptides, vide infra, required a mixed solvent system (tol/dcm) to fully solubilize starting materials and so further optimization studies were performed in this solvent mixture. Increasing the amount of silane to 3 equiv. allowed for full conversion and isolation of **4** in 73% yield. Notably, using amides of this type, the parent BCF catalyst requires forcing conditions (130 °C, 8 eqv. Si–H[20]) to achieve lesser conversions. To examine the generality of this reaction we performed the reduction of several tertiary alkyl amides (Table 2), which proceeded in good to excellent yield under these conditions. While N-aryl amides were reduced in good yield, the reduction of N-Bn amide (**18**) resulted in complex mixtures of products. The reduction of 2-oxindoles did not give the expected indoline (**19**).[29]

The application of similar conditions to N-benzoyl amides with 2.5 (or 3.5) equivalents of Me_2EtSiH led to incomplete conversion of starting material. The tertiary amine products could be isolated in a moderate yield of 55% with long reactions times or gentle heating (60 °C). The enhanced reactivity of a secondary silane (Et_2SiH_2, 2.5 eqv) proved more productive, and provided full conversion of starting material and isolation in 85% yield (Table 3). Both electron donating (-OMe) and withdrawing (-NO_2, -Br) substituents in the para-position were well tolerated under these conditions and gave high yields of product (92-99%). Arenes containing substituents in the ortho position (2,4-Cl, 2-Br), however, were untouched even after extended reaction times (~72 h). Cyclic N-benzoyl amides were also reduced in good yield (**26**). Benzamide, a primary amide, is not a viable substrate under these conditions.

Table 2: Reduction of alkyl tertiary amides

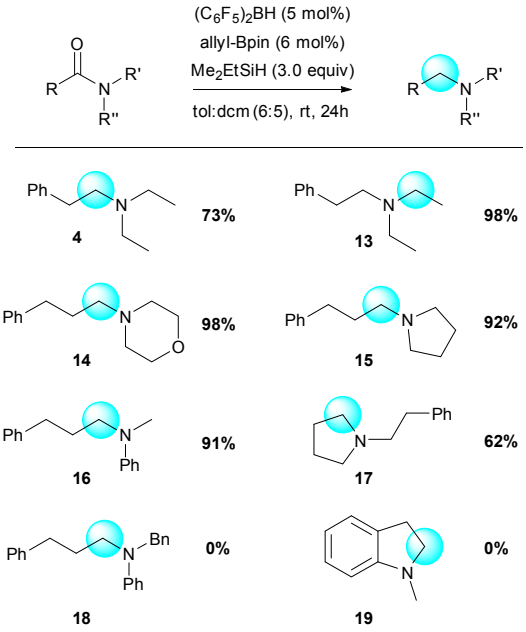
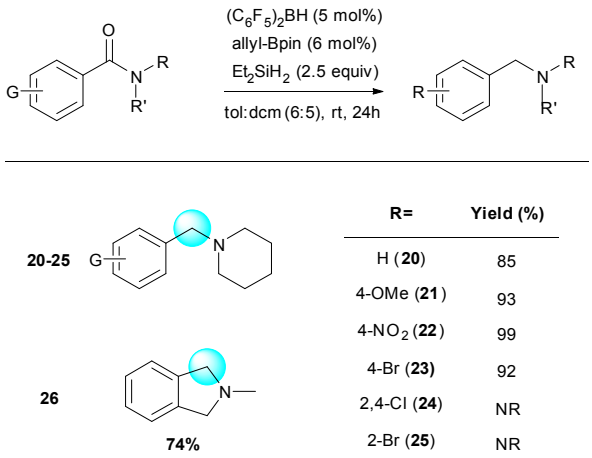


Table 3: Reduction of tertiary benzoyl amides



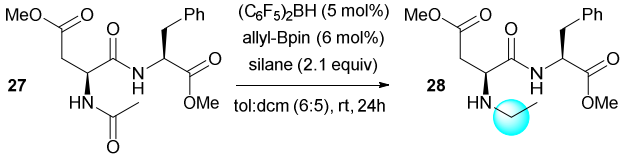
R=	Yield (%)
H (**20**)	85
4-OMe (**21**)	93
4-NO_2 (**22**)	99
4-Br (**23**)	92
2,4-Cl (**24**)	NR
2-Br (**25**)	NR

BCF mediated hydrosilylation conditions are known to reduce cyclic ethers, aryl ethers, and aryl nitro groups. Considering the lack of reduction of these groups in **21** and **22**, we concluded that the bias of **7** towards amide reduction may provide functional group tolerance and selectivity in more complex systems. Inspired by the Rh-catalysed reduction of peptides by Beller et. al.[9] we chose to examine these oligo-amides. The variability of functionality and the presence of enolizable stereocenters would showcase the potential of **7** as a selective catalyst for amide reduction.

Given the diverse silane effects in Tables 2 and 3, we performed a screen to optimize conditions for the reduction of aspartame derived dipeptide **27** (Table 4). In all cases, reduction of the acetamide was the major product with no

evidence for reactivity at the internal amide. This result is consistent with the

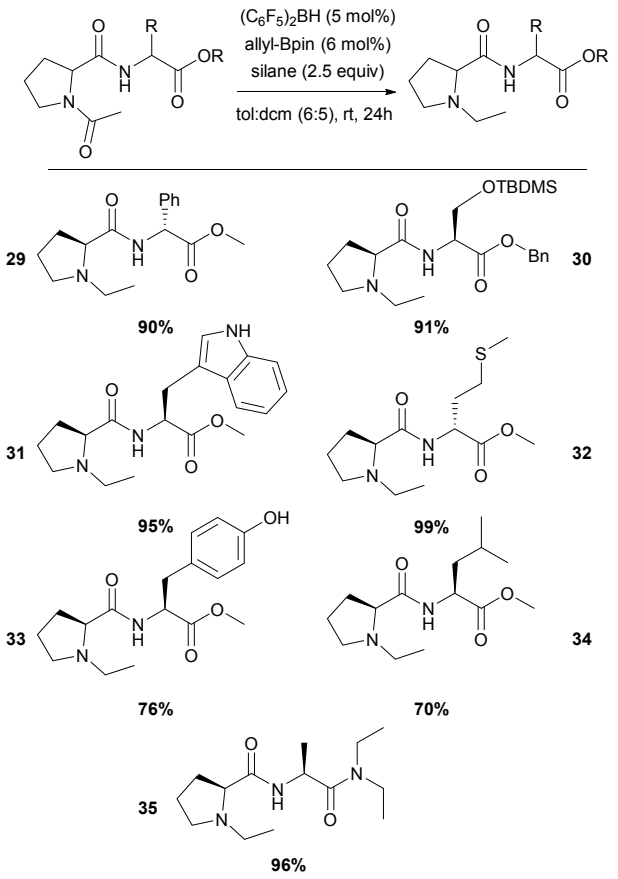
Table 4: Silane screen for dipeptide reduction



Silane	Yield (%)	Me_2EtSiH equiv	Yield (%)
Et_3Si-H	79	2.1	87
Me_2EtSi-H	87	2.5	93 (85)
Et_2SiH_2	69	3.0	96 (87)
$MePhSiH_2$	78		
TMDS	60		
$PhSiH_3$	25		

[a]Yields were assessed by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. Isolated yields are given in parenthesis.

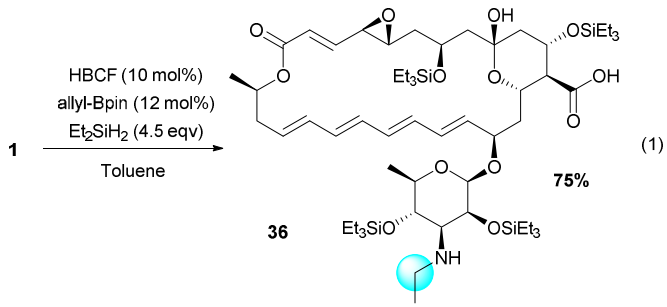
Table 5: N-Acetyl Proline dipeptide reductions



observation that **7** is sensitive to sterically encumbered amides. Tertiary silanes gave the highest yield of the desired product followed by secondary and primary silanes. A slight increase in the number of equivalents aided in achieving full conversion of starting material and allowed for isolation of **28** in 85% yield. Given the high yield of this system coupled with the lack of observable diastereomers (^{1}H-NMR), we reasoned that epimerization of the enolizable stereocenters is not problematic under these conditions.

To examine the breadth of functional groups that may be applicable to selective reduction of dipeptides, N-Acetyl proline was coupled to several amino acids and subjected to the optimized reaction conditions (Table 5). In all cases **7** selectively reduced the proline acetamide over the internal secondary amide in good to excellent yield (70-99%). Methyl and benzyl esters are well tolerated by the reaction conditions as are TBDMS-ethers, thioethers, and indoles. The reduction of **33**'s parent amide required additional equivalents of silane to achieve satisfactory yields as partial dehydrogenative silylation of the phenol moiety occurs, which required a deprotection step prior to chromatography. Triamide **35,** which contains two tertiary amides, is still selectively reduced at the acetamide.

To gain further insight into the selectivity and efficiency of **7** in complex environments, we examined the reduction of **1** (Equation 1). We found that the acetamide is selectively reduced in 75% yield, a significant improvement over the previously reported catalyst **2** (57% yield).[21] Furthermore, the results indicate that TES-ethers, epoxides, olefins, enoates, and acetals are tolerated under these reaction conditions.



(1)

In summary, we have developed a readily synthesized heteroleptic boron catalyst that is capable of reducing alkyl tertiary amides and benzamides in excellent yield. This catalyst exhibits good functional group tolerance and high fidelity in functionally rich environments.

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Conflicts of interest

There are no conflicts to declare

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