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Versatile, mild, and selective reduction of various carbonyl groups using an electron-deficient boron catalyst†

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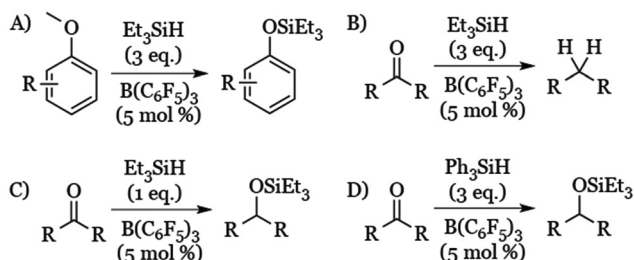
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A mild and selective new method was discovered to reduce acetanilides and other carbonyl compounds. Unlike sodium borohydride, which is selective in reducing aldehydes and ketones, this new protocol is uniquely selective in reducing acetanilides and nitriles over other carbonyl containing functional groups. Additionally, β -ketoamides were shown to be reduced at the ketone preferentially over the amide.

Electron-deficient boron Lewis acids have recently been utilized by the synthetic community for a variety of diverse applications.¹ These include forming frustrated Lewis acid–base pairs for metal-free hydrogenation reactions^{1b,2} and co-catalyzing olefin polymerization reactions.³ Two of the more synthetically useful are the deprotection of methyl aryl ethers⁴ (Scheme 1A) and the reduction of carbonyl groups to the corresponding alkanes (Scheme 1B) or silyl ethers, depending on the number of equivalents (Scheme 1C)⁵ and nature of silane employed (Scheme 1D).⁶ The silyl ethers, accessed by

only using 1 equivalent of triethylsilane,^{5,7} can then be mildly deprotected to the corresponding alcohols using a fluoride source such as tetrabutylammonium fluoride (TBAF).⁸ A boron Lewis acid was also shown to selectively cleave a very complex methyl aryl ether⁹ when other standard deprotection conditions such as boron tribromide treatment caused complete decomposition.¹⁰ The most common electron-deficient borane employed for these reactions is tris(pentafluorophenyl)borane⁷ ($B(C_6F_5)_3$) in conjunction with a trialkylsilane, most often triethylsilane. A remarkable quality of $B(C_6F_5)_3$ that sets it apart from most boron-based Lewis acids of equal strength, such as boron trifluoride, is that it has been shown to be much more hydrolytically stable and even catalytically active in aqueous systems.¹¹ Aldehydes, ketones, esters, lactones, acid chlorides, alcohols, carboxylic acids, and ethers have all been reduced, depending on conditions and silane equivalents to silyl ethers, alcohols or alkanes.⁵ More recently, non-symmetric cyclic ethers were also shown to be reduced regioselectively using these conditions.¹² Although this boron/silane system has proven capable of carrying out these critical transformations, little is known about the chemoselectivity¹³ of the overall processes. Additionally, the conditions have not been used to selectively reduce amides or nitriles to date. Therefore, we sought to gain a more thorough understanding of the selectivity of the reaction, along with its applicability toward the reduction of other carbonyl-derived functional groups such as amides and nitriles.

The most commonly employed conditions to reduce an amide to its corresponding amine utilize highly reactive and non-selective lithium aluminum hydride ($LiAlH_4$).¹⁴ While effective, the functional group tolerance of $LiAlH_4$ is meager at best, competitively reacting with aldehydes and ketones, all carboxylic acid derivatives, nitriles, imines, oximes, azides, epoxides, alkyl halides and nitro groups.¹⁵ Additionally, $LiAlH_4$



Scheme 1 Known reactivity of $B(C_6F_5)_3$ and Et_3SiH with aryl methyl ethers and aldehydes and ketones. Depending on the amount and type of silane employed, the carbonyl reduction can form either silyl ethers or alkanes.

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reacts violently with water requiring the use of anhydrous ether solvents and caution must be taken during the workup of the reaction. Clearly a mild and selective alternative approach would be of great interest to the synthetic community. To initially screen the reactivity of carbonyl-containing compounds *versus* ethers we purchased a set of selectivity probes shown in Scheme 2. In all three cases treatment with 2 equivalents of silane and 10 mol% borane catalyst was selective in reducing and deoxygenating the carbonyl functionalities while leaving the aryl ether intact. It should be noted that treatment with excess triethylsilane eventually reacts with the methyl aryl ethers as well.

Moving on to probe the relative reactivity of the catalytic $B(C_6F_5)_3/Et_3SiH$ system to the reduction of acetanilide amides, a set of functionalized acetanilides were purchased and other anilines were acetylated to their corresponding acetanilide derivatives.¹⁶ The addition of 3 equivalents of triethylsilane and a catalytic amount of $B(C_6F_5)_3$ in non-anhydrous dichloromethane cleanly and efficiently accomplished the reduction of the acetanilides without any indication of significant by-product formation (Table 1). In addition, we were able to show that even more sterically hindered *N*-substituted acetanilides such as *N*-methylacetanilide are also susceptible to reduction under these conditions, even though they require the use of a less sterically hindered silane (diethyl silane) and elevated temperatures (Table 1, entry 5). To our knowledge, this represents the first report of such a mild reduction of an acetanilide to the corresponding *N*-ethylaniline. In addition, these substrates clearly show that both electron-rich and electron-deficient acetanilides are capable of being reduced using this system, even though the electron-rich variant required a higher catalyst loading to accomplish the task (Table 1, entry 2). The reactions proceed efficiently at room temperature without the need of anhydrous solvents or an inert gas atmosphere.

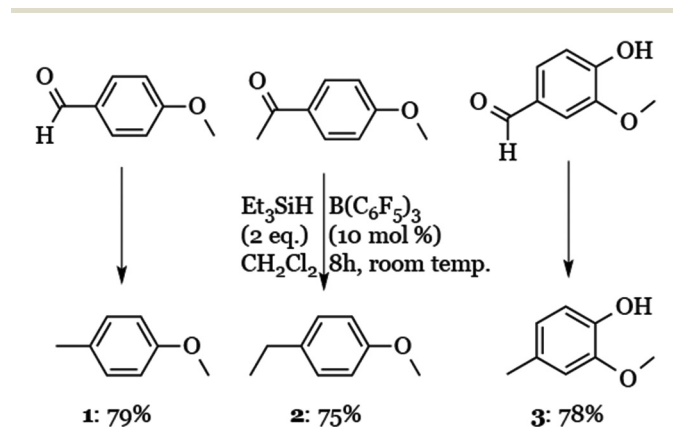
The next question to be answered was what the selectivity would be when more than one carbonyl-containing functional group was present. To probe this, two dual-functionalized aromatic compounds were used, the first being an amide-ketone (Table 1, entry 6) and the second an amide-ester (Table 1,

entry 7). Not only were the amides reduced again under these conditions, but they were also selectively deoxygenated over the “more reactive” ketone and ester in each case. This reaction is therefore quite complimentary to reduction by sodium borohydride, which has long been known to selectively reduce aldehydes and ketones while being incapable of reducing amides. It seems the reaction indeed likely undergoes “pre-coordination” of the silyl group with the more nucleophilic amide carbonyl oxygen and is subsequently attacked by an *in situ* formed borohydride nucleophile as previously reported.^{6a} In addition to being complementary to sodium borohydride, the mild nature of these conditions clearly make it an obvious replacement for the harsh conditions of lithium aluminum hydride otherwise needed to accomplish the comparable reduction of an amide.

The successful reduction of the more sterically hindered *N*-methylacetanilide with diethylsilane when the standard conditions proved ineffective prompted an additional examination of the generality of this reaction. Therefore several different silanes were screened to test their relative reactivity. To accomplish this, another tertiary silane (Ph_3SiH) along with a secondary (Et_2SiH_2) and a primary silane ($PhSiH_3$) were used (Table 2). Each time an amide was tested first by treatment with 3 molar equivalents of silane. Under these conditions, the triphenyl silane struggled to generate adequate product formation, the diethyl silane worked equally well as the triethyl silane, and the monophenyl silane resulted in decomposition. Even with ten equivalents of triphenyl silane the reaction still struggled, suggesting a potential steric hindrance to reactivity. Stepping down to two molar equivalents of monophenyl silane eliminated the decomposition initially observed, cleanly deoxygenating the amide. Therefore, it is concluded that the less sterically hindered the silane is, the more reactive it is in this process.

In an effort to further investigate the reduction of amide groups, a set of alkyl-based amides were purchased or synthesized through acetylation of the corresponding amine. All attempts to apply these conditions to the various alkyl-amides proved unsuccessful. Even when the equivalents of silane and borane were increased and the reactions were heated in 1,2-dichloroethane with more reactive silanes, the alkyl-amides were completely unreactive (Scheme 3). Therefore, in a complex system containing multiple amide functionalities, these conditions could be used to selectively reduce the acetanilides present while leaving the alkyl amides unreacted.

The inability to reduce alkyl amides led us to investigate competition experiments that sought to better explain this lack of reactivity. Along these lines an alkyl amide was mixed 1 : 1 with various acetanilides and the mixture was subjected to the standard reaction conditions (Scheme 4). Surprisingly, it appears the alkyl amide actually has some form of inhibitory effect under these reaction conditions, as all of the acetanilides screened were now unreactive when in the presence of an equivalent of alkyl amide. Not until 1.5 equivalents of borane and 10 equivalents of triethylsilane were used did we observe



Scheme 2 Selective aldehyde and ketone deoxygenation in presence of methyl aryl ethers.

Table 1 Mild reduction of acetanilides to secondary amines in the presence of a variety of functional groups

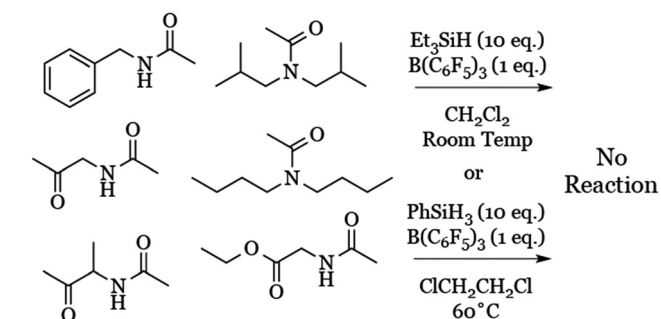
Entry	Acetanilide	Product	Et ₃ SiH (eq.)	Yield
1			3	91%
2 ^a			3	82%
3			3	87%
4			3	94%
5 ^b			5	74%
6			2	88%
7			2	87%

Conditions 10 mol% B(C₆F₅)₃ 0.1 M in dichloromethane, 8 hours, room temperature, ambient atmosphere. ^a Entry 2 required 50 mol% B(C₆F₅)₃ to achieve reaction completion. ^b Entry 5 required heating at 60 °C in 1,2-dichloroethane and more reactive diethylsilane. All yields reported are isolated yield after purification by silica gel chromatography.

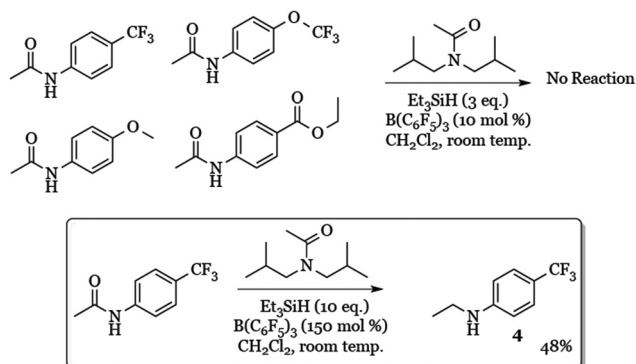
Table 2 Probing the effect of varying the sterics of the silane reducing agent on the reaction progress

Entry	Silane	Equivalents	% Conversion
1	Et ₃ SiH	3	100
2	Ph ₃ SiH	3	18
3	Ph ₃ SiH	10	20
4	Et ₂ SiH ₂	2	50
5	Et ₂ SiH ₂	3	100
6	PhSiH ₃	3	Degradation
7	PhSiH ₃	2	100

conversion of the acetanilide to the corresponding *N*-ethylaniline. This inhibitory effect will be the focus of future investigations.

**Scheme 3** Alkyl-amides unreactive even under forcing conditions.

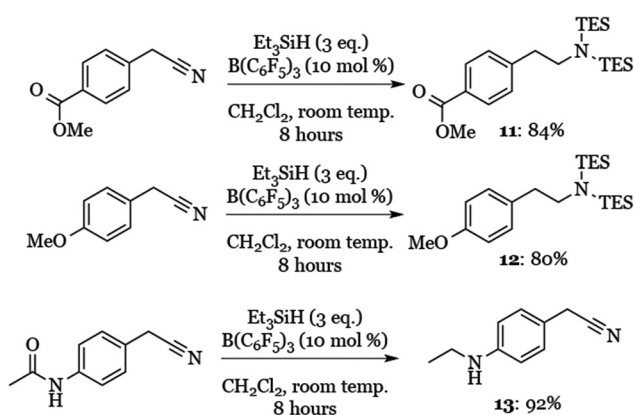
The successes of selective acetanilide reduction prompted us to explore the potential reduction of another carbonyl derivative that typically requires harsh conditions to reduce: the largely unreactive nitrile group. Due to the known



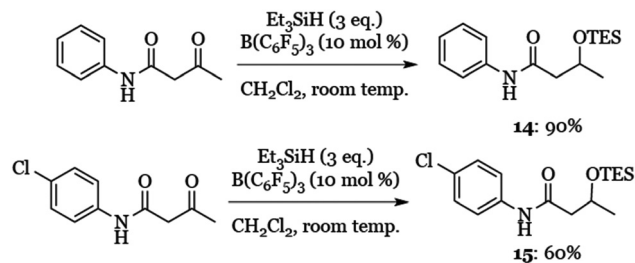
Scheme 4 Inhibitory effect of alkyl amides on the reduction of acetanilides.

nucleophilicity of the nitrogen atom of a nitrile,¹⁷ we hypothesized our reduction system could also successfully reduce a nitrile. The choice of nitriles also extended the selectivity screening of this reaction by testing the relative reactivity of a few different functional groups. Both of the first two substrates cleanly reduced the nitrile functionality while leaving the ester and methyl aryl ether intact (Scheme 5).

Another interesting aspect of the nitrile reduction is that both of these products were isolated as the corresponding *N,N*-bis(triethylsilyl) amine. Comparing nitrile reduction to amide reduction, the latter involves overall deoxygenation, likely resulting in formation of a disilylether byproduct. The nitrile reduction, however, involves successive silyl activation of the nitrile and hydride additions, resulting in the incorporation of two silyl groups and two hydride equivalents. No attempts were made to remove the silyl group, although treatment with TBAF would very likely liberate the free amine in each case. The third substrate in Scheme 5 was used to probe the relative reactivity of an amide compared to a nitrile. Both functionalities are typically challenging to reduce and require harsh conditions, so we sought to compare their reactivity under these conditions. By employing our standard conditions, the amide



Scheme 5 Competition reactions between nitriles and esters, methyl aryl ethers, and amides.



Scheme 6 Reduction of β -keto-amides results in TES-ethers of the ketone even when treated with excess silane reagent.

was cleanly deoxygenated while the nitrile remained intact. Therefore, acetanilides appear to reduce quite chemoselectively¹³ under these conditions.

In a further examination of the selectivity of the carbonyl reductions, we sought to determine if the proximity of the carbonyl groups would affect the reaction outcome. To accomplish this, two β -ketoamides were used (Scheme 6). Interestingly, both examples resulted in ketone reduction rather than amide as observed in Table 1. Also, regardless of the number of equivalents of silane used, the reaction outcome was the same and we never observed any deoxygenation of either of the carbonyl groups. A possible explanation for this change in reactivity could originate from the previously reported mechanistic study.^{6a} If the initial rate-determining step for the process involves the carbonyl oxygen coordinating to the silyl group, and the amide previously proved the better nucleophile for the task, then it might be assumed that the same initial coordination occurs. Due to the proximity of the neighboring ketone in these cases, the silyl could chelate or bridge between the two carbonyl groups, thus activating both for nucleophilic attack by the borohydride. At this point the more electrophilic ketone is attacked and the resulting species remains chelated until the reaction is complete and the product is isolated. This also explains the lack of subsequent reactivity.

Conclusions

The relative reactivities of a variety of functional groups with a silane and an electron-deficient boron catalyst were examined. Carbonyl reduction was found to be faster than methyl aryl ether cleavage. The known reactivity was extended to acetanilide amides and nitriles to produce aryl amines and silyl-protected amines respectively. Locally distant ketones and esters proved to be less reactive than their corresponding acetanilide amides, while β -ketoamides were shown to react at the ketone exclusively and stop prior to deoxygenation. Acetanilide amides were found to be more reactive than nitriles cleanly affording the corresponding ethyl aniline derivative without any reduction of the nitrile functionality. Finally, the reaction was shown to work with a variety of silane reagents, although the sterically hindered triphenyl silane was limited in utility.

These results help shed light onto the relative reactivity of various functional groups under these mild reduction conditions.

Notes and references

- (a) Y. Hoshimoto, T. Kinoshita, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2015, **54**(40), 11666–11671; (b) D. W. Stephan and G. Erker, *Angew. Chem., Int. Ed.*, 2010, **49**(1), 46–76; (c) N. A. McGrath, E. S. Bartlett, S. Sittihan and J. T. Njardarson, *Angew. Chem., Int. Ed.*, 2009, **48**(45), 8543–8546.
- D. W. Stephan, *Dalton Trans.*, 2009, (17), 3129–3136.
- (a) Y. X. Chen, M. V. Metz, L. T. Li, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.*, 1998, **120**(25), 6287–6305; (b) Y. X. Chen, C. L. Stern, S. T. Yang and T. J. Marks, *J. Am. Chem. Soc.*, 1996, **118**(49), 12451–12452; (c) P. A. Deck, C. L. Beswick and T. J. Marks, *J. Am. Chem. Soc.*, 1998, **120**(46), 12167–12167.
- V. Gevorgyan, M. Rubin, S. Benson, J. X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**(19), 6179–6186.
- V. Gevorgyan, M. Rubin, J. X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**(5), 1672–1675.
- (a) D. J. Parks, J. M. Blackwell and W. E. Piers, *J. Org. Chem.*, 2000, **65**(10), 3090–3098; (b) S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2008, **47**(32), 5997–6000.
- D. J. Parks and W. E. Piers, *J. Am. Chem. Soc.*, 1996, **118**(39), 9440–9441.
- R. D. Crouch, *Tetrahedron*, 2013, **69**(11), 2383–2417.
- N. A. McGrath, J. R. Binner, G. Markopoulos, M. Brichacek and J. T. Njardarson, *Chem. Commun.*, 2011, **479**(1), 209–211.
- T. Kosak, *Eur. J. Org. Chem.*, 2015, 7460–7467.
- K. Ishihara, N. Hanaki, M. Funahashi, M. Miyata and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1995, **68**(6), 1721–1730.
- D. J. Mack, B. Y. Guo and J. T. Njardarson, *Chem. Commun.*, 2012, **48**(63), 7844–7846.
- B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, 1973, **95**(20), 6840–6842.
- A. E. Finholt, A. C. Bond and H. I. Schlesinger, *J. Am. Chem. Soc.*, 1947, **69**(5), 1199–1203.
- L. A. Paquette, T. Ollevier and V. Desyroy, *Lithium Aluminum Hydride. e-EROS Encyclopedia of Reagents for Organic Synthesis*, 2004.
- E. Blondiaux and T. Cantat, *Chem. Commun.*, 2014, **50**(66), 9349–9352.
- (a) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**(12), 4045–4048; (b) H. Plaut and J. J. Ritter, *J. Am. Chem. Soc.*, 1951, **73**(9), 4076–4077; (c) E. Callens, A. J. Burton and A. G. M. Barrett, *Tetrahedron Lett.*, 2006, **47**(49), 8699–8701.