Stoichiometric Reductions of Alkyl-Substituted Ketones and Aldehydes to Borinic Esters

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| Complete List of Authors: | Longobardi, Lauren; University of Toronto, Chemistry  
                                 Tang, Connie; University of Toronto, Chemistry  
                                 Stephan, Douglas; University of Toronto, Department of Chemistry |
A series of alkyl-substituted ketones are shown to activate hydrogen in the presence of B(C6F5)3, affording the corresponding borinic esters RR’CHOB(C6F5)2. The mechanism is shown to proceed via H2 activation, hydride delivery and protonation of a C=O group. The aliphatic aldehyde Et2C–CHO reacts with B(C6F5)3 or BPh3 to give boron enolates Et2C=CH(OBAr2) (Ar = C6F5, Ph). These latter species are amenable to FLP-catalyzed reduction to the corresponding borinic esters.

Ketone reductions can be readily achieved by exploiting transition metal systems based on precious metal Ru and Rh complexes. More recently, interest in reductions based on Earth-abundant elements has been motivated by economic and environmental advantages. To this end, Fe-based catalysts have emerged. The widely utilized classic boron and aluminum hydrides and their derivatives3 are based on abundant elements, although these stoichiometric reagents are often used in large excess. The field of main group hydrogenations has seen dramatic growth in recent years with the development of frustrated Lewis pairs (FLPs) chemistry. These combinations of sterically-encumbered Lewis acids and bases have found utility as hydrogenation catalysts for a myriad of unsaturated substrates including imines,5 protected nitriles, aziridines,6,7 enamines,7 silyl enol ethers,8 N-heterocycles,9 olefins,10 and poly-aranes,11 and most recently alkynes have been reduced to cis-alkenes.12 In addition, stoichiometric FLP reductions of anilines to cyclohexylammonium derivatives13 has been extended to pyridines and other N-heterocycles.14

Efforts to extend the reactivity of FLPs to oxygen-based donors have found limited success due to the high oxophilicity of the electrophilic boranes employed. In an early report, we showed that the H2-activated linked P/B system Mes2PCH2CH2B(C6F5)3 could deliver hydride to benzaldehyde, forming the corresponding phosphonium borate zwitterions.5,15 Subsequently Repo and Rieger published analogous chemistry using bulky nitrogen bases,16 while Erker et al demonstrated 1,4-addition of FLPs to conjugated yrones.17 Nonetheless, the computational investigations by the groups of Privalov18 and Wang19 suggests that ketone reductions using B(C6F5)3 as a catalyst are energetically viable.

Despite the current advances, and computational support,20 FLP-reduction of ketones and aldehydes remains an ongoing challenge. Repo and co-workers reported the first experimental evidence that carbonyl compounds could behave as FLP bases capable of H2 activation (Scheme 1).20 Using benzaldehyde and benzophenone in combination with B(C6F5)3 and H2 they observed reduction to toluene and diphenylmethane, respectively, at elevated temperatures in dichloromethane. Using toluene as the solvent, they observed low conversion to benzylic alcohol from benzaldehyde, and Friedel-Crafts alkylation products from benzophenone. We were interested in exploring FLP carbonyl chemistry further and, in particular, whether alkyl-substituted ketones and aldehydes would behave in an analogous fashion to those bearing aryl substituents.

Scheme 1. FLP reductions of benzaldehyde and benzophenone.

As an initial experiment, 1 equivalent of B(C6F5)3 was combined with 4-heptanone 1a in toluene. An adduct was formed at room temperature as evidenced by a broad singlet in the 11B NMR spectrum at 9.5 ppm. This mixture was heated to 110 °C under 4 atm of H2 for 24 hours. Complete conversion of the ketone to a new boron-containing product 2a with the concurrent formation of HC6F5 was observed. Removal of the toluene solvent followed by purification yielded product 2a, which showed a broad singlet at 39.3 ppm in the 11B NMR spectrum, and 3 peaks at -132.3, -150.8, and -161.9 ppm in the 19F NMR. These data suggest the formation of a three-coordinate boron species. In the 1H NMR spectrum, in addition to expected aliphatic peaks, the species 2a exhibited a quintet integrating to 1H at 4.20 ppm. Collectively, these data are in

Lauren E. Longobardi,a Connie Tanga and Douglas W. Stephan*a,b

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agreement with previous reports of borinic esters\textsuperscript{16} and thus confirms the formulation of product 2a as \(\text{Pr}_2\text{CHOB(C}_6\text{F}_{5})_2\) (Scheme 2). The reactivity of dialkylketone 1a stands in contrast to the previously reported FLP hydrogenation chemistry of the aryl-substituted ketones where the \(\text{C}–\text{O}\) bond is further reduced to afford the fully saturated alkane.\textsuperscript{20}

\[
\begin{align*}
\text{O} & \quad 1\text{a} & 1\text{equiv. B(C}_6\text{F}_{5})_3 & \quad 4 \text{ atm H}_2 & \quad \text{toluene, 110 °C} & \quad \text{2a} \quad + \text{HCF}_5 \\
\text{O} & \quad \text{2a} & & & & & \text{2a} \quad >99 (99) \\
\text{2b} & & & & & & \text{2b} \quad >99 (99) \\
\text{2c} & & & & & & \text{2c} \quad 98 (83) \\
\text{2d} & & & & & & \text{2d} \quad 94 \\
\text{2e} & & & & & & \text{2e} \quad 97 (91) \\
\text{2f} & & & & & & \text{2f} \quad 85 \\
\text{2g} & & & & & & \text{2g} \quad >99 \\
\text{1h} & & & & & & \text{1h} \\
\text{1i} & & & & & & \text{1i} \\
\end{align*}
\]

\textbf{Scheme 2. Reduction of 1a to the corresponding borinic ester 2a.}

In an effort to probe the generality of this transformation, the corresponding reactivity of a variety of alkyl-substituted ketones was explored (Table 1). Diethylketone (1b) and acetone (1c) were shown to give the corresponding borinic esters 2b and 2e, respectively, and were isolated in high yields. Ketones bearing \(\beta\)-substituents were tolerated (1d), and cyclic ketones were also shown to undergo the analogous reduction (1e). Substrates with one branched substituent (1f and 1g) were tolerated, however for 2,4-dimethyl-3-pentanone (1h) the hydrogenation was prohibitively slow. Similarly, di-\textit{tert}-butyl ketone (1i) could not be reduced. These latter observations were attributed to steric inhibition and are in accord with previous hydrogenation attempts by Repo.\textsuperscript{12} In further support of the steric inhibition, it is interesting to note that the combination of 1i with B(C\(_6\)F\(_5\)_3) at room temperature does not result in adduct formation, as evidenced by a shift at 60.8 ppm in the \(^{11}\text{B}\) NMR spectrum. With the exception of the sterically crowded systems, reductive formation of the boron-alkoxides proved to be quite general for dialkylketones, proceeding with full conversion and with high isolated yields.

\textbf{Table 1. Scope of reduction of ketone with B(C\(_6\)F\(_5\)_3)/H\(_2\) to borinic esters. NMR yields are reported, with representative isolated yields in parentheses.}

Mechanistically, it is clear that elevated temperatures encourage dissociation of the ketone from B(C\(_6\)F\(_5\)_3). The resulting acid/base combination of ketone and B(C\(_6\)F\(_5\)_3) then acts as a FLP, enabling H\(_2\) activation, and generating an oxonium borohydride species of the form [R\(_2\)COH][HB(C\(_6\)F\(_5\))]. Despite the fact that THF ring-opening was observed by reactions of P/B FLPs, ether-borate combinations were shown to activate H\(_2\) and effect the catalytic hydrogenation of olefins.\textsuperscript{21} More recently, Ashley and co-workers have shown that this notion could be extended to a series of boranes, B\(_n\)(C\(_6\)F\(_5\))\(_n\) (where \(n=0–3\)), which activate H\(_2\) in combination with THF.\textsuperscript{22} In the present case, following activation of H\(_2\) by ketone/borane, two pathways can be envisioned. Delivery of the hydride to the carbonyl carbon affords the corresponding alcohol and B(C\(_6\)F\(_5\)_3) in \textit{sit}u. However, B(C\(_6\)F\(_5\)_3) is not stable to alcohol functionalities at the elevated temperature required to initiate the reaction with H\(_2\) and thus subsequent protonation of a C\(_6\)F\(_5\)_3 group on B(C\(_6\)F\(_5\)_3) results in the generation of a formal B–O bond (Scheme 3, pathway 1) with loss of HCF\(_5\). An alternative pathway (Scheme 3, pathway 2) could involve the direct protonation of the anion [HB(C\(_6\)F\(_5\))\(_3\)] by the acidic cation [R\(_2\)COH], liberating HCF\(_5\), and generating Piers’ borane HB(C\(_6\)F\(_5\))\(_2\).\textsuperscript{23} Rapid ketone hydroboration would generate the observed product, R\(_2\)COB(C\(_6\)F\(_5\)_2).

\[
\begin{align*}
\text{O} & \quad R & \quad R & \quad \text{H} & \quad \text{HCF}_5 & \quad \text{B(C}_6\text{F}_{5})_2 \\
\text{O} & \quad \text{B(C}_6\text{F}_{5})_2 & & & & \text{B(C}_6\text{F}_{5})_2 \\
\text{O} & \quad \text{B(C}_6\text{F}_{5})_2 & & & & \text{B(C}_6\text{F}_{5})_2 \\
\text{O} & \quad \text{B(C}_6\text{F}_{5})_2 & & & & \text{B(C}_6\text{F}_{5})_2 \\
\end{align*}
\]

\textbf{Scheme 3. Reaction pathways for reductive pathway to borinic esters.}

To probe the mechanism, cyclohex-2-en-1-one 1j was used as a substrate (Scheme 4). If the reaction proceeds through pathway 1, hydride delivery would be observed after initial H\(_2\) activation. Since hydride is a soft nucleophile, 1,4-addition to the protonated enone would be expected. This would generate cyclohexanone in its enol form, which would then rapidly tautomerize to its keto form. The uptake of another equivalent of H\(_2\), would then generate a cyclohexyloboronic ester. However, if Piers’ borane is generated \textit{in situ} (pathway 2), the ketone would undergo hydroboration, leaving the alkene functionality unchanged. This was confirmed by addition of Piers’ borane to 1j. Indeed, in the presence of B(C\(_6\)F\(_5\)_3) and H\(_2\), substrate 1j undergoes complete reduction to give the borinic ester 2e, where both the olefin and the resultant keto tautomer are reduced, supporting the mechanistic postulate of pathway 1. It is noteworthy that this was further supported by the formation of borinic ester 2e via direct treatment of B(C\(_6\)F\(_5\)_3) with cyclohexanol in toluene at 110 °C.
Aliphatic aldehydes were also evaluated as substrates under similar reduction conditions. In general, complex mixtures of products were generated upon treatment of a variety of aldehydes with B(C$_2$F$_3$)$_3$ and H$_2$ in toluene at 110 °C. Efforts to isolate individual products were unsuccessful. However, in the case of aldehyde Et$_2$CHCHO 3a, which bears an α-substituent, loss of HC$_2$F$_3$ and clean conversion to a new product 4a was evident from the peak at 39.8 ppm in the $^{11}$B NMR spectrum and peaks at -131.8, -148.1, and -160.9 ppm in the $^{19}$F NMR spectrum. The $^1$H NMR spectrum of 4a, while similar to the anticipated borinic ester, showed the absence of the expected shift in the 3.5-4 ppm range and instead showed a new singlet at 6.37 ppm. Collectively these data support the formulation of 4a as the boron enolate product Et$_2$C=CHOB(C$_2$F$_3$)$_2$. In this case, the substrate was not hydrogenated, but rather 3a reacted as an enol with B(C$_2$F$_3$)$_3$ effecting the formation of 4a and liberating HC$_2$F$_3$ (Scheme 5). Indeed, when the reaction was repeated in the absence of H$_2$ the same product 4a was observed. Pleasingly, this reactivity is also demonstrated with the less electron-deficient borane BPH$_3$, generating enolate 4b and benzene. It is interesting to note that this enol-like reactivity was not observed for any α-substituted ketones. In addition, the reactions of this enol with boranes is analogous to generating enolate (like reactivity was not observed for any α-substituted ketones.

Products 4a and 4b were also shown to be amenable to FLP-catalyzed hydrogenation (Scheme 5). Using conditions reported for the reduction of silyl enol ethers, the isolated substrates in toluene were treated with 20 mol% B(C$_2$F$_3$)$_3$ and the bidentate phosphine C$_{10}$H$_8$(PPh$_2$)$_2$ under 4 atm of H$_2$ at 110 °C to give the borinic esters 5a and 5b, respectively. Hydrogenation was also found to proceed with catalytic phosphine, or with catalytic B(C$_2$F$_3$)$_3$, however in these cases the reaction was much slower and generated unidentified impurities.

![Scheme 5. Synthesis of the boron enolates 4a and 4b and reduction to boronic esters 5a and 5b.](image)

**Conclusions**

A range of aliphatic ketones activate H$_2$ in the presence of B(C$_2$F$_3$)$_3$ and undergo stoichiometric reduction to give the corresponding borinic ester products, with concurrent cleavage of a C-B bond to liberate HC$_2$F$_3$. This observation stands in contrast to earlier reports of FLP hydrogenations of aryl-substituted ketones where the C-O bond is cleaved. Reactions of linear aliphatic aldehydes were not clean, although 3a, bearing an α-substituent, was shown to react through its enol form with B(C$_2$F$_3$)$_3$ or BPH$_3$ affording boron enolate products, which were amenable to further FLP-catalyzed hydrogenation. The H$_2$ activation achieved by the combination of aliphatic ketones and an electrophilic borane proceeds to give transient formation of the corresponding alcohol, which reacts further providing a unique approach to borinic esters. We are continuing to explore the utility of these species in FLP chemistry. In addition, efforts are underway to find alternative hydrogenation conditions that avoid protonolytic formation of borinic esters. In this fashion we hope to achieve catalytic metal-free ketone hydrogenation.

**Notes and references**

*Department of Chemistry, 80 St George St University of Toronto, Toronto, Ontario, Canada M5S3H6 E-mail: dstephan@chem.utoronto.ca

Chemistry Department-Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia

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