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

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

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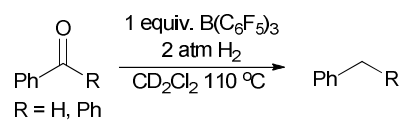
A series of alkyl-substituted ketones are shown to activate hydrogen in the presence of $B(C_6F_5)_3$, affording the corresponding borinic esters $RR'CHOB(C_6F_5)_2$. The mechanism is shown to proceed via H_2 activation, hydride delivery and protonation of a C_6F_5 group. The aliphatic aldehyde Et_2CHCHO reacts with $B(C_6F_5)_3$ or BPh_3 to give boron enolates $Et_2C{=}CH(OBAr_2)$ (Ar = C_6F_5, 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.[1] 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.[2] The widely utilized classic boron and aluminum hydrides and their derivatives[3] 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 pair (FLP) chemistry.[4] 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,[5-6] enamines,[7] silyl enol ethers,[8] N-heterocycles,[9] olefins,[10] and poly-arenes,[11] and most recently alkynes have been reduced to *cis*-alkenes.[12] In addition, stoichiometric FLP reductions of anilines to cyclohexylammonium derivatives[13] 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 H_2-activated linked P/B system $Mes_2PCH_2CH_2B(C_6F_5)_2$ 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 ynones.[17] Nonetheless, the computational investigations by the groups of Privalov[18] and Wang[19] suggests that ketone reductions using $B(C_6F_5)_3$ 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 H_2 activation (Scheme 1).[20] Using benzaldehyde and benzophenone in combination with $B(C_6F_5)_3$ and H_2 they observed reduction to toluene and diphenylmethane, respectively, at elevated temperatures in dichloromethane. Using toluene as the solvent, they observed low conversion to benzyl 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 $B(C_6F_5)_3$ was combined with 4-heptanone **1a** in toluene. An adduct was formed at room temperature as evidenced by a broad singlet in the ^{11}B NMR spectrum at 9.5 ppm. This mixture was heated to 110 °C under 4 atm of H_2 for 24 hours. Complete conversion of the ketone to a new boron-containing product **2a** with the concurrent formation of HC_6F_5 was observed. Removal of the toluene solvent followed by purification yielded product **2a**, which showed a broad singlet at 39.3 ppm in the ^{11}B NMR spectrum, and 3 peaks at -132.3, -150.8, and -161.9 ppm in the ^{19}F NMR. These data suggest the formation of a three-coordinate boron species. In the ^{1}H 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

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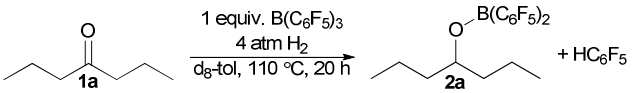
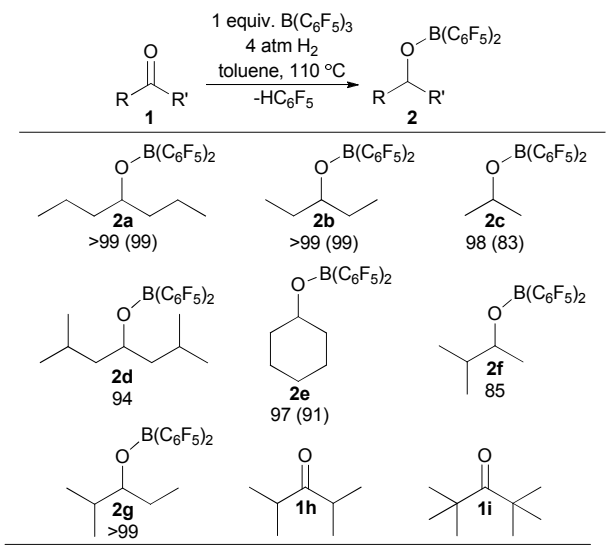
agreement with previous reports of borinic esters[16] and thus confirms the formulation of product **2a** as $Pr_2CHOB(C_6F_5)_2$ (Scheme 2). The reactivity of dialkylketone **1a** stands in contrast to the previously reported FLP hydrogenation chemistry of the aryl-substituted ketones where the C−O bond is further reduced to afford the fully saturated alkane.[20]



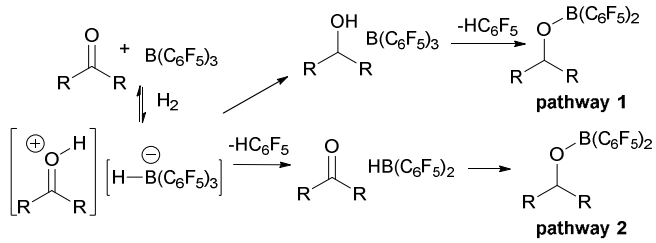
Scheme 2. Reduction of **1a** to the corresponding borinic ester **2a**.

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 **2c**, respectively, and were isolated in high yields. Ketones bearing β-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-*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.[12] In further support of the steric inhibition, it is interesting to note that the combination of **1i** with $B(C_6F_5)_3$ at room temperature does not result in adduct formation, as evidenced by a shift at 60.8 ppm in the ^{11}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.

Table 1. Scope of reduction of ketone with $B(C_6F_5)_3/H_2$ to borinic esters. NMR yields are reported, with representative isolated yields in parentheses.

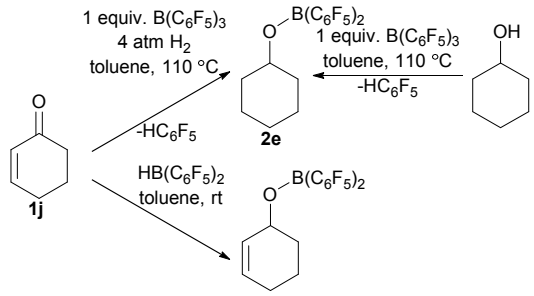


Mechanistically, it is clear that elevated temperatures encourage dissociation of the ketone from $B(C_6F_5)_3$. The resulting acid/base combination of ketone and $B(C_6F_5)_3$ then acts as a FLP, enabling H_2 activation, and generating an oxonium borohydride species of the form $[R_2COH][HB(C_6F_5)_3]$. Despite the fact that THF ring-opening was observed by reactions of P/B FLPs, ether-borane combinations were shown to activate H_2 and effect the catalytic hydrogenation of olefins.[21] More recently, Ashley and co-workers have shown that this notion could be extended to a series of boranes, $B(C_6Cl_5)_n(C_6F_5)_{3-n}$ (where n=0-3), which activate H_2 in combination with THF.[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 $B(C_6F_5)_3$ *in situ*. However, $B(C_6F_5)_3$ 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_6F_5 group on $B(C_6F_5)_3$ results in the generation of a formal B−O bond (Scheme 3, pathway 1) with loss of HC_6F_5. An alternative pathway (Scheme 3, pathway 2) could involve the direct protonation of the anion $[HB(C_6F_5)_3]$ by the acidic cation $[R_2COH]$, liberating HC_6F_5 and generating Piers' borane $HB(C_6F_5)_2$.[23] Rapid ketone hydroboration would generate the observed product, $R_2COB(C_6F_5)_2$.



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 cyclohexylborinic ester. However, if Piers' borane is generated *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 $B(C_6F_5)_3$ 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 $B(C_6F_5)_3$ with cyclohexanol in toluene at 110 °C.



Scheme 4. Hydrogenation of an α,β-unsaturated ketone to the fully- saturated borinic ester **2e**.

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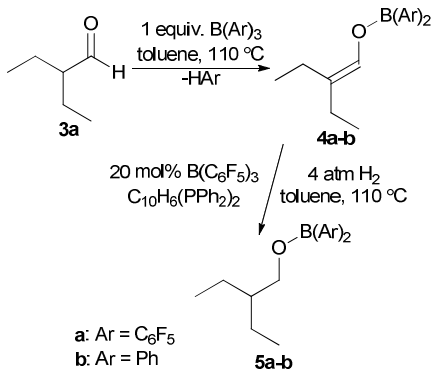
Aliphatic aldehydes were also evaluated as substrates under similar reduction conditions. In general, complex mixtures of products were generated upon treatment of a variety of aldehydes with $B(C_6F_5)_3$ and H_2 in toluene at 110 °C. Efforts to isolate individual products were unsuccessful. However, in the case of aldehyde Et_2CHCHO **3a**, which bears an α-substituent, loss of HC_6F_5 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 ^1H 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 $Et_2C{=}CH(OB(C_6F_5)_2)$. In this case, the substrate was not hydrogenated, but rather **3a** reacted as an enol with $B(C_6F_5)_3$ effecting the formation of **4a** and liberating HC_6F_5 (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 the latter step in the mechanism for reduction of ketones described above and further supports the proposed reaction pathway (Scheme 3, pathway 1).

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,[8a] the isolated substrates in toluene were treated with 20 mol% $B(C_6F_5)_3$ and the bidentate phosphine $C_{10}H_6(PPh_2)_2$ 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 $B(C_6F_5)_3$, 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 borinic esters **5a** and **5b**.

Conclusions

A range of aliphatic ketones activate H_2 in the presence of $B(C_6F_5)_3$ and undergo stoichiometric reduction to give the corresponding borinic ester products, with concurrent cleavage of a B-C bond to liberate HC_6F_5. 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 $B(C_6F_5)_3$ 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

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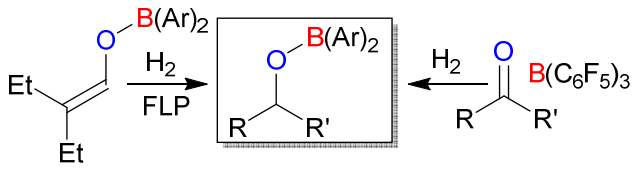
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