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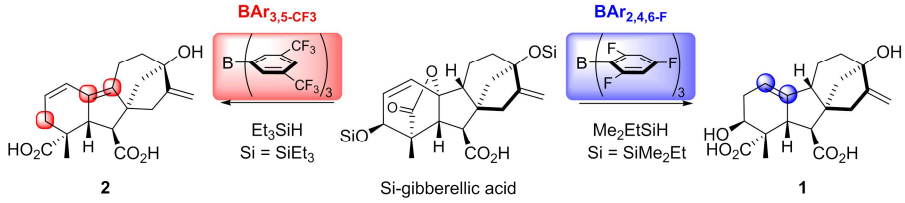

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ABSTRACT

Reductive late-stage functionalization of gibberellic acid is reported using three fluoroarylborane Lewis acids; ($B(C_6F_5)_3$, $B(3,5\text{-}C_6H_3(CF_3)_2)$, and $B(2,4,6\text{-}C_6H_2F_3)_3$) in combination with a tertiary silane and a borane (HBCat) reductant. In each case, C–O bond activation occurs, and different products are obtained depending on the reductant and catalyst employed.

We are very pleased to dedicate this article to Prof. Steve Davies for his many contributions to the Tetrahedron Journals and to the broader chemistry community.

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1. Introduction

Late stage functionalization (LSF) of natural products is a useful medicinal chemistry tool, but is challenging to execute as it requires a synthetic method able to chemo- and site-selectively manipulate complex structures, which, by their nature, usually contain a diverse array of off-target reactive groups.[1,2] Figure 1 demonstrates the LSF principle for the site-selective deoxygenation of erythromycin A, enabled either by a selectively-defining *O*-thiocarbonylation or -phosphitylation with a peptide catalyst (Fig. 1(a)).[3,4] Metal catalysts for deoxygenation are also feasible as recently demonstrated for the ruthenium-catalyzed primary alcohol reduction of cholic alcohol (Fig. 1(b)).[5] A similar preference for primary deoxygenation (silane reductant) was demonstrated using the main group Lewis acid $B(C_6F_5)_3$ on a diosgenin derivative (Fig. 1(c)).[6] $B(C_6F_5)_3$-catalyzed hydrosilylative deoxygenations have additionally been used to chemo-selectively reduce the hemiacetal of dihydroartemisinin or to open the lactone ring of gibberellic acid with an accompanying allylic transposition (Fig. 1(c)).[7]

Although the commercially available $B(C_6F_5)_3$ has been the workhorse catalyst, fluorinated arylboranes have also been investigated for the reduction of diverse functional groups, with one form typically exhibiting superior reactivity to the others.[8–10] Our group recently discovered that tuning the position of fluorination led to catalysts for site-selective deoxygenation that yielded divergent products from a set of common cellulosic starting materials.[11] Site-selective modifications in complex

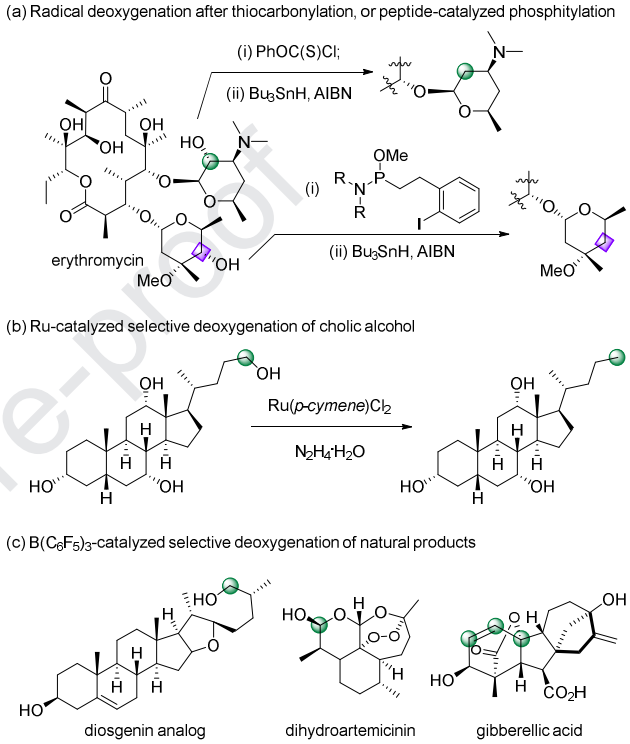


Figure 1. Selective deoxygenation of natural products.

natural products such as natamycin have also been reported using various fluoroaryl borane catalysts and silanes as reductants.[7] The choice of reductant (e.g. borane versus silane) can also alter which product is formed, as seen with carbohydrates under $B(C_6F_5)_3$-catalyzed conditions.[12] These results led us to ask how modifications to the fluoroaryl borane catalyst and the reductant influences the selectivity for the deoxygenation of a multi-functional test molecule such as gibberellic acid.[13] Trialkylsilanes (Me_2EtSiH or Et_3SiH) and catecholborane (HBCat) were selected as the reductants while the following three fluoroarylboranes were chosen based on their differing Lewis acidity and steric profiles: $B(C_6F_5)_3$, $B((3,5\text{-}CF_3)_2C_6H_3)_3$ ($BAr_{3,5\text{-}CF3}$), and $B(2,4,6\text{-}F_3C_6H_2)_3$ ($BAr_{2,4,6\text{-}F}$).

2. Results and Discussion

As previously computed by Heiden, the three fluoroaryl borane Lewis acids in this study have hydride affinities (kcal/mol) that decrease from $B(C_6F_5)_3$ to $BAr_{3,5\text{-}CF3}$ to $BAr_{2,4,6\text{-}F}$ (Fig. 2(a)).[14] These hydricity values correspond to the negative free energy of hydride formation from the Lewis acid and H^-. For the current study, we additionally computed electrostatic potential surfaces to compare both the Lewis acid and conjugate hydride forms; more negative regions of electron distribution are visualized by red (Fig. 2(b)). Not surprisingly, the borohydrides are overall more negative than the neutral boranes. Unexpected, however, was the difference between $BAr_{3,5\text{-}CF3}$ and $BAr_{2,4,6\text{-}F}$ which have a similar hydride affinity. The computed surfaces indicate that the boron center in $BAr_{3,5\text{-}CF3}$ is the most electron deficient of the three (most blue) while the hydride derived from $BAr_{2,4,6\text{-}F}$ is the most negatively charged of all three (most red). We conclude from these data that hydride affinity (a difference) might not provide the full story of the reactivity of the Lewis acids and their conjugate hydrides since it is possible that one form might play a more important role in a given transformation.

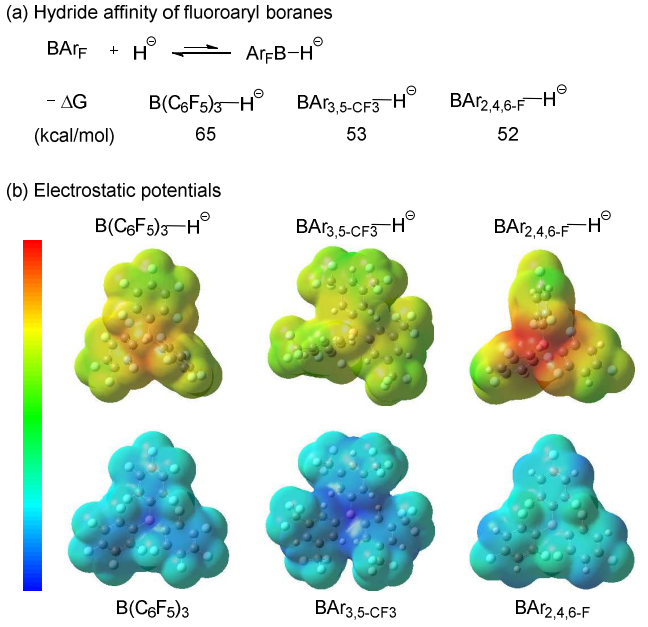
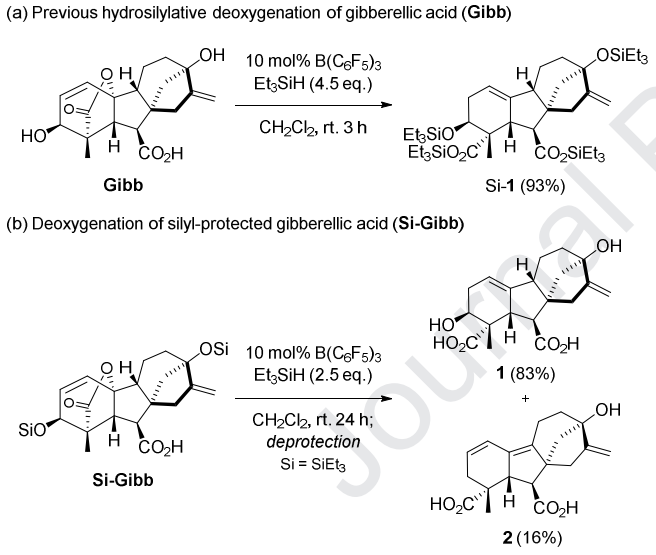


Figure 2. Calculated hydride affinity (Heiden) and electrostatic surfaces of the tested fluoroaryl boranes

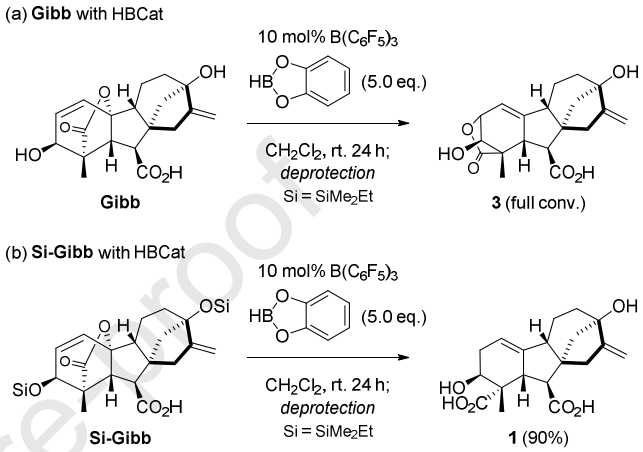
In the study comparing the three catalysts for the site-selective deoxygenation of cellulose-derived carbohydrates, the most significant differences were noted between $B(C_6F_5)_3$ and $BAr_{3,5\text{-}CF3}$.[11] For multiple carbohydrate starting materials the two catalysts favored different products. Although no definitive reasons were apparent, it was noted that the boron resting state for $B(C_6F_5)_3$-catalyzed reactions was $B(C_6F_5)_3{-}H^-$ while in the latter, it was the Lewis acid form. The higher nucleophilicity of $BAr_{3,5\text{-}CF3}{-}H^-$ presumably promoted its consumption. In this study $BAr_{2,4,6\text{-}F}$ was typically a less reactive version of $B(C_6F_5)_3$.[15]

The previously reported $B(C_6F_5)_3$-catalyzed hydrosilylative deoxygenation of free gibberellic acid afforded the tetrasilyl-protected diester Si-**1** in 93% yield *via* a cascade of dehydrosilylation, and reductive olefin migration/ lactone opening (Scheme 1(a)).[7] To enhance the starting material solubility and to avoid vigorous hydrogen evolution, the allylic alcohols of gibberellic acid were pre-silylated (Me_2EtSi-, Et_3Si-; **Si-Gibb**), and tested under ambient reaction conditions with excess Et_3SiH. Unlike the results obtained with **Gibb** (Scheme 1(a)), **Si-Gibb** provided **1** (83%) along with the conjugated diene **2** (16%) (Scheme 1(b)).[16] Although it is unclear why pre-silylated **Si-Gibb** promotes elimination to **2**, all $B(C_6F_5)_3$-catalyzed deoxygenations favor product **1** as the major species.



Scheme 1. Hydrosilylative deoxygenation of **Gibb** and **Si-Gibb**.

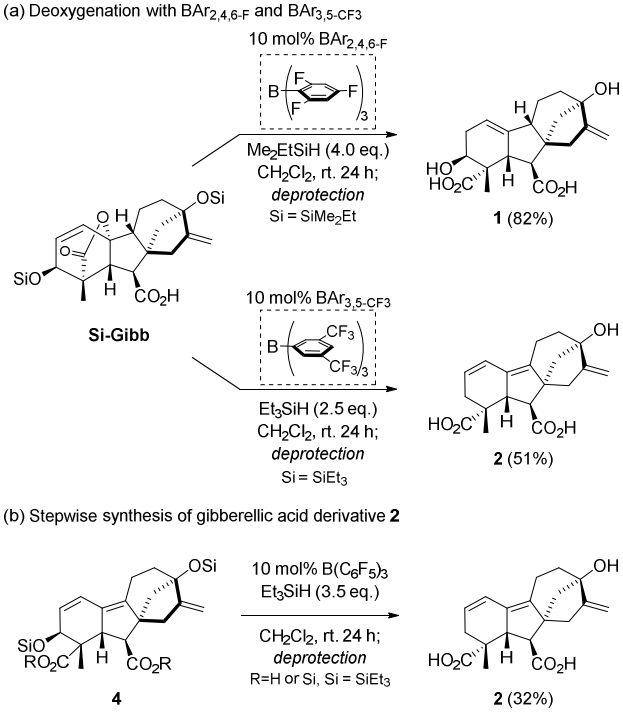
Since free gibberellic acid and silyl protected gibberellic acid react slightly differently, both forms were tested with the alternative reductant, catecholborane (HBCat). Interestingly, different products, **1** or **3**, were obtained from **Si-Gibb** and **Gibb** after hydrolysis (Scheme 2). As evidenced from gas evolution on mixing either **Gibb** or **Si-Gibb** with HBCat (no catalyst necessary), the free alcohols and carboxylic acids were borylated, making the resulting borylated compounds the actual starting materials. Under these conditions isomerization to known **3** occurs in contrast to **Si-Gibb**, which converts to **1** (Scheme 2). *In situ* monitoring of the reactions by ^{19}F and ^{11}B NMR spectroscopy reveal that the fluoroarylborane catalyst rests as $(C_6F_5)_3B{-}H^-$ in the reaction using **Si-Gibb** whereas it rests as various $B(C_6F_5)_3$ Lewis adducts in reactions using **Gibb**. These observations agree with our previous DFT study on the silyl/boryl oxonium ions that can be formed from 2-propanol.[12] These calculations showed that a diboryl oxonium is significantly higher in energy than a mixed silyl-boryl or disilyl oxonium ion. In other words, boryl protected ethers are insufficiently Lewis basic to support the formation of a putative [diboryl oxonium][$(C_6F_5)_3B{-}H^-$] Lewis pair. In this situation a Lewis acid catalyzed allylic transposition becomes competitive over heterolytic cleavage of HBCat. Thus, the formation of **1** through C–O bond activation/cleavage predominates when relatively more basic silyl ethers are present under $B(C_6F_5)_3$-catalyzed conditions, while non-reductive pathways dominate when the less basic boryl ester intermediates are involved.



Scheme 2. Deoxygenation with HBCat as reductant.

Next, the less Lewis acidic fluoroarylboranes, $BAr_{2,4,6\text{-}F}$ and $BAr_{3,5\text{-}CF3}$, were tested with **Si-Gibb** and silane reductants. Although $B(C_6F_5)_3$ generates a mixture of **1** and **2**, each compound can be prepared as the sole product by changing the catalyst (Scheme 3(a)). With 10 mol% $BAr_{2,4,6\text{-}F}$, Me_2EtSi-protected gibberellic acid was fully converted to **1** and isolated in a good yield (82%). Even though the yield was a little lower than that obtained with $B(C_6F_5)_3$ and **Gibb**, **2** was not detectable by *in situ* $^{13}C\{^1H\}$ NMR. In contrast, using 10 mol% of $BAr_{3,5\text{-}CF3}$ resulted in allylic alcohol reduction coupled with lactone opening and elimination. *In situ* $^{13}C\{^1H\}$ NMR monitoring indicated a lack of detectable intermediates, with **Si-Gibb** being smoothly converted to **2**.[17]

We next sought to synthesize **2** from conjugated diene **4** *via*



selective allylic alcohol reduction using a fluoroarylborane catalyst and silane (Scheme 3(b)). Silyl protected diene **4** was prepared *via* a previously reported procedure in 64% yield from gibberellic acid.[13] Under $B(C_6F_5)_3$-catalyzed hydrosilylative deoxygenation conditions, 32% of reduced allylic alcohol **2** was obtained after 24 h, with only trace amounts of **2** being formed when $BAr_{3,5\text{-}CF3}$ was the catalyst. Few examples of hydrosilylative allylic alcohol reductions with fluoroarylborane catalysts are known although several examples of C–O reductions on cyclic ethers have been reported.[18,19]

Unlike $B(C_6F_5)_3$ catalyzed reactions, *in situ* spectroscopic studies of the $BAr_{2,4,6\text{-}F}$ and $BAr_{3,5\text{-}CF3}$ reactions provided no clear evidence for how the borane speciated. In an attempt to observe a difference in the behavior of the catalysts an additional 20 mol% of an external Lewis base (PPh_3) was added, which can promote the heterolysis of the silane into a borohydride/silylphosphonium ion pair.[20] In the case of $BAr_{2,4,6\text{-}F}$ the rate of forming **1** and **3** slowed and resonances for $H\text{–}BAr_{2,4,6\text{-}F}^-$ were observed in the ^{19}F NMR (-100.2 ppm for *o*-F, and -120.1 ppm for *p*-F) along with its cation $Me_2EtSi\text{-}PPh_3^+$ (-3.29 ppm) by ^{31}P NMR.[20,21] By contrast, addition of 20 mol% PPh_3 to the $BAr_{3,5\text{-}CF3}$ catalyzed reaction completely shut down its reduction to **2**, and instead provided only partial conversion of **Si-Gibb** to **3**. As discussed in Figure 1, despite having a similar net hydride affinity, both the borohydrides and borane Lewis acids have different electrostatic potential surfaces. In addition to these electrostatic differences, the lack of *ortho*-F groups in $BAr_{3,5\text{-}CF3}$ makes it more sterically accessible to both the hydride source (Piers mechanism) and other competing Lewis bases.[9,22–24] The balance of these forces is especially complex in a multi-functional structure like gibberellic acid and so the diverging reactivity patterns is difficult to pin down to a specific feature of the catalysts.

Scheme 3. Divergent deoxygenation with fluoroarylboranes.

3. Conclusion

Selective activation and cleavage of C–O bonds in gibberellic acid has been achieved employing different fluoroarylborane Lewis acid catalysts. Although the precise mechanistic reasons for the diverging behavior could not be unambiguously disentangled, a number of differences were noted, including changes in the electrostatic surfaces of the borane Lewis acid and their conjugate hydrides. Experimental studies noted that $B(C_6F_5)_3$, which has the highest hydride affinity, rests as the borohydride. The partially fluorinated catalysts have lower hydride affinities and neither build up significant quantities of borohydride during catalysis. However, when PPh_3 is added to a reaction the $BAr_{2,4,6\text{-}F}$ catalyst converts to the borohydride *in situ* while $BAr_{3,5\text{-}CF3}$ does not. It is tempting to ascribe the difference in reaction selectivities to the propensity of the catalysts to form borohydride versus borane resting states, however, it is still too early to tell if this is the ultimate source of the divergent behavior.

4. Experimental section

4.1. General information

All reactions were performed at ambient temperature (25 ºC, RT) unless otherwise specified. All workup procedures were performed under air with reagent grade reagents unless otherwise specified. Column chromatography was performed using SilaFlash P60 40-63 μm (230-400 mesh). Thin layer chromatography (TLC) was performed on SiliCycle Silica Gel 60 F254 plates and was visualized with ceric ammonium molybdate (CAM) stain. All NMR spectra were recorded on a Bruker Avance 600 MHz spectrometer at standard temperature and pressure. All deuterated solvents were used as received from Cambridge Isotope Laboratories, Inc. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. The following abbreviations are used in reporting NMR data: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; ddd, doublet of doublet of doublets; and m, multiplet. Where necessary, 2D COSY, and HSQC data were used for peak assignment. High Resolution Mass spectra were obtained on Q Exactive™ HF-X Hybrid Quadrupole-Orbitrap™ Mass spectrometer.

All chemicals were used as received, or otherwise described on how it was treated before use. Me_2EtSiH and Et_3SiH were purchased from Gelest, and degassed *via* three freeze-pump-thaw cycles and stored over molecular sieves in the glovebox. Catecholborane was purchased from Sigma-Aldrich, distilled prior to use, taken into a nitrogen filled glovebox, and stored at -48 °C. $B(C_6F_5)_3$ was purchased from Strem and used as received. $BAr_{2,4,6\text{-}F}$ and $BAr_{3,5\text{-}CF3}$ were synthesized *via* known methods.[10,24]

*4.2. $B(C_6F_5)_3$ catalyzed reaction with **Si-Gibb** and silane*

In a N_2-filled glove box, $B(C_6F_5)_3$ (4.9 mg, 0.010 mmol, 0.10 equiv) was placed in a 1 dram vial and dissolved in 0.2 mL of CH_2Cl_2. To the catalyst solution was added Me_2EtSiH (32 μL, 0.241 mmol, 2.50 equiv) and mixed. In a separate vial, **Me_2EtSi-Gibb** (50 mg, 0.096 mmol, 1.00 equiv) was diluted with 0.3 mL of CH_2Cl_2. The catalyst and borane mixture was then added to the substrate solution in one portion. The reaction mixture was transferred to an NMR tube and sealed with a septum cap. After 24 h, the mixture was transferred to a vial and rinsed three times with 0.5 mL of MeOH. After concentrating the resulting solution in vacuo, the crude residue was purified by silica gel chromatography (30:1 CH_2Cl_2/MeOH to 20:1 to 10:1 to 5:1) to yield **1** (83%, 28 mg) and **2** (16%, 5.0 mg).

Compound **1**: ^1H NMR (600 MHz, Acetone-d_6) δ 5.19 (br s, 1H), 5.06 (br s, 1H), 4.90 (br s, 1H), 4.04 (dd, *J* = 4.3, 2.0 Hz, 1H), 3.17 (d, *J* = 5.5 Hz, 1H), 3.16 – 3.12 (m, 1H), 2.77 (dt, *J* = 18.2, 3.5 Hz, 1H), 2.68 (dt, *J* = 16.3, 3.0 Hz, 1H), 2.49 (br s, 1H), 2.28 – 2.23 (m, 1H), 2.13 (m, 1H), 1.96 – 1.88 (m, 1H), 1.74 (dd, *J* = 11.0, 2.9 Hz, 1H), 1.69 – 1.58 (m, 2H), 1.49 – 1.39 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (151 MHz, Acetone-d_6) δ 177.5, 176.2, 156.6, 142.1, 111.0, 105.7, 79.3, 70.5, 50.5, 50.0, 49.8, 49.7, 48.8, 47.2, 46.6, 40.1, 38.8, 33.4, 22.2, 19.4. HRMS (EI) calculated for $C_{19}H_{24}O_6Na$ $[M+Na]^+$:371.1465; found 371.1459.

Compound **2**: ^1H NMR (600 MHz, Methanol-d_4) δ 5.85 (d, *J* = 9.8 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 5.10 (t, *J* = 2.5 Hz, 1H), 3.15 – 3.01 (m, 1H), 2.98 – 2.81 (m, 2H), 2.75 – 2.64 (m, 1H), 2.60 – 2.42 (m, 2H), 2.31 – 2.12 (m, 1H), 2.06 (dd, *J* = 10.1, 2.6 Hz, 1H), 2.03 – 1.89 (m, 1H), 1.73 (td, *J* = 11.9, 6.4 Hz, 1H), 1.64 (ddd, *J* = 10.7, 7.0, 2.6 Hz, 1H), 1.59 (dd, *J* = 10.1, 2.5 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (151 MHz, Methanol-d_4) δ 178.2, 177.8, 156.0, 136.5, 132.4, 128.9, 127.8, 105.8, 80.0, 57.1, 55.9, 53.9, 52.4, 40.6, 40.5, 26.1, 24.5, 21.6. HRMS (EI) calculated for $C_{19}H_{22}O_5Na$ $[M+Na]^+$: 353.1360; found: 353.1370.

4.3. $B(C_6F_5)_3$ catalyzed reaction with HBCat

In a N_2-filled glove box, $B(C_6F_5)_3$ (3.6 mg, 0.007 mmol, 0.10 equiv) was placed in a 1 dram vial and dissolved in 0.2 mL of CH_2Cl_2. To the catalyst solution was added HBCat (37 μL, 0.350

mmol, 5.00 equiv) and mixed. In a separate vial, **Me_2EtSi-Gibb** (36 mg, 0.070 mmol, 1.00 equiv) was diluted with 0.3 mL of CH_2Cl_2. The catalyst and borane mixture was then added to the substrate solution in one portion. The reaction mixture was transferred to an NMR tube and sealed with a septum cap. After 24 h, the mixture was transferred to a vial and rinsed three times with 0.5 mL of MeOH. After concentrating the resulting solution in vacuo, the crude residue was purified by silica gel chromatography (100% CH_2Cl_2 to 30:1 CH_2Cl_2/MeOH to 20:1 to 10:1 to 5:1) to yield **1** as a clear film in 90% yield (22.0 mg, average over two runs).

4.4. Selective deoxygenation with $BAr_{2,4,6\text{-}F}$

In a N_2-filled glove box, $BAr_{2,4,6\text{-}F}$ (3.2 mg, 0.008 mmol, 0.10 equiv) was placed in a 1 dram vial and dissolved in 0.2 mL of CH_2Cl_2. To the catalyst solution was added Me_2EtSiH (38 μL, 0.308 mmol, 4.00 equiv) and mixed. In a separate vial, **Me_2EtSi-Gibb** (40 mg, 0.077 mmol, 1.00 equiv) was diluted with 0.3 mL of CH_2Cl_2. The catalyst and silane mixture was then added to the substrate solution in one portion. The reaction mixture was transferred to an NMR tube and sealed with a septum cap. After 24 h, the mixture was transferred to a vial and rinsed three times with 0.5 mL of MeOH. After concentrating the resulting solution in vacuo, the crude residue was purified by silica gel chromatography (20:1 CH_2Cl_2/MeOH to 10:1 to 8:1 to 5:1) to yield **1** as a clear film in 82% yield (22.0 mg).

4.5. Selective deoxygenation with $BAr_{3,5\text{-}CF3}$

In a N_2-filled glove box, $BAr_{3,5\text{-}CF3}$ (4.5 mg, 0.007 mmol, 0.10 equiv) was placed in a 1 dram vial and dissolved in 0.2 mL of CH_2Cl_2. To the catalyst solution, was added Et_3SiH (28 μL, 0.174 mmol, 2.50 equiv) and mixed. In a separate vial, **Et_3Si-Gibb** (40 mg, 0.070 mmol, 1.00 equiv) was diluted with 0.3 mL of CH_2Cl_2. The catalyst and silane mixture was then added to the substrate solution in one portion. The reaction mixture was transferred to NMR tube and sealed with a septum cap. After 24 h, the mixture was transferred to a vial and rinsed three times with 0.5 mL of MeOH. After concentrating the resulting solution in vacuo, the crude residue was purified by silica gel chromatography (20:1 CH_2Cl_2/MeOH to 10:1 to 8:1 to 5:1) to yield **2** as a clear film in 51% yield (15.7 mg, average over 3 runs).

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://doi.org/

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- Gibberellic acid derivatives are synthesized with fluoroarylborane catalysts.
- An example of selective deoxygenation in a natural product
- Selective deoxygenation is possible with silane and borane reductants.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: