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Moisture-Tolerant Frustrated Lewis Pair Catalyst for Hydrogenation of Aldehydes and Ketones

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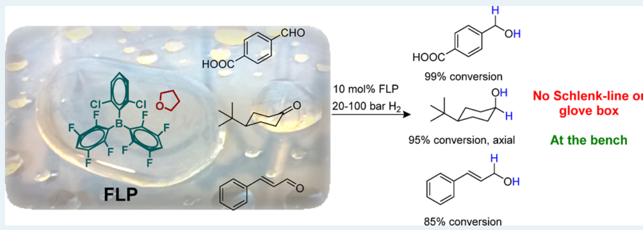
Supporting Information

ABSTRACT: In this paper, we report on the development of a bench-stable borane for frustrated Lewis pair catalyzed reduction of aldehydes, ketones, and enones. The deliberate fine-tuning of structural and electronic parameters of Lewis acid component and the choice of Lewis base provided for the first time, a moisture-tolerant FLP catalyst. Related NMR and DFT studies underpinned the unique behavior of this FLP catalyst and gave insight into the catalytic activity of the resulting FLP catalyst.



KEYWORDS: *frustrated Lewis pair, hydrogenation, catalysis, moisture tolerant, carbonyl*

1. INTRODUCTION

Frustrated Lewis pair (FLP) chemistry, introduced by Stephan and co-workers, is a new paradigm in small-molecule activation and catalysis.[1] This approach employs sterically encumbered Lewis acid−base pairs that impede stable Lewis adduct formation. As a consequence, a "quasi-metastable" state emerges that can abruptly release the strain energy in the ensuing bond-activation step.[2] FLP chemistry has actually empowered main group elements to emulate the cooperative donor−acceptor properties of transition metals, and it has significantly expanded the capacity of bifunctional, cooperative catalysis.[3]

FLP-catalyzed hydrogenation, a striking and emblematic application of the field, is undergoing a surge of upheaval that is largely fueled by the aspirations to develop metal-free hydrogenation technology.[4] A number of papers have been published in this area that chronicle the constant interplay between conceptual catalyst development and exploration of applicability.[5] Recently, one of the long-unsolved limitations has been resolved, in which Ashley[6a] and Stephan[6b,c] described the FLP-mediated reduction of aldehydes and ketones. Despite the many advances, the scope and practicality of FLP-mediated hydrogenation still lag behind transition-metal-based strategies. Because of the appreciably hard nature of the Lewis acidity of the boron center,[6e] the FLP catalyst improvement always confronts with the dilemma of substrate and/or product inhibition and moisture sensitivity. As such, the substrate scope is restricted as certain functionalities are not tolerated, and the hydrogenation process requires the rigorous exclusion of water.[7] This restriction represents a considerable synthetic hurdle that must be overcome to realize the full potential of FLP catalysis.

In a dual attempt to further the FLP-catalyzed hydrogenation in the scope and practicality, we aimed to develop new catalysts that combine improved substrate scope and functional group tolerance with a significantly upgraded user-friendliness. Herein, we report the development of such an FLP system that has both an amplified application profile and also an unprecedented moisture tolerance.

The most common, privileged Lewis acid that has been used for the FLP-based small-molecule activation and catalytic hydrogenation is the tris(pentafluorophenyl)-borane (**1a**). Despite its availability and proven worthiness in hydrogenation, the applicability of this borane has been limited owing to its low functional group tolerance and moisture sensitivity. Accordingly, efforts have been directed to modify the parent Lewis acid **1a** to reduce the incompatibility with substrates encompassing nitrogen or oxygen centered Lewis basic sites (Scheme 1). So far, two strategies have been successfully implemented: the mitigation of electron-deficiency of the boron center[8] (Scheme 1, FLP-2, **1b**) that tempers the strength of competing dative bonds, and the size-exclusion approach (Scheme 1, FLP-3, **1c−e**)[9,10] that retards the binding to Lewis acidic center via enhanced sterical repulsion (F-strain). Although the size-exclusion developments provided Lewis acids **1d,e** that have stabilities toward moisture in the solid state and could be weighed in air, their catalytic applications in hydrogenation still require rigorously dried solvents and reagents.[9a,10a] Thus, the tempting prospect of moisture tolerant FLP hydrogenation catalysis has not been realized.

Apparently, the water inhibition of FLP hydrogenation catalysts should be considered as the consequence of an FLP reactivity (i.e., a cooperative interaction of the Lewis acid−base pair with water) and not only a borane−water interaction.[7]

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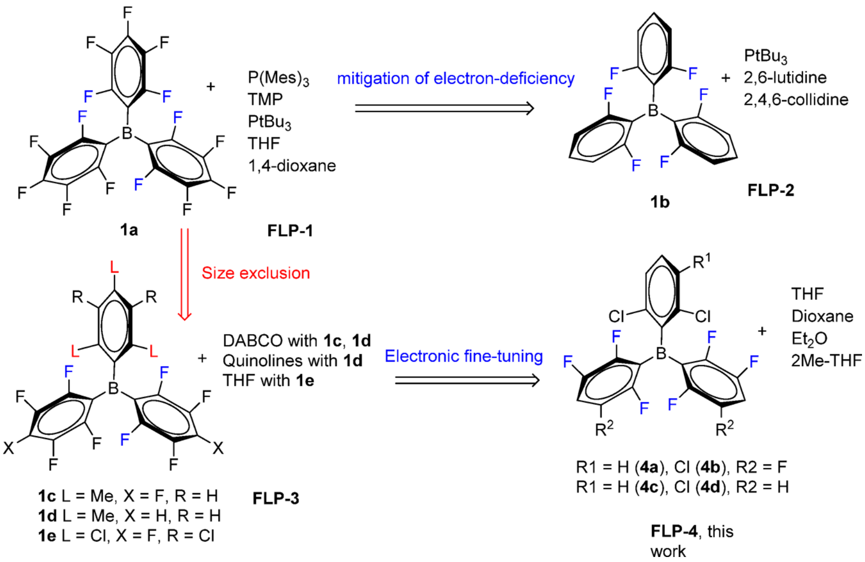
Scheme 1. Design Concepts in FLP Hydrogenation



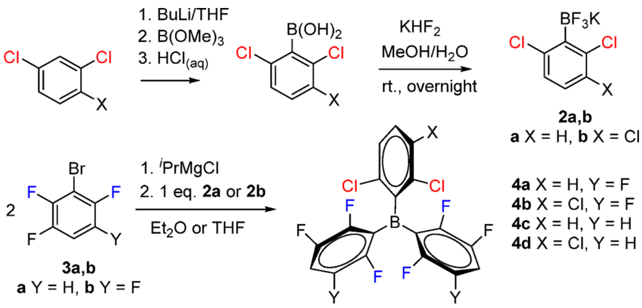
Whereas the appropriate fine-tuning of the Lewis acidic boron can attenuate the strength of the dative complex with water, the applied Lewis base can restore or even enhance the inhibitory effect via strong H-bonding interactions or even deprotonation of the bound water. Accordingly, an attractive, dual acid–base optimization approach was considered to address the challenge of moisture-tolerant FLP hydrogenation catalysis. This development requires the first and foremost identification of a suitable class of Lewis basic component of the FLP, which guides the selection of the Lewis acidic component as well (and also the selection of tolerated functional groups in the substrate). In this regard, careful design of steric and electronic factors of Lewis acid is required to maintain the preferential hydrogen activation ability while minimizing the side reaction of the water with the FLP. We thus envisioned that using a Lewis acid with an appropriate size-exclusion design in a weakly basic ethereal type solvent might result in a moisture tolerant FLP hydrogenation catalyst. (Scheme 1, FLP-4). Initial attempts to employ our previously developed Lewis acid **1d**, however, were not successful. The **1d**/THF combination was found to be inactive in the hydrogenation of activated olefins. Obviously, deliberate enhancement of the Lewis acidity was required to afford boranes that could activate hydrogen with THF.[11] Therefore, we envisaged the development of isosteric analogues of **1d** having chlorines instead of methyl groups at *ortho* position of the mesityl ring. This replacement was expected not only to increase the Lewis acidity but also to hinder the protodeborylative decomposition of boranes during the FLP catalysis.

2. RESULTS

2.1. Catalyst Development. With these structural requirements in mind, we embarked on the synthesis of a series of Lewis acidic triaryl-boranes **4a–d** endowed with the same steric bulk around the boron atom.

The introduction of halogen atoms (F or Cl) in meta positions was expected to permit the electronic fine-tuning of boranes to secure the necessary acidity strength for FLP hydrogen activation in THF. Although varieties of routes have been probed, the synthetic route outlined in Scheme 2 was the method of choice owing to its simplicity, scalability, and high yields. This methodology provided a rapid and unified entry to various unsymmetrical borane derivatives **4a–d** in multi 10 g scales from easily accessible fluoroborates **2a,b** and commercially available fluorinated aryls **3a,b**.

Scheme 2. Synthesis of Boranes 4a–d with Size-Exclusion Design



2.2. Catalytic Application. To explore the feasibility of the synthesized Lewis acid components **4a–d** in catalytic hydrogenation, we selected the hydrogenation of benzaldehyde (**5**), *trans*-chalcone (**6**) and cyclohexanone **7** in THF as model reactions. Gratifyingly, all boranes **4a–d** (Table 1, entries 1–4) were found to be amenable to promote the reduction of benzaldehyde (**5**) to the corresponding alcohol **8a** and its condensation side product dibenzylether (**8b**). Although every borane **4a–d** could reduce the sterically more accessible olefin bond[12] in **6** to afford 1,3-diphenylpropane-1-one (**9a**) (Table 1, entries 5–8), only tetrafluoro-boranes (**4a,b**) could convert it further to 1,3-diphenylpropan-1-ol (**9b**) (Table 1, entries 5, 6). Next, the effect of the ethereal solvents, the Lewis basic component of the FLP, on catalytic efficiencies was investigated. As highlighted in Table 1 (entries 9–14), the catalytic hydrogenations could be accomplished in a variety of ethereal solvents ranging from the relatively basic 2-Me-THF to the weakly basic diethyl ether. Nevertheless, we observed that these solvents influenced the selectivity of the hydrogenation. Not only can a higher conversion be achieved (Table 1, entry 5 vs 9), but also, the formation of the **10b** condensation side-product could be suppressed by the choice of the solvent (Table 1, entry 12 vs entries 13, 14). These results demonstrate that the selectivity of FLP-catalyzed hydrogenation (i.e., olefin

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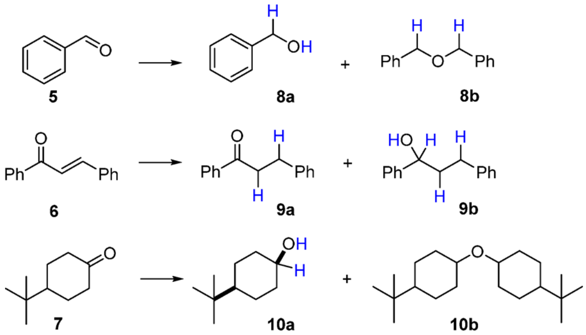
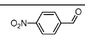
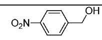
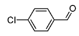
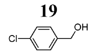
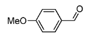
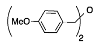
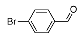
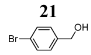
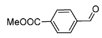
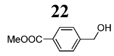
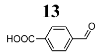
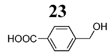
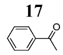
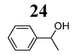
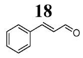
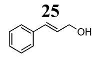
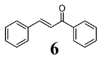
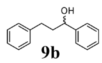
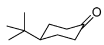
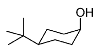
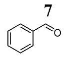
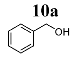
Table 1. FLP Hydrogenation of Carbonyls 5−7 in Ethereal Solvents[a]



entry	catalyst	solvent	substrate	conversion[b]
1	**4a**	THF	**5**	99% (93% **8a**, 7% **8b**)
2	**4b**	THF	**5**	99% (88% **8a**, 12% **8b**)
3	**4c**	THF	**5**	99% (94% **8a**, 6% **8b**)
4	**4d**	THF	**5**	99% (91% **8a**, 9% **8b**)
5	**4a**	THF	**6**	99% (30% **9a**, 70% **9b**)
6	**4b**	THF	**6**	99% (30% **9a**, 70% **9b**)
7	**4c**	THF	**6**	83% (**9a**)
8	**4d**	THF	**6**	99% (**9a**)
9	**4a**	2-Me-THF	**6**	99% (21% **9a**, 79% **9b**)
10	**4a**	1,4-dioxane	**6**	99% (84% **9a**, 16% **9b**)
11	**4a**	Et_2O	**6**	99% (67% **9a**, 33% **9b**)
12	**4a**	THF	**7**	87% (87% **10a**, 13% **10b**)
13	**4a**	2-Me-THF	**7**	99% (90% **10a**, 10% **10b**)
14	**4a**	1,4-dioxane	**7**	99% (97% **10a**, 3% **10b**)

[a]Reaction conditions: 100 bar of H_2, 50 °C, 10 mol % catalyst, 1.0 mmol substrate in 1.25 mL of abs. ethereal solvents, 40 h for benzaldehyde (**5**) and 112 h for trans-chalcone (**6**) and 4-^{t}Bu-cyclohexanone (**7**). [b]All conversions were determined by ^1H NMR integration of crude products and reinforced by GC-MS measurements.

Table 2. Substrate Scope of the Catalytic FLP Hydrogenation with 4a,b

Entry	Substrate	Product	Conversion[a]	Yield
1	 **11**	 **19**	99%[b]	95%[b]
2	 **12**	 **20**	99%[b]	93%[b]
3	 **15**	 **21**	99%[c]	73%[c]
4	 **16**	 **22**	98%[b]	75%[b]
5	 **13**	 **23**	99%[b]	76%[b]
6	 **17**	 **24**	81%[b], 99%[d]	76%[d]
7	 **18**	 **25**	85%[e]	60%[e]
8	 **14**	 **26**	85%[b]	60%[b,f]
9	 **6**	 **9b**	99% (33% **9a**, 66% **9b**)[e]	21% **9a**, 45% **9b**[e]
10	 **7**	 **10a**	98% (95% **10a**, 5% **10b**)[g]	65%[g]
11	 **5**	 **8a**	99% (88% **8a**, 12% **8b**)[b]	75%[b]

[a]All conversions were determined by ^1H NMR integration of crude products and reinforced by GC-MS measurements. [b]Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 40 h, 10 mol % catalyst **4a**, 20 bar, 55 °C. [c]Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 40 h, 10 mol % catalyst **4a**, 20 bar, 80 °C. [d]Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 136 h, 10 mol % catalyst **4b**, 100 bar, 55 °C. [e]Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 137 h, 10 mol % catalyst **4a**, 100 bar, 55 °C. [f]Beside the isolation of **26**, 21% dicinnamic-ether was also isolated. [g]Reaction conditions: 1.0 mmol substrate in 1.25 mL of Et_2O, 88 h, 10 mol % catalyst **4a**, 20 bar, 55 °C.

vs keto, keto vs aldehyde) can be beneficially altered by deliberate tuning of the Lewis acidity and/or choice of ethereal solvent.

Having identified boranes **4a,b** as competent, as well as easily available Lewis acids for carbonyl reductions, we next focused on exploring their scope and limitation (Table 2). A variety of electron-deficient and electron-rich aromatic aldehydes underwent the hydrogenation to give benzyl alcohols **19−24** (entries 1−6). Most importantly, the applied pressure of hydrogen could be reduced from 100 to 20 bar in most cases of aldehydes. The process tolerated functional groups such as nitro, halogen, and methoxy (entries 1−4). Notably, there was no detectable dehalogenation during the reduction of 4-chloro and 4-bromobenzaldehydes (entries 2, 4). To our surprise, not only ester (entry 5) but also carboxylic group was tolerated during the catalytic reduction. Thus, 4-formylbenzoic acid (**17**) could be reduced to the alcohol **24** (entry 6), although it was necessary to apply higher pressure and more acidic catalyst **4b** to realize a full conversion.

In addition to aromatic aldehydes, the FLP reduction of some challenging ketones and aldehydes were also examined. We found that acetophenone (**18**) could be converted cleanly to the corresponding benzylalcohol **25** as no ether formation and no water elimination (to afford styrene) occurred; however, utilization of a hydrogen pressure of 100 bar and longer reaction time was required. Interestingly, cinnamaldehyde (**14**) was chemoselectively hydrogenated at the carbonyl without the saturation of the olefin bond. The only observed side reaction was ether formation. 4-^{t}Bu-cyclohexanone (**7**) could be reduced selectively to the corresponding *cis* alcohol **10a** (entry 10) at lower pressure (20 bar). Thus, the transiently formed borohydride only attacks the carbonyl group of **7** equatorially, because of the steric demand of the reducing agent.

Next, our major objective, the enticing prospect of moisture-tolerant hydrogenation, was probed. Notably, when borane **4a** was brought out from the glovebox and stored in an open vial, it quickly, within a few hours, absorbed 1.5 equiv of water. However, the resulting hydrate displayed a remarkable stability in the solid state and retained the same unvaried chemical and physical properties after a 2 month storage.[13] Encouraged by the stability of **4a** hydrate, we pursued to investigate whether the water interferes with the hydrogenation activity of **4a** (Table 3, entry 1−5). To our delight, water, being present in more than 1 equivalent with respect to the catalyst, was found to be compatible with this catalyst in THF; even technical grade THF could be used as a solvent without compromising the conversion. Notably, the presence of water had an impact on the selectivity of the reduction: cinnamaldehyde (**14**) could be reduced more efficiently (entry 5).

Because the desired catalytic reduction could be performed when more than 1.5 equiv of water to the borane **4a** was present, our catalyst development rendered the water binding

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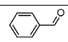
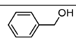
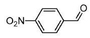
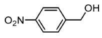
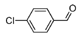
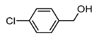
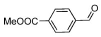
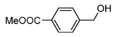
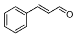
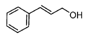
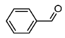
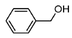
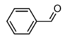
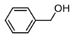
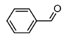
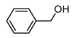
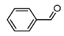
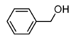
Table 3. Investigation of the Moisture Tolerance in the FLP Hydrogenation of Carbonyls[a]

Entry	Catalyst	Solvent	Substrate	Product	Conversion[b]
1	**4a**	THF	 **5**	 **8a**	99%
2	**4a**	THF	 **11**	 **19**	99%
3	**4a**	THF	 **12**	 **20**	99%
4	**4a**	THF	 **13**	 **23**	99%
5	**4a**	THF	 **14**	 **26**	99%[c]
6	**1a**	1,4-dioxane	 **5**	 **8a**	29%
7	**1a**	1,4-dioxane	 **5**	 **8a**	5%[d]
8	**1a**	THF	 **5**	 **8a**	18%
9	**1a**	THF	 **5**	 **8a**	0%[d]

[a]Reaction conditions: 1.0 mmol substrate in 1.25 mL of puriss. grade THF, 50 °C, 40 h, 10 mol % **4a**·1.5 H_2O, 100 bar of H_2. [b]All conversions were determined by ^{1}H NMR integration of crude products and reinforced by GC-MS measurements. [c]Beside the formation of **26** (83%), the following side products were detected: 12% 3-phenyl-1-propanol, 5% propanol, 5% dicinnamic-ether. [d]Borane **1a** was exposed to moisture in an open vial for 3 days.

to **4a** reversible in the applied ethereal-type basic solvent.[14] The efficiency and superior moisture tolerance of **4a** was also demonstrated in a side-by-side comparison to the benchmark borane catalyst **1a**. Despite its outstanding application profile in FLP chemistry, catalyst **1a** was markedly less efficient catalyst in aldehyde **5** reduction using THF or 1,4-dioxane as solvents (Table 3, entries 6, 8).[15] Most importantly, this catalyst required rigorously inert conditions, otherwise markedly reduced or no conversion were observed (Table 3, entries 6, 8 vs 7, 9).

To our knowledge, the application of **4a**/THF catalyst is the first example in the FLP field that process does not require inert techniques containment (without glovebox and Schlenk-line technique) during the entire synthetic operation. Therefore, reaction mixtures were conveniently prepared in an open flask using technical grade solvent and charged into a pressure vessel, allowing to upgrade the practicality of the FLP-catalyzed hydrogenation.

2.3. NMR and Theoretical Studies. Despite the established importance of structural fine-tuning of the Lewis acid component in moisture tolerant FLP-catalyzed hydrogenation, our understanding regarding the structural and electronic factors that affect water coordination in **4a**/THF, substrate/product bindings and also the hydrogenation process itself is limited. Thus, our investigations were extended toward NMR complexation studies and DFT calculations to gain a deeper insight and provide structural and thermochemical foundations for the above observations.

First, a variable-temperature complexation study was undertaken to probe the strength and dynamic behavior of borane **4a** complexes relevant to the hydrogenation of benzaldehyde (**5**). We explored the association ability of borane **4a** with benzaldehyde (**5**), benzylalcohol (**8a**) and water in the applied THF solvent. As summarized in Figure 1, these combinations were characterized by ^{10}B NMR spectroscopy at 20 and 50 °C

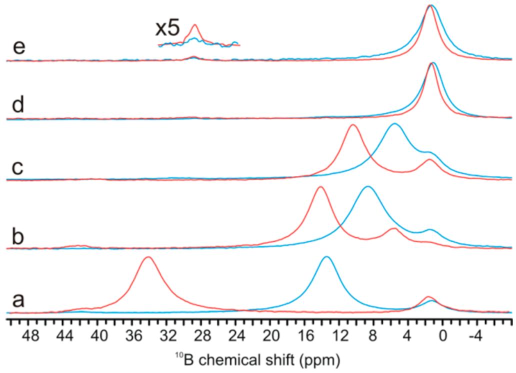


Figure 1. ^{10}B NMR complexation study of borane **4a**, ^{10}B NMR spectra in THF at 20 °C − blue lines and at 50 °C − red lines: (a) borane **4a**, (b) 4a and 10 equiv of benzaldehyde (**5**), (c) **4a** and 10 equiv of benzylalcohol (**8a**), (d) **4a** and 3 equiv of water, (e) **4a** and 3 equiv of water and 10 equiv of benzaldehyde (**5**).

temperatures (blue and red lines, respectively). Importantly, the Lewis acid **4a** formed a dative complex with the Lewis basic solvent THF (Figure 1, blue spectra a). However, the **4a**-THF adduct is sufficiently weak, so the solvent molecule can easily dissociate at higher temperature or it can be displaced by benzaldehyde (**5**), benzyl alcohol (**8a**), and water. Both substrate **5** and product **8a** could bind to the reactive boron center; however, we observed a balanced population of free and datively bound states at higher temperature as the resonance signals moved downfield (δ = 63.4 ppm for free **4a** in benzene).[16] Finally, the complexation capacity of water was assessed by using a 3 molar excess of water over borane **4a**. It is apparent that water formed the strongest dative complex and could exert the highest inhibitory effect on the catalytic cycle among the investigated Lewis bases. Nevertheless, the dative adduct was kinetically labile at elevated temperature, as evidenced by the observation of a resonance signal around 28 ppm. As a consequence of dynamic equilibrium between the free and the datively bound states, a small amount of free borane **4a** is always available for FLP reactions, which is in accord with the observed catalytic FLP reactivity in the presence of water. Finally, it is important to note that catalyst **4a** was found to be quite robust in the presence of water, as no hydrolytic decomposition of **4a** was observed when the THF solutions (in experiments d and e) were held at 50 °C for 2 h and cooled back to 20 °C.[16]

Datively bound 1:1 complexes formed between borane **4a** and selected oxygen-based Lewis bases (**5**, **8a**, THF, and H_2O) were subject to computational analysis.[17] Our results indicated that the experimentally observed trend regarding the strength of complexation could only be reproduced with the inclusion of explicit solvent (THF) molecules in the model. We found that THF formed strong hydrogen bonds with the OH group of the complexed alcohol and water, which provided significant stabilization for these species. As a result of these stabilizing H-bonding interactions, the **4a**−**8a**(THF) and **4a**−H_2O-$(THF)_2$ adducts (see Figure 2) become thermodynamically more favored than the **4a**−**5** and **4a**−THF complexes, which is consistent with our NMR observations.

The association ability of the predecessor Lewis acids **1a** and **1e** with water and benzylalcohol (**8a**) was also considered for comparison (Figure 2). Although water tends to form a moderately strong adduct with **4a** (with association free energy of ΔG = −5.3 kcal/mol), the more acidic boranes, **1e**, but

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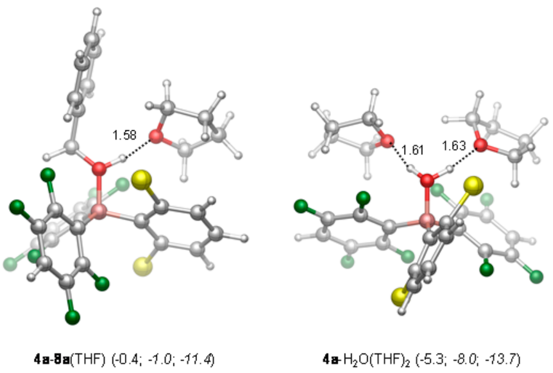

Figure 2. Optimized structures of THF-stabilized **4a**−**8a** and **4a**−H_2O adducts. Computed association Gibbs free energies (in kcal/mol, at 25 °C; with respect to dissociation limits) are shown in parentheses (data in italics refer to boranes **1e** and **1a**, respectively). O···H bond distances are given in Å.

especially **1a**, gave notably stronger THF-stabilized water complexes (ΔG = −8.0 and −13.7 kcal/mol for **1e** and **1a**, respectively).[18] The THF-induced aqua complex stabilization in this series can range from the competitive to the irreversible water inhibition, and it can also result in the complete loss of hydrogenation reactivity as observed in previous reports.

The mechanism of catalytic hydrogenation of carbonyl compounds using borane **4a** was also investigated computationally. The free-energy diagram of the entire catalytic cycle is shown in Figure 3. In these calculations, benzaldehyde (**5**) was

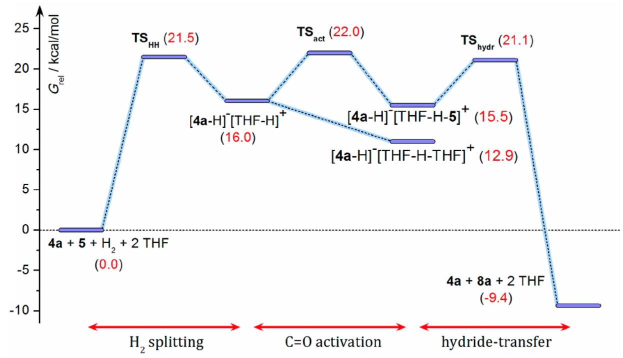

Figure 3. Gibbs free-energy diagram computed for the entire catalytic cycle.

used as a substrate and we aimed to identify and characterize the main elementary steps of the catalytic process. The envisioned catalytic cycle is initiated by the heterolytic H_2 splitting, which may occur via two alternative pathways corresponding to H_2 activation by the **4a**/THF and **4a**/**5** pairs. According to the computed free energies, H_2 activation by **4a**/THF is clearly favored kinetically (computed barriers are 21.5 and 25.1 kcal/mol, respectively).

The ion pair intermediate [**4a**−H]$^-$[THF−H]$^+$ can be stabilized considerably by the association of an additional solvent molecule yielding the [**4a**−H]$^-$[THF−H−THF]$^+$ species.[5m] In this ion pair, the proton is solvated by two THF molecules via strong H-bonds; nevertheless, the H_2 splitting step remains still rather endergonic. The substrate molecule **5** can similarly associate with [**4a**−H]$^-$[THF−H]$^+$ resulting in the [**4a**−H]$^-$[THF−H−**5**]$^+$ ion pair. This intermediate involves a highly electrophilic substrate, and therefore, the hydride transfer from [**4a**−H]$^-$ can easily occur, thereby yielding the alcohol product **8a** and regenerating the borane. The free energy of transition state of hydride transfer is predicted to be 21.1 kcal/mol.

It is apparent that the transition states associated with the three basic steps of the cycle (H_2 cleavage, substrate activation, and hydride transfer) are found to have very similar free energies; therefore, none of these steps can be identified as rate-determining in the catalytic process. Our results, however, provide solid support for the mechanism proposed previously by Stephan and Ashley,[6a,b] which considers the borane/ether pair to induce H_2 splitting and Brønsted acid activation of the substrate.

CONCLUSION

In summary, new FLP catalysts for the hydrogenation of carbonyls have been developed. The dual steric and electronic fine-tuning of Lewis acidic component not only allowed to markedly expand the substrate scope in carbonyl reduction but also rendered the water inhibition of the catalyst reversible. Accordingly, this advance alleviates one of the key restrictions of the FLP chemistry, the enhanced sensitivity toward water. Therefore, all synthetic manipulations can be performed at the laboratory bench without the reliance and dependence on inert techniques, and there is no need for purification of the solvents and reagents. Continuing investigation of the catalyst design and application of this catalyst in other hydrogenation processes are currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01299.

Detailed synthesis of the new boranes with their full characterization, reaction conditions and NMR spectra, detailed NMR investigation of borane (**4a**)−H_2O complex, theoretical studies, calculation data, and supplementary figures (PDF)

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Notes

The authors declare no competing financial interest.

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(7) The coordination of water to **1a** is known to be reversible in toluene. Accordingly without an appropriately strong base, the water binding to this borane is reversible (for a relevant work, see: Bergquist, C.; Bridgewater, B. M.; Harlan, C. J.; Norton, J. R.; Friesner, R. A.; Parkin, G. J. *J. Am. Chem. Soc.* **2000**, *122*, 10581−10590. In the presence of amines, however, the borane catalyst **1a** becomes sensitive even to trace amount of water and aldehydes. Therefore, appropriate scavengers were utilized during FLP hydrogenation (see in. Thomson, J. W.; Hatnean, J. A.; Hastie, J. J.; Pasternak, A.; Stephan, D. W.; Chase, P. A. *Org. Process Res. Dev.* **2013**, *17*, 1287−1292 Interestingly, even ethereal type of solvent can be a sufficiently strong base to render water binding irreversible. For example, complete loss of FLP hydrogenation activity was reported by Ashley and co-workers when adding 1.0 equiv of water to **1e**/dioxane FLP hydrogenation catalyst (see ref 6a).

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(11) Ashley and co-workers reported that borane **1e** having highly electron-deficient boron center is a poor catalyst for catalytic FLP hydrogenation of acetone, see ref 6a.

(12) Similar selectivity has been observed during FLP reduction of carvone and unsaturated crotyl-aldimine (see ref 9c).

(13) Borane **4b** shows the same water tolerance as **4a** in catalytic hydrogenation, further work in progress.

(14) Although the water binding to **4a** was rendered reversible, large excess of water (>20 equiv) inhibited the hydrogenation reaction.

(15) THF is more basic than 1,4-dioxane, and this might be the reason that it was a less efficient donor solvent for catalysis in the case of **1a** (see also ref 6a).

(16) For more details, see the Supporting Information.

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(17) For the applied computational methodology and a detailed analysis, see the Supporting Information.

(18) The relative stabilities of borane-$H_2O(THF)_2$ adducts obtained for the borane = **4a**, **1e**, **1a** series parallel well with the Lewis acidities of boranes. The computed hydride affinities are 40.7, 44.5, 49.4 kcal/mol (see Supporting Information).

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