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

Ádám Gyömöre, Mária Bakos, Tamás Földes, Imre Pápai*, Attila Domján, Tibor Soós*

Institute of Organic Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2, 1117 Budapest, Hungary

KEYWORDS: frustrated Lewis pair; hydrogenation; catalysis; moisture tolerant; carbonyl

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 for 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.

1. INTRODUCTION

Frustrated Lewis pair (FLP) chemistry, introduced by Stephan and coworkers, is a new paradigm in small-molecule activation and catalysis.^[1] This approach employs sterically encumbered Lewis acid-base pairs that impedes 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 could be resolved, namely 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.

ACS Catalysis

2. DISCUSSION

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.



Scheme 1. Design concepts in FLP hydrogenation

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] 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 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.

3. RESULTS

3.1 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.



Scheme 2. Synthesis of boranes 4a-d with size-exclusion design

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 10g scales from easily accessible fluoroborates **2a**,**b** and commercially available fluorinated aryls **3a**,**b**.

3.2 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 corresponding alcohol 8a and its condensation side product dibenzylether (8b). Whereas, every borane 4a-d could reduce the sterically more accessible olefin bond^[12] in 6 to afford 1,3-diphenylpropane-1one (9a) (Table 1, entries 5-8), only tetrafluoro-boranes (4a,b) could convert it further to 1,3diphenylpropan-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 Me-THF to the weakly basic diethyl ether. Nevertheless, we observed that these solvents influenced the selectivity of the hydrogenation. Not only higher conversion can 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 14). These results demonstrate that the selectivity of FLP-catalyzed hydrogenation (i.e. olefin vs. keto, keto vs. aldehyde) can be beneficially altered by deliberate tuning of the Lewis acidity and/or choice of ethereal solvent.

Table 1. FLP hydrogenation of carbonyls 5-7 in ethereal solvents.^a



Entry	Catalyst	Solvent	Substrate	Conversion ^b
1	4 a	THF	5	99% (93% 8a, 7% 8b)
2	4b	THF	5	99% (88% 8a , 12% 8b)
3	4 c	THF	5	99% (94% 8a , 6% 8b)
4	4d	THF	5	99% (91% 8a, 9% 8b)
5	4 a	THF	6	99% (30% 9a , 70% 9b)
6	4b	THF	6	99% (30% 9a , 70% 9b)
7	4 c	THF	6	83% (9a)
8	4d	THF	6	99% (9a)
9	4 a	2-Me-THF	6	99% (21% 9a , 79% 9b)
10	4a	1,4-dioxane	6	99% (84% 9a , 16% 9b)
11	4a	Et ₂ O	6	99% (67% 9a , 33% 9b)
12	4 a	THF	7	87% (87% 10a , 13% 10b)
13	4a	2-Me-THF	7	99% (90% 10a , 10% 10b)
14	4 a	1,4-dioxane	7	99% (97% 10a , 3% 10b)

^a Reaction conditions: 100 bar H₂, 50 °C, 10 mol% catalyst, 1.0 mmol substrate in 1.25 mL of abs. ethereal solvents, 40h for benzaldehyde (5) and 112h for trans-chalcone (6) and 4-tBu-cyclohexanone (7). ^b All conversions were determined by ¹H-NMR integration of crude products and reinforced by GC-MS measurements.

Having identified boranes **4a,b** as competent, and 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 bar 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.

Entry	Substrate	Product	Conversion ^a	Yield
1	0 ₂ N-()-0 11	0 ₂ N-()-OH 19	99% ^b	95% ^b
2			99% ^b	93% ^b
3	мео-		99% ^c	73% ^c
4	Br-() 16		98% ^b	75% ^b
5	MeOOC	меоосон 23	99% ^b	76% ^b
6	ноос-	ноосОн	81% ^b , 99% ^d	76% ^d
7		25 ^{OH}	85% ^e	60% ^e
8	14	Состон 26	85% ^b	60% ^{b,f}
9		он 9b	99% (33% 9a , 66% 9b) ^e	21% 9a , 45% 9b ^e
10		OH	98% (95% 10a , 5% 10b) ^g	65% ^g
11	5	10а Он 8а	99% (88% 8a , 12% 8b) ^b	75% ^b

Table 2. Substrate scope of the catalytic FLP hydrogenation with 4a,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, 40h, 10 mol% catalyst **4a**, 20 bar, 55°C. ^c Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 40h, 10 mol% catalyst **4a**, 20 bar, 80°C. ^d

ACS Catalysis

Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 136h, 10 mol% catalyst **4b**, 100 bar, 55°C. ^e Reaction conditions: 1.0 mmol substrate in 1.25 mL of THF, 137h, 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 Et₂O, 88 h, 10 mol% catalyst **4a**, 20 bar, 55°C.

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-^tBu-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 glove box and stored in an open vial, it quickly, within a few hours, absorbed 1.5 equivalent 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 one 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
eff	iciently	(ent	ry 5).									

Entry	Catalyst	Solvent	Substrate	Product	Conversion ^b		
1	4a	THF		ОН	99%		
			5	8 a			
2	4a	THF	O ₂ N	O ₂ N-	99%		
			11	19			
3	4a	THF	ci-	CI	99%		
			12	20			
4	4a	THF	MeOOC	MeOOC	99%		
			13	23			
5	4a	THF	O O	ОН	99% ^c		
			14	26			
6	1a	1,4-		ОН	29%		
-		dioxane	5	8 a			
7	19	1,4-		OH OH	5% ^d		
/	14	dioxane	5	8a	570		
				<u></u> Он			
8	1 a	THF	5	8 a	18%		
				,── OH			
9	1 a	THF			$0\%^{d}$		
,	14	1111	5	ða			

Table 3. Investigation of the moisture tolerance in the FLP hydrogenation of carbonyls.^a

^a Reaction conditions: 1.0 mmol substrate in 1.25 mL of puriss. grade THF, 50 °C, 40h, 10 mol% $4a \cdot 1.5 H_2O$, 100 bar H₂. ^b All conversions were determined by ¹H-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.

Since the desired catalytic reduction could be performed when more than one and half equivalent of water to the borane **4a** was present, our catalyst development rendered the water binding to **4a**

Page 11 of 20

ACS Catalysis

reversible in the applied etheral-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 glove box and Schlenk-line technique) during the entire synthetic operation. So, 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.

3.3 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 ¹⁰B NMR spectroscopy at 20 °C and 50 °C 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 ($\delta = 63.4$ ppm for free **4a** in benzene).^[16] Finally, the complexation capacity of water was assessed by using 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 hours and cooled back to 20 °C.^[16]



Figure 1.¹⁰B NMR complexation study of borane **4a**, ¹⁰B NMR spectra in THF at 20 °C – blue lines and at 50 °C -red lines: (a) borane **4a**, (b) 4a and 10 equiv. benzaldehyde (**5**), (c) **4a** and 10 equiv. benzaldehyde (**5**), (d) **4a** and 3 equiv. water, (e) **4a** and 3 equiv. water and 10 equiv. benzaldehyde (**5**).

Datively bound 1:1 complexes formed between borane **4a** and selected oxygen-based Lewis bases (**5**, **8a**, THF and H₂O) 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-**H₂O(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). While water tends to form a moderately

 strong adduct with **4a** (with association free energy of $\Delta G = -5.3$ kcal/mol), the more acidic boranes, **1e**, but especially **1a**, gave notably stronger THF-stabilized water complexes ($\Delta G = -8.0$ 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 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 H₂ splitting, which may occur via two alternative pathways corresponding to H₂ activation by the **4a**/THF and **4a**/**5** pairs. According to the computed free energies, H₂ activation by **4a**/THF is clearly favored kinetically (computed barriers are 21.5 and 25.1 kcal/mol, respectively).



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.

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 H₂ 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, therefore, the hydride transfer from $[4a-H]^{-}$ can easily occur 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.



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

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 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

The Supporting Information is available free of charge on the ACS Publication website at DOI:

Detailed synthesis of the new boranes with their full characterization, reaction conditions and NMR spectra, detailed NMR investigation of borane (4a)-H₂O complex, theoretical studies, calculation data, and supplementary figures

AUTHOR INFORMATION

Corresponding Author

*E-mail: <u>soos.tibor@ttk.mta.hu</u>, <u>papai.imre@ttk.mta.hu</u>. Tel.: +36-1-382-6401, +36-1-382-6979.

ACKNOWLEDGEMENT

Á. Gy., M. B., and T. S. acknowledge the Lendület program for financially supporting this work.

This work was also supported by the Hungarian Scientific Research Fund (OTKA, K-81927).

REFERENCES

(1) Pioneering work: a) Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124. Reviews on FLP chemistry: b) Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2015**, *54*, 6400–6441. c) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 306–316. d) Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 46–76. e) Flynn, S. R.; Wass, D. F. *ACS Catal.*, **2013**, *3*, 2574–2581. f) *Frustrated Lewis Pairs I-II*, Erker, G.; Stephan, D. W., Eds.; Top. Curr. Chem., Springer: Heidelberg, **2013**.

(2) Recent selected examples of FLP reactivities: a) Chernichenko, K.; Kótai, B.; Pápai, I.; Zhivonitko, V.; Nieger, M.; Leskelä, M.; Repo, T. Angew. Chem. Int. Ed. 2015, 54, 1749; Forrest, S. J. K.; Clifton, J.; Fey, N.; Pringle, P. G.; Sparkes, H. A.; Wass, D. F. Angew. Chem. Int. Ed. 2015, 54, 2223-2227. c) Longobardi, L. E.; Wolter, V.; Stephan, D. W. Angew. Chem. Int. Ed. 2015, 54, 809-812. d) Xu, X.; Kehr, G.; Daniliuc, C. G.; Erker, G. J. Am. Chem. Soc. 2014, 136, 12431–12443. e) Courtemanche, M.-A.; Legare, M.-A.; Maron, L.; Fontaine, F.-G. J. Am. Chem. Soc. 2014, 136, 10708–10717. f) Liedtke, R.; Scheidt, F.; Ren, J.; Schirmer, B.; Cardenas, A. J. P.; Daniliuc, C. G.; Eckert, H.; Warren, T. H.; Grimme, S.; Kehr, G.; Erker, G. J. Am. Chem. Soc. 2014, 136, 9014–9027. g) Holthausen, M. H.; Mahdi, T.; Schlepphorst, C.; Hounjet, L. J.; Weigand, J. J.; Stephan, D. W. Chem. Commun. 2014, 50, 10038-10040. h) Stephan, D. W.; Erker, G. Chem. Sci. 2014, 5, 2625-2641. i) Klatt, T.; Markiewicz, J. T.; Samann, C.; Knochel, P. J. Org. Chem. 2014, 79, 4253–4269. j) Lawrence, E. J.; Oganesyan, V. S.; Hughes, D. L.; Ashley, A. E.; Wildgoose, G. G. J. Am. Chem. Soc. 2014, 136, 6031-6036. k) Sajid, M.; Kehr, G.; Daniliuc, C. G.; Erker, G. Angew. Chem. Int. Ed. 2014, 53, 1118-1121. 1) Wang, X.; Kehr, G.; Daniliuc, C. G.; Erker, G. J. Am. Chem. Soc. 2014, 136, 3293-3303. m) Xu, T.; Chen, E. Y.-X. J. Am. Chem. Soc. 2014, 136, 1774–1777. n) Pereira, J. C. M.; Sajid, M.; Kehr, G.; Wright, A. M.; Schirmer, B.; Qu, Z.-W.; Grimme, S.; Erker, G.; Ford, P. C. J. Am. Chem. Soc. 2014, 136, 513–519. o) Sajid, M.; Lawzer, A.; Dong, W.; Rosorius, C.; Sander, W.; Schirmer, B.; Grimme, S.; Daniliuc, C. G.; Kehr, G.; Erker, G. J. Am. Chem. Soc. 2013, 135, 18567–18574. p) Li, H.; Aquino, A. J. A.; Cordes, D. B.; Hung-Low, F.; Hase, W. L.; Krempner, C. J. Am. Chem. Soc. 2013, 135, 16066-16069. q) Unsinn, A.; Wunderlich, S. H.; Jana, A.; Karaghiosoff, K.; Knochel, P. Chem. Eur. J. 2013, 19, 14687-14696. r) Piedra-Arroni, E.; Ladaviere, C.; Amgoune, A.; Bourissou, D. J. Am. Chem. Soc. 2013, 135, 13306-13309. s) Kelly, M. J.; Gilbert, J.; Tirfoin, R.; Aldridge, S. Angew. Chem. Int. Ed. 2013, 52, 14094-14097. t) Mahdi, T.; Stephan, D. W. Angew. Chem. Int. Ed. 2013, 52, 12418-12421. u) Jiang, Y.; Blacque, O.; Fox, T.; Berke, H. J. Am. Chem. Soc. 2013, 135, 7751-7760. v) Menard, G.; Hatnean, J. A.; Cowley, H. J.; Lough, A. J.; Rawson, J. M.; Stephan, D. W. J. Am. Chem. Soc. 2013, 135, 6446–6449. w) Holtrichter-Rosmann, T.; Isermann, J.; Rosener, C.; Cramer, B.; Daniliuc, C.-G.; Kosters, J.; Letzel, M.; Wurthwein, E.-U.; Uhl, W. Angew. Chem. Int. Ed. 2013, 52, 7135–7138. x) Groll, K.; Manolikakes, S. M.; Jourdin, X. M.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. Angew. Chem. Int. Ed. 2013, 52, 6776-6780.

(3) Recent investigations about the activation mode of FLP: a) Pu, M.; Privalov, T. ChemPhysChem 2014, 15, 3714–3719. b) Pu, M.; Privalov, T. Inorg. Chem. 2014, 53, 4598–

4609. c) Rocchigiani, L.; Ciancaleoni, G.; Zuccaccia, C.; Macchioni, A. J. Am. Chem. Soc. 2014, 136, 112–115. d) Ponec, R.; Beran, P. J. Phys. Chem. A 2013, 117, 2656–2663. e) Rokob, T. A.; Bakó, I.; Stirling, A.; Hamza, A.; Pápai, I. J. Am. Chem. Soc. 2013, 135, 4425–4437. f) Zeonjuk, L. L.; Vankova, N.; Mavrandonakis, A.; Heine, T.; Roschenthaler, G.-V.; Eicher, J. Chem. Eur. J. 2013, 19, 17413–17424. g) Dang, L. X.; Schenter, G. K.; Chang, T.-M.; Kathmann, S. M.; Autrey, T. J. Phys. Chem. Lett. 2012, 3, 3312–3319. h) Wiegand, T.; Eckert, H.; Ekkert, O.; Frohlich, R.; Kehr, G.; Erker, G.; Grimme, S. J. Am. Chem. Soc. 2012, 134, 4236–4249.

(4) a) Shi, L.; Zhou, Y.-G. *ChemCatChem* **2015**, *7*, 54–56. b) Hounjet, L. J.; Stephan, D. W. Org. Process Res. Dev. **2014**, *18*, 385–391. c) Paradies, J. *Angew. Chem Int. Ed.* **2014**, *53*, 3552–3557. d) Fontaine, F.-G.; Courtemanche, M.-A.; Legare, M.-A. *Chem. Eur. J.* **2014**, *20*, 2990–2996. e) Stephan, D. W. *Org. Biomol. Chem.* **2012**, *10*, 5740-5746.

(5) Recent examples of FLP mediated reductions: a) Tussing, S.; Greb, L.; Tamke, S.; Schirmer, B.; Muhle-Goll, C.; Luy, B.; Paradies, J. Chem. Eur. J. 2015, 21, 8056-8059. b) Lindqvist, M.; Borre, K.; Axenov, K.; Kótai, B.; Nieger, M.; Leskelä, M.; Pápai, I.; Repo, T. J. Am. Chem. Soc. 2015, 137, 4038-4041. c) Eisenberger, P.; Bestvater, B. P.; Keske, E. C.; Crudden, C. M. Angew. Chem. Int. Ed. 2015, 54, 2467-2471. d) Chatterjee, I.; Oestreich, M. Angew. Chem. Int. Ed. 2015, 54, 1965–1968. e) Zhang, Z.; Du, H. Angew. Chem. Int. Ed. 2015, 54, 623-626. f) Mohr, J.; Oestreich, M. Angew. Chem. Int. Ed. 2014, 53, 13278-13281. g) Clark, E. R.; Ingleson, M. J. Angew. Chem. Int. Ed. 2014, 53, 11306-11309. h) Kalz, K. F.; Brinkmeier, A.; Dechert, S.; Mata, R. A.; Meyer, F. J. Am. Chem. Soc. 2014, 136, 16626-16634. i) Wei, S.; Du, H. J. Am. Chem. Soc. 2014, 136, 12261-12264. j) Wang, G.; Chen, C.; Du, T.; Zhong, W. Adv. Synth. Catal. 2014, 356, 1747–1752. k) Jochmann, P.; Stephan, D. W. Angew. Chem. Int. Ed. 2013, 52, 9831–9835. 1) Chernichenko, K.; Madarász, A.; Pápai, I.; Nieger, M.; Leskelä, M.; Repo, T. Nat. Chem. 2013, 5, 718–723. m) Hounjet, L. J.; Bannwarth, C.; Garon, C. N.; Caputo, C. B.; Grimme, S.; Stephan, D. W. Angew. Chem. Int. Ed. 2013, 52, 7492–7495. n) Wang, Y.; Chen, W.; Lu, Z.; Li, Z. H.; Wang, H. Angew. Chem. Int. Ed. 2013, 52, 7496-7499. o) Menard, G.; Tran, L.; Stephan, D. W. Dalton Trans. 2013, 42, 13685-13691. p) Ines, B.; Palomas, D.; Holle, S.; Steinberg, S.; Nicasio, J. A.; Alcarazo, M. Angew. Chem. Int. Ed. 2012, 51, 12367-12369. r) Mahdi, T.; Heiden, Z. M.; Grimme, S.; Stephan, D. W. J. Am. Chem. Soc. 2012, 134, 4088-4091.

(6) a) Scott, D. J.; Fuchter, M. J.; Ashley, A. E. J. Am. Chem. Soc. 2014, 136, 15813–15816.
b) Mahdi, T.; Stephan, D. W. J. Am. Chem. Soc. 2014, 136, 15809–15812. c) Mahdi, T. Stephan D. W. Angew. Chem. Int. Ed. 2015, 54, 8511–8514. d) For non-catalytic version, see: Lindqvist, M.; Sernala, N.; Sumerin, V.; Chernichenko, K.; Leskelä, M.; Repo, T. Dalton Trans. 2012, 41, 4310-4312. e) Britovsek, G. J. P.; Ugolotti, J.; White, A. J. P. Organometallics 2005, 24, 1685–1691. f) Longobardi, L. E.; Tang, C.; Stephan, D. W. Dalton Trans. 2014, 43, 15723–15726.

(7) The coordination of water to **1a** is known to be reversible in toluene. Accordingly without appropriately strong base, the water binding to this borane is reversible (for a relevant work, see: Bergquist, C.; 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 coworkers when adding 1.0 equiv. of water to 1e/dioxane FLP hydrogenation catalyst (see in ref. 6a).

(8) a) Greb, L.; Daniliuc, C.-G.; Bergander, K.; Paradies, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 5876–5879. b) Greb, L.; Daniliuc, C.-G.; Bergander, K.; Paradies, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 5876–5879. c) Nicasio, J. A.; Steinberg, S.; Ines, B.; Alcarazo, M. Chem. Eur. J. **2013**, *19*, 11016–11020.

(9) a) Erős, G.; Nagy, K.; Mehdi, H.; Pápai, I.; Nagy, P.; Király, P.; Tárkányi, G.; Soós, T. *Chem. Eur. J.* **2012**, *18*, 574–585. b) Soós, T. *Pure Appl. Chem.* **2011**, *83*, 667–675. c) Erős, G.; Mehdi, H.; Pápai, I.; Rokob, T. A.; Király, P.; Tárkányi, G.; Soós, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 6559–6563.

(10) a) Scott, D. J.; Fuchter, M. J.; Ashley, A. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 10218–10222. b) Ashley, A. E.; Herrington, T. J.; Wildgoose, G. G.; Zaher, H.; Thompson, A. L.; Rees, N. H.; Kraemer, T.; O'Hare, D. J. Am. Chem. Soc. **2011**, *133*, 14727–14740.

(11) Ashley and coworkers 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 that might be the reason that it was less efficient donor solvent for catalysis in case of 1a (see also ref. 6a).

(16) For more details see the Supporting Information.

(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).

TABLE OF CONTENT:



ACS Paragon Plus Environment