HYDROGEN AND WATER SPLITTING BY FRUSTRATED LEWIS PAIRS AND REACTIONS THEREOF

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DOCTORAL DISSERTATION

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ABSTRACT

The principle of combining a Lewis acid (LA) and a Lewis base (LB), prevented from the formation of classical Lewis adduct and thus possessing reactive potential, is known as frustrated Lewis pair (FLP). This powerful, yet simple concept allowed for a wide range of reactivities unprecedented for main group chemistry and is perceived as an alternative to transition metal catalysis. Among such reactivities, hydrogen activation and catalytic hydrogenations of unsaturated organic substrates, perhaps remain the most remarkable ones.

In the literature review, our focus is limited to hydrogen activation and reactions thereof, and furthermore, FLPs comprising boron-centered LAs. First, mechanistic aspects of the process are discussed, including principles of assessment and modulation of Lewis acidity. Further, the review covers hydrogenation catalysis with FLPs, including hydrogenation of polar and non-polar substrates, functional group- and moisture- tolerant catalysts, and enantioselective hydrogenations. A separate section is devoted to intramolecular FLPs as a distinct subclass of FLPs.

The results and discussion part summarizes the key findings reported in the attached original publications and can be divided into two subtopics. First is devoted to the development of linked FLPs aimed for generation of parahydrogen-induced hyperpolarization (PHIP). The phenomenon occurs upon parahydrogen (p-H₂) pairwise splitting and causes substantial amplification of NMR signals of p-H₂ originating fragments and neighboring nuclei. Therefore, the method can be promising for sensitivity enhancement in, e.g., NMR (MRI) signal imaging. In this work, the series of phenylene bridged ansa-aminoboranes (AABs) varied in the chemical environment around B were synthesised, and their ability to generate PHIP upon addition of p-H₂ at ambient conditions was demonstrated. Kinetic, thermodynamic, and NMR parameters favorable for the efficient production of PHIP with such FLPs were formulated. Replacement of quadrupolar ¹⁴N nucleus of the amine site with ¹⁵N in the series led to spontaneous polarization transfer to nitrogen and strong signal enhancements. Further efforts were dedicated to overcoming the incompatibility of ansa-FLPs with water, bringing closer their realization as PHIP contrast agents in biologically relevant media. In this regard, thorough design of LA-LB active sites resulted in ansa-phosphinoborane capable of both H₂ and H₂O splitting in a reversible manner. Quite unexpectedly, this compound featured stoichiometric reduction of H₂O to H₂ via a proton “umpolung” mechanism.

The second part is devoted to synthesizing (+)-camphor-based chiral boranes for asymmetric hydrogenation of imines. This study resulted in a highly enantioselective catalyst easily accessible from the synthetic point of view and shed light on the origin of the enantioselectivity.
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


VI **Kristina Sorochkina**, Konstantin Chernichenko, Vladimir Zhivonitko, Martin Nieger, and Timo Repo. Water reduction and hydrogen addition in aqueous conditions with ansa-phosphinoborane, *under preparation*

The publications are referred to in the text by their roman numerals.
AUTHOR’S CONTRIBUTION

**Paper I:** The author performed the syntheses, characterizations, and preliminary experiments with dihydrogen under the supervision of Dr. K. Chernichenko and Prof. T. Repo. Dr. B. Kótai, T. Földes and Prof. I. Papai carried out computational work. Assoc. Prof. V. Zhivonitko performed and analysed PHIP experiments with the help of V.-V. Telkki and I. Koptyug, and drafted the manuscript. All authors took part in the manuscript revision.

**Paper II:** The author performed minor syntheses and analyses. Dr. Chernichenko performed major experimental work with the help of Dr. M. Lindqvist. Dr. M. Nieger performed the X-ray structural analysis. Dr. B. Kótai and Prof. I. Pápai carried out computational work. Prof. T. Repo supervised the study.

**Paper III:** The author performed synthesis, characterization, and preliminary experiments with dihydrogen under the supervision of Dr. K. Chernichenko and Prof. T. Repo. Assoc. Prof. V. Zhivonitko performed PHIP and thermochemistry experiments and drafted the manuscript. All authors took part in the manuscript revision.

**Paper IV:** The author performed experimental work and drafted the manuscript under the supervision of Dr. K. Chernichenko and Prof. T. Repo. Dr. M. Nieger performed the X-ray structural analysis. Dr. K. Chernichenko carried out computational work. All authors took part in the manuscript revision.

**Paper V:** The author performed experimental work under Dr. K. Chernichenko and Prof. T. Repo's supervision and drafted corresponding part of the manuscript. Dr. M. Nieger and Dr. M. Bolte performed the X-ray structural analysis. Dr. A. Hamza carried out computational studies with the help of Dr. B. Kótai and D. Berta. Prof. I.Papai drafted theoretical part of the manuscript. All authors took part in the manuscript revision.

**Paper VI:** The author performed experimental work under Dr. K. Chernichenko and Prof. T. Repo's supervision and drafted the manuscript. Dr. K. Chernichenko carried out computational studies. Assoc. Prof. V. Zhivonitko performed PHIP experiments. Dr. M. Nieger performed the X-ray structural analysis. All authors took part in the manuscript revision.
ABBREVIATIONS

AAB – ansa-aminoboranes
Alk – alkyl
Ar – aryl
Bn – benzyl
bPh – biphenyl
(t)Bu – (tert-)butyl
CPME – cyclopentyl methyl ether
Cy – cyclohexyl
DABCO – 1,4-diazabicyclo[2.2.2]octane
Dipp – 2,6-diisopropylphenyl
DFT – density functional theory
DQF OPSY – double-quantum filtering only parahydrogen spectroscopy
EC – encounter complex
Et – ethyl
ee – enantiomeric excess
eq. – equivalent
EWG – electron-withdrawing group
ΔG – Gibbs free energy
ΔH – enthalpy change
HIA – hydride ion affinity
HOESY – heteronuclear Overhauser effect spectroscopy
HOMO – highest occupied molecular orbital
iPr – prop-2-yl
Fc – ferrocene
FIA – fluoride ion affinity
FLP – frustrated Lewis pairs
FRP – radical frustrated pairs
GEI – global electrophilicity index
HIA – hydride ion affinity
HSAB – hard and soft acid base theory
ItBu – N,N-di(tert-butyl)imidazol-2-ylidene
LA – Lewis acid
LB – Lewis base
LUMO – lowest occupied molecular orbital
MD – molecular dynamics
Me – methyl
Mes – mesityl, 2,4,6-trimethylphenyl
MRI – magnetic resonance imaging
MS – molecular sieves
NMR – nuclear magnetic resonance
Ph – phenyl
PHIP – parahydrogen-induced hyperpolarization
PMP – para-methoxyphenyl
ppm – part per million
PTFE – polytetrafluoroethylene
RT – room temperature
(S,S)-diop - 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
SET – single electron transfer
Ts – tosyl
TBAF – tetra-n-butylammonium fluoride
TMS – trimethylsilyl
TS – transition state
PMP – 4-methoxyphenyl
TMP – 2,2,6,6-tetra-methylpiperidine
1 INTRODUCTION

When combined in the solution, Lewis acid (LA) and Lewis base (LB) usually form Lewis adduct, and, consequently, their reactivity is quenched. However, the formation of Lewis adduct can be precluded by sufficient steric hindrance, preserving acidity of LA and basicity of LB. While this was known since the 1940s, only six decades later, it was discovered that a combination of sterically separated LA and LB can unleash its reactive potential upon heterolytic splitting of $\sigma$- and $\pi$-bonds (Fig. 1). Such reactivity was translated into a powerful concept known as frustrated Lewis pairs (FLPs).

![Figure 1](image_url)

The majority of FLPs derive from abundant main group elements and exhibit a spectacular range of reactivities, making them a potential alternative for transition metal catalysis. FLP reaction types can be categorized into 3 classes (Fig. 2):

a) Heterolytic splitting of $\sigma$-bonds (Fig. 2, A). Such reactivity commonly occurs with sufficiently acidic bonds: $\text{H}_2$, $\text{XH}$ (X=halogen, OH, OR), $\text{spC-H}^{2-4}$ and $\text{sp}^2\text{C-H}$-bonds. FLPs also commonly react with hydridic bonds such as B-$\text{H}$ bonds of boranes$^{5, 6}$ and Si-$\text{H}$ bonds of silanes.$^{7-9}$ Cleavage of heteroatomic bonds such as $\text{C-F}^{10, 11}$ and S-S in disulfides$^{12}$ was also reported.

b) Dipolar addition to unsaturated compounds (Fig. 2, B-B”). 1,2-Addition was reported with alkenes and alkynes, C=O bond containing compounds including $\text{CO}_2$,$^{13-15}$ with isothiocyanates,$^{14}$ nitroso compounds,$^{13}$ and $\text{SO}_2$. 1,3-Addition occurs with $\text{N}_2\text{O}$.$^{17, 18}$
c) 1,1-Addition (Fig. 2, C’). Such reactivity was reported with NO, CO, difluorocarbene and azides.

Despite the diverse range of FLP reactivities, only a few were translated into practically important transformations. Among them, hydrogen activation and hydrogenation catalysis are particularly developed.

The landmark discovery reported by Stephan et al. in 2006 described the first example of a metal-free system, namely phosphinoborane 1, which could heterolytically split H₂ in a reversible manner (Fig. 3). Subsequent reports on H₂ splitting by ethylene bridged P/B system and simple combinations of sterically demanding boranes and phosphines or amines demonstrated the generality of the FLP notion. Concurrently, 1 was shown to affect catalytic hydrogenation of bulky imines, aziridines, and protected nitriles.

Triarylboranes dominate FLP chemistry as Lewis acidic components due to their robustness, hydrolytic stability, and synthetic accessibility. The library of the boranes utilized in FLPs is rapidly expanding, yet, commercial and its derivatives perhaps remain the most common. The range of LAs beyond boranes comprises neutral Al, Ga, In, Sn, cationic borenium,
phosphonium\textsuperscript{9}, silylium\textsuperscript{36, 37} and methylacridinium\textsuperscript{38} species. Lewis bases are typically represented by bulky amines, phosphines and less often by ethereal bases. Examples of more exotic LBs in FLPs include N-heterocyclic carbenes\textsuperscript{39, 40} and silylenes.\textsuperscript{37, 41} Transition metal-centered LAs and LBs were also actively explored in FLP chemistry.\textsuperscript{42, 43}

Besides impressive expansion throughout the periodic table and broadening the scope of transformations enabled by FLPs, the paradigm itself is conceptually evolving. It was realized that sterical “frustration” is not a prerequisite for FLP reactivity. For instance, even robust classical Lewis adducts such as of 6 with Verkade’s base P(MeNCH\textsubscript{2}CH\textsubscript{2})\textsubscript{3}N undergo FLP reactions under ambient conditions.\textsuperscript{44} Reactive FLPs can be generated from classical Lewis adducts upon external stimuli such as light or heat, which opens possibility of controlled/switchable reactivity.\textsuperscript{45, 46} More recently there has been growing interest in radical frustrated pairs (RFP), a concept that has emerged from the initial observation that single electron transfer (SET) may occur within classical FLP systems.\textsuperscript{47} The ability of RFP to operate by a radical mechanism has been already utilized for a few synthetic transformations,\textsuperscript{48, 49} and more advances are expected here.\textsuperscript{50}
2 SCOPE OF THE THESIS

This work is a continuation of the pioneering research conducted by our group in the field of FLP chemistry. The present thesis focuses on the heterolytic splitting of hydrogen by boron-centred FLPs and its further utilization in 1) NMR signal amplification employing parahydrogen-induced hyperpolarization (PHIP) and 2) asymmetric hydrogenations. Moisture sensitivity of FLPs is one of the major obstacles for their practical implementations, and in particular, for the realization of FLP mediated PHIP in biologically relevant media. Therefore, much work has been directed towards inhibiting interactions of FLPs of our interest with water.

The results and discussion part describes the central findings reported in the attached original publications I-VI. In publications I and II (partly), the family of ansa-aminoboranes with altered aromatic substituents at boron site were explored. Publication I discloses a detailed study on their interaction with normal hydrogen and parahydrogen. Here, the common ability of ansa-aminoboranes to produce PHIP in a continuous manner is demonstrated, and kinetic and thermodynamic parameters of hydrogen splitting are derived using NMR spectroscopy. In publication II, one of the family members is reported in the context of internal sp²C-H bond borylation, illustrating the unique ability of such metal-free systems to cleave relatively strong C-H bonds. In publication III, ¹⁵N labeled analog ansa-aminoboranes were synthesized and subjected to PHIP experiments. Here, substantially higher NMR signal enhancements are achieved due to the replacement of quadrupolar ¹⁴N nucleus and spontaneous polarization transfer to ¹⁵N nuclei. Publication IV reports ansa-phoshinoborane, which does not react with hydrogen or water. Being in sharp contrast with the high moisture sensitivity of N-centred analogs reported in publications I-III, this observation shifted our interest towards P-centred ansa-systems. In the publication VI, more Lewis acidic at boron site ansa-phosphinoborane is shown to split both hydrogen and water reversibly. It also featured unprecedented stoichiometric reduction of water to molecular hydrogen. The reaction mechanism is investigated by kinetic and computational studies. Finally, in publication V, a highly enantioselective catalyst in the hydrogenation of imines, (+)-camphor-based chiral borane, is reported together with detailed computational studies on the origin of enantioselectivity.
3 LITERATURE REVIEW

3.1 MECHANISTIC BASIS OF H₂ SPLITTING BY FLPs

3.1.1 THERMODYNAMIC CONSIDERATIONS

Due to the simplicity of H₂ splitting by FLPs, its thermodynamic analysis is relatively simple and accurate. Papai et al. reported solvent-phase Gibbs free energies ($\Delta G$) of H₂ splitting calculated for a large set of reported inter- and intramolecular FLPs. Calculated $\Delta G$ fall in a wide range from +30 to -40 kcal/mol. Computed energies, with few exceptions, are consistent with observed reactivities: negative values were obtained for the reactive systems, and positive (typically above 10 kcal/mol) for unreactive ones, while values for the systems which activate H₂ reversibly lay slightly below zero (-0.1 to -2.5 kcal/mol). The overall process of H₂ addition to non-linked D/A or linked D~A pairs (where D is a donor (LB) and A is an acceptor (LA)) can be split into several chemically meaningful steps. The respective partitioning scheme depicted in Fig. 4 includes the following steps: FLP preparation (dative bond breaking), heterolytic H₂ bond cleavage, proton attachment to base, hydride attachment to acid, and stabilizing interactions associated with the formation of ionic pair. Cleavage of H₂ is the most energy consuming step with calculated value of $\Delta G_{HH} = +128,8$ kcal/mol in toluene and is constant for all FLPs. The additional energy $\Delta G_{prep}$ is required for dissociation of a weak adduct of LA and LB if such adduct is formed (0-12 kcal/mol for most FLPs).

![Diagram](image)

**Figure 4** Partitioning of the reaction free energy using Born-Haber cycle formalism. D: donor (Lewis base); A: acceptor (Lewis acid).
These two endergonic steps have to be counterbalanced by the negative energy values of the last three steps to achieve favorable thermodynamics of H₂ cleavage. Protonation of D and hydride attachment to A is the major exergonic steps in the cycle. Corresponding ΔG_{pa} and ΔG_{ha} values are Gibbs free energies of the proton affinity of the donor (PA, basicity) and hydride affinity of the acceptor (HA, hydricity) reflecting on the Lewis donor and acceptor strengths, respectively.

Calculated basicities are plotted on an energy scale in Fig. 5. The values corresponding to conventional amines, phosphines, and their derivatives within linked systems range from -60 to -40 kcal/mol. Carbo[n]e[I]tBu stands out as most basic (ΔG_{pa} = -80 kcal/mol) and least basic (C₆F₅)₃P (ΔG_{pa} = -7 kcal/mol) lies on the opposite edge of the scale.

Reported hydricity values⁵¹, ⁵⁴ are summarized on an energy scale in Fig. 6. The scale starts from parental B(C₆F₅)₃ (ΔG_{pa} = -72.5 kcal/mol), followed by its intramolecular derivatives from the substitution of one p-F with phosphino group. Other intramolecular boranes bearing two C₆F₅ rings lie in a fairly narrow range of ΔG_{pa} = -60 to -55 kcal/mol. In the series of non-linked boranes on the scale, hydricity gradually reduces with decreasing number of halogens in the aromatic rings. In fact, boranes with lower (stronger) calculated hydricity than this of 6 have been reported more recently and discussed in section 3.1.3.

Basicities and hydricities strongly depend on the electron effect of substituents: electron-withdrawing groups increase the strength of LA and decrease the strength of LB; the effect is opposite for electron-donating substituents. In the series, non-linked boranes acidity gradually drops with decreasing number of halogens, but also steric plays a remarkable role.

![Figure 5](image)  
**Figure 5** Calculated Gibbs free energies of proton attachment to the Lewis donor. ⁵¹
The final term $\Delta G_{\text{stab}}$ represents Gibbs free energy of the formation of ion pair from separated ions $\text{DH}^+$/A$^-$ or $\text{A}^-$/D$^+$. For intermolecular systems it is binding free energy, including a positive entropic term as two ions associate into one ionic complex. Quantitative analysis $\Delta G_{\text{stab}}$ values account for a narrow range of -14 to -24 kcal/mol presumably due to the structural similarity of the considered pairs (neutral charge, shielding bulky substituents, narrow distribution of distances $d_{\text{DA}}$). For intermolecular systems stabilization effect $\Delta G_{\text{stab}}$ is thought to be an interplay of multiple weak interactions, such as electrostatics, dispersion, repulsion, solvation effects, etc. For instance, weak correlation between $\Delta G_{\text{stab}}$ and reciprocal distances $1/d_{\text{DA}}$, observed in the gas phase, becomes undetectable in the solvent phase. For intramolecular systems $\Delta G_{\text{stab}}$ is reasoned differently; namely, it measures how much hydride attachment enhances basicity ($\text{D}^-\text{A}$ vs. $\text{D}^-\text{AH}^-$), and proton attachment enhances acidity ($\text{D}^-\text{A}$ vs. $\text{A}^-\text{DH}^+$), reflecting acid-base cooperative effect. Stabilization interaction $\Delta G_{\text{stab}}$ of the linked systems falls in a broader range (-21 to -65 kcal/mol) and is substantially stronger. Such difference is presumably attributed to the aforementioned cooperative effect and smaller entropic loss: in the last step number of species does not change, unlike for intermolecular systems. Additionally, $\Delta G_{\text{stab}}$ showed a linear correlation with $1/d_{\text{DA}}$, pointing that the acid/base cooperation is distance-dependent.

This analysis revealed the fundamental difference between inter- and intramolecular systems: for the former (unless they form a dative complex and somewhat resembles intramolecular case), thermodynamics is determined by cumulative acid-base strength, while for later, $\Delta G_{\text{stab}}$ makes a significant contribution and can even become a decisive factor for overall thermodynamics. This peculiarity was utilized in the design of intramolecular FLPs with substantially less acidic boryl sites.55
3.1.2 KINETIC CONSIDERATIONS

Direct kinetic exploration of FLP reactions with H₂ due to experimental constraints related to adding gaseous and poorly soluble H₂ to the reaction mixture and controlling its concentration; eventually, the reaction rate can become diffusion controlled. For this reason, mechanistic views on hydrogen splitting and hydrogenation pathways primarily rely on computational studies.

Splitting H₂ by non-linked FLPs involves three molecules and is typically rapid under mild conditions. Due to the low probability of termolecular collision scenario, the process was postulated to be stepwise, comprising the association of two reactants before the reaction with the third. The possibility of binary interaction binding of H₂ to borane or a base (phosphine) has experimental grounds. Adducts H₂…BH₃⁵⁶ and R₃P…H₂⁵⁷ were detected in an argon matrix. Activation of H₂ in some cases occurs in the absence of base: as with antiaromatic boroles,⁵⁸, ⁵⁹ or with boranes (MesF)₂BD,⁶⁰ DB(C₆F₅)₂ and BD₃-THF⁶¹, which undergo D/H exchange under H₂ pressure to form analog hydroboranes. However, mechanistic investigations accompanying these examples suggest that observed reactivities arise from specific structural features and can not be generalized for all FLPs.

Computational studies of prototypical reaction ⁵/⁶+H₂ in the gas phase revealed that H₂ interactions with either borane or phosphine are repulsive. Rather loosely bound complex ⁵-⁶ (Fig. 7), known as encounter complex (EC), was located at the minima of the potential energy surface.⁶² The EC is characterized by P-B distance 4 Å and weak overlap of P/B frontier orbitals. The association energy was found to be 11-15 kcal/mol, depending on the level of calculations,⁶²-⁶⁵ and arises from multiple weak C-H…F interactions and dispersion forces (presumably lp-π interaction between phosphorus lone pair and C₆F₅ ring)⁶³. Varying P-B distance within the range of 3.7 -4.7 Å corresponds to only 2 kcal/mol interval on the energy scale, reflecting the high structural flexibility of the EC.

![Figure 7](image)

**Figure 7** Preassociation of FLP components into EC is proposed to rationalize high reactivity towards H₂.

The second step of the process is hydrogen splitting. For the ⁵/⁶+H₂ system, a single early transition state TS1 (TS) was located 10.4 kcal/mol above reactants EC+H₂.⁶² It featured nearly linear PHHB unit and maintained CH···F
and van der Waals contacts between the phosphine and borane molecules as in EC. A later study on 5/6 and other FLPs conducted at higher level of theory provided more accurate structural parameters for corresponding TSs; in particular, the PHHB unit appeared to be L-shaped (Fig. 8).\textsuperscript{66} All computed TSs\textsuperscript{52, 62, 64, 66} feature the following geometry: 1) H\textsubscript{2} molecule is slightly stretched, suggesting an early TS (0.77-0.99 Å) 2)D–H (where D is P- or N-centered donor) and H–B distances shorter than the sum of van der Waals radii, meaning that H\textsubscript{2} interacts simultaneously with donor and acceptor centers 3) DHH unit is nearly linear and HHB unit notably bent 4) borane unit is pyramidalized. Analysis of the TS electronic structure revealed notable HH bond polarization featuring bond orders 0.7-0.8. From a molecular orbital point of view synergetic electron transfer from lone pair orbital of the Lewis base to $\sigma^*$($H_2$) and from $\sigma$($H_2$) to the empty orbital of the Lewis acid, leading to polarization, weakening and ultimate heterolytic HH bond cleavage. Thus, H\textsubscript{2} molecule acts as a bridge between the phosphine and borane fragments, enabling an electron transfer that was prevented in the frustrated complex.

Presumably, the preorganization of active sites and flexibility of the EC ensures its rapid interaction with upcoming H\textsubscript{2}. Calculated activation barriers are quite low: 0-8 kcal above EC+H\textsubscript{2} for most of the calculated TSs. The distortion of EC accounts for only a minor contribution to activation energy (2.4 kcal out of the total activation energy of 7.4 kcal), and the rest arises from the work required for hydrogen diffusion in the EC cavity (distort the three fragments and to create the orbital overlaps) and therefore is entropy controlled.

Whether or not EC represents an actual reactive species is still debatable. Classical MD simulations pointed that EC in toluene is unfavorable, yet, it is presented at 0.5% concentration.\textsuperscript{67} In the solution, the stabilizing interactions within EC are significantly weaker, and it does not exhibit preferential orientation.\textsuperscript{68} Based on MD simulations, the pair 2,6-lutidine/6 exist in

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure8.png}
\caption{Transition state for the system tBu$_3$P + B(C$_6$F$_5$)$_3$ + H$_2$}
\end{figure}
separated solvent cages rather than in the associated form. Nevertheless, experimental evidence of EC formation was offered by neutron scattering and NMR studies in ionic liquids. Combined $^{19}$F, $^1$H HOESY NMR studies provided further evidence of association of Mes$_3$P/6 or tBu$_3$P/6 in the solution based on observation of C-H···F interactions. These associates, however, did not feature preferential orientation.

Recently direct kinetic study of H$_2$ activation with Mes$_3$P/6 by isothermal calorimetry has been reported. Obtained experimental data could be well modeled as a single termolecular reaction with the rate constant 0.61 M$^{-2}$ s$^{-1}$ at 303 K. However, the identical rate law would apply for the pathway involving an EC, assuming that the encounter complex formation is a rapid equilibrium prior to the rate-determining H$_2$ activation step:

$$D/A \xrightleftharpoons{k_1}{k_{-1}} D...A \xrightarrow{k_2} DH^+/AH^-$$

$$v = (k_1 k_2 / k_{-1}) [D][A][H_2]$$

Figure 9 Two-step activation of H$_2$ by FLP and the associated rate law.

Determination of activation parameters revealed that the reaction is entropy controlled. At the same time, virtually no kinetic isotope effect was observed in the experiments with D$_2$. Together, these observations suggest that the diffusion of H$_2$ into the “encounter complex pocket” is an actual rate-limiting step, that is followed by hydrogen cleavage. Enthalpic barrier was found as small as $\Delta H^\ddagger = 3.3$ kcal mol$^{-1}$ and $\Delta G^\ddagger = 17.7$, yet its non-zero value indicates that the reaction proceeds via the transition state. In the view of EC concept, intramolecular FLP with spatially close active centres represents a particular case of such, which brings kinetic advantage in the reaction with H$_2$.

### 3.1.3 ALTERING LEWIS ACIDITY

Energy partitioning analysis illustrated the importance of quantification of LA and LB strengths for rational FLP design. In a big portion of FLP reactions, including hydrogen splitting, LB accepts a proton, and its strength can be well correlated with proton affinity (PA) or Brønsted basicity in the solution, of which tabular values are widely available. In contrast, there is no universal choice of Lewis acidity scale. Commonly employed metrics are defined with respect to complementary bases, that vary significantly in their nature. Therefore, it is essential to compare these metrics and understand their limitations.

Assessment of Lewis acidity by spectroscopic methods (Fig. 10) is widespread. Gutmann–Becket method measures Lewis acidity (Gutmann number NA) based on the change in $^{31}$P NMR chemical shift of Et$_3$PO upon
coordination with LA (Fig. 10) Childs method utilizes crotonaldehydes as the complementary base and assesses $^1$H NMR chemical shift of H$_3$ proton upon complexation with LA. Computational measures of Lewis acidity (Fig. 10) derive thermodynamic parameters of adduct formation between LB and LA in question. For instance, hydride affinity (HA) and fluoride ion affinity (FIA) calculate the enthalpy change upon binding of H$^-$ or F$^-$ correspondingly to LA in question in a gas phase via isodesmic reactions. Naturally, these methods can be used in a predictive manner.

Figure 10 Methods for determination of the Lewis acidity.

The ability of LA to accept electron density without regard to a particular base can be evaluated based on electrochemically measured reduction potential. Global Electrophilicity Index (GEI, $\omega$) is another intrinsic Lewis acidity metric, which is defined as $\omega = \chi^2/2\eta$, where $\chi$ electronegativity, and $\eta$ is hardness. Both $\chi$ and $\eta$ values can be derived from computed one-electron energies of the frontier molecular orbital $E_{HOMO}$ and $E_{LUMO}$ of the optimized LA structure. Hence, GEI represents a “cheaper” computational method than FIA and HIA, where structural optimizations of several species are needed.

Attenuation of Lewis acidity is a common strategy to achieve compatibility of FLP systems towards polar functional groups; besides, upon H$_2$ activation less acidic boranes give intermediates, that are stronger hydride donors. This facilitates the subsequent hydride transfer step. In this context number of tempered boranes achieved by simply F/H replacements in parental 6 were explored in the past years. Recently, Stephan et al. systematically assessed Lewis acidities within the library of 20 partially fluorinated analogs of 6 by GEI (Fig.11, compounds 9). The latter nearly linearly correlated with an absolute number of fluorines in the structure; however, slight deviations were observed depending on the position of F atoms: those in meta position have slightly stronger electron withdrawal effect than in para positions. Importantly, boranes with the same number of ortho, meta, and para F have the same GEI regardless of their distribution among the rings, which is valuable insight from a synthetic point of view. This study also revealed that, given that steric congestion around boron is the same, GEI is in good
agreement with Childs scale, while FIA scale - with Gutmann-Beckett scale, which was rationalized by HSAB theory.

Generation of stronger Lewis acidic boranes than 6 appeared to be a challenging task. Fluorine has the strongest positive inductive effect among halogens, however, its back-donation of lone electron pair to the aromatic system is also prominent. Hammett parameter, which reflects combined mesomeric and inductive effect of the substituent, is substantially greater for Cl (σ_{para}=0.23) than F (σ_{para}=0.06)(more positive value denotes greater electron withdrawing group). Investigation on the electronic structure of the series B(C6F5)3-n(C6Cl5)n, n = 0-3 (6, 10a-c, Fig.11) confirmed that boron atom becomes more electron deficient concurrently with the replacement of each C6F5 with C6Cl5 according to 11B NMR chemical shifts, computed electron charges on B atom, and reduction potentials measured by cyclic voltammetry. In the later work, calculated HIAs energies for 10b and 10c were found to be 0.4 and 1.1 kcal lower relative to 6 (stronger affinities). In contrast, Lewis acidity estimated by Gutmann-Beckett and Childs methods within the series 10a-c followed the opposite trend due to the increasing steric hindrance. Repulsion with bulkier Cl around boron center upon interaction with bigger donors (front strain) and higher energetic costs for pyramidization of B center caused by repulsion of sterically bulky CsCl5 fragments at the back (back strain) disfavor B-O bond formation.

Even for a smaller donor like H2O, contribution of steric to Lewis acidity overrides electronics: unlike 6-H2O, its bulkier homolog 10a releases water under vacuum or in the solution upon addition of molecular sieves and pristine 10c could be recovered after refluxing in a toluene/H2O mixture for several days. These observations illustrate the basis for the size-exclusion principle in FLP design: steric modulation around boron to discriminate donors by size. Since H2 is the smallest possible molecule, such an approach can inhibit interaction of borane with other donors without compromising on reactivity towards H2.

![Figure 11](image-url)  
*Highly Lewis acidic boranes.*
Recently Mitzel et al. reported a super Lewis acid, the tris-(perfluorotolyl) borane 11 (Fig.11). Replacement of F with stronger electron acceptor CF₃ (σ_para=0.54) in the para-positions of 6 does not impose energetic penalties associated with the front and back strains compared to 6. Guttmann-Beckett and FIA values of 11 were found to be about 10% higher than those of 6, and HIA was found 12.6 kcal stronger. Substantial enhancement of Lewis acidity can be achieved by rendering pyramidalization of planar trivalent B centre. Thus, Lewis acidities of non-halogenated boranes 12a and 12b evaluated by the HIA scale are comparable to those of 6, and are slightly stronger according to the FIA scale. 91

Size-exclusion design was successfully applied in the development of functional groups and moisture tolerant boranes. In the related work, 54 Soós and Pápai systematically investigated the broad series of halogenated triarylboranes BYX₂ (13-17, Fig.11) with default steric congestion around boron: Y ring bears at least two Cl or two Me (those two substituents are isosteric) in ortho-position, and each X ring bears at least two ortho F substituents. Calculated gas-phase HIs plotted against the number of F in the X ring for each small series (13 a-d, 14 a-d, 15 a-d, 16 a-c, 17b,c) gave nearly linear trends with about 5 kcal step for each additional F on X ring with more prominent effect at meta-positions. Interestingly, that H/Cl replacement in the Y ring affected HA to less extend, presumably because of the lower level of the conjunction of B center with bulkier aromatic ring, which is forced perpendicular to ipso-C atoms.

3.2 FLP CATALYSED HYDROGENATIONS

3.2.1 HYDROGENATION OF DOUBLE BONDS

Since the products of H₂ splitting by FLPs possess ionic character, FLPs were explored as catalysts in hydrogenation of polar substrates at first, including imines, N-heterocycles, enamines, silyl ethers, enones, and ynones. The FLP hydrogenation catalyst may comprise both LA and LB components, separated or linked, or a single LA. Shortly after the first report on FLP-catalysed hydrogenation by 1, it was discovered that 6 alone could catalyse the reduction of sterically hindered imines and N-heterocycles 92-95. These early reports postulated the mechanism where the substrate functions as a basic component giving iminium hydroborate pair upon H₂ splitting with borane (Fig. 12, Cycle A). Subsequent hydride transfer from boron to iminium carbon yields amine-borane adduct, dissociating to release free borane and the product. Since the latter is also a viable base for hydrogen activation, the process might occur through the autoinduced catalytic cycle (Fig. 12, Cycle B, where the base is the produced amine). Paradies et al. showed that whether hydrogenation proceeds via catalytic cycle A or B is determined by Lewis acidity of borane. 96, 97 While 6 is unselective with regard to Lewis base (imine or amine), catalysis with less
acetic boranes $9a$ B(2,6-F$_2$Ph)$_3$ and $9b$ B(2,4,6-F$_3$Ph)$_3$ proceeds via autoinduced cycle B due to higher activation energies (2 kcal mol$^{-1}$) for H$_2$ splitting by the imine versus amine.

Stoichiometric reaction between imine-borane pair and H$_2$ occurs at room temperature, but further activation of H$_2$ by formed amine-borane adduct requires heating due to high dissociation energy. Thus, hydrogenation of imines$^{92, 93}$ or N-heterocycles such as substituted quinolines, phenanthroline, acridines$^{94}$, indoles$^{93, 95}$ catalysed by 6 proceeds with sufficiently hindered substrates at elevated temperatures (Fig. 13a,b). Naturally, strong binding with amine and other functional groups present in the system can hamper or completely quench catalyst activity. To overcome this limitation, Soós et al.$^{98, 99}$ exploited the size-exclusion principle in the design of hydrogenation catalyst comprising sterically shielded MesB(C$_6$F$_5$)$_3$ (13d) and DABCO (20) or quinuclidine (21), compact bases that could ensure H$_2$ activation regardless the substrate nature. These catalytic systems enabled hydrogenations of double bonds of sterically accessible imines, enamines and enones at room temperatures and featured high functional group tolerance and chemoselectivity. (Fig. 13, c). More chemically robust borane modification 13c broadened substrate scope to sterically accessible quinolines and, notably, retained activity after exposure to air. The reduction could be accomplished without an external base at elevated temperature (Fig. 13, d).
The use of single component borane 6 as a catalyst is appealing but limited by the basicity of substrates/product: hydrogenation of substrates with diminished basicity requires forcing conditions or auxiliary base. Anticipating that the strong-donor solvent can operate as a base, Ashley et al. probed sterically shielded boranes B(C₆F₅)₃-n(C₆Cl₅)n, n = 1-3 (10a-c) in the hydrogenation of imines in THF (Fig. 13, e). Among the series, 10a was found to be particularly effective, while 10c did not show any reactivity, presumably due to excessive steric bulk. As was discussed previously, 10a is more Lewis acidic with respect to hydride and at the same time less acidic with respect to O-donors compared to 6. Hence, weakly bound pair 10a/THF is capable of hydrogen activation under mild conditions, upon which highly Brønsted acidic protonated THF is formed. This allowed hydrogenation of the weakly basic imines, furans, pyrroles. Air stability of 10a and utilization of “greener” polar solvent which enables solubilising of a broader range of potential substrates, make the protocol especially handy.
FLPs with properly prearranged LA-LB centres can be considered as 100% EC. As this kinetic advantage results in facile hydrogen splitting, they were expected to be superior catalysts over intermolecular counterparts. Indeed, one of the first intramolecular systems reported by Erker et al., ethylene-bridged 4 (Fig. 14), appeared to be far more active in the hydrogenation of imines and enamines than the previously reported FLP catalysts. For instance, hydrogenation of imine 7 occurred at room temperatures under 2.5 atm H\(_2\) in 3 hours. On the other hand, 22 reacts with H\(_2\) instantly to form an adduct \(22-H_2\), but the latter poorly performed as a catalyst in the hydrogenation of imines. Later, various intramolecular systems (23-28) were reported to effect hydrogenations of imines and enamines, yet again not overperforming activity of non-linked systems. Presumably, the energetic disadvantages of hydrogen transfer from the intramolecular hydrogen adducts hamper catalyst activity despite facile H\(_2\) splitting.

![Figure 14](image)

Intramolecular FLP hydrogenation catalysts.

Like for imines, hydrogenation of enamines and silyl enol ethers occurs via activation of carbonyl group by protonation, followed by hydride attack on activated carbon. Reduction of enamines was effected by catalysts 4, MesB(C\(_6\)F\(_5\))\(_3\) (13d) /DABCO, \(^{98}\) 22-28.\(^{101-106}\) Hydrogenations of poorly basic silyl enol ethers typically requires FLP catalysts comprising an auxiliary base, such as commercially available phosphines in combinations with 6.\(^{106-108}\) FLP-promoted reduction of enones and ynone occurs in the reverse order than that for imines: hydride transfer to Michael position is followed by protonation. Hence, generation of more nucleophilic hydroborate species derived from less Lewis acidic boranes facilitates the reaction. Borane 13d effected hydrogenation of activated double bond of carvone to dihydrocarvone,\(^{98}\) and borane 10a hydrogenated CH\(_2\)=CHC(O)On-Bu in THF.\(^{109}\) Erker et al. reported 29 in combination with DABCO as effective catalyst for the reduction of ynone and a small series of enones.
3.2.2 ASYMMETRIC HYDROGENATION

Remarkable efforts were dedicated to the development of an asymmetric version of hydrogenation catalysis with FLPs (Fig. 15, 16). From a practical point of view, steric induction by LB is an attractive approach as plenty of bench stable chiral amines and phosphines are readily available. However, hydrogenation of PhCMe=NPh employing commercial chiral phosphines in combination with B(C6F5)3 resulted in only 25% ee when (S,S)-diop 30 was used.95 Reaction required prolonged heating at 100°C, which likely diminished the enantioselectivity. Unproductive attempts to employ chiral bases in FLP hydrogenations can be rationalized from mechanistic point of view. In the corresponding catalytic cycle (Fig. 12) hydride transfer to prochiral imine is an enantioselectivity determining step, and it does not involve base directly. Additionally, imine or amine can be involved in the competing autoinduced process, decreasing enantioselectivity.

Generation of chiral (at boron) intermediate borohydrides then should be a more efficient strategy, but due to the trigonal geometry of boranes and limited choice of substituents dictated by the Lewis acidity requirements, it is practically hard to implement.110, 111 Instead, Lewis acidic boron center is typically installed on the chiral backbone. The first FLP-type asymmetric hydrogenation was reported by Klankermayer et al., employing (+)-α-pinene derived borane 31 as a sole catalyst.93 Imine PhCMe=NPh 32a was reduced with full conversion under relatively mild conditions, albeit with only 13% ee. Subsequently, enantioselectivity was substantially improved by employing 35a derived from (1R)-(+)−camphor scaffold. Hydroboration of alkene 33 with Piers’ borane 34 gave a diastereomeric mixture of boranes in the ratio 1:4. They could be separated upon hydrogen activation in the presence of tBu3P via kinetically controlled crystallization, as adduct 35b forms faster than 35a. In hydrogenations of imines 35a showed poor ee while 35b provided products with up to 99% yields and up to 83% ee. Its intramolecular analog 36112 was obtained as exclusive stereoisomer after the hydroboration step. Catalyst 36 gave lower enantioselectivities than 35b, but, interestingly, its zwitterionic hydrogen adduct featured high stability and could be recycled 5 times without loss of enantioselectivity.

Intramolecular ansa-aminoboranes were found to be active hydrogenation catalysts under mild conditions (room temperature), which is essential for achieving high ees. Therefore, their analogs bearing chiral amine moieties were probed in the hydrogenation of imines.113 Rigid and bulky chiral amine moiety in the structure of ansa-ammonium borane 37 was expected to ensure generation of chiral at nitrogen ammonium center with high enantioselectivity. Nevertheless, 37 obtained upon the reaction of corresponding ansa-aminoborane with H2 was isolated as a mixture of two diastereomeric hydrogen adducts, indicating low asymmetric induction already at the hydrogen activation step. In hydrogenation experiments, 37 reached 35% ee for imines and 37% ee for quinolines at most. In contrast, chiral intramolecular ansa-ammonium borate 38 based on a binaphthyl
scaffold was proved to be highly selective in the hydrogenation of a wide range of structurally different substrates at mild conditions. The catalyst was particularly effective in the hydrogenation of acetophenone, N-alkyl and -benzyl imines (76-83% ee) and enamines (47-99% ee), giving excellent conversions.

Figure 15  FLP catalysts for chiral hydrogenation.
Du et al. developed a family of efficient FLP catalysts bisboranes 40 derived from the axially chiral 1,1'-binaphthyl scaffold. 115 Bisboranes 40 can be cleanly generated by hydroboration of corresponding terminal bis-alkenes 39 with 34a. The catalyst can be assembled in situ, which eliminates the necessity for tedious isolation (separation of diastereomers), storage, and handling of the moisture sensitive organoboranes. Screening of the wide palette of 3,3'-diaryl substituted bisboranes in the hydrogenation of model imine 32a revealed that enantioselectivity is sensitive to the bulkiness of the Ar substituent.116 The most sterically hindered bisborane 40a gave the highest ees, and further screening with various imines at mild conditions (20 bar, room temperature) gave ees in the range of 74-89% and high conversions (63-99%). The results are similar to those obtained for 35a, albeit broader substrate scope was explored bearing halides and ethers. Bisboranes 40 were successfully applied in stereoselective hydrogenations of polysubstituted N-heterocycles such as 2,3-disubstituted quinoxalines using 40b,117 2,3,4-trisubstituted quinolines using 40c,118 2,3- and 2,4-disubstituted quinolines using 40b,119 and others.120 Highly enantioselective hydrogenations of silyl enol ethers were achieved with 40b in combination with external base tBu3P (5).121 Corresponding secondary alcohols were obtained after deprotection by TBAF in excellent yields (93-99%) and enantiopure almost in all cases.

Wang et al. introduced a family of C2-symmetric bicyclic bisboranes prepared by hydroboration of internal diene 41 with 34a or its analog HB(p-C6F4H)2 34b.122 Diastereomers 42 and 43 could be selectively prepared from 41 depending on the temperature. Generated in situ at 80°C 43a afforded hydrogenations of imines with excellent activity (turnover number is up to 200) and enantioselectivity (up to 95% ee) at -40°C and thus outperformed catalysts 35a and 40a. Subsequently, the same group reported a series of spiral-bicyclic bisboranes 46. In situ generated 46a was particularly selective in the hydrogenation of 2-alkyl, -vinyl, and -allyl substituted quinolines. Enantioselective reduction 2-aryl and 2-hetaryl substituted quinolines was achieved with the combination of 46a / P(3,5-(CF3)2Ph)3.

The long-standing problem of asymmetric hydrogenation of carbonyl compounds has been resolved recently by using achiral boranes in combination with chiral oxazoline 47, thus, representing a rare example of successful utilization of chiral base to induce chirality in FLP catalysed reductions.123 Ketones were reduced to corresponding alcohols using B(p-C6F4H)3(9c)/47 in 43–97% yields with 50–87% ee. Hydrogenation of enones and chromones to ketones was achieved in high yields and up to 95% ee.

In addition to direct hydrogenation, other types of FLP-catalysed asymmetric reductions such as hydrosilylation and transfer hydrogenation were successfully explored.120
3.3 HYDROGENATION OF C=O BONDS AND WATER TOLERANCE

Commercially available B(C₆F₅)₃ (6),¹²⁴,¹²⁵ is a strong Lewis acid, somewhat between BCl₃ and BF₃,¹²⁶ but possesses the substantial steric bulk, is thermally robust, and moisture stable compared to boron halides. In fact, some reactions catalysed by 6 can be carried out in aqueous solutions.¹²⁴,¹²⁵,¹²⁷ In FLP-type reactions when combined with strong bases such as phosphine or amine, 6 exhibits high functional group sensitivity, especially towards O-H bonds. Marked inhibition occurs through H₂O coordination to form complex 6-H₂O, which, being a very strong Brønsted acid,¹²⁶ in the presence of strong LB, is further deprotonated to an ion pair [6-OH]⁻[LBH]+ (Fig. 17, a). While the formation of 6-H₂O is reversible, its deprotonation is typically not. Even without base upon heating complex 6-H₂O undergoes protodeboronation to form 48 induced by proton transfer from the coordinated water to C₆F₅ substituent.

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Figure 16  Asymmetric FLP catalysed hydrogenations of polar double bonds.
Deactivation of FLPs by (a) water or (b,c) ROH.

Figure 17

Deactivation of FLPs by (a) water or (b,c) ROH.

The reaction of phosphonium borohydride 4 with the ketone led to its reduction and concurrent irreversible formation of FLP adduct with the produced alcohol (Fig. 17, b). Theoretical studies suggested feasibility of the direct H₂ activation by ketone or aldehyde/6 pairs. Indeed, experimental attempts to hydrogenate carbonyl substrates using 6 in toluene resulted in the stoichiometric reduction due to subsequent reaction of the borane with the formed alcohols leading to C-B bond cleavage and formation of ether 49, 129, 130.

Taking a closer look at the deactivation pathway of 6 by water or alcohols under basic conditions, one can conclude that the strength of LB is essential, and irreversible deprotonation of the complexes 6-H₂O or 50 can be
prevented when a weaker LB is used. Consistent with these considerations, two independent studies reported hydrogenation of aldehydes and ketones mediated by 6 in combination with weak ethereal LBs such as Et₂O and 1,4-dioxane. The proposed mechanism is depicted in Fig. 18. Here, H₂ activation occurs between 6 and ethereal solvent (solvent-assisted pathway, Fig. 18, Route A). Being a strong Brønsted acid, protonated ether activates the carbonyl compound followed by hydride transfer from borohydride species to form a borane-alcohol adduct. The latter does not undergo deprotonation with the weak ethereal LB. Since H₂ activation between Et₂O/6 was demonstrated and employed in hydrogenation catalysis earlier, and taking into the account overwhelming excess of the ethereal donor compared to the carbonyl compound, the substrate assisted pathway was thought to be unlike. (Fig. 18, Route B). It was further shown that 6 remains an active catalyst in the hydrogenation of carbonyl compounds in 1,4-dioxane even in the presence of multiple equivalents of water. Thus, the reaction could be performed in commercial moist solvents in air, albeit under more forcing conditions and longer reaction times.

Figure 19 (a) Reduction of carbonyls, and (b) reductive esterification under moist conditions.

Hydrogenation of carbonyl compounds under moist conditions was also independently reported by Soós et al. using borane 16c in technical grade THF (Fig. 19, a). In this work, functional group/water tolerance was ensured by weakly basic conditions along with employing a less acidic borane designed according to the size-exclusion principle. As an extension of this work, the same group demonstrated the utility of 17c in reductive esterification of aldehydes and ketones (Fig. 19, b). The sole borane 17c in THF provided dual function catalysis: Brønsted acid-assisted formation of acetal/ketal 52 followed by FLP-type reduction. Both high H₂O tolerance attributed to the
catalyst and selective reduction of in situ formed acetals rather than starting carbonyls are remarkable.

In fact, deprotonation of water adduct 6-H2O, which occurs in the presence of stronger LBs, was proved to be reversible: hydroxyborate [6-OH]- releases H2O upon protonation by [HPtBu3]+ - conjugated Brønsted acid of moderate base PtBu3 under forcing conditions.137 Borane 6 in an amount of just 1 mol% catalysed reductive amination of aldehydes and ketones with anilines using 1.2 equivalents of hydrosilane as a reductant in the presence of up to 100 equivalents of water, derived from imine formation and the use of non-purified solvents (Fig. 20). In the presence of arylamines, boron species exists in catalytically inactive hydroxyborate form [6-OH]-. However, heating to 100°C unlocks reprotonation of [6-OH]- to 6-H2O and further dissociation to release free 6 enough to effect FLP type Si-H bond activation and subsequent reactivity. This methodology could not be applied to more basic alkylamines due to the irreversible deprotonation of 6-H2O. Thus, compatibility of 6/amine pair with H2O was found to be limited to those amines whose conjugate acids have pKa<16 in MeCN. In the subsequent work, the range of substrates was complemented with alkylamines using less acidic borane BPh3 (54) as a catalyst. In the presence of more basic alkylamines, catalyst is preserved in the form of AlkNH2-54 and [54-OH][AlkNH3]+, with weaker aromatic amines equilibrium shifts towards H2O-54, which is prone to deactivation via protodeboronation. Therefore, 54 was only effective for amines whose conjugate acids have pKa>12 in MeCN. Both pathways of catalyst deactivation could be minimized employing moderately Lewis acidic and sterically accessible for coordination of amine borane B(3,5-Cl2C6H3)3 (55). This catalyst effected reductive amination with a wide range of both aliphatic and aromatic amines corresponding to conjugate acids in the pKa range 10.6-18.5 in MeCN.

Despite notable water tolerance, neither of the aforementioned boranes were capable of reductive amination using H2 as a reductant under the reported conditions. Presumably, in the case of 6 H2 activation is kinetically precluded due to the very low concentration of free borane, while boranes 54 and 55 do not reach sufficient cumulative strength in combination with imines/amines presented in the system. This challenge was resolved by Soós et al. yet again applying the size-exclusion principle in the borane design. Sterically crowded at boron (2,6-Cl2C6H3)2(2-Cl-6-F-C6H3) (56) in combination with moderately strong and compact base DABCO provided a viable catalyst for reductive amination carbonyls with aryl- and alkylamines and H2. The system tolerated high contents of water; for instance, 37% aqueous solution of formaldehyde could be used as a reagent. Shortly after Ogoshi et al. reported a similar methodology employing more electrophilic borane 57 as a sole catalyst in the presence of molecular sieves.138 This work featured impressive substrate scope bearing a wide range of functional groups, including carboxyl, hydroxyl, and additional amino groups (Fig. 21).
3.4 INTRAMOLECULAR FLPS AMONG OTHERS

As was discussed previously in section 3.1.1, intramolecular systems with spatially close LA and LB centers have the thermodynamic advantage over intermolecular analogs due to larger stabilization interactions $\Delta G_{\text{stab}}$. From the kinetic point of view, intramolecular FLPS are somewhat similar to EC and typically feature faster hydrogen addition rates. These features gave grounds to search for superior hydrogenation catalysts among intramolecular systems.

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**Figure 20** Reductive amination of carbonyls with aryl and alkyl amines under "wet" conditions using hydrosilane as a reductant.

**Figure 21** Reductive amination of carbonyls using $H_2$ as a reductant.

It is also worth noting that there has been growing interest in alternative approach to disfavouring FLPS deactivation by $H_2O/O-H$ bonds by the replacement of B centre into a heavier element to result in a still strong but softer and less oxophilic Lewis acid.\(^{139}\)
Phosphonium borate 4 (Fig. 22) was shown to be a far more active catalyst in the hydrogenation of imines and enamines than its FLP predecessors. Dihydrogen addition rates to 3 and to its intermolecular analog Mes₃P/6 are comparable, and so are corresponding activation energies: 21.5 kcal/mol for 3+H₂⁶⁵ compared to 17.7 kcal/mol for Mes₃P/6+H₂.⁷² Thus, despite 3 having notably less acidic LA site than 6, it retains high activity towards H₂ likely due to the cooperative effect of the linked system. The following hydrogen transfer step from 4 to the substrate occurs rapidly so that the prior H₂ activation becomes the rate limiting step.¹⁴⁰ Calculated Gibbs free energies of the formation of adducts [Mes₃PH]⁺[6-H]- and 4 in toluene are -11.6 and -2.4 kcal/mol⁵¹ correspondingly. Naturally, close-to-zero thermodynamics of intermediate 4 favors hydrogen transfer and, therefore, hydrogenation occurs faster. Attempts to obtain phosphinoborane 58a with shorter methylene linker led to the spontaneous formation of undesirable heterocycle 58c, which likely proceeds via activation of the ortho-C-F bond by the frustrated P/B centres followed by [1,3]-F shift.¹⁴¹ Surprisingly, 61 bearing simply Ph instead C₆F₅ rings were still capable for H₂ activation under mild conditions.⁵⁵ Calculated Gibbs free energies of the formation of hypothetical adduct 58-H₂ and adduct 4 in toluene are -14.8 and -0.7 kcal/mol respectively, whereas activation barriers are 16.6 and 22.6 kcal/mol respectively. These numbers suggest that thermodynamics of H₂ splitting are more sensitive to the electronic effect of LA part than the kinetics and this observation seems to be general for intramolecular systems.¹⁴²

Ansa-aminoborane 22¹⁰¹ with substantially more basic TMP group rapidly converts into zwitterionic salt 22-H₂ under 1 atm of H₂ (Fig. 23). Salt 22-H₂ appeared to be air and moisture stable and could be reverted to 22 upon reflux at 110°C in 20 hours. The activation barrier and Gibbs free energy were calculated to be 14.4 kcal/mol¹⁰¹ and -12 kcal/mol respectively. Combined studies on the structure of 22-H₂ by X-ray and neutron diffraction, DFT calculations, and NOE NMR revealed a strong dihydrogen bond between former H₂ atoms with partially covalent character (1.5-1.8 Å, and 1.78 Å according to X-ray analysis). Such bonding is favorable for facile H₂ release, yet, notable thermodynamic stability of 22-H₂ limited catalyst performance and despite facile H₂ activation the reaction required
prolonged heating (typical conditions: 1 bar H\textsubscript{2}, 110°C 6-24 h). Low conversions were observed with sterically accessible and also less basic substrates. With the latter proton transfer seems to become the rate limiting step. In a good agreement with this assumption, further reducing the basicity of amine moiety accelerated H\textsubscript{2} release. For instance, 37-H\textsubscript{2} converts to 37 six times faster and demonstrated substantially improved catalytic activity.

Figure 23  Dihydrogen activation with ansa-aminoboranes.

Removal of the methylene linker between the aromatic ring and amine moiety in 22 provides a more rigid ortho-phenylene scaffold. In fact, the first example of ortho-phenylene templated FLP system 61 was reported by Piers et al. a few years before the breakthrough discovery of heterolytic H\textsubscript{2} splitting by the system 1\textsuperscript{,143} Compound 61 formed adducts with acidic molecules HCl and H\textsubscript{2}O, yet it failed to activate H\textsubscript{2} due to insufficient basicity of -NPh\textsubscript{2} site. Almost a decade later, our group reported -TMP- and -NMe\textsubscript{2} substituted analogs 62 and 63, which both readily activated H\textsubscript{2} under mild conditions.\textsuperscript{144} Adduct 63-H\textsubscript{2} appeared to be extremely stable not releasing H\textsubscript{2} even upon prolonged heating, presumably due to strong electrostatic stabilization within rigid 6-member ring C-N-H-H-B-C. In contrast, 62 reacted with hydrogen slower but reversibly. Unlike 63, compound 62 exists as an internal B-N adduct. Since additional energy is required to break B-N bond, H\textsubscript{2} activation is slower than this with 63. Significant stabilization of the internal adduct 62 is the driving force for the reverse H\textsubscript{2} release. Due to the excessive steric hindrance and thermodynamic stability 63-H\textsubscript{2} could not transfer H\textsubscript{2} to any polar substrates, while 62 effected hydrogenations of sterically accessible substrates. It was noted that upon heating at 80°C adduct 62-H\textsubscript{2} easily
undergoes intramolecular protodeboronation to give *ansa*-aminohydroborane 64. The latter was found to be an efficient catalyst in the hydrogenation of internal alkynes into *cis*-alkenes. Mechanistic studies revealed that the process occurs via hydroboration of alkyne with 64, followed by H₂ cleavage and subsequent intramolecular protodeboronation to release alkenes and regenerate 64.\textsuperscript{145}

The cooperative effect of phenylene bridged B/N sites appeared to be so powerful that even *ansa*-aminoborane 65 bearing weakly acidic -BH₂ existed in dynamic equilibrium with corresponding adduct 65-H₂ under moderate pressures and temperatures in CD₂Cl₂.\textsuperscript{143} Gibbs free energy of \(-1.1\) kcal/mol was obtained from VT \(^1\)H NMR study. The kinetic analysis of H₂ release from 65-H₂ using spin-saturation transfer NMR provided free activation energy of 18.3 kcal/mol.

Besides application in catalysis, *ansa*-FLPs have the ability to produce parahydrogen-induced polarization (PHIP).\textsuperscript{146} Parahydrogen (pH₂) is one of the spin isomers of molecular hydrogen, in which the two nuclear spins are antiparallel (spin of I = 0). Parahydrogen is NMR silent unless it loses symmetry upon pairwise addition to a catalyst or unsaturated substrate, producing spin polarization well above the thermal level. In the recorded NMR spectra, the signals of the former pH₂ nuclei can exhibit orders of magnitude increased intensities. Thus, the addition of pH₂ to 60 allowed for the detection of NH and BH PHIP signals in the corresponding adduct 60-H₂* (Fig. 24). PHIP signals disappear upon the nuclei spin relaxation, which results in the observation of just the thermal spectrum. However, since hydrogen uptake by 60 is reversible at elevated temperatures, PHIP signals can be observed as long as pH₂ is supplied to the solution. In contrast, 22 PHIP was only observed after first bubbling due to the irreversible character of the hydrogen uptake.

**Figure 24** (a) Dynamic chemical equilibrium occurring upon pH₂ bubbling through the solution of 60 at 90°C and corresponding \(^1\)H NMR spectra: (b) single shot spectrum, (c) DQF OP-SY spectrum.

Certain NMR pulse sequences allow to filter out crowded \(^1\)H NMR spectra leaving only PHIP signals. Polarization can also be transferred (spontaneously
or by magnetic field manipulations) to other nuclei, such as $^{13}$C and $^{15}$N, which are coupled to pH$_2$-originated protons. These technics are promising for NMR applications, e.g. MRI, since they provide the possibility to enhance signals of compounds in a background-free mode. Apart from NMR/MRI sensitivity boosting, PHIP is useful in mechanistic studies of reactions involving pH$_2$. Observation of PHIP serves as evidence of pairwise mechanism of H$_2$ addition/transfer. It also allows to 'light up' trace amounts of intermediate products or coordination compounds.
4 RESULTS AND DISCUSSION

This chapter will briefly cover the results published in publications I-V. More thorough discussions and experimental details can be found in the attached publications and corresponding supplementary materials, which are available free of charge on the publishers’ webpages.

4.1 NON-HALOGENATED ANSA-AMINOBORANES FOR HIGHLY REVERSIBLE HYDROGEN ACTIVATION I, II

The ability of ansa-FLPs to produce PHIP is attributable to their unique bifunctional structure, which allows them to fulfill very specific prerequisites:

• Locking pairwise-split H₂ within the H₂ adduct
• Spacious proximity of H₂ originated hydrogens (J-coupling)
• Reversibility of H₂ addition
• High H₂ addition rates

In this work, we aimed to unlock the potential of ansa-FLPs as MRI contrasting tags utilizing PHIP. This would require achieving biocompatibility of pH₂ activation process: aqueous media, ambient temperature, and pressure. In the proof-of-principle study, compound 60 enabled continuous production of PHIP only at elevated temperatures, while compound 22 effected PHIP only in the beginning of pH₂ bubbling through the sample due to irreversible formation of the adduct. Besides, both compounds required strictly dry conditions to preserve their reactivity.

We envisioned that phenylene bridged FLPs can provide more favorable parameters for effecting PHIP under ambient conditions: neutral thermodynamics of H₂ addition along with high reaction rates. In such systems, strong electron withdrawing C₆F₅ groups, which are detrimental both in terms of reversibility and moisture sensitivity, can be replaced with substantially less electron withdrawing substituents without sacrificing reactivity towards H₂. Accordingly, we proposed the series of ansa-aminoboranes (AABs) represented by the general structure 69 (Fig. 25), where boron is substituted by various non-halogenated aryls (phenyl, 2-isopropylphenyl, mesityl, 2,2-diisopropylphenyl and 2-bisphenyl). Steric hindrance of the aryl substituents was systematically altered with the aim to disfavour B-O bond and, thus, overcome moisture sensitivity.
Compounds 69-Ph, 69-Mes and 69-Dipp were prepared from the precursor lithium salt 66 and corresponding diarylboron chlorides or fluorides. Due to steric hindrance the reaction between 66 and Dipp$_2$BF required forcing conditions (60°C, 12 hours) and 69-Dipp was obtained as crude oil without further purification (see Appendix, A). Compound 69-iPr was prepared from the salt 66 by one-pot protocol via formation of ansa-dichloraminoborane 67 and subsequent addition of 2 equivalents of ortho-isopropylphenyl lithium. Intriguingly, treatment of 67 with 2 equivalents of 2-lithiumbiphenyl gave compound 69-bPh rather than expected bis(2-biphenyl)borylamine 68, as was confirmed by the single-crystal X-ray diffraction analysis. Compound 69-bPh is a product of a spontaneous intramolecular C−H insertion of one of the ortho-biphenyl substituents attached to the boron atom (reported separately in Publication II).

Hydrogen activation was probed with AABs 69 at room temperature under 10 bars of H$_2$ in CD$_2$Cl$_2$. To our delight, all AABs except the bulkiest 69-Dipp reacted with H$_2$ under these conditions. According to $^1$H and $^{11}$B NMR 69-iPr, -Mes, -bPh existed in dynamic equilibrium with their adducts with H$_2$ (Fig. 26), and corresponding conversions are indicated in the Table 1 (column 2). Compound 69-Ph fully converted to the adduct 69-Ph-H$_2$ within
10 minutes, however, after the solution was left standing under argon atmosphere for 24 hours it underwent partial dehydrogenation (70% conversion back to 69-Ph) confirming reversibility of hydrogen uptake at room temperature. Compound 69-Dipp did not react with H₂ under these conditions, nor H/D scrambling was observed after the solution of 69-Dipp was left under 5 bars of H₂/D₂ mixture (1:1) for 5 days. Ḥ NMR of 69-Dipp revealed that CH protons corresponding to isopropyl groups are non-equivalent and appear as four separate septets, indicating rotational constraints. Along with unfavorable thermodynamics, conformational rigidity might prevent 69-Dipp to adopt geometry needed for H₂ splitting.

The existence of a dynamic equilibrium between AAB and AAB-H₂ allowed us to determine thermodynamic and kinetic parameters using NMR spectroscopy. Equilibrium constants were determined based on the known initial concentrations of AABs, and ratios of AAB, AAB-H₂ and H₂ signals derived from the integration of Ḥ NMR signals according to the equation: \( K_c = \frac{[\text{AAB-H}_2]}{[\text{AAB}] \times [\text{H}_2]} \). Additionally, \( k_{\text{dis}} \) were determined using the spin saturation transfer method upon the reaction with normal H₂. \(^{148,143}\)

<table>
<thead>
<tr>
<th>AAB</th>
<th>AAB-H₂, % a</th>
<th>T (°C)</th>
<th>( k_{\text{dis}} \times 10^5 \text{(s}^{-1}) )</th>
<th>( K_c \times 10^{-3} \text{(M}^{-1}) )</th>
<th>ΔG</th>
</tr>
</thead>
<tbody>
<tr>
<td>69-Ph</td>
<td>100</td>
<td>0</td>
<td>5.1</td>
<td>7.1</td>
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<td></td>
<td></td>
<td>30</td>
<td>540.2</td>
<td>0.3</td>
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</tr>
<tr>
<td>69-iPr</td>
<td>90</td>
<td>0</td>
<td>0.2b</td>
<td>3.2c</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td>10</td>
<td>1.0b</td>
<td>1.2c</td>
<td>3.2</td>
</tr>
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<td></td>
<td></td>
<td>20</td>
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<td></td>
<td>30</td>
<td>17.9</td>
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<td>0.5b</td>
<td>0.014c</td>
<td>0</td>
</tr>
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<td></td>
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<td>10</td>
<td>2.2b</td>
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<td>30</td>
<td>32.2</td>
<td>0.001</td>
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<tr>
<td>69-bPh</td>
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<td>-</td>
<td>3.0</td>
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<td>69-Dipp</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| a Measured at RT, 10 bars H₂. b Predicted from the Eyring plots using linear regression. c Calculated by extrapolating experimental data.

Experiments with pH₂ were conducted with AABs 69-Ph, 69-iPr and 69-Mes at various temperatures. Fig. 27a-c shows Ḥ NMR spectra (¹⁴N-decoupled) recorded at 20°C after pH₂ bubbling via PTFE capillary through the 0.05 M AAB solutions for 10 seconds. Antiphase PHIP signals appear for
NH and BH signals. The chart on the Fig. 27 shows combined results for the experiments conducted at various temperatures.

Figure 27  $^{14}$N-decoupled $^1$H NMR spectra acquired at 20°C in the experiments with (a) 69-Ph, (b) 69-iPr and (c) 69-Mes. The antiphase signals of -NH and -BH groups are marked with '*' and '#' correspondingly. (d) Bar chart of PHIP signal amplitudes obtained from the NH proton for the AABs 69-Ph, -iPr, -Mes (0.05 M solutions) at different temperatures. The numbers above each bar represents the measured signal enhancement factors for these signals.

The amplitude of PHIP signal depends on kinetic and thermodynamic parameters, nuclear relaxation times and $J_{HH}$ coupling constants in a rather complex way (Publication I, equation 11). First, it is proportional to AAB's initial concentration, which was the same for all measured samples. Higher $K_c[H_2]_0$ values increase the amplitude by shifting the equilibrium towards higher total concentrations of AAB-$H_2$, including hyperpolarized AAB–$H_2^*$. Further, nuclear polarization evolves upon the establishment of the chemical equilibrium during pumping of $pH_2$ into the solution of AAB; on the other hand, nuclear relaxation destroys polarization diminishing PHIP signals. Therefore, fast equilibrium establishment and particularly high $k_{dis}$ (note, addition and dissociation rates are interconnected as $k_{as} = K_c k_{dis}$) allow minimizing negative contribution of the nuclear relaxation. In turn, long relaxation times $T_{1NH}$ and $T_{1BH}$ are beneficial for PHIP. Another detrimental factor for PHIP is the mutual cancelation of the antiphase doublets due to line broadening. Accordingly, smaller $J_{HH}$ and shorter $T_{2NH}$ and $T_{2BH}$ relaxation times enhance broadening and decrease overall signal intensity. Larger $k_{dis}$ (faster exchange) also enhances the line broadening. One can note that the effect of $k_{dis}$ on the amplitude is dual: when $k_{dis}$ is too low, nuclear relaxation becomes significant, while when $k_{dis}$ is too high, it enhances self-cancellation of the signal. However, the values of $k_{dis}$ at which its negative contribution starts to overrun and cause signal amplitude to decline are well above those
achieved with compounds 69. Therefore, we can assume this negative contribution is insignificant.

Among all listed parameters, only parameters $K_c$ and $k_{dis}$ varied significantly depending on the chemical structure of 69 and temperature. As can be noted from Table 1, compound 69-Ph has overall longer (more favorable) $K_c$ and $k_{dis}$ values compared to 69-iPr and 69-Mes. Indeed, in the temperature range -20°C to 10°C it shows higher PHIP amplitudes than those observed for 69-iPr and 69-Mes. With 69-Ph PHIP was observed even at sub-zero temperatures in the experiments. Similarly, signal amplitudes achieved with 69-iPr notably overrun those with 69-Mes. However, one can note that in the case of 69-iPr and 69-Mes PHIP amplitudes increase with temperature, while in the case of 69-Ph it passes a maximum at 0°C and at 20°C 69-iPr shows the highest efficiency in the generation of PHIP. Increase of PHIP signal intensity with temperature is expected as $k_{dis}$ grows exponentially. Therefore, abnormal decrease of PHIP signal in the case of 69-Ph may indicate a competing process of non-pairwise H$_2$ splitting at higher temperatures. Steric bulk of 69-iPr and 69-Mes prevents such possibility.

Despite the hydrophobic and crowded environment around boron, all synthesized AABs reacted with water instantly and irreversibly, except 69-Dipp, which did not show a sign of reaction or complexation with water. $^1$H and $^{11}$B NMR revealed that the 69-Mes adduct instantly reacts with water after its solution in toluene being exposed to moist air. The structure of the adduct 69-Mes-H$_2$O was confirmed by single-crystal X-ray diffraction analysis. In the solid state 69-Mes-H$_2$O features (N)H···O hydrogen bond (1.68(2) Å), as was also observed in the previously reported adduct 62-H$_2$O. Interestingly, B-O and (N)H···O bonds in 69-Mes-H$_2$O are only insignificantly elongated compared to those in 62-H$_2$O.

Figure 28  Heterolytic splitting of H$_2$O by 69-Mes to give zwitterionic adduct 69-Mes-H$_2$O, its X-ray crystal structure, and analogues formation of previously reported 62-H$_2$O for comparison. Selected bond lengths (Å) and angles (°): 69-Mes-H$_2$O: B-O 1.53(0), (N)H-O 1.68(2), NH 0.93(2), N-O 2.56(9), N-H-O 160; 62-H$_2$O: B-O 1.52(1), (N)H-O 1.67, NH 0.93, N-O 2.53(3), N-H-O 152.
4.2 $^{15}$N-LABELED ANSA-AMINOBORANES FOR PHIP III

Compounds $69$-Ph, -iPr, and -Mes generated only modest levels of PHIP signal intensity (20-fold at most). Apart from thermodynamic and kinetic parameters, relaxation times affect the signal amplitudes. In the hyperpolarized adduct AAB-$H_2^*$, both nuclei $^{14}$N (I=1) and $^{11}$B (I=3/2) to which $H_2$ originating protons are attached are quadrupole and have long relaxation times and consequently rapidly quench hyperpolarization. Thus, the replacement of $^{14}$N (I=1) with $^{15}$N (I=1/2) was expected to affect signal amplitudes. Besides, hyperpolarization can be transferred from the former $H_2$ nuclei to the neighbouring heteronuclei such as $^{15}$N, $^{13}$C, and $^{31}$P being observed longer than on protons (due to the longer relaxation times of heteronuclei compared to protons) The signal of heteronuclei then can be monitored as background free signal, which is of special interest for MRI application. Therefore, we synthesized a series $^{15}$N-labeled analog AABs $75$-Ph, -Mes, -iPr according to Fig. 29. Starting from phorone $70$ and $^{15}$N-ammonium chloride, we synthesized lithium salt $74$ in 4 steps. Target AABs $75$ were obtained from $74$ following the same procedures as described for the non-labeled compounds (Fig. 25).

![Synthesis of $^{15}$N-labeled ansa-aminoboranes $75$.](image)

$^1$H NMR experiments recorded after bubbling of $H_2$ (91%) through the samples of AABs $75$-Ph, -Mes, and -iPr revealed appearance of amplified NH and BH signals with amplitudes comparable to those observed with non-labeled compounds. However, spontaneous hyperpolarization of $^{11}$B and $^{15}$N nuclei was observed under the same experimental conditions in $^{11}$B and $^{15}$N NMR spectra. These results are remarkable since rendering hyperpolarization transfer from the former $H_2$ nuclei to the neighbouring heteronuclei typically requires modification of the equipment setup or use of sophisticated pulse sequences. In the $^{11}$B NMR of $75$-iPr-$H_2$, the BH signal appeared as an antiphase doublet with a 10-fold enhancement compared to the thermal signal. The enhancements for the $^{15}$NH signals in the reactions performed at 20 ºC were: 150 for $75$-Ph, 350 for $75$-iPr, and 300 for $75$-Mes.
4.3 WATER TOLERANT ANSA-PHOSPHINOBORANE IV

Compound 69-Mes appeared to reach a steric threshold in reactivity towards both H₂ and H₂O. Since sterical adjustment at the boron site exceeded its limit, we anticipated that introducing a weaker P-centred Lewis basic site could render H₂O addition notably reversible. To explore this hypothesis, we synthesised ansa-phosphinoborane 77 in one step from commercially available materials (Fig. 30). The crystal structure of 77 depicted in Fig. 30 revealed no P-B interaction (P-B distance 3.17(7) Å). To our surprise compound 77 was completely inert towards both H₂ (10 bars) and water at ambient and elevated temperatures.

![Synthesis of 77 and its X-ray crystal structure; hypothetic adducts of 77 with H₂ and H₂O (exo- and endo-forms)](image)

Figure 30 Synthesis of 77 and its X-ray crystal structure; hypothetic adducts of 77 with H₂ and H₂O (exo- and endo-forms)

Table 2. Calculated Gibbs free energies (kcal/mol) of H₂ and H₂O-adducts with 77

<table>
<thead>
<tr>
<th>Adduct</th>
<th>C₆H₆</th>
<th>CH₂Cl₂</th>
<th>MeOH</th>
<th>MeCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>77-H₂-endo</td>
<td>8.0</td>
<td>4.5</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>77-H₂-exo</td>
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<td>6.7</td>
<td>5.4</td>
<td>5.3</td>
</tr>
<tr>
<td>77-H₂O-endo</td>
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<td>9.5</td>
<td>10.5</td>
<td>9.1</td>
</tr>
<tr>
<td>77-H₂O-exo</td>
<td>5.4</td>
<td>5.5</td>
<td>7.7</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*a Solution-phase Gibbs free energies for equilibriums 77 + H₂ ⇌ 77-H₂ and 77 + H₂O ⇌ 77-H₂O

In agreement with experimental observations, DFT calculations showed that formation of adducts 77-H₂ and 77-H₂O is endergonic (Table 2). For each adduct two isomeric forms were investigated: endo, where two ionic fragments of the split molecule are bound (PH···HB or PH···O(H)B), and exo without such bonding due to inverted P centre. For H₂ addition in all solvents product
77-H₂-endo appeared to be by about 2 kcal/mol more stable than 77-H₂-exo, which is promising in light of the importance of H–H bonding for hydrogen release. In contrast, H₂O adduct 77-H₂O-exo is 3-4 kcal/mol more stable than 77-H₂O-endo. Previously reported adducts of FLPs with HX molecules typically feature intramolecular bonding H⋯X (where X=OH, F, Cl)\(^{143, 153, 154}\), whereas in the case of 77-H₂O sterics seems to disfavour such corresponding isomer. However, the most inspiring observation was that the addition of H₂ in more polar solvents is more energetically favourable than this of H₂O, confirming that our goal to discriminate these two molecules based on the size is feasible.

### 4.4 WATER REDUCTION AND HYDROGEN ADDITION IN AQUEOUS CONDITIONS WITH ANSA-PHOSPHINOBORANE VI

The above experimental and DFT studies on compound 77 encouraged us to explore further ansa-phosphinoborane scaffold. To unlock FLP reactivity, we reverted to Lewis acidic site adjustment. Anticipating that the replacement of Me with Cl substituents in ortho-positions to B will increase its electron deficiency while retaining the necessary sterics, we synthesised ansa-phosphinoborane 80 in three steps depicted in Fig. 31.

![Figure 31](image)

Upon exposure of 80 to 10 bars of H₂ in CD₂Cl₂, it produced corresponding adduct 80-H₂ quantitatively in 5 minutes; the latter was comprehensively characterized by \(^1\)H and heteronuclear NMR spectroscopy. Isotope scrambling experiments confirmed that H₂ splitting is highly reversible. After the solution of 80-H₂ in C₆D₆ was kept under 5 bars of H₂/D₂ mixture at room temperature for 12 hours, the said gas mixture was converted to HD in \(~75\)%.

Water adduct 80-H₂O rapidly formed upon exposure of 80-H₂ solution to air. Adduct
**80-H₂O** was prepared separately by reacting 80 with H₂O in CH₂Cl₂ followed by recrystallization. Single crystal X-ray diffraction showed that in the solid state, **80-H₂O** adopts *exo*-conformation (Fig. 32). Interestingly, it features B-O bond length of 1.46 Å, which is notably shorter than this in *endo*-adducts **62-H₂O** and **69-Mes-H₂O** (1.52 and 1.53 Å respectively).

The observed reactivity of 80 towards H₂ and H₂O was investigated by DFT calculations. In good agreement with the experiments, both H₂ and H₂O addition to 80 were found to be exergonic. The solution Gibbs free energies of formation of **80-H₂O-exo** and **80-H₂O-endo** isomers were calculated to be -3.3 and -1.9 kcal/mol respectively. Intriguingly, calculations showed that the addition of H₂ is more endergonic, predicting energies of **80-H₂-exo** and **80-H₂-endo** to be -5.0 and -6.2 kcal/mol respectively.

In the course of NMR monitoring of **80-H₂O** in the moist mixtures of CD₂Cl₂/CD₃CN we have noted the formation of a new species, accompanied by the appearance of H₂ singlet peak both at room and elevated temperatures. The unknown compound was cleanly produced by heating 80 with 3 equivalents of H₂O in CH₂Cl₂/CH₃CN under inert conditions, isolated, and identified as phosphinoborane oxide **80-O** (Fig. 32). Its crystal structure featured B-O-P fragment characterised by B-O and P-O bond lengths of 1.56(9) and 1.55(0) Å respectively.

![Figure 32](image)

**Figure 32** Reactivity of 80 with H₂ and H₂O; X-ray crystal structures of **80-H₂O** (left) and **80-O** (right).

![Figure 33](image)

**Figure 33** Synthesis of 80 and its X-ray crystal structure.
To confirm that 80 produces an equimolar amount of hydrogen upon the reaction with H2O we set up the following experiment in the two-chamber reactor: a mixture of 80 and 2 equivalents of H2O was placed in chamber A to generate H2, which further reduced ethyl cinnamate (equimolar amount with respect to 80) placed in the chamber B (Fig. 33). After 24 hours 1H NMR analysis of the crude product from chamber B revealed close to the quantitative formation of ethyl 3-phenylpropionate.

Indirect reaction between H2O and R3P is employed as a source of hydrogen in a number of chemical transformations, such as Mitsunobu reaction or reductive S-S bond cleavage. To the best of our knowledge direct displacement of hydrogen with phosphines from H2O was not reported so far. The reaction R3P + H2O → R3PO + H2 is thermodynamically favorable but kinetically precluded due to the inability of reactants to adopt reasonable configuration to progress towards the products. In fact, geometry distortion can render P(III) center reactive towards polar E-H bonds. This was demonstrated for constrained ONO-supported P(III) complex, which undergoes formal oxidative addition of H2O to form P(V) complex.

Considering other non-metals, examples of H2O reduction to H2 are scarce. To understand the mechanism of H2O reduction with 80 we carried out kinetic studies employing 31P NMR spectroscopy. The inverse gated proton decoupling pulse sequence ensured quantitative measurements whereas utilization of non-deuterated solvent, namely 1:1 CH3CN/CH2Cl2 mixture, prevented any isotopic exchange side effects. We collected kinetic data at various precise concentrations of H2O and were surprised to discover that reaction rates are higher at lower concentrations of H2O. At 65°C the reaction obeys the second order in 1-H2O and the reverse first order in H2O. However, similar experiments carried out at 25°C revealed first order in 1-H2O along with -0.5 order in water. Combined kinetic and computational DFT studies suggested the mechanism depicted in Fig. 34.

In order to reduce computational costs, DFT calculations were performed for the des-chloro analog of 80, ansa-phosphinoborane 81. Adduct 81-H2O exists in rapid equilibrium with the free 81. The LA center of the latter abstracts water-originated hydrogen atom from the PH in the form of hydride (umpolung of the proton) concurrently with OH migration from the boron to the phosphorus atom. Borohydride 81-H then reacts with phosphoxonium 81-OH to give 81-O, free 81, and H2 via proton-hydride recombination. According to the calculations, the hydride abstraction step is rate-determining with the kinetic barrier of 27.5 kcal/mol (in CH2Cl2). It involves both water adduct 80-H2O and free 80, giving the first kinetic orders in each of these compounds. Since 80-H2O and free 80 exist in rapid equilibrium, the expected kinetic orders 2 in 80-H2O and -1 in H2O are consistent with the ones observed at 65°C. The alternative unimolecular process featured too high kinetic barrier of 42.5 kcal/mol; besides, it does not conform with the observed kinetics.
DFT studies of the water reduction mechanism with a model deschlorophosphinoborane \(81\). Solution phase Gibbs free energies computed at the \(\omega B97XD/6-311++G(3df,3pd)\) level of theory (DFT) are given in kcal/mol with respect to \(81-H_2O\)-exo in dichloromethane (blue), acetonitrile (black), and water (red).

The results above pointed to the presence of free \(80\) in wet solvents. Hence, we could expect to detect formation of \(80-H_2\) under such conditions upon addition of \(H_2\). The solution of \(80\) in CD\(_2\)Cl\(_2\)/CD\(_3\)CN, containing 6 equivalents of H\(_2\)O, was pressurized with 10 bars of H\(_2\) in the gas-tight heavy wall NMR tube and heated at 80°C for an hour, followed by \(^1^H\) and heteronuclear NMR analysis. The reaction mixture contained two major species \(80-H_2O\) and \(80-O\) but also minor species \(80-H_2\) (about 13%). Prolonged observation and reliable quantitative monitoring of \(80-H_2\) were impossible due to its rapid oxidation and interference of H/D exchange. Similar experiments with pH\(_2\) confirmed the formation of \(80-H_2\) by displaying amplified PH and BH PHIP signals. Lower levels of hyperpolarization were observed at \(^{31}P\) and \(^{11}B\) nuclei. The occurrence of PHIP proves that the detected \(80-H_2\) is a product of direct H\(_2\) activation by \(80\), rather than an intermediate formed in the course of the reduction of H\(_2\)O.

### 4.5 CATALYTIC ASYMMETRIC HYDROGENATION WITH CAMPHOR-BASED CHIRAL BORANE \(^V\)

When this study was initiated, the highest ees in the FLP-type hydrogenation of imines were obtained with Klankermayer’s (1R)-(+) -camphor-based \(35a\) (up to 83%). This and related reports, however, lacked understanding of the factors governing the enantiocontrol. To address this issue, our collaborators conducted detailed computational DFT studies on the hydrogenation of
PhCMe=NPhe 32a catalysed by 35a. The reaction was found to be kinetically controlled, and in the stereoselectivity-determining hydride transfer step from borohydride 35a-H to iminium salt 32a-H+, several TSs were located within just 5 kcal/mol range. Based on the set of the obtained TSs the enantioselectivity was computed as 80.7%, which is consistent with the experimental ee of 79%. The lowest TS, which leads to the major R enantiomer of 32a was just 1.5 kcal/mol below the following TS leading to the minor S enantiomer. An essential role in the stabilization of TSs played weak non-covalent interactions, namely π-π stacking, CH3-π, and Ph-Ph intermolecular contacts. Weak interactions of the Ph group of the catalyst with 32a-H+ seemed to be particularly important, and preliminary calculations suggested that introduction substituents at meta positions would lead to a greater energetic separation of the two lower transition states, increasing the enantioselectivity.

We were interested to assess the meta substituted analogs of 35a experimentally. We started with a computationally examined candidate, borane 84a, which was predicted to provide 99.1% ee in the model reaction. Borane 84a was synthesized following the procedure established for 35a (Figure 35). Fortunately, separation of diastereoisomers 84a and 84b did not require kinetic recrystallization as was described in the said procedure for 35a and 35b. Hydroboration of alkene 83 with Piers’ borane under solvent-free conditions gave a mixture of 84a and 84b in 7:1 ratio. Pure 84a was isolated from the mixture by simple recrystallization from pentane at -20°C and its structure was confirmed by single crystal X-ray diffraction analysis.

Unfortunately, catalyst 84a did not overperform previously reported 35a, reaching only 75% ee at most in the hydrogenation of the model substrate 32a, albeit at high conversions. Nevertheless, we decided to investigate another candidate, borane 88 bearing bulky tBu substituents, design of which was guided by chemical intuition. In fact, the most successful chiral FLP catalysts reported
by Du et al. carried substantial steric bulk, which seemed to be a decisive element of the stereocontrol (see section 3.2.2). In the recent report, it was claimed that dispersion interactions rather than steric bulk might be the origin of enantiocontrol with catalyst containing such substituents.158

To obtain 88 we developed alternative procedure depicted in Fig. 36, because the addition of 3,5-tBu2-PhLi or 3,5-tBu2-PhMgBr to the starting (1R)-(+)-camphor led to its enolization. The last hydroboration step carried out under solvent-free conditions gave exclusively one diastereomer 88 in a quantitative yield. Recrystallization of 88 from n-pentane at -20°C gave crystals suitable for X-ray crystallographic analysis.

Figure 36 Synthesis of chiral borane 88 and its X-ray crystal structure.

Table 3. Asymmetric hydrogenation of imines with 88.a

<table>
<thead>
<tr>
<th>Substrate (0.25 mmol), PhMe (0.5 ml), conversion by 1H NMR spectroscopy, ee by HPLC (Chiralcel OD-H or OJ-H column)</th>
<th>89f</th>
<th>89g</th>
<th>89h c,d</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 25 °C:</td>
<td>99%, 93% ee (S)</td>
<td>99%, 33% ee (R)</td>
<td>99%, 21% ee (S)</td>
</tr>
<tr>
<td>At -15 °C:</td>
<td>99%, 95% ee (S)</td>
<td>99%, 96% ee (S)</td>
<td></td>
</tr>
</tbody>
</table>

a Substrate (0.25 mmol), PhMe (0.5 ml), conversion by 1H NMR spectroscopy, ee by HPLC (Chiralcel OD-H or OJ-H column). c Reaction time 48 h. d 10 mol% of 88
To our delight, when 88 was probed as a catalyst in hydrogenation of model imine 32a quantitative hydrogenation was observed in 24 hours along with 92% ee. The solvent effect on the stereoselectivity was found to be insignificant. We examined catalyst 88 in the hydrogenation of a small series of imines (Table 3), among which N-aryl-substituted-imines 35b-c and N-cyclohexyl substituted 35f gave full conversions and similarly high ees in the range of 91-94%. Enantioselectivity dropped dramatically in the hydrogenation of benzyl-substituted imine 35g (33% ee). Hydrogenation of quinoline 35h required higher catalyst loading and prolonged time to achieve the full conversion (10 mol%, 48h) with only 21% ee. Enantioselectivity could be slightly improved upon lowering the temperature to -15°C, as was demonstrated in the hydrogenation of selected imines 35a,d (95% and 96% ee respectively). As high enantioselectivities in FLP mediated hydrogenation of imines were reported recently by Wang et al. utilizing bicyclic borane 43a at -40°C (up to 95% ee).
5 CONCLUSIONS

Frustrated Lewis pairs exhibit an impressive range of reactivities, yet, just a few were translated into practically valuable processes. One of them, activation of H₂, was employed in hydrogenation catalysis. FLP-type hydrogenation rapidly progressed in terms of substrate scope, functional group tolerance, and selectivity. Besides application in catalysis, intramolecular FLPs have the ability to generate parahydrogen-induced hyperpolarization (PHIP) upon addition of parahydrogen (pH₂). The phenomenon is associated with NMR signal amplification of pH₂ derived hydrogens and possibly neighboring nuclei by orders of magnitude. Therefore, linked FLPs have the potential as PHIP contrast agents in NMR and MRI. The reversibility of pH₂ addition and exchange rates are essential for the efficient production of PHIP. To that end, ortho-phenylene bridged (ansa) FLPs have the advantage of flexibility in terms of strength and sterics of LA and LB sites. This, in turn, ensures high tunability of thermodynamic and kinetic parameters of H₂ addition.

We synthesized the series of ansa-aminoboranes 69-Ph, -iPr, -Mes, -bPh, and -Dipp bearing non-halogenated sterically varying aryls at B site. Reduced acidity of the boryl sites in these compounds allowed to achieve thermodynamically neutral and, consequently, highly reversible H₂ addition at ambient temperatures and pressures. Compound 69-Mes represented a steric threshold for reactivity, as more hindered 69-Dipp was inert to H₂ and H₂O. Compound 69-bPh existed as a zwitterionic adduct formed upon a spontaneous intramolecular splitting of one of the C−H bonds of the ortho-biphenyl substituents by B/N centers. This compound was reported as a demonstration of the ability of ansa-aminoboranes to activate more challenging sp²C−H bonds.

Being pressurised with H₂, compounds 69-Ph, -iPr, -Mes existed in dynamic chemical equilibrium with the corresponding hydrogen adducts, and respective thermodynamic and kinetic parameters (Kᵣ and kᵈⁱˢ) were extracted using NMR spectroscopy. All three compounds provided amplified NH and BH PHIP signals with modest enhancements (up to 20 fold). PHIP could be generated continuously (as long as pH₂ was supplied in the solution) at ambient pressures and temperatures, which is optimal in the context of applications. Compound 69-Ph featured the most suitable characteristics (higher Kᵣ and kᵈⁱˢ values) and demonstrated higher levels of PHIP at subzero temperatures. An abnormal decrease in PHIP level was observed at higher temperatures for 69-Ph, likely indicating switching on non-pairwise activation mode. It was not the case with sterically more bulky 69-iPr and 69-Mes, and at room temperature 69-iPr was found to be the most optimal candidate.

Apart from thermodynamic and kinetic parameters, the NMR properties of the nuclei involved in PHIP, such as relaxation times (T₁ and T₂) are crucial.
Nuclei with longer relaxation times generate stronger PHIP signals with longer observation windows. Introducing $^{15}$N nuclei instead of quadrupole $^{14}$N within the series 75-Ph, -iPr, -Mes led to spontaneous hyperpolarization transfer from p-H$_2$ derived nuclei to $^{15}$N and $^{11}$B. PHIP signals of $^{15}$NH$^+$ exhibited up to 350-fold enhancement.

Despite steric hindrance around B, all compounds except 69-Dipp reacted with H$_2$O irreversibly, which means their incompatibility with biological media. In contrast, a structural analog of 69-Mes, where -TMP is replaced with weaker Lewis basic moiety -PCy$_2$, ansa-phosphinoborane 77 is completely inert towards H$_2$ and also H$_2$O. Computational analysis predicted that its hypothetical H$_2$ adduct is more thermodynamically favorable than the H$_2$O adduct and suggested that steric plays the key role in destabilizing the latter.

The above observation encouraged us for further development of the ansa-phosphinoborane scaffold. We synthesized 80, where chlorines in ortho-positions to B were intended to unlock FLP reactivity but retain the comparable sterics as its predecessor 77. Compound 80 activates both H$_2$ and H$_2$O in a reversible manner. This allowed detecting adduct 80-H$_2$ in moist solvents, which was demonstrated in experiments with the thermal polarization and parahydrogen. Compound 80 oxidizes to 80-O upon unprecedented for phosphines stoichiometric reduction of H$_2$O to H$_2$. Combined kinetic and computational studies revealed that the reaction occurs via PH$^+$ proton umpolung triggered by Lewis acidic site of the free 80, which exists in rapid equilibrium with 80-H$_2$O.

In another part of this work, a modification of previously reported (1R)-(+)-camphor based catalyst 35a, new chiral borane 88 was synthesized. It was superior to the parental catalyst, giving up to 96% ee in the hydrogenation of imines. Alteration of 35a leading to 88 was suggested by a computational study carried out by our collaborators and partially by chemical intuition. In addition, unlike 35a, preparation of 88 did not involve a tedious separation procedure.

In this thesis, thorough structural adjustment guided by complementary theoretical and experimental studies allowed to extend the boundaries of FLPs in a few directions. Firstly, we made a step further towards the practical implementation of FLP mediated PHIP. Secondly, we developed one of the most enantioselective FLP catalyst known to date. However, it was not the rational design, but serendipity, which led us to the discovery of unanticipated stoichiometric reduction of water by one of the studied ansa-phosphinoborane. The comprehensive mechanistic study provided a solid basis to further developments in this direction. Certainly, it may help to translate peculiar stoichiometric reactions into catalytically viable processes capable of converting cheap and abundant H$_2$O into H$_2$, the substance in greater-than-ever demand.
6 REFERENCES


149. Niegger, M.; Sorochkina, K.; Chernichenko, K.; Repo, T., CCDC 2121061: Experimental Crystal Structure Determination, **2021**, DOI: 10.5517/ccdc.csd.cc2964b0


A. Preparation of 69-Dipp

Starting material 2-iodo-1,3-diisopropylbenzene was synthesized from 2,6-diisopropylaniline according to the reported procedure (Bolstad, D. B. et al., J. Med. Chem. 2008, 51, 6839-6852). At -78°C, tert-butyllithium (2.82 ml of 1.7 M solution in hexane, 4.8 mmol) was added dropwise to a vigorously stirring solution of 2-iodo-1,3-diisopropylbenzene (691 mg, 2.4 mmol) in 6 ml of diethyl ether. The mixture was stirred additionally for 15 min at -60°C, warmed up to room temperature and stirred for another 1 h. Then the solution was cooled to -90°C, and BF₃·OEt₂ (0.15 ml, 170 mg, 1.2 mmol) was added via syringe in one portion. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure; the residue was suspended in 10 ml of toluene and filtered. The filter cake was washed with additional portions of toluene (5x1 ml), and the filtrate was evaporated to dryness yielding 403 mg bis(2,6-diisopropylphenyl) fluoroborane (Dipp₂BF): as slightly yellow oil (95.4%), which was used without further purification. ¹H NMR (500 MHz, CD₂Cl₂, 25°C): δ 7.21 (m, 2H), 7.05 (m, 4H), 3.17 (m, 4H), 1.13 (d, J₃H = 6.7 Hz, 24H). ¹⁹F NMR (282 MHz, C₆D₆): δ -178.27 (s). Obtained as described above, Mes₂BF was redissolved in 6 ml of toluene and the solution was cooled to -70°C. The solution of [2-(2,2,6,6-tetramethylpiperidin-1-yl)phenyl]lithium (66) (270 mg, 1.2 mmol) in 4 ml of toluene was added via syringe in one portion. The mixture was allowed to warm to room temperature and heated in an oil bath at 60°C overnight. The solvent was removed under reduced pressure; the residue was suspended in 10 ml of toluene and filtered. The filter cake was washed with additional portions (5x1 ml) of toluene and the filtrate was evaporated to dryness yielding 0.610 mg (>90%) of crude yellow oil containing ansa-aminoborane 69-Dipp as major compound and residual amount of unreacted Mes₂BF. ¹H NMR (500 MHz, C₆D₆): δ 7.54 (dd, JHH = 7.6, 1.9 Hz, 1H), 7.34 (t, JHH = 7.8 Hz, 1H), 7.27 (m, 1H), 7.23-7.18 (m, 3H), 7.11-7.06 (m, 2H), 7.04-6.98 (m, 2H), 3.88 (hept, JHH = 6.8 Hz, 2H), 3.42 (hept, JHH = 6.2 Hz, 2H), 3.02 (hept, JHH = 7.3, 6.6 Hz, 2H), 2.49 (hept, JHH = 6.8 Hz, 2H), 1.58-1.44 (m, 12H), 1.37-1.31 (m, 4H), 1.25 (d, JHH = 6.8 Hz, 3H), 1.23-1.06 (m, 8H overlapped with protons of residual starting material), 0.98 (d, JHH = 6.5 Hz, 3H), 0.83 (s, 3H), 0.77 (m, 6H), 0.69 (s, 3H), 0.62 (d, JHH = 6.4 Hz, 3H), 0.58 (d, JHH = 6.6 Hz, 3H).
Figure 37  $^1$H NMR (300 MHz, C$_6$D$_6$, 25°C) and $^{19}$F (282 MHz, C$_6$D$_6$, 25°C) spectra of compound Mes$_2$BF, precursor of 69-Dipp.

Figure 38  $^1$H NMR (300 MHz, C$_6$D$_6$, 25°C) spectrum of compound of crude 69-Dipp.