Frustrated Lewis Pairs: Metal-free Hydrogen Activation and More

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Dedicated to Professor Thomas Kauffmann on the occasion of his 85th birthday
Sterically encumbered Lewis acid and Lewis base combinations do not undergo the ubiquitous neutralization reaction to form “classical” Lewis acid/Lewis base adducts. Rather, both the unquenched Lewis acidity and basicity of such sterically “frustrated Lewis pairs” (FLPs) is available to carry out unusual reactions. Typical examples of frustrated Lewis pairs are inter- or intramolecular combinations of bulky phosphines or amines with strongly electrophilic $\text{RB(C}_6\text{F}_5)_2$ components. Many examples of such frustrated Lewis pairs are able to cleave dihydrogen heterolytically. The resulting $\text{H}^+/\text{H}^-$ pairs (stabilized for example, in the form of the respective phosphonium cation/hydridoborate anion salts) serve as active metal-free catalysts for the hydrogenation of, for example, bulky imines, enamines, or enol ethers. Frustrated Lewis pairs also react with alkenes, aldehydes, and a variety of other small molecules, including carbon dioxide, in cooperative three-component reactions, offering new strategies for synthetic chemistry.

1. Introduction

In 1923 Gilbert N. Lewis classified molecules that behave as electron-pair donors as bases and conversely electron-pair acceptor systems as acids.\[1\] Lewis acids are characterized by low-lying lowest unoccupied molecular orbitals (LUMOs) which can interact with the lone electron-pair in the high-lying highest occupied molecular orbital (HOMO) of a Lewis base. These notions of Lewis acids and bases were used to rationalize numerous reactions. For example, the combination of a simple Lewis acid and Lewis base results in neutralization similar to the corresponding combination of Brønsted acids and bases.\[2\] However, in the case of Lewis acids and bases, instead of forming water, the combination results in the formation of a Lewis acid/base adduct. This principle described by Lewis has come to be a primary axiom of chemistry.\[1–3\] Lewis acid/base chemistry is central to our understanding of much of main-group and transition-metal chemistry and a guiding principle in understanding chemical reactivity in general.

While much chemical history can be considered in terms of the interaction of Lewis acids and bases, occasionally since 1923, researchers have encountered systems that appear to deviate from Lewis’ axiom. In 1942, Brown and co-workers\[4\] while examining the interaction of pyridines with simple boranes, noted that although most of these combinations of Lewis acids and bases formed classical Lewis adducts, lutidine formed a stable adduct with $\text{BF}_3$ but did not react with $\text{BMe}_3$ (Scheme 1).\[5\] Based on an examination of molecular models, they attributed this result to the steric conflict of the ortho-methyl groups of lutidine with the methyl groups of the borane. While Brown et al. noted this anomaly, they did not probe the impact on subsequent reactivity.

In 1959, Wittig and Benz described that 1,2-didehydrobenzene, generated in situ from $\text{o}$-fluorobromobenzene, reacts with a mixture of the Lewis base triphenylphosphine and the Lewis acid triphenylborane to give the $\text{o}$-phenylene-bridged phosphonium-borate 5 (Scheme 2).\[6\] A few years later, Tochtermann, then a member of the Wittig school, observed the formation of the trapping product 7, instead of the usual formation of polybutadiene through anionic polymerization, upon addition of $\text{BPh}_3$ to the butadiene monomer/trityl anion initiator mixture. Both researchers realized the special nature of the bulky Lewis pairs that did not yield the classical Lewis acid/base adduct. This situation led Tochtermann to describe such a non-...
quenched Lewis pair using the German term “antagonistisches Paar”.[7]

2. Frustrated Lewis Pairs and H2 Activation: The Beginning

2.1. \((\text{C}_6\text{H}_2\text{Me}_3)_2\text{PH}(\text{C}_6\text{F}_4)\text{BH}(\text{C}_6\text{F}_5)_2\): Reversible H2 Activation

The Stephan group, in exploring the reactivity of maingroup systems, queried the impact of systems in which Lewis acid and Lewis base functions were incorporated into the same molecule and sterically precluded from quenching each other. To this end, the zwitterionic salt 9a (Scheme 3), obtained from the nucleophilic aromatic substitution reaction of B(\text{C}_6\text{F}_5)_3 with dimesitylphosphine, was treated with Me_2SiHCl (8), yielding 10a cleanly (Scheme 3). The zwitterionic species 10a is a rare example of a molecule that contains both protic and hydridic fragments. Indeed, it was anticipated that this species might spontaneously lose H2, however, this was not the case. On the contrary, this species was air and moisture stable and as such quite robust. Nonetheless, heating this species to 150°C prompted the elimination of H2 generating the orange-red phosphino-borane 11a (Scheme 3).[8] This conversion was confirmed with X-ray crystallographic data for 10a, 11a, and the THF adduct of the generated phosphino-borane, 12 (Figure 1). Compound 11a was also accessible directly from 9a by treatment with a Grignard reagent (Scheme 3). This species 11a proved to be monomeric in solution, as both the B and P centers are sterically congested precluding dimerization or higher aggregation. As such, this molecule can be described as a sterically “frustrated Lewis pair”.

Doug Stephan attended McMaster University followed by the University of Western Ontario earning a PhD in 1980. He was a NATO postdoctoral Fellow at Harvard University (R. H. Holm) and in 1982 joined the faculty at Windsor, and was subsequently promoted through the ranks to University Professor in 2002. Most recently his group uncovered “frustrated Lewis pairs” and their chemistry. He has received a number of awards. In 2008, he took up a position as Professor of Chemistry and Canada Research Chair in Inorganic Materials and Catalysis at the University of Toronto. For 2009–11, he was awarded a Killam Research Fellowship.

Gerhard Erker studied chemistry at the University of Köln. He received his doctoral degree at the University Bochum in 1973 (W. R. Roth). After a post-doctoral stay at Princeton University (M. Jones, Jr.) he did his habilitation in Bochum and then joined the Max-Planck-Institut für Kohlenforschung in Mülheim as a Heisenberg fellow. He became a Chemistry Professor at the University of Würzburg (1985) and then (1990) at the University of Münster. For his scientific achievements he received many awards. He was the President of the German Chemical Society (GDCh) in 2000–2001 and a member of the Senate of the Deutsche Forschungsgemeinschaft (2002–2008).
Both compounds 10a and 10b were found to react with benzaldehyde to effect carbonyl insertion into the B–H bond affording the related zwitterionic compounds 13 (R = C₆H₄Me₃, 13a; tBu, 13b; Scheme 4).

![Scheme 4. Reactions of 10a and 10b with benzaldehyde.](image)

The elimination of H₂ from 10a is perhaps not surprising however, a remarkable finding is that addition of H₂ to the phosphino-borane 11a at 25°C resulted in the rapid and facile regeneration of the zwitterionic salt 10a (Scheme 3). The loss of H₂ from 10a also results in a dramatic color change from colorless to orange-red (λmax: 455 nm; ε = 487 L cm⁻¹ mol⁻¹; Figure 2). Weak π-donation from P, and electron acceptance by B has been proposed to account for the intense color of the related acetylene-based phosphino-borane Ph₂PC≡CB-(C₆H₄Me₃). In addition, it is noteworthy that phosphine-borane adducts R₂PH(BH₃) thermally or catalytically eliminate H₂ to give cyclic and polymeric phosphino-boranes.

This remarkable finding represents the first non-transition-metal system known that both releases and takes up dihydrogen. X-ray data for 14b were unexceptional although it is noted that the cations and anions pack such that the BH and PH units are oriented towards each other with the BH···HP separation of 2.75 Å (Figure 3). Despite this orientation in the solid state, heating of this species to 150°C did not liberate H₂, in contrast to 10a (Section 2.1). The combination of (C₆H₄Me₃)₅P and B(C₆F₅)₃ was also shown to activate D₂ affording [D₂]-14a (Scheme 5).

![Scheme 5. Heterolytic activation of H₂ or D₂ by phosphine/borane combinations.](image)

The observation described in Section 2.2 prompted questions regarding the generality of this heterolytic H₂ activation. In probing this question, solutions of the phosphines R₃P (R = tBu, C₆H₄Me₃) with B(C₆F₅)₃ were examined. These mixtures showed no evidence of a Lewis acid/base neutralization reaction. Indeed, the NMR spectroscopic data for these mixtures showed resonance signals identical to the individual constituents even on cooling to −50°C.[8b] In a facile and straightforward manner, exposure of these mixtures to an H₂ atmosphere resulted in the rapid generation of the salt 14 (R = C₆H₄Me₃, 14a, tBu 14b; Scheme 5) resulting from the heterolytic cleavage of dihydrogen.[11] The observation described in Section 2.2 prompted questions regarding the generality of this heterolytic H₂ activation. In probing this question, solutions of the phosphines R₃P (R = tBu, C₆H₄Me₃) with B(C₆F₅)₃ were examined. These mixtures showed no evidence of a Lewis acid/base neutralization reaction. Indeed, the NMR spectroscopic data for these mixtures showed resonance signals identical to the individual constituents even on cooling to −50°C.[8b] In a facile and straightforward manner, exposure of these mixtures to an H₂ atmosphere resulted in the rapid generation of the salt 14 (R = C₆H₄Me₃, 14a, tBu 14b; Scheme 5) resulting from the heterolytic cleavage of dihydrogen.[11]
These unprecedented three-component reactions appear to result from the interaction of H$_2$ with the residual Lewis acidity and basicity derived from the frustrated Lewis pair. The range of Lewis acidity and basicity required for this facile heterolytic activation of H$_2$ was also probed. Reaction of tBu$_3$P and BPh$_3$ with H$_2$ slowly gave 15 (Scheme 5) although the salt was only isolated in 33% yield. The analogous combination of (C$_6$H$_2$Me$_3$)$_3$P and BPh$_3$, (C$_6$F$_5$)$_3$P and B-(C$_6$F$_5$)$_3$, or tBu$_3$P and B(C$_6$H$_2$Me$_3$)$_3$ resulted in no reactions with H$_2$, despite the fact that no adducts were detected spectroscopically for these pairs of Lewis acids and bases. Based on these observations, it was concluded that a combined aggregate Lewis acidity and basicity is required to effect the activation of H$_2$ by a frustrated Lewis pair.

2.3. The Intramolecular FLP (C$_6$H$_2$Me$_3$)$_2$PCH$_2$CH$_2$B(C$_6$F$_5$)$_3$

The Erker group, in targeting new systems capable of H$_2$ activation, sought to develop linked phosphine-boranes. They noted that Tilley et al. had developed the synthesis of the phosphino-borane of the form (Ph$_2$PCH$_2$CH$_2$BR)$_2$ (17a R$^1$ = cyclohexyl (Cy); 17b BR$^1_2$ = 9-borabicyclo[3.3.1]nonyl (9-BBN)) through the regioselective hydroboration of Ph$_2$PCH=CH$_2$ (16a) with either (Cy$_2$BH)$_2$ or the 9-BBN reagent.[12] These systems have been exploited as “ambi-
philic” ligands[13] affording such complexes as the zwitterionic nickel species 18. Targeting the incorporation of more electrophilic boron fragments, the Erker group treated 16a with “Piers’ borane”[14] HB(C$_6$F$_5$)$_3$. (19). In this case, the classical Lewis acid/base adduct 20 (Scheme 6, Figure 4) was formed.[15] In contrast, the corresponding allyl- and butenyl phosphines 21 (21a: R = Ph, 21b: tBu) and 23 (CH$_2$=CHCH$_2$PPh$_2$) underwent clean hydroboration with HB-(C$_6$F$_5$)$_3$ to yield the bifunctional phosphine-borane products, 22 (R = Ph 22a, tBu 22b) and 24 (Figure 5), respectively (Scheme 6). These species formed strong intramolecular phosphorus/boron Lewis acid/base adducts.[16,17,18] Studies of the conformational properties revealed heteroalkane-like behavior.

In contrast to the above systems, reaction of the bulkier (dimesityl)vinylphosphine 16b with 19 produces the clean hydroboration product, 25a/26a (Scheme 7).[19] While this product was not characterized by X-ray diffraction, it was fully characterized spectroscopically. Theoretical analysis revealed that the global minimum for this monomeric bifunctional system features a four-membered heterocyclic struc-

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**Scheme 6.** Hydroboration of alkenyl phosphines.

**Scheme 7.** Synthesis and reactivity of 25a.
ture with a weak P···B interaction\textsuperscript{[20]} [(P···B) calcd. 2.21 Å]. This geometry is supported in part by favorable π–π-stacking interactions\textsuperscript{[21]} between an electron-poor C\textsubscript{6}F\textsubscript{5} arene ring on the boron and a parallel electron-rich mesityl substituent at phosphorus (Figure 6). Density functional theory (DFT) calculations also identified a gauche and an antiperiplanar conformation. These geometries are of similar energy, both calculated ca. 8 to 12 kcal mol\textsuperscript{-1} higher in energy than the global minimum depending on the employed method.\textsuperscript{[22]}

Exposure of a solution of 25\textsubscript{a} to an atmosphere of H\textsubscript{2} (1.5 bar) at ambient temperature immediately produced the zwitterionic product 27\textsubscript{a} (Scheme 7) as a white precipitate (Figure 7). Heterolytic activation of H\textsubscript{2} to give a phosphonium-borate salt was confirmed by characteristic NMR spectral features. The corresponding reaction with D\textsubscript{2} gave the corresponding D\textsubscript{2}-labeled zwitterionic product [D\textsubscript{2}]\textsubscript{-}27\textsubscript{a}.

Figure 6. DFT calculated structure of the intramolecular P–B Lewis pair 25\textsubscript{a}.

The product 27\textsubscript{a}, formed through the heterolytic splitting of H\textsubscript{2} by the intramolecular frustrated Lewis pair 25\textsubscript{a}, shows a typical hydrido borate reactivity. It rapidly reduces benzaldehyde stoichiometrically to give the benzylalcohol derivative 28 that was characterized by X-ray diffraction (Scheme 7, Figure 8).\textsuperscript{[19]}

To obtain experimental information regarding the thermal ring-opening, several chiral derivatives were prepared by incorporation of substituents in the alkyl-chain linking boron and phosphorus\textsuperscript{[15]}. The substituted derivatives with substituents \textit{alpha}- (R = CH\textsubscript{3}, 26\textsubscript{b}, Ph 26\textsubscript{c}) or \textit{beta}- (R = SiMe\textsubscript{3}, 26\textsubscript{d}) to phosphorus were prepared by analogous hydroboration reactions of suitably substituted alkenyl(dimethyl)phosphines of the form (C\textsubscript{6}H\textsubscript{2}Me\textsubscript{3})\textsubscript{2}PCR\textsubscript{1}=CHR\textsubscript{2} (R\textsubscript{1} = CH\textsubscript{3}, R\textsubscript{2} = H 16\textsubscript{b}; R\textsubscript{1} = Ph, R\textsubscript{2} = H 16\textsubscript{c}; R\textsubscript{1} = H, R\textsubscript{2} = SiMe\textsubscript{3} 16\textsubscript{d}) (Scheme 8) with Piers/C\textsubscript{29} borane. Owing to the presence of a chiral center in the bridge, the NMR spectra of each of these compounds feature signals arising from pairwise diastereotropic mesityl and C\textsubscript{6}F\textsubscript{5} groups. The rapid equilibration of the open-chain and four-membered donor–acceptor forms of these phosphine-boranes does not affect the geometry at phosphorus, this remains pseudo-tetragonal and hence retains prochirality. In contrast, the rapid equilibration results in the coalescence of the respective NMR signals arising from the C\textsubscript{6}F\textsubscript{5} rings on the boron center, as it interconverts from trigonal-planar geometry in the open isomer to tetrahedral geometry in the cyclic form. From the line-shape analysis of the temperature-dependent \textsuperscript{19}F NMR resonances (Figure 9) of the p-F atoms of the pair of C\textsubcript{6}F\textsubscript{5} substituents for 26\textsubscript{b}, a Gibbs activation energy\textsuperscript{[23]} for the reversible ring opening was determined to be Δ\textsubscript{G}^{\ddagger,\text{dis}} (280 K) \approx (11.7 \pm 0.4) kcal mol\textsuperscript{-1}. The substituted analogues 26\textsubscript{c} and 26\textsubscript{d} showed similar B–P dissociation energies.

Whereas compound 25\textsubscript{b} reacts with H\textsubscript{2} to give the zwitterionic product 27\textsubscript{b} (Scheme 8) at ambient temperature, the other analogues 26\textsubscript{c} and 26\textsubscript{d} did not react with H\textsubscript{2} under similar conditions.\textsuperscript{[15]}

Figure 7. Molecular structure of the zwitterion 27\textsubscript{a}.

Figure 8. Molecular structure of 28.

3. Other Phosphorus/Boron Systems in H₂ Activation

3.1. Alkenylene-Linked FLPs

The developments outlined in Section 2.3 prompted an examination of related alkenylene-linked phosphine/borane systems. Such systems are readily derived from hydroboration of \(\text{tBu}_2\text{P}(	ext{C}_6\text{H}_2\text{Me}_3)\text{CCH}_3\) with \(\text{19}\).\(^{24}\) The resulting orange product \(\text{29a}\) is inert to dihydrogen at ambient conditions but reacts cleanly at 60 bar \(\text{H}_2\) to give the corresponding zwitterionic phosphonium hydridoborate \(\text{30a}\) (Scheme 9).\(^{25}\) This product exhibits the typical \(^1\text{H}\) NMR doublet and quartet signals for the \(\text{P–H}\) and the \(\text{B–H}\) units, respectively. The dihydrogen splitting reaction was also confirmed by the corresponding \(\text{D}_2\) experiment affording \([\text{D}_2]\text{30a}\).

The corresponding hydroboration reactions of \((\text{C}_6\text{H}_5\text{Me}_3)\text{PC}≡\text{CCH}_3\) with \(\text{19}\) \(^{24}\) resulted in a non-quenched Lewis pair that activated \(\text{H}_2\) (1.5 bar) to yield the phosphonium hydridoborate salt \(\text{32}\) (Scheme 12).\(^{28}\) A single proton rapidly exchanges between the two phosphine sites of the \(\text{P–H}\) and the \(\text{B–H}\) units, respectively. The dihydrogen splitting reaction was also confirmed by the corresponding \(\text{D}_2\) experiment affording \([\text{D}_2]\text{30a}\).

The corresponding hydroboration reactions of \((\text{C}_6\text{H}_5\text{Me}_3)\text{PC}≡\text{CPh}\) with Piers’ borane gave the corresponding bright-red bifunctional products \(\text{29b}\) (\(\text{R} = \text{CH}_3\)) and \(\text{29c}\) (\(\text{Ph}\)), respectively. Both species are inactive toward \(\text{H}_2\) even at elevated \(\text{H}_2\) pressure (60 bar). However, upon mixing these compounds with the very reactive ethylene-linked hydrogen activation product \(\text{27a}\), rapid proton and hydride transfer occurs to give equilibria affording \(\text{30b}\) (\(\text{R} = \text{CH}_3\)) and \(\text{30c}\) (\(\text{R} = \text{Ph}\); Scheme 10 and Scheme 11). Employing this proton/hydride transfer equilibrium, it was possible to effect the complete conversion to \(\text{30a–c}\) using a catalytic amount of \(\text{27a}\) (10 mol %) in the presence of \(\text{H}_2\) (2.5 bar). Alternatively, this conversion was also effected employing a catalytic amount of \(\text{tBu}_3\text{P}\) (15 mol %; Scheme 11). Similarly the corresponding dideuteride \([\text{D}_2]\text{30}\) was obtained by the catalytic reaction using \(\text{D}_2\).\(^{25}\) In the case of \(\text{30b}\), the structure of the zwitterion was confirmed crystallographically (Figure 10).

3.2. Bisphosphino Naphthalene

The Erker group has also developed a new intermolecular frustrated Lewis pair based on 1,8-bis(diphenylphosphino)naphthalene (31)\(^{30}\) which is capable of heterolytic \(\text{H}_2\) cleavage. Combining this bidentate phosphine with \(\text{B}-(\text{C}_6\text{F}_5)_3\)\(^{27}\) in a 1:1 molar ratio resulted in a non-quenched Lewis pair that activated \(\text{H}_2\) (1.5 bar) to yield the phosphonium hydridoborate salt \(\text{32}\) (Scheme 12).\(^{29}\) A single proton rapidly exchanges between the two phosphine sites of the...
bisphosphine, although this exchange process is slowed at low temperature as evidenced by $^{31}$P NMR spectral data. This unsymmetrical structure was also confirmed crystallographically (Figure 11). The approach of the phosphonium cation and [HB(C$_6$F$_5$)$_3$] anion featured a rather close PH–HB contact$^{30}$ of 2.08 Å. This zwitterion liberated H$_2$ at 60°C regenerating the mixture of 31 and B(C$_6$F$_5$)$_3$, thus providing the second reported system capable of metal-free reversible activation of H$_2$.

### 3.3. Phosphinometallocene-Based FLPs

The use of ferrocene as a sterically demanding substituent on phosphorus has also been explored.$^{31}$ To this end, the mono- and bis(phosphino)ferrocenes [(η$^5$-C$_5$H$_4$PrBu$_2$)FeCp] (33; Cp = C$_5$H$_5$), [(η$^5$-C$_5$H$_4$PrBu$_2$)Fe(C$_5$Ph$_2$)] (34), and [(η$^5$-C$_5$H$_4$Pr$_2$)Fe] (R = iPr 35, tBu 36) were combined with B(C$_6$F$_5$)$_3$. In the case of 33, 35, and 36, reaction with B(C$_6$F$_5$)$_3$ results in the mono-para-substitution products of the form [(η$^5$-C$_5$H$_4$PrBu$_2$)FeBF(C$_6$F$_5$)$_2$]FeCp] (37), [(η$^5$-C$_5$H$_4$PrBu$_2$)FeBF(C$_6$F$_5$)$_2$]Fe(η$^5$-C$_5$H$_4$PrBu$_2$)] (38; Scheme 13) and a di-para-substitution product [(η$^5$-C$_5$H$_4$Pr$_2$)FeBF(C$_6$F$_5$)$_2$]Fe].

Species 38 was converted into 39 by reaction with silane. Subsequent addition of B(C$_6$F$_5$)$_3$ effected the heterolytic activation of H$_2$, yielding 40. The more sterically encumbered ferrocene 34 forms a frustrated Lewis pair with B(C$_6$F$_5$)$_3$, which reacts with H$_2$ to give 41 (Scheme 13, Figure 12).

A related early-transition-metal metallocene derivative has been shown to exhibit similar frustrated Lewis pair activation of H$_2$: The zirconocene complex 42 forms a frustrated Lewis pair with B(C$_6$F$_5$)$_3$ which heterolytically activates dihydrogen under very mild conditions to yield the salt 43 (Scheme 14).$^{32}$

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**Scheme 13.** Frustrated Lewis pairs derived from phosphinoferrrocenes/B(C$_6$F$_5$)$_3$.

**Scheme 14.** Activation of H$_2$ by the zirconium complex 42.
3.4. FLPs with \(B(p\text{-C}_6\text{F}_4\text{H})_3\)

Of the first frustrated Lewis pairs capable of heterolytic activation of \(\text{H}_2\), only the initial arene-linked system and subsequently the system based on bis(phosphino)naphthalene/\(\text{B(C}_6\text{F}_5\text{)}_3\) were capable of facile and reversible \(\text{H}_2\) activation. Indeed, the simple salts, such as \(14\text{a, 14b, and 15b}\), do not liberate \(\text{H}_2\) even upon heating to above 100 °C.\(^{[11]}\) Thus, modification of the borane partners of the pairs were considered. While the early data implied that a strongly Lewis acidic system was required, the Stephan group targeted a Lewis acid designed to preclude attack by the phosphine in the \(\text{para}\) position and yet be Lewis acidic enough to effect \(\text{H}_2\) activation. To address these issues the borane \(B(p\text{-C}_6\text{F}_4\text{H})_3\) \((45)\) was prepared by treatment of \(\text{BF}_3(\text{OEt})_2\) with the appropriate Grignard reagent (Scheme 15).\(^{[33]}\) Initially, this species was isolated as the diethylether adduct \(44\); sublimation resulted in the isolation of the base-free borane.

This borane in combination with \(\text{PR}_3\) \((R=\text{tBu, Cy, } \alpha\text{-C}_6\text{H}_4\text{Me})\) rapidly activates \(\text{H}_2\) at 25 °C yielding the corresponding phosphonium hydridoborates \(\text{R}_2\text{PH} \land \text{B(C}_6\text{F}_4\text{H})_3\) \((46\text{a,b})\) (Figure 13), \(\alpha\text{-C}_6\text{H}_4\text{Me} \text{46c}\). The case of \(46\text{c}\) stands in contrast to previous two-component systems, in that this salt loses \(\text{H}_2\) under vacuum at 25 °C (Scheme 16).\(^{[13]}\) The reverse reaction to the starting frustrated Lewis pair is slow, it is only 85% after 9 days at 25 °C. At 80 °C, this process is accelerated, and is completed in 12 h.

\begin{align*}
\text{H}_2 + \text{B(C}_6\text{F}_4\text{H})_3 & \rightarrow \text{R}_2\text{PH} \land \text{B(C}_6\text{F}_4\text{H})_3
\end{align*}

Scheme 16. Reversible H\(_2\) activation at 25 °C by 46c.

3.5. Phosphido-Boranes as FLPs

Given that frustrated Lewis pairs are derived from the combination of unquenched donor and acceptor sites, the Stephan group queried the possibility that such fragments could be directly bound to each other. With this in mind, the phosphido-boranes \(47\) \((R=\text{Et 47a, Ph 47b})\) and \(48\) \((R=\text{Cy 48c, tBu 48d})\) were prepared\(^{[34]}\) from the reaction of secondary lithium phosphides \(\text{R}_2\text{PLi \ (R=Et, Ph, Cy, tBu)}\) with \(\text{B(C}_6\text{F}_5\text{)}_2\text{BCl}\). While sterically undemanding substituents on phosphorus resulted in the formation of dimeric products \(47\text{a,b}\) (Scheme 17), more sterically demanding groups gave the monomeric species, \(48\text{a,b}\) (Figure 14) which retain the donor and acceptor properties at phosphorus and boron, respectively. In the case of \(48\text{b}\) the geometries about boron and phosphorus are pseudo-trigonal planar with a very short B–P distance of 1.786(4) Å.\(^{[34]}\)

Despite the geometries in the solid state, DFT calculations of the monomeric phosphido-boranes indicate that the HOMO B–P \(\pi\) bonding orbital is significantly polarized. Indeed, this polarization presumably accounts for the slow reaction of these species with \(\text{H}_2\) (4 atm) at 60 °C affording the

\begin{align*}
\text{R}_2\text{PH} \land \text{B(C}_6\text{F}_4\text{H})_3 + \text{H}_2 & \rightarrow \text{R}_2\text{PH} \land \text{B(C}_6\text{F}_4\text{H})_3
\end{align*}

Scheme 17. Synthesis and reactions of phosphido-boranes.

Figure 13. X-ray crystal structure of the salt 46b.

Figure 14. X-ray crystal structure of 48b.
phosphine-borane adducts 49 (R = Cy 49a, tBu 49b) in 48 h (Scheme 17). The B–P distance in the product of H₂ activation, 49b, at 1.966(9) Å, is dramatically longer than in the precursor 48b (Figure 15). In contrast, the dimeric phosphido-boranes show no reaction under similar conditions after 4 weeks.

DFT studies of this activation of H₂ showed that H₂ initially attacks the Lewis acidic boron center, using the H–H bond as a Lewis base. Subsequent H₂ rotation such that the H–H bond lies parallel to the B–P bond occurs and the H–H bond is split with formation of the new P–H bond. Coordination of H₂ to boron provides an approximately 22 kcal mol⁻¹ barrier for the process. Subsequent steps are essentially barrier-less. The overall reaction is exothermic (−43 kcal mol⁻¹) consistent with the irreversibility of the reaction.[34]

4. Carbon/Boron and Nitrogen/Boron Systems in H₂ Activation

4.1. Carbenes in FLP Activation of H₂

Following the initial report of the metal-free activation of H₂ by 11a, Bertrand and co-workers[51] demonstrated that N-heterocyclic carbenes (NHCs) did not react with H₂, the alkylaminocarbenes 50 reacts both with H₂ or NH₃ resulting in heterolytic cleavage of the H–H and N–H bond, respectively. These reactions afford the clean production of 51 and 52, respectively. (Scheme 18). In contrast to NHCs, monoamino-carbenes apparently provide the required balance of Lewis basicity/acidity to activate H₂ or NH₃.

Subsequently, the Stephan[52] and Tamm[37] research groups simultaneously reported the use of sterically hindered N-heterocyclic carbenes and B(C₆F₅)₃ in frustrated Lewis pair chemistry. Initially, it was established that the carbone 53a, although considered bulky in transition-metal chemistry, forms a stable, classical Lewis acid/base adduct 54 with B(C₆F₅)₃ (Scheme 19).

However, a frustrated Lewis pair is formed from the related carbene 53b and the borane. Tamm et al. showed that these two components, on prolonged standing, react to give B(C₆F₅)₃ substitution on the backbone of the carbene, affording a zwitterionic product 55 (Scheme 20). Nonetheless, exposure of the freshly generated frustrated Lewis pair mixture to H₂ results in the immediate formation of the imidazolium hydridoborate salt 56 (Scheme 20, Figure 16). Similarly the Tamm et al. have shown this frustrated Lewis pair also effects the ring opening of THF giving 57 (Scheme 20).

In addition, carbene 53b was also shown to react with B(C₆F₅)₃ adducts of ammonia or amines 58a–f (see Scheme 21). In the case of 58a–c, the reaction results in the rapid N–H activation and formation of imidazolium amido-borates 59a–c (Scheme 21). In the case of 59a, X-ray methods revealed a B–N bond length of 1.532(8) Å (Figure 17). In

![Figure 15. X-ray crystal structure of 49b.](image1)

![Scheme 19. Formation of 54.](image2)

![Scheme 20. Frustrated Lewis pair chemistry of 53b/B(C₆F₅)₃.](image3)

![Scheme 18. Activation of H₂ and NH₃ by alkylamino-carbenes.](image4)

![Figure 16. X-ray structure of the salt 56.](image5)
contrast, while alkylamines are thought to react similarly, a subsequent reaction is detected: the imidazolium protonates an arene ring on boron to give C$_6$F$_5$H, and the amido-borane (60d–f. Scheme 21) with concurrent regeneration of the carbene. Consequently, the formation of the amido-borane can also be achieved catalytically in the presence of a 5 mol% of carbene.$^{[36]}$

4.2. Imines and Amines in FLP Activation of H$_2$

The stoichiometric reaction between imine tBuN$^==C$Ph(H) and B(C$_6$F$_5$)$_3$, with H$_2$ provides the amine-borane 61 (Scheme 22). This result infers the transient formation of an iminium hydridoborate which then undergoes hydride transfer to the iminium carbon atom affording the amine adduct. Further heating of this product at 80°C for 1 h under H$_2$ (4–5 atm) resulted in additional H$_2$ activation to give salt 62 (Scheme 22).$^{[38]}$ The X-ray crystal structure of 62 shows a B–H–H–N close contact of 1.87(3) Å (Figure 18), consistent with a nontraditional proton–hydride hydrogen bond$^{[30]}$ similar to that seen in 14a.$^{[11]}$ The analogous reactions of the more sterically encumbered ketimine diisopropylphenyl-N=CMe(tBu) with B(C$_6$F$_5$)$_3$ under H$_2$ yielded the iminium cation salt 63 (Scheme 22). This result suggests that the steric congestion precludes hydride transfer to the iminium carbon.$^{[38]}$

Reactions of iPr$_2$NEt and iPr$_2$NH with B(C$_6$F$_5$)$_3$ gave 50:50 mixtures of the corresponding ammonium salts 64 (R = Et 64a, H 64b) with the zwitterionic products of amine dehydrogenation 65 and 66 (Scheme 23).$^{[39]}$ Nonetheless, exposure of mixtures of iPr$_2$NH or Me$_2$C$_6$H$_4$NH with B(C$_6$F$_5$)$_3$ to H$_2$ gave quantitative formation of the ammonium-borate 64b and 67, respectively (Scheme 23). Reactions employing BPh$_3$ in place of B(C$_6$F$_5$)$_3$ resulted in no reaction prompting the speculation that CF–HN interactions (in addition to the difference in Lewis acidity) play a role in bringing amine and borane in close proximity permitting cooperative activation of H$_2$.$^{[39]}$

In a similar fashion, the research groups of Repo and Rieger have very recently reported a linked amine-borane system 68/69 derived from tetramethylpiperidine...
This system exhibits the ability to effect reversible H₂ activation and will be discussed in Section 6.3.

4.3. Zirconocene Amines in FLP Chemistry

The Erker group has demonstrated that even a relatively unobstructed secondary amine functionality attached to the Cp ring of a Group 4 bent metalloocene framework can be used as a suitable base in a frustrated amine/B(C₆F₅)₃ Lewis pair. Addition of one molar equivalent of B(C₆F₅)₃ to the doubly aminomethyl-substituted zirconocene substrate 70 generated a frustrated Lewis pair that rapidly reacted with H₂ under ambient conditions (2 bar, 25 °C) to form the organometallic monoammonium/hydridoborate salt 71.[41] Addition of a second equivalent of B(C₆F₅)₃ eventually afforded the zirconocene-bis(ammonium)/2[HB(C₆F₅)₃] product 72. Both the synthesis of 70 by means of a metal-free hydrogenation procedure as well as the use of the 71/72 systems (Scheme 25) as effective metal-free hydrogenation catalysts are described in Section 6.3.

4.4. Lutidine in FLP Chemistry

While pyridines are known to form adducts with B-(C₆F₅)₃,[42] the Stephan group was prompted to study the case of lutidine after considering the early work of Brown et al.[4] (see Section 1.) Reaction of 2,6-lutidine and B(C₆F₅)₃ gave rise to broad ¹H and ¹³F NMR spectra, suggesting the establishment of an equilibrium between free lutidine/B-(C₆F₅)₃ and the Lewis acid/base product (2,6-Me₂C₅H₃N)B-(C₆F₅)₃, 73[43] (Scheme 26). At low temperature, the ¹³F NMR resonance signals sharpened and were consistent with the presence of primarily a disymmetric product. Determination of the equilibrium constants as a function of temperature gave ΔH = −42(1) kJ mol⁻¹ and ΔS = −131(5) J mol⁻¹ K⁻¹. Indeed upon cooling solutions of this mixture to −40 °C, the classical adduct 73 was isolable as X-ray quality crystals (Figure 19).[43] The structure reflects the steric congestion in that the B–N bond length of 1.661(2) Å, was found to be significantly longer than that in (py)B(C₆F₅)₃ (1.628(2) Å; py = pyridine).[42] The observation of an equilibrium at room temperature suggested that frustrated Lewis pair chemistry may be accessible. Treatment of lutidine/B(C₆F₅)₃ with H₂ (1 atm, 2 h) gave the pyridinium salt 74 (Scheme 26, Figure 20 (top)). Similarly, treatment of lutidine/B(C₆F₅)₃ with THF yielded the zwitterionic species 75 (Scheme 26, Figure 20 (bottom)).

The formation of both classical products and frustrated Lewis pair products from lutidine/borane affirm that these reaction pathways are not mutually exclusive. Moreover, this finding points to the possibility that classical Lewis acid/base adducts may serve as precursors for new reaction pathways, despite the fact that such compounds have been regarded as unreactive.[43]
Mechanistic Studies of \( \text{H}_2 \) Activation by FLPs

The details of the mechanism of action of frustrated Lewis pairs on \( \text{H}_2 \) have been the subject of study. In the first report of reversible \( \text{H}_2 \) activation by an frustrated Lewis pair system, Stephan and co-workers\[8\] speculated on intramolecular processes based on initial indications of first-order kinetics for the loss of \( \text{H}_2 \) from \( 10a \). Efforts to confirm this experimentally have indicated that, at the elevated temperatures required to observe \( \text{H}_2 \) loss, the back-reaction is facile and rapid. The consequence is misleading kinetic data. \[44\]

Efforts to study the uptake of \( \text{H}_2 \) by phosphine/borane systems is also challenging as the reaction is rapid at low \( \text{H}_2 \) pressures even at \( 60^\circ\text{C} \). Moreover the control of \( \text{H}_2 \) concentrations in solution is experimentally difficult, leading to reactions that are diffusion controlled. Based on early computational studies\[45\] of the interaction of BH\(_3\) and \( \text{H}_2 \), it was speculated that the activation of \( \text{H}_2 \) is initiated by Lewis acid activation of \( \text{H}_2 \) leading to protonation of the Lewis base. While this intuitively seems reasonable, it is noteworthy that previous low-temperature matrix-isolation work has demonstrated phosphines do interact with \( \text{H}_2 \) presumably via nucleophilic attack of the \( \text{H}_2 \) in an end-on fashion.\[46\]

Computational studies by Pápai and co-workers\[47\] suggest generation of a phosphine-borane “encounter complex”, stabilized by \( \text{H} \cdot \cdot \cdot \text{F} \) interactions. In this “species” the boron and phosphorus centers approach but fail to form a dative bond as a result of steric congestion. Interaction of \( \text{H}_2 \) in the reactive pocket between the donor and acceptor sites (Figure 21) results in heterolytic cleavage of \( \text{H}_2 \). A related mechanism has been described for \( 11 \).[80]

Calculations reported by the Tamm group\[37\] showed the transition state for the activation of \( \text{H}_2 \) by carbene and borane gave rise to a carbene-borane “encounter complex” similar to that proposed by Pápai et al.

Very recent computational studies by Grimme et al.\[49\] of the (quasi)linear \( \text{P} \cdot \cdot \cdot \text{H} \cdot \cdot \cdot \text{B} \) activation mechanism of \( 11 \) (see Figure 21) cast some doubt on the “reality” of the corresponding transition state. According to these new results, a transition state in a linear arrangement only appears for rather large \( \text{P} \cdot \cdot \cdot \text{B} \) distances over 4.5 \( \text{Å} \). Such values seem to be artificially induced by the quantum chemical method (B3LYP) which is well-known to overestimate steric congestion. With properly dispersion-corrected density functionals\[49b\] no linear transition state exists and only one minimum with a rather large \( \text{P} \cdot \cdot \cdot \text{H} \) distance of about 1.67 \( \text{Å} \) could be found. This points to an alternative bimolecular mechanism in which the “entrance” of \( \text{H}_2 \) into the “frustrated” \( \text{P} \cdot \cdot \cdot \text{B} \) bond is rate-determining. Further theoretical studies to address this important question are currently underway.

According to DFT calculations\[49a\] \( \text{B(C}_6\text{F}_5)_3 \) forms the van der Waals complex \( 76 \) with \( \text{H}_2 \) (Scheme 27), although this is unlikely to contribute to the \( \text{H}_2 \) activation pathway. However, it is noteworthy that Piers et al. have exploited a related reaction to prepare HB(C\(_6\text{F}_5\))\(_2\) through direct treatment of B(C\(_6\text{F}_5\))\(_3\) with triethylsilane.\[14\]

Unfortunately, the \( \text{H}_2 \) splitting reaction does not provide stereochemical information. However, such information is available in the related B(C\(_6\text{F}_5\))\(_3\)-catalyzed hydrosilylation reaction of ketones\[50\] and related substrates.\[51\] Piers et al. have shown that this reaction proceeds by Lewis acid\[14\] activation of the silane rather than by the carbonyl compound.\[16,52\] Hydride transfer from Si to B followed by (or concomitant with) carbonyl addition to the silylium ion then generates an intermediate \( 77 \) activated for hydride addition en route to the hydrosilylation product \( 78 \) (Scheme 28).\[50\]

In a very elegant study, Oestreich et al. determined that the B(C\(_6\text{F}_5\))\(_3\)-induced hydrosilylation of acetoephone with the highly optically enriched chiral silane \( 79 \) (“Oestreich silane”)\[54\] proceeds with inversion of the configuration at
This result rules out the involvement of a free silylium ion and indicates an S$_N$2-type process with a Walden inversion at the silicon atom. Subsequent cleavage of the Si–C$_0$ bond of (Si$_R$$R'_2$$Si$) by treatment with $i$/Bu$_2$AlH proceeds with retention of configuration at Si. Interestingly, the alcohol (81) which is set free in the final step of the reaction sequence was found to be enantiomerically enriched (38% ee) (Scheme 29). This process is a remarkable asymmetric induction given that the system involves only a single-point of attachment.

**6. Metal-Free Catalytic Hydrogenation**

**6.1. Catalytic Hydrogenations by Phosphine/Borane FLPs**

Soon after the discovery of metal-free activation of H$_2$ by the frustrated Lewis pair 10a/11a, the application of this finding for hydrogenation catalysis was envisioned. This notion was reinforced by the analogy to the Noyori-hydrogenation catalysts. In those systems, a metal complex effects heterolytic cleavage of H$_2$ yielding a metal hydride and a protonated ligand. Frustrated Lewis pairs effect similar heterolytic H$_2$ activation without the need for a transition metal. However, for hydrogenation to be catalytic, proton and hydride transfer from a phosphonium hydridoborate to a substrate must occur with regeneration of the frustrated Lewis pair. This frustrated Lewis pair would reactivate H$_2$ and be available for subsequent substrate reduction. In the first exploration of this concept, the salts 10a and 10b were treated with aldimes. Stoichiometric addition resulted in the formation of the amine adducts (R$_2$P)(C$_6$F$_4$)B(C$_6$F$_5$)$_2$(NHRCH$_2$R').

Sterically less encumbered imines were reduced by the phosphonium-borate catalyst by using B(C$_6$F$_5$)$_3$ as a protecting group. As B(C$_6$F$_5$)$_3$ is a stronger Lewis acid than the boron center in the catalyst (11), reduction proceeds because the amine formed does not inhibit activation of H$_2$ by the phosphine-borate catalyst. A similar strategy was applied to nitriles. Thus, 90–93 were reduced to give the corresponding amine-B(C$_6$F$_5$)$_3$ products 94–97 in near quantitative yields using a phosphonium-borate catalyst (Scheme 32). While this strategy demonstrates the principle of metal-free hydrogenation of imines and nitriles, it is recognized that B(C$_6$F$_5$)$_3$ is not
an inexpensive protecting reagent and must be used stoichiometrically.\[57\]

The \(25a/27a\) pair is an even more active catalyst for the metal-free hydrogenation of imines as it operates effectively at ambient conditions. For some substrate types, it is the most active metal-free hydrogenation catalysts to date. For example, the \(25a/27a\) system catalyzes the hydrogenation of the aldime \(98a\) at ambient conditions (25\(\degree\)C, 1.5 bar \(H_2\)) although in this case at least 20 mol\% of the catalyst system are required. In contrast, catalytic hydrogenation of the related ketimine \(98b\) is much more effective (Scheme 33), complete hydrogenation is achieved with 5\% of the metal-free \(P/B\) catalyst system under very mild reaction conditions.\[25\]

Since it is conceivable that these reactions proceed by means of the corresponding iminium-ion intermediates, other substrates amenable to iminium-ion formation were considered as they might also be suitable substrates for metal-free catalytic hydrogenation by \(PH^+/BH^-\) systems. Indeed, this turns out to be the case. The Erker group observed that the ethylene-linked system \(27a\) reacts rapidly with the enamine \(100a\) to form the amine \(101a\) with re-formation of the frustrated Lewis pair precursor \(25a\).\[23\] This reaction can be carried out catalytically (Scheme 34). With 10 mol\% of the catalyst \(27a\) a practically quantitative conversion of the enamine \(100a\) into the amine \(101a\) was achieved at 25\(\degree\)C and under 1.5 bar \(H_2\) in toluene solution. A variety of examples (\(100b–e\)) gave similar results. In some cases, 3 mol\% of catalyst was sufficient to achieve near-complete enamine hydrogenation under these mild reaction conditions.\[41\] In the case of the very bulky enamine \(100e\), slightly more forcing conditions were required. Using 50 bar \(H_2\), 70\(\degree\)C, and 10 mol\% catalyst, the amine \(101e\) was isolated in over 80\% yield.\[58\]

The salt \(32\), derived from heterolytic cleavage of \(H_2\) by the frustrated Lewis pair \(31/B(C_6F_5)_3\), rapidly transfers proton and hydride stoichiometrically to the silyl enolether \(102a\) at room temperature. The reaction can also be carried out catalytically at 25\(\degree\)C and 2 bar \(H_2\) using 20 mol\% of the \(31/B(C_6F_5)_3\) catalyst system. Similarly, this catalyst hydrogenates a variety of silyl enolethers (\(102a–d\); Scheme 35) giving good yields of the corresponding silyl ether products (\(103a–d\)).\[28,59\] In the case of the silyl enolether \(102e\) only a stoichiometric hydrogenation was observed under the typically mild conditions, however, the apparent product inhibition could be
overcome using more forcing reaction conditions (60 bar H2, 70°C).

6.2. Substrates as Bases in FLP Catalysts

Having demonstrated the metal-free catalytic hydrogenation of imines, the Stephan group then probed the notion that the substrate could serve as the base-partner of an frustrated Lewis pair. Thus employing a catalytic amount of B(C6F5)3 in the presence of an imine substrate (and H2), it was indeed possible to effect the catalytic reduction of the imine to the corresponding amine. In this fashion, the simple combination of an imine substrate and H2 results in reduction of imines (82–84) to amines (86–88) under conditions similar to those described in Section 6.1 for the phosphino-borane catalysts. Mechanistically these reductions proceed by H2 cleavage and protonation of the imine to give iminium cations which are then attacked by hydridoborate affording the amine (Scheme 36). [38]

It is noteworthy that in cases where the imine is a poor base, as in 83, addition of a catalytic amount of P(C6H2Me3)3 gave an accelerated and essentially quantitative hydrogenation in 8 h, compared to 41 h in the absence of phosphine. The acceleration was attributed to the enhanced ability of phosphine/borane to cleave H2 heterolytically. In a similar fashion, the nitrile-borane adducts, 91 and 92 were reduced to 95 and 96 under H2 in the presence of a catalytic amount of P(C6H2Me3)3 and B(C6F5)3, whereas in the absence of phosphine no reduction was observed (Scheme 37). [38]

Analogous reductions employing B(C6F5)3, in combination with imine substrates were subsequently reported by Chen and Klankermayer. [60] In one example, they showed that employing the chiral borane 106 in the asymmetric reduction of imine 104 to amine 105 (Scheme 38) gave an enantiomeric excess of 13% ee. [60]

6.3. Catalytic Hydrogenations Employing Amine-Borane FLPs

The research groups of Repo and Rieger [40] have employed the linked amine-borane 68/69 in the catalytic hydrogenation of imines and enamines. (Scheme 39). [40] While generally this catalyst was effective, affording near quantitative reduction of the substrates, sterically less-encumbered substrates, such as 109, 111, 113, 115 were only hydrogenated in 4% yield.

Following the demonstration that ammonium/[HB-(C6F5)3] salts can be used for catalytic hydrogenation reactions, the organometallic zirconocene-based ammonium [B]H+ salt 72 was also studied. It was shown to efficiently catalyze the hydrogenation of the bulky imines 117a,b as well as of the silyl enol ether 102b to the respective saturated products (Scheme 40). [41] In these cases, the use of 3–9 mol %
of the catalyst system was sufficient for high product conversion under mild reaction conditions.

The conformationally rigid dienamine 120 can readily be obtained by Mannich coupling of acetyl groups at the ferrocene framework (Scheme 41). Stoichiometric reaction of 120a, b with the zwitterion 27a gave an approximately 1:1 mixture of the mono(dihydrogen) and bis(dihydrogen) addition products 121a, b and 122a, b (see Schemes 41 and 42). Experimental evidence indicates that 122 may originate from a slow subsequent hydrogenation reaction of 121 under the specific reaction conditions employed. The product 121a was characterized by X-diffraction (Figure 22). In contrast, the substrates 120a, b are catalytically hydrogenated with 5 mol % of 27a under H2 to selectively yield the formal 1,4-hydrogenation products 121a, b with only marginal amounts of the saturated products.


Scheme 41. Catalytic 1,4-hydrogenation of 120.

Figure 22. Molecular structure of the 1,4-hydrogenation product 121a.

The iminium-ion intermediate of this catalytic metal-free hydrogenation was independently prepared by selective protonation of the dienamine 120a with HCl in diethyl ether. Subsequent anion exchange gave 123[BF4]-. Remarkably, protonation of 120a with the zirconocene-ammonium/[HB(C6F5)3] system 72 gave 123[HB(C6F6)3], which was isolated and characterized by an X-ray crystal structure analysis (Scheme 42 and Figure 23). These systems apparently represent borderline cases in which the ferrocenyl-stabilized iminium ions are slow to react with hydride. Thus, the system 123[HB(C6F5)3] is stable and isolable, whereas treatment of 123[BF4]- with the slightly more nucleophilic reagent 27a results in the formation of the respective stoichiometric hydrogenation products 121a and 122a.
6.4. Hydrogenations using Ammonia-Borane

The systems 29 do not activate \( \text{H}_2 \) by themselves under typical conditions, but they do react rapidly with ammonia-borane.\[^{[66]}\] Treatment of (\( \text{H}_3\text{N} \))\( \text{BH}_3 \) with a stoichiometric amount of 29b in [D\(_8\)]THF gave 30b. This reaction can be adapted for the catalytic metal-free hydrogenation of the bulky imine 98b. Thus, treatment of an imine/(\( \text{H}_3\text{N} \))\( \text{BH}_3 \) mixture with a catalytic amount of 29b (ca. 10 mol\%) in THF resulted in the rapid formation of the corresponding amine 99b and borazine (Scheme 43).\[^{[67]}\]

6.5. Other Metal-Free Catalytic Hydrogenation Reactions

There are a variety of other metal-free hydrogenation reactions reported in the literature, some of which are catalytic. An early example was reported by Walling and Bollyky.\[^{[68]}\] They had observed that benzophenone is reduced to diphenylmethanol with dihydrogen in the presence of the strong base, potassium tert-butoxide. The reaction conditions were quite forcing, typically using over 100 bar \( \text{H}_2 \) pressure and a high reaction temperature (ca. 200°C).\[^{[69]}\] Berkessel et al. studied this reaction in some detail\[^{[70]}\] and proposed a reaction pathway (Scheme 44) related to the asymmetric ruthenium-complex-catalyzed Noyori hydrogenation\[^{[71]}\] of prochiral ketones.

Metal-free hydrogenation can be induced by strong acids under forcing conditions. Aromatic hydrocarbons as well as cyclic alkenes and dienes were hydrogenated using \( \text{H}_2 \) at elevated pressure, in the presence of strong acids, such as HF/\( \text{TaF}_5 \), HF/\( \text{SbF}_5 \) or HBr/AlBr\(_3\). This approach gave saturated hydrocarbon products, some with rearranged carbon frameworks.\[^{[72]}\] Köster et al. reported borane-catalyzed hydrogenation of condensed arenes to fully or partly hydrogenated derivatives at high temperature (ca. 200°C) and under high \( \text{H}_2 \) pressures.\[^{[73]}\] Haenel et al. described a related procedure for the liquefaction of coal using homogeneous borane catalysts.\[^{[74]}\]

Dihydropyridines are increasingly used as alternative hydrogen sources for the organocatalytic hydrogenation of carbonyl and imine substrates by means of proton and hydride transfer. Asymmetric hydrogenation using chiral Brønsted acids has become an increasingly important variant.\[^{[75]}\] In this regard, it should not be forgotten that NADH (124), provides a metal-free hydrogenation in natural systems (Scheme 45) which bears some relation mechanistically to the metal-free reduction with the PH\(^+\)/BH\(_3\)/C\(_0\) systems.\[^{[76]}\]

In an early example, Sander et al. showed that the strongly electrophilic carbene difluorovinylidene reacts directly with \( \text{H}_2 \) in an argon matrix at 20–30 K with practically no activation barrier to yield 1,1-difluoroethene (125; Scheme 46).\[^{[77]}\] Formal insertion of examples of monoamino carbenes into the H—H bond in solution were recently reported by Bertrand et al.\[^{[78]}\] (Scheme 18). Remotely related
7. Applications in Organometallic Chemistry

There are a variety of systems reported that contain trivalent phosphorus and trivalent boron centers connected by unsaturated organic linkers. [13,20c,24c-e] The photophysical properties of such “conjugated phosphine-borane” systems have been examined. [79] Some of these π-conjugated P/B systems form internal adducts, [80] while some show reactivities reminiscent of frustrated Lewis pairs, undergoing bifunctional addition reactions to organometallic substrates. For example, the products 127 and 128 were formed by such addition reactions employing the P/B system 126 (Scheme 47). [81,82]

Carrying out organic functional-group transformations on many organometallic frameworks is tedious owing to the often high sensitivity of these metal-containing compounds. This is especially true for many early-transition-metal systems for which only recently a variety of suitable methods for organic functional-group interconversion are beginning to emerge. [61b–e,83] Metal-free catalytic hydrogenation using frustrated Lewis pair catalysts provides a suitably mild method for such sensitive systems. Below some examples are described.

Treatment of 6-dimethylaminofulvene (129) [84] with lithium anilides results in exchange of the amino component with formation of the formally imino-substituted cyclopentadiene 130. [85] Protonation under carefully controlled conditions with the Bronsted acid acetylacetone, gave the bulky sec-aminofulvene 131. This species was subsequently metallated by treatment with the [(Me₂N)₂ZrCl₂(thf)]₂ to give 132 (Scheme 48). The functionalized bent metallocene forms a frustrated Lewis pair with B(C₆F₅)₃, which under H₂ (2 bar H₂, 25°C) effects a “quasi-autocatalytic” metal-free hydrogenation reaction of the imino groups giving the aminomethyl-substituted zirconocene complex 70 (Figure 24).

The ansa-metalocene 133 was easily available by acid-catalyzed intramolecular Mannich coupling of the respective bis(enamino)-substituted zirconocene. [61b–e] In the analogous [3]ferrocenophane derivatives 120, catalytic hydrogenation opened a pathway for the synthesis of a variety of useful ligands for asymmetric catalysis. [62,86] Carrying out similar hydrogenation reactions of the unsaturated bridge of the ansa-zirconocene systems 133 was difficult because of the high sensitivity of these systems. However, metal-free catalytic hydrogenation offered a solution to this problem. The ansa-zirconocene 133 was selectively 1,4-hydrogenated to 134 using the catalyst system 27a [63] (Scheme 49). The proton/hydride transfer reaction is thought to follow a similar course as in the ferrocene system 120 discussed above. Protonation of 133 with a variety of Bronsted acids followed by treatment with NH⁺/BH⁻ system 72 gave the corresponding ansa-zirconocene-derived conjugated iminium salts [135][X] ([X] = [HB(C₆F₅)] or [ZrCl₃]; Scheme 49, Figure 25). [64]

Sometimes organometallic Lewis base components complicate the reactions. For example, treatment of “Ugi’s amine” (N,N-dimethyl-1-ferrocenylethylamine) with methyl
iodide and then by dimesitylphosphine gave rise to complex 136a. Reaction with B(C₆F₅)₃ and H₂ results in loss of the phosphine fragment. Complex 136a probably forms a frustrated Lewis pair with B(C₆F₅)₃, which under very mild conditions reacts with H₂ to yield ethylferrocene and the (C₆H₂Me₃)₂P(H)B(C₆F₅)₃ adduct. It is assumed that this reaction proceeds via the salt 138a. However, under the reaction conditions this intermediate salt is unstable towards SN1-substitution, leading to hydride from [HB(C₆F₅)₃] effecting displacement of HP(C₆H₂Me₃)₂ with anchimeric assistance by the iron center (Scheme 50).

The analogous reaction was also observed in the related 3]ferrocenophane series. The product 137 was independently synthesized and characterized (Figure 26). The assumed reaction course was supported by the observed stereoselective formation of the trans-product, trans-[D₁]-137, upon treatment of the 136b/B(C₆F₅)₃ frustrated Lewis pair with D₂ (Scheme 51).

Surprisingly, the analogous reaction of the closely related ortho-bromo- or ortho-iodo[3]ferrocenophane derivative 136c.d features a different outcome. The frustrated Lewis pairs 136c.d/B(C₆F₅)₃ split H₂ heterolytically to yield the stable organometallic phosphonium/hyridoborate salts

Scheme 49. Selective 1,4-hydrogenation of ansa-zirconocenes 133. X = HB(C₆F₅)₃⁺.

Figure 25. A view of the cationic part of the ansa-zirconocene iminium salt [135][ZrCl₄].

Scheme 50. Reaction of the frustrated Lewis pair of 136a with hydrogen.

Scheme 51. Proposed reaction path for the formation of 137.

Scheme 52. Formation of the salt 138.

138c.d (Scheme 52). The X-ray crystal structure analysis of 138d (Figure 27) features a close PH–halide contact that might make the HP(C₆H₂Me₃)₂ moiety a slightly less-favorable leaving group in this special case. 
8. Activation of Other Small Molecules by FLPs

As frustrated Lewis pairs retain most of the typical reactivities of their Lewis base and Lewis acid components, they undergo reactions that are characteristic for each separate component. However, in addition they add cooperatively to a variety of substrates. This extends the scope of their potential use far beyond their application for metal-free heterolytic H₂ activation and metal-free hydrogenation catalysis. In this section, this emerging development is illustrated with selected examples.

8.1. Ring Opening of THF

Wittig and Rücker, in 1950, described the reaction of Ph₃CNa with THF(BPh₃). Conventional thought would have predicted that treatment of the Lewis acid/base adduct with a strong nucleophile would simply result in the displacement of the weaker donor by the stronger, resulting in formation of the stronger acid/base adduct. However, Wittig and Rücker reported that the trityl anion effected THF ring opening affording the anion [Ph₃C(CH₂)₄OBPh₃]⁻ (Scheme 53). Since this early study, the ability of Lewis acidic centers to promote THF ring-opening reactions has been observed for a number of systems. For example, in 1992 Breen and Stephan showed that treatment of [ZrCl₄(thf)₂] with PCy₃ gave the zwitterionic dimer [{Cl₄Zr(µ-O-CH₂)₄PCy₃}]₂⁻ (Scheme 53). Related combinations of Lewis acids and Lewis bases exhibit similar THF ring-opening chemistry. These include systems involving Lewis acidic transition metals, such as U[70] Sm[71] Ti[72] and Zr[70,74] and main-group Lewis acids including carborane[75] alane[76] tellurium species[77] and borane[78] in combination with either nitrogen- or phosphorus-based Lewis bases (Scheme 53). The most pertinent of these to the present discussion is the zwitterionic species R₂PH(CH₂)₄OB(C₆F₅)₃ (R = tBu, C₆H₂Me₃) derived from the treatment of (THF)B-(C₆F₅)₃ with sterically encumbered phosphines.

8.2. para-Substitution Reactions

In reactions of sterically encumbered amines with trityl cation, conventional Lewis behavior was not observed, rather, the trityl cation abstracts a proton from the carbon alpha to the nitrogen atom yielding an iminium cation. In related chemistry, reactions of pyridine with trityl cation also failed to prompt quaternization of the nitrogen center. Instead, it was suggested that pyridine attacks the carbon para to the carbocation although this report was subsequently disputed. In 1998, Doering et al. described the reaction of the Lewis acid B(C₆F₅)₃, which is isoelectronic to the trityl cation, with the ylide Ph₃PCHPh. It was shown that the classical Lewis adduct, (Ph₃PCHPh)B(C₆F₅)₃, formed reversibly at room temperature and rearranged at higher temperature to effect attack at the para-position of one of the C₆F₅ rings. Concurrent fluoride transfer to B affords the zwitterionic phosphonium-borate [Ph₃PCHPh(C₆F₄)BF(C₆F₅)₂] (Scheme 54).

In a related study of the reactions of trityl borates with Lewis donors, bulky phosphines (R = tBu, iPr, Cy) were unable to attack the central carbocation and instead effected nucleophilic substitution at the carbon para to the carbocation, giving the salts 140 or 141 (Scheme 55). More recently, this reactivity has been shown to be general and the para-substitution was demonstrated to occur for classical phosphine adducts of B(C₆F₅)₃ under warming, yielding the air- and moisture-stable zwitterions 142, 9a, 143 (Scheme 55). Analogous species are obtained with smaller phosphines after the combined toluene solutions of the reagents are heated under reflux.

8.3. Addition to Boron

The boron center in 25a is quite Lewis acidic. Therefore, it adds a variety of typical, small, donor ligands. Among them a sometimes unwanted reaction partner is the H₂O molecule. Reaction of 25a with H₂O occurs in a well-defined way if
insufficient precautions are taken to exclude moisture from reaction mixtures. Addition of \( \text{H}_2\text{O} \) to the \( \text{B}((\text{C}_6\text{F}_5)_2) \) unit substantially increases the Brønsted acidity of the water molecule.[106] Rapid intramolecular deprotonation by the adjacent mesityl \( \text{P} \) base then rapidly leads to the formation of \( 144 \) (Scheme 56, Figure 28). The [B]-OH unit in \( 144 \) is still quite acidic. Therefore, it may react further with \( 25\text{a} \) if present in an excess, ultimately providing compound \( 145 \) (Figure 29, B1-O: 1.578(3) Å, angle B1-O-B2: 131.3(2)°).[107]

The frustrated Lewis pair \( 25\text{a} \) adds terminal alkynes in a similar fashion. Thus \( 146 \) is produced from the reaction of \( 25\text{a} \) with 1-pentyne in good yield (Scheme 57, Figure 30; \( 146 \):

\[
\begin{align*}
\text{B} - & \text{C}_3 1.589(4) /\text{C}138, \\
\text{C}_3 - & \text{C}_4 1.198(4) /\text{C}138; \\
\text{B} - & \text{C}_3 1.622(4) /\text{C}138, \\
\text{C}_3 - & \text{N}_1: 1.138(3) /\text{C}138).
\end{align*}
\]

tert-Butylisocyanide adds cleanly to the boron center of \( 25\text{a} \) to give the adduct \( 147 \). Even some imines react in a similar way. For example, dicyclohexylcarbodiimide forms the Lewis acid/Lewis base adduct \( 148 \) with \( 25\text{a} \) (Scheme 57, Figure 31).[107]

\[\text{Scheme 55. } \text{para-} \text{substitution reactions of Lewis acids with phosphines.}\]

\[\text{Scheme 56. } \text{Reaction of } 25\text{a} \text{ with water.}\]

\[\text{Scheme 57. } \text{Addition products with } 25\text{a}.\]

\[\text{Figure 28. } \text{A view of the molecular structure of the product } 144 \text{ of } \text{H}_2\text{O} \text{ addition to the frustrated Lewis pair } 25\text{a}.\]

\[\text{Figure 29. } \text{Molecular structure of } 145.\]

\[\text{Figure 30. } \text{Addition products with } 25\text{a}.\]

\[\text{Figure 31. } \text{Addition products with } 25\text{a}.\]

8.4. Reactions with Carbonyl Groups

Frustrated Lewis pairs undergo 1,2-addition reactions to carbonyl compounds. Addition to the reactive C=O bond of isocyanates is common. Typical examples are the formation of \( 149\text{a} \) from \( 25\text{a} \) and phenylisocyanate[108] and the related reversible formation of \( 149\text{b} \) from the “ambiphilic”
Benzaldehyde adds rapidly to 25a to form the six-membered heterocycle 149c which adopts a distorted chair conformation in the solid state (Scheme 58, Figure 32). In the case of the reaction of cinnamic aldehyde, it was not clear whether the frustrated Lewis pair 25a would add to the electron-deficient C=C double bond or the carbonyl function. Experiment shows that 1,2-addition to the carbonyl group is preferred (149d; Scheme 58).

The Stephan group has also demonstrated that frustrated Lewis pairs add to alkenes. For example, exposure of a solution of tBu3P and B(C6F5)3 to ethylene resulted in the formation of the zwitterionic species \([\text{tBu}_3\text{P}(\text{C}_2\text{H}_4)\text{B}(\text{C}_6\text{F}_5)\text{B}](\text{Scheme 59}).\) Similarly, the products \([\text{tBu}_3\text{P}((\text{CH}(\text{R})\text{CH}_2)\text{B}(\text{C}_6\text{F}_5)\text{B}]( R = \text{CH}_3, \text{C}_4\text{H}_9), \) were derived from propylene and 1-hexene, respectively. In addition, reaction of \(\text{CH}_2=\text{CH}(\text{CH}_2)\text{PR}_2 ( R = \text{tBu}, \text{C}_6\text{H}_2\text{Me}_3) \) with B(C6F5)3 generates the cyclic phosphonium-borate 151d (Scheme 59). In all of these products, the boron center adds to the less-hindered carbon atom. The structures of these compounds were confirmed by X-ray data (Figure 33, Figure 34). Mechanistically, activation of the alkene by the Lewis acid is thought to initiate these reactions, prompting
attack by the phosphine at the more-substituted carbon of the alkyne. Older IR studies have demonstrated the formation of BF₃–ethylene and BF₃–propylene complexes in an argon matrix at 93–125 K, supporting this notion of Lewis acid-activation of alkenes. In addition computational studies have suggested weak π-donation complexes for ethylene–alane and ethylene–borane adducts.

Similarly, the Stephan group has probed the related reactions of frustrated Lewis pairs with conjugated dienes. Again, in these cases, addition reactions are observed, although the regiochemistry is predominantly that of 1,4-addition. Thus in the reaction of iBu₃P/B(C₆F₅)₃ with butadiene, 2,3-diphenylbutadiene, 2,3-dimethylbutadiene, and 1,3-cyclohexadiene, 1,4-addition products were isolated in 50–60% yield (Scheme 60, Figure 35). These reaction mixtures contain other species that may arise from other stereoisomers or 1,2-addition products although these latter byproducts could not be isolated or fully characterized.

In a theoretical study, Papai et al. described the reaction of the iBu₃P/B(C₆F₅)₃ pair with ethylene as an antarafacial asynchronous concerted 1,2-addition reaction (Scheme 61).

The intramolecular frustrated Lewis pair 25a undergoes a rapid and regioselective 1,2-addition reaction to the electron-rich ethylvinylether to yield compound 153 (Scheme 62 and Figure 36).

In related chemistry, Erker and co-workers showed that the reaction of 25a with norbornene gives the exo-2,3-addition product 154 selectively (Figure 37). Comparison with DFT data indicated that the product 154 was formed under kinetic control. This means that product formation occurs either in a stepwise reaction with very rapid trapping of
Results of a detailed theoretical analysis favor the concerted mechanism. The DFT analysis located a transition-state structure characterized by a markedly stronger B–C than P–C interaction (Figure 38), suggesting an asynchronous concerted cis addition. The reaction might be considered as a "two-site cheletropic" reaction type.[107,114] Norbornadiene undergoes an analogous two-fold exo addition reaction with the frustrated Lewis pair 25a[107]

Frustrated Lewis pairs may also add to alkynes.[115] Combinations of B(C₆F₅)₃ or (PhMe)Al(C₆F₅)₃ with (α-C₆H₄Me)₃P generated frustrated Lewis pairs, these react with PhC≡CH to give the zwitterionic species 157 and 158 (Scheme 63, Figure 39). In marked contrast the reaction of B(C₆F₅)₃ or (PhMe)Al(C₆F₅)₃[116] and tBu₃P with PhC≡CH gave the salts 155 and 156, respectively, in near quantitative yields (Figure 40).

The isolated and classical Lewis acid/base adduct Ph₃PB(C₆F₅)₃ was also shown to react with PhC≡CH to give the addition product, Ph₃PC(Ph)=C(H)B(C₆F₅)₃.[115] This result is surprising in that for the adduct Ph₃PB(C₆F₅)₃ no evidence of dissociation is found by NMR spectroscopy. This accessibility of frustrated Lewis pair chemistry from classical Lewis acid/base adducts suggests the possibility that many more examples of compounds, otherwise thought to be unreactive, may indeed offer access to new reactivity.

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8.6. Activation of B–H Bonds

Frustrated Lewis pairs have also been shown to prompt the activation of the B–H bond of catecholborane. Thus treatment of tBu2RP (R = tBu, C6H4Ph) and B(C6F5)3 with catecholborane affords the products 159 (Scheme 64, Figure 41).[117] These reactions are presumed to proceed by initial coordination of phosphine to catecholborane, thus activating the B–H bond for hydride abstraction by B(C6F5)3. DFT calculations were used to address the nature of the resulting cations. This approach led to the localization of the positive charge on the phosphorus atom, which prompts the description of these species as borylphosphonium cations rather than as a phosphate-stabilized borenium cations. Nonetheless, this cation is the first three-coordinate boron cation, ligated by oxygen donors.[118]

8.7. Activation of CO2

Owing to its role as a greenhouse gas, the development of new methods for both the sequestering of CO2 and its use as an alternative C1 chemical feedstock is rapidly gaining increasing attention.[119] Chemical conversion of CO2 often utilizes the special properties of metal complexes.[120] The ruthenium-based hydrogenation of CO2 to formic acid derivatives is a prominent example.[121] There are a number of reactions of main-group-element reagents with CO2, such as the trapping reaction with amines[122] or main-group-metal amides,[123] or the conversion of CO2 into bicarbonate induced by organic bases in the presence of hydroxide.[124] Some chelate complexes of zinc catalyze the addition of CO2 to epoxides.[125] Recently, N-heterocyclic carbenes (NHCs) were shown to add to CO2 and to induce its organocatalytic addition reactions to organic substrates[126] or its reduction to methanol.[127]

In a collaborative report, Stephan et al. and Erker et al. found that CO2 reacts with frustrated Lewis pairs in a straightforward fashion.[22] For example, the components of the tBu2P/B(C6F5)3 pair add to CO2 at room temperature in bromobenzene with P−C and O−B bond formation, yielding the product 160 (Scheme 65, Figure 42). Cleavage and
liberation of CO₂ occurs upon heating to +70°C, indicating that the CO₂ addition reaction is reversible.

Similarly, the intramolecular frustrated Lewis pair 25a also reacts with CO₂ under analogous reaction conditions. Pressuring a solution of 25a in pentane with CO₂ (2 bar) leads to the precipitation of the adduct 161. In this case, the carboxylation of the frustrated Lewis pair is reversible as the product 161 rapidly loses CO₂ in solution at temperatures above −20°C to reform the starting material 25a. At temperatures below this limit, compound 161 can be handled without decomposition. Single crystals of compound 161 were obtained at −36°C. (Figure 43) The examples 160 and 161 may be regarded as phosphonium analogues of carbamic acid derivatives.

Grimme et al. examined these reactions of CO₂ by DFT calculations. The detailed theoretical analysis revealed that the CO₂ addition reaction to 25a to yield 161 is close to thermoneutral, whereas the analogous addition of the open /Bu₃P/B(C₆F₅)₃ pair is remarkably exothermic. Analysis of the 25a/CO₂ system showed the formation of a weakly bound van der Waals complex of CO₂ and the open isomer (26a), followed by a concerted addition reaction to 161 (calculated activation energy: 7.7 kcal mol⁻¹ from the van der Waals complex). In contrast to the very unsymmetrical transition state found in the corresponding addition reaction of 25a to norbornene (see Section 8.3), both the formation of the P–C and the O–B bonds are almost equally advanced in the cyclic transition state (Figure 44) of the 25a/CO₂ addition reaction.

9. Conclusions

The concept of “frustrated Lewis Pairs” (FLPs) advanced herein is rooted in the early observations of Brown, Wittig, and Tochtermann. However in the flurry of research that has taken place in recent years, frustrated Lewis pairs have developed from chemical curiosities into a new strategy for the activation of a variety of small molecules.

The remarkable ability of these systems to reversibly activate hydrogen presents a new line of thought for those developing and applying hydrogenation catalysis and perhaps even for the field of hydrogen storage. While any commercial impact of catalytic systems derived from frustrated Lewis pairs developed to date remains to be seen, the potential for metal-free hydrogenation catalysis is an attractive notion given the reductions in both cost of production and of environmental impact of these main-group catalysts.

While H₂ activation is of broad interest to the chemical community, the demonstration that frustrated Lewis pairs are capable of reactions with alkenes, dienes, alkynes, boranes, and CO₂ suggests a parallel between the chemistries of frustrated Lewis pairs and that of transition metals. In organometallic chemistry, the activation of small molecules is known to be the first step towards a mediated transformation. This analogy suggests that new patterns of reactivity and catalysis will emerge from these early findings of small-molecule activation by frustrated Lewis pairs.

Finally and perhaps more generally, the notion of frustrated Lewis pairs draws attention to the importance of molecular interactions that are not in themselves chemically productive and are generally not discernible spectroscopically. The attractive forces that bring the Lewis acid and Lewis base together in a frustrated Lewis pair are such interactions. While these forces do not prompt a chemical transformation, they offer a new “species” capable of unique reactivity. Fundamental understanding of such systems will be critical to the further development of their unique reactivity. Moreover, the application of these concepts in other, as yet unstudied systems, may provide the roots for further discovery.
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