"Frustrated Lewis pairs": a concept for new reactivity and catalysis

Douglas W. Stephan*

The concept of "frustrated Lewis pairs" is described and shown to result in molecular systems capable of unique reactivity as well as applications in catalysis.

Introduction

In 1923 Lewis[1] put forth a description of acids and bases categorizing molecules as electron pair donors or acceptors that is central to our understanding of much of main group and transition metal chemistry. A primary axiom of this descriptor of chemical reactivity is the notion that the combination of Lewis acids and bases results in the formation of simple Lewis acid–base adducts. A classic undergraduate demonstration of this concept is the formation of the ammonia–borane adduct, $NH_3 \cdot BH_3$, upon combination of the Lewis acid borane with the Lewis base ammonia. The concept of donor–acceptor adduct formation is the basis of transition metal coordination chemistry. As examples, the extensive use of Lewis-acidic B- and Al-based activators in olefin polymerization catalysis[2–13] and in a large number of organic transformations are noted.[14–20] Similarly, Lewis base donor ligands are inherent to homogeneous transition metal catalysis. Indeed, many of the developments of new applications of organometallic chemistry hinged on designed control of specific steric and electronic properties as well as the stereochemistry of ligands. The principles of Lewis acidity–basicity also extend to surface science and solid state chemistry, accounting for the adsorption of materials to either surfaces or within cavities as well

Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ontario, M5S 3H6, Canada. E-mail: dstephan@chem.utoronto.ca; Tel: +1 416-946-3294

as the assembly of complex arrays of electron donor and acceptors. It is clear that the concept put forth by Lewis almost 90 years ago, which offered a molecular-orbital-based rationale for acid/base reactions that describes dative donor–acceptor adducts,[1] is a powerful tool for explaining and understanding much of modern chemistry. This principle is indeed accepted and employed across the discipline.

In this article, we describe findings that illustrate an interesting corollary to Lewis' principle. Herein we discuss our initial studies of "frustrated Lewis pairs" (FLPs). In such systems, sterically hindered Lewis donors and acceptors are combined.[21] Their steric demands preclude formation of simple Lewis acid–base adducts, allowing for the subsequent actions of both Lewis acids and bases on other molecules. This concept of FLPs has been extended to demonstrate new reactivity, ultimately leading to new approaches in catalysis. The advent of this new notion in reactivity presents both opportunities and challenges for chemists across the discipline.

Non-classical reactivity of Lewis acid–base pairs

Our initial formulation of the concept of FLPs evolved during a study of simple reactions of trityl borate with Lewis donors such as amine, pyridines and phosphines.[22] In general these reactions followed conventional chemistry affording classical Lewis acid–base adducts of the form $[LCPh_3][B(C_6F_5)_4]$ (Scheme 1A).

Douglas W. Stephan

Doug Stephan attended McMaster University and earned a PhD at the University of Western Ontario in 1980. He was a NATO postdoctoral Fellow at Harvard University and in 1982 he joined the faculty at Windsor, where he was subsequently promoted through the ranks, being named University Professor in 2002. Author of over 190 scientific articles, his research interest focuses on transition metal and main group chemistry, including early–late heterobimetallics, Ti–S, Zr–P and Zr=PR chemistry, catalysts for P–H activation as well as catalysts for olefin polymerization. This latter work resulted in numerous patents and is currently in commercial practice. Most recently, Stephan's group has uncovered the concept of "frustrated Lewis pairs". Stephan received the 2001 Alcan Award (Canadian Society for Chemistry) and in 2003 was awarded an NSERC of Canada Synergy Award and a Humboldt Research Award (Germany). In 2004 he received the Ciapetta Lectureship (North American Catalysis Society) and in 2005, Stephan was awarded the LeSueur Memorial Award from the Society for Chemical Industry and named a Canada Research Chair at Windsor. In January 2008, he took up a position as Professor of Chemistry and Canada Research Chair in Inorganic Materials and Catalysis at the University of Toronto.

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However, reactions of [CPh₃][B(C₆F₅)₄] with sterically encumbered phosphines such as PR₃, R = *i*Pr, Cy, *t*Bu, resulted in nucleophilic attack at the *para*-position of an aryl ring of the trityl cation, giving species of the form [(*i*Pr₃PC₆H₄)Ph₂CH][B(C₆F₅)₄] or [(R₃PC₆H₅)CPh₂][B(C₆F₅)₄] (R = Cy, *t*Bu) (Scheme 1C).[22] In related reactions of the phosphines with THF–B(C₆F₅)₃, it is generally observed that the stronger Lewis base simply replaces THF forming the corresponding borane–phosphine adduct (Scheme 1B). However, reactions of sterically demanding phosphines followed an alternate path, giving rise to nucleophilic ring opening of THF giving butoxy-tethered R₃HP(CH₂)₄OB(C₆F₅)₃ phosphonium borates (Scheme 1D).[23] These results were interpreted in terms of the inability of the Lewis acid and base to form simple adducts as a result of the steric congestion. Nonetheless, as the steric frustration leaves the Lewis acidity and basicity unquenched, these centers are available for further reactivity. These initial findings prompted us to explore the "frustrated Lewis pairs" (FLPs) concept as an avenue to new reactivity.
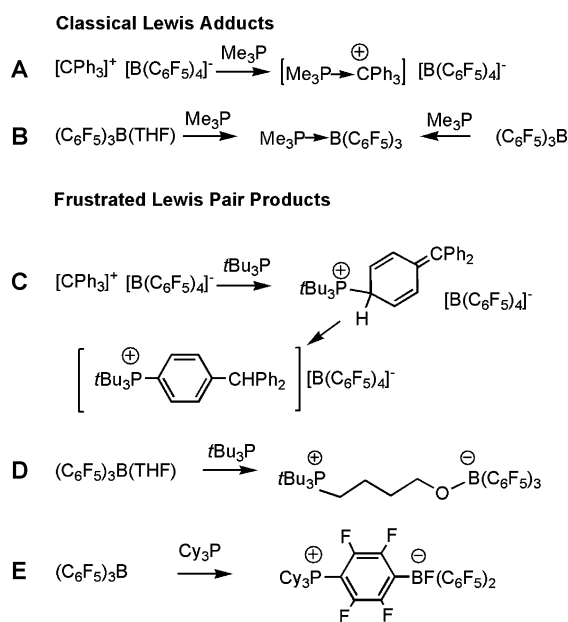

Scheme 1 Reactivity of "classical" and "frustrated" Lewis pairs.

We began with an examination of the reactions of the Lewis acid B(C₆F₅)₃ with sterically hindered tertiary or secondary phosphines R₃P (R = *i*Pr, Cy) or R₂PH (R' = *t*Bu, C₆H₂Me₃-2,4,6).[24] Consistent with FLP reactivity there was no evidence of simple Lewis acid–base adduct formation. Instead, white, air- and moisture-stable solids formulated as [R₃P(C₆F₄)BF(C₆F₅)₂] (Scheme 1E) or [R'₂PH(C₆F₄)BF(C₆F₅)₂] were isolated.[25] The nature of these products is consistent with steric congestion precluding coordination to B and thus facilitating nucleophilic attack by the phosphine at the more accessible, electrophilic *p*-carbon of an arene ring. Substitution occurs with concurrent fluoride transfer to B. In a similar fashion, Erker and coworkers have described the thermal rearrangement of the ylide adduct (Ph₃PCHPh)B(C₆F₅)₃ to the *para*-substituted species [Ph₃PCHPh(C₆F₄)BF(C₆F₅)₂].[26]

Activation of small molecules by FLPs

The BF fluoride in the products [R₃P(C₆F₄)BF(C₆F₅)₂] or [R'₂PH(C₆F₄)BF(C₆F₅)₂] could be simply exchanged for hydride by reaction with Me₂SiClH. These products were particularly interesting to us, as these molecules contain both protic and hydridic centres. Thermolysis of the species [(C₆H₂Me₃-2,4,6)₂PH(C₆F₄)BH(C₆F₅)₂] results in the liberation of H₂ and the generation of the species [(C₆H₂Me₃-2,4,6)₂P(C₆F₄)B(C₆F₅)₂].[25] It is noteworthy that this species is a unimolecular FLP in that no intermolecular coordination of P to B is evident in solution or the solid state. Perhaps more astounding however is the fact that exposure of a solution of this phosphino–borane to H₂ at 25 °C led to the re-formation of the zwitterionic salt [(C₆H₂Me₃-2,4,6)₂PH(C₆F₄)BH(C₆F₅)₂] (Scheme 2A). This finding represents the first non-transition metal system that reversibly releases and takes up hydrogen.
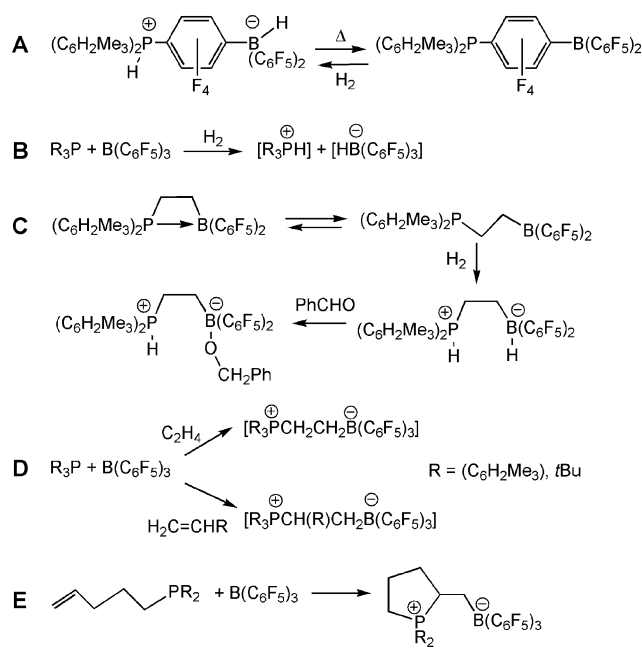
Scheme 2 Activation of H₂ and olefins by FLPs.

H₂ is also activated by simple combinations of phosphines and boranes.[27] The key, again, is that the Lewis acidity and basicity is not quenched by donor–acceptor adduct formation. Thus, 1:1 mixtures of R₃P (R = *t*Bu, C₆H₂Me₃) with B(C₆F₅)₃ were prepared and showed no evidence of adducts formation even on cooling to −50 °C. However, exposure of this mixture to 1 atm H₂ resulted in the formation of [R₃PH][HB(C₆F₅)₃] (Scheme 2B).[27] In contrast to [(C₆H₂Me₃)₂PH(C₆F₄)BH(C₆F₅)₂],[25] heating of these salts did not liberate H₂ even with heating to above 100 °C. Similarly, combination of *t*Bu₃P and BPh₃ were seen to activate H₂ to some extent giving [*t*Bu₃PH][HBPh₃] in only 33% yield. In contrast, reactions of (C₆H₂Me₃)₃P and BPh₃, (C₆F₅)₃P and B(C₆F₅)₃ or *t*Bu₃P and BMes₃ resulted in no reaction at 25 °C under an atmosphere of H₂. On the other hand, Ph₃P and Me₃P reacts with B(C₆F₅)₃ under H₂ at 25 °C to give the classical Lewis acid–base adducts R₃P·B(C₆F₅)₃ (R = Ph, Me). These observations suggest that the activation of H₂ requires not only a sterically

frustrated Lewis pair but a favorable combination of Lewis acidity and basicity as well.

The Erker group have recently extended such activation of H_2 to include alkyl-linked phosphino-boranes.[28] The species $[(C_6H_2Me_3)_2PCH_2CH_2B(C_6F_5)_2]$ was shown to exist in an equilibrium between the four-membered intramolecular donor–acceptor ring complex and the open unlinked form. Exposure of this species to H_2 resulted in formation of the zwitterionic species $[(C_6H_2Me_3)_2PHCH_2CH_2BH(C_6F_5)_2]$. This species was also shown to react with benzaldehyde, affording $[(C_6H_2Me_3)_2PHCH_2CH_2B(OR)(C_6F_5)_2]$, demonstrating the potential of such systems to act as reducing agents (Scheme 2C).[28]

The reactivity of such FLPs with olefins has also been investigated. Indeed, purging of a solution of combination of tBu_3P and $B(C_6F_5)_3$ with ethylene resulted in the formation of the zwitterionic species $[tBu_3PCH_2CH_2B(C_6F_5)_3]$ (Scheme 2D).[29] Similarly, reactions with propylene and 1-hexene with tBu_3P and $B(C_6F_5)_3$ afforded $[tBu_3P(CH(R)CH_2B(C_6F_5)_3]$ (R = CH_3, C_4H_9), respectively (Scheme 2D). Of particular note is the regiochemistry, as these species yield a B-methylene unit with the substituted carbon adjacent to P. An interesting twist on this reactivity is derived from the inclusion of the olefinic unit in a substituent on the phosphine. Thus, the phosphines $CH_2=CH(CH_2)_3PR_2$ (R = tBu, $C_6H_2Me_3$) were reacted with $B(C_6F_5)_3$ to generate the cyclized phosphonium borate $[R_3PCH(C_3H_6)CH_2B(C_6F_5)_3]$ (R = tBu, $C_6H_2Me_3$) (Scheme 2E).[29]

The mechanistic details of these reactions of FLPs with small molecules are the subject of on-going studies. Initially, Lewis acid activation of the substrate molecule followed by attack of the Lewis base seems a reasonable postulate. Such a notion is supported for reactions of H_2 by some computations for borane–H_2 adducts. However, it should be noted that matrix isolation work suggests interaction of phosphine with H_2. In the case of activation of olefins, experimental precedent for such a proposition is based on IR studies of van der Waals BF_3–ethylene and BF_3–propylene complexes generated in an argon matrix at 93–125 K reported by Herrebout and van der Veken.[30] Computational studies have also suggested weak π-donation complexes for ethylene–alane and -borane adducts.[31,32]

Following our publication of the reversible activation of H_2 by phosphino–boranes, Bertrand and coworkers[33] described a very interesting and related system. These researchers showed that some carbene derivatives react both with H_2 or NH_3 to effect the heterolytic cleavage of H–H or N–H bonds. Supported by molecular orbital calculations, these reactions were described in terms of the orthogonal lone pair and vacant p-orbital on the carbene carbon. To our way of thinking, Bertrand's work illustrates that carbenes can be described as unique FLPs in that the donor and acceptor site reside on the same atom (Scheme 3).
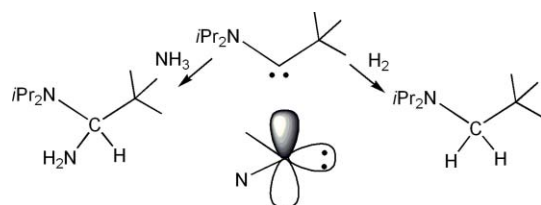
Scheme 3 Activation of H_2 and NH_3 by a carbene.

Tuning Lewis acidity

The generation of the *para*-substituted derivatives of $B(C_6F_5)_3$ derived from the reactivity of FLPs offered a convenient and readily accessible means for tuning the Lewis acidity of B centres. Reaction of species of the form $[R_2PH(C_6F_4)BF(C_6F_5)_2]$ with a Grignard reagent afforded a facile route to the phosphino–borane species $R_2P(C_6F_4)B(C_6F_5)_2$.[24] On the other hand, reaction of the fluoride zwitterions with Me_2SiHCl and subsequent reaction with $[Ph_3C][B(C_6F_5)_4]$ afforded compounds of the form $[(R_3P)(C_6F_4)B(C_6F_5)_2]$ $[B(C_6F_5)_4]$ and $[(R_2PH)(C_6F_4)B(C_6F_5)_2]$ $[B(C_6F_5)_4]$.[24] Thus, these synthetic routes provided a family of borane derivatives with both electron-donating phosphine and electron-withdrawing phosphonium groups in the *para*-position. This affords variations in the Lewis acidity while maintaining the steric features about the B centre. Employing the Gutmann–Beckett and Childs methods for determining Lewis acid strength, it was demonstrated that the cationic boranes are much more Lewis-acidic than $B(C_6F_5)_3$, while the acidity of the phosphine–boranes is diminished, as expected (Scheme 4).[24]
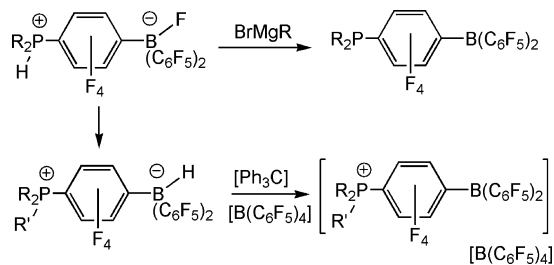
Scheme 4 Preparation of phosphino–borane and phosphonium–borane derivatives.

Metal-free catalytic hydrogenation

A more interesting and perhaps creative application of the chemistry of FLPs is derived from the notion that a catalytic cycle for metal-free hydrogenation could be derived from activation the action of H_2 upon $(C_6H_2Me_3)_2P(C_6F_4)B(C_6F_5)_2$.[34] If one could effect transfer of proton and hydride from $(C_6H_2Me_3)_2PH(C_6F_4)BH(C_6F_5)$ to a substrate, this would regenerate the phosphino–borane, allowing activation of H_2 once again, thus providing a catalytic cycle for reduction. To this end, the phosphonium borates $(R_2PH)(C_6F_4)BH(C_6F_5)_2$ (R = $C_6H_2Me_3$, tBu) were shown to effect the catalytic reduction of imines to the corresponding amines cleanly and in high yield at temperatures between 80 and 120 °C and H_2 pressures of 1–5 atm.[34] It should be noted, however, that a common feature of the imines that are reduced is the inclusion of sterically demanding substituents on N. This requirement was shown to be necessary, as reduction of a less hindered imine affords an amine that binds tightly to the borane centre of the phosphino–borane, precluding further H_2 activation. The mechanism of reduction in these cases was probed and shown to involve initial protonation of the imine by the phosphonium centre followed by borohydride attack of the iminium salt.[34]

In systems where such steric bulk is not present such as $PhCH=NCH_2Ph$, sequestering the N lone pair by coordination

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to $B(C_6F_5)_3$ allowed catalytic imine reduction to proceed. In addition, alkyl and aryl $B(C_6F_5)_3$-bound nitriles are also successfully reduced to the corresponding primary amine–borane adducts.[34] In addition, catalytic reductive ring opening of an unactivated *N*-aryl aziridine functionality is achieved under similar conditions. Mechanistically, reduction of $B(C_6F_5)_3$-bound imines or nitriles is believed to proceed *via* initial hydride transfer affording an amido–borate species, with subsequent protonation of N affording the corresponding amine–borane adduct.[34] Thermal dissociation provides the free phosphino–borane, which then activates H_2 and re-enters the catalytic cycle (Scheme 5).
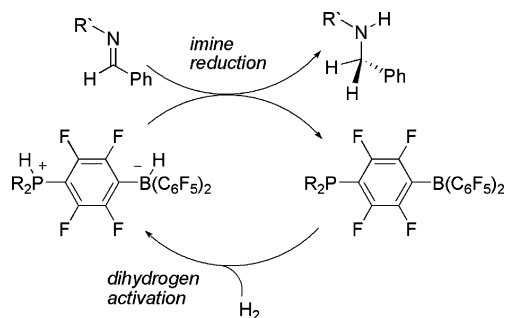
Scheme 5 Mechanism of hydrogenation of imines catalyzed by phosphino–borane.

In very recent work, we have also shown that the sterically hindered imine substrates themselves can act as the Lewis base partner of an FLP.[35] Thus, combination of such an imine, $B(C_6F_5)_3$ and H_2 results in reduction of conditions similar to those described for the phosphino–borane catalysts.

The above studies are rare examples of transition metal-free hydrogenation catalysis. Generally, previous examples have achieved catalysis under rather forcing conditions. For example, hydrogenation of benzophenone was achieved using 20 mol% KO*t*Bu and H_2 at 200 °C and >100 bar H_2.[36] Alternatively, trialkylboranes and H_2 effect hydrogenation of olefins by successive hydroboration–hydrogenolysis reactions at >200 °C and 15 atm.[37–40] Organocatalysts have been developed for hydrogenations of enones and imines; however, such systems use a Hantzsch ester as the stoichiometric source of hydrogen.[41–45] Therefore, the finding that FLP catalysts can effect hydrogenation under relatively mild conditions is a major advance in this area. Clearly, this approach replaces expensive precious metal catalysts, offering the potential benefit of significantly lower cost and diminished environmental impact from heavy metal pollutants.

Implications and future directions

These early results unveil the concept of FLPs and generate the potential of a new strategy to reactivity and catalysis. Clearly, the studies to date are limited but they do demonstrate that small molecule activation can be effected by simple combination with readily available Lewis acids and bases. From the perspective of an organometallic/inorganic chemist, this aspect seems ripe for exploitation. Activation of a range of small molecules, the development of new metal-free catalytic processes and uncovering ways to extend the range of application and control stereochemistry are all aspects that are indeed being actively pursued in our labs.

Taking another perspective, it is interesting to speculate on the breadth and generality of the notion of FLPs. For example, can one extend this concept to a range of other Lewis-acidic and Lewis-basic elements, including transition metals? Specifically, can one employ early metal cations as the Lewis acid-component of a FLP? In this regard it is interesting to note that in examining base-stabilized cations of the form $[CpTi(NPR_3)Me(PR_3)]$ $[MeB(C_6F_5)_3]$, it was observed that bulky phosphines such as PR_3 ($R = C_6H_2Me_3$, *t*Bu) did not coordinate to Ti. Do such combinations generate a transition-metal-based FLP? Can the reactivity of such systems be exploited for unique transition metal chemistry or catalysis? These questions are also being probed.

In broader terms, important questions relate to the extension of the concept of FLPs to organic chemistry. As but one example, the early finding of metal-free catalytic hydrogenation prompts questions regarding applications to organic chemistry and the potential to develop FLP hydrogenation catalysis for a range of organic substrates. An obvious extension of these findings is the potential to develop metal-free catalysts for asymmetric hydrogenations. On the other hand, the finding that olefins are activated suggests that FLPs have the potential to effect the activation of other bonds, presenting a new strategy for methodology development.

While the investigations on the chemistry of FLPs are still in their infancy, this concept has the potential to be broadly applicable to a number of areas. Early reports certainly suggest that this corollary to Lewis theory promises a new window of opportunity for the study of reactivity and catalysis in molecular chemistry. However, a broader view suggests that the organic chemistry community has the potential to exploit this concept in novel ways. The development of new FLPs and the utilization of the resulting catalysts will undoubtedly emerge, giving rise to unique approaches to a range of applications in catalysis and synthetic methodologies of use to the organic chemist.

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