

Frustrated Lewis Pairs

Enabling via Inability

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The fundamental concept of Lewis acid–base interactions have played a substantial role in the progress of chemistry and enriched its understanding, most significantly in the evolution of coordination compounds. In the last 7 years, the chemistry of Lewis Pairs (i.e., acids and bases) has witnessed a different kind of revolution. Molecular frustration, arising from restrictions preventing Lewis acid–base adduct formation has attracted significant attention in metal-free catalysis and activation of small molecules¹. In this article, the basic concepts of such frustrated Lewis Pairs are discussed.

1. Introduction

In the modern advancement of chemistry and its day-to-day applications, a major part is occupied by catalysis and activation of chemical bonds. Activation of apparently indolent chemical bonds forms the pillars of modern petroleum, polymer and other related chemical industries (such as production of methanol, acetic acid, etc.). Until recently, the concepts of catalysis were inseparably related only to the families of transition metals. Having a significant number of valence d-orbitals, transition metal compounds show various possible oxidation states or coordination modes and these flexibilities of transition-metal-based systems have boosted their study as catalysts and chemical bond activators. In spite of being expensive, their efficient behaviour has led to their application in the industry. However, issues of cost-effectiveness, toxicity and availability have necessitated the search for organic alternatives in all fields of chemistry in the last few decades. For example, in the last two decades, a significant advancement has been achieved in fields of organic light emitting diodes (OLEDs), organic thin film transistors (OFETs), and



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Keywords

Lewis acidity/basicity, steric congestion, catalysis, H₂ activation.



¹ Activation of small molecules i.e., reactions and chemistry of important species like CO_2 , N_2 etc. is often extremely important from the viewpoints of chemistry and its possible applications. It is often involved with production of energy-rich materials from highly stable chemical species, removal of certain chemical species or chemical synthesis.

organic solar cells (OSCs), and last but not the least, organocatalysis. The apparent safety and comfort associated with the term organic have now made it an extremely appealing research and marketing statement.

Until 2006, metal-free organic systems capable of activating small important molecular systems such as dihydrogen (H_2), carbon monoxide (CO), carbon dioxide (CO_2) and other covalent bonds (e.g., C–H) bonds were unknown to chemists. In the last few years, a single class of compounds known as Frustrated Lewis Pairs (FLPs) has changed our concepts in this regard and has created opportunities in metal-free catalysis and much more.

2. What Governs Lewis Acidity or Basicity?

In 1923, Gilbert N Lewis classified compounds/molecules as Lewis acids and Lewis bases according to their ability to accept or donate electron pairs (*Figure 1*). Lewis bases, with their highest occupied molecular orbitals (HOMO) can donate electron pairs to other species; whereas Lewis acids can accept electron pairs owing to the presence of their lowest unoccupied molecular orbitals (LUMO). Like Bronsted acids and bases, Lewis acids and bases combine together resulting in neutralisation. However, in this case, new Lewis acid–base adducts are formed rather than salt and water

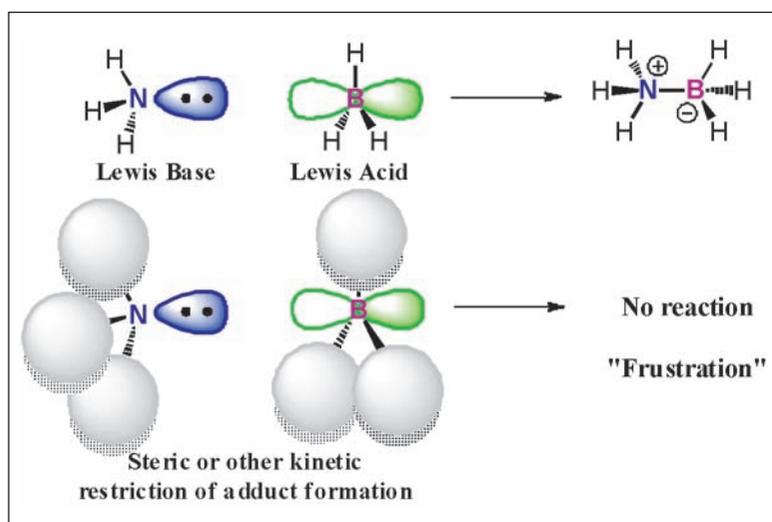


Figure 1. Lewis acid–base interactions.



(Figure 1, ammonia–borane adduct formation). Formation of a Lewis acid–base adduct is one of the most fundamental concepts and a pillar of modern chemistry. A large part of main group chemistry and the entire transition-metal coordination chemistry can be understood and generalised according to Lewis acid–base concepts. If Lewis acid–base chemistry is so all encompassing, the natural question is: ‘How can molecular Lewis Pairs be frustrated?’¹

3. What Governs frustration in Lewis Pairs?

Attempts to form Lewis acid–base adducts in sterically overcrowded systems have failed for a long time. In 1942, Brown *et al.* noticed that the Lewis acid–base adduct formation observed among pyridines and simple boranes was not followed by Lutidine (**1**) and BMe_3 . However, under similar conditions, Lutidine forms a Lewis acid–base adduct (**2**) with BF_3 (Figure 2). After scrutinizing the molecular models of these compounds, Brown *et al.* attributed this result to the steric hindrance of methyl groups in BMe_3 by the *ortho*-methyl groups of Lutidine. Wittig and Benz (1959) and Tochtermann (1966) also observed similar non-classical behaviour of sterically encumbered Lewis acid–base pairs. Tochtermann described these systems as ‘Antagonistisches Paar’ meaning antagonistic pair. However, the unprecedented reactivity of such

¹ The word frustration is derived from the Latin word *frustratio* (related to *frustra*) meaning ‘in vain’ or ‘disappointment’. Even without being a psychologist, one can infer that frustration is a sense of apparent failure to do something which is not impossible. Sometimes, it causes serious alterations to one’s emotions and responses, or it may also inspire one to do something better and more important than the previously targeted task.

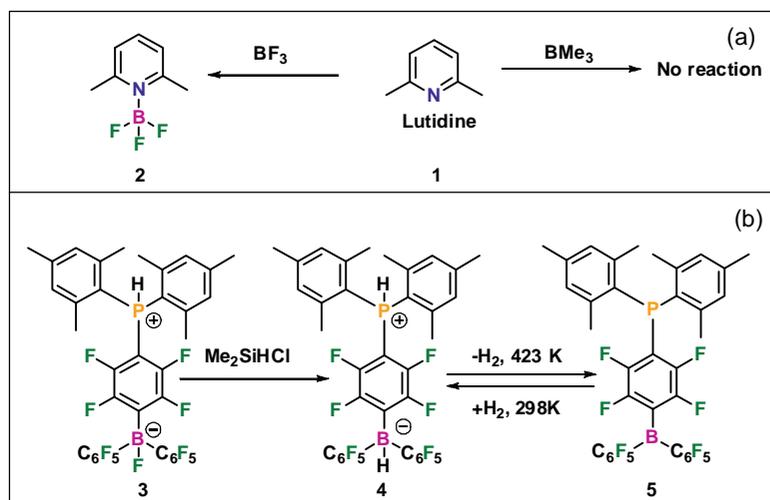


Figure 2. Reactivity of Lutidines towards boranes (a) and the first example of FLP system (b).

Lewis Pairs (LPs) was yet to be understood and applied, which had to wait until 2006. Stephan and co-workers (2006), for the first time, illustrated the reactivity of such FLPs (*Figure 2*).

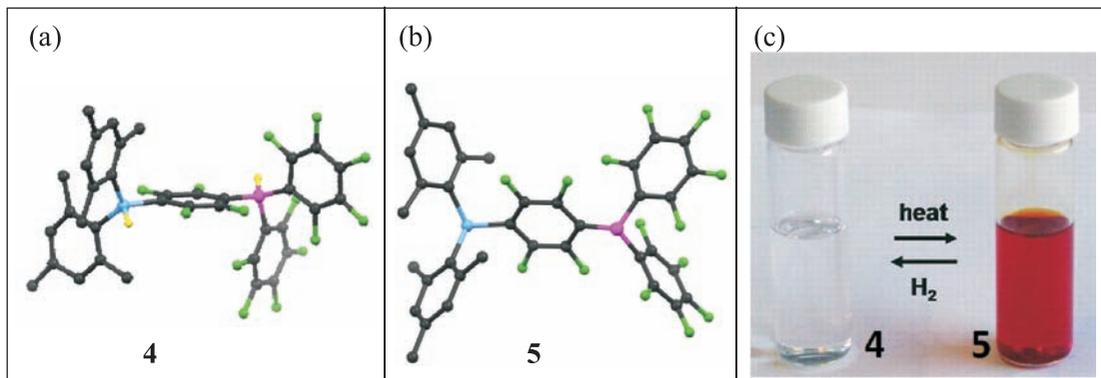
4. The Breakthrough!

The zwitterionic salt **3** obtained from aromatic nucleophilic substitution reaction of $B(C_6F_5)_3$ with dimesitylphosphine, was treated with Me_2SiHCl , yielding compound **4** in a clean reaction. Compound **4**, at that time, was a rare example of a metal-free system containing both protic and hydridic fragments. The species was air and moisture stable and by itself, quite robust. However, heating of the species near $150^\circ C$ resulted in elimination of H_2 and formation of compound **5**. The conversion was confirmed by X-ray diffraction analysis of **4** and **5** (*Figure 3*).

Figure 3. X-ray (single crystal) obtained structures of **4** (a) and **5** (b) (C = black, P = sky blue, F = green, B = magenta, H = yellow, solvent molecules and irrelevant hydrogen atoms omitted for clarity) and the photograph (c) of THF solutions of **4** and **5**.

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The sterically congested compound was found to be monomeric in solution with no signs of dimerisation or higher aggregation and could be described as a steeric FLP. A remarkable finding was that the addition of H_2 to the phosphinoborane **9** at $25^\circ C$ resulted in rapid and facile formation of **4**. The reaction could also be monitored by naked eye as the dark red colour of **5** ($\lambda_{max} = 455 \text{ nm}$; $\epsilon = 487 \text{ L cm}^{-1} \text{ mol}^{-1}$) disappeared with formation of colourless **4**. This represented the first example of a non-transition metal system which could both release and take up dihydrogen. This unique reactivity was undoubtedly a result of the combination of a sterically crowded strong Lewis acid with a Lewis base where steric demands prevent the classical adduct formation. The elec-

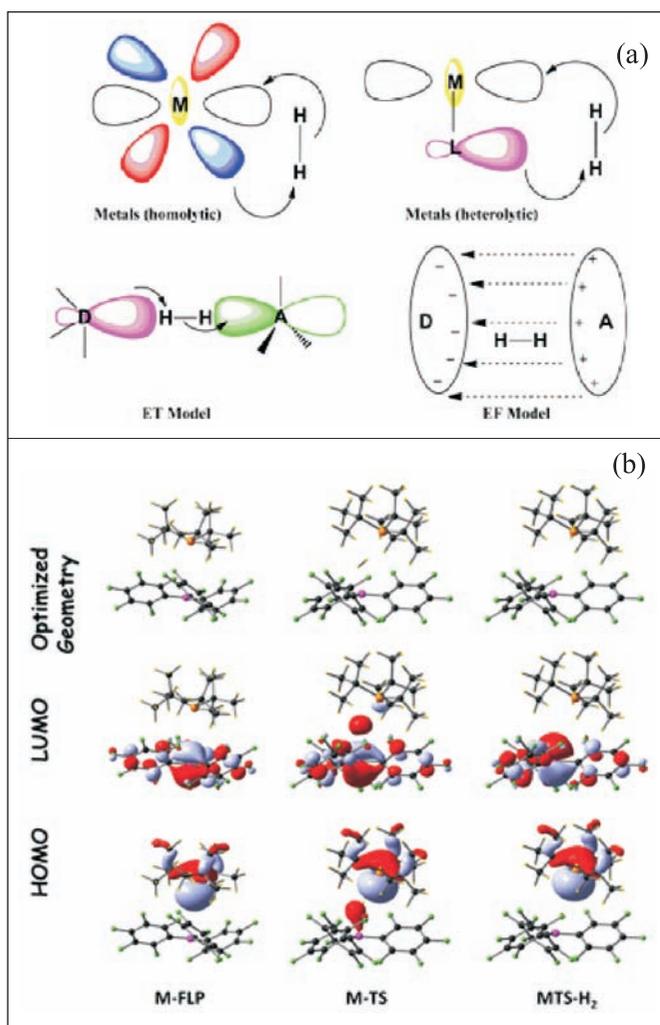


tronic thirst of the phosphine moiety to donate electrons and the thirst of the borane to gain an electron pair (i.e., the state of frustration), could be overcome upon heterolytic cleavage of H_2 . The strength of the constituent Lewis acids and Lewis bases were also found to be very important in achieving such behaviour. Thus, in most of the cases, strong Lewis acids like Piers' borane, i.e., $B(C_6F_5)_3$ or related fluorinated boranes and relatively strong phosphine bases (e.g., tri-tert-butylphosphine) received considerable attention. Soon, it was found that the non-interacting mixtures of these molecules (e.g., mixture of $B(C_6F_5)_3$ and tri-tert-butylphosphine) can act as FLPs with the capability to heterolytically cleave H_2 .

5. In Search of How

The mechanism of such reactivity in FLP systems is still an unsolved puzzle. Whereas our concepts about transition metal-based dihydrogen activation is well-established in literature, the FLPs are still not bound by a single rule. Two alternative reactivity models have been proposed to qualitatively describe such a heterolytic cleavage of H_2 by FLPs (Figure 4). Both models assume that the course of the reaction passes through intermediates consisting of preorganised Lewis acid–base partners. The electron transfer (ET) model suggests that hydrogen activation is accompanied by synergistic e-donation with the concurrent involvement of active centres and the bridging dihydrogen, similar to transition-metal-based systems. Whereas, the electric field (EF)

Figure 4. Proposed mechanisms of heterolytic dihydrogen activation by FLPs compared to transition-metal-based systems (a) and DFT-obtained geometries and FMOs of model systems (b). (Colour codes: C = black, P = sky blue, F = green, B = magenta, H = yellow.)



model proposes that the breaking of heterolytic bond occurs as a result of polarization of H_2 by the strong EF present in the cavity of the reactive species.

Recent studies by Pápai and co-workers suggest that the EF model might be inappropriate to understand the actual occurrences at a molecular level. The ET model suggests bond weakening via orbital overlap at intermediate steps based on computational studies (*Figure 4*). Computations with a model FLP system consisting of $P(t-Bu)_3$ and $B(C_6F_5)_3$ (i.e., **M-FLP**) reveals a preorganised face-to-face orientation of the active sites. The H_2 -bound transition-state (**MTS**) structure shows a bent $B \cdots H \cdots H \cdots P$ geometry with significant amount of orbital overlap. This bent geometric unit can be explained by the simplistic EF model. To understand contributions of the orbitals at this stage, energy calculation after removal of the dihydrogen unit from the transition-state structure (i.e., **MTS- H_2**) was also performed. **M-FLP** and **MTS- H_2** consist of a HOMO dominated by the Lewis basic phosphine centre, whereas the LUMO is dominated by the empty p_π orbital of the borane unit. Evidently, FMOs of the Lewis acid and Lewis base participate actively during the course of reaction.

6. General Behaviour of FLPs

The lack of a perfect theoretical basis has not affected the pace of experimental progress in this field as researchers have continuously explored different possible ways to achieve FLP systems. Lewis basic amines were also found to act similar to phosphine. As reported by Reiger and co-workers (2008), reaction of $B(C_6F_5)_3$ with iPr_2NEt and iPr_2NH gives a 1:1 mixture of corresponding ammonium salts **6** and **7**, respectively (*Figure 5*). These reactions also produce zwitterionic products of amine dehydrogenation **8** and **9**. However, exposure of mixtures of iPr_2NH or $Me_4C_5H_6NH$ with $B(C_6F_5)_3$ to H_2 results in the quantitative formation of ammonium borate **7** and **10** (*Figure 5*).

Stephan et al. (2009) explored the reactivities of the Lutine– $B(C_6F_5)_3$ pair. This combination was found to act as a boundary



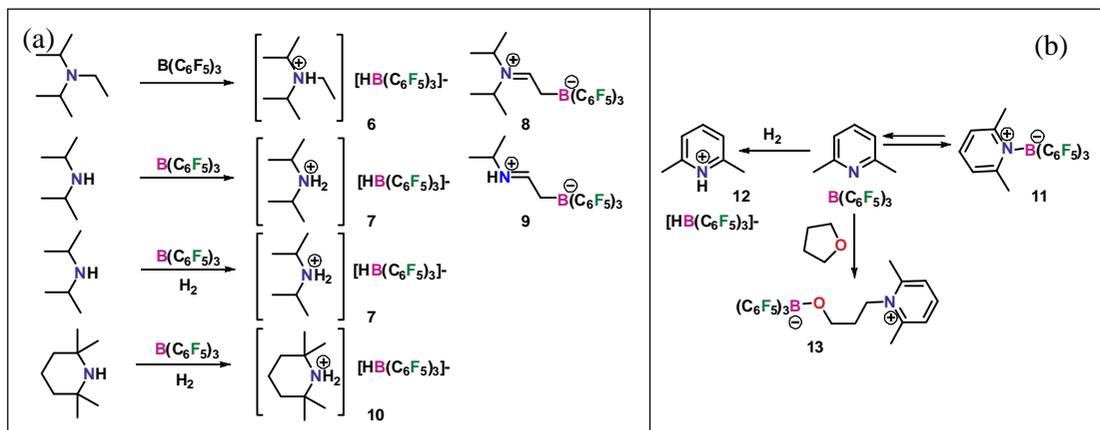


Figure 5. Dihydrogen activation by amine–borane pairs (a) and Lutidine–borane pair (b).

between classical Lewis Pairs and FLPs (Scheme 12). Unlike previously reported systems, Lutidine and $B(C_6F_5)_3$ undergo reversible adduct formation (**11**) such as classical Lewis Pairs (Figure 5). However, the reactivity of the system towards H_2 is not diminished. Upon exposure to H_2 atmosphere, the formation of zwitterionic salt (**12**) with 87% yield was observed. These results indicate that the two different types of reactivities of Lewis Pairs may not be mutually exclusive.

The real state-of-the-art approach in amine–borane-based FLPs was illustrated by Stephan and co-workers (2013) (Figure 6). In a new approach, they buried the amine functionality inside steri-

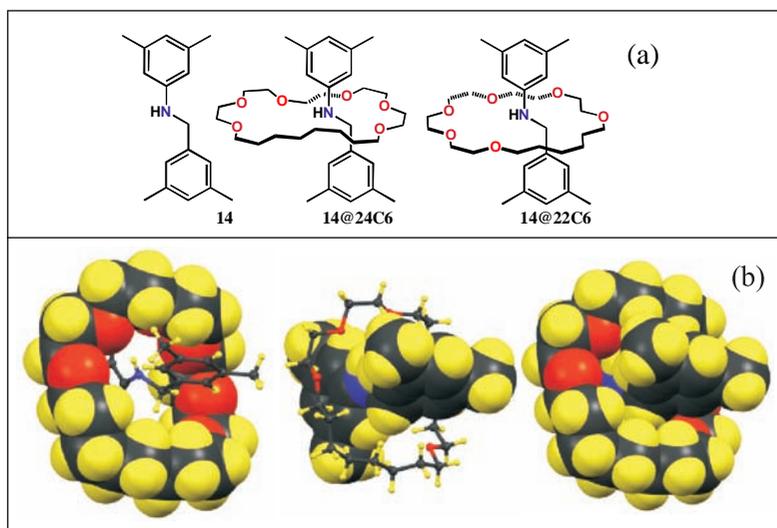


Figure 6. Structures of **14**, **14@24C₆**, **14@22C₆** (a). X-ray (single crystal) obtained structures of **14@24C₆** (b) (C = black, O = red, H = yellow, N = blue). The three perspectives, respectively, represent the alkylether unit, the axle and the entire rotaxane in space-filling models.

cally protected rotaxane cavities. The amine **14**, containing 1,3-dimethylphenyl and 1,3-dimethylbenzyl groups, was selected as the Lewis acid axle for incorporation into a [2]rotaxane. The two rotaxanes **14@24C₆** and **14@22C₆** with differently sized macrocyclic wheels (24- and 22-membered) and the compound **14** as axle were prepared. **14** reacts with B(C₆F₅)₃ in DCM forming classical Lewis adduct **14-B(C₆F₅)₃**. However, **14@24C₆** reacts with H₂ (4 atm) in presence of B(C₆F₅)₃ in toluene, resulting in the formation of [14H@24C₆]+[HB(C₆F₅)₃]- (61%). Whereas, **14@22C₆** reacts with H₂ (4 atm) in the presence of B(C₆F₅)₃ in hexane to give [14H@22C₆]+[HB(C₆F₅)₃]- (60%). These results demonstrate that a sterically unencumbered base (*Figure 6*) can be included in a FLP reactivity region without any covalent modification.

Although most of the studies on FLPs contain fluorine-substituted electron-deficient boranes as the Lewis acid counterpart, recent efforts to utilise other related Lewis acids in FLP chemistry have been successful. Stephan and co-workers (2010) demonstrated the utilisation of phosphine–alane mixtures as effective FLP catalysts (*Figure 7*). A 1:1 solution of PMes₃/AlX₃ (X = Cl **15** / X = Br **16**) in bromobenzene results in the formation of weak Lewis adducts. When these solutions were exposed to CO₂ in

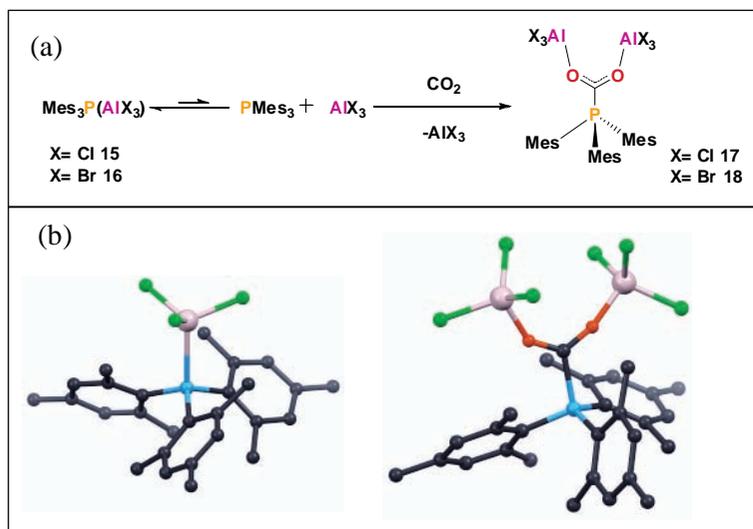
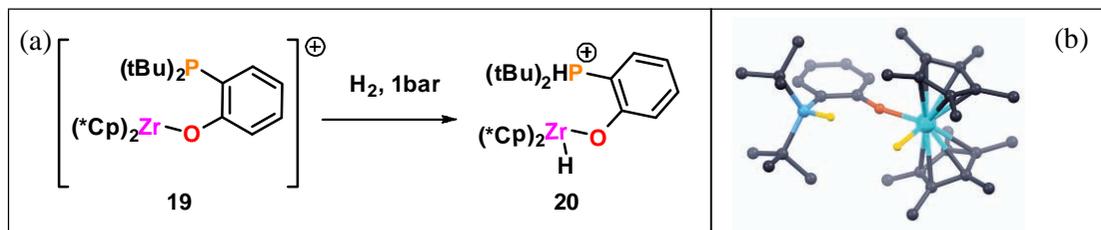


Figure 7. CO₂ activation by a phosphine–alane Lewis pair (a) and X-ray obtained structures of **15** and **17** (b) (C = black, P = sky blue, F = green, Al = pink, O = red; hydrogen atoms omitted for clarity).



$\text{C}_6\text{D}_5\text{Br}$ in sealed NMR tubes, the formation of $\text{Mes}_3\text{P}(\text{CO}_2)(\text{AlX}_3)$ ($\text{X} = \text{Cl}$ **17** / $\text{X} = \text{Br}$ **18**) was observed. In these compounds, the phosphines are bound to the C atom of CO_2 whereas the AlX_3 units are bonded to the O atoms (Figure 7). The reactions of these complexes with ammonia borane and subsequent addition of H_2O resulted in formation of MeOH. This type of room temperature conversion of CO_2 to MeOH was a milestone in FLP chemistry. Later in 2011, these types of FLPs were further explored for stoichiometric reduction of CO_2 to CO. Recently; other non-interacting Lewis acid–base pairs such as phosphine–alanes and amine–alanes have also been significantly utilised as FLP systems. Also, the concept of FLPs has been well-exploited in the design of transition-metal-based catalyst systems. In 2011, Erker and co-workers reported Zr–phosphine-based FLPs which can act as catalytic hydrogenation reagents (Figure 8). Following this trend, Ti-, Re- and Ru-based frustrated Lewis Pairs have also been reported.

7. Applications and Potentials

The primary drawback of the metal-free FLP systems was their stoichiometric reaction processes rather than catalytic activity. However, this drawback has been overcome in many situations in diverse examples of FLP systems enhancing their prospective practical potential in chemists' view. Metal-free hydrogenation of unsaturated compounds using FLP systems is now a well-studied subject in literature. Stephan and co-workers have shown that FLPs such as **5** (5 mol %) can catalytically reduce imines under mild conditions. Imines with sterically encumbered nitrogen are reduced cleanly in high yield at 80–120°C under H_2 pressure of 1–5 atm. The imine could be easily separated by filtration through a plug of silica gel, affording the pure product.

Figure 8. H_2 activation by **19** (a) and X-ray obtained structure of **20** (b) (C = black, P = sky blue, Zr = cyan, O = red, H = yellow, residual molecules and irrelevant hydrogen atoms omitted for clarity).

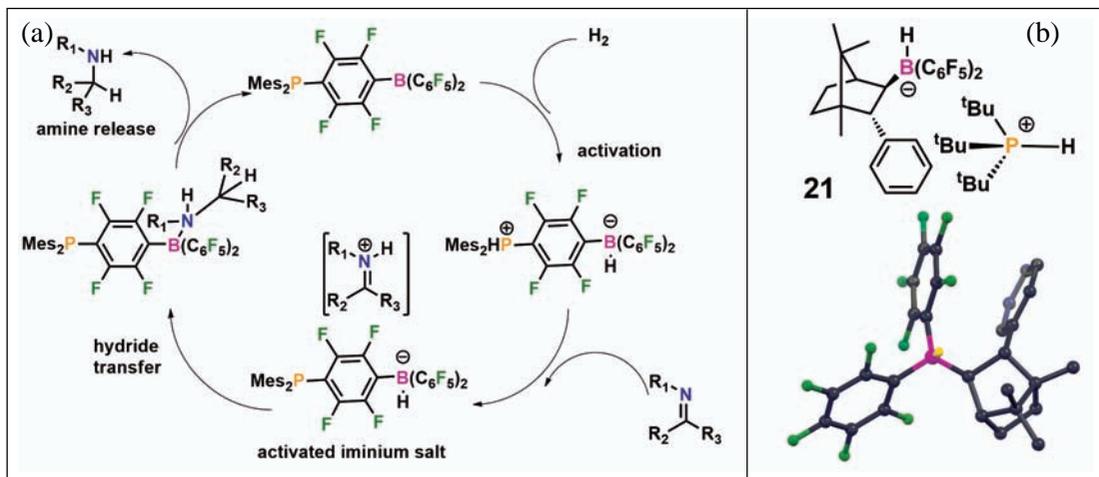
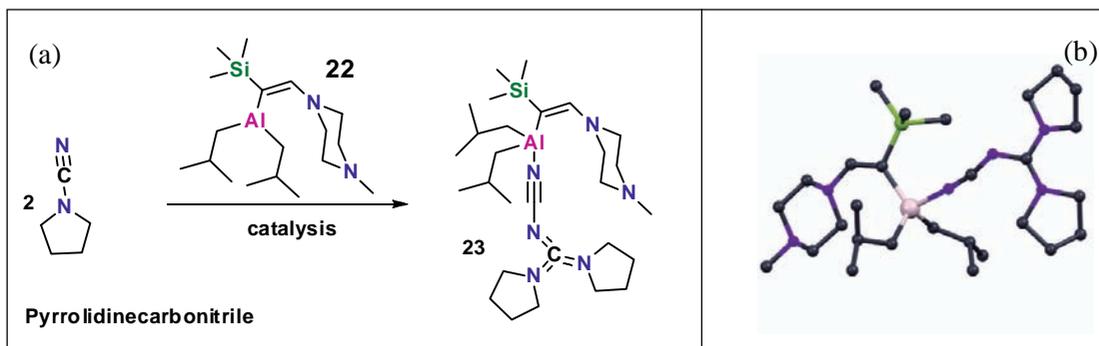


Figure 9. Mechanism of catalytic reduction of amine by **5** (a) and chiral FLP **21** (b). X-ray obtained structure of anionic part of **21** (C = black, F = green, B = magenta, H = yellow, residual molecules and irrelevant hydrogen atoms omitted for clarity).

Figure 10. Catalytic oligomerization of pyrrolidine-carbonitrile by **22** (a). X-ray (single crystal) obtained structure of **23** (b) (C = black, N = blue, Si = green, Al = pink, hydrogen atoms omitted for clarity).

This catalyst has been successfully commercialised in recent times and so it has found its way into modern chemical laboratories. Significant progress in such hydrogenation has been achieved using modified synthetic protocols and additives. In 2010, Klankermayer and co-workers added the element of chirality in this newly born concept of FLPs (*Figure 9*). Utilising the zwitterionic chiral phosphonium-borate **21**, enantioselective hydrogenation of imines was achieved. Following this report, chiral FLP systems have also attracted significant attention in chiral synthetic processes.

Apart from small molecule activations and catalytic hydrogenations, FLPs have also been utilised in other chemical processes by different research groups around the world. For example, Uhl and co-workers have recently developed an aluminium–nitrogen-based Lewis pair as an effective catalyst for the oligomerization



of cyanamides (*Figure 10*). Interestingly, formation of the thermodynamically favoured cyclic trimer was suppressed. When FLP **22** reacts with pyrrolidinecarbonitrile, it results in the formation of the FLP-bound acyclic dimer **23**. Formation of such unlikely oligomers, which are inaccessible otherwise, opens new opportunities for studies on properties of such systems.

8. Conclusions and Outlook

The last seven years of modern chemistry have witnessed a glimpse of the enormous potential in FLP systems. A concept conceived nearly 80 years ago was reinvented in an entirely new fashion resulting in unprecedented outcomes. It is a young concept with enormous potential, which, with further nourishment from chemists around the globe, will surely grow to be one of the most important areas of modern chemistry.

Suggested Reading

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