RESEARCH ARTICLE

FRUSTRATED LEWIS PAIRS:
CONCEPTS, MECHANISMS, AND APPLICATIONS

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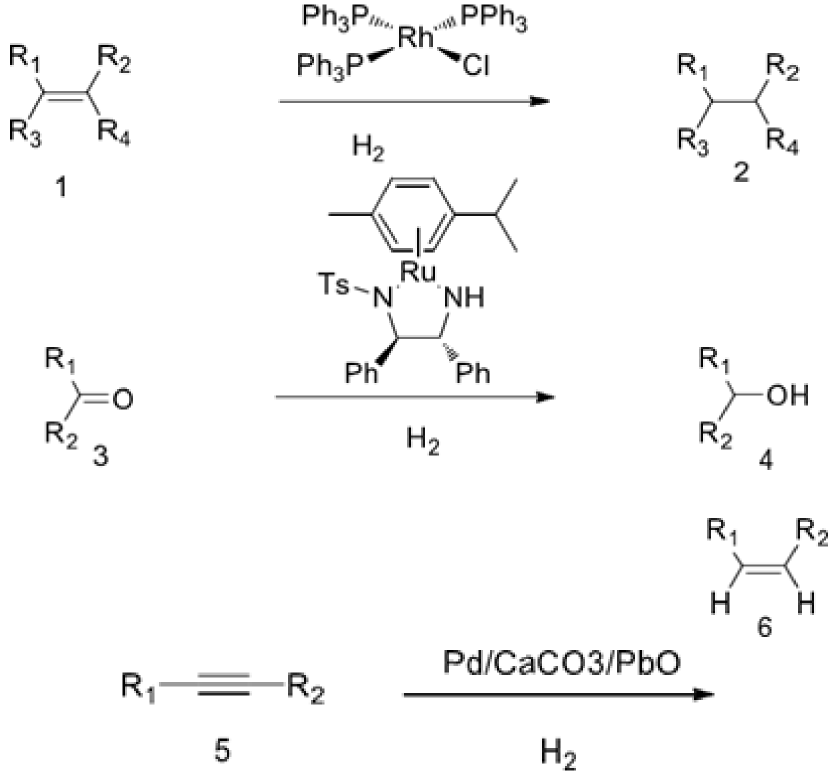
Abstract:

The discovery of Frustrated Lewis Pairs (FLPs) has revolutionized the field of main-group chemistry by enabling metal-free activation of Hydrogen (H_2) and other small molecules. FLPs are unique combinations of sterically encumbered Lewis acids and bases that cannot form conventional adducts, leaving their reactive sites accessible for cooperative bond activation. Since the pioneering report of H_2 activation by FLPs in 2006, their scope has rapidly expanded from stoichiometric reactivity to catalysis, most notably in hydrogenation reactions. This chapter provides a comprehensive overview of the evolution of FLP chemistry from its conceptual foundation to its broad application in catalytic hydrogenation. It highlights key breakthroughs in the hydrogenation of imines, nitriles, aziridines, olefins, alkynes, enones, carbonyl compounds, silyl enol ethers, anilines, and N-heterocycles, as well as recent advances in enantioselective FLP catalysis. The mechanistic aspects of H_2 activation, innovative intramolecular FLP designs, and the growing application of FLPs in CO_2 capture and polymerization are also discussed. This review underscores the potential of FLPs as sustainable, metal-free catalysts and outlines emerging directions for their application in synthetic and green chemistry.

Keywords: Frustrated Lewis Pairs, Metal-Free Catalysis, Hydrogen Activation, Catalytic Hydrogenation, Main-Group Chemistry.

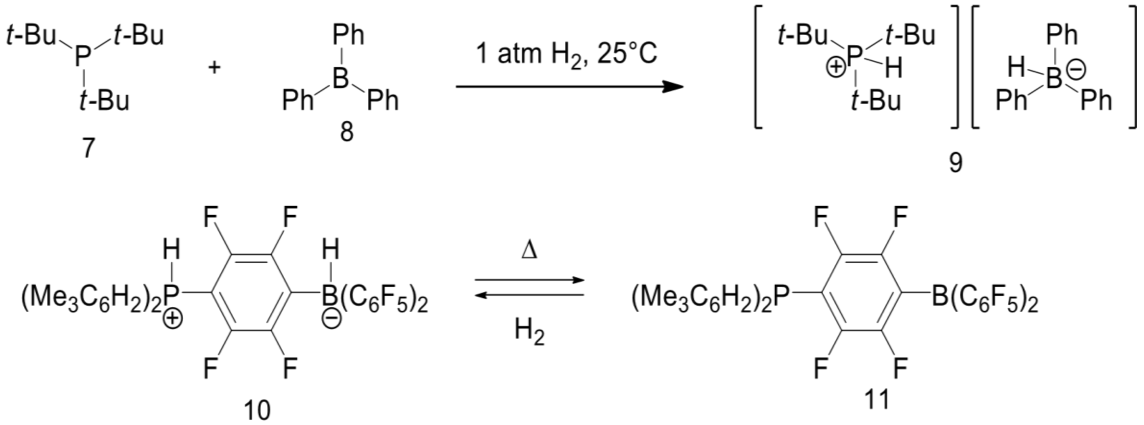
1. Introduction:

Catalytic hydrogenation of unsaturated compounds using H_2 is one of the most powerful and widely applied transformations in both academic research and industrial processes. Traditionally, transition metal-based catalysts have been employed for the hydrogenation of diverse unsaturated organic compounds, including olefins, alkynes, arenes, imines, aldehydes, and ketones. Heterogeneous catalysts are commonly used to achieve such reductions, while homogeneous catalysts based on precious metals such as Rhodium (Rh), Iridium (Ir), Palladium (Pd), Platinum (Pt), and Ruthenium (Ru) often offer greater selectivity. These homogeneous systems are particularly valuable because they can be tailored for enantioselective syntheses, operate under milder conditions, and provide higher turnover numbers. Consequently, they have become indispensable in large-scale industrial hydrogenation. For example, classic catalysts such as Wilkinson's catalyst ([$RhCl(PPh_3)_3$]), the Ryoji Noyori catalyst, and Lindlar's catalyst are widely used (Scheme 1). While these metalbased systems are renowned for their high product selectivities, the high cost and limited natural abundance of these metals necessitate the development of strategies for their recovery and recycling.[1-4]



Scheme 1: Various hydrogenation reactions using metal catalysts

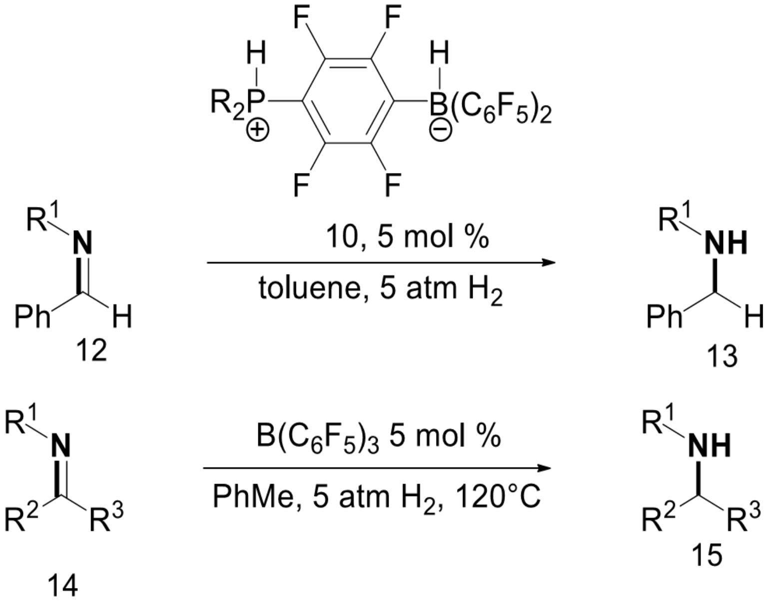
In 2006, a groundbreaking alternative approach was introduced: the activation of H_2 by metalfree systems. This concept challenged nearly a century of dogma in synthetic chemistry. It was based on the principle that certain combinations of Lewis acids and Lewis bases-when sterically hindered from forming classical adducts, retain their Lewis acidity and basicity, enabling them to interact cooperatively with small molecules. Initially explored for stoichiometric reactivity, this concept was later expanded to catalysis. The most striking discovery was that such systems could activate H_2, overturning the long-held belief that metals are indispensable for this process. This innovation paved the way for using simple main-group species as catalysts in hydrogenation reactions. Today, Frustrated Lewis Pairs (FLPs) represent a rapidly growing field in main-group chemistry. For example, while a mixture of $B(C_6F_5)_3$ and tBu3P shows no reactivity at room temperature, the addition of H_2 rapidly yields the salt [$^tBu_3PH$][$HB(C_6F_5)_3$] (Scheme 2). Such acid–base combinations are termed FLPs and exemplify the ability of steric hindrance to unlock novel reactivity.[5-6]



Scheme 2: Activation of H_2 by frustrated lewis pairs

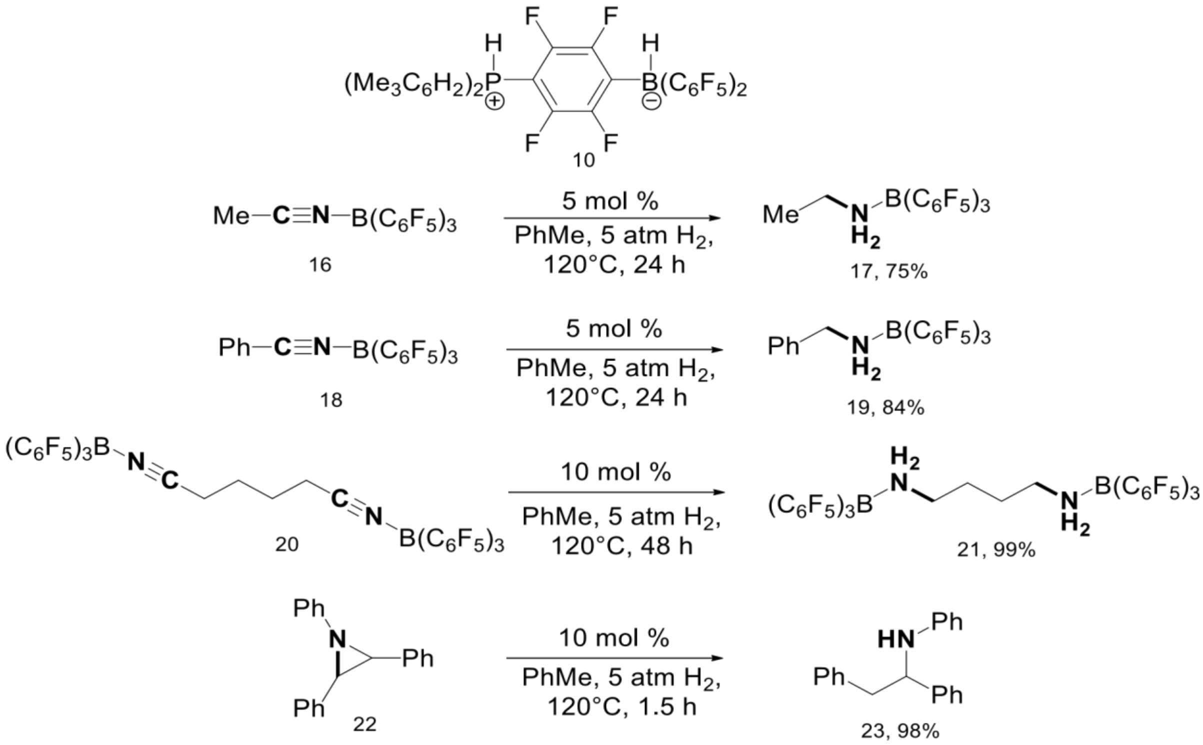
2. Hydrogenation of Imines, Nitriles, and Aziridines

The first report of metal-free catalytic hydrogenation demonstrated that FLP systems could reduce imines, nitriles, and aziridines. In these pioneering studies, 5 mol% of the phosphonium–borate catalyst **11** was employed at 80–120 °C under 1–5 atm of H_2 (Scheme 3). Remarkably, imine substrates were later shown to act as the basic component of FLPs. When combined with a catalytic amount of $B(C_6F_5)_3$ under 4 atm of H_2, imines were efficiently hydrogenated to the corresponding amines. The same catalyst system was also applied to diimines, furnishing the corresponding diamines with ease.[7-9]



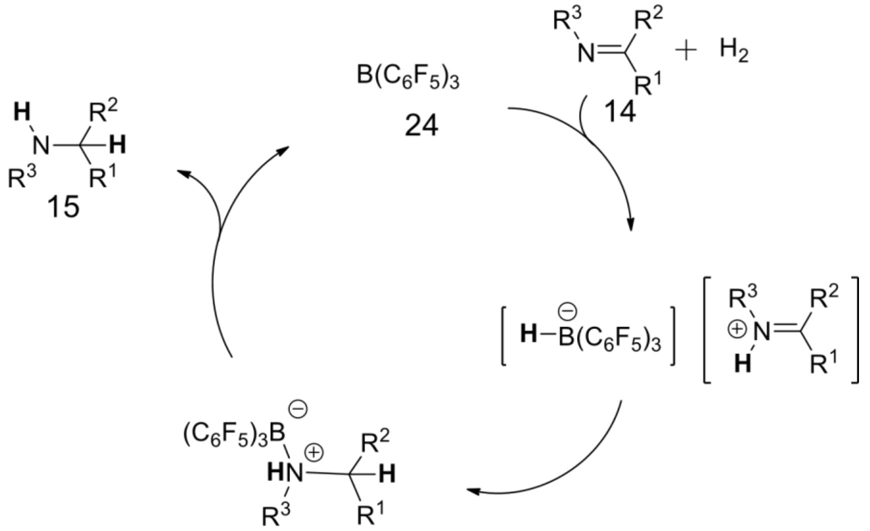
Scheme 3: Hydrogenation of Imine

Because nitriles form strong, stable adducts with boranes, they are typically resistant to hydrogenation. However, when preformed nitrile–borane adducts were used as substrates with catalytic amounts of 11, hydrogenation proceeded slowly yet ultimately afforded good yields of amine–borane adducts (Scheme 4). Interestingly, cis-1,2,3-triphenylaziridine underwent ring-opening hydrogenation to the corresponding amine in the presence of either catalyst 11 or a $B(C_6F_5)_3$/PMes3 combination.[8]



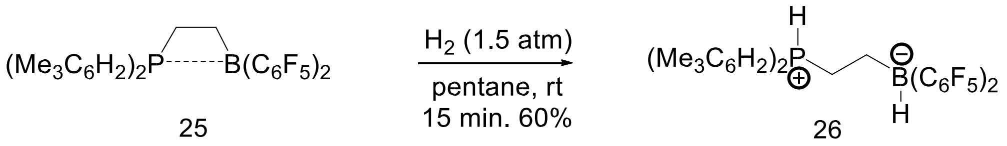
Scheme 4: Hydrogenation nitriles and aziridine

Mechanistically, imine hydrogenation by FLPs proceeds via heterolytic cleavage of H_2 by a Lewis base donor and a boron Lewis acid acceptor. This generates either an iminium hydridoborate intermediate directly or proceeds via proton transfer from a transient phosphonium cation to nitrogen. The iminium cation then abstracts a hydride from the hydridoborate, yielding the amine product and regenerating the borane catalyst (Scheme 5).[7-8]



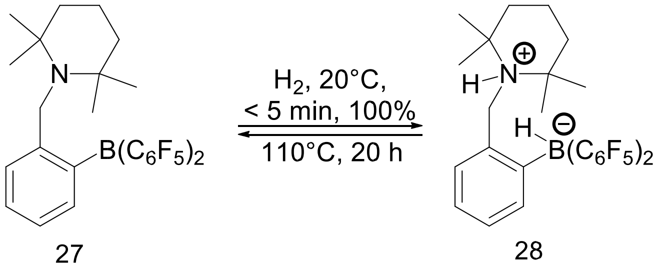
Scheme 5: mechanism of the hydrogenation of imine

Following these studies, Gerhard Erker and co-workers developed an intramolecular FLP in which the P and B centers are tethered by an ethylene linker, Mes2PCH2CH2B(C6F5)2 (3; Scheme 6).[10] The close proximity of the Lewis acidic and basic sites, combined with steric congestion, prevents P–B bond formation and facilitates H_2 activation. This catalyst effectively reduced imines and enamines at 25 °C under 1.5 atm of H_2, although higher catalyst loadings (up to 10 mol%) were required.



Scheme 6: H2 activation by intramolecular FLP

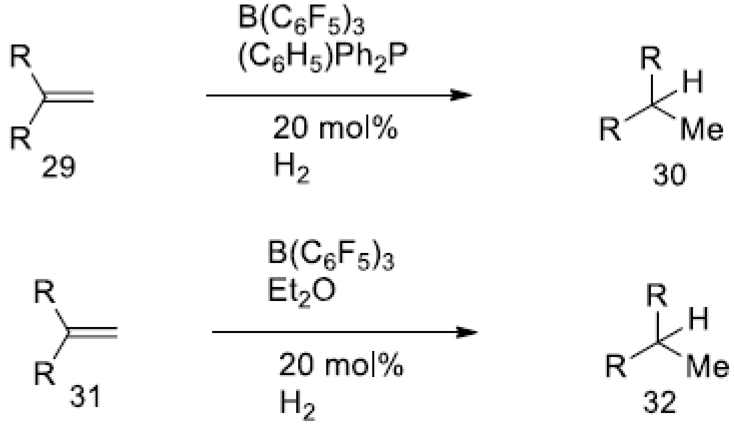
Later, Tiina Repo and colleagues designed a novel "molecular tweezer" FLP bearing a piperidine moiety tethered to an electrophilic borane (C5H6Me4NH(CH2C6H4)BH(C6F5)2, 4; Scheme 7). This system catalyzed the hydrogenation of imines and enamines using 4 mol% catalyst at 110 °C and 2 atm of H_2, demonstrating impressive activity.[1]



Scheme 7: H2 activation by intramolecular FLP

3. Catalytic Hydrogenation of Olefins

To expand FLP hydrogenation beyond heteroatom-containing substrates, Douglas W. Stephan and co-workers explored olefin reduction. They found that heterolytic H_2 activation using electron-deficient (C6F5)Ph2P and $B(C_6F_5)_3$ produced a highly acidic phosphonium species at −80 °C, which enabled protonation of 1,1-disubstituted olefins and subsequent hydride capture (Scheme 8). Initially, 20 mol% of the P/B FLP catalyst was used, but the base pTol2NMe allowed catalyst loading to be reduced to 5 mol%. Later studies also showed that Et2O and $B(C_6F_5)_3$ could heterolytically cleave H_2 and catalyze olefin hydrogenation
despite forming ether–borane adducts.[12-13]



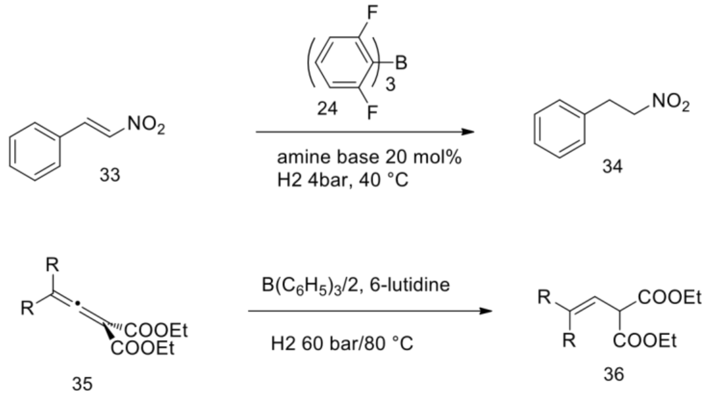
Scheme 8: Catalytic Hydrogenation olefins

4. Catalytic Hydrogenation of Allene−Ester, Enone and β- nitrostyrenes

In efforts to further broaden the substrate scope, Paradies and co-workers[14] extended FLP reductions to include β- nitrostyrenes using (2,6-$C_6H_3F_2$)$_3$B/2,6-lutidine at 40 °C (Scheme 9), while

Alcarazo and co-workers[15] showed that B(C6F5)3 with either (1,4)diazabicyclo[2.2.2]octane (DABCO) or 2,6-lutidine (10−15 mol %) can catalytically hydrogenate allenic esters (Scheme 9).

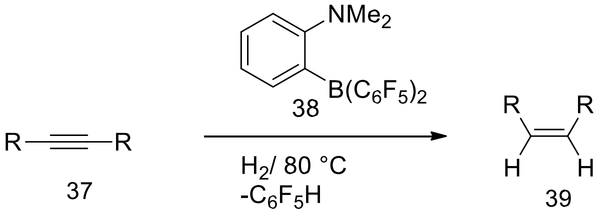
Similarly, enones were reduced in a combined hydrogenation/hydrosilylation using [2,2]-bis(phosphino)paracyclophane/B(C6F5)3 catalysts (Scheme 9).[16] While the ynone PhC$\equiv$C(O)tBu was stoichiometrically reduced with $R(R)C\equiv C(C_6F_5)B(C_6F_5)_2$ and $^tBu_3P$ under H_2 to afford the cis-enone product,[17] the use of DABCO permitted catalytic reduction, although the trans-enone was obtained.



Scheme 9: Catalytic Hydrogenation of Allene−Ester and β- nitrostyrenes

5. Catalytic Hydrogenation of alkynes

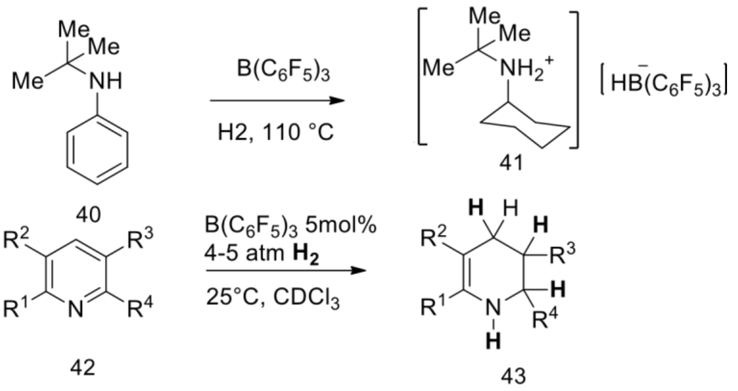
Repo and co-workers[18] further broadened the substrate scope, effecting selective hydrogenation of nonfunctionalized internal alkynes to give cisalkenes using the intramolecular FLP $C_6H_4(NMe_2)B(C_6F_5)_2$ under H_2 at 80 °C. Interestingly, activation of H_2 liberates C_6F_5H and generates $C_6H_4(NMe_2)BH(C_6F_5)$ (Scheme 10), which effects hydroboration of the alkyne, while subsequent activation of H_2 prompts protonolysis to afford the cis-alkene and regenerate the catalyst.



Scheme 10: Catalytic Hydrogenation of alkynes

6. Catalytic Hydrogenation of anilines and N-heterocycles

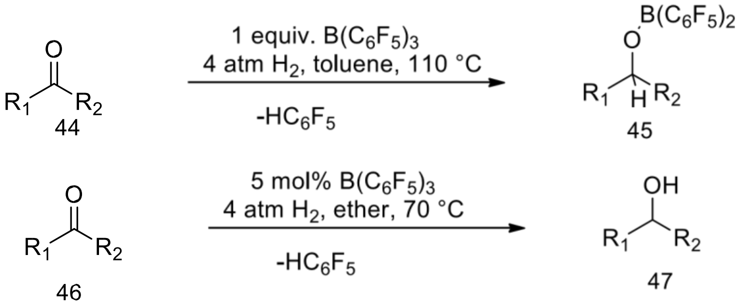
Activation of H_2 by $^tBuNHPh/B(C_6F_5)_3$ at 25 °C afforded $[tBuNH_2Ph][HB(C_6F_5)_3]$,[19] but prolonged heating at 110 °C for 96 h under H_2 gave $[tBuNH_2Cy][HB(C_6F_5)_3]$ (Scheme 11). The reduction of the N-bound arene ring was subsequently generalized for a series of bulky secondary anilines, yielding the corresponding cyclohexylammonium salts in high yields. Such FLP aromatic reductions were extended to N-heterocycles, including hindered pyridines, quinolines, acridines, and quinoxalines.[20] In these cases, treatment with $B(C_6F_5)_3$ and H_2 at 110 °C for 16−60 h resulted in the corresponding saturated species. Interestingly, the nominal “pyridine” and “aniline” rings of benzoquinoline are reduced while the remote ring remains untouched (Scheme 11).



Scheme 11: Catalytic Hydrogenation of anilines and N-heterocycles

7. Catalytic Hydrogenation of carbonyl compounds

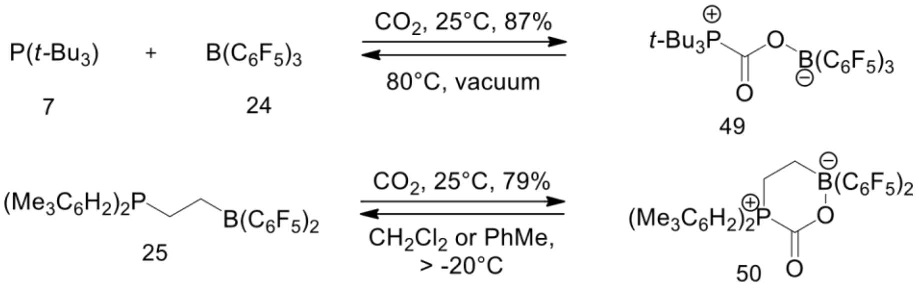
Reactions of FLPs, H2, and benzaldehyde resulted in the stoichiometric formation of phosphonium alkoxyborates.[21] More recently, stoichiometric reactions of ketones and $B(C_6F_5)_3$ in the presence of H_2 in toluene generated C_6F_5H and borinic esters $ROB(C_6F_5)_2$ (Scheme 12). Interestingly, when ether[22] or dioxane60 was used as the solvent, catalytic reduction of ketones in the presence of H_2 using 5 mol % $B(C_6F_5)_3$ at 70 °C was achieved for a series of ketones (Scheme 12). The dramatic solvent effect is consistent with a mechanism initiated by ketone/borane heterolytic cleavage of H_2. In toluene, the protonated ketone cleaves a B−C bond, liberating C_6F_5H, while in ether the protonated ketone forms hydrogen bonds with the solvent, allowing hydride transfer from the hydridoborate to the carbonyl carbon.



Scheme 12: Catalytic Hydrogenation of carbonyl compounds

8. Stoichiometric reactions of CO_2 with FLPS

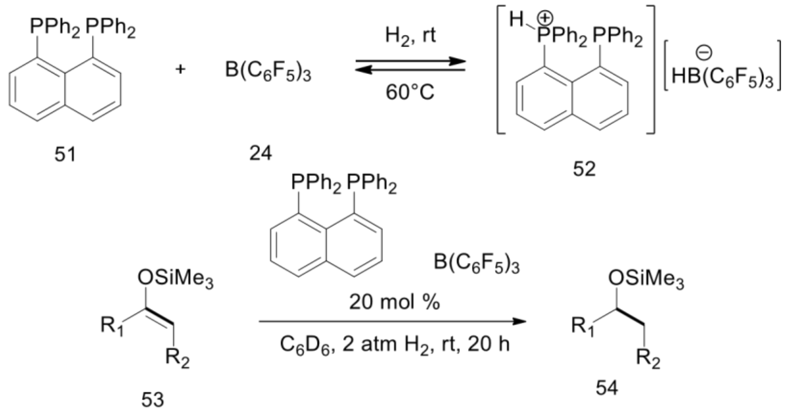
The classic inter and intramolecular FLPs capture CO_2 to give the addition products $tBu_3PCO_2B(C_6F_5)_3$ and $Mes_2P(CH_2)_2B(C_6F_5)_2(CO_2)$ (Scheme 13).[23] The thermodynamics of this capture of CO2 has been recently determined by microfluidic methods.



Scheme 13: Stoichiometric reactions of CO_2 with FLPS

9. Catalytic Hydrogenation of silyl enol ethers

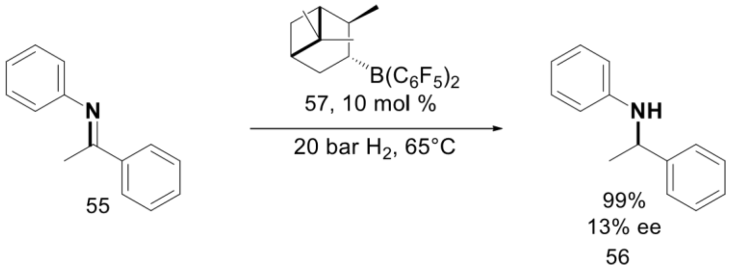
The scope of substrates reduced by FLP catalysts was expanded by the Erker group to include silyl enol ethers. This feat was initially accomplished using the FLP combination of bis-phosphine $C_{10}H_6(PPh_2)_2$ and $B(C_6F_5)_3$ which under H_2 affords the salt, $[C_{10}H_6(PPh_2)_2H][HB(C_6F_5)_3]$ (Scheme 14).[24] The FLP catalyzes hydrogenation of silyl enol ethers under 2 atm of H_2 at 25 °C, although 20 mol % of catalyst was employed.



Scheme 14: Catalytic Hydrogenation of silyl enol ethers

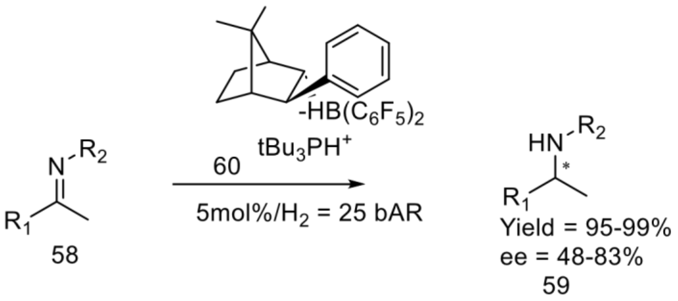
10. Enantioselective Hydrogenation by FLPS

Despite the extremely rapid growth of FLP catalysis, the asymmetric reactions have been far less developed. In 2008, Klankermayer and co-workers reported the first FLP-catalyzed asymmetric hydrogenation of imines with 13% ee (Scheme 15).[25]



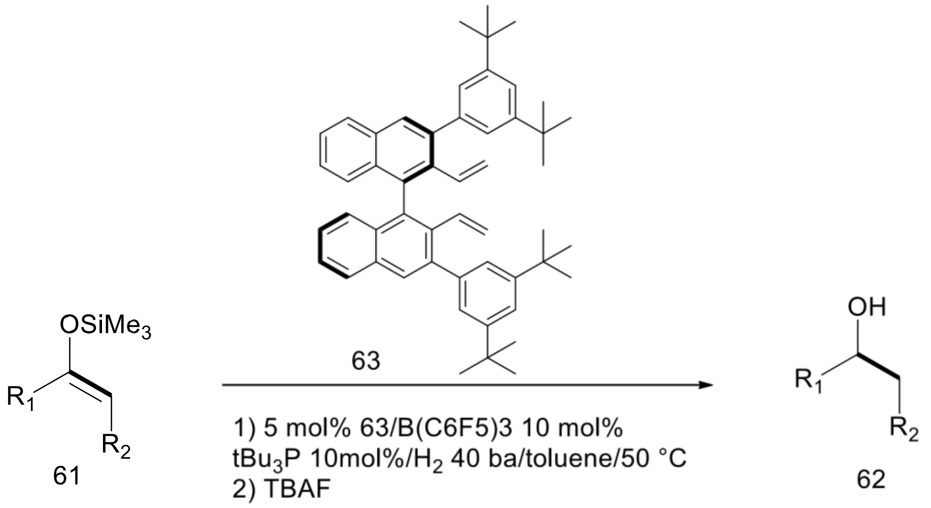
Scheme 15: Enantioselective Hydrogenation of imines

Later, this was improved to 83% by the same group using the combination of chiral borane and phosphine (Scheme 16).[26]



Scheme 16: Enantioselective Hydrogenation of imines

In 2011, Repo and co-workers employed chiral ansa-ammonium borates as catalysts to obtain up to 37% ee.[27] Haifeng Du group employed the in situ generated chiral borane catalysts by the hydroboration of chiral dienes with Pier's borane[28] for the asymmetric hydrogenation of imines to give up to 89% ee (Figure 1).[29] Moreover, the hydrogenation of chiral imines using $B(C_6F_5)_3$ has also been reported by Stephan and coworkers.[30] Accordingly, the development of highly enantioselective reactions with a broad substrate scope is a challenging but important subject in this area. Very recently, Du and coworkers reporteded enantioselective hydrogenation Using a simple combination of tri-tertbutylphosphine and chiral borane generated in situ by the hydroboration of chiral diene with $HB(C_6F_5)_2$ as a frustrated Lewis pair catalyst, a highly enantioselective metal-free hydrogenation of silyl enol ethers was successfully realized to furnish a variety of optically active secondary alcohols in 93−99% yields with 88->99% ee (Scheme 17).



Scheme 17: enantioselective metal-free hydrogenation of silyl enol ethers

Conclusion:

In less than a decade since their discovery, FLPs have evolved from a conceptual curiosity to a transformative tool in catalysis. Initially developed for the metal-free hydrogenation of imines, FLPs have since demonstrated remarkable versatility, catalyzing the hydrogenation of diverse functional groups including enamines, enones, anilines, heterocycles, silyl enol ethers, and even carbonyl compounds. Advances in enantioselective FLP catalysis further underscore the untapped potential of these systems. Beyond hydrogenation, FLPs have been shown to activate a variety of small molecules-including olefins, alkynes, disulfides, B–H and C–H bonds, CO_2, N2O, cyclopropanes, enynes, enones, and diynes-heralding their broader application in synthetic chemistry. Moreover, their use in greenhouse gas capture and polymerization reactions (e.g., acrylates, styrenes) highlights their growing real-world impact. Importantly, the concept is no longer confined to main-group elements; the emergence of allcarbon and metal-based FLPs demonstrates its expanding reach. As more researchers embrace this powerful concept, FLP chemistry is poised to deliver even more exciting and practical innovations.

Conflict of Interest:

The author declares that there is no conflict of interest regarding the publication of this chapter.

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