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Frustrated Lewis pair chemistry: early concepts, scope, and recent developments with 9-phosphatriptycenes

This article is part of the PhD thesis of the author, under the supervision of Prof. G. Berionni (experimental part) and Prof. B. Champagne (computational part).

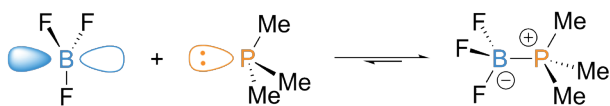
Abstract

Frustrated Lewis pairs (FLPs) chemistry provide new prospects in metal-free catalysis. Since their discovery in 2006 and the definition of the concept, these sterically hindered combinations of Lewis acids and bases have been increasingly used as catalysts for hydrogenation reactions. Over the years the scope of substrates expanded significantly, and mechanistic investigations shed light into their reactivity. Still challenges and limitations remain, and the hydrogenation of weakly reactive substrates such as “unactivated” olefins cannot be achieved by classical FLP systems. The groups of Prof. G. Berionni and Prof. B. Champagne at UNamur investigated the use of 9-phosphatriptycenes in this context. Due to their unique reactivity compared with other arylphosphines, these cage-shaped Lewis bases allowed for the first time the metal-free hydrogenation of unactivated olefins with FLP catalysts.

1. Frustrated Lewis pair chemistry

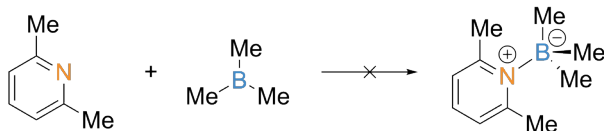
1.1. From the Lewis theory to the definition of frustrated Lewis pairs

The pioneer work of Gilbert Lewis on acids and bases in 1923 led to the development of one of the most important and unifying theories of reactivity in modern chemistry.¹ Lewis defined acids and bases as, respectively, electron-pair acceptors and donors. According to him, both react to form covalently bonded adducts, effecting a mutual stabilization (*i.e.* quenching) of the two compounds, as shown with the example of the association of trimethylphosphine with boron trifluoride (Scheme 1). Both compounds are unstable to air, but the Lewis adduct they form is stable in air and water. The concept of donor-acceptor adduct formation is ubiquitous in all aspects of chemistry, spanning from the coordination chemistry of transition metals, the rationalization of reaction mechanisms, the adsorption at the surface of materials in solid state chemistry or polymer science, up to the development of new catalysts.



Scheme 1. Reaction of a Lewis acid (boron trifluoride) and a Lewis base (trimethylphosphine), to form a Lewis adduct. The lone pair of electrons of the phosphorus atom overlaps the empty 2p orbital of the boron atom to form a covalent bond.

Frustrated Lewis pair chemistry provides new prospects in acid-base chemistry, where the reactivity of Lewis acids and bases are combined while preventing mutual quenching. This point is detailed below. According to the Lewis theory [1], a Lewis base (*e.g.* PR_3) combines with a Lewis acid (*e.g.* BX_3) to form a covalent adduct ($\text{R}_3\text{P} \rightarrow \text{BX}_3$). However, the subtle effect of steric hindrance on their association was investigated later. In their 1942 report, Brown and coworkers studied the effect of steric strain on carbon-carbon bond rotation by comparing the stability of a series of amine-borane adducts (the B-N bond being isosteric to the C-C bond). They observed that the 2,6-lutidine does not coordinate with trimethylborane due to the excessive steric strain the B-N bond formation would generate (Scheme 2) [2].

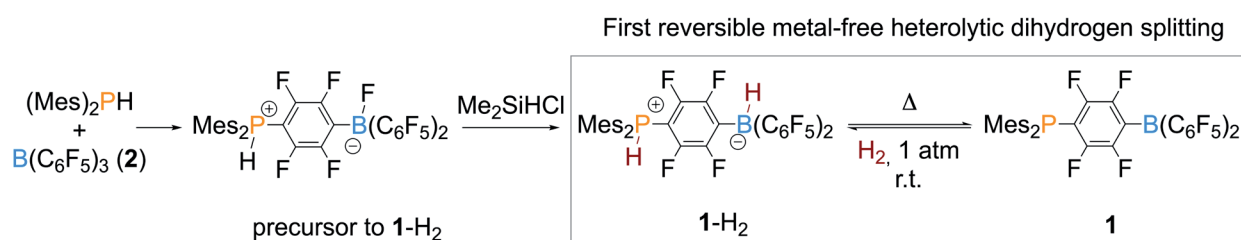


Scheme 2. Absence of reaction between 2,6-lutidine and trimethylborane.

In 2006, Stephan discovered that a phosphine-borane compound (**1**) was able to reversibly react with and release dihydrogen (H_2) [3]. The reaction

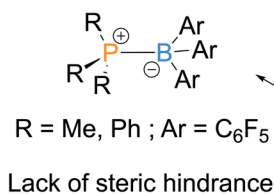
of **1** with H_2 is spontaneous at room temperature under 1 atm of dihydrogen while H_2 release is triggered by heating above 100°C (Scheme 3). Due to steric hindrance, dimesitylphosphine (Mes_2PH , $\text{Mes} = 2,4,6\text{-trimethylphenyl}$) and tris(pentafluorophenyl)borane **2** did not form the classical Lewis adduct but instead, under heating, generated the precursor to **1** *via* nucleophilic aromatic substitution at the *para* position of a C_6F_5 ring of **2**, leading to this seminal discovery. It constituted the first reported reversible metal-free hydrogen activation. While other phosphine-borane systems are capable of releasing H_2 , the unique stability of **1** (*i.e.* the lack of polymerization or cyclization) is due to the steric hindrance around the P and B centers and allows its reversible reaction with H_2 .

In his subsequent report, Stephan investigated the steric and electronic parameters influencing this reactivity [4]. More classical and simple frustrated pairs than **1** were shown to cleave dihydrogen, such as the $\text{PtBu}_3/\text{B}(\text{C}_6\text{F}_5)_3$ or $\text{PMes}_3/\text{B}(\text{C}_6\text{F}_5)_3$ combinations. Not all phosphine/borane pairs are suitable however, as the steric hindrance in the acid or the base must be sufficient to prevent the formation of the Lewis adduct, while their acidity/basicity must remain high enough for reacting with dihydrogen. On the one hand, the combinations PMes_3 or $\text{PPh}_3/\text{B}(\text{C}_6\text{F}_5)_3$ for instance are lacking in steric repulsions and form a classical Lewis adduct. On the other hand, $\text{PMes}_3/\text{BMes}_3$ or $\text{P}(\text{C}_6\text{F}_5)_3/\text{B}(\text{C}_6\text{F}_5)_3$ do not react spontaneously with H_2 at room temperature because they are electronically deactivated, either the acid or the base is not reactive enough to cleave dihydrogen (Scheme 4) [4].

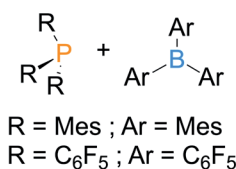
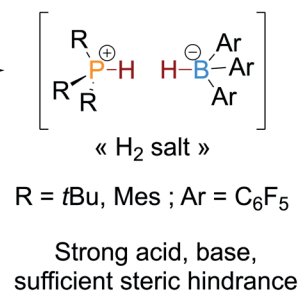


Scheme 3. First example of reversible heterolytic hydrogen splitting reported by Stephan.

a) Formation of the Lewis adduct



b) Absence of reaction

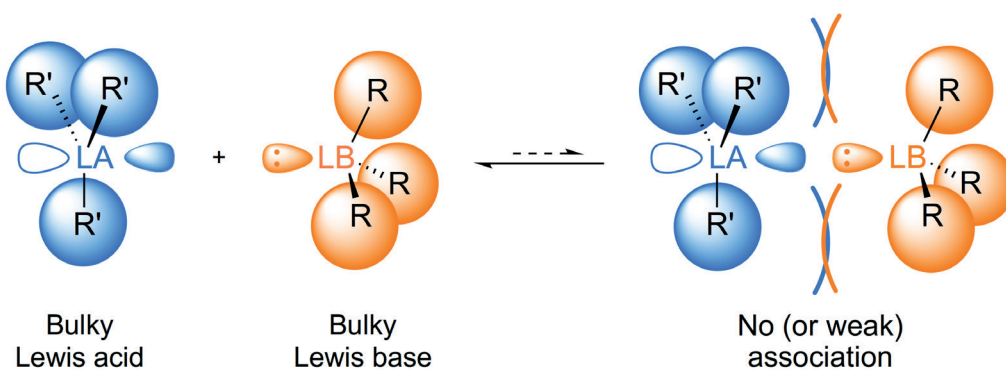
c) Heterolytic dihydrogen splitting
(hydrogen activation)

Scheme 4. Reactions of Lewis acid-base combinations in the presence of dihydrogen according to their substitution pattern.

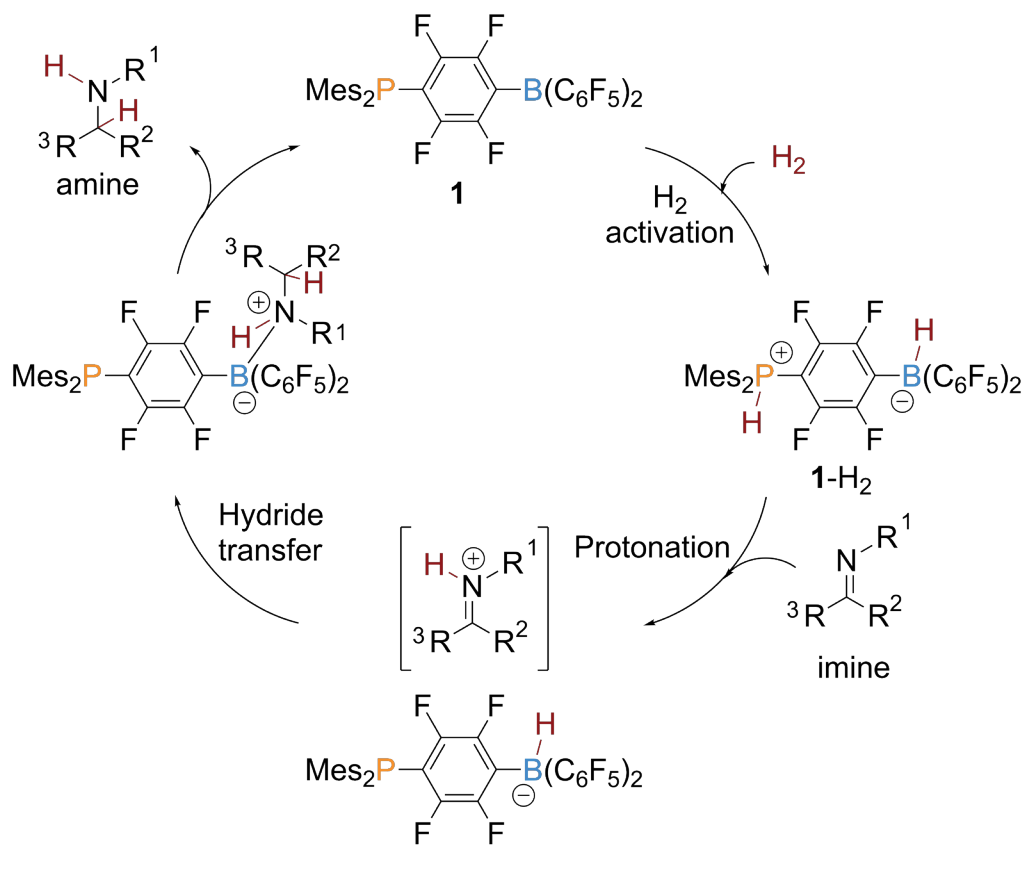
These observations eventually led to the formal definition of “frustrated Lewis pairs” (FLPs) as sterically hindered Lewis acids and bases that cannot form the corresponding Lewis adduct because of steric repulsions (Scheme 5) [5-6]. These bifunctional systems display completely new reactivity patterns and even some catalytic properties since both Lewis acid and base are now able to act synergistically on a reagent of small size in a “three-component” type reaction.

Stephan next demonstrated the ability of these systems to perform the metal-free hydrogenation of unsaturated substrates, namely imines and

nitriles, and the reductive ring-opening of aziridines with dihydrogen [7]. The hydrogenation reaction was proposed to proceed as follows: first, the heterolytic splitting of H_2 , generating formally a proton (phosphonium) at the Lewis base and an hydride (borohydride) at the Lewis acid, followed by proton transfer to the imine then hydride transfer to the iminium moiety, forming a new B-N bond, finally followed by the release of the corresponding amine and regeneration of the catalyst (Scheme 6). Hydrogenations with FLP systems was an important part of my PhD work, and a more detailed subsection on this reactivity is detailed hereafter.



Scheme 5. Stephan's definition of a frustrated Lewis pair.



Scheme 6. Proposed mechanism for an imine hydrogenation by FLP system **1**. Scheme adapted from reference [8] with permission from the Royal Society of Chemistry.

1.2. Reactivity of frustrated Lewis pairs

1.2.1. First hydrogenations and hydrogenation of alkenes and alkynes

Hydrogenation reactions are among the most widely used chemical transformations, especially in pharmacochemical industries and synthetic organic chemistry [9-10]. Ever since the founding work of Sabatier in the beginning of the 20th century, homogeneous and heterogeneous transition-metal-based catalysts were used for these transformations [11-13]. However, the limited resources and toxicity of these elements incite chemists to develop alternatives [14-17]. As shown above, frustrated Lewis pairs are able to catalyze the hydrogenation of unsaturated substrates and thus constitute appealing surrogates to transition metal catalysts for this transformation. While other transition-metal-free systems are known to catalyze hydrogenations, they either require harsh

conditions or use other sources of hydrogen, such as Hantzsch's ester (in hydride transfer reactions) or hydrogen transfer reagent surrogates [18-25]. FLPs offer the advantage of reacting directly with H₂. In addition, the reactivity of the Lewis acid and base can be finely tuned to target different types of substrates. Over the years, these systems were extensively used for transition-metal-free hydrogenations of unsaturated compounds, notably imines, alkenes, aromatics, and carbonyl compounds. Several comprehensive publications have reviewed these hydrogenation reactions, their scope and limitations [8, 26-28].

As mentioned above, the first report of FLP-catalyzed hydrogenation described the transformation of imines, nitriles and aziridines to the corresponding amine. The phosphonium hydridoborate salt of **1** and another *t*Bu-substituted derivative were used as catalysts [7]. The reaction yields were dependent on the steric and electronic

parameters of the substrates. For example, bulky substituents were necessary for the reaction to proceed catalytically or electronically deactivated imines required longer reaction times. These observations shed light on some mechanistic aspects of the reaction, suggesting that proton transfer is indeed the initial step, and highlighting the possible coordination of the Lewis acid moiety to the substrate. Eventually, the hydrogenation of bulky imines and the reductive ring-opening of aziridines could be achieved with $\text{B}(\text{C}_6\text{F}_5)_3$ as lone catalyst, the substrate itself acting as Lewis base for hydrogen heterolytic cleavage [29-30].

Notably, the group of Erker developed an intramolecular system capable of activating H_2 , which was able to perform the hydrogenation of imines under milder conditions than the ones previously reported (25°C , 1.5 atm H_2 w.r.t. $80\text{--}120^\circ\text{C}$, 1-5 atm H_2) [31]. Allegedly, this difference in reactivity arises from the intramolecular character of the FLP system that reduces the entropy of activation, and from a lower Lewis acidity at the boron than in $\text{B}(\text{C}_6\text{F}_5)_3$. Other systems were developed afterwards, varying the

linker, the Lewis base, or the Lewis acid (Figure 1) [32-33]. Using weaker and bulkier Lewis acid was also investigated [34-35]. Interestingly, Ashley discovered that the solvent (THF) can act as Lewis base for FLP reactions with bulky, air-stable boranes [including $\text{B}(\text{C}_6\text{Cl}_5)(\text{C}_6\text{F}_5)_2$] [35]. This was the first instance where FLP reactivity is achieved without significant steric hindrance in one of the reactive partners. Eventually, it was even observed that systems forming classical Lewis adducts can serve as FLP-type catalysts if the LA-LB bond can be dissociated at high temperature. In addition to imines, this first generation of FLP catalysts (Figure 1) also allowed the hydrogenation of electron-rich polarized double-bonds: silyl-enol-ethers and enamines. These substrates display a more nucleophilic carbon-carbon double bond than that of regular olefins.

The hydrogenation of more challenging substrates relied on the improvement of existing systems and the development of new types of FLPs. A second generation of FLP catalysts was thus developed with Lewis bases or acids with a tuned reactivity, adapted to the type of substrates targeted. In 2012,

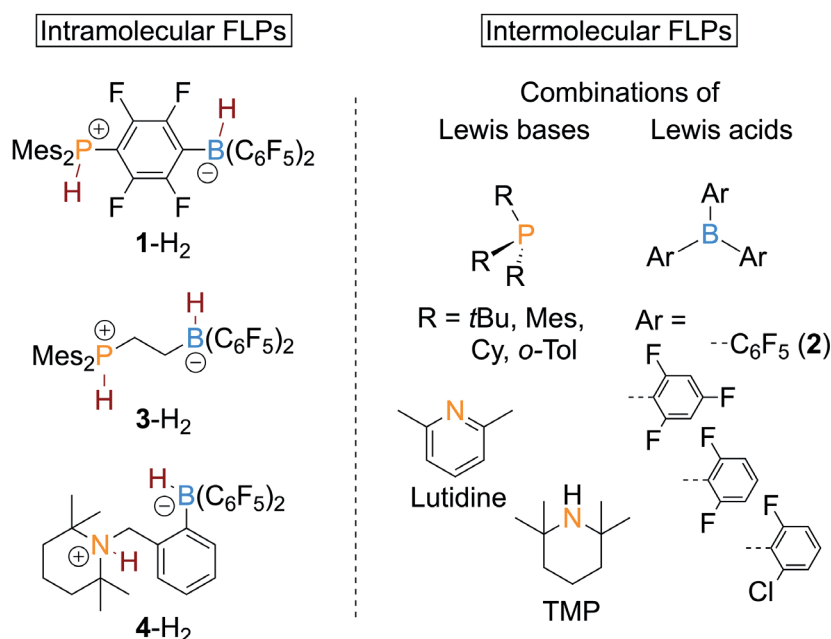


Figure 1. Selected examples of intra- and intermolecular frustrated Lewis pairs. Note that intramolecular FLPs are usually stored and handled in their « H_2 salt» state (denoted by “- H_2 ”) and are thus shown in this form.

the group of Paradies in collaboration with Stephan reported the first hydrogenation of olefins [36]. For this transformation, they used deactivated Lewis bases such as $\text{P}(\text{C}_6\text{F}_5)(\text{Ph})_2$ (Scheme 7a). Upon hydrogen activation, these weaker bases generate a phosphonium cation with enhanced Brønsted acidity, able to protonate a carbon-carbon double bond. The carbenium ion formed after protonation is stabilized by conjugation with either aryl substituents or neighboring unsaturated bonds in the substrate. The borohydride then adds on the carbocation to yield the alkane as product. These FLP systems appear not to react spontaneously with dihydrogen at room temperature, and low temperatures (between -60°C and -80°C) are needed to observe the phosphonium and borohydride by NMR spectroscopy. However, it does not prevent the hydrogenation to proceed at room temperature, and olefins are reduced in reaction times between 12 h and 96 h, with longer times and higher temperatures required for less reactive double bonds (up to 240h and 70°C). Interestingly, Stephan showed that dialkylethers/ $\text{B}(\text{C}_6\text{F}_5)_3$ combinations can catalyze 1,1-diphenylethylene hydrogenation, although requiring higher pressures of H_2 to proceed [37]. Similarly, polycyclic aromatic cycles and N-heteroaromatics are partially reduced with these FLP catalysts [38-41].

In contrast to this reactivity, Alcarazo showed that olefins can also act as hydride acceptors if the resulting carbanion is stabilized by electron-withdrawing groups (Scheme 7b). In this case, the hydride transfer happens first and is followed by the protonation step [42-44].

While not technically an FLP catalyst, Wang's hydrogenation of aliphatic olefins catalyzed by Piers' borane [bis(pentafluorophenyl)borane, $\text{HB}(\text{C}_6\text{F}_5)_2$] is worth mentioning (Scheme 7c) [45]. These less reactive alkenes are not readily hydrogenated by standard FLP systems. Their formal hydrogenation is achieved by initial hydroboration of the alkene by the borane, followed by σ -bond metathesis with H_2 , or hydrogenolysis, of the carbon-boron bond (Scheme 7d). The metal-free catalytic hydrogenation of olefins was already known in the literature (Scheme 7e), dating back to the

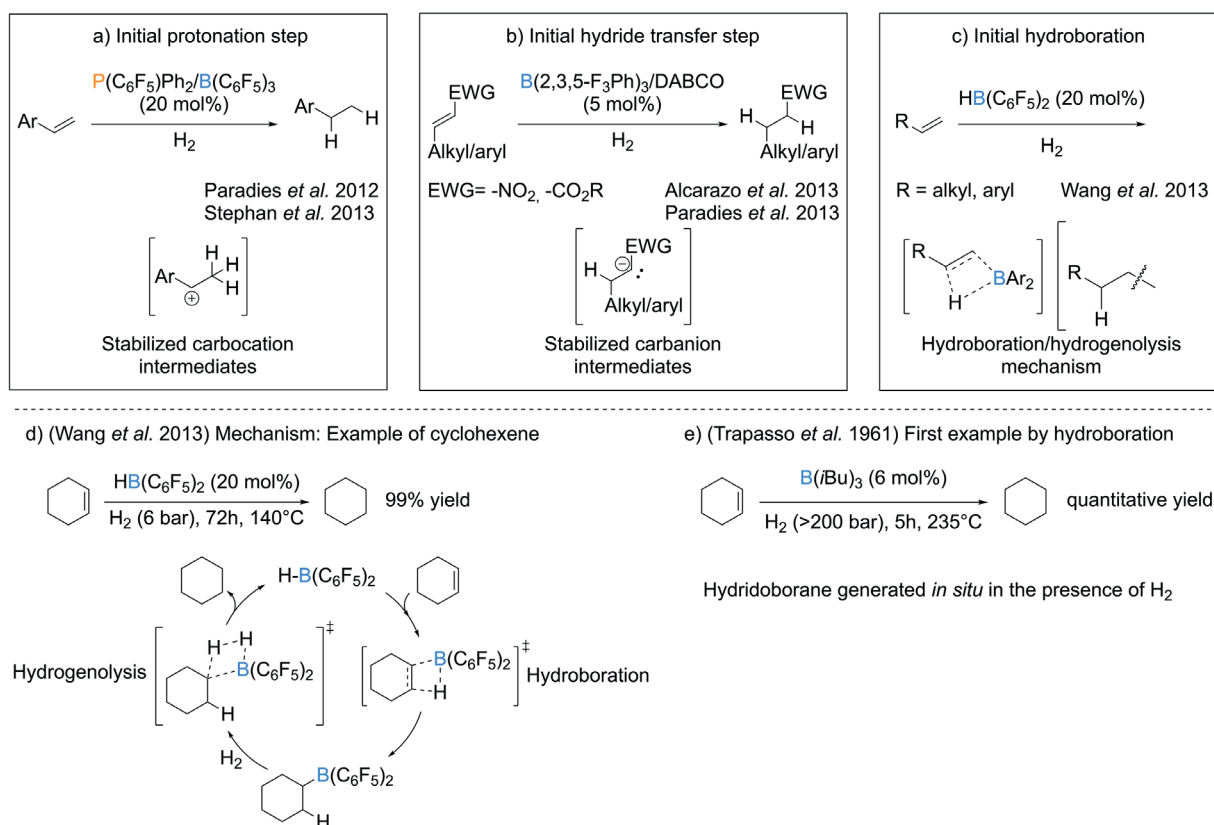
1960's [46-47], but the reaction of Wang *et al.*, performed at 140°C under 6 bar of hydrogen pressure and 20 mol% catalyst, constitutes the first reported example of metal-free-catalyzed hydrogenation of aliphatic, unactivated alkenes, under relatively mild conditions. They took advantage of the better reactivity of Piers' borane for hydroborations compared to classical boranes to perform this challenging reaction [48].

The first step toward the hydrogenation of alkynes was reported by the group of Erker. Their intramolecular FLP **3** reduced ynones into the corresponding enones [49]. The hydrogenation of simple alkynes however was reported later by Repo and coworkers [50]. Using an *ansa*-aminoborane system **6**, they performed the hydrogenation of alkynes to *cis*-alkenes under mild conditions (Scheme 8). The actual catalyst **6** is generated by reacting the pre-catalyst **5** at 80°C under H_2 atmosphere. The new B-H bond allows the following hydroboration of the substrate, generating a bulky bifunctional system **7** which cleaves H_2 to form the corresponding ammonium hydridoborate salt **7-H₂**, eventually releasing the *cis*-alkene *via* protodeborylation. Hydrogenation with this system only yields the *cis*-alkene (*Z*). Subsequent work by Du described the selective hydrogenation to *cis*- or *trans*-alkenes catalyzed by $\text{HB}(\text{C}_6\text{F}_5)_2$, in a similar fashion as Wang for unactivated alkenes [51].

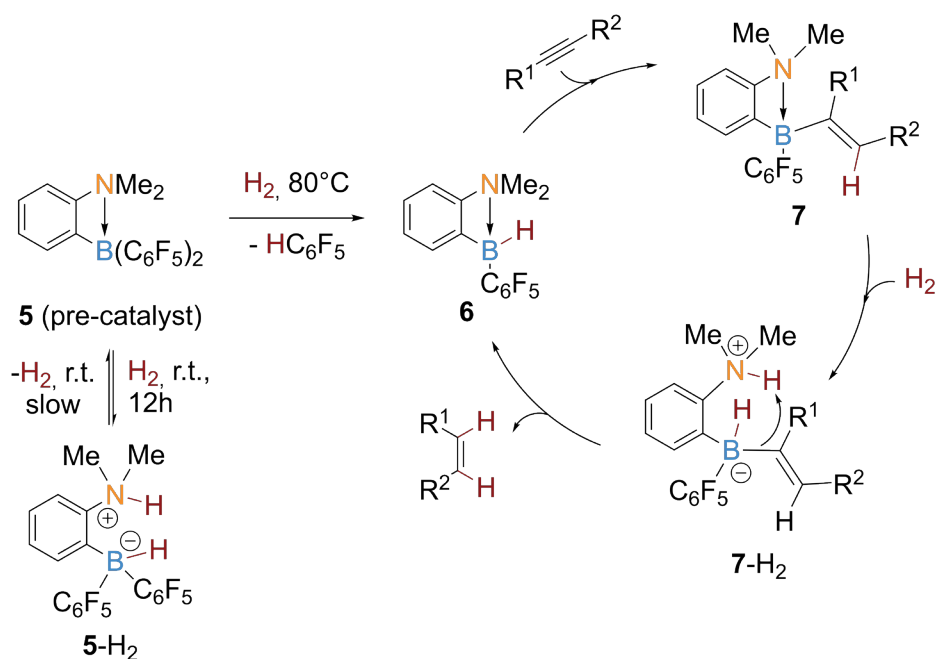
1.2.2. Hydrogenation of carbonyl derivatives

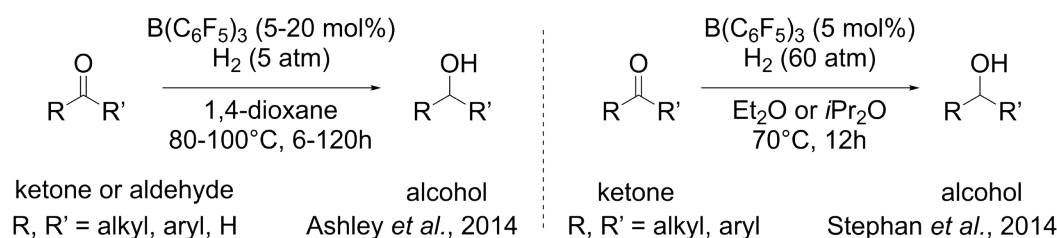
The use of ethereal solvents developed by Stephan and Ashley allowed the hydrogenation of aldehydes and ketones. These substrates turned out to be more challenging than their imines analogues due to the lower basicity of the oxygen atom. By computational investigation, Privalov reported that the process of activating H_2 with a ketone in combination with $\text{B}(\text{C}_6\text{F}_5)_3$ was possible [52]. Early efforts however were unsuccessful and only led to the formation of the corresponding alkoxyboranes and the deactivation of the catalyst [53-54]. Eventually, the groups of Ashley and Stephan solved this problem by using respectively THF or diethyl ether/diisopropyl ether as solvents (Scheme 9) [55-56].

Three pathways of olefins hydrogenation



Scheme 7. Metal-free-catalyzed hydrogenations of olefins, either by FLPs or Piers' borane. DABCO = 1,4-diazabicyclo[2.2.2.]octane.

Scheme 8. Formation of the catalyst **6** and mechanism of FLP-catalyzed hydrogenation of alkynes to cis-alkenes.



Scheme 9. FLP-catalyzed hydrogenation of ketones and aldehydes by Ashley and Stephan.

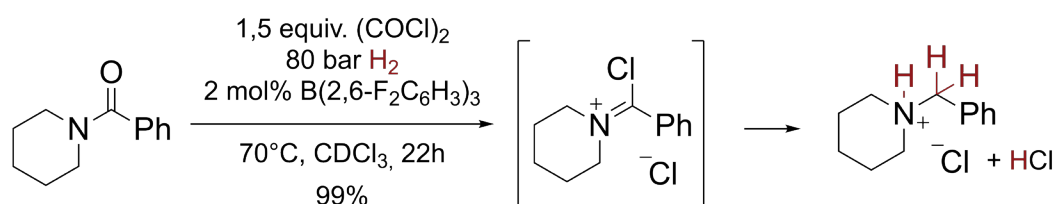
Investigating the reactivity of the Lewis acid also expanded the scope of FLP chemistry. Soós *et al.* reported the use of bulkier and weaker Lewis acids for the hydrogenation of Michael acceptors, previously limited by their coordination to the oxygen atom, and carbonyl compounds [32, 35, 57]. The first water-tolerant FLPs were developed this way, allowing the catalysis of a new reaction by FLPs, reductive aminations, not considered earlier since it generates water as by-product [58-59].

The reduction of amides is one of the major ways to form functionalized amines [60]. The use of transition metal catalysts is well-developed but poses issues of selectivity (formation of a mixture of the corresponding amine and alcohol) and of tolerance with sensitive functional groups (*e.g.* halogens, alkynes, nitro). Paradies reported the first hydrogenation of amides by FLPs [61]. This reaction required $(\text{COCl})_2$ as additive to convert the amide in the corresponding chloroiminium ion before reduction to the ammonium (Scheme 10) [62]. Later improvements using a phosphine oxide in combination with triphosgene $[\text{CO}(\text{OCCl}_2)_2]$ to generate the chloroiminium intermediate were reported [63]. Similarly, esters eluded

FLP hydrogenation until recently, when Ashley reported their direct hydrogenation catalyzed by an organotin Lewis acid in combination with lutidine [64].

1.2.3. Enantioselective hydrogenations catalyzed by FLPs

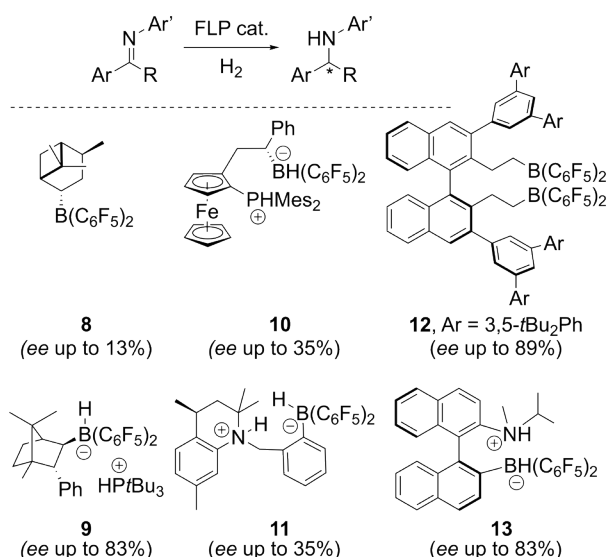
In 2008, Klankermayer and his group opened the door of asymmetric catalysis with FLP catalysts when they used an alkenylborane derived from (+)- α -pinene (8, Scheme 11) to catalyze the enantioselective hydrogenation of imines [30]. This first chiral catalyst only led to limited enantiomeric excess (13% ee) but later improvements using a camphor scaffold (9, Scheme 11) led to ee values up to 83% for the same reaction [65-66]. Other chiral FLP systems were developed as well: Erker *et al.* used a ferrocene-based catalyst (10, Scheme 11) for asymmetric imine reduction with up to 69% ee [67-68]. Building on earlier work with intramolecular FLPs [33], Repo and coworker synthesized a series of ansa-ammonium borates systems including some chiral versions (11, Scheme 11) able to yield up to 35% ee [69]. Notably, the group of Du reported



Scheme 10. Paradies' hydrogenation of amide through a chloroiminium intermediate.

a straightforward method to access chiral Lewis acid catalysts based on the binaphthyl chiral scaffold [70]. Their catalyst **12** (Scheme 11) is generated in situ by double hydroboration of binaphthyl diene with Piers' borane [$\text{HB}(\text{C}_6\text{F}_5)_2$] and displays good enantioselectivity with up to 89% ee. Another well-performing system for asymmetric imine hydrogenation based on the naphthyl scaffold (**13**, Scheme 11) was reported by Repo. These bifunctional "chiral molecular tweezers" led to ee values up to 83% for imines and up to 99% for enamines [71].

Asymmetric hydrogenation of imines



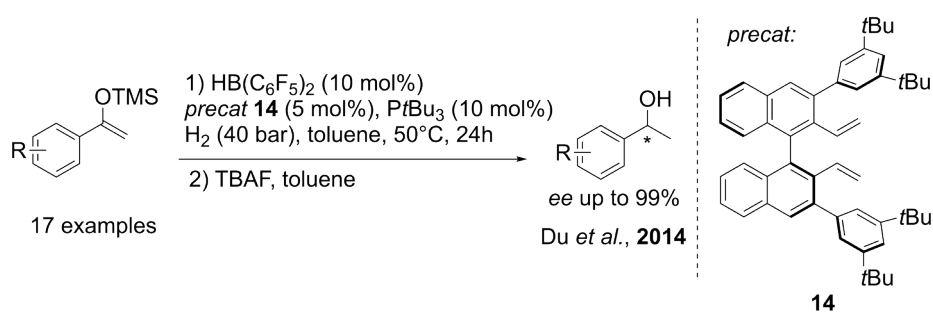
Scheme 11. General reaction of asymmetric hydrogenation of imines and selected examples of chiral FLP systems.

Other substrates were targeted as well, for example variations of Du's catalyst allowed the

hydrogenation of silyl enol ethers (**14**, Scheme 12) and N-heterocycles with good enantioselectivity [72–76].

1.2.4. Investigations on the mechanism of H_2 activation

Understanding the reactivity of frustrated Lewis pairs and the mechanism of hydrogen activation remains a challenge. To this end, many research groups have undertaken computational studies, mostly employing Density Functional Theory, to gain insight into the complex reactivity of FLPs [77–84]. In particular, the mechanism of H_2 activation by acid-base combinations was a source of long-lasting debates. Shortly after the seminal discoveries of Stephan, in 2008, Pápai and co-workers reported a quantum chemical study of the activation of dihydrogen by the typical FLP tris(*tert*-butyl)phosphine (Pt-Bu_3) and tris(pentafluorophenyl)borane ($\text{B}(\text{C}_6\text{F}_5)_3$) [77]. They pointed out that the splitting of the hydrogen molecule is neither due to a preliminary borane- H_2 or phosphine- H_2 complexation but to a concerted mechanism: a simultaneous breaking of the H–H bond and formations of P–H and B–H covalent bonds. The preliminary borane- H_2 complex was initially hypothesized because H_3BH_2 interactions were previously observed experimentally [85–86]. In the case of $\text{B}(\text{C}_6\text{F}_5)_3$ however, the weak electron-donation from the π -system to the vacant boron orbital is sufficient to prevent this interaction, due to Pauli repulsions. Instead, they suggested that the Lewis acid and the Lewis base associate first through weak interactions, without direct P–B

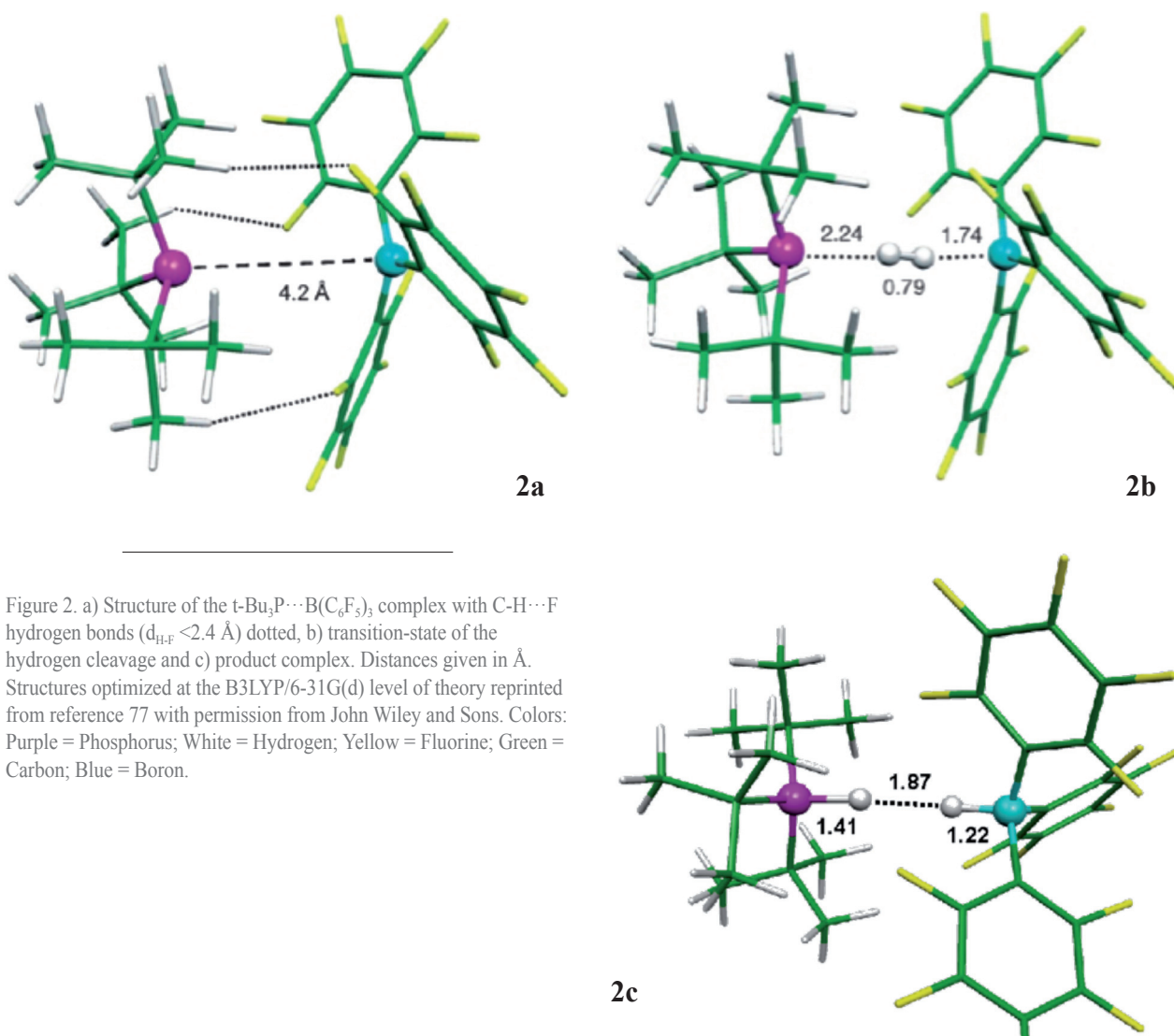


Scheme 12. Asymmetric hydrogenation of silyl enol ethers and deprotection to the secondary alcohol by Du et al. TBAF= tetrabutylammonium fluoride, TMS = trimethylsilyl.

charge transfer (mainly dispersion interactions and C-H $\cdots$ F hydrogen bonds), to form a cavity in which H₂ can be inserted (Figure 2). The H-H bond heterolytic cleavage happens subsequently through a transition state stabilized by the same weak intermolecular interactions between the phosphine and the borane to form the product, itself further stabilized by a P-H $\cdots$ H-B electrostatic interaction.

Their mechanism was later detailed based on a molecular orbital approach [87]. The LA-LB complex retains the HOMO of the base and the LUMO of the acid mostly unchanged but aligned in a way to ease orbital overlaps with H₂. The latter molecule inserted in the cavity undergoes a significant polarization (symmetry breaking) that alters its orbital configuration (mixing between the HOMO and LUMO of H₂) resulting

in a H₂ molecule acting both as a better electron pair acceptor and electron pair donor than in the unperturbed system (Scheme 13, left). The actual heterolytic splitting happens next through a simultaneous and electron transfer, resulting in the phosphonium and borohydride ion pair. H₂ acts as a bridge between the acid and base centers, breaking its σ bond to release the frustration. Interestingly, they drew a parallel between this reactivity and the other modes of H₂ splitting, homolytic or heterolytic, in metal complexes or by singlet carbenes, identifying FLP-H₂ activation as the newest member in this category (Scheme 13, right). In view of all these results and the stabilization occurring in the product of the reaction, they could explain why, experimentally, this reaction happened quantitatively and under mild conditions.



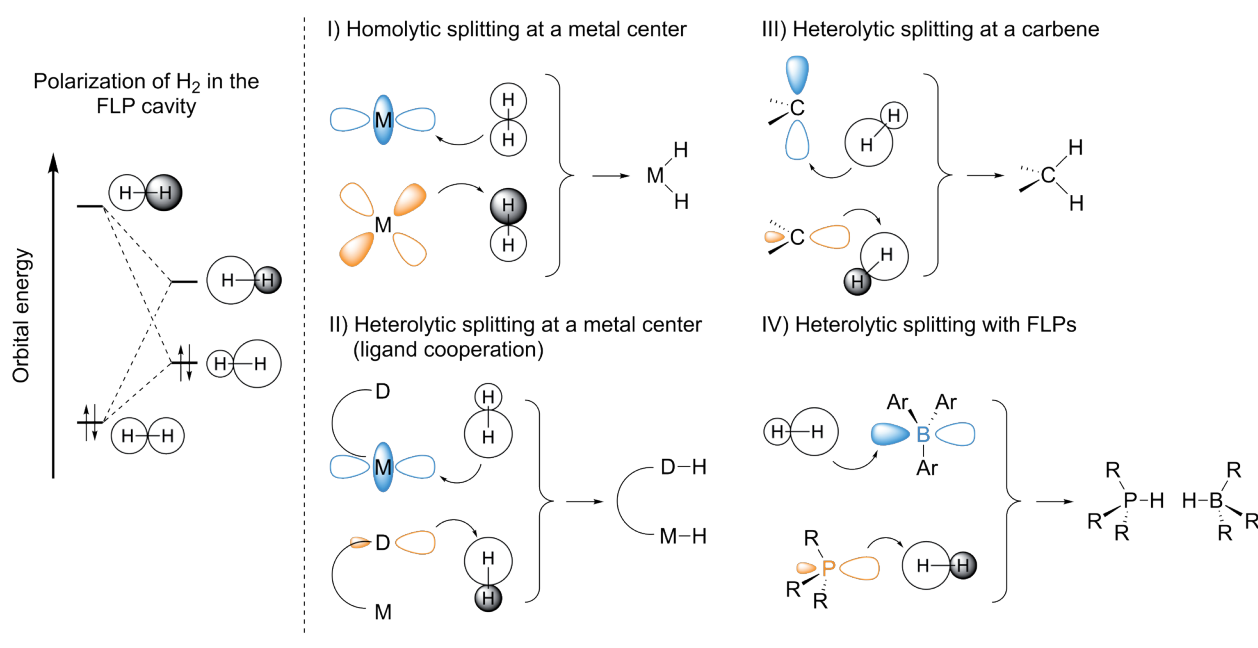
Similarly, Guo and Li invoked the same mechanism to explain the splitting of H_2 by Stephan's first intramolecular FLP system **1** [88], contrary to the mechanism proposed in that initial report [3].

Next were investigated the factors influencing the thermodynamics of H_2 activation by several acid-base combinations [78]. To this end, a partitioning of reaction energies was undertaken, identifying several unfavorable and favorable contributions, the former consisting in the H_2 cleavage itself and the preparation energy of the Lewis pair (breaking of eventual dative LA-LB bonds or weak interactions to "make space" for H_2 insertion), the latter consisting in the stabilizations brought by proton attachment to the Lewis base, the hydride attachment to the acid and the coulombic interactions in the ion pair product. Isolating these contributions allowed to pinpoint the individual effects of the acid, of the base, and of the nature of the FLP itself (either intra- or intermolecular). A notable conclusion from the report was that intermolecular FLPs displayed a good correlation between the strength of the acid-base combination and the ease of H_2 cleavage, while intramolecular FLPs benefited from a reduced

entropy penalty, so that weaker intramolecular acid-base combinations were still able to activate H_2 . In a later report, Vankova *et al.* drew similar conclusions for reaction kinetics [82]. Both articles stress the importance of tuning the size and properties of the Lewis base and of the Lewis acid to best exploit the reactivity with H_2 .

In 2010, Grimme and Erker challenged the so-called "electron transfer" mechanism of Papaï, described above [89]. Their initial claim was that the previous work of Papaï was questionable, mainly due to a poor theoretical treatment (namely the small, poorly flexible, basis set, the use of the B3LYP functional, and the lack of proper benchmark study for the method) that did not (sufficiently) consider the interactions between the bulky substituents, mainly London dispersion forces, and led to inaccurate transition state structures. Using the B97-D⁹⁰/TZVPP^[1] [91] method in combination with single point calculations at the higher-level

¹ TZVPP' corresponding to Alrich's triple ζ valence basis set with either two sets of polarization functions for P, B and H (TZVPP) or one set for all other atoms (TZVP).



Scheme 13. (left) Orbital deformation resulting from mixing between HOMO and LUMO. (right) Modes of H_2 splitting in a metal complex (I, II), at a carbene (III) and by FLPs (IV). In orange and in blue are shown filled and empty orbitals respectively, filled orbital of H_2 shown in full white, empty in black and white. Heterolytic splitting modes involve a polarized H_2 moiety. Scheme adapted from reference 87 with permission from John Wiley and Sons.

SCS-MP2 [92] /CBS [93-94], they probed the potential energy surface in the cavities (Figure 2a) created in FLP systems at several P-B and H-H distances and concluded that once H_2 was inside the cavity, its dissociation was practically barrierless. They attributed the observed kinetic barrier to the H_2 entrance into the cavity. According to their mechanism, the electric field generated between the acid and the base centers is sufficient to split the H_2 molecule, the phosphorus and boron then acting merely as the hydride acceptor and donor. To support this view, they simulated a strong electric field acting on H_2 , without FLP system, and showed that the heterolytic splitting was spontaneous (Figure 3). According to them, there is no need to invoke orientation and deformation of molecular orbitals to explain FLP reactivity.

To summarize both conceptual views, in the electron transfer mechanism, FLPs activate H_2 by adequate orbital overlaps, allowing electron transfer. The reaction barrier is due to the transition state of H_2 splitting. In the electric field mechanism, FLPs activate H_2 through its polarization owing to the electric field generated by the LA and LB moieties. The reaction barrier is due to preparation or entrance of H_2 in the cavity. Investigations in the following years discussed the

possibilities of both mechanisms. Camaioni *et al.* studied a series of small molecules combinations (NH_3/BX_3 , $X = H, F, Cl$) in their reaction with H_2 [95]. They optimized their structures using B3LYP-D/DZVP2 method and refined electronic energies at the G3(MP2)-B3LYP [96] and CCSD(T) levels of theory. Given the study was not experimental, they could decide to ignore the fact that the small molecules would normally form Lewis adducts and focused instead on the energy decomposition analysis of their reaction with H_2 . They concluded that favorable orbital overlaps were the main stabilizing factor in reaction energy. Electrostatic interactions, which include the interactions through the electric field generated by the FLP, were significant as well but could not alone be accountable for the reactivity of the system.

Rokob, Papaï and co-workers eventually addressed the previous comments of Grimme on the theoretical method. New in-depth studies, extensively comparing both conceptual views, were reported [81, 97]. Inter- and intramolecular FLPs with several types of Lewis acids and bases were considered, eventually supporting the electron-transfer mechanism, and highlighting the limitations of the electric field view. To further support their claim, they performed a

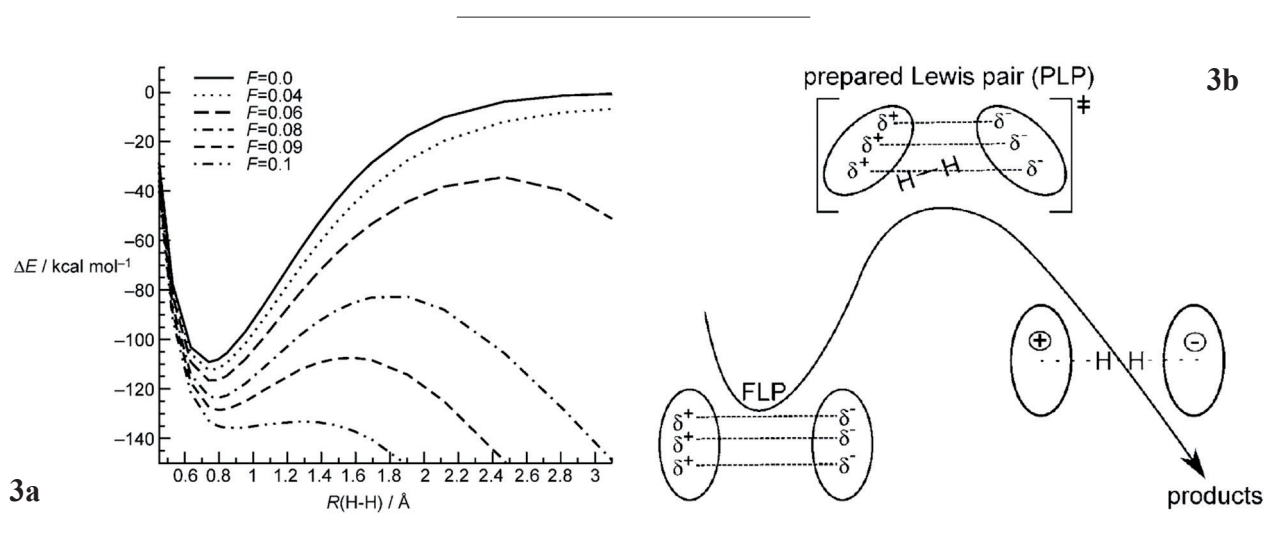


Figure 3. (left) Potential energy curves of H_2 dissociation (computed at the FCI/aug-cc-pVQZ) in electric fields of varying strength, note that for a strong enough field ≥ 0.1 a.u. ($1 \text{ a.u.} = 5.1422 \cdot 10^{11} \text{ V.m}^{-1}$), the dissociation is almost barrierless. (right) Representation of FLP H_2 activation with the electric field model, a typical range of field strength inside a FLP is between 0.04 and 0.06 a.u. Schemes reprinted from reference [89] with permission from John Wiley and Sons.

preliminary benchmark study, investigating the effect of the method on the results and settled on the use of the ω B97X-D exchange correlation functional, a range-separated hybrid functional including an empirical dispersion correction term, with the 6-311G(d,f) basis set. Eventually, they proposed a general mechanism for intermolecular FLP systems, regardless of the nature of the LA and LB considered, divided in three main steps: i) preorganization through weak interactions, ii) simultaneous interaction of H_2 with both LA and LB (*i.e.* H_2 polarization) and iii) electron transfer through cooperative and . The mechanism differs between systems in the way H_2 , the electron donor and the acceptor are positioned.

These discussions pointed out the need for a robust computational method and how inappropriate exchange-correlation functionals or basis sets can lead to inaccurate structures, energies, or scientific conclusions. Even though the electron transfer model has been generally adopted overtime, especially since the molecular orbital approach allowed a deeper understanding and the establishment of guidelines for the development of new systems, continuous improvements and contributions were added over the years. The addition of Molecular Dynamics studies are worth mentioning, which allowed the group of Ensing to shed light on the asynchronous nature of the transition state and the individual roles of the acid and base on the kinetics [98-100]. Giving more depth to the established models, Privalov described more complex orbital interactions, in which both σ and σ^* orbitals of H_2 in the cavity are coupled with the HOMO and LUMO respectively of the FLP system [101]. In essence, the understanding

of reaction mechanisms and the interactions between all involved compounds through computational studies is crucial to predict the properties of FLPs and to design new ones.

1.2.5. Small molecules capture, carbon dioxide hydrogenation and methane activation

The reactivity of FLP systems is not limited to dihydrogen, several small molecules can be captured by FLPs, such as CO , CO_2 , SO_2 and N_2O (Figure 4) [102-108]. Reaction conditions are similar to the original H_2 reports [4]: the FLP spontaneously traps these small molecules at room temperature and atmospheric pressure of the gas. Contrary to H_2 however, no catalytic system has yet been developed with these molecules. They require a stoichiometric amount of phosphine-borane, which is why one talks of small molecules “capture” instead of “activation”.

The activation of CO_2 , a potent greenhouse gas [109], is a very attractive transformation, which led researchers to further investigate its reactivity with FLP catalysts. Its conversion with dihydrogen into formic acid or methanol is an attractive method to generate C_1 building blocks in chemical synthesis or as a chemical storage of H_2 in the context of renewable energy management [110-112]. This transformation is well-studied in heterogenous catalysis [113-114], with electrochemical reduction [115] as well as with transition metal in homogeneous catalysis [116], but an efficient metal-free alternative is still lacking [117]. Wang reported a $B(C_6F_5)_3$ -catalyzed hydrogenation of carbon dioxide without transition metal but using instead potassium metal (K) in the reaction mixture under harsh conditions. A first proof of concept

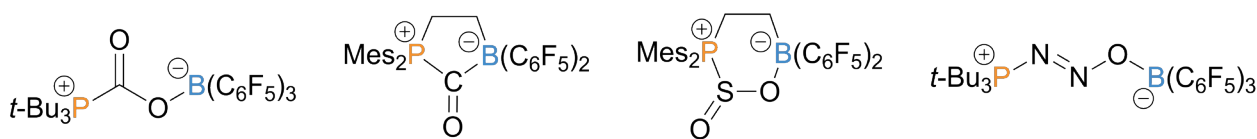
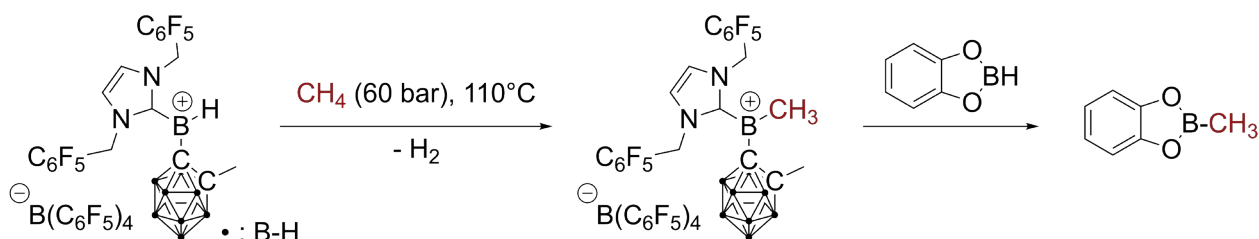


Figure 4. CO_2 , CO , SO_2 and N_2O molecules captured by FLPs.



Scheme 14. Activation and borylation of methane by a borenium complex.

that CO_2 can be hydrogenated into methanol in low yield with a FLP in stoichiometric amount was described [118] by Ashley but ultimately led to the destruction of the FLP catalyst. Another stoichiometric reaction was reported by Stephan and Fontaine in 2015 [119]. More recent computational investigations hinted at the feasibility of the catalytic transformation of CO_2 into formic acid by FLPs, which is encouraging [120-122]. Eventually, Stephan's group reported the hydrogenation of CO_2 with H_2 in the presence of silyl halides, leading selectively to either disilyl acetals or methoxysilanes [123].

Another compound of great interest that cannot yet be activated by FLPs is methane (CH_4). Methane is, alongside carbon dioxide, one of the major gases responsible for global warming and its conversion into value-added products would be most profitable. Again, transition metals proved to be efficient catalysts for this challenging transformation. Periana and coworkers developed the first catalytic conversion of methane into a methanol derivative using a Pt (II) complex [124]. More recently, the groups of Sanford and Mindiola developed catalytic C-H borylations of methane using Ir, Rh and Ru complexes [125-126].

FLPs were obvious candidates for developing metal-free alternatives for the activation of methane. However, while carbon dioxide displays some reactivity with FLP systems, no reaction with methane was reported to this day. Several theoretical studies tried to address this problem by understanding the reasons behind this difficulty: they concluded that the lack of reactivity with FLP systems is mainly due to a substantial barrier of activation, resulting from unfavorable structural

reorganizations in the CH_4 moiety and the Lewis acids during the reaction, and also to weaker orbital interactions with the FLP system compared to H_2 and CO_2 [79, 127-129]. Alternatively, the group of Wang reported more recently that the activation and functionalization of methane can be achieved with a borenium cation complex, effecting its borylation (Scheme 14) and its addition on a silyl acetylene, demonstrating that reactivity with methane is possible without transition metal complexes [130].

As shown in above-detailed examples, the hydrogenation of, or the reactivity with, new and challenging substrates is strongly reliant on the development of new Lewis acids and Lewis bases, specifically designed to address limitations in the field [131-133]. In parallel, it is also crucial to understand these limitations and the parameters affecting their reactivity, for which quantum chemical calculations are necessary. Phosphines are ideal Lewis base candidates in FLP chemistry and were widely used and studied in this field [36, 134]. Their development is an important field of research, especially since they can also be applied as ligands in organometallic chemistry.

1.3. Aim of the project: merging FLP and 9-phosphatriptycene chemistry

An understudied and yet promising class of phosphines are 9-phosphatriptycene derivatives. The 9-phosphatriptycene (**15**, Figure 5) is a strongly pyramidalized ring-strained phosphine with its phosphorus atom in the bridgehead 9-position of the tricyclic [2.2.2]-octatriene inner motif. While heteroderivatives of the triptycene were synthesized in the decades following the

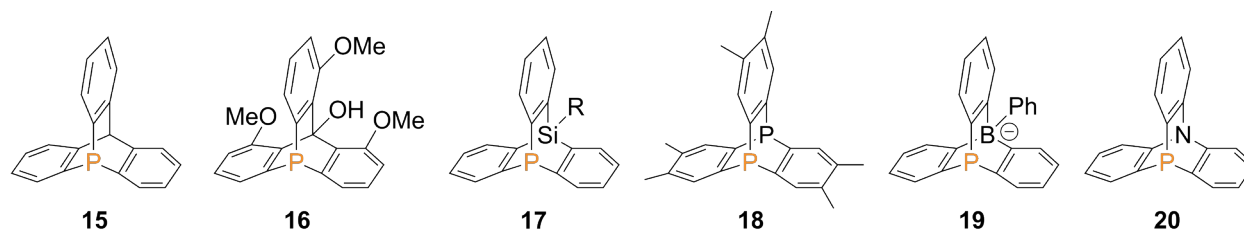


Figure 5. Phosphatriptycene **15** and reported derivatives **16-20** [142-143].

parent triptycene, they found little applications until their use as ligands in the early 2000's [135-137]. Among them, the 9-phosphatriptycene was first synthesized in 1974 by Bickelhaupt in five steps with 3% overall yield [136].

In the past two decades, several new developments and syntheses were made on the phosphatriptycene and its derivatives. A new synthetic pathway was designed by the group of Kawashima in 2003 that uses phosphatriptycene oxide intermediates to access methoxy substituted phosphatriptycenes (**16**, Figure 5) [138]. Other oxide derivatives were later described by the same group [139]. Tsuji, Tamao *et al.* reported the synthesis of new 9-phospha-10-silatriptycenes **17** and derivatives as well as a study of their structure and properties [140]. In order to have a better solubility in common organic solvents, the group of Mazaki introduced methyl groups on phosphorus- and antimony-based diheteratriptycenes [141]. These methyl groups were added on the 2, 3, 6, 7, 12 and 13-positions (**18**). A significantly greater

challenge, however, is to add substituents in positions 1, 8 and 14 (*i.e.* in *ortho*-position relative to the phosphorus), and no example of triptycenes with this interesting substitution pattern has been reported so far.

The parent 9-phosphatriptycene was never reportedly tested as a Lewis base in FLPs or in any other organocatalysis. It possesses however interesting properties relevant to these applications. The scaffold is very robust and can be heated to high temperatures without degradation. Adding substituents in *ortho*-position to the phosphorus allows to tune both the electronic and steric properties of the phosphine, which is helpful in the context of FLP chemistry. My PhD thesis aimed at developing and studying 9-phosphatriptycene derivatives and probe their application in FLP chemistry. More specifically, the goal of this investigation was to develop our fundamental understanding of structure-property relationships in cage-shaped phosphines, especially at the electronic level, while targeting

applied objectives such as finding solutions to current limitations in the field of FLP catalysis.

The FLP part of the PhD project was divided into three main objectives. First, a new synthesis to access *ortho*-substituted 9-phosphatriptycene was developed, since these compounds displayed the highest potential in FLP chemistry. Next, a fundamental investigation of the steric and electronic properties was undertaken, shedding light into the parameters affecting the reactivity of these phosphines. In addition, a DFT tool to accurately predict their pK_a was developed, highlighting their weak basicity compared to regular triarylphosphines. Finally, 9-phosphatriptycenes were used for the first time as Lewis bases in FLP catalysis, taking advantage of their weak basicity to allow the hydrogenation of unactivated olefins, a challenging family of substrates.

2. Synthesis, study and application of 9-phosphatriptycenes to FLP chemistry

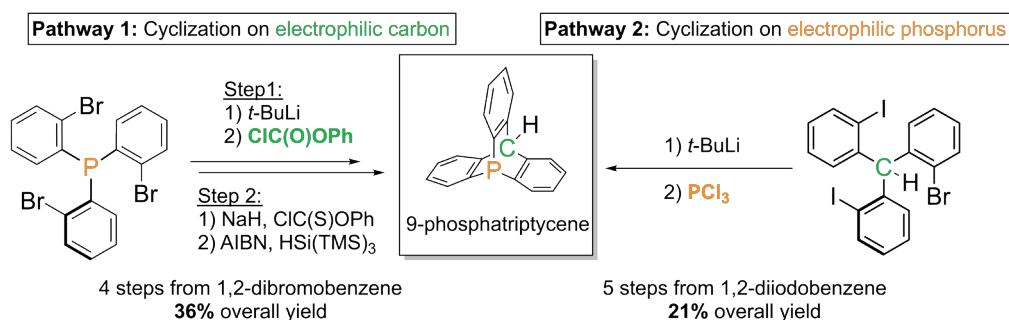
2.1. Synthesis of *ortho*-substituted 9-phosphatriptycenes

In 2018, our group published two new synthetic approaches to the parent 9-phosphatriptycene (**15**), as well as a combined experimental and theoretical investigation of its steric and electronic properties [144]. On the one hand, it can be obtained *via* an *ortho*-tribrominated phosphine precursor that undergoes a triple

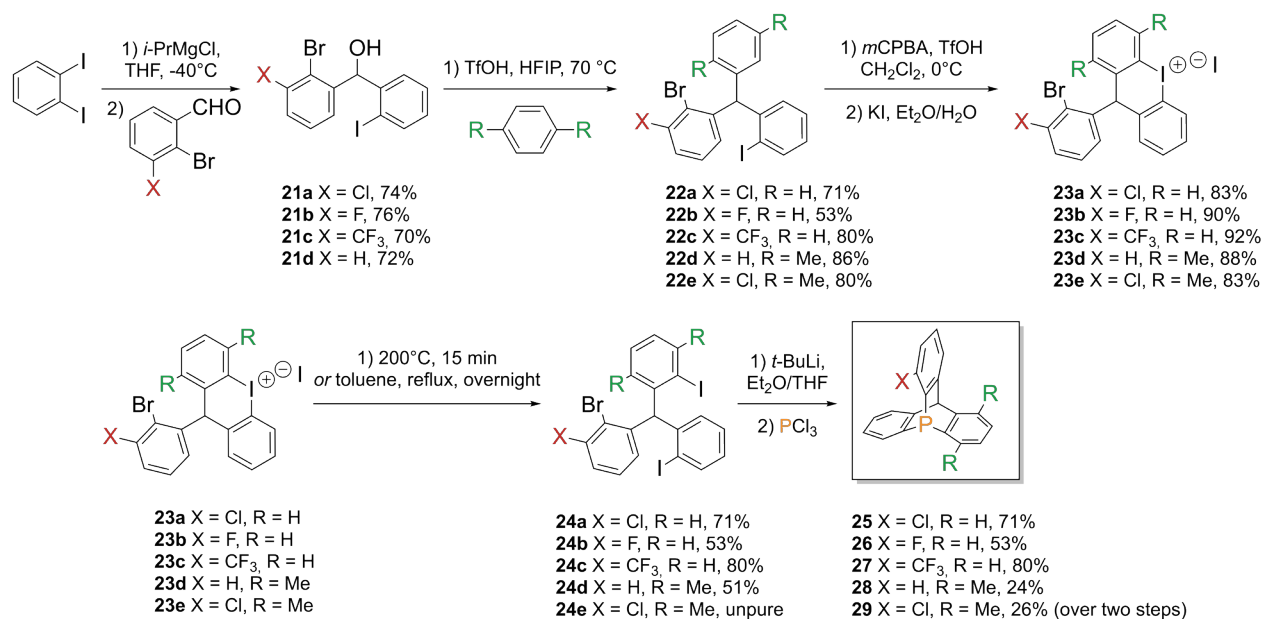
lithium-halogen exchange, then cyclizes on phenylchloroformate to give a 9-phospha-10-hydroxytriptycene that is further reduced into the target 9-phosphatriptycene in two steps using a Barton-McCombie deoxygenation (Scheme 15, Pathway 1). On the other hand, a trihalogenated triphenylmethane precursor [145] can be used for lithiation and cyclization on a phosphorus-based electrophile, namely PCl_3 , to obtain 9-phosphatriptycene (Scheme 15, Pathway 2).

A new five-step synthesis to access *ortho*-substituted 9-phosphatriptycenes was developed during my PhD, starting from and adapting the strategy based on triphenylmethane precursors mentioned above (Scheme 16) [146]. While the synthesis based on phosphine precursors is more efficient for the parent compound (Scheme 15), it failed at yielding *ortho*-substituted derivatives due to intermediates with excessive steric strain. The alternative strategy involving triarylmethane precursors was used instead and is detailed below.

Starting from 1,2-diiodobenzene, iodine/magnesium exchange by *i*-PrMgCl and reaction with 2-bromo-3-chlorobenzaldehyde yielded the diphenylmethanol derivative **21a**. Following a modified procedure of Moran [147], a Friedel-Crafts reaction with benzene produced **22a**. Next, iodine oxidation with *m*CPBA, intramolecular S_EAr and triflate/iodide anion metathesis generated the iodonium salt **23a**. Heating of the later, either neat at 200°C for 15-20 min or overnight in refluxing toluene yields



Scheme 15. Formation of 9-phosphatriptycene via two synthetic pathways.



Scheme 16. Synthesis of ortho-substituted 9-phosphatriptycene derivatives. This synthesis was developed in collaboration with Dr. Lei Hu.

trihalogenated triphenylmethane precursor **24a**. Other substituted derivatives can be obtained with the same method, either by changing the starting aldehyde (X = F, CF₃ to yield **26** and **27**) and/or using *para*-xylene instead of benzene for the Friedel-Crafts reaction (R = Me, yielding **28** and **29**). For the first time, *ortho*-substituted 9-phosphatriptycenes were synthetically accessible, which is the first step in applying their reactivity to catalysis.

2.2. Reactivity study of 9-phosphatriptycenes

The choice of 9-phosphatriptycenes as Lewis base candidates in FLP catalysis is strategic not only due to their tunable steric hindrance but also due to their intrinsic reactivity. The cage-like structure of the 9-phosphatriptycene **15** and its derivatives **25-29** imposes a strong pyramidalization on the phosphorus center with respect to other triarylphosphines. This structural constraint impacts the electronic configuration of the phosphorus and induces a high *s* character of its lone pair. Interestingly, it was highlighted that this triptycene scaffold effected a weakening of the Lewis basicity of the phosphorus atom compared to the reference triphenylphosphine (PPh₃). This was evidenced experimentally by the

evaluation of the Lewis Basicity (*LB*) parameter, as introduced by Mayr, with a *LB* value of 7.63 for **15** with respect to 14.27 for PPh₃, corresponding to a ~10⁶ times weaker Lewis basicity towards C-centered Lewis acids [148-149].

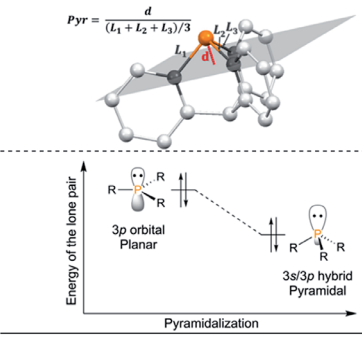
In a recent investigation, the low basicity of 9-phosphatriptycenes was highlighted computationally by the accurate prediction of their conjugate phosphonium p*K*_a in water and acetonitrile [150]. Since Lewis bases react in FLP hydrogenations by the proton transfer from their conjugate acid (Scheme 6), the appropriate reactivity parameter to consider for characterization is their p*K*_a. This prediction method is based on the DFT (M06-2X/6-311G[d] with IEFPCM solvation for water or acetonitrile) determination of Dp*K*_a's improved by correlation with experimental values from the literature [151-152] (RMSD = 0.2 and 0.5 p*K*_a units in water and acetonitrile respectively). The reactivity investigation, supported by NBO calculations yielding information on the electronic state of the phosphorus atom (*e.g.* the hybridization of its orbitals), shed light into the origin of the low basicity of 9-phosphatriptycenes. As the phosphorus atom is constrained into the triptycene scaffold, its pyramidalization (pyramidalization parameter, defined below) increases relative to

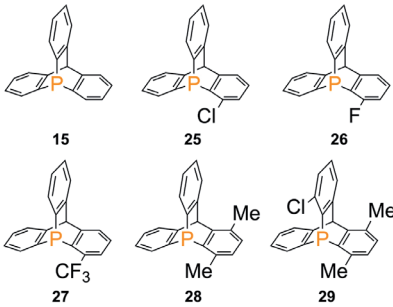
non-strained phosphines, resulting in an increase of the P lone pair 3s character (see Welsh diagram below). Since 3s orbitals are more stable than 3p orbitals, the global energy of the phosphorus lone pair is reduced and so is its reactivity, explaining the significantly lower pKa predicted for these compounds. Then, changing the *ortho*-substituents allows to further fine-tune the reactivity of the phosphine. Table 1 summarizes the pKa values and main NBO results highlighting this pattern.

2.3. Application to FLP catalysis

In FLP catalysis, deactivated Lewis bases find applications in the hydrogenation of weakly

reactive substrates such as olefins. Since the base is weak, its conjugate acid (obtained after H₂ activation) is strong, more prone to protonate weakly reactive substrates. Still, “unactivated” olefins, such as aliphatic alkenes, are still a challenge. In a first FLP application studied in this project, 9-phosphatriptycenes were shown to be able to hydrogenate 1,1-diphenylethylene at room temperature, a reaction already reported in the literature, but serving as a proof of concept that such phosphines can serve as Lewis bases in FLP catalysis [150]. More interestingly, 9-phosphatriptycenes derivatives allowed for the first time the hydrogenation of unactivated alkenes with an FLP catalyst: after optimization





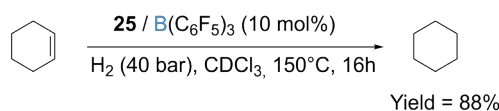
15 25 26

27 28 29

Phosphines	Est. pKa (MeCN)	Est. pKa (H ₂ O)	ε _{LP} (eV)	Pyr	3s _{LP} (%)	3p _{LP} (%)
PPh₃	7.62 ^[a]	3.28 ^[a]	-11.66	0.452	45.4	54.6
15 (-H)	-0.7	-2.9	-12.78	0.536	49.9	50.1
25 (-Cl)	-2.6	-4.2	-12.95	0.538	50.8	49.2
26 (-F)	-2.5	-4.1	-12.93	0.540	50.7	49.3
27 (-CF₃)	-2.9	-4.5	-12.99	0.538	50.9	49.1
28 (-Xyl)	0.2	-2.2	-12.71	0.534	49.9	50.1
29 (Cl, Xyl)	-1.5	-3.5	-12.88	0.536	50.8	49.2

[a] Experimental values.

Table 1. Estimated (Est.) pKa's in acetonitrile (MeCN) and water (H₂O) of the conjugate phosphonium of selected phosphines, pyramidalization parameter (Pyr), energy of the phosphorus lone pair (ε_{LP}), its 3s and 3p characters.



Scheme 17. Optimized conditions for the hydrogenation of cyclohexene with 1-chloro-9-phosphatriptycene **25** and BCF. NMR yield indicated.

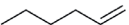
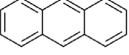
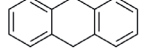
Entry	Substrate	Product	Conversion (%) ^[a]	¹ H NMR yield (%) ^[a]
1			100	72
2			100	60
3			100	70
4			84	76
5			61 ^[b]	57 ^[b]
6			0	0
7			33	20
8			26	3

Table 2. Substrate scope of hydrogenation with 1-chloro-9-phosphatriptycene **25** and BCF as catalyst.

Conditions: 10 mol% catalyst, Solvent= CDCl₃, 150°C, 16h, 40 bar H₂. [a] Triphenylmethane or 1,3,5-trimethoxybenzene used as ¹H NMR internal standard for yield determination. [b] Reaction time increased to 72h.

of the catalyst and the conditions, the combination of tris(pentafluorophenyl)borane (BCF) as Lewis acid and 1-chloro-9-phosphatriptycene as Lewis base reduced cyclohexene to cyclohexane at 150°C overnight under high dihydrogen pressure (40 bar) with up to 88% yield (Scheme 17) [153].

Comparison with other deactivated Lewis bases highlighted the effect of the triptycene scaffold on the phosphorus reactivity since no other phosphine was able to catalyze this reaction as effectively, even the ones bearing deactivating groups, such as P(2-Br-C₆H₄)₃, P(4-Cl-C₆H₄)₃ or P(C₆F₅)Ph₂. Eventually, a scope of substrates was undertaken, showing that these conditions tolerate cyclic and acyclic olefins, even the ones bearing deactivating groups, but steric hindrance in the substrate hampers the reaction (Table 2). So far thus, substrates are limited to mono- and di-substituted olefins, or trisubstituted ones with limited steric hindrance.

Inserting phosphorus into the triptycene scaffold and using 9-phosphatriptycene as organocatalysts thus solved a lasting issue in FLP catalysis, namely the hydrogenation of unactivated alkenes.

In addition to this applied outcome, it is also a fundamental proof of concept that targeting the structure of main group elements such a phosphorus is an effective but underdeveloped tool that can be used in combination with the usual strategy consisting in changing the nature and number of substituents (*i.e.* electron-withdrawing or -donating groups).

3. Conclusions

Frustrated Lewis pair chemistry opened a new door in acid-base reactivity and catalysis. Over the years, from the definition of early concepts to deeper mechanistic and scope investigations, this new field of organocatalysis has developed very quickly. Currently, the synthesis of new Lewis acids and bases is inherent to solving limitations in metal-free catalysis, such as the hydrogenation of unactivated alkenes. In this context, 9-phosphatriptycenes are appealing solutions since they display both the steric hindrance necessary for FLP reactivity and the weak basicity necessary for the hydrogenation of less reactive substrates. My PhD project allowed

to expand the reactivity of FLP catalyst with the use of 9-phosphatriptycenes. A new synthesis giving access to a series of *ortho*-substituted derivatives was developed. Then a reactivity investigation to understand the origin of their weak basicity was undertaken, showing that the increased pyramidalization of the phosphine due

to the triptycene scaffold stabilizes the phosphorus lone pair, resulting in a weaker reactivity. Finally, the high acidity of the conjugate phosphonium of 9-phosphatriptycenes was taken advantage of to allow for the first time the hydrogenation of unactivated alkenes by FLP catalysis.

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