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Design of frustrated Lewis pair catalysts for metal-free and selective hydrogenation*

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Abstract: After a short introduction to place our work in a proper context, this account summarizes our theoretical and synthetic results in the field of frustrated Lewis pair (FLP) chemistry.

Keywords: catalysis; chemoselectivity; frustrated Lewis pair chemistry; hydrogen; metal-free hydrogenation.

INTRODUCTION

In 1923, Gilbert N. Lewis introduced an ingenious idea that greatly broadened and generalized the definition of an acid and a base [1]. Since then this paradigm has become one of the central and fundamental concepts of chemistry, which has been especially useful to explain and predict chemical reactivities in polar reactions. It has also long been noted that the strength of the dative bond in a Lewis acid–base pair is strongly influenced by steric factors, which can even prevent the formation of a donor–acceptor adduct [2]. The inherent potential offered by the simultaneous presence of unquenched Lewis acid (LA) and base (LB) was rarely exploited, and these systems remained only exotic textbook or literature examples until quite recently [3,4]. Then, in 2006, Stephan and co-workers brought into sharp focus their synthetic potential in a series of landmark experiments [5,6]. They showed that the incapability of Lewis acid–base adduct formation in a "frustrated Lewis pair" (FLP) was a key element to unprecedented chemical transformations among which the activation of molecular hydrogen excels [5a,b]. As reported [5b], stoichiometric mixtures of $PR_3/B(C_6F_5)_3$ pairs (R = *t*Bu and $C_6H_2Me_3$) showed no evidence of the formation of Lewis acid–base adducts according to NMR, but the exposure of their solutions to H_2 at 1 atm pressure at 25 °C resulted in the facile formation of $[R_3PH][HB(C_6F_5)_3]$ products (eq. 1).

$$R_{3}P + BAr_{3} \xrightarrow{H_{2}} R_{3}P^{+}H + HB^{-}Ar_{3}$$

$$R = tBu, Mes; Ar = C_{6}F_{5}$$
(1)

Although the field of FLPs is still young [7] and definitively a large body of fundamental chemistry is left to be investigated and developed, in my opinion, the above simple and fascinating reaction is one of the greatest achievements in modern chemistry. It was a long and commonly held perception that the activation of the apolar hydrogen molecule is the characteristic of transition metals at ambient conditions. Hence, this main-group element-based and metal-free activation represents a clear scientific novelty, and this field has a great potential to induce a paradigm shift within chemistry.

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Additionally, Stephan's results unambiguously indicate that there still exists a scientific "terra incognita" within main-group chemistry, a field that was otherwise thought to provide no further radical developments.

Stephan and co-workers also proposed two mechanistic scenarios to rationalize their findings (Fig. 1) [5b]. The hydrogen-splitting reaction was rather facile, which can hardly be explained in terms of a termolecular collision between the reactants. Therefore, they presumed the formation of hydrogen-bounded precomplexes with the LA or LB. First, a side-on interaction of H₂ with $B(C_6F_5)_3$ was assumed to precede the dissociation process (path a). However, no evidence for the formation of the $(C_6F_5)_3B\cdots H_2$ species was found in related experiments [5b]. As an alternative pathway (path b), the end-on approach of H₂ to PR₃ was also raised, but again, weak R₃P\cdots H₂ interactions have been detected only at cryogenic conditions [8].



Fig. 1 Proposed mechanism for metal-free hydrogen activation.

DISCUSSION

Because of our keen interest in bifunctional organocatalysis [9], this bifunctional, metal-free activation of molecular hydrogen caught our attention. As a first step, we were interested in the mechanism of this peculiar reaction, because it seemed rather elusive and nonconventional at first sight.

As we have seen above, there were no solid proofs to select or support any of the proposed mechanistic models, which can be a sign that an alternative mechanism was operating upon hydrogen cleavage. This possibility triggered us, and the following two considerations dictated the construction of a preliminary model. (a) Nature abhors a gradient [10]—this rather simple, but fundamental law can be applied to FLPs. Considering the steric effect as a mode to generate gradient at the molecular level (it has the effect of separating the electrophilic center from the nucleophilic center in the dative complex), it can be expected that the resulting dissociated system counters the gradient via developing an organized structure, a bifunctional molecular complex. (b) Although NMR studies of FLPs provided definitive information about the non-existence of a stable donor–acceptor complex; the formation of any transient, short-lifetime bifunctional complexes between the molecules of the FLPs cannot be ruled out due to the inherent limited capability of NMR to detect those types of intermediates.

Along this line, as a first hypothesis, we assumed that one electron is thermally transferred from the highest occupied molecular orbital (HOMO) of the phosphine to the lowest unoccupied molecular orbital (LUMO) of the boron-centered LA. Thus, a transient radical ion pair would be formed which is held together by the Coulombic force (eq. 2). Then this highly reactive bifunctional system can induce the hydrogen cleavage.

$$R_{3}P + BAr_{3} - \left(R_{3}P^{+} B^{-}Ar_{3}\right)$$
⁽²⁾

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This proposal initiated a joint cooperation with Imre Pápai and his group, who are specialists in theoretical chemistry at our institute. We found no theoretical evidence in support of previously suggested mechanisms ([5b], Fig. 1), and it turned out very quickly that there was no need for electron transfer to generate a radical ion pair; even the secondary interactions lead to an association between the molecules of an FLP (Fig. 2) [11]. The bonding in this encounter or "frustrated" complex can be characterized as a combination of London dispersion forces and multiple C–H···F hydrogen bonds. As predicted by the calculation, the association energy was $\Delta E = -11.5$ kcal mol⁻¹, which is roughly the half of the interaction energy of a classical Lewis adduct. Additionally, the theoretical work revealed a unique characteristic of the $[(tBu)_3P]$ ···· $[B(C_6F_5)_3]$ encounter complex. It has a high structural flexibility, the phosphine–borane (P–B) distance in $[(tBu)_3P]$ ···· $[B(C_6F_5)_3]$ can be varied in a quite broad range at only a small energetic cost. This feature seems to be the consequence of the dominating non-directional secondary interactions.



Fig. 2 Frustrated complex and its synergistic hydrogen cleavage.

The flexible nature of the frustrated $[(tBu)_3P]\cdots [B(C_6F_5)_3]$ complex allows an easy entrance for the small H₂ molecule, which can reach the vicinity of the P···B axis of the adduct. In this bifunctional environment, the H₂ can interact with both active centers of the P–B pair, which directly lead to the heterolytic cleavage of the hydrogen molecule. In other words, the frustrated complex ensures for the hydrogen an unfilled empty orbital on boron and a donor orbital from the phosphorus in a spatiotemporal manner [12]. Thus, the FLP complex fulfills a similar function as the frontier orbitals on transition metals, although these frontier orbitals are secured by two nuclei.

After providing a reasonable mechanistic picture for the hydrogen activation by FLPs, one puzzling question remained—why do FLP systems have such a high reactivity? To understand this quandary better, one has to use a reference point which is a hypothetical classical Lewis pair having the same intrinsic acid–base properties. As can be concluded from this theoretical work (Fig. 3), the frustration has a deeper and broader meaning, it is not only a steric effect, but it also implies a strain, which can be utilized for bond activation. Accordingly, the frustration lowers the activation barrier and increases the exothermicity of the overall process by reactant-state destabilization.



Fig. 3 Frustration as a method to generate reactant-state destabilization.

The FLP concept has immediately attracted an immense scientific interest, and several groups made important and fundamental contributions [7]. Using steric hindrance as a critical design element, numerous inter- and intramolecular combinations of bulky Lewis acid–base pairs were effectively probed for the heterolytic cleavage of hydrogen (Scheme 1). This remarkable capacity of FLPs was then exploited in metal-free hydrogenation procedures first by Stephan [13], then later by Erker [14], and Repo and Rieger [15].



Scheme 1 Representative examples of FLP hydrogenation catalysts and their application in hydrogenations.

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Besides the area of FLP hydrogenation, several interesting FLP reactivities on a diverse set of substrates appeared in the literature (Fig. 4). As reported [7], the bifunctional and unquenched nature of the FLPs makes them capable of reacting with alkenes, dienes, acetylenes, isocyanides, N_2O [16], and CO_2 . While these reactivities definitively represent a breakthrough in main-group chemistry, its enhanced and non-orthogonal nature obviously limits the synthetic applicability of FLPs in the catalytic hydrogenation. Additional limitation stems from the hard-type nature of the applied LAs, because they could easily form an inhibitory dative complex with common organic molecules, such as tetrahydrofuran (THF).



Fig. 4 Selected examples of the reactivity of FLPs.

To address the issue of the broader utility in FLP hydrogenation, we envisioned that the LA component with sterically even more congested boron center may be advantageous [17]. Thus, the steric demands imposed on the boron center by additional proximal substituents are such that they can prevent or markedly decrease the complexation ability with normal Lewis bases but still allow the cleavage of the small hydrogen molecule. A potential drawback, however, is that the steric shielding around the boron center can be accompanied by decreased or lost FLP hydrogen splitting capacity. Therefore, not only the structure of the LA component, but also the size and steric demand of the LB component has to be tuned in order to generate an effective system for hydrogen activation. To use an analogy, a smaller ship size is necessary to explore narrow and out-of-the-way fjords that the big ships simply cannot enter. Additionally, we expected that the increased shielding around boron center could preclude the addition of this modified FLP to olefins, thus creating a unique opportunity to investigate the chemoselectivity of FLP hydrogenations.

The design concept for increased functional-group tolerance FLP hydrogenation catalyst is outlined in Fig. 5. The previously reported FLP hydrogen activation systems utilized mostly tris(pentafluorophenyl)borane (1), and we thought its slight modification could afford an improved FLP catalyst for hydrogenation. We selected mesitylborane $B(C_6F_5)_2(Mes)$ (2) (Mes = mesityl = 2,4,6-trimethylphenyl) as a possible bulky LA, because the ortho methyl groups were expected to render the boron atom even less accessible by common organic bases than that of 1. Besides the structural optimization of the LA component, it was obvious that we have to tune the LB component for the envisioned FLP. By combining sterically and electronically different commercially available amines with borane 2, we began to explore their utility in metal-free FLP hydrogenation of a bulky benzaldimine (Fig. 6) [18]. This study highlighted the importance of the dual optimization of both LA and LB components to attain capable FLP catalysts, and also supported the validity of the original idea. For example, there was a striking difference in the catalytic efficiency of TMP (5) or DABCO (6) based FLP systems that stemmed from their markedly different activity in the hydrogen activation.



Fig. 5 Illustration of the design concept for improved FLP hydrogenation catalysts.



Fig. 6 Optimization of Lewis base component for FLP hydrogenation.

Having identified the most efficient LA/LB combinations for metal-free hydrogenation, we began to investigate their scope, functional-group tolerance, and possible selectivity [16]. First, we selected substrates which were already studied in metal-free hydrogenations using the more active intramolecular FLP systems (Scheme 2). The obtained results demonstrated that the novel intermolecular FLP catalysts using DABCO or the related quinuclidine bases (2/6 and 2/7) showed the expected functional-group tolerance. Not only the methoxy functionality was tolerated in **8a**, but also the sterically less demanding enamine **8b** and benzyl imine **8c** underwent hydrogenation, although the efficiency of these processes was LB-dependent.

Next, the hydrogenation of more challenging substrates (8d-f) was probed. First, an allyloxy derivative 8d was evaluated. Similarly to the previous benzaldimines, smooth reduction to the secondary amine 9d took place. Most importantly, neither cleavage of the allyl group nor the FLP addition to the double bond occurred. Additionally, the reduction of the nonactivated double bond was not observed during the reaction. In an attempt to achieve chemoselective hydrogenation, the reduction of crotyl



Scheme 2 Hydrogenation of selected substrates to evaluate functional group selectivity and chemoselectivity.

imine **8e** was examined, but both imine and activated double bond functionalities were saturated in the case of FLP **2**/**7** catalyst. However, the efficiency of the processes again depends on the basicity of the LB constituent. Using the less efficient **2**/**6** pair, not only the reaction rate decreased but also the presence of an intermediate **9e'** with a saturated olefin bond could be detected. Finally, the reduction of carvone (**8f**) was probed because it is a frequently studied test reaction in transition-metal-based catalytic hydrogenation methods. Contrary to the conventional palladium- and platinum-catalyzed hydrogenation, the FLP catalyst **2**/**6** could selectively reduce the activated olefin bonds and afforded dihydrocarvone (**9f**), thus illustrating the power and potential of FLP-catalyzed hydrogenation. It is also

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remarkable that neither olefin migration nor terminal olefin saturation was observed. It seems plausible that the steric demands around the C=O bond in the substrate dictates the chemoselectivity of this metal-free hydrogenation.

SUMMARY

In summary, our theoretical work provided a reasonable mechanistic picture for the FLP hydrogen activation. The emerging model suggests the formation of a preorganized, loosely bound bifunctional precomplex held together by secondary interactions. This transient, energetically strained complex then acts as a highly reactive species for H–H bond activation. Additionally, based on a conceptual framework, we developed frustrated Lewis acid–base catalytic systems in which the enhanced steric shield-ing around the LA center could prevent or markedly decrease undesired FLP reactivities but still allowed the cleavage of the small hydrogen molecule. This simple modification allowed us to realize unprecedented orthogonal reactivity and chemoselectivity in FLP hydrogenation.

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