

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/154755/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Guerzoni, Michael G., Dasgupta, Ayan, Richards, Emma and Melen, Rebecca L. 2022. Enantioselective applications of frustrated Lewis pairs in organic synthesis. *Chem Catalysis* 2 (11) , pp. 2865-2875. 10.1016/j.checat.2022.09.007

Publishers page: <http://dx.doi.org/10.1016/j.checat.2022.09.007>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



# Enantioselective applications of frustrated Lewis pairs in organic synthesis

Michael G. Guerzoni,<sup>1</sup> Ayan Dasgupta,<sup>1,2</sup> Emma Richards,<sup>1</sup> and Rebecca L. Melen<sup>1,3,\*</sup>

## SUMMARY

The field of asymmetric catalysis has witnessed tremendous development since its discovery, and this has recently culminated in the Nobel prize given to Benjamin List and David MacMillan “for the development of asymmetric organocatalysis.” In this perspective, we aim to highlight a less-represented class of catalysts, which can be also employed in enantioselective transformations: cooperative main-group Lewis acids and Lewis bases. Since 2007, this concept has been strongly associated with the term frustrated Lewis pair (“FLP”). Chiral FLPs have been applied in hydrogenation reactions whereby the enantioselective transformation is accomplished by using an FLP containing either a chiral Lewis acid or a chiral Lewis base. Chiral intramolecular FLPs have also been employed for this purpose. This perspective will look at the recent developments in enantioselective FLP catalysis and will suggest new directions for the field, taking inspiration from the ongoing research in the area of enantioselective cooperative catalysis.

## INTRODUCTION

Asymmetric synthesis is the branch of chemistry that includes the construction of molecules while controlling the outcome of any stereogenic centers. Medicinal chemistry and agro-chemistry strongly rely on such reactions, given that changes in the absolute configuration of just one stereogenic center can have tremendous biological effects.<sup>1</sup> Although the first example of asymmetric synthesis was reported back in 1889 (now known as the Kiliani-Fischer synthesis),<sup>2</sup> it was not until the early 1950s that such chemistry found its deserved place among the synthetic community. In the same period, transition-metal catalysis was flourishing, and transition metals were used for many transformations, so it is not surprising that asymmetric synthesis has been strongly developed by relying on those elements in combination with chiral ligands.<sup>3</sup> However, in recent times, chemical research has shifted toward a greener and more sustainable approach, involving the elimination (or at least the reduction) of the use of transition metals that are known to be toxic as well as expensive.<sup>4,5</sup> In this regard, p-block elements have proved to be a valid alternative, so it is reasonable to consider asymmetric synthesis carried out by these elements instead.<sup>6</sup> A stepping stone into the application of main-group elements in synthetic transformations arose from Stephan and co-workers in 2006,<sup>7</sup> where a sterically encumbered Lewis acid (LA) and Lewis base (LB) cooperatively activated dihydrogen gas. Following this work, the term frustrated Lewis pair (FLP) became popular among the scientific community.<sup>8–10</sup> Although hydrogen activation and hydrogenation catalysis with metals is well reported, the FLP dihydrogen cleavage was the first example of reversible H<sub>2</sub> activation in the absence of metals.<sup>11,12</sup> The unquenched

## THE BIGGER PICTURE

Application of chiral Lewis acids or chiral Lewis bases in modern synthetic organic chemistry is one of the most common methods to induce asymmetry in chemical reactions and to afford molecules possessing defined stereochemical elements. Although high enantioselectivities (>98%) are often desired, it is not always possible to reach those values.

Difficulties arise also when multiple stereocenters are formed, since the enantiocontrol might be challenging to achieve. By employing the concept of frustrated Lewis pairs, which relies on two active sites working together to activate substrate(s), and by taking inspiration from cooperative catalysis, where “both the nucleophile and the electrophile are simultaneously activated by two separate and distinct catalysts to conduct a single chemical transformation,” it would be possible to develop an FLP system where both the Lewis acid and the Lewis base are chiral, establishing a chiral pocket between the two sites capable of inducing high degrees of enantioselectivity.

reactivities of FLPs cleave H<sub>2</sub> heterolytically to afford a LA-LB zwitterion species (activation step). This species can then transfer H<sub>2</sub> to an unsaturated substrate in a reduction reaction. For most substrates (such as imines or alkenes), proton transfer occurs first, followed by hydride attack from the LA component to the unsaturated substrate (hydride transfer step) to generate the hydrogenated product. This groundbreaking discovery prompted the birth of many works in the field of FLP reductions, especially of ketones and imines, among others.<sup>11</sup> Following the work developed by Noyori on the asymmetric hydrogenation of ketones,<sup>13</sup> the natural evolution in FLP chemistry has been directed toward accomplishing similar transformations with control of the stereogenic centers (Scheme 1). Given the fact that FLP systems rely on two sites that work cooperatively to raise the highest occupied molecular orbital (HOMO) and/or lower the lowest unoccupied molecular orbital (LUMO) of the reactant(s),<sup>14</sup> it might be inferred that by judicious choice of a chiral LA and LB, an FLP system can be developed that can catalyze the synthesis of enantioenriched molecules. This perspective aims to highlight recent developments in the field of chiral FLPs and to provide an outlook for new possibilities in the area of enantioselective FLP cooperative catalysis. This perspective is comprised of three sections: FLPs bearing chiral LAs, FLPs bearing chiral LBs, and chiral intramolecular FLPs, followed by an outlook for future directions in the field.

### Chiral LA components within an FLP

The majority of the reports of enantioselective FLP catalysis have focused on using chiral LAs. The reason for this is that typically in hydrogenation reactions (e.g., of imines, carbonyls), the LA (or rather its hydride) is responsible for delivering the hydrogen atom to the prochiral center. This section will focus on chiral LAs of the type R\*B(Ar<sup>F</sup>)<sub>2</sub> (Ar<sup>F</sup> = C<sub>6</sub>F<sub>5</sub>, p-HC<sub>6</sub>F<sub>4</sub>) (where R\* is chiral) as well as chiral borenium cations, which have been used with achiral LBs in an FLP fashion (Figure 1A). In R\*B(Ar<sup>F</sup>)<sub>2</sub> compounds, the enantioselectivity induced in a chemical reaction depends on the chiral ligand bound to the boron atom. In general, chiral LAs of the type R\*B(Ar<sup>F</sup>)<sub>2</sub> are synthesized from the hydroboration reaction between Piers' borane (HB(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>)<sup>15</sup> or HB(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> and a chiral auxiliary containing a ChC or C=C functionality. The chiral auxiliary can be divided into three main groups: chiral pool, binaphthyl, and spiro/bicyclic ligands.<sup>16–18</sup>

One of the earliest examples of enantioselective hydrogenations of imines, reported by Klankermayer and co-workers, employed a chiral LA (1) derived from (+)-α-pinene without the presence of an additional LB. In this scenario, the substrate (imine) acts as the LB component of the FLP. The chiral LA catalyst 1, in combination with the imine substrate, proved to be proficient in activating H<sub>2</sub> and simultaneously reducing the imine substrate, as evidenced by full conversion of the imine starting material to the amine product. However, low ees (13%) were obtained.<sup>19</sup> The poor enantioselectivity was attributed by the authors to the tendency of the borane to undergo isomerization via retrohydroboration and rehydroboration at room temperature, which in turn lowers the enantioselectivity.<sup>20,21</sup> However, a recent study on the origin of selectivity in FLP-type hydrogenation of imines proposed that the poor ee can be also attributed to the low chiral environment around the B–H bond of the borohydride active species.<sup>22</sup> Just two years later, the same group developed new chiral LAs (2 and 3) derived from (1R)-(+)-camphor. It was suggested that the aryl ring in the chiral camphor backbone is significant in leading to higher enantioselectivities (up to 83% with full conversion of the starting material into product) through interactions with one of the C<sub>6</sub>F<sub>5</sub> rings. In this case, it is important to highlight the need of an additional LB (PtBu<sub>3</sub>) to form the FLP with 2 or 3. In these reactions, the catalyst employed was the H<sub>2</sub>-activated species [2/3–H][H–PtBu<sub>3</sub>],

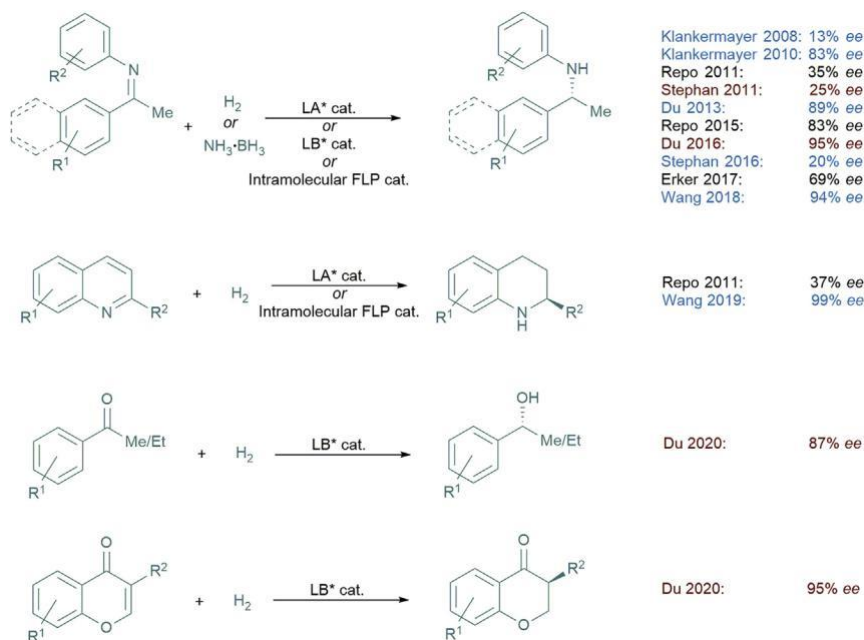
---

<sup>1</sup>Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT Cymru/Wales, UK

<sup>2</sup>Present address: Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK

<sup>3</sup>Lead contact

\*



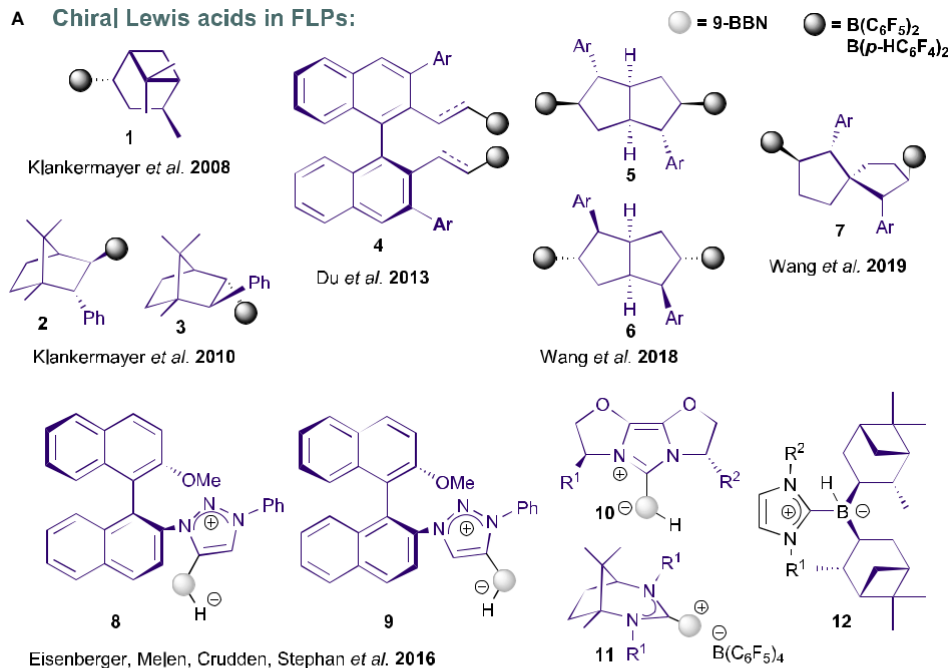
**Scheme 1. Representative substrates employed in enantioselective hydrogenation reactions** Blue: reductions accomplished by employing a chiral LA and an achiral LB. Red: reductions accomplished by employing a chiral LB and an achiral LA. Black: reductions accomplished by employing chiral intramolecular FLPs. Maximum ees in each reaction are reported.

with  $[2-H][H-PtBu_3]$  giving the best enantioselectivities. It was later demonstrated that the enantioselectivity with these types of catalysts can be altered and tuned by judicious choice of the aromatic ring on the chiral skeleton.<sup>19</sup>

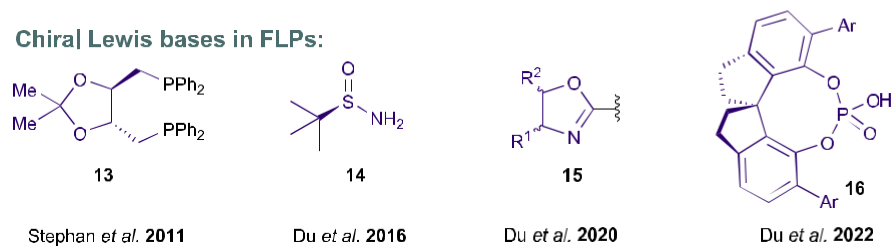
Another factor that is important for dictating the enantioselectivity in a reaction is the rigidity of the catalyst. In this regard, binaphthyl derivatives have become very popular as chiral ligands for the synthesis of a range of chiral LAs.<sup>23–25</sup> Their effectiveness is exemplified by the results of Du and co-workers, who employed compounds of type 4 in the hydrogenation of imines, enhancing the ee up to 89%.<sup>26</sup> In this reaction, the active catalyst 4 is generated in situ from the double hydroboration of a chiral binaphthyl terminal diene with  $HB(C_6F_5)_2$ . Subsequently, Du and co-workers have applied this approach to the asymmetric hydrogenation (up to 99% ee) of other sub-strates such as diimines, quinolines, quinoxalines, and silyl enol ethers using chiral binaphthyl-derived terminal dienes/diynes as the precatalyst.<sup>22</sup> While most enantio-selective FLP chemistry to date has focused on hydrogenation catalysis, it has also shown that these systems are also suitable catalysts for asymmetric hydrosilylation<sup>23,27,28</sup> and halocyclization<sup>29</sup> reactions.

During the thriving growth of enantioselective catalysis by means of chiral LAs, Wang et al. developed a class of chiral ligands for enantioselective FLP chemistry based upon bicyclo/spiro compounds. A rigid [3.3.0] fused bicyclopentane system (21; Scheme 2) was found to be a suitable chiral precursor.<sup>30</sup> Upon hydroboration of 21 with  $HB(C_6F_5)_2$ , the chiral LAs (5 or 6) were afforded. Interestingly, during the synthesis of the bicyclo catalyst, the authors discovered that the reaction temperature controls the formation of the product. When the *cis*-C<sub>2</sub>-symmetric bicyclic [3.3.0] diene 21 is exposed to  $HB(C_6F_5)_2$  or  $HB(p-HC_6F_4)_2$  at 25 C, anti-Markovnikov hydro-boration of both double bonds occurs, delivering the kinetic isomer 6, where the two Lewis acidic sites are on the less sterically hindered face.<sup>23</sup> However, when the same

**A Chiral Lewis acids in FLPs:**



**B Chiral Lewis bases in FLPs:**



**C Chiral intramolecular FLPs:**

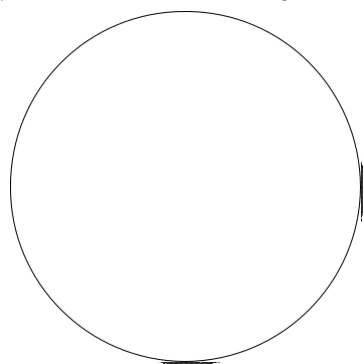
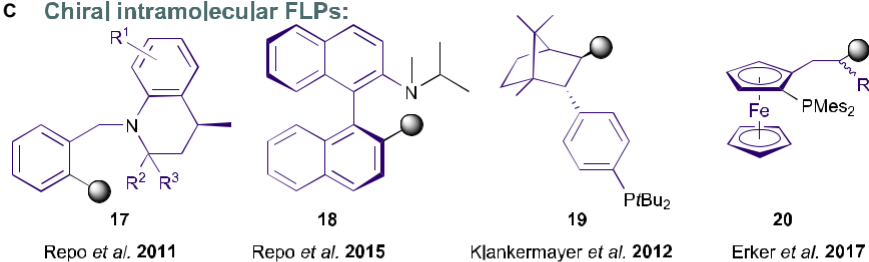


Figure 1. Overview of the chiral Lewis acids and Lewis bases employed in FLP-type chemistry

(A) Chiral Lewis acids employed in FLP chemistry.

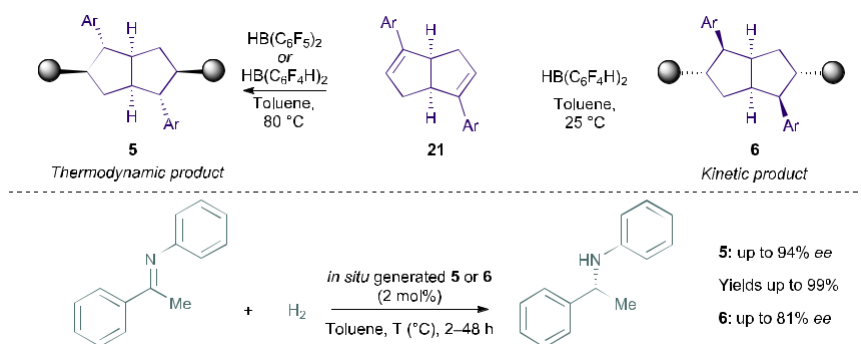
(B) Chiral Lewis bases employed in FLP chemistry.

(C) Chiral intramolecular FLPs.

reaction is carried out at 80 C, the thermodynamically controlled product 5 is observed, where the two Lewis acidic sites point toward each other on the same face of the bicyclic scaffold (Scheme 2, top). Interestingly, catalyst 5 or 6 is formed from 21 and HB(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> via four-membered ring transition states. Out of two possibilities, (1) addition of HB(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> to the unsaturated substrate from the bottom (cis to the hydrogen atoms on the fused carbon atoms) or (2) top (trans to the hydrogen atoms on the fused carbon atoms) face, the authors found that bottom-face addition required a lower activation barrier compared with top-face addition, which is more exothermic. Due to the large energy barrier, conversion of the kinetic isomer 6 to the thermodynamic isomer 5 was found to be not feasible at 25 C but was possible at 80 C. Furthermore, the authors concluded from the calculated energy profile diagram that the release of HB(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> from its dimeric form is quite endothermic, which accounts for its slow hydroboration at 25 C. These catalysts were then employed in the hydrogenation of imines with ees of up to 94% for the thermodynamic isomer 5 (Scheme 2, bottom). The authors observed that the formation of R enantiomer is energetically more favored compared with the S enantiomer. The superior selectivity of catalyst 5 compared with catalyst 6 was investigated by computational means. Density functional theory (DFT) calculations showed that, in the rate-limiting step (hydrogen activation), the ease of interaction between two Lewis acidic sites has a strong contribution to enantiocontrol due to several weak interactions between the two B(p-HC<sub>6</sub>F<sub>4</sub>). The ratio between the two enantiomers formed in the reaction was also found to be heavily dependent on the steric bulk brought by the two aryl (Ar) groups present on the bicyclic core in 21. When using more sterically demanding substituents such as Ar = p-tBuC<sub>6</sub>H<sub>4</sub> or Ar = m-tBu<sub>2</sub>C<sub>6</sub>H<sub>2</sub>, higher ees resulted than with smaller Ar = p-FC<sub>6</sub>H<sub>4</sub>. In a subsequent study, the same catalyst proved to be ineffective toward the reduction of quinolines, shining light on one of the major downsides of the highly acidic boranes often used in FLP chemistry: their tendency to strongly coordinate small molecules.

The lack of activity was attributed to the insufficient steric hindrance around the boron center of the catalyst, which was able to coordinate the substrate thereby poisoning itself.<sup>31</sup> Hence, a more sterically encumbered chiral LA was developed, based on a spiro-bicyclo ligand 7. The new spiro-bicyclic LA 7 was found to be even more proficient than the bicyclic compounds 5/6 due to the greater steric demand around the boron atom as well as the increased rigidity of the catalyst, promoting the asymmetric hydrogenation of differently functionalized quinolines with ees of up to 99% and yields up to 98%.

As seen above, one of the most common methods to make chiral LAs is to take a chiral unsaturated scaffold and subject it to hydroboration with HB(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub> to generate R\*B(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>. The inclusion of C<sub>6</sub>F<sub>5</sub> groups is necessary to increase the Lewis acidity of the boron center required for H<sub>2</sub> activation and catalysis. An alternative method to increase the Lewis acidity is to turn to borenium cations where the positive charge on the boron center renders them strong LAs. In this regard, Eisenberger, Melen, Crudden, Stephan et al. have laid the foundations for future developments in this field by employing chiral carbenes as ligands with easily accessible 9-BBN (8–11) or by using achiral carbenes with diisopinocampheylborane (Ipc<sub>2</sub>BH) (12).<sup>32</sup> Although the initial results proved to be unfruitful in terms of steric inductions (up



**Scheme 2. Hydrogenation of imines with a chiral bicyclic bisborane**

Top: active catalyst synthesis; bottom: reaction conditions and enantioselectivities obtained.

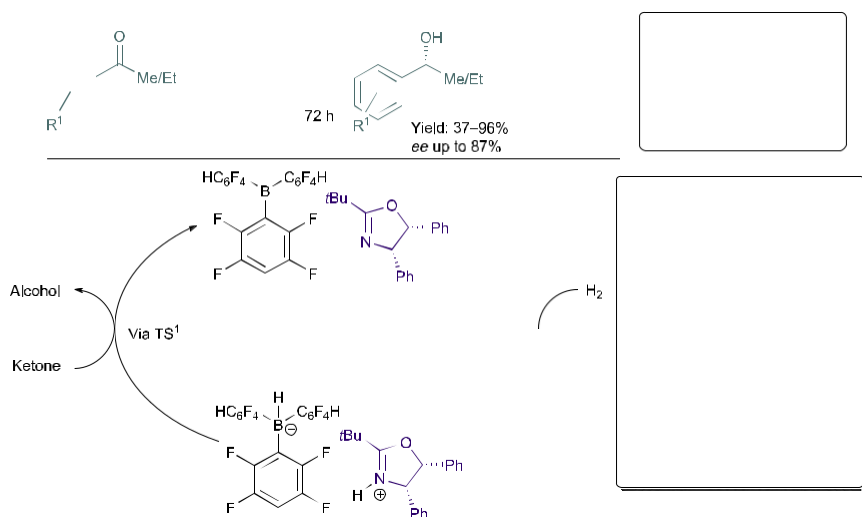
to 20% ee), some of the catalysts were proficient in hydrogenating imines with quantitative yields, indicating the potential for future development in this field.

From the above discussion, it can be understood that three main aspects need to be considered when designing chiral LAs for enantioselective FLP catalysis with high asymmetric inductions. Firstly, the stability of the catalyst is important, and processes such as retrohydroboration should be minimized. Secondly, a rigid catalyst is desirable to promote a tighter transition state. Finally, the bulkiness around the boron atom is significant to avoid poisoning of the catalyst with coordinating molecules. By keeping in mind these parameters, it is potentially possible to develop highly efficient chiral LAs that can be employed not only in FLP hydrogenation reactions with a suitable LB but also in other FLP- or LA-catalyzed reactions such as hydrosilylation, C–C bond formation, C–H and C–X activation, and cycloaddition reactions.<sup>33–38</sup>

### Chiral LB components within an FLP

Chiral LBs are commonplace as organocatalysts;<sup>39</sup> however, their application in enantioselective FLP catalysis is much less known (Figure 1B). According to the explanation given by Du and co-workers, the asymmetric induction by the LB tends to be heavily limited for two main reasons. Firstly, this can be due to the competition between the chiral LB and the achiral substrate (imine, ketone, etc.) with the LA, both of which can act as the LB component of the FLP. Secondly, this can be due to the order and position that the hydride (delivered by the LA) and the proton (delivered by the LB) are conveyed to the substrate.<sup>40</sup> For example, in the case of imine hydro-genation, initial protonation of the nitrogen by the chiral LB means there is no chiral environment close to the prochiral carbon atom of the imine, and little to no asymmetric induction arises. Moreover, as evidenced by the work of Pa'pai et al., when imines are reduced in FLP chemistry, the role of the LB is limited at best, since the imine itself can act as the LB in the FLP, giving rise to a much more stable and accessible transition state for the hydrogen transfer step.<sup>19</sup>

The first example of asymmetric induction involving a chiral Lewis basic component of an FLP in hydrogenation reactions was shown by the work of Stephan and co-workers in 2011. Here, the ligand (S,S)-DIOP (13) afforded the reduced aliphatic amine with only 25% ee, despite full conversion of the starting ketimine.<sup>41</sup> To date, due to the issues highlighted above, there are only a few further examples of enantioselective hydrogenation with an FLP system where the asymmetric induction is due to a chiral LB rather than a chiral LA. In 2016, a chiral tert-butylsulfonamide (14) was employed toward the reduction of imines with extremely high yields and ees (78%–99% and 84%–95%, respectively) using ammonia borane as a hydrogen



**Scheme 3.** Catalytic asymmetric hydrogenation of acetophenone by a chiral Lewis base and an achiral Lewis acid

Top: reaction scheme; bottom: catalytic cycle with configuration-determining transition state (insert).

source.<sup>42</sup> Interestingly, the active FLP catalyst is obtained by the reaction between the LA  $\text{HB}(\text{C}_6\text{F}_5)_2$  and the chiral LB tert-butylsulfonamide (14) generating 14/  $\text{BH}(\text{C}_6\text{F}_5)_2$ . In the presence of the imine substrate, a highly ordered eight-membered transition state is formed where the proton and hydride transfer occurs in a concerted fashion, giving a high degree of enantioselectivity in the reduced product generating the amine and  $\text{tBuS}(=\text{O})\text{NHB}(\text{C}_6\text{F}_5)_2$ . Hydrogenation of  $\text{tBuS}(=\text{O})\text{NHB}(\text{C}_6\text{F}_5)_2$  using ammonia borane then regenerates 14/ $\text{BH}(\text{C}_6\text{F}_5)_2$ . In 2020, a later study investigated the use of chiral oxazolines (15) as LBs in the FLP hydrogenation of ketones and enones. The weak Lewis basicity of oxazolines renders them suitable for the enantioselective hydrogenation of carbonyl compounds as they form strong Brønsted acids following  $\text{H}_2$  activation.<sup>43</sup> In this work, the authors exposed a series of prochiral ketones to various chiral bis-oxazoline/oxazoline- $\text{B}(\text{p}\text{-HC}_6\text{F}_4)_3$  FLPs to determine which chiral LB could give the best results in terms of yields and enantio-selectivities of the incipient alcohols. Notably  $\text{B}(\text{p}\text{-HC}_6\text{F}_4)_3$  was used as the LA component of the FLP due to its weaker Lewis acidity and therefore greater nucleophilicity of the hydride in the  $\text{H}_2$  activated species. In the optimization, it was re-revealed that the mono-oxazoline (15,  $\text{R}^1 = \text{R}^2 = \text{Ph}$ ) moiety gave the best yields and ees of up to 87% for acetophenone derivatives (Scheme 3). Aliphatic ketones were also reduced to the corresponding alcohols using the same chiral LB/achiral LA system, albeit the ees were drastically lower (50% ee). Calculations suggested that the high enantioselectivity was driven by non-covalent interactions (p-p and hydrogen bonding) in transition state  $\text{TS}^1$  (Scheme 3), which decreases the flexibility of the conformation in the transition state. The proton and hydride are then transferred in a concerted manner to the substrate. With non-aromatic substrates, such p-p interactions cannot occur, and therefore the ee is negatively affected. By slightly tuning the LA and the chiral oxazoline, this methodology could be extended to the reduction of enones derived from b-tetralone and 3-substituted chromones. These reactions were found to be regioselective toward the reduction of only the double bond with yields of 86%–99% and ees ranging from 33%–95%. The same group later demonstrated the asymmetric FLP hydrogenation of 3-fluorinated chromones using the chiral oxazoline/achiral borane FLP system, yielding 3-fluorinated chromanones in 89%–99% yields with 75%–88% ees.<sup>44</sup> From these results, it can be inferred that



to exploit chiral LBs in enantioselective FLP chemistry, it is crucial to consider all the possible non-covalent interactions between the FLP catalyst and the substrate, as well as the reaction mechanism, to prevent detachment of the chiral LB from the prochiral system before having performed the asymmetric induction. One concept to avoid some of the associated problems with competition for the LB was recently reported by Du. Here, the authors explored alternative approaches based upon relay catalysis by using an achiral borane and a chiral phosphoric acid for the asymmetric hydrogenation of chromones giving up to 95% ee.<sup>45</sup> Furthermore, in 2022, Du et al. reported the asymmetric transfer hydrogenation of benzoxazinones using a catalytic chiral phosphoric acid (16; 0.5 mol %) under H<sub>2</sub> in good to excellent yields (69%–98%) and ees (64%–99%). Dihydrophenanthridine was used as the hydrogen donor, and catalytic amounts (5 mol %) of borane LA [B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(4-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>] were employed to the reaction to swift the hydrogenation of phenanthridine for the regeneration of catalyst.<sup>46</sup>

Despite these remarkable examples, chiral LBs have found limited applications in asymmetric FLP hydrogenation for the reasons described above. However, a broader use of chiral LBs in FLP catalysis could be envisioned by taking inspiration from asymmetric organocatalysis<sup>47,48</sup>—a flourishing field for which David MacMillan and Benjamin List were recently awarded the Nobel Prize for their efforts toward the “development of asymmetric organocatalysis.” Moving away from hydrogenation, FLP catalysis taking advantage of nucleophilic organocatalysts<sup>49</sup> could be envisioned for other transformations. Likewise, inspiration could be taken from the work by Scheidt et al. on the cooperative catalysis by carbenes and LAs for the stereoselective synthesis of  $\gamma$ -lactams,<sup>50</sup> which shows a very strong parallelism with FLP chemistry whereby the cooperative action of an LB (carbene) and an LA (Mg<sup>2+</sup>) simultaneously activate the substrate(s). In their work, the authors uncovered the ability of a chiral LB derived from an N-heterocyclic carbene (NHC) to raise the HOMO of an  $\alpha,\beta$ -unsaturated aldehyde with a concomitant lowering of the LUMO of the N-acyl hydrazones by means of an achiral LA (Mg<sup>2+</sup>), with ees up to 97%. In our opinion, this concept of cooperative catalysis can be thus extended to FLP chemistry, where the frustration might lead to a chiral cooperation.

### Intramolecular chiral FLPs

The final class of chiral FLP systems are those in which the Lewis acidic and basic sites are embedded within the same scaffold (Figure 1C). It is evident that chiral intramolecular FLPs might be highly desirable when it comes to enantioselective transformations, since a system where both the active sites are on the same scaffold possesses fewer degrees of freedom, which in turn would make the transition state more ordered. In this regard, the first example of a chiral intramolecular FLP arises from the work of Repo et al.<sup>51</sup> In their seminal work, the authors described the synthesis of a so-called “ansa-amino borane” catalyst (17), which, upon hydrogen activation, forms an “ansa-ammonium borate,” capable of reducing a large variety of imines, including quinolines. Interestingly, the basicity of the amine within the chiral catalyst plays a pivotal role in the catalyst activity. Highly basic amines efficiently activated hydrogen but were less effective at delivering the proton to the imine substrate as they are weaker Brønsted acids. On the contrary, catalysts with less basic amines proved to be superior, as the resulting H<sub>2</sub> activated species has a weaker N–H bond (more Brønsted acidic). Although high conversions were obtainable (up to 100%), poor ees were observed (up to 37%). Improved results instead were obtained by the same group a few years later by changing the chiral backbone and using a bi-naphthyl skeleton (18).<sup>52</sup> The amino-borane binaphthyl scaffold showed improved control of chiral induction, allowing the reduction of imines and enamines with ees

of up to 99%. Remarkably, several positive aspects were found to be beneficial for both the activity and the asymmetric induction of the new catalyst: (1) the Lewis acidic site has been directly attached to the aromatic ring of the chiral binaphthyl fragment, hence preventing the known phenomenon of retrohydroboration; (2) due to the two perpendicular naphthyl moieties, the Lewis basic and acidic sites are positioned in close proximity to each other to form an FLP but are far enough in space to prevent mutual quenching; and (3) such close proximity prevented the catalyst from poisoning by the small amines formed in the reaction. Finally, DFT calculations showed once again how pivotal non-covalent interactions in the transition state for hydride transfer were for controlling the asymmetry in the reduction process. The transition state showed that the B–H functionality was embedded in a chiral environment, allowing selective hydride transfer to the iminium species.

Intramolecular B/P systems have also been developed, with one of the earliest examples being a derivative of the camphor borane 2 described earlier. Introduction of a *p*-tBu<sub>2</sub>P group to the phenyl ring afforded the intramolecular chiral FLP 19.<sup>53</sup> Application of the H<sub>2</sub> activated FLP in the hydrogenation of imines gave ees of up to 76%. Ferrocenyl derivatives with planar chirality have also been employed as scaffolds for intramolecular B/P FLPs. Initial studies using a planar-chiral ferrocene-based FLP (pS)-(20) (R = H) gave just 26% ee for imine reduction with H<sub>2</sub>.<sup>54</sup> Modification of this catalyst to introduce an additional chiral center next to the boron atom led to an improved catalyst (pS,R)-(20) (R = Ph), which gave ees of up to 70%.<sup>55</sup>

### Conclusions and outlook

In this short perspective, we highlight some of the recent advances and developments in enantioselective FLP chemistry. Although FLP chemistry has been flourishing for over 15 years, comparatively few studies have been undertaken in the realm of enantioselective transformations, and the field lags far behind that of transition-metal-catalyzed asymmetric reactions and enantioselective organocatalysis. However, recent studies in this field have demonstrated the potential for chiral FLPs in enantioselective catalysis to sustain further impactful discoveries in this area. To date, many examples in the literature include a chiral LA in an FLP system or utilize a chiral intramolecular FLP, both of which are challenging to synthesize. On the contrary, only a few examples are known so far where the LB is the chiral component in the FLP. However, experimental and computational understanding of reaction mechanisms and transition states have been crucial in understanding the enantiocontrol in these reactions.

By exploiting the ability of both the components within an FLP to raise the HOMO and lower the LUMO of the reactants, such systems could be exploited in a similar manner to that observed for cooperative catalysis. Cooperative catalysis, sometimes also referred to as cooperative dual catalysis,<sup>56</sup> contemporaneous dual catalysis,<sup>57</sup> or simply synergistic catalysis,<sup>58</sup> is a common tool available to the synthetic community where “both the nucleophile and the electrophile are simultaneously activated by two separate and distinct catalysts to conduct a single chemical transformation.”<sup>53</sup> This has clear parallels to FLP chemistry, where the two catalytic sites are kept separate and therefore active by steric frustration. Thus, inspiration for future directions in enantioselective FLP chemistry can be taken from the field of cooperative catalysis. This can lead to new chiral FLP catalysts as well as alternative reactions to the archetypal enantioselective FLP hydrogenation described in this perspective. An interesting concept would be to employ intermolecular FLPs with a chiral LA and a chiral LB to develop selective and fully stereodivergent methods to access chiral molecules containing multiple stereocenters, such as that reported for metal/ amine-based systems elegantly shown by Carreira and co-workers in 2013.<sup>59</sup>

## Resource availability

### Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Prof. Rebecca L. Melen ([MelenR@cardiff.ac.uk](mailto:MelenR@cardiff.ac.uk)).

## Materials availability

This study did not generate new materials.

## Data and code availability

This study did not generate any datasets.

## ACKNOWLEDGMENTS

M.G.G., E.R., A.D., and R.L.M. would like to acknowledge the Leverhulme Trust for Funding (RPG-2020-016).

## AUTHOR CONTRIBUTIONS

Writing – original draft, M.G.G. and R.L.M.; writing – review & editing, M.G.G., E.R., A.D., and R.L.M.; funding acquisition, E.R. and R.L.M.; supervision, E.R. and R.L.M.

## DECLARATION OF INTERESTS

R.L.M. is on the journal's editorial advisory board.

## REFERENCES

- Brooks, W.H., Guida, W.C., and Daniel, K.G. (2011). The Significance of chirality in drug design and development. *Curr. Top. Med. Chem.* 11, 760–770. <https://doi.org/10.2174/156802611795165098>.
- Fischer, E., and Hirschberger, J. (Ueber Mannose. II, 1889). *Ber. Dtsch. Chem. Ges.* 22, 365–376. DOI: 10.1002/cber.188802101343
- Hayashi, T., and Kumada, M. (1982). Asymmetric synthesis catalyzed by transition-metal complexes with functionalized chiral ferrocenylphosphine ligands. *Acc. Chem. Res.* 15, 395–401. <https://doi.org/10.1021/ar00084a003>.
- Clark, J.H. (1999). Green chemistry: challenges and opportunities. *Green Chem.* 1, 1–8. <https://doi.org/10.1039/a807961g>.
- Hunter, P. (2015). Essentially deadly: living with Humans and plants have evolved various mechanisms to deal with and even adopt toxic heavy metals. *EMBO Rep.* 16, 1605–1608. <https://doi.org/10.15252/embr.201541601>.
- Power, P.P. (2010). Main-group elements as transition metals. *Nature* 463, 171–177. <https://doi.org/10.1038/nature08634>.
- Welch, G.C., San Juan, R.R., Masuda, J.D., and Stephan, D.W. (2006). Reversible, metal-free hydrogen activation. *Science* 314, 1124–1126. <https://doi.org/10.1126/science.1134230>.
- Stephan, D.W. (2008). Frustrated Lewis pairs: a concept for new reactivity and catalysis. *Org. Biomol. Chem.* 6, 1535–1539. <https://doi.org/10.1039/b802575b>.
- Stephan, D.W., and Erker, G. (2015). Frustrated Lewis pair chemistry: development and perspectives. *Angew. Chem. Int. Ed. Engl.* 54, 6400–6441. <https://doi.org/10.1002/anie.201409800>.
- Stephan, D.W. (2021). Diverse uses of the reaction of frustrated Lewis pair (FLP) with hydrogen. *J. Am. Chem. Soc.* 143, 20002–20014. <https://doi.org/10.1021/jacs.1c10845>.
- Lam, J., Szkop, K.M., Mosafari, E., and Stephan, D.W. (2019). FLP catalysis: main group hydrogenations of organic unsaturated substrates. *Chem. Soc. Rev.* 48, 3592–3612. <https://doi.org/10.1039/C8CS00277K>.
- Li, N., and Zhang, W. (2020). Frustrated Lewis Pairs: discovery and overviews in catalysis. *Chin. J. Chem.* 38, 1360–1370. <https://doi.org/10.1002/cjoc.202000027>.
- Noyori, R., Ohkuma, T., Kitamura, M., Takaya, H., Sayo, N., Kumobayashi, H., and Akutagawa, S. (1987). Asymmetric hydrogenation of *b*-keto carboxylic esters. A practical, purely chemical access to *b*-hydroxy esters in high enantiomeric purity. *J. Am. Chem. Soc.* 109, 5856–5858. <https://doi.org/10.1021/ja00253a051>.
- Moberg, C. (2015). Lewis acid-lewis base catalysis. *Coop. Catal.* 35–66. <https://doi.org/10.1002/9783527681020.ch2>.
- Parks, D.J., von H Spence, R.E., and Piers, W.E. (1995). Bis(pentafluorophenyl)borane: synthesis, properties, and hydroboration chemistry of a highly electrophilic borane reagent. *Angew. Chem. Int. Ed. Engl.* 34, 809–811. <https://doi.org/10.1002/anie.199508091>.
- Meng, W., Feng, X., and Du, H. (2020). Asymmetric catalysis with chiral frustrated Lewis pairs. *Chin. J. Chem.* 38, 625–634. <https://doi.org/10.1002/cjoc.202000011>.
- Shi, L., and Zhou, Y.-G. (2015). Enantioselective metal-free hydrogenation catalyzed by chiral frustrated Lewis pairs. *ChemCatChem* 7, 54–56. <https://doi.org/10.1002/cctc.201402838>.
- Paradies, J. (2018). Chiral borane-based Lewis acids for metal free hydrogenations. *Chiral Lewis Acids* 62, 193–216. [https://doi.org/10.1007/3418\\_2016\\_173](https://doi.org/10.1007/3418_2016_173).
- Chen, D., and Klankermayer, J. (2008). Metal-free catalytic hydrogenation of imines with tris(perfluorophenyl) borane. *Chem. Commun.* 2130–2131. <https://doi.org/10.1039/b801806e>.
- Parks, D.J., Piers, W.E., and Yap, G.P.A. (1998). Synthesis, properties, and hydroboration activity of the highly electrophilic borane bis(pentafluorophenyl)borane, HB(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>. *Organometallics* 17, 5492–5503. <https://doi.org/10.1021/om980673e>.
- Chen, D., Wang, Y., and Klankermayer, J. (2010). Enantioselective hydrogenation with chiral frustrated Lewis Pairs. *Angew. Chem. Int. Ed. Engl.* 49, 9475–9478. <https://doi.org/10.1002/anie.201004525>.
- Hamza, A., Sorochkina, K., Ko'tai, B., Chernichenko, K., Berta, D., Bolte, M., Nieger, M., Repo, T., and Pa'pai, I. (2020). Origin of stereoselectivity in FLP-catalyzed asymmetric hydrogenation of imines. *ACS Catal.* 10, 14290–14301. <https://doi.org/10.1021/acscatal.0c04263>.
- Ren, X., and Du, H. (2016). Chiral frustrated Lewis pairs catalyzed highly enantioselective hydrosilylations of 1, 2-dicarbonyl compounds. *J. Am. Chem. Soc.* 138, 810–813. <https://doi.org/10.1021/jacs.5b13104>.

24. Meng, W., Feng, X., and Du, H. (2018). Frustrated Lewis pairs catalyzed asymmetric metal-free hydrogenations and hydrosilylations. *Acc. Chem. Res.* 51, 191–201. <https://doi.org/10.1021/acs.accounts.7b00530>.
25. Feng, X., Meng, W., and Du, H. (2022). Chiral dienes: from ligands to FLP catalysts. *Chin. J. Chem.* 40, 1109–1116. <https://doi.org/10.1002/cjoc.202100854>.
26. Liu, Y., and Du, H. (2013). Chiral dienes as “ligands” for borane-catalyzed metal-free asymmetric hydrogenation of imines. *J. Am. Chem. Soc.* 135, 6810–6813. <https://doi.org/10.1021/ja4025808>.
27. Liu, X., Wang, Q., Han, C., Feng, X., and Du, H. (2019). Chiral frustrated Lewis pairs catalyzed highly enantioselective hydrosilylations of ketones. *Chin. J. Chem.* 37, 663–666. <https://doi.org/10.1002/cjoc.201900121>.
28. Du, H., Ren, X., Han, C., and Feng, X. (2017). A borane-catalyzed metal-free hydrosilylation of chromones and flavones. *Synlett* 28, 2421–2424. <https://doi.org/10.1055/s-0036-1588474>.
29. Han, C., Feng, X., and Du, H. (2021). Asymmetric halocyclizations of 2-vinylbenzyl alcohols with chiral FLPs. *Org. Lett.* 23, 7325–7329. <https://doi.org/10.1021/acs.orglett.1c02361>.
30. Tu, X.S., Zeng, N.N., Li, R.Y., Zhao, Y.Q., Xie, D.Z., Peng, Q., and Wang, X.C. (2018). C2-Symmetric bicyclic bisborane catalysts: kinetic or thermodynamic products of a reversible hydroboration of dienes. *Angew. Chem. Int. Ed. Engl.* 57, 15096–15100. <https://doi.org/10.1002/anie.201808289>.
31. Li, X., Tian, J.J., Liu, N., Tu, X.S., Zeng, N.N., and Wang, X.C. (2019). Spiro-bicyclic bisborane catalysts for metal-free chemoselective and enantioselective Hydrogenation of quinolines. *Angew. Chem. Int. Ed. Engl.* 58, 4664–4668. <https://doi.org/10.1002/anie.201900907>.
32. Lam, J., Guñther, B.A.R., Farrell, J.M., Eisenberger, P., Bestvater, B.P., Newman, P.D., Melen, R.L., Crudden, C.M., and Stephan, D.W. (2016). Chiral carbene-borane adducts: precursors for borenium catalysts for asymmetric FLP hydrogenations. *Dalton Trans.* 45, 15303–15316. <https://doi.org/10.1039/c6dt02202b>.
33. Crudden, C.M., Glasspoole, B.W., and Lata, C.J. (2009). Expanding the scope of transformations of organoboron species: carbon-carbon bond formation with retention of configuration. *Chem. Commun.* 2009, 6704–6716. <https://doi.org/10.1039/b911537d>.
34. Kan, S.B.J., Huang, X., Gumulya, Y., Chen, K., and Arnold, F.H. (2017). Genetically programmed chiral organoborane synthesis. *Nature* 552, 132–136. <https://doi.org/10.1038/nature24996>.
35. Nori, V., Pescioli, F., Sinibaldi, A., Giorgianni, G., and Carlone, A. (2022). Boron-based Lewis acid catalysis: challenges and perspectives. *Catalysts* 12, 5. <https://doi.org/10.3390/catal12010005>.
36. Rao, B., and Kinjo, R. (2018). Boron-based catalysts for C C bond-formation reactions. *Chem. Asian J.* 13, 1279–1292. <https://doi.org/10.1002/asia.201701796>.
37. Li, F., Tian, D., Fan, Y., Lee, R., Lu, G., Yin, Y., Qiao, B., Zhao, X., Xiao, Z., and Jiang, Z. (2019). Chiral acid-catalyzed enantioselective C H functionalization of toluene and its derivatives driven by visible light. *Nat. Commun.* 10, 1774. <https://doi.org/10.1038/s41467-019-09857-9>.
38. Zhang, M., and Wang, X.C. (2021). Bifunctional borane catalysis of a hydride transfer/enantioselective [2+2] cycloaddition cascade. *Angew. Chem. Int. Ed. Engl.* 60, 17185–17190. <https://doi.org/10.1002/anie.202106168>.
39. Denmark, S.E., and Beutner, G.L. (2008). Lewis base catalysis in organic synthesis. *Angew. Chem. Int. Ed. Engl.* 47, 1560–1638. <https://doi.org/10.1002/anie.200604943>.
40. Gao, B., Feng, X., Meng, W., and Du, H. (2020). Asymmetric hydrogenation of ketones and enones with chiral Lewis base derived frustrated Lewis pairs. *Angew. Chem. Int. Ed. Engl.* 132, 4528–4534. <https://doi.org/10.1002/ange.201914568>.
41. Stephan, D.W., Greenberg, S., Graham, T.W., Chase, P., Hastie, J.J., Geier, S.J., Farrell, J.M., Brown, C.C., Heiden, Z.M., Welch, G.C., and Ullrich, M. (2011). Metal-free catalytic hydrogenation of polar substrates by frustrated Lewis pairs. *Inorg. Chem.* 50, 12338–12348. <https://doi.org/10.1021/ic200663v>.
42. Li, S., Li, G., Meng, W., and Du, H. (2016). A Frustrated Lewis pair catalyzed asymmetric transfer hydrogenation of imines using ammonia borane. *J. Am. Chem. Soc.* 138, 12956–12962. <https://doi.org/10.1021/jacs.6b07245>.
43. Gao, B., Feng, X., Meng, W., and Du, H. (2020). Asymmetric hydrogenation of ketones and enones with chiral Lewis base derived frustrated Lewis pairs. *Angew. Chem. Int. Ed. Engl.* 59, 4498–4504. <https://doi.org/10.1002/ange.201914568>.
44. Dai, Y., Meng, W., Feng, X., and Du, H. (2022). Chiral FLP-catalyzed asymmetric hydrogenation of 3-fluorinated chromones. *Chem. Commun.* 58, 1558–1560. <https://doi.org/10.1039/d1cc06964k>.
45. Chen, J., Gao, B., Feng, X., Meng, W., and Du, H. (2021). Relay catalysis by achiral borane and chiral phosphoric acid in the metal-free asymmetric hydrogenation of chromones. *Org. Lett.* 23, 8565–8569. <https://doi.org/10.1021/acs.orglett.1c03286>.
46. Gao, B., Meng, W., Feng, X., and Du, H. (2022). Regenerable dihydrophenanthridine via borane-catalyzed hydrogenation for the asymmetric transfer hydrogenation of benzoxazinones. *Org. Lett.* 24, 3955–3959. <https://doi.org/10.1021/acs.orglett.2c01314>.
47. Xiang, S.-H., and Tan, B. (2020). Advances in asymmetric organocatalysis over the last 10 years. *Nat. Commun.* 11, 3786. <https://doi.org/10.1038/s41467-020-17580-z>.
48. MacMillan, D.W.C. (2008). The advent and development of organocatalysis. *Nature* 455, 304–308. <https://doi.org/10.1038/nature07367>.
49. Hyodo, K., and Nakamura, S. (2020). Catalytic enantioselective decarboxylative nucleophilic addition reactions using chiral organocatalysts. *Org. Biomol. Chem.* 18, 2781–2792. <https://doi.org/10.1039/D0OB00127A>.
50. Raup, D.E.A., Cardinal-David, B., Holte, D., and Scheidt, K.A. (2010). Cooperative catalysis by carbenes and Lewis acids in a highly stereoselective route to  $\gamma$ -lactams. *Nat. Chem.* 2, 766–771. <https://doi.org/10.1038/nchem.727>.
51. Sumerin, V., Chernichenko, K., Nieger, M., Leskela, M., Rieger, B., and Repo, T. (2011). Highly active metal-free catalysts for hydrogenation of unsaturated nitrogen-containing compounds. *Adv. Synth. Catal.* 353, 2093–2110. <https://doi.org/10.1002/adsc.201100206>.
52. Lindqvist, M., Borre, K., Axenov, K., Ko'tai, B., Nieger, M., Leskela, M., Pa'pai, I., and Repo, T. (2015). Chiral molecular tweezers: synthesis and reactivity in asymmetric hydrogenation. *J. Am. Chem. Soc.* 137, 4038–4041. <https://doi.org/10.1021/ja512658m>.
53. Ghattas, G., Chen, D., Pan, F., and Klankermayer, J. (2012). Asymmetric hydrogenation of imines with a recyclable chiral frustrated Lewis pair catalyst. *Dalton Trans.* 41, 9026–9028. <https://doi.org/10.1039/C2DT30536D>.
54. Wang, X., Kehr, G., Daniliuc, C.G., and Erker, G. (2014). Internal adduct formation of active intramolecular C4-bridged frustrated phosphane/borane Lewis pairs. *J. Am. Chem. Soc.* 136, 3293–3303. <https://doi.org/10.1021/ja413060u>.
55. Ye, K., Wang, X., Daniliuc, C.G., Kehr, G., and Erker, G. (2017). A ferrocene-based phosphane/borane Frustrated Lewis pair for asymmetric imine reduction. *Eur. J. Inorg. Chem.* 2017, 368–371. <https://doi.org/10.1002/ejic.201600834>.
56. Sammis, G.M., Danjo, H., and Jacobsen, E.N. (2004). Cooperative Dual Catalysis : Application to the Highly Enantioselective Conjugate Cyanation of Unsaturated Imides. *J. Am. Chem. Soc.* 126, 9928–9929. <https://doi.org/10.1021/ja046653n>.
57. Trost, B.M., and Luan, X. (2011). Contemporaneous dual catalysis by coupling highly transient nucleophilic and electrophilic intermediates generated in situ. *J. Am. Chem. Soc.* 133, 1706–1709. <https://doi.org/10.1021/ja110501v>.
58. Allen, A.E., and Macmillan, D.W.C. (2012). Synergistic catalysis : a powerful synthetic strategy for new reaction development. *Chem. Sci.* 2012, 633–658. <https://doi.org/10.1039/c2sc00907b>.
59. Krautwald, S., Sarlah, D., Schafroth, M.A., and Carreira, E.M. (2013). Enantio- and diastereodivergent dual catalysis:  $\alpha$ -Allylation of branched aldehydes. *Science* 340, 1065–1068. <https://doi.org/10.1039/c2sc00907b>.