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# Advancing Metal-Free Asymmetric Hydrogenation: From FLP Catalyst Design to Synthetic Innovations

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*Abstract:* Asymmetric hydrogenation (AH) is one of the most important transformations in organic synthesis, enabling efficient access to enantioenriched molecular building blocks used in pharmaceuticals, agrochemicals, and fine chemicals. AH is largely dominated by catalysts based on precious transition-metals. However, concerns over cost, supply, and toxicity have intensified interest in developing metal-free alternatives. Frustrated Lewis pairs (FLPs) – combinations of sterically encumbered Lewis acids and bases – have emerged as a promising metal-free platform for AH, yet they face significant challenges that must be addressed to enable widespread adoption. Our group aims to contribute to this effort by developing new chiral FLP catalysts for AH and exploring FLP-mediated transformations beyond hydrogenation. In this perspective, we summarize the state-of-the-art, outline current challenges, and discuss opportunities to advance the field towards sustainable catalysis.

**Keywords:** Asymmetric synthesis · Boron catalysis · Frustrated Lewis pairs · Homogeneous hydrogenation

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## 1. Introduction

Few catalytic transformations have shaped organic synthesis as profoundly as homogeneous asymmetric hydrogenations (AHs), which are widely used in academia and industry to convert simple unsaturated substrates into enantiomerically enriched products.[1,2] Within the broad toolkit of asymmetric methods,[3] AHs stand out for their high efficiency, scalability, and the use of dihydrogen ($H_2$) as a clean and inexpensive reductant. Historically, AHs have relied on precious transition-metal catalysts, which deliver excellent performance across diverse substrates.[2] Notable industrial applications include the Ir-catalyzed synthesis of (*S*)-Metolachlor (>100 kilotons annually),[4] and the Rh-catalyzed production of L-DOPA.[5]

Reliance on precious metals, however, raises sustainability concerns: they are scarce, their prices are volatile, and their toxicity has prompted increasingly strict regulations on residual metal content in pharmaceuticals and fine chemicals.[6] This has created strong incentives to develop alternative catalytic systems that reduce or eliminate metal use. While bio- and organocatalysis have revolutionized asymmetric synthesis – achievements recognized by the 2018 and 2021 Nobel Prizes in Chemistry – effective metal-free catalysts remain underdeveloped for transformations requiring activation of small molecules with strong chemical bonds, such as hydrogenations (bond dissociation energy of $H_2$ = 104 kcal·mol$^{-1}$).[7]

Motivated by this challenge, our group has joined efforts to advance metal-free AHs through the rational design of chiral frustrated Lewis pairs (FLPs).[8] In this perspective, we highlight the current state of FLP-catalyzed AHs, discuss key challenges, and outline opportunities for future development. For brevity, we focus on selected representative examples and direct interested readers to recent reviews for comprehensive coverage.[9,10]

## 2. Hydrogenation With Frustrated Lewis Pairs (FLPs)

In 2006, Stephan and coworkers reported a seminal discovery: a sterically encumbered borane Lewis acid (LA) and a phosphine Lewis base (LB) could synergistically split $H_2$ in a heterolytic fashion (Scheme 1A).[11] Steric hindrance prevented formation of a classical LA–LB adduct, leaving the pair 'frustrated' and thus reactive towards $H_2$. This breakthrough represented the first example of reversible, metal-free $H_2$ activation and shortly after enabled the first catalytic hydrogenation of imines without metals.[12]

The general mechanism of FLP-catalyzed hydrogenation is shown in Scheme 1B.[13] The cycle begins with heterolytic cleavage of $H_2$, generating a hydridic LA–H$^-$ and a protonated

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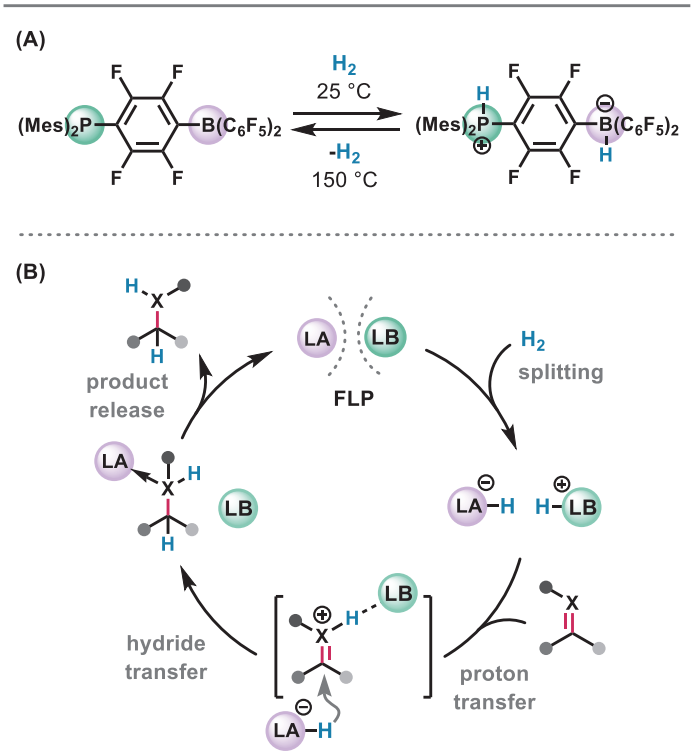



Scheme 1. Frustrated Lewis Pairs: discovery (A) and general hydrogenation mechanism (B).

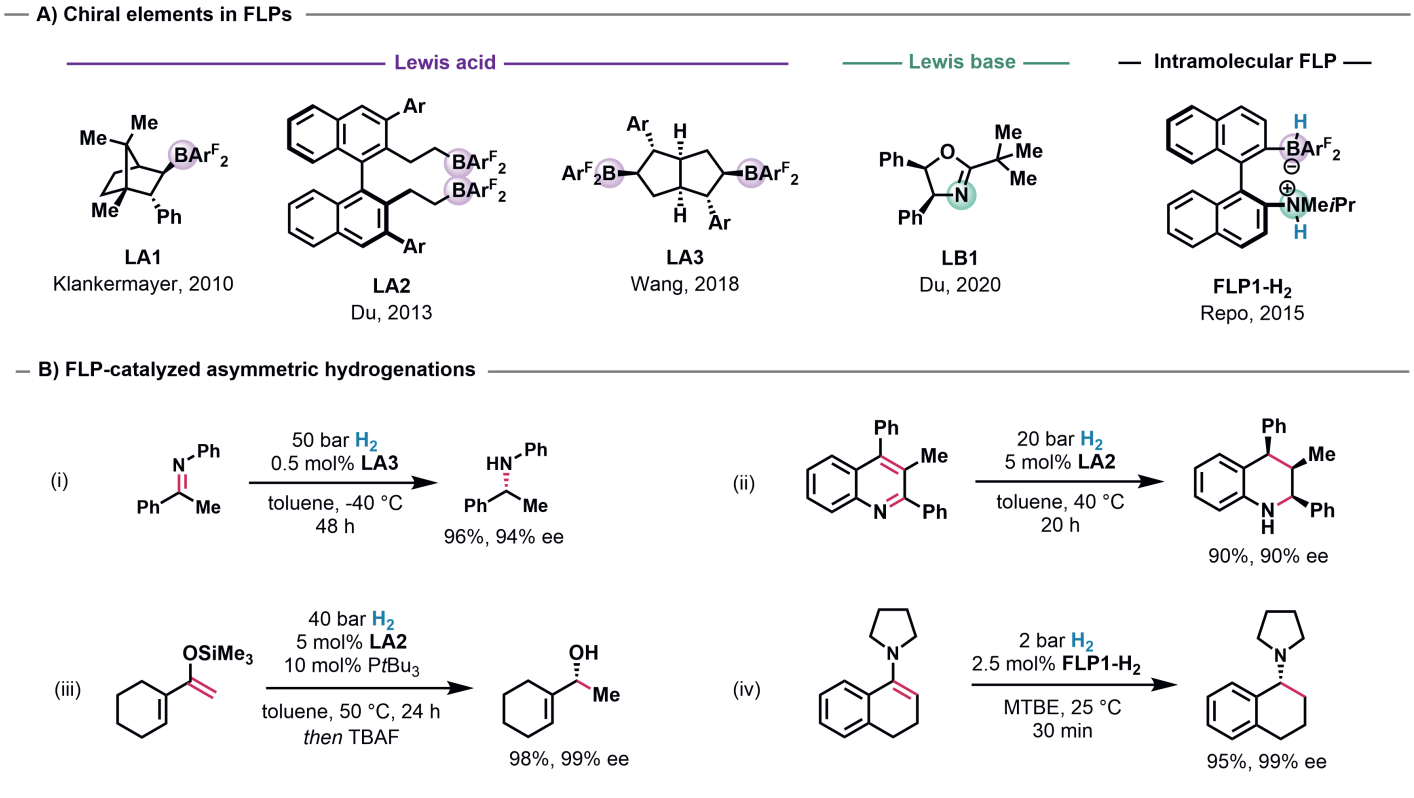
LB–H⁺ species. Hydrogenation then proceeds typically *via* protonation of the unsaturated substrate by LB–H⁺, which activates it electrophilically for subsequent hydride delivery from LA–H⁻. Product release regenerates the FLP, closing the catalytic cycle. Since these pioneering reports, FLP chemistry has expanded impressively, now encompassing the activation of other small molecules (*e.g.* $CO_2$, $N_2O$) and strong chemical bonds, with applications ranging from organic synthesis to polymerizations.[14–17] Recognizing its transformative potential, IUPAC recently listed FLPs among its 2024 Top Ten Emerging Technologies in Chemistry, citing them as "*innovations with outstanding potential to open new opportunities in chemistry, sustainability, and beyond*."[18]

### 2.1 *State-of-the-art in Asymmetric Hydrogenation*

To date, several chiral FLP catalysts for asymmetric hydrogenation (AH) have been developed,[9,10] which can be broadly grouped into three categories based on the source of chirality (Scheme 2A):

i) **Chiral Lewis acids (LA*)**. This is the most explored approach, which relies on the chiral LA to enantioselectively deliver the hydride to the prochiral substrate. A pioneering example is the camphor-derived borane **LA1** reported by Klankermayer and coworkers in 2010,[19] which in combination with tri-*tert*-butyl phosphine ($t$Bu$_3$P) as the LB, catalyzed imine AH to chiral amines with up to 20 turnovers (TON) and 83% *ee*. Later catalyst developments include Du's axially chiral bis-borane **LA2**[20] and Wang's bicyclic bis-borane **LA3**,[21] both of which showed excellent performance in imine AH. Notably, **LA3** achieved 200 TON – among the highest activities reported in FLP-catalyzed AH – and enantioselectivities of up to 94% *ee* in *N*-aryl ketimine reduction (Scheme 2B-i). **LA2** also promoted hydrogenation of aza-heteroarenes; for example, it afforded multisubstituted tetrahydroquinolines with high enantio- and diastereoselectivity (Scheme 2B-ii).[22] In these cases, the substrates themselves served as the LB. Furthermore, combining **LA2** with $t$Bu$_3$P as the LB gave access to chiral alcohols from silyl enol ethers (Scheme 2B-iii).[23]

ii) **Chiral Lewis bases (LB*)**. Here, stereocontrol arises from the protonated chiral LB (LB–H⁺), which can be viewed as a 'chiral proton' that transfers H⁺ to the substrate, directing the subsequent




Scheme 2. Selected examples of chiral FLP components and their application in asymmetric hydrogenation.

facial-selective hydride delivery. This approach is less developed because the chiral LB may compete with basic substrates for FLP formation and may dissociate from the protonated substrate before hydride transfer, both of which undermine stereocontrol. A notable example is Du's oxazoline-based **LB1**, which enabled metal-free AH of carbonyl compounds (see Section 2.3).[24]

iii) **Intramolecular FLPs**. Here, the chiral information is embedded in a single scaffold that covalently links the LA and LB. These systems often exhibit efficient $H_2$ activation due to entropically favored LA–LB preorganization,[13,25] but their reduced synthetic modularity compared with intermolecular congeners has limited their exploration. A representative example is Repo's axially chiral binaphthyl-derived ammonium–borohydride **FLP1–H$_2$**,[26] which hydrogenates *N*-alkyl imines and enamines with up to 99% *ee* under mild conditions (2 bar $H_2$, 25 °C; Scheme 2B-iv).

### 2.2 *Remaining Challenges*

Although remarkable advances have been achieved, several challenges remain that must be addressed for FLPs to become broadly adopted in AH. These include:

– **Moisture sensitivity**. Because boron is highly oxophilic, most FLPs are readily deactivated by water or hydroxyl-containing molecules and therefore require rigorously anhydrous conditions and glovebox handling. Elegant strategies such as decreasing Lewis acidity, sterically shielding the boron center, or replacing boron with less oxophilic elements (*e.g.* tin) have improved stability,[27] but were mainly demonstrated in achiral systems. Chiral FLPs remain generally intolerant to moisture.

– **Recyclability**. FLP catalyst recovery is rare and often labor-intensive.[28,29] A promising direction involves combining chiral FLPs with porous covalent organic frameworks (COFs), which was recently applied to the AH of α,β-unsaturated esters and enabled catalyst reuse for five cycles with negligible activity loss.[30]

– **Substrate scope**. Current applications of FLP-catalyzed AH are largely restricted to aza-unsaturated substrates (imines, aza-arenes).[9] Other valuable classes, such as ketones or unactivated olefins, remain elusive. This contrasts with the well-established AH of ketones and olefins using transition-metal catalysts.[31]

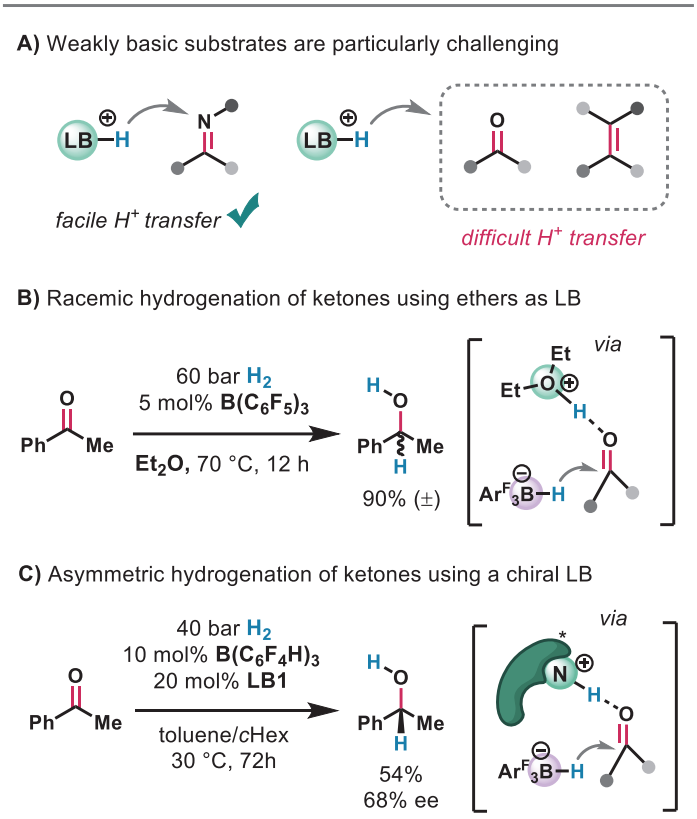
Addressing these shortcomings is essential to translate the conceptual appeal of FLPs into a widely adopted AH platform.

### 2.3 *Expanding the Substrate Scope*

The stronger performance of existing FLPs with imines and related aza-substrates is generally attributed to two main factors. First, these substrates can act as LBs themselves and form effective FLPs; second, their relatively high Brønsted basicity ($pK_aH \approx 6$)[32] facilitates proton transfer from the LB–H$^+$ species, a key step in the catalytic cycle.[13] In contrast, weakly basic substrates such as ketones or unfunctionalized olefins are far more difficult to protonate, and therefore pose a greater challenge for FLP-catalyzed hydrogenation (Scheme 3A).

A clever workaround was introduced by Stephan and coworkers, who exploited ether solvents as the LB.[33] Upon $H_2$ activation, the resulting protonated ethers are strong Brønsted acids ($pK_a \approx -3$),[32] being capable of efficiently protonating weakly basic substrates. This strategy enabled hydrogenation of olefins and ketones, although in a racemic fashion (Scheme 3B).[33–35] Importantly, ethers bind reversibly to the boron LA, preventing its deactivation despite boron's high oxophilicity. Remarkably, these systems also exhibit enhanced moisture tolerance, allowing practical open-air reaction setups.[36,37]

Despite these advances, enantioselective variants remain underdeveloped. To date, the only reported example is Du's 2020 study on AH of carbonyl compounds (Scheme 3C).[24] The authors employed an FLP composed of a chiral oxazoline **LB1** and an achiral borane LA. Although relatively high catalyst loadings were required (20 mol% of **LB1**) and enantioselectivities were modest (68% *ee* for acetophenone, up to 83% *ee* for selected substrates), the work demonstrated that stereocontrol can be achieved with an LB as the sole chiral component of the FLP. DFT studies suggested that non-covalent interactions (π–π stacking and hydrogen-bonding) facilitate concerted proton/hydride transfer, thereby enabling enantioinduction.




Scheme 3. FLP-catalyzed hydrogenations of weakly basic substrates: challenges and solutions.

## 3. Opportunities and Our Approach

Although remarkable progress has been achieved in FLP-catalyzed AH over the past two decades, the development of chiral catalysts – particularly for weakly basic substrates – remains an important open challenge. In general, designing chiral catalysts is among the most demanding tasks in chemical science. Because enantioselectivity hinges on subtle energetic differences between competing transition states (often just a few kJ·mol$^{-1}$), even minor structural modifications can profoundly alter both reactivity and stereocontrol.

To tackle this, we pursue a systematic, iterative workflow in which mechanistic principles first guide the rational design of potential catalyst scaffolds. A small library (~10 members) is then synthesized to rapidly map structure-performance relationships. Both experimental and computational studies are conducted to gain insights into activity and selectivity, and those insights feed directly into subsequent design cycles until an effective catalyst emerges. Notably, the initial step of identifying a suitable scaffold is often the most critical and challenging part of this workflow.

### 3.1 *Design of Chiral FLPs for Asymmetric Hydrogenation*

Inspiration can be drawn from powerful transition-metal catalysts that hydrogenate through outer-sphere mechanisms reminiscent of FLPs.[38] A prominent example is Noyori's Ru–TsDPEN system, which achieves excellent enantioselectivity *via* a

well-organized cyclic transition state: the metal delivers a hydride while the ligand's N–H group simultaneously transfers a proton to the substrate (Fig. 1).[39] By analogy, chiral intramolecular FLPs can promote concerted proton/hydride transfer by enforcing spatial organization of the LA and LB while preventing dissociation. Compared to bimolecular systems,[24,40] covalently linking the reactive sites should favor more ordered transition states and thereby enhance stereocontrol. Success in this strategy requires both (i) a chiral backbone that places the LA and LB at a proper distance and orientation, and (ii) stereoelectronic complementarity between the two sites to ensure efficient $H_2$ activation.

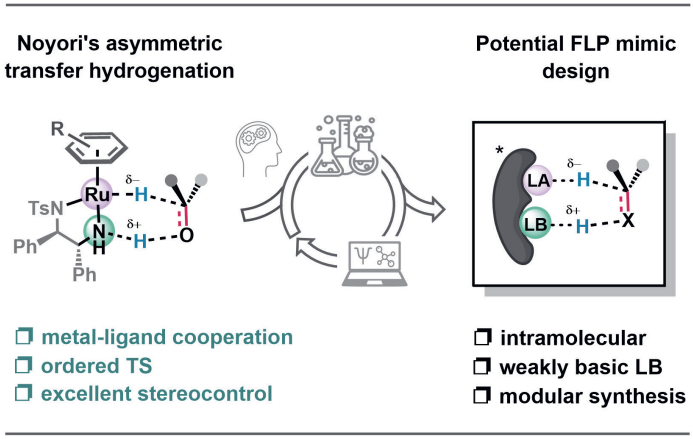



Fig. 1. Metallo-mimetic design concept for a chiral intramolecular FLP.

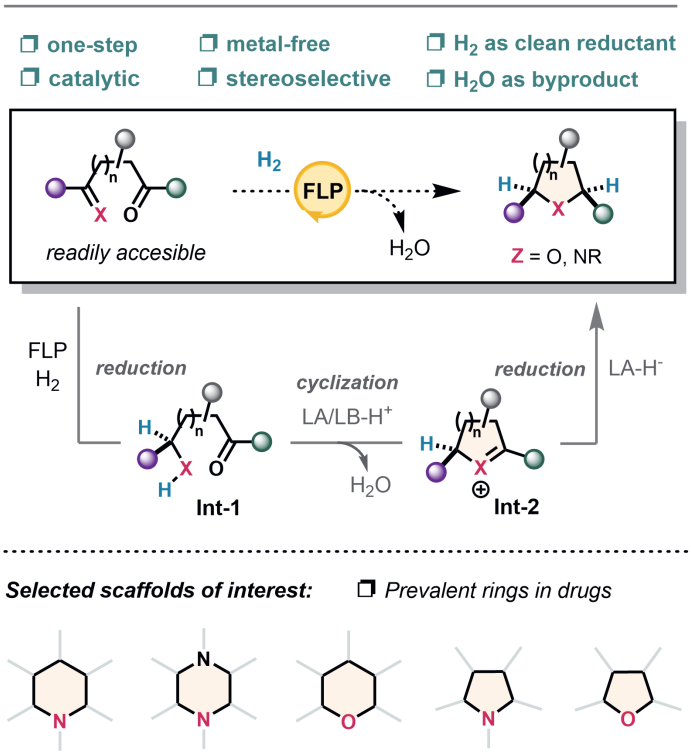
For backbones, proven chiral FLP frameworks such as camphor or 1,1´-bi-2-naphthol (BINOL) provide logical starting points. In terms of donor/acceptor pairing, studies suggest that combining a strong LA with a weak LB, or vice versa, is most effective.[41] For weakly basic substrates, the strong-LA/weak-LB combination seems particularly attractive: weak LBs (*e.g.* oxazolines, electron-deficient phosphines or amines) generate strongly Brønsted acidic conjugates (LB–$H^+$), which efficiently protonate the substrate (*vide supra*). To accelerate discovery, modular synthetic strategies are desirable; for instance, routes enabling late-stage diversification of the LB would streamline library construction and facilitate more efficient screening.

Given the multiple parameters that require optimization, computational methods can play an important role in design. FLPs lacking *d*-orbitals are generally more amenable to accurate modelling than transition-metal catalysts. Pioneering studies have already demonstrated the potential of density functional theory (DFT)[42–45] and machine learning[46,47] to predict FLP activity and selectivity, although these approaches remain less mature than in other organocatalyst families such as chiral phosphoric acids.[48] By integrating modular synthesis, mechanistic insight, and computational prediction, we aim to accelerate the discovery of effective chiral FLPs for the AH of challenging substrates. Ongoing efforts in our group are already showing promising results, and further details will be reported in due course.

### 3.2 *Reaction Development Beyond Hydrogenation*

In parallel with FLP catalyst design, we aim to exploit the unique reactivity of these systems beyond hydrogenation. Borane Lewis acids display broad catalytic versatility, enabling diverse transformations such as cycloadditions, C–H functionalization, and many others.[49–51] Building on this foundation, we envision cascade processes in which FLP-mediated hydrogenation is directly coupled with downstream functionalization.

A particularly attractive application is the stereoselective synthesis of saturated aza- and oxa-heterocycles (Scheme 4, bottom). These 3D scaffolds are prevalent in pharmaceuticals, where they can improve pharmacokinetic properties, metabolic stability, and target selectivity.[52–54] Conventional synthetic approaches often require multiple steps – for example, cyclization of linear precursors into unsaturated heterocycles (*e.g.* hetero-Diels–Alder, Paal-Knorr, condensation reactions),[55] followed by transition-metal-catalyzed hydrogenation.[56,57]




Scheme 4. Our strategy for FLP-catalyzed direct synthesis of saturated heterocycles (top), and selected scaffolds of interest (bottom).

A more efficient alternative could be a catalytic process that merges cyclization and hydrogenation in a single step, directly converting simple unsaturated precursors into saturated heterocycles (Scheme 4, top). FLPs, which combine Lewis acid reactivity with the ability to activate $H_2$, are ideally suited for this purpose. In such a process, hydrogenation of a polar unsaturated moiety (*e.g.* an imine or ketone) generates a nucleophilic amine or alcohol intermediate (**Int-1**). This species undergoes Lewis- or Brønsted-acid-mediated cyclization to form an electrophilic onium intermediate (**Int-2**), which is then reduced by the LA–$H^-$, affording the product in one step and generating water as the only byproduct. Potential challenges include controlling chemoselectivity in the initial reduction, suppressing competing aromatization pathways, and mitigating catalyst deactivation by water.

In line with this concept, we recently developed a catalytic, diastereoselective reductive cycloetherification of diketones, delivering *cis*-2,5-tetrahydrofurans and *cis*-2,6-disubstituted-tetrahydropyrans in a single step.[58] Beyond its immediate synthetic utility, this transformation illustrates how FLP catalysis can streamline access to valuable molecular scaffolds while minimizing waste, thereby opening new opportunities for sustainable synthesis.

## 4. Closing Remarks

Asymmetric hydrogenation remains one of the most powerful strategies for synthesizing chiral molecules that are central to pharmaceuticals, agrochemicals, and functional materials. Over the past two decades, FLPs have emerged as promising metal-free catalysts for hydrogenation. Despite their potential, chiral

FLPs still face challenges in catalytic performance, stability, and substrate scope, which limit their widespread adoption.

By combining rational catalyst design with the development of new transformations beyond hydrogenation, our research aims to tackle some of these challenges and push the boundaries of main-group catalysis. We hope to contribute meaningfully to this rapidly evolving field and to advance the broader goal of a more sustainable chemistry.

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