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CHEMCATCHEM Highlights

Enantioselective Metal-Free Hydrogenation Catalyzed by Chiral Frustrated Lewis Pairs

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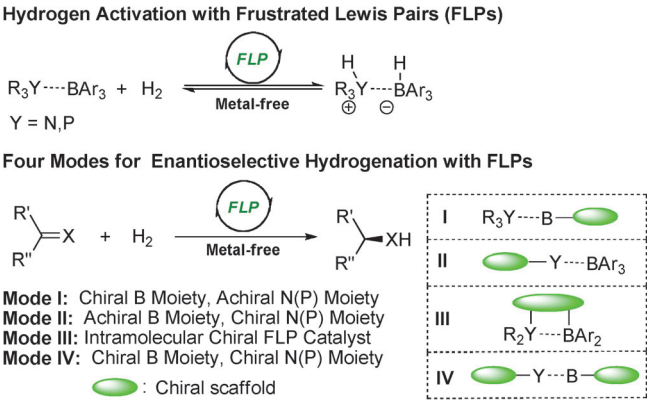
Bulky Lewis acids and Lewis bases do not undergo neutralization to form classical Lewis acid–base adducts because of steric hindrance. The Lewis acids and Lewis bases involved in this phenomenon are termed "frustrated Lewis pairs" (FLPs).[1] The synergy between the unquenched acid and base endows the Lewis pair with the ability to activate small molecules, in particular hydrogen. A milestone discovery in this field was reported by Stephan and co-workers in 2006, in which a phosphine–borane compound was reported to reversibly activate hydrogen under mild conditions.[1b] Since then, FLP chemistry has developed into a cutting-edge concept. Most of the reported FLPs, generally based on the strong Lewis acid $B(C_6F_5)_3$ accompanied by a bulky amine or phosphine, may serve as hydrogenation catalysts. Recently, metal-free hydrogenation using FLP catalysts has been regarded as a promising application of FLP chemistry. FLP catalytic systems are able to hydrogenate a wide range of unsaturated substrates, such as imines, enamines, enol ethers, and heterocycles.[1d,e]

Enantioselective hydrogenation, which is still dominated by transition-metal catalysts, plays a pivotal role in organic synthesis. Considering the increasingly stringent limits on the amount of metal impurities found in drug compounds, the development of an effective metal-free catalyst for enantioselective hydrogenation to synthesize chiral molecules is a long-term challenge. FLP-type enantioselective hydrogenation is a rational extension of this hydrogenation chemistry owing to its significant potential for the transition-metal-free synthesis of chiral molecules. However, FLP-type catalytic enantioselective hydrogenation has remained relatively unexplored. This strategy is hampered by the design and synthesis of an effective chiral borane reagent because this class of air-sensitive compound cannot be purified by the usual chromatography techniques. Another issue confronting researchers is that the stereoselectivity of borane connected to the chiral scaffold through a single σ bond is difficult to control because two perfluorophenyl groups are necessary to keep enough Lewis acidity for H_2 activation. To realize FLP-type catalytic enantioselective hydrogenation, four kinds of chiral FLP catalysts can be considered (Scheme 1), mode I: chiral B moiety, achiral N(P) moiety; mode II: achiral B moiety, chiral N(P) moiety; mode III: intramolecular chiral FLP; mode IV: chiral B moiety, chiral N(P) moiety. Great progress has been made in the rational design of chiral FLP catalysts based on modes I–III in recent years, but mode IV remains to be explored (Figure 1).



Scheme 1. Enantioselective metal-free hydrogenation by means of an FLP strategy.

In mode I, the chiral B–H species resulting from H_2 activation is expected to undergo an asymmetric hydride transfer to pro-

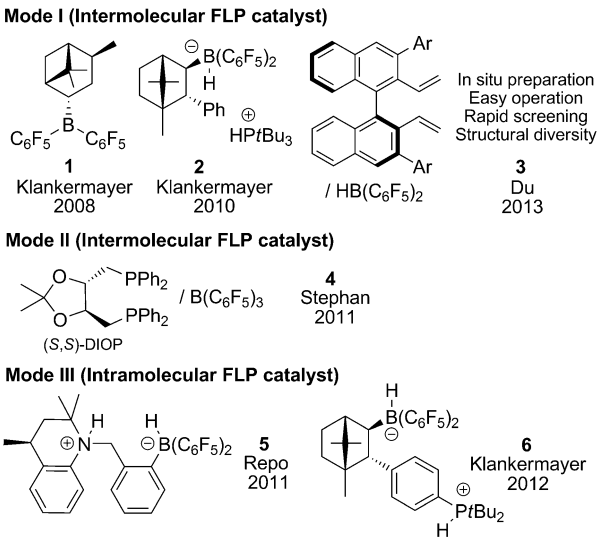


Figure 1. FLP catalysts for enantioselective metal-free hydrogenation.

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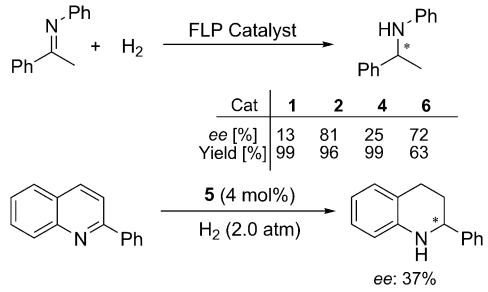
chiral substrates. Chiral boranes were prepared through direct hydroboration of chiral olefins with bis(pentafluorophenyl)borane ($HB(C_6F_5)_2$) in the pioneering work of Klankermayer and co-workers.[2] Compound **1**, derived from (+)-α-pinene, was first evaluated in FLP-type enantioselective hydrogenation of imines.[2a] The results demonstrated the possibility of metal-free hydrogenation by means of chiral FLP catalysis, albeit with only 13% *ee*. Further investigation proved that (+)-camphor is a more suitable chiral structural motif for FLP-type enantioselective hydrogenation.[2b] The hydroboration of (1*R*,4*R*)-1,7,7-trimethyl-2-phenylbicyclo-[2,2,1]hept-2-ene with $HB(C_6F_5)_2$ resulted in two, inseparable, diastereoisomers. With the aid of tBu_3P, the stable FLP salt was achieved after hydrogen-gas activation. Fortunately, two diastereomeric FLP salts can be isolated through kinetically controlled H_2-activated product formation. High conversion and significant enantioselectivity could be obtained by employing the FLP salt, **2**, as a catalyst for the hydrogenation of a series of imines. Notably, the crystal structure of **2** suggests that the phenyl ring in the chiral scaffold is parallel to one of the C_6F_5 rings and the fixed conformation of the catalyst is important for the control of enantioselectivity in the asymmetric hydrogenation.

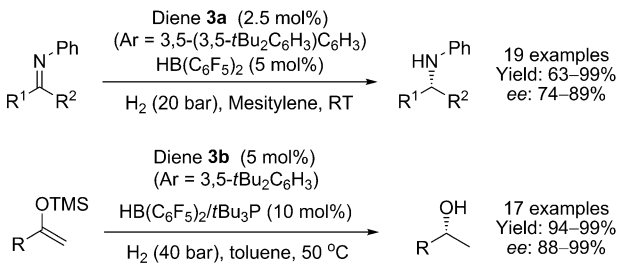
Stephan and co-workers described a very interesting attempt to employ chiral phosphine (*S*,*S*)-DIOP and $B(C_6F_5)_3$ as a mode II FLP catalyst for the hydrogenation of imines.[3] This strategy may work in controlling stereoselectivity if a hydrogen-bond interaction exists between the imine and chiral phosphonium cation as the hydride ion is transferred. Although low selectivity (25% *ee*) was obtained in this work, the mode II FLP catalyst is still worth exploring because a huge number of chiral Lewis bases can be identified. (Scheme 2)



Scheme 2. Enantioselective hydrogenation of imines and quinolines by means of an FLP strategy.

Mode III intramolecular FLP catalysts have also been developed. A novel phosphonium hydride borate zwitterion, **6**, was synthesized with the same chiral precursor as that used for Klankermayer's catalyst **2**.[2c] This catalyst exhibits high stability, and can be purified by using column chromatography. Moreover, the high stability of the chiral FLP catalyst enables effective recycling in hydrogenation. Full conversion and 76% *ee* were maintained after four consecutive runs. Repo and co-workers reported an intramolecular N/B FLP catalyst, **5**, in 2011, in which a chiral amine moiety, as the Lewis base part, was introduced into a borane molecule.[2d] The activity of *ansa*-ammonium borate can be simply adjusted by tuning the basicity and steric hindrance of the amine moiety. A wide substrate scope was investigated and full conversion was achieved. Unfortunately, only up to 37% *ee* was obtained when 2-phenylquinoline was used as substrate. This result suggested that the chiral structure of the amine was too far away from the boron functionality to offer effective enantioselective induction during the hydride-transfer process.

Very recently, some developments in this area have been reported by the group of Du.[4] They envisioned a powerful mode I FLP catalyst and reported that chiral binaphthyl dienes containing two terminal olefin groups can generate enantiomerically pure catalyst in situ by direct hydroboration. This strategy is a clever detour to avoid the tedious purification of the chiral borane catalyst. A variety of chiral boranes for FLP-type hydrogenation was achieved by changing the 3,3′-substituted groups. Therefore, optimization of the reaction conditions could be performed with a wide scope of catalysts. The feasibility of this strategy was initially examined in the enantioselective metal-free hydrogenation of imines. Significant improvement of enantioselectivity was successfully achieved with under mild conditions. A variety of chiral amines were synthesized in excellent yields and 74–89% *ee* (Scheme 3), which represents the best enantioselectivity of FLP-type hydrogenation of imines. Encouraged by this achievement, Du's group explored the enantioselective hydrogenation of silyl enol ethers with the above-mentioned catalysts. The direct hydrogenation of ketones to prepare chiral alcohols is a straightforward method to these valuable compounds, but is extremely difficult using FLP catalysts because of the strong oxophilicity of borane. Hydrogenation of silyl enol ethers provides an ideal alternative approach to chiral alcohols, and is suitable for FLP catalysis. The 3,3′-Substitutents of binaphthyl diene greatly affected the enantioselectivity of the hydrogenation reaction and the diene bearing 3,3′-(3,5-*t*Bu)$_2$phenyl proved to be the best FLP-catalyst precursor after evaluation. With the combination of chiral borane generated in situ and tBu_3P, the enantioselective hydrogenation of silyl enol ethers was realized. After treatment with tetrabutylammonium fluoride (TBAF), a variety of chiral secondary alcohols were furnished with 88–99% *ee*.



Scheme 3. Highly enantioselective hydrogenation of imines and silyl enol ethers catalyzed by Du's chiral FLP.

In conclusion, these results demonstrate the successful application of FLP chemistry, a completely new H_2-activation mode, in catalytic asymmetric hydrogenation. We believe that the FLP catalyst for hydrogenation will have a significant

impact on this field, which is still dominated by chiral transition-metal catalysts, and could provide an effective metal-free pathway for the synthesis of valuable chiral amines and alcohols. However, to achieve better enantioselectivity, reaction activity, and a wider substrate scope further research is required. Theoretically, a mode IV FLP catalyst would offer several combinations of chiral B moeity and chiral N(P) moiety and would enable rapid screening of catalysts. Although the relevant catalyst has not yet been reported, it is predicted that mode IV will provide more opportunities in the search for efficient catalysts.

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Keywords: boranes · enantioselectivity · hydrogenation · frustrated Lewis pairs · metal-free catalysis

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