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Frustrated Lewis Pairs

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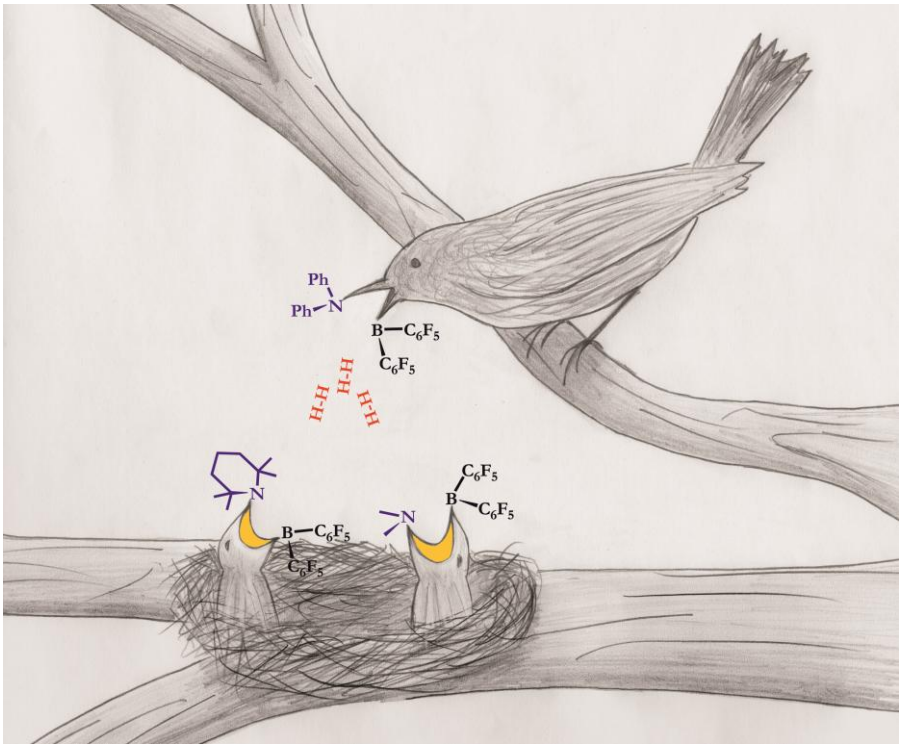

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COMMUNICATION

Asymmetric hydrogenation of imines with a recyclable chiral frustrated Lewis pair catalyst†

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A camphor based chiral phosphonium hydrido borate zwitterion was synthesised and successfully applied in the enantioselective hydrogenation of imines with selectivities up to 76% ee. The high stability of the novel chiral FLP-system enables effective recycling of the metal-free catalyst.

Combinations of sterically demanding electron pair donor and acceptor compounds do not form the expected classical Lewis acid–base adducts, but the special nature of this arrangement enabled the unprecedented activation of small molecules and paved the way towards effective metal-free catalytic transformations.[1] In 2006 Douglas W. Stephan demonstrated for the first time that intramolecular combinations of strong Lewis acid and base allow the heterolytic cleavage of molecular hydrogen *via* the formation of a phosphonium borate zwitterion.[2] This species was robust, air and moisture stable and only heating to 150 °C prompted the elimination of hydrogen, regenerating the intramolecular phosphine–borane frustrated Lewis pair (FLP).[3] This remarkable activation could subsequently be generalised and combinations of sterically hindered phosphines and boranes were not only able to activate hydrogen, but also emerged as effective hydrogenation catalysts. However, these synthetically readily accessible intermolecular FLP systems demonstrated reduced stability in the presence of air and moisture, thus complicating the effective recycling of the metal-free catalysts.

Taking into consideration the uniqueness of intramolecular frustrated Lewis pairs, the phosphine–borane **1**[4] could be established in 2007 as one of the most active metal-free dihydrogen activators. Moreover, this metal-free system served as an effective catalyst for hydrogenation of various unsaturated substrates,[5] and adds to different organic carbonyl compounds (Fig. 1).[6] In 2010 intermolecular frustrated Lewis pairs based on chiral boranes could be synthesised and **2** was reported as a catalyst for enantioselective hydrogenation of imines with an enantiomeric excess up to 83%.[7] Recently, Bernhard Rieger and Timo Repo described the chiral intramolecular FLP **3** with high air and moisture stability, foreshadowing the extended applicability of these systems. This catalyst could be used in the enantioselective hydrogenation of imines with a moderate catalytic loading leading to an enantiomeric excess up to 37% ee.[8] Herein we report on a novel efficient and highly stable chiral FLP, able to easily activate hydrogen and to act as a catalyst for metal-free enantioselective hydrogenation of prochiral imines with high selectivity.

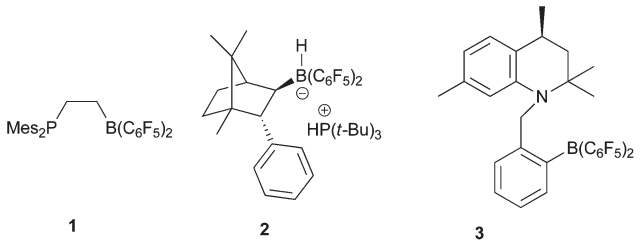

Fig. 1 Frustrated Lewis pairs as effective metal-free catalysts.

The synthesis strategy of the FLP is based on the already established chiral intermolecular FLP system **2**, and the stability of this novel catalyst is expected to be strongly enhanced with retained activity and selectivity, due to the comparable Lewis acidity of the borane fragment. The synthesis of the intramolecular phosphine–borane FLP catalyst is presented in Scheme 1. Reaction of (1*R*)-(+)-camphor **4** with (4-bromophenyl) magnesium bromide **5** gave the corresponding tertiary alcohol **6**. Subsequent dehydration using thionyl chloride/pyridine resulted in (1*R*,4*R*)-2-(4-bromophenyl)-1,7,7-trimethyl-2-phenylbicyclo [2.2.1]hept-2-ene **7** in 45% yield.[9] Lithiation of compound **7** using *t*-BuLi and nucleophilic substitution with di-*tert*-butylchlorophosphine afforded di-*tert*-butyl(4-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2yl)-phenyl)phosphine **8**. Hydroboration of the unsaturated compound **8** using Piers borane (bis(pentafluorophenyl)borane)[10] in *n*-pentane at 100 °C provided diastereomerically pure borane **9**, which was used without further purification for hydrogen activation at room temperature and ambient pressure. The resulting phosphonium hydrido borate zwitterion **10** could be effectively purified using column chromatography with dichloromethane as eluent, already indicating the expected increased stability of the chiral system in comparison to the hitherto existing chiral metal free catalysts, which decomposed under these conditions. After the purification the solvent was removed and compound **10** could be isolated as a colourless powder in 40% yield. Phosphonium hydrido borate **10** could be fully characterised by multinuclear NMR analysis. The

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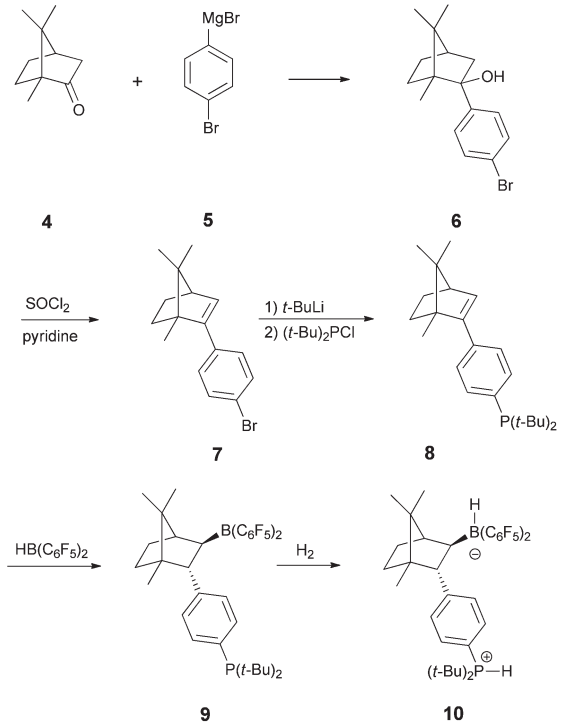


Scheme 1 Synthetic pathway to chiral FLP catalyst **9** and the phosphonium hydrido borate zwitterion **10**.

$^{31}P\{^{1}H\}$-NMR spectrum of **10** reveals a singlet resonance at δ = 53.7 ppm, and the $^{19}F\{^{1}H\}$-NMR spectrum shows two sets of signals for the diastereotopic C_6F_5 rings [(*ortho*) $\delta = -132.36$ (d, J_{F-F} = 21.9 Hz, 2F), (*ortho*) −132.83 (dm, J_{F-F} = 19.32 Hz, 2F), (*para*) −165.73 (t, J_{F-F} = 23.4 Hz, 1F), (*para*) −165.93 (t, J_{F-F} = 20.8 Hz, 1F), (*meta*) −167.61 (m, 2F), (*meta*) −167.82 (m, 2F)]. In the ^{1}H-NMR spectrum a broad signal at 2.85 ppm corresponding to BH, and a doublet at 5.71 ppm (J_{P-H} = 477 Hz) for PH could be observed. The ^{11}B-NMR displays a doublet at $\delta = -19.25$ ppm (J_{B-H} = 81.6 Hz).

Crystallisation of compound **10** in a mixture of dichloromethane and *n*-pentane resulted in crystals suitable for X-ray crystallographic analysis. The unit cell contains two independent molecules with identical absolute configuration (1*R*,2*R*,3*R*,4*S*) and one of them is shown in Fig. 2.

Having this new chiral FLP in hand, catalytic transformations with various prochiral imines as substrates were performed and the results are summarised in Table 1. Using 2 mol% catalyst **10** at 65 °C and 25 bar hydrogen pressure, imines *N*-(1-phenylethylidene)aniline **11a**, *N*-(1-(2-naphthyl)ethylidene)aniline **11b**, and *N*-phenyl-(1-(4-chlorophenyl)ethylidene)aniline **11c** were hydrogenated at a conversion of 70%, 51%, and 33% (Table 1, entries 1–3). After two days of reaction time, 72% ee, 76% ee, and 72% ee could be obtained for the chiral amine products. Extending the reaction time from 2 to 3 days for imine **11a** increased the conversion to 90% with comparable enantioselectivity (Table 1, entry 4). The more activated methoxy substituted imines *N*-(1-phenylethylidene)-4-methoxyaniline **11d** and *N*-(1-(2-naphthyl)-ethylidene)-4-methoxyaniline **11e** could be more easily hydrogenated and full conversion was obtained within 2 days with a selectivity from 73% ee to 76% ee (Table 1, entries 5 and 6).

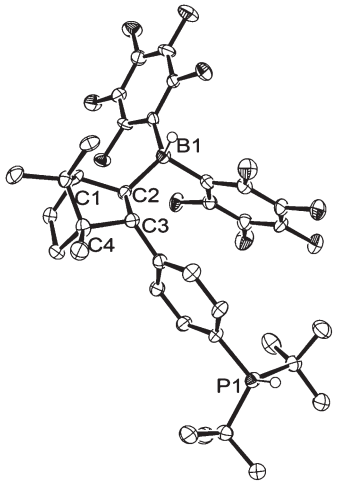
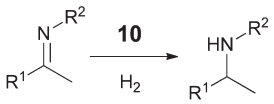


Fig. 2 Molecular structure of catalyst **10** in the crystal. Hydrogen atoms and solvent molecules were omitted for clarity except for the hydrogen atoms bonded to boron and phosphorus.

Table 1 Enantioselective hydrogenation of imines using chiral intramolecular FLPs **10**



11 12

11a:R^1=Ph, R^2=Ph
11b:R^1=2-Naphthyl, R^2=Ph
11c:R^1=4-Cl-C_6H_4, R^2=Ph
11d:R^1=Ph, R^2=4-MeO-C_6H_4
11e:R^1=2-Naphthyl, R^2=4-MeO-C_6H_4
11f:R^1=4-MeO-C_6H_4, R^2=4-Cl-C_6H_4
11g:R^1=4-MeO-C_6H_4, R^2=4-MeO-C_6H_4
11h:R^1=4-MeO-C_6H_4, R^2=Ph

Entry[a]	Substrate	Conversion[e] [%]	Isolated yield [%]	ee[f] [%]
1	**11a**	70	63	72 (*R*)
2	**11b**	51	32	76 (−)
3	**11c**	33	21	72 (−)
4[b]	**11a**	90	79	72 (*R*)
5	**11d**	>99	95	73 (*R*)
6	**11e**	>99	94	76 (+)
7	**11f**	70	51	72 (+)
8[c]	**11g**	>99	95	76 (+)
9[d]	**11h**	>99	95	70 (−)

[a] Reaction conditions: catalyst loading (2.0 mol%), imine (0.5 mmol), H_2 (25 bar), 1 mL toluene, T = 65 °C, 2 days. [b] Reaction time: 3 days. [c] Reaction time: 1 day. [d] Reaction time: 5 days, catalyst loading (0.5 mol %). [e] Yield was determined by ^{1}H NMR analysis. [f] % ee was determined by HPLC or GC methods using a chiral column, absolute configurations assigned by comparison of retention times and optical rotations with literature values.

Replacing one methoxy function with a chlorine group, the conversion in the transformation of *N*-[1-(4-chlorophenyl)ethylidene]-*p*-anisidine **11f** decreased slightly to 70% within 2 days with a selectivity of 72% ee (Table 1, entry 7).

Full conversion was achieved within only one day of reaction time at a notable enantioselectivity of 76% ee with the substrate incorporating two methoxy substituents (*N*-[1-(4-methoxy)-phenyl]ethylidene-4-methoxyaniline **11g**) (Table 1, entry 8). In order to demonstrate the applicability of the catalytic system, the catalyst loading was reduced to 0.5 mol% in the hydrogenation

Table 2 Recycling experiments with catalyst **10** and imine **11g**

Entry[a]	Catalyst-run	Conversion [%]	ee [%]
1	1st	>99	76 (+)
2	2nd	>99	76 (+)
3	3rd	>99	76 (+)
4	4th	>99	76 (+)
5	5th	70	76 (+)

[a] Reaction conditions: catalyst loading (2.5 mol%), H_2 (25 bar), imine **11g** (1.42 mmol), 1 mL toluene, T = 65 °C. Reaction time: 24 h; yield was determined by ^{1}H NMR analysis; % ee was determined by HPLC, absolute configurations assigned by comparison of retention times and optical rotations with literature values.

of imine *N*-(1-(4-methoxyphenyl)ethylidene)aniline **11h** and, consequently, the amine could be obtained with an enantioselectivity of 70% ee in 95% yield. The recyclability of catalyst **10** was investigated in more detail in the hydrogenation of imine **11g** (Table 2). After the first hydrogenation experiment catalyst **10** was precipitated under air with pentane, the supernatant solution was separated and analysed, showing full conversion and an enantioselectivity of 76% ee (Table 2, entry 1). The recycled solid catalyst **10** was subsequently retransferred to the autoclave, mixed with toluene and substrate, and pressurized with 25 bar hydrogen. Four consecutive runs demonstrated a constant enantioselectivity of 76% ee and full conversion, confirming the effectiveness and stability of the novel chiral FLP catalyst (Table 2, entries 1–4).

Conclusions

In summary a novel chiral FLP salt was successfully synthesised and fully characterised. The stable catalyst was able to selectively hydrogenate prochiral imines with an enantioselectivity up to 76% ee at low catalyst loading. Furthermore, the increased recyclability in comparison to the related chiral intermolecular system demonstrates the effectiveness of the modified catalyst design. Further investigation regarding the scope and the hydrogenation mechanism of the chiral FLP catalyst is underway and will be presented in the near future.

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