**Abstract:** In recent years ‘frustrated Lewis pairs’ (FLPs) have been shown to be effective metal-free catalysts for the hydrogenation of many unsaturated substrates. Even so, limited functional-group tolerance restricts the range of solvents in which FLP-mediated reactions can be performed, and all FLP-mediated hydrogenations reported to date carried out in non-donor hydrocarbon or chlorinated solvents. Herein we report that the bulky Lewis acids $B(C_6Cl_5)x(C_6F_5)_y$ ($x = 0–3$) are capable of heterolytic H$_2$ activation in the strong-donor solvent THF, in the absence of any additional Lewis base. This allows metal-free catalytic hydrogenations to be performed in donor solvent media under mild conditions; these systems are particularly effective for the hydrogenation of weakly basic substrates, including the first examples of metal-free catalytic hydrogenation of furan heterocycles. The air-stability of the most effective borane, $B(C_6Cl_5)(C_6F_5)_3$, makes this a practically simple reaction method.

Since the initial reports into their reactivity by Stephan et al., frustrated Lewis pairs (FLPs) have attracted great interest for their ability to act as metal-free polar hydrogenation catalysts.[1] By rational modification of both the Lewis acidic and Lewis basic components, FLPs have been developed that are effective for the reduction of a wide range of unsaturated substrates, both polar (e.g. imines, enol ethers)[2] and non-polar (e.g. 1,1-diphenylethylene).[3] In addition to H$_2$, FLPs have been shown to readily react with a wide variety of other functional groups including ethers,[4] carbonyls,[5] and weakly acidic C–H[6] and N–H bonds.[7] Though impressive, this diverse reactivity has generally rendered FLPs incompatible with many common organic solvents. In particular, the ubiquity in FLP chemistry of very strong, air-sensitive, Lewis acids, such as $B(C_6F_5)_3$ (1a) and derivatives thereof, has significantly limited the use of donor solvents, such as ethers, which tend to form strong classical donor–acceptor adducts. For many FLPs this coordination is followed by nucleophilic cleavage of the activated C–O bond (Scheme 1). Therefore, ring-opening of THF was one of the first reported FLP-mediated transformations, and as such is often viewed as an archetypal FLP reaction.[8] Consequently, only a few explicit reports exist of H$_2$ activation by FLPs in donor-solvent media, all of which were based on stoichiometric phosphine or amine bases, and none of which described any subsequent catalytic hydrogenation reactivity.[9]

Recent work has shown that near-stoichiometric mixtures of 1a (Figure 1) and specific ethers (Et$_2$O, crown ethers) are capable of acting as hydrogenation catalysts in non-donor solvents, such as CD$_2$Cl$_2$, neatly demonstrating that such ethers are not fundamentally incompatible with FLP H$_2$ activation chemistry.[10] Meanwhile, Paradies and co-workers have reported use of the THF adduct of $B(2,6-F_2C_6H_3)_3$, as a convenient source of the borane for certain P/B and N/B FLP-catalyzed hydrogenations.[11] These results led us to speculate that, with an appropriate Lewis acid, not only should FLP-mediated hydrogenation be possible in stronger donor ethereal solvents, but such solvents might reveal the need for an additional “frustrated” Lewis base, by performing that role themselves.

The use of reaction media other than hydrocarbons and chlorinated solvents is inherently appealing; the low polarity of the hydrocarbons limits their effectiveness at solubilizing many potential polar substrates ($\epsilon_{\text{FAME}} = 2.38$, c.f. $\epsilon_{\text{THF}} = 7.52$, $\epsilon_{\text{DCM}} = 8.93$),[11] while chlorinated solvents have become increasingly unattractive as chemists become more concerned about the ‘greenness’ of their reactions.[12]

Previously, we have investigated the extremely hindered boranes $B(C_6Cl_5)x(C_6F_5)_y$ ($x = 1–3$, Figure 1) and found that although electrophilicity increases with the number of

\[
\begin{align*}
\text{C}_4\text{F}_5 & \quad \text{C}_4\text{Cl}_5 \\
\text{C}_4\text{F}_5 & \quad \text{C}_4\text{Cl}_5 \\
\text{C}_3\text{Cl}_5 & \quad \text{C}_3\text{Cl}_5 \\
\text{C}_2\text{Cl}_5 & \quad \text{C}_2\text{Cl}_5 \\
\text{C}_1\text{Cl}_5 & \quad \text{C}_1\text{Cl}_5
\end{align*}
\]

Figure 1. Boranes 1a–1d, studied for hydrogenation efficacy in THF solvent.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405531.
perchlorophenyl groups, Lewis acidity decreases as a result of increasing steric hindrance.\textsuperscript{[13]} Significantly, and unlike 1a, these boranes were also found to demonstrate appreciable stability to air and moisture. Herein we describe investigations into the behavior of this family of boranes in the donor-solvent THF, and report the ability of such solutions to effectively catalyze the hydrogenation of even weakly basic substrates, using an operationally simple method that does not require the addition of an auxiliary Lewis base.

Although 1a binds strongly to THF, we envisioned that the strength of this interaction might be reduced by increasing steric bulk. Rational modification of the Lewis acid has been shown to lead to improved functional-group tolerance in FLP-catalyzed hydrogenation reactions.\textsuperscript{[10,14]} Thus B(C\textsubscript{6}Cl\textsubscript{5})\textsubscript{3} (1b), though more electrophilic than 1a,\textsuperscript{[13]} is found to bind the solvent only weakly when dissolved in neat THF. The reversibility of the binding is clear from variable-temperature (VT) NMR analysis of THF solutions of 1b: below 0°C the \textsuperscript{11}B NMR shift remains constant at \(\delta = 3.8\) ppm, consistent with the four-coordinate 1b-THF adduct (c.f. \(\delta = 3.3\) ppm for 1a-THF in CD\textsubscript{2}Cl\textsubscript{2}).\textsuperscript{[15]} Upon warming, however, the resonance signal moves progressively downfield, reaching \(\delta = 23.9\) ppm at 60°C, indicative of a shift in the equilibrium towards free, uncoordinated Lewis pair.\textsuperscript{[17]}

THF solutions of B(C\textsubscript{6}Cl\textsubscript{5})(C\textsubscript{6}F\textsubscript{5})\textsubscript{2} (1c), which is bulkier still, show no sign of coordination at all at room temperature (\(\delta = 63.5\) ppm, c.f. \(\delta = 64.1\) ppm in PhMe). Only upon cooling to \(-40\)°C do signals consistent with a THF adduct become apparent in the \(\textsuperscript{19}F\) NMR spectrum (see Supporting Information). We observed no evidence for adduct formation with THF instead as a result of hydride abstraction from the solvent can be discounted based on the observation of the \textsuperscript{11}B borohydride resonance signal as a doublet in both protoe and deutero THF, as well as the lack of any reaction in the absence of H\textsubscript{2} (Scheme 2b). Conclusive evidence is provided by using D\textsubscript{2} in place of H\textsubscript{2}, which replaces the \textsuperscript{11}B doublet at \(\delta = -19.6\) ppm with a singlet at the same shift, and a comparable signal in the \textsuperscript{1}H spectrum diagnostic of [THF-D]\textsubscript{2}, or a solvate thereof (Figure 2).

Further evidence for H\textsubscript{2} activation is provided by THF solutions of B(C\textsubscript{6}Cl\textsubscript{5})(C\textsubscript{6}F\textsubscript{5})(D\textsubscript{2}) (1d). After heating to 60°C for 1h under H\textsubscript{2} (4 bar), new resonance signals can clearly be observed at \(\delta = 11.34\) ppm and \(\delta = -8.7\) ppm (d, \(J = 91\) Hz)\textsuperscript{[8c]} in the room temperature \textsuperscript{1}H and \textsuperscript{11}B NMR spectra, respectively. Clearly H\textsubscript{2} activation in this manner generates a substantially acidic proton (the p\textsubscript{K\textsubscript{a}} of protonated THF has been measured as \(-2.05\) in aqueous H\textsubscript{2}SO\textsubscript{4}).\textsuperscript{[21]} Strong Brønsted acids can initiate polymerization of THF\textsuperscript{[19d]} as can strong Lewis acids, including 1a.\textsuperscript{[21]} Nevertheless, during the course of our studies no evidence for borane or proton-catalyzed polymerization of THF was detected for solutions of 1a-d under H\textsubscript{2}, even after prolonged heating.\textsuperscript{[21]} Nor, during our subsequent investigations into catalytic hydrogenation, was

\begin{align*}
\text{[H\textsubscript{2}]} & \rightarrow \text{[THF]} \\
\text{[THF]} & \rightarrow \text{[H\textsubscript{2}]} \\
\end{align*}
any FLP-mediated ring-opening of the solvent observed, even in the presence of relatively basic imines.

**1a** has been shown to catalyze the hydrogenation of bulky imines in PhMe through a FLP mechanism. However, since the reaction relies on the substrate to act as the frustrated Lewis base for initial H₂ activation, it works relatively poorly for less electron-rich, and hence less basic, imines. The bulky electron-deficient N-tosyl imine **2a**, for example, was reported to require forcing conditions, in particular high H₂ pressures, to achieve appreciable conversion (Table 1, entries 1 and 2).

In contrast, the same imine was rapidly reduced in the presence of **1b** in [D₆]THF under much milder conditions (5 mol% **1b**, 60 °C, 4 bar H₂, 3 h), as was the related substrate **2b** (Table 1, entries 3 and 4). Furthermore, the air-stability of **1b** meant the initial reaction mixture could be conveniently prepared under air using pre-dried solvent, without the need for use of a glovebox (Table 1, entry 5). In addition to **2b**, the bulky N-aryl imines **2c** and **2d** were also successfully reduced (Table 1, entries 6 and 7), as was the less bulky N-aryl imine **2e**, although in this final case slightly higher catalyst loadings were necessary to achieve complete conversion, owing to reversible binding of **1b** to the product **3e** (Table 1, entry 8).

Notably, when the hydrogenation experiments were repeated in a non-basic solvent (C₇D₈) rather than in [D₆]THF, under otherwise identical conditions, the weakly basic substrates **2a** and **2b** showed no evidence of hydrogenation (Table 1, entries 9 and 10). Conversely, the relatively basic imines **2d** and **2e** both show appreciable conversions in C₇D₈ (Table 1, entries 12 and 13). This divergent reactivity is consistent with hydrogenation occurring by two distinct mechanisms. In the first, H₂ activation by **1b/THF** is followed by sequential proton and hydride transfer to generate the product amine (Scheme 3, route a). In the second mechanism, H₂ is activated instead by a **1b/substrate** FLP in the manner described by Stephan et al., with subsequent transfer of hydride to the protonated imine (Scheme 3, route b).

**Table 1**: FLP-mediated hydrogenation of imines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>[B] (mol %)</th>
<th>t [h]</th>
<th>Yield [%][f]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a,d]</td>
<td><strong>2a</strong></td>
<td>C₇H₈</td>
<td>80</td>
<td>1a (10)</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>2[a,d]</td>
<td><strong>2a</strong></td>
<td>C₇H₈</td>
<td>80</td>
<td>1a (10)</td>
<td>22</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td><strong>2a</strong></td>
<td>[D₆]THF</td>
<td>60</td>
<td>1b (5)</td>
<td>3</td>
<td>&gt;99 (98)[m]</td>
</tr>
<tr>
<td>4</td>
<td><strong>2b</strong></td>
<td>[D₆]THF</td>
<td>60</td>
<td>1b (5)</td>
<td>3</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td><strong>2a</strong></td>
<td>THF</td>
<td>60</td>
<td>1b (5)</td>
<td>3</td>
<td>&gt;99[m]</td>
</tr>
<tr>
<td>6</td>
<td><strong>2c</strong></td>
<td>[D₆]THF</td>
<td>60</td>
<td>1b (5)</td>
<td>8</td>
<td>&gt;99 (99)[m]</td>
</tr>
<tr>
<td>7</td>
<td><strong>2d</strong></td>
<td>[D₆]THF</td>
<td>80</td>
<td>1b (5)</td>
<td>18</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td><strong>2e</strong></td>
<td>[D₆]THF</td>
<td>60</td>
<td>1b (15)</td>
<td>8</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td><strong>2a</strong></td>
<td>C₇D₈</td>
<td>60</td>
<td>1b (5)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td><strong>2b</strong></td>
<td>C₇D₈</td>
<td>60</td>
<td>1b (5)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td><strong>2c</strong></td>
<td>C₇D₈</td>
<td>60</td>
<td>1b (5)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td><strong>2d</strong></td>
<td>C₇D₈</td>
<td>80</td>
<td>1b (5)</td>
<td>18</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td><strong>2e</strong></td>
<td>C₇D₈</td>
<td>80</td>
<td>1b (15)</td>
<td>8</td>
<td>26</td>
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<tr>
<td>14</td>
<td><strong>2a</strong></td>
<td>Dioxane</td>
<td>60</td>
<td>1b (5)</td>
<td>41</td>
<td>96</td>
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<tr>
<td>15</td>
<td><strong>2b</strong></td>
<td>[D₆]THF</td>
<td>60</td>
<td>1c (5)</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>16</td>
<td><strong>2a</strong></td>
<td>[D₆]THF</td>
<td>80</td>
<td>1a (10)</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>17</td>
<td><strong>2a</strong></td>
<td>[D₆]THF</td>
<td>80</td>
<td>1d (5)</td>
<td>72</td>
<td>0</td>
</tr>
</tbody>
</table>

**Scheme 3**: Proposed mechanisms for hydrogenation of imines by activation of H₂ using either a) THF solvent or b) substrate as a frustrated Lewis base.

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H2SO4) but may also partially be attributed to its reduced polarity relative to THF (ε_dioxane = 2.22, ε_THF = 7.52), which will make cleavage of H2 into ionic H+H− adducts less favorable (Scheme 3, route a). Some variation of the borane is also tolerated: use of 1c leads to a reduction in reaction rate, but otherwise only a minor change in outcome (Table 1, entry 15). In fact, even 1a is observed to effectively catalyze hydrogenation at slightly higher temperatures (Table 1, entry 16); clearly under these conditions, coordination of THF is sufficiently reversible to allow some H2 activation to occur. No reaction is observed with 1d, suggesting [1d·H]+ to be a much poorer hydride donor. Given that 1B NMR spectroscopic analysis suggests the equilibrium between 1d and [1d·H]+ under H2 favors 1d, this lack of reactivity is most likely due to kinetic (steric) rather than thermodynamic factors (Table 1, entry 17).

Given the success of 1b as a hydrogenation catalyst for electron-poor imines we were interested in its ability to effect hydrogenation of other weakly basic substrates. To date the only reported example of FLP-mediated hydrogenation of a weakly basic aromatic heterocycle describes the reduction of indoles under very high pressures of H2. Nevertheless, admission of just 5 bar H2 to a mixture of 1b and N-methyl pyrrole (4a) or 2,5-dimethylpyrrole (4b) in THF led to formation of the reduced species 5H+[1b·H]+ (Scheme 4). No catalytic turnover was observed due to the relatively low acidity of the pyrrolidinium borohydride products (although it should be noted that the reduction of the pyrroles only reported example of FLP-mediated hydrogenation of any additional Lewis base. Solutions of 1b in particular are effective catalysts for the metal-free hydrogenation of a variety of substrates by a solvent-assisted mechanism. Compound 1b shows appreciable stability in air, which further increases the practicality of this system relative to the 1a-derived alternatives.

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[17] Because the limiting 19F or 11B resonance signals of free 1b in THF are not known, it is unfortunately not possible to extract thermodynamic activation parameters for the reversible binding of THF to 1b from these spectra.


[20] Although the number of THF molecules coordinated to the proton has not been determined, a coordination number of two would be consistent with previous observations.[9] See also: I. Krossing, A. Reisinger, Eur. J. Inorg. Chem. 2005, 1979–1989, and references therein.


[24] In fact, it appears that the presence of an atmosphere of H₂ inhibits polymerization of THF by 1a (see Supporting Information).


[26] pKₐ differences of this magnitude have been shown to significantly affect the rate of alkene hydrogenation by FLP catalysts based on weakly basic phosphines. See: L. Greb, S. Tussing, B. Schirmer, P. Oña-Burgos, K. Kaupmees, M. Lõkov, I. Leito, S. Grimme, J. Paradies, Chem. Sci. 2013, 4, 2788–2796.
