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PERSPECTIVE

"Frustrated Lewis pair" hydrogenations

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This perspective article discusses developments of metal-free hydrogenation catalysts derived from "frustrated Lewis pair" (FLP) systems. The range of catalysts uncovered and the applications to reductions of imines, aziridines, enamines, silyl enol ethers, diimines, metallocene derivatives and nitrogen-based heterocycles are described. In addition, FLP aromatic reduction of aniline derivatives to the cyclohexylamine analogs is discussed. The potential applications of these metal-free reductions are considered.

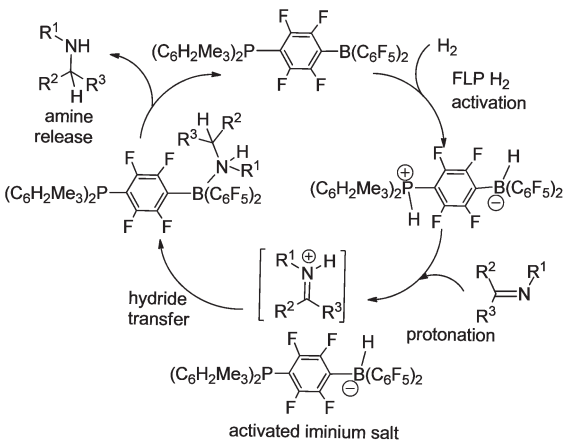
Introduction

Five years ago, the term "frustrated Lewis pairs" (FLPs) was first used to describe combinations of Lewis acids and bases in which steric demands precluded the formation of classical Lewis acid–base adducts.[1] Although the phenomenon of steric demands precluding adduct formation had been previously recognized by Brown *et al.*,[2] Wittig and Benz[3] and Tochtermann[4] as early as 70 years ago, the implications for further reactivity was not considered at that time.

In 2006, we discovered that sterically encumbered phosphorus and borane acids and bases could activate H_2.[5,6] This first metal-free heterolytic cleavage of H_2 prompted a variety of further studies demonstrating the unique reactivity of FLPs and their ability to activate a variety of small molecules. Several comprehensive reviews[7–10] have chronicled the rapid growth of FLP chemistry over the last few years; each in turn describing the growing knowledge of FLP reactivity. We have now reached a point in the development of this emerging field where some aspects of FLP chemistry may be of synthetic utility to the organic chemist. Specifically, this perspective article focuses on FLP hydrogenations. Herein, we illustrate the variety of FLP catalysts that have been studied and discuss the range of substrates where FLP reductions have been shown to be effective in catalyzing hydrogenation. It is our hope that this review will stimulate both the application and further development of new synthetic strategies that exploit the paradigm of FLP reductions.

Mechanism of FLP hydrogenations

The ability of simple combinations of sterically encumbered Lewis acids and bases (*i.e.* an FLP) to heterolytically cleave H_2 generated the following question: Can one effect consecutive delivery of proton and hydride to an organic substrate? If so, this would yield a *metal-free* hydrogenation system that would regenerate the FLP to further activate H_2, yielding a catalytic process. Indeed, this hypothesis was first demonstrated to be true for nitrogen-based unsaturated molecules. The mechanism of such metal-free imine reductions has been shown to proceed *via* initial protonation of the imine, followed by hydride transfer from the hydridoborate to the iminium carbon (Scheme 1).[11,12] This net transfer of proton and hydride from the phosphonium-borate to the imine regenerates the Lewis acid–base pair, which are then available for subsequent activation of H_2 regenerating the phosphonium-borate. This mechanism is consistent with the observed reactivity trends in which the electron-rich imine, *t*BuN=CPh(H) is reduced significantly faster than the electron-poor imine, $PhSO_2N$=CPh(H). In addition, the phosphonium-borate $(Cy_3P)(C_6F_4)BH(C_6F_5)_2$ [13] was shown not to react with imine. These results are consistent with initiation of the imine reduction *via* protonation.



Scheme 1 Mechanism for FLP hydrogenation of imine.

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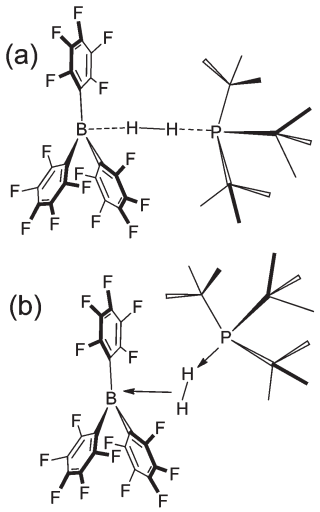


Fig. 1 Depictions of computed encounter-complex geometries.

In subsequent studies it was recognized that an FLP is also generated by the simple combination of a catalytic amount of the Lewis acid $B(C_6F_5)_3$ in the presence of the basic substrate. In this case, the substrate and the Lewis acid catalyst can combine to act as an FLP and activate H_2 forming the iminium cation. Subsequently, the hydride from the borate transfers to the generated iminium carbon to afford the corresponding amine regenerating the Lewis acid catalyst. In studying this reactivity, further support for the intermediary activated iminium species is evidenced by the isolation of the salt $[(C_6H_2Me_3)NH{=}C(Me)tBu]$-$[HB(C_6F_5)_3]$ from the stoichiometric reaction of the imine and $B(C_6F_5)_3$ under H_2.[11] Presumably, in this case, the iminium carbon-atom is too sterically hindered to allow hydride transfer from the borohydride anion. Computational studies by Papai and coworkers[14] support this proposed mechanism.

Intimate details of the process of H_2 activation and other small molecules by FLPs have been examined computationally by the groups of Papai *et al.*[15–18] and Grimme *et al.*[19–22] Both studies suggest the generation of an "encounter complex" where the Lewis acid and base are in close approach but stop short of adduct formation. However, the details of the geometry of the subsequent interaction with H_2 differ in the two models. Papai's model (Fig. 1(a)) suggests the polarization of H_2 by the electric field generated by the FLP. On the other hand, the Grimme model (Fig. 1(b)) is consistent with "side-on" H_2 donation to the B center and with concurrent donation of from P to the H_2 σ* orbital. It is noteworthy that experimental efforts to observe an "encounter complex" have not been successful.

FLP hydrogenations: catalysts and substrates

Applying this FLP approach to the reduction of nitrogen-based substrates began with our initial report of the hydrogenation of sterically encumbered imines and aziridines in the presence of 5 mol% of the phosphonium-borate $(R_2PH)(C_6F_4)BH(C_6F_5)_2$ (**1**) (R = 2,4,6-$Me_3C_6H_2$ **1a**, *t*Bu **1b**) (Fig. 2) at 80–120 °C under 1–5 atm of H_2.[12] In this fashion, imines that incorporate sterically demanding substituents on nitrogen are reduced cleanly, in high yields (Table 1) with reaction times typically ranging from

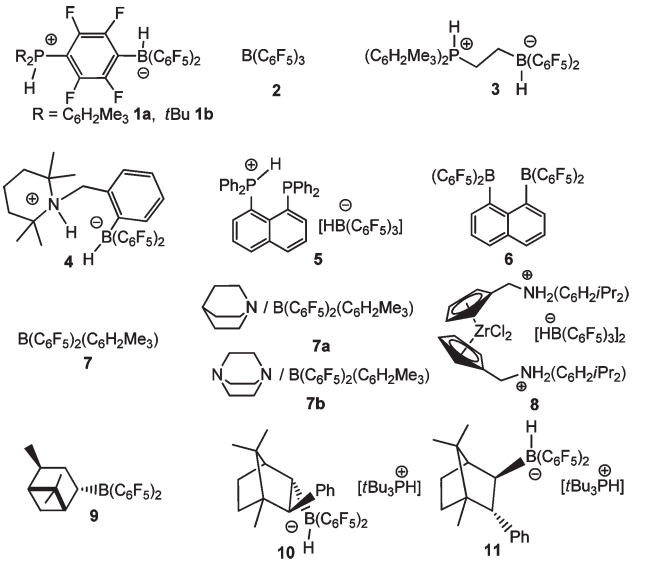


Fig. 2 FLP hydrogenation catalysts.

1–24 h (Scheme 2). The product amines are readily separated from residual catalyst *via* filtration through a plug of silica gel. Similarly, catalytic reductive ring opening of an unactivated *N*-aryl aziridine is readily accomplished under similar conditions (Table 1, Scheme 2).

In a subsequent report, we established that analogous reductions of sterically encumbered imines and aziridines could also be achieved using $B(C_6F_5)_3$ (**2**)[11] as the catalyst (Table 1). Interestingly, for electron-poor imines addition of a catalytic equivalent of $P(C_6H_2Me_3)_3$ accelerated hydrogenation as a result of the enhanced ability of the phosphine/borane to effect the heterolytic cleavage of H_2.

Following the initial reports, employing the ethylene linked phosphonium-borate $(C_6H_2Me_3)_2PH(C_2H_4)BH(C_6F_5)_2$ (**3**) (Fig. 2) as a hydrogenation catalyst was reported by the Erker group.[22,23] Perhaps because the boron in this species is less Lewis acidic than that in $B(C_6F_5)_3$, this catalyst proved to be more active.[23] For example, the imines *t*BuN=CHPh and *t*BuN=CMePh were reduced at 25 °C under 1.5 atm H_2 using this catalyst (Table 1). However, it is noteworthy that higher catalyst loadings (10 mol%) were required for these reductions. While the cause of this is not unequivocally understood, residual moisture in the imine is thought to be the issue. The Erker group further reported the use of this catalyst at 10 mol% in the reduction of a series of enamines. For example, the enamine $C_5H_{10}NC_6H_{10}$ was reduced to the amine $C_5H_{10}NC_6H_{12}$ at 25 °C and 1.5 atm H_2 in toluene. In some cases, the catalyst loadings were reduced to 3 mol% (Table 1)[24] while the reduction of the very bulky enamine $PhC(NC_5H_{10}){=}CH_2$ required more forcing conditions (50 atm H_2, 70 °C, 10 mol% catalyst) to achieve 80% yield (Scheme 3).

Repo and Rieger subsequently developed a related catalyst based on the linked amine–borane species $C_5H_6Me_4NH$-$(CH_2C_6H_4)BH(C_6F_5)_2$ (**4**) (Fig. 2) derived from tetramethylpiperidine.[25] This species was shown to catalyze the near quantitative hydrogenation of imines as well as enamines utilizing 4 mol% of catalyst, at 110 °C under 2 atm H_2.[25] Interestingly, this catalyst is also effective for sterically unencumbered imine

Table 1 Hydrogenation by FLP catalysts

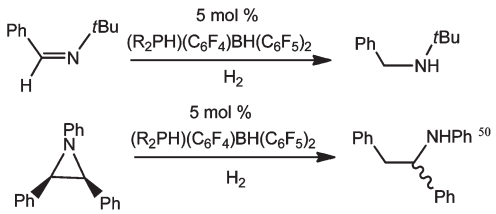
	mol%	*T* (°C)	*P* (atm)	*t* (h)	*y*
$(C_6H_2Me_3)_2PH(C_6F_4)BH(C_6F_5)_2$ 1a[12,23,29]					
PhCH=N*t*Bu	5	80	1	1	79
PhCH=NSO_2Ph	5	120	5	11	97
PhCH=$NCHPh_2$	5	140	5	1	88
PhCH=NCH_2Ph	5	120	5	48	5
PhCH=$NCH_2Ph(B(C_6F_5)_3)$	5	120	5	46	57
MeC≡$N(B(C_6F_5)_3)$	5	120	5	24	75
PhC≡$N(B(C_6F_5)_3)$	5	120	5	24	84
$(CH_2CH_2C{\equiv}N(B(C_6F_5)_3))_2$	10	120	5	48	99
PhCHCHPhNPh	10	120	5	1.5	98
$ClC_5H_3N(CH{=}NCH_2CH_2F)$	5	124	120	4	54
$ClC_5H_3N(CH{=}NCH_2CH_2F)$	5	124	120	20	46
$PhCH_2CH_2N((CH_2)_2)_2C{=}NPh$	5	117	120	20	26
$C_{10}H_{10}{=}NCH_2Ph$	5	120	120	4	93
$C_{10}H_{10}{=}NCH_2Ph$	5	120	120	20	100
$C_{10}H_{10}{=}NCH_2Pr$	5	124	120	20	78
$tBu_2PH(C_6F_4)BH(C_6F_5)_2$ 1b[12]					
PhCH=N*t*Bu	5	80	1	1	98
PhCH=NSO_2Ph	5	120	5	16	87
$ClC_5H_3N(CH{=}NCH_2CH_2F)$	5	120	120	4	10
$ClC_5H_3N(CH{=}NCH_2CH_2F)$	5	117	120	20	10
$PhCH_2CH_2N((CH_2)_2)_2C{=}NPh$	5	120	120	20	25
$C_{10}H_{10}{=}NCH_2Ph$	5	120	120	4	90
$C_{10}H_{10}{=}NCH_2Ph$	5	124	120	20	100
$C_{10}H_{10}{=}NCH_2Pr$	5	124	120	20	100
$B(C_6F_5)_3$ 2[11,3 f,32]					
PhCH=N*t*Bu	5	80	1	2	89
PhCH=NSO_2Ph	5	120	5	41	94
PhCH=$NCHPh_2$	5	120	5	1	99
PhCH=$N(SO_2C_6H_4Me)$	10	80	10	22	7
PhCH=$N(SO_2C_6H_4Me)$	10	80	20	22	97
PhCH=$N(SO_2C_6H_4Me)$	10	100	20	22	91
PhCH=$N(SO_2C_6H_4Me)$	10	100	30	22	99
$C_6H_4CMe_2CMe{=}N$	10	100	40	22	0
$C_6H_4CMe_2CMe{=}N$	10	140	20	22	21
$C_6H_4CMe_2CMe{=}N$	10	140	40	22	53
$Ph_2C{=}NtBu$	5	120	5	1	98
PhCMe=$NC_6H_2Me_3$	5	120	5	8	94
PhCMe=NPh	2.5	80	10	22	19
PhCMe=NPh	5	80	10	22	68
PhCMe=NPh	10	80	10	22	99
PhCMe=NPh	10	50	10	22	29
PhCMe=NPh	5	80	20	22	99
PhCHCHPhNPh	5	120	5	2	95
$C_6H_4CH{=}CHNMe$	1	80	103	18	0
$C_6H_4CH{=}CHNMe$	10	80	103	18	98
$C_6H_4CH{=}CMeNMe$	1	80	103	18	21
$C_6H_4CH{=}CMeNMe$	10	80	103	18	98
$C_6H_4CH{=}CPhNMe$	1	80	103	18	37
$C_6H_4CH{=}CPhNMe$	10	80	103	18	91
C_9H_6N(2-Ph)	5	25	4	4	80
C_9H_6N(2-Me)	5	50	4	16	74
C_9H_6N(8-Me)	10	80	4	6	88
$C_{13}H_9N$(acridine)	5	25	4	2	80
$C_{13}H_9N$(phenanthroline)	5	25	4	3	84
$(CH_2{=}NC_6H_2Me_3)_2$	5	120	4	24	99
$(CH_2{=}NC_6H_4iPr)_2$	5	120	4	24	99
$(C_5H_3N)(MeC{=}N(C_6H_4$-4-iPr)$_2$	5	120	4	24	99
$(C_5H_3N)(MeC{=}N(C_6H_3$-2,6-$iPr_2)_2$	5	120	4	24	99
$(C_5H_3N)(MeC{=}N(C_6H_2$-2,4,6-$Me_3)_2$	5	120	4	24	99
$ClC_5H_3N(CH{=}NCH_2CH_2F)$	5	120	120	4	13
$ClC_5H_3N(CH{=}NCH_2CH_2F)$	5	120	120	20	31
$C_{10}H_{10}{=}NCH_2Pr$	5	124	120	20	100
1-$CF_3C_6H_4$(2-C(Me)=NCH_2Ph)	2	117	120	16	95
PhC(Me)=NCH(Me)*t*Bu	10	80	5	48	100

Table 1 *(Contd.)*

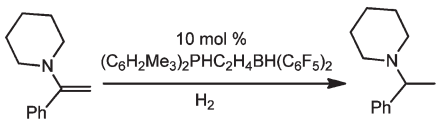
	mol%	*T* (°C)	*P* (atm)	*t* (h)	*y*
$PhC(Me){=}NCH(Me)C_6H_{11}$	10	80	5	48	100
PhC(Me)=NCH(Me)Ph	10	80	5	48	72
PhC(Me)=NCH(Me)Ph	10	25	115	23	100
PhC(Et)=NCH(Me)Ph	10	80	5	48	100
PhC(iPr)=NCH(Me)Ph	10	80	5	48	100
PhC(Et)=NCH(Et)	10	80	5	24	100
$C_7H_7Me_3{=}NCH_2Ph$	10	115	5	120	100
$C_7H_7Me_3{=}NPh$	10	115	5	120	92
$C_6H_6Me(iPr){=}NCH_2Ph$	10	115	5	120	100
$C_6H_6Me(iPr){=}NPh$	20	115	5	120	100
$C_6H_6Me(iPr){=}NPh$	10	115	5	120	66
$(C_6H_2Me_3)_2PH(C_2H_4)BH(C_6F_5)_2$ 3[23]					
PhCH=N*t*Bu	20	25	2.5	—	87
PhCMe=N*t*Bu	5	25	2.5	3	70
$PhC(NC_5H_{10}){=}CH_2$	10	25	2.5	—	99
$(C_5H_{10}N)C{=}CH(CH_2)_4$	5	25	2.5	—	88
$O(CH_2CH_2)_2NC{=}CH(CH_2)_4$	3	25	2.5	—	78
$CH_2C(C_5H_4)CH{=}C(NMe_2)C_5H_4ZrCl_2$	20	25	2.5	—	27
$(CH_2C(C_5H_4)CH{=}C(NMe_2)$-$C_5H_4)Fe$	5	25	2.5	—	77
$CH_2C(C_5H_4)CH{=}C(N((CH_2)_2)_2CH)_2C_5H_4Fe$	5	25	2.5	—	99
$(CH_2C(C_5H_4)CH{=}C(N((CH_2)_2)_2O)_2)C_5H_4)Fe$	5	25	2.5	—	99
$C_5H_6Me_4NH(CH_2C_6H_4)BH(C_6F_5)_2$ 4[33]					
PhCH=NCH_2Ph	8	110	2	12	99
PhCH=NMe	4	110	2	24	4
$PhCH_2CMe{=}NMe$	4	110	2	24	4
$MeOC_6H_4CMe{=}NCH_2Ph$	4	110	2	6	99
$ClC_6H_4CMe{=}NCH_2Ph$	4	110	2	6	99
$(C_5H_{10}N)C{=}CH(CH_2)_4$	4	110	2	12	85
$[C_{10}H_6(PPh_2)_2H][HB(C_6F_5)_3]$ 5[26]					
$Ph(Me_3SiO)C{=}CH_2$	20	25	2	20	93
$tBu(Me_3SiO)C{=}CH_2$	20	25	2	20	89
$(Me_3SiO)C{=}CH(CH_2)_4$	20	25	2	20	86
$(Me_3SiO)C{=}CH(CH_2)_3$	20	25	2	20	85
$Me(Me_3SiO)C{=}CH_2$	20	25	60	3	99
$C_{10}H_6(B(C_6F_5)_2)_2$ 6[27]					
PhCH=$NCHPh_2$	5	120	15	1	99
PhCH=N*t*Bu	10	120	15	1	99
PhCH=NPh	10	120	15	1	78
PhCH=NCH_2Ph	10	120	15	6	5
PhCH=NC_6H_4Cl	10	120	15	1	99
$ClC_6H_4CH{=}NC_6H_4Cl$	10	120	15	1	99
$NO_2C_6H_4CH{=}NPh$	10	120	15	1	99
$B(C_6F_5)_2(C_6H_2Me_3)$ 7[34]					
C_9H_7N	10	105	4	17	80
C_9H_6N(2-Me)	10	105	4	17	86
C_9H_6N(8-Me)	10	105	4	17	84
C_9H_6N(2-Ph)	10	105	4	17	93
$C_{13}H_9N$(acridine)	10	105	4	17	99
C_9H_6N(6-OMe)	10	105	4	17	63
C_9H_5N(6-OMe)(2-Me)	10	105	4	17	79
C_9H_6N(8-Br)	10	105	4	17	82
C_9H_5N(6-Br)(2-Me)	10	105	4	17	80
C_9H_5N(8-Cl)(2-Me)	10	105	4	17	84
C_9H_6N(2-CH=CHPh)	10	105	4	17	82
C_9H_5N(6-CH=CHPh)(2-Me)	10	105	4	17	79
C_9H_5N(5-CH=CHPh)(2-Me)	10	105	4	17	78
$[CH(CH_2CH_2)_3NH][HB(C_6F_5)_2(C_6H_2Me_3)]$ 7a[28]					
PhCH=N*t*Bu	10	20	4	42	81
$MeOC_6H_4CH{=}NtBu$	10	20	4	42	75
PhCH=NCH_2Ph	10	20	4	42	49
$MeO(CH_2CHCH_2O)C_6H_3CH{=}NtBu$	10	20	4	42	72
$CH_3CH{=}CHCH{=}NtBu$	10	20	4	42	97
$O(CH_2CH_2)_2NC{=}CH(CH_2)_4$	10	20	4	42	73
$[N(CH_2CH_2)_3NH][HB(C_6F_5)_2(C_6H_2Me_3)]$ 7b[28]					
PhCH=N*t*Bu	10	20	4	42	99

Table 1 *(Contd.)*

	mol%	*T* (°C)	*P* (atm)	*t* (h)	*y*
$MeOC_6H_4CH{=}NtBu$	10	20	4	42	98
$PhCH{=}NCH_2Ph$	10	20	4	42	16
$MeO(CH_2CHCH_2O)C_6H_3CH{=}NtBu$	10	20	4	42	99
$CH_3CH{=}CHCH{=}NtBu$	10	20	4	42	24
$O(CH_2CH_2)_2NC{=}CH(CH_2)_4$	10	20	4	42	92
$(CH_2{=}CMe)C_6H_6MeO$	20	20	4	14	87
$[(C_5H_4CH_2NH(C_6H_3iPr_2))_2ZrCl_2][HB(C_6F_5)_3]_2$ 8[24]					
$tBuCH{=}NC_6H_3Me_2$	6	25	2	—	99
$tBuCH{=}NC_6H_3iPr_2$	2	25	2	—	99
$tBu(Me_3SiO)C{=}CH_2$	5	25	2	—	85
(α-pinenyl)$B(C_6F_5)_2$ 9[32]					
PhCMe=NPh	10	65	20	22	99
(α-Ph-pinenyl)$B(C_6F_5)_2$ 10[35]					
PhCMe=NPh	5	65	25	15	99
PhCMe=NPh	5	65	25	15	99
PhCMe=NPh	5	65	25	15	95
$PhCMe{=}N(C_6H_4Me)$	5	65	25	15	37
$PhCMe{=}N(C_6H_3iPr_2)$	5	65	25	15	0
$MeOC_6H_4CMe{=}NPh$	5	65	25	15	96
$PhCMe{=}NC_6H_4OMe$	5	65	25	15	99
$(C_{10}H_7)CMe{=}NPh$	5	65	25	15	93
$(C_{10}H_7)CMe{=}NC_6H_4OMe$	5	65	25	15	96



Scheme 2 Examples of imine and aziridine hydrogenation by an FLP.

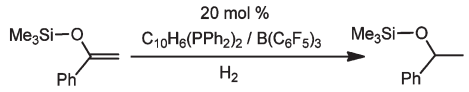


Scheme 3 Enamine hydrogenation by an FLP.

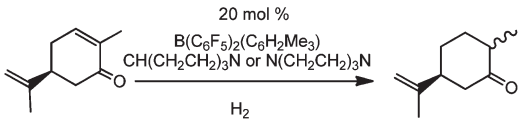
substrates such as $PhCH_2C(Me){=}NMe$ (Table 1). This presumably results from the steric congestion about the boron center which precludes adduct formation with either the substrate imine or the product amine.

The Erker group also uncovered FLP reductions employing the combination of the bis-phosphine $C_{10}H_6(PPh_2)_2$ and $B(C_6F_5)_3$ as a catalyst.[26] This pair generates the salt $[C_{10}H_6(PPh_2)_2H]$ $[HB(C_6F_5)_3]$ (**5**) (Fig. 2) under H_2 at 25 °C. The FLP was shown to catalytically hydrogenate silyl enol ethers affording the corresponding silyl ether under relatively mild conditions of 2 atm H_2 pressure and 25 °C (Table 1, Scheme 4).[26] Again, the steric demands of the substrate are crucial in these reactions as reduction of the sterically less-hindered silyl enol ether, $Me_3SiO(Me)C{=}CH_2$, required more forcing reaction conditions of 60 atm H_2 and 70 °C.

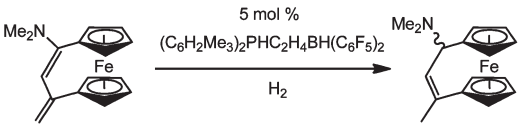
In a related strategy, Berke and co-workers achieved hydrogenations of imines employing the Lewis acid 1,8-bis-(dipentafluorophenylboryl)naphthalene, $C_{10}H_6(B(C_6F_5)_2)_2$ (**6**)[27]



Scheme 4 Silyl enol ether hydrogenation by an FLP.



Scheme 5 Carvone hydrogenation by an FLP.



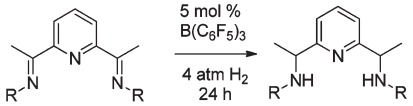
Scheme 6 FLP hydrogenation of a metallocene.

(Fig. 2) under 15 atm H_2 at 120 °C (Table 1). Mechanistic studies suggested that H_2 activation *via* a "super Lewis acidic activation pathway" involving both boron centers has a higher barrier than "external" activation of H_2 at just one boron center.

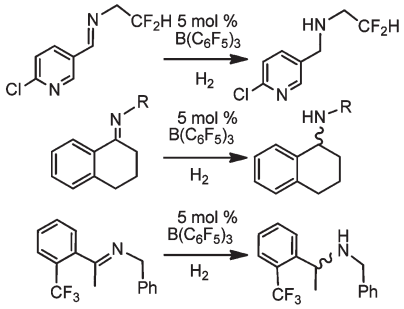
In further efforts to extend the functional group tolerance the Soos group have developed a clever approach based on "size exclusion".[28] Prompted by the notion that steric congestion about the Lewis acid center could preclude reaction with donor molecules but allows reaction with H_2, Soos and coworkers explored the utility of $B(C_6F_5)_2(C_6H_2Me_3)$. For example, the species $B(C_6F_5)_2(C_6H_2Me_3)$ **7** in combination with one of the nitrogen-bases $CH(CH_2CH_2)_3N$ or $N(CH_2CH_2)_3N$, acts as catalyst (**7a** and **7b**) for the reduction of imines at 20 °C and 4 atm H_2 (Table 1).[28] Interestingly, the additional steric congestion about the boron center presumably accounts for the ability of these catalysts to reduce $MeO(CH_2CHCH_2O)C_6H_3CH{=}NtBu$ which incorporates both ether and vinyl functional groups. In addition, these catalyst systems effect the complete hydrogenation of $CH_3CH{=}CHCH{=}NtBu$. Even the conjugated olefinic bond in carvone was hydrogenated, although this reaction was quite slow (6 days) (Scheme 5).

The Erker group has also constructed FLP catalysts on an organometallic scaffold. For example, the zirconocene-salt, $[(C_5H_4CH_2NH_2(C_6H_3iPr_2))_2ZrCl_2][HB(C_6F_5)_3]_2$ (**8**)[24] (Fig. 2), behaves as an FLP hydrogenation catalyst for imines and silyl enol ethers (Table 1). In addition, FLP hydrogenations can also be effected on metallocene-based substrates. For example, the diene–amine complex $(CH_2C(C_5H_4)CH{=}C(NR_2)C_5H_4)Fe$ was hydrogenated using H_2 in the presence of the phosphonium borate (**3**) affording the product $(CH_3C(C_5H_4){=}CHCH(NR_2)$-$C_5H_4)Fe$ in high yields (Scheme 6). However, the substrate $(CH_2C(C_5H_4)CH{=}C(NMe_2)C_5H_4)ZrCl_2$ could only be reduced to $(CH_3C(C_5H_4){=}CHCH(NMe_2)$ $C_5H_4)ZrCl_2$ in 27% yield (Table 1).[29]

This reduction strategy can also be applied to diimines. For example, simple diimines, as well as pyridyldiimines were easily reduced to the corresponding diamines in the presence of the catalyst $B(C_6F_5)_3$ (**2**) (Scheme 7).[30] Similarly, the imine precursors



Scheme 7 FLP hydrogenation of a diimine.



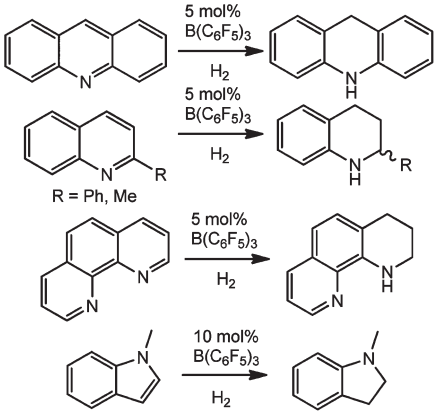
Scheme 8 FLP hydrogenations of several imine substrates.

to potential herbicides, the *N*-propyl and benzyl analogs of the antidepressant sertraline, and $CF_3C_6H_4CMe{=}NCH_2Ph$, a precursor to anti-cancer and herbicide candidates were readily reduced using this FLP strategy (Scheme 8). In contrast, reduction of fentanyl, a potent analgesic narcotic was low yielding; presumably a result of coordination of the amine center in the substrate to the boron center of the catalyst.

Functional group tolerance testing for FLP hydrogenation using either phosphine-boranes, (**1**) or the borane (**2**) showed that these catalysts remained active in the presence of naphthalene, bulky ethers, n-hexyl acrylate, bulky amines and alkyl and aryl halides.[30] However, the activity was reduced in the presence of $PhNMe_2$, $tBuNH_2$, carbamate esters, ketones or aldehydes. Moreover, these catalysts were not functional in the presence of $2,4,6\text{-}Me_3C_6H_2OH$, but tolerated the presence of $2,6\text{-}tBu_2C_6H_3OH$. These data suggest that the first generation of FLP reduction catalysts have functional group tolerance that is limited to either non-polar substituents or sterically encumbered donor functionalities. Nonetheless, optimization of the conditions for imine reduction showed that using highly pure imine substrates, FLP reduction can be effected with as little as 0.1 mol% catalyst at 130 °C and 120 atm H_2.

In early efforts to adapt FLP reductions to catalytic asymmetric hydrogenations, Chen and Klankermayer[32] reported the reduction of PhN=CPh(Me) to the corresponding chiral amine using $(\alpha\text{-pinenyl})B(C_6F_5)_2$ (**9**) to give a 13% enantiomeric excess in the product. However, building on this strategy, they subsequently developed other derivatives of these chiral boranes[35] (**10**, **11**) which afforded hydrogenation of prochiral imines with enantiomeric excesses as high as 83%. In our own efforts,[36] we have employed **2** to catalyze the hydrogenation of chiral imines with diastereoselectivity. While phenethylamine derivatives gave varying diastereomeric excesses ranging from 0 to 68%, camphor or menthone derived imines were reduced with >95% diastereomeric excess.

To broaden the scope of substrates, our group has applied FLP hydrogenations to substituted nitrogen-heterocycles including substituted quinolines, phenanthroline, acridine and several indole derivatives (Scheme 9). For example, using a catalytic



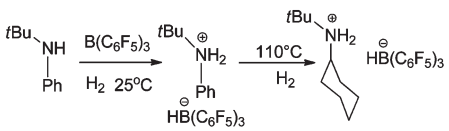
Scheme 9 FLP hydrogenations of nitrogen-based heterocycles.

amount of (**2**) under H_2,[31,37–39] the substituted quinolines and phenanthroline are reduced in 4 h at 25 °C. These species take up two equivalents of H_2 thus saturating the nitrogen-containing ring. In the case of indole derivatives, higher pressures of H_2 (103 bar) and 80 °C for 18 h were required.

It is noteworthy that in a recent paper Soos and co-workers[34] have also employed the sterically encumbered borane $B(C_6F_5)_2(C_6H_2Me_3)$ to effect the FLP hydrogenation of a series of nitrogen-based heterocycles in yields generally exceeding 80%.

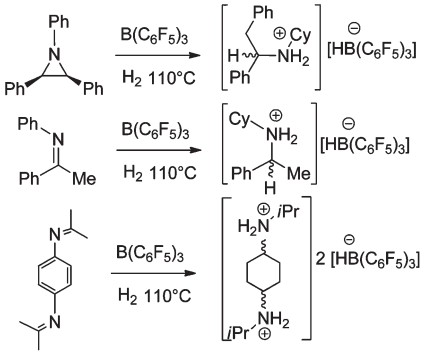
Aniline reductions

Consistent with FLP activation of H_2, the combination of the amine *t*BuNHPh with an equivalent of (**2**) in C_6D_5Br or pentane solutions under H_2 (4 atm) at 25 °C for 12 h resulted in the formation of $[tBuNH_2Ph][HB(C_6F_5)_3]$.[40] However, we have recently reported that subsequent heating of the above reaction mixture to 110 °C for 96 h under H_2 results in the reduction of the *N*-bound aromatic ring affording $[tBuNH_2Cy][HB(C_6F_5)_3]$ (Scheme 10). This remarkable reduction has also been achieved with a variety of other aniline derivatives. For example, hydrogenation with an equivalent of $B(C_6F_5)_3$ of iPrNHPh afforded $[iPrNH_2Cy][HB(C_6F_5)_3]$ while hydrogenation of PhCyNH or Ph_2NH gave $[Cy_2NH_2][HB(C_6F_5)_3]$. In a similar fashion, iPrNH(2-MeC_6H_4), iPrNH(4-RC_6H_4) (R = Me, OMe), iPrNH(3-MeC_6H_4) and iPrNH(3,5-$Me_2C_6H_3$) were reduced with $B(C_6F_5)_3$ in toluene under H_2 (4 atm) at 110 °C affording the arene-reduced products $[iPrNH_2(2\text{-}MeC_6H_{10})][HB(C_6F_5)_3]$, $[iPrNH_2(4\text{-}RC_6H_{10})][HB(C_6F_5)_3]$ (R = Me, OMe), $[iPrNH_2(3\text{-}MeC_6H_{10})][HB(C_6F_5)_3]$ and $[iPrNH_2(3,5\text{-}Me_2C_6H_9)][HB(C_6F_5)_3]$ in yields ranging from 61–82%.[40]

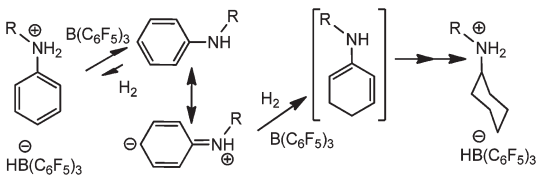


Scheme 10 Hydrogenation of *t*-butylaniline.

This same strategy was applied to *cis*-1,2,3-triphenylazirdine. Treatment with one equivalent of $B(C_6F_5)_3$ at 110 °C for 96 h, yielded the salt $[CyNH_2CHPhCH_2Ph][HB(C_6F_5)_3]$.[40] It is noted



Scheme 11 Hydrogenation of aniline- and diamine benzene derivatives.



Scheme 12 Proposed reaction pathways to anilinium and cyclohexylammonium salts.

that only the *N*-bound phenyl ring is selectively reduced. In a similar fashion the imines PhN=CMePh and $(Me_2C{=}N)_2C_6H_4$ are reduced to $[PhCH(Me)NH_2Cy][HB(C_6F_5)_3]$ and $[(iPrNH_2)_2C_6H_{10}][HB(C_6F_5)_3]_2$, respectively (Scheme 11).

Computational studies suggest that the FLP activation of H_2 by amine *t*BuNHPh and $B(C_6F_5)_3$ is energetically 9.7 kcal mol^{-1} lower than the FLP. At elevated temperatures, this barrier yields equilibrium conditions allowing for the rotation of the amine, providing a van der Waals complex in which the *para*-carbon of the arene ring is oriented towards the boron atom. FLP activation in this case has low energy barrier of 8.7 kcal mol^{-1}, resulting in a net free activation enthalpy (*i.e.* relative to the FLP) of 23.8 kcal mol^{-1}. The resulting transient intermediate product $[tBuNHC_6H_6][HB(C_6F_5)_3]$ undergoes subsequent hydrogenation completing the arene reduction (Scheme 12).[40] The reaction is concluded with the activation of H_2 by the generated cyclohexylamine and borane. The greater basicity of the reduced ammonium salt precludes the loss of H_2 and results in the termination of the reaction with the formal uptake of 4 equivalents of H_2. This view is also consistent with the observation that no arene reduction is seen for hydrogenation of the more basic amine iPr_2NPh with $B(C_6F_5)_3$ under H_2 yielding only $[iPr_2NHPh][HB(C_6F_5)_3]$. These FLP hydrogenations of the *N*-phenyl amines are rare examples of homogeneous hydrogenations of aromatic rings and the first to be metal-free (Table 2).

Future considerations

It has been almost 100 years since the work of Sabatier uncovered the ability of heterogeneous metals to catalyze hydrogenations. Indeed, with the advent of homogeneous catalysts in the 1960s, the ability of transition metals to activate H_2 became part

Table 2 Aniline hydrogenations

Aniline	Product cation	*t* (h)	Y %
*t*BuNHPh	$[tBuNH_2Cy]^+$	96	30
iPrNHPh	$[iPrNH_2Cy]^+$	36	93
CyNHPh	$[Cy_2NH_2]^+$	36	88
Ph_2NH	$[Cy_2NH_2]^+$	96	65
$iPrNH(2\text{-}MeC_6H_4)$	$[iPrNH_2(2\text{-}MeC_6H_{10})]^+$	36	77
$iPrNH(4\text{-}MeC_6H_4)$	$[iPrNH_2(4\text{-}MeC_6H_{10})]^+$	36	73
$iPrNH(4\text{-}MeOC_6H_4)$	$[iPrNH_2(4\text{-}MeOC_6H_{10})]^+$	36	61
$iPrNH(3\text{-}MeC_6H_4)$	$[iPrNH_2(3\text{-}MeC_6H_{10})]^+$	36	82
$iPrNH(3,5\text{-}Me_2C_6H_3)$	$[iPrNH_2(3,5\text{-}Me_2C_6H_9)]^+$	72	48
$PhN(C_2H_2Ph_2)$	$[CyNH_2(CH(Ph)CH_2Ph)]^+$	96	50
PhN=C(Me)Ph	$[CyNH_2CH(Me)Ph]^+$	96	57
$(Me_2C{=}N)_2C_6H_4$	$[(iPrNH_2)_2C_6H_{10}]^{2+}$	72	64

of the dogma of organometallic chemistry. However, the discovery of the FLP heterolytic cleavage of H_2 has begun to alter this view. To date, the FLP approach to hydrogenation has been applied to imines, aziridines, enamines, silyl enol ethers, diimines, metallocene derivatives and nitrogen-based heterocycles as well as the unprecedented *metal-free* reduction of aromatic derivatives. While the area is only five years old, it is clear that new developments will continue to emerge and find applications in academic and potentially industrial settings.

In terms of potential applications, one of the key advantages is that FLP reductions offer the possibility of effecting hydrogenation without transition metal residue in the products. It is well known that the removal of transition metal catalyst residue from pharmaceutical products constitutes a significant cost for the drug industry. Similarly, the total absence of metal contaminants is critical for materials used in electronic applications. The first generation of FLP catalysts required high Lewis acidity to effect H_2 activation and this presented significant limitations in terms of substrate scope. Nonetheless, recent work on specifically designed FLP catalysts by Soos and co-workers[15,28] have shown improved range of applications and thus further improvements are likely to be the subject of future studies. Fine control of the catalysts is likely to broaden the range of substrates which can be reduced. Aspects of catalyst selectivity are also in the early stages of study, but the cutting-edge work of Klankermayer *et al.*[32,35] has already demonstrated the potential of FLP catalysts for asymmetric hydrogenation. These seminal works may foreshadow the application of FLP reductions in syntheses of compounds of pharmaceutical interest.

The more recent finding of aromatic reduction of aniline derivatives[40] provides an unprecedented approach to metal-free reduction of an aromatic ring. The scope studied to date is limited, but it is clear that this finding should provide synthetic chemists with an unconventional strategy to cyclic amine derivatives.

In all of these FLP reductions, the underlying message to the synthetic chemists is clear: a new tool for hydrogenation has been added to the chemists' toolbox. It is our hope that synthetic chemists will find creative new uses for this tool.

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