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FORUM ARTICLE

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Metal-Free Catalytic Hydrogenation of Polar Substrates by Frustrated Lewis Pairs

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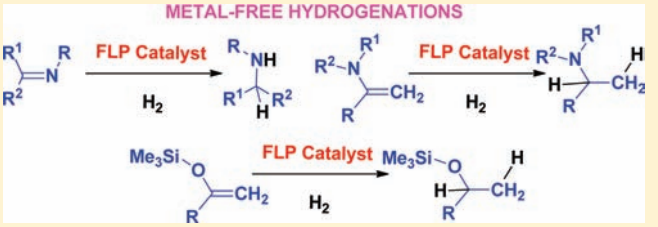
Supporting Information

ABSTRACT: In 2006, our group reported the first metal-free systems that reversibly activate hydrogen. This finding was extended to the discovery of "frustrated Lewis pair" (FLP) catalysts for hydrogenation. It is this catalysis that is the focal point of this article. The development and applications of such FLP hydrogenation catalysts are reviewed, and some previously unpublished data are reported. The scope of the substrates is expanded. Optimal conditions and functional group tolerance are considered and applied to targets of potential commercial significance. Recent developments in asymmetric FLP hydrogenations are also reviewed. The future of FLP hydrogenation catalysts is considered.



INTRODUCTION

The addition of molecular hydrogen (H_2) to an unsaturated organic molecule defines a process known as hydrogenation. This seemingly facile transformation is used in a very diverse range of applications. Indeed, the breadth of the application of this chemical process is unparalleled in the chemical industry. Large-scale commercial use of hydrogenation is required for the upgrading of crude oil, production of bulk commodity materials, as well as fine chemicals used in the food, agricultural, and pharmaceutical industries.[1] The atom economy and cleanliness of the transformation makes hydrogenation "arguably the most important catalytic method in synthetic organic chemistry both on the laboratory and the production scale".[2]

Catalytic hydrogenation of unsaturated compounds began with the discovery by Sabatier in 1897 that traces of nickel could mediate the catalytic addition of H_2 to olefins. This discovery of the use of nickel as a heterogeneous catalyst culminated in a share of the 1912 Nobel Prize with Grignard. The onset of organometallic chemistry and the discoveries of ruthenium- and rhodium-based hydrogenation catalysts by Wilkinson and others in the 1960s prompted the evolution of homogeneous transition-metal-based hydrogenation catalysts for a variety of substrates. These catalysts operated by the interaction of H_2 with the metal to effect oxidative addition, affording intermediate dihydride complexes.[3] In the 1990s, Noyori discovered that transition-metal complexes incorporating amido ligands effect heterolytic cleavage of H_2. This results in a metal hydride and protonation of the amide ligand to give an amine. Outer-sphere transfer of the proton and hydride to a substrate affords a distinct strategy to hydrogenation.[4,5]

With these well-established precedents, it was generally accepted dogma within inorganic and organometallic chemistry that the activation of H_2, and small molecules, required the action of a coordinatively unsaturated transition-metal center. Nonmetal catalysts for hydrogenation reactions had received very limited attention. Organocatalytic hydrogenations of enones and imines was possible; however, these systems required a Hantzsch ester as the stoichiometric source of H_2.[6−10] In some sense, these systems mimic NADH[11] in natural systems because the transfer of H_2 is thought to proceed via proton and hydride transfer. Such reductions have been extended to asymmetric systems with the use of chiral Brønsted acids.[8,12−15] While these systems support the view that consecutive transfer of proton and hydride to a substrate can be mediated by non-transition-metal species, the development of nonmetal hydrogenation catalysts that employ H_2 seemed unlikely because so few main-group species were known to react with H_2. Sander et al.[16,17] reported that the reaction of H_2 with difluorovinylidene generated in an argon matrix at 20−30 K to give 1,1-difluoroethene ($F_2C{=}CH_2$; Scheme 1b) and showed no significant activation barrier.[16−20] This work clearly foreshadowed the more recent work of Bertrand and co-workers,[21] in which the reaction of H_2 with monoaminocarbenes resulted in conversion to the corresponding amine (Scheme 1c). An early report described the use of KO^{t}Bu as a catalyst to hydrogenate benzophenone at 200 °C and >100 bar of H_2 (Scheme 1a).[22] In a similar sense, strong acids such as HF-TaF_5, HF-SbF_5, or HBr-$AlBr_3$ were used to catalyze

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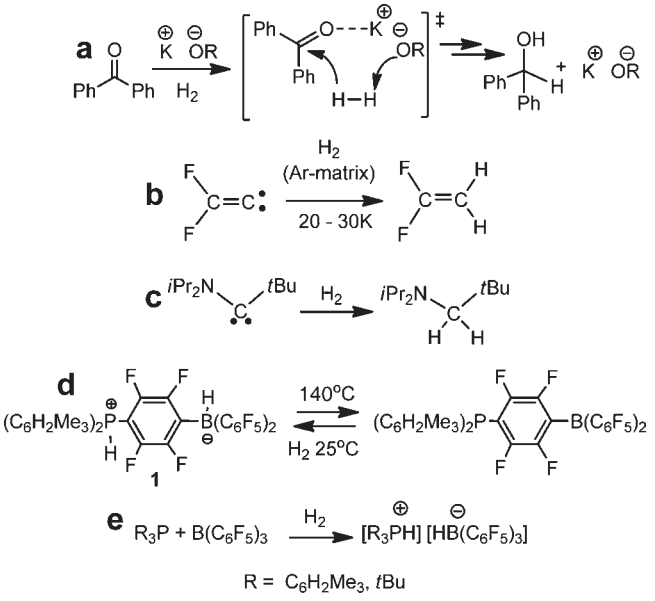
Scheme 1. Nonmetal Reactions with H_2



the reduction of aromatics, cyclic alkenes, and dienes using H_2 at elevated pressure, although in some cases, rearrangement of the carbon frameworks was observed.[23−25] In related work, Köster et al. reported the complete or partial reduction of arenes using BH_3 as the catalyst at 200 °C and high H_2 pressures.[26,27] A related borane-catalyzed process has also been described by Haenel to effect the liquefaction of coal.[28]

In terms of isolable molecular nonmetal species that react with H_2, Power and co-workers were the first to report the uncatalyzed addition of H_2 to a main-group substrate. In that work, digermanium and ditin alkyne analogues were reduced with H_2 to gives mixtures of products.[29,30] Subsequently, in 2006, we reported the first reversible activation of H_2 by a nonmetal system with the interconversion of phosphonium borate (2,4,6-$Me_3C_6H_2)_2PH(C_6F_4)BH(C_6F_5)_2$ (**1**; Scheme 1d) and the corresponding phosphine−borane species (2,4,6-$Me_3C_6H_2)_2P(C_6F_4)B(C_6F_5)_2$. Heating of the salt **1** above 140 °C liberates H_2, while the zwitterion **1** is regenerated by simple exposure of the phosphine−borane to H_2 at 25 °C.[31] In a subsequent report, we demonstrated that this ability to activate H_2 was not limited to this novel linked phosphine−borane system but rather that simple, sterically demanding combinations of monomolecular phosphines and boranes could effect such an activation of H_2.[32] For example, while the combination of $^tBu_3P$ and $B(C_6F_5)_3$ results in no apparent reaction, the addition of H_2 results in an immediate reaction, affording $[^tBu_3PH][HB(C_6F_5)_3]$ (Scheme 1e). In subsequent papers, we and others have described a series of combinations of sterically encumbered Lewis acids and bases that are capable of similar activation of H_2. Such systems are now commonly referred to as "frustrated Lewis pairs" (FLPs), and their general reactivity with small molecules has recently been reviewed.[33−36]

The ability to activate H_2 with non-transition-metal systems presents questions about the potential for hydrogenation catalysis. The concept is simple. Activation of H_2 by an FLP followed by the delivery of proton and hydride to an organic substrate would regenerate the FLP and provide the saturated product. Thus, in this Forum Article, we focus on the development of FLP

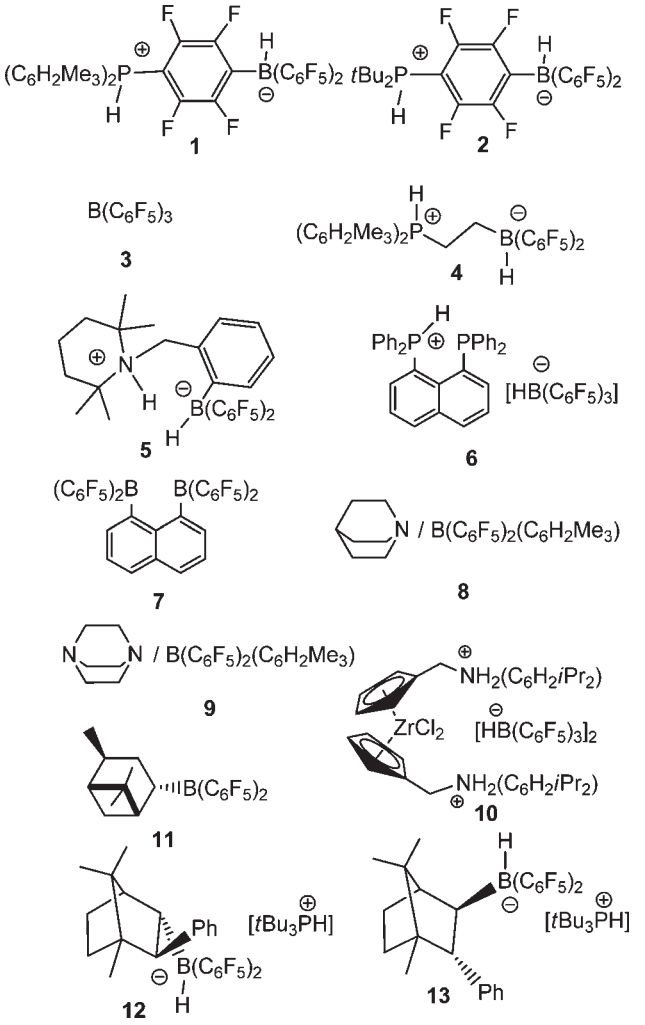


Figure 1. Catalysts for FLP hydrogenation.

hydrogenation catalysts, integrating a review of recent progress with the report of previously unpublished data. The latter work expands the scope of substrates, describes optimal conditions, and evaluates functional group tolerance. In addition, recent work on the aspects of catalytic asymmetric hydrogenation and the hydrogenation of targets of commercial significance is reported.

RESULTS AND DISCUSSION

Initial FLP Hydrogenation of Imines, Nitriles, and Aziridines. The reduction of imines is a synthetic method to generate secondary and primary amines used in the pharmaceutical and fine chemical industries.[37−39] In our first report of metal-free catalytic hydrogenation using H_2 and mild conditions, we described the reduction of imines using the phosphonium borate $(R_2PH)(C_6F_4)BH(C_6F_5)_2$ [R = 2,4,6-$Me_3C_6H_2$ (**1**), ^{t}Bu (**2**); Figure 1].[40] For example, imines, which include sterically demanding substituents on nitrogen, are reduced cleanly in high yield at 80−120 °C under H_2 pressures of 1−5 atm using 5 mol % **1** or **2** as the catalyst (Scheme 2a and Table 1). Separation of the amine products involves simple filtration through a plug of silica gel, affording pure amine product, as evidenced by NMR spectroscopy. In a similar fashion, catalytic reductive ring opening

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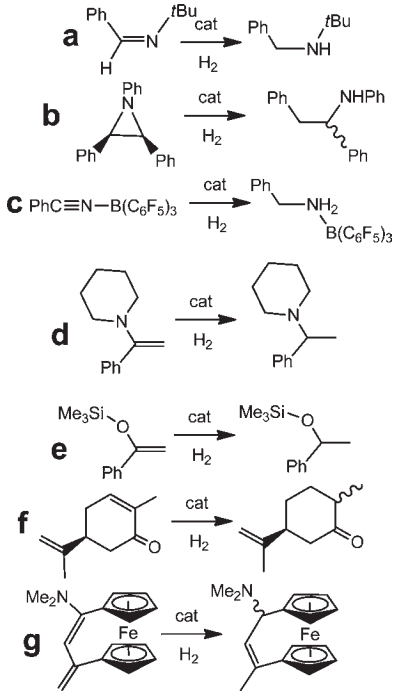
Scheme 2. Examples of FLP Hydrogenation



of an unactivated *N*-arylaziridine functionality is achieved under similar conditions (Scheme 2b and Table 1).

In the case of sterically less demanding imines, only stoichiometric reduction is observed.[40] Similarly, nitriles are not catalytically reduced. These observations are attributable to the formation of classical Lewis acid−base adducts. Such strong binding to the boron center of the catalyst inhibits the catalytic cycle. Recognizing that $B(C_6F_5)_3$ is more Lewis acidic than the boron center in the dehydrogenated phosphine−borane catalyst **1**, one strategy to reduce a sterically unencumbered imine or nitrile is to employ the corresponding $B(C_6F_5)_3$ adducts as substrates. In this fashion, the phosphonium borate **1** can be used as a hydrogenation catalyst to reduce a borane-bound imine or nitrile to give the corresponding amine−borane adducts.[41] For example, the imine−borane adduct $(PhCH{=}NCH_2Ph)B(C_6F_5)_3$ is reduced to $(PhCH_2NHCH_2Ph)B(C_6F_5)_3$, while $(PhCN)B(C_6F_5)_3$ and $(CH_2CH_2CN)_2(B(C_6F_5)_3)_2$ are reduced to $(PhCH_2NH_2)B(C_6F_5)_3$ and $(CH_2CH_2CH_2NH_2)_2(B(C_6F_5)_3)_2$, respectively (Scheme 2c and Table 1). It is certainly true that using $B(C_6F_5)_3$ as a "protecting group" is hardly a practical approach; nonetheless, these transformations do demonstrate that the principle of FLP reduction can be extended to sterically unencumbered C−N double and triple bonds.

The mechanism of these metal-free reductions is thought to proceed via protonation of the imine, followed by hydride transfer from the hydridoborate (Scheme 3). This results in liberation of the FLP, which is then available to react with H_2, regenerating phosphonium borate. The fact that the electron-rich imine ^{t}BuN=CPh(H) is reduced significantly faster than the electron-poor imine $PhSO_2N{=}CPh(H)$ is consistent with this proposed mechanism. In addition, it was shown that there is no stoichiometric reaction of the phosphonium borate $(Cy_3P)(C_6F_4)BH(C_6F_5)_2$[42] with the imine ^{t}BuN=CPh(H), indicating that the reductions are initiated by proton transfer and not delivery of the B−H hydride. Further, stoichiometric reactions of imines and **1** at 25 °C afforded generation of $((2,4,6\text{-}Me_3C_6H_2)_2P)(C_6F_4)B(C_6F_5)_2(^t\text{BuNHCH}_2\text{Ph})$, while under H_2, the ion pair $[^t\text{BuNH}_2\text{CH}_2\text{Ph}][^t\text{Bu}_2\text{PC}_6\text{F}_4\text{BH}(C_6F_5)_2]$ is generated. These observations are also consistent with the proposed mechanism in which elevated temperatures between 80 and 120 °C promote amine dissociation and enhance the rate of catalytic reduction. It is important to note that while imines, nitriles, and aziridines are efficiently reduced in a catalytic manner, aldehydes react in a stoichiometric fashion, affording the phosphonium alkoxyborate zwitterions $R_2PHC_6F_4B(C_6F_5)_2OCH_2Ph$ exclusively. This view is consistent with the oxophilicity of boron and the strength of the B−O bond. The proposed mechanism based on these experimental data was subsequently supported by the computational studies of Papai and co-workers.[43]

Lewis Acid Catalyzed Hydrogenation. The discovery of metal-free hydrogenation by FLPs prompted the suggestion that when using a sterically encumbered basic substrate, it should be possible to effect hydrogenation using only a catalytic amount of Lewis acid. Indeed, the combination of a catalytic amount of $B(C_6F_5)_3$ (**3**) (Figure 1) with an imine substrate under H_2 with mild heating was shown to afford the corresponding amines, which were isolable in high yields[44] (Table 1). Mechanistically, this is thought to be similar to the process described above, with the only difference being that the initial activation of H_2 results from the action of an FLP derived from **3** and the sterically demanding imine. This activation generates a transient iminium hydridoborate. Subsequent transfer of the hydride from boron to the iminium carbon affords the amine−borane adduct, while thermally induced release of the amine regenerates free **3**, which is then available for further H_2 activation. In support of this view, it is noteworthy that efforts to hydrogenate the ketimine $(C_6H_2Me_3)N{=}CMe(^t\text{Bu})$ fail, affording only the intermediate iminium hydroborate $[(C_6H_2Me_3)HN{=}CMe(^t\text{Bu})][HB(C_6F_5)_3]$ (Scheme 4). Presumably, this is attributable to the steric demands about the iminium carbon, which precludes hydride transfer. While these observations suggest that phosphine is not required for FLP hydrogenation of imines, it is noteworthy that, in cases where the imine is a poor base, the 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 heterolytic cleavage of H_2.

Expanding the Scope of FLP Hydrogenation Catalysts and Substrates. Shortly after our initial reports, the Erker group developed the phosphonium borate $(C_6H_2Me_3)_2PHC_2H_4BH(C_6F_5)_2$ **4** (Figure 1), which proved to be an even more active catalyst, effecting the metal-free hydrogenation of imines at ambient conditions (Table 1).[45] For example, this catalyst effects the reduction of ^{t}BuN=CHPh and ^{t}BuN=CMePh at 25 °C under 1.5 bar of H_2. In the former case, there is a need for higher catalyst loadings, which is not unambiguously understood. However, this may be attributable to residual moisture in the imine (vide infra).

The linked amine−borane species derived from tetramethylpiperidine, $C_5H_6Me_4NHCH_2C_6H_4BH(C_6F_5)_2$ (**5**; Figure 1) was developed by the research groups of Repo and Rieger. This species has been shown to be effective for the hydrogenation of several imines and enamines,[46] affording near-quantitative yields of the reduced products. As appears typical, this catalyst was also less effective in the case of sterically less encumbered imine substrates such as $PhCH_2C(Me){=}NMe$ (Table 1).

With the target of expanding the scope of FLP reductions, the Erker group recognized that FLP hydrogenation could be applied

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Table 1. FLP Hydrogenation of Imines, Enamines, Azirdines, Nitriles, and Silylenol Ethers

substrate	catalyst (mol %)	T (°C)	P (atm)	t (h)	yield (%)	ref
		Aldimines				
PhCH=N^{t}Bu	**1** (5)	80	1	1	79	40
PhCH=NSO$_2$Ph	**1** (5)	120	5	11	97	40
PhCH=NCHPh$_2$	**1** (5)	140	5	1	88	40
PhCH=NCH$_2$Ph	**1** (5)	120	5	48	5	40
PhCH=NCH$_2$Ph(B(C$_6$F$_5$)$_3$)	**1** (5)	120	5	46	57	40
PhCH=N^{t}Bu	**2** (5)	80	1	1	98	40
PhCH=NSO$_2$Ph	**2** (5)	120	5	16	87	40
PhCH=N^{t}Bu	**3** (5)	80	1	2	89	44
PhCH=NSO$_2$Ph	**3** (5)	120	5	41	94	44
PhCH=NCHPh$_2$	**3** (5)	120	5	1	99	44
PhCH=N(SO$_2$C$_6$H$_4$Me)	**3** (10)	80	10	22	7	58
PhCH=N(SO$_2$C$_6$H$_4$Me)	**3** (10)	80	20	22	97	58
PhCH=N(SO$_2$C$_6$H$_4$Me)	**3** (10)	100	20	22	91	58
PhCH=N(SO$_2$C$_6$H$_4$Me)	**3** (10)	100	30	22	99	58
C$_6$H$_4$CMe$_2$CMe=N	**3** (10)	100	40	22	0	58
C$_6$H$_4$CMe$_2$CMe=N	**3** (10)	140	20	22	21	58
C$_6$H$_4$CMe$_2$CMe=N	**3** (10)	140	40	22	53	58
PhCH=N^{t}Bu	**4** (20)	25	2.5		87	45
PhCH=NCH$_2$Ph	**5** (8)	110	2	12	99	46
PhCH=NMe	**5** (4)	110	2	24	4	46
PhCH=NCHPh$_2$	**7** (5)	120	15	1	99	50
PhCH=N^{t}Bu	**7** (10)	120	15	1	99	50
PhCH=NPh	**7** (10)	120	15	1	78	50
PhCH=NCH$_2$Ph	**7** (10)	120	15	6	5	50
PhCH=NC$_6$H$_4$Cl	**7** (10)	120	15	1	99	50
ClC$_6$H$_4$CH=NC$_6$H$_4$Cl	**7** (10)	120	15	1	99	50
NO$_2$C$_6$H$_4$CH=NPh	**7** (10)	120	15	1	99	50
PhCH=N^{t}Bu	**8** (10)	20	4	42	81	51
MeOC$_6$H$_4$CH=N^{t}Bu	**8** (10)	20	4	42	75	51
PhCH=NCH$_2$Ph	**8** (10)	20	4	42	49	51
MeO(CH$_2$CHCH$_2$O)C$_6$H$_3$CH=N^{t}Bu	**8** (10)	20	4	42	72	51
CH$_3$CH=CHCH=N^{t}Bu	**8** (10)	20	4	42	97	51
PhCH=N^{t}Bu	**9** (10)	20	4	42	99	51
MeOC$_6$H$_4$CH=N^{t}Bu	**9** (10)	20	4	42	98	51
PhCH=NCH$_2$Ph	**9** (10)	20	4	42	16	51
MeO(CH$_2$CHCH$_2$O)C$_6$H$_3$CH=N^{t}Bu	**9** (10)	20	4	42	99	51
CH$_3$CH=CHCH=N^{t}Bu	**9** (10)	20	4	42	24	51
^{t}BuCH=NC$_6$H$_3$Me$_2$	**10** (6)	25	2		99	47
^{t}BuCH=NC$_6$H$_3$^{i}Pr$_2$	**10** (2)	25	2		99	47
		Ketimines				
Ph$_2$C=N^{t}Bu	**3** (5)	120	5	1	98	44
PhCMe=NC$_6$H$_2$Me$_3$	**3** (5)	120	5	8	94	44
PhCMe=NPh	**3** (2.5)	80	10	22	19	58
PhCMe=NPh	**3** (5)	80	10	22	68	58
PhCMe=NPh	**3** (10)	80	10	22	99	58
PhCMe=NPh	**3** (10)	50	10	22	29	58
PhCMe=NPh	**3** (5)	80	20	22	99	58
PhCMe=N^{t}Bu	**4** (5)	25	2.5	3	70	45
PhCMe=NCH$_2$Ph	**5** (4)	110	2	6	99	46
PhCMe=NMe	**5** (4)	110	2	12	99	46
PhCH$_2$CMe=NMe	**5** (4)	110	2	24	4	46
MeOC$_6$H$_4$CMe=NCH$_2$Ph	**5** (4)	110	2	6	99	46

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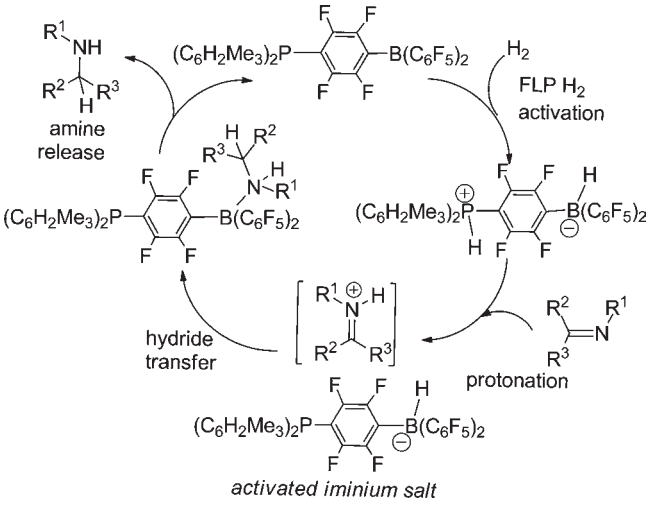
Table 1. Continued

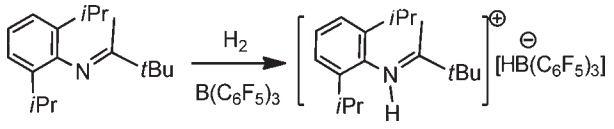
substrate	catalyst (mol %)	T (°C)	P (atm)	t (h)	yield (%)	ref
$ClC_6H_4CMe{=}NCH_2Ph$	**5** (4)	110	2	6	99	46
	Protected Nitriles					
$MeC{\equiv}N(B(C_6F_5)_3$	**1** (5)	120	5	24	75	40
$PhC{\equiv}N(B(C_6F_5)_3)$	**1** (5)	120	5	24	84	40
$(CH_2CH_2C{\equiv}N(B(C_6F_5)_3)_2$	**1** (10)	120	5	48	99	40
	Aziridines					
PhCHCHPhNPh	**1** (10)	120	5	1.5	98	40
PhCHCHPhNPh	**3** (5)	120	5	2	95	44
	Enamines					
$PhC(NC_5H_{10}){=}CH_2$	**4** (10)	25	2.5		99	45
$(C_5H_{10}N)C{=}CH(CH_2)_4$	**4** (5)	25	2.5		88	45
$O(CH_2CH_2)_2NC{=}CH(CH_2)_4$	**4** (3)	25	2.5		78	45
$(C_5H_{10}N)C{=}CH(CH_2)_4$	**5** (4)	110	2	12	85	46
$O(CH_2CH_2)_2NC{=}CH(CH_2)_4$	**8** (10)	20	4	42	73	51
$O(CH_2CH_2)_2NC{=}CH(CH_2)_4$	**9** (10)	20	4	42	92	51
	Silyl Enol Ethers					
$Ph(Me_3SiO)C{=}CH_2$	**6** (20)	25	2	20	93	49
$^tBu(Me_3SiO)C{=}CH_2$	**6** (20)	25	2	20	89	49
$(Me_3SiO)C{=}CH(CH_2)_4$	**6** (20)	25	2	20	86	49
$(Me_3SiO)C{=}CH(CH_2)_3$	**6** (20)	25	2	20	85	49
$Me(Me_3SiO)C{=}CH_2$	**6** (20)	25	60	3	99	49
$^tBu(Me_3SiO)C{=}CH_2$	**10** (5)	25	2		85	47
	Eneone					
$(CH_2{=}CMe)C_6H_6MeO$	**9** (20)	20	4	14	87	51
	Dieneamines					
$(CH_2C(C_5H_4)CH{=}C(NMe_2)C_5H_4)ZrCl_2$	**4** (20)	25	2.5		27	48
$(CH_2C(C_5H_4)CH{=}C(NMe_2)C_5H_4)Fe$	**4** (5)	25	2.5		77	48
$(CH_2C(C_5H_4)CH{=}C(N(CH_2CH_2)_2CH)_2C_5H_4)Fe$	**4** (5)	25	2.5		99	48
$(CH_2C(C_5H_4)CH{=}C(N(CH_2CH_2)_2O)_2)C_5H_4)Fe$	**4** (5)	25	2.5		99	48

Scheme 3. Proposed Mechanism of Hydrogenation



to species where an iminium ion intermediate was accessible. Employing this creative approach, they showed that 10 mol % of **4** effected the reduction of the enamine $C_5H_{10}NC_6H_{10}$ to the

Scheme 4. Hydrogenation of Sterically Encumbered Imine



amine $C_5H_{10}NC_6H_{12}$ at 25 °C and 1.5 bar of H_2 in a toluene solution.[45] In a similar sense, this strategy was applied to a series of enamines with catalyst loadings as low as 3 mol % catalyst (Scheme 2d and Table 1).[47] The very bulky enamine $PhC(NC_5H_{10}){=}CH_2$ was reduced to the corresponding amine in >80% yield yet required more forcing conditions of 50 bar of H_2, 70 °C, and 10 mol % catalyst.

Employing a related strategy, Erker et al.[48] further broadened the scope of FLP reductions, uncovering that a 20 mol % bis(phosphine) $C_{10}H_6(PPh_2)_2{-}B(C_6F_5)_3$ combination generated $[C_{10}H_6(PPh_2)_2H][HB(C_6F_5)_3]$ (**6**; Figure 1), which is an effective catalyst for hydrogenation of silylenol ethers to give silyl ether products under comparatively mild conditions, 2 bar of H_2 pressure and 25 °C (Scheme 2e and Table 1).[49] The less sterically hindered silyl enol ether $Me_3SiO(Me)C{=}CH_2$ it was necessary to employ the more forcing reaction conditions of

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60 bar of H_2 at 70 °C to effect the catalytic reduction of silyl enol ether to the corresponding silyl ether.

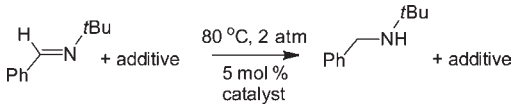
Modified Lewis acid catalysts were probed by Berke and coworkers.[50] These researchers explored the use 1,8-bis(dipentafluorophenylboryl)naphthalene, $C_{10}H_6(B(C_6F_5)_2$ (**7**; Figure 1), to reduce a variety of imines under 15 bar of H_2 at 120 °C (Table 1). These authors also explored the mechanism of action of this bis(borane) and suggested that hydrogen activation via the so-called "super Lewis acidic activation pathway" involving both boron centers has a higher barrier than the "external" access of H_2 to just one boron center.

In a related approach to Lewis acid modification, the group of Soos et al. has demonstrated that the straightforward modification of the borane to $B(C_6F_5)_2(C_6H_2Me_3)$ had a significant impact on the range of substrates that could be reduced.[51] In combination with $CH(CH_2CH_2)_3N$ or $N(CH_2CH_2)_3N$, the borane $B(C_6F_5)_2(C_6H_2Me_3)$ was used to generate catalysts **8** and **9** (Figure 1), respectively which were effective for the reduction of conventional aldimines (Table 1). In addition, these catalysts lead to the reduction of $MeO(CH_2CHCH_2O)$-$C_6H_3CH{=}N^tBu$, which incorporates both ether and vinyl functional groups. Interestingly, these catalyst systems led to the full reduction of $CH_3CH{=}CHCH{=}N^tBu$ to nBuNH^{t}Bu. Even more dramatic, however, was the finding that the conjugated olefinic bond in carvone was reduced, although this required 6 days of reaction (Scheme 2f).

The Erker group[47] has also expanded the realm of FLP catalysts to include unusual metallocene derivatives. For example, the zirconocene salt $[(C_5H_4CH_2NH(C_6H_3{}^iPr_2))_2ZrCl_2]$-$[HB(C_6F_5)_3]_2$ (**10**; Figure 1), which incorporates pendant bulky ammonium fragments, was shown to act as an FLP catalyst for the hydrogenation of bulky imines and silyl enol ethers to corresponding saturated products. In these examples, catalyst loadings ranged between 2 and 6 mol % (Table 1). These same authors also showed that FLP reductions could be applied to metallocene-based substrates. Thus, the dieneamine complexes $(H_2C{=}C(C_5H_4)CH{=}C(NR_2)C_5H_4)Fe$ and $(H_2C{=}C(C_5H_4)CH{=}C(NR_2)C_5H_4)$-$ZrCl_2$ were reduced under H_2 in the presence of the phosphonium borate **4** to give $(CH_3C(C_5H_4){=}CHCH(NR_2)C_5H_4)Fe$ and $(CH_3C(C_5H_4)CH{=}CH(NR_2)C_5H_4)ZrCl_2$, respectively (Table 1).[48] In the case of the ferrocene derivatives, the products were isolated in yields ranging from 77 to 99%, whereas the zirconocene product was isolated in 27% yield.

Optimized Conditions for Catalysis. Efforts to uncover optimized conditions for the reduction of PhCH=N^{t}Bu as a standard imine were undertaken with the catalysts **2** or **3**, with variations in the pressures of H_2 ranging from 25 to 120 atm, in the reaction temperatures from 25 to 130 °C, and in the catalyst loadings from 5 to 0.1 mol %. Increasing H_2 pressures had a dramatic impact on the reaction time. When 2 mol % catalysts were employed, increasing the pressure of H_2 from 25 to 103 atm at 25 °C led to increased conversion as a function of time. In the case of **1**, the species PhCH=N^{t}Bu was quantitatively reduced in 2 h, whereas with **3**, this reaction was complete in 1 h. In general, reduction of the catalyst loading slowed the reaction. However, this could be overcome by altering the reaction conditions and time. For example, reduction of the catalyst from 5 mol % to as low as 0.3 mol % catalyst resulted in quantitative reduction in 18 h at 120 atm of H_2 and 100 °C. Further reduction to 0.1 mol % catalyst was also possible if the temperature was raised to 130 °C. However, in this case, it was necessary to remove traces of water from the imine substrate by distillation from $Al(iBu)_3$ prior to reduction. This finding is interesting because it points out the dileterious effect of trace H_2O on the catalyst efficiency. Nonetheless, at this catalyst loading, FLP reductions become cost competitive with stoichiometric $LiAlH_4$ reductions. In addition, this approach offers the advantage of minimal workup because simple flash chromatography removes the catalyst from the product. This stands in contrast to stoichiometric reductions, where workup by quenching of the reaction generates heat, H_2 gas, and significant amounts of aqueous aluminum hydroxide waste.

Table 2. Product Yields of Catalytic Hydrogenation in the Presence of a Stoichiometric Additive[a]



	catalyst			catalyst	
additive	**2**	**3**	additive	**2**	**3**
naphthalene	100	100	Me_3Si methacrylate	0	0
MeO^{t}Bu	100	16	^{i}PrPhNC(O)O^{t}Bu	0	0
MeOPh	100	100	^{t}BuNH$_2$	0	0
2,4,6-$Me_3C_6H_2OH$ trimethylphenol	5	0	^{i}Pr$_2$NH	49	82
2,6-^{t}Bu$_2C_6H_3OH$	100	100	2-^{t}Bu$C_6H_4NH_2$	0	0
p-anisaldehyde	0	0	$PhNMe_2$	4	31
4-heptanone	6	0	Ph_2NMe	100	100
(*t*-Bu)$_2$CO	12	3	Ph_3N	100	100
L-(−)-fenchone	98	0	$C_6H_2Me_3Br$	100	85
hexyl acrylate	100	100	$PhCH_2Br$	0	0
			$C_8H_{17}Br$	100	95

[a] Reaction conditions: 80 °C, 10 atm of H_2, 5 mol % catalyst, imine−additive ratio 1:1.

Functional Group Tolerance. The classical method for functional group tolerance testing would involve the preparation of a large series of substrates that incorporate a variety of additional functional groups. Such an approach would require labor-intensive and tediously repetitive synthesis of substrate molecules. In an effort to acquire a large array of data in an expeditious manner, we chose an alternative that would allow an automated and combinatorial methodology. In this approach, the catalyst efficiency for the hydrogenation of a standard substrate was assessed in the presence of an equal amount of an additive containing a functional group. PhCH=N^{t}Bu was used as our standard substrate, and a large variety of additives were screened employing a Chem-Speed ASW1000 robotic reactor system (Table 2). While this approach provides information on the catalyst tolerance for a particular functional group. It does not provide information on the more subtle impact of electronic perturbations to the substrate as a result of the incorporation of a particular functional group. Nonetheless, this approach is expeditous and should be useful as a primary screen.

Automated hydrogenation trials were performed at 80 °C under 10 atm of H_2 pressure, and the reactions were allowed to run for 8 h using 5 mol % **2** or **3** as the catalyst. In all cases, the reactions were conducted at least in triplicate to ensure reproducibility. Following the reaction, samples were dispensed to NMR tubes for spectroscopic examination. To support the validity of this additive approach, the imines $(p$-$MeOC_6H_4)CH{=}N^tBu$,

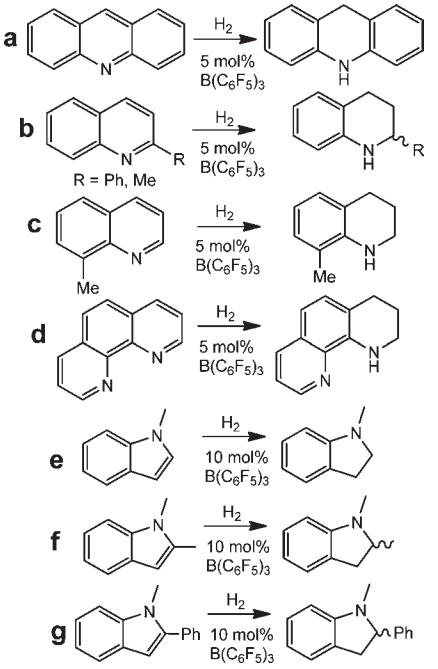
(m-$MeOC_6H_4$)CH=N^{t}Bu, and (p-$(Me_2)NC_6H_4$)CH=N^{t}Bu were prepared and employed as substrates. For both catalysts **2** and **3**, the efficiency of the imine reductions mimicked the data acquired from the corresponding additive experiments. While this does not constitute a comprehensive evaluation of the method, these data do suggest that this bimolecular approach to functional group tolerance is a valid first approximation.

The combinatorial hydrogenation data confirm that the efficient reduction of PhCH=N^{t}Bu was achieved for both catalysts in the presence of naphthalene, MeOPh, n-hexyl acrylate, $MePh_2N$, Ph_3N, and alkyl and aryl halides. It should be noted that while $PhCH_2Br$ does not inhibit hydrogenation of the imine, the product amine is quarternized to the benzylammonium bromide salt. In the case of MeO^{t}Bu, catalysis by ^{t}Bu$_2$PC$_6$F$_4$B(C$_6$F$_5$)$_2$ is quantitative, whereas with B(C$_6$F$_5$)$_3$, only 16% conversion is observed, consistent with competitive binding of the additive to the borane. Higher conversions with the bifunctional phosphine−borane catalyst are also consistent with the reduced Lewis acidity. In a similar observation, the phosphine−borane catalyst **2** tolerates the presence of L-fenchone, whereas **3** does not. While both catalysts give sigificant conversion in the presence of ^{i}Pr$_2$NH, both are much less effective in the presence of $PhNMe_2$ ^{t}BuNH$_2$, carbamate esters, ketones, or aldehydes. These latter observations are consistent with the known stoichiometric reaction of R$_2$PHC$_6$F$_4$BH(C$_6$F$_5$)$_2$ with aldehyde to give R$_2$PHC$_6$F$_4$B(OCH$_2$R′)(C$_6$F$_5$)$_2$. In a similar sense, both catalysts were not functional in the presence of 2,4,6-$Me_3C_6H_2OH$. Surprisingly, these catalysts tolerate the presence of 2,6-^{t}Bu$_2$C$_6$H$_3$OH, where quantitative hydrogenation of the imine is observed. Thus, these functional group data infer that FLP catalysts for the reduction of imines are tolerant of weakly donating arenes, halides, ethers, and amines. In addition, these catalyst also tolerate sterically encumbered amines, ketones, and alcohols in some cases. Collectively, the present data, together with extensive hydrogenation data reported to date, suggest that it may be possible to design new Lewis acidic catalyst partners for FLP activation of H_2 that are contrived to avoid deactivation by coordinating donor fragments in substrates. In this fashion, the breadth of applications could be broadened.

More Substrates. In an effort to further expand the substrate scope for FLP reductions, we have recently probed the reduction of substituted N-heterocycles such as substituted quinolines, phenanthrolines, and acridines (Scheme 5a−d and Table 3). These are reduced to varying degrees catalytically by B(C$_6$F$_5$)$_3$ under an atmosphere of H_2.[52] While acridine was shown to take up 1 equiv of H_2, substituted quinolines and phenanthrolines were shown to take up 2 equiv of H_2 to saturate the N-containing ring. This is attributed to tautomerization of the initial hydride attack product. This view was supported by isolation of the $NSiEt_3$ analogue derived from the catalytic hydrosilylation of 2-phenylquinoline using Et_3SiH, a reaction that is mechanistically similar to hydrogenation.[53] Herein, we also report the hydrogenation of several indole derivatives to the corresponding dihydroindoles[54−56] (Scheme 5e−g), using B(C$_6$F$_5$)$_3$, higher pressures of H_2 (103 bar), and 80 °C for 18 h. While as little as 1 mol % affected the reaction to some extent, 10 mol % catalyst was required for an effective reduction.

Another useful application of FLP reductions was derived from the hydrogenation of diimines (Scheme 6). Thus, for example, the diimines (CH_2=NR)$_2$ and (MeCH=NR)$_2$ (R = $C_6H_2Me_3$, C$_6$H$_3$^{i}Pr$_2$) are quantitatively reduced to the corresponding diamines,[57] using 5 mol % **3** and 5 atm of H_2 at 120 °C

Scheme 5. Reduction of N-Heterocycles



(Table 1). In a similar fashion, the pyridine−diimines (C$_5$H$_3$N)-(MeC=NR)$_2$ (R = C$_6$H$_4$-4-^{i}Pr, C$_6$H$_2$-2,4,6-Me$_3$, C$_6$H$_3$-2,6-^{i}Pr$_2$) are reduced quantitatively to the diamines using 4 atm of H_2 (Table 1). In the case of (C$_5$H$_3$N)(MeCHNH(C$_6$H$_3$^{i}Pr$_2$))$_2$, the nature of the product was confirmed unambiguously by X-ray crystallography (Figure 2).

When optimized conditions are employed and with the recognized functional group tolerance limitations of the present FLP catalysts, hydrogenation that could yield reductions of relevant to commercially significant amines can be investigated (Table 4). One such case involves hydrogenation of the imine with a pendant pyridine fragment (Figure 3a) because this species is a potential herbicide. However, attempts to effect FLP-catalyzed high-pressure reductions yielded generally low yields. Maximum yields of 54% were achieved using 4 mol % **1** as the catalyst for 4 h at 124 bar of H_2 pressure and 120 °C. In a similar sense, the imine precursor to fentanyl, a potent analgesic narcotic (Figure 3b), was only reduced to a limited extent with the hydrogenation catalysts **1** and **2**. This observation was attributed, in part, to coordination of the amine to the boron center of the catalysts and the loss of C_6F_5H, as suggested by ^{19}F NMR spectra of the reaction mixtures. In contrast, the N-propyl analogue of the antidepressant sertraline (Figure 3c) showed good conversion to amine products with 5 mol % catalysts **1** (78%) and **2** and **3** (100%) at 124 bar over the course of 20 h at 120 °C. Freshly prepared samples of the corresponding benzylimine (Figure 3d) were also reduced in high yields using 5 mol % **1** or **2** under similar conditions, although the reaction time could be reduced in these cases to 4 h. Similarly, the ketimine $CF_3C_6H_4CMe$=NCH_2Ph (Figure 3e), a precursor to anticancer and herbicide candidates, was effectively reduced in 16 h at 117 bar and 120 °C using 2 mol % phosphonium borate catalyst **1**.

Toward Catalytic Asymmetric Hydrogenation by FLPs. The ability of FLP systems to effect hydrogenation prompts questions about controlling the stereochemistry of hydrogen

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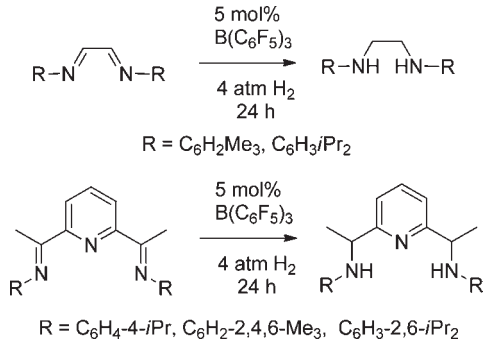
Table 3. FLP Hydrogenation of N-Heterocycles and Diimines

substrate	catalyst (mol %)	T (°C)	P (atm)	t (h)	yield (%)	ref
		Indoles				
$C_6H_4CH{=}CHNMe$	**3** (1)	80	103	18	0	herein
$C_6H_4CH{=}CHNMe$	**3** (10)	80	103	18	98	herein
$C_6H_4CH{=}CMeNMe$	**3** (1)	80	103	18	21	herein
$C_6H_4CH{=}CMeNMe$	**3** (10)	80	103	18	98	herein
$C_6H_4CH{=}CPhNMe$	**3** (1)	80	103	18	37	herein
$C_6H_4CH{=}CPhNMe$	**3** (10)	80	103	18	91	herein
		Quinolines				
C_9H_6N(2-Ph)	**3** (5)	25	4	4	80	52
C_9H_6N(2-Me)	**3** (5)	50	4	16	74	52
C_9H_6N(8-Me)	**3** (10)	80	4	6	88	52
		N-Heterocycles				
$C_{13}H_9N$ (acridine)	**3** (5)	25	4	2	80	52
$C_{13}H_9N$ (phenanthroline)	**3** (5)	25	4	3	84	52
		Dimines				
$(CH_2{=}NC_6H_2Me_3)_2$	**3** (5)	120	4	24	99	herein
$(CH_2{=}NC_6H_4{}^{i}Pr)_2$	**3** (5)	120	4	24	99	herein
$(C_5H_3N)(MeC{=}N(C_6H_4\text{-}4\text{-}{}^{i}Pr)_2$	**3** (5)	120	4	24	99	herein
$(C_5H_3N)(MeC{=}N(C_6H_3\text{-}2,6\text{-}{}^{i}Pr_2)_2$	**3** (5)	120	4	24	99	herein
$(C_5H_3N)(MeC{=}N(C_6H_2\text{-}2,4,6\text{-}Me_3)_2$	**3** (5)	120	4	24	99	herein

Scheme 6. Reduction of Diimines



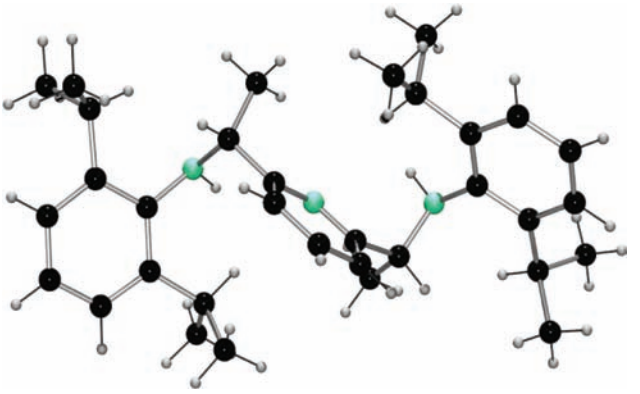


Figure 2. ORTEP of the reduced pyridine−diamine $(C_5H_3N)(MeCH\text{-}NH(C_6H_3{}^{i}Pr_2))_2$.

addition. That is, can one perform asymmetric hydrogenation employing chiral analogues of FLPs? One strategy to this end involves the use of chiral phosphines, a class of chiral Lewis bases that has been well studied (Table 5). However, efforts to reduce PhCMe=NPh under 4 atm of H_2 using catalyst loadings of 20 mol % $B(C_6F_5)_3$ and a chiral phosphine required heating of the reactions to 50−100 °C to produce PhCHMeNHPh. Use of the ligand (*R*)-binap or (*S*,*S*)-chiraphos gave exclusively racemic mixtures of the amine, while the corresponding catalysis using the ligand (*S*,*S*)-diop at 100 °C gave a modest enantiomeric excess of 25%. In retrospect, it is perhaps not surprising that this approach appears flawed. Mechanistic studies of hydrogenation by FLPs suggest that the role of the phosphonium cation is to transfer the proton to the imine. Employing a chiral phosphine is only going to impact the induced chirality if it remains in close proximity to the iminium as the hydride is transferred to the imine carbon center. The above data suggest that NH···P hydrogen bonding is weak at best and thus has a minimal effect.

Given that above, a better strategy would be based on the use of a chiral borane. In the first report demonstrating the possibility of chiral induction by an FLP catalyst, Chen and Klankermayer[58] described the asymmetric hydrogenation of PhN=CPh(Me) to the corresponding amine by employing the chiral borane (α-pinenyl)$B(C_6F_5)_2$ (**11**; Table 5). This particular system gave only a 13% enantiomeric excess in the product amine. In a more recent report, these same authors[59] synthesized the related hydrogenation catalysts **12** and **13** derived from camphor. These systems dramatically improved the asymmetric induction, affording hydrogenation of prochiral imines with enantiomeric excesses as high as 83% (Table 5).

In a very recent study,[60] we have shown that $B(C_6F_5)_3$ catalyzes the hydrogenation of chiral imines with diastereoselectivity. In the case of phenethylamine derivatives, diastereomeric excesses ranged from 0 to 68% (Figure 4 and Table 6). However,

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Table 4. Hydrogenation of Commercially Relevant Imines (Figure 3)

substrate	catalyst (mol %)	*P* (atm)	*T* (°C)	*t*(h)	yield (%)
a	**1**(5)	124	120	4	54
a	**2**(5)	120	120	4	10
a	**3**(5)	120	120	4	13
a	**1**(5)	124	120	20	46
a	**2**(5)	117	120	20	10
a	**3**(5)	120	120	20	31
b	**2**(5)	120	120	20	25
b	**1**(5)	117	120	20	26
c	**2**(5)	120	120	4	90
c	**1**(5)	120	120	4	93
c	**2**(5)	124	120	20	100
c	**1**(5)	120	120	20	100
d	**3**(5)	124	120	20	100
d	**2**(5)	124	120	20	100
d	**1**(5)	124	120	20	78
e	**3**(2)	117	120	16	95

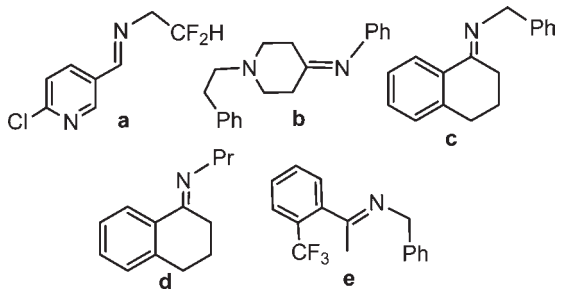

Figure 3. Examples of Commercially Relevant Imines.

camphor- or menthone-derived imines were reduced with >95% diastereomeric excess (Figure 4 and Table 6), although for high yields they require 10−20 mol % $B(C_6F_5)_3$ as a catalyst at 115 °C, 4 atm, and up to 5 days of reaction time. In contrast, stoichiometric reductions of these imines using $Na[BH_3(CN)]$ or $Na[BH(OAc)_3]$ gave high chemical yields but significantly lower diastereoselectivities. Thus, these FLP reductions offer high diastereoselectivities and the atom economy of catalysis.

Future Directions. The catalytic incorporation of H_2 into organic substrates mediated by hetero- or homogeneous transition-metal materials has been known for over 100 years. In contrast, the analogous transformation mediated by main-group systems was reported less than 5 years ago. These findings offer a new paradigm for hydrogenation. The development of catalysts of this kind has been applied to an increasing variety of polar organic substrates. These developments have been reviewed and augmented herein. In addition, innovations targeting asymmetric synthesis or the ability to reduce a broader range of substrates may be useful products of commercial interest. The work of Soos et al. demonstrates that altering the substituents on boron is one viable approach to this end. Alternatively, we are exploring the ability of other Lewis acidic centers to both activate H_2 and effect hydride transfer to a broader range of substrates. Of particular interest would be FLP systems, which effect reductions of ketones, aldehydes, or even olefins. While the latter target seems extremely challenging, it should be noted that the ability to effect hydrogenation of any kind without a transition metal seemed highly unrealistic just 5 years ago. With this in mind, there can be no doubt that, as the substrate−catalyst space expands for FLP hydrogenation, this approach will continue to blossom as a new tool in the synthetic chemists' tool kit.

EXPERIMENTAL SECTION

General Considerations. All preparations and manipulations were performed on a double-manifold N_2/vacuum line with Schlenk-type glassware or in a N_2-filled VAC glovebox. Solvents (Aldrich) were dried using an Innovative Technologies solvent system and degassed before use. NMR spectra were obtained on a Bruker Avance 400 MHz spectrometer, and spectra were referenced to residual solvent (^{1}H and ^{13}C) or externally (^{11}B, $BF_3\cdot OEt_2$; ^{19}F, $CFCl_3$; ^{31}P, 85% H_3PO_4). Chemical shifts are reported in ppm. NMR solvents were purchased from Cambridge Isotopes, dried over CaH_2 or sodium benzophenone, vacuum distilled prior to use, and stored over 4 Å molecular sieves in the glovebox. $B(C_6F_5)_3$ was purchased from Boulder Scientific Co. Combustion analysis was performed in-house on a Perkin-Elmer CHN analyzer. A series of hydrogenation experiments were performed in a combinatorial manner employing the Chem-Speed ASW1000 robotic reactor system. In some cases, hydrogenation experiments were done in a Parr pressure reactor. Details are provided below.

General Procedure for FLP Hydrogenation Catalysis. In a N_2-filled glovebox, the imine substrate (0.5 mmol) was weighed in a vial and dissolved in toluene (2 mL). To this was added catalyst (5 mol %), and the imine−catalyst solution was thoroughly mixed and then transferred to a 31 mL Parr pressure reactor equipped with a magnetic stir bar. The reactor was assembled and sealed inside the glovebox. Once removed, it was further tightened. The reactor and its contents were purged three times with H_2, which was first passed through a gas purifier (Matheson model 8010). The reactor was then heated to the appropriate temperature, pressurized with H_2, and stirred for the listed reaction time. Conversions were determined through ^{1}H NMR spectroscopy.

Example Procedures. *Reduction of $C_6H_4CH{=}CHNMe$.* The catalyst **3** (9.7 mg, 0.0184 mmol, 10 mol %) was transferred to a vial containing 1-methylindole (24.8 mg, 0.189 mmol) with 1 mL of toluene-d_8. The vial was equipped with a stir bar and sealed in a Parr bomb. The bomb was pressurized with 103 atm of H_2 at 80 °C and stirred for 18 h. The bomb was depressurized and cooled to room temperature. The reaction mixture was then transferred to an NMR tube. Indoline products were identified by comparison of ^{1}H NMR spectra to literature values.[54−56]

Reduction of Pyridinediimines. These reductions were done in an analogous manner, and thus only one preparation is detailed. To a Schlenk tube fitted with a Teflon tap was added the imine $(C_5H_3N)(MeC{=}N(C_6H_3\text{-}2,6\text{-}^iPr_2)_2$ (337 mg, 0.70 mmol) followed by $B(C_6F_5)_3$ (18 mg, 0.0035 mmol, 5 mol %). The reaction was freeze−pump−thawed three times, and then 4 atm of H_2 was added. The sealed tube was then heated to 120 °C for 24 h. Conversions were monitored by NMR spectroscopy, which showed them to be quantitative.

$(C_5H_3N)(MeCHNH(C_6H_3\text{-}2,6\text{-}^iPr_2)_2$. ^{1}H NMR ($C_6D_5CD_3$): δ 12.04−12.16 (Ar, 10H), 6.81 (py, 1H), 6.46 (py, 2H), 4.39 (br, 2H, NH), 4.29 (q, 2H, $CH(CH_3)$), 3.42 (sept, 2H, $CH(CH_3)_2$), 1.65 (d, 6H, $CH_3(CH)$), 1.31 (d, 12H, $(CH_3)_2(CH)$), 1.15 (d, 12H, $(CH_3)_2(CH)$). X-ray crystals were obtained by slow evaporation from a toluene solution.

$(C_5H_3N)(MeCHNH(C_6H_4\text{-}4\text{-}^iPr)_2$. ^{1}H NMR ($C_6D_5CD_3$): 8.32 (d, Ar), 8.09 (t, Ar),7.81 (t, Ar), 7.66 (t, Ar), 7.50 (t, Ar), 7.70−7.25

Table 5. Enatioselective Hydrogenation of Ketimines

substrate	catalyst (mol %)	T (°C)	P (atm)	t (h)	yield (%)	ee	ref
PhCMe=NPh	**3**/(*R*)-binap (20)	50	4	240	99	0	herein
PhCMe=NPh	**3**/(*S*,*S*)-chiraphos (20)	50	4	240	99	0	herein
PhCMe=NPh	**3**/(*S*,*S*)-diop (20)	50	4	240	33	6	herein
PhCMe=NPh	**3**/(*S*,*S*)-diop (20)	100	4	96	99	25	herein
PhCMe=NPh	**11** (10)	65	20	22	99	13	58
PhCMe=NPh	**12**/**13** (5)	65	25	15	99	20	59
PhCMe=NPh	**13** (5)	65	25	15	99	48	59
PhCMe=NPh	**13** (5)	65	25	15	95	79	59
PhCMe=N(C_6H_4Me)	**13** (5)	65	25	15	37	74	59
PhCMe=N($C_6H_3{}^iPr_2$)	**13** (5)	65	25	15	0		59
MeOC_6H_4CMe=NPh	**13** (5)	65	25	15	96	81	59
PhCMe=NC_6H_4OMe	**13** (5)	65	25	15	99	81	59
($C_{10}H_7$)CMe=NPh	**13** (5)	65	25	15	93	80	59
($C_{10}H_7$)CMe=NC_6H_4OMe	**13** (5)	65	25	15	96	83	59

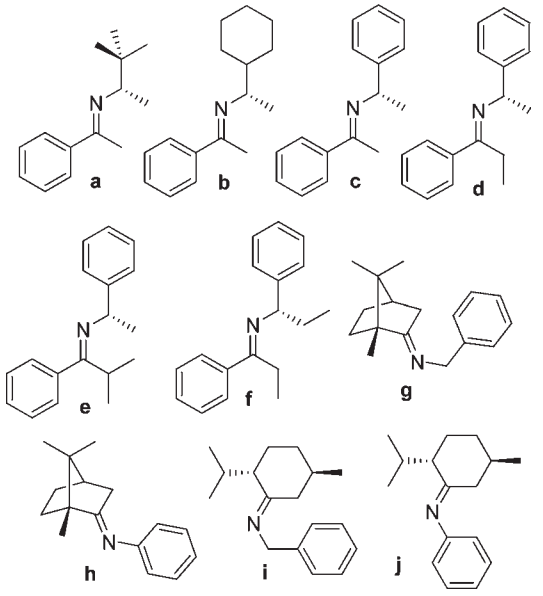

Figure 4

(m, Ar), 4.60 (CH(CH_3)), 4.42 (br, NH), 2.90 (CH(CH_3)$_2$), 2.73 (CH(CH_3)$_2$), 2.39 (d, CH_3(CH)), 1.47−1.55 (m, CH_3(CH)), 1.27 (d, CH_3(CH)),1.15 (d, CH_3(CH)).

(C_5H_3N)(MeCHNH(C_6H_2-2,4,6-Me_3)$_2$. ^{1}H NMR ($C_6D_5CD_3$): 8.45 (d, Ar), 8.20 (d, Ar), 7.87 (t, Ar), 7.65 (t, Ar), 7.46 (t, Ar), 6.70−7.23 (m, Ar), 4.41 (CH(CH_3)), 4.15 (br, NH), 2.14−2.28 (m, CH_3), 1.98 (m, CH_3), 1.35−1.45 (m, CH_3), 1.47−1.55 (m, CH_3(CH)), 1.27 (d, CH_3(CH)), 1.15 (d, CH_3(CH)).

X-ray Data Collection, Reduction, Solution, and Refinement. Single crystals were coated in Paratone-N oil in the glovebox, mounted on a MiTegen Micromount, and placed under a N_2 stream. The data were collected on a Bruker Apex II diffractometer. The data were collected at 150(±2) K for all crystals. Data reduction was performed using the *SAINT* software package, and an absorption correction was applied using *SADABS*. The structures were solved by direct methods using XS and refined by full-matrix least squares on F^2 using XL as implemented in the *SHELXTL* suite of programs.[61] All non-hydrogen atoms were refined anisotropically. Carbon-bound hydrogen atoms were placed in calculated positions using an appropriate riding model and coupled isotropic temperature factors (see the Supporting Information).

Table 6. Diastereoselective Hydrogenation of Chiral Imines with $B(C_6F_5)_3$ (Figure 4)

substrate	catalyst (mol %)	T (°C)	P (atm)	t (h)	yield (%)	de	major isomer
a	10	80	5	48	100	0	
b	10	80	5	48	100	11	*S*,*R*
c	10	80	5	48	72	36	*S*,*S*
c	10	25	115	23	100	62	*S*,*S*
d	10	80	5	48	100	39	*S*,*S*
e	10	80	5	48	100	45	*S*,*R*
f	10	80	5	24	100	65	*S*,*S*
g	10	115	5	120	100	99	*R*,*R*,*R*
h	10	115	5	120	92	98	*R*,*R*,*R*
i	10	115	5	120	100	99	*R*,*S*,*R*
j	20	115	5	120	100	99	*R*,*S*,*S*
j	10	115	5	120	66	96	*R*,*S*,*S*

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Vries, J. G. d.; Elsevier, C. J. *The Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, Germany, 2007.
(2) Spindler, F., Blaser, H.-U., Vries, J. G. d., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 1193.
(3) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 2nd ed.; John Wiley & Sons: New York, 1994.
(4) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2000**, *19*, 2655.
(5) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466.
(6) Adolfsson, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3340.
(7) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(8) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683.
(9) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.
(10) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660.
(11) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407.
(12) Akagawa, K.; Akabane, H.; Sakamoto, S.; Kudo, K. *Tetrahedron: Asymmetry* **2009**, *20*, 461.
(13) Rueping, M.; Antonchick, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562.
(14) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.
(15) Marcelli, T.; Hammar, P.; Himo, F. *Chem.—Eur. J.* **2008**, *14*, 8562.
(16) Sander, W.; Hübert, R.; Kraka, E.; Gräfenstein, J.; Cremer, D. *Chem.—Eur. J.* **2000**, *6*, 4567.
(17) Sander, W.; Koetting, C. *Chem.—Eur. J.* **1999**, *5*, 24.
(18) Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4744.
(19) Bettinger, H. F.; Filthaus, M.; Neuhaus, P. *Chem. Commun.* **2009**, 2186.
(20) Kötting, C.; Sander, W. *J. Am. Chem. Soc.* **1999**, *121*, 8891.
(21) Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007**, *316*, 439.
(22) Berkessel, A.; Schubert, T. J. S.; Mueller, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 8693.
(23) Kimura, T.; Takahashi, T.; Nishiura, M.; Yamamura, K. *Org. Lett.* **2006**, *8*, 3137.
(24) Siskin, M. *J. Am. Chem. Soc.* **1974**, *96*, 3640.
(25) Wristers, J. *J. Am. Chem. Soc.* **1975**, *97*, 4312.
(26) Yalpani, M.; Köster, R. *Chem. Ber.* **1990**, *123*, 719.
(27) Yalpani, M.; Lunow, T.; Köster, R. *Chem. Ber.* **1989**, *122*, 687.
(28) Haenel, M. W.; Narangeral, J.; Richter, U.-B.; Rufińska, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1061.
(29) Peng, Y.; Ellis, B. D.; Wang, X.; Power, P. P. *J. Am. Chem. Soc.* **2008**, *130*, 12268.
(30) Spikes, G. H.; Fettinger, J. C.; Power, P. P. *J. Am. Chem. Soc.* **2005**, *127*, 12232.
(31) Welch, G. C.; Juan, R. R. S.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124.
(32) Welch, G. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2007**, *129*, 1880.
(33) Stephan, D. W. *Org. Biomol. Chem.* **2008**, *6*, 1535.
(34) Stephan, D. W. *Dalton Trans.* **2009**, 3129.
(35) Stephan, D. W. *Chem. Commun.* **2010**, *46*, 8526.
(36) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46.
(37) Clarke, M. L.; Roff, G. J. In *The Handbook of Homogeneous Hydrogenation*; Vries, J. G. d., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 413.
(38) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
(39) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
(40) Chase, P. A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 8050.
(41) Mountford, A. J.; Lancaster, S. J.; Coles, S. J.; Horton, P. N.; Hughes, D. L.; Hursthouse, M. B.; Light, M. E. *Inorg. Chem.* **2005**, *44*, 5921.
(42) Welch, G. C.; Prieto, R.; Dureen, M. A.; Lough, A. J.; Labeodan, O. A.; Holtrichter-Rossmann, T.; Stephan, D. W. *Dalton Trans.* **2009**, 1559.
(43) Rokob, T. A.; Hamza, A.; Stirling, A.; Papai, I. *J. Am. Chem. Soc.* **2009**, *131*, 2029.
(44) Chase, P. A.; Jurca, T.; Stephan, D. W. *Chem. Commun.* **2008**, 1701.
(45) Spies, P.; Schwendemann, S.; Lange, S.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7543.
(46) Sumerin, V.; Schulz, F.; Nieger, M.; Leskela, M.; Repo, T.; Rieger, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 6001.
(47) Axenov, K. V.; Kehr, G.; Frohlich, R.; Erker, G. *J. Am. Chem. Soc.* **2009**, *131*, 3454.
(48) Schwendemann, S.; Tumay, T. A.; Axenov, K. V.; Peuser, I.; Kehr, G.; Fröhlich, R.; Erker, G. *Organometallics* **2010**, *29*, 1067.
(49) Wang, H. D.; Fröhlich, R.; Kehr, G.; Erker, G. *Chem. Commun.* **2008**, 5966.
(50) Jiang, C. F.; Blacque, O.; Berke, H. *Chem. Commun.* **2009**, 5518.
(51) Eros, G.; Mehdi, H.; Papai, I.; Rokob, T. A.; Kiraly, P.; Tarkanyi, G.; Soos, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 6559.
(52) Geier, S. J.; Chase, P. A.; Stephan, D. W. *Chem. Commun.* **2010**, *46*, 4884.
(53) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440.
(54) Hirano, M.; Osakada, K.; Nohira, H.; Miyashita, A. *J. Org. Chem.* **2001**, *67*, 533.
(55) Costa, M. F. D.; da Costa, M. R. G.; Marcelo Curto, M. J. *J. Organomet. Chem.* **2001**, *626*, 233.
(56) Chapman, O. L.; Eian, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5329.
(57) Chen, H.; Bartlett, R. A.; Dias, H. V. R.; Olmstead, M. M.; Power, P. P. *Inorg. Chem.* **1991**, *30*, 2487.
(58) Chen, D. J.; Klankermayer, J. *Chem. Commun.* **2008**, 2130.
(59) Chen, D. J.; Wang, Y. T.; Klankermayer, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9475.
(60) Heiden, Z. M.; Stephan, D. W. *Chem. Commun.* **2011**, DOI:10.1039/C1CC10438A.
(61) Sheldrick, G. M. *SHELXTL*; Bruker AXS Inc.: Madison, WI, 2000.