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Metal-free diastereoselective catalytic hydrogenations of imines using $B(C_6F_5)_3$†

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Reductions of chiral ketimines effected under H_2 by catalytic amounts of $B(C_6F_5)_3$ result in moderate to excellent diastereoselectivities. In the case of camphor and menthone derived imines, the reductions proceeded with greater than 95% diastereoselectivity.

About 70% of all new chemicals produced today incorporate a chiral center. In the pharmaceutical industry the most favorable process for the introduction of a chiral center into a chemical is through asymmetric hydrogenation. Currently most imines reductions involve the use of stoichiometric reagents such as $NaBH_4$ or $NaBH_3CN$.[1–3] Although these reagents work well, their use on industrial scales does generate waste disposal issues. While metal-based catalysts have been shown to reduce imines to amines,[4–7] new guidelines of United States Pharmacopeia dramatically have lowered the allowable metal impurities such as Ru, Ir, Rh, and Os in pharmaceuticals.[8,9] This has prompted new interest in metal-free hydrogenation processes. While stoichiometric reductions of organic species utilizing Hantzsch's ester as a source of H_2 have garnered some attention,[10–13] it has only been with the recent discovery of "frustrated Lewis pairs (FLPs)",[14–18] that the possibility of metal-free hydrogenation catalysts has been demonstrated. In our initial report of such catalysis we showed that the species $R_2PHC_6F_4BH(C_6F_5)_2$ (R = *t*Bu, $C_6H_2Me_3$) effectively catalyzes the hydrogenation of primarily aldimines in excellent isolated yields.[19] Subsequently, we showed that analogous hydrogenations of imines, aziridines, and protected nitriles are effected by catalytic amounts of the Lewis acid $B(C_6F_5)_3$.[20] Subsequently, other researchers have extended FLP reductions to include the hydrogenation of imines, enamines and silylenol ethers.[21–30]

The potential of this finding for applications in asymmetric synthesis is a logical and highly desirable extension. Indeed, given that FLP reductions can be viewed as a catalytic version of borohydride reductions, this prospect has been foreshadowed in the work of Brown and Corey[31,32] who developed stoichiometric chiral borohydride reagents some years ago. A preliminary effort to effect an enantioselective FLP hydrogenation was described by Chen and Klankermayer.[33] In that case a chiral borane was used to reduce a ketimine, resulting in ee of 13%. In a very recent paper,[34] this group has extended this strategy, developing chiral borane catalysts for the enantioselective imine reduction with ee's as high as 84%. In this report, we demonstrate catalytic hydrogenation of chiral ketimines using $B(C_6F_5)_3$ as a catalyst. In the case of camphor and menthonimine derivatives, these reductions proceed with high diastereoselectivity.

A series of ten ketimines with chiral substituents derived from α-phenethylimine, camphor-imine and methonimine, **1–10** were prepared (Fig. 1). Hydrogenations of a series of chiral imines using $B(C_6F_5)_3$ as the catalyst were studied. Heating toluene solutions of (*S*)-*t*BuCH(Me)N=C(Me)Ph **1** (Fig. 1) with 10 or 20 mol% of $B(C_6F_5)_3$ at 80 °C under 5 atm H_2 for 48 h resulted in the complete reduction of the imine **1** to the corresponding amine. However, in this case, there was no diastereoselectivity. Analogous catalytic hydrogenations of imines: (*S*)-CyCH(Me)N=C(Me)Ph **2**, (*S*)-PhCH(Me)N=C(Me)Ph **3**, (*S*)-PhCH(Me)N=C(Et)Ph **4**, (*S*)-PhCH(Me)N=C(*i*Pr)Ph **5**,

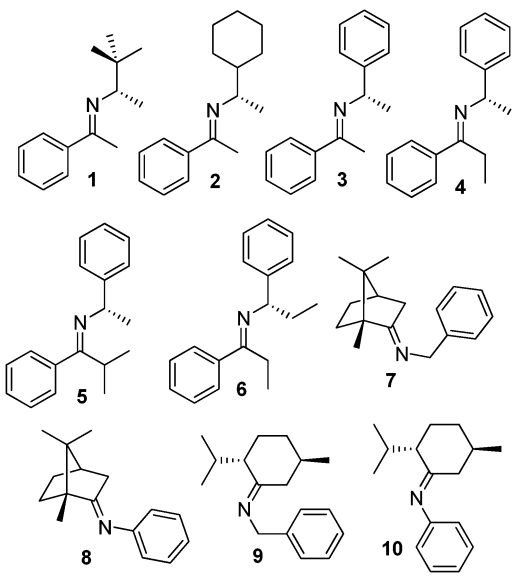

Fig. 1 Chiral imines.

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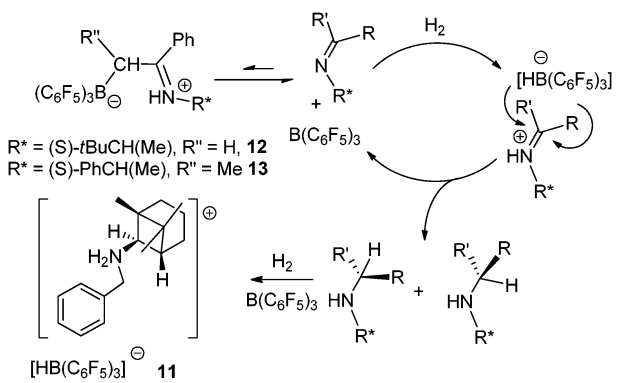
† Electronic supplementary information (ESI) available: Experimental procedures, sample calculations of borohydride cone angles, and 3D coordinates of borohydrides. CCDC 809425–809427. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10438a

and (*S*)-PhCH(Et)N=C(Et)Ph **6** led to the quantitative reduction to the corresponding amine. NMR data of the product amines revealed that reduction afforded a mixture of diastereomers with increasing diastereoselectivity ranging from 11 to 65% (Table 1). Both the yield and diastereoselectivity were improved by using higher pressure of H_2 at lower temperature. Thus at 25 °C and 115 atm H_2, 10 mol% of $B(C_6F_5)_3$ effected the quantitative catalytic hydrogenation of **3** to the corresponding amine with an improved diastereomeric ratio of 62%. Identical results were obtained for the hydrogenation of **3** using the less Lewis acidic borane, $B(C_6F_4H)_3$.[35]

More forcing conditions were required for the catalytic reduction of the following imines: *N*-benzyl-D-camphorimine **7**, *N*-phenyl-D-camphorimine **8**, *N*-benzyl-menthonimine **9**, and *N*-phenyl menthonimine **10** (Fig. 1). Heating these reaction mixtures for 5 days and at 115 °C under 5 atm of H_2 gave complete reduction using 10 or 20 mol% of $B(C_6F_5)_3$. In all of these cases, high diastereoselectivities ranging from 95–99% were obtained. The stereochemistry of the preferred diastereomer was unambiguously established in the case of **7**. Stoichiometric reaction of the imine **7** with $B(C_6F_5)_3$ under H_2 afforded *R*,*R*,*R*-*N*-benzyl-camphorammonium *tris*-pentafluorophenyl-hydridoborate salt, [*R*,*R*,*R*-C_6H_9(Me)-(CMe_2)(NH_2CH_2Ph)][$HB(C_6F_5)_3$] **11** which was crystallographically characterized (Scheme 1 and Fig. 2), confirming the stereochemistries about C(1), C(2) and C(5).

In the case of the imines **1–6**, the hydride transfer is less discriminating presumably as a result of the free rotation of the chiral substituent about the C–N bond. This postulate is also consistent with the increased diastereoselectivities with increasing steric congestion about the imine fragment. To further garner insight into the reactions of imine reduction, stoichiometric reactions of imines with $B(C_6F_5)_3$ in the presence and absence of H_2 were undertaken. For example, upon stoichiometric reaction of imines **1** or **4** with $B(C_6F_5)_3$ results in ready addition to the enamine-tautomers affording the products (*S*)-*t*BuCH(Me)NHC($CH_2B(C_6F_5)_3$)Ph **12** and (*S*)-PhCH(Me)NHC(CH(Me)$B(C_6F_5)_3$)Ph **13** (Scheme 1, Fig. 3 and ESI†). The formation of these species was confirmed spectroscopically and crystallographically. The research groups of Piers[36] and Basset[37] have previously observed similar additions of $B(C_6F_5)_3$ to enamine tautomers. While these species (from imines **1–6**) are formed in



Scheme 1 Proposed mechanism for hydrogenation and formation of **11–13**.

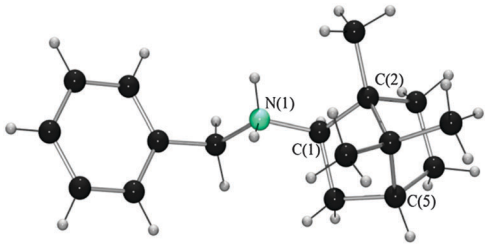


Fig. 2 POV-ray depiction of the cation of **11**. Carbon = black, hydrogen = white, and nitrogen = green.

Table 1 Catalytic hydrogenation of chiral imines with $B(C_6F_5)_3$

Imine	$B(C_6F_5)_3$/ mol%	P_{H_2}/ atm	*T*/°C	*t*/h	Conv. (%)	de	Major isomer
1	20	5	80	48	100	0	—
1	10	5	80	48	100	0	—
2	20	5	80	48	100	21	*S*,*R*
2	10	5	80	48	100	11	*S*,*R*
3	10	5	80	48	72	36	*S*,*S*
3	10	115	25	23	100	62	*S*,*S*
4	20	5	80	48	100	39	*S*,*S*
4	10	5	80	48	100	39	*S*,*S*
5	20	5	80	48	100	45	*S*,*R*
5	10	5	80	48	100	45	*S*,*R*
6	20	5	80	24	100	68	*S*,*S*
6	10	5	80	24	100	65	*S*,*S*
7	20	5	115	120	100	99	*R*,*R*,*R*
7	10	5	115	120	100	99	*R*,*R*,*R*
8	20	5	115	120	100	95	*R*,*R*,*R*
8	10	5	115	120	92	98	*R*,*R*,*R*
9	20	5	115	120	100	99	*R*,*S*,*R*
9	10	5	115	120	100	99	*R*,*S*,*R*
10	20	5	115	120	100	99	*R*,*S*,*S*
10	10	5	115	120	66	96	*R*,*S*,*S*

equilibrium, under H_2 the reduction of the free-imine results in the ultimate consumption of the imine and enamine. Nonetheless, the accessibility of the enamine in these cases, generates the possibility of a mutarotation, thus diminishes facial preference generated by the chiral substituent.

Mechanistically these reductions are thought to proceed *via* the previously proposed FLP hydrogenation mechanism. The imine acts as the base partner together with $B(C_6F_5)_3$ to heterolytically cleave H_2. The resulting anion $[HB(C_6F_5)_3]^-$ then transfers the hydride to the carbon-atom of the iminium cation affording the amine and regenerating the $B(C_6F_5)_3$ which is then available for further reduction. It is clear that in the case of the camphorimines and menthonimines **7–10**, the transfer of the hydride from $[HB(C_6F_5)_3]^-$ to the corresponding iminium cations proceeds almost exclusively *via* approach of the anion toward one of the two diastereotopic faces of the iminium cations. While this explanation offers some insight into the selectivity, the formation of differing diastereomers from **9** and **10** remains unexplained.

For comparative purposes the precursors imines were also reduced stoichiometrically using the reducing agents $NaBH_3CN$ and $NaBH(OAc)_3$ (Table 2). While the product amines were obtained in quantitative yields under mild conditions, the diastereoselectivities for these reagents were markedly different from those obtained from the catalytic hydrogenations. $NaBH_3CN$ gave rise to reduction products with

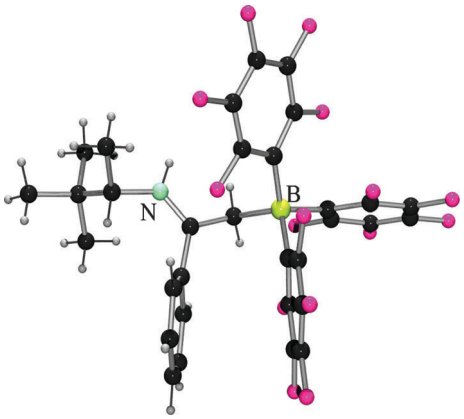


Fig. 3 POV-ray depiction of **12**. Carbon = black, hydrogen = white, nitrogen = green, boron = yellow, and fluorine = pink.

Table 2 Diastereoselectivity of stoichiometric reduction of chiral imines with $NaBH_3CN$ and $NaHB(OAc)_3$

	Reductant			Reductant	
Imine	$NaBH_3CN$	$NaHB(OAc)_3$	Imine	$NaBH_3CN$	$NaHB(OAc)_3$
1	3	58	**6**	24	66
2	6	58	**7**	15	85
3	25	70	**8**	35	79
4	30	68	**9**	1	66
5	26	38	**10**	10	31

Reactions with $NaBH_3CN$ and $NaBH(OAc)_3$ employed acetic acid as the proton source.

diastereoselectivities ranging between 1–35% while those from $NaBH(OAc)_3$ gave rise to diastereoselectivities from 31 to 85%.

Collectively it appears that proximity of the chiral center to the unsaturated-carbon center of the imine rather than the nitrogen atom facilitates higher diastereoselectivities. In addition, these reduction data suggest that the steric bulk around the borohydride anion is key to diastereoselectivity. The catalytic reductions of the camphor– and menthone–imines result in the near quantitative diastereoselectivities. This is attributed to the significantly larger $[HB(C_6F_5)_3]^-$ anion in comparison to $[BH_3CN]^-$ and $[BH(OAc)_3]^-$ anions used in stoichiometric reductions. This view is supported by computed cone angles of 186°, 163° and 92° for the borohydrides, $[HB(C_6F_5)_3]^-$, $[HB(OAc)_3]^-$ and $[BH_3CN]^-$, respectively (ESI†).

The reduction of chiral imines with $B(C_6F_5)_3$ resulted in excellent diastereoselectivities when the chiral center is near the unsaturated carbon center. This is attributed to the larger effect of proximity of the chiral center on the approach of the sterically bulky $[HB(C_6F_5)_3]^-$. The presence of the chiral center near the unsaturated nitrogen center had a less impact on the diastereoselectivity of the hydrogenation. Further mechanistic studies and the application of FLP-based hydrogenation catalysts continue to be a subject of intense efforts in our laboratories.

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