BAr^F_3-Catalyzed Imine Hydroboration with Pinacolborane Not Requiring the Assistance of an Additional Lewis Base

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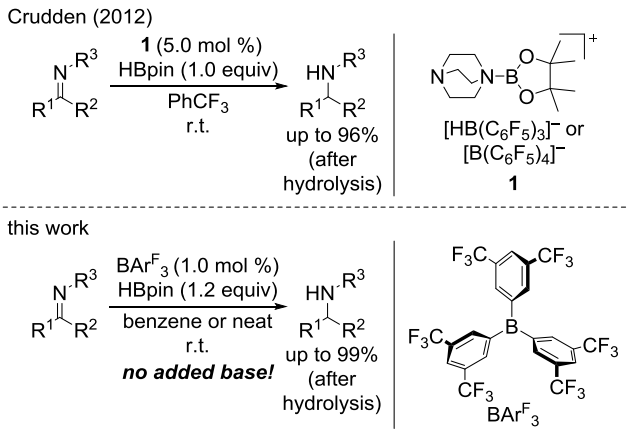
Supporting Information Placeholder

ABSTRACT: The rarely used boron Lewis acid tris[3,5-bis(trifluoromethyl)phenyl]borane (BAr^F_3) is found to be an excellent catalyst for metal-free hydroboration of imines. In the presence of 1.0 mol % of BAr^F_3, several ketimines and aldimines undergo hydroboration with pinacolborane (HBpin) at room temperature without the aid of an external Lewis base. BAr^F_3 is more reactive than other Lewis-acidic boranes, including often-used tris(pentafluorophenyl)borane [$B(C_6F_5)_3$]. The steric hindrance imparted by the six fluorine atoms *ortho* to the boron center in $B(C_6F_5)_3$ accounts for this. Mechanistic control experiments indicate conventional Lewis-acid catalysis involving imine activation and hydride transfer from HBpin.

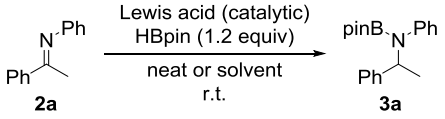
Catalytic imine hydroboration is a straightforward way of preparing ubiquitous amines.[1] However, the number of protocols, of which the majority makes use of transition metals as catalysts, is still limited,[2] and imine hydroboration relying on main-group elements as catalysts is currently attracting attention.[3] In 2012, Crudden and co-workers reported a metal-free imine hydroboration at room temperature where the actual catalyst **1** is generated from the combination of $B(C_6F_5)_3$ or $[Ph_3C]^+[B(C_6F_5)_4]^-$, DABCO (1,4-diazabicyclo[2.2.2]octane), and pinacolborane (HBpin). Hence, this transformation is initiated by $B(C_6F_5)_3$ or the trityl cation but catalyzed by the borenium ion **1** (Scheme 1, top).[4] We recently found that tris[3,5-bis(trifluoromethyl)phenyl]borane (BAr^F_3)[5] promotes the hydroboration of alkenes with HBpin while tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] does not.[6] Detailed mechanistic studies unveiled electron-deficient Ar^F-substituted hydroboranes generated by substituent redistribution between BAr^F_3 and HBpin are the real catalysts. Herein, we disclose that BAr^F_3 is also competent to catalyze the hydroboration of imines with HBpin at room temperature without the assistance of an external Lewis base (Scheme 1, bottom).

Scheme 1. Imine Hydroboration at Room Temperature Catalyzed by Boron Lewis Acids



We began investigating this imine hydroboration using ketimine **2a** as the model substrate (Table 1). No reaction was observed after 18 h at room temperature without a catalyst (entry 1). We then tested different boron Lewis acids. Triphenylborane (BPh_3) was not sufficiently Lewis acidic (entry 2). Similar to Crudden's findings,[4] strongly Lewis-acidic $B(C_6F_5)_3$ showed poor catalytic activity, furnishing 36% conversion after 18 h (entry 3). In stark contrast, BAr^F_3 cleanly led to quantitative conversion of the imine to the amine (entry 4). Lowering the catalyst loading from 2.0 to 0.30 mol % was not detrimental, again providing full conversion (entry 5). We note here that $[Ph_3C]^+[B(C_6F_5)_4]^-$ did not react at all (entry 6). Also, $HB(C_6F_5)_2$, known as Piers' borane, showed hardly any conversion (entry 7)[7] while $HBAr^F_2{\cdot}SMe_2$ performed as efficiently as BAr^F_3 (entry 8 vs entry 3).[8] Using 1.0 mol % of BAr^F_3 as catalyst, we compared the reaction rates in several solvents at 1 h reaction time (entries 9–13). Benzene emerged as best, affording 58% conversion (entry 9); full consumption of the imine was obtained after 18 h, and the free amine was isolated in 87% yield after hydrolysis (entry 14). For the sake of completeness, $B(C_6F_5)_3$ was also probed in benzene yet without any improvement over the neat reaction, even with 5.0 mol % (entry 15 vs entry 3).—Although the present study is about the striking reactivity difference between BAr^F_3 and $B(C_6F_5)_3$, we nevertheless tried BCl_3 and $BF_3{\cdot}OEt_2$ as catalysts in benzene as the solvent (entries 16 and 17). With 20 mol % catalyst loading, BCl_3 still performed poorly but $BF_3{\cdot}OEt_2$ was able to mediate the imine hydroboration with quantitative conversion.

Table 1. Optimization of the Catalytic Imine Hydroboration[a]

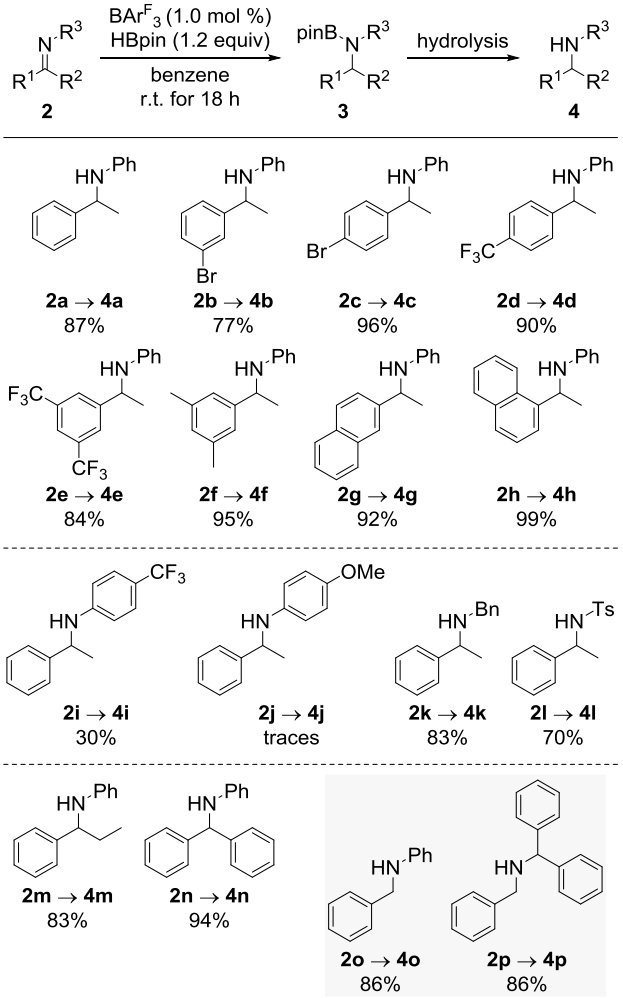


entry	Lewis acid	mol %	time (h)	solvent	conv[b] (%)[c]
1	—	—	18	neat	0
2	BPh_3	2.0	18	neat	0
3	$B(C_6F_5)_3$	2.0	18	neat	36
4	BAr^F_3	2.0	18	neat	100
5	BAr^F_3	0.30	18	neat	100
6	$[Ph_3C]^+[B(C_6F_5)_4]^-$	10	18	neat	0
7	$HB(C_6F_5)_2$	3.0	18	neat	5
8	$HBAr^F_2{\cdot}SMe_2$	3.0	18	neat	100
9	BAr^F_3	1.0	1	benzene	58
10	BAr^F_3	1.0	1	toluene	30
11	BAr^F_3	1.0	1	$PhCF_3$	37
12	BAr^F_3	1.0	1	CH_2Cl_2	34
13	BAr^F_3	1.0	1	1,2-$Cl_2C_2H_4$	37
14	BAr^F_3	1.0	18	benzene	100 (87)[c]
15	$B(C_6F_5)_3$	5.0	6	benzene	<5
16	BCl_3	20	18	benzene	27
17	$BF_3{\cdot}OEt_2$	20	18	benzene	99

[a]All reactions were performed on a 0.1 mmol scale either neat or in solvent (1 M) in a sealed tube. [b]Determined by GLC analysis using tetracosane as internal standard. [c]Isolated yield of the free amine after hydrolysis and purification by flash chromatography on silica gel.

With the optimal conditions in hand, we assessed the scope of this hydroboration reaction (Scheme 2). Various N-phenyl-protected ketimines **2a**–**h** with either electron-withdrawing (Br and CF_3) or -donating groups (Me) on the benzene ring were tested. Full conversion was observed throughout, giving the corresponding amines **4a**–**h** in 77 to 99% yield after aqueous workup. We then investigated the effect of different protecting groups on the nitrogen atom. A CF_3 substituent in the *para* position of the phenyl group (as in **2i**) resulted in a dramatic decrease of substrate reactivity while a MeO substituent in the same position (as in **2j**) completely thwarted the reaction. Changing of the protecting group from phenyl to benzyl (as in **2k**) or tosyl (as in **2l**) did not bring about any significant reactivity difference and good yields were obtained in both cases. Moreover, ketimines **2m** and **2n** derived from α-methyl acetophenone and benzophenone, respectively, were also suitable substrates. Finally, aldimines **2o** and **2p** also proved to be good substrates, both undergoing the hydroboration in 86% yield (gray box).

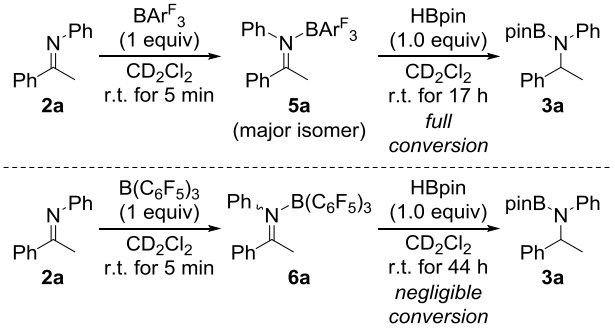
Scheme 2. BAr^F_3-Catalyzed Hydroboration of Ketimines and Aldimines



To gain insight into the mechanism of this facile imine hydroboration, several stoichiometric control experiments were performed. No interaction between the model ketimine **2a** and HBpin was observed by ^1H and ^{11}B NMR spectroscopy when mixing equimolar amounts of these reactants in CD_2Cl_2 (see the Supporting Information for details). Equimolar amounts of **2a** and BAr^F_3 immediately formed the expected Lewis pair **5a** in CD_2Cl_2; **5a** was assigned to be the thermodynamically more stable isomer by multinuclear NMR measurements.[9] Subsequent treatment of **5a** with stoichiometric HBpin resulted in smooth reduction, and full conversion was reached after 17 h (Scheme 3, top). Notably, the catalyst BAr^F_3 precipitated from the solution after completion of the reaction. In-situ formation of hydroboranes $[H_nBAr^F_{3-n}]_2$ (n = 1 and 2) as well as $[(Ar^F)(H)B(\mu\text{-}H)_2BAr^F_2]$ as potential catalysts (cf. Table 1, entry 8) from ligand exchange between BAr^F_3 and HBpin was not observed.[6] Importantly, the diagnostic formation of Ar^F-Bpin was not detected in both the stoichiometric and the catalytic setups. This stands in contrast to our previous study of alkene hydroboration where that substituent redistribution occurs.[6] We believe that the σ-basic imine as opposed to the π-basic alkene prevents that process because of its better coordi-

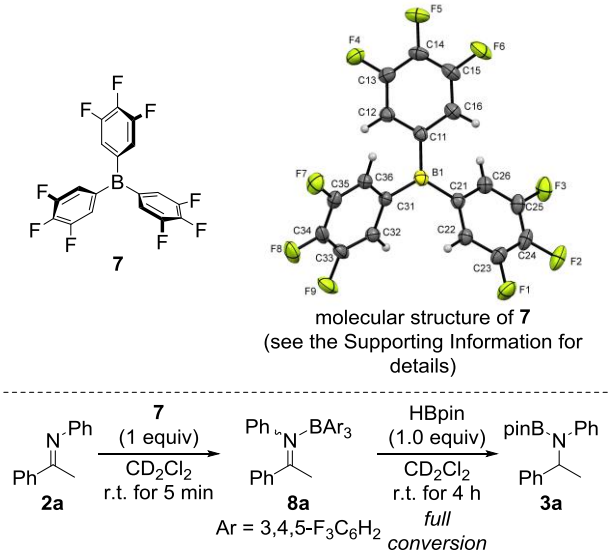
nating ability. Furthermore, neither the formation of any borenium or boronium ions nor the presence of hydridoborate $[HBAr^{F}_{3}]^{-}$ as the counteranion was seen in the NMR spectra. This essentially excludes the possibility of borenium-ion catalysis (cf. Scheme 1, top).[4,10] Directly mixing **2a**, HBpin, and BAr^{F}_{3} in CD_2Cl_2 had the same outcome. For comparison, we repeated the same experiment with $B(C_6F_5)_3$ where rapid formation of the expected Lewis adduct **6a** was also found. However, **6a** was reluctant to react with HBpin, and only traces of reduction were observed after 44 h (Scheme 3, bottom).— Competition experiments in CD_2Cl_2 (treatment of **5a** with $B(C_6F_5)_3$ and **6a** with BAr^{F}_{3}, respectively) revealed that the formation of **6a** is strongly favored over **5a**. It must be noted though that the solubility of BAr^{F}_{3} is rather poor, potentially shifting the equilibrium toward **6a**.

Scheme 3. Stoichiometric Control Experiments: BAr^{F}_{3} Against $B(C_6F_5)_3$



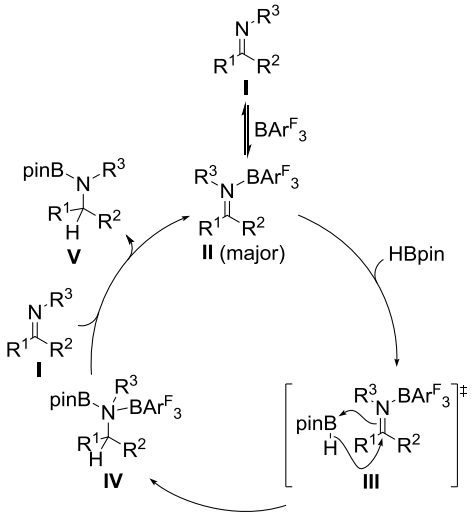
According to literature data,[5a] the Lewis acidities of BAr^{F}_{3} and $B(C_6F_5)_3$ are quite similar, depending on the Lewis base and, hence, on the relative Lewis-acidity scale. We therefore thought that the big difference in catalytic activity between the two could be ascribed to steric effects. $B(C_6F_5)_3$ with its six *ortho* fluorine atoms in the proximity of the boron center is far more sterically hindered than BAr^{F}_{3}. To support this hypothesis, we prepared tris(3,4,5-trifluorophenyl)borane (**7**)[11] devoid of *ortho* substitution (Scheme 4, top). In line with our assumption, this borane exhibited excellent activity in catalytic imine hydroboration, and full conversion was achieved after 4 h at room temperature (not shown). A control experiment with stoichiometric formation of the Lewis adduct analogous to those outlined above (cf. **2a** → **5a** or **6a** → **3a**, Scheme 3) confirmed this result (**2a** → **8a** → **3a**, Scheme 4, bottom).

Scheme 4. Molecular Structure of Tris(3,4,5-trifluorophenyl)borane and Stoichiometric Control Experiment



Based on literature precedence[12] and consistent with our experimental observation, we postulate the following mechanism for the BAr^{F}_{3}-catalyzed imine hydroboration (Scheme 5). BAr^{F}_{3} coordinates to the imine nitrogen atom, thereby lowering the LUMO of the imine (**I** → **II**). Lewis adduct **II** is then reduced to **IV** by HBpin, likely through transition state **III** (**II** → **III** → **IV**). Transfer of BAr^{F}_{3} from Lewis adduct **IV** to the more Lewis-basic imine **I** eventually furnishes the N-borylated amine **V** and closes the catalytic cycle (**IV** → **V**).

Scheme 5. Postulated Catalytic Cycle for Imine Hydroboration



In conclusion, the strong boron Lewis acids BAr^{F}_{3} as well as tris(3,4,5-trifluorophenyl)borane have been uncovered as efficient catalysts for imine hydroboration. Unlike the previous report by Crudden and co-workers,[4] the new protocol did not require the aid of an external Lewis base. A conventional mechanism for Lewis-acid catalysis was shown to be operative. Control experiments corroborated that the steric hindrance imparted by the *ortho* fluorine atoms in $B(C_6F_5)_3$ accounts for

the enormous reactivity difference between BAr^F_3 and widely used $B(C_6F_5)_3$. The present work is another example of a catalysis where $B(C_6F_5)_3$ fails to react effectively.[6]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website to include optimization data, experimental procedures, characterization of new compounds and spectral data.

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Notes

The authors declare no competing financial interests.

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(7) The lack of catalytic activity was not due to stoichiometric imine hydroboration. As verified by NMR measurements, $HB(C_6F_5)_2$ forms an adduct with the imine that does not react further with HBpin.

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(10) Unlike Crudden's initiation of the borenium-ion catalysis with $[Ph_3C]^+[B(C_6F_5)_4]^-$ in the *presence* of DABCO,[4] absolutely no reduction occurs with catalytic (see Table 1, entry 6) as well as stoichiometric amounts of the trityl cation in the *absence* of Lewis bases other than the imine. Instead, imine dimerization through trityl-cation-mediated enamine formation was obtained from an equimolar combination of the three reactants dissolved in CD_2Cl_2 while HBpin remained untouched; HBpin was found to be degraded by stoichiometric treatment with $[Ph_3C]^+[B(C_6F_5)_4]^-$ in independent experiments in CD_2Cl_2 or C_6D_6.

(11) Tris(3,4,5-trifluorophenyl)borane (**7**) was prepared by treatment of 3,4,5-trifluorophenyllithium with $BF_3{\cdot}OEt_2$ at –78 °C; the pure borane was obtained after 2-fold sublimation (see the Supporting Information for details).

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