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COMMUNICATION

Frustrated Lewis pair catalyzed hydrodehalogenation of benzyl-halides

Tongtong Wang^{a,b}, Maotong Xu^a, Andrew R. Jupp^a, Shi-Ming Chen,^a Zheng-Wang Qu^{*c}, Stefan Grimme^c, and Douglas W. Stephan^{*a}Received 00th January 20xx,
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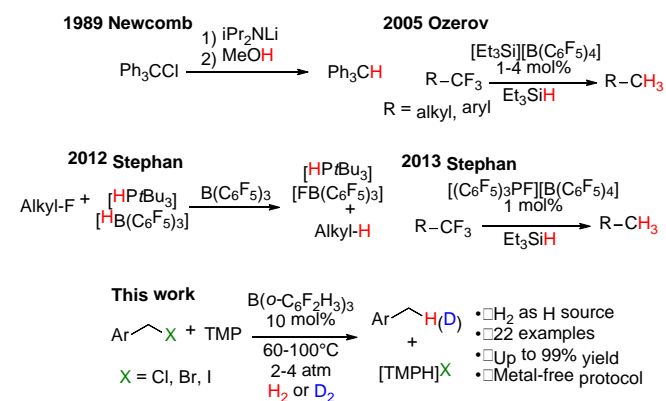
Abstract: 10 mol% B(*o*-C₆F₂H₃)₃ in the presence of excess tetramethylpiperidine (TMP) and H₂ (or D₂) is shown to catalyze the hydrogenative dehalogenation of benzyl-halides to give corresponding toluene derivatives. These reactions proceed via an initial FLP activation of H₂ yielding the ammonium hydridoborate [TMPH][HB(*o*-C₆F₂H₃)₃]. This species act in analogy to an FLP to cooperatively activate C–X bond (X = Cl, Br, I) of benzyl-halides delivering hydride and generating the corresponding ammonium halide salts.

Organic halides are useful reagents and have found versatile applications in synthetic chemistry and industry. However, such species are both toxic¹ while CFC and related species are known to be resistant to degradation under ambient conditions leading to detrimental environmental effects.² Hydrodehalogenation, which replaces the halogen with a hydrogen atom represents one method to degrade toxic organic halides to the less toxic hydrocarbons. While this process is dominated by transition metal catalysts,^{3–12} alkali metal reagents are also known to stoichiometrically reduce trityl halides (Scheme 1).¹³ Recently, Wilson and coworkers¹⁴ have employed a molecular calcium hydride species to effect hydrodehalogenation of halobenzenes, while others have developed photochemical processes for C–X activation.^{15, 16}

Metal-free processes have also been explored. For example, the highly Lewis acidic main group species such as B(C₆F₅)₃¹⁷ [(C₆F₅)₃PF][B(C₆F₅)₄]¹⁸ and [Et₃Si][B(C₆F₅)₄]^{19, 20} have also exhibited excellent reactivity in the hydrodehalogenation reactions of C–F bonds (Scheme 1). In these reactions Et₃SiH is used as the source of hydride.

The emergence of frustrated Lewis pairs (FLPs) has led to metal-free reductions.^{21–24} Numerous studies have exploited such combinations of Lewis acids and bases in the presence of H₂ to effect the reduction of a wide range of unsaturated organic substrates including imines, enamines, silyl enol ethers, alkenes, alkynes, aromatic species, aldehydes, and ketones.²² In addition, we have previously employed the product of H₂ activation, [*t*-Bu₃PH][HB(C₆F₅)₃] as a stoichiometric source of hydride.²⁵ That being said, efforts to exploit FLPs and H₂ for catalytic hydrodehalogenation have remained unexplored.

Benzyl-halides are suspected to be carcinogenic and are known to have direct effects on water and soil organisms, leading to indirect toxic effects on birds, mammals and humans.²⁶ Herein, we devise a strategy to exploit FLP activation of H₂ to catalytically deliver hydride effecting the reduction of a range of benzyl-halides to the corresponding toluene derivatives under mild conditions. Mechanistic insights are provided by extensive DFT studies.



Scheme 1. Stoichiometric and catalytic transition metal-free approaches to hydrodehalogenation reactions.

The Lewis acid, B(*o*-C₆F₂H₃)₃ has a low affinity for binding of chloride, bromide, or iodide ions in CHCl₃ solution. This stands in contrast to the stronger Lewis-acid B(C₆F₅)₃ that binds chloride with a computed affinity of -5.7 kcal/mol. The even higher affinities of

^a Department of Chemistry, University of Toronto, 80 St. George St, Toronto, ON, Canada, M5S3H6, dstephan@chem.utoronto.ca

^b College of Chemistry, Faculty of Chemical, Environmental and Biological Science and Technology, Dalian University of Technology, Dalian, China 116023

^c Mulliken Center for Theoretical Chemistry, University of Bonn, Beringstrasse 4, 53115 Bonn, Germany, Email: qu@thch.uni-bonn.de

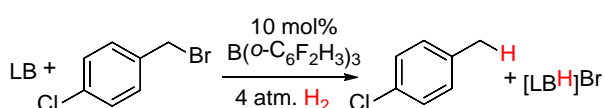
† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: Experimental, spectroscopic and computations details are deposited See DOI: 10.1039/x0xx00000x

$B(C_6F_5)_3$ and $B(o-C_6F_2H_3)_3$ for fluoride ions of -41.6 and -29.5 kcal/mol, respectively, have been exploited for stoichiometric C-F activation of alkylfluorides.^{17, 27} However, these strong interactions precluded a catalytic role for boranes.

Thus, targeting FLP mediated hydrogenolysis of haloalkanes, we reckoned that $B(o-C_6F_2H_3)_3$ in the presence of a strong base, would activate H_2 in the presence of an alkylhalide. To test this notion, 4-chloro-benzyl bromide was combined with 10 mol% $B(o-C_6F_2H_3)_3$ with various bases at varying temperature in C_6D_6 or $CDCl_3$ (Table 1, entry 1-8). Using 2,4,6-collidine (Col) as a Lewis base (entry 1, 2), no reactions were observed at 60 °C. The use of stronger Lewis base, 2,2,6,6-tetramethylpiperidine (TMP), resulted in hydrodehalogenation reaction, affording the product, 4-chloro-toluene in 7% and 12% after 16 h at room temperature in C_6D_6 and $CDCl_3$, respectively (entry 3, 4). Increasing the reaction temperature to 60 °C significantly accelerated the catalysis, giving rise to yields of 74% and 80%, respectively, after 16 h (entry 5, 6). Still longer reaction times (23 h) boosted the yields of 4-chloro-toluene to 86% and 90%, respectively (entry 7, 8).

Table 1. Optimization of reaction conditions for catalytic hydrodehalogenation of 4-chloro-benzyl bromide.



	Base (LB)	Solvent	Time h	Temp °C	Yield ^a %
1	Col	C_6D_6	23	60	0
2	Col	$CDCl_3$	23	60	0
3	TMP	C_6D_6	16	25	7
4	TMP	$CDCl_3$	16	25	12
5	TMP	C_6D_6	16	60	74
6	TMP	$CDCl_3$	16	60	80
7	TMP	C_6D_6	23	60	86
8	TMP	$CDCl_3$	23	60	90

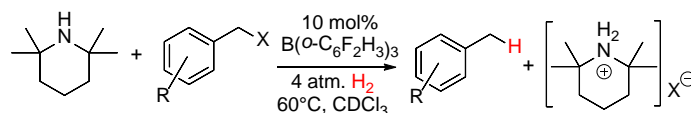
^a Yield determined by 1H NMR integration, 10 μ L toluene was added as internal standard

Under similar conditions, using $CDCl_3$ as the solvent at 60 °C and TMP as the base, a series of benzyl bromides including 4- $BrC_6H_4CH_2Br$, 2- $BrC_6H_4CH_2Br$, 2- $IC_6H_4CH_2Br$, 3,4- $F_2C_6H_3CH_2Br$, 3- $FC_6H_4CH_2Br$, 3-(CN) $C_6H_4CH_2Br$ and 2,2'-($C_6H_4CH_2Br$)₂ were reduced to the corresponding toluene derivatives (Table 2, entry 1-7). Generally, the yields were high, ranging from 81-99% except for 3-(CN) $C_6H_4CH_2Br$, where a yield of 53% was seen (entry 6). The reduced yield in the latter case is presumably due to the electron-withdrawing effects of CN on the phenyl ring. This could result in a less stable benzyl cation intermediate or alternatively could give rise to a dative interaction with the Lewis acid. The latter is suggested by the ^{11}B chemical shift observed at *ca* -3 ppm for the initial reaction mixture.

The corresponding reactions of benzyl iodides also proceed in a similar fashion. Thus, treatment of $C_6H_5CH_2I$, 2- $BrC_6H_4CH_2I$, 2-

$IC_6H_4CH_2I$ and 4- $ClC_6H_4CH_2I$ with 10 mol% $B(o-C_6F_2H_3)_3$ and TMP resulted in the reduction to the corresponding toluene derivatives in yields ranging from 83-95%, (Table 2, entry 8-11), although the reactions times were increased to 36 h. In the same vein, the catalytic hydrodechlorination of benzyl chlorides was probed. The substrates $C_6H_5CH_2Cl$, 4-*t*Bu $C_6H_4CH_2Cl$, 2,4,6- $C_6H_2Me_3CH_2Cl$ and 4- $BrC_6H_4CH_2Cl$ were reduced at 60 °C after 21-36 h to the corresponding toluene derivatives in yields from 86-95% (entry 12-15). The more electron-deficient species 3,4- $F_2C_6H_3CH_2Cl$ and 4-(NO₂) $C_6H_4CH_2Cl$ were also reduced although the yields were lower (60 and 58% respectively, entry 16, 17). Hydrodehalogenation of non-benzylic alkylhalides (entry 18) led to poor reactivity, even with prolonged heating (60 h) at elevated temperatures (120 °C). For example, the alkane product from $CH_3(CH_2)_6Br$, heptane was obtained in 36% yield. These observations suggest that reduction of the C-X by borohydride is facilitated by the electron withdrawing character the aryl of benzylhalides as well as the π -conjugation stabilization of the resultant carbocation upon halide anion removal. This view is consistent with the lesser reactivity of alkyl halides where the halide substituted carbon is less electrophilic.

Table 2. Catalytic hydro-dehalogenation of alkylhalides

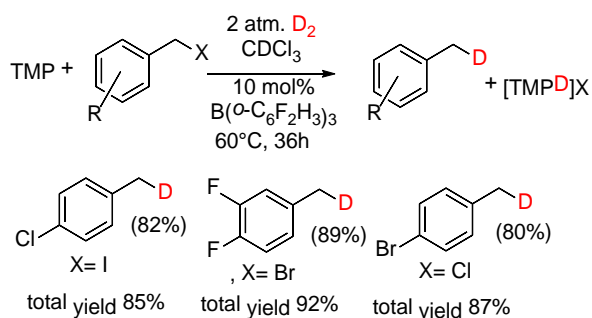


	Substrate	Time (h)	Yield ^a (%)
1	4- $BrC_6H_4CH_2Br$	21	99
2	2- $BrC_6H_4CH_2Br$	21	81
3	2- $IC_6H_4CH_2Br$	21	96
4	3,4- $F_2C_6H_3CH_2Br$	21	99
5	3- $FC_6H_4CH_2Br$	21	83
6	3-(CN) $C_6H_4CH_2Br$	36	53
7	2,2'-($C_6H_4CH_2Br$) ₂	36	96
8	$C_6H_5CH_2I$	21	83
9	2- $BrC_6H_4CH_2I$	36	94
10	2- $IC_6H_4CH_2I$	36	85
11	4- $ClC_6H_4CH_2I$	36	95
12	$C_6H_5CH_2Cl$	36	87
13	4- <i>t</i> Bu $C_6H_4CH_2Cl$	36	86
14	2,4,6- $C_6H_2Me_3CH_2Cl$	21	95
15	4- $BrC_6H_4CH_2Cl$	36	87
16	3,4- $F_2C_6H_3CH_2Cl$	36	60
17	4-(NO ₂) $C_6H_4CH_2Cl$	36	58
18	$CH_3(CH_2)_6Br$	60	36 ^b
19	$C_6H_5CH_2Br$	33	94

^aYield determined by 1H or $^{19}F\{^1H\}$ NMR integration; ^b performed at 120 °C in C_6D_6

This methodology was shown to be scalable. To this end, 5.00 grams of 4- $BrC_6H_4CH_2Br$ (20 mmol) was treated with TMP and 5 mol% $B(o-C_6F_2H_3)_3$ under H_2 at 60 °C. The 1H NMR spectrum of the crude reaction mixture after 36 h showed a 98% conversion rate. Subsequent work-up afforded an isolated yield of 2.37 g (70%) of white crystalline product, 4- $BrC_6H_4CH_3$ (m.p. 28.5 °C)

This methodology was also used to deuterate benzyl-halides. Thus, the combination of 4-BrC₆H₄CH₂Cl, 3,4-F₂C₆H₃CH₂Br or 4-ClC₆H₄CH₂, with TMP and 10 mol% B(*o*-C₆F₂H₃)₃ in CDCl₃ under D₂ (2 atm) for 36 h at 60 °C afforded 4-BrC₆H₄CH₂D, 3,4-F₂C₆H₃CH₂D and 4-ClC₆H₄CH₂D, in yields of 82, 89, 80%, respectively (Scheme 2). Each product exhibited the expected 1:1:1 triplet in the ¹H NMR spectrum at approximately 2.3 ppm with a proton-deuterium coupling of 2 Hz. The lower yields of these deuterated species in comparison to the hydrogenated analogues may result from the reversibility of FLP-H₂ activation which lead to isotopic dilution of the D₂ with the proton from TMP, thereby lowering the yield of the deuterated product (see ESI).



Scheme 2. Catalytic deuterodehalogenation of benzyl-halides. percentage deuterium incorporation is indicated. (Protonated species also generated due to H/D scramble with TMP (see ESI).

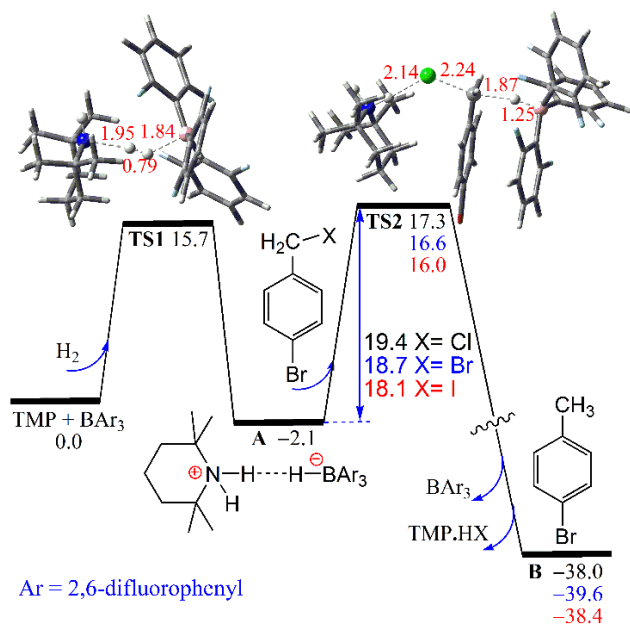


Figure 1. DFT-computed free energy paths for the B(2,6-C₆F₂H₃)₃ catalyzed hydrodehalogenation of benzyl-halides with H₂ in the presence of excess TMP. For ball-and-stick models, crucial B, C, N, H and Cl atoms are highlighted by pink, grey, blue, white, and green balls, with selected bond lengths shown in Å.

To gain deep mechanistic insights, extensive DFT calculations were performed at the dispersion-corrected PW6B95-D3/def2-QZVP + COSMO-RS // TPSS-D3/def2-TZVP + COSMO level in CHCl₃ solution.²⁸⁻³⁸ The final PW6B95-D3 free energies (in kcal/mol, at 298 K and 1 M concentration) are discussed. The first H₂ activation step is -2.1 kcal/mol exergonic over a free energy barrier of 15.7 kcal/mol (via transition state **TS1**) yielding the contact ion pair [TMPH][HB(*o*-C₆F₂H₃)₃] that is 3.4 kcal/mol more stable than the separated ions. Subsequent cooperative B-H...C-Cl...H-N type C-Cl bond activation of 4-BrC₆H₄CH₂Cl with [TMPH][HB(*o*-C₆F₂H₃)₃] is -35.9 kcal/mol exergonic over a higher barrier of 19.4 kcal/mol (via **TS2**) to form the desired product 4-BrC₆H₄CH₃ and [TMPH]Cl, regenerating B(*o*-C₆F₂H₃)₃ for further reaction. The overall FLP-catalyzed hydrodehalogenation of 4-BrC₆H₄CH₂Cl using H₂ and TMP is thus -38.0 kcal/mol exergonic and is rate-limited by the C-Cl bond activation. This barrier is reduced by 0.7 and 1.3 kcal/mol for C-Br and C-I bonds, respectively. While this suggests the gradually increasing reactivity of benzyl C-X bonds in the order of X = Cl < Br < I, experimentally data are generally consistent with this trend, although this is impacted by additional substitution. Interestingly, alkylhalide substrates of the form CH₃(CH₂)₃X (X = Cl, Br, I) are computed to have higher barriers ranging from 23.8 to 26.3 kcal/mol depending on the halide. This latter observation is consistent with the poorer reactivity observed (Table 2, entry 18).

Conclusions

In conclusion, we have reported the facile use of a judicious selected FLP catalyst affords a protocol for the reduction of benzyl-halides that proceeds under relatively mild conditions. In these cases, the ammonium cation and the hydridoborate anion act in tandem as an FLP to activate the C-X bond, delivering hydride and eliminating the ammonium halide salt. The utility of this protocol in further chemistry and the development of other FLP-catalyzed processes are the subjects of on-going efforts.

Conflicts of interest

There are no conflicts to declare.

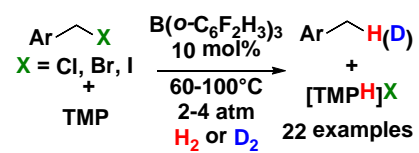
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FLP Hydrodehalogenation Catalysis

The FLP $\text{B}(\text{o}-\text{C}_6\text{F}_2\text{H}_3)_3$ / tetramethylpiperidine (TMP) in the presence of H_2 (or D_2) catalyzes the hydrodehalogenation of benzyl-halides affording the corresponding toluene derivatives.