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Metal-Free Aromatic Hydrogenation: Aniline to Cyclohexyl-amine Derivatives

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Supporting Information

ABSTRACT: Hydrogenation of the *N*-bound phenyl rings of amines, imines, and aziridine is achieved in the presence of H_2 and $B(C_6F_5)_3$, affording the corresponding *N*-cyclohexylammonium hydridoborate salts.

Hydrogenation is a conceptually simple reaction in which molecular hydrogen is added to an unsaturated organic molecule. Such reactions are used in a diverse range of applications, including the upgrading of crude oil paper production and the generation of commodity and fine chemicals for 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] It was early in the 20th century when Sabatier discovered that amorphous metals could catalyze the hydrogenation of olefins. In the 1960s, the advent of organometallic chemistry led Wilkinson and others to uncover homogeneous ruthenium and rhodium based hydrogenation catalysts[3] that operate via oxidative addition of H_2 to transition metal centers.[4] Further advancements in hydrogenations came in the 1980s with the development of asymmetric hydrogenation catalysts by Noyori[5] and Knowles.[6]

Despite these advancements in hydrogenation catalysis, over the last century, catalytic reduction of aromatic rings remains challenging. This is typically attributed to the inherent stability resulting from aromaticity. While a tantalum-based homogeneous catalyst system has been described by Rothwell et al.,[7] a majority of catalysts used for hydrogenation of aromatic substrates are heterogeneous cobalt or nickel catalysts on oxide supports, used at temperatures greater than 200 °C and H_2 pressures on the order of 200 atm.[8] Köster and co-workers have demonstrated that hydroboration and subsequent hydrogenolysis effects the conversion of naphthalenes to tetralins[9] and anthracenes to coronenes[10] at 170−200 °C and 25−100 atm of hydrogen. More recently, we have reported metal-free systems capable of reversible heterolytic activation of H_2.[11] On the basis of these "frustrated Lewis pairs" (FLPs),[12] we[12b,13] and others,[14] have developed metal-free hydrogenation catalysts for a variety of imines, enamines, silylenol ethers, diimines, and *N*-heterocyclic compounds. In this communication, we describe metal-free hydrogenation of *N*-bound aromatic rings to the corresponding cyclohexylamine derivatives. While these reductions are stoichiometric, these reactions represent rare examples of homogeneous aromatic reductions that are metal-free and performed under comparatively mild conditions.

The combination of the amine *t*BuNHPh with an equivalent of $B(C_6F_5)_3$ in C_6D_5Br or pentane solutions initially results in no apparent reaction. However, following the exposure of this solution to H_2 (4 atm.) at 25 °C, the gradual precipitation of a solid was observed. After standing for 12 h, the white product **1** can be isolated in 82% yield. NMR data for **1** obtained in C_6D_5Br revealed a ^{11}B NMR resonance at −24.0 ppm exhibiting one bond B−H coupling of 78 Hz.[15] These data, together with the resonances in the ^{19}F NMR observed at −133.5, −161.3, and −165.0 ppm were consistent with the presence of the anion $[HB(C_6F_5)_3]^-$.[11a] The ^1H NMR data showed a broad resonance at 7.15 ppm attributable to an NH_2 fragment, integrating to two protons, as well as the signals assignable to the phenyl and tbutyl groups. These data were consistent with the formulation of **1** as $[t\text{BuNH}_2\text{Ph}][HB(C_6F_5)_3]$.

In contrast, repetition of the above reaction in toluene with heating to 110 °C for 96 h led to the formation of a new product **2**. Subsequent workup and characterization by NMR spectroscopy revealed the presence of the anion $[HB(C_6F_5)_3]^-$. The ^1H NMR data displayed a broad resonance at 5.07 ppm attributed to an NH_2 moiety while aromatic resonances were no longer observed. Instead, multiplets at 2.72, 1.55, 1.45, 1.31, 1.17, and 0.90 ppm, along with a sharp singlet at 0.91 ppm, were observed. These data were consistent with the identity of **2** as $[t\text{BuNH}_2\text{Cy}][HB(C_6F_5)_3]$ (Scheme 1).

Monitoring the reaction by ^1H NMR spectroscopy showed the gradual growth of methylene resonances with the corresponding disappearance of the aromatic signals. After 48 h, the cyclohexylamine product constituted approximately 81% of the reduced product in solution although it was obtained in 30% isolated yield.

In an analogous fashion, treatment of *i*PrNHPh with an equivalent of $B(C_6F_5)_3$ in toluene under H_2 (4 atm) at 110 °C for 36 h resulted in reduction of the aromatic ring affording the salt $[i\text{PrNH}_2\text{Cy}][HB(C_6F_5)_3]$ **3** in 93% yield. Similar treatment of PhCyNH or Ph_2NH afforded $[Cy_2NH_2][HB(C_6F_5)_3]$ **4** in yields of 88 and 65%, respectively. In addition to the NMR spectroscopy data, the formulations of **3** and **4** were unambiguously confirmed crystallographically (Figure 1).[16]

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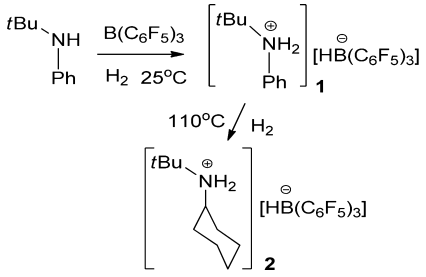
Scheme 1. Synthesis of Compounds 1 and 2



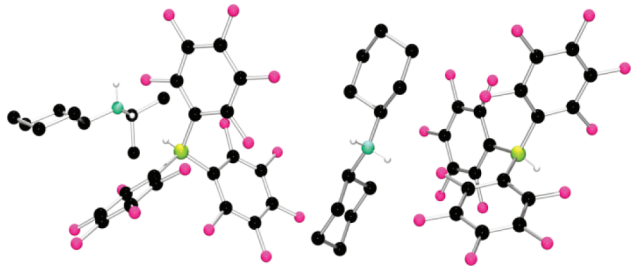


Figure 1. POV-ray drawings of (left) **3** and (right) **4**. C, black; F, pink; N, blue-green; B, yellow-green; H, gray. Hydrogen atoms except for NH and BH groups are omitted for clarity.

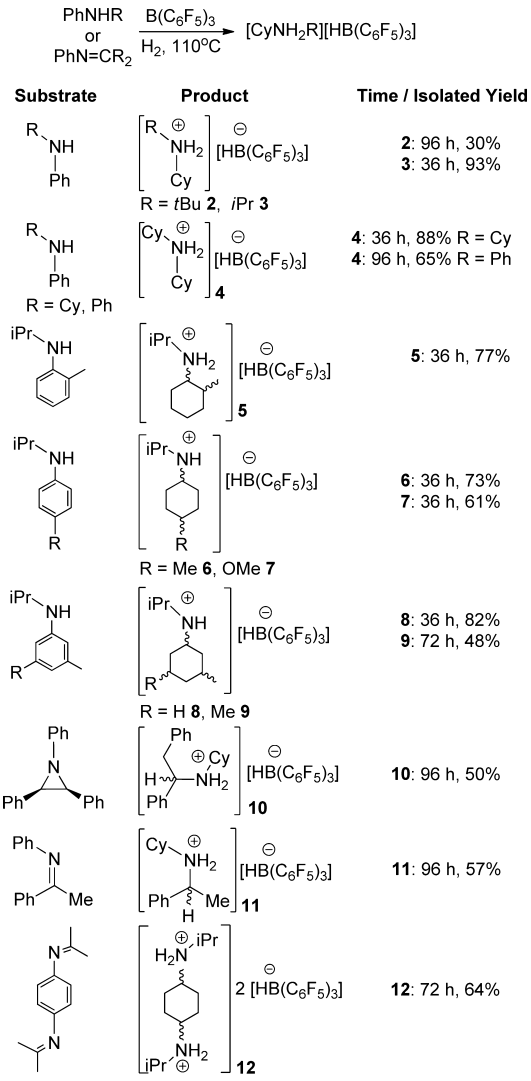
Additional substrates explored in analogous reductions included, *i*PrNH(2-MeC$_6$H$_4$), *i*PrNH(4-RC$_6$H$_4$) (R = Me, OMe), *i*PrNH(3-MeC$_6$H$_4$), and *i*PrNH(3,5-Me$_2$C$_6$H$_3$). affording the arene-reduced products [*i*PrNH$_2$(2-MeC$_6$H$_{10}$)][HB(C$_6$F$_5$)$_3$] **5**, [*i*PrNH$_2$(4-RC$_6$H$_{10}$)][HB(C$_6$F$_5$)$_3$] (R = Me **6**, OMe **7**), [*i*PrNH$_2$(3-MeC$_6$H$_{10}$)][HB(C$_6$F$_5$)$_3$] **8**, and [*i*PrNH$_2$(3,5-Me$_2$C$_6$H$_9$)][HB(C$_6$F$_5$)$_3$] **9** in yields of 77, 73, 61, 82, and 48%, respectively (Table 1). In cases where reduction affords a chiral center, mixtures of diastereomers were observed.

We have previously reported the catalytic hydrogenative ring-opening of *cis*-1,2,3-triphenylazirdine using 5 mol % B(C$_6$F$_5$)$_3$ to give PhNHCHPhCH$_2$Ph.[13d] However, employing 1 equiv of B(C$_6$F$_5$)$_3$ at 110 °C for 96 h resulted in the reduction of the *N*-bound phenyl ring yielding the salt [CyNH$_2$CHPhCH$_2$Ph][HB(C$_6$F$_5$)$_3$] **10**. The ^{1}H NMR data were in keeping with the formulation of the cation with the notable presence of resonances at 5.88 and 4.61 ppm, ascribed to the NH$_2$ and methine fragments, respectively, in addition to the phenyl, cyclohexyl, methylene, and BH signals. ^{19}F and ^{11}B NMR spectra displayed the characteristic resonances of the anion [HB(C$_6$F$_5$)$_3$]$^-$.

Reduction of the imine PhN=CMePh, to the corresponding amine, has also been previously reported to occur upon exposure of the imine to H$_2$ using 10 mol % B(C$_6$F$_5$)$_3$.[13c] However, on heating the substrate to 110 °C for 96 h under H$_2$ (4 atm) and in the presence of 1 equiv of B(C$_6$F$_5$)$_3$, reduction of the *N*-bound aromatic ring is also observed, affording the species[CyNH$_2$PhCH(Me)][HB(C$_6$F$_5$)$_3$] **11**. The reduction of (Me$_2$C=N)$_2$C$_6$H$_4$ was observed on heating for 72 h, in the presence of 2 equiv of B(C$_6$F$_5$)$_3$, yielding 64% of the product [(*i*PrNH$_2$)$_2$C$_6$H$_{10}$][HB(C$_6$F$_5$)$_3$]$_2$ **12** (Table 1).

The mechanism of these reductions is the subject of ongoing study. To this end, quantum chemical calculations were performed at the dispersion-corrected *meta*-double hybrid level (PW6P95 functional), employing large triple-ζ type basis sets, and TPSS-D3 optimized geometries.[17] This final

Table 1. Reductions of *N*-Phenyl Substrates to *N*-Cyclohexylammonium Salts



theoretical level denoted as PWP95-D3/def2-TZVPP//TPSS-D3/def-TZVP provides reaction energies with an estimated accuracy of about 1−2 kcal/mol. Solvation effects of toluene were considered using the COSMO-RS continuum solvation model (for details see Supporting Information). The optimized structures, computed relative energies, free enthalpies *G* (298 K) of **1** and **2**, important intermediates and the H$_2$-addition transition state (TS) are shown in Figure 2. The theoretical results support a mechanism initiated by the dissociation of the weak amine-borane adducts. FLP activation of H$_2$ yields the salt **1** which is computed to be 9.7 kcal/mol lower in energy but the free enthalpy difference is close to zero. Hence, under equilibrium conditions, it can be considered as a resting state of the reaction. Rotation of the amine such that the arene *para*-position is oriented towards the boron atom afford a van der Waals complex (Figure 2, vdW-complex) which benefits from significant pi-stacking stabilization. Similar to the reaction of classical FLPs,[18] this pairing can effect H$_2$-splitting in the 'cavity' formed by the borane and the arene ring with a relatively low energy barrier of 8.7 kcal/mol. The effective free activation enthalpy (i.e., relative to the resting state) is computed to be 21.2 kcal/mol which is in agreement with the experimentally observed reactivity at elevated temperatures.

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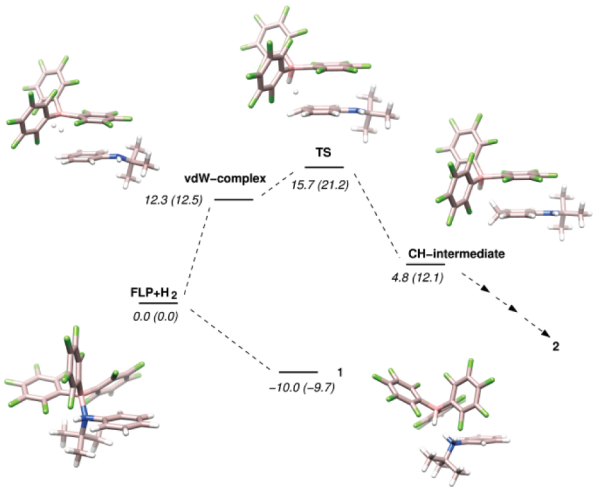
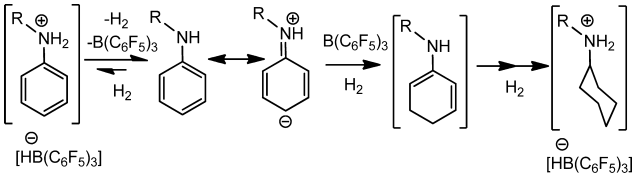


Figure 2. Optimized structures, energies (in parentheses), and free enthalpies *G* (298K) are relative to FLP + H_2 (all data are in kcal/mol) for the first step of the reaction mechanism. Computations refer to the PWP95-D3/def2-TZVPP//TPSS-D3/def-TZVP level of theory (for details see Supporting Information).

The H–H distance in the TS structure is about 0.97 Å, significantly longer than that seen for P/B based FLPs (0.78–0.8 Å) indicating a somewhat 'later' TS. The corresponding H–H and C–H covalent Wiberg bond orders are 0.33 and 0.41 Å, respectively, while the B–H bond order is 0.63 Å, indicating approximately half-broken and half-formed bonds in the TS. The transient intermediate product (Figure 2, CH-intermediate) of the reaction is an ion pair of $[tBuNHC_6H_6][HB(C_6F_5)_3]$ showing a completely rehybridized carbon atom in the *para*-position and an almost planar NHR=C unit in the cation. This species has similar energy and free enthalpy to the vdW-complex. While the anticipated complexity of subsequent hydrogenation steps to **2** has limited further computations, it is clear that access to the arene–$B(C_6F_5)_3$ vdW-complex is key in initiating the arene reduction.

This view of the mechanism is consistent with the observation of species **1** as the initial product of hydrogenation and the subsequent thermal access to the arene reduced species **2** (Scheme 2). It is noteworthy that even under prolonged

Scheme 2. Proposed Reaction Pathways to Anilinium and Cyclohexylammonium Salts



heating of the more basic amine iPr_2NPh with $B(C_6F_5)_3$ under H_2 yields only the salt $[iPr_2NHPh][HB(C_6F_5)_3]$ **13**. The nature of this species was confirmed spectroscopically and crystallographically (see Supporting Information). This suggests that the greater basicity of the N center in iPr_2NPh both facilitates and stabilizes **13** relative to the corresponding FLP, thus, inhibiting access to the corresponding arene–borane vdW complex and subsequent arene reduction.

In summary, we have demonstrated that *N*-phenyl amines are reduced under H_2 in the presence of an equivalent of $B(C_6F_5)_3$ to yield the corresponding cyclohexylamine derivatives under mild conditions. In these reactions, the borane mediates uptake of 4 equiv of H_2, terminating with a final FLP activation of H_2 affording the cyclohexylammonium salts. These results represent the first stoichiometric, homogeneous, metal-free hydrogenations of aromatic rings. We are actively studying a broadening range of substrates for arene hydrogenations and the application of this new methodology in targeted syntheses.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental, computational, and crystallographic data are deposited. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Materials and methods are available as supporting material on Science Online.
(16) Crystallographic parameters of **3**: $P2(1)/c$, a = 9.7241(8) Å, b = 14.7348(12) Å, c = 18.8022(15) Å, b = 98.826(4)°, V = 2662.1(4) Å^3; Data, 4685; Variables, 401; R = 0.0361, Rw(all) = 0.0898; GOF, 1.007. Crystallographic parameters of **4**: $P2(1)/n$, a = 12.6342(6) Å, b = 18.1939(8) Å, c = 12.8612(6) Å, b = 90.269(2)°, V = 2956.3(2) Å^3; Data, 5207; Variables, 424; R = 0.0352, Rw = 0.0866; GOF, 1.024.
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