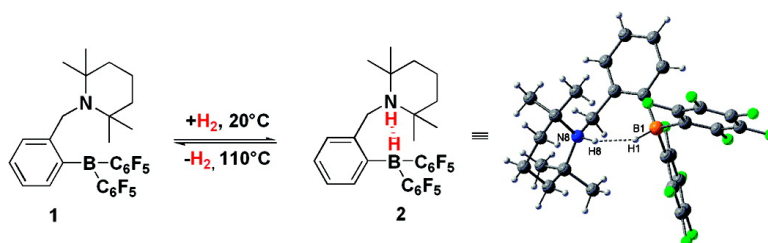


Molecular Tweezers for Hydrogen: Synthesis, Characterization, and Reactivity

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Molecular Tweezers for Hydrogen: Synthesis, Characterization, and Reactivity

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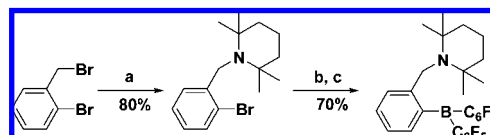
Amine formation is a fundamental reaction in chemical synthesis.¹ The importance of amines and their derivatives such as amides and sulfamides in food, agrochemical, and pharmaceutical industries is well recognized.^{2,3} Although countless methods are known for the synthesis of amines, preparations under mild conditions, without generation of waste, and without the use of transition-metals is a challenging goal.⁴ Among the various methods, the widely used transition-metal-catalyzed reductions of imines, enamines, and nitriles are probably the most important.⁵ Unfortunately, transition-metal catalysts are not only expensive, but their complete removal from the reaction product is generally required in the production of pharmaceutical intermediates due to toxicity concerns.⁶ Alternatively, main-group hydride reagents such as NaBH₄ and LiAlH₄ afford stoichiometric reductions, but involve tedious procedures and produce toxic chemical waste.⁷ Metal-free reductions of imines by organocatalysts, in combination with Hantzsch ester as the hydrogen source, are known.⁸ Recently, several atom-economical transition-metal-free methods such as Lewis acid-catalyzed amination,⁹ hydrosilylation,¹⁰ and intermolecular hydroamination¹¹ were reported. More recently, the first nonmetal system which is able to reversibly activate H₂ was shown in pioneering studies by Stephan and co-workers to be an effective catalyst for the hydrogenation of bulky imines.^{12–14} Herein we report the metal-free catalytic hydrogenation of nonsterically demanding imines and enamines.

Understanding the actual mechanism of splitting and liberating H₂ by nonmetals and the nature of dihydrogen bond interaction in these compounds is essential for learning how to design metal-free systems for H₂ storage and new hydrogenation catalysts.^{15–17} Although the liberation of H₂ is expected to be thermodynamically uphill, it is envisioned that if the energetic cost is small enough, facile hydrogen liberation can take place.

We recently reported the hydrogen activation by 2,2,6,6-tetramethylpiperidine (TMPNH) in combination with B(C₆F₅)₃.¹⁸ Whereas this reaction leads to the stable hydrogenated ionic product [TMPNH₂]⁺[BH(C₆F₅)₃]⁻, an extraordinary intermediate with a strong N–H···H–B dihydrogen bond between the cation and the anion was detected by nuclear magnetic resonance (NMR) spectroscopy. This observation prompted us to investigate a similar intramolecular system for H₂ activation where active B and N centers are located close to each other.¹⁹ In this respect we designed the *ansa*-compound N-TMPN-CH₂C₆H₄B(C₆F₅)₂ **1** and developed an effective procedure for the synthesis of a dehydrogenated product **1** starting from 2-bromobenzylbromide, 2,2,6,6-tetramethylpiperidine and (C₆F₅)₂BCl.²⁰

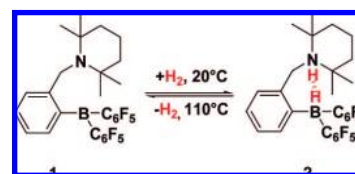
The bright yellow oil **1** was isolated in total yield of 55% and exhibited a single boron resonance in the ¹¹B NMR spectrum at

Scheme 1. Synthesis of Compound **1**^a



^a Reagents and conditions: (a) acetone, 95 °C, 48 h, 1.1 equiv K₂CO₃, 0.1 equiv KI, 1 equiv TMPNH; (b) –70 °C, Et₂O, 2 equiv *t*-BuLi; (c) –20 to 20 °C, 12 h, (C₆F₅)₂BCl.

Scheme 2. Reversible H₂ Activation by System **1, 2**



65.48 ppm indicative of three-coordinate boron (Scheme 1). Moreover, the difference in the chemical shifts $\Delta\delta_{p,m} = 13.61$ ppm of the F atoms in the para and meta positions of the C₆F₅ fragments refers to a neutral boron center.¹⁰

Compound **1** reacted rapidly with H₂ in toluene solution at 20 °C to give a white suspension of **2** in quantitative yield (Scheme 2). The NMR spectroscopic data exhibited a ¹¹B NMR signal at –20.39 ppm (doublet, ¹J_{BH} = 77 Hz) and the difference in the chemical shifts of the F atoms ($\Delta\delta_{p,m} = 3.68$ ppm) indicated an anionic four-coordinate borate.¹⁰ The ¹H NMR spectrum showed quartet and a broad singlet resonances at 3.91 ppm (B–H, ¹J_{BH} = 74 Hz) and 7.55 ppm (N–H), respectively. The observation that the methyl groups in catalyst **2** occur as two singlets (1:1 ratio) accounts for a significant barrier of rotation around the N-benzyl bond. Furthermore, the NMR data revealed that the conversion to **2** was completed in less than 5 min. An X-ray crystallographic study of **2** (Figure 1) showed that the N–H···H–B dihydrogen bond (DHB) is rather short (1.78 Å).^{21,22} Thus, the air- and moisture-stable catalyst **2** has been prepared on a gram scale (up to 5 g) by an efficient three-step synthesis from readily available precursors (Schemes 1, 2).

Interestingly, when a toluene solution of **2** (0.1M) was refluxed at 110 °C in a closed system under reduced pressure, or a flow of argon for 3 h, a 50% conversion of **2** to the bright yellow starting compound **1** was observed. Continuing the reaction up to 20 h resulted in the quantitative recovery of product **1**. These findings are in contrast to the nonbridged systems where the bound hydrogen cannot be released thermally after activation.¹⁸

To gain further insight into the mechanism of these reactions and the nature of the N–H···H–B dihydrogen-bond interaction, we studied theoretically the structure, reaction path, and energetics.

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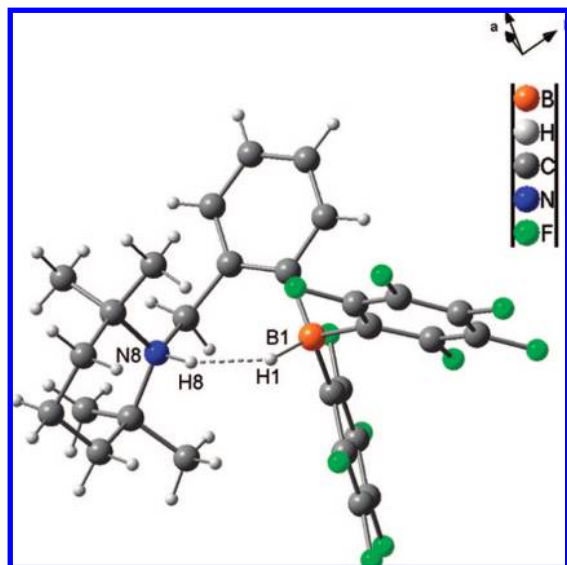


Figure 1. Experimental X-ray structure of **2** (solvent molecules are omitted for clarity).

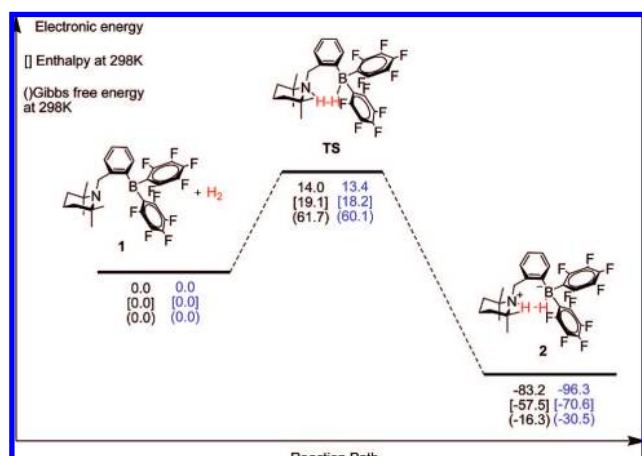


Figure 2. Energies (kJ/mol) of the hydrogen activation reaction by **1** calculated at the PBE/6-31G(d) level of theory: black color, gas phase; blue color, solution in benzene.

Until now, a broad spectrum of DHB interactions, including medium (1.2–1.7 Å) and short (0.8–1.2 Å) distances, were discussed only from a theoretical point of view.²³ Furthermore, in earlier studies of dihydrogen bonds, the partial charges $A-H^{\delta+} \cdots B-H^{\delta-}$ were often emphasized.²⁴

Both compound **2** and the simplified system $[NH_4]^+[HB(CH_3)_2(CH_2F)]^-$ (**2a**) were considered.^{25,26} The reaction path found (Figure 2) is similar to the reported concerted Lewis acid–Lewis base (LA–LB) mechanisms for the hydrogen splitting by similar phosphine–borane systems.^{27,28}

The structure of the starting compound **1** was identified as a minimum on the PBE potential energy surface. This *ansa*-aminoborane makes use of the concept of molecular tweezers for hydrogen. Owing to the constraint geometry and C–H \cdots F–C interactions, which are common for this class of substances,²⁹ the boron and nitrogen atoms are oriented toward and in close but noncoordinative contact to each other (a B–N distance of 3.43 Å was detected). A hydrogen molecule can easily fit into this void and may interact with both active centers of the amine–borane pair.

An early transition state (TS) with a short H–H distance of 0.78 Å has been located and represents the highest stationary point on

Table 1. Catalytic Hydrogenation of Imines and Enamines by the Nonmetal Compound **2**: Catalyst **2** (0.01 mmol, 4%), Substrate (0.25 mmol), and Toluene (0.7 mL) Were Refluxed (110°C) under 2 atm of H₂ Pressure

Entry	Substrate	Time (h)	Amine	Yield (%) ^a
1		12		99 ^b
2		6		99
3		12		99
4		24		4
5		24		4
6		6		99
7		6		99
8		12		85

^a Determined by ¹H NMR spectroscopy. ^b Catalyst **2** (0.02 mmol, 8%).

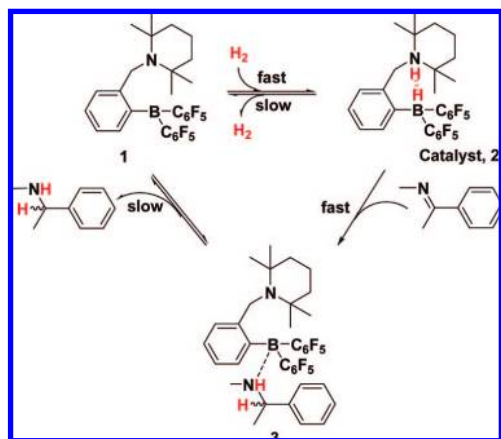
the reaction pathway and describes an essentially direct route from system **1** and H₂ to catalyst **2**.

The optimized structure of **2** is consistent with the X-ray data in that the NH and BH bonds are oriented toward each other. The calculated H \cdots H distance of 1.51 Å indicates the presence of a strong partially covalent dihydrogen bond.²³ That it is shorter than the apparent experimental value of 1.78 Å, may largely be due to the tendency of the X-ray technique to yield too short X–H bonds, compared to neutron technique.^{21,30,31} Furthermore, not only the short H \cdots H contact, but also the experimental topological parameters such as the N–H \cdots H (154°) and B–H \cdots H (125°) angles show that the dihydrogen bond interaction in **2** is partially covalent in nature.

For **2**, the calculated B \cdots N distance $R(B-N) = 3.32$ Å, where R is the distance between two opposite unit charges, is close to the obtained experimental data (3.36 Å). Then the Coulomb attraction becomes $-1/R = -0.16$ atomic units = -413 kJ/mol. This is comparable with the amount of energy required for the heterolytic cleavage of the H–H bond, 432 kJ/mol.³² According to this calculation the Coulomb attraction between the entire cation and the entire anion can pay for the loss of the strong Heitler–London covalent bond of H₂, or “Coulomb pays for Heitler–London”.³³ The two hydrogen atoms in system **2** (NH, BH) can be reunited and thermally released due to the constraint geometry of this *ansa*-ammoniumborate.²⁰

To continue our experimental investigation, we examined the reduction of imines with catalyst **2**. Previous nonmetal systems have shown stoichiometric reductions of the imine substrate PhCH₂N=CPh(H), because the resulting dibenzylamine inhibits the active boron center because of adduct formation.^{13,34,35} At the outset, when a toluene solution of catalyst **2** (4 mol percent) with the imine from benzaldehyde and benzylamine was refluxed under 2 atm of H₂ for 24 h, a 51% conversion of imine to amine was observed. Continuing the reaction for up to 48 h gave 60% conversion. To increase the yield, we heated the starting imine with 8 mol percent of catalyst **2** under the same H₂ pressure (2 atm) in toluene for 12 h. This setup resulted in the formation of dibenzylamine in 99% yield (Table 1, entry 1). Moreover, a stoichiometric

Scheme 3. Proposed Mechanism for the Catalytic Hydrogenation of Imines by **2**



reduction of the substrate $\text{PhCH}_2\text{N}=\text{CPh}(\text{H})$ with **2** occurs rapidly upon mixing at 80 °C and no side-products were detected in these reactions.

These data support a proposed mechanism for the catalytic hydrogenation of imines (Scheme 3). An important step is the suppression of the activity of the catalyst by amine–borane adduct formation (**3**), and hence the sensitivity to steric factors at the α positions of the imine is crucial. Repeating the reaction either with $p\text{-R-C}_6\text{H}_4\text{CH}_2\text{N}=\text{CPh}(\text{CH}_3)$ or $\text{CH}_3\text{N}=\text{CPh}(\text{CH}_3)$ (where R is H, Cl, or MeO) led to selective hydrogenation, providing *N*-benzyl- α -methylbenzylamines or *N*-methyl- α -methylbenzylamine, respectively, in almost quantitative yields (Table 1, entries 2, 3, 6, 7).³⁶ However, even small changes in the carbonyl or amine site geometry of the imines can significantly affect the reactivity. Thus, when less steric imines such as $\text{CH}_3\text{N}=\text{CPh}(\text{H})$, and $\text{CH}_3\text{N}=\text{CCH}_2\text{Ph}(\text{CH}_3)$ were reduced with catalyst **2**, the corresponding amines were obtained only in 4% yield (Table 1, entries 4, 5). Furthermore, the cyclohexanone piperidine enamine was hydrogenated to *N*-cyclohexylpiperidine in good yield (Table 1, entry 8).

In summary, we have devised the first *ansa*-aminoborane which is able to reversibly activate H_2 under mild conditions through an intramolecular mechanism. The structural and theoretical findings show that the dihydrogen interaction in our molecular tweezers is partially covalent in nature. Moreover, the results reported here highlight the substantial scope for the preparation of amines by nonmetal catalytic reduction of imines and enamines.

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Supporting Information Available: Experimental procedures, characterization data of all new compounds, copies of NMR spectra, and X-ray crystallography data of **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>. Structure parameters for compound **2** are also available free of charge from Cambridge Crystallographic Data Centre under reference number CCDC-694515.

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