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FLP Catalyzed Reduction of N-Heterocyclic Compounds: A Three Nuclei NMR Approach

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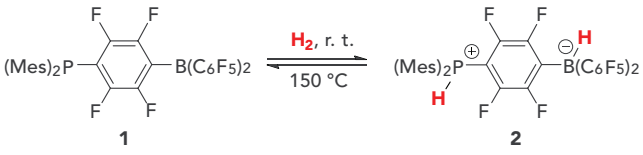
INTRODUCTION

In 2006, Doug Stephan *et al.*[1] reported the first reversible metal free activation of molecular hydrogen, employing so-called frustrated Lewis pairs (FLP, **Scheme 1**).



Scheme 1. Reversible metal free activation of molecular hydrogen.[1]

FLP catalysts consist of a Lewis acid/Lewis base pair. For phosphine borane **1**, the phosphorous atom with its free electron pair acts as the Lewis base while the electropositive boron atom has the role of the Lewis acid. The perfluorated phenyl groups as electron withdrawing substituents amplify the acidity of the borane whereas the mesitylene substituents are electron donating and increase the pK_a of the phosphine. Stephan found that the zwitterionic species **2** liberates molecular hydrogen under elevated temperatures and reversely, phosphine borane **1** activates H_2 at room temperature. Based on this reactivity, a large number of methods has been developed for effective catalyzed transformations like hydrogenations,[2] dehydrogenations,[3] and others[4] in absence of any (transition) metal atom. For FLP catalyzed hydrogenation reactions, among others, imines, enones, enamines, silyl enol ethers, and N-heterocyclic compounds have been found to be suitable substrates **(Figure 1)**.[5]

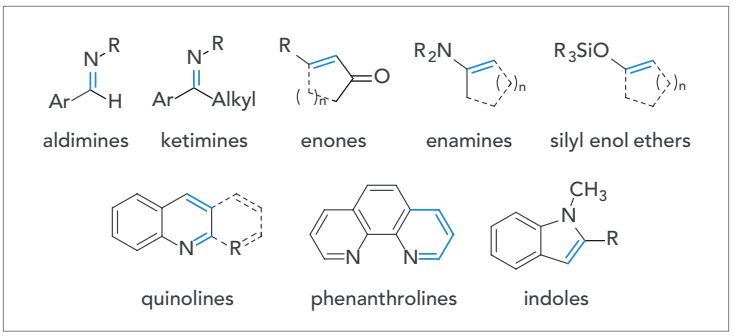


Figure 1. Substrate scope for the FLP catalyzed hydrogenation (R = H, Alkyl, Ar).[5]

Many FLP systems consists entirely of NMR active nuclei. Due to this fact it is very common in this research area to investigate new reactions mainly by NMR spectroscopy. Analyzing the ^{1}H, ^{11}B, ^{19}F, ^{13}C, ^{31}P, or ^{15}N NMR spectra of the reaction mixtures allows to investigate the mechanism or measure the kinetics by following the interaction of the catalyst with the substrates during the reaction.

Frustrated Lewis Pairs Catalyzed Reduction of N-Heterocyclic Compounds

The basic and acidic centers of an FLP are sterically hindered by large substituents so they cannot form a classical unreactive Lewis adduct. As the FLP cannot achieve the favorable low energetic state of a dative bond between the Lewis base and the Lewis acid (**Figure 2**, left), it forms a frustrated complex (**Figure 2**, right). In this complex, the reactivity of the active centers (electropositive acid, electronegative base) is preserved. This facilitates the heterolytic bond cleavage of molecular hydrogen and the resulting proton and hydride can be transferred to an unsaturated substrate.

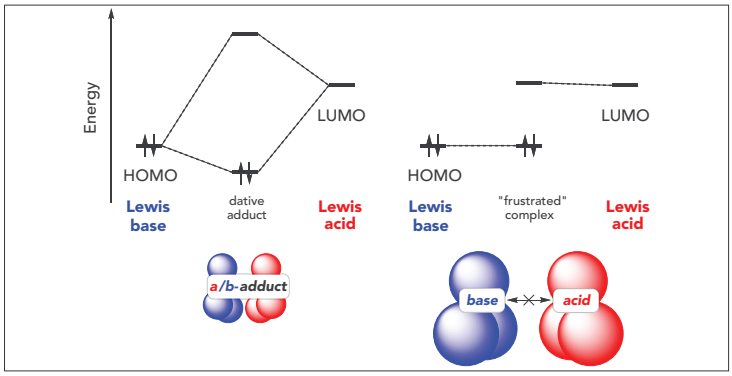
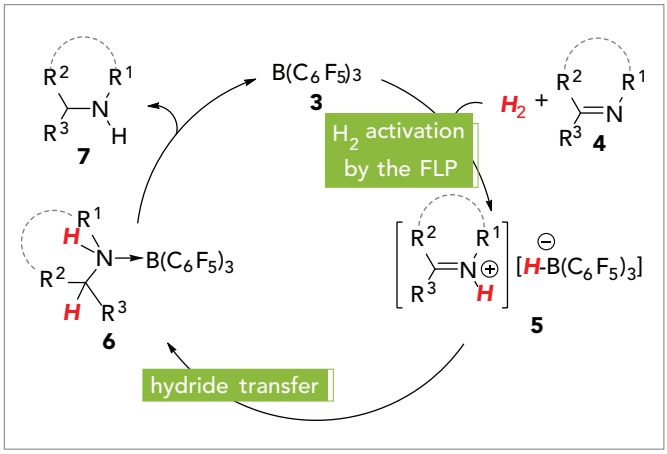


Figure 2. The FMOs of a classical Lewis pair building a dative adduct (left) and an FLP (right).[6]

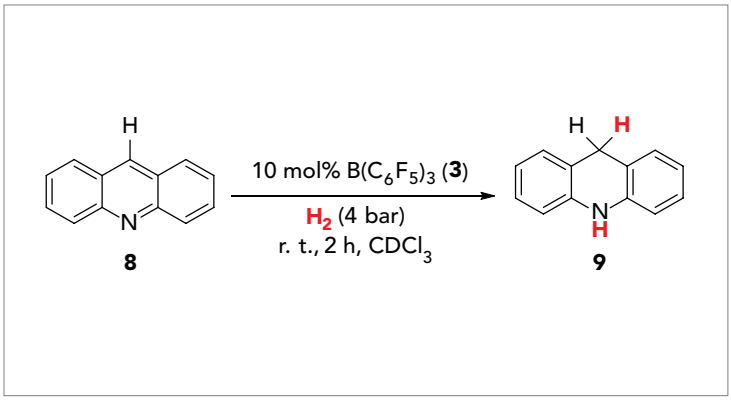
Regarding the hydrogenation of nitrogen-containing compounds like imines or N-heterocyclic compounds, the addition of a Lewis base is not needed, as the substrate itself acts as the base. The general mechanism of the reduction of nitrogen-containing substrates is depicted in **Scheme 2**.



Scheme 2. General mechanism of the FLP catalyzed reduction of imine-derivatives.[2a, 7]

As an initial step, the FLP (consisting of borane **3** and imine **4**), activates molecular hydrogen forming the iminium borate **5**. Hydride transfer leads to the reversible amino borane adduct **6**. Cleavage of amine **7** regenerates the perfluorinated phenyl borane **3**.

Here, we investigated the FLP catalyzed hydrogenation of quinoline **8**[8] (**Scheme 3**).

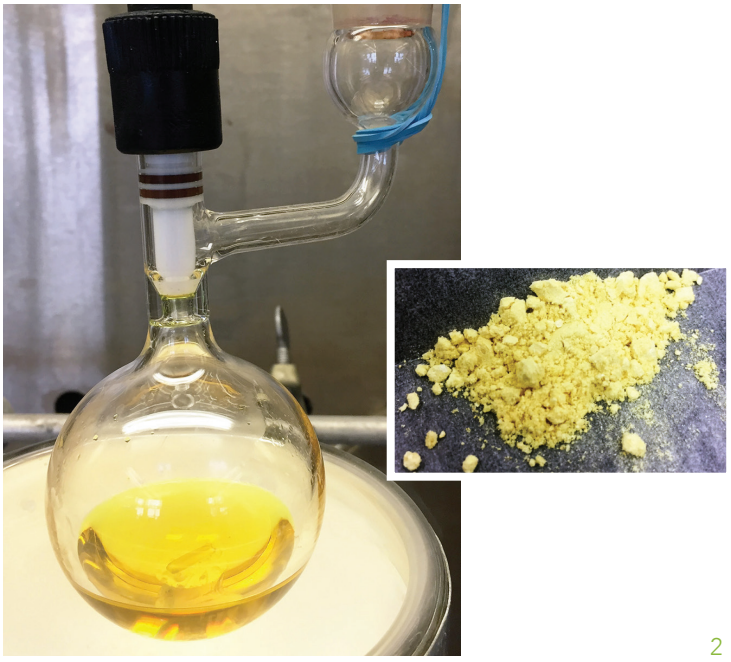


*Scheme 3. FLP catalyzed reduction of acridine (**8**).[8]*

Acridine (**8**) is reduced to 9,10-dihydroacridine (**9**) employing 10 mol% of the strong Lewis acid **3**. Again, the addition of an additional Lewis base to this reaction mixture is not needed, quinoline **8** and borane **3** form the active FLP. The reaction proceeds under very mild conditions.

EXPERIMENTAL PROCEDURE

Based on a literature procedure,[8] in a 100 mL thick-walled glass vessel, acridine (1.00 g, 5.58 mmol, 1.00 equiv.) and 10 mol% $B(C_6F_5)_3$ were dissolved in 15 mL of toluene under an inert atmosphere. The resulting solution was freeze-pump-thawed for three cycles and then charged with 1 atm of H_2 at 77 K (which equals approx. 4 atm at r.t.). The mixture was stirred for 3 hours at room temperature. Then, 15 mL of ethyl acetate was added, and the mixture was filtered through a short plug of silica. The solvents were removed under reduced pressure and the product dried *in vacuo*. The obtained yellow solid was analyzed via ^{1}H, ^{11}B, and ^{19}F NMR spectroscopy on the NMReady-60PRO.



Hydrogen, Boron and Fluorine

This app note focuses on the identification of the product mixture by discussing the corresponding ^{1}H, ^{19}F, and ^{11}B NMR spectra. The ^{1}H NMR spectrum of the product mixture reveals that the main species indeed is 9,10-dihydroacridine (**9**, **Figure 3**). The singlet at 4.07 ppm can be assigned to the methylene group (red). Also, the broad signal at 5.94 ppm refers to the amine N*H* group (blue).

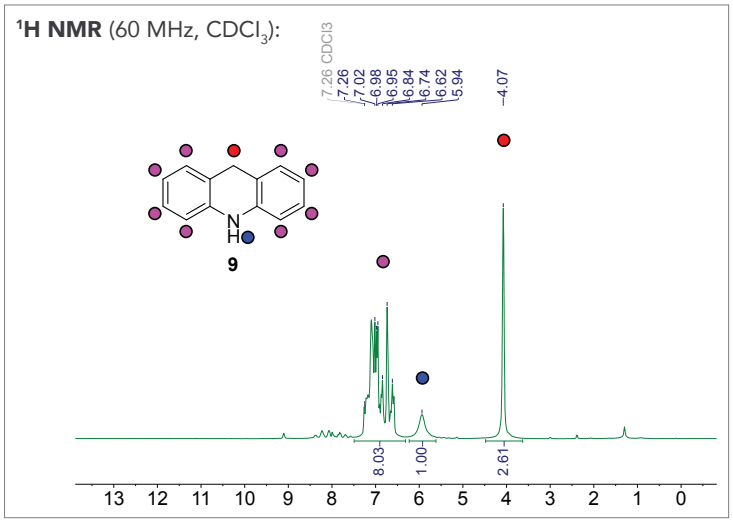


Figure 3. 60 MHz ^{1}H NMR spectrum of the product mixture in $CDCl_3$, 256 scans, 1 s delay.

The relative integral area of the methylene signal is a little bit higher than expected, but this can be attributed to the different relaxation time of the protons in the molecule. A longer delay would provide more accurate integrations.

In the range of 7.5 – 9.5 ppm signals of a by-product can be observed. As a boron catalyst was employed, these signals are further investigated taking the ^{11}B NMR spectrum of the product mixture into account (**Figure 4**, left).

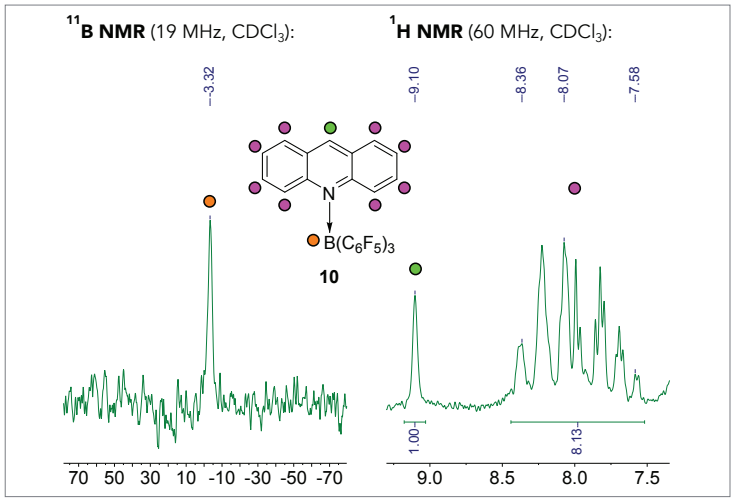


Figure 4. ^{11}B NMR spectrum (left) and the zoomed region of the ^{1}H NMR spectrum (right).

^{11}B is by nature a less NMR sensitive nucleus than ^{1}H which is the reason for the noisier baseline in this spectrum. However, the signal at –3.32 ppm in the ^{11}B-NMR spectrum (**Figure 4**, left) can be clearly observed and the chemical shift is typical[9] for B-N adducts. Interestingly, due to the integration ratio of the aromatic signals in the ^{1}H NMR spectrum (**Figure 4**, right) the present by-product must be the acridine-borane adduct **10**.

The highly sensitive ^{19}F NMR spectroscopy of the mixture confirms the interpretations above, as only one signal set (*ortho-*, *meta-*, *para-*Position of the perfluorated benzene rings) is observed. The pattern and the chemical shifts observed (**Figure 5**) are typical for this kind of complex:[8] ^{19}F NMR (57 MHz, $CDCl_3$): δ [ppm] = –134.96 - –135.38 (m, 6F, *ortho*-C_6F_5) - –159.97- –160.68 (m, 3F, *para*-C_6F_5)- –164.47- –165.40 (m, 6F, *meta*-C_6F_5).

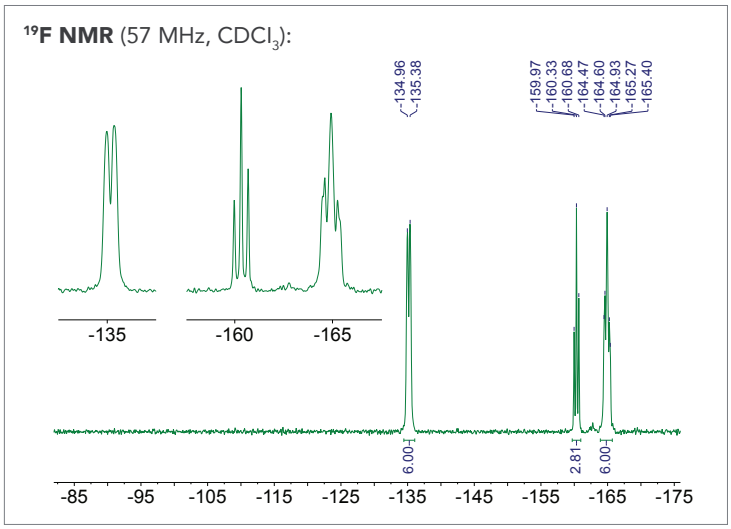


*Figure 5. 57 MHz ^{19}F NMR spectrum confirms that the $B(C_6F_5)_3$ catalyst is present as the B-N adduct **10** only.*

Naturally, at 60 MHz the resolution of the spectra is lower compared to a high-field instrument. However, the spectra observed allow for the identification of the by-product being present in the mixture as low as 10 mol%. Remarkably, even the ^{11}B NMR signal of this side product can be detected and is perfectly in agreement with the ^{1}H NMR and ^{19}F NMR spectra.

CONCLUSION

In summary, an FLP catalyzed reduction of N-Heterocyclic compounds was experimentally performed on Acridine (**8**). The product and side product were successfully characterized employing ^{1}H, ^{11}B, and ^{19}F NMR spectroscopy at 1.4 Tesla. The obtained spectra prove to be sufficient for R&D purposes.

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