Dihydrogen Activation

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Pyridylidene-Mediated Dihydrogen Activation Coupled with Catalytic Imine Reduction**

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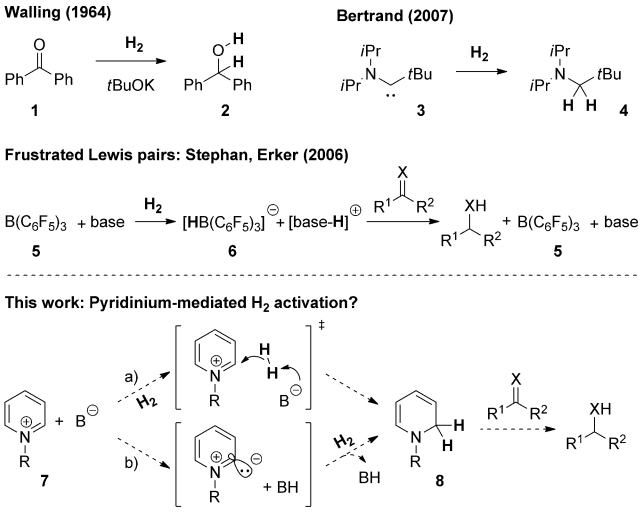
Dedicated to Professor Albert Eschenmoser on the occasion of his 90th birthday

Abstract: *In recent years, dihydrogen activation at non-metallic centers has received increasing attention. A system in which dihydrogen is trapped by a pyridylidene intermediate that is generated from a pyridinium salt and a base is now reported. The dihydropyridine formed in this process can act as reducing agent towards organic electrophiles. By coupling the hydrogen-activation step with subsequent hydride transfer from the dihydropyridine to an imine, a catalytic process was established. Treatment of the N-phenylimine of phenyl trifluoromethyl ketone with 5–20 mol % of N-mesityl-3,5-bis(2,6-dimethylphenyl)pyridinium triflate and 0.3–1.0 equivalents of $LiN(SiMe_3)_2$ under 50 bar of hydrogen gas resulted in high conversion into the corresponding amine.*

Catalytic hydrogenation with H_2 as the reductant is of central importance in organic synthesis. In general, a transition-metal catalyst is required for H_2 activation, dissociation of the H–H bond, and transfer of the hydrogen atoms to the substrate. However, there are examples of transition-metal-free systems for H_2 activation. In 1964, Walling and Bollyky showed that *t*BuOK catalyzed the hydrogenation of benzophenone at high temperature and pressure through a mechanism that involves heterolytic splitting of H_2 (Scheme 1).[1] More recently, Bertrand and co-workers reported a stoichiometric reaction of H_2 with a singlet (alkyl)(amino)carbene leading to an amine.[2] A breakthrough in the development of non-metallic catalytic systems for H_2 activation was achieved by the groups of Stephan and Erker, based on the concept of frustrated Lewis pairs (FLPs).[3] FLPs that consist of a perfluorinated aryl borane and a sterically demanding base cannot form a stable Lewis acid–base complex owing to steric constraints and were shown to reversibly split H_2 and catalyze the hydrogenation of various functional groups.[3,4] Although



Scheme 1. H_2 activation by non-metallic systems.

a range of phosphorus, nitrogen, and carbon Lewis bases have been used, the choice of the Lewis acid component appears to be restricted to highly reactive fluorinated aryl boranes, which have shown limited functional-group compatibility and require glove-box or Schlenk techniques. Therefore, it would be desirable to explore other types of potential hydride acceptors to generalize the concept of FLP-mediated H_2 activation and to enhance its scope.

The base-induced H_2 splitting and reduction of benzophenone (Scheme 1)[1] suggests that carbon-centered electrophiles might serve as Lewis acid components in FLPs. Among possible carbon-centered hydride acceptors, pyridinium salts seem particularly attractive because the corresponding dihydropyridines resulting from H_2 activation may act as reducing agents towards organic electrophiles,[5] offering the possibility to couple H_2 activation with subsequent hydride transfer to an organic substrate. The reaction could then be rendered catalytic in the pyridinium salt as in NADH-mediated biological redox processes.

A pyridinium salt is expected to be a stronger hydride acceptor than benzophenone and should therefore react under milder conditions with a weaker base through a mechanism as shown in Scheme 1 (pathway a). An analogous process based on a formamidinium cation as the hydride acceptor had been proposed for a hydrogenase from methanogenic archaea that was originally thought to be metal-free.[6] Although later on the enzyme was shown to contain an iron atom that was involved in H_2 activation,[7] the results

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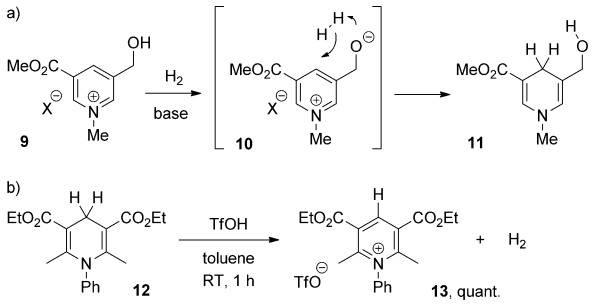
from DFT studies indicated that a hypothetical H–H bond cleaving process of this type would be energetically feasible.[6]

An alternative mechanism that may be considered for H_2 activation by pyridinium salts involves deprotonation to a highly reactive pyridylidene,[8] which inserts into the H–H bond in analogy to aminocarbene **3**[2] (Scheme 1, pathway b). In contrast to the amine produced from an aminocarbene, the resulting dihydropyridine could serve as a hydride donor, and therefore, a catalytic hydrogenation process via a pyridylidene intermediate would be conceivable. To examine the feasibility of these concepts, we synthesized various pyridinium salts and investigated their reactivity towards H_2 in the presence of a base. Herein, we report the results of our studies that have led to a pyridinium-based system for H_2 activation and catalytic imine reduction.

First experiments were carried out on hydroxymethyl-substituted pyridinium salt **9** (Scheme 2a). DFT calculations



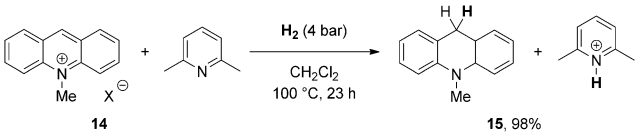
Scheme 2. Initial studies on H_2 activation by pyridinium salts and bases. Tf = trifluoromethanesulfonyl.

suggested that the alkoxide pyridinium zwitterion **10** could react with H_2 through a concerted, strongly exothermic process leading to the corresponding 1,4-dihydropyridine with an activation barrier of approximately 13 kcal mol^{-1}.[9] Unfortunately, subsequent experiments failed despite the low barrier predicted by DFT calculations. When pyridinium salt **9** or related hydroxyalkyl-substituted derivatives were treated with base under H_2 atmosphere (up to 100 bar), only decomposition products were observed with no evidence of H_2 activation.

Attempts to reduce pyridinium salts in an intermolecular process with H_2 and various external bases, such as LiN(SiMe$_3$)$_2$, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), phosphazenes, phenolates, or *N*-ethyldiisopropylamine (DIPEA) also failed. Although dihydropyridine **12** was formed in 28% yield upon treatment of **13** with DIPEA in toluene at 100 °C under 35 bar of H_2, deuteration experiments with D_2 revealed that this product did not arise from H_2 activation.[9] Based on literature precedence,[10] we assume that the observed reduction occurred through nucleophilic addition of DIPEA (or **13** deprotonated at one of the methyl groups) and subsequent hydride transfer from the resulting dihydropyridine to another molecule of **13**.

However, one notable observation was made in this context: When 1,4-dihydropyridine **12** was treated with CF_3SO_3H (Scheme 2b) the aromatized *N*-phenyl Hantzsch ester was formed by release of H_2. This process, which finds precedent in the hydride extrusion from orthoamides reported by Erhardt and Wuest,[11] is the reversal of the proposed H_2 activation by pyridinium salts, implying that such a pathway is, in principle, feasible based on the concept of microscopic reversibility.

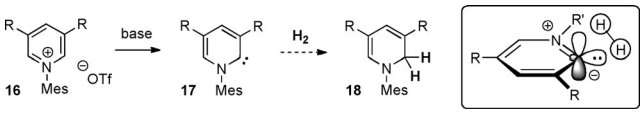
After completion of these studies, Clark and Ingleson reported successful H_2 activation experiments with *N*-methylacridinium salt **14** (Scheme 3).[12] Using 2,6-lutidine as the



Scheme 3. H_2 activation with acridinium salt **14** and a base, reported by Clark and Ingleson.[12] X = tetra(3,5-dichlorophenyl)borate.

base under 4 bar of H_2, they achieved 98% conversion into dihydroacridine **15** after 23 hours at 100 °C. They also achieved the in situ reduction of the *N*-*tert*-butylimine of benzaldehyde under these conditions. However, only 25% conversion into the corresponding amine was observed after 72 hours, and consequently, a catalytic version of this process has not been described. Nevertheless, these results demonstrate that carbon-centered Lewis acids with an electron-deficient pyridinium core may act as hydride acceptors in FLPs.

In view of our failed H_2 activation attempts based on pathway a in Scheme 1, we turned our attention to the alternative pathway b, involving a pyridylidene intermediate. After initial unsuccessful experiments with *N*-aryl Hantzsch esters and nicotinamide derivatives, we chose 1,3,5-triarylpyridinium salt **16** for further investigations because Itami and co-workers had shown that it forms pyridylidene **17** in the presence of a strong base (Scheme 4).[13]



Scheme 4. Proposed H_2 activation by pyridylidene derivatives. R = 2,6-Me$_2$C$_6$H$_3$.

DFT calculations predicted a relatively low activation energy of 20 kcal mol^{-1} for the concerted addition of H_2 to the carbenoid center of pyridylidene **17**, suggesting that the proposed reaction would be feasible within a chemically reasonable temperature range.[9] The calculated transition state (Figure 1) closely resembles that reported for the analogous reaction of aminocarbene **3** (Scheme 1).[2]

Pyridinium salt **16** was deprotonated by treatment with LiN(SiMe$_3$)$_2$ (2.25 equiv) in THF or THF/toluene at room temperature for 20 min, as described by Itami and co-workers.[13] After subsequent stirring under H_2 atmosphere (1–100 bar) at elevated temperature, traces of 1,2-dihydropyridine **18** were detected. In pure toluene, conversion into **18**

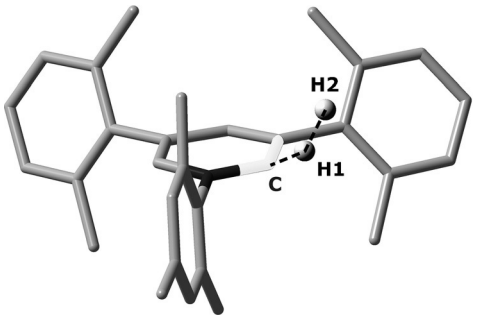


Figure 1. Calculated transition state for the reaction of H_2 with pyridylidene **17**.

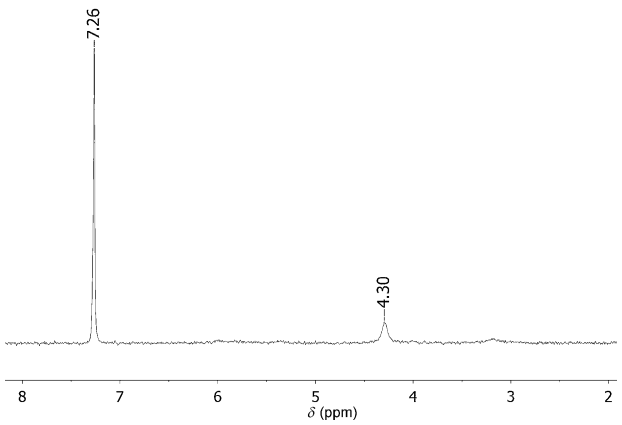
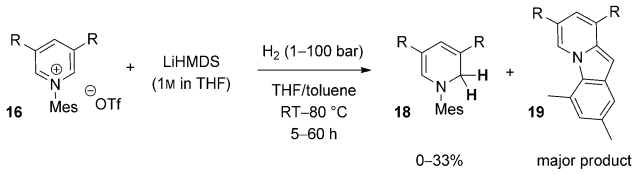


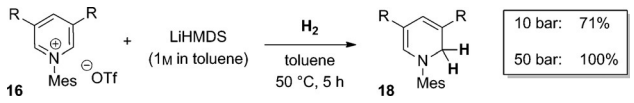
Figure 2. ^2H NMR spectrum for the D_2 splitting experiment; $CHCl_3$ with $CDCl_3$ (7.26 ppm) was used as the internal standard.

increased to 13–33% (Scheme 5). In all experiments, compound **19** was obtained as the major product. Its formation from pyridylidene by intramolecular activation of one of the arylmethyl groups had already been observed by Itami and co-workers.[13]



Scheme 5. Initial H_2 activation studies. R = 2,6-$Me_2C_6H_3$.

To suppress this undesired reaction, the H_2 pressure was applied immediately after the addition of $LiN(SiMe_3)_2$ (2.25 equiv). Using this procedure, conversion into 1,2-dihydropyridine **18** reached 71% after five hours at 50 °C in toluene under 10 bar of H_2. Furthermore, raising the pressure to 50 bar led to full conversion (Scheme 6).



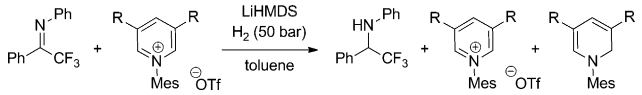
Scheme 6. H_2 activation under the optimized conditions. R = 2,6-$Me_2C_6H_3$.

Deuteration experiments confirmed the role of H_2 as the reductant: When the reaction was conducted under 50 bar of D_2 at 50 °C for five hours, clear evidence for deuterium incorporation at the C2 position of dihydropyridine **18** was obtained. The ^2H NMR spectrum (Figure 2) showed a resonance at 4.3 ppm in accordance with the chemical shift of the CH_2 group of authentic **18** in the ^1H NMR spectrum. The reaction with D_2 proved to be slower than that with H_2, as indicated by the presence of 40% of the starting material. Extending the reaction time to 24 hours resulted in full consumption of **16**. The kinetic isotope effect k_H/k_D predicted by DFT calculations for this reaction is 3.2 at 323 K,[9] which is in qualitative agreement with the reaction times required for full conversion (H_2: 5 h; D_2: 24 h). ^1H NMR analysis confirmed the incorporation of deuterium at the methylene group of **18**, but the measured deuterium content was only 68%. As D_2 with a purity of 99.98% was used, we assume that the observed hydrogen incorporation results from hydride transfer between dihydropyridine and the pyridinium salt under the reaction conditions or from base-induced H/D exchange of H_2.[14]

In view of the well-documented reactivity of dihydropyridines as hydride donors,[5] we next explored the possibility to couple H_2 activation with in situ hydride transfer to an organic substrate. Imine **20** was chosen for these experiments as it does not contain acidic protons and is expected to be a good hydride acceptor owing to the electron-withdrawing CF_3 group. When a 1:1 mixture of imine **20** and pyridinium salt **16** was subjected to the optimized conditions for H_2 activation for five hours, 46% conversion into amine **21** was observed, along with 80% of a 70:30 mixture of dihydropyridine **18** and pyridinium salt **16** (Table 1, entry 1). Extension of the reaction time to 13 hours resulted in 95% conversion into the amine (entry 2). Notably, 75% of dihydropyridine **18** and no pyridinium salt **16** were detected, implying that more than one equivalent of H_2 had been consumed, and **18**, acting as a hydride donor, had been almost fully regenerated. These findings suggest that a catalytic process based on this reaction might be possible.

Indeed, the reaction with one equivalent of base but only 20 mol% of pyridinium salt **16** led to full reduction of the imine (entry 3), affording amine **21** in 82% yield after column chromatography. Moreover, reducing the catalyst loading to 5 mol% still resulted in 85% conversion into amine **21** (entry 4). In a control experiment without pyridinium salt **16**, no amine was formed (entry 5), ruling out base-induced heterolytic H_2 splitting as in the reduction of benzophenone with KO*t*Bu (see Scheme 1).[1] Initial attempts to reduce the amount of base below one equivalent resulted in a drastic drop in conversion under the standard conditions. However, at elevated temperatures, the amine could be obtained in high yields with substoichiometric amounts of base (entries 6–8). With 0.5 equivalents of LiHMDS and 0.2 equivalents of pyridinium salt **16** at 80 °C, the amine was formed in almost

Table 1: H_2 activation coupled with imine reduction.[a]



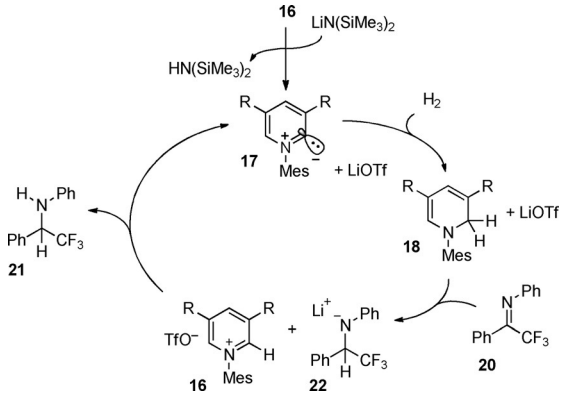
20 **16** **21** **16** **18**

Entry	**16** [equiv]	LiHMDS [equiv]	*t* [h]	*T* [°C]	**21**[a] [%]	**16**+**18**[d] [%]	**18/16**
1	1	2.25	5	50	46	80	70:30
2	1	2.25	13	50	95[b]	75	>97:3
3	0.2	1	5	50	100 (82)[c]	95	>97:3
4	0.05	1	5	50	85[b]	95	>97:3
5	–	2.25	5	50	0	–	–
6[e]	0.2	0.5	5	80	97	n.d.	n.d.
7[e]	0.2	0.3	5	80	76	n.d.	n.d.
8[e]	0.2	0.3	5	100	69	n.d.	n.d.

20 (1 equiv) used for all entries, R = 2,6-$Me_2C_6H_3$. [a] Conversion based on quantitative ^{19}F NMR analysis of the crude reaction mixture. [b] Formation of side products detected. [c] Yield of pure isolated product. [d] Based on the starting amount of **16**; determined by ^1H NMR analysis using **21** as an internal standard. [e] Experiments with substoichiometric amounts of base were less reproducible than those with 1 equivalent of LiHMDS. In four runs with 0.3 equivalents of LiHMDS at 80 °C, **21** was obtained in 24, 28, 57, and 76 % yield. n.d.: not determined.

quantitative yield. With only 0.3 equivalents of LiHMDS and 0.2 equivalents of **16**, up to 76 % conversion into the amine was observed, implying that the lithiated amine resulting from hydride transfer is sufficiently basic to deprotonate the pyridinium salt and regenerate the active pyridylidene intermediate. This was confirmed by an NMR experiment, which demonstrated that upon deprotonation of amine **21** with one equivalent of LiHMDS and subsequent addition of **16**, pyridylidene **17** was formed as evidenced by trapping with S_8.[9] Based on these results and DFT calculations,[9] a catalytic cycle for the observed imine reduction is proposed in Scheme 7.[15,16]

In conclusion, pyridylidene **17** generated from pyridinium salt **16** has been shown to be an efficient H_2 trapping agent. The observed addition of H_2 to the carbenoid center of **17** has precedent in the reaction of aminocarbene **3** described by Bertrand and co-workers (Scheme 1).[2] However, in contrast to the amine **4** produced from **3**, which lacks reactivity as a hydride donor, dihydropyridine **18** can act as a reducing agent towards an imine. Therefore, a catalytic process becomes possible through H_2 activation with subsequent hydride transfer (Scheme 7). Our findings and the *N*-methylacridinium-mediated heterolytic H_2 splitting reported by Clark and Ingleson[12] demonstrate the potential of pyridinium salts for H_2 activation and catalytic hydrogenation. Variations of the electronic and steric properties of pyridinium salt and base will provide a means for the further development of catalytic systems of this type.



Scheme 7. Proposed catalytic cycle. R = 2,6-$Me_2C_6H_3$.

Keywords: catalytic hydrogenation · dihydrogen activation · NADH analogues · pyridinium salts · pyridylidenes

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[15] The Li ions introduced with the base may play a role in the catalytic cycle by coordinating to the imine, thereby facilitating hydride transfer. This would explain why phosphazene bases did not induce H_2 activation, although they deprotonated the pyridinium salt as shown by trapping experiments with S_8.
[16] In principle, it should be possible to start the catalytic cycle from dihydropyridine **18** without using an external base. However, preliminary experiments along these lines with and without LiOTf as an additive have been unsuccessful thus far.

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