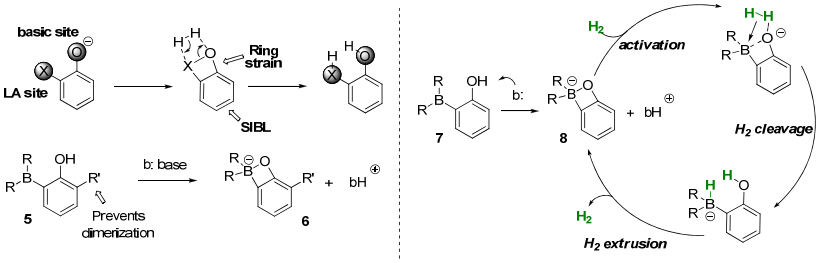
Dihydrogen Activation at Non-Metallic Centers (DANMC)

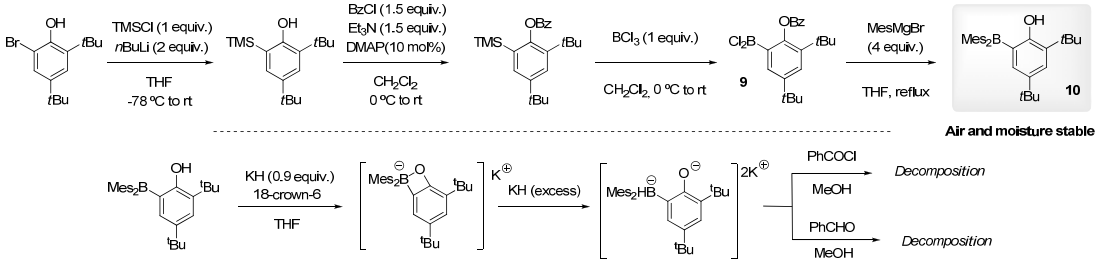
Project summary and research goals. The primary goal of this project is to develop new systems for heterolytic dihydrogen activation and catalytic hydrogenation, which contain non-fluorinated-triarylboranes as hydride acceptor and a basic oxygen as proton acceptor. Systems of this type would considerably enhance the scope of nonmetal-based catalytic hydrogenation, because the electrophilic centers involved are less Lewis acidic than the fluorinated arylboranes used so far.[i] Our proposed alternative to FLPs is based on the formation of a strained benzo-1,2-oxetane,[ii] in which the energy released upon ring-opening will be the driving force to effect the heterolytic splitting of dihydrogen (Scheme 4). We propose that the energetic cost of the H-H splitting will be compensated by the synergistic combination of three factors: (1) liberation of the ring strain in the four-membered ring, coupled with (2) the energy released as a result of the partial localization of the π-cloud in the aromatic ring (SIBL),[iii] and finally (3) the inherent Lewis acidity of boron, which should facilitate formation of the corresponding borohydride.



Scheme 1. *Proposed working model*

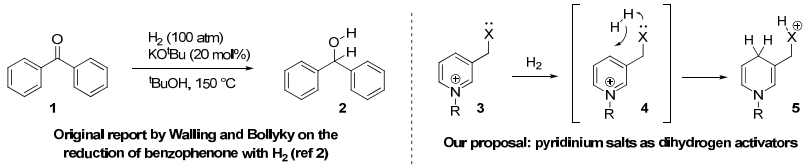
Specifically, we have explored the use of a triarylboron compound in which one of the aryl groups bears a hydroxyl group ortho to the boron atom (Scheme 1, **5**). Upon basic treatment, the phenol is deprotonated, and interaction of the anion with the nearby electron-deficient boron results in formation of a tetracoordinate 1,2-oxaboretanide. This borate **6** should be thermodynamically unstable because of two main reasons: first, the high strain of the four-membered ring. Second, participation of the aryl group in the four-membered ring implies a partial localization of the π-cloud, which results in destabilization of the ground state of the molecule. Our system posseses two features that should facilitate the process: variation of the substituents on boron R to tune the Lewis acidity of the system, thus facilitating formation of the desired borohydride, and potential introduction of bulky *ortho* substituents in the aromatic ring to help prevent dimerization (which might result in diminished reactivity). A simplified mechanistic cycle for the proposed dihydrogen activation is outlined in Scheme 1 (right). (i) Treatment of **7** with a base results in formation of a phenolate, and subsequent formation of borate **8**. (ii) Interaction of the antibonding σ* orbital of H_2 with a non-bonding lone pair of oxygen, facilitated by the basicity of oxygen. (iii). H_2 cleavage, where the lone pair of oxygen populates the antibonding σ* orbital of H_2, consequently weakening both the H-H and the B-O bonds. At that point the H_2 σ-bonding orbital donates into the vacant p orbital of boron, and heterolytic cleavage occurs. (iv). H_2 extrusion to reform the borate.

Experimental results. Preparation of the target phenol-boranes. One of the main obstacles in the proposed research topic has been the synthesis of the required aryl boranes. Numerous attempts have been performed over the course of the first part of this research project, but the vast majority of them have only met with failure. However, A synthetic approach has been designed that capitalizes on the use of a dichloroborane (Scheme 2).[iv] Following this sequence, compound **10** (Scheme 2, top) was synthesized in four steps from the corresponding commercially available bromophenol in 18% overall yield (unoptimized). With this product in our hands, we were able to form quantitative amounts of the desired borohydride by treatment with KH (Scheme 2, bottom). Unfortunately, this borohydride was shown to be unreactive in the presence of a number of substrates (aldehydes or acyl chlorides), and we decided to explore a conceptually different approach (see below).



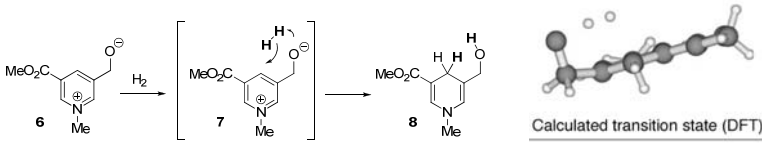
Scheme 2. Preparation and reactivity of the target hydroxyl-boranes

A pyridinium-based alternative. The primary goal of this project is to develop new systems for heterolytic dihydrogen activation and catalytic hydrogenation, which contain an iminium or pyridinium group as hydride acceptor and a basic oxygen or nitrogen function as proton acceptor. Systems of this type would considerably enhance the scope of nonmetal-based catalytic hydrogenation, because the electrophilic centers involved are less Lewis acidic than the fluorinated arylboranes used so far. Walling and Bollyky demonstrated over forty years ago the ability of ketones to act as hydride acceptors in H_2 activation processes (Scheme 3, left).[v] Compared to benzophenone, a pyridinium compound is expected to be a much stronger hydride acceptor. Additionally, reactions which generate sterically unhindered nucleophiles such as water, primary or secondary alcohols, lead to deactivated Lewis base borane adducts and, therefore, cannot be carried out catalytically with borane-based systems. Pyridinium salts, on the other hand, are less Lewis acidic and should survive in the presence of moderate nucleophiles. Thus, with a hydrogen-activating pyridinium derivative, catalytic hydrogenation of aldehydes or ketones or iminium ions formed in situ from a carbonyl compound or an α,β-unsaturated aldehyde seems possible. Furthermore, the intramolecular nature of H_2 activation which involves a concerted action of the pyridinium salt and the base should significantly lower the activation energy and H_2 splitting should occur under milder reaction conditions. Thus, the first objective of our studies is to develop an efficient system for heterolytic H_2 activation containing basic alcoxides and amines as an alternative to bulky phosphines as proton acceptor, and a pyridinium salt as a hydride acceptor (**3** in Scheme 3, right).



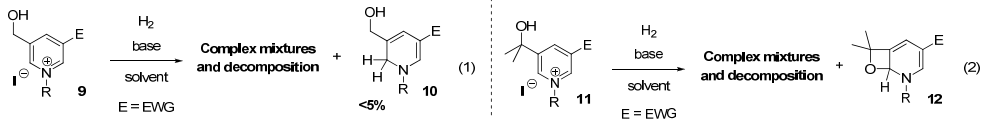
Scheme 3

Experimental results. *1. Pyridinium alcoxides.* Preliminary DFT calculations were performed on the system shown in Scheme 2. A reaction path involving a concerted, strongly exothermic reaction of the zwitterionic pyridinium derivative with dihydrogen was found, leading to the corresponding 1,4-dihydropyridine with an activation barrier of *ca.* 13 kcal/mol. MP2 calculations, which yield more realistic transition state energies, gave a value of 21 kcal/mol. In the transition state shown below (Scheme 4), one hydrogen atom strongly interacts with the basic oxygen atom, while the electrophilic center at C(4) interacts with the elongated σ-bond of the dihydrogen molecule. Obviously, the calculated energies are not reliable numbers, and further calculations including solvent effects, which should give more realistic transition state energies, are underway. Nevertheless, the results show that this reaction is, at least in principle, a feasible process.



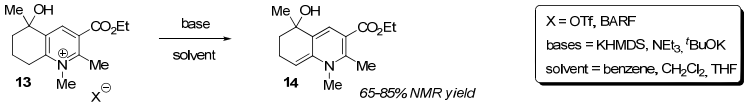
Scheme 4

With this results in hand, our first efforts were devoted to the development of systems which incorporate a pyridinium ring and a free alcohol placed in a position in principle ideal to adopt the required conformation. In this context, we were able to prepare and test several model substrates such as those indicated in Scheme 3. Unfortunately, no success was achieved with the systems tested thus far; our tests often lead to either decomposition of the starting material, or to complex reaction mixtures from which no products originated from dihydrogen activation could be detected. Problems associated with the nucleophilicity of these alcoxides occasionally led to the formation of intramolecular addition of the alcoxide to the electrophilic pyridinium. Nevertheless, we were able to extract valuable conclusions from these experiments: 1. Disproportionation process take place when primary alcohols are used (Scheme 5, eq. 1). 2. Our studies indicate that pyridinium salts undergo nucleophilic addition in the presence of alcohols even if that entails formation of strained four-membered heterocycles (Scheme 5, eq. 2).



Scheme 5

With this information in our hands, we revised our model system and prepared a second generation of potential pyridinium-based dihydrogen activators. The main difference between the two models is the introduction of a rigid carbon backbone that in theory should preclude intramolecular nucleophilic addition of the deprotonated alcohols to the pyridine ring. Additionally, this new design included tertiary alcohols in order to prevent disproportionation reaction as well as intermolecular nucleophilic additions. Once a synthetic route to prepare the desired salts was found, we treated them with a series of different bases and tested their reactivity at different temperatures and under different hydrogen pressures (Scheme 6). In all cases we observed formation of varying amounts of analogues of **14**, which can be explained by the presence of acidic protons next to the pyridinium ring.



Scheme 6

2. Pyridinium amines. We have simultaneously worked on nitrogen analogues of the systems indicated above. These are interesting because they incorporate less basic and less nucleophilic amines, which in principle should help to overcome the problems indicated in section 1. Computational studies show values that correspond to a feasible process with a calculated activation energy for the hydrogen splitting by a model substrate slightly over 30 kcal/mol (Figure 1, right). Although high, this activation energy required for the process could be reached by using more forcing conditions such as elevated temperature or high pressure. The calculations also show an energetic difference of around 5 kcal/mol between substrate and product, which suggests that the process might be reversible under the reaction conditions. A straightforward route for the preparation of pyridinium salts which incorporate amines as basic fragments has been developed which allows for variations and tuning of basicity with relative ease, thus enabling facile exploration of new substrates. Following this general route the compounds indicated below (Figure 1, left) have been prepared and tested in reactions with H_2, but no reactivity has been yet observed.

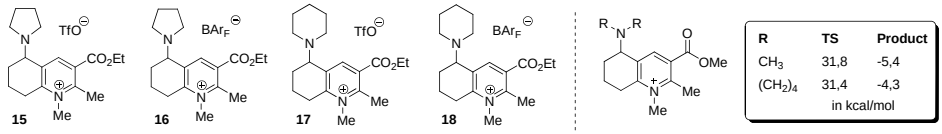


Figure 1

One of the main problems associated with pyridinium salts pertains to the relatively low stability of pyridinium salts, and their high sensitivity to water. For that reason, NMR analysis of the crude reaction mixtures is our preferred analytical method. In particular, ^{2}D-NMR should be an ideal method for detecting even trace amounts of deuterium incorporation, since incorporation of deuterium into the pyridinium salts can only be explained via activation of D_2. Additionally, the calculated values of kinetic isotope effect are not dramatically high even at elevated temperature and pressure, which suggests that the reaction with deuterium or hydrogen gas should proceed at similar rates. With that idea in mind, reactions of several amine-pyridinium systems with deuterium gas have been tested. In this context, the results obtained thus far have been inconclusive: although evolution of the starting material has been observed in several instances, NMR analysis suggests that these products mainly decompose under high reaction temperatures and pressured ranging from 50-100 bar.

3. Pyridinium imidines. Present directions of the project are directed towards the design of more robust systems, as well as tuning the basicity of the nitrogen. Along these lines, systems containing more basic amines such as imidines are currently being explored, and replacement of the methyl group on nitrogen by a more robust benzyl group is being tested. An easy way to prepare multigram quantities of model imidine **19** (Figure 2) has been found, and several other derivatives with different counterions have been prepared. As usual, we have sought to find theoretical support for our working hypothesis by means of DFT studies. We have examined the effect that substitution on both the aromatic ring and the imidine would have on the activation barrier for the H_2 splitting, and we have found that very similar results (26.1-31.6 kcal/mol) for the different substitution patterns studied. We expect to be able to test this system very soon.

Conclusions. In summary, progress has been made towards the development of novel systems for heterolytic dihydrogen activation and catalytic hydrogenation. Promising results were obtained using an approach based on a pyridinium group as hydride acceptor and a basic oxygen or nitrogen function as proton acceptor. Although at the current stage of the project our main goal has not yet been achieved, we have identified several problems and drawbacks in substrate design. Solutions to these problems (which are mainly associated with stability, basicity and electrophilicity of the pyridinium salts) have been formulated, and are currently underway in our laboratories. Importantly, ample theoretical support for our working hypothesis has been achieved: our studies support the viability of our proposal, throwing activation energy values in the range of 20-30 kcal/mol. Although these barriers are high, in principle they should be reachable at high temperatures. In light of our results, we remain confident that proof of principle for the proposed research project will soon be found.

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[iii] (a) W. H. Mills, I. G. Nixon, *J. Chem. Soc.* **1930**, 2510. (b) Heteroatom case: A. Stanger, *J. Am. Chem. Soc.* **1998**, *120*, 12034.
[iv] a) D. Kaufmann, *Chem. Ber.* **1987**, *120*, 853. b) Kaufmann, *Chem. Ber.* **1987**, *120*, 901.
[v] C. Walling, L. Bollyky, *J. Am. Chem. Soc.* **1964**, *86*, 3750.