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Synthetic Methods |*Hot Paper*|

α-Hydroxymethylation of Pyridines at a Frustrated Lewis Pair Template

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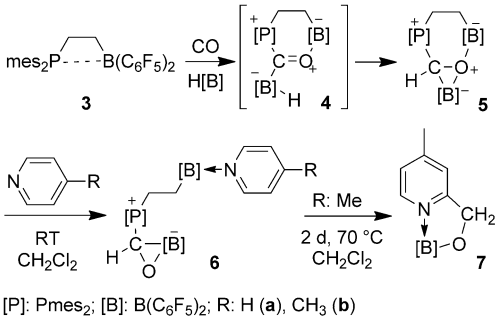
Abstract: The "η^2-formylborane" moiety formed by CO reduction with $HB(C_6F_5)_2$ at a P/B frustrated Lewis pair template undergoes a hydroxymethylation reaction at the α-position to nitrogen in pyridine or isoquinoline. The analogous reaction with pyrimidine revealed a mechanism related to the Tschitschibabin reaction.

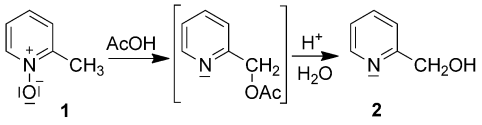
Reactive arenes readily undergo single or even multiple hydroxymethylation reactions with suitable electrophilic reagents. The situation is different with pyridines which only reluctantly enter into the electrophilic aromatic substitution sequences. When they do, they are usually converted to the 3-substituted derivatives. Consequently, α-hydroxymethylated pyridines are mostly prepared by principally different protocols. The parent compound α-hydroxymethylpyridine (**2**) is for example, conveniently prepared by treatment of 2-picolin-*N*-oxide (**1**) with acetic acid derivatives (Boekelheide reaction, Scheme 1).[1] α-Substitutions of pyridines on the other hand can readily be achieved by routes involving nucleophilic attack at the 2-position with subsequent removal of hydride. The Tschitschibabin (Chitchibabin) reaction[2] or the Ziegler alkylation and arylation[3] are prominent examples. We have now found a mechanistically related α-hydroxymethylation reaction at pyridine and related substrates using a carbon monoxide derived nucleophilic reagent generated and controlled at a vicinal phosphane borane frustrated Lewis pair (P/B FLP).[4] First examples and a mechanistic evaluation will be presented in this account.

We had recently shown that the vicinal P/B FLP **3**[5] reacted readily with a 1:1 mixture of Piers borane $[HB(C_6F_5)_2]$ and carbon monoxide to give the FLP template stabilized "η^2-formylborane" system **5** (Scheme 2).[6] This reaction is unusual since [B]–H boranes were shown not to be able to reduce carbon monoxide by themselves for thermodynamic reasons but just form the respective adducts, the borane carbonyls.[7] $[HB(C_6F_5)_2]$ is no exception. We could show that it forms the borane carbonyl $[(C_6F_5)_2BH{\cdot}CO]$ which we could isolate at low temperature and characterize by X-ray diffraction.[8] The formation of **5** was thought to proceed by the FLP/borane carbonyl addition product **4** as an intermediate which apparently lifts the thermodynamic restriction imposed for simple formylborane formation.[6] We had shown that the FLP/(η^2-formyl)borane adduct **5** is opened with pyridines to give **6** [R: H (**a**), Me (**b**)].[8]



Scheme 2. FLP route to the pyridine derivative **7**.

We have now treated compound **5** with an excess of 4-methylpyridine (ca. 5 molar equivalents) under slightly more forcing conditions (Scheme 2). The reaction mixture (in dichloromethane) was kept for 2 days at 70 °C in a sealed NMR tube. Workup including column chromatography (silica gel, CH_2Cl_2) and crystallization then gave the hydroxymethylated pyridine derivative **7** in 64% yield as a colorless crystalline solid. Compound **7** was characterized by X-ray diffraction. The X-ray crystal structure analysis showed that the (η^2-formyl)borane of the precursor **5** had been cleaved from the FLP framework and combined with the added pyridine reagent (Figure 1). The strongly Lewis acidic boron center is found attached to the Lewis basic pyridine nitrogen as expected and the former formyl carbon atom has now formed a carbon–carbon bond with the adjacent pyridine C2 center, but it was at the same time further reduced. Overall, a selective boryloxymethylation reaction at the pyridine C2 carbon had been achieved. In solution compound **7** shows the ^{19}F NMR signals of a pair of symmetry-equivalent C_6F_5 substituents at boron (^{11}B: $\delta = 6.4$ ppm). It shows the ^1H NMR feature of the newly formed



Scheme 1. The Boekelheide reaction.

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[+] *X-ray crystal structure analyses.*

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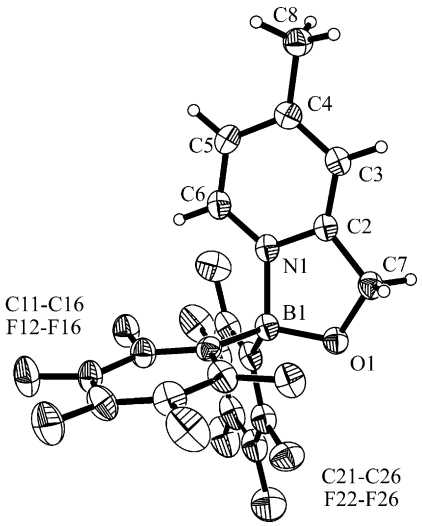


Figure 1. A view of the molecular structure of the hydroxymethylation product **7** (thermal ellipsoids are shown with 30% probability). Selected bond lengths [Å] and bond angles [°]: N1-B1 1.619(4), B1-O1 1.453(4), O1-C7 1.404(3), C2-C3 1.381(4), C2-C7 1.492(4), C2-N1 1.342(3), N1-C6 1.349(4), C6-C5 1.372(4), N1-B1-O1 100.0(2), B1-O1-C7 113.0(2), O1-C7-C2 106.7(2), C7-C2-N1 109.8(2), C2-N1-B1 109.1(2).

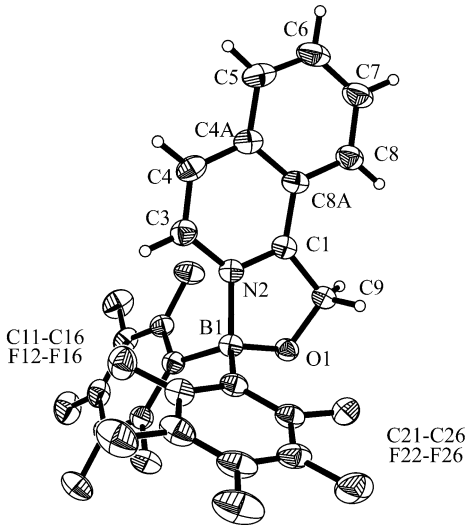
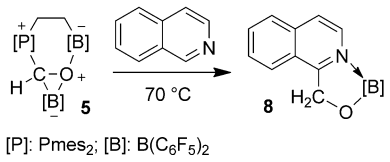


Figure 2. Molecular structure of compound **8** (thermal ellipsoids are shown with 30% probability). Selected bond lengths [Å] and bond angles [°]: N2-B1 1.611(3), B1-O1 1.459(3), O1-C9 1.400(2), C3-N2 1.378(3), N2-C1 1.318(2), C1-C9 1.488(3), C4-C4A 1.416(3), N2-B1-O1 99.5(2), B1-O1-C9 111.4(2), O1-C9-C1 106.4(2), C9-C1-N2 109.5(2), C3-N2-B1 129.2(2).

CH_2 group at $\delta = 5.28$ ppm (^{13}C: $\delta = 69.6$ ppm). Compound **7** was deborylated by treatment with aqueous NaOH to give the respective free hydroxymethylpyridine derivative (for details see the Supporting Information).

We then treated **5** with isoquinoline (5 molar equivalents). Under the analogous conditions we obtained the hydroxymethylation derivative **8** selectively, isolated as a colorless crystalline solid in 80% yield (Scheme 3). The X-ray crystal structure



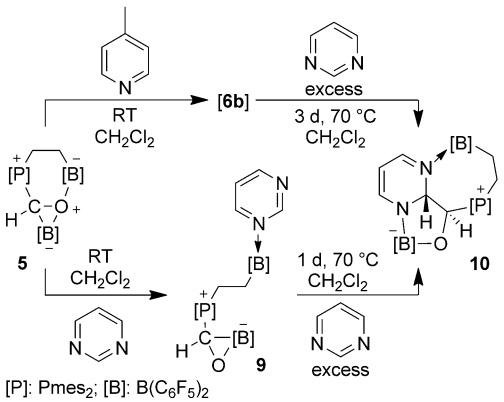
Scheme 3. Formation of the isoquinoline derivative **8**.

analysis confirmed the attachment of the CH_2–O[B] group (originally from the (η^2-formyl)$B(C_6F_5)_2$ unit in **5**) at the C1 position of the isoquinoline fragment (Figure 2). Again, the boron atom is found attached to the nitrogen. Compound **8** shows the expected NMR features [CH_2–O[B]: $\delta = 5.86$ ppm (^1H), $\delta = 70.0$ ppm (^{13}C), $\delta = 7.6$ ppm (^{11}B)].

The outcome of the reaction of **5** with pyrimidine gave us an indication about the pathway followed in this hydroxymethylation reaction. The treatment of **5** with pyrimidine at room temperature followed by crystallization at $-35\,^\circ C$ gave the ring opened addition product **9** which still contained the intact (η^2-formyl)borane subunit attached at phosphorus (Scheme 4). Compound **9** was characterized by X-ray diffraction (Figure 3) and by spectroscopy (for details see the Supporting Information).

We achieved the C–C coupling reaction between the η^2-formyl borane unit with the pyrimidine reagent in the following way: treatment of **6b** (in situ generated from **5** and 4-methylpyridine) with a large excess of pyrimidine (ca. 13 molar equivalents) followed by thermolysis of the mixture for 3 days at 70 °C resulted in the formation of the N-borylated dihydropyrimidine product **10**. It was isolated in 16% yield after column chromatography and washing with CH_2Cl_2.

The X-ray crystal structure analysis of **10** revealed the formation of the annulated five-membered heterocycle that was formed by addition of the components of the (η^2-formyl)borane unit to the N=C bond of pyrimidine (Figure 4). The 2-hydrogen is still attached and it is *trans*-oriented to the C–H hydrogen of the former formyl group. The remaining [P]–CH_2CH_2–[B] FLP framework is still present, probably caused by the strong internal B2–N3 coordination.



Scheme 4. Reaction of **5** or **6** with pyrimidine.

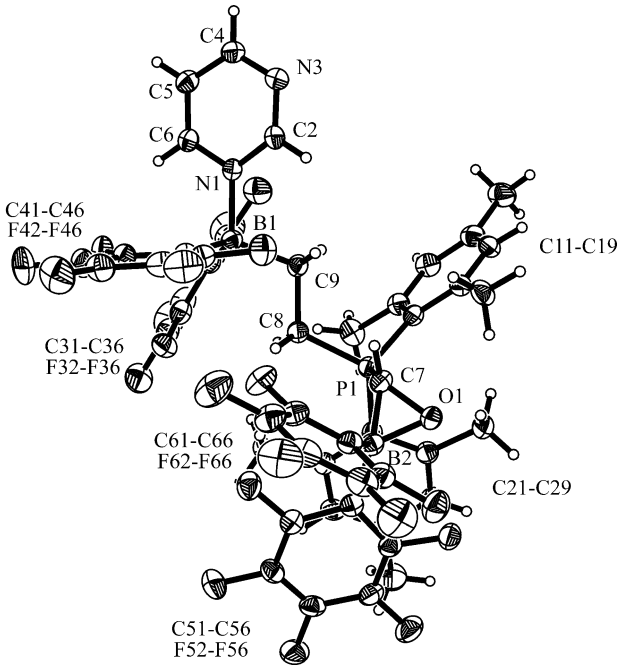


Figure 3. The molecular structure of the pyrimidine adduct **9** (thermal ellipsoids are shown with 30% probability). Selected bond lengths [Å] and bond angles [°]: N1-B1 1.634(4), C9-B1 1.634(5), C8-C9 1.536(5), P1-C8 1.819(3), P1-C7 1.783(4), C7-O1 1.435(4), C7-B2 1.596(5), B2-O1 1.471(5), B2-C7-O1 57.7(2), C7-O1-B2 66.6(2), O1-B2-C7 55.6(2).

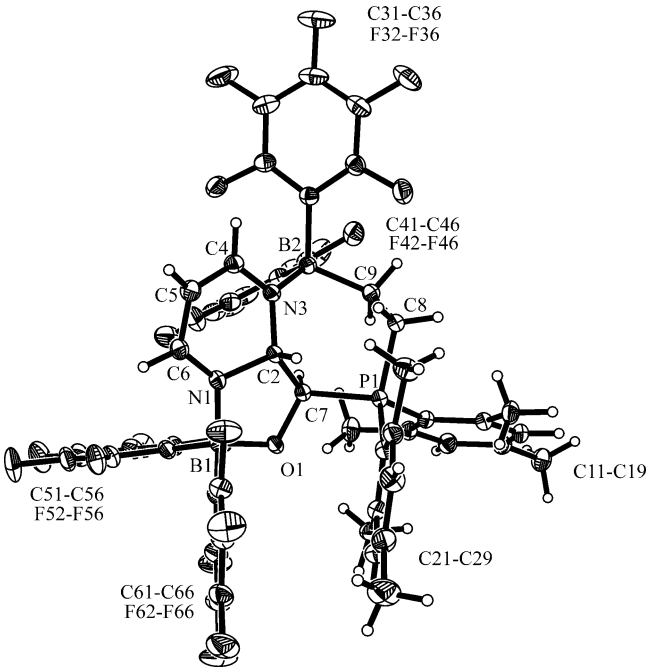
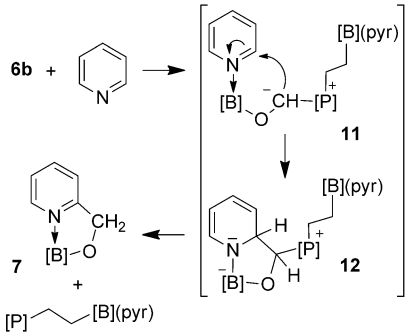


Figure 4. A view of the molecular structure of compound **10** (thermal ellipsoids are shown with 30% probability). Selected bond lengths [Å] and bond angles [°]: N3-B2 1.601(3), N1-B1 1.567(3), N3-C2 1.467(3), N1-C2 1.458(2), B1-O1 1.473(2), P1-C7 1.858(2), N3-C4 1.324(3), N1-C6 1.311(3), B2-N3-C2 124.5(2), N1-B1-O1 100.7(2), C2-C7-O1 107.1(2), C6-N1-B1 133.7(2), C4-N3-C2 111.5(2), N1-C2-N3 112.4(2), C2-N1-B1 110.6(2), C7-O1-B1 113.4(2).

This leads us to propose a general reaction pathway as schematically depicted in Scheme 5. The reaction could be initiated by coordination of the respective pyridine reagent to the boron atom of the FLP framework of **5** to give **6** (Scheme 2)[8] followed by opening of the (η^2-formyl)borane subunit by a second equivalent of the pyridine nucleophile to give a stabilized carbanion (i.e., the phosphorus ylide intermediate **11**). This would activate this moiety for nucleophilic attack at the pyridine α-position to give **12**. Hydride migration with extrusion of the good FLP phosphane leaving group would provide an attractive short route to the α-hydroxymethylated pyridine product with concurrent formation of the FLP pyridine adduct **3**·pyridine.



Scheme 5. Mechanistic scheme of the formation of compound **7**.

Our study shows that frustrated Lewis pair chemistry has provided a pathway for hydroxymethylation of pyridines by means of a typical nucleophilic aromatic substitution pathway, thereby offering a potential alternative method to the Boeckelheide reaction. Our reaction is similar in its essential course to the Tschitschibabin amination of pyridines or the Ziegler pyridine alkylation and arylation reactions. In those classical reactions hydride is the leaving group, in our closely related case hydride is not set free but utilized for reduction of the CO-derived formyl group by 1,2-hydride shift. We think that this is another example that demonstrates the potential frustrated Lewis pair chemistry has in developing new chemical reactions.

Experimental Section

A solution of pyridine/isoquinoline (ca. 10 equiv) in dichloromethane (ca. 0.9 mL) was added to powdered compound **5** (up to 0.3 mmol) to give a clear reaction solution. The resulting colorless solution was sealed in an NMR tube and heated at 70 °C (oil-bath temperature) for 2 days. The dark brown reaction mixture was diluted with CH_2Cl_2 (2 mL) and loaded onto a column (SiO_2, CH_2Cl_2). The obtained product (**7** or **8**) was further purified by crystallization (toluene/*n*-pentane; 1:4) at −35 °C.

For the detailed reaction procedures and analytical data please see the Supporting Information. CCDC-1028144 (**7**), -1028145 (**8**), -1028146 (**9**) and -1028147 (**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: boron · frustrated Lewis pairs · hydroxymethylation · phosphorus · pyridine

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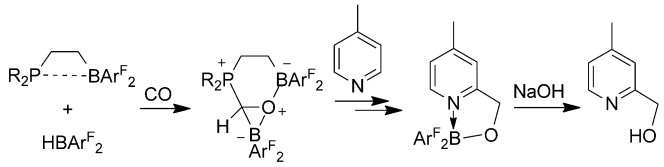

The "η^2-formylborane" moiety, formed by CO reduction with $HB(C_6F_5)_2$ and a P/B frustrated Lewis pair template, hydroxymethylates pyridine or isoquinoline by a reaction pathway related to the Tschitschibabin reaction (see scheme).

Synthetic Methods

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α-Hydroxymethylation of Pyridines at a Frustrated Lewis Pair Template