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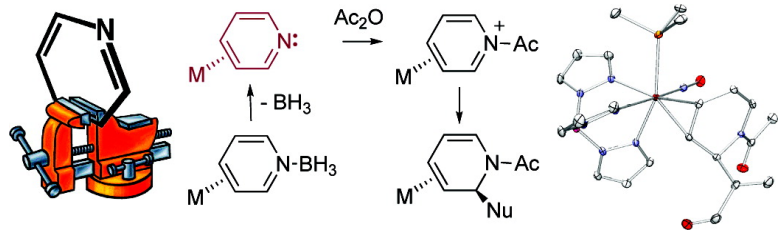

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Efficient Synthesis of an η^2-Pyridine Complex and a Preliminary Investigation of the Bound Heterocycle's Reactivity

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Over the past two decades, our group has sought to develop new methods of functionalizing aromatic molecules.[1,2] Our approach exploits the ability of certain π-basic transition metal complexes to bind aromatic molecules through two carbons, thereby localizing the remaining uncoordinated π-system. In this manner, η^2-arene, η^2-pyrrole, and η^2-furan complexes have been utilized in novel organic syntheses.[1−3] However, the development of parallel chemistry for pyridines, diazines, diazoles, and other basic aromatic heterocycles has been hampered by the thermodynamic preference of the transition metal to coordinate at nitrogen (Scheme 1, Path A). While such coordination for pyridines can be avoided by strategic placement of substituents (e.g., 2,6-disubstituted pyridines),[4] we desired a more general method for the preparation of dihapto-coordinated complexes of basic heterocycles.

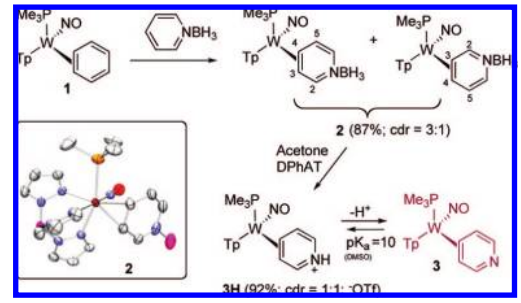
Scheme 1. Synthetic Strategies

Using pyridine as a test case, our strategy was first to form a complex with a corresponding pyridinium ion, in which N coordination was no longer possible. Once the heterocycle was coordinated, we planned to remove the N-substituent and utilize the η^2-pyridine ligand prior to its evolution to the N-bound isomer.[4] Unfortunately, when the synthon TpW(NO)(PMe_3)(η^2-benzene) (**1**) was subjected to either pyridinium or methylpyridinium triflate, the tungsten complex underwent oxidative degradation (Scheme 1, Path B).[4] We reasoned that a pyridine−borane adduct, being neutrally charged, would be less oxidizing than its cationic analog and hence could potentially form an isolable complex (Scheme 1, Path C).

True to expectation, the treatment of TpW(NO)(PMe_3)(η^2-benzene)[5] with pyridine−borane (PB; Aldrich) generated a new compound, TpW(NO)(PMe_3)(3,4-η^2-PB), isolated as a 3:1 mixture of coordination diastereomers (**2**; 87%; Scheme 2). The major isomer features five correlated ring proton resonances, two of which (2.18 and 3.76 ppm) being well upfield of the ^{1}H NMR signals for uncoordinated PB. The anodic peak potential ($E_{p,a}$ = +0.47 V @100 mV/s; NHE) of **2** is between those of the neutral η^2-pyridine (0.00 V) and η^2-pyridinium complexes (+0.83 V).[4] The X-ray structure of **2** (Scheme 2) depicts the major coordination diastereomer present in solution,[6] in which C4 is adjacent to the PMe_3 ligand.

Treatment of a suspension of **2** in ether with acidified acetone (DPhAT = diphenylammonium triflate) smoothly unmasks the

Scheme 2. Improved Synthesis of Pyridinium **3H**



nitrogen,[7] and the previously reported pyridinium complex **3H** is isolated as an orange microcrystalline solid (92%; cdr = 1:1).[4] The preparation of **3H** from **1** in 80% yield over two steps represents a vast improvement from the impractical 14% reported from trapping procedures[4,8] and enables direct access to the parent η^2-pyridine complex (**3**) on a synthetic scale.

The basicity of the η^2-pyridine **3** was found to be markedly greater than that for pyridine itself (pK_a(DMSO) of **3H** = 10; *cf.* 3.4 for pyH^+), owing to the tungsten backbonding; hence we attempted its acylation. Deprotonation of **3H** with 2,6-di-*tert*-butylpyridine (DTBP) in the presence of acetic anhydride results in the acetylpyridinum complex, **4**. The initial coordination diastereomer ratio (cdr = 4:1)[6] is improved to >10:1 upon heating (55 °C for 5.5 h),[6] and **4** was ultimately isolated in 94% yield (cdr >10:1).[9] This complex shows a CO stretching feature at 1733 cm^{-1} (IR) and CO and CN bond lengths of 1.19 and 1.41 Å (X-ray), respectively, consistent with an acetylpyridinium species (resonance form **a** in Figure 1). However the ^{13}C signal at 169.8 ppm and weak interaction between W and C2 (2.88 Å *cf.* 3.22 Å for W−C5) in **4** indicate partial allyl/amide character (resonance form **b**).[5] While acylpyridinum ions are commonly invoked as intermediates in pyridine (e.g., DMAP) catalyzed acylation reactions, they are normally far too unstable to isolate.[10,11] In the case of **4**, electron donation from tungsten not only allows its isolation but also renders the acetylpyridinium ligand *stable to water*, even at elevated temperatures (55 °C; 0.5 h; 30 equiv of water in acetone solution).

To determine if **4** was a viable acylation agent, we treated this complex with an acetone solution of morpholine (Scheme 3) and monitored the reaction with ^{31}P NMR. A 4 ppm upfield shift in ^{31}P

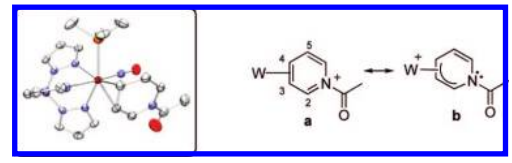


Figure 1. POV-Ray diagram and resonance forms of **4**.

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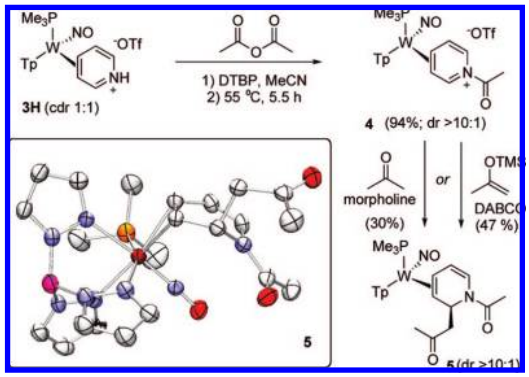
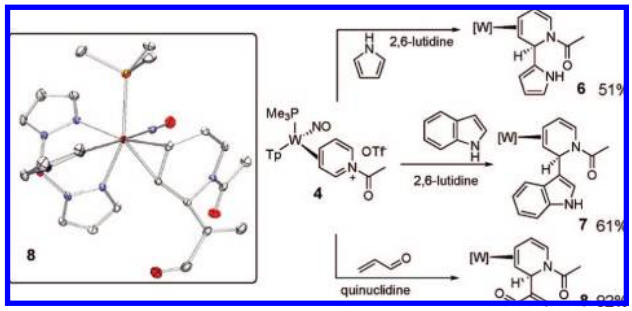
Scheme 3. Tandem Addition of Acetone (30% Ellipsoids)



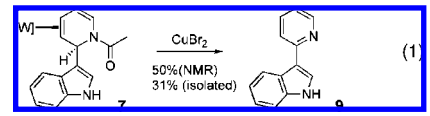
NMR and a cyclic voltammogram with an $E_{p,a}$ of +0.54 V signaled that a neutral tungsten species had been produced. To our surprise, spectroscopic analysis of the isolated product, **5**, indicates that acetone has added to C2 of the pyridinium ring (Scheme 2). 2D NMR and X-ray diffraction studies confirm that the addition is highly stereoselective, with the presumed enol, enolate, or enamine intermediate adding *anti* to the metal. A more efficient method to synthesize **5** was ultimately found using the silyl-enol ether of acetone with DABCO added to remove the TMS group.[12] This Mukiama−Mannich variation has the additional advantage that the product spontaneously precipitates from the CH_3CN/DME solution.

Encouraged by this mild and selective C2 nucleophilic addition, we explored several other reagents that could serve as mild carbon nucleophiles for the Mannich reaction. Both pyrrole and indole successfully undergo reactions at C2 of the acetylpyridinum complex under mild conditions to form **6** and **7**, respectively. Pyrrole selectively reacts at the α carbon (**6**; 51%) while indole undergoes electrophilic substitution at the β carbon of the heterocycle (**7**; 61%) (Scheme 4). Notably, these aza−Friedel−Crafts alkylations proceed only in the presence of a modest base (2,6-lutidine). As with the acetone adduct **5**, spectroscopic analysis confirms complete control of the stereochemistry at C2. Alternatively, the treatment of the acetylpyridinum complex **4** with acrolein and quinuclidine resulted in an aza−Morita−Baylis−Hillman reaction to form the enone **8** (92%),[13] where X-ray data again confirm addition to pyridine *anti* to coordination. Attempts to carry out C2 nucleophilic addition reactions with pyridinium complex **3** or with free *N*-acetylpyridinium (prepared *in situ* from pyridine and Ac_2O) were unsuccessful.

Scheme 4. Aza-Friedel−Crafts and Baylis−Hillman Reactions



The successful liberation of 3-(pyridin-2-yl)-1*H*-indole (**9**; 31% isolated, unoptimized; eq 1) was accomplished by treating complex **7** with 2.5 equiv of the oxidant $CuBr_2$. Unfortunately, the dihydropyridine ring was also oxidized. Other methods for decomplexation are currently under investigation that will conserve the C2 stereocenter. (2-Piperidyl)indoles are common components of monoterpenoid indole alkaloids;[14] the reaction sequence of **3H** → **9** illustrates an approach to form (2-pyridyl)indoles that does not involve cross-coupling methods or arylmetallic reagents, is tolerant of oxygen and water, and does not require harsh acids or bases. This reaction sequence is complementary to that observed by Corey et al. in which weak nucleophiles successfully were added to a triflylpyridinium intermediate to generate 1,4-dihydropyridines.[15]



In contrast to the reactivity of **4**, organic acylpyridiniums[16,17] or η^6-pyridine complexes[18] typically require strong nucleophiles such as metalloenolates and Grignard reagents to overcome the aromatic stabilization of the pyridine ring. Furthermore, without the use of directing groups, such nucleophilic addition reactions are often plagued by poor regioselectivity.[16,17]

This preliminary study shows that a borane adduct can be an effective synthon for the preparation of π-complexes of basic N-heterocycles that otherwise could bind through nitrogen. Once the heterocycle is coordinated through the π-system, the nitrogen can be deprotected and chemically accessed, pre-empting its coordination to the metal. In the present case, tungsten coordination of pyridine increases the basicity and nucleophilicity of the nitrogen, resulting in its facile acetylation. Yet remarkably, this *dearomatized* acetylpyridinium complex regio- and stereoselectively combines with mild carbon nucleophiles to give C2-substituted dihydropyridine complexes that could potentially be elaborated into highly functionalized piperidines. Further modification of the resulting enamide functionality is currently under investigation.

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Supporting Information Available: CIF files for **2**, **4**, **5**, and **8** ^{1}H and ^{13}C NMR of all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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