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Base-Free, Acceptorless, and Chemoselective Alcohol Dehydrogenation Catalyzed by an Amide-Derived *NNN*-Ruthenium(II) Hydride Complex

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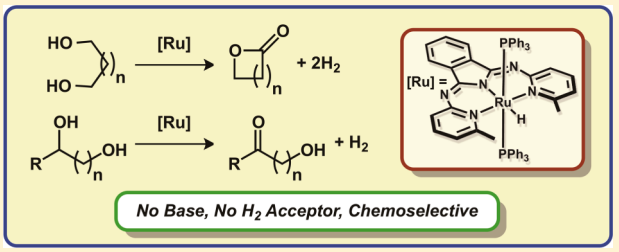
Supporting Information

ABSTRACT: The bmpi (1,3-bis(6′-methyl-2′-pyridylimino)-isoindoline) pincer Ru(II) hydride complex catalyzes base-free, acceptorless, and chemoselective dehydrogenation of alcohols with liberation of dihydrogen under moderate (<120 °C) conditions. Primary alcohols and diols are converted to ester and lactone products with high conversion efficiencies. The catalyst system is remarkably selective for the oxidation of secondary alcohols in the presence of primary alcohols.



In the past decade, catalytic alcohol dehydrogenation reactions have evolved as an atom-economic methodology to generate H_2 from biologically relevant alcohols[1] and/or to reveal a reactive organic fragment that can undergo follow up reactivity to form higher order liquid products.[2] In the absence of an added H_2 acceptor, primary alcohols can couple to form esters, with concomitant release of H_2, which is a variant of acceptorless dehydrogenative coupling (ADC) reactivity. Recently, this reaction class has seen substantial growth, typified by catalytic systems incorporating bifunctional metal−ligand scaffolds capable of promoting ADC.[3] For high atom economy, reactions that function in the absence of exogenous additives are particularly desirable, when this trait is coupled with mild reaction conditions. However, many alcohol dehydrogenation catalysts require the addition of super-stoichiometric quantities (with respect to Ru catalyst) of a basic reagent for efficient catalysis.[4] The bases (e.g., K^{t}BuO) are highly caustic, require specialized equipment, and also contribute to unwanted waste products; thus, systems that operate under base-free conditions are highly desirable.

Most known catalysts that effect alcohol dehydrogenation and/or ADC reactivity incorporate pincer-type ligand frameworks that can operate by a ligand−metal cooperative mechanism. Often containing a central pyridine ring, the pincer framework can exhibit multifunctionality by dearomatization/aromatization of the pyridinyl group, which ensues from the deprotonation/protonation of a methylene spacer.[3,5] We targeted an alternative anionic *NNN* pincer framework that substitutes the methylene spacer groups with an imine linker whose orbitals preclude concerted hydrogen transfer to an adjacent acceptor, in order to probe whether a cooperative mechanism is required for efficient dehydrogenation.[6] Herein, we report the synthesis and characterization of new pincer-ligated ruthenium complexes, which efficiently catalyze the dehydrogenation of primary and secondary alcohols without the requirement of added hydrogen acceptor or base.

To promote rapid dehydrogenation reactivity, we targeted amide-derived *NNN* pincer Ru complexes that incorporate the bmpi (1,3-bis(6′-methyl-2′-pyridylimino)isoindoline) ligand.[6,7] Metalation was achieved by addition of the deprotonated bmpi ligand to $Ru(PPh_3)_3Cl_2$ over 21 h in THF solvent, which afforded Ru(bmpi)(PPh_3)Cl (**1**)[8] in 92% yield (Figure 1). The $^{31}P\{^1H\}$ NMR spectrum of **1** exhibits a singlet at 43.50 ppm, while the ^1H NMR spectrum features a single set of ligand-based resonances, including a singlet at 1.71 ppm, consistent

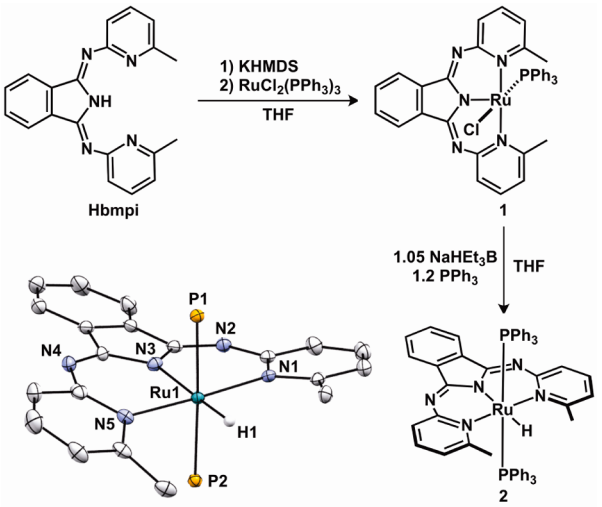


Figure 1. Synthesis of HRu(bmpi)(PPh_3)$_2$ (**2**) and ORTEP diagram of complex **2** with thermal ellipsoids at the 50% probability level. PPh_3 phenyl groups and hydrogen atoms, except for the hydride, are omitted for clarity.

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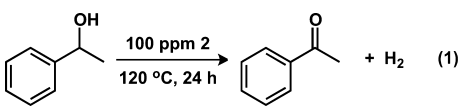
with symmetric binding of the bmpi ligand. This molecule represents the first reported ruthenium complex with a bpi (1,3-bis(2′-pyridylimino)isoindoline) ligand having substituents ortho to the pyridyl nitrogens.[7b,9]

Ruthenium hydride complexes are implicated as catalytic intermediates in alcohol dehydrogenation with pincer-type ligands;[3b−d,5,10] thus, we targeted hydride variants of Ru−bmpi complexes. The complex HRu(bmpi)(PPh_3)$_2$ (**2**) was isolated in 89% yield by allowing **1** to react with 1.05 equiv of $NaHEt_3B$ and 1.2 equiv of PPh_3 in THF solution at room temperature for 2 h (Figure 1). The $^{31}P\{^1H\}$ NMR spectrum of **2** exhibits a singlet at 50.97 ppm, and the ^1H NMR spectrum revealed a solution structure consistent with C_2 symmetry. A single peak for the ortho-substituted CH_3 units was visualized at 3.12 ppm, in addition to a high-field triplet resonance at −9.58 ppm (J_{PH} = 20.0 Hz); the latter resonance is consistent with a hydride ligand trans to an amido nitrogen.[11] Crystals suitable for single-crystal X-ray diffraction were obtained from vapor diffusion of pentane into a THF solution of **2**, and the solid-state structure of **2** (Figure 1) confirmed the proposed geometry, exposing a distorted-octahedral geometry around the Ru(II) center with a hydride ligand (located from the difference map) trans to the pyrrolidine nitrogen atom.

The ability of **1** and **2** to effect catalytic transfer hydrogenation with ^{i}PrOH was evaluated using acetophenone as the substrate. Heating a 0.1 M acetophenone ^{i}PrOH solution containing 0.5 mol % of **1** and 1.0 mol % of KO^{t}Bu to 80 °C for 1 h resulted in quantitative conversion (99%) of acetophenone to 1-phenylethanol. No reaction took place in the absence of a base. Complex **2** effected similar hydrogenative transformations with fewer required reagents. For example, *without* added base, under the reaction conditions listed above, complex **2** catalytically reduced acetophenone to 1-phenylethanol in 99% conversion within 1 h.

In addition to transfer hydrogenation reactivity by **2**, we hypothesized that dehydrogenation of ^{i}PrOH should also be possible without an added hydrogen acceptor. Indeed, in the absence of an exogenous ketone, such as acetophenone, ^{i}PrOH was consumed within 2 h at 80 °C using 10 mol % of **2** in C_6D_6. H_2 and acetone were confirmed as the sole reaction products by in situ examination of the reaction mixture in a sealed NMR tube.[12] ^1H NMR spectroscopic analyses revealed the formation of acetone and dihydrogen in equimolar quantities after 1 h at 80 °C, observed as singlets at 1.55 and 4.47 ppm, respectively.[13] This catalyst system was found to be remarkably active, and when using 20 ppm of **2**, a turnover number (TON) of 314 and turnover frequency (TOF) of 51 h^{-1} were obtained, on heating to reflux for 6 h.[14] In situ analysis of the dehydrogenation reaction revealed the release of free PPh_3 during catalysis, as visualized by ^{31}P NMR spectroscopy. Phosphine dissociation from **2** under catalytic conditions is consistent with an inner-sphere type pathway, which requires an open coordination site for substrate binding.

In order to investigate contributors to the overall reaction efficiency, 1-phenylethanol was chosen as a model 2° alcohol substrate (eq 1 and Figure 2). This substrate exhibits a



(1)

dehydrogenation reaction profile (Figure S7, Supporting Information) similar to that of ^{i}PrOH and, due to its low volatility, is amenable to reaction sampling by GCMS and/or ^1H NMR spectroscopy. When the dehydrogenation reaction was monitored over 24 h in an open system inside an inert-atmosphere glovebox, the reaction profile displayed two regions: a linear region (where the maximum rate was measured) and culmination. The reaction profile was linear after 4 min[15] and reached culmination after approximately 12 h (Figure 2, Standard).

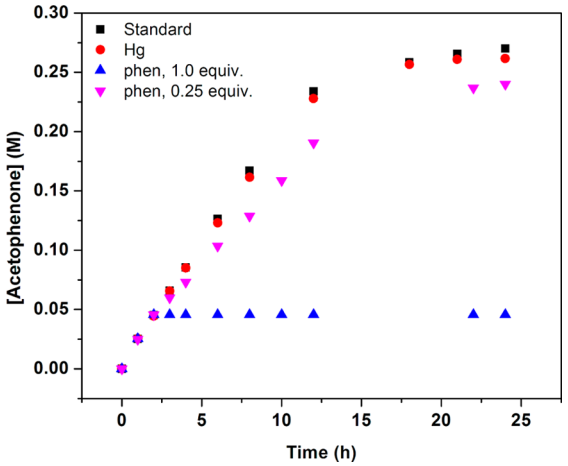


Figure 2. Reaction profiles of 1-phenylethanol dehydrogenation with and without added catalyst poisons. Conditions for each curve were identical ([**2**] = 7.44 × 10^{-4} M; [1-phenylethanol] = 7.53 M; [Ph-TMS] = 0.53 M; 120 °C) with the following modifications: (black ■) no modifications; (red ●) Hg(0) added after 2 h; (blue ▲) 1.0 equiv of 1,10-phenanthroline added after 2 h; (pink ▼) 0.25 equiv of 1,10-phenanthroline added after 2 h.

The catalyst identity of Ru-catalyzed transfer hydrogenation reactions with alcohols was recently reported to be distinct from that of a presumed homogeneous precursor, which formed catalytically active *heterogeneous* Ru(0) nanosized clusters.[16] Accordingly, we undertook initial experiments to probe whether complex **2** participates as a homogeneous catalyst or as a precursor to a heterogeneous species. Among the myriad techniques that collectively can be used to establish the catalyst identity, reproducible kinetic data and poisoning experiments are regarded as highly supportive evidence for homogeneous catalysis.[17] Consistent with an operative homogeneous system, the catalytic activity was unaffected by Hg(0) (~800 equiv) addition (Figure 2, Hg), when added *during catalysis*. Additionally, a substoichiometric ligand poisoning experiment was conducted.[18] Complete poisoning with 1,10-phenanthroline required 1 equiv (~ 25% decrease in the rate was observed with 0.25 equiv), inconsistent with a heterogeneous system, where low surface area aggregates are typically poisoned by ≪1 equiv of added ligand poison.[18] Finally, in the absence of any poisoning reagent, highly reproducible (nonsigmoidal) reaction kinetic profiles were observed (Figure S9, Supporting Information). The combined results of these tests suggest that the active catalytic species is indeed a homogeneous ruthenium complex.

The rates of alcohol dehydrogenation by structurally related Ru−PNP complexes are often dramatically increased by base additives,[4] and thus we examined whether complex **2** exhibited similar reactivity toward bases. Addition of 1−1000 equiv of KO^{t}Bu to the dehydrogenation reaction noted above (Table S1, Supporting Information) modified the reaction rate in a manner dependent on the quantity of base additive. Increasing

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the amount of base up to 100 equiv nearly doubled the reaction rate; however, at 1000 equiv, the reaction rate was suppressed. We hypothesized that, in the presence of excess base, KO^{t}Bu or ^{t}BuOH could compete with 1-phenylethanol coordination, thus impeding catalytic activity by diverting a competitive β-hydride elimination pathway. In support, a control experiment using 1000 equiv of ^{t}BuOH also exhibited a decreased reaction rate (Table S1, Supporting Information), consistent with rate suppression by ^{t}BuOH.

The release of H_2 provides a large entropic contribution to the overall thermodynamic profile of acceptorless alcohol dehydrogenation at a given temperature.[19] Thus, we probed H_2 pressure effects on 1-phenylethanol dehydrogenations (Figure 3) to examine how the overall conversion efficiency would be

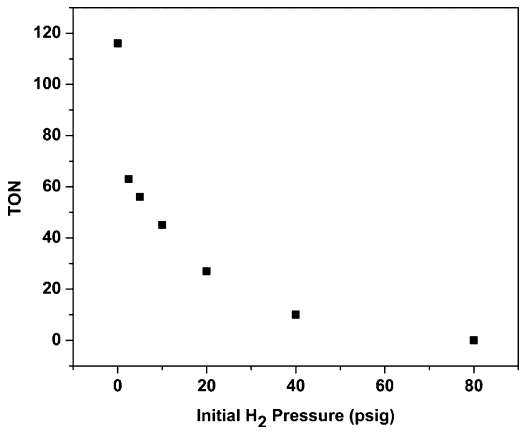
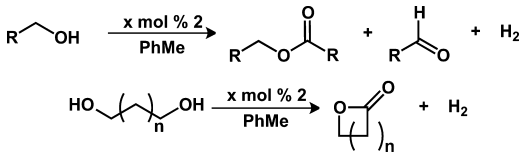


Figure 3. Dependence of 1-phenylethanol dehydrogenation catalyzed by **2** on the initial H_2 pressure. Conditions: **2** (4.1×10^{-3} mmol), Ph-TMS (2.9 mmol), and 5 mL of 1-phenylethanol (41 mmol) were charged with H_2 in a Fisher-Porter tube and heated to 120 °C for 24 h.

attenuated by elevated pressure. As expected, the reaction was found to be highly sensitive to pressure, and the dehydrogenation reaction was significantly inhibited (66% decrease in TON) when it was performed in a sealed vessel (80 mL headspace). Under as little as 2.5 psig of H_2 initial pressure, we observed a further, sharp decrease in TON (81%), which continued to decrease with increased pressure up to 80 psig (0% conversion). Note that complete product inhibition was not observed at moderate pressures (40 psig of H_2; 10 turnovers for dehydrogenation in 24 h). To determine whether the H_2 pressure effect was the result of rapid equilibration or a kinetic effect (inhibiting H_2 release), a dehydrogenation experiment was performed in a sealed NMR tube using 0.15 mol % of **2** in 2-propanol-d_8. HD was not observed in the ^{1}H NMR spectrum after the reaction mixture was heated to 90 °C for 24 h, suggesting that equilibration of H_2/D_2 is not an operative pathway under the operating conditions and instead inhibition is likely due to a kinetic effect that inhibits H_2 release with increasing pressure. Furthermore, although dehydrogenations are inhibited by product release, pressures of at least 8 psig could be obtained from vessels (5 mL of alcohol; 80 mL of headspace) sealed at ambient pressure. This observation is noteworthy if considering dehydrogenation of biorenewable alcohols as a means to release H_2 for use as an energy carrier, where elevated pressures are required for H_2 transport.[20]

We next sought to explore the ADC reactivity of primary alcohols and diols, whose dehydrogenation products contain highly reactive aldehyde fragments. Consistent with our results for the dehydrogenation of secondary alcohols, primary alcohols were similarly dehydrogenated to afford esters with no required additives under moderate reaction conditions. For instance, when *n*-butanol was used as a substrate, butyl butyrate was generated in 99% yield after 7 h at 111 °C (Table 1, entry 2). High yields of ester products were not general, and when benzyl alcohol was used as a substrate, 50% conversion to benzyl benzoate and 8% conversion to the aldehyde were noted. Furthermore, the conversion of ethanol, a biorelevant alcohol, to ethyl acetate proceeded with low conversion (Table 1, entry 1).[21]

Table 1. Dehydrogenation of Primary Alcohols to Esters and of Diols to Lactones Catalyzed by 2[a]



entry	alcohol or diol	amt of **2** (mol %)	time (h)	conversn (%)[b]	yield of ester or lactone (%)[b]
1	ethanol	1	24	9[c]	9[c]
2	*n*-butanol	1	7	99	99
3	benzyl alcohol	5	24	58	50
4	1,4-butanediol	1	24	88	88
5	1,5-pentanediol	5	24	99	99

[a]Conditions: alcohol (0.5 mmol), **2**, and 2 mL of toluene were refluxed in an open system under N_2. [b]Determined by GC-MS. [c]Determined by ^{1}H NMR spectroscopy.

Intramolecular reactivity was explored with aliphatic diol substrates, which were converted in high yields to the corresponding lactones. For instance, yields of 88% and 99% were obtained for γ-butyrolactone and δ-valerolactone (Table 1, entries 4 and 5), respectively, from 1,4-butanediol and 1,5-pentanediol. Several groups have previously reported homogeneous base-free catalytic oxidation of diols to lactones using a hydrogen acceptor (i.e., acetone) as the solvent.[22] However, to the best of our knowledge, only three accounts[3c,10a,23] of acceptorless *and* base-free catalytic oxidation of diols to lactones have been reported, and two[3c,10a] of these reports require significantly high temperatures (>200 °C). Thus, complex **2** is only the second reported example of catalytic ADC reactivity of diols to lactones that does not require an added hydrogen acceptor and base and occurs under moderate (<120 °C) conditions.

Guided by our results that demonstrated distinct conditions were required for the oxidation of primary and secondary alcohols, we reasoned that **2** should be capable of chemoselective oxidations of secondary alcohols in the presence of primary alcohols. Indeed, using temperatures lower than those required for ADC reactivity (90 °C), **2** chemoselectively oxidized the secondary alcohol moiety in 1-phenyl-1,2-ethanediol (**3**) in the absence of exogenous base or hydrogen acceptor additives and **4** was obtained as the only product, produced in 70% yield, which demonstrates the high chemoselectivity of **2** for alcohol dehydrogenation (eq 2). Because the methine C−H bond of **3** is weakened with respect to the primary alcohol due to the adjacent phenyl group, we investigated whether alkanediols of less disparate bond strengths can be similarly oxidized chemoselectively. Gratifyingly, when 1,3-butanediol (**5**) was subjected to modified

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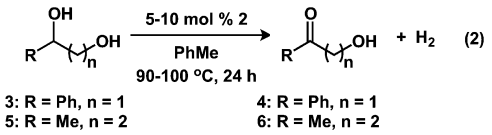

dehydrogenation conditions (15 mol % of **2**, 100 °C) selective oxidation of the secondary alcohol was achieved (eq 2) as the sole reaction product in 52% yield. To the best of our knowledge, such chemoselective oxidation of secondary alcohols in the presence of primary alcohols by homogeneous catalysis are exceptionally rare.[24]

In conclusion, we have developed an amide-derived *NNN*-Ru(II) hydride complex capable of catalyzing acceptorless dehydrogenation and dehydrogenative couplings of secondary and primary alcohols/diols, respectively, without requirements of added exogenous base or acceptor additives. Although prior reports demonstrated ADC reactivity of primary alcohols to esters and H_2, few catalysts accomplish this without base or acceptor additives.[3a,d,5,22a,25] Thus, when base-free, acceptorless alcohol oxidation catalysts under moderate (<120 °C) conditions are compared, the activity of **2** ranks among the best known ADC catalysts. In addition, **2** is particularly noteworthy because it mediates the chemoselective oxidation of secondary alcohols in the presence of primary alcohols without exogenous base or hydrogen acceptor additives, a difficult selective transformation.[24b] Work is ongoing to elucidate the mechanism of alcohol dehydrogenation, as well as the coupling reactivity of primary alcohols. Furthermore, we are targeting catalytic dehydrogenations of alternate polar substrates in order to examine the scope of ADC reactions with alcohols and/or amines.

■ ASSOCIATED CONTENT

Supporting Information

CIF files, text, figures, and tables giving crystallographic data for **1** and **2**, experimental procedures, and characterizations of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Different conditions were used: 15 mol % of **2** in 0.7 mL of ^{i}PrOH using phenyltrimethylsilane as an internal standard.

(13) The yield of hydrogen gas was determined using Ph-TMS as an internal standard and corrected for dissolved and free H_2, using Henry's Law, with a constant of 0.01907.

(14) When it is dissolved in solution, complex **2** is air-sensitive; thus, catalytic dehydrogenation is not tolerated in air.

(15) Monitoring the internal reaction temperature as a function of time required 3.85 min for the reaction solution to reach 120 °C (Figure S8, Supporting Information), consistent with temperature equilibration as the primary contributor to the induction period.

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