JOC Article

Using a Two-Step Hydride Transfer To Achieve 1,4-Reduction in the Catalytic Hydrogenation of an Acyl Pyridinium Cation

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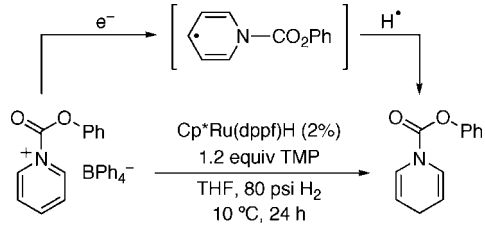
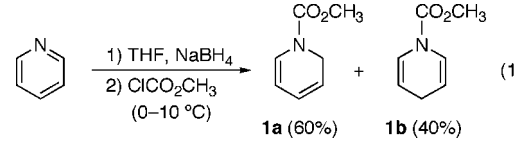
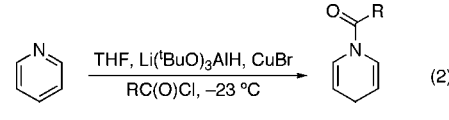


The stoichiometric reduction of *N*-carbophenoxypyridinium tetraphenylborate (**6**) by CpRu(P−P)H (Cp = η^5-cyclopentadienyl; P−P = dppe, 1,2-bis(diphenylphosphino)ethane, or dppf, 1,1′-bis(diphenylphosphino)ferrocene), and Cp*Ru(P−P)H (Cp* = η^5-pentamethylcyclopentadienyl; P−P = dppe) gives mixtures of 1,2- and 1,4-dihydropyridines. The stoichiometric reduction of **6** by Cp*Ru(dppf)H (**5**) gives only the 1,4-dihydropyridine, and **5** catalyzes the exclusive formation of the 1,4-dihydropyridine from **6**, H_2, and 2,2,6,6-tetramethylpiperidine. In the stoichiometric reductions, the ratio of 1,4 to 1,2 product increases as the Ru hydrides become better one-electron reductants, suggesting that the 1,4 product arises from a two-step ($e^-/H^\bullet$) hydride transfer. Calculations at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31G* level support this hypothesis, indicating that the spin density in the *N*-carbophenoxypyridinium radical (**13**) resides primarily at C4, while the positive charge in **6** resides primarily at C2 and C6. The isomeric dihydropyridines thus result from the operation of different mechanisms: the 1,2 product from a single-step H^- transfer and the 1,4 product from a two-step ($e^-/H^\bullet$) transfer.

Introduction

In 1972, Stout, Takaya, and Meyers reported a synthesis of 1,4-dihydropyridines via the addition of an azide to a 2,3-diazabicycloheptene to form an aziridine (followed by hydrolysis, oxidation, and N_2 extrusion).[1,2] Dihydropyridines may also be prepared by the reduction of pyridinium salts. However, in a 1982 review with Stout entitled *Recent Advances in the Chemistry of Dihydropyridines*, Meyers noted that "the formation of dihydropyridines by the reduction of pyridines and pyridinium salts is complicated by the fact that mixtures of 1,2- and 1,4-dihydropyridines result".[3] For example, Fowler obtained both *N*-carbomethoxy-1,2-dihydropyridine and *N*-carbomethoxy-1,4-dihydropyridine by treating a mixture of pyridine and sodium borohydride with methyl chloroformate (eq 1).[4] Comins concluded in 1984 that "a 1-acyl substituent stabilizes the dihydropyridine system" and found that both *N*-(alkylcarbonyl)- and *N*-(alkoxycarbonyl)-1,4-dihydropyridines can be prepared by a completely regioselective (but stoichiometric) reduction with $Li(^tBuO)_3AlH/CuBr$ (eq 2).[5]





In general, a 1,4-dihydropyridine is more stable thermodynamically than its 1,2 isomer.[6−9] Fowler measured in 1972 a substantial positive $\Delta G°$, 2.3 kcal/mol, for eq 3 at 91.6° in

(1) Meyers, A. I.; Stout, D. M.; Takaya, T. *J. Chem. Soc., Chem. Commun.* **1972**, 1260–1261.
(2) Stout, D. M.; Takaya, T.; Meyers, A. I. *J. Org. Chem.* **1975**, *40*, 563–569.
(3) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243.

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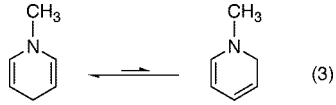
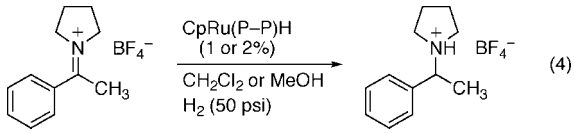
DMSO,[10] and Eisner and Sadeghi reported in 1978 the Rh-catalyzed isomerization of **1a** to **1b**.[11] The reduction of a pyridinium cation to a 1,2-dihydropyridine is thus usually the result of kinetic control.



(3)

We have previously shown that half-sandwich ruthenium hydride complexes catalyze the hydrogenation of the C=N bonds in iminium cations (eq 4)[12] and the rings in aziridinium cations (eq 5).[13] In the present work, we have investigated the reactivity of the Ru hydride complexes **2**−**5** toward the acyl pyridinium cation **6**[14] and the ability of **5** to *catalyze* the hydrogenation of **6**. The water-soluble Ru catalyst **7** and the Rh catalyst **8** have been shown to catalyze the 1,4 hydrogenation of NAD^+ models as well as $NADP^+$.[15−17]



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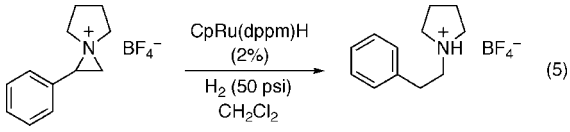
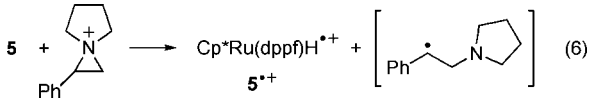
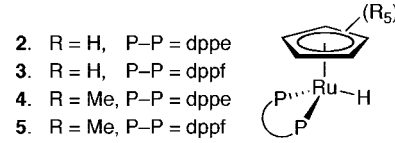


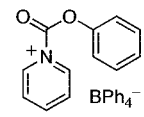
(5)

While investigating the hydrogenation of aziridinium cations, we observed the formation of the radical cation $\mathbf{5}^{\bullet+}$ in eq 6,[13] suggesting electron transfer. Multistep mechanisms beginning with e^- transfer have often been suggested as an alternative to the single-step transfer of hydride, particularly for H^- transfers from NAD(P)H and its analogues.[18] Scheme 1 shows a possible multistep pathway, involving an $H^\bullet$ transfer (HAT)[19,20] after the initial single-electron transfer (SET);[21,22] the possibility that the "$H^\bullet$" step involves the separate transfer of H^+ and e^- has also been considered.[22−25] We have therefore considered the possibility of e^- transfer during the reaction of the Ru hydrides **2**−**5** with the pyridinium cation **6** and have examined the electrochemical oxidation of **2**−**5** and the electrochemical reduction of **6**.

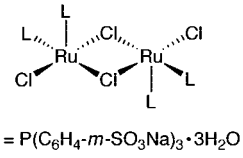


(6)



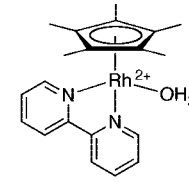


6



L = $P(C_6H_4\text{-}m\text{-}SO_3Na)_3 \cdot 3H_2O$

7



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Results and Discussion

Stoichiometric and Catalytic Reactions. All four Ru−H complexes quantitatively transfer H^- to **6**, giving the 1,2- and 1,4-dihydropyridines **9a** and **9b** (Table 1). The resulting 16-electron Ru cations are trapped by excess CH_3CN in entries 1−4 or solvent CD_3CN in entries 5−8. These stoichiometric reactions proceed readily at room temperature, although entries 6 and 8 require heating to dissolve the sparingly soluble **3** and **5**. The trend in the product distribution among the different hydride complexes is the same in CD_2Cl_2 and CD_3CN. In both solvents, **5** (Hembre's hydride,[26] Cp*Ru(dppf)H) is remarkably selective, giving only the 1,4-dihydropyridine.

The product ratios in Table 1 are different for each hydride, remain constant after each reaction, and are obviously the result of kinetic control. Thermodynamic control (recall the reported slow isomerization of **1a** to **1b**[11]) would give the 1,4 product **9b**. Only the formation of **9b** (*and none of* **9a**) was observed when the reaction in entry 4 was monitored by ^1H NMR at 228 K.

The iminium and aziridinium cations in eqs 4 and 5 are hydrogenated by an ionic mechanism, where H^- and H^+ are transferred in separate steps.[12,13] In eqs 4 and 5, the tertiary amine product removes H^+ from an H_2 complex, regenerates the hydride complex, and makes the reaction *catalytic* in Ru, with H_2 as the ultimate reductant. If we attempt to make the

(4) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321–1323.
(5) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1984**, *49*, 3392–3394.
(6) Damji, S. W. H.; Fyfe, C. A. *J. Org. Chem.* **1979**, *44*, 1757–1761.
(7) Keay, J. G. *Adv. Heterocycl. Chem.* **1986**, *39*, 1–77.
(8) 1,2-Dihydropyridines are significantly stabilized by a methoxy substituent at the 2 position, and in such cases are often more stable than their 1,4 counterparts: Doddi, G.; Ercolani, G.; Mencarelli, P. *J. Org. Chem.* **1992**, *57*, 4431–4434.
(9) Another counterexample is reported in: Feith, B.; Weber, H. M.; Maas, G. *Chem. Ber.* **1986**, *119*, 3276–3296.
(10) Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 5926–5927.
(11) Eisner, U.; Sadeghi, M. M. *Tetrahedron Lett.* **1978**, 299–302, The isomerization of **1a** was said to be "incomplete" after 5 days, but the 1,4 isomer **1b** remained unchanged under the same conditions.
(12) Guan, H.; Iimura, M.; Magee, M. P.; Norton, J. R.; Zhu, G. *J. Am. Chem. Soc.* **2005**, *127*, 7805–7814.
(13) Guan, H.; Saddoughi, S. A.; Shaw, A. P.; Norton, J. R. *Organometallics* **2005**, *24*, 6358–6364.
(14) King, J. A.; Bryant, G. L. *J. Org. Chem.* **1992**, *57*, 5136–5139.
(15) Wagenknecht, P. S.; Penney, J. M.; Hembre, R. T. *Organometallics* **2003**, *22*, 1180–1182.
(16) Lo, H. C.; Fish, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 478–481.
(17) Hollmann, F.; Schmid, A.; Steckhan, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 169–171.
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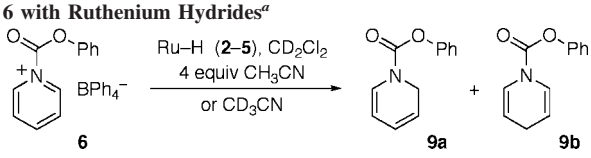
(24) Ohno, A.; Shio, T.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2045–2048.
(25) Yuasa, J.; Yamada, S.; Fukuzumi, S. *J. Am. Chem. Soc.* **2006**, *128*, 14938–14948.
(26) Hembre, R. T.; McQueen, J. S.; Day, V. W. *J. Am. Chem. Soc.* **1996**, *118*, 798–803.

TABLE 1. Product Distributions of the Stoichiometric Reduction of 6 with Ruthenium Hydrides[a]

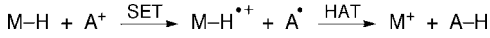


6 9a 9b

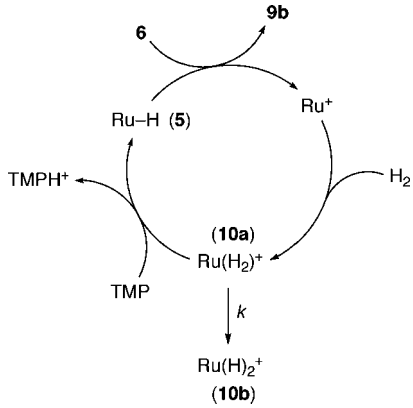
entry	complex	solvent	9a	9b
1[b]	**2**	CD_2Cl_2	52	48
2[b]	**3**	CD_2Cl_2	30	70
3[b]	**4**	CD_2Cl_2	4	96
4[b]	**5**	CD_2Cl_2		100
5[c]	**2**	CD_3CN	23	77
6[d]	**3**	CD_3CN	15	85
7[c]	**4**	CD_3CN	2	98
8[d]	**5**	CD_3CN		100

[a] General reaction conditions: 0.02 mmol of **6**, 0.02 mmol of hydride complex, 700 μL of solvent, product ratio determined by ^{1}H NMR integration. [b] 0.08 mmol of CH_3CN, room temperature. [c] Room temperature. [d] 75 °C, 2 h.

SCHEME 1



SCHEME 2



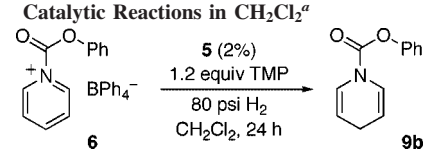
reduction of the pyridinium cation **6** in Table 1 catalytic, the dihydropyridine products **9a** and **9b** are not sufficiently basic to deprotonate the H_2 complex (**10a**), so a non-nucleophilic base must be added (Scheme 2). TMP (2,2,6,6-tetramethylpiperidine) fulfills this requirement and makes the reaction catalytic; DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and NEt_3 react with **6**.

Isomerization of the cationic dihydrogen complex $Cp^*Ru(dppf)(H_2)^+$ **10a** to the *trans*-dihydride complex (**10b**)[27] competes with the catalytic cycle, as TMP is not basic enough to deprotonate **10b**. Such isomeric dihydrogen and dihydride complexes are readily distinguished by the T_1 (min) of their ^{1}H NMR hydride resonances;[28] the dihydrogen resonance of **10a** has a typically short T_1 (min) of 11.5 ms (218.5 K, 300 MHz), while that of the dihydride resonance of **10b** is much longer, 0.151 s (195.2 K, 300 MHz).

An attempt to catalyze the hydrogenation of **6** with **5** at room temperature in CH_2Cl_2 gave only 28% conversion to **9b** (Table 2). The ^{1}H NMR analysis of a reaction aliquot showed the presence of **10b**, confirming that the isomerization reaction (**10a** → **10b**) is responsible for stopping catalysis.

Because the **10a** → **10b** isomerization shuts down the catalytic cycle, it is important to know its rate. The protonation of **5** at

TABLE 2. Catalytic Reactions in CH_2Cl_2[a]

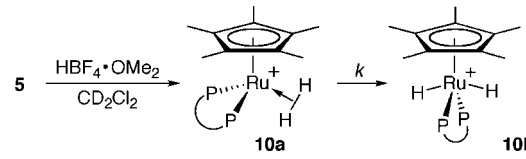


6 9b

T, °C	% conversion[b]
rt	28
10	58
0	38

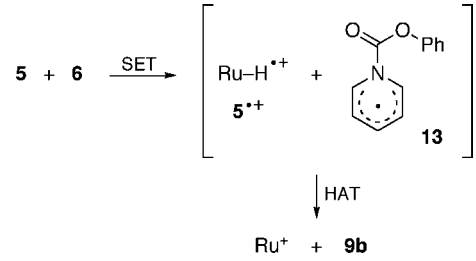
[a] General reaction conditions: 0.50 mmol of **6**, 0.60 mmol of TMP, 0.01 mmol of **5**, 10 mL of CH_2Cl_2, 80 psi H_2, 24 h. [b] Determined by ^{1}H NMR integration.

SCHEME 3



10a 10b

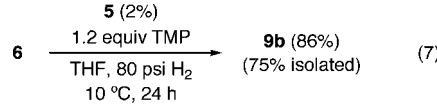
SCHEME 4



room temperature gives **10a**, which rapidly isomerizes to **10b** (Scheme 3). At lower temperatures, the isomerization (a first-order reaction) can be followed by ^{1}H NMR. At 0 °C, $k = 1.32(2) \times 10^{-3}$ s^{-1} in CD_2Cl_2, giving **10a** a half-life of about 9 min at this temperature. Belkova has recently reported $k = 1.53 \times 10^{-3}$ s^{-1} for the isomerization of protonated **4** ($Cp^*Ru(dppe)(H_2)^+$ → *trans*-$Cp^*Ru(dppe)(H)_2^+$) at 260 K.[29]

One would expect lower temperatures to decrease the rate of catalyst deactivation, slowing the unwanted (intramolecular) isomerization of **10a** → **10b** relative to the needed (intermolecular) proton transfer from the H_2 ligand of **10a** (note the relatively large $\Delta H^{\ddagger}$ for isomerization reported by Belkova).[29] Unfortunately, **6** is not very soluble in CH_2Cl_2 below room temperature; a reaction at 0 °C in CH_2Cl_2 gave only a modest improvement in conversion over the room temperature reaction (Table 2). An intermediate temperature of 10 °C gave a significant improvement in the conversion of **6** to **9b** in CH_2Cl_2.

The solubility of **6** is much greater in THF than in CH_2Cl_2. Using THF at 10 °C gave 86% conversion to **9b** (eq 7); aqueous workup and flash chromatography gave pure **9b** in 75% yield (with respect to the initial **6**). To the best of our knowledge, this is the first catalytic hydrogenation of an *N*-acylpyridinium cation that gives a 1,4 product exclusively.



(7)

(27) Hembre, R. T.; McQueen, J. S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 65–67.
(28) Luo, X. L.; Crabtree, R. H. *Inorg. Chem.* **1990**, *29*, 2788–2791.
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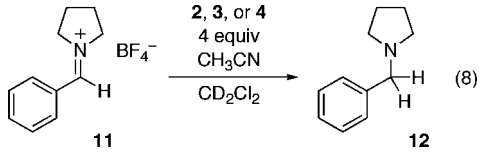
TABLE 3. Cyclic Voltammetry

compd	potential[a]	process
CpRu(dppe)H (**2**)	−0.16[b]	Ru(III/II)
CpRu(dppf)H (**3**)	−0.31[c]	Ru(III/II)
Cp*Ru(dppe)H (**4**)	−0.51[d]	Ru(III/II)
Cp*Ru(dppf)H (**5**)	−0.63[d]	Ru(III/II)
6	−0.87[e]	reduction
11	−1.42[e]	reduction

[a] Potentials in volts (V) in CH_2Cl_2 vs Fc/Fc^+. [b] E_{pa}, irreversible, 50 mV/s. [c] E_{pa}, quasireversible, $I_a/I_c = 1.25$, $E_{pa} - E_{pc} = 0.09$, 50 mV/s. [d] $E_{1/2}$, reversible, 50 mV/s. [e] E_{pc}, irreversible, 200 mV/s.

Probing the Mechanism of H⁻ Transfer. The reactivities of the hydride ligands in the Ru complexes **2**−**5** are influenced by the nature of the chelating bisphosphine and by the extent of substitution on the Cp ring. For example, **2** readily transfers H^- to the iminium cation in eq 4, while the hydride ligand of **4** is basic enough to deprotonate that cation.[12] The dppf ligand makes **3** and **5** unusually good one-electron reducing agents,[26] but it does not make them better hydride donors: complexes **2**, **3**, and **4** (*but not* **5**) react with the iminium cation **11** (eq 8).



11 **12** (8)

The difference in reactivity between **5** with **6** and **5** with **11** led us to suspect a two-step mechanism for H^- transfer from **5** to **6**, with e^- transfer preceding $H^\bullet$ transfer. Hembre found that **5** is easily oxidized by ferrocenium or trityl cation.[26,27]

Although the potentials of **2**,[30,31] **4**,[29] and **5**[26] have been reported, they were obtained in THF. We therefore performed cyclic voltammetry on **2**−**5** (and **6** and **11** for comparison) in CH_2Cl_2 (Table 3).

Under our conditions, the cyclic voltammogram of **2** is sufficiently irreversible (see the Supporting Information) to leave some doubt about its thermodynamic potential relative to that of **3**. However, the order of the *reversible* potentials of **4** and **5** implies that the thermodynamic potential of **3** must be more negative than that of **2** and that the order of the reduction potentials of the hydride complexes, from least to most negative, is **2**, **3**, **4**, and **5**. *This order correlates with the increase in* **9b**/**9a** as we go from **2** to **5** in Table 1.

From their irreversible potentials in Table 3 it appears that **6** is more easily reduced than **11** and that an SET mechanism for H^- transfer is much more plausible with **6** than with **11**. The $E_{1/2}$ of **5** is close to the E_{pc} of **6** but not to the E_{pc} of **11**, suggesting that an e^- transfer mechanism is available for the reaction of **5** with **6** (which occurs) but not for the reaction of **5** with **11** (which does not occur).

Indirect evidence for an initial electron transfer in the reaction of **5** with **6** (Scheme 4) was obtained by ^1H NMR. At 228 K, the hydride signal of **5** was broadened, and after 1 h a significant amount of **10a** was present (see the Supporting Information). The broadening arose from self-exchange with $Ru-H^{\bullet+}$ (**5**$^{\bullet+}$).[13] The **10a** came from disproportionation (eq 9) and proton transfer (eq 10), a sequence known to result in the formation of dihydrogen complexes from $Ru-H^{\bullet+}$.[31]

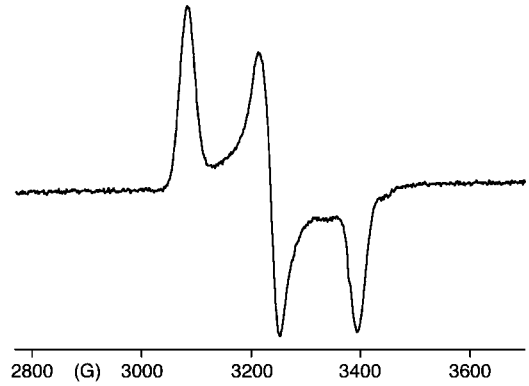


FIGURE 1. X-band EPR spectrum of **5**$^{\bullet+}$ at 77 K (from the reaction of **5** with **6** in CH_2Cl_2 at 223 K).

$$2Ru-H^{\bullet+} \rightarrow Ru-H + Ru-H^{2+} \quad (9)$$

$$Ru-H + Ru-H^{2+} \rightarrow Ru(H_2)^+ + Ru^+ \quad (10)$$

EPR evidence for the formation of **5**$^{\bullet+}$ was obtained by mixing CH_2Cl_2 solutions of **5** and **6** at 223 K. The reaction mixture, initially orange, became green after 10 min. The X-band EPR, recorded at 77 K after quenching the reaction in liquid nitrogen, clearly showed the presence of **5**$^{\bullet+}$ (Figure 1).[32] Apparently at this temperature, the second step (HAT) in Scheme 4 is slow relative to the first step (SET), permitting the accumulation of some **5**$^{\bullet+}$.

Computational Results. A two-step mechanism for the reaction of **5** with **6** involves not only **5**$^{\bullet+}$ but also the radical **13** as a short-lived intermediate (Scheme 4). Further evidence for this mechanism is available from various quantum mechanical calculations. Mulliken population analysis[33] provides a means of assessing radical character as well as charge at any atomic center. In the case of radical character, the atomic spin density (S) is given by the difference in α and β electron density (D_α and D_β) at the atomic center of interest. By definition, α-electrons are assigned positive spin and β-electrons are assigned negative spin, such that the atomic spin density at a particular atomic center is given by eq 11. One unpaired electron on an atomic center is ideally given by $S = 1$, while a closed shell atom is ideally given by $S = 0$. However, atomic spin densities are often noninteger and deviate from these ideal numbers.

$$S = D_\alpha - D_\beta \quad (11)$$

For the radical **13**, different resonance structures place the unpaired electron on C2, C4, or C6. Mulliken population analysis at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31G* level shows that the radical resides primarily para to nitrogen, at C4. In contrast, the positive charge in the pyridinium cation **6** resides primarily at C2 and C6 (Figure 2). Our results vary little across basis sets and regardless of whether implicit solvation is included. Our results are consistent with calculations performed as early as 1970 in which Hückel theory and SCF quantum calculations were used to show that the electron density of the 7-(π-electron) pyridine anion resides primarily at the 4 position.[34] Semiempirical methods AM1 and MNDO have also

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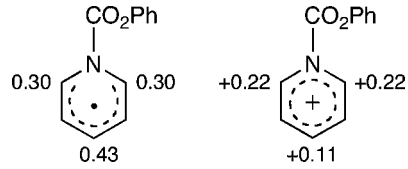
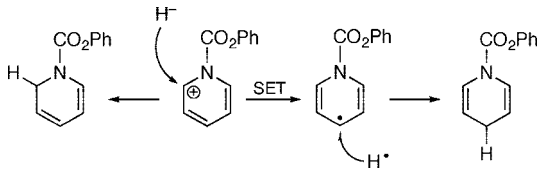


FIGURE 2. Calculated atomic spin densities (**13**) and charges (**6**) at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31G* level.

SCHEME 5



been used to show that the kinetic regioselectivity for nucleophilic attack on the pyridinium ring is governed by the electron density at each carbon.[8]

Single- and Multistep Mechanisms. The first explanation of the regioselectivity of nucleophilic attack on pyridinium cations[8,35] was offered by Kosower in 1956. He noted the formation of charge-transfer complexes between I^- and pyridinium cations[36] and suggested that nucleophiles which could form such complexes added to the 4 position while other nucleophiles preferred the 2/6 position.[37] Later, Klopman suggested that the regioselectivity was the result of the hard/soft character of the nucleophile, with the total charge density (charge control) directing hard nucleophiles to the 2/6 position while the coefficient of C4 in the LUMO (frontier orbital control) directed soft nucleophiles to the 4 position.[38] Doddi, Ercolani, and Mencarelli have noted[8] the frequent misuse of Klopman's analysis to explain results that have arisen from thermodynamic control rather than from the kinetic control he assumed.

The regioselectivities we obtain for the transfer of H^- from Ru hydrides to **6** arise entirely from kinetic control. Our results suggest that, at least with Ru hydrides, the 1,2 and 1,4 products arise from the operation of different mechanisms. Mulliken population analysis confirms that the positive charge in the cation **6** resides predominantly at C2 and C6, whereas the spin density in the radical **13** resides predominantly at C4. A single-step H^- transfer is likely to be charge controlled and reduction at C2/C6 will be electronically favored, although steric factors may result in a mixture; the e^- transfer at the beginning of a multistep mechanism will favor $H^•$ transfer to C4 (Scheme 5). As our Ru hydrides become better one-electron reductants, they give greater percentages of the 1,4 reduction product, until **5** gives only the 1,4 product.

Other reductants that result exclusively in 1,4-dihydropyridines are ones we expect to be particularly good at single-electron transfer. Examples include sodium dithionite,[7] the copper hydride (probably polynuclear) formed from Li-(^{t}BuO)$_3$AlH and CuBr,[5] and the formyl complex [Ru(bpy)$_2$(CO)(CHO)]$^+$.[39]

Indeed, the importance of single-step or multistep mechanisms in determining the regiochemistry of nucleophilic attack on pyridinium cations is implied by much previous literature. In his 1995 review of the *Regioselectivity of the Reactions of Pyridinium and Quinolinium Salts with Various Nucleophiles*, Poddubnyi cited various calculations as predicting "the highest spin density for the γ position" of the radicals formed by e^- transfer, and concluded that an "SET mechanism...gives rise to γ-selectivity...whereas the polar...mechanism...is characteristic of α-selective addition".[35]

Experimental Section

General Procedures. All air-sensitive compounds were prepared and handled under an N_2/Ar atmosphere using standard Schlenk and inert-atmosphere box techniques.

N-Carbophenoxypyridinium tetraphenylborate (**6**) was prepared by the method of King[14] and recrystallized from $CH_2Cl_2-Et_2O$. *N*-Benzylidenepyrrolidinium tetrafluoroborate (**11**),[40] Cp*Ru(dppf)H (**5**),[26] CpRu(dppf)H (**3**),[41] Cp*Ru(dppe)H (**4**),[29] and CpRu(dppe)H (**2**)[42] were prepared by the literature methods. CD_2Cl_2 and CD_3CN were degassed and stored over 3 Å molecular sieves. CH_2Cl_2 was deoxygenated and dried by two successive columns (Q-5, activated alumina). THF was distilled from sodium/benzophenone under an N_2 atmosphere.

General Electrochemical Procedure. Cyclic voltammetry was performed with a BAS CV-50W potentiostat. The supporting electrolyte for all solutions except the reference electrode was 0.10 M $[Bu_4N]PF_6$ in CH_2Cl_2. The cell consisted of a 1.6 mm diameter platinum disk working electrode, a platinum wire auxiliary electrode, and a silver wire reference electrode (0.01 M $AgNO_3$ + 0.10 M $[Bu_4N]PF_6$ in CH_3CN). The reference electrode was separated from the sample solutions with a porous Vycor tip (Bioanalytical Systems, MF-2042). Fc/Fc^+ was used as an external reference and was found to be +0.22 V with respect to our reference electrode. All samples were prepared under an N_2/Ar atmosphere and further purged with Ar before measurement. Analyte concentrations were 0.001 M. Cyclic voltammograms of the hydride complexes (**2**−**5**) were recorded at 50 mV/s. Cyclic voltammograms of **6** and **11** were recorded at 200 mV/s. All potentials are reported in volts (V) vs Fc/Fc^+.

General Hydrogenation Procedure. *CAUTION! Always shield pressurized vessels!* Under an inert atmosphere, **6** (0.26 g, 0.50 mmol) and **5** (7.9 mg, 0.01 mmol) were combined in a Fischer−Porter bottle. THF or CH_2Cl_2 (10 mL) and 2,2,6,6-tetramethylpiperidine (TMP, 0.10 mL, 0.6 mmol) were added, and the apparatus was charged with H_2 (80 psi). The reaction mixture was stirred rapidly for 24 h at room temperature. For lower temperature reactions, the sealed apparatus was cooled in a salt−water bath at 0 or 10 °C for 5 min prior to charging with H_2. The temperature was maintained for 24 h by placing the sealed apparatus, salt−water bath, magnetic stir plate, and shielding inside an appropriately set refrigerator. A 1 mL aliquot of the reaction mixture was evaporated and the residue dissolved in CD_2Cl_2. The percent conversion was determined by comparing the ^{1}H NMR integrations of the product peaks with that of 3.0 μL of added CH_3CN.

Variable-Temperature NMR. Probe temperatures were calibrated with an ethylene glycol or methanol (99.97% MeOH + 0.03% HCl) chemical shift thermometer.[43,44]

Cp*Ru(dppf)(H$_2$)$^+$ (10a). $HBF_4 \cdot OMe_2$ (0.01 mmol) and 400 μL of CD_2Cl_2 were added to a screw-cap NMR tube with a Teflon-

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coated septum insert. The NMR tube was cooled in an acetone/CO_2 bath while connected to an N_2 bubbler. Separately, **5** (0.01 mmol) was dissolved in 400 μL of CD_2Cl_2 and then added slowly to the cold NMR tube with a syringe. The tube was quickly shaken and inserted into a precooled NMR probe. ^{1}H NMR (300 MHz, 195.2 K, CD_2Cl_2): δ −8.12 (s, br, Ru(H_2), 2H), 1.21 (s, Cp*, 15H), 4.11 (s, dppf Cp, 2H), 4.22 (s, dppf Cp, 2H), 4.29 (s, dppf Cp, 2H), 4.49 (s, dppf Cp, 2H), 7.30−7.70 (m, Ar, 20H). ^{31}P {^{1}H} NMR (121.5 MHz, 195.2 K, CD_2Cl_2): δ 55.09. T_1 measurements (300 MHz) of the dihydrogen resonance: T_1 = 12.6(2) ms, 195.2 K; 11.5(2) ms, 218.5 K; 12.8(2) ms, 238.9 K.

***trans*-Cp*Ru(dppf)(H)$_2^+$ (10b).** The title dihydride complex[27] may be prepared by treating **5** with $HBF_4 \cdot OMe_2$ at room temperature or by warming a solution of **10a** to room temperature. ^{1}H NMR (300 MHz, 279.5 K, CD_2Cl_2): δ −7.80 (t, Ru*(H)*$_2$, J_{P-H} = 25.8 Hz, 2H), 1.24 (s, Cp*, 15H), 4.19 (s, dppf Cp, 4H), 4.21 (s, dppf Cp, 4H), 7.58−7.66 (m, Ar, 12H), 7.85−7.96 (m, Ar, 8H). ^{31}P {^{1}H} NMR (121.5 MHz, 279.5 K, CD_2Cl_2): δ 58.33. T_1 measurements (300 MHz) of the dihydride resonance: T_1 = 0.224(4) s, 178.0 K; 0.151(2) s, 195.2 K; 0.223(5) s, 218.5 K; 0.253(5) s, 238.9 K; 0.323(5) s, 258.9 K; 0.439(7) s, 279.5 K.

Isomerization Kinetics. A solution of **10a** (0.04 M in CD_2Cl_2) was prepared as described above and inserted into an NMR probe precooled to 0 °C. The reaction was followed by the integration of the dihydrogen complex peak at δ 4.59 (s, dppf Cp, 2H) in comparison with the integration of the residual solvent peak at δ 5.32. The average of three experiments gave a first-order rate constant of 1.32(2) × 10^{-3} s^{-1} for the disappearance of **10a**.

***N*-Carbophenoxy-1,2-dihydropyridine (9a).** Compound **9a** as prepared by the literature method[45] was contaminated with 6% of the isomeric 1,4-dihydropyridine (**9b**). Two conformers of **9a** (in a 3/4 ratio) were observed at room temperature. ^{1}H NMR (300 MHz, 298 K, CD_3CN): δ 4.36 (s, CH_2, major), 4.56 (s, CH_2, minor), 5.29 (m, 1H), 5.62 (m, 1H), 5.90 (m, 1H), 6.65−6.95 (m, N−C*H*, 1H), 7.15 (m, Ar, 2H), 7.26 (m, Ar, 1H), 7.41 (m, Ar, 2H). An averaged spectrum was observed at 340 K: δ 4.46 (s, br, CH_2, 2H), 5.31 (m, 1H), 5.64 (m, 1H), 5.92 (m, 1H), 6.83 (m, N-C*H*, 1H), 7.15 (m, Ar, 2H), 7.26 (m, Ar, 1H), 7.41 (m, Ar, 2H).

***N*-Carbophenoxy-1,4-dihydropyridine (9b).**[5] The hydrogenation of 0.50 mmol of **6** (see General Hydrogenation Procedure) in 10 mL of THF at 10 °C for 24 h gave a yellow solution. An aliquot (1 mL) was evaporated, and ^{1}H NMR (in CD_2Cl_2 + 3.0 μL CH_3CN internal standard) indicated 86% conversion to **9b**. The remainder of the reaction solution was evaporated to give a yellow residue. The residue was extracted with 4 × 5 mL of Et_2O. The Et_2O solution was washed with 1 M NH_4Cl (2 × 10 mL) and satd $NaHCO_3$ (2 × 10 mL), dried over $MgSO_4$, and evaporated to give a yellow solid. The solid was dissolved in an 8/2 mixture of hexanes/Et_2O and loaded on a flash column (230−400 mesh silica, 14 cm × 1 cm diameter). The product was eluted with an 8/2 mixture of hexanes/Et_2O. Evaporation of the solvent gave the product, a white crystalline solid, in 75% yield (corrected for the aliquot removed, and with respect to **6**). ^{1}H NMR (300 MHz, 298 K, CD_3CN): δ 2.87 (m, CH_2, 2H), 5.02 (br, β-C*H*, 1H), 5.07 (br, β-C*H*, 1H), 6.76 (d, α-C*H*, J = 7.8 Hz, 1H), 6.91 (d, α-C*H*, J = 8.7 Hz, 1H), 7.17 (m, Ar, 2H), 7.27 (m, Ar, 1H), 7.42 (m, Ar, 2H). An averaged spectrum (due to fast rotation about the N−C(O) bond) was observed at 340 K: δ 2.88 (m, CH_2, 2H), 5.06 (br, β-C*H*, 2H), 6.84 (br, α-C*H*, 2H), 7.19 (m, Ar, 2H), 7.27 (m, Ar, 1H), 7.42 (m, Ar, 2H). FAB$^+$ MS (*m*-NBA): *m*/*z* for [M + 1]$^+$ calcd 202.0868, found 202.0867.

Stoichiometric Hydride Transfer from Ruthenium Hydrides to 6 in CD_2Cl_2. The Ru hydride (0.02 mmol) and **6** (0.02 mmol) were dissolved in 700 μL of CD_2Cl_2 at room temperature. CH_3CN (0.08 mmol) was added, and the product ratio was measured by ^{1}H NMR integration.

Stoichiometric Hydride Transfer from Ruthenium Hydrides to 6 in CD_3CN. The Ru hydride (0.02 mmol) and **6** (0.02 mmol) were dissolved in 700 μL of CD_3CN at room temperature; the product ratio was measured by ^{1}H NMR integration. The hydride complexes **3** and **5** are sparingly soluble in CD_3CN. For reactions with **3** or **5**, the NMR tube was heated in a 75 °C oil bath and shaken to mix the contents every 20 min. Once most of the yellow **3** or **5** had dissolved (about 2 h), the tube was removed from the bath and the product ratio determined by ^{1}H NMR integration.

Stoichiometric Hydride Transfer from Ruthenium Hydrides to 11 in CD_2Cl_2. The Ru hydride (0.02 mmol) and **11** (0.02 mmol) were dissolved in 700 μL of CD_2Cl_2 at room temperature. CH_3CN (0.08 mmol) was added, and the ^{1}H NMR spectrum was recorded. Complexes **2**, **3**, and **4** transferred hydride to **11**, giving the tertiary amine (**12**). In these cases, the CD_2Cl_2 solution was evaporated, the residue extracted with Et_2O, the Et_2O solution evaporated, and the resulting residue dissolved in $CDCl_3$. The ^{1}H NMR spectra matched the reported spectrum of **12**.[46] The hydride complex **5** did not react with **11** in CD_2Cl_2.

Low-Temperature Reaction of 5 with 6 (^{1}H NMR). CH_3CN (0.08 mmol), **6** (0.02 mmol), and 550 μL of CD_2Cl_2 were added to a screw-cap NMR tube with a Teflon-coated septum insert. The NMR tube was cooled in an acetone/CO_2 bath while connected to a N_2 bubbler. Separately, **5** (0.02 mmol) was dissolved in 250 μL of CD_2Cl_2 and then added slowly to the cold NMR tube with a syringe. The tube was quickly shaken and inserted into a precooled NMR probe. The reaction was monitored by 300 MHz ^{1}H NMR at 228.0 K for 1 h, during which time the only dihydropyridine product formed was **9b**.

Low-Temperature Reaction of 5 with 6 (EPR). An EPR tube (quartz, 3 mm) was charged with **6** (200 μL, 0.02 M in CH_2Cl_2). The tube was sealed with a septum and cooled in a hexanes/CO_2 bath at 223 K while connected to a N_2 bubbler. Separately, **5** (200 μL, 0.02 M in CH_2Cl_2) was slowly added to the cold EPR tube with a syringe. The mixture, initially orange, became green after 10 min and was then quenched in liquid N_2. The X-band EPR spectrum was obtained at 77 K with a Bruker EMX EPR spectrometer with a TE_{102} rectangular cavity.

Computational Methods

Both the radical (**13**) and the pyridinium cation (**6**) were subjected to conformational searching using Macromodel 6.0[47] and the OPLS 2001 force field.[48] The lowest energy structures were subsequently minimized at the DFT-UB3LYP/6-31G* level[49−51] in both vacuum and implicit solvent (dichloromethane) using Jaguar 7.0.[52] Single-point calculations were also performed at the UB3LYP/6-311++G(3df,3pd)//UB3LYP/6-31G* level. Spin densities and atomic charges were determined by Mulliken population analysis.[33]

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Supporting Information Available: Lists of ^{1}H NMR peaks for **6** and **11**, ^{1}H NMR spectra of **9a** and **9b** (298 and 340 K) and **10a** (195.2 K), a ^{1}H NMR spectrum from (and detailed comments on) the low-temperature reaction of **5** with **6**, kinetic data for **10a** → **10b**, computational details for **6** and **13**, and cyclic voltammograms of **2**, **3**, **4**, **5**, **6**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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