Transfer Hydrogenation of Carbonyl Compounds Catalyzed by a Ruthenium−Acetamido Complex: Evidence for a Stepwise Hydrogen Transfer Mechanism

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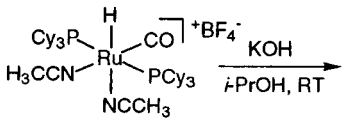
Summary: The ruthenium−acetamido complex, prepared from the reaction of $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$ *with KOH in 2-propanol, was found to be an effective catalyst for the transfer hydrogenation of carbonyl compounds and imines. Observation of both the inverse deuterium isotope effect and the competitive inhibition by added phosphine provided strong evidence for a stepwise mechanism of proton and hydride transfer via a coordinatively unsaturated ruthenium−amido species.*

The transition-metal-catalyzed transfer hydrogenation of ketones and imines has been shown to be an effective method for forming chiral alcohols and amines.[1−3] For example, Noyori achieved highly enantioselective transfer hydrogenation reactions of ketones and imines by using chiral Ru^{II}−TsDPEN catalysts, and recently proposed a concerted mechanism of hydrogen transfer involving metal-to-ligand "bifunctional" hydrogen activation on the basis of both experimental and computational results.[2] Several other Ru and Rh catalysts with chiral nitrogen ligands have also been shown to give high enantioselectivity toward the hydrogenation of ketones and imines.[3] The "N−H effect" of the amide ligand has been suggested as an important factor for promoting the catalyst activity for these systems.[4] On the basis of a detailed kinetic and mechanistic study of benzaldehyde reduction mediated by Shvo's bimetallic HOC_5Ph_4−Ru^{II}−hydride complex, Casey recently proposed a concerted transfer mechanism of proton and hydride via a monomeric ruthenium−hydride complex.[5] As part of ongoing efforts to study ruthenium-catalyzed hydrogenation reactions,[6] we have begun to explore the catalytic activity of coordinatively unsaturated ruthenium−amido complexes. Here we report the synthesis of the ruthenium−acetamido complex $[(PCy_3)_2(CO)(CH_3CONH)(i\text{-PrOH})RuH]$ (**1**) and its catalytic activity toward the transfer hydrogenation of carbonyl compounds and imines.

The acetamido complex **1** was prepared from the nucleophilic addition of OH^- to the cationic complex $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$ (**2**) (eq 1).[7] Thus, the



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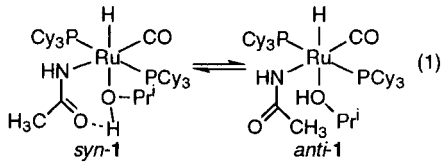

syn-**1** *anti*-**1**

treatment of **2** (200 mg, 0.23 mmol) with KOH (26 mg, 2.0 equiv) in 2-propanol at room temperature cleanly formed the ruthenium−acetamido complex **1**, which was isolated in 75% yield as a colorless crystalline solid after recrystallization in 2-propanol at 0 °C. The initially colorless crystals of **1** slowly turned to a pale yellow powder, apparently due to desolvation at room temperature, but the desolvated complex **1** was found to exhibit the same spectral features as the solvent-coordinated one. The ^1H NMR spectrum of **1** in CD_2Cl_2 at room temperature showed a broad metal−hydride peak at δ −18.38 ($w_{1/2}$ = 102 Hz), which split into a 10:1 ratio of

(1) Recent reviews: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051−1069. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (c) Fehring, V.; Selke, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1827−1830. (d) Sánchez-Delgado, R. A.; Rosales, M. *Coord. Chem. Rev.* **2000**, *196*, 249−280.

(2) TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine. (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288. (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (c) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478.

(3) (a) Sammakia, T.; Strangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104−6105. (b) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817−3818. (c) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749−2751. (d) Cao, P.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 2127−2129. (e) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186−2187. (f) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291−2293. (g) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841−843.

(4) (a) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580−9588 and references therein. (b) Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *J. Am. Chem. Soc.* **1998**, *120*, 1441−1446. (c) Guiral, V.; Delbecq, F.; Sautet, P. *Organometallics* **2000**, *19*, 1589−1598. (d) Bernard, M.; Delbecq, F.; Sautet, P.; Fache, F.; Lemaire, M. *Organometallics* **2000**, *19*, 5715−5722.

(5) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090−1100.

(6) (a) Yi, C. S.; Lee, D. W. *Organometallics* **1999**, *18*, 5152−5156. (b) Yi, C. S.; Lee, D. W.; He, Z.; Rheingold, A. L.; Lam, K.-C.; Concolino, T. E. *Organometallics* **2000**, *19*, 2909−2915. (c) Lee, H. M.; Smith, D. C., Jr.; He, Z.; Stevens, E. D.; Yi, C. S.; Nolan, S. P. *Organometallics* **2001**, *20*, 794−797.

(7) See the Supporting Information for the synthetic procedure and the characterization data of **2**.

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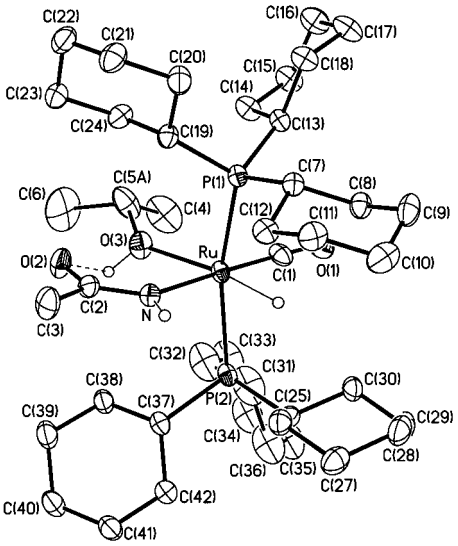


Figure 1. Molecular structure of **1** drawn with 30% thermal ellipsoids.

distinct peaks δ −18.31 (t, J_{PH} = 20.4 Hz) and δ −14.25 (t, J_{PH} = 19.2 Hz) at −50 °C.[8] These peaks were assigned to *syn*-**1** and *anti*-**1** rotational isomers, respectively. The amide C−N bond rotational barrier estimated from the ^{1}H and ^{31}P VT NMR analysis ($\Delta G^{\ddagger}$ = 15.0 kcal/mol at 35 °C) was found to be similar to organic carbonyl amides.[9]

The molecular structure of **1** showed the syn configuration of the amido carbonyl group with respect to the coordinated 2-propanol ligand (Figure 1). The syn configuration was apparently facilitated by a strong hydrogen-bonding interaction between the carbonyl oxygen and the alcohol groups, as evidenced by a relatively short distance between two oxygen atoms (O(3)−O(4) = 2.580(4) Å). Also, a relatively short C−N bond distance (C(2)−N = 1.322(5) Å) along with a low carbonyl amide stretching frequency ($\nu_{C=O}$ = 1545 cm^{-1}) suggested the extensive π-delocalization of the amide ligand.

The complex **1** was found to be an effective catalyst for the transfer hydrogenation of carbonyl compounds and imines (Table 1, Supporting Information). For example, the treatment of acetophenone (120 mg, 1.0 mmol) with **1** (4 mg, 0.5 mol %) in 2-propanol (1 mL) cleanly produced the alcohol **3a** in >95% isolated yield after 6 h at 80 °C. Both aryl- and alkyl-substituted ketones and imines were readily hydrogenated at 80 °C. For *trans*-4-phenyl-3-buten-2-one, alkene hydrogenation was initially favored over carbonyl reduction at 50 °C to give 4-phenyl-2-butanone (95% selectivity), but the alcohol product **3c** was eventually formed at 80 °C after 12 h (entry 3). In general, the reaction rate was found to be very slow at low temperature, but it can be substantially increased by adding 10 equiv of CuCl for acetophenone with 0.5 mol % of **1** (95% yield after 2 days at room temperature).[10]

The following preliminary results were obtained from probing the catalytic hydrogenation of acetophenone. (1) The presence of an acetamido ligand was found to greatly promote the catalytic activity of **1**, since neither the chloride complex [$(PCy_3)_2$(CO)RuHCl] nor the acetate complex $(PCy_3)_2$(CO)(CH_3CO_2)RuH (**4**) was effective under similar reaction conditions. These results, along with recent revelations on the Ru−amido complexes,[11] confirmed the importance of a basic amide ligand to catalytic activity. (2) The product Ph(CH_3)CDOH (95% D) was exclusively formed when $(CH_3)_2$CDOH (98% D, Cambridge Isotopes) was employed, while Ph(CD_3)CHOD (>90% D) with extensive deuterium incorporation on both the hydroxy and methyl groups resulted from $(CH_3)_2$CHOD.[12] These results showed the regiospecific hydrogen transfer from 2-propanol to acetophenone. (3) The reaction was found to be strongly inhibited by added PCy_3. For example, the addition of 2 equiv of PCy_3 to the reaction mixture led to ca. 90% rate reduction compared to the reference reaction. Furthermore, the double-reciprocal plots of the initial rate vs [$PhCOCH_3$] with added PCy_3 (0.2 and 0.5 equiv) showed that the catalyst was competitively inhibited by PCy_3 (Figure 1, Supporting Information). (4) The rate of the reaction was found to be first order in [$PhCOCH_3$] (0.2−2.8 M) and zero order in [2-propanol] (0.4 M-4.0 M) in C_6D_6. Unexpectedly, a nonlinear rate dependence on [**1**] was observed under these reaction conditions; thus, a modest rate increase (~60%) resulted upon increasing [**1**] from 1.7 to 27 mM.[13] The reaction rate was virtually independent of [**1**] under the relatively low catalyst concentrations (1.7−5 mM), and a simple empirical rate law was obtained in this case ($-d[PhCOCH_3]/dt = k_{obs}[PhCOCH_3]$ with k_{obs} = 1.3 × 10^{-4} s^{-1} at 80 ± 1 °C in C_6D_6).[14] (5) An inverse deuterium isotope effect was observed from both $(CH_3)_2$CHOH/$(CH_3)_2$CHOD and $(CH_3)_2$CHOH/$(CD_3)_2$CDOD for the hydrogenation of acetophenone in the presence of 1.0 mol % of **1** (k_{OH}/k_{OD} = 0.7 ± 0.1 and k_{CHOH}/k_{CDOD} = 0.7 ± 0.2 at 80 °C). In contrast, a normal deuterium isotope effect was observed for a 1:1 mixture of $(CH_3)_2$CHOH and $(CH_3)_2$CDOH under the competitive reaction conditions (k_{CH}/k_{CD} = 1.9 ± 0.2 at 80 °C).

While a detailed reaction mechanism still remains to be established, these results are consistent with a stepwise mechanism of proton and hydride transfers via an unsaturated ruthenium−amido species (Scheme 1). An inverse deuterium isotope effect has been commonly observed for stepwise hydrogen transfer reactions,[15] particularly in specific acid- and enzyme-catalyzed hydrogen transfer reactions[16] and in C−H bond activation reactions,[17] where the reaction mechanism is typically characterized by a fast and reversible step followed

(8) Two separate NH proton peaks (δ 5.39 and 4.79, 1:10 ratio) as well as a broad OH proton peak (δ 3.12) were also observed at −50 °C.

(9) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Deerfield Beach, FL, 1985; Chapter 2.

(10) (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897. (b) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627−1628.

(11) (a) Fulton, J. R.; Bouwkamp, M. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 8799−8800. (b) Kaplan, A. W.; Bergman, R. G. *Organometallics* **1998**, *17*, 5072−5085.

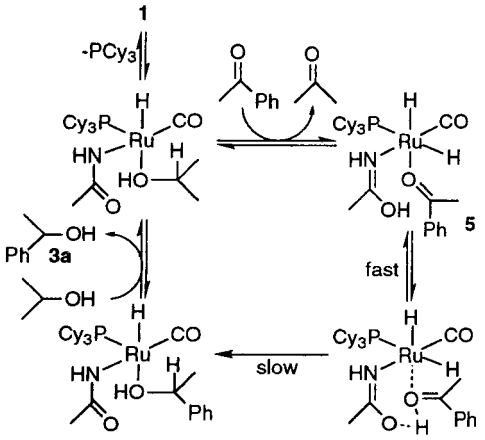
(12) The deuterium incorporation at the methyl group can be readily explained from the keto−enol tautomerization of acetophenone.

(13) The nonlinear [catalyst] dependence has been observed for cases where active catalysts are generated from monomer/dimer preequilibrium and/or ligand dissociation, and in asymmetric catalysis. For recent examples, see: (a) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402−411 and the references therein. (b) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848−1855.

(14) Similar kinetic behavior was observed in 2-propanol with a slightly higher reaction rate under low [**1**].

(15) Bullock, R. M. In *Transition Metal Hydrides*; Dedieu, A., Ed.; VCH: Weinheim, Germany, 1992; Chapter 8.

Scheme 1



by a rate-limiting step. The observed inverse isotope effect (k_{OH}/k_{OD} = 0.7) is consistent with a stepwise mechanism involving a rapid and reversible proton transfer followed by a rate-determining step of hydride transfer. The observation of both competitive rate inhibition by added PCy_3 and a normal isotope effect (k_{CH}/k_{CD} = 1.9) further suggests a Michaelis−Menten type of kinetics with the hydride transfer from the metal center to the carbonyl substrate as the rate-determining step.[18] Previously, ruthenium−dihydride complexes have been commonly proposed as key intermediate species in hydrogenation reactions,[19] and in our case, the formation of the dihydride species **5** can be envisioned from the initial dissociation of the PCy_3 ligand followed by hydrogen transfer from 2-propanol. Recently, normal deuterium isotope effects have been observed for concerted hydrogenation transfer reactions, such as in the dehydrogenation of 2-propanol by the Ru^{II}−TsDPEN catalyst[2a] and in the reduction of benzaldehyde by the hydroxy−ruthenium−hydride complex (k_{CH}/k_{CD} = 1.5−1.6), with an additive effect for the latter example (k_{CHOH}/k_{CDOD} = 3.6).[5] The observation of an inverse isotope effect is clearly different from these results. In a related ionic hydrogenation of ketones and imines, Bullock and Norton proposed a stepwise mechanism of proton transfer followed by a rate-limiting hydride transfer for the catalytic reaction.[20]

When the complex **1** was treated with excess $(CD_3)_2$CDOD at room temperature, a facile H/D exchange of the NH proton was observed (>95% D after 10 min), whereas the incorporation of 90% deuterium in the metal hydride required over 10 days. This result, along with the observation of hydrogen bonding between two oxygen atoms (O(3)−O(4)), further implies that the proton transfer may be facilitated by a hydrogen-bonding interaction between the acetamido group and the carbonyl substrate, possibly via an iminol-to-amide tautomerization of the acetamido ligand. Crabtree showed that a similar iminol-to-amide tautomerization led to strong Ir−H···H−X intramolecular hydrogen-bonding interactions (X = O, N) for the cationic iridium−acetamido complexes.[21] We also believe that the catalyst's ability to form unsaturated species is an important factor for promoting the stepwise mechanism. For both Noyori's Ru^{II}−TsDPEN and Shvo's complexes, the concerted mechanism was favored because the generation of coordinatively unsaturated species for these complexes would require energetically unfavorable ring slippage and/or dissociation of a chelating ligand. Further research is currently underway to probe the effect of catalyst-to-substrate hydrogen bonding on the transfer hydrogenation reactions.

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Supporting Information Available: Text giving the experimental procedures and characterization data for **1**, **2**, and **4** and tables giving the X-ray crystallographic data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Dover: Mineola, NY, 1987; Chapter 4. (b) *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: London, 1977; pp 157−161.

(17) (a) Schultz, R. H.; Bengali, A. A.; Tauber, M. J.; Weiller, B. H.; Wasserman, E. P.; Kyle, K. R.; Moore, C. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7369−7377. (c) Wang, J.-H.; Chiang, C.-M. *J. Am. Chem. Soc.* **2000**, *122*, 11521−11522.

(18) According to the kinetic expression developed by Casey and coworkers,[5] the observed inverse isotope effect of k_{OH}/k_{OD} = 0.7 would result from the normal isotope effects of k_{OH}/k_{OD} = 3.0 and k_{CH}/k_{CD} = 2.0, an inverse *equilibrium* isotope effect of k_1/k_{-1} = 0.5, and $k_1 = 10k_2$ for the proposed stepwise mechanism. Also, the fact that PhCHDOH (95% D) without significant loss of deuterium atom was formed from the reaction of PhCDO (98% D, Aldrich) in 2-propanol is inconsistent with a mechanism involving reversible hydride transfer.

(19) (a) Aranyos, A.; Csjernyik, G.; Szabó, K. J.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351−352. (b) Laxmi, Y. R. S.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611−612. (c) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2000**, *19*, 2655−2657.

(20) (a) Bullock, R. M.; Voges, M. H. *J. Am. Chem. Soc.* **2000**, *122*, 12594−12595. (b) Magee, M. P.; Norton, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 1778−1779.

(21) (a) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. F. *Acc. Chem. Res.* **1996**, *29*, 348−354. (b) Lee, J. C., Jr.; Peris, E.; Rheingold, A. L.; Crabtree, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 11014−11019. (c) Gruet, K.; Crabtree, R. H.; Lee, D.-H.; Liable-Sands, L.; Rheingold, A. L. *Organometallics* **2000**, *19*, 2228−2232.