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An Unexpected Possible Role of Base in Asymmetric Catalytic Hydrogenations of Ketones. Synthesis and Characterization of Several Key Catalytic Intermediates

Robin J. Hamilton and Steven H. Bergens*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

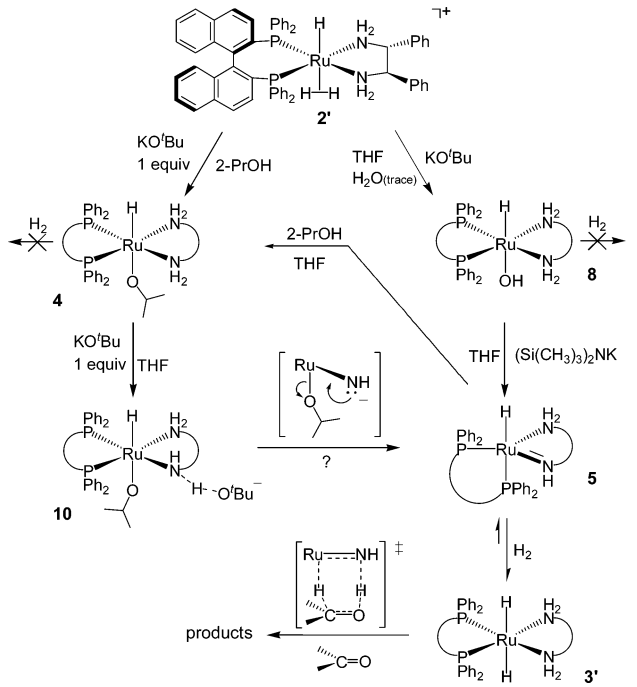
Received July 28, 2006; E-mail: steve.bergens@ualberta.ca

We report direct observations and reactivity studies of several catalytic intermediates in enantioselective ketone hydrogenations that reveal an unexpected role of added base in these systems. Among the most significant advances in enantioselective catalysis is Noyori et al.'s development of the catalyst system *trans*-Ru(diphosphine)Cl_2(diamine) plus base in 2-PrOH.[1] This remarkable system and its variants hydrogenate aryl−alkyl, vinyl−alkyl, and certain alkyl−alkyl ketones with high enantiomeric excess, turnover numbers, and frequencies.[1d,e] The mechanism of these ketone hydrogenations has been the subject of intense study.[1d,2−5] Most attempts to observe intermediates in these hydrogenations are impeded by long initiation times to convert stable precursors into less stable catalytic intermediates and by decomposition of active catalyst species via β-hydride elimination from the amine ligand.[2f] Further, the key hydrogen atoms in the catalytic cycle, the N−H, Ru−H, and Ru−η^2-H_2 functionalities, all undergo rapid H−D exchange at room temperature, impeding ^{1}H NMR studies of the catalytic cycle in 2-PrOH-d_8. As a result of these difficulties, most mechanistic studies must resort to less direct approaches, including kinetics and isotope labeling studies on catalytic mixtures, use of nonprotic solvents, and model compounds containing non-indigenous ligands.

Noyori et al. made the distinguishing mechanistic proposition for these hydrogenations—that the enantioselective step is a bifunctional, ligand-assisted addition of a nucleophilic hydride ligand on Ru and a protic hydrogen on nitrogen to the carbon and oxygen atoms of the ketone, respectively, through a pericyclic six-membered TS (Scheme 1, bottom).[1b,d] Using model compounds, Morris et al. established that one role of the added base is to generate the active, dihydride catalysts *trans*-Ru(diphosphine)$(H)_2$(diamine).[2a] Base-free catalyst precursors, such as *trans*-Ru((*R*)-tol-BINAP)(H)(η^1-BH_4)-((*R*,*R*)-dpen) (**1**, tol-BINAP = 2,2′-bis(ditolylphosphino)-1,1′-binaphthyl, dpen = 1,2-diphenylethylenediamine), have been developed by Noyori et al.[1c] They proposed that, in the absence of added base, hydrogenations using **1** proceed through the cationic, η^2-H_2 intermediate *trans*-[Ru((*R*)-tol-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]$^+$ (**2**). As is the case with most of these catalytic hydrogenations, the rate of reaction using **1** increases, peaks, and then decreases as base is added in increasing concentrations. The initial increase in rate with added base was accounted for by proposing that the η^2-H_2 compound **2** reacts to generate the dihydride compound *trans*-[Ru-((*R*)-tol-BINAP)$(H)_2$((*R*,*R*)-dpen)] (**3**) faster in the presence of base.[1d] Although the conversion of the η^2-H_2 compound **2** into **3** was identified as a key step in these hydrogenations, the difficulties encountered when studying these systems (vide supra) made direct information about this step impossible to obtain at the time.

We recently reported a high yielding, low-temperature synthesis of the BINAP-containing cationic η^2-H_2 intermediate *trans*-[Ru-((*R*)-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]$^+$ (**2′**, BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl) in 2-PrOH-d_8 containing CH_2Cl_2-d_2.[6] We found that the η^2-H_2 group in **2′** is extremely labile, it is readily displaced by BH_4^- to form **1′**, and it retains a high degree of free H_2 character. Further, **2′** is inactive toward the hydrogenation of acetophenone under 4 atm H_2, 30 °C, and 2000 equiv of ketone unless 1 equiv of *t*-BuOK or BH_4^- is added as base. Compound **2′** therefore does not generate **3′** without added base under these conditions. We now report our study of the key reaction of **2′** with base and H_2 under various conditions.

Scheme 1



Flushing the H_2 from 2-PrOH solutions of **2′** with Ar results in decomposition, presumably by loss of H_2 and β-H elimination from the dpen ligand. Reaction of **2′** with 1 equiv of *t*-BuOK under H_2 (∼2 atm H_2, 2-PrOH, −80 °C) immediately[7] formed the 2-propoxide compound *trans*-Ru((*R*)-BINAP)(H)(2-PrO)((*R*,*R*)-dpen) (**4**), by replacement of the labile η^2-H_2 ligand (Scheme 1). The results from previous studies infer that **4** may be in equilibrium either with the amide [Ru((*R*)-BINAP)(H)((*R*,*R*)-NH(CH(Ph))$_2$$NH_2$))] (**5**)[2b] or with the cationic solvento compound *trans*-[Ru((*R*)-BINAP)(H)(solvent)-((*R*,*R*)-dpen)]$^+$ (**6**).[1d] Unexpectedly, we found no evidence for the amide **5**, the solvento compound **6**, nor the *trans*-dihydride **3′** after prolonged exposures of 2-PrOH solutions of **4** to H_2 gas (∼10 h, ∼2 atm, 22 °C) in the absence of base. This unexpected stability of **4** may result from intra-[5] or intermolecular H-bonding between the 2-PrO^- ligand and an N−H group or 2-PrOH, respectively.[8]

The N−H groups in the dihydrogen compound **2′** undergo H−D exchange with 2-PrOH-d_8 upon mixing at −80 °C. The hydride and η^2-H_2 ligands begin to exchange with 2-PrOH-d_8 and free H_2 upon warming to ∼ −60 °C. The N−H groups are therefore kinetically, at least, the most acidic protons in **2′**. To prevent both H−D

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exchange and formation of the 2-propoxide **4**, we prepared **2′** in THF-d_8. THF is a stronger ligand for these compounds than 2-PrOH. Unlike in 2-PrOH, warming THF-d_8 solutions of the η^2-H_2 compound **2′** under ~2 atm H_2 reveals an equilibrium that shifts from ~84% **2′** at −80 °C to a ~ 2:1 mixture of **2′** and the solvento compound *trans*-[Ru((*R*)-BINAP)(H)(THF-d_8)((*R*,*R*)-dpen)]$^+$ **7** at −50 °C. Compound **7** is the THF-d_8 analogue of the 2-PrOH adduct **6**, a catalytic intermediate proposed by Noyori et al. to react with H_2 and form **2′**.[1d,e] We found that this equilibrium in THF-d_8 shifts back to the η^2-H_2 compound when cooled to −80 °C, and it shifts to **7** when the H_2 is replaced with Ar. Also unlike 2-PrOH, the THF-d_8 adduct **7** does not decompose via β-elimination at ~22 °C.

To study the reaction with base, we found that reaction of **2′** with ~1 equiv of *t*-BuOK in THF-d_8 at −60 °C immediately formed the hydroxide analogue of **4**, *trans*-Ru((*R*)-BINAP)(H)(OH)((*R*,*R*)-dpen) (**8**, Scheme 1). We found it extremely difficult to keep all traces of H_2O from THF-d_8 to avoid the facile replacement of η^2-H_2 in **2′** by hydroxide to form **8**, analogous to the reaction in 2-PrOH (vide supra). Like the 2-propoxide compound **4**, the hydroxide compound **8** did not react with H_2 gas (~2 atm, ~22 °C) to generate the dihydride **3′**. Reaction of the hydroxide **8** with ~1 further equiv of *t*-BuOK in THF-d_8 at −60 °C, however, quickly produced a new compound that we formulate as the N···$H_{equatorial}$···O−*t*-Bu− hydrogen-bonded species **9**.[9] This formulation is based upon the similarities between the signals in the NMR spectra of **9** and **8**, except for shifts in the N−H signals for **9**, the largest shift was ~1.6 ppm upfield by a N−$H_{equatorial}$. The analogous compound **10** forms when the 2-propoxide **4** reacts with ~1 equiv of *t*-BuOK in THF-d_8 (Scheme 1). Significant to the catalytic hydrogenation, both compounds **9** and **10** quickly react with H_2 gas (~2 atm H_2, −80 °C, <10 min) to generate the key catalytic intermediate, *trans*-dihydride **3′**, which is stable at low *T* in THF-d_8. Morris et al. reported a tentative observation of **3′** in benzene based upon P and Ru−H NMR signals.[2a] We hypothesize that these hydrogen additions proceed via deprotonation of the hydrogen bonded −N···H···OR^- group in **9** and **10** to effect an intramolecular elimination of the hydroxide or alkoxide ligand, respectively, to form the amide **5** (Scheme 1, middle). The amide **5** then reacts with H_2 to produce **3′**. Although a pathway involving β-H elimination is not ruled out, this hypothesis is supported by the reaction of the hydroxide **8** with ~1 equiv of the stronger, hindered base $((CH_3)_3Si)_2NK$ in the absence of H_2 gas in THF-d_8 at ~ −60 °C (Scheme 1) to immediately form the amide **5**, another intermediate in these catalytic hydrogenations. The amide **5** was stable at low *T* in THF-d_8, but decomposed at room temperature, presumably via β-hydride elimination.[2f] Our identification of **5** is in part based upon comparisons to the model amide Ru((*R*)-BINAP)(H)(NH-$(C(CH_3)_2)_2NH_2$) (**11**), prepared by Morris et al. in benzene.[2a] Consistent with the results we obtained in wet THF, the amide **5** in dry THF-d_8 reacts immediately at −60 °C with H_2O or 2-PrOH (~5 equiv) to completely form the hydroxide **8** or the 2-propoxide compound **4**, respectively (Scheme 1).[10] In contrast, Morris et al. proposed that the corresponding reaction between the amide $Ru(PPh_3)_2(H)(NH(C(CH_3)_2)_2NH_2)$ (**12**) and $Ph(CH_3)CHOH$ is slow, reversible, and does not go to completion. They suggested for this type of equilibrium in 2-PrOH that added base shifts the reaction toward the free amide by decreasing the net acidity the solvent.[2b]

As has been proposed for these and related catalytic hydrogenations, we found that the amide **5** reacts quickly with H_2 (~2 atm H_2, −80 °C, <5 min) to generate the *trans*-dihydride **3′** (Scheme 1).[1d,2a,3a] Reaction of the dihydride **3′** with D_2 in THF-d_8 caused H−D exchange at the Ru−H and the N−H_{axial} groups. Addition of H_2 to the amide **5** is reversible,[2b] and it is the axial N−H's that participate in this exchange. We also found that the dihydride **3′** could also be prepared by reacting the η^2-H_2 compound **2′** with $((CH_3)_3Si)_2NK$ under H_2 in dry THF-d_8.

This report details the first low-temperature syntheses and conclusive characterizations of the illusive intermediates **7**, **5**, **3′**, and a new intermediate, **10**. Our results show that any amide **5** formed during a catalytic hydrogenation will quickly react with the 2-PrOH solvent to form the 2-propoxide **4**. This observation, along with both the facile displacement of the η^2-H_2 ligand in **2′** by 2-propoxide and the reversibility of H_2 addition to **3′**, confirms Morris et al.'s suggestion[2b] from model studies that the formation of **4** is in strong competition with H_2 for the amide **5** during these catalytic hydrogenations. Unlike the suggestion of Morris et al., however, we find the formation of **4** is fast, complete, and not kinetically reversible in the absence of base under our conditions. We propose that adding base increases the rate of these hydrogenations by promoting the base-assisted elimination of 2-propoxide from **4** to form the amide **5** (Scheme 1). It has been proposed that addition of H_2 to the amide **5** to produce **3′** is the turnover limiting step of these hydrogenations carried out in the presence of excess base.[1d,2b] Our direct observations show that H_2 addition to the amide **5** occurs at high rates at −80 °C. We predict, therefore, that this hydrogen addition is turnover limiting in the presence of excess base because the steady-state concentration of **5** is low during the catalytic hydrogenation.

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Supporting Information Available: Experimental procedures and spectral characterization of all species. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931−7944. (c) Ohkuma, T.; Koizumi, M.; Muniz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508−6509. (d) Sandoval, C. A.; Ohkuma, T.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc*. **2003**, *125*, 13490−13503. (e) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288−8289.

(2) (a) Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7473−7474. (b) Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 15104−15118. (c) Rautenstrauch, V.; Hoang-Cong, X.; Churlaud, R.; Abdur-Rashid, K.; Morris, R. H. *Chem.—Eur. J.* **2003**, *9*, 4954−4967. (d) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201−2237. (e) Li, T.; Churlaud, R.; Lough, A. J.; Abdur-Rashid, K.; Morris, R. H. *Organometallics* **2004**, *23*, 6239−6247. (f) Abbel, R.; Abdur-Rashid, K.; Faatz, M.; Hadzovic, A.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 1870−1882.

(3) (a) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc*. **2001**, *123*, 1090−1100. (b) Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, *127*, 3100−3109. (c) Casey, C. P.; Johnson, J. B. *Can. J. Chem.* **2005**, *83*, 1339−1346.

(4) Hedberg, C.; Kallstrom, K.; Arvidsson, P. I.; Brandt, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 15083−15090.

(5) Baratta, W.; Chelucci, G.; Gladiali, S.; Siega, K.; Toniutti, M.; Zanette, M.; Zangrando, E.; Rigo, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 6214−6219.

(6) Hamilton, R. J.; Leong, C. G.; Bigam, G.; Miskolzie, M.; Bergens, S. H. *J. Am. Chem. Soc*. **2005**, *127*, 4152−4153.

(7) All reaction times are approximate. See Supporting Information.

(8) Fulton, J. R.; Holland, A. W.; Fox, D. J.; Bergman, R. G. *Acc. Chem. Res.* **2002**, *35*, 44−56.

(9) For a similar example of H-bonding, see: Fulton, J. R.; Sklenak, S.; Bouwkamp, M. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 4722−4737.

(10) For a similar addition, see: Koike, T.; Ikariya, T. *Organometallics* **2005**, *24*, 724−730.

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