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Experimental Investigations of a Partial Ru−O Bond during the Metal−Ligand Bifunctional Addition in Noyori-Type Enantioselective Ketone Hydrogenation

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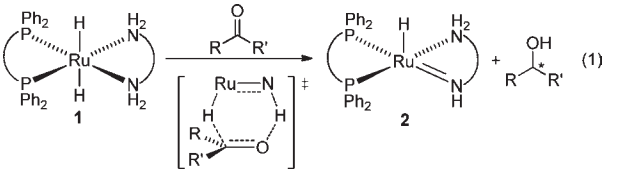
Supporting Information

ABSTRACT: The transition state for the metal−ligand bifunctional addition step in Noyori's enantioselective ketone hydrogenation was investigated using intramolecular trapping experiments. The bifunctional addition between the Ru dihydride *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] and the hydroxy ketone 4-HOCH$_2$C$_6$H$_4$(CO)CH$_3$ at −80 °C exclusively formed the corresponding secondary ruthenium alkoxide *trans*-[Ru((*R*)-BINAP)(H)(4-HOCH$_2$C$_6$H$_4$CH(CH$_3$)O)((*R*,*R*)-dpen)]. Combined with the results of control experiments, this observation provides strong evidence for the formation of a partial Ru−O bond in the transition state.

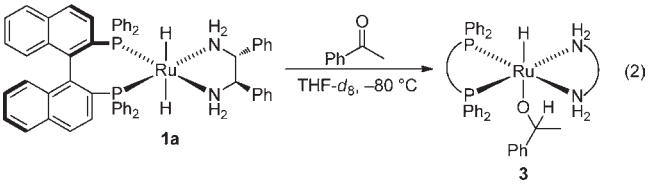
Among the most important advances in enantioselective catalysis is Noyori's discovery of the carbonyl hydrogenation catalyst system *trans*-[Ru(diphosphine)(Cl)$_2$(diamine)] + base.[1] Many bifunctional catalyst systems for asymmetric hydrogenations[2] and transfer hydrogenations[3] have been developed on the basis of this discovery. A wide variety of ketones have been hydrogenated with remarkable activities and enantioselectivities using these catalysts in academia[1c,3b,4] and industry,[5] forming important bioactive compounds.[1b,5] In recent developments, less reactive carbonyl compounds, including esters, imides, and amides, have also been hydrogenated using these catalyst systems.[6] Further, active iron-catalyzed carbonyl hydrogenations and transfer hydrogenations are also being developed.[7,8]

The mechanisms of these hydrogenations are being studied by several research groups using methods that include kinetics of product formation,[9] deuterium exchange studies,[10] computational studies,[11] and stoichiometric reactions of intermediates and model compounds.[12] The prominent feature of these studies is the metal−ligand bifunctional addition, first proposed by Noyori et al.[1b] Specifically, the hydridic Ru−H and the protic N−H in catalysts such as **1** add to the carbon and oxygen, respectively, of the carbonyl group via a six-membered pericyclic transition state to form the product alcohol and Ru amide **2** (eq 1). This step accounts for the high activity and C=O/C=C selectivity of 18-electron species such as **1** toward these hydrogenations. Amide **2** then undergoes addition of dihydrogen to regenerate **1**. Alcohol-assisted variants of this mechanism have been also proposed.[13,11b]



The bifunctional addition between dihydride **1** and the ketone has been studied mostly by means of density functional theory calculations on model compounds such as *trans*-[Ru(PH$_3$)$_2$(H)$_2$(ethylenediamine)][11] and direct experimental studies of related compounds such as Ru(η^6-*p*-cymene)(H)((*S*,*S*)-TsDPEN) [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine][9c,14] *trans*-[Ru((*R*)-BINAP)(H)$_2$(H$_2$NCMe$_2$CMe$_2$NH$_2$)] [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl],[9b,12a] and [2,5-Ph$_2$-3,4-Ar$_2$(η^5-C$_4$COH)]Ru(CO)$_2$H (Ar = Ph, 4-MeC$_6$H$_4$).[9a,15,16] The conclusions of these studies support the bifunctional addition (eq 1).

We recently reported the low-temperature, high-yield preparation and study of the Noyori ketone hydrogenation catalyst *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] (**1a**) (eq 2).[12c] We discovered that the addition between **1a** and 1 equiv of acetophenone was complete upon mixing at −80 °C. Unexpectedly, the products of the addition at −80 °C were not the corresponding Ru amide Ru((*R*)-BINAP)(H)((*R*,*R*)-HNCHPhCHPhNH$_2$) (**2a**) and 1-phenylethanol. Instead, the corresponding Ru alkoxide **3** was formed without an observable intermediate (eq 2).[12d] Alkoxides such as **3** undergo facile base-assisted elimination of the alkoxide ligand at −80 °C to generate amide **2a**. The amide rapidly and reversibly adds H$_2$ to form **1a** at −80 °C. Ru alkoxides have been observed experimentally with related systems,[17,9b] and computational studies have predicted their presence as well.[11a−c,f]



Scheme 1 illustrates the likely pathways for the formation of alkoxide **3**. The first is the conventional bifunctional addition to form amide **2a** and the alcohol, that then rapidly react to form **3**

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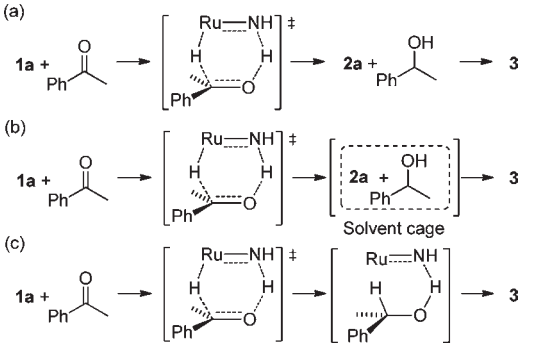
Scheme 1. Possible Mechanisms for the Formation of 3



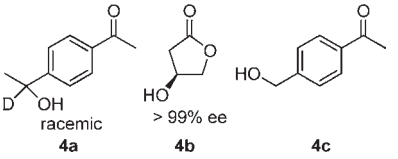


Figure 1. Structures of intramolecular trapping agents.

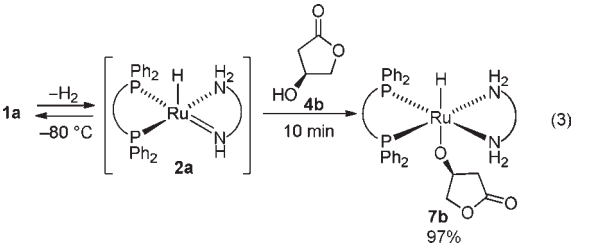
[pathway (a) in Scheme 1]. We note that the addition between **1a** and acetophenone in the presence of excess 2-PrOH as an intermolecular trap formed **3** exclusively.[12d] The result of this intermolecular trapping experiment can be explained if **2a** and 1-phenylethanol are formed within a solvent cage or with a sufficiently strong hydrogen bond between the OH group of the alcohol and the nitrogen of the amide ligand [pathway (b) or (c) in Scheme 1]. Casey proved that a combination of pathways (b) and (c) occurs in the hydrogenation of imines catalyzed by [2,5-Ph_2-3,4-(4-MeC_6H_4)$_2$(η^5-C_4COH)]Ru(CO)$_2$H.[15]

Previously, Casey and Bäckvall reported intramolecular trapping experiments to elucidate the mechanism for hydrogenation of imines catalyzed by [2,5-Ph_2-3,4-Ar_2(η^5-C_4COH)]Ru(CO)$_2$H (Ar = Ph, 4-MeC_6H_4).[15,16] We now report the first such intramolecular trapping experiments for the Noyori ketone hydrogenation to investigate the mechanism of the bifunctional addition with this system.

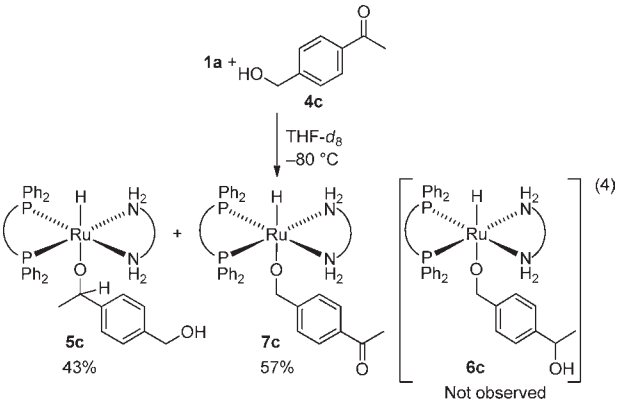
We prepared solutions of Ru dihydride **1a** for this study by reacting mixtures of *trans*-[Ru((*R*)-BINAP)(H)(L)((*R*,*R*)-dpen)]BF_4 (L= η^2-H_2 or THF-d_8), 0.7−1 equiv of KN(Si(CH$_3$)$_3$)$_2$, and H_2 (~2 atm) at −78 °C in THF-d_8 in an NMR tube.[12c] Less than 1 equiv of KN(Si(CH$_3$)$_3$)$_2$ was used in order to avoid the presence of excess base, that can catalyze the elimination of the alkoxide ligand from the Ru alkoxide products.[18] As such base-assisted eliminations are rapid even at −78 °C, they would erase the kinetic regiochemistry of the bifunctional addition.[12c] For the intramolecular trapping experiments, layers of frozen THF-d_8 solutions of the intramolecular trapping agent (top) and dihydride **1a** (bottom) were thawed and mixed under ~2 atm H_2 at −80 °C in a precooled NMR probe.

A series of intramolecular trapping agents were prepared and screened to find a suitable candidate (Figure 1). Consistent with the high activity of **1a** toward the reduction of acetophenone, the trapping agent **4a** rapidly underwent bifunctional addition with Ru dihydride **1a** upon thawing at −80 °C to form the corresponding Ru alkoxide product(s). However, it was impossible to unambiguously identify the product(s) because of overlapping and broad signals in the NMR spectra.

Unexpectedly, the reaction between the hydroxylactone trapping agent **4b** and **1a** resulted in exclusive rapid formation of Ru alkoxide **7b** and H_2 (eq 3). **7b** was characterized by ^{1}H, ^{31}P, ^{1}H−^{13}C gHSQC, and ^{1}H−^{1}H gCOSY NMR experiments. **7b** was produced through reversible formation of amide **2a** from **1a** via the elimination of H_2. As mentioned above, our previous isotope-labeling studies showed that addition of H_2 to **2a** forms **1a** in a rapid and reversible manner at −78 °C. Although the addition is reversible, it strongly favors the dihydride. The reactivity of the lactone carbonyl in **4b** toward the addition with **1a** is lower than that of ketone carbonyls.[6f] The relatively low reactivity at the lactone carbonyl explains why this trapping agent reacted with the small amount of amide **2a** instead of undergoing the expected bifunctional addition.



Conversely, the bifunctional addition reaction between dihydride **1a** and ketone **4c** was rapid upon thawing at −80 °C and formed Ru alkoxides **5c** and **7c** in 43 and 57% yield, respectively (eq 4). This reaction was carried out a total of four times with the same result. *Most importantly, no formation of trapped alkoxide* ***6c*** *was observed.*



The alkoxide **7c** was formed via the same mechanism as discussed for the formation of **7b** (eq 3). Thus, elimination of H_2 from **1a** formed Ru amide **2a**, that rapidly reacted with the alcohol group in the unreduced ketone−alcohol **4c** to form alkoxide **7c**. Despite the rapid nature of the addition of ketone groups to **1a**, more than 50% of **1a** reacted through addition of the primary alcohol trap in **4c** with amide **2a**. This bias toward alcohol addition is explained by two factors. First, sterically less hindered primary alcohols coordinate more strongly than secondary alcohols. Second, primary alcohols are more acidic than secondary alcohols.[19] The formation of **7c** does not impact the mechanism of formation of **5c**, the net Ru−H insertion product. The identities of the Ru alkoxides **5c**, **6c**, and **7c** were determined unambiguously by means of ^{1}H, ^{31}P, ^{1}H−^{13}C gHSQC, and

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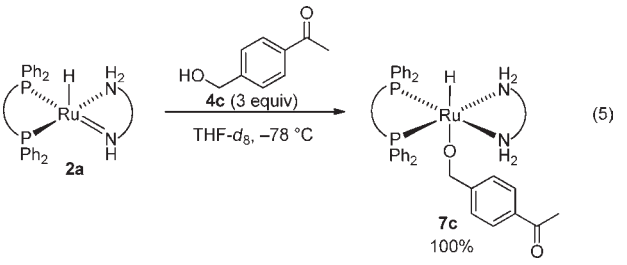
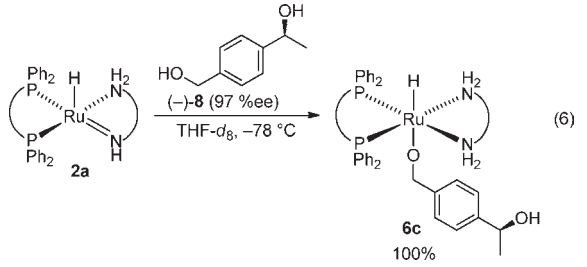
^{1}H−^{1}H gCOSY NMR experiments. Ketone−primary alkoxide **7c** was also prepared independently by the reaction between Ru amide **2a** and **4c** (eq 5).



(5)

In a control competition experiment, Ru amide **2a** and 1 equiv of the diol product (−)-**8** (97% ee) were reacted in THF-d_8 at −78 °C. The (−)-enantiomer was chosen in order to match the major product expected to form upon addition of **1a** and **4c** at −80 °C. We reported that the stoichiometric addition between **1a** and acetophenone at −80 °C in THF-d_8 forms (*S*)-(−)-1-phenylethanol in 83% ee and that the optical rotation of the major enantiomer from hydrogenation of **4c** is (−).[12d] Surprisingly, the reaction of amide **2a** with diol (−)-**8** at −80 °C in THF-d_8 *exclusively* formed **6c**, the product of addition of the primary alcohol group, which was the species that was *not* formed by the bifunctional addition of **4c** to **1a** (eq 6).

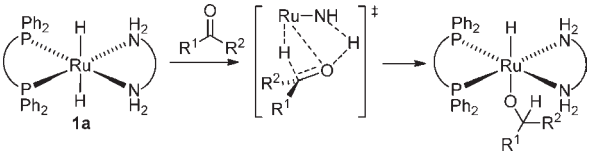


(6)

As discussed above, the high selectivity toward the formation of the primary alkoxide is explained by the higher acidity and lower steric crowding of the primary alcohol. Thus, there exists a strong bias toward the formation of primary alkoxide **6c** over secondary alkoxide **5c** in this reaction. Therefore, if amide **2a** and diol **8** were formed within a solvent cage during the bifunctional addition between dihydride **1a** and alcohol−ketone **4c**, primary alkoxide **6c** should have been formed form as a major product as a result of molecular tumbling within the solvent cage. The exclusive formation of secondary alkoxide **5c** upon addition between **1a** and **4c** is conclusive evidence that the reaction path via the formation of the free amide and diol within a solvent cage (Scheme 1b) does *not* operate during the addition of **4c** to **1a** under these conditions.

On the basis of these intramolecular trapping experiments, the closest fit among the pathways for the bifunctional addition shown in Scheme 1 is (c), that proceeds via the formation of a hydrogen bond between the amide nitrogen in **2a** and the secondary alcohol proton in the product that is sufficiently strong to prevent the formation of the favored primary alkoxide **6c** (Scheme 1c). Formation of such a hydrogen bond must be associated with diminished π donation from the amide nitrogen to Ru, thereby resulting in coordination unsaturation at Ru. Further, this hydrogen bond results in a partial negative charge on oxygen. Such coordination unsaturation would promote the formation of a Ru−O bond during the addition. The interaction

Scheme 2. Proposed Transition State with a Partial Ru−O Bond



between the carbonyl carbon and the hydride on Ru has an electrophilic component that is promoted by hydrogen bonding between the N−H group and the carbonyl oxygen. Thus, the interaction is similar to addition of CO_2 to an 18-electron metal hydride and alkyl. We note that Darensbourg has established a precedent for partial metal−oxygen bond formation during the electrophilic attack of CO_2 on 18-electron metal−alkyl complexes.[20] Further, this pathway is one of those proposed for the Ru(H)$_2$(phosphine)$_4$-catalyzed hydrogenation of CO_2.[21] For example, Perutz reported that addition between *cis*-[Ru(H)$_2$(Me$_2$PCH$_2$CH$_2$PMe$_2$)$_2$] and CO_2 at −50 °C quickly formed the corresponding Ru carboxylate products in toluene-d_8 without dissociation of the diphosphine ligands.[21a] It is therefore reasonable to propose a transition state that contains a partial Ru−O bond during the bifunctional addition of ketones to **1a** (Scheme 2).

A continuum between pathway (c) in Scheme 1 and the pathway in Scheme 2 is likely the current best description of the metal−ligand bifunctional addition. The strength of the partial Ru−N double bond (Scheme 1) and Ru−O bond (Scheme 2) depends on the particulars (ligand structure, solvent, substrate, etc.) of each hydrogenation system. A similar conclusion has been drawn for the mechanisms of late transition metal-catalyzed C−H bond activation, which has been proposed to proceed via a continuum between σ-bond metathesis and an oxidative addition/reductive elimination sequence.[22]

In conclusion, this paper presents the first intramolecular trapping experiments to elucidate a reaction mechanism for the formation of Ru alkoxides in Noyori carbonyl hydrogenations. The results prove that the solvent cage mechanism [pathway (b) in Scheme 1] is not operative during the addition between **1a** and **4c** under these conditions. Thus, the current most probable mechanisms are those involving the formation of a sufficiently strong hydrogen bond between amide **2a** and the product alcohol [(c) in Scheme 1] and/or the concerted formation of Ru alkoxides (Scheme 2).

■ ASSOCIATED CONTENT

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

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(18) The yield of **1a** was 70−80% when prepared under these conditions. The remaining Ru species consisted of small amounts of decomposition side products that formed during the steps required to prepare **1a** along with the Ru hydroxide compound *trans*-[Ru((*R*)-BINAP)(H)(OH)((*R*,*R*)-dpen)] formed from trace amounts of water.[12c]

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