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Base-Catalyzed Bifunctional Addition to Amides and Imides at Low Temperature. A New Pathway for Carbonyl Hydrogenation.

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ABSTRACT: Mono- or di-deprotonation at the N-H groups of the Noyori ketone hydrogenation catalyst *trans*-[RuH_2((*R*)-BINAP)((*R*,*R*)-dpen)] (**1a**) yields *trans*-M[RuH_2((*R*,*R*)-HNCHPhCHPhNH$_2$)((*R*)-BINAP)], where M = K^+ (**8-K**) or Li^+ (**8-Li**), or *trans*-M_2[RuH_2((*R*,*R*)-HNCHPhCHPhNH)((*R*)-BINAP)] where M = Li^+ (**8-M'$_2$**) that have unprecedented activity towards the hydrogenation of amide and imide carbonyls at low temperatures in THF-d_8. Details into the origins of the enantioselection for the desymmetrization of *meso*-cyclic imides by hydrogenation with **8-K** are also described herein.

INTRODUCTION

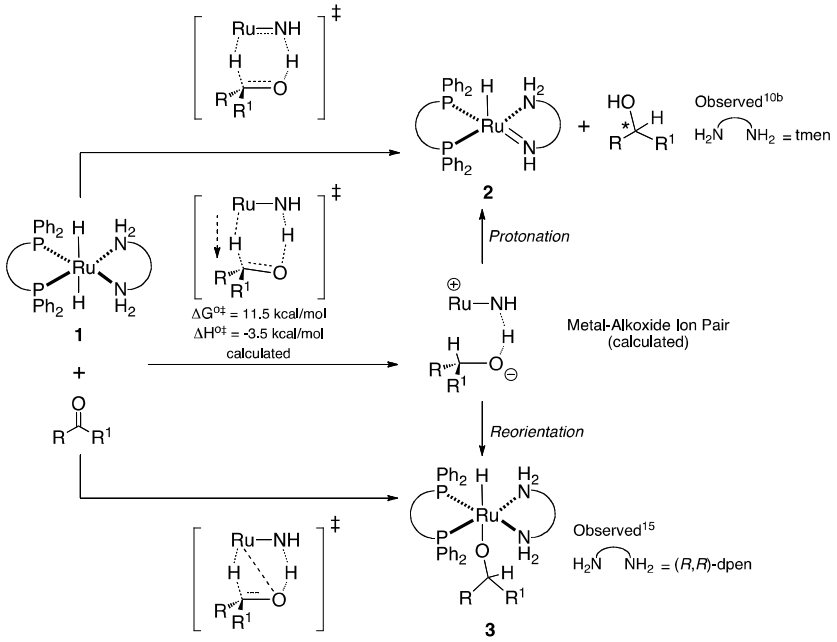
The catalytic hydrogenation of carboxylic acid derivatives such as imides, esters, and amides is a key, emerging class of sustainable chemistry. These hydrogenations will likely replace the use of stoichiometric, wasteful aluminum- and boron-hydrides for industrial-scale carbonyl reductions because they typically produce only the desired product and excess hydrogen gas that can simply be recycled, or burned to provide energy and water.[1] Hydrogenations of imides, esters, and amides have historically required impractical temperatures, pressures, times, and catalyst loadings to overcome the low reactivity of their carbonyl groups.[2] There is, however, a revolution underway in catalytic hydrogenation. Within the last decade, there have been numerous reports of catalysts that hydrogenate esters,[2b, 3] imides,[4] imines,[5] nitriles,[6] and even amides[3d, 7] with high turnover numbers and rates under practical conditions. Curiously, the reported systems tend to be most active in THF solvent and often in the presence of high ratios of base to catalyst. A handful of systems are active in the absence of base in THF.[2b, 3b, 8] Most of these catalysts operate by the ligand-assisted bifunctional addition.

Noyori's discovery of the bifunctional addition to ketones is a landmark moment in the history of asymmetric catalysis because it made available the first practical methodology to enantioselectively hydrogenate ketones in high yields for use in synthesis of pharmaceuticals, insecticides, flavors, and fragrances.[9] The parent system for bifunctional ketone hydrogenations are mixtures of *trans*-[$RuCl_2$(diamine)(diphosphine)] and base that react to form *trans*-dihydrides, such as **1** (Scheme 1), as the active catalyst. The ligand-assisted bifunctional addition was first proposed to proceed with a nucleophilic hydride on ruthenium, and a protic hydrogen on nitrogen, that add in a concerted manner to the carbon and oxygen of the carbonyl group to form the product alcohol and the Ru-amide, **2** (Scheme 1, top).

The pathways for these bifunctional additions have been heavily studied with model systems,[10] isotope studies,[11] product-forming kinetics,[12] trapping experiments,[13] and calculations.[14] We recently reported a solvent-cage, intramolecular trapping NMR study that shows that the bifunctional addition of an aryl-alkyl-ketone to *trans*-[RuH_2((*R*)-BINAP)((*R*,*R*)-dpen)], (**1a**) [BINAP: 2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl, dpen: 1,2-diphenyl-ethylenediamine] forms the ruthenium-alkoxide, **3**, without formation of product alcohol and the corresponding Ru-amide as intermediates upon thawing at −80°C .[15] This experiment was biased towards scrambling of the free Ru-amide **2** and alcohol, even in a solvent cage on timescales faster than NMR, as such, it is strong evidence that they *are not* the products of this addition under these conditions. An analogous Os-alkoxide was isolated by Bertoli *et al*,[10e] and alkoxides were observed or proposed to form with other bifunctional systems.[16] Our group has also observed analogous Ru-alkoxides as products for rapid addition reactions between **1a** and ketones,[17] and lactones at low temperatures.[3e] Based on the unexpected result from our intramolecular trapping study, we proposed a transition state that contains a partial Ru-O bond rather than a partial Ru=N bond as described in the original mechanism (Scheme 1, bottom).[15] A recent computational study on the addition of acetophenone to the catalyst model *trans*-[RuH_2(1,2-bis(phosphino)ethane)(ethylenediamine)] concluded that the reaction proceeds via a stepwise pathway, with a rate-limiting hydride transfer from Ru to the hydrogen bonded carbonyl to form a metal-alkoxide ion pair with the alkoxide hydrogen bonded to a N-H group in the Ru cation ($\Delta G^{\circ\ddagger}$ for the addition = 11.5 kcal/mol, $\Delta H^{\circ\ddagger}$ = -3.5 kcal/mol) (Scheme 1, middle). This species then either undergoes proton transfer from a N-H group to the alkoxide to form **2** and the alcohol, or the alkoxide undergoes a simple rotation to form the model coordinated alkoxide **3**.[14n] The pathway forming **3** is consistent with our experimental observations on the catalyst system. Similar results were obtained from a computational study on the addition of acetone or acetophenone to (*S*)-[RuH((*R*,*R*)-OCH(Ph)CH(Ph)NH$_2$)(η^6-C_6H_6)] and (*S*)-[RuH(η^6-$(CH_3)_3C_6H_3$)((*R*,*R*)-Tsdpen)] [Tsdpen: (1R,2R)-(-)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine].[14o] More refined experiments and calculations will provide further insights into the mechanism of these additions.

Aided by mechanistic understandings,[17] we recently developed the first enantioselective desymmetrization of *meso*-cyclic imides via monohydrogenation (eq. 1).[4c] For example, the

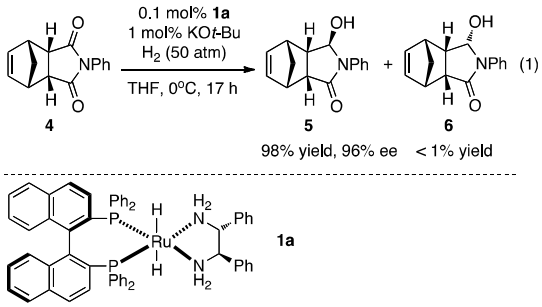
monohydrogenation of the *endo meso*-cyclic imide **4** by **1a** formed the *trans*-hydroxy lactam **5** with five new stereogenic centres in 96% *ee* (eq. 1). We now report a mechanistic investigation on this desymmetrization that uncovers a new, highly facile *base-catalyzed* bifunctional addition to imide- and amide-carbonyl groups at low temperatures.



Scheme 1. Proposed mechanisms for the Bifunctional Addition

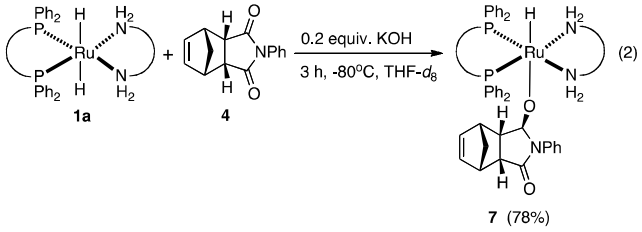
RESULTS AND DISCUSSION

We prepared the Ru-dihydride **1a** in the rigorous absence of water and excess inorganic base by reacting mixtures of *trans*-[RuH(*L*)((*R*)-BINAP)((*R*,*R*)-dpen)]BF_4 ($L=\eta^2$-H_2 *or* THF-d_8) with 0.9 equiv. of $KN[Si(CH_3)_3]_2$ or KO*t*-Bu as base under H_2 (~2 atm) at −78°C in THF-d_8.[17b] All the reactions reported in this paper are carried out in THF-d_8, unless reported otherwise. Less than 1 equiv. of base was used to ensure that no residual base remained after the formation of **1a**. These preparations form mixtures of **1a**, the conjugate acids $HN[Si(CH_3)_3]_2$ or HO*t*-Bu (depending on which base was used), and KBF_4 (0.9 equiv. each).



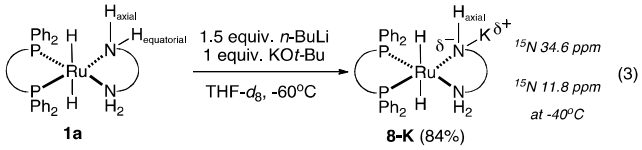
The stoichiometric addition reaction between **1a** and the *meso*-cyclic imide **4** only formed small amounts of what appeared to be catalyst decomposition after ~ 3.3 h at −60°C. Further warming resulted in more decomposition. To our surprise, the addition between **1a** and **4** *does* occur in the presence of *catalytic* amounts of KOH (0.2 equiv. relative to Ru and imide substrate) at −80°C to give the alkoxide **7** as the major product in 78% yield after 3 h (eq. 2).

There are no prior reports of a *base-catalyzed bifunctional addition*. This is the first observed instance of base promoting the activity of the fully hydrogenated catalyst in a carbonyl reduction. To investigate this unexpected phenomenon, we reacted 1 equiv. of anhydrous KOH with the imide **4** at −80°C, but observed, no net reaction.[18] Similarly, no net reaction was observed between **1a** and either KOH, or excess $KN[Si(CH_3)_3]_2$ (>1.0 equiv. relative to Ru), in the presence of the conjugate acid $HN[Si(CH_3)_3]_2$ at −80°C. Further, the reaction between $KN[Si(CH_3)_3]_2$ and **4** lead to mixtures of unidentified species that also did not react with **1a** at −80°C.



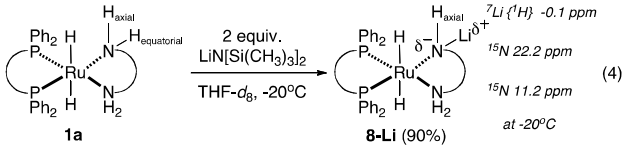
These observations do not exclude a reversible reaction between **1a** and base that lies to the side of the dihydride. To explore this possibility, we employed a variant of Schlosser's base,[19] prepared by reacting a mixture of **1a**, HO*t*-Bu, and KBF_4 with a mixture of *n*-BuLi and KO*t*-Bu (2.5 and 1.0 equiv. respectively) to form a new intermediate, the *trans*-Ru-dihydride amidate, **8** (Figure 1) in 84% yield at −60°C (eq. 3). This is the first experimental observation of such a species in a carbonyl hydrogenation. The Ru-amidate (**8**) resulted from the deprotonation of one of the protic N-H groups in the dpen ligand. **8** was not isolatable, but was fully

characterized at −80°C in anhydrous THF-d_8 using ^{1}H, ^{31}P{^{1}H}, ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC, TOSCY and TROESY NMR experiments. The signals for all three N-H's were identified in the ^{1}H NMR spectrum, with the N-H$_{amidate}$ at δ 0.22 ppm, N-H$_{axial}$ at δ 2.8 ppm, and N-H$_{equatorial}$ at δ 2.9 ppm. The amidate ligand is best described as singly-bonded to the coordinatively saturated ruthenium center in **8**, with the lone pair on nitrogen in an equatorial disposition and coordinated to the cation, which is likely potassium *i.e.* **8-K**.[20] Based upon kinetic studies, Chen *et al* proposed in 2001 that a similar species forms during ketone hydrogenations. Specifically, they proposed that an axial, cation-selective binding site (*e.g.* K^+ over Li^+) allows deprotonation of an axial N-H in **1a** to form **8-K$_{axial}$**, which differs from the equatorial disposition we observe in **8-K**. In a manner related to the original pathway for the bifunctional addition, the addition of a ketone to **8-K$_{axial}$** was proposed to form the product alkoxide ionically bonded to K^+ which was also bonded to the nitrogen in the Ru-amide (**2**). This species would react with H_2 to regenerate **8-K$_{axial}$** and the product alcohol faster than **2** reacts with H_2 to form **1a**.[21] Subsequent studies were unable to confirm this pathway.[10b, 12a] It is unlikely that activation of hydrogen is the slow step in imide or amide hydrogenations.



(3)

Although detectable amounts of **8-K** were not observed in the NMR of a mixture of **1a** with KN[Si(CH$_3$)$_3$]$_2$ and HN[Si(CH$_3$)$_3$]$_2$ (1.5 and 1.0 equiv. respectively), we reasoned that the lithium salt, LiN[Si(CH$_3$)$_3$]$_2$ would deprotonate **1a** to a further extent, as the conjugate base **8** would be stabilized by the coordination of lithium to the free lone pair in the amidate ligand. Indeed, reacting a 1:1:1 mixture of **1a**, HN[Si(CH$_3$)$_3$]$_2$, and LiBF$_4$ with 2.0 equiv. LiN[Si(CH$_3$)$_3$]$_2$ forms the lithium adduct **8-Li** in 90% yield at −20°C (eq. 4). This compound was also not isolatable, but was fully characterized in solution at −20°C with the same NMR experiments used to characterize **8-K**.



(4)

The ^{1}H NMR signals for the amidate, axial, and equatorial N-H's of **8-Li** at −20°C were δ −0.2 ppm, δ 2.5 ppm, and δ 2.6 ppm respectively. Figure 1 compares the most significant regions of the ^{1}H and ^{31}P{^{1}H} NMR spectra for the *trans*-Ru-dihydrides **1a**, **8-K**, and **8-Li**. There are two signals for the inequivalent phosphorous centers in the ^{31}P{^{1}H} NMR of **8-K** and **8-Li**. Each species has one signal with a chemical shift similar to that of **1a**, and another shifted upfield by 7.0-9.0 ppm. One of the hydride signals in *trans*-Ru-amidate **8-K** overlaps with the Ru-hydride signal of **1a**, while the other is shifted upfield by 1.1 ppm to δ –6.1 ppm. TROESY experiments show a negative ROE correlation between the signals at δ –6.1 ppm for the hydride and at δ 0.2 ppm for the N-H$_{amidate}$. Thus, the signal at δ –6.1 ppm is definitively from the Ru-hydride adjacent to the N-H$_{amidate}$, and it is very likely that the amidate N-H in **8-K** is axially oriented in the deprotonated dpen moiety. We had previously reported evidence that KO*t*-Bu forms a hydrogen bond with the N-H$_{equatorial}$ of the Ru-alkoxide *trans*-[RuH(2-PrO)((*R*)-BINAP)((*R*,*R*)-dpen)].[17b] Therefore, these observations combined, suggest that the equatorial N-H's in coordinated dpen are either more accessible and/or more acidic than the axial N-H's.

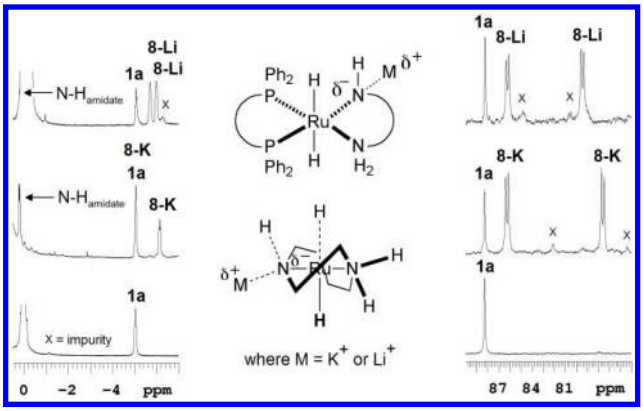
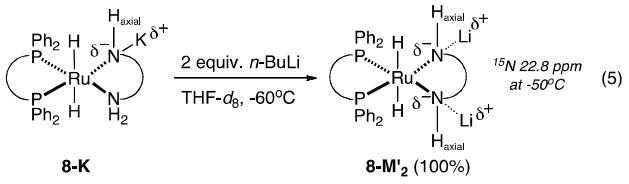


Figure 1. Comparison of the δ 0.5 to δ −7 ppm ^{1}H (left) and δ 90 to δ 75 ppm ^{31}P{^{1}H} (right) NMR spectra for the *trans*-Ru-dihydrides **1a** (bottom), **8-K** (middle) and **8-Li** (top)

The Ru-hydride signals in **8-Li** are slightly shifted from those of **8-K**. The upfield signal for the Ru-hydride adjacent to the N-H$_{amidate}$ in **8-Li** was comparable to that of **8-K**. However, the Ru-hydride next to the NH$_2$ group in **8-Li** is at –5.5 ppm, ~0.5 ppm upfield from those in the neutral dihydride, **1a**. These subtle differences in ^{1}H NMR show that Li^+ is coordinated to the lone pair on the N-H$_{amidate}$ in **8-Li**. Unlike, **8-K**, however, no ROE correlations could be observed between the N-H$_{amidate}$ adjacent to the Ru-hydride in **8-Li**. Thus, the orientation of the N-H$_{amidate}$ could not be unambiguously assigned. Similarities between the ^{1}H and ^{31}P{^{1}H} NMR data of **8-K** and **8-Li**, and the smaller size of Li^+ compared to that of K^+, lead us to propose that the N-H$_{amidate}$ in **8-Li** is axial. Although there are several reports of neutral, 18-electron compounds containing singly-bonded amide ligands (*i.e.* Ru-NH$_2$) in the literature,[22] compounds **8-K** and **8-Li** are to our knowledge, the first characterized examples of late transition-metal singly-bonded K- and Li-amidates.

Remarkably, we found that adding 2 equiv. *n*-BuLi to **8-K** at −60°C resulted in a *second deprotonation*, to form the *trans*-dihydride-diamidate (**8-M'$_2$**, M' = K or Li) in quantitative yield (eq. 5, Figure 2).



(5)

This compound was fully characterized in solution at −50°C using the same NMR experiments used to characterize **8-K** and **8-Li**. The $^{31}P\{^{1}H\}$ NMR of **8-M'$_2$** consisted of a singlet at δ 76.8 ppm. The C_2-dissymmetrical nature of the compound resulted in equivalent hydride, N-$H_{amidate}$ and C*H*(Ph) signals located respectively at δ −6.6 ppm, δ −0.15 ppm and δ 2.9 ppm in the ^{1}H NMR. TROESY NMR experiments showed significant ROE correlations between the Ru-hydrides and amidate N-H's, and C*H*(Ph) signals. Thus, the amidate N-H's in **8-M'$_2$** are axially oriented with respect to the Ru-hydride, and the coordinating metals occupy equatorial positions (Figure 2). We could not unambiguously assign the identity of **M'**. We propose that the coordinating metal is Li^+ due to its higher stoichiometric ratio and its stronger Lewis acidity.

We utilized ^{1}H-^{15}N HSQC NMR to gather information on the different nitrogen environments in these compounds in an attempt to identify the cation in **8-M'$_2$**. The $^{15}NH_2$ and $^{15}N^{-}H$ chemical shifts for **8-K** were 11.8 and 34.6 ppm at –40°C, respectively, while those for **8-Li** were 11.2 and 22.2 ppm at –20°C. The ^{15}N data for **8-M'$_2$** was 22.8 ppm at −50°C. The similarity between the $^{15}N^{-}H$ chemical shifts in **8-Li** and **8-M'$_2$** support the assignment of **M'$_2$** as Li^+.[23]

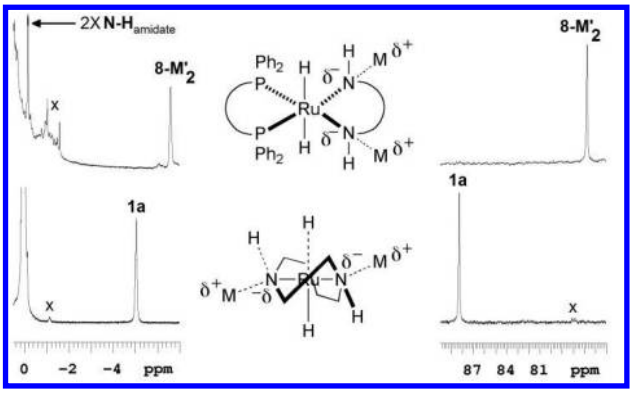
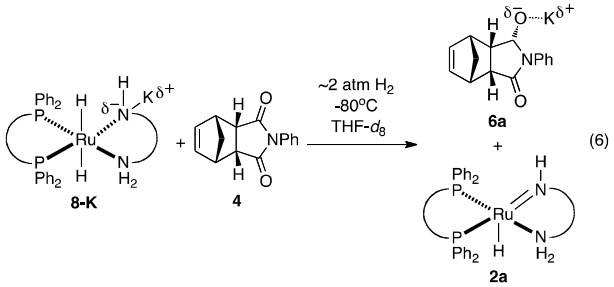
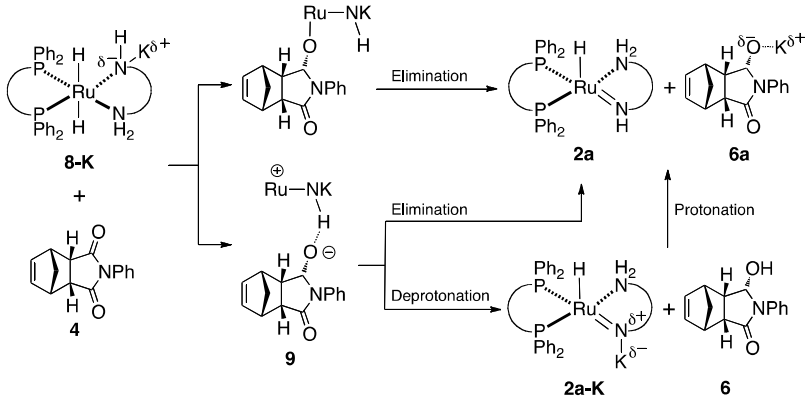


Figure 2. Comparison of the δ 0.5 to δ −7 ppm ^{1}H (left) and δ 90 to δ 75 ppm $^{31}P\{^{1}H\}$ (right) NMR spectra for the trans-Ru-dihydrides **1a** (bottom), and **8-M'$_2$** (top)

Unlike the slow decomposition reaction between the *meso*-cyclic imide **4** and the neutral dihydride **1a**, the addition of **4** to **8-K** was *complete* on mixing at −80°C. Unexpectedly, the products of the addition were the Ru-amide [RuH((*R*,*R*)-NH(CH(Ph))$_2$NH$_2$)((*R*)-BINAP)], **2a**, and the potassium alkoxide of the *cis*-hydroxy lactam, **6a** (eq. 6). This is a hitherto unobserved, active pathway for the bifunctional addition. We believe that **8-K** is dramatically more active than **1a** because the amidate group increases the electron density at the Ru-center, making the hydride ligand more nucleophilic towards the imide carbonyl group.

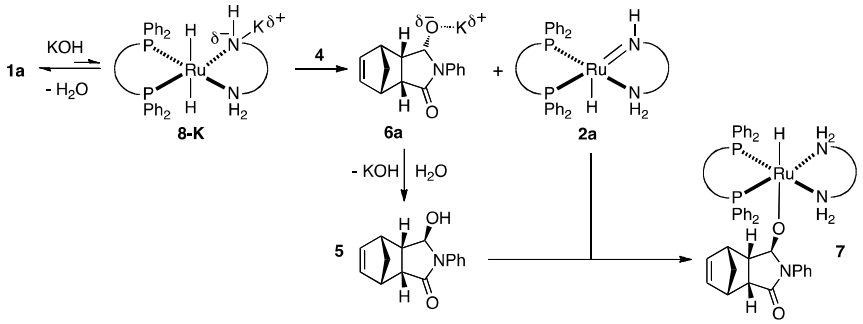


We reported previously that the additions of ketones and lactones to **1a** generate the corresponding Ru-alkoxide, as does the KOH-catalyzed addition of **4** to **1a** at −80°C (*vide supra*). We also showed that the Ru-2-propoxide, *trans*-[RuH(2-PrO)((*R*)-BINAP)((*R*,*R*)-dpen)], and related compounds are inactive towards ketone hydrogenations in the absence of base under our conditions.[17b] These Ru-alkoxide compounds do, however, undergo a *base-assisted elimination* reaction where, an N-H group in the dpen ligand is deprotonated, and 2-propoxide is eliminated to generate the Ru-amide, **2a**. If the product of the addition of **4** to **8-K** is the Ru-alkoxide corresponding to those we observed for the additions of ketones and esters to **1**,[17b] such a species would be predisposed to undergo this elimination to form the alkoxide **6a** and **2a** (Scheme 2, top). If the addition proceeds by rapid hydride transfer to form the corresponding alkoxide ion pair, **9**, (Scheme 2, middle) this species presumably can also eliminate the alkoxide **6a** to form **2a**. Alternatively, the alkoxide in **9** can deprotonate the N-H group to form the alcohol and the potassium amide **2a-K** (Scheme 2, bottom). Proton transfer forms the observed product mixture. These additions could also proceed with K^+ directly involved in the bifunctional addition, as proposed by Chen and co-workers for the addition of ketones to **8-K$_{axial}$** (via **8-K** rearrangement). A sequence of steps analogous to those in Scheme 2 would form the observed products.



Scheme 2. Possible pathways for the formation of **2a** and **6a** from **8-K**

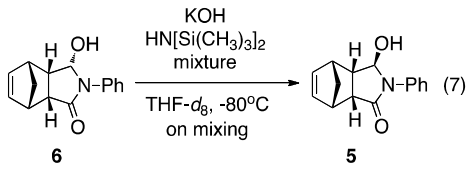
The addition of the imide **4** to **8-Li** is slower than the corresponding potassium analogue, **8-K**, but still forms the Ru-amide **2a** and the lithium alkoxide of the *cis*-hydroxy lactam (**6b**) in ~8% yield after 15 min at −60°C. The excess $LiN[Si(CH_3)_3]_2$ (2.0 equiv. relative to **1a**) also resulted in some decomposition of **4**. It is well established that Li^+ forms stronger adducts to N-containing bases than K^+. Thus the Ru center in **8-K** is more electron rich, and thereby the hydride ligands are more nucleophilic than those in **8-Li**.



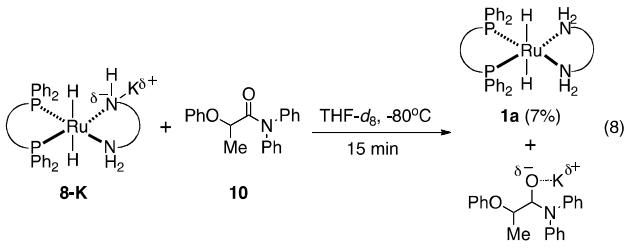
Scheme 3. Mechanism for the formation of **7** from **1a** catalyzed by KOH

The KOH-catalyzed addition of **4** to **1a** likely proceeds by the reaction of **4** with small amounts of **8-K** that would be present in solutions of **1a** and KOH. This addition forms the Ru-amide, **2a**, and the potassium salt of the mono-reduced product **6a**. **6a** would then react with the conjugate acid (H_2O) to form the *trans*-hydroxy lactam **5** and regenerate KOH (Scheme 2). To complete the pathway, we carried out control experiments that showed that the *trans*-hydroxy lactam **5** adds on mixing at −80°C to the Ru-amide **2a** to form the *trans*-Ru-alkoxide (**7**), which is the product of the KOH-catalyzed addition.

We note that the kinetic product of the hydrogenation is the *cis*-hydroxy lactam (**6**) formed by addition to the least-hindered, convex face of the imide carbonyl in **4**. The *trans*-alcohol **5**, however, is the favored thermodynamic product. We carried out control experiments that show the rapid *cis*-(**6**) to *trans*-(**5**) isomerization is catalyzed by KOH in THF-d_8 at −80°C, thereby explaining the formation of the *trans*-alkoxide, **7** as the observed product from the addition of **4** to **1a** catalyzed by KOH (eq. 7, Scheme 3).



Upon further investigation of this new pathway for the bifunctional addition, we found, remarkably, that **8-K** underwent the addition reaction with the *amide*, N, N′-diphenyl-2-phenoxypropionamide (**10**) starting at −80°C in THF-d_8 (eq. 8). The net products of the addition were the neutral dihydride **1a** (formed by the reaction of the Ru-amide, **2a**, with excess H_2) and a mixture of organic potassium salts. Hydrolysis of these salts with excess 2-propanol-d_8 forms the product alcohol and amine from the complete reduction of the α-chiral amide via C-N cleavage.[24] It is noteworthy that no deuterium incorporation was observed in the α-position of the product alcohol, showing that **8-K** did not simply deprotonate the amide **10** to form **1a** under our conditions. Consistent with our previous observations, the *trans*-Ru-dihydride-amidate, **8-Li** was somewhat less reactive towards **10** than **8-K**, undergoing the addition starting at −60°C.



We reported that the catalytic desymmetrization-hydrogenation of **4** by **1a** (0.1 mol% Ru, 1.0 mol% KO*t*-Bu, 0°C, 50 atm, 17 h) generates the *trans*-hydroxy lactam **5** in 96% *ee* and 98% yield under mild conditions (eq. 1)].[4c] Our control experiments show that KO*t*-Bu catalyzes the addition of **4** to **1a** at −80°C, but also undergoes a slow decomposition reaction with the substrate **4** shown above with K- and Li-$N[Si(CH_3)_3]_2$. Thus, during the catalytic desymmetrization-hydrogenation, a portion of the KO*t*-Bu is consumed by reaction with **4**, and some is converted into KOH by reaction with the residual H_2O in the system. The KOH then acts as the co-catalyst for the hydrogenation. To confirm this scenario, we carried out control experiments that showed that the *ee* and absolute configuration of the stoichiometric addition of **4** to **1a**, carried out in the presence of added trace water, were the same as the catalytic hydrogenation reaction.

We determined the absolute configuration of the major enantiomer of **5** with X-ray crystallography. This determination shows that the major enantiomer of the hydrogenation results from addition to the convex face of the *S*-side enantiotopic carbonyl (all stereogenic centres on the norbornene backbone adopt the *S* configuration upon reduction) of **4**, as shown in Figure 3. The unique combination of the structural and conformational rigidity of **4** and **1a**, the requirement for addition to the convex face of the enantiotopic *S*-side carbonyl, and the published studies of the enantioselection of aryl ketones to **1a**, make the origins of enantioselection for

these hydrogenations readily apparent. Specifically, the new reaction pathway proceeds through bonding interactions between the carbonyl, Ru-H, and the axially orientated N-$H_{amidate}$ of the *trans*-deprotonated dihydride (**8-*M*** where *M* = K^+ or Li^+). Figure 3 represents the stereoelectronic consequences for this addition to the convex faces of the *S*-side ($\mathbf{TS_A}$) and *R*-side ($\mathbf{TS_B}$) carbonyls of **4**.

Inspection of molecular models shows that the *N*-phenyl group projects deeply into the spatial domain of the BINAP ligand, resulting in strong steric repulsions in $\mathbf{TS_B}$ (Figure 3). The *endo*-geometry of **4**, and the addition to the convex face of the *S*-side carbonyl, result in no appreciable steric crowding in $\mathbf{TS_A}$. Further, the geometry of $\mathbf{TS_A}$ allows for the stabilizing $NH_{equitorial}$-π attraction, by lone equatorial N-H in the deprotonated dpen moiety.[25] This simple, well-defined model thereby explains the high preference for addition to the *S*-side of **4**. Addition to the other Ru-H in **8** is also possible, which would replace the N-H-π interaction by a N-K^+-π interaction, but the same steric forces would form the same major enantiomer.

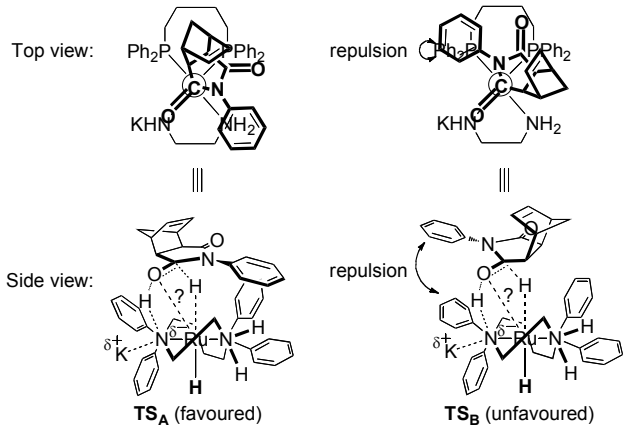


Figure 3. Possible geometries for the addition between **8-X** (where X = K or Li) and **4**

CONCLUSIONS

These studies revealed the first intermediates in the hydrogenations of imides and amides, as well as a facile, new base-catalyzed pathway for the bifunctional addition mechanism to unreactive carbonyls. Deprotonation of the dihydride **1a** gives rise to electron-rich species with unprecedented reducing power towards organic carbonyls, including carboxylic acid derivatives. We believe such deprotonations are a key feature in our amide, ester and imide hydrogenations (and others with high base to catalyst ratios) and will in principle, lead to more powerful catalysts from most bifunctional catalysts with a coordinated N-H group, or with an acidic group that is in conjugation with an unsaturated nitrogen ligand. The high enantioselectivity of the desymmetrization of imides by monohydrogenation was explained using simple and well-defined models based on current literature and the results of these investigations. A combination of NMR rate measurements (to obtain activation parameters), isotope labeling, and trapping studies, with computational studies will provide further insights into the mechanism of these additions. We are currently exploring such experimental studies and the use of the variants of **8** as catalysts for the hydrogenation of less reactive carboxylic acid and carbonic acid derivatives.

EXPERIMENTAL SECTION

Stoichiometric Reactions. Experimental details are found in the Supporting Information.

ASSOCIATED CONTENT

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

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(18) We first reacted the dihydride **1a** with the standard substrate for these hydrogenations, acetophenone in the rigorous absence of water and base at −80 °C. The addition occurred rapidly to the alkoxide, *trans*-[RuH((Ph)(Me)CHO)((*R*)-BINAP)((*R*,*R*)-dpen)]. This result is consistent with our previous findings. Reference 16 (b).

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(23) Unfortunately, no useful information could be gathered from the $^7Li\{^1H\}$ NMR of **8-M'$_2$** owing to the presence of numerous lithium species in the reaction mixture. The $^7Li\{^1H\}$ NMR of **8-Li**, however, was obtained at –20°C and consists of a singlet at –0.1 ppm.

(24) Aldehyde was not observed in the worked-up reaction mixture. We attribute this to its facile reduction by the Ru-dihydride, **1a**, at higher temperatures.

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