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Mechanism of Asymmetric Hydrogenation of Acetophenone Catalyzed by Chiral η^6-Arene–*N*-Tosylethylenediamine–Ruthenium(II) Complexes

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Abstract: Chiral arene–*N*-tosylethylenediamine–Ru^{II} complexes can be made to effect both asymmetric transfer hydrogenation and asymmetric hydrogenation of simple ketones through a slight functional modification and by switching reaction conditions. $[Ru(OSO_2CF_3)\{(S,S)\text{-TsNCH-}(C_6H_5)CH(C_6H_5)NH_2\}(\eta^6\text{-}p\text{-cymene})]$ catalyzes the asymmetric hydrogenation of acetophenone in methanol to afford (*S*)-1-phenylethanol with 96% *ee* in 100% yield. Like the transfer hydrogenation catalyzed by similar Ru catalysts with basic 2-propanol or a formic acid/triethylamine mixture, this hydrogenation proceeds through a metal–ligand bifunctional mechanism. The reduction of the C=O function occurs via an intermediary 18e RuH species in its outer coordination sphere without metal–substrate interaction. The high catalytic efficiency relies on the facile ionization of the Ru triflate complex in methanol. The turnover rate is dependent on hydrogen pressure and medium acidity and basicity. The RuCl analogue can be used as a precatalyst, albeit less effectively. Unlike the well-known diphosphine–1,2-diamine–Ru^{II}-catalyzed hydrogenation that proceeds in a basic alcohol, this reaction takes place under slightly acidic conditions, creating new opportunities for asymmetric hydrogenation.

Keywords: asymmetric catalysis · homogeneous catalysis · hydrogenation · reaction mechanisms · ruthenium · transfer hydrogenation

Introduction

The principle of "practical elegance" should always be pursued in developing chemical synthesis.[1] In this regard, the development of efficient asymmetric hydrogenation (AH) continues to be an important and substantial challenge in modern chemistry.[2] Despite the tremendous efforts made to discover useful AH catalysts, there still remains much potential for the continued development of these reactions. In fact, only a limited number of truly efficient catalysts have been found. Furthermore, because of the structural and functional diversity of unsaturated organic compounds, no universal catalysts exist.

So far AH catalysts have been discovered largely by coincidence, trial-and-error approaches, and combinatorial screening of various chiral transition-metal complexes. However, the notion of "molecular catalysis" provides a logical way to search for efficient AH reactions, because any molecule, by definition, can be designed and synthesized at will. The only necessary condition toward this goal is to acquire reliable, detailed knowledge of the reaction mechanism.[3] A well-designed three-dimensional structure of the catalyst is not enough. The efficiency is highly dependent on the structures of unsaturated substrates, the properties of the central

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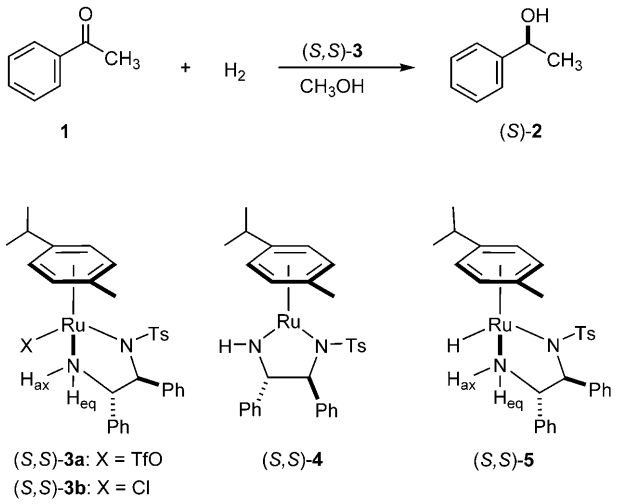
metal atom and the auxiliary anionic or neutral ligands of the catalyst, and the reaction conditions, such as hydrogen pressure, temperature, solvent, and additive.[4] We present herein a mechanism-based development of AH of aromatic ketones in the presence of chiral Ru complexes that are widely used for asymmetric transfer hydrogenation (ATH).[5]

Results and Discussion

The asymmetric reduction of ketones to chiral alcohols is most effectively achieved by AH by using H_2[2,5] or ATH by using organic reducing agents[6] with the aid of chiral transition-metal complexes. AH[3,4,7,8] and ATH[9–11] are linked mechanistically, because both reactions commonly involve a metal hydride species under catalytic conditions. However, most of the existing catalysts are effective for only one of these reactions.[12–14] Our long-term mechanistic investigation[7,9–11] has led to the discovery of a catalytic system that allows both AH and ATH by selecting appropriate functional and conditional parameters.[6] As illustrated in Scheme 1, acetophenone (**1**) is hydrogenated to (*S*)-1-phenylethanol ((*S*)-**2**) with 95–96% *ee* in the presence of a newly devised chiral Ru triflate complex, [Ru(OSO_2CF_3){(*S,S*)-TsNCH(C_6H_5)CH(C_6H_5)NH_2}(η^6-*p*-cymene)] ([Ru(OTf){(*S,S*)-Ts-dpen}(cymene)]; (*S,S*)-**3a**).[15] This AH reaction proceeds most effectively in methanol under slightly acidic conditions, in contrast to ATH, which proceeds best in 2-propanol with the Ru chloride (*S,S*)-**3b** under basic conditions.[6] Furthermore, this procedure provides the sole method for the enantioselective hydrogenation of simple ketones under acidic conditions.[16] Hydrogenation of **1** catalyzed by (*S,S*)-**3b** proceeds in methanol (but not 2-propanol) to give (*S*)-**2** in 96% *ee*, but this AH is three times slower than that catalyzed by **3a**. The following demonstrates that this AH takes place through a metal–ligand bifunctional mechanism (Scheme 2).



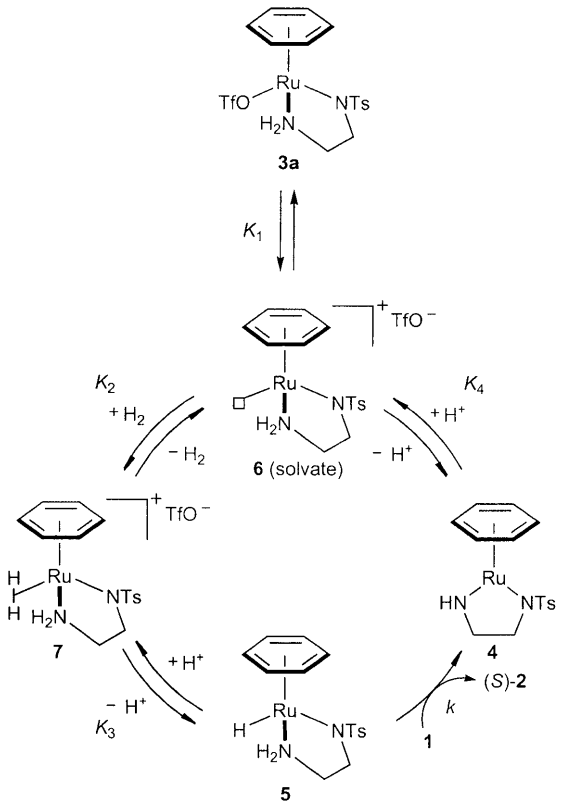
Scheme 1. Asymmetric hydrogenation of acetophenone (**1**) catalyzed by the chiral η^6-arene–Ts-dpen–Ru complex (*S,S*)-**3**. Ts = *p*-toluenesulfonyl; dpen = (*S,S*)-1,2-diphenylethylenediamine; Tf = trifluoromethanesulfonyl.

Synthesis and Solution Behavior of the Chiral Ru Catalyst

The Ru triflate complex (*S,S*)-**3a** was synthesized in 61% yield by slow addition of TfOH to the amido complex (*S,S*)-**4** in CH_2Cl_2 at 4 °C.[15] Its formation could be monitored in CD_2Cl_2 solvent by NMR spectroscopy. The isolated solid complex gave correct elemental analysis. The structure of (*S,S*)-**3a** was substantiated by comparing the NMR spectrum to that of (*S,S*)-**3b**.[9] The (*S,S*)-Ts-dpen ligand forms a skewed, δ conformation with respect to the five-membered *N,N*-chelate ring, which bears two equatorial phenyl substituents. The metal complexation allows a clear distinction between the NH_2 protons, H_{ax} (axial) and H_{eq} (equatorial) and generates an *R* configuration at the Ru center.[9–11,17] Table 1 contrasts the ^{1}H NMR spectra of solutions of (*S,S*)-**3** in CD_2Cl_2 and in CD_3OH. The spectrum suggests that (*S,S*)-

Abstract in Japanese:

キラルなアレーン／*N*-トシルエチレンジアミン－Ru(II)錯体は僅かな官能基の修正や反応条件の変化を施すだけで、単純ケトンの水素移動型不斉還元と不斉水素化の双方を行うことができる。Ru(OSO_2CF_3)[(*S,S*)-TsNCH(C_6H_5)CH(C_6H_5)NH_2-(η^6-*p*-シメン)はメタノール中でアセトフェノンを不斉水素化して、96% eeの(*S*)-1-フェニルエタノールを100%の収率で与える。同様のRu触媒を用いる塩基性2-プロノールまたは蟻酸／トリエチルアミン混合物をによる水素移動型還元と同じく、本水素化は金属－配位子二官能性反応機構によって進行する。C=O基の還元は中間体である18電子系RuH種によって、金属－基質の相互作用を経ずにその配位外圏で起る。高い触媒効率はメタノール中でRuトリフラート錯体が容易にイオン化するために得られる。触媒回転速度は水素圧と溶媒の酸性および塩基性度に依存する。Ru塩化物も触媒として用いることができるが、効率は低下する。既知のジホスフィン／1,2-ジアミン－Ru(II)触媒による水素化反応が塩基性条件で進行するのと対照的に、本反応は微酸性条件で起るので、不斉水素化反応の新たな可能性を開くものである。



Scheme 2. Mechanism of the asymmetric hydrogenation of **1** catalyzed by the chiral Ru complex (*S,S*)-**3a** under acidic conditions. Substituents in the arene and ethylenediamine ligands are omitted for clarity.

Table 1. Comparison of 1H NMR data for NH_2 protons in (*S,S*)-**3**.[a]

Ru complex	Solvent	δ (NH_{ax}) [ppm]	δ (NH_{eq}) [ppm]
(*S,S*)-**3a**	CD_2Cl_2	4.70	5.68
	CD_3OH	3.45	7.59
(*S,S*)-**3b**	CD_2Cl_2	3.59	5.51
	CD_3OH	3.39	7.10

[a] Obtained with a 21 mM solution at 30 °C.

3a in CD_2Cl_2 is largely an 18e octahedral complex, in which H_{ax} and H_{eq} have similar chemical shifts, $\delta = 4.70$ and 5.68 ppm, respectively. Most notably, in the polar alcoholic solvent, the signal for H_{eq} is significantly shifted downfield to $\delta = 7.59$ ppm ($\Delta\delta = 1.91$ ppm), whereas the resonance for H_{ax} at $\delta = 3.45$ ppm shows an upfield shift ($\Delta\delta = 1.25$ ppm). The chemical shifts in CD_3OH were independent of concentration in the 5–21 mM range. Thus, the RuOTf complex (*S,S*)-**3a** is ionized in methanol and exists mostly as an ion pair, [Ru^+\{(*S,S*)-Ts-dpen\}(cymene)]TfO^- ((*S,S*)-**6**). The Ru center is expected to be solvated with methanol to form an 18e complex.[18] Furthermore, the spatially more accessible NH_{eq} is more strongly hydrogen bonded to methanol or to a TfO^- anion and hence magnetically deshielded. As a consequence of the N–H_{eq} polarization, the electron density of the nitrogen atom is enhanced, resulting in magnetic shielding of the NH_{ax} nucleus. Consistent with this view, NH_{eq} of (*S,S*)-**3a** underwent rapid H/D exchange in CD_2Cl_2/CD_3OD (1:1). The isotope exchange was completed within 3 min at 25 °C, whereas NH_{ax} required 12 min for full exchange. The RuCl analogue (*S,S*)-**3b** exhibited a similar but smaller change in NMR signal in going from CD_2Cl_2 and CD_3OH as solvent (Table 1), but its NH_2 protons underwent comparable H/D exchange with CD_3OD.[18] Thus the Ru–Cl bond is less polar than the Ru–OTf linkage but would be more ionized under catalytic conditions in a dilute solution in methanol.

The precursor (*S,S*)-**4** was stable in methanol (the solvent of choice for AH) at 0 °C, as judged by NMR spectroscopy in CD_3OH, but, upon warming, dehydrogenated the alcohol to afford the RuH species (*S,S*)-**5**.[9] At 25 °C, approximately half was converted into (*S,S*)-**5** after 1.5 h. However, when an equimolar amount of TfOH in CD_3OH was added quickly to (*S,S*)-**4** in CD_2Cl_2 at 25 °C, (*S,S*)-**6** was produced quantitatively. Removal of this solvent from solution gave (*S,S*)-**3a**, as confirmed by the spectrum in CD_2Cl_2.

Mechanistic Scenario

The mechanistic model of Scheme 2 explains the overall aspects of the AH of **1** catalyzed by (*S,S*)-**3a** (Scheme 1). The catalytic reaction proceeds through a metal–ligand bifunctional mechanism,[10,11] as fully supported by the experimental findings. The Ru triflate precatalyst **3a** is easily ionized in methanol to give an ion pair **6** (solvate). The electrophilic Ru center reversibly accommodates an H_2 molecule to form the η^2-H_2 complex **7**.[19] Deprotonation of the H_2 ligand by bulk solvent generates the RuH species **5**,[20] which reduces the ketone **1** to give (*S*)-**2** enantioselectively and the Ru amide **4**. The reduction of the C=O function occurs in the outer coordination sphere of **5** without any metal–substrate interaction.[7,10,11,19,21] The Ru center donates a hydride and the NH_2 ligand delivers a proton through a Ru-H-C-O-H_{ax}-N six-membered pericyclic transition state. This step is irreversible under the AH conditions. Finally, protonation at the basic nitrogen ligand of **4**, regenerating **6**, completes the catalytic cycle.

This mechanistic model is constructed by assuming the effective relative acidity of η^2-H_2 in **7** > methanol solvent > NH_2 in **6**. Likewise, the basicity of :NH in the 16e Ru amide **4** must be comparable with that of the reaction medium. The turnover rate of hydrogenation of **1** is determined by the equilibrium constants K_1–K_4 and the rate constant k. The concentration of **5** must be maximized to allow high catalytic efficiency. In view of the facile ionization of the Ru–OTf bond of (*S,S*)-**3a** in methanol as established by NMR spectroscopy (Table 1), the K_1 value is very large. The equilibrium positions of the K_2, K_3, and K_4 steps are determined by H_2 pressure, medium basicity, and medium acidity, respectively. The equilibrium constant K_3 is also very large as judged from the high stability of the RuH species **5** in pure methanol. Only acidic conditions cause the reverse process **5**→**7**. Although the purple amido Ru complex **4** is hardly protonated by pure alcohols,[9] a solution of **3a** in

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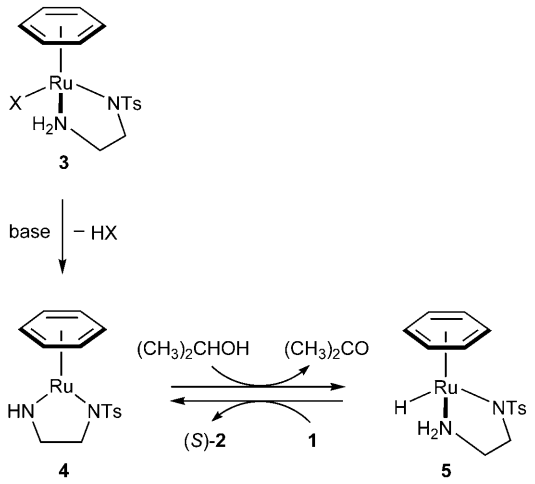
methanol retains a yellow color with or without H_2 gas. Thus the K_4 equilibrium is mostly shifted toward the regeneration of **6** under the acidic steady-state hydrogenation conditions. Overall, the K_2 step appears to control the concentration of **5**. The AH reaction catalyzed by (*S,S*)-**3b** is essentially the same, but is less effective owing to the lower K_1 value.

This AH cycle is mechanistically linked with ATH of **1** catalyzed by the Ru chloride (*S,S*)-**3** in 2-propanol (Scheme 3).[9–11,22] In contrast to the present AH, the ATH



Scheme 3. Mechanism of the asymmetric transfer hydrogenation of **1** catalyzed by the chiral Ru complexes (*S,S*)-**3** under basic conditions. Substituents in the arene and ethylenediamine ligands are omitted for clarity.

reaction requires a strong base to effect the elimination of HX (X = Cl, OTf) from the precatalyst either via the ion pair **6** or by a dcb (dissociative conjugate base) mechanism.[23] When preformed **4** is used as catalyst, an extra base is unnecessary for ATH. However, addition of an acid totally diminishes the catalytic activity.[6,9] The common 16e species **4** then dehydrogenates 2-propanol to form the RuH intermediate **5**, which reduces **1** to give (*S*)-**2** with the same 95–96% *ee*.[24] The current more acidic conditions (Scheme 1) quench **4** rapidly to form **6**, thereby prohibiting the possible ATH pathway. Because dehydrogenation of (*S*)-**2** is prevented for the same reasons, the stereochemical outcome of AH is determined kinetically by the irreversible step **1**+**5**→**2**+**4**. The ATH catalyst **4** reacts with H_2 only at very high pressure under neutral or basic conditions.[9] Thus the acidic medium appears to change the hydrogen source from 2-propanol to H_2.

The observed high catalytic efficiency is ascribed to the ready formation of catalytic **6** from **3a** under the reaction conditions. Furthermore, in accord with the subtle acid/base interplay in this metal–ligand bifunctional mechanism,[10,11] the acidity and basicity of the alcoholic medium is suitably adjusted.

Kinetics

The hydrogenation was conducted under various conditions in a glass autoclave equipped with a sampling needle connected to a stop valve. Because of the delicate acidity/basicity balance in this AH, the reaction vessel must be silanized to obtain high reproducibility.[25] Aliquots were taken from an active hydrogenation mixture and analyzed by GC with a chiral column. Data were collected for the reaction under the following conditions: [**1**] = 0.22–3.23 M in methanol, [(*S,S*)-**3a**] = 0.44–0.49 mM, [TfOH] = 0–320 μM, P_{H_2} = 5–20 atm, and T = 50 °C. Figure 1 illustrates a typical reaction profile. As shown in Figure 1a, there was a direct relation-

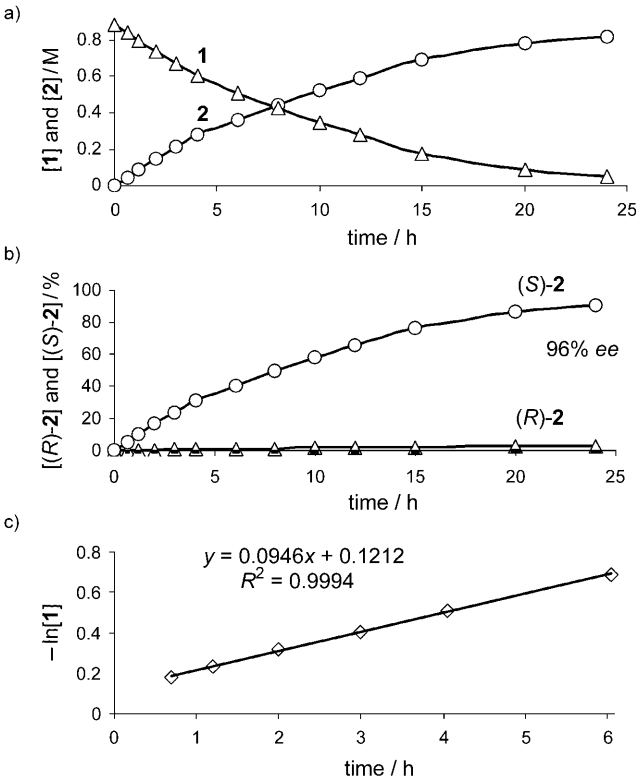


Figure 1. Typical reaction profile. a) Relative [**1**] and [**2**] versus reaction time. Reaction conditions: solvent = CH_3OH, [**1**] = 0.89 M, [(*S,S*)-**3a**] = 0.44 mM, S/C = 2000, [TfOH] = 35 μM, P_{H_2} = 20 atm, 50 °C. b) Relative (*S*)- and (*R*)-**2** product in a). c) Determination of the observed rate constant (k_{obs}, gradient of −ln[**1**] versus reaction time) for data in part a).

ship between substrate expenditure and product formation, without any side reactions. The enantioselectivity ((*S*)-**2** obtained with 96% *ee*) remained constant throughout the reaction (Figure 1b). Notably, no apparent incubation period was seen under the experimental conditions, with the initial consumption of **1** (< 50% conversion) being nearly constant. This suggests that the precatalyst (*S,S*)-**3a** enters the steady-state catalytic cycle simply by ionization. As illustrated in Figure 1c, the system follows pseudo-first-order kinetics in [**1**], with the initial (typically 1–6 h) linearity for the expression $\ln[\mathbf{1}]_t = k_{obs}(t) + \ln[\mathbf{1}]_0$ ([**1**]$_0$ = initial concentration of **1**, t = 0) allowing the determination of the observed rate k_{obs}.

Methanol is the best solvent for this AH. The reaction in less polar 2-propanol or *tert*-butyl alcohol was slower. The rate of hydrogenation increased proportionally with increasing initial concentration of the precatalyst (Figure 2a) and H_2 pressure (Figure 2b), whereas the dependence on

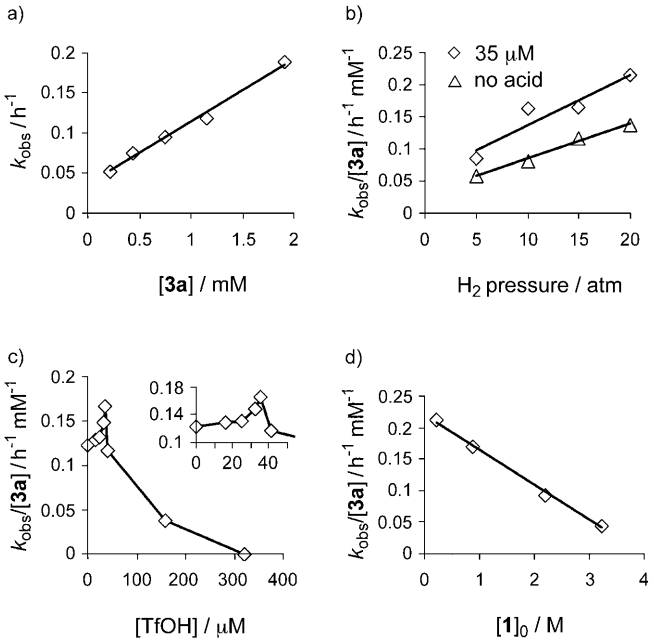


Figure 2. Dependence of hydrogenation rate on: a) concentration of **3a** ([**1**] = 0.88–0.89 M, [(*S,S*)-**3a**] = 0.22–1.91 mM); b) hydrogen pressure ([**1**] = 0.86–0.88 M, [(*S,S*)-**3a**] = 0.44–0.46 mM, [TfOH] = 0 or 35 μM); c) acid concentration ([**1**] = 0.85–0.88 M, [(*S,S*)-**3a**] = 0.44–0.49 mM; and d) initial concentration of **1** ([**1**]$_0$ = 0.22–3.23 M, [(*S,S*)-**3a**] = 0.44–0.46 mM, S/C = 500–7500). Unless otherwise stated: solvent = CH_3OH, [TfOH] = 35 μM, S/C = 2000, P_{H_2} = 15 atm, 50 °C.

[TfOH] showed initial rate enhancement followed by inhibition about an optimum value (Figure 2c). The unique substrate inhibition shown in Figure 2d is discussed below. Thus, this AH reaction follows first-order kinetics in [**1**] in the reaction system, [**3a**]$_0$, and H_2 pressure. The hydrogenation kinetics reflects **5** undergoing a bimolecular reaction with the ketone substrate **1**, with the rate law given by $-d[\mathbf{1}]/dt = k[\mathbf{1}][\mathbf{5}]$, in which [**5**] is highly dependent on the reaction parameters:

a) **Acidity dependence**: The mechanistic model in Scheme 2 suggests that the balance between the acidity and basicity of the reaction medium plays an important role.[26] In fact, the addition of TfOH was found to have a modest but distinct effect on catalytic efficiency. As shown in Figure 2c, the rate was steadily enhanced with small increments in acid concentration and reached a maximum with [TfOH] = 35 μM, resulting in an overall 1.5-fold enhancement of turnover frequency (TOF) relative to the reaction without acid. Beyond this point, however, TOF dropped gradually until the hydrogenation effectively stopped at [TfOH] > 300 μM. Such an effect was previously observed in the AH of **1** in *basic* 2-propanol catalyzed by a binap–1,2-diamine–Ru complex that takes place through a similar metal–ligand bifunctional mechanism.[7] The protic conditions must suitably shift the K_3 and K_4 equilibria toward product formation. Pure methanol ($pK_a = 15.5$)[27] is not sufficiently acidic to ensure protonation of **4** to give **6**.[9,28] Instead, the alcohol is dehydrogenated by **4** to give **5** and formaldehyde.[9] However, the steady-state conditions contain 1 equivalent of TfOH per Ru center, which effectively converts **4** into **6** at the cost of methanol dehydrogenation. The presence of a slight excess of TfOH further facilitates this step. The bulk solvent, however, must serve as a base as well to deprotonate **7**, giving **5**. Thus an increase in the concentration of TfOH suppresses this step. In fact, when TfOH in CD_3OH was added to a solution of **5** in CD_2Cl_2, **6** was formed with concomitant evolution of (hydrogen) gas. Furthermore, addition of a large amount of TfOH would result in the removal of the Ts-dpen ligand from the Ru center.[26] In fact, (*S,S*)-**3a** decomposed upon addition of TfOH in CD_3OD (NMR spectroscopic evidence). Experimentally, the optimum conditions were attained with [TfOH] = 35 μM. Beyond this point, the tendency for the system to generate **5** becomes exceedingly disfavored, and the rate decreases accordingly.

b) **Effects of hydrogen pressure**: The H_2 pressure influenced the catalytic rate significantly in accord with Scheme 2. The hydrogenation was very slow under an atmospheric pressure of H_2 owing to reduction in [**7**]. The TOF steadily increased over a 5- to 20-atm range with an optimum [TfOH] of 35 μM (Figure 2b). This twofold increase is a consequence of the enhanced steady-state concentration of **5** and reflects the equilibration between **6** and **7** with K_2. A similar pressure effect, that is, a 2.5-fold rate enhancement, was seen in the absence of extra TfOH. Thus, with a given medium acidity/basicity, an increase in H_2 pressure suffices to augment the catalytic performance. No pressure effect was seen on enantioselectivity.

c) **Substrate inhibition**: We observed an interesting substrate inhibition. As stated above (Figure 1c), this reaction follows first-order kinetics with respect to the concentration of ketone in the reaction system, [**1**], but not for the initial concentration of ketone, [**1**]$_0$.[29] Instead, as shown in Figure 2d, the reaction suffered an inhibitory effect from **1** in a 0.2–3.2 M range. This influence does not contradict the pseudo-first-order kinetics of Figure 1c. The rate decline with increasing [**1**]$_0$ arises from an event outside the steady-state catalytic cycle of Scheme 2, and is ascribed to the reversible formation of a phenacyl-Ru complex from the amido Ru species **4** and ketone **1**.[30] In fact, when a purple solution of **1** in CD_3OD (1.0 M) containing (*S,S*)-**4** (S/C = 200) was left to stand at 25 °C for 5 h, the ketone was recovered with 40% deuteration at the methyl group. Furthermore, $C_6H_5CD(OD)CH_{3-x}D_x$ was obtained in 9% yield. As expected, the H/D exchange and reduction were suppressed considerably by the use of (*S,S*)-**3a**.

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Hydrogen Source

Methanol, ethanol, 2-propanol, and other secondary alcohols are known to serve as hydrogen donors in ATH of aromatic ketones catalyzed by η^6-arene/Ts-dpen–Ru^{II} complexes (Scheme 3).[9] However, when AH of **1** was conducted in CD_3OH containing (*S,S*)-**3a** without or with TfOH (35 μM) (S/C = 1000, [**3a**] = 0.44 mM, P_{H_2} = 15 atm, T = 50 °C), (*S*)-**2** was obtained with 96% *ee*, with only 10% and < 5% deuterium incorporation at C1, respectively. Thus this reaction is largely a net hydrogenation using H_2 as a hydrogen donor. The alcohol solvent is involved in the AH reaction, but merely as a proton donor and a base. Under such reaction conditions, the cationic amino Ru complex **6** is equilibrated with a small amount of the neutral amido complex **4**, if any, but reacts overwhelmingly with H_2 to achieve AH. In the reaction without extra TfOH, ATH with **4** may be partially contaminated, increasing the extent of deuteration with CD_3OH.

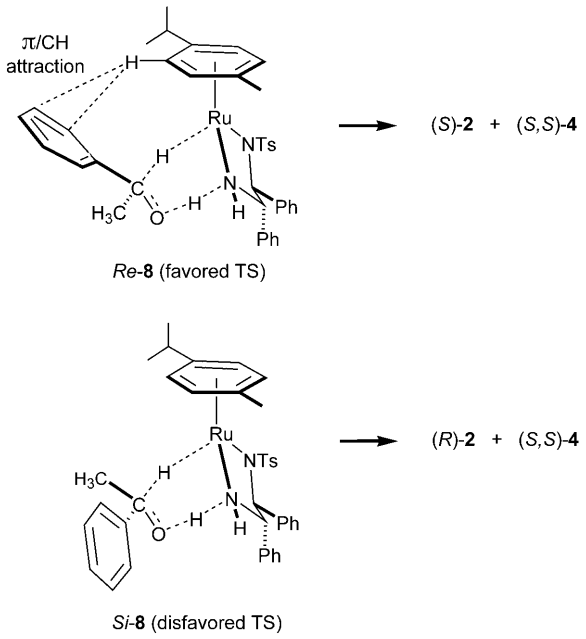
Reducing Ru Species

Scheme 2, coupled with the above discussion, indicates that the resting state is virtually dependent on H_2 pressure. When a solution of (*S,S*)-**3a** in CD_3OH was kept under an atmosphere of H_2 (10 atm) for 20 min, the RuH complex **5** was detected by NMR spectroscopy ($\delta = -5.61$ ppm), albeit in ≈1% yield. This species stayed in methanol, even in the absence of H_2 gas, consistent with a large K_3 constant. No RuH was formed in the absence of H_2 gas. These observations suggest that **5** is the resting state under high H_2 pressure, while **6** is the major species at low pressure. The conditions required for NMR spectroscopy led to **5** in a low yield owing to the very low H_2 concentration relative to **6**. However, the actual catalytic conditions with a high H_2/Ru ratio would produce the RuH much more readily. The intermediate **5** then undergoes the turnover-limiting reduction of a ketone. The same Ru compound, acting as an intermediate of ATH, was synthesized separately from **4** and 2-propanol and fully characterized by X-ray crystallographic analysis and NMR spectroscopy.[9,24]

Enantioselection

When the AH of **1** was conducted with (*S,S*)-**3a** under the standard conditions at 20 atm in methanol with [TfOH] = 35 μM, the enantiomeric excess of (*S*)-**2** remained constant (95.5 ± 0.5% *ee*), independent of the substrate concentration and/or conversion (Figure 1b). Thus the stereo-determining step of AH is irreversible. This is contrasted with the reversible ATH catalyzed by (*S,S*)-**3b** in basic 2-propanol that showed a deterioration of the *ee* value as a function of conversion.[6] Notably, AH of **1** under TfOH-free conditions occasionally showed a small, conversion-dependent decrease in the enantiomeric excess of the product to 94–95% *ee*. This may be due to partial contamination by ATH (Scheme 3).

The absolute stereochemistry and enantiomeric purity of the major product are essentially identical to those observed in ATH catalyzed by (*S,S*)-**3b**,[6,9] implying that both AH and ATH involve the common chiral RuH intermediate **5** with the *R* configuration at Ru.[17] This hydrogenative complex **5**, which bears an NH_2 ligand, acts as a 1,4-dipole that matches the C=O dipole well. Its reaction with **1** occurs via a Ru-H-C-O-H_{ax}-N six-membered pericyclic transition structure instead of the classical 2+2 mechanism involving a metal alkoxide intermediate.[10,11] Neither the ketone substrate nor the alcohol product interacts with the Ru center. The ketone utilizes the π face rather than the σ plane in the transition state. Scheme 4 illustrates two diastereomeric



Scheme 4. Origin of enantioselection in the asymmetric hydrogenation of **1**.

transition states, *Re*-**8** and *Si*-**8**, leading to (*S*)-**2** and (*R*)-**2**, respectively. Here, importantly, the "spatially more congested" *Re* structure is favored over the *Si* isomer.[21,31] We consider that this enantioselectivity originates from the CH/π attraction between the cymene ligand in the Ru complex and the phenyl ring of the ketone **1**. The crystallographic structure of (*S,S*)-**5** and the theoretical calculation on the model transition states suggest that the attraction between $C(sp^2)H$ in cymene and the *ortho* and *meta* carbon atoms in **1** is used for the stabilization of *Re*-**8**.[10,11,21]

Conclusions

The metal–ligand bifunctional mechanism can be utilized for AH and ATH under various conditions. Earlier, we developed chiral η^6-arene–Ts-dpen–Ru^{II} complexes for ATH of simple aromatic ketones in basic 2-propanol or a formic

acid/triethylamine mixture.[6] Both Ru chloride and triflate precatalysts can be used. We now showed that the Ru complexes catalyze AH by using hydrogen gas under slightly acidic conditions. This procedure is complementary to the binap/1,2-diamine–Ru^{II}-catalyzed AH that proceeds under basic conditions.[7] The chemical properties of the Ru center and the nitrogen ligand attached to Ru can be suitably perturbed by the electronic differences between the arene and diphosphine ligands.

Experimental Section

General

All manipulations were conducted in oven-dried glassware by using standard Schlenk techniques under argon gas (99.998%, purified through a BASF R3–11 catalyst at 80°C). THF and diethyl ether were distilled from Na/benzophenone and stored in Schlenk tubes with a Na mirror, $(CH_3)_2CHOH$, $(CH_3)_3COH$, and CH_2Cl_2 were freshly distilled from CaH_2, and CH_3OH was distilled from Mg powder. All solvents were degassed by three freeze-thaw cycles prior to use. $[D_8]$THF, CD_2Cl_2, CD_3OD, and CD_3OH were purchased from Aldrich, and stored in Schlenk tubes (teflon taps) over CaH_2, and freshly cold-distilled and degassed prior to use. Trifluoromethanesulfonic acid (TfOH, >99%) and chlorotrimethylsilane (TMSCl) were obtained from Kanto Chemical Co., Inc. (*S*,*S*)-1,2-Diphenylethylenediamine was purchased from Kankyo Kagaku Company. Di-μ-chloro-bis(*p*-cymene)chlororuthenium(II) was purchased from Acros Organics. Acetophenone (**1**), purchased from Aldrich, was washed with a solution of KOH (1.0 M) and purified by distillation from CaH_2 or K_2CO_3. Hydrogen gas (99.99999%) was obtained from Nippon Sanso. Unless otherwise stated, all reagents were used without further purification. The amino Ru complexes [RuCl{(*S*,*S*)-Ts-dpen}(cymene)] ((*S*,*S*)-**3b**) and [RuH{(*S*,*S*)-Ts-dpen}(cymene)] ((*S*,*S*)-**5**) and the amido complex [Ru{(*S*,*S*)-Ts-dpen}(cymene)] ((*S*,*S*)-**4**) were synthesized according to literature procedures.[9]

Gas chromatography (GC) analysis was conducted on a Hewlett Packard 6890 instrument equipped with a CP-Chirasil-DEX CB (df = 0.25 μm, 0.32 mm i.d., 25 μm, Varian). ^{1}H and ^{13}C NMR data were collected on JEOL α-400 NMR, Bruker DMX-500, Bruker AMX-400, or Varian Mercury vx 300 spectrometers. Chemical shifts are expressed in parts per million (ppm) relative to $Si(CH_3)_4$, benzene, or toluene (δ = 0.0, 7.16, and 2.09 ppm for ^{1}H NMR and δ = 0.0, 128, 20.4 ppm for ^{13}C NMR, respectively). Standard pulse sequences for 2D acquisitions were employed for DQF-COSY, ^{1}H,^{31}P-HSQC, and ^{1}H,^{13}C-HMQC. For NOESY, mixing times of 20 and 40 ms were used. The spectra were processed and analyzed with Bruker XWINNMR software.

Synthesis

(*S*,*S*)-**3a**: (*S*,*S*)-**4** (302 mg, 0.50 mmol) was placed in a 100-mL Schlenk tube equipped with a teflon-coated magnetic stirrer bar, and the air was replaced with argon. CH_2Cl_2 (40 mL) was added to the flask. The mixture was cooled to 4°C in an ice bath, and TfOH in CH_2Cl_2 (0.083 M; 6.0 mL) was added dropwise over 30 min. The mixture was then stirred at room temperature for 1 h. The volume of the mixture was reduced to ≈10 mL in vacuo and stored at −40°C for 12 h. The resulting brown precipitate was washed with cold CH_2Cl_2 (4°C), and the volatile components were removed in vacuo to yield (*S*,*S*)-**3a** (228 mg, 61%). ^{1}H NMR (400 MHz, 21 mM in CD_2Cl_2, T = 30°C): δ = 1.30 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 1.33 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 2.12 (s, 3H; CH_3 in cymene), 2.27 (s, 3H; CH_3 in Ts), 2.76 (m, 1H; $CH(CH_3)_2$), 3.75 (m, 1H; $CHNH_2$), 4.21 (d, ^3J(H,H) = 8 Hz, 1H; CHNTs), 4.70 (m, 1H; NH_{ax}), 5.68 (m, 1H; NH_{eq}), 5.84 (d, ^3J(H,H) = 6 Hz, 1H; aromatic CH in cymene), 5.94 (m, 2H; aromatic CH in cymene), 6.11 (d, ^3J(H,H) = 6 Hz, 1H; aromatic CH in cymene), 6.63–7.25 ppm (m, 14H; aromatic CH in Ts-dpen), absolute assignments were aided by 2D NMR spectroscopic analysis;[32] ^{13}C NMR (100.4 MHz, 10 mM in $[D_8]$THF): δ = 18.6, 21.1, 22.6, 22.8, 31.4, 70.3, 73.2, 82.4, 82.9, 84.2, 84.3, 97.0, 101.2, 127.0, 127.8, 128.1, 128.6, 128.7, 128.8, 129.2, 130.0, 139.7, 139.9, 140.3, 143.6 ppm; elemental analysis: calcd (%) for $C_{32}H_{35}F_3N_2O_5RuS_2$: C 51.26, H 4.70, N 3.74; found: C 51.09, H 4.47, N 3.74.

NMR Experiments on (S,S)-3

A) **Spectral analysis of (*S*,*S*)-3a in different solvents**: a) CD_2Cl_2: Data described above. b) CD_3OH: ^{1}H NMR (400 MHz, 21 mM in CD_3OH, T = 30°C): δ = 1.30 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 1.40 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 2.23 (s, 3H; CH_3 in cymene), 2.37 (s, 3H; CH_3 in Ts), 3.01 (m, 1H; $CH(CH_3)_2$), 3.45 (br t, 1H; NH_{ax}), 3.67 (m, 1H; $CHNH_2$), 4.02 (d, ^3J(H,H) = 11 Hz, 1H; CHNTs), 5.64 (d, ^3J(H,H) = 6 Hz, 1H; aromatic CH in cymene), 6.00–6.05 (m, 3H; aromatic CH in cymene), 6.60–7.18 (m, 14H; aromatic CH in Ts-dpen), 7.59 ppm (m, 1H; NH_{eq}). The fully deuterated solvent was used, because the NH_2 protons underwent slow H/D exchange under such conditions. Absolute assignments were aided by 2D NMR spectroscopic analysis.[32]

B) **Spectral analysis of (*S*,*S*)-3b in different solvents**: a) CD_2Cl_2: ^{1}H NMR (500 MHz, 21 mM in CD_2Cl_2, T = 30°C): δ = 1.37 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 1.39 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 2.24 (s, 3H; CH_3 in cymene), 2.35 (s, 3H; CH_3 in Ts), 3.09 (m, 1H; $CH(CH_3)_2$), 3.59 (dd, ^3J(H,H) = 11, 14 Hz, 1H; $CHNH_2$), 3.59 (dd, ^3J(H,H) = 9, 14 Hz, 1H; NH_{ax}), 3.83 (d, ^3J(H,H) = 11 Hz, 1H; CHNTs), 5.51 (br d, ^3J(H,H) = 9 Hz, 1H; NH_{eq}), 5.58–5.66 (m, 4H; aromatic CH in cymene), 6.52–7.12 ppm (m, 14H; aromatic CH in Ts-dpen). b) CD_3OH: ^{1}H NMR (300 MHz, 21 mM in CD_3OH, T = 25°C) δ = 1.35 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 1.36 (d, ^3J(H,H) = 7 Hz, 6H; $C(CH_3)_2$), 2.26 (s, 3H; CH_3 in cymene), 2.39 (s, 3H; CH_3 in Ts), 3.16 (m, 1H; $CH(CH_3)_2$), 3.39 (br t, 1H; NH_{ax}), 3.61 (br t, 1H; $CHNH_2$), 3.90 (d, ^3J(H,H) = 11 Hz, 1H; CHNTs), 5.59–5.72 (m, 4H; aromatic CH in cymene), 6.54–7.20 (m, 14H; aromatic CH in Ts-dpen), 7.10 ppm (br; NH_{eq}). Absolute assignments were aided by 2D NMR spectroscopic analysis.[32]

C) **H/D exchange**: a) (*S*,*S*)-**3a** with CD_3OD: First, the ^{1}H NMR spectrum of (*S*,*S*)-**3a** was obtained in CD_2Cl_2 at 25°C. CD_3OD (99.8% deuterated) was added to this solution at the designated t = 0 min. ^{1}H NMR spectra were recorded at designated time intervals, and the declining integration value (int%) of the amine protons was monitored relative to the unchanged CHNTs integration (δ = 4.05 ppm, defined as constant 100% H). For NH_{ax}, H/D exchange (int%) was monitored by the decline in the triplet multiplicity for $CHNH_2$ owing to the overlap of its resonance with that of the CD_3OD solvent. 1) $[(S,S)\text{-}\mathbf{3a}]_T$ = 21.3 mM, $V(CD_2Cl_2) = V(CD_3OD)$ = 0.25 mL. For NH_{eq} ($\delta \approx 7.5$ ppm), int (%) (t, min): >95 (<3). For NH_{ax}, int (%) (t, min): 50 (3), 75 (5), 90 (7), >95 (12). 2) $[(S,S)\text{-}\mathbf{3a}]_T$ = 21.1 mM, $V(CD_2Cl_2)$ = 0.40 mL, $V(CD_3OD)$ = 0.10 mL. For NH_{eq} ($\delta \approx 7.5$ ppm), int (%) (t, min): >95 (<2). For NH_{ax} int (%) (t, min): 20 (2), 30 (4), 50 (6), 60 (8), 80 (10), >95 (>15). b) (*S*,*S*)-**3b** with CD_3OD: The same experimental procedure described in a) above was followed. 1) $[(S,S)\text{-}\mathbf{3b}]_T$ = 21.3 mM, $V(CD_2Cl_2) = V(CD_3OD)$ = 0.25 mL. The extent of H/D exchange for NH_{eq} with time could not be determined accurately owing to overlap in the region of the signals for the aryl protons. For NH_{ax}, H/D exchange was monitored by the decline in the triplet multiplicity for $CHNH_2$ (br) owing to the overlap of its resonance with that of the CD_3OD solvent; int (%) (t, min): >95 (10). 2) $[(S,S)\text{-}\mathbf{3b}]_T$ = 21.1 mM, $V(CD_2Cl_2)$ = 0.40 mL, $V(CD_3OD)$ = 0.10 mL. For NH_{ax}, int (%) (t, min): 50 (2); 55 (4); 60 (6); 65 (8); 70 (10); 80 (14); >95 (>20).

D) **Addition of TfOH to (*S*,*S*)-5**: A solution of TfOH in CD_3OD (0.05 M, 0.22 mL, 1 equiv) was added slowly to a solution of (*S*,*S*)-**5** (8.0 mg) in CD_2Cl_2 (0.28 mL) at 25°C. Bubbling was evident upon mixing. The ^{1}H NMR spectrum (400 MHz, CD_2Cl_2/CD_3OH 1:1) was indistinguishable from that of (*S*,*S*)-**6**: δ = 1.41 (d, ^3J(H,H) = 7 Hz, 3H; $C(CH_3)_2$), 1.30 (d, ^3J(H,H) = 7 Hz, 3H; $C(CH_3)_2$), 2.22 (s, 3H; CH_3 in cymene), 2.35 (s, 3H; CH_3 in Ts), 3.05 (m, 1H; $CH(CH_3)_2$), 3.61 (br t, 1H; NH_{ax}), 3.69 (m, 1H; $CHNH_2$), 4.03 (d, ^3J(H,H) = 11 Hz, 1H; CHNTs), 5.68 (d, ^3J(H,H) = 6 Hz, 1H; aromatic CH in cymene), 6.11–6.17 (m, 3H; aromatic CH in cymene), 6.61–7.20 (m, 14H; aromatic CH in Ts-dpen), 7.63 (br d, 1H; NH_{eq}). Removal of solvent in vacuo yielded a yellow product: the ^{1}H NMR (400 MHz, CD_2Cl_2) was indistinguishable from the spectrum of (*S*,*S*)-**3a** given above.

E) **Experiments under H_2 atmosphere**: a) CD_3OH: An accurately measured mass of (*S*,*S*)-**3a** was placed in a predried (120 °C) glass autoclave containing a magnetic stirring bar, which was then maintained under high vacuum for at least 5 min prior to purging with argon. Dry and degassed CD_3OH was added under an argon atmosphere. Hydrogen was introduced, set to 10 atm, and stirring commenced. After 20 min, the H_2 pressure was slowly decreased to 1 atm, and an aliquot was directly collected into an NMR tube fitted with a Young tap under an H_2 atmosphere. ^{1}H NMR analysis (500 MHz, CD_3OH) showed resonances consistent with (*S*,*S*)-**5**[9] in ca. 1% yield, $\delta = -5.61$ ppm (RuH). For the same mixture but in the absence of H_2 gas, no new species were detected by ^{1}H NMR spectroscopy. **b)** CD_2Cl_2: The same procedure as above was followed in CD_2Cl_2 solvent. No new species were detected by ^{1}H NMR spectroscopy.

Hydrogenations

A) **Standard**: A pre-dried (120 °C) glass autoclave containing a magnetic stirring bar was silanized with TMSCl (≈1 mL) and then maintained under high vacuum for 10 min at 50 °C. An accurately measured mass of (*S*,*S*)-**3a** was then added, and the mixture was maintained under high vacuum for 5 min before purging with argon. Into a predried Schlenk tube were placed accurately measured amounts of a ketone substrate, a solution of TfOH in CH_3OH (0.1 M), and CH_3OH solvent such that the necessary [(*S*,*S*)-**3a**], S/C ratio, and [TfOH] were obtained. The reaction mixture was degassed by three freeze–thaw cycles and added to the autoclave under an argon atmosphere. H_2 was introduced at 5 atm pressure with several quick release–fill cycles before being set to the desired pressure. The mixture was stirred for the required time. The conversion and *ee* value of the alcohol product, (*S*)-l-phenylethanol [(*S*)-**2**], were determined by GC analyses of the purified product: CP-Chirasil-DEX CB column, $P = 41$ kPa, $T = 105$ °C, t_R ((*R*)-**2**) = 20.9 min, t_R ((*S*)-**2**) = 24.6 min. Conditions: CH_3OH solvent, [(*S*,*S*)-**3a**] = 0.44 mM, [**1**] = 0.88 M, P_{H_2} = 15 atm, no TfOH, S/C = 2000, $T = 50$ °C, $t = 24$ h; conversion = 90%; 96% *ee*.

B) **Kinetics**: Hydrogenations were conducted in a glass autoclave equipped with a sampling needle connected to a three-way stop valve.[7] This experimental setup allowed for samples to be taken from the reaction mixture for GC and NMR analyses. A predried (120 °C) glass autoclave containing a magnetic stirrer bar was silanized with TMSCl (≈1 mL) and then maintained under high vacuum for 10 min at 50 °C. An accurately measured mass of (*S*,*S*)-**3a** was then added, and the mixture was maintained under high vacuum for 5 min before purging with argon. Into a predried Schlenk tube were placed accurately measured amounts of a ketone substrate, a solution of TfOH in CH_3OH (0.1 M), and CH_3OH solvent such that the required [(*S*,*S*)-**3a**], S/C ratio, and [TfOH] were obtained. The reaction mixture was degassed by three freeze–thaw cycles and added to the autoclave under an argon atmosphere. H_2 was introduced under 5 atm pressure with several quick release-fill cycles before being set to the desired pressure. Stirring and timing ($t = 0$ min) were immediately commenced. Reaction samples were obtained (2 drops into a hexane-filled GC sample tube) at specified time intervals, and the extent of substrate consumption and the *ee* value of (*S*)-**2** were determined by GC analyses as described in **A** above. a) Dependence on **[3a]**: Hydrogenation conditions: [(*S*,*S*)-**3a**] = 0.22–1.91 mM, [**1**] = 0.88–0.89 M, P_{H_2} = 15 atm, [TfOH] = 35 μM (0.01 M TfOH in CH_3OH), S/C = 2000, $T = 50$ °C, CH_3OH solvent. Samples were collected at 0.5–1-h intervals. b) Dependence on [TfOH]: Hydrogenation conditions: [(*S*,*S*)-**3a**] = 0.44–0.49 mM, [**1**] = 0.85–0.88 M, P_{H_2} = 15 atm, [TfOH] = 0–320 μM (0.01 M TfOH in CH_3OH), S/C = 2000, $T = 50$ °C, CH_3OH solvent. Samples were collected at 0.5- or 1-h intervals. c) Dependence on H_2 pressure: Hydrogenation conditions: [(*S*,*S*)-**3a**] = 0.44–0.46 mM, [**1**] = 0.86–0.88 M, P_{H_2} = 5–20 atm, [TfOH] = 0 or 35 μM (0.01 M TfOH in CH_3OH), S/C = 2000, $T = 50$ °C, CH_3OH solvent. Samples were collected at 0.5- or 1-h intervals. d) Dependence on [ketone]: Hydrogenation conditions: [(*S*,*S*)-**3a**] = 0.44–0.46 mM, [**1**] = 0.22–3.23 M, P_{H_2} = 15 atm, [TfOH] = 35 μM (0.01 M TfOH in CH_3OH), S/C = 500, 2000, 5000, 7500, $T = 50$ °C, CH_3OH solvent. Samples were collected at 0.5- or 1-h intervals. e) Reaction with the Ru chloride (*S*,*S*)-**3b**: Conditions: [(*S*,*S*)-**3b**] = 0.44 mM, [**1**] = 0.88 M, P_{H_2} = 15 atm, no TfOH, S/C = 2000, $T = 50$ °C, CH_3OH. Samples were collected at 2-h intervals. $k_{obs} = 0.037\ h^{-1}\,mM^{-1}$ (three-times slower than with (*S*,*S*)-**3a**).

C) **Deuterium content**: Hydrogenation conditions: [(*S*,*S*)-**3a**] = 0.44 mM, [**1**] = 0.45 M, P_{H_2} = 15 atm, [TfOH] = 0, 35 μM (0.01 M TfOH in CH_3OH), S/C = 1000, $T = 50$ °C, $t = 12$ h, CH_3OH solvent. ^{2}H incorporation determined by ^{1}H- and ^{2}H NMR spectroscopic analysis of purified (*S*)-**2**: 1) 10% for TfOH-free conditions; 2) <5% for reaction with [TfOH] = 35 μM.

D) **Transfer Hydrogenation under Basic Conditions:** An accurately measured mass of (*S*,*S*)-**3a** was placed into a predried (120 °C) Schlenk flask. Under an argon atmosphere, a solution of **1** in CH_3OH or $(CH_3)_2CHOH$ containing KO*t*Bu was added such that the desired [**1**], [KO*t*Bu], and S/C ratio were obtained. Sample aliquots of the reaction mixture were analyzed by GC. a) $(CH_3)_2CHOH$: Conditions: [(*S*,*S*)-**3a**] = 0.50 mM, [**1**] = 0.50 M, [KO*t*Bu] = 15 mM, S/C = 1000, $T = 25$ °C; conversion = 90% (t = 12 h), 97% *ee*; conversion > 99% (t = 24 h), 96% *ee*. b) CH_3OH: Conditions: [(*S*,*S*)-**3a**] = 0.50 mM, [**1**] = 0.50 M, [KO*t*Bu] = 15 mM, S/C = 1000, T = 25 °C; conversion = 24% (t = 12 h), 96% *ee*; conversion = 38% (t = 24 h), 96% *ee*.

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