CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200800246

VIP

The Hydrogenation/Transfer Hydrogenation Network in Asymmetric Reduction of Ketones Catalyzed by [$RuCl_2$(binap)(pica)] Complexes

Christian A. Sandoval,*[a] Yuehui Li,[a] Kuiling Ding,[a] and Ryoji Noyori*[b]

Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Abstract: Chiral binap/pica-Ru^{II} complexes (binap = (*S*)- or (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; pica = α-picolylamine) catalyze both asymmetric hydrogenation (AH) of ketones using H_2 and asymmetric transfer hydrogenation (ATH) using non-tertiary alcohols under basic conditions. The AH and ATH catalytic cycles are linked by the metal–ligand bifunctional mechanism. Asymmetric reduction of pinacolone is best achieved in ethanol containing the Ru catalyst and base under an H_2 atmosphere at ambient temperature, giving the chiral alcohol in 97–98% *ee*. The reaction utilizes only H_2 as a hydride source with alcohol acting as a proton source. On the other hand, asymmetric reduction of acetophenone is attained with both H_2 (ambient temperature) and 2-propanol (>60 °C) with relatively low enantioselectivity. The degree of contribution of the AH and ATH cycles is highly dependent on the ketone substrates, solvent, and reaction parameters (H_2 pressure, temperature, basicity, substrate concentration, H/D difference, etc.).

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

Introduction

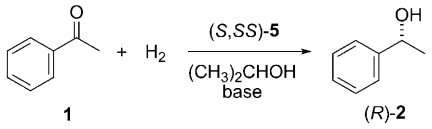
General Background

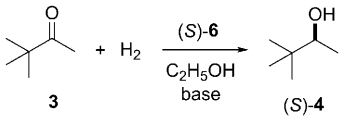
Asymmetric hydrogenation (AH) of ketones by molecular catalysts is a fundamental transformation in modern organic synthesis and is of current industrial relevance.[1,2] Generation of chiral alcohols by AH has been best achieved using transition-metal-based catalysts possessing appropriately designed chiral ligand(s).[1,3,4] Notably, no universal catalysts exist because of the structural diversity of ketones. As shown in Scheme 1, the binap/dpen-Ru^{II} complexes (*S,SS*)-**5** (dpen = 1,2-diphenylethylenediamine) catalyze the AH of acetophenone (**1**) to (*R*)-1-phenylethanol ((*R*)-**2**) under mild conditions in 2-propanol containing an inorganic or organic strong base. For example, use of (*S,SS*)-**5a** with a substrate-to-catalyst (S/C) molar ratio of 100000 led to (*R*)-**2** in 99% *ee* quantitatively.[4b,5a] This method allows for AH of various aromatic, heteroaromatic, and olefinic ketones.[4,5] However, AH of sterically congested *tert*-alkyl ketones is achievable only by replacing the symmetrical 1,2-diamine in **5** by pica (α-picolylamine), an unsymmetrical NH_2/pyridine hybrid ligand, and by using ethanol instead of 2-propanol as solvent.[6] Thus, the binap/pica-Ru complex (*S*)-**6a** catalyzes the AH of pinacolone (**3**) in basic ethanol with an S/C ratio of up to 100000, resulting in the chiral carbinol (*S*)-**4** in 97% *ee* (Scheme 1).[6a] Thus, this method allows, for the first time, the efficient and general preparation of *tert*-alkyl carbinols with high enantiomeric purity.

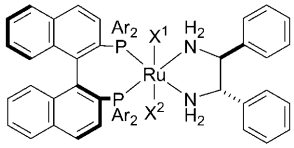
The efficiency of AH is highly dependent on the properties of the metal and the auxiliary anionic or neutral ligands, and reaction conditions including H_2 pressure, temperature, solvent, and additives. Notably, in the reactions of Scheme 1, the use of Ru complexes having an NH_2 ligand is essential because of the operation of the metal–ligand bifunctional mechanism.[7–13] Furthermore, the reaction system must be slightly basic for mechanistic reasons, although AH of **1** and **3** is attainable without an extra strong base by the use of the

[a] Prof. Dr. C. A. Sandoval, Y. Li, Prof. Dr. K. Ding
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (China)
Fax: (+86) 21-5492-5480
E-mail: sandoval@mail.sioc.ac.cn

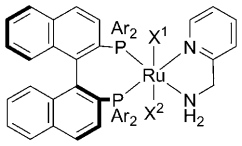
[b] Prof. Dr. R. Noyori
Department of Chemistry and
Research Center for Materials Science
Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
Fax: (+81) 52-783-4177
E-mail: noyori@chem3.chem.nagoya-u.ac.jp





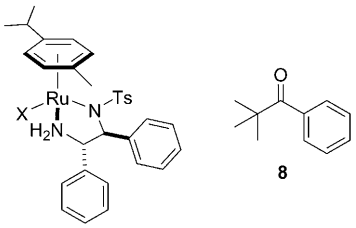


(*S*,*SS*)-**5a**: Ar = 3,5-$(CH_3)_2C_6H_3$
$X^1 = X^2 = Cl$
(*S*,*SS*)-**5b**: Ar = 4-$CH_3C_6H_4$
$X^1 = X^2 = Cl$
(*S*,*SS*)-**5c**: Ar = 4-$CH_3C_6H_4$
$X^1 = H$, $X^2 = BH_4$



Ar = 4-$CH_3C_6H_4$

(*S*)-**6a**: $X^1 = X^2 = Cl$
(*S*)-**6b**: $X^1 = H$, $X^2 = BH_4$



(*S*,*S*)-**7a**: X = Cl
(*S*,*S*)-**7b**: X = OSO_2CF_3

Scheme 1. Asymmetric hydrogenation (AH) catalyzed by chiral Ru complexes.

Abstract in Japanese:

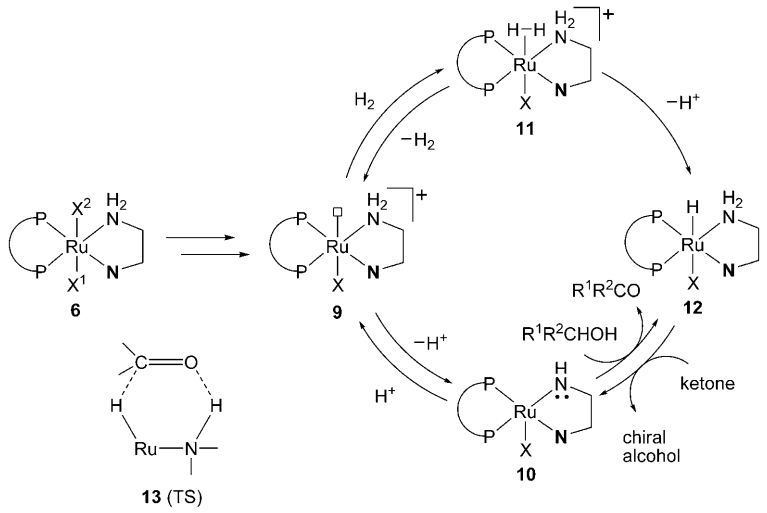
キラルなBINAP/PICA—ルテニウム(Ⅱ)錯体(BINAP = (*S*)-または(*R*)-ビス(ジフェニルホスフィノ)-1, 1'-ビナフチル、PICA = α-ピコリルアミン)は、塩基性条件下に、ケトン類の水素ガスによる不斉水素化(AH)と非三級アルコールによる不斉水素移動還元(ATH)の双方を触媒する。両触媒サイクルは金属—配位子二官能性機構を介して結ばれている。ピナコロンの還元は、ルテニウム触媒を含むエタノール中で水素雰囲気下、常温で効果的に進み、鏡像体過剰率97—98%のキラルなアルコールを与える。反応はもっぱら水素ガスをヒドリド源とし、アルコールはプロトン源として働くに過ぎない。他方、アセトフェノンの還元は水素ガス(常温)でも2-プロパノール(>60 °C)でも起り、エナンチオ選択性は比較的低い。AHとATHサイクルの寄与の割合は、ケトン基質、溶媒および反応パラメーター(水素圧、温度、塩基性、基質濃度、H/Dの相違など)に大きく依存する。

H/BH_4 catalyst **5c** or **6b** owing to the generation of a tiny amount of base by alcoholysis of the BH_4 anion. Sometimes asymmetric transfer hydrogenation (ATH) becomes possible using functionally similar Ru catalysts and organic reducing agents such as 2-propanol and formic acid.[9,14] Since the AH reaction generally proceeds via metal hydride or dihydride species formed by splitting of H_2 molecules, one might expect that common intermediates are generated from the same catalyst precursor and organic reagents. The mechanistic linkage between hydrogenation and transfer hydrogenation offers novel opportunities to exploit an efficient reduction through appropriate catalyst design and careful consideration of reaction parameters.[7–9,14–17] In fact, we recently discovered that the chiral arene Ru complexes **7**, well-known ATH catalysts, promote not only ATH but also AH simply by switching the conditions from basic 2-propanol to acidic methanol.[18] The identical sense and degree of enantioselectivity (*S,S* to *S*, 96% *ee*) shown in the ATH and AH of **1** suggests the involvement of the same RuH intermediate. Despite such potential, however, most of the existing chiral catalysts are effective for only one of these reactions, either ATH or AH.[19–22]

Network of Asymmetric Hydrogenation (AH) and Asymmetric Transfer Hydrogenation (ATH) Catalyzed by the binap/pica-Ru System

In principle, both H_2 and 2-propanol, or other non-tertiary alcohols possessing α-hydrogen atom(s), act as potential hydride donors for the reduction of ketones. Our earlier studies[6,7] suggest the possible existence of the AH/ATH linkage in the reaction catalyzed by the binap/pica-Ru complex **6**, as illustrated in Scheme 2. Exposure of the precatalyst **6** to an alcoholic medium with or without base, depending on the nature of the anionic ligand(s), readily generates the cationic amino Ru complex **9** (solvate), which is in equilibrium with the neutral amido complex **10** through proton relay. The 16e cation **9** catalyzes AH of ketones, whereas **10** with a partial Ru–N double bond can promote ATH of ketones with non-tertiary alcohols. The AH reaction starts with the η^2-H_2 complex **11**, which is deprotonated to give the reducing 18e RuH species **12**. The simultaneous delivery of a hydride on Ru and a proton of the NH_2 ligand to an approaching prochiral ketone produces a chiral alcohol and **10**. This reduction occurs via a six-membered pericyclic TS of type **13** in an outer coordination sphere without Ru/carbonyl interaction. Protonation on the amido nitrogen atom of **10**, regenerating catalytic **9**, completes the AH cycle. Alcohol-assisted heterolytic cleavage of H_2 by **10** via its short-lived η^2-H_2 complex can directly generate **10**, though this is a minor pathway. On the other hand, **10** dehydrogenates an alcohol, typically 2-propanol, via **13** to form RuH **12**, which reacts with a ketone to give a chiral alcohol and **10**. Thus, both the AH and ATH cycles generate active RuH species **10** through distinctly different pathways and by using different hydride sources. A non-tertiary alcohol provides a hydride and proton for ATH but is used only as a proton source

CHEMISTRY
AN ASIAN JOURNAL



Scheme 2. Mechanistic network of asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) of ketones catalyzed by binap/pica-Ru complexes **6**. The stereochemistry of the Ru complexes (X^1/X^2 = Cl/Cl or H/BH_4; X = H, OR; P–P = binap; **N** = sp^2 nitrogen atom) is not specified.

Results and Discussion

Asymmetric Reduction of Pinacolone (3)

Confirmation of the AH mechanism. When an ethanol solution of **3** containing (*S*)-**6a** (S/C = 2000 to 100000) and a small amount of KO-*t*-C_4H_9 was stirred under 1–20 atm of H_2 at 25 °C for several hours, (*S*)-**4** was obtained in 100 % yield and in 97–98 % *ee*.[6a] Phosphazenes, metal-free strong organic bases, can be used in place of metal alkoxides. The reaction with the chloride-free H/BH_4 complex (*S*)-**6b** took place smoothly without added base, giving the same result. Many lines of evidence indicate that this reduction is indeed AH, rather than ATH: 1) The reaction consumes H_2 gas; 2) The reduction occurs, albeit less effectively, even in *tert*-butyl alcohol, which has no α-hydrogen atoms; (3) Reaction of **3** using CD_3CD_2OH as solvent did not cause any deuterium incorporation. Under optimum AH conditions with CD_3CD_2OH ([(*S*)-**6a**] = 0.1 mM, [**3**] = 0.20 M, [KO-*t*-C_4H_9] = 20 mM, T = 25 °C, $P(H_2)$ = 1 atm, V_T = 10 mL), (*S*)-**4** is obtained in 97 % *ee* as expected. Even at 80 °C, non-deuterated (*S*)-**4** was obtained with the same *ee* value. Attempted ATH of **3** using ethanol without H_2 gas ([(*S*)-**6a**] = 0.1 mM, [**3**] = 0.2 M, [KO-*t*-C_4H_9] = 4 mM, T = 80 °C, V_T = 10 mL) resulted in a poor conversion, only 1 % after 1 h (TOF (turnover frequency) = 20 h^{-1}), giving **4** with no enantiomeric excess. Although the ATH reactivity was improved in 2-propanol under similar conditions, the reduction remained inefficient (TOF = 460 h^{-1} at 80 °C, 23 % conversion after 1 h, (*S*)-**4** in 85 % *ee*). Use of **6b** did not improve the ATH reactivity. Thus, it is clear that, under our AH catalytic conditions, the degree of competition from ATH is negligible at both ambient and elevated temperatures.

Solvent effects. Alcoholic solvents appear to influence strongly the catalytic activity and enantioselectivity in AH of **3**.[23] Ethanol is the best solvent, forming (*S*)-**4** with 97 % *ee*.[6a] Reduction in 2-propanol proceeds smoothly but gives (*S*)-**4** in only 36 % *ee*, whereas the AH in *tert*-butyl alcohol occurs with reversal of the asymmetric sense, affording (*R*)-**4** in 68 % *ee*. No reduction takes place in pure methanol, but (*S*)-**4** with 97–99 % *ee* is produced in a methanol/*tert*-butyl alcohol (>3:7) mixture. The stereochemical outcome is interpreted in terms of an 18e *cis*-[RuH(OR)(binap)(pica)] intermediate(s) (*cis*-configurated **12**, X = OR) as the dominant reactive species (Scheme 2). In an H_2 atmosphere, various RuH structures can be generated, but this species is kinetically very appropriate for asymmetric reduction of **3**. In view of the different enantioselectivity in during AH. The concentration of **12** would limit the turnover rate of both AH and ATH, and the product stereochemistry is determined by the TS **13**. AH of a ketone is irreversible, whereas ATH could be reversible because of the structural similarity of the starting materials and products, namely, ketones and (secondary) alcohols.

Scheme 2 does not define the geometry of the Ru complexes. In order for **12** to reduce ketones via a **13**-type TS, the H/N,**N** ligands on Ru must have a *fac* relationship. The AH/ATH network involves **9**, **10**, and **11** as common intermediates, but they may or may not have the same stereochemistry. For **12**, five (X = H; one *trans* and four *cis* isomers) or six reactive stereoisomers (X = OR; two *trans* and four *cis* isomers) are possible. These are interchangeable in solution via pentacoordinate species, if formed, and the equilibrium ratio is variable according to the reaction conditions. The catalyst precursor (*S*)-**6a**, for instance, is a mixture of five diastereomers in benzene or toluene at room temperature, although the content of the most dominant isomer is increased to less than 95 % by heating at 80 °C. Throughout the catalytic reaction, the solution remains yellowish orange, indicating that the formal 16e complex **10** is not a major entity under the steady-state conditions.

This study actually stemmed from the work of Baratta and co-workers on the transfer hydrogenation of simple ketones in basic 2-propanol, effected by achiral and chiral Ru complexes which are structurally similar to **6**.[11] In this regard, since our first publication in 2005,[6] we have received many inquiries as to whether our AH of **3** to (*S*)-**4** using (*S*)-**6** (Scheme 1) truly uses H_2, rather than alcohol, as reducing agent. This paper reports that our conclusion is correct and that the degree of ATH during AH is highly dependent on the ketone structure, catalyst, and reaction conditions.

sluggish ATH, intermediary RuH complexes **12** would have different structures. Hydrogenation of **3** catalyzed by **6** is much faster and more enantioselective than the reaction with the binap/dpen-Ru complexes **5**, which are excellent catalysts for the AH of **1**.[4,7]

Function of diamine ligands. As seen in Scheme 1, the AH reactions of **1** and **3** catalyzed by (*S,SS*)-**5** or (*S*)-**6**, respectively, possessing the same (*S*)-binap ligand display an opposite sense of asymmetric induction. We consider that this is due to the structural difference in reducing species, *trans*-[RuH_2(binap)(dpen)][7] versus *cis*-[RuH(OR)(binap)-(pica)].[6] The function of the C_2-symmetric dpen ligand in **5** in AH of the aromatic ketone **1** is twofold. An NH_2 moiety donates a proton to the carbonyl oxygen atom and the other NH_2 unit attracts *electrostatically* the phenyl ring of **1** (NH/π interaction) to stabilize the TS to form (*R*)-**2** enantioselectively.[7] The latter function is absent in the NH_2/pyridine-hybrid pica ligand of (*S*)-**6**. Thus, the asymmetric bias in the AH of **3** catalyzed by (*S*)-**6**, leading to (*S*)-**4**, results from the difference in steric bulk between the *tert*-butyl and methyl groups.

Asymmetric Reduction of Acetophenone (1)

Pivalophenone (**8**), an aromatic analogue of **3**, is smoothly hydrogenated with the binap/pica-Ru catalyst **6a** in basic ethanol to give the chiral alcohol with 97% *ee* in 100% yield.[6a] The asymmetric sense is identical with that observed for the bulky dialkyl ketone **3**. Notably, however, the simplest aromatic ketone **1** behaves differently from *tert*-butyl ketones. In fact, both (*S*)-**6a** and (*S*)-**6b** are poor for AH of **1**, giving (*R*)-**2** in only 54 and 58% *ee*, respectively, in ethanol under the optimum conditions for AH of **3**.

Interestingly, Barrata and co-workers reported that the structurally similar *cis*-[$RuCl_2$\{(*R,S*)-josiphos\}\{(±)-MePyme\}] catalyzes the ATH (not AH) of **1** in basic 2-propanol at 60 °C, giving (*R*)-**2** in 96% *ee*.[11b,24] In this regard, we found that the simpler *cis*-[$RuCl_2$\{(*R,S*)-josiphos\}(pica)] gave (*R*)-**2** in 83% *ee* by AH in 2-propanol (conditions: [Ru] = 0.1 mM, [**1**] = 0.2 M, [KO-*t*-C_4H_9] = 4 mM, $P(H_2)$ = 2 atm, T = 25 °C, V_T = 10 mL). The enantioselectivity is the same as that obtained by ATH without H_2 gas under the same conditions but at 80 °C.[11a,25] The temperature effect is not significant. Thus, the degree of competition by ATH during AH of **1** becomes relevant in reaction in non-tertiary alcohols such as 2-propanol (Scheme 2), and offers an opportunity to probe the mechanistic relationship between the two related pathways.

Reaction profiles and kinetics. Figure 1 shows typical profiles of reduction of **1** catalyzed by (*S*)-**6a** in 2-propanol. An observed rate constant (k_{obs}) was determined under the standard AH conditions ([(*S*)-**6a**] = 0.1 mM, [**1**] = 0.20 M, [KO-*t*-C_4H_9] = 4 mM, $P(H_2)$ = 2 atm, T = 25 °C, $(CH_3)_2$CHOH solvent, V_T = 10 mL) and the ATH conditions ([(*S*)-**6a**] = 0.1 mM, [**1**] = 0.20 M, [KO-*t*-C_4H_9] = 4 mM, T = 80 °C, $(CH_3)_2$CHOH solvent, V_T = 10 mL). Ketone **1** was converted into (*R*)-**2** smoothly for both systems without formation of any side-products (Figure 1a,b). For AH, addition of an aliquot of **1** (t = 0), once steady-state conditions have been achieved, yields a pseudo-first-order dependence on [**1**], allowing for k_{obs} determination according to: $\ln[\mathbf{1}]_t = -k_{obs}(t) + \ln[\mathbf{1}]_0$ ([**1**]$_0$ = initial concentration of **1**, t = 0; Figure 1c). Typically, a TOF of 6000 h^{-1} was observed ($P(H_2)$ = 2, T = 25 °C). No ATH took place at room temperature. For ATH at 80 °C, k_{obs} could be directly determined from the reaction profile (Figure 1d). At this temperature, TOF approached 14000 h^{-1}. Importantly, for both systems, the TOF was not limited by [**1**] under the conditions used, showing saturation kinetics.

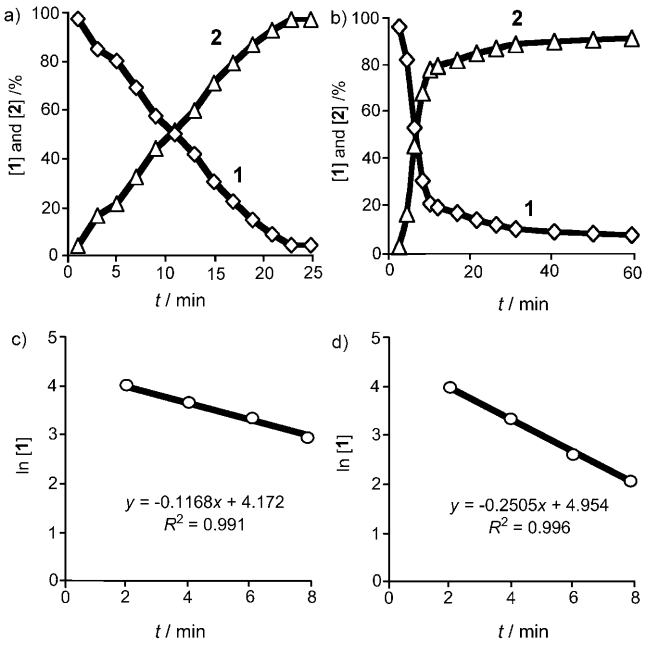


Figure 1. Reaction profiles for a) asymmetric hydrogenation (AH) and b) asymmetric transfer hydrogenation (ATH) of acetophenone (**1**) catalyzed by [$RuCl_2$\{(*S*)-tolbinap\}(pica)] ((*S*)-**6a**). Calculation of k_{obs} for c) AH and d) ATH. Conditions: for AH, [(*S*)-**6a**] = 0.10 mM; [**1**] = 0.20 M, [KO-*t*-C_4H_9] = 4 mM, $P(H_2)$ = 2 atm, T = 25 °C, $(CH_3)_2$CHOH solvent (V_T = 10 mL); for ATH, [(*S*)-**6a**] = 0.10 mM, [**1**] = 0.20 M, [KO-*t*-C_4H_9] = 4 mM, T = 80 °C, $(CH_3)_2$CHOH solvent (V_T = 10 mL).

The enantioselectivity of AH catalyzed by (*S*)-**6a** or (*S*)-**6b** in 2-propanol was constant ((*R*)-**2** in 18–19% *ee*). On the other hand, the *ee* value of (*R*)-**2** obtained by ATH using a 0.1–0.2 M solution decreased slowly with time owing to the inherent reversibility.[9,14,17] The reduction gave (*R*)-**2** with 45% *ee* at 50% conversion and 39% *ee* at 96% conversion, and further decreased to 30% *ee* when the reaction period was prolonged. Furthermore, the reaction became slower with increasing substrate concentration. Incomplete conversion and lower enantioselectivity were observed at higher [**1**] (a lower 2-propanol amount) even after a long reaction period, for example, (*R*)-**2** in 33% yield and 37% *ee* under the conditions: [(*S*)-**6a**] = 0.80 mM, [**1**] = 1.6 M, [KO-*t*-C_4H_9] = 20 mM, T = 80 °C, $(CH_3)_2$CHOH solvent, t = 2 h, V_T = 2 mL. ATH of the aryl ketone **1** (TOF = 14000 h^{-1}), giving (*R*)-**2** in 40% *ee*, proceeded much faster than that of the bulky di-

alkyl ketone **3** under the same conditions (TOF = 460 h^{-1}, (*S*)-**4** in 85% *ee*). Use of ethanol as solvent resulted in very poor reactivity (TOF = 80 h^{-1}) to afford (*R*)-**2** in 28% *ee*.

Solvent effect on enantioselection. As was seen in the reaction of **3**, the enantioselectivity of AH catalyzed by (*S*)-**6a** was solvent-dependent, giving (*R*)-**2** in 54% *ee* in ethanol, 19% *ee* in 2-propanol, and 13% *ee* in *tert*-butyl alcohol under the standard AH conditions at 25°C. AH of **1** proceeded smoothly in *tert*-butyl alcohol, a solvent incapable of undergoing ATH, albeit with low enantioselection. Use of (*S*)-**6b** at 25°C gave (*R*)-**2** in 58% *ee* (ethanol) or 18% *ee* (2-propanol).

ATH of **1** at 80°C catalyzed by (*S*)-**6a** and 2-propanol or ethanol as solvent gave (*R*)-**2** in 40% *ee* (93% conversion after 0.6 h) and 28% *ee* (4% conversion after 1 h), respectively. Reaction with (*S*)-**6b** in 2-propanol led to (*R*)-**2** in 39% *ee* with 96% conversion.

Reaction in H_2 atmosphere. The reaction profiles and corresponding k_{obs} values were obtained for AH (and ATH) of **1** catalyzed by (*S*)-**6** under different experimental conditions. For all determined k_{obs} values, linearity ($R^2 > 0.98$) was maintained for a conversion range of greater than 60% (TON = 1200). Table 1 lists selected kinetic data obtained. Most importantly, the reduction of **1** at ambient temperature proceeded solely by AH with H_2 acting as the only hydride source. No reaction was observed at 25°C under the ATH conditions (Table 1, entry 1). This was confirmed by several trials. Upon addition of 1 atm of H_2 to the same catalytic system, **1** was hydrogenated to give (*R*)-**2** (Table 1, entry 2). The reduction rate increased significantly with increasing H_2 pressure. Thus, k_{obs} values of 4.8, 9.3, and 100.8 $M^{-1}s^{-1}$ were obtained at 2, 4, and 20 atm, respectively, under otherwise analogous conditions.

Temperature effect on the degree of ATH. During AH in 2-propanol, increasing the reaction temperature clearly resulted in competitive degrees of ATH. Thus, at 60°C, reduction of **1** with **6a** proceeded by ATH (in the absence of H_2) although with incomplete conversion (50–58%, TOF = 1150–1250 h^{-1}, several trials). Raising the temperature to 80°C further increased the ATH rate (k_{obs} = 10.5 $M^{-1}s^{-1}$, TOF = 14000 h^{-1}) and conversion (96%). Thus, 2-propanol solvent can readily act as a hydride source at elevated temperatures. Practically the same rate was observed under 1 atm of H_2, although the reduction rates were further enhanced with increasing H_2 pressure. Thus, k_{obs} values of 9.8, 27.8, and 33.3 $M^{-1}s^{-1}$ were found at 80°C for 1, 2, and 4 atm of H_2, respectively, corresponding to a 4.4- (2 atm) and 5.3-fold increase (4 atm) over the rate for ATH in the absence of H_2.

A survey of the reaction at 80°C (Table 1) reveals that the overall reduction at very low H_2 pressure (0.5 atm) is faster than the reduction in the absence of H_2. Importantly, however, the reaction rate actually decreases when the pressure of H_2 is further increased to 1 atm. Since, in principle, the independent rate for the ATH at elevated temperature should remain constant, the variation in reduction rate appears to reflect changes in the relative concentrations of interchangeable AH- and ATH-active species and, possibly, inactive complexes. Although the rate for AH increases with increasing pressure, the ATH cycle dominates under low-pressure, high-temperature conditions (Scheme 2). Facile (re)generation of **12** from ATH-active **10** would increase the degree of ATH and, consequently, the overall reduction rate.[7] At higher pressures, the drive toward AH is a similar consequence of the mass balance for participating species, particularly the increased [**11**] and then [**12**].

Basicity effect on the degree of ATH. The basicity of the system is crucial to the overall catalysis, because proton relay is involved in the competing AH and ATH cycles. Thus, the reduction rate at 2 atm of H_2 and 25°C (conditions: [(*S*)-**6a**] = 0.1 mM, [**1**] = 0.20 M, [KO-*t*-C_4H_9] = 4 mM, $P(H_2)$ = 2 atm, T = 25°C, $(CH_3)_2CHOH$ solvent, V_T = 10 mL) was enhanced by increasing the solution basicity. The k_{obs} values changed from 3.6 to 4.8, 5.3 and 7.0 $M^{-1}s^{-1}$ for [KO-*t*-C_4H_9] of 0, 4, 20, and 100 mM, respectively.

The chloride-free H/BH_4-Ru complex (*S*)-**6b** catalyzes the AH of **1** in 2-propanol without the addition of a strong base,[6a] affording (*R*)-**2** with 27% *ee* in 99% yield. Notably, this complex, though slightly basic in 2-propanol, is a feeble catalyst

Table 1. Observed rate constants (k_{obs}, gradient of ln[**1**] versus reaction time) for asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) of acetophenone (**1**) in 2-propanol catalyzed by [$RuCl_2${(*S*)-tolbinap}(pica)] ((*S*)-**6**).[a]

Entry	Cat.	T [°C]	H_2 [atm]	[KO-*t*-C_4H_9] [mM]	k_{obs} [10^{-3} s^{-1}]	k_{obs}/[**6**] [$M^{-1}s^{-1}$]	*ee* (*R*)-**2** [%]
1	(*S*)-**6a**	25	0	4	no reaction		–
2	(*S*)-**6a**	25	2	4	1.9	4.8	19
3	(*S*)-**6b**	25	2	0	1.5	3.6	27
4	(*S*)-**6a**	25	2	20	2.1	5.3	17
5[b]	(*S*)-**6a**	25	2	20	0.7	1.8	13
6	(*S*)-**6a**	25	2	100	2.8	7.0	15
7	(*S*)-**6a**	25	4	4	3.7	9.3	19
8	(*S*)-**6a**	25	20	4	40.3	100.8	19
9[c]	(*S*)-**6a**	60	0	4	0.5	1.3	45
10	(*S*)-**6a**	80	0	4	4.2	10.5	40
11	(*S*)-**6a**	80	0.5	4	5.6	14.0	38
12	(*S*)-**6b**	80	1	0	1.5	3.8	29
13	(*S*)-**6a**	80	1	4	3.9	9.8	33
14	(*S*)-**6a**	80	1	20	8.0	20.0	38
15	(*S*)-**6a**	80	1	100	3.8	9.5	35
16	(*S*)-**6a**	80	2	4	11.1	27.8	34
17	(*S*)-**6a**	80	4	4	13.3	33.3	31
18	(*S*)-**6a**	80	8	4	15.6	39.0	21

[a] Conditions: for AH, [(*S*)-**6**] = 0.10 mM; [**1**] = 0.20 M, $(CH_3)_2CHOH$ solvent (V_T = 10 mL), > 90% conversion; for ATH, [**6**] = 0.10 mM, [**1**] = 0.20 M, $(CH_3)_2CHOH$ solvent (V_T = 10 mL), > 90% conversion. [b] Solvent = *t*-C_4H_9OH. [c] Maximum conversion was 57%.

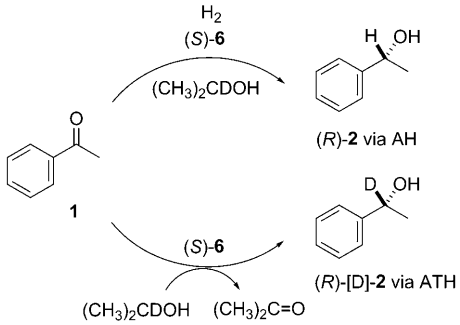
for the ATH of **1** even at 80 °C in the absence of added base, giving only 23 % conversion after 4 h ([**6b**] = 0.1 mM, [**1**] = 0.20 M, $(CH_3)_2CHOH$ solvent, V_T = 10 mL). Upon addition of KO-*t*-C_4H_9 (4 mM) under otherwise identical conditions, ATH proceeded smoothly ($k_{obs} = 6.27\,M^{-1}s^{-1}$). The *ee* value of (*R*)-**2** obtained with or without KO-*t*-C_4H_9 was similar, 39 % versus 37 %. Further increase in the base concentration, however, had a detrimental effect on the reactivity, giving only 60 % and 42 % conversions after 1 h at a [KO-*t*-C_4H_9] of 20 or 100 mM, respectively. Under competing AH/ATH conditions, the observed reduction rates reflect the enhanced AH and reduced ATH reactivity with increasing [KO-*t*-C_4H_9] with k_{obs} values of 9.8, 20.0, and $9.5\,M^{-1}s^{-1}$ obtained with [KO-*t*-C_4H_9] of 4, 20, and 100 mM.

The role of the base is critical to both the AH and ATH pathways, as expected from the mechanistic scenario of Scheme 2. In the AH cycle, a basic medium favors the turnover-limiting deprotonation of η-H_2 complex **11** under steady-state conditions, in addition to the elimination of HCl from **6** forming the catalysts **9** and **10**. A strong base is necessary for ATH as well, because the amido Ru complex **10** must be generated in a significant concentration from the cationic amino complex **9**. However, at very high base concentrations, ATH is hindered for unknown reasons.

Enantioselectivity in AH and ATH. Because of the NH_2/pyridine hybrid structure of pica, the Ru catalyst **6** is unable to clearly differentiate the phenyl and methyl group in **1**. Although the enantioselectivity was subject to the reaction conditions, a higher enantioselectivity was obtained for the reduction of **1** by ATH (40 %) compared to that by AH (15–19 %) for this system. Consequently, the higher enantioselectivity reflects an increased degree of ATH. AH of **1** at 25 °C, in the absence of ATH, gives (*R*)-**2** in 15–19 % *ee* under various conditions, while at 80 °C the product enantioselectivity ranges from 21 % (8 atm) to 40 % (0 atm) depending on the H_2 pressure (Table 1).

As noted earlier, the chiral arene-Ru catalyst (*S,S*)-**7b** catalyzes both AH and ATH of **1**, giving (*S*)-**2** with the same 96 % *ee*, owing probably to the involvement of a common RuH species, though the conditions vary from slightly acidic to basic.[18] Likewise, *cis*-[$RuCl_2${(*R*,*S*)-josiphos}(pica)][11a] affords the same degree of chiral induction, (*R*)-**2** with 83 % *ee*, for AH (25 °C) and ATH (80 °C) of **1** in 2-propanol containing KO-*t*-C_4H_9. Despite some difference in reaction temperature, this observation is in accord with Scheme 2, which contains a common RuH intermediate **12** for AH and ATH. These phenomena are in contrast to the present AH and ATH catalyzed by **6**. Here, the different degree of enantioselection in AH and ATH suggests the participation of different chiral RuH species—for example, species with different geometries and/or auxiliary X groups. In view of the similar behavior of precatalysts **6a** and **6b**, chloride would not be involved in the catalytic intermediates. The equilibrium ratio of different RuH species **12** is variable depending on the reaction conditions, because their precursors **10** may have different chemical properties including the Lewis acidity of Ru and the basicity of amido nitrogen. However, more elaborate reaction pathways cannot be ruled out under these reaction conditions.

Hydride source in AH and ATH. Scheme 2 suggests that, if **6** does not cause the H/D exchange between H_2 and $(CH_3)_2CDOH$ to any great degree,[7] AH must exhibit no deuteration in **2**, since RuH species **12** is generated only from H_2.[26] On the other hand, ATH in $(CH_3)_2CDOH$ solvent is expected to lead to a deuterated product at the C-1 position, [D]-**2**, since dehydrogenation of the secondary alcohol generates a RuD complex, [D]-**12**, as reducing species.[9,27] This was the case, as shown in Scheme 3. Under



Scheme 3. Hydride source in asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) of **1** in 2-propanol catalyzed by [$RuCl_2${(*S*)-tolbinap}(pica)] ((*S*)-**6a**).

1 atm of H_2 in $(CH_3)_2CDOH$ (98 % D content; [(*S*)-**6a**] = 0.1 mM, [**1**] = 0.2 M, [KO-*t*-C_4H_9] = 4 mM, V_T = 10 mL), hydrogenation of **1** proceeded smoothly at 25 °C, giving (*R*)-**2** in 17 % *ee* with no detectable deuterium incorporation (**2**/[D]-**2** = 100:0). No decrease in D content was seen in the recovered $(CH_3)_2CDOH$. Thus, at ambient temperature, a net AH occurs overwhelmingly by using H_2 with alcohol solvent acting merely as a proton donor. Without H_2, no reduction occurred at 25 °C. Heating **1** at 80 °C in $(CH_3)_2CDOH$ in the absence of H_2, under otherwise analogous conditions, yielded a mixture of (*R*)-**2** and (*R*)-[D]-**2** (37 % *ee*) in the ratio of 2:98 (^1H NMR). These observations are fully consistent with Scheme 2. This result also indicates that ATH-active RuH **12** does not undergo isotope exchange by protonation with 2-propanol solvent. This in turn suggests that deprotonation of **11**, depending on its geometry and X, to **12** is virtually irreversible.[26i,28]

Deuterium isotope effect. 2-Propanol does not reduce **1** at 25 °C in the presence of **6** and a strong base, but does so smoothly at 80 °C. Furthermore, $(CH_3)_2CDOH$ cleanly acts as a hydride source for generation of active [D]-**12** under the ATH conditions. Notably, the rate for ATH using $(CH_3)_2CDOH$ at 80 °C differs significantly from that with non-deuterated $(CH_3)_2CHOH$. Competition experiments using a $(CH_3)_2CHOH/(CH_3)_2CDOH$ (1:1) solvent mixture gave the product in a **2**/[D]-**2** ratio of 80:20, corresponding to a fourfold decrease in reactivity for the C_α-deuterated solvent.[29] In comparison, AH proceeded with similar rates in $(CH_3)_2CHOH$ and $(CH_3)_2CDOH$ at 25 °C ($k_{obs\text{-}H}/k_{obs\text{-}D}$ of 1.1,

$k_{obs\text{-}D}$/[**6a**] = 4.3 M^{-1}s^{-1}; **2**/[D]-**2** = 100:0), although the isotope effect could not be determined at elevated temperature owing to the influence of competing ATH.

Competition of AH and ATH with H_2/$(CH_3)_2$CDOH. Reduction of **1** with H_2/$(CH_3)_2$CDOH and (*S*)-**6a** at 80 °C and 0.5 to 8 atm ([(*S*)-**6a**] = 0.1 mM, [**1**] = 0.2 M, [KO-*t*-C_4H_9] = 4 mM, V_T = 10 mL) gave (*R*)-**2** with a **2**/[D]-**2** ratio ranging from 52:48 to 98:2 (Scheme 3). Table 2 summarizes the results. Bearing in mind the isotope effects on the reactivity in ATH (k_H/k_D = 4), the (*R*)-**2**/(*R*)-[D]-**2** ratio provides an approximate measure of the degree of ATH and AH under a given condition. At 80 °C, the participation of ATH is considerably high at low H_2 pressures (0.5–2 atm) and remains significant, accounting for about 40 % of the total conversion even at 4 atm. At the higher pressure of 8 atm, however, the degree of AH increases dramatically giving an AH/ATH ratio as high as 98:2 (Table 2, entry 11). These findings are consistent with the observed *ee* values for (*R*)-**2**, which decrease gradually from 26 % (0.5 atm) to 17 % (8 atm) as the pressure increases (Table 2, entry 3 and 11). By decreasing the temperature to 60 °C and the H_2 pressure to 1 atm, the degree of ATH decreases to give an AH/ATH ratio of 78:22 (48 % conversion; Table 2, entry 5). The lower enantioselectivity of the reaction in $(CH_3)_2$CDOH (26 % *ee*; Table 2, entry 6) in comparison to the value with $(CH_3)_2$CHOH, 33 % (Table 1, entry 13), similarly reflects the reduced ATH rate. These observations agree with the above arguments.

Table 2. Degree of deuterium incorporation in (*R*)-1-phenylethanol ((*R*)-**2**) and AH/ATH ratio for asymmetric reduction of acetophenone (**1**) with H_2/$(CH_3)_2$CDOH catalyzed by [$RuCl_2$[(*S*)-tolbinap](pica)] ((*S*)-**6a**).[a]

Entry	H_2 [atm]	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]	**2**/[D]-**2**
1	0	25	9	no reaction	–	–
2	0	80	9	98	37	2:98
3	0.5	80	4	93	26	52:48
4	1	25	9	99	17	100:0
5	1	60	8	87	17	78:22[b]
6	1	80	4	99	26	58:42
7[c]	1	80	5	96	22	64:36
8[d]	1	80	1	97	25	72:28
9	2	80	4	84	15	63:37
10	4	80	4	99	19	86:14
11	8	80	0.5	>99	17	98:2

[a] Conditions: [**6a**] = 0.1 mM; [**1**] = 0.2 M; [KO-*t*-C_4H_9] = 4 mM; $(CH_3)_2$CDOH solvent (V_T = 10 mL). [b] Maximum conversion was 48 %. [c] [KO-*t*-C_4H_9] = 100 mM. [d] (*S*)-**6b** was used as catalyst, [KO-*t*-C_4H_9] = 0 mM.

Conclusions

The ability of binap/pica-Ru complexes **6** to efficiently catalyze AH of bulky *tert*-alkyl ketones such as **3** is ascribed to the functional/structural characteristics of the hybrid pica ligand in addition to the chiral recognition capability of binap. The reaction utilizes only H_2 gas as a hydride source even in alcoholic solvents having α-hydrogen atom(s). The pica complexes effect both AH and ATH of the aromatic ketones including **1** but cannot rival the dpen catalysts **5** in terms of reactivity and enantioselectivity. In general, the relative significance of the AH and ATH cycle is subject to the particular catalyst ligand-framework structure, ketonic substrates, and reaction parameters (solvent, H_2 pressure, temperature, basicity, concentration, H/D difference, etc.), and reflect a delicate balance for the catalytic species under steady-state conditions.

Experimental Section

General

All manipulations were conducted in oven-dried glassware using standard Schlenk techniques employing Ar gas (99.998 %, purified through a BASF R3-11 catalyst at 80 °C). Toluene, benzene, hexane, and ether were distilled from metal sodium/benzophenone and stored in Schlenk tubes with a sodium mirror. CH_2Cl_2, CH_3CH_2OH, and $(CH_3)_2CHOH$ were freshly distilled from CaH_2 prior to use. DMF was distilled from CaH_2 and stored in a Schlenk tube with molecular sieves (4 Å). $CDCl_3$, $(CH_3)_2CDOH$, CD_3CD_2OH, [D_8]toluene, and [D_6]benzene were purchased from Aldrich Chemical Company (Milwaukee, WI), stored in Schlenk tubes (teflon taps) over CaH_2, and freshly distilled and degassed prior to use.

[$RuCl_2(\eta^6$-benzene)]$_2$ and α-picolylamine (pica) were purchased from Aldrich Chemical Co. CaH_2 was purchased from Tianjin Beidouxing Fine Chemicals. $NaBH_4$ was purchased from Shanghai Chemical Company. KO-*t*-C_4H_9 (purified by sublimation) was purchased from Tokyo Chemical Industry Co. Acetophenone (**1**) and pinacolone (**6**) were purchased from Shanghai Chemical Company and purified by distillation from CaH_2. (*S*)-2,2′-Bis(di-4-tolylphosphino)-1,1′-binaphthyl ((*S*)-tolbinap) was purchased from AZmax. H_2 gas (99.9999 %) was obtained from Shanghai Pujiang Specialty Gases Co., Ltd. [$RuCl_2$[(*S*)-tolbinap](pica)] ((*S*)-**6a**),[6a] [$RuH(\eta^1$-BH_4)[(*S*)-tolbinap](pica)] ((*S*)-**6b**),[5a] *trans*-[$RuCl_2$[(*S*)-tolbinap]{(*S*,*S*)-dpen}] ((*S*,*SS*)-**5b**),[4a] and *cis*-[$RuCl_2$[(*R*,*S*)-josiphos]-(pica)][11a] were synthesized according to the procedures in the literature.

Gas chromatography (GC) analysis was conducted on a Hewlett Packard 6890 instrument equipped with a BETA-DEX 120 fused silica capillary column (df = 0.25 μm, 0.25 mm i.d., 30 m, Supelco). ^{1}H- and ^{13}C NMR data were collected on a JEOL α-400 NMR, Bruker DMX-500 or AMX-400, and 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).

Synthesis of Ru Complexes

[$RuCl_2$[(*S*)-tolbinap](pica)] ((*S*)-**6a**): [$RuCl_2(\eta^6$-benzene)]$_2$ (105.5 mg, 0.21 mmol) and 2 equivalents of (*S*)-tolbinap (286.0 mg, 0.42 mmol) were dissolved in DMF (5 mL) and placed in a 10 mL Schlenk flask under an Ar atmosphere. Ar was bubbled through the solution for 5 min. The suspension was then heated at 100 °C for 10 min. Following solvent removal under vacuum, pica (45.4 mg, 0.42 mmol) was added together with CH_2Cl_2 (3 mL). The solution was stirred for 2 h. Reduction of the volume to about 0.5 mL and addition of hexane (2 mL) yielded a yellow precipitate. The supernatant was removed by filtration and the resulting powder was dried in vacuo to give (*S*)-**6a** in 86 % yield (322.0 mg) as a mixture of stereoisomers. Heating at 80 °C for 30 min in toluene resulted in the Ru complex consisting predominantly of a single isomer (>95 %). This was used for hydrogenation and transfer hydrogenation without further purification. ^{1}H NMR (400 MHz, [D_6]benzene): δ = 1.78 (s, 3, CH_3), 1.90 (s, 3, CH_3), 2.28 (s, 3, CH_3), 2.33 (s, 3, CH_3), 2.86 (br s, 1, N*H*H), 3.22 (br s, 1, NH*H*), 3.95 (br s, 1, CH*H*), 4.93 (br s, 1, C*H*H), 6.19–8.36 ppm (m, 32, ar-

omatics); ^{31}P (161.7 MHz, [D$_6$]benzene): $\delta = 44.74$ (d, $J = 35.6$ Hz), 41.93 ppm (d, $J = 35.6$ Hz).

[RuH(η^1-BH$_4$){(*S*)-tolbinap}(pica)] ((*S*)-**6b**): Compounds (*S*)-**6a** (50.2 mg, 0.052 mmol) and NaBH$_4$ (30.1 mg, 0.81 mmol) were placed in a 20 mL Schlenk flask in an Ar atmosphere. Addition of a 1:1 mixture of degassed benzene and C_2H_5OH (5 mL) immediately resulted in a pale red solution. This mixture was stirred at 40 °C for about 1 min, and then immediately frozen in a liquid N_2 bath. The solvent was removed in vacuo. The residue was extracted with benzene (5 mL), and the solution was filtered through a celite pad. The filtrate was concentrated to about 0.3 mL, and hexane (3 mL) was added to precipitate a pale yellow solid. The supernatant was removed by filtration and the resulting powder was dried in vacuo to give (*S*)-**6b** (28.2 mg, 60 %): ^1H NMR (400 MHz, [D$_6$]benzene): $\delta = -13.82$ (t, 1, $J = 23.9$ Hz, RuH), −0.75 (br s, 4, BH$_4$), 1.51 (m, 1, N*H*H), 1.82 (m, 1, C*H*H), 1.85 (s, 3, CH$_3$), 1.90 (s, 3, CH$_3$), 2.13 (s, 3, CH$_3$), 2.16 (s, 3, CH$_3$), 2.28 (m, 1, CH*H*), 3.29 (m, 1, NH*H*), 5.26–8.81 ppm (m, 44, aromatics); ^{31}P (161.7 MHz, [D$_6$]benzene): $\delta = 71.6$ (d, $J = 41.4$ Hz), 74.2 ppm (d, $J = 41.4$ Hz). Complex (*S*)-**6b** was used for hydrogenations immediately after synthesis.

Hydrogenation

Standard procedure: a) Acetophenone (**1**) as substrate: Accurately weighed amounts of (*S*)-**6a** (2.3 mg, 0.4 mM) and solid KO-*t*-C$_4$H$_9$ (13.5 mg, 20 mM) were placed in a pre-oven-dried (120 °C) 100 mL glass autoclave containing a magnetic stirring bar and subjected to high vacuum for at least 5 min before purging with argon. Freshly distilled solvent (5.5 mL) and purified **1** (0.56 mL, 0.80 M) were placed into a predried Schlenk flask, degassed by running Ar through the solution (5 min), then added to the autoclave in an Ar atmosphere. H_2 was introduced under 4 atm pressure with several quick release–fill cycles before being reduced to the desired pressure. The solution was vigorously stirred at 25 °C and H_2 consumption was monitored. Following the designated reaction time, the H_2 was released, and a small aliquot of the crude product mixture was analyzed by chiral GC to determine the conversion and *ee* value of **2**: BETA-DEX 120 fused silica capillary column (df = 0.25 μm, 0.25 mm i.d., 30 m, Supelco); $P = 100.7$ kPa; $T = 120$ °C; t_R of (*R*)-**2**: 14.8 min; t_R of (*S*)-**2**: 15.8 min. b) Pinacolone (**3**) as substrate: The same procedure was used as in (a). Following the designated reaction time, the H_2 was released, and a small aliquot of the crude product mixture was analyzed by chiral GC to determine the conversion and *ee* value of **4**: CP-Chirasil-DEX CB column (df = 0.25 μm, 0.32 mm i.d., 25 m); $P = 41.5$ kPa; $T = 60$ °C; t_R of (*R*)-**4**: 17.2 min; t_R of (*S*)-**4**: 17.9 min.

Hydrogenation profile measurement: a) Hydrogenations were conducted in a glass autoclave equipped with a sampling needle connected to a three-way stop valve as previously described.[7a] This experimental setup allowed for samples to be taken from, or added to, the reaction mixture in an H_2 or Ar atmosphere. An accurately measured mass of (*S*)-**6** was placed into 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. Into a predried Schlenk tube were placed accurately measured amounts of **1**, KO-*t*-C$_4$H$_9$, and a solvent such that desired [(*S*)-**6**], [**1**], S/C ratio, and [KO-*t*-C$_4$H$_9$] values were obtained. The reaction mixture was degassed by three freeze–thaw cycles and added under Ar to the autoclave. If needed, the autoclave was placed in a prewarmed oil bath set at the desired reaction temperature. H_2 was introduced under 4 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 (two drops into an ether-filled GC sample tube) at specified time intervals (t), and the degree of substrate consumption and *ee* value of **2** were determined by GC. Conditions: [(*S*)-**6a** or (*S*)-**6b**] = 0.1 mM; [**1**] = 0.2 M; $P(H_2) = 1$–8 atm; [KO-*t*-C$_4$H$_9$] = 0, 4, 20, or 100 mM; S/C = 2000; $T = 25$, 60, or 80 °C; $t = 0.5$–9 h; $V_T = 10$ mL, solvent = $(CH_3)_2CHOH$ or $(CH_3)_3COH$. b) The experimental setup and sample preparation were the same as in (a). Assuming a similar reaction profile under the same experimental conditions, a predetermined period of time was allowed such that an estimated >95% amount of substrate was consumed. Following sample collection, an aliquot of **1** was added as follows: Degassed (three freeze–thaw cycles) and distilled **1** (0.23 mL) and $(CH_3)_2CHOH$ (3.8 mL) were added to a predried thick-walled Schlenk glass autoclave. The argon atmosphere was changed to H_2. This system was connected to the hydrogenation autoclave through high-pressure tubing, and the contents were added ($t = 0$ min) using a positive pressure flow of H_2. Samples were then obtained at regular time intervals (t), and the degree of substrate consumption and enantioselectivity were determined by GC. Conditions: [(*S*)-**6a**] = 0.1 mM; [**1**] = 0.2 M; $P(H_2) = 2$ atm; [KO-*t*-C$_4$H$_9$] = 0, 4, 20, 100 mM; S/C = 1000 (+2000 for aliquot of **1**); $T = 25$ °C; $t = 1$–9 h; $V_T = 10$ mL, solvent = $(CH_3)_2CHOH$.

Kinetic k_{obs} determination: The observed reaction rate constant (k_{obs}) was derived from the gradient for the expression $\ln[\mathbf{1}]_t = -k_{obs}(t) + \ln[\mathbf{1}]_0$ from data collected for reaction profiles in **a** and **b**; t = reaction time; t_0 = initial sampling time; $[\mathbf{1}]_0 = [\mathbf{1}]$ at $t = 0$. Data points covering greater than 60 % consumption of **1** were used where the linearity (R^2) was greater than 0.98.

Deuterium content: Hydrogenations were conducted using the standard procedure with $(CH_3)_2CDOH$ or CD_3CD_2OH as solvent. Conditions: [(*S*,*SS*)-**5a** or (*S*)-**6a**] = 0.1 mM; [**1**] = 0.2 M; $P(H_2) = 1$–2 atm; [KO-*t*-C$_4$H$_9$] = 0, 20, or 100 mM; S/C = 1000; $T = 25$, 60, or 80 °C; $t = 4$–9 h; $V_T = 2$ or 10 mL. The deuterium content was determined by ^1H NMR analysis of purified (*S*)-**2**. The relaxation time needed to be extended (DL = 20 s) to obtain accurate and reproducible integration values. Deuterium incorporation was verified by ^2H NMR analysis. The results are given in Table 2.

Transfer Hydrogenation

Standard procedure: An accurately measured mass of (*S*,*SS*)-**5** (or (*S*)-**6**) and KO-*t*-C$_4$H$_9$ were placed into a predried (120 °C) Schlenk flask, and $(CH_3)_2CHOH$ and **1** were added such that desired [**1**], [KO-*t*-C$_4$H$_9$], and S/C values were obtained. The mixture was then placed into a prewarmed oil bath set at the desired reaction temperature. Sample aliquots of the reaction mixture were taken at designated time intervals (t), and the degree of substrate consumption and *ee* value of **2** were determined by GC. Conditions: [(*S*,*SS*)-**5** or (*S*)-**6**] = 0.1 mM; [**1**] = 0.2 M; [KO-*t*-C$_4$H$_9$] = 0, 4, 20, or 100 mM; S/C = 1000; $T = 25$, 60, or 80 °C; $t = 1$–5 h; $V_T = 2$ or 10 mL.

Kinetic k_{obs} determination: The observed reaction rate constant (k_{obs}) was derived as described above. Data points covering greater than 60 % consumption of **1** were used where the linearity (R^2) was greater than 0.98.

Deuterium content: Transfer hydrogenations were conducted as described above using $(CH_3)_2CDOH$ as solvent. Conditions: [(*S*,*SS*)-**5** or (*S*)-**6**] = 0.1 mM; [**1**] = 0.2 M; [KO-*t*-C$_4$H$_9$] = 4 mM; S/C = 1000; $T = 25$ or 80 °C; $t = 9$ h; $V_T = 10$ mL. Deuterium incorporation was determined as described above.

Acknowledgements

The Chinese Academy of Sciences (No. O7210122R0), the National Science Foundation (No. 20620140429), and the Japan Society for Promotion of Science (No. 15350079) are acknowledged for their financial support. The authors would like to thank Kanto Chemical Co., Inc. for providing some of the deuterated solvents.

[1] Reviews: a) T. Ohkuma, R. Noyori in *Comprehensive Asymmetric Catalysis*, *Vol. 1* (Ed.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 6.1; b) T. Ohkuma, M. Kitamura, R. Noyori in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, chap. 1; c) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; d) *Transition Metals for Organic Synthesis* (2nd Edition) (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 29–113; e) *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U, Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; f) *The Handbook of Homo-*

geneous Hydrogenation, Vol. 1–3 (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**.

[2] a) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; R. Noyori, *Adv. Synth. Catal.* **2003**, *345*, 15–32; b) W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096–2107; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007; W. S. Knowles, *Adv. Synth. Catal.* **2003**, *345*, 3–13. Recent advances in this field were described in *Acc. Chem. Res.* **2007**, *40*, issue no. 12.

[3] a) M. Kitamura, R. Noyori in *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**, pp. 3–52; b) R. Noyori, M. Kitamura, T. Ohkuma, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5356–5362.

[4] a) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792–1796; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703–1707; b) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73.

[5] Selected recent publications: a) T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509; b) T. Hamada, T. Torii, K. Izawa, R. Noyori, T. Ikariya, *Org. Lett.* **2002**, *4*, 4373–4376; c) T. Ohkuma, J. Li, R. Noyori, *Synlett* **2004**, *8*, 1383–1386.

[6] a) T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289; b) N. Arai, K. Suzuki, S. Sugizaki, H. Sorimachi, T. Ohkuma, *Angew. Chem. Int. Ed.* **2008**, *47*, 1770–1773.

[7] a) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; b) R. Noyori, C. A. Sandoval, K. Muñiz, T. Ohkuma, *Phil. Trans. R. Soc. A* **2005**, *363*, 901–912; c) C. A. Sandoval, T. Ohkuma, Y. Yamaguchi, K. Kato, R. Noyori, *Magn. Reson. Chem.* **2006**, *44*, 66–75.

[8] a) P. Cao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 2127–2129; b) K. Abdur-Rashid, A. J. Lough, R. H. Morris, *Organometallics* **2000**, *19*, 2655–2657; c) R. Hartmann, P. Chen, *Angew. Chem.* **2001**, *113*, 3693–3697; *Angew. Chem. Int. Ed.* **2001**, *40*, 3581–3585; d) K. Abdur-Rashid, M. Faatz, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2001**, *123*, 7473–7474; e) K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2002**, *124*, 15104–15118; f) C. J. A. Daley, S. H. Bergens, *J. Am. Chem. Soc.* **2002**, *124*, 3680–3691; g) R. Abbel, K. Abdur-Rashid, M. Faatz, A. Hadzovic, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2005**, *127*, 1870–1882; h) R. J. Hamilton, S. H. Bergens, *J. Am. Chem. Soc.* **2006**, *128*, 13700–13701.

[9] See also: a) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478; b) R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931–7944.

[10] a) K. Muñiz, *Angew. Chem.* **2005**, *117*, 6780–6785; *Angew. Chem. Int. Ed.* **2005**, *44*, 6622–6627; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406.

[11] a) W. Baratta, E. Herdtweck, K. Siega, M. Toniutti, P. Rigo, *Organometallics* **2005**, *24*, 1660–1669; b) W. Baratta, G. Chelucci, E. Herdtweck, S. Magnolia, K. Siega, P. Rigo, *Angew. Chem.* **2007**, *119*, 7795–7798; *Angew. Chem. Int. Ed.* **2007**, *46*, 7651–7654.

[12] Selected hydrogenation systems: a) K. Abdur-Rashid, A. J. Lough, R. Morris, *Organometallics* **2000**, *19*, 2655–2657; b) M. Ito, M. Hirakawa, K. Murata, T. Ikariya, *Organometallics* **2001**, *20*, 379–381; c) K. Abdur-Rashid, A. J. Lough, R. H. Morris, *Organometallics* **2001**, *20*, 1047–1049; d) K. Abdur-Rashid, M. Faatz, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2001**, *123*, 7473–7474; e) K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2002**, *124*, 15104–15118; f) V. Rautenstrauch, X. Hoang-Cong, R. Churlaud, K. Abdur-Rashid, R. H. Morris, *Chem. Eur. J.* **2003**, *9*, 4954–4967; g) W. Baratta, P. Da Ros, A. Del Zotto, A. Sechi, E. Zangrando, P. Rigo, *Angew. Chem.* **2004**, *116*, 3668–3672; *Angew. Chem. Int. Ed.* **2004**, *43*, 3584–3588; h) K. Abdur-Rashid, R. Guo, A. J. Lough, R. H. Morris, D. Songa, *Adv. Synth. Catal.* **2005**, *347*, 571–579; i) R. J. Hamilton, C. G. Leong, G. Bigam, M. Miskolzie, S. H. Bergens, *J. Am. Chem. Soc.* **2005**, *127*, 4152–4153; j) R. Abbel, K. Abdur-Rashid, M. Faatz, A. Hadzovic, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2005**, *127*, 1870–1882; k) D. Xue, Y.-C. Chen, X. Cui, Q.-W. Wang, J. Zhu, J.-G. Deng, *J. Org. Chem.* **2005**, *70*, 3584–3591; l) K. Abdur-Rashid, R. Abbel, A. Hadzovic, A. J. Lough, R. H. Morris, *Inorg. Chem.* **2005**, *44*, 2483–2492; m) W. Chen, W. Mbafor, S. M. Roberts, J. Whittall, *Tetrahedron: Asymmetry* **2006**, *17*, 1161–1164; n) H. Huang, T. Okuno, K. Tsuda, M. Yoshimura, M. Kitamura, *J. Am. Chem. Soc.* **2006**, *128*, 8716–8717; o) T. Ohkuma, N. Utsumi, M. Watanabe, K. Tsutsumi, N. Arai, K. Murata, *Org. Lett.* **2007**, *9*, 2565–2567; p) N. Arai, H. Ooka, K. Azuma, T. Yabuuchi, N. Kurono, T. Inoue, T. Ohkuma, *Org. Lett.* **2007**, *9*, 939–941; q) L. A. Saudan, C. M. Saudan, C. Debieux, P. Wyss, *Angew. Chem.* **2007**, *119*, 7617–7620; *Angew. Chem. Int. Ed.* **2007**, *46*, 7473–7476; r) M. L. Clarke, M. B. Diaz-Valenzuela, A. M. Z. Slawin, *Organometallics* **2007**, *26*, 16–19; s) M. Ito, A. Sakaguchi, C. Kobayashi, T. Ikariya, *J. Am. Chem. Soc.* **2007**, *129*, 290–291.

[13] Selected non-hydrogenation systems: a) K. Murata, H. Konishi, M. Ito, T. Ikariya, *Organometallics* **2002**, *21*, 253–255; b) M. Ito, M. Hirakawa, A. Osaku, T. Ikariya, *Organometallics* **2003**, *22*, 4190–4192; c) M. Watanabe, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2003**, *125*, 7508–7509; d) T. Ikariya, H. Wang, M. Watanabe, K. Murata, *J. Organomet. Chem.* **2003**, *689*, 1377–1381; e) K. Majima, R. Takita, A. Okada, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845; f) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; g) H. Wang, M. Watanabe, T. Ikariya, *Tetrahedron Lett.* **2005**, *46*, 963–966; h) R. Guo, R. H. Morris, D. Song, *J. Am. Chem. Soc.* **2005**, *127*, 516–517; i) J. Zhao, J. F. Hartwig, *Organometallics* **2005**, *24*, 2441–2444; j) R. Guo, C. Elpelt, X. Chen, D. Song, R. H. Morris, *Org. Lett.* **2005**, *7*, 1757–1759; k) K. Abdur-Rashid, R. Guo, A. J. Lough, R. H. Morris, D. Song, *Adv. Synth. Catal.* **2005**, *347*, 571–579; l) M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc.* **2005**, *127*, 6172–6173; m) T. Koike, T. Ikariya, *Organometallics* **2005**, *24*, 724–730.

[14] a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; b) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061; c) K. Everaere, A. Mortreux, J.-F. Carpentier, *Adv. Synth. Catal.* **2003**, *345*, 67–77; d) J.-B. Sortais, V. Ritleng, A. Voelklin, A. Holuigue, H. Smail, L. Barloy, C. Sirlin, G. K. M. Verzijl, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, M. Pfeffer, *Org. Lett.* **2005**, *7*, 1247–1250; e) W. Baratta, G. Chelucci, S. Gladiali, K. Siega, M. Toniutti, M. Zanette, E. Zangrando, P. Rigo, *Angew. Chem.* **2005**, *117*, 6370–6375; *Angew. Chem. Int. Ed.* **2005**, *44*, 6214–6219; f) M. T. Reetz, X. Li, *J. Am. Chem. Soc.* **2006**, *128*, 1044–1045; g) W. Baratta, M. Bosco, G. Chelucci, A. Del Zotto, K. Siega, M. Toniutti, E. Zangrando, P. Rigo, *Organometallics* **2006**, *25*, 4611–4620; h) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236; i) W. Baratta, K. Siega, P. Rigo, *Chem. Eur. J.* **2007**, *13*, 7479–7486.

[15] For a mechanistic discussion, see: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*; Wiley, New York, **1994**, chap. 2; b) J. Halpern in *Asymmetric Synthesis Vol. 5*, (Ed.: J. D. Morrison), Academic Press, New York, **1994**, chap. 1; c) J. M. Brown, *J. Organomet. Chem.* **2004**, *689*, 4006–4015; d) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201–2237; e) *Mechanisms in Homogeneous Catalysis*, (Ed.: B. Heaton), Wiley-VCH, Weinheim, **2005**, chap. 1.

[16] a) D. S. Moore, S. D. Robinson, *Chem. Soc. Rev.* **1983**, *12*, 415–452; b) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books: Mill Valley, **1987**.

[17] a) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–288; b) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588; c) D. G. I. Petra, J. N. H. Reek, J.-W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leewen, *Chem. Eur. J.* **2000**, *6*, 2818–2829; d) M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem.* **2001**, *113*, 2900–2903; *Angew. Chem. Int.*

Ed. **2001**, *40*, 2818–2821; e) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237–248.

[18] a) T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. A. Sandoval, R. Noyori, *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725; b) C. A. Sandoval, T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, R. Noyori, *Chem. Asian J.* **2006**, *1*, 102–110; c) T. Ohkuma, K. Tsutsumi, N. Utsumi, N. Arai, R. Noyori, K. Murata, *Org. Lett.* **2007**, *9*, 255–257.

[19] Phosphine/osmium complexes with an NH_2 ligand catalyze the AH and ATH of **1**: a) W. Baratta, M. Ballico, G. Chelucci, K. Siega, P. Rigo, *Angew. Chem.* **2008**, *120*, 4434–4437; *Angew. Chem. Int. Ed.* **2008**, *47*, 4362–4365; b) W. Baratta, M. Ballico, A. Del Zotto, K. Siega, S. Magnolia, P. Rigo, *Chem. Eur. J.* **2008**, *14*, 2557–2563.

[20] Binap/Ru complexes effect AH and ATH of unsaturated carboxylic acids: a) T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174–3176; b) J. M. Brown, H. Brunner, W. Leitner, M. Rose, *Tetrahedron: Asymmetry* **1991**, *2*, 331–334.

[21] Achiral (cyclopentadienone)Ru carbonyl complexes effect AH and ATH of **1**: a) Y. Blum, D. Czarkle, Y. Rahamim, Y. Shvo, *Organometallics* **1985**, *4*, 1459–1461; b) C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana, *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100.

[22] See also: a) T. Langer, G. Helmchen, *Tetrahedron Lett.* **1996**, *37*, 1381–1384; b) T. Sammakia, E. L. Stangeland, *J. Org. Chem.* **1997**, *62*, 6104–6105; c) Y. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* **1999**, *18*, 2291–2293; d) Y. Arikawa, M. Ueoka, K. Matoba, Y. Nishibayashi, M. Hidai, S. Uemura, *J. Organomet. Chem.* **1999**, *572*, 163–168; e) F. Naud, C. Malan, F. Spindler, C. Rüggeberg, A. T. Schmidt, H.-U. Blaser, *Adv. Synth. Catal.* **2006**, *348*, 47–50.

[23] Enantioselectivity of AH of **1** using **5** is solvent-independent, while the rate is highly influenced by the nature of alcoholic solvents.[7]

[24] Josiphos = 1-[diarylphosphano]-2-[1-(dicyclohexylphosphano)ethyl]-ferrocene. MePyme = 1-methyl-1-(pyridine-2-yl)methanamine.

[25] ATH experiments were conducted at a maximum temperature of 80 °C, since this was the highest attainable temperature for AH reaction profile experiments in 2-propanol (safety and practical reasons).

[26] a) J. M. Brown, D. Parker, *Organometallics* **1982**, *1*, 950–956; b) T. Ohta, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1990**, *31*, 7189–7192; c) M. T. Ashby, J. Halpern, *J. Am. Chem. Soc.* **1991**, *113*, 589–594; d) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 11703–11714; e) A. S. C. Chan, C. C. Chen, T. K. Yang, J. H. Huang, Y. C. Lin, *Inorg. Chim. Acta* **1995**, *234*, 95–100; f) J. M. Brown, M. Rose, F. I. Knight, A. Wienland, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 242–251; g) I. D. Gridnev, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2000**, *122*, 10486–10487; h) M. Kitamura, M. Tsukamoto, Y. Bessho, M. Yoshimura, U. Kobs, M. Widhalm, R. Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6649–6667; i) A. Berkessel, T. J. S. Schubert, T. N. Müller, *J. Am. Chem. Soc.* **2002**, *124*, 8693–8698; j) Y. Ishibashi, Y. Bessho, M. Yoshimura, M. Tsukamoto, M. Kitamura, *Angew. Chem.* **2005**, *117*, 7453–7456; *Angew. Chem. Int. Ed.* **2005**, *44*, 7287–7290; k) C. J. A. Daley, J. A. Wiles, S. H. Bergens, *Inorg. Chim. Acta* **2006**, *359*, 2760–2770.

[27] a) O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058; b) I. Yamada, R. Noyori, *Org. Lett.* **2000**, *2*, 3425–3427; c) J. B. Johnson, J.-E. Bäckvall, *J. Org. Chem.* **2003**, *68*, 7681–7684; d) C. P. Casey, J. B. Johnson, *J. Org. Chem.* **2003**, *68*, 1998–2001.

[28] D_2 and $(CH_3)_2CHOH$ undergo D/H isotope exchange in the presence of KO-*t*-C_4H_9 without Ru catalyst.

[29] A kinetic isotope effect, k_H/k_D, of 1.5 was seen in the ATH of **1** in 2-propanol catalyzed by (*S,S*)-**7a**.[9a]

Received: June 23, 2008
Published online: September 15, 2008

