Hydrogenation versus Transfer Hydrogenation of Ketones: Two Established Ruthenium Systems Catalyze Both

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Abstract: The established standard ketone hydrogenation (abbreviated HY herein) precatalyst [$Ru(Cl)_2$((*S*)-tolbinap){(*S*,*S*)-dpen}] ((*S*),(*S*,*S*)-**1**) has turned out also to be a precatalyst for ketone transfer hydrogenation (abbreviated TRHY herein) as tested on the substrate acetophenone (**3**) in *i*PrOH under standard conditions (45 °C, 45 bar H_2 or Ar at atmospheric pressure). HY works at a substrate catalyst ratio (s:c) of up to 10^6 and TRHY at s:c $< 10^4$. Both produce (*R*)-1-phenylethan-1-ol ((*R*)-**4**), but the *ee* in HY are much higher (78–83 %) than in TRHY (4–62 %). In both modes, *i*PrOK is needed to generate the active catalysts, and the more there is (1–4500 equiv), the faster the catalytic reactions. The *ee* is about constant in HY and diminishes in TRHY as more *i*PrOK is added. The ketone TRHY precatalyst [$Ru(Cl)_2$((*S*,*S*)-cy$P_2(NH)_2$)] ((*S*,*S*)-**2**), established at s:c = 200, has also turned out to be a ketone HY precatalyst at up to s:c = 10^6, again as tested on **3** in *i*PrOH under standard conditions. The enantioselectivity is opposite in the two modes and only high in TRHY: with (*S*,*S*)-**2**, one obtains (*R*)-**4** in up to 98 % *ee* in TRHY as reported and (*S*)-**4** in 20–25 % *ee* in HY. *i*PrOK is again required to generate the active catalysts in both modes, and again, the more there is, the faster the catalytic reactions. The *ee* in TRHY are only high when 0.5–1 equivalents *i*PrOK are used and diminish when more is added, while the (low) *ee* is again about constant in HY as more *i*PrOK is added (0–4500 equiv). The new [Ru(H)(Cl)((*S*,*S*)-cy$P_2(NH)_2$)] isomers (*S*,*S*)-**9A** and (*S*,*S*)-**9B** (mixture, exact structures unknown) are also precatalysts for the TRHY and HY of **3** under the same conditions, and (*R*)-**4** is again produced in TRHY and (*S*)-**4** in HY, but the lower *ee* shows that in TRHY (*S*,*S*)-**9A**/(*S*,*S*)-**9B** do not lead to the same catalysts as (*S*,*S*)-**2**. In contrast, the *ee* are in accord with (*S*,*S*)-**9A**/(*S*,*S*)-**9B** leading to the same catalysts as (*S*,*S*)-**2** in HY. The kinetic rate law for the HY of **3** in *i*PrOH and in benzene using (*S*,*S*)-**9A**/(*S*,*S*)-**9B**/*i*PrOK or (*S*,*S*)-**9A**/(*S*,*S*)-**9B**/*t*BuOK is consistent with a fast, reversible addition of **3** to a five-coordinate amidohydride (*S*,*S*)-**11** to give an (*S*,*S*)-**11**-substrate complex, in competition with the rate-determining addition of H_2 to (*S*,*S*)-**11** to give a dihydride [$Ru(H)_2$((*S*,*S*)-cy$P_2(NH)_2$)] (*S*,*S*)-**10**, which in turn reacts rapidly with **3** to generate (*S*)-**4** and (*S*,*S*)-**11**. The established achiral ketone TRHY precatalyst [$Ru(Cl)_2$(eth$P_2(NH)_2$)] (**12**) has turned out to be also a powerful precatalyst for the HY of **3** in *i*PrOH at s:c = 10^6 and of some other substrates. Response to the presence of *i*PrOK is as before, except that **12** already functions well without it at up to s:c = 10^6.

Keywords: asymmetric catalysis · homogenous catalysis · ketone hydrogenation · ruthenium · transfer hydrogenation

Introduction

Among the most spectacular recent developments in asymmetric catalysis are the Ru^{II}-catalyzed, highly chemo- and enantioselective reductions of ketones, in particular of unsaturated ketones in which the C=C double bonds are left entirely intact. There are two ways of doing this. One is an enantioselective Ru^{II}-catalyzed version of the Meerwein–Ponndorf–Verley reduction, thus the redox reaction between the substrate and most typically excess *i*PrOH to give selectively one product alcohol enantiomer;[1–8] this is called transfer hydrogenation, abbreviated TRHY herein. Here *i*PrOH is both the reducing agent and the solvent. The other way is enantioselective hydrogenation with molecular H_2 as the reducing agent,[9–11, 22] abbreviated HY herein, and here *i*PrOH is usually also the solvent of choice.

The TRHY have been studied longer and by numerous groups and a multitude of systems has been described. Among the most advanced catalysts are the [Ru(amidoalkoxy)(ar-

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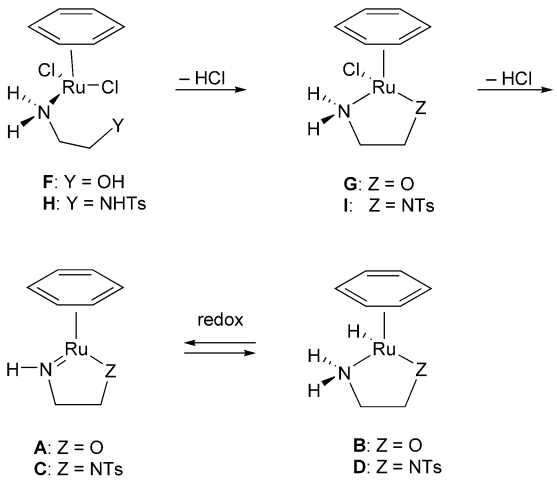
DOI: 10.1002/chem.200304884

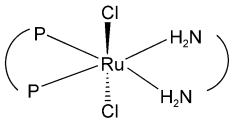
ene)]/[Ru(H)(aminoalkoxy)(arene)][1] (**A**/**B**) and [Ru(bisamido)(arene)]/[Ru(H)(aminoamido)(arene)][2] (**C**/**D**) redox pairs (Scheme 1). The method is mature and well understood, but has several disadvantages: the substrate–catalyst ratios (s:c) are low—typically 10^2–10^3; one is obliged to work with



Scheme 1.

dilute solutions to shift the equilibrium concentration of the product alcohol—typically around 0.1M in *i*PrOH; the *ee* is subject to erosion at long reaction times because the reversibility of the fast step that leads to the major enantiomer eventually comes into play. There are also advantages, namely the existence of catalysts that produce alcohols in high *ee* and the simplicity of the operation. The method is therefore often proposed as an operationally simpler alternative to HY that is suitable for small and medium scale applications.

The HY are a more recent discovery. The Noyori group's HY precatalysts [$Ru(Cl)_2$(bisphosphane)(diamine)] **E** essentially constitute a single group, which performs outstandingly.[9, 11] A representative example is [$Ru(Cl)_2$((*S*)-tolbinap)((*S*,*S*)-dpen)] (*S*),(*S*,*S*)-**1**[9e,f, 12]. These precatalysts are



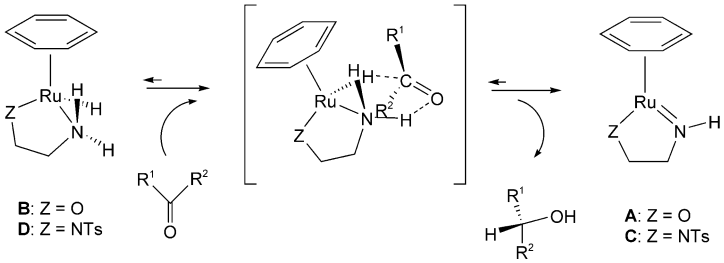
general type **E**
(*S*),(*S*,*S*)-**1**: P-P = (*S*)-TolBINAP, H_2N-NH_2 = (*S*,*S*)-DPEN
(*S*),(*S*,*S*)-**13**: P-P = (*S*)-BINAP, H_2N-NH_2 = (*S*,*S*)-DPEN

transformed in situ into the active catalysts by treatment with base in *i*PrOH under H_2. The active catalysts are suspected to be hydridoamido/dihydride redox pairs;[9m,q] we will discuss this in detail further on in this section, as well as later in the section on HY kinetics. From the industrial viewpoint, with a view to application on a large scale, HY has a much greater potential because very large s:c ratios can be reached—the highest s:c on record is about 2×10^6,[9f] more than 10^3 to 10^4 times higher than in TRHY. HY have two further important advantages: no erosion of the enantioselectivity (see further on in this section) and they can be run at much higher concentrations, typically around 2M in *i*PrOH. A certain disadvantage is that they normally require autoclaves.

Academe has focussed almost exclusively on enantioselective TRHY and HY, but HY of ketones to give achiral or racemic alcohols or to give mixtures of diastereoisomeric alcohols and of all kinds of aldehydes just using very low loadings of achiral or racemic precatalysts already have considerable industrial potential, because such HY can replace reductions by means of the traditional hydride reagents ($NaBH_4$, $LiAlH_4$, polymethylhydrosiloxane, etc.). Most of these reagents are difficult to handle and require a heavy workup, involving hydrolysis and a separation, plus the disposal of the large amounts of inorganic hydroxides produced. In HY, one normally uses H_2 in large excess, but it can be recycled and is one of the ideal reactants: lowest possible molecular weight, total atom economy, very low cost, effortless separation on degassing.

Until very recently, mechanistic investigations, both experimental and theoretical, have concentrated on TRHY rather than on HY, and on the TRHY that use the redox couples of type **A**/**B** and **C**/**D** (Scheme 1) mentioned above. For both types, representative catalysts are identified and the mechanisms largely understood. Thus upon treatment of an amino alcohol with a [{$Ru(Cl)_2$(arene)}$_2$] in *i*PrOH in the presence of a base, the active catalysts are formed in four steps, $\rightarrow$**F**$\rightarrow$**G**$\rightarrow$**A**$\rightarrow$**B**[1e,g–i,k,n,q, 8d] (Scheme 1). Compound **F** is the first [$Ru(Cl)_2$(aminoalcohol)(arene)] precatalyst to be formed. Then follow two consecutive dehydrochlorinations. The first gives the [Ru(Cl)(aminoalkoxy)(arene)] precatalyst **G** and the second the [Ru(amidoalkoxy)(arene)] catalyst **A**. Catalyst **A** is the dehydro form of the redox pair and is coupled with its reduced form [Ru(H)(aminoalkoxy)(arene)] **B** by the redox reaction with *i*PrOH; see below. Once formed, **A** and **B** function alone; base is only required to generate **A** from **F** and **G**. When a diamine is used instead of an amino alcohol, the redox pair **C**/**D** is formed via the analogous sequence $\rightarrow$**H**$\rightarrow$**I**$\rightarrow$**C**$\rightarrow$**D**.[1i,q, 2c,f, 8d] Most of the **C**/**D** pairs have one amido function *N*-tosylated, but there are some specific exceptions in which they bear just alkyl or aryl groups.[2b,g]

The reduced forms **B** and **D** both contain a near-planar *syn*-H-Ru-N-H motif at the active site, and a common general mechanism for the redox step has been proposed (Scheme 2).



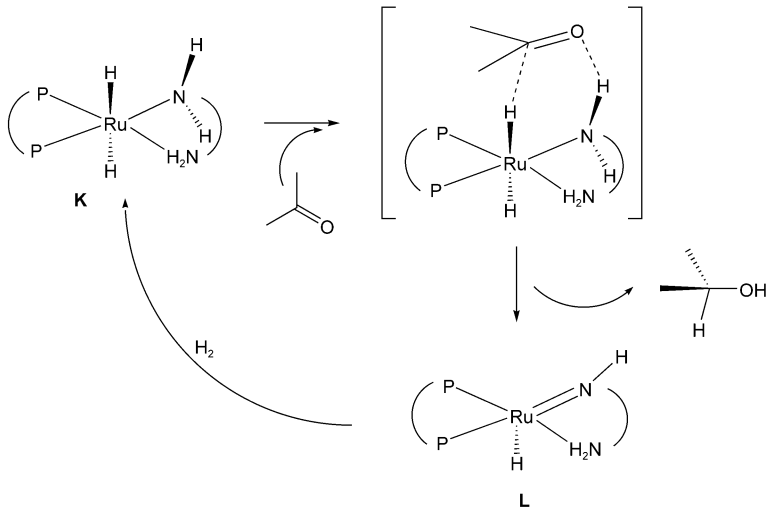
Scheme 2.

In the sense of the reduction of the substrate ketone, the hydridic H on Ru and the protic H on N in **B** and **D** are more or less simultaneously transferred from the H-Ru-N-H site to the carbonyl dipole ("metal–ligand bifunctional catalysis",[1i]

"concerted hydride and proton transfer"[4d]) via a six-membered transition state. The resulting **A** and **C**, with an active Ru=N site, then revert back to **B** and **D** by the same reaction in reverse, with *i*PrOH to give acetone, through transfer of the hydroxyl and α-C-bound hydrogen atom.

Numerous other Ru^{II}-based TRHY systems are known and the corresponding precatalysts are almost always dichlorides generated in situ; these are also treated with base to transform them in situ into the active catalysts. Among these are systems where one can imagine that a catalyst with an active H-Ru-N-H site is involved although that is not established[5] and others that seem to utilize a different mechanism,[6] but the latter conclusion is not made in the literature, nor are there suggestions as to what that latter mechanism may be.

The Noyori group's advanced $[Ru(Cl)_2(bisphosphane)(diamine)]$ HY precatalysts **E** are likewise transformed into the active catalysts by treatment with base in situ in *i*PrOH, but under H_2. Nothing concrete was known about these active catalysts until recently, but it was suspected that they probably also have a *syn*-H-Ru-N-H motif at the active site and reduce ketones as in the TRHY mechanism just discussed.[8e, 9e, 11b,c, 22] This is depicted in Scheme 3 in terms of a dihydride of the type **K**; reduction of the ketone by **K** gives the dehydro form **L**. The regeneration of the H-Ru-N-H catalyst **K** from the Ru=N catalyst **L** then occurs by the reaction of **L** with H_2, not *i*PrOH as in TRHY. Some of us recently provided experimental support for this sequence;[9m,p,q,s] we will discuss this evidence in later sections.



Scheme 3.

We were struck by the following situation: although the mechanism of the reduction step is viewed as being essentially the same, TRHY and HY are otherwise treated completely apart in the literature. Papers either deal with TRHY or with HY, but never with both. In particular, (pre)catalysts are also either used for TRHY or for HY, but never for both. The goal of the present work is to discover new HY systems by examining known TRHY systems, or in other words by running cross tests. A two point rationale can be spelled out for this:

1) Within the constraints of the Meerwein – Ponndorf – Verley equilibria, an Ru^{II} catalyst redox pair that works in the HY of ketones in *i*PrOH is likely to also work in the TRHY with *i*PrOH as the reducing agent, owing to the principle of microscopic reversibility, provided the pair is stable in the absence of H_2.
2) Systems that work in TRHY should also work in HY if the reduced form H-Ru-N-H of the TRHY redox pair can be regenerated by addition of H_2 to the dehydro form Ru=N rather than by the backward reaction with *i*PrOH.[13]

For point 2 above, if the addition of H_2 is efficient enough, then it outpaces and replaces the slow, unfavorable backward reaction with *i*PrOH, and this is then the essential advantage in HY. The reduced form of the catalyst is then formed much more rapidly; the step in which the substrate is reduced is, therefore, also rapid, effectively irreversible, and thus not subject to erosion of the enantioselectivity with time.

Strikingly, there are no systematic cross tests in the literature. To the best of our knowledge, there are just a very few papers that deal with advanced systems and in which the activities in both modes are mentioned in passing or can be inferred: these are listed in Table 1.

Reference [14] provides the only positive cross test from HY to TRHY that we know of in the area; however, the TRHY experiment was not run in *i*PrOH but in (*S*)-1-*deutero*-1-phenylethan-1-ol/THF, and it seems that the mechanistic significance was not recognized. Further, it is established that the structurally related Shvo catalyst is active in both HY and TRHY, but the experiments in the two modes were also carried out in different solvents.[4] The rest of the reported tests we know of concern early systems with lower activities and are again not true cross tests, because the conditions were also not the same.[15] There is also a paper in which the differing performance of (different) HY and TRHY systems on the same class of substrates is compared.[1m]

We reiterate that there are striking similarities, but also differences, in the literature recipes that are used to generate

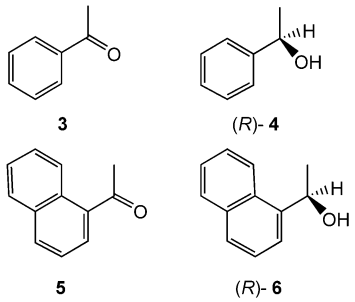
Table 1. Known cross tests.

(Pre)catalyst type	TRHY	HY
[Ru(H)(aminoamido)(arene)]	active[10]	almost inactive[10]
[Ru(H)(Cp*)(diamine)]	almost inactive[10]	active[10]
$[Ru(Cl)_2(PPh_3)_3]/NH_2$-CH_2-CH_2-NH_2/*i*PrOH/KOH	almost inactive[9a]	very active[9a]
$[Ru(Cl)_2(PPh_3)_2(NH_2$-CH_2-CH_2-$NH_2)]$/*i*PrOH/KOH	active[14]	very active[9f]
Shvo catalyst	active[4]	active[4]

the catalysts in TRHY and HY and that were discussed above. As outlined, the precatalysts in TRHY and HY were always different until the present study; nevertheless, they are usually dichlorides in both cases. In both cases, the standard solvent (*i*PrOH) is the same, but the substrate/product concentrations are normally much lower in TRHY than in HY. In both cases, the active catalyst is produced by dehydrochlorination reactions induced by addition of base.[1–3, 5–9, 11] In HY, the catalysts are generated by this reaction in the presence H_2.[13] In both cases, the base is typically *i*PrOK, but much more is usually used in HY than in TRHY: about 5000 times more in two systems we deal with herein ((*S*,*S*)-**2**-based TRHY at s:c 200, 0.5 equiv *i*PrOK;[3a,b] (*S*),(*S*,*S*)-**1**-based HY at s:c 2.4×10^6, 2.4×10^4 equiv *i*PrOK[9f, 16]). *i*PrOK is most often generated from commercially available *t*BuOK that is added to the solvent *i*PrOH; MeONa, *i*PrONa, KOH, NaOH, and K_2CO_3 are also used. It seems that these dosages were developed empirically, and only recently have explanations been advanced; see later. A consequence of the different amounts of base that are used or required and of the presence of H_2 in HY[13] could be that, starting from the same precatalyst, different catalysts are formed in TRHY and HY. A further complication is that several isomers with different geometries may be accessible for any given catalyst. The conclusions of points 1 and 2 above would nevertheless apply to all of these catalysts. Accordingly, we decided to carry out the first systematic cross tests and to study the effect of varying the amount of *i*PrOK in both modes.

Results and Discussion

Cross tests with [Ru(Cl)$_2$((*S*)-tolbinap)((*S*,*S*)-dpen)] ((*S*),(*S*,*S*)-1): For completeness, we began by testing the standard HY precatalyst [Ru(Cl)$_2$((*S*)-tolbinap)((*S*,*S*)-dpen)] ((*S*),(*S*,*S*)-**1**) for TRHY activity. Table 2 lists the published record result for the HY of the standard substrate acetophenone (**3**) at s:c 2.4×10^6 and a typical result from the same paper for 1-acetonaphthone (**5**) at s:c 10^5 (to give compound **6**) which is more convenient for rapid screening, and then our tests with **3** from s:c 10^4 to 10^6 with and without H_2 and in the presence of varying amounts of *i*PrOK, mainly under standard HY conditions, that is, at 2.1 M substrate concentration. HY is slow with one equivalent *i*PrOK and works well with 5–4500 equivalents at s:c 10^5 to 10^6. The HY rates increase as more base is added, while the *ee* for the product (*R*)-1-phenylethan-1-ol ((*R*)-**4**) are about constant throughout this range.



In the absence of H_2 under otherwise the same conditions, slow TRHY occurs at s:c 10^4 to 10^5, which also produces (*R*)-**4**, but the *ee* are much lower than in HY, decrease as more base is added, and also decrease with time; this last decrease being probably due to equilibration. We also did one run under typical TRHY conditions (cf. next section and Table 3), at s:c 200 (Table 2, TRHY4). It also works, but the *ee* is now in

Table 2. Conversions and *ee* for the precatalyst [Ru(Cl)$_2$((*S*)-tolbinap)((*S*,*S*)-dpen)] ((*S*),(*S*,*S*)-**1**) in the hydrogenation (HY, "H_2") and transfer hydrogenation (TRHY, "no H_2") of acetophenone (**3**), 1-acetonaphthone (**5**) and cyclohexyl methyl ketone (**7**).

Run	Conditions[a]	Substrate	Precatalyst/ *i*PrOK/Substrate	Conversion 1[b]	*ee* 1[c]	Conversion 2[b]	*ee* 2[c]
ref. [9f]	45 bar H_2, **30 °C**, **2.4 M**	**3**	$1/2.4 \times 10^4/2.4 \times 10^6$	100/48	80 (*R*)	–	–
ref. [9f]	**10 bar H_2**, **30 °C**, **2.4 M**	**5**	$1/455/10^5$	100/40	98 (*R*)	–	–
HY1	45 bar H_2, 60 °C, 2.1 M	**3**	$1/90/10^6$	32/3	78 (*R*)	37/14	79 (*R*)
HY2	45 bar H_2, 60 °C, 2.1 M	**3**	$1/450/10^6$	100/3	79 (*R*)	–	–
HY3	45 bar H_2, 60 °C, 2.1 M	**3**	$1/1/10^5$	0.4/24	n.d.	–	–
HY4	45 bar H_2, 60 °C, 2.1 M	**3**	$1/5/10^5$	95/1.5	80 (*R*)	100/3	80 (*R*)
HY5	45 bar H_2, 60 °C, 2.1 M	**3**	$1/90/10^5$	100/1.5	78 (*R*)	–	–
HY6	45 bar H_2, 60 °C, 2.1 M	**3**	$1/450/10^5$	100/1.5	80 (*R*)	–	–
HY7[d]	45 bar H_2, 60 °C, 2.1 M	**3**	$1/4500/10^5$	100/3	83 (*R*)	–	–
TRHY1	no H_2, 60 °C, 2.1 M	**3**	$1/450/10^5$	2/3	42 (*R*)	4/24	26 (*R*)
TRHY2[d]	no H_2, 60 °C, 2.1 M	**3**	$1/4500/10^5$	11/3	11 (*R*)	23/20	4 (*R*)
TRHY3[d]	no H_2, 60 °C, 2.1 M	**3**	$1/4500/10^4$	25/1.5	13 (*R*)	87/20	9 (*R*)
TRHY4	no H_2, **45 °C**, **0.1 M**	**3**	1/0.5/200	11/3	62 (*R*)	15/24	52 (*R*)
HY8	45 bar H_2, 60 °C, 2.1 M	**7**	$1/90/10^5$	0/24	–	–	–
HY9	45 bar H_2, 60 °C, 2.1 M	**7**	$1/450/10^4$	97/3	20[e]	–	–

[a] The standard conditions throughout Tables 2–4, 7 are 45 bar H_2 for HY, Ar at atmospheric pressure for TRHY, 60 °C, ca. 2.1 M solution of the substrate in *i*PrOH. Runs were typically carried out on a 20 mmol scale. Conditions that are different from these standard ones are indicated in bold face. Precatalyst/base/substrate = mol *i*PrOK (generated by adding *t*BuOK) and mol substrate per mol precatalyst. [b] Conversion 1 = conversion in %, usually at the first control (GC) after *n* h; conversion 2 = conversion in % at the maximal reaction time (when the run was stopped) in h, thus 100/48 means 100% conversion within ≤48 h. [c] *ee* 1 and 2: corresponding *ee* in % for the alcohols (*R*)- or (*S*)-1-phenylethan-1-ol (*R*)- or (*S*)-**4**, (*R*)- or (*S*)-1-(1-naphthalenyl)ethan-1-ol (*R*)- or (*S*)-**6**, and (*R*)- or (*S*)-1-cyclohexylethan-1-ol (*R*)- or (*S*)-**8**. The selectivities for the product alcohols throughout were normally close to 100% and rarely, at high base concentration, down to about 96%. [d] The actual experiment was done with (*R*),(*R*,*R*)-**1**. For clarity, the table lists these results mirrored to the (*S*),(*S*,*S*)-**1** series. [e] (*R*) or (*S*) was not assigned.

Table 3. Results for $[Ru(Cl)_2((S,S)\text{-}cyP_2(NH)_2)]$ ((*S*,*S*)-**2**) with acetophenone (**3**) as the substrate.

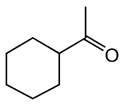
Run	Conditions[a]	Precatalyst/ *i*PrOK/Substrate	Conversion 1[b]	*ee* 1[c]	Conversion 2[b]	*ee* 2[c]
ref. [3a]	no H_2, **23 °C**, **0.1M**	1/0.5/200	91/25	97 (*R*)	–	–
ref. [3a]	no H_2, **45 °C**, **0.1M**	1/0.5/200	93/7	97 (*R*)	–	–
TRHY1	no H_2, **45 °C**, **0.1M**	1/0.5/200	32/1.5	94 (*R*)	88/9	90 (*R*)
TRHY2	no H_2, **45 °C**, **0.1M**	$1/1/10^4$	5/6	98 (*R*)	14/46	98 (*R*)
TRHY3	no H_2, **45 °C**, **0.1M**	$1/450/10^4$	12/5	96 (*R*)	43/40	92 (*R*)
TRHY4	no H_2, **45 °C**, 2.1M	$1/1/10^4$	4/6	96 (*R*)	8/47	92 (*R*)
TRHY5	no H_2, **45 °C**, 2.1M	$1/90/10^4$	8/6	92 (*R*)	30/47	90 (*R*)
TRHY6	no H_2, **45 °C**, 2.1M	$1/450/10^4$	9/6	82 (*R*)	43/47	64 (*R*)
TRHY7	no H_2, **45 °C**, 2.1M	$1/900/10^4$	14/6	53 (*R*)	44/47	46 (*R*)
TRHY8	no H_2, **45 °C**, 2.1M	$1/4500/10^4$	24/7	8 (*R*)	86/100	6 (*R*)
TRHY9	no H_2, **45 °C**, 2.1M	$1/1/10^5$	0.1/48	n.d.		
TRHY10	no H_2, **45 °C**, 2.1M	$1/450/10^5$	1.7/22	92 (*R*)	2/48	92 (*R*)
HY1	45 bar H_2 **45 °C**, 2.1M	$1/1/10^5$	4/7	26 (*S*)	35/23	25 (*S*)
HY2	45 bar H_2 **45 °C**, 2.1M	$1/1/10^5$	12/6	24 (*S*)	15/24	20 (*S*)
HY3	45 bar H_2 **45 °C**, 2.1M	$1/450/10^5$	36/7	24 (*S*)	100/23	23 (*S*)
HY4	45 bar H_2 **45 °C**, 2.1M	$1/450/10^5$	79/3.5	24 (*S*)	100/6.5	23 (*S*)
HY5	45 bar H_2 **45 °C**, 2.1M	$1/4500/10^5$	26/2	24 (*S*)	100/4	24 (*S*)
HY6	45 bar H_2 60 °C, 2.1M	$1/0/10^5$	1/3	16 (*S*)	2/24	13 (*S*)
HY7	45 bar H_2 60 °C, 2.1M	$1/90/10^5$	12/3	19 (*S*)	99/6	19 (*S*)
HY8[d]	45 bar H_2 60 °C, 2.1M	$1/90/10^5$	3/3	n.d.	100/24	20 (*S*)
HY9	45 bar H_2 60 °C, 2.1M	$1/450/10^5$	62/3	22 (*S*)	100/6	20 (*S*)
HY10[d]	45 bar H_2 60 °C, 2.1M	$1/450/10^5$	100/3	19 (*S*)	–	–
HY11[d]	45 bar H_2 60 °C, 2.1M	$1/4500/10^5$	100/3	20 (*S*)	–	–
HY12[d]	45 bar H_2 60 °C, 2.1M	$1/90/10^6$	19/3	20 (*S*)	100/22	20 (*S*)
HY13[d]	45 bar H_2 60 °C, 2.1M	$1/450/10^6$	23/3	25 (*S*)	100/24	18 (*S*)
HY14	45 bar H_2 **45 °C**, 2.1M, **benzene**	$1/450/10^4$	0/24	–	–	–
HY15	45 bar H_2 **45 °C**, 2.1M, **benzene**	$1/450/10^5$	0/24	–	–	–

[a] See footnote [a] in Table 2. [b] See footnote [b] in Table 2. [c] See footnote [c] in Table 2. [d] Actual run done with (*R*,*R*)-**2** and mirrored.

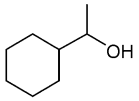
between those seen in HY and under HY conditions in the absence of H_2; the reaction also does not go to completion.

Point 1 in the Introduction is thus further confirmed,[14] but there is a surprise: in this first strict cross test from HY to TRHY for an enantioselective system, the enantioselectivities are different. The system has turned out to be optimal for HY in that only HY gives high enantioselectivity.

Table 2 also lists results on the HY of cyclohexyl methyl ketone (**7**) by means of (*S*),(*S*,*S*)-**1**. Ketone **7** is unaffected



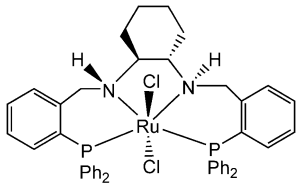
7



8

after 24 h at s:c 10^5 in the presence of 90 equivalents of *i*PrOK, while **3** is completely converted within 1.5 h under these conditions, but **7** is readily hydrogenated (to give compound **8**) at s:c 10^4 and by using 450 equivalents *i*PrOK. This is in line with our general experience in this area: **3** and its derivatives are always the most reactive substrates; see also section on HY by means of precatalyst **12** (see later).

Cross tests with $[Ru(Cl)_2((S,S)\text{-}cyP_2(NH)_2)]$ ((*S*,*S*)-2): We chose the Gao–Noyori–Ikariya TRHY precatalyst $[Ru(Cl)_2((S,S)\text{-}cyP_2(NH)_2)]$ ((*S*,*S*)-**2**)[3, 12] for a first cross test



(*S*,*S*)-**2**

from TRHY to HY, because it so much resembles a typical HY precatalyst such as (*S*),(*S*,*S*)-**1**; recall that the best-understood TRHY systems, the redox couples **A**/**B** and **C**/**D** and their precursors (Scheme 1), contain some similar elements, but have otherwise quite different structures. The tetradentate ligand $cyP_2(NH)_2$ in (*S*,*S*)-**2** provides essentially the same coordination environment as the combined bidentate TolBINAP and DPEN ligands in (*S*),(*S*,*S*)-**1**, except that (*S*,*S*)-**2** has NH sites and (*S*),(*S*,*S*)-**1** NH_2 sites.[12] It is known that (*S*,*S*)-**2**[3a] has the P and NH sites arranged around the Ru in the same way as in (*S*),(*S*,*S*)-**1**,[9f] that is, in a plane with the Cl above and below and in the same order, P, NH, NH, P in (*S*,*S*)-**2** and P, NH_2, NH_2, P in (*S*),(*S*,*S*)-**1**. The flexibilities of the environments, bidentate/bidentate and tetradentate, are clearly different, and, therefore, different precatalyst geometries and especially catalyst geometries could be accessible in the two systems. These active catalysts have not yet been identified. In view of all of this, it was truly intriguing that only opposite and unique reactivities had been reported: only TRHY in the case of the (*S*,*S*)-**2**[3d] and only HY in he case of (*S*),(*S*,*S*)-**1**,[9e,f] without mention of the opposite mode.

We were once more in for a surprise: again with acetophenone (**3**) as the substrate, (*S*,*S*)-**2** works very efficiently in HY as regards the rate, but the enantioselectivity is *opposite* to, and unfortunately much lower than, that in TRHY. Table 3 shows the published TRHY results at s:c 200 at 23 °C and 45 °C, controls without H_2 at s:c from 200 up to 10^5 with varying amounts of base added, at 0.1 M (standard for TRHY) and 2.1 M (standard for HY) at 45 °C, and then under 45 bar H_2 at s:c 10^5 and up to 10^6, at 45 °C and 60 °C, again with varying amounts of base added. Here TRHY has turned out to be the better method in that it gives a high *ee*, but the HY activity is otherwise very high, at about the same level as that of the very good HY system based on (*S*),(*S*,*S*)-**1**. Thus only half of the potential of the system was known, and the tantalizing question is just why high enantioselectivity is only attained in TRHY, at the cost of 10^4 times more catalyst. Intriguingly, one can conclude outright that the active catalysts that are *both* generated from (*S*,*S*)-**2** *must be different* in TRHY and HY, and yet the basic mechanisms for the reduction steps similar as outlined.

In detail, the data in Table 3 show that HY already proceeds slowly in the absence of base; this is not TRHY because the enantioselectivity is opposite to that for TRHY. One equivalent *i*PrOK already suffices to make the HY really go, but the HY rate increases as more base is added up to 4500 equivalents, while the enantioselectivity is about the same over that entire range. In the parallel TRHY runs, thus without H_2 but otherwise using the HY conditions, the (opposite) enantioselectivity decreases, while the rate increases as more and more base is added (Figure 1). Some further tuning would be needed to determine the optimal amount of base with regard to *ee* and rate. The drop in *ee* when more base is added is already seen at low conversion and is thus due mainly to catalyst modification and not to racemization via equilibration. Note that Table 3 lists several HY runs in duplicate, showing that reproducibility is not perfect (throughout this paper), but that the above conclusions (rate versus amount of base present) are on solid ground.

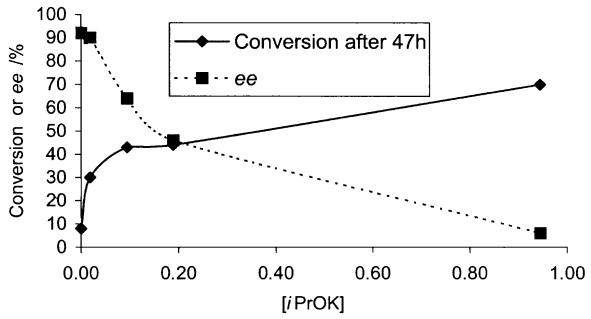
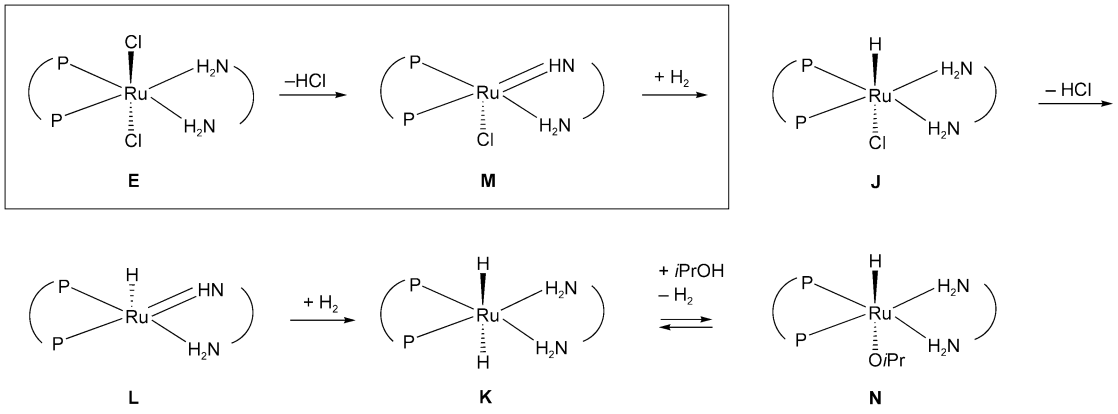


Figure 1. Effect of added *i*PrOK on TRHY activity using (*S*,*S*)-**2**.

Work by some of us and new results that are discussed in the next two sections cover HY of **3** in benzene as the solvent. In the second of these sections, we show that HY, by what is presumably the active catalyst pair that we also obtain from (*S*,*S*)-**2** upon treatment with base, is about 10 times faster in *i*PrOH than in benzene at ambient temperature. To correlate these results, we also tested the (*S*,*S*)-**2**-based HY under our standard conditions in benzene rather than *i*PrOH as the solvent, which confirm this large solvent effect. We saw no conversion within 24 h at s:c 10^5 and 10^4 (450 equiv *i*PrOK, Table 3, runs HY14 and HY15). We continued this calibration with a more reactive system (complex **12**; see later).

Cross tests with the [Ru(H)(Cl)((*S*,*S*)-cyP$_2$(NH)$_2$)] isomers (*S*,*S*)-9 A and (*S*,*S*)-9 B: Some of us recently prepared and characterized hydridochlorides of the type [Ru(H)(Cl)(bisphosphane)(diamine)] (**J**) and dihydrides of the type [Ru(H)$_2$(bisphosphane)(diamine)] (**K**) (Scheme 4) along with related complexes.[9m,p,q,s] Both types were potential HY catalysts that could be formed from the dichloride precatalysts [Ru(Cl)$_2$(bisphosphane)(diamine)] (**E**) under the HY conditions. They were tested only in HY and in benzene solution or starting with the neat substrate, and it was concluded, that, in these media, the hydridochlorides **J** are inactive and the dihydrides **K** active. It was further shown that the hydridochlorides **J** are transformed into dihydrides **K**, the hydrogenated form of the catalysts, by treatment with one equivalent *i*PrOK in benzene under H_2. This involves dehydrochlorination of **J** to give the dehydro form **L**, which then adds H_2, thus **J** → **L** → **K** (Scheme 4). In the catalytic cycle (Scheme 3), **K** then reacts with the substrate ketone to give **L** and the product alcohol, and **L** then again adds H_2.

This would seem to suggest the sequence **E** → **M** → **J** → **L** → **K** leading from the first dichloride precatalyst **E** to the redox pair **L**/**K** (Scheme 4), but there is so far no evidence for

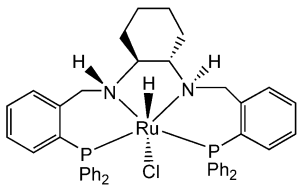


Scheme 4.

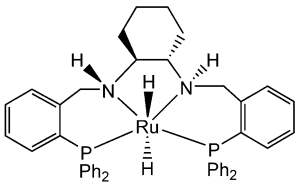
the postulated first elimination of HCl and the first addition of H_2, **E** → **M** → **J** (Scheme 4, "boxed in"). Further, things are unfortunately *more* complicated in the standard solvent *i*PrOH (the hydrides of type **J** and **K** were observed by ^{1}H NMR spectroscopy in [D$_6$]benzene and the HY then monitored in the same solvent) and less is still known about the active catalyst(s) in this medium. Thus it is not yet known whether the hydridochlorides **J** are involved at all in *i*PrOH, either as precatalysts or as catalysts. On the other hand, it is very likely that the amidohydride/dihydride redox pairs **L**/**K** are also the active catalyst pairs in the HY in *i*PrOH. However, the situation is complicated by the fact that **K** and *i*PrOH are in equilibrium with complexes of the type [Ru(H)(*i*PrO)(bisphosphane)(diamine)] (**N**) and H_2 (Scheme 4).[9s] The more base and the more H_2 is present, the more this equilibrium favors the dihydrides **K**;[9s] the dihydrides **K** and the amidohydrides **L** may be too basic to survive in *i*PrOH alone and would thus be stabilized in the presence of base as proposed for related systems.[9s] H_2 gas is probably also required to stabilize **K**. The complexes **N** are also potential precatalysts and/or active catalysts, but nothing concrete is yet known about their role, except that partial β-hydride elimination **N** → **K** plus acetone has been also observed in the absence of H_2, as another possible mode of generation of **K**.[9s]

Therefore, in the hope of learning more about the active catalysts in TRHY and HY based on the use of [Ru(Cl)$_2$((*S*,*S*)-cyP$_2$(NH)$_2$)] ((*S*,*S*)-**2**), we tried to synthesize the complexes [Ru(H)(Cl)((*S*,*S*)-cyP$_2$(NH)$_2$)] ((*S*,*S*)-**9**), corresponding to **J** in Scheme 4) and [Ru(H)$_2$((*S*,*S*)-cyP$_2$(NH)$_2$)] ((*S*,*S*)-**10**), corresponding to **K** in Scheme 4, in order to test them in both TRHY and HY and, thus, to verify whether and if so how they are involved in the (*S*,*S*)-**2**-based processes.

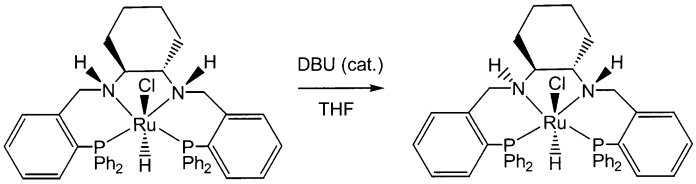
Refluxing an equimolar mixture of [Ru(H)(Cl)(PPh$_3$)$_3$] and the tetradentate ligand (*S*,*S*)-cyP$_2$(NH)$_2$ in THF as described previously[9m,p,q,s] resulted in the near-quantitative formation of a mixture of two new diastereoisomeric hydridochloro complexes (*S*,*S*)-**9A** and (*S*,*S*)-**9B**. Two sets of dd (doublet of doublets) and two AB patterns with similar chemical shifts and coupling constants were observed in the ^{1}H and ^{31}P{^{1}H} NMR spectra, respectively. Further, we found that isomer **A** can be isomerized to isomer **B** in THF in the presence of a catalytic amount of DBU or *t*BuOK, but not Et$_3$N. Presumably this reaction proceeds by means of deprotonation to give an amido intermediate that is then protonated on the opposite side. Scheme 5 depicts this isomerization in terms of tentative structures for **A** and **B**.



(*S*,*S*)-**9**



(*S*,*S*)-**10**



(*S*,*S*)-**9A** (*S*,*S*)-**9B**

Scheme 5.

Table 4 lists the tests with **3** as the substrate using a 60:40 mixture of the [Ru(H)(Cl)((*S*,*S*)-cyP$_2$(NH)$_2$)] isomers (*S*,*S*)-**9A** and (*S*,*S*)-**9B**, and (*S*,*S*)-**9B** alone. TRHY activity was tested in the absence of base or with very little base added, 0.5 equivalents *i*PrOK, because of the procedure given in reference [3a], see Table 3. TRHY is very slow in the absence of base, and works in its presence. We obtain the same product enantiomer (*R*)-1-phenylethan-1-ol ((*R*)-**4**) as in the case of (*S*,*S*)-**2**, but the *ee* are much lower. The mixture {**A**+**B**} and **B** alone are thus not the active catalysts in the (*S*,*S*)-**2**-based

Table 4. Results for the [Ru(H)(Cl)((*S*,*S*)-cyP$_2$(NH)$_2$)] isomers ((*S*,*S*)-**9A** and (*S*,*S*)-**9B**) with acetophenone (**3**) as the substrate.[a]

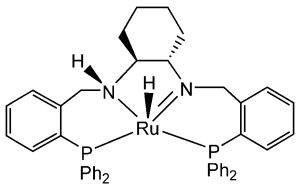
Run	Isomer Ratio	Conditions[a]	Precatayst/ *i*PrOK/Substrate	Conversion 1[b]	*ee* 1[c]	Conversion 2[b]	*ee* 2[c]
TRHY1[d]	**A**/**B** = 60:40	no H_2, **45 °C**, **0.1 M**	1/0/200	4/3	44 (*R*)	7/24	37 (*R*)
TRHY2[d]	**A**/**B** = 60:40	no H_2, **45 °C**, **0.1 M**	1/0.5/200	54/3	20 (*R*)	89/24	7 (*R*)
TRHY3[d]	**B** alone	no H_2, **45 °C**, **0.1 M**	1/0.5/200	72/1.5	13 (*R*)	95/24	5 (*R*)
HY1[d]	**A**/**B** = 60:40	45 bar H_2, **45 °C**, 2.1 M	1/1/10^6	5/3	31 (*S*)	7/20	34 (*S*)
HY2[d]	**A**/**B** = 60:40	45 bar H_2, **45 °C**, 2.1 M	1/90/10^6	1/1	35 (*S*)	6/24	22 (*S*)
HY3[d]	**A**/**B** = 60:40	45 bar H_2, **45 °C**, 2.1 M	1/450/10^6	18/3	27 (*S*)	40/24	24 (*S*)
HY4	**B** alone	45 bar H_2, **45 °C**, 2.1 M	1/90/10^6	100/3	27 (*S*)	–	–
HY5	**B** alone	45 bar H_2, **45 °C**, 2.1 M	1/90/10^5	100/3	26 (*S*)	–	–
HY6	**B** alone	45 bar H_2, **45 °C**, 2.1 M	1/90/10^4	100/3	26 (*S*)	–	–

[a] See footnote [a] in Table 2. [b] See footnote [b] in Table 2. [c] See footnote [c] in Table 2. [d] Actual run done with [Ru(H)(Cl)((*R*,*R*)-cyP$_2$(NH)$_2$)] (*R*,*R*)-**9** and mirrored.

TRHY and are not transformed into them under the reaction conditions.

HY with the mixture {**A**+**B**} and **B** alone also works, and we obtain the same enantiomer (*S*)-**4** with *about* the same *ee* as in the case of (*S*,*S*)-**2**. Addition of 1 to 450 equivalents *i*PrOK speeds up the HY in the case of the mixture {**A**+**B**}. The use of **B** alone was only tested in the presence of 90 equivalents *i*PrOK, but at an s:c of 10^5 to 10^6. In terms of rate, **B** performs much better than the mixture {**A**+**B**} although we do not understand why this is so. Compound **B** also performs much better than (*S*,*S*)-**2**, probably because the active catalysts are more directly generated starting from the hydridochloride **B** than from the dichloride (*S*,*S*)-**2**. The fact that the *ee* are similar suggests that the active catalyst(s) in these HY and the (*S*,*S*)-**2**-based HY could be the same.

HY kinetics using (*S*,*S*)-9 A and (*S*,*S*)-9 B as the precatalysts: Since (*S*,*S*)-**9 A** and (*S*,*S*)-**9 B** are the catalyst precursors we have in hand at present that are probably the closest (in terms of reaction steps) to the active HY catalysts, we used them (rather than the dichloride precatalyst (*S*,*S*)-**2**) to investigate the kinetics of the HY. The resulting rate law is also valid for the HY based on (*S*,*S*)-**2** if our assumption that (*S*,*S*)-**2** and (*S*,*S*)-**9** are both transformed into the same active redox pair (*S*,*S*)-**11**/(*S*,*S*)-**10** under the HY conditions is correct. Table 5



(*S*,*S*)-**11**

Table 5. Observed and calculated initial rates of production of (*S*)-1-phenylethan-1-ol ((*S*)-**4**; 23–26% *ee*)[a] by the HY of acetophenone **3** in *i*PrOH/*i*PrOK at 293 K using a 1:1 precatalyst mixture (*S*,*S*)-**9 A** plus (*S*,*S*)-**9 B**.

Run	[Ru^{tot}] [$\times 10^5$ M]	[H_2] [$\times 10^2$ M][b]	[*i*PrOK] [$\times 10^2$ M]	[**3**] [M]	Rate [$\times 10^4$ M s^{-1}]	Rate [$\times 10^4$ M s^{-1}][c]
1	4.0	1.91	1.79	0.167	7.8	7.8
2	4.0	1.91	3.57	0.333	6.6	6.7
3	4.0	1.91	5.36	0.500	5.3	5.8
4	6.0	1.91	3.57	0.333	10.7	10.0
5	4.0	1.91	1.79	0.333	6.6	6.7
6	4.0	1.91	1.79	0.500	6.5	5.8
7	4.0	3.29	1.79	0.500	10.1	10.1

[a] Actually (*R*,*R*)-**9 A** and (*R*,*R*)-**9 B** were used so that (*R*)-**4** was produced; however for consistency the results have been mirrored. [b] Obtained from ref. [20]; 0.0191 M and 0.0329 M correspond to 6 and 12 bar H_2. [c] Calculated by means of Equation (1).

lists the results of a study of the effect of variation of the concentrations of the reactants on the rates of the HY of **3** in *i*PrOH at room temperature catalyzed by a 1:1 mixture of the isomers (*S*,*S*)-**9 A** and (*S*,*S*)-**9 B**.

The conditions for the kinetic runs were different from the standard conditions listed in Tables 2–4, and 7 (see later) in order to put the rates of reaction into a conveniently and reliably measurable range at 293 K (estimated error for the rate constants about 10%), 6–11 bar H_2, 0.167–0.555 M **3**, substrate/precatalyst ratios 4175–25000 [with respect to the total of the isomers (*S*,*S*)-**9 A** plus (*S*,*S*)-**9 B**)].

Alkoxide base (*i*PrOK generated from *t*BuOK added to excess *i*PrOH) served to generate the catalyst as usual, but at the resulting, purposely high catalyst concentrations, the alkoxide concentration does *not* significantly affect the HY rate as in the runs under the preparative standard conditions, where the catalyst concentrations are much lower. The rate of 1-phenylethan-1-ol (**4**) production as monitored by GC and NMR spectroscopy increased approximately linearly with total Ru concentration and H_2 pressure ([H_2] has a linear relationship with pressure). The *ee* for the (*S*)-**4** produced by HY at 293 K by use of the mixture (*S*,*S*)-**9 A** plus (*S*,*S*)-**9 B** range between 23 to 26%. This range is similar to the range of values 22 to 35% reported in Tables 2–4 for temperatures of 318 and 333 K.

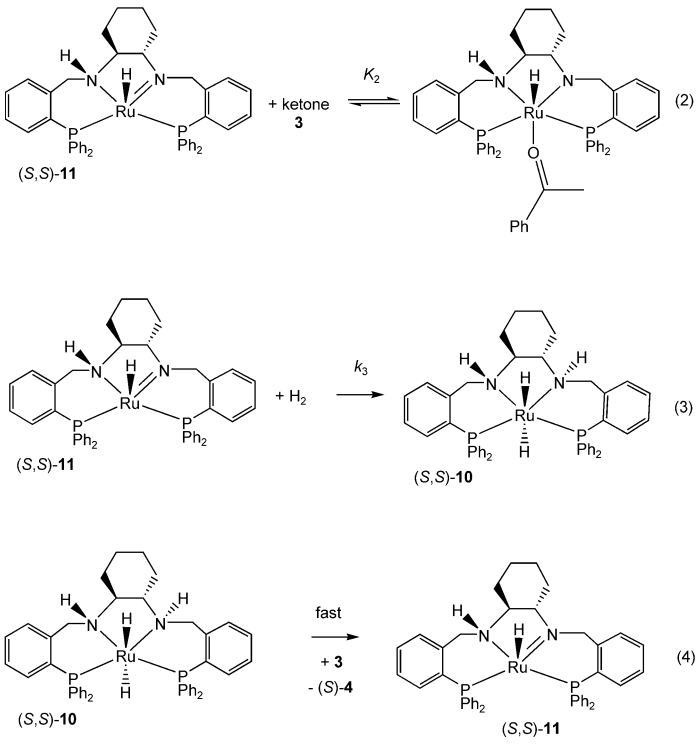
The results given in Table 5 lead to the rate law of Equation (1) (derivation, see the Experimental Section, for *i*PrOH, $k_3 = 1.23 \times 10^3\,M^{-1}s^{-1}$, $K_2 = 1.20\,M^{-1}$), in which [Ru^{tot}] is the total Ru concentration and [H_2] is the concentration of dissolved H_2. The rates that are calculated on the basis of Equation (1) are also listed in Table 5.

$$\text{rate} = k_3[Ru^{tot}][H_2]/(1 + K_2[\text{acetophenone}]) \quad (1)$$

This rate law is consistent with a fast, reversible addition of acetophenone (**3**) to a five-coordinate Ru amidohydride species (*S*,*S*)-**11** with a Ru=N double bond to give an amidohydride–acetophenone complex [Eq. (2)] and probably also an enolate complex [Ru(H)(O-C(Ph)=CH_2)((*S*,*S*)-cy$P_2(NH)_2$)]. This acts in competition with the rate-determining addition of H_2 to (*S*,*S*)-**11** to give a dihydride complex [Ru(H)$_2$((*S*,*S*)-cy$P_2(NH)_2$)] ((*S*,*S*)-**10**) [Eq. (3)]. Compound (*S*,*S*)-**10** corresponds to **K** and (*S*,*S*)-**11** to **L** in Scheme 3, but (*S*,*S*)-**10** may have the hydride ligands *trans* (as depicted) or *cis* to each other. It must react very rapidly with the substrate **3** to generate the alcohol (*S*)-**4** and regenerate the amidohydride complex (*S*,*S*)-**11** [Eq. (4)]. The ketone complexes must be much less active HY catalysts than the amidohydride complex (*S*,*S*)-**11**. The ketone and/or the enolate complexes have not been directly observed. However, related complexes [Ru(H)((*R*)-binap)(HN$CMe_2CMe_2NH_2$)(O=C(Ph)Me)] and [Ru(H)((*R*)-binap)($H_2NCMe_2CMe_2NH_2$)(O-C(Ph)=CH_2)] have been characterized.[9]

A cross test with TRHY conditions identical to those of the HY in the kinetic runs (as in run 5 in Table 5, 895 equiv *i*PrOK), but without H_2, produced the alcohol (*R*)-**4** in 72% *ee*; however, the conversion was only 3% after two days.

The effect of a change in solvent from *i*PrOH to benzene, which was used previously[9m,p,q,s] (and to *t*BuOK as the base), was also investigated. Since *t*BuOK is only moderately soluble in benzene,[17] there is an induction period until the generation of the catalyst from the precatalyst, *t*BuOK, and H_2 gas is complete. In the absence of base, the precatalyst (*S*,*S*)-**9** is



inactive under these conditions. Therefore, these runs were done by activating the precatalyst with *t*BuOK under H_2 for 45 min before adding **3**. The results are listed in Table 6.

Table 6. Observed and calculated initial rates of production of (*S*)-1-phenylethan-1-ol ((*S*)-**4**; *ee* 17–24 %)[a] by the HY of acetophenone **3** in benzene/*t*BuOK mixtures at 293 K using a 1:1 precatalyst mixture (*S*,*S*)-**9A** plus (*S*,*S*)-**9B**.

run	$[Ru^{tot}]$ $[\times 10^4\,M]$	$[H_2]$ $[\times 10^2\,M]$[b]	[**3**] [M]	[*t*BuOK] $[\times 10^2\,M]$	Rate $[\times 10^4\,M\,s^{-1}]$	Rate $[\times 10^4\,M\,s^{-1}]$[c]
1	2.0	1.59	0.167	5.4	1.2	1.1
2	2.0	1.59	0.084	1.8	1.8	1.8
3	2.0	1.59	0.167	1.8	1.1	1.1
4	2.0	1.59	0.333	1.8	0.7	0.7
5	2.0	1.59	0.167	1.8	1.1	1.1
6	1.0	1.59	0.167	0.9	0.4	0.6
7	4.0	1.59	0.167	1.8	2.2	2.2
8	2.0	3.18	0.167	1.8	2.0	2.2
9	2.0	2.52	0.167	1.8	1.9	1.8

[a] See footnote [a] in Table 5. [b] See footnote [b] in Table 5. [c] Calculated by means of Equation (1).

The rate law appears to be the same as that for *i*PrOH, [Eq. (1)] above, with $k_3 = 1.3 \times 10^2\,M^{-1}s^{-1}$, $K_2 = 16\,M^{-1}$ in the case of benzene.

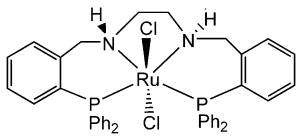
The rates of alcohol production that are calculated on the basis of Equation (1) (Table 6) are in excellent agreement with the observed values. Therefore, there is substrate inhibition and the chemistry is again described by reactions given in Equations (2)–(4). The activation of H_2 by the amido complex (*S*,*S*)-**11** is again the rate-limiting step, but it is approximately ten times slower in benzene ($k_3^{(benzene)} = 1.3 \times 10^2\,M^{-1}s^{-1}$) than in *i*PrOH ($k_3^{(iPrOH)} = 1.23 \times 10^3\,M^{-1}s^{-1}$). The more polar alcohol solvent favors the heterolytic splitting of H_2. In addition the acetophenone adduct is more stable ($K_2^{(benzene)} = 16\,M^{-1}$) in benzene than in *i*PrOH ($K_2^{(iPrOH)} = 1.20\,M^{-1}$).

Calibrations with HY using the dichloride precatalysts (*S*,*S*)-**2** and **12** (see below) under our standard conditions in benzene are provided in other sections. Under these standard conditions, the HY in benzene are also much slower.

Attempts to generate dihydrides of type (*R*,*R*)-10 and to observe the active TRHY catalyst that is generated from the dichloride (*S*,*S*)-2: Preparatively, it should be simpler to generate the dihydrides (*R*,*R*)-**10** by treating the hydridochloride(s) (*R*,*R*)-**9** with HB*s*Bu_3K rather than by dehydrochlorination and addition of H_2.[9m,p,q,s] When a mixture (*R*,*R*)-**9A** plus (*R*,*R*)-**9B** was treated with HB*s*Bu_3K in THF at room temperature under N_2, a mixture of isomeric dihydrides of type (*R*,*R*)-**10** [Eqs. (3) and (4)] was indeed generated. This was ascertained by analysis by NMR spectroscopy (in C_6D_6, see the Experimental Section); this demonstrated the presence of a *trans*-dihydride (*R*,*R*)-**10** (t at −5.5 ppm for RuH) and a *cis*-dihydride (*R*,*R*)-**10** (ddd at −4.5 and dt at −15.5 ppm for RuH) along with a third isomer. However, when this reaction was repeated (this time with (*S*,*S*)-**9A** plus (*S*,*S*)-**9B** and under Ar), the resulting THF solution manipulated and dosed under Ar at ambient temperature, and then tested under TRHY and HY conditions, practically no reaction occurred; this suggests that this mixture of hydrides is too unstable to handle under these conditions.

Attempts to observe the active catalyst in TRHY as it is formed from the dichloride precatalyst (*S*,*S*)-**2** upon treatment with *i*PrOK in *i*PrOH at ambient temperature and up to 60 °C (see above, Table 3) by NMR spectroscopy failed. The reason for this is probably the low solubility of (*S*,*S*)-**2** in *i*PrOH. We actually use mostly finely dispersed "stock suspensions" rather than true stock solutions of (*S*,*S*)-**2** in *i*PrOH in our TRHY and HY experiments. The reaction mixtures in TRHY and HY at the beginning of the reaction (containing the total of the substrate **3**) appear to be homogenous (see the Experimental Section), but even the concentrations used in TRHY are too low to permit the detection of the catalyst by NMR.

HY with [Ru(Cl)$_2$(ethP_2(N$H)_2$)] (12): Since we also wanted achiral HY catalysts, we tested the ethano-bridged precatalyst [Ru(Cl)$_2$(ethP_2(N$H)_2$)] (**12**),[12, 18a] which is a simple achiral analogue of (*S*,*S*)-**2** that was again (like (*S*,*S*)-**2**) already known to be a TRHY precatalyst;[18b] see Table 7.



12

HY with **12** work beautifully and are much more rapid than those with **2**. Complex **12** already performs quite well at s:c 10^6 without base, and already gives record rates at s:c 10^6 with

Table 7. HY of acetophenone (**3**) and three further substrates by using the precatalyst $[Ru(Cl)_2(ethP_2(NH)_2)]$ **12**.

Run	Conditions[a]	Substrate	Precatalyst/ *i*PrOK/substrate	Conversion 1[b]	Conversion 2[b]
1	45 bar H_2, 60 °C, 2.1 M	**3**	1/0/10^5	85/3	98/6
2	45 bar H_2, 60 °C, 2.1 M	**3**	1/5/10^5	100/1.5	–
3	45 bar H_2, 60 °C, 2.1 M	**3**	1/450/10^5	100/1.5	–
4	45 bar H_2, 60 °C, 2.1 M	**3**	1/0/10^6	24/3	100/30
5	45 bar H_2, 60 °C, 2.1 M	**3**	1/0/10^6	8/3	99/30
6	45 bar H_2, 60 °C, 2.1 M	**3**	1/90/10^6	100/3	–
7	45 bar H_2, 60 °C, 2.1 M	**3**	1/6.2 × 10^4 DBU/10^6[c]	2.6/3	32/24
8	45 bar H_2, 60 °C, 2.1 M	**3**	1/500 KBAF/10^6[c]	3/3	6/24
9	45 bar H_2, 60 °C, 2.1 M	**3**	1/500 KBAF/6.2 × 10^4 DBU/10^6[c]	25/3	100/24
10	45 bar H_2, 60 °C, 2.1 M, **benzene**	**3**	1/450/10^4	0/6	99/24
11	45 bar H_2, 60 °C, 2.1 M, **benzene**	**3**	1/450/10^5	23/24	–
12	45 bar H_2, 60 °C, 2.1 M	**7**	1/5/10^5	0/72	–
13	45 bar H_2, 60 °C, 2.1 M	**7**	1/450/10^5	0/72	–
14	45 bar H_2, 60 °C, **3.1 M**	**7**	1/5/10^4	0/28	–
15	45 bar H_2, 60 °C, **3.1 M**	**7**	1/450/10^4	0/28	–
16	45 bar H_2, 60 °C, **3.1 M**	**7**	1/4500/10^4	99/3	–
17	45 bar H_2, 60 °C, 2.1 M	**14**	1/90/10^6	0/23	–
18	45 bar H_2, 60 °C, 2.1 M	**14**	1/90/10^5	100/1	–
19	45 bar H_2, 60 °C, 2.1 M	**14**	1/450/10^5	100/1	–
20	45 bar H_2, 60 °C, **3.1 M**	**14**	1/450/10^5	100/1	–
21	45 bar H_2, 60 °C, 2.1 M	**16**[d]	1/450/10^5	2/3	96/24

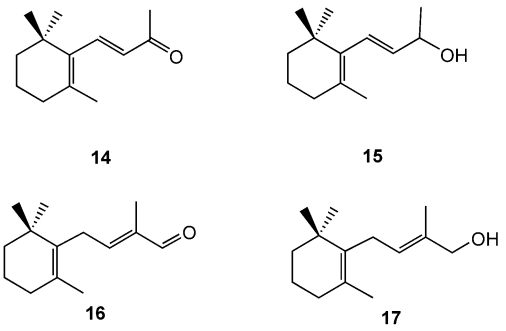
[a] See footnote [a] in Table 2. [b] See footnote [b] in Table 2. [c] KBAF and/or DBU in plac of *i*PrOK. [d] Compound **16** is (*E*)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)buten-2-al.

90 equivalents *i*PrOK. In terms of rate, (*S*,*S*)-**2** performs about the same as (*S*),(*S*,*S*)-**1**. For the latter, the published record *overall* TOF (TOF = turnover frequency) is $5 \times 10^4\ h^{-1}$ at 30 °C (complete conversion within 48 h, 45 bar) at a TON (TON = turnover number = s:c) of 2.4×10^6 and in the presence of 2.4×10^4 equivalents *i*PrOK.[16] In the case of **12**, we reach an overall TOF $\geq 3.3 \times 10^5\ h^{-1}$ at 60 °C (3 h, 45 bar) at a TON of 10^6 in the presence of 90 equivalents *i*PrOK.

We used **12** to further calibrate the difference in the rate of the HY of **3** in *i*PrOH versus benzene, which we had begun with (*S*,*S*)-**2**, see earlier sections. Runs HY10 and HY11 in Table 7 at s:c 10^5 and 10^4 demonstrate again that the reaction is very much slower in benzene, but we at least now achieve near-complete conversion at s:c 10^4 within 24 h.

HY with **12** works well in *i*PrOH in the absence of *i*PrOK at the s:c 10^6 level and still responds strongly to its presence, and we see similar responses in the case of (*S*),(*S*,*S*)-**1** and (*S*,*S*)-**2**. We already discussed the explanation for this that was provided by some of us:[9s] the less acidic the *i*PrOH medium is, and the higher the H_2 pressure, the more the corresponding dihydrides are favored, see above. An earlier explanation is Chen and Hartmann's conclusion that K^+ ion is a cocatalyst in the HY.[19] From experiments using $[Ru(Cl)_2((S)\text{-binap})((S,S)\text{-dpen})]$ ((*S*),(*S*,*S*)-**13**)[12] in *i*PrOH at s:c ≈2000 and using **3** as the substrate, they deduced that both a base and K^+ ions are needed: according to them, the base (*i*PrO^-) serves to generate the dehydro form of the catalyst by dehydrochlorination (cf. Scheme 4, **J** → **L** in the catalytic cycle), and K^+ can then intervene in, and accelerate the addition and cleavage of H_2 (cf. Scheme 3, **L** → **K**) and the subsequent reduction step (cf. Scheme 3, **K** + substrate → **L** + product alcohol). They tested for the effect of K^+ by using K^+ tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (KBAF) as the K^+ source and the role of base by using DBU (which generates *i*PrO^- and $DBUH^+$), and found that only when both are added is the effect of adding *t*BuOK reproduced (50 °C, 5 bar H_2). In the hope of accelerating our HY yet further and to see whether both explanations (refs. [9s] and [19]) are valid, we repeated their tests in the case of **12** at the extreme s:c 10^6 level; see Table 7. These tests were negative: the combined presence of 500 equivalents KBAF and 6.2×10^4 equivalents DBU, which generates about 500 equivalents *i*PrO^-, and should thus have about the same effect as 500 equivalents *i*PrOK, gives about the same performance as **12** *alone*, while KBAF and DBU each alone actually slow down the reaction. Note in passing, that, from a practical viewpoint, it is much simpler and much less costly to add *i*PrOK.

We tested this very active achiral system on some further representative substrates: again cyclohexyl methyl ketone **7** as a saturated analogue of acetophenone (**3**), β-ionone (**14**), to give compound **15**, as an α,β-unsaturated analogue of **3**, and also the α,β-unsaturated aldehyde (*E*)-2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)buten-2-al (**16**) to give compound **17**. All three are hydrogenated much more slowly than **3**, and **7**



is the least reactive. To obtain conversions that are comparable to those for **3**, one needs 100 times more precatalyst **12** in the case of **7** and **16**, and ten times more in the case of **14**, and in the case of **7** more base as well. As already noted at the beginning of the Results and Discussion, these HY systems are best at dealing with acetophenones. The reasons for this are presently not clearly understood. For steric and electronic reasons, **7** is more difficult to hydrogenate than **3**. For **16**, catalyst deactivation by CO abstraction from the aldehyde could be a problem. Changes in the polarity of the medium could also be a factor. We chose substrates **14** and **16** also to

reconfirm the chemoselectivities, and the C=C double bonds are indeed not affected.

Conclusion

Our results provide 1) positive cross tests from TRHY to HY and vice versa, and 2) establish at the same time that, nevertheless, for a given system (i.e., starting out with the *same* precatalyst), different catalysts (or different mixtures of catalysts) operate in the two modes. Further, we find (under our standard conditions) that the response to base is different in the two modes: while added *i*PrOK speeds up both HY and TRHY, the enantioselectivity is not affected in HY and is lowered in TRHY.

The active catalysts in the HY in the standard solvent *i*PrOH are almost certainly amidohydride/dihydride redox couples of the type **L**/**K** (Scheme 3), such as (*S*,*S*)-**11**/(*S*,*S*)-**10** [Eqs. (2)–(4)], and the dihydrides **K** are only accessible or much more accessible under H_2 and in the presence of *i*PrOK. Accordingly, higher concentrations of **3** actually reduce the activity of the system for HY by competing for the five-coordinate amidohydride complex (*S*,*S*)-**11** with a Ru=N double bond [Eq. (2)]; the addition of H_2 to (*S*,*S*)-**11** to give a dihydride species (*S*,*S*)-**10** [Eq. (3)] is the turnover-limiting step, while the reaction of (*S*,*S*)-**10** with **3** to give (*S*)-1-phenylethan-1-ol ((*S*)-**4**) [Eq. (3)] is very fast; the heterolytic splitting of H_2 at the complex (*S*,*S*)-**11** is much faster in *i*PrOH than in benzene, because the higher dielectric constant of *i*PrOH and its ability to form hydrogen bonds to stabilise the polar transition state.

What the active catalysts in the parallel TRHY are is still something of a mystery. This is surprising because the $[Ru(Cl)_2((S,S)\text{-}cyP_2(NH)_2)]$–(*S*,*S*)-**2**-based TRHY were discovered at about the same time as the Ru(H)(aminoalkoxy)(arene)]/[Ru(H)(amidoalkoxy)(arene)][1] and [Ru(H)(aminoamido)(arene)]/[Ru(H)(bisamido)(arene)][2] systems (Scheme 1). We have at least excluded that the hydridochlorides $[Ru(H)(Cl)((S,S)\text{-}cyP_2(NH)_2]$ **9A** and **9B** are the active catalysts in the (*S*,*S*)-**2**-based TRHY and shown that they are not transformed into them under the reaction conditions. We note that the stereochemical outcomes in our experiments suggest the following. In TRHY, for a given system, *different* catalysts (different entities or isomers with different geometries, perhaps different mixtures) are formed from different precatalysts (e.g., from the dichloride (*S*,*S*)-**2** versus the hydridochloride (*S*,*S*)-**9**). The geometries of the TRHY catalyst (whose identity is still unknown) and of the dihydride HY catalyst, which are formed from the same precatalyst (e.g., from (*S*,*S*)-**2**), must also different. Different mixtures may of course also be involved here.

Further unraveling of these complex mechanisms is thus still a rather daunting challenge, but meeting it will be worthwhile, because only then will we fully understand the exceptionally potent systems that already exist, will the discovery of new and perhaps even better HY catalysts become less arduous. It is clearly also worthwhile to run further cross tests, especially for the numerous TRHY systems that have been proposed, including those where the enantioselectivity is unsatisfactory.

Experimental Section

Ligands and precatalysts: All ligands and their Ru^{II} complexes were prepared by combining glove box and standard Schlenk techniques using Ar or N_2. The ligands, $(S,S)\text{-}cyP_2(NH)_2$,[21e,f] its enantiomer, and $ethP_2(NH)_2$,[21a,c] and the derived complexes, $[Ru(Cl)_2((S,S)\text{-}cyP_2(NH)_2)]$ ((*S*,*S*)-**2**),[3a,b, 21d] its enantiomer, and $[Ru(Cl)_2(ethP_2(NH)_2)]$ (**12**),[18a, 21b] are known compounds and were prepared according to the literature.

Preparation of $[Ru(H)(Cl)((S,S)\text{-}cyP_2(NH)_2)]$ as a mixture of two isomers (*S*,*S*)-9A and (*S*,*S*)-9B: THF (2 mL) was added to a mixture of $[Ru(H)(Cl)(PPh_3)_3]$ (300 mg, 0.34 mmol) and $(S,S)\text{-}cyP_2(NH)_2$ (225 mg, 0.34 mmol), and the resulting solution refluxed for 1 h. After cooling to ambient temperature, the solution was filtered and hexanes (10 mL) were added to the filtrate, precipitating a pale yellow solid. Yield: 254 mg (94%). The NMR spectra indicate the presence of a mixture of two isomers. ^1H NMR (360 MHz, C_6D_6, 25 °C), isomer **A**: $\delta = -17.1$ ppm (br); isomer **B**: -17.8 ppm (br t); $^{31}P\{^1H\}$ NMR, isomer **A**: $\delta = 69.9$ (d, $^2J_{PP} = 32.4$ Hz), 63.2 ppm (d, $^2J_{PP} = 32.4$ Hz); isomer **B**: 65.4 (d, $^2J_{PP} = 31.5$ Hz), 61.1 ppm (d, $^2J_{PP} = 31.5$ Hz); elemental analysis calcd (%) for $C_{44}H_{45}ClN_2P_2Ru$ (800.3): C 66.0, H 5.7, N 3.5; found C 67.5, H 6.1, N 3.3 (the presence of hexane of crystallisation would explain the discrepancies).

Preparation of (*S*,*S*)-9B on the NMR scale: Upon treatment with base (10 equiv) of a mixture of $[Ru(H)(Cl)((S,S)\text{-}cyP_2(NH)_2)]$ (*S*,*S*)-**9A** + (*S*,*S*)-**9B** (ca. 1:1, 40 to 80 mg) in [D_8]THF or C_6D_6 (0.7 mL) at ambient temperature, isomer **A** was transformed into isomer **B** (rapidly with *t*BuOK, more slowly with DBU, no reaction with NEt_3). In the case of DBU, the hydride peaks in the ^1H NMR spectrum sharpen to clear dd patterns [isomer **A**: -17.1 (dd, $^2J_{HP} = 33$ Hz, $^2J_{HP} = 28.8$ Hz; isomer **B**: -17.8 (dd, $^2J_{HP} = 32.4$ Hz, $^2J_{HP} = 32.1$ Hz)] in the course of the rearrangement. Isolation after isomerization with DBU in C_6D_6: precipitation with pentanes, stirring (2 h), filtration, and rinse with pentanes produces a yellow solid.

Generation of isomeric dihydrides $[Ru(H_2)((R,R)\text{-}cyP_2(NH)_2)]$ ((*R*,*R*)-10): Under N_2, $HBsBu_3K$ in THF (100 mg of a 1.0 M solution in THF, 0.12 mmol) was diluted with THF (1.0 mL), and the resulting solution was added to the mixture of **9A** and **9B** (100 mg, 0.12 mmol) and the mixture stirred for 4 h. The suspension was then filtered and the filtrate exaporated to dryness. The solids were extracted with C_6D_6 (1 mL total). The ^1H and ^{31}P NMR spectra for this C_6D_6 solution show the presence of three hydride species. The two major isomers are assigned as a *trans*-dihydride (37%) and an unsymmetrical *cis*-dihydride (45%). *trans*-(*R*,*R*)-**10**: ^1H NMR (360 MHz, 25 °C): $\delta = -5.55$ ppm (t, $J_{HP} = 16.7$ Hz); $^{31}P\{^1H\}$ NMR: $\delta = 78.7$ ppm (s). Note that a symmetrical *cis*-dihydride structure would give similar spectra, but the position of the hydride resonance at -5.5 ppm is typical of other *trans*-dihydrides we have observed previously.[9q] cis-(*R*,*R*)-**10**: ^1H NMR: $\delta = -4.49$ (ddd, $J_{HPtrans} = 96.0$, $J_{HPcis} = 29.1$, $J_{HH} = 6.0$ Hz), -15.48 ppm (dt, $J_{HH} = 6.0$, $J_{HP} = 19.2$ Hz); $^{31}P\{^1H\}$ NMR: $\delta = 71.33$ (d, $J_{PP} = 38.6$ Hz), 70.27 ppm (d). Unknown hydride: ^1H NMR: $\delta = -7.12$ ppm (dd, $J_{HP} = 29$, 22 Hz); $^{31}P\{^1H\}$ NMR: $\delta = 78.2$ ppm (br).

Standard HY and TRHY runs: The HY and TRHY runs listed in Tables 2–4, 7 were carried out in cylindrical open glass inserts placed inside a 70 mL stainless steel autoclave (manufactured at Firmenich) fitted with two valves, one for pressurizing/degassing and the other for taking samples by septum/syringe. The autoclave was charged and sealed in a glove box operated with Ar. H_2 gas (99.99990%) was used as received. All substrates and solvents were distilled from appropriate drying agents under Ar.

General procedure for catalytic HY—representative example for a standard run (run HY12 in Table 3): Use of (*R*,*R*)-**2** for the HY of acetophenone (**3**), precatalyst/base/substrate ratio 1:90:10^6, 2.1 M in *i*PrOH; actual mmolar ratios (2×10^{-5}):(1.8×10^{-3}):20. Volumetry: automatic pipettes with a disposable plastic heads were used.

A 0.02 M milky yellow/white suspension/solution of (*R*,*R*)-**2** (low solubility) was prepared by dissolving/suspending (*R*,*R*)-**2** (9.9 mg, 0.01 mmol) in *i*PrOH (500 μL) with magnetic stirring (5 min). A 0.002 M yellow/white suspension/solution of (*R*,*R*)-**2** was then prepared by diluting 100 μL

(0.002 mmol) of the 0.02 M solution with *i*PrOH (900 μL) and stirring (5 min). A 0.18 M solution of *i*PrOK was prepared by dissolving *t*BuOK (202 mg, 1.8 mmol) in *i*PrOH (10 mL). The glass insert of the autoclave was successively charged, 1) with *i*PrOH (7.2 mL), 2) with the 0.18 M solution of *i*PrOK (10 μL, 1.8×10^{-3} mmol), 3) acetophenone (**3**, 2.4 g, 20 mmol), and 4) with the 0.002 M solution of (*R*,*R*)-**2** (10 μL, 2×10^{-5} mmol). The resulting mixture was colorless and homogenous upon inspection with the eye. The charged insert was placed inside the autoclave, the autoclave was sealed and pressurized with 45 bar of H_2, and its contents magnetically stirred and heated to 60 °C with an oil bath. Samples for analysis by GC were withdrawn with septum and syringe under a flow of H_2 after taking the autoclave out of the heating bath and degassing. The autoclave was then repressurized with H_2 and the HY continued.

Kinetics: HY reactions were run at 293 K at constant H_2 pressures except during the brief sampling periods that lasted 5 to 2 s by using a 50 mL Parr reactor. The reactor was flushed several times with Ar and H_2 at the pre-set pressure prior to charging. Aliquots of the reaction mixture were quickly withdrawn with a syringe under a flow of H_2 at regular intervals (the minimum interval was 120 s) by venting the reactor. Concentrations of acetophenone (**3**) and 1-phenylethan-1-ol (**4**) were determined by ^{1}H NMR spectroscopy (in C_6D_6) or GC (in *i*PrOH and C_6D_6). The temperature was maintained at 293 K by use of a constant temperature water bath. Initial rates were taken from the first linear portion of the plot of alcohol concentration versus time. This linear portion continued to at least 60% conversion before a slowing of the reaction was observed. In some cases an induction period was observed before this rate was established.

In C_6D_6 as the solvent: A stock solution of (*R*,*R*)-**9A** + (*R*,*R*)-**9B** (1.00×10^{-3} M) was prepared by dissolving the mixture of isomers (20 mg, 0.025 mmol) in C_6D_6 (25 mL). A catalyst–base mixture was prepared by pipetting the required amount of the stock solution of (*R*,*R*)-**9A** + (*R*,*R*)-**9B** onto a weighed amount of *t*BuOK and then adding C_6D_6 to give a final volume of 3 mL. This mixture was introduced into the autoclave and allowed to react under H_2 for 45 min. A solution of **3** in C_6D_6 (2 mL) was then added to start the reaction. Samples were taken at intervals of between 2 and 10 min for analysis by NMR spectroscopy and GC. The pressure was released for about 5 s while the sample was withdrawn against a flow of H_2.

In *i*PrOH as the solvent: Stock solutions of (*R*,*R*)-**9A** + (*R*,*R*)-**9B** (2.00×10^{-3} M) and *t*BuOK (0.089 M) were prepared by dissolving the required amount of (*R*,*R*)-**9A** + (*R*,*R*)-**9B** (40 mg, 0.05 mmol) in toluene (25 mL) and of *t*BuOK (250 mg, 2.23 mmol) in *i*PrOH (25 mL). The required amount of (*R*,*R*)-**9A** + (*R*,*R*)-**9B** solution (50 to 200 μL) and toluene were then mixed to make up a total volume of 200 μL. To this was added the solution of *t*BuOK in *i*PrOH (1–3 mL), then the desired amount of **3**, and finally the required amount of *i*PrOH to give a final volume of 5 mL. The resulting solution was then introduced into the autoclave and placed under H_2 to start the reaction.

Rate law derivation for Equation (1):

$[Ru^{tot}] = [\mathbf{11}] + [\text{ketone adduct}]$

$K_2 = [\text{ketone adduct}]/([\mathbf{11}][\text{ketone}])$

therefore:

$[\mathbf{11}] = [Ru^{tot}]/(1 + K_2[\text{ketone}])$

$\text{rate} = k_3[H_2][\mathbf{11}]$

therefore:

$\text{rate} = d[\text{alcohol}]/dt = k_3[H_2][Ru^{tot}]/(1 + K_2[\text{ketone}])$

GC analyses: Chrompack Chirasil-Dex CB 25 m × 0.25 mm capillary column, H_2 as carrier gas.

[1] Pairs Ru(amidoalkoxy)(arene)]/[Ru(H)(aminoalkoxy)(arene)] **A/B**: a) J. Takehara, S. Hashiguchi, A. Fujii, S.-I. Inoue, T. Ikariya, R. Noyori, *Chem. Commun.* **1996**, 233–234; b) M. Palmer, T. Walsgrove, M. Wills, *J. Org. Chem.* **1997**, *62*, 5226–5228; c) D. A. Alonso, D. Guijarro, P. Pinho, O. Temme, P. G. Anderson, *J. Org. Chem.* **1998**, *63*, 2749–2751; d) M. Wills, M. Gamble, M. Palmer, A. Smith, J. Studley, J. Kenny, *J. Mol. Catal. A* **1999**, *146*, 139–148; e) D. G. I. Petra, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, A. M. van Loon, J. G. de Vries, H. E. Schoemaker, *Eur. J. Inorg. Chem.* **1999**, 2335–2341; f) K. Evereaere, J.-F. Carpentier, A. Mortreux, M. Bulliard, *Tetrahedron: Asymmetry* **1999**, *10*, 4663–4666; g) D. A. Alonzo, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588; h) J. A. Kenny, K. Versluis, A. J. R. Heck, T. Walsgrove, M. Wills, *Chem. Commun.* **2000**, 99–100; i) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478; j) C. G. Frost, P. Mendonça, *Tetrahedron: Asymmetry* **2000**, *11*, 1845–1848; k) M. Henning, K. Püntener, M. Scalone, *Tetrahedron: Asymmetry* **2000**, *11*, 1849–1858; l) D. A. Alonso, S. J. M. Nordin, P. Roth, T. Tarnai, P. G. Anderson, M. Thommen, U. Pittelkow, *J. Org. Chem.* **2000**, *65*, 3116–3122; m) I. Yamada, R. Noyori, *Org. Lett.* **2000**, *2*, 3425–3427; n) K. Everaere, A. Mortreux, M. Bulliard, J. Brussee, A. van der Gen, G. Nowogrocki, J.-F. Carpentier, *Eur. J. Org. Chem.* **2001**, 275–291; o) A. J. Sandee, D. G. I. Petra, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2001**, *7*, 1202–1208; p) S. J. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt, P. G. Andersson, *Chem. Eur. J.* **2001**, *7*, 1431–1436; q) M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem.* **2001**, *113*, 2900–2903; *Angew. Chem. Int. Ed.* **2001**, *40*, 2818–2821; r) J. W. Faller, A. R. Lavoie, *Org. Lett.* **2001**, *3*, 3703–3706; s) J. W. Faller, A. R. Lavoie, *Organometallics* **2002**, *21*, 2010–2012; t) J. W. Faller, A. R. Lavoie, *Organometallics* **2002**, *21*, 3493–3495; u) M. Pastó, A. Riera, M. A. Pericàs, *Eur. J. Org. Chem.* **2002**, 2337–2341.

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[12] BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; TolBINAP = the di-*p*-tolyl analogue of BINAP; DPEN = 1,2-diphenylethylenediamine; $cyP_2(NH)_2$ = *N*,*N*′-bis[*o*-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine; $ethP_2(NH_2)$ = *N*,*N*′-bis[*o*-(diphenylphosphino)-benzyl]ethylenediamine.

[13] One can go full circle. If the addition of H_2 is feasible, then it may be reversible. In that case, TRHY/*i*PrOH systems would generate H_2. This is thermodynamically uphill, so only very low partial H_2 pressures would be available, but the H_2 could escape from an open reactor, and the TRHY and HY systems would merge into one. (See: a) D. Morton, D. J. Cole-Hamilton, *J. Chem. Soc. Chem. Commun*. **1988**, 1154 – 1156; b) D. Morton, D. J. Cole-Hamilton, I. Utuk, M. Paneque-Sosa, M. Lopez-Poveda, *J. Chem. Soc. Dalton Trans.* **1989**, 489 – 495.) If so, TRHY presumably still dominates when no H_2 is introduced, and HY takes over when it is and as the pressure is increased. It seems that nobody has checked whether H_2 is generated in the advanced Ru^{II}/*i*PrOH TRHY systems. We also did not make any such checks in the present work because our central interest is in bona fide HY.

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[15] $[Ru(H)_2(H_2)(PPh_3)_3]$ is the classic Ru^{II} catalyst for the HY of cyclohexanone. In the proposed catalytic cycle, it reduces cyclohexanone, and the resulting $[Ru(H)_2(PPh_3)_3]$ then reacts with H_2 to give back $[Ru(H)_2(H_2)(PPh_3)_3]$: a) D. E. Linn, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 2969 – 2974. $[Ru(H)_2(PPh_3)_3]$ {normally generated from $[Ru(Cl)_2(PPh_3)_3]$ by treatment with base in *i*PrOH), but see: b) Y. Lin, Y. Zhou, *J. Organomet. Chem.* **1990**, *381*, 135 – 138} is apparently the active catalyst in the related TRHY of ketones: c) E. Mizushima, M. Yamaguchi, T. Yamagishi, *Chem. Lett.* **1997**, 237 – 238; E. Mizushima, M. Yamaguchi, T. Yamagishi, *J. Mol. Catal. A* **1999**, *148*, 69 – 75; d) A. Aranyos, G. Csjernyik, K. L. Szabo, J.-E. Bäckvall, *Chem. Commun.* **1999**, 351 – 352, 2131. $[RuH(Tp^*)(H_2)_2]$ catalyzes the HY of ketones in heptanes in the absence of base and their TRHY in *i*PrOH/NaOH: e) C. Vicente, G. B. Shulpin, B. Moreno, S. Sabo-Etienne, B. Chaudret, *J. Mol. Catal. A* **1995**, *98*, L5 – L8. The $[Ru(H)(Cl)(bis(1\text{-}pyrazolyl)methane)(1,3\text{-}cod)]$/NaOH/MeOH system catalyzes, inter alia, the HY of cyclohexanone and, in *i*PrOH instead of MeOH, its TRHY: f) F. A. Jalon, A. Otero, A. Rodriguez, M. Perez-Manrique, *J. Organomet. Chem.* **1996**, *508*, 69 – 74. $[Ru(Cl)_2((R_2(phosphino))\text{-}(2'\text{-}pyridyl)methane)_2]$/*i*PrOH/NaOH systems have TRHY activity, and HY activity with $NH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$ added: ref. [6k].

[16] The catalyst base ratio (c:b) = 2.4×10^4 at s:c 2.4×10^6 corresponds to a substrate/base ratio (s:b) = 100.

[17] About 0.18 M at ambient temperature: W. von E. Doering, R. S. Urban, *J. Am. Chem. Soc.* **1956**, *78*, 5938 – 5942.

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Received: February 25, 2003 [F4884]

