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Rapid, productive and stereoselective hydrogenation of ketones*

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Abstract: $RuCl_2$(phosphine)$_2$(1,2-diamine) complexes act as excellent precatalysts for homogeneous hydrogenation of simple ketones which lack any functionality capable of interacting with the metallic center. This newly devised catalytic system allows preferential saturation of a C=O function over a coexisting C=C linkage in 2-propanol containing an alkaline base. Furthermore, the stereoselectivity of the reaction is easily controlled by the electronic and steric properties (bulkiness and chirality) of the ligands as well as the reaction conditions.

Selective reduction of carbonyl compounds to alcohols has relied heavily on the use of metal hydride reagents. Our goal is to replace such stoichiometric reductions by catalytic hydrogenation, because the latter is obviously more beneficial, particularly for large-scale reactions. Here we describe a very practical homogeneous hydrogenation of ketones catalyzed by $RuCl_2$(phosphine)$_2$(1,2-diamine) and an inorganic base. The precatalysts can be preformed or generated *in situ* by mixing the phosphine–$RuCl_2$ complex and an appropriate 1,2-diamine in 2-propanol. The reaction is normally conducted at room temperature and at < 8 atm of hydrogen. The new method shows promise for the synthesis of a wide range of achiral and chiral alcohols from ketonic substrates. This chemistry is entirely different from the BINAP–Ru catalyzed asymmetric hydrogenation of functionalized ketones developed earlier in our laboratories [1].

RAPID HYDROGENATION OF SIMPLE KETONES

Preformed $RuCl_2$(phosphine)$_2$(1,2-diamine) complexes serve as stable precatalysts for rapid and productive hydrogenation of ketones. For example, when a 2.1 M solution of cyclohexanone in 2-propanol containing *trans*-$RuCl_2(P(C_6H_4\text{-}4\text{-}CH_3)_3)_2(NH_2(CH_2)_2NH_2)$ and *t*-C_4H_9OK (ketone:Ru:base = 100 000:1:450) was hydrogenated at 10 atm of hydrogen at 60 °C for 2 h, cyclohexanol was produced in 96% yield [2]. The reaction was extremely rapid with an initial turnover frequency (TOF) [3] of 563 000 h^{-1} (or 156 s^{-1}). The Ru complexes are among the most reactive (pre)catalysts known for homogeneous hydrogenation of ketones. The reaction rate and productivity of reaction of the preformed phosphine/diamine complexes are some two orders of magnitude higher than those obtained with the *in situ* generated complexes [4], while the selectivities (*vide infra*) of both systems are very similar. Although the real catalyst formed under the hydrogenation conditions remains to be elucidated, we consider that the reducing species is RuHX (phosphine)$_2$ (diamine) (X=H, or OR).

CARBONYL-SELECTIVE HYDROGENATION

Currently available hydrogenation catalysts, either homogeneous or heterogeneous, are mostly selective for C=C functions over C=O bonds. Despite extensive efforts for over a century, there are no general catalysts effecting C=O selective hydrogenation in the presence of an olefinic linkage [5]. We found that a ternary system consisting of $RuCl_2$(phosphine)$_3$, 1,2-diamine, and an alkaline base or a system comprising *trans*-$RuCl_2$(phosphine)$_2$(1,2-diamine) and an alkaline base meets this requirement.

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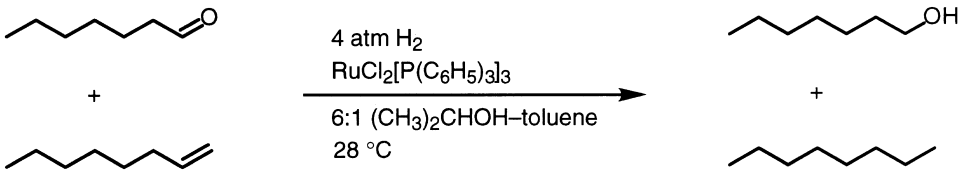
An intermolecular competition experiment using an equimolar mixture of heptanal and 1-octene with $RuCl_2(P(C_6H_5)_3)_3$ in a 6:1 2-propanol–toluene mixture at 4 atm of hydrogen at 28 °C showed that the terminal olefin is 250-fold more reactive than the aldehyde. However, when one equiv of $NH_2(CH_2)_2NH_2$ and 2 eq. of KOH with respect to Ru were added, the aldehyde was hydrogenated 1500-fold faster than the olefin [6]. The very small quantities of the diamine and the base changed the C=C/C=O selectivity profile by a factor of 375 000. Under such conditions, benzaldehyde was 450-fold more reactive than styrene and acetophenone was hydrogenated 1500-fold faster than α-methylstyrene (Scheme 1).

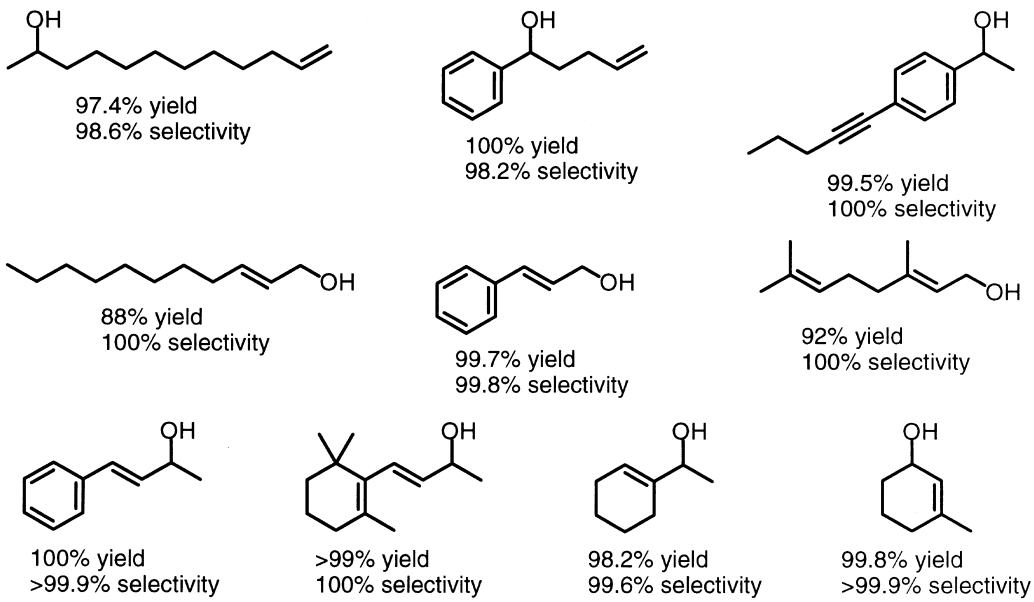


aldehyde:olefin:Ru = 500:500:1

additive	time, min	1-heptanol:octane
no base	150	1:250
$NH_2(CH_2)_2NH_2$ and KOH (Ru:diamine:KOH = 1:1:2)	10	1500:1

Scheme 1

This chemoselective hydrogenation is applicable to a variety of carbonyl compounds having an olefinic or internal acetylenic bond. Certain α,β-unsaturated aldehydes and ketones are also hydrogenated selectively to allylic alcohols by this method [2,6], The excellent C=O selectivity is reminiscent of that attained by stoichiometric $NaBH_4$ reduction (Scheme 2).

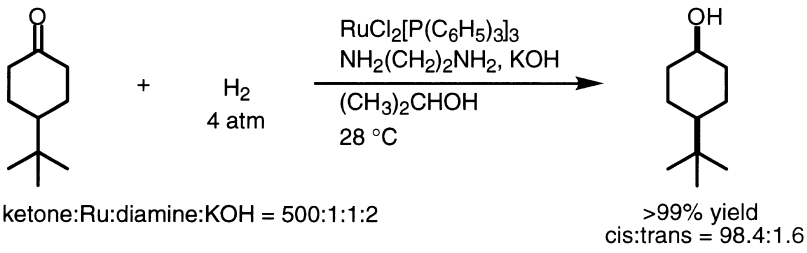


Scheme 2

DIASTEREOSELECTIVE HYDROGENATION

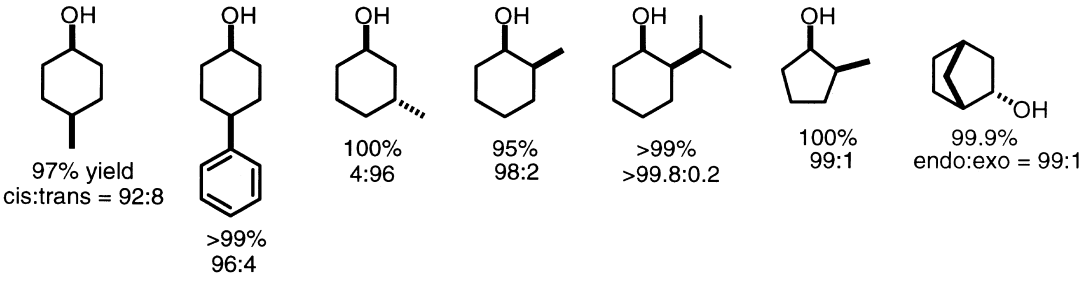
Diastereoselective reduction of ketones has been accomplished mainly with boron-based hydride reagents [7]. The new hydrogenation catalyzed by phosphine/diamine Ru complexes is very useful for this

purpose. For example, hydrogenation of 4-*t*-butylcyclohexanone, a conformationally anchored ketone, with the $RuCl_2(P(C_6H_5)_3)_3$–$NH_2(CH_2)_2NH_2$–KOH system took place preferentially from the less crowded equatorial direction to give a 98.4:1.6 mixture of *cis*-4-*t*-butylcyclohexanol and its *trans* isomer [8]. Use of preformed *trans*-$RuCl_2(P(C_6H_4\text{-}4\text{-}CH_3)_3)_2(NH_2(CH_2)_2NH_2)$ and *t*-C_4H_9OK (ketone:Ru:base 50 000:1:250, 10 atm, 60 °C) effected rapid hydrogenation with a TOF of 178 000 h^{-1} (or 49 s^{-1}) (Scheme 3) [2].



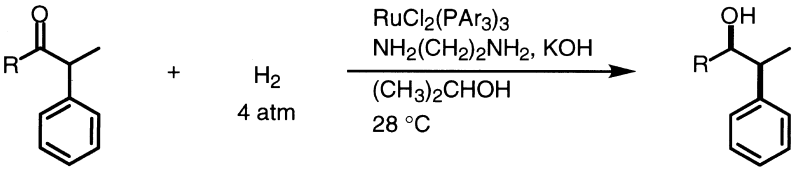
Scheme 3

Some other cyclic ketones can be hydrogenated with a high diastereoselectivity (Scheme 4) [8].



Scheme 4

Hydrogenation of 1-phenylethyl ketones, conformationally flexible substrates, displayed a high Cram selectivity [8]. The extent of diastereoselectivity compares well with that obtained with the stoichiometric L-Selectride reagent (Scheme 5) [9].

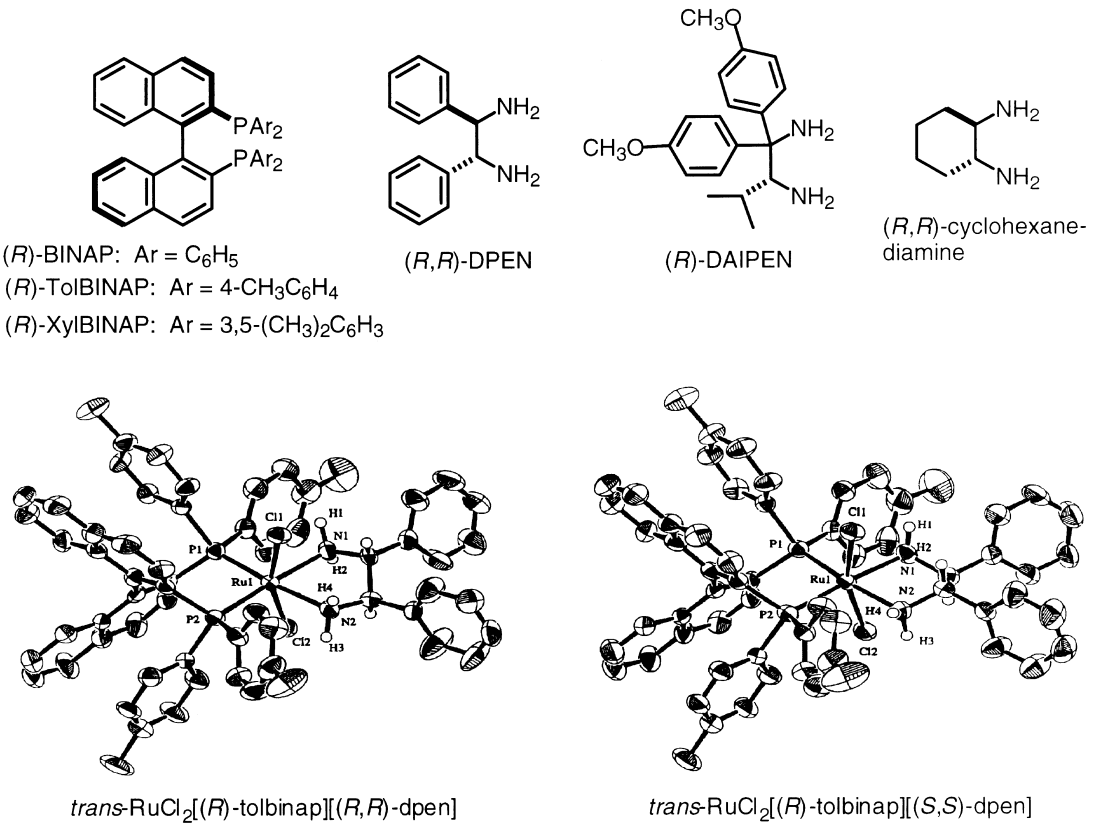


R in ketone	Ar in PAr_3	% yield	syn:anti
C_6H_5	C_6H_5	99	98:2
n-C_4H_9	C_6H_5	96	93:7
CH_3	4-$CH_3OC_6H_4$	99	96:4

Scheme 5

ENANTIOSELECTIVE HYDROGENATION

Although various chiral catalysts effect asymmetric reduction, no single catalyst can be universal [5,10,11]. This hydrogenation system copes flexibly with the diverse situations by modification of catalyst structures and reaction parameters. A wide variety of chiral Ru catalysts can be obtained by combinations of chiral diphosphine and diamine ligands. Both preformed mixed-ligand complexes and *in situ* generated complexes are usable [2,4], the former exhibiting a higher turnover number (TON) [3]. Single-crystal X-ray analysis of the structures of the (*R*)-TolBINAP/(*R*,*R*)-DPEN Ru complex and the diastereomeric (*R*)-TolBINAP/(*S*,*S*)-DPEN complex revealed that both complexes have a distorted octahedral geometry of the Ru center [2]. The (*R*,*R*)-DPEN ligand forms a λ chelate ring, whereas the *S*,*S* diamine creates a δ five-membered ring. ^{1}H and ^{31}P NMR analyses showed that these diastereomers exist as a single conformer in benzene-d_6 (Scheme 6).

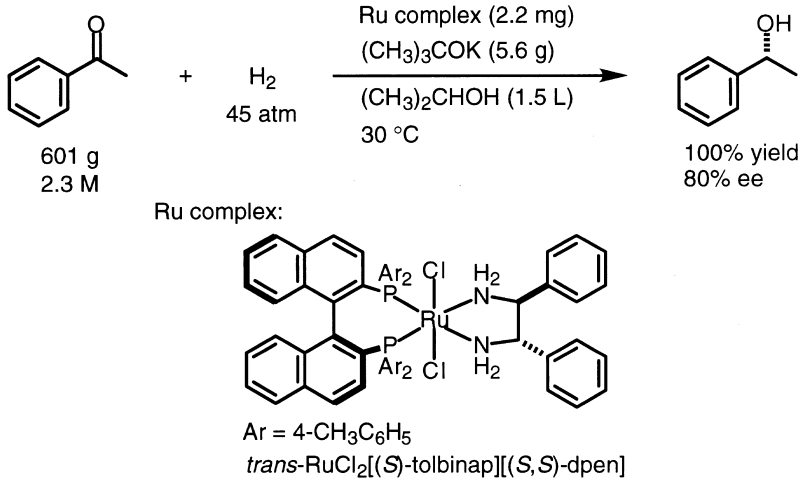


Scheme 6

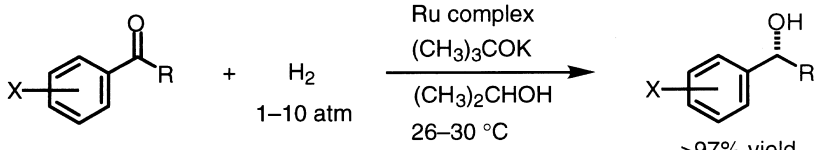
Rapid, highly productive asymmetric hydrogenation can be achieved with chiral diphosphine/diamine complexes. When a mixture of acetophenone (601 g), the TolBINAP/DPEN complex (2.2 mg), and *t*-C_4H_9OK (5.6 g) in 2-propanol (1.5 L) was stirred under 45 atm of hydrogen at 30 °C for 48 h, the *R* alcohol was obtained in 80% enantiomer excess and in 100% yield. The TON was at least 2400 000, while the TOF at 30% conversion was 228 000 h^{-1} (or 63 s^{-1}) [2]. The enantioselectivity was greatly improved by the use of the (*S*)-XylBINAP/(*S*)-DAIPEN complex (ketone:Ru:*t*-C_4H_9OK = 100 000:1:400, 8 atm, 28 °C), giving (*R*)-1-phenylethanol in 99% enantiomer excess (Scheme 7) [12].

With the XylBINAP/DAIPEN Ru catalyst, various 2′-, 3′-, and 4′-substituted acetophenones have been hydrogenated with high enantioselectivity. This hydrogenation permits many ring substituents including F, Cl, Br, I, CF_3, OCH_3, $COOCH(CH_3)_2$, NO_2, and NH_2 (Scheme 8) [12].

2,2,2-Trifluoroacetophenone and its derivatives were also hydrogenated in high yield with high enantioselectivity (Scheme 9) [12].



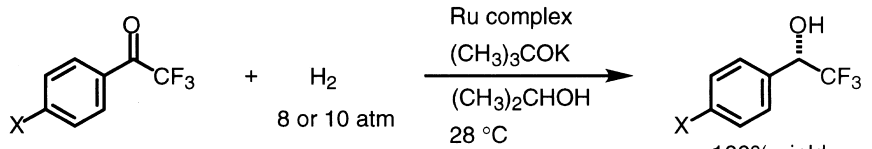
Scheme 7



ketone:Ru = 500:1 (1 atm) to 100 000:1
Ru complex = *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen]

R (X = H)	% ee	X ($R = CH_3$)	% ee	X ($R = CH_3$)	% ee
CH_3	99	2-, 3-, 4-CH_3	99, 100, 98	2-, 3-, 4-CF_3	99, 99, 99.6
C_2H_5	99	4-*n*-C_4H_9	98	2-, 3, 4-CH_3O	92, 99, 100
$(CH_3)_2CH$	99	2-, 3-, 4-F	97, 98, 97	4-$(CH_3)_2CHOCO$	99
cyclo-C_3H_5	96	2-, 4-Cl	98, 98	4-NO_2	99.8
		2-, 3-, 4-Br	96, 99.5, 99.6	4-NH_2	99
		4-I	99		

Scheme 8



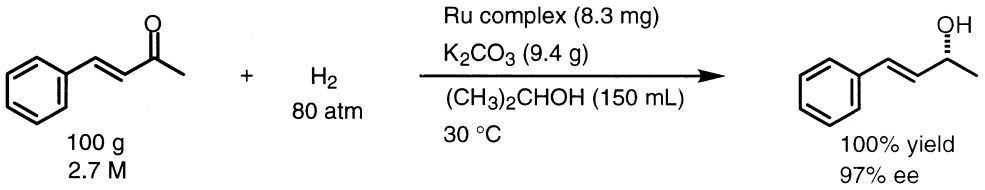
ketone:Ru = 2000–11 000:1
Ru complex = *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen]

X	% ee
H	96
Cl	94
Br	94
CH_3O	96

Scheme 9

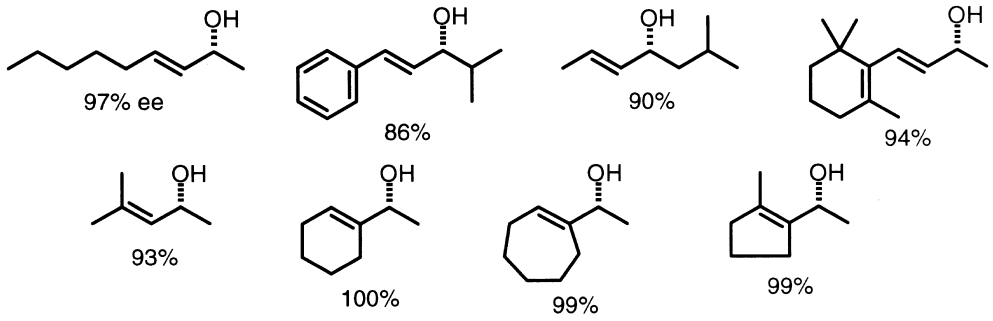
Asymmetric hydrogenation of alkenyl ketones remained difficult because of conformational flexibility and the presence of two kinds of unsaturated moieties, C=C and C=O. In addition, some simple enones are sensitive to basic conditions. Fortunately, this long-standing problem has been solved by the use of the XylBINAP/DAIPEN Ru complex and the weakly basic K_2CO_3 in place of conventional KOH or

t-C_4H_9OK. Reaction of benzalacetone (100 g) in 2-propanol (150 mL) containing the (*S*)-XylBINAP/(*S*)-DAIPEN complex (8.3 mg) and K_2CO_3 (9.4 g) (ketone:Ru = 100 000:1, 2.7 M solution) at 80 atm of hydrogen gave the *R* alcohol in 97% enantiomer excess [12]. Enones with various substitution patterns were converted to their corresponding allylic alcohols with high enantiomer excess. β-Ionone, a dienone, is convertible to β-ionol in 94% enantiomer excess. Like in the reaction of aromatic ketones, the combination of the *S* diphosphine and *S* diamine (or *R* and *R*) is crucial for obtaining a high level of enantioselection (Schemes 10 and 11).



ketone:Ru:K_2CO_3 = 100 000:1:10 000
Ru complex = *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen]

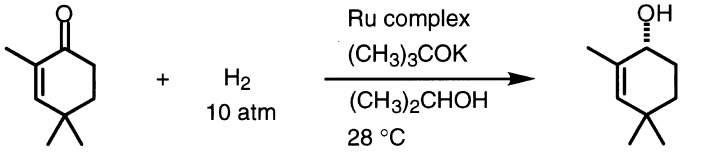
Scheme 10



conditions: 8 or 10 atm H_2, *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-diamine] + K_2CO_3 or *t*-C_4H_9OK in 2-propanol

Scheme 11

Certain cyclic α,β-unsaturated ketones can be used as substrates. For example, reaction of 2,4,4-trimethyl-2-cyclohexenone in the presence of the (*S*)-TolBINAP/(*R*,*R*)-DPEN Ru complex and *t*-C_4H_9OK (ketone:Ru = 10 000:1, 10 atm, 28 °C) produced (*R*)-2,4,4-trimethyl-2-cyclohexenol in 94% enantiomer excess and in 100% yield [2,13], No conjugate reduction took place. Here the combination of the *S* diphosphine and the *R*,*R* diamine is necessary for high enantioselection. The *R* and *S* cyclohexenols, coupled with the Claisen reaction, are convertible to a series of carotenoid-derived odorants and other bioactive terpenes (Scheme 12) [14].

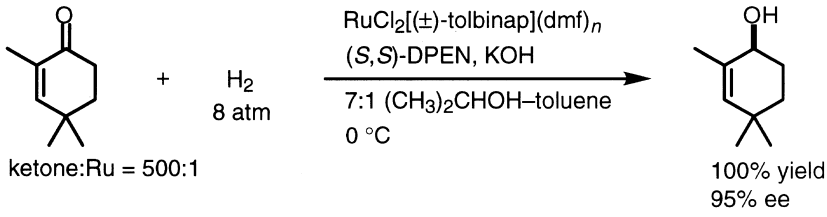


ketone:Ru = 10 000:1
Ru complex = *trans*-$RuCl_2$[(*S*)-tolbinap][(*R*,*R*)-dpen]

Scheme 12

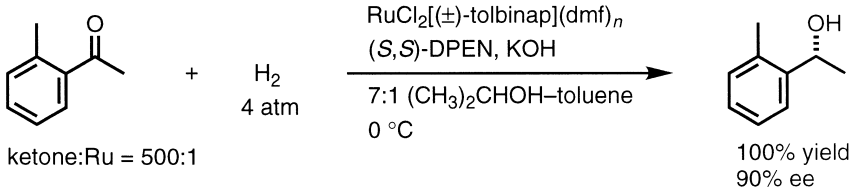
This important asymmetric hydrogenation is effected by using a racemic diphosphine Ru complex with the aid of a nonracemic 1,2-diamine. Thus, when the cyclohexenone was hydrogenated with (±)-$RuCl_2$(tolbinap)$(dmf)_n$ (*S*,*S*)-DPEN, and KOH in a 2-propanol–toluene mixture at 8 atm at 0 °C, the *S* allylic alcohol was obtained in 95% enantiomer excess and 100% yield [15]. The observed enantioselectivity reflects the relative turnover numbers of the competing (*R*)-TolBINAP/(*S*,*S*)-DPEN and

(*S*)-TolBINAP/(*S*,*S*)-DPEN catalytic cycles, and the ratio is determined by the relative concentrations and reactivities of the coexisting diastereomeric diphosphine/diamine Ru catalysts. Under this condition (*S*,*S*)-DPEN selectively activates the (*R*)-TolBINAP–Ru enantiomer of the racemate. Analysis indicates that the *R*/*S*,*S* cycle, with an *S*:*R* enantioselectivity of 98:2, turns over 121 times faster than the *S*/*S*,*S* cycle, having an *S*:*R* selectivity of 37:63 (Scheme 13).



Scheme 13

Notably, the relative significance of the diastereomeric cycles, *R*/*S*,*S* and *S*/*S*,*S*, as well as the sense and degree of asymmetric induction is highly dependent on the structures of ketonic substrates. When 2′-methylacetophenone was used as substrate, (*S*,*S*)-DPEN enhanced the activity of the (*S*)-TolBINAP–Ru complex more than the (*R*)-TolBINAP enantiomer. The hydrogenation catalyzed by (±)-$RuCl_2$(tolbinap)$(dmf)_n$ (*S*,*S*)-DPEN, and *t*-C_4H_9OK afforded (*R*)-1-(2-methylphenyl)ethanol in 90% enantiomer excess and 100% yield [15]. In this case, the *S*/*S*,*S* cycle with an *S*:*R* enantioselectivity of 1.3:98.7 occurred 13 times faster than the *R*/*S*,*S* cycle, having an *S*:*R* selectivity of 54:46 (Scheme 14).



Scheme 14

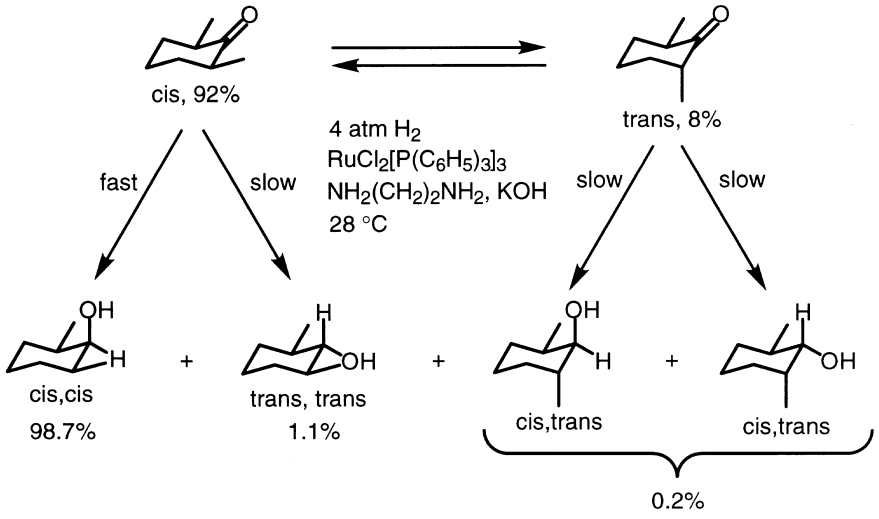
DYNAMIC KINETIC DISCRIMINATION OF STEREOISOMERS

Stereoisomeric ketones are hydrogenated at different rates. A configurationally labile α-substituted ketone undergoes stereomutation easily in basic 2-propanol, leading to a new type of stereoselective hydrogenation based on kinetic discrimination [16].

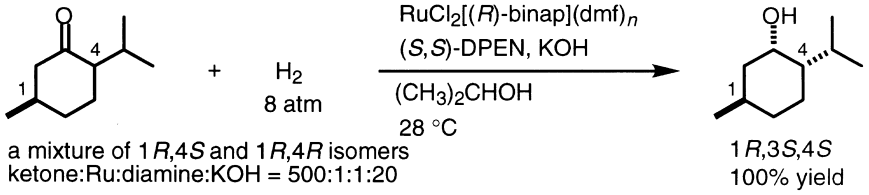
2,6-Dimethylcyclohexanone is in a rapid equilibrium between the *cis* and *trans* isomers (92:8), which can be differentiated kinetically. The *trans* isomer is rather unreactive because the equatorial approach of the Ru hydride species to the carbonyl carbon is blocked by the axially oriented methyl substituent at the α position. Therefore, hydrogenation of the diastereomeric mixture in the presence of a $RuCl_2(P(C_6H_5)_3)_3$–$NH_2(CH_2)_2NH_2$–KOH catalyst system in 2-propanol at 4 atm gave the *cis*,*cis*, *trans*,*trans* and *cis*,*trans* alcohols in a 98.7:1.1:0.2 ratio [8]. The distribution of the *cis*,*trans* isomer (0.2%) is much less than the equilibrium population of the *trans*-dimethyl ketone (8%) (Scheme 15).

(−)-Menthone is in an equilibrium with isomenthone. These epimers were differentiated kinetically by hydrogenation with an (*R*)-BINAP/(*S*,*S*)-DPEN Ru catalyst system, leading exclusively to (+)-neomenthol (Scheme 16) [8].

Dynamic kinetic resolution provides a useful method to convert racemic α-substituted ketones stereoselecively to a single stereoisomer among four possible isomers. Hydrogenation of (±)-2-isopropylcyclohexanone in the presence of an (*S*)-BINAP/(*R*,*R*)-DPEN Ru catalyst and KOH at 4 atm afforded a 99.8:0.2 mixture of the *cis*-1*R*,2*R* alcohol in 93% enantiomer excess and the *trans*-1*R*,2*S* isomer in 28% enantiomer excess [8]. Computer-aided analysis of the reaction revealed that: (i) the inherent 1*R*,2*R*:1*S*,2*S*:1*R*,2*S*:1*S*,2*R* selectivity is 97.26:2.57:0.10:0.07; (ii) under this reaction condition, the *R*

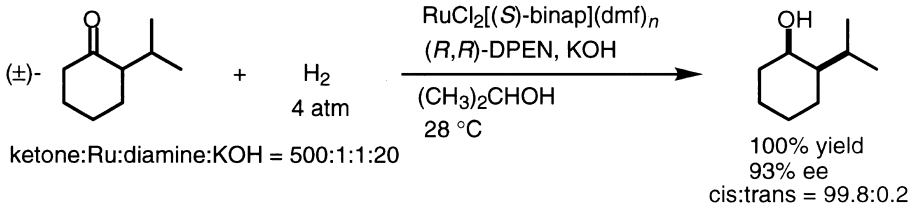


Scheme 15



Scheme 16

ketone is hydrogenated 36-fold faster than the *S* enantiomer; (iii) the slow-reacting *S* ketone undergoes *in situ* stereochemical inversion 47-fold faster than hydrogenation; (iv) the extent of the substrate-based asymmetric induction (*cis*/*trans*) is 192; and (v) the catalyst-controlled asymmetric induction (*R**/*S**) is 7.2. The kinetic and stereochemical factors are well coupled to accomplish the diastereo- and enantioselective hydrogenation (Scheme 17).



Scheme 17

ACKNOWLEDGEMENTS

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REFERENCES

1 R. Noyori. *Asymmetric Catalysis in Organic Synthesis*. Chap. 2. Wiley, New York (1994).

2 H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori. *Angew. Chem. Int. Eds.* **37**, 1703 (1998).

3 TON = mols product per mol catalyst. TOF = TON per h or s.

4 T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori. *J. Am. Chem. Soc.* **117**, 2675 (1995).

5 T. Ohkuma, R. Noyori. In *Transition Metals for Organic Synthesis* (M. Beller, C. Bolm, eds), Vol. 2, Chap. 1.1.3. Wiley-VCH, Weinheim (1998), and references cited therein. For C=O selective asymmetric transfer hydrogenation, see: R. Noyori, S. Hashiguchi. *Acc. Chem. Res.* **30**, 97 (1997).

6 T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori. *J. Am. Chem. Soc.* **117**, 10417 (1995).

7 Selected reviews: H. C. Brown, S. Krishnamurthy. *Tetrahedron* **35**, 567 (1979); A. P. Davis. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th edn (G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, eds), Vol. E21d, p. 3988. Thieme, Stuttgart (1995); H. C. Brown, P. V. Ramachandran. In *Reductions in Organic Synthesis* (A. F. Abdel-Magid, ed.), Chap. 1. American Chemical Society, Washington, DC (1996), and references cited therein.

8 T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, R. Noyori. *J. Org. Chem.* **61**, 4872 (1996).

9 H. C. Brown, S. Krishnamurthy. *J. Am. Chem. Soc.* **94**, 7159 (1972); S. Krishnamurthy, H. C. Brown. *J. Am. Chem. Soc.* **98**, 3383 (1976).

10 E. J. Corey, C. J. Helal. *Angew. Chem. Int. Eds.* **37**, 1986 (1998), and references cited therein.

11 T. Ohkuma, R. Noyori. In *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, eds), Vol. 1, Chap. 6.1. Springer, Berlin (1999).

12 T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori. *J. Am. Chem. Soc.* **120**, 13529 (1998).

13 T. Ohkuma, H. Ikehira, T. Ikariya, R. Noyori. *Synlett* 467 (1997).

14 K. Mori, P. Puapoomchareon. *Liebigs Ann. Chem.* 1053 (1991). R. Croteau, F. Karp. In *Perfumes: Art, Science and Technology* (P. M. Müller, D. Lamparsky, eds), Chap. 4. Blackie Academic & Professional, London (1991).

15 T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori. *J. Am. Chem. Soc.* **120**, 1086 (1998). See also: K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori. *Angew. Chem. Int. Eds.* **38**, 495 (1999), and references cited therein.

16 M. Kitamura, M. Tokunaga, R. Noyori. *J. Am. Chem. Soc.* **115**, 144 (1993). M. Kitamura, M. Tokunaga, R. Noyori. *Tetrahedron* **49**, 1853 (1993). R. Noyori, M. Tokunaga, M. Kitamura. *Bull. Chem. Soc. Jpn.* **68**, 36 (1995).