32
Enantioselective Ketone and β-Keto Ester Hydrogenations (Including Mechanisms)

Takeshi Ohkuma and Ryoji Noyori

Enantioselective hydrogenation of β-keto esters is a well-established procedure to produce chiral β-hydroxy esters in high optical purity [1–4]. Many important biologically active compounds have been synthesized through this procedure, even on a commercial scale [1–4]. Ru complexes [5] bearing appropriate chiral phosphine ligands [6–8] provide excellent catalytic efficiency for this reaction. Certain chiral Rh catalysts [3, 4] and heterogeneous Ni catalysts [9] are also utilized. The recent development of the chiral diphosphine/diamine–Ru catalyst enables rapid and stereoselective hydrogenation of simple ketones without a hetero-atom functionality close to the carbonyl group [2, 4]. These enantioselective transformations are summarized in the present chapter.

32.1
Chiral Ligands

In enantioselective hydrogenation of ketonic substrates, the excellent catalytic performance such as high turnover number (TON), turnover frequency (TOF = TON h^{-1} or s^{-1}), and enantioselectivity is achievable only when (pre)catalysts are prepared by the appropriate combination of metal species and chiral ligands [6–8, 10, 11]. Stereo-repulsive interaction between substituents of ligands and substrates is normally utilized for the regulation of stereochemistry. The metal and ligand must be carefully selected because of the diversity of substrate structures [1–5]. Chiral diphosphine ligands with a C_2 symmetry (see Fig. 32.1) have played a main role in this respect. Recently, however, various effective C_1 phosphine ligands as well as phosphinite ligands have been developed, the structures of which are illustrated in Figures 32.2 and 32.3, respectively. Chiral amine and imine ligands (Fig. 32.4) are also useful, particularly when they are coupled with a chiral diphosphine ligand in the hydrogenation of simple ketones [2, 4, 5]. Immobilized BINAPs are detailed in Figure 32.5.

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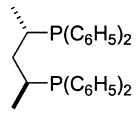
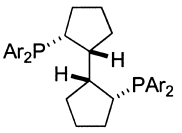
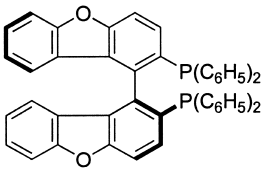


(*S*,*S*)-BDPP
(SKEWPHOS)

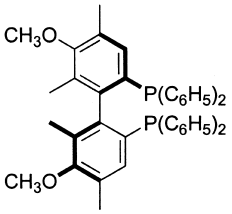


(*R*,*R*)-BICP

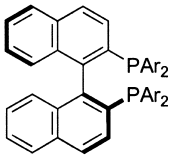


(*S*)-BIFAP

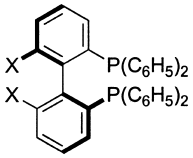
BICP: Ar = C_6H_5
1Aa: Ar = 3,5-$(CH_3)_2C_6H_3$
1Ab: Ar = 3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$



(*R*)-BIMOP



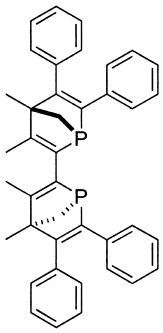
(*S*)-BINAP



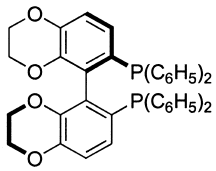
(*S*)-BIPHEMP

BINAP: Ar = C_6H_5
TolBINAP: Ar = 4-$CH_3C_6H_4$
XylBINAP: Ar = 3,5-$(CH_3)_2C_6H_3$
DTBBINAP: Ar = 3,5-$(t\text{-}C_4H_9)_2C_6H_3$
(absolute configuration unknown)

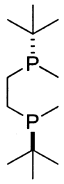
BIPHEMP: X = CH_3
MeO-BIPHEP: X = CH_3O



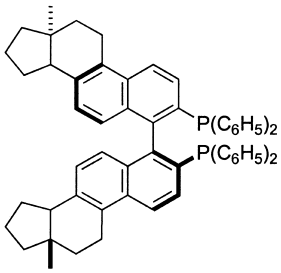
(*R*,*R*)-BIPNOR



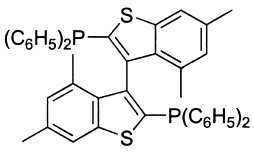
(*R*)-BisbenzodioxanPhos



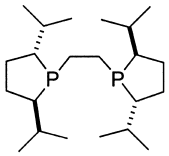
(*R*,*R*)-*t*-Bu-BisP*



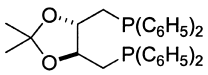
(*S*)-bis-steroidal phosphine



tetraMe-BITIANP
(absolute configuration unknown)

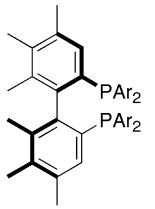


(*R*,*R*)-*i*-Pr-BPE

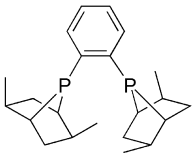


(*S*,*S*)-DIOP

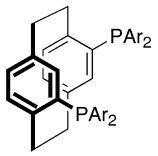
Fig. 32.1 C_2-chiral phosphine ligands.



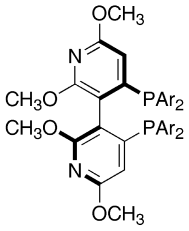
(*R*)-Xyl-HexaPHEMP
Ar = 3,5-$(CH_3)_2C_6H_3$



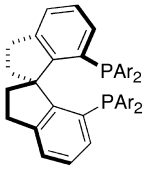
(*R*,*S*,*R*,*S*)-Me-PennPhos



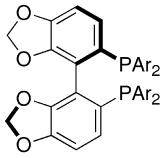
(*S*)-[2.2]PHANEPHOS
PHANEPHOS: Ar = C_6H_5
xylyl-PHANEPHOS: Ar = 3,5-$(CH_3)_2C_6H_3$



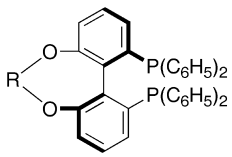
(*R*)-P-Phos
P-Phos: Ar = C_6H_5
Tol-P-Phos: Ar = 4-$CH_3C_6H_4$
Xyl-P-Phos: Ar = 3,5-$(CH_3)_2C_6H_3$



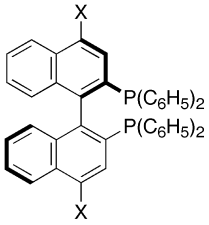
(*S*)-Xyl-SDP
Ar = 3,5-$(CH_3)_2C_6H_3$



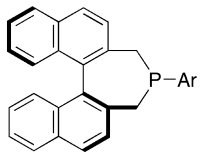
(*R*)-SEGPHOS
SEGPHOS: Ar = C_6H_5
DTBM-SEGPHOS:
Ar = 4-CH_3O-3,5-(*t*-$C_4H_9)_2C_6H_2$
(absolute configuration unknown)



(*R*)-TunaPhos
C3TunaPhos: R = $(CH_2)_3$
C4TunaPhos: R = $(CH_2)_4$



(*R*)-**1B**
1Ba: X = $BrNH_3CH_2$
1Bb: X = $(CH_3)_3Si$



(*S*)-**1C**
Ar = 4-$CH_3OC_6H_4$

Fig. 32.1 (continued)

32.2
β-Keto Esters and Analogues

32.2.1
β-Keto Esters

The enantioselective hydrogenation of *β*-keto esters is important, because the resulting optically active *β*-hydroxy esters are converted to useful chiral building blocks [1–4]. The development of BINAP–Ru(II) catalysts allowed the highly enantioselective hydrogenation of *β*-keto esters. As shown in Figure 32.6, methyl-

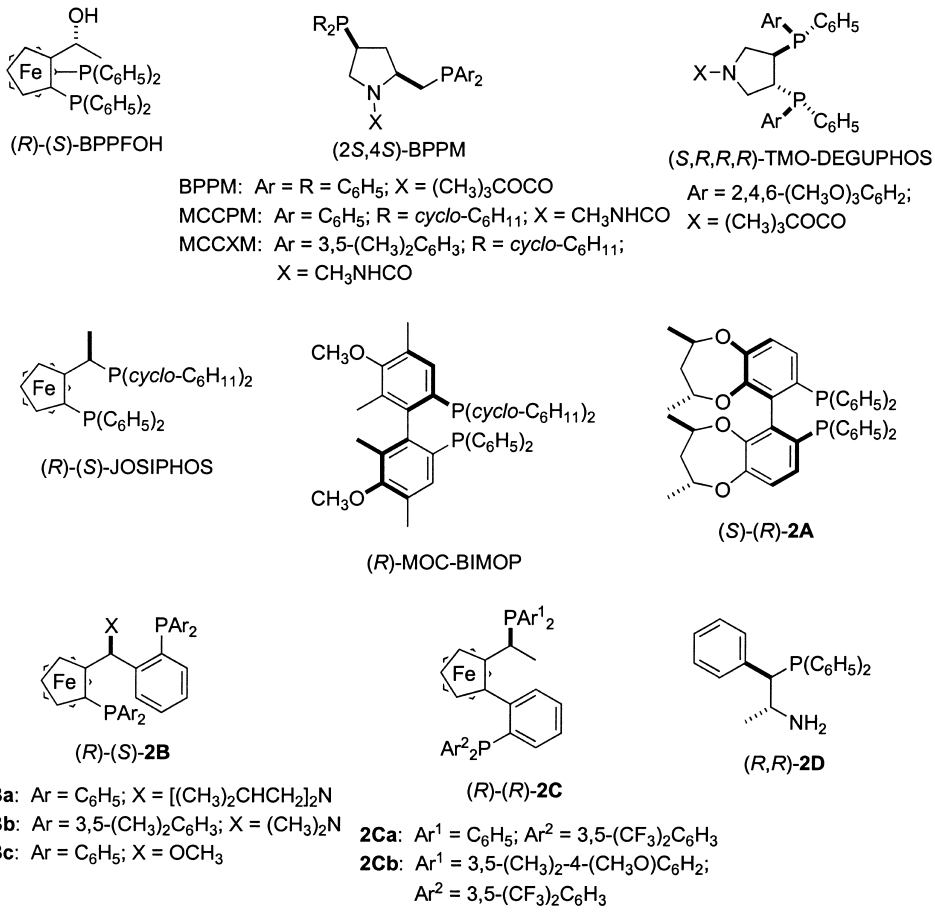


Fig. 32.2 Phosphine ligands with C_1 chirality.

3-oxobutanoate was hydrogenated in methanol containing an (*R*)-BINAP–Ru(II) complex to give (*R*)-methyl-3-hydroxybutanoate in >99% ee quantitatively [1, 2, 12]. The anionic halogen ligands on the Ru center are crucial to achieve high catalytic activity. Ru complexes with a formula of RuX_2(binap) (X=Cl, Br, or I; empirical formula with a polymeric form) [12] or $RuCl_2$(binap)$(dmf)_n$ (oligomeric form) [13] catalyze the hydrogenation of a wide variety of *β*-keto esters with a substrate:catalyst molar ratio (SCR) as high as 10000. Several isolated or *in-situ*-prepared BINAP–Ru complexes show a similar performance [14]. The hydrogenation is accelerated by an addition of strong acid [14b,d, 15]. The use of more sterically demanding XylBINAP as a chiral ligand gives 99.9% ee [16]. Even a racemic XylBINAP–Ru complex can be used for this reaction in the presence of 0.5 equiv. of (*S*)-DM-DABN, a chiral aromatic diamine, as a poisoning compound [16]. Here, the *R* alcohol is obtained in 99.3% ee due to the selective

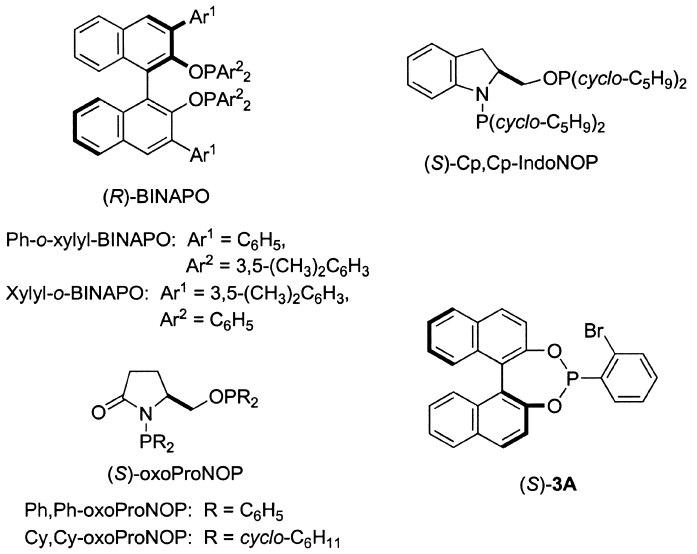


Fig. 32.3 Phosphinite ligands.

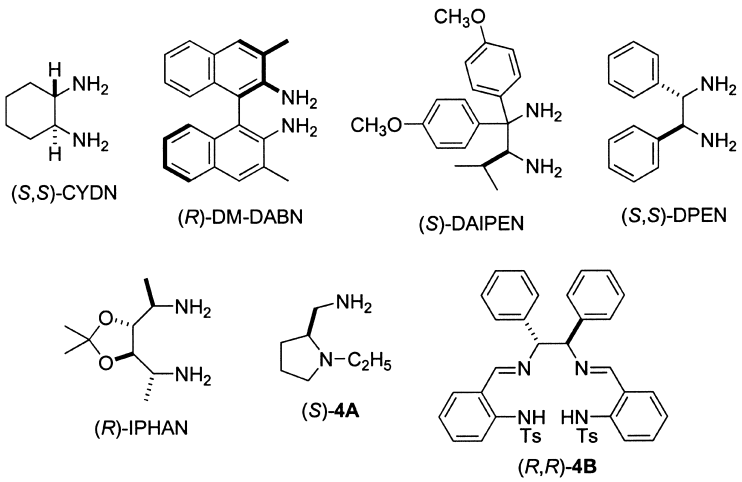
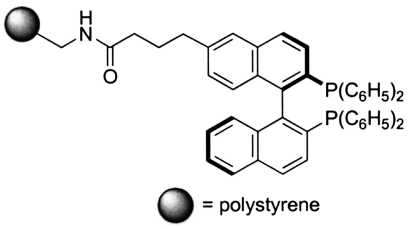
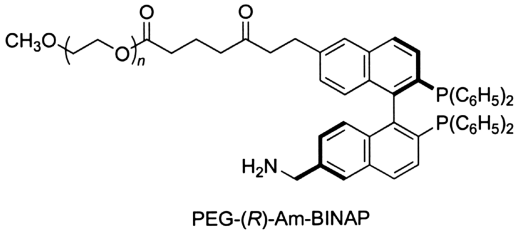


Fig. 32.4 Amine and imine ligands.

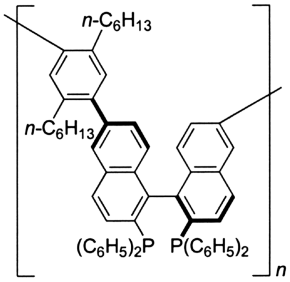
formation of a feebly active (*S*)-XylBINAP/(*S*)-DM-DABN–Ru complex. Other useful biaryl diphosphines include BIPHEMP [14m], BIMOP [17], MeO-BIPHEP [18], C4TunaPhos [19], BIFAP [20], BisbenzodioxanPhos [21], P-phos [22], tetraMe-BITIANP [23], bis-steroidal phosphine [24], and **2A** [25]. The reaction can be run in aqueous phase by use of a BINAP derivative with ammonium functions **1Ba** [11b, 26, 27]. Hydrogenation catalyzed by a Ru complex bearing *i*-Pr-BPE, proceeds smoothly under a low pressure of H_2, probably due to the



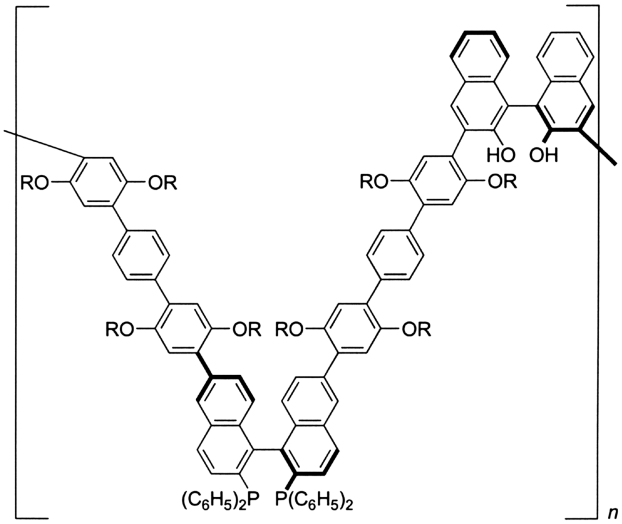
(*R*)-APBBINAP



PEG-(*R*)-Am-BINAP



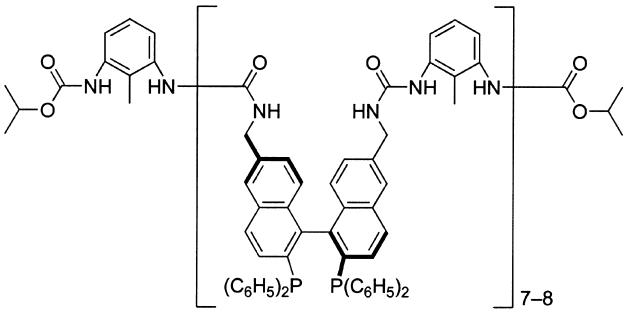
(*R*)-poly(BINAP)



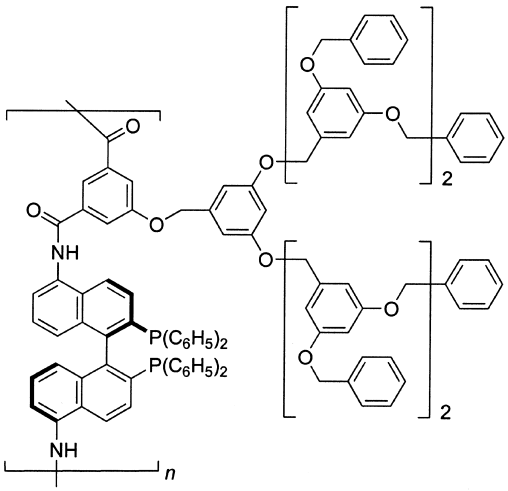
R = *n*-C_6H_{13}

(*R*,*R*)-poly(BINOL-BINAP)

Fig. 32.5 Polymer-bound BINAPs.



(*R*)-poly-NAP



(*R*)-**5A**

Fig. 32.5 (continued)

electron-donating ability of the aliphatic diphosphine ligand [28]. A Ru complex with *t*-Bu-BisP* having chiral centers on the phosphorus atoms also shows high enantioselectivity [7a, 29]. $Ru(OCOCF_3)_2$([2.2]-phanephos) in the presence of $(n\text{-}C_4H_9)_4NI$ catalyzes the reaction of β-keto esters at a low temperature and under a low H_2 pressure, without the addition of a strong acid [30]. A Ru complex prepared from $Ru[\eta^3\text{-}CH_2C(CH_3)CH_2](cod)$, 2 equiv. of chiral monophosphine **1C**, and HBr catalyzes the hydrogenation of methyl-3-oxobutanoate with an optical yield of 95% [31]. C_1-chiral ferrocenyl ligands [8] are also useful. Ru complexes with **2Ba** [32] and **2Cb** [33], and a JOSIPHOS–Rh complex [34] yield chiral alcohols in 98.6, 95, and 97% ee, respectively. A C_2-symmetric bisphosphinite ligand, Ph-*o*-xylyl-BINAPO, is also useful in the Ru-catalyzed reaction [35]. Some

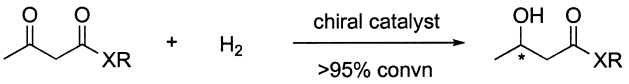


Fig. 32.6 Enantioselective hydrogenation of β-keto carboxylic acid derivatives.

XR	Chiral catalyst (SCR) [a]	Solvent	H_2 [atm]	Temp. [°C]	ee [%]	Con-fig.	TON	TOF [h^{-1}]
OCH_3	$RuCl_2$[(*R*)-binap] (2000)	CH_3OH	100	23	>99	*R*	1980	55
OCH_3	$RuCl_2$[(*R*)-binap](dmf)$_n$ (1960)	CH_3OH	100	25	99	*R*	1960	49
OCH_3	$RuCl_2$[(*R*)-binap](dmf)$_n$ (2330)	CH_3OH	4	100	98	*R*	2330	388
OCH_3	$[NH_2(C_2H_5)]_2$[{RuCl[(*R*)-binap]}$_2$(μ-Cl)$_3$] (1410)	CH_3OH	100	25	>99	*R*	1340	33
OCH_3	[RuI{(*S*)-binap}C_6H_6]I (2380)	CH_3OH	100	20	99	*R*	2380	99
OCH_3	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-[(*S*)-binap] + HBr (50)	CH_3OH	1	rt	97 [b]	*S*	40	0.8
OCH_3	*trans*-$RuCl_2$[(*R*)-binap]py_2 + HCl (1000)	CH_3OH	3.7	60	99.9	*R*	1000	42
OCH_3	[$RuCl_2$(cod)]$_n$–(*R*)-BINAP (100)	CH_3OH	4	rt	99	*R*	100	4
OCH_3	$RuCl_2$[(*R*)-xylbinap](dmf)$_n$ (1500)	CH_3OH	100	rt	99.9	*R*	1500	94
OCH_3	$RuCl_2$[(±)-xylbinap](dmf)$_n$ –0.5 (*S*)-DM-DABN (750)	CH_3OH	100	rt	99.3	*R*	750	47
OCH_3	$RuCl_2$[(*S*)-bis-steroidal phosphine](dmf)$_n$ (1270)	CH_3OH	100	100	99	*S*	1270	1270
OCH_3	$RuBr_2$[(*S*)-biphemp] (200)	CH_3OH	5	50	>99	*S*	200	3
OCH_3	[RuI_2(*p*-cymene)]$_2$–(*R*)-BIMOP (2000)	1:1 CH_3OH–CH_2Cl_2	10	30–40	100	*R*	2000	100
OCH_3	$RuCl_3$–(*S*)-MeO-BIPHEP (100)	CH_3OH	4	50	99	*S*	100	25
OCH_3	$RuCl_2$[(*R*)-c4tunaphos]-(dmf)$_n$ (100)	CH_3OH	51	60	99.1	*R*	100	5
OCH_3	$RuCl_2$[(*S*)-(*R*)-**2A**](dmf)$_n$ (667)	79:1 CH_3OH–CH_2Cl_2	3.4	70	99.4	*S*	667	28
OCH_3	$RuCl_2$[(*S*)-bifap](dmf)$_n$ (1000)	CH_3OH	100	70	100	*S*	1000	500
OCH_3	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-[(*R,R*)-*i*-pr-bpe] + HBr (500)	9:1 CH_3OH–H_2O	4	35	99.3	*S*	500	25
OCH_3	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-[(*S,S*)-*t*-bu-bisp*] + HBr (200)	10:1 CH_3OH–H_2O	6	70	97 [c]	*R*	172	17
OCH_3	Ru$(OCOCF_3)_2$[(*S*)-[2.2]-phanephos] + (n-$C_4H_9)_4$NI (125–250)	10:1 CH_3OH–H_2O	3	–5	96	*R*	<250	<14
OCH_3 [d]	[RuI_2(*p*-cymene)]$_2$–(*R*)-(*R*)-**2Cb** + HCl (1000)	CH_3OH	5	80	95	*S*	>990	>62

XR	Chiral catalyst (SCR) [a]	Solvent	H_2 [atm]	Temp. [°C]	ee [%]	Con-fig.	TON	TOF [h^{-1}]
OCH_3 [d]	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*S*)-**1B** + HBr (100)	CH_3OH	60	100	95	*R*	99	12
OCH_3	$[RuCl_2$(*p*-cymene)$]_2$–(*S*)-Ph-*o*-Xylyl-BINAPO (100)	3:1 C_2H_5OH–CH_2Cl_2	5.4	50	96	*S*	100	5
OCH_3	$RuCl_2$[(*R*)-poly-nap](dmf)$_n$ (1000)	CH_3OH	40	50	99	*R*	1000	71
OCH_3	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-[peg-(*R*)-am-binap] + HBr (10 000)	CH_3OH	100	50	99	*R*	10 000	208
OC_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*S*)-BINAP + HBr (3000)	C_2H_5OH [e]	4	50	99	*S*	>2970	>165
OC_2H_5	$RuCl_2$[(*R*)-bisbenzodiox-anephos](dmf)$_n$ (1000)	C_2H_5OH	3.4	80–90	99.5	*R*	1000	<42
OC_2H_5	$RuCl_2$[(*S*)-p-phos](dmf)$_n$ (400)	10:1 C_2H_5OH–CH_2Cl_2	3.4	70	98.6	–	400	<33
OC_2H_5	$RuCl_2$[(–)-tetrame-bitianp] (1000)	CH_3OH	100	70	99	*R*	950	475
OC_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*R*)-(*S*)-**2Ba** + HBr (200)	C_2H_5OH	50	50	98.6	*S*	200	11
OC_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*R*)-**1Aa** + HBr (1000)	H_2O	40	50	98	*R*	1000	67
OC_2H_5	$[Rh(nbd)_2]BF_4$–(*R*)-(*S*)-JOSIPHOS (100)	CH_3OH	20	rt	97	*S*	100	7
$OC(CH_3)_3$	$[NH_2(C_2H_5)]_2$[{RuCl[(*R*)-binap]}$_2$(μ-Cl)$_3$] + HCl (2170)	CH_3OH	3	40	>97	*R*	2170	271
NH_2	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-[(*S*,*S*)-*t*-bu-bisp*] + HBr (71)	10:1 CH_3OH–H_2O	6	50	89	*R*	71	7
NHC_6H_5	$[NH_2(C_2H_5)]_2$[{RuCl[(*R*)-binap]}$_2$(μ-Cl)$_3$] (500)	CH_3OH	30	60	>95	*R*	495	10
$N(CH_3)_2$	$RuBr_2$[(*S*)-binap] (680)	C_2H_5OH	63	27	96	*S*	680	8
SC_2H_5	$RuCl_2$[(*R*)-binap] (530)	C_2H_5OH	95	27	93 [f]	*R*	218	3

a) SCR = substrate : catalyst molar ratio.
b) 80% yield.
c) 86% yield.
d) Methyl-3-oxopentanoate.
e) 0.3 equiv. to substrate.
f) 42% yield.

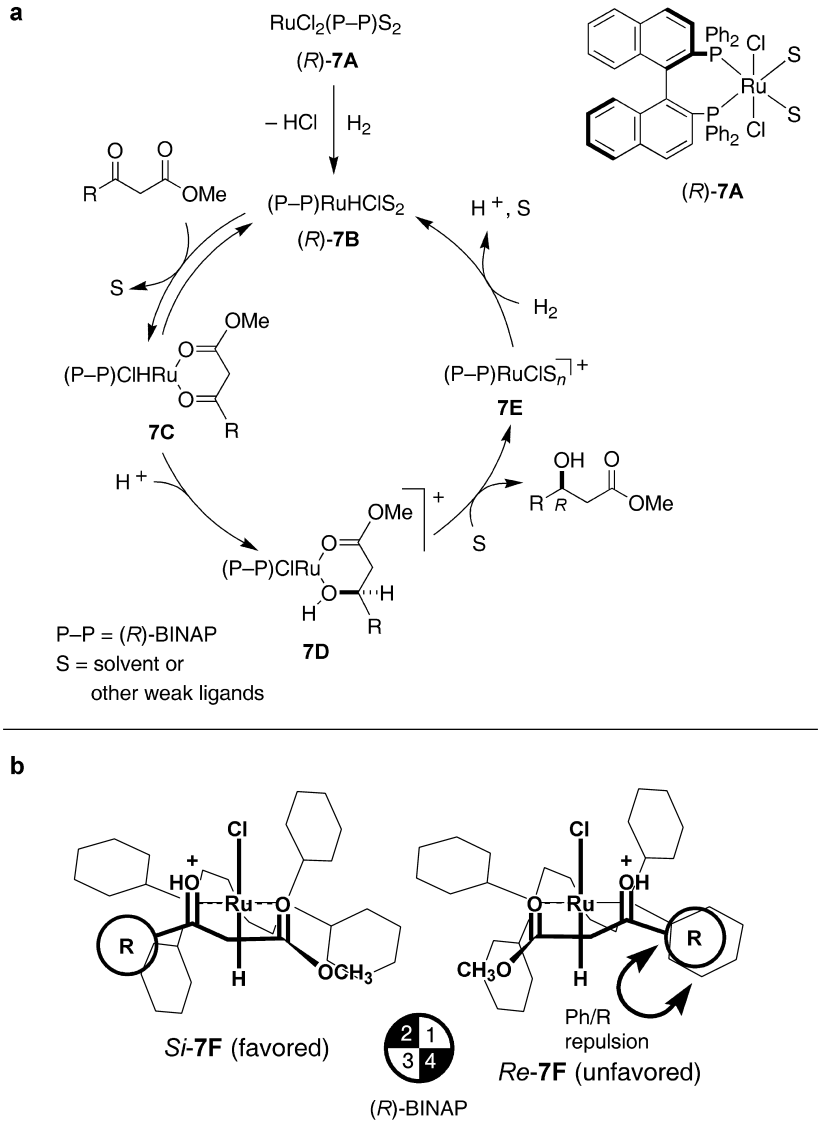


Fig. 32.7 (*R*)-BINAP–Ru-catalyzed hydrogenation of β-keto esters. (a) Catalytic cycle. (b) Transition-state models.

reusable catalysts have been developed for this reaction. An oligomeric Poly-NAP–Ru catalyst can be used five times in the hydrogenation, with an SCR of 1000 [36]. A Ru complex with PEG-Am-BINAP is applicable to the reaction with an SCR of 10 000 in methanol [37]. This complex can be separated as a precipitate by addition of ether to the reaction mixture. It is reusable four times, with an SCR of 100 per batch. A Ru complex of APBBINAP which is a BINAP li-

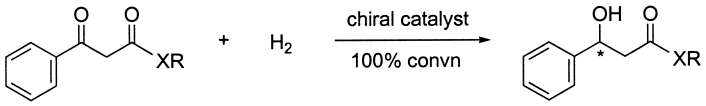


Fig. 32.8 Hydrogenation of benzoylacetic acid derivatives.

XR	Chiral catalyst (SCR) [a]	Solvent	H_2 [atm]	Temp. [°C]	ee [%]	Config.	TON	TOF [h^{-1}]
OC_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-(cod)–(*S*)-Meo-BIPHEP + HBr (50)	C_2H_5OH	1	50	97 [b]	*R*	45	3
OC_2H_5	[$NH_2(C_2H_5)$]$_2$[{RuCl[(*R*)-segphos]}$_2$(μ-Cl)$_3$] (10 000)	C_2H_5OH	30	80	97.6	*S*	10 000	1667
OC_2H_5	$RuCl_2$[(*S*)-tol-p-phos](dmf)$_n$ (800)	1 : 1 C_2H_5OH–CH_2Cl_2	20	90	96.4	*R*	800	400
OC_2H_5	$RuCl_2$[(*S*)-(*R*)-**2A**](dmf)$_n$ (667)	79 : 1 CH_3OH–CH_2Cl_2	3.4	70	97.7	*R*	667	28
OC_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-(cod)–(*R*)-(*S*)-**2Bc** + HBr (200)	C_2H_5OH	50	50	98	*R*	200	–
OC_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-(cod)–(*S*)-**1C** + HBr (100)	C_2H_5OH	60	100	95	*S*	99	12
OC_2H_5	[$RuCl_2$(*p*-cymene)]$_2$–(*S*)-Xylyl-*o*-BINAPO (100)	3 : 1 C_2H_5OH–CH_2Cl_2	5.4	50	99	*R*	100	5
$NHCH_3$	$RuCl_2$[(*R*)-binap](dmf)$_n$ (1800)	CH_3OH	14	100	>99.9 [c]	*S*	900	50

a) SCR = substrate : catalyst molar ratio.
b) 90% yield.
c) 50% yield.

gand bound on polystyrene [38], and an immobilized BINAP–Ru complex in a polydimethylsiloxane membrane [39] are also usable for this transformation. β-Keto dimethylcarboxamides and thioesters are also hydrogenated with BINAP–Ru complexes enantioselectively [40, 41]. A Ru complex with a *t*-Bu-BisP* is useful for the reaction of a β-keto amide [7a, 29].

A mechanistic model for the asymmetric hydrogenation of β-keto esters catalyzed by (*R*)-BINAP–Ru complex is shown in Figure 32.7. The $RuCl_2$ precatalyst (*R*)-**7A** reacts with H_2 to give the active RuHCl (*R*)-**7B** with removal of HCl [2]. The substrate and **7B** reversibly form the σ-chelate complex **7C**, whose geometry is unfavorable for metal-to-carbonyl hydride transfer. Protonation at carbonyl-oxygen then increases the electrophilicity of the carbonyl-carbon, with conversion of σ-coordination to π-interaction causing facile hydride migration onto the carbonyl

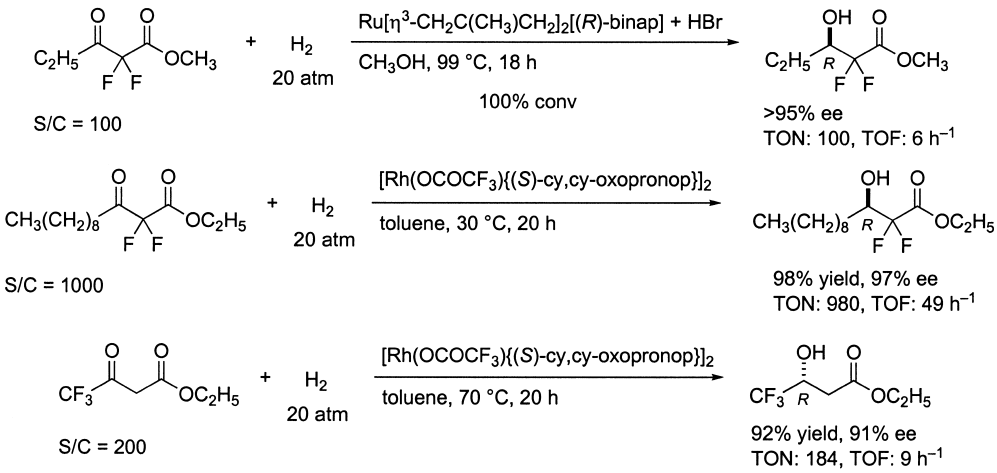


Fig. 32.9 Hydrogenation of fluorinated β-keto esters.

carbon. The hydroxy ester ligand of **7D** is replaced by solvent molecules, giving **7E**. Regeneration of **7B** by heterolysis of H_2 with **7E** completes the catalytic cycle.

The high level of enantiofacial selection is made in the hydride transfer step **7C** → **7D** [2]. The chelating geometry in the transition state **7F** decreases the activation energy. The chiral environment derived from (*R*)-BINAP clearly differentiates diastereomeric *Si*-**7F** and *Re*-**7F** (Fig. 32.7b). The *Si* structure affording the *R* alcohol is much more favored than the *Re* structure, which suffers from the Ph/R repulsion.

Figure 32.8 shows examples of enantioselective hydrogenation of benzoylacetic acid derivatives. The ethyl ester is hydrogenated in the presence of an (*R*)-SEGPHOS–Ru complex with an SCR of 10000 under 30 atm of H_2 to afford the *S* alcohol in 97.6% ee quantitatively [42]. The small dihedral angle of the SEGPHOS–Ru complex (65°) may have a major influence on the high enantioselectivity. MeO-BIPHEP [14q, 18], Tol-P-Phos [43], **2A** [25], ferrocenyl diphosphine **2Bc** [44], and the monodentate phosphine **1C** [31] also show high enantioselectivity. A Ru complex with the diphosphinite ligand Xylyl-*o*-BINAPO gives the hydroxy ester in 99% ee [35]. Reaction of *N*-methylbenzoylacetamide with an (*R*)-BINAP–Ru catalyst gives the *S* alcohol in an enantiomerically pure form, albeit in 50% yield [45].

α,α-Difluoro-*β*-keto esters are hydrogenated with an (*R*)-BINAP–Ru complex to yield the (*R*)-hydroxy esters in >95% ee (Fig. 32.9) [46]. The sense of enantioselection is consistent with that of reaction of nonfluorinated substrates. A Cy,Cy-OxoProNOP–Rh complex also shows high enantioselectivity for the hydrogenation of fluorinated *β*-keto esters [47]. The sense of enantioface-selection depends heavily on the fluorinated position. Reaction of ethyl-2,2-difluoro-3-oxododecanoate catalyzed by an (*S*)-Cy,Cy-OxoProNOP–Rh complex gives the *R* (*β*) alcohol in 97% ee. By contrast, ethyl-4,4,4-trifluoro-3-oxobutanoate is converted to the *R* (*α*) alcohol in 91% ee with the same catalyst.

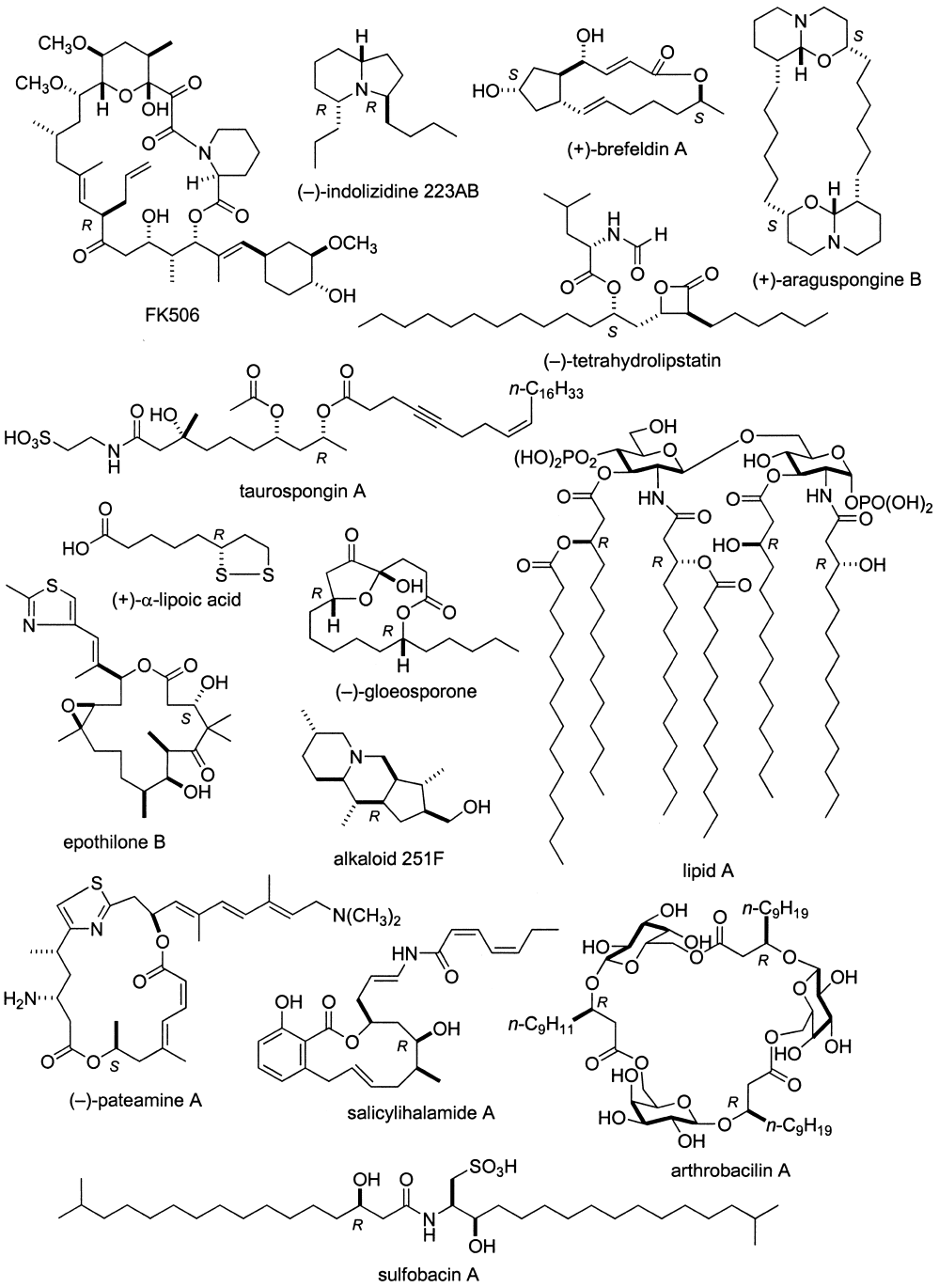


Fig. 32.10 Examples of biologically active compounds obtainable through BINAP–Ru-catalyzed hydrogenation of β-keto esters.

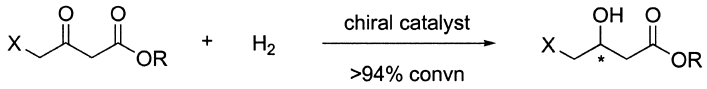


Fig. 32.11 Hydrogenation of difunctionalized ketones.

X	R	Chiral catalyst (SCR) [a)]	H_2 [atm]	Temp. [°C]	ee [%]	Con-fig.	TON	TOF [h^{-1}]
$C_6H_5CH_2OCH_2$	CH_3	$RuBr_2$[(*S*)-binap] (370)	50	26	99	*S*	148	0.8
CH_3O	CH_3	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-[(*R*,*R*)-*i*-pr-bpe] + HBr (500)	4	35	95.5	*R*	500	25
$C_6H_5CH_2O$	C_2H_5	$RuBr_2$[(*S*)-binap] (560)	100	28	78	*R*	543	12
$C_6H_5CH_2O$	C_2H_5	$RuBr_2$[(*S*)-binap] (560)	100	100	98	*R*	554	111
$C_6H_5CH_2O$	C_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*R*)-Meo-BIPHEP + HBr (3000)	8	80	98	*S*	3000	63
$[(CH_3)_2CH]_3SiO$	C_2H_5	$RuBr_2$[(*S*)-binap] (290)	100	27	95	*R*	290	3
Cl	C_2H_5	$RuBr_2$[(*S*)-binap] (1080)	77	24	56	*R*	1080	26
Cl	C_2H_5	$RuBr_2$[(*S*)-binap] (1300)	100	100	97	*R*	1300	19500
Cl	C_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-[(*R*,*R*)-*i*-pr-bpe] + HBr (500)	4	35	76	*R*	500	25
Cl	C_2H_5	$RuCl_3$–(*S*)-MeO-BIPHEP (100)	4	120	92	*R*	100	17
Cl	C_2H_5	$[NH_2(C_2H_5)]_2$[{RuCl[(*R*)-segphos]}$_2$(μ-Cl)$_3$] (2500)	30	90	98.5	*S*	2500	1250
Cl	C_2H_5	$RuCl_2$[(*R*)-bisbenzodioxanephos](dmf)$_n$ (1000)	3.4	80–90	97	*S*	1000	<83
Cl	C_2H_5	$RuCl_2$[(*S*)-p-phos](dmf)$_n$ (2780)	3.4	80	98	–	2780	<232
Cl	C_2H_5	$[RuCl_2(p\text{-cymene})]_2$–(*S*)-Ph-*o*-Xylyl-BINAPO (100)	5.4	50	98	*R*	100	5
$Cl(CH_3)_2NH$	C_2H_5	[RhCl(cod)]$_2$–(2*S*,4*S*)-MCCXM (100)	20	50	85	*S*	100	5
$Cl(CH_3)_3N$	C_2H_5	$[NH_2(C_2H_5)]_2$[{RuCl[(*R*)-binap]}$_2$(μ-Cl)$_3$] (–)	100	25	96 [b)]	*S*	–	–

a) SCR = substrate : catalyst molar ratio.
b) 75% yield.

The BINAP–Ru(II)-catalyzed enantioselective hydrogenation of β-keto esters is used for the synthesis of a wide range of important natural and man-made compounds [1–4, 48]; some examples of these are listed in Figure 32.10, wherein chiral centers created by the enantioselective reaction are labeled with *R* or *S*.

The enantioselective hydrogenation of ketones which have two heteroatoms on both sides of the carbonyl group tends to give lower enantioselectivity due to the competitive interaction of the functionalities with the catalyst. The extent depends

on the electronic and steric properties of the coordinating groups. Methyl-5-benzyloxy-3-oxopentanoate is hydrogenated with the (*S*)-BINAP–Ru catalyst to afford the *S* alcohol in 99% ee (Fig. 32.11) [40]. The sense and degree of enantioselection is the same as that in the reaction of methyl-3-oxobutanoate, but the situation is changed when 4-benzyloxy- and 4-chloro-3-oxobutanoate are employed as substrates, with only moderate optical yields (78% and 56%, respectively) being obtained by reaction at room temperature. However, the optical yield is increased to 98% and 97%, respectively, when the reactions are conducted at 100 °C [49]. The analogous substrate connecting a bulky triisopropylsilyloxy group at the C4 position is reduced with high enantioselectivity even at room temperature [49]. β-Keto ester possessing a chlorotrimethylammonium function is also reduced with a high optical yield [14m]. Ru catalysts with other C_2-chiral biaryl diphosphines [14q, 18, 21, 22, 42] and Ph-*o*-Xylyl-BINAPO [35], a bisphosphinite, show similar enantioselectivity. Methyl-4-methoxy-3-oxobutanoate is hydrogenated with an *i*-Pr-BPE–Ru complex to afford the hydroxy ester in 95.5% ee even at 35 °C, whereas the ee-value obtained by the reaction of 4-chloro ketone is 76% [28]. An MCCXM–Rh complex catalyzes hydrogenation of the 4-chlorodimethylammonium derivative to yield the alcohol in 85% ee [50].

The BINAP–Ru-catalyzed hydrogenation of difunctional ketones has been applied to the asymmetric synthesis of several bioactive compounds (see Fig. 32.12) [1, 49–51]. Stereocenters derived from the BINAP–Ru are labeled by *R* or *S*.

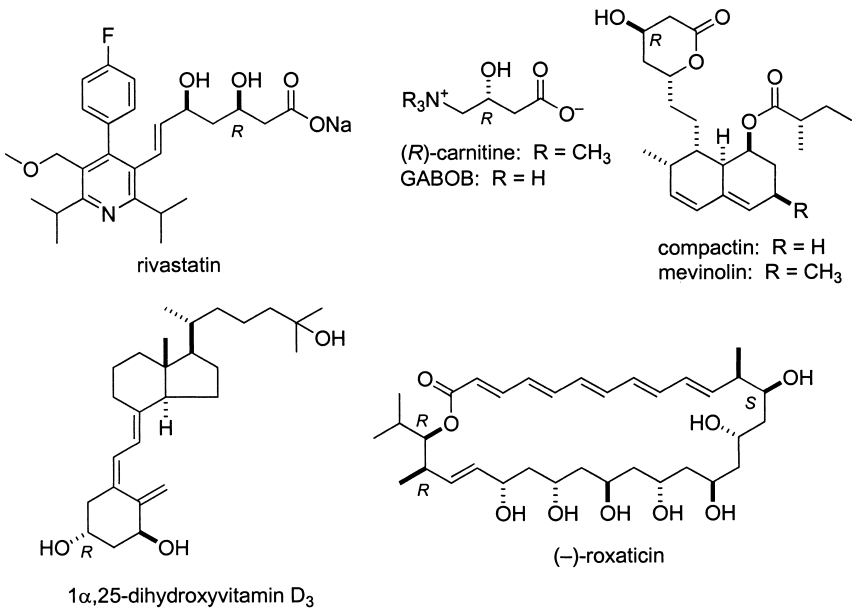
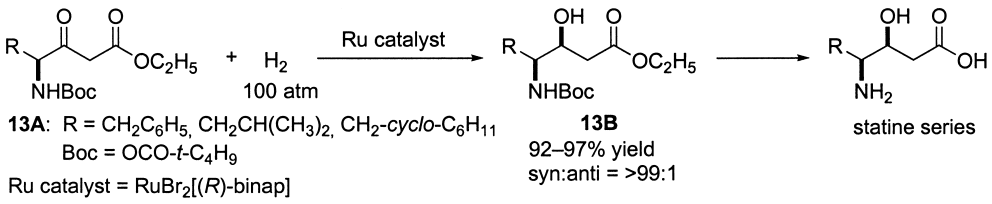
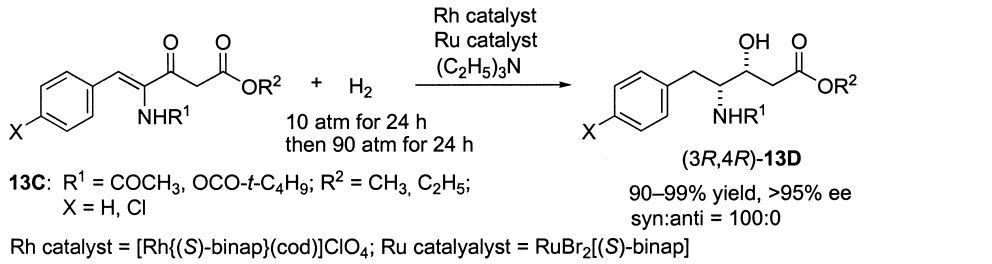
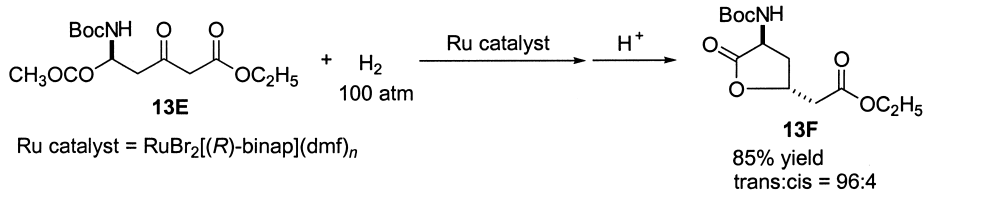


Fig. 32.12 Examples of biologically active compounds obtainable through BINAP–Ru-catalyzed hydrogenation of difunctionalized ketones.







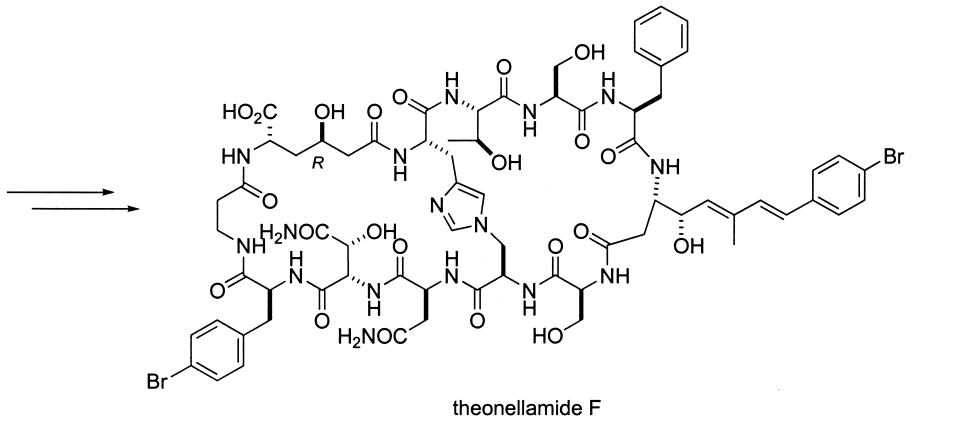
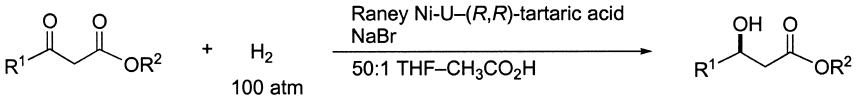


Fig. 32.13 Diastereoselective hydrogenation of chiral β-keto esters.

BINAP–Ru is effective for the diastereoselective hydrogenation of some chiral β-keto esters (Fig. 32.13). Reaction of *N*-Boc-protected (*S*)-γ-amino β-keto esters **13A** catalyzed by the (*R*)-BINAP–Ru complex results in the *syn* alcohols **13B** exclusively [52]. The stereocenter at the β-position is controlled by the chirality of the catalyst; therefore, use of the *S* catalyst affords the *anti* isomer, as predicted. Derivatives of statine, a key component of the aspartic proteinase inhibitor pep-



Raney Ni-U = ultrasonic irradiated Raney Ni

Fig. 32.14 Hydrogenation of β-keto esters catalyzed by modified Raney Ni.

R^1	R^2	Temperature [°C]	Time [h]	ee [%]
CH_3	CH_3	100	4	86
C_2H_5	CH_3	60	34	94
n-C_6H_{13}	CH_3	60	52	90
$(CH_3)_2CH$	CH_3	60	71	96
cyclo-C_3H_5	CH_3	60	48	98.6
CH_3	$(CH_3)_2CH$	60	45	87
CH_3	$(CH_3)_3C$	60	40	88

statine, are efficiently synthesized by this method [1, 52]. Tandem hydrogenation of *N*-acetyl- or *N*-Boc-protected γ-amino γ,δ-unsaturated β-keto esters **13C** in the presence of an (*S*)-BINAP–Rh and –Ru catalyst gives (3*R*,4*R*)-**13D** exclusively [53]. First, enantioselective reduction of the olefinic moiety catalyzed by the BINAP–Rh complex occurs preferentially at low H_2 pressure, after which the carbonyl group is reduced with the BINAP–Ru catalyst under high pressure of H_2. The hydrogenation of an *N*-Boc-protected (*S*)-δ-amino β-keto ester **13E** in the presence of the (*R*)-BINAP–Ru complex followed by an acid-catalyzed cyclization affords selectively the *trans* lactone **13F**, which is a useful intermediate for the synthesis of theonellamide F, an antifungal agent [54].

Highly enantioselective hydrogenation of β-keto esters is achieved by using a Raney Ni catalyst modified by tartaric acid and NaBr (Fig. 32.14) [9, 55]. The catalyst should be prepared under controlled conditions including suitable pH (3–4), temperature (100 °C), and concentration of the modifier (1%) to achieve an optimum stereoselectivity. The addition of NaBr, an achiral modifier, is important. Furthermore, ultrasonic irradiation of the catalyst tends to increase the activity and enantioselectivity [9f,g]. Ultrasonication may remove nonselective sites of the catalyst surface.

Enantioselective hydrogenation of β-keto esters catalyzed by the modified Raney Ni is useful for the synthesis of biologically active compounds, as shown in Figure 32.15 [56–58]. A large-scale synthesis of (–)-tetrahydrolipstatin (orlistat), a pancreatic lipase inhibitor (F. Hoffmann-La Roche AG), is carried out using this method [58].

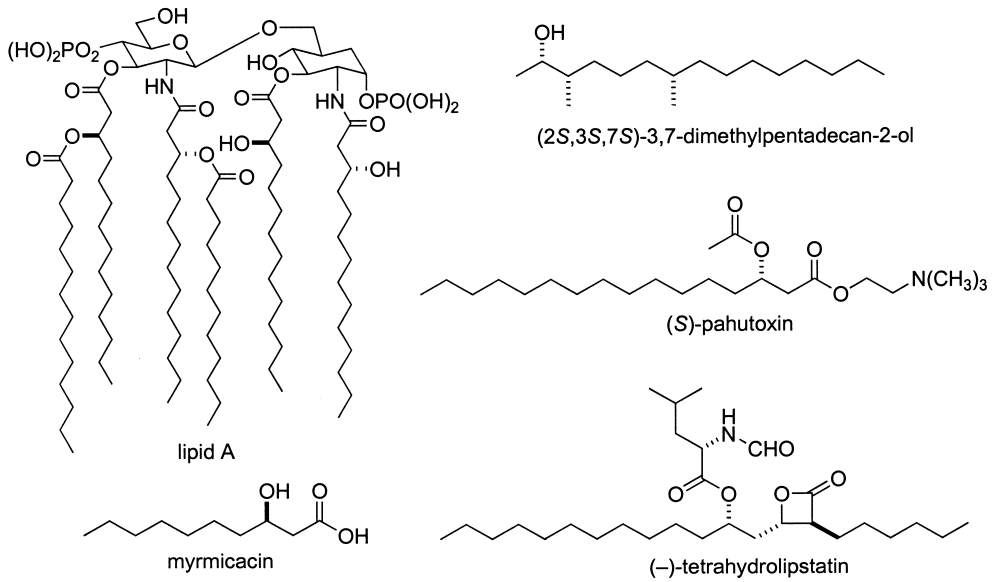


Fig. 32.15 Examples of biologically active compounds obtainable through asymmetric hydrogenation of β-keto esters catalyzed by modified Raney Ni.

32.2.2 1,3-Diketones

Double hydrogenation of 1,3-diketones in the presence of an appropriate chiral catalyst yields the chiral 1,3-diols with an excellent diastereo- and enantioselectivity (Fig. 32.16). When 2,4-pentanedione is hydrogenated with an (*R*)-BINAP–Ru catalyst, enantiomerically pure (*R,R*)-2,4-pentanediol (*anti*:*syn* = 99:1) is obtained quantitatively [40, 59]. Dissymmetric 5-methyl-2,4-hexanedione and 1-phenyl-1,3-butanedione are also reduced stereoselectively to give the chiral *anti* diols. Ru complexes bearing other ligands such as C_2-chiral BIPHEMP [60] and BDPP [61] as well as C_1-symmetric **2Ca** [33] show similar stereoselectivity. The hydrogenation of methyl-3,5-dioxohexanoate catalyzed by a BINAP–Ru complex gives an 81:19 mixture of the *anti* (78% ee) and *syn* dihydroxy esters [62]. The stereoselective outcome shows that the C3 carbonyl group is preferentially reduced over the C5 carbonyl function. Hydrogenation of ethyl-2,4-dioxopentanoate with an (*S*)-MeO-BIPHEP–Ru catalyst followed by *in-situ* cyclization affords an 84:16 mixture of (3*R*,5*S*)-3-hydroxy-5-methyltetrahydrofuran-2-one in 98% ee and the 3*R*,5*R* isomer in 87% ee [63]. A Ru complex bearing a chiral ferrocenyl diphosphine (*S*)-(*R*)-2Bc catalyzes the hydrogenation of 1,3-diphenyl-1,3-propanedione with almost perfect diastereo- and enantioselectivity [44]. A BIPHEMP–Ru complex is also usable [64]. The BINAP–Ru-catalyzed hydrogenation of 1,5-dichloro-2,4-pentanedione results in the chiral *anti* diol in 92–94%

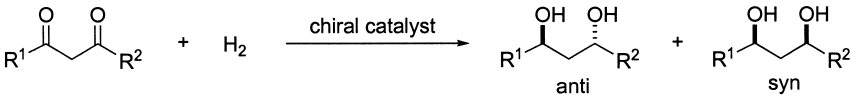


Fig. 32.16 Hydrogenation of 1,3-diketones to give the chiral 1,3-diols.

R^1	R^2	Catalyst (SCR) [a]	H_2 [atm]	Temp. [°C]	Yield [%]	dr [b]	ee [%] [c]	TON	TOF [h^{-1}]
CH_3	CH_3	$RuCl_2$[(*R*)-binap] (2000)	72	30	100	99:1	100	2000	22
CH_3	CH_3	RuHCl[(*R*)-biphemp]-$[P(C_6H_5)_3]$ + HCl (2000)	100	50	100	99:1	>99.9	2000	83
CH_3	CH_3	$[RuCl_2(C_6H_6)]_2$–(*R*,*R*)-BDPP (1695)	80	80	100	75:25	97	1695	106
CH_3	CH_3	$[RuI_2(p\text{-cymene})]_2$–(*R*)-(*R*)-**2Ca** + HCl (1000)	100	80	>99	>99:1	97	>990	>58
CH_3	$(CH_3)_2CH$	$[NH_2(C_2H_5)_2]$[{RuCl[(*R*)-binap]}$_2(\mu$-Cl)$_3$] (500)	50	50	92	97:3	98	460	23
CH_3	C_6H_5	$RuBr_2$[(*R*)-binap] (360)	83	26	98	94:6	94	360	6
CH_3	CH_3O-$COCH_2$	$[NH_2(C_2H_5)_2]$[{RuCl[(*R*)-binap]}$_2(\mu$-Cl)$_3$] (– [d])	100	50	100 [e]	81:19	78	–	–
CH_3	C_2H_5OCO	$RuBr_2$[(*S*)-meo-biphep] (200)	100	80	>99 [f]	84:16	98	>198	5
C_6H_5	C_6H_5	$RuCl_2$[(*R*)-biphemp] (170)	100	40	70	94:6	87	119	2
C_6H_5	C_6H_5	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-(cod)–(*S*)-(*R*)-**2Bc** + HBr (200)	50	50	100	>99.5:0.5	>99	200	–
$ClCH_2$	$ClCH_2$	$[NH_2(C_2H_5)_2]$[{RuCl[(*R*)-binap]}$_2(\mu$-Cl)$_3$] (– [d])	85	102	– [d]	– [d]	92–94	–	–

a) SCR = substrate : catalyst molar ratio.
b) *Anti* : *syn* diastereomeric ratio.
c) % ee of the *anti* diol.
d) Not reported.
e) A mixture of diol and δ-lactone.
f) (3*R*,5*S*)-3-Hydroxy-5-methyltetrahydrofuran-2-one.

ee, which is a synthetically useful chiral polyfunctionalized compound [65]. Under appropriate conditions, mono-hydrogenation of 1-phenyl-1,3-butanedione catalyzed by $[NH_2(C_2H_5)_2]$[{RuCl[(*R*)-binap]}$_2(\mu$-Cl)$_3$] occurs selectively to give (*R*)-1-phenyl-3-hydroxybutan-1-one (Fig. 32.17) [59]. As shown in Figure 32.18, the asymmetric hydrogenation of 1,3-diketones catalyzed by a BINAP–Ru complex is used for the synthesis of bioactive compounds with contiguous polyhydroxy groups [66].

A chirally modified Raney Ni catalyzes the hydrogenation of 1,3-diketones selectively to give the *anti* 1,3-diols in about 90% ee (Fig. 32.19) [67]. Natural compounds such as africanol and ngaione are synthesized via this method [68].

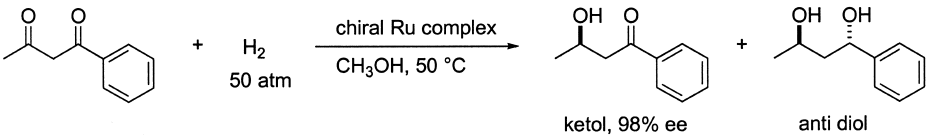


Fig. 32.17 Mono-hydrogenation of 1-phenyl-1,3-butanedione catalyzed by a BINAP–Ru complex.

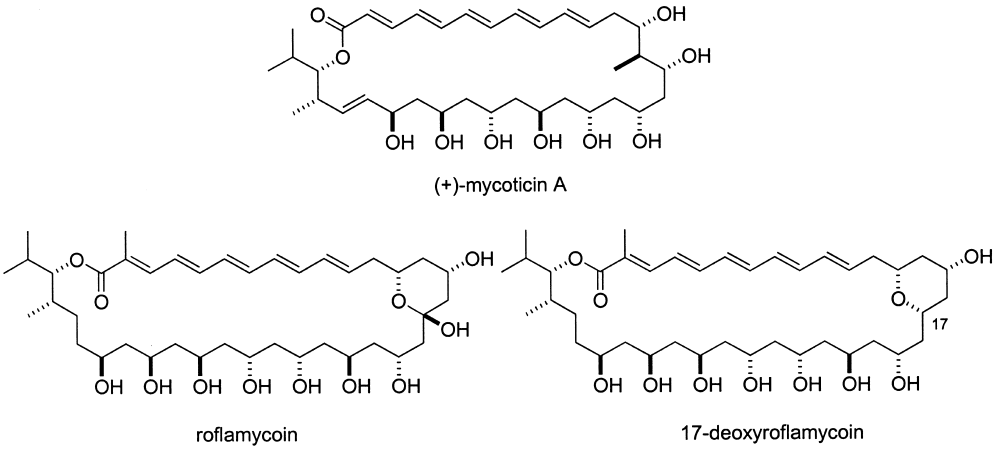


Fig. 32.18 Examples of biologically active compounds obtainable through BINAP–Ru-catalyzed hydrogenation of 1,3-diketones.

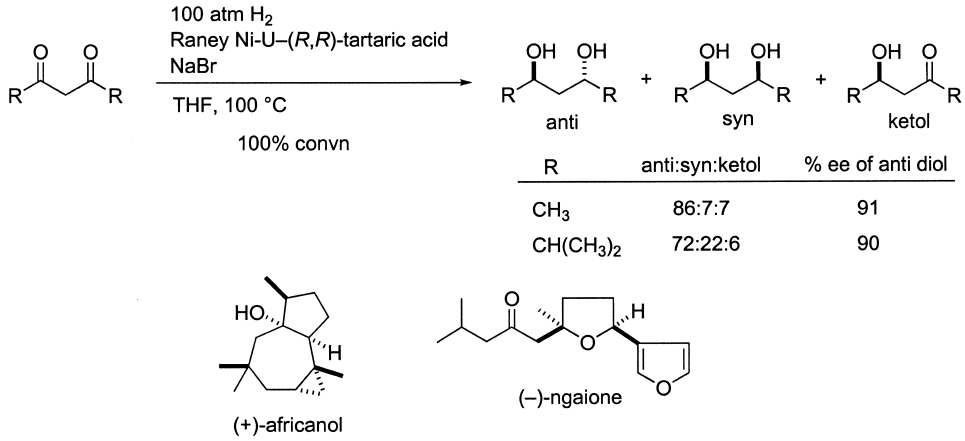


Fig. 32.19 Hydrogenation of 1,3-diketones catalyzed by modified Raney Ni.

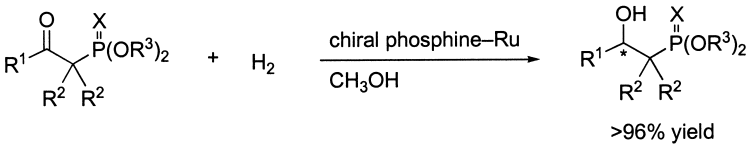


Fig. 32.20 Hydrogenation of β-keto phosphonates.

R^1	R^2	R^3	X	Chiral phosphine (SCR) [a]	H_2 [atm]	Temp. [°C]	ee [%]	Con-fig.	TON	TOF [h^{-1}]
CH_3	H	CH_3	O	(*R*)-BINAP (1220)	4	25	98	*R*	1208	17
CH_3	H	C_2H_5	O	(*S*)-BINAP (50)	1	50	99	*S*	50	1
CH_3	H	C_2H_5	O	(*R,R*)-BDPP (50–100)	30	rt	95	*R*	<100	<2
CH_3	CH_3	CH_3	O	(*R*)-BINAP (370–530)	4	50	98	*R*	<514	<9
n-C_5H_{11}	H	CH_3	O	(*S*)-BINAP (100)	100	rt	98	*S*	100	1
$(CH_3)_2CH$	H	CH_3	O	(*S*)-BINAP (370–530)	4	80	96	*S*	<509	<32
C_6H_5	H	CH_3	O	(*R*)-BINAP (370–530)	4	60	95	*R*	<509	<3
n-C_5H_{11}	H	CH_3	S	(*S*)-MeO-BIPHEP (100)	100	rt	94	*S*	100	1
$(CH_3)_2CH$	H	CH_3	S	(*S*)-MeO-BIPHEP (100)	10	rt	93	*S*	100	1

a) SCR = Substrate : catalyst molar ratio.

32.2.3
β-Keto Phosphonates, Sulfonates, and Sulfones

Enantioselective hydrogenation of β-keto phosphonates in the presence of an (*R*)-BINAP–Ru complex under 1–4 atm H_2 and at room temperature provides the (*R*)-β-hydroxy phosphonates in up to 99% ee (Fig. 32.20) [69]. The sense of enantioface selection is the same as that observed in the reaction of β-keto carboxylic esters (see Fig. 32.14). A BDPP–Ru catalyst is also usable [70]. Similarly, β-keto thiophosphonates are hydrogenated with a MeO-BIPHEP–Ru catalyst with up to 94% optical yield [69 b].

BINAP–Ru catalysts also show high enantioselectivity in the hydrogenation of β-keto sulfonates. Reaction of sodium β-keto sulfonates with (*R*)-BINAP–Ru catalyst quantitatively gives the (*R*)-β-hydroxy sulfonates in up to 97% ee (Fig. 32.21) [15]. In the same manner, hydrogenation of β-keto sulfones in the presence of an (*R*)-MeO-BIPHEP–Ru catalyst affords the (*R*)-hydroxy sulfones in >95% ee [71].

Figure 32.22 shows the diastereoselective hydrogenation of (*R*)-β-keto sulfoxides with Meo-BIPHEP–Ru catalysts [72]. The *R* chiral center of the substrate matches with the *S* catalyst, giving the *S,R* alcohols in >99 : 1 selectivity, whereas reactions with the *R* catalyst affords a 6 : 94 to 10 : 90 mixture of the *S,R* and *R,R* diastereomeric alcohols. The diastereoselection is controlled mainly by the configuration of the catalyst.

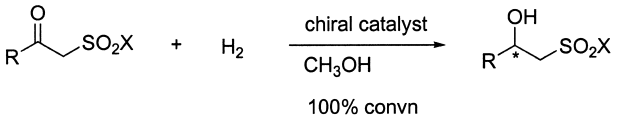


Fig. 32.21 Hydrogenation of β-keto sulfonates.

R	X	Chiral catalyst (SCR) [a]	H_2 [atm]	Temp. [°C]	ee [%]	Config.	TON	TOF [h^{-1}]
CH_3	ONa	$RuCl_2$[(*R*)-binap](dmf)$_n$ + HCl (200)	1	50	97	*R*	200	8
n-$C_{15}H_{31}$	ONa	$RuCl_2$[(*R*)-binap](dmf)$_n$ + HCl (200)	1	50	96	*R*	200	8
$(CH_3)_2CH$	ONa	$RuCl_2$[(*R*)-binap](dmf)$_n$ + HCl (200)	1	50	97	*R*	200	8
C_6H_5	ONa	$RuCl_2$[(*R*)-binap](dmf)$_n$ + HCl (200)	1	50	96	*R*	200	67
CH_3	C_6H_5	$RuBr_2$[(*R*)-meo-biphep] (100)	1	65	>95	*R*	100	4
n-C_5H_{11}	C_6H_5	$RuBr_2$[(*R*)-meo-biphep] (100)	1	65	>95	*R*	100	4
cyclo-C_6H_{11}	C_6H_5	$RuBr_2$[(*R*)-meo-biphep] (100)	1	65	>95	*R*	100	4
C_6H_5	C_6H_5	$RuBr_2$[(*S*)-meo-biphep] (100)	75	40	>95	*S*	100	4

a) SCR = Substrate : catalyst molar ratio.

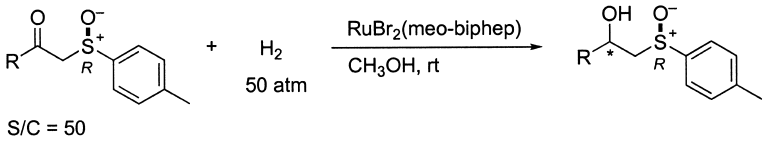


Fig. 32.22 Diastereoselective hydrogenation of β-keto sulfoxides.

R	MeO-BIPHEP	Time [h]	Yield [%]	*S,R:R,R*	TON	TOF [h^{-1}]
n-C_6H_{13}	*S*	25	82	>99:1	41	2
n-C_6H_{13}	*R*	25	74	6:94	37	2
C_6H_5	*S*	63	70	>99:1	35	0.6
C_6H_5	*R*	63	95	10:90	48	0.8

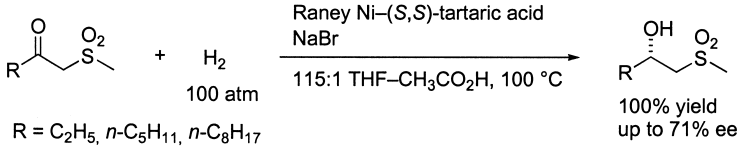


Fig. 32.23 Hydrogenation of β-keto sulfones catalyzed by modified Raney Ni.

Enantioselective hydrogenation of β-keto sulfones in the presence of (*S,S*)-tartaric acid modified Raney Ni gives the *S* alcohols in up to 71% ee (Fig. 32.23) [73].

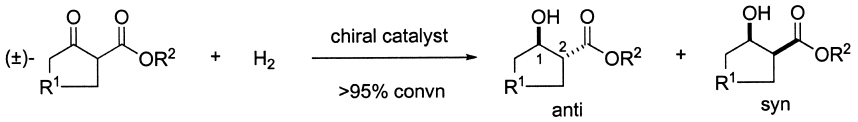


Fig. 32.24 Hydrogenation of racemic 2-alkoxycarbonyl cycloalkanones via dynamic kinetic resolution.

R^1	R^2	Catalyst (SCR) [a]	Solvent	H_2 [atm]	dr [b]	*Anti* alcohol		TON	TOF [h^{-1}]
						ee [%]	Config.		
CH_2	CH_3	[RuCl{(*R*)-binap}C_6H_6]Cl (1820)	CH_2Cl_2	100	99:1	92	1*R*,2*R*	1820	30
CH_2	CH_3	[RuI{(*S*)-binap}(*p*-cymene)]I (1370)	CH_2Cl_2 [c]	100	99:1	95	1*S*,2*S*	1302	33
CH_2	CH_3	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-[(*R*,*R*)-*i*-pr-bpe] + HBr (500)	9:1 CH_3OH–H_2O	4	96:4	98.3	1*S*,2*S*	500	25
CH_2	CH_3	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-[(*S*,*S*)-*t*-bu-bisp*] + HBr (200)	10:1 CH_3OH–H_2O	6	84:16	96	– [d]	200	20
CH_2	CH_3	$RuCl_2$[(+)-tetrame-bitianp] (1000)	CH_3OH	100	93:7	99	1*R*,2*R*	1000	500
CH_2	C_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*R*)-BINAP + HBr (100)	CH_3OH	20	97:3 [e]	94	1*R*,2*R*	50	25
$(CH_2)_2$	C_2H_5	[RuCl{(*R*)-binap}C_6H_6]Cl (530)	CH_2Cl_2	100	95:5	90	1*R*,2*R*	530	9
$(CH_2)_2$	C_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*S*)-BINAP + HBr (100)	CH_2Cl_2	20	74:26	91	1*S*,2*S*	100	33
$(CH_2)_2$	C_2H_5	Ru[η^3-$CH_2C(CH_3)CH_2]_2$-(cod)–(*R*)-(*S*)-**2Bb** + HBr (200)	C_2H_5OH	50	92:8	>99	1*R*,2*R*	<200	<3
$(CH_2)_3$	CH_3	[RuCl{(*R*)-binap}C_6H_6]Cl (910)	CH_2Cl_2	100	93:7	93	1*R*,2*R*	910	11

a) SCR = substrate : catalyst molar ratio.
b) *Anti* : *syn* diastereomeric ratio.
c) Contaminated with <1% of water.
d) Not determined.
e) 50% conversion.

32.2.4 Dynamic Kinetic Resolution

It is possible that hydrogenation of racemic *α*-mono-substituted *β*-keto esters provides four stereoisomers of the corresponding hydroxy esters. Fortunately, enantioselective hydrogenation of such racemic compounds can selectively yield

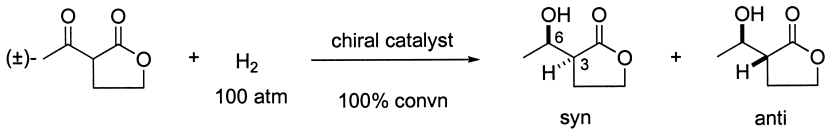


Fig. 32.25 Hydrogenation of 3-acetyltetrahydrofuran-2-one via dynamic kinetic resolution.

Catalyst (SCR) [a]	Solvent	dr [b]	*Syn* alcohol		TON	TOF [h^{-1}]
			ee [%]	Config.		
[RuCl{(*R*)-binap}C_6H_6]Cl (1350)	C_2H_5OH	98:2	94	3*S*,6*R*	1350	18
[RuI_2(*p*-cymene)]$_2$–(*S*)-BINAP (770)	3:1 CH_3OH–CH_2Cl_2	99:1	97	3*R*,6*S*	770	19
$RuCl_2$[(+)-tetrame-bitianp] (1000)	CH_3OH	96:4	91	3*S*,6*R*	1000	20

a) SCR = substrate : catalyst molar ratio.
a) *Syn* : *anti* diastereomeric ratio.

a single stereoisomer of products through the *in-situ* racemization under appropriate conditions, because the α position of β-keto esters is configurationally labile [1]. In fact, as shown in Figure 32.24, racemic 2-methoxycarbonylcyclopentanone is hydrogenated with [RuCl{(*R*)-binap}C_6H_6]Cl in CH_2Cl_2 instead of conventional methanol and ethanol to afford the 1*R*,2*R* hydroxy-ester in 92% ee with a 99:1 *anti*-selectivity [74, 75]. The diastereoselectivity decreases to some extent with increasing ring-size of the substrate, while the enantioselectivity is not affected. High stereoselectivity is obtainable by hydrogenation with Ru catalysts bearing *i*-Pr-BPE [28], *t*-Bu-BisP* [29], tetraMe-BITIANP [23], and a chiral ferrocenyl diphosphine **2Bb** [32] in alcoholic solvents. The enantioselective hydrogenation through dynamic kinetic resolution is the result of catalyst-based intermolecular enantioselective induction and substrate-based intramolecular enantioselective induction, as well as suitable kinetic parameters [76]. The computer-aided analysis of (*R*)-BINAP–Ru-catalyzed hydrogenation of racemic 2-ethoxycarbonylcycloheptanone in CH_2Cl_2 reveals that the *R* keto ester is hydrogenated 9.8-fold faster than the *S* isomer, and that equilibration between both enantiomers of the substrate occurs 4.4-fold faster than hydrogenation of the slow-reacting *S* substrate. Hydrogenation of racemic 3-acetyltetrahydrofuran-2-one catalyzed by the (*R*)-BINAP–Ru complex gives the 3*S*,6*R* (*syn*) product exclusively (Fig. 32.25) [14n, 74b]. A tetraMe-BITIANP–Ru catalyst is also usable [23].

This chemistry is applicable to the hydrogenation of acyclic compounds such as α-acylamino-, α-ammonio-, α-amidomethyl-, and α-chloro-substituted β-keto esters (Fig. 32.26) [14n, 74a, 77–79]. The (*R*)-BINAP–Ru-catalyzed hydrogenation of the α-acylamino and α-amidomethyl ketones in CH_2Cl_2 leads to the 2*S*,3*R* (*syn*) alcohols in up to 98% ee [14n, 74a]. The use of sterically hindered

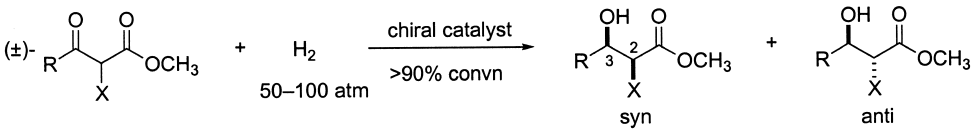


Fig. 32.26 Hydrogenation of acyclic α-substituted β-keto esters via dynamic kinetic resolution.

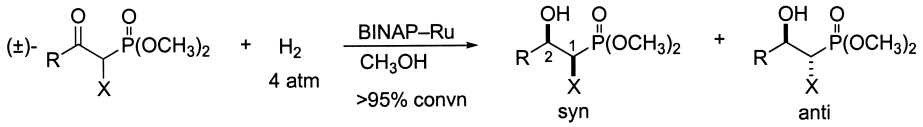
R	X	Catalyst (SCR) [a]	Solvent	dr [b]	Major diastereomer		TON	TOF [h^{-1}]
					ee [%]	Config.		
CH_3	CH_3CO-NH	$RuBr_2$[(*R*)-binap] (270)	CH_2Cl_2	99:1	98	2*S*,3*R*	270	5
CH_3	CH_3CO-NH	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$ [(*R*)-binap] + HCl (100)	CH_3OH	76:24	95	2*S*,3*R*	90	<2
CH_3	$(CH_3)_2C$-HCONH	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$ [(*R*)-binap] + HBr (100)	CH_3OH	77:23	92	2*S*,3*R*	90	<2
$(CH_3)_2$-CH	C_6H_5CO-NH [c]	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$ [(*R*)-bisbenzodioxanphos] + HBr (50)	CH_2Cl_2 [d]	>99:1	98	2*S*,3*R*	45	2
$(CH_3)_2$-CH	$ClNH_3$ [e]	$RuCl_2$[(*S*)-binap](dmf)$_n$ (26)	CH_2Cl_2	1:>99 [f]	98	2*S*,3*S*	21	4
$(CH_3)_2$-CH	$ClNH_3$ [c]	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$ [(*S*)-bisbenzodioxanphos] + HBr (50)	1:10 C_2H_5OH–CH_2Cl_2 [g]	1:99	97	2*S*,3*S*	45	2
Ar [h]	$ClNH_3$	[IrCl(cod)]$_2$–(*R*)-MeO-BIPHEP + NaI + $NaOCOCH_3$ (33)	CH_3CO_2H	1:>99 [i]	95	2*R*,3*R*	29	0.3
Ar [i]	CH_3CO-NH	$RuBr_2$[(*R*)-binap] (265)	CH_2Cl_2	99:1	94	2*S*,3*R*	265	2
CH_3	phthali-mide	[$NH_2(C_2H_5)_2$][{RuCl[(*R*)-c3tunaphos]}$_2$(μ-Cl)$_3$] (– [k])	CH_3OH	3:97	>99	2*R*,3*R*	–	–
CH_3	C_6H_5CO-$NHCH_2$	[$NH_2(C_2H_5)_2$][{RuCl[(*R*)-binap]}$_2$(μ-Cl)$_3$] (100)	CH_2Cl_2	94:6	98	2*S*,3*R*	100	5
CH_3	C_6H_5CO-$NHCH_2$	[RuI{(*S*)-binap}-(*p*-cymene)]I (100)	99.5:0.5 CH_2Cl_2–H_2O	94:6	97	2*R*,3*R*	98	2
CH_3	C_6H_5CO-$NHCH_2$	[RuI_2(*p*-cymene)]$_2$–(+)-DTBBINAP (1000)	1:7 CH_3OH–CH_2Cl_2	99:1 [l]	99	2*S*,3*R*	550	14
CH_3	C_6H_5CO-$NHCH_2$	[$NH_2(C_2H_5)_2$][{RuCl[(–)-dtbm-segphos]}$_2$(μ-Cl)$_3$] (– [k])	– [k]	99.3:0.7	99.4	2*S*,3*R*	–	–
CH_3	Cl [c]	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-(cod)–(*R*)-BINAP (200)	CH_2Cl_2	1:99	99	2*R*,3*R*	200	40

R	X	Catalyst (SCR) [a]	Solvent	dr [b]	Major diastereomer		TON	TOF [h^{-1}]
					ee [%]	Config.		
CH_3	CH_3	Ru[η^3-$CH_2C(CH_3)CH_2$]$_2$-[(*R*,*R*)-*i*-pr-bpe] + HBr (500)	9:1 CH_3OH–H_2O [m]	58:42	96	2*R*,3*R*	500	25
CH_3	CH_3	[RuCl{(*R*)-binap}C_6H_6]Cl (625)	CH_2Cl_2	32:68	94 [n]	2*R*,3*R* [n]	625	10

a) SCR = substrate : catalyst molar ratio.
b) *Syn* : *anti* diastereomeric ratio.
c) Ethyl ester.
d) 130 atm H_2.
e) Benzyl ester.
f) 82% yield after conversion to the benzyl amide.
g) 12 atm H_2.
h) 4-Benzyloxyphenyl.
i) 88% yield after conversion to the benzyloxycarbonyl amide.
j) 3,4-Methylenedioxyphenyl.
k) Not reported.
l) 55% conversion.
m) 4 atm H_2.
n) Value of the *syn* alcohol.

ligands, DTBBINAP and DTBM-SEGPHOS, results in excellent stereoselectivity, affording the almost pure *syn* α-amidomethyl β-hydroxy ester [14n, 42]. BisbenzodioxanPhos also induces high stereoselectivity [78b]. Highly *anti*-selective hydrogenation with the BINAP– or BisbenzodioxanPhos–Ru complex is achieved by using α-amino β-keto ester hydrochlorides (R = alkyl) instead of the acylamino compounds in CH_2Cl_2 or a 1:10 mixture of ethanol and CH_2Cl_2 [78, 79]. An (*R*)-MeO-BIPHEP–Ir complex catalyzes the hydrogenation of methyl α-amino benzoylacetate hydrochlorides in acetic acid to afford the 2*R*,3*R* (*anti*) products selectively [80]. Addition of $NaOCOCH_3$ and NaI is essential to attain high enantioselectivity. Hydrogenation of an α-phthalimide β-keto ester catalyzed by the (*R*)-C3TunaPhos–Ru complex in methanol selectively gives the 2*R*,3*R* (*anti*) product in >99% ee [81]. An α-chloro β-keto ester is hydrogenated with a BINAP–Ru dimethallyl complex to give predominantly the *anti* chloro alcohol in 99% ee [77b]. Hydrogenation of a simple α-methyl β-keto ester gives low diastereoselectivity, while the ee-value of the product remains high [28, 74]. Similarly, the BINAP–Ru-catalyzed hydrogenation of α-acylamino- or α-bromo-substituted β-keto phosphonates affords selectively the corresponding *syn* alcohols in up to >98% ee (Fig. 32.27) [69a, 82]. The mode of stereoselection is the same as that observed in the reaction of α-substituted β-keto carboxylic esters.

The stereoselective hydrogenation of α-substituted β-keto carboxylates and phosphonates via dynamic kinetic resolution catalyzed by a BINAP–Ru com-



BINAP–Ru = $RuCl_2(binap)(dmf)_n$

Fig. 32.27 Hydrogenation of α-substituted β-keto phosphonates via dynamic kinetic resolution.

R	X	BINAP (SCR) [a]	Temp. [°C]	dr [b]	*Syn* alcohol		TON	TOF [h^{-1}]
					ee [%]	Config.		
CH_3	CH_3CONH	*R* (590)	25	97:3	>98	1*R*,2*R*	590	9
C_6H_5	CH_3CONH	*R* (100)	45	98:2	95	1*R*,2*R*	100	0.8
CH_3	Br	*S* (590)	25	90:10 [c]	98	1*R*,2*S*	561	6

a) SCR = substrate : catalyst molar ratio.
b) *Syn* : *anti* diastereomeric ratio.
c) Contaminated with 15% of a debrominated compound.

plexes is now widely used for the synthesis of important bioactive compounds, as well as some chiral diphosphines [1–4, 69a, 74, 83]. Some examples are listed in Figure 32.28. The stereocenter according to the BINAP–Ru chemistry is labeled by *R* or *S*. The chiral 2-acetoxyazetidinone, a key intermediate in the synthesis of carbapenems, is synthesized through the BINAP–Ru-catalyzed hydrogenation of methyl-2-benzamidomethyl-3-oxobutanoate via dynamic kinetic resolution on an industrial scale at Takasago International Corporation (Fig. 32.29) [1, 2, 84].

32.3 Simple Ketones

32.3.1 Alkyl Aryl Ketones

The hydrogenation of simple ketones was difficult. Because of the absence of hetero-atoms near the carbonyl function, these ketones cannot form a stable cyclic transition state, as shown in the reaction of β-keto esters (see Fig. 32.7) [2]. Most neutral or cationic metal-catalysts bearing monodentate or bidentate chiral phosphine ligands produced unsatisfactory results [4]. A breakthrough in this field was achieved by the development of Ru catalysts bearing both BINAP and a chiral 1,2-diamine on the center metal [2, 85]. Hydrogenation of 601 g acetophenone with only 2.2 mg *trans*-$RuCl_2$[(*S*)-tolbinap][(*S*,*S*)-dpen] in alkaline-base containing 2-propanol at 30 °C, under 45 atm of H_2 completes in 48 h, resulting

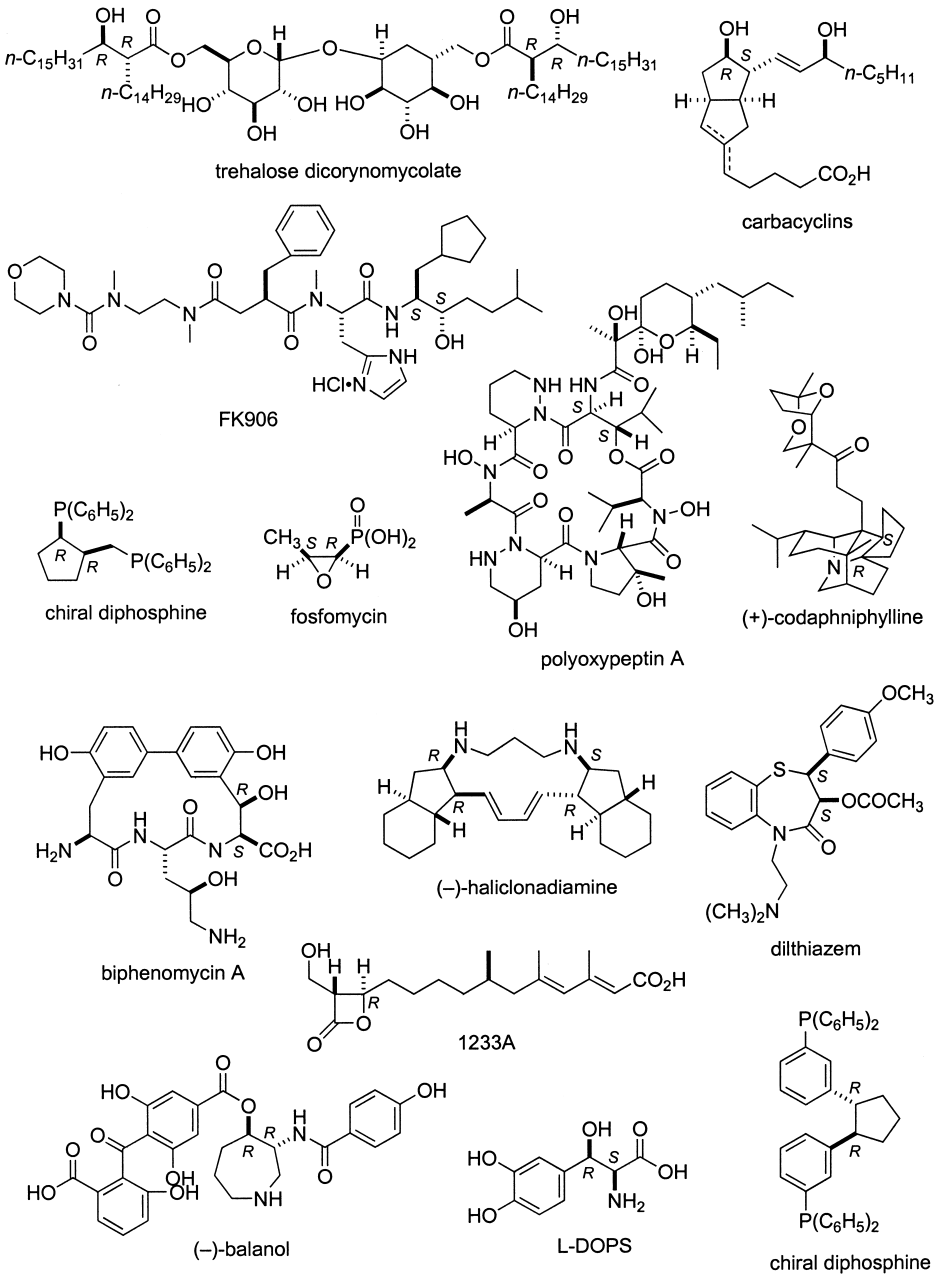


Fig. 32.28 Examples of bioactive compounds and chiral diphosphines obtainable by BINAP–Ru-catalyzed hydrogenation via dynamic kinetic resolution.

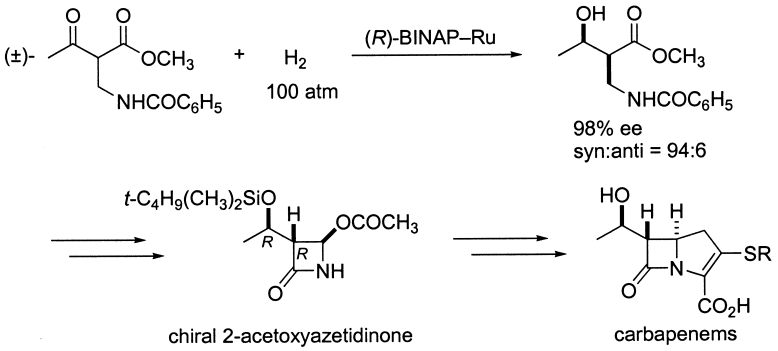


Fig. 32.29 Industrial synthesis of a carbapenem intermediate by BINAP–Ru-catalyzed hydrogenation.

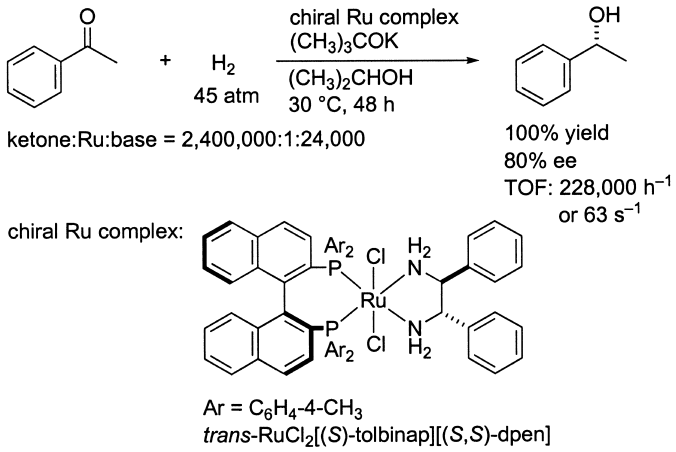
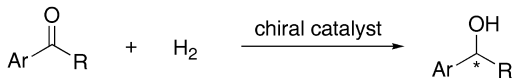


Fig. 32.30 Rapid hydrogenation of acetophenone catalyzed by the TolBINAP/DPEN–Ru complex.

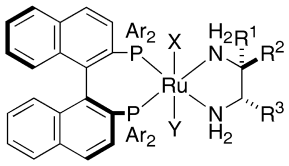
in (*R*)-1-phenylethanol in 80% ee (Fig. 32.30) [86]. The TON reaches 2 400 000, while the TOF at 30% conversion was calculated as 228 000 h^{-1} or 63 s^{-1}.

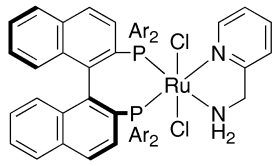
Highly enantioselective hydrogenation of simple ketones has been achieved by the use of the catalyst consisting of *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] (or the *R*/*R* combination) and $(CH_3)_3COK$ [(*S*,*S*)- or (*R*,*R*)-**31D**] in 2-propanol (Fig. 32.31) [87]. For example, hydrogenation of acetophenone catalyzed by (*S*,*S*)-**31D** with an SCR of 100 000 under 8 atm H_2 quantitatively gives (*R*)-1-phenylethanol in 99% ee. The combination of XylBINAP and DPEN (**31E**) also shows excellent enantioselectivity. This reaction tolerates many functionalities on the aryl ring such as F, Cl, Br, I, CF_3, OCH_3, $CO_2CH(CH_3)_2$, NO_2, and NH_2 [87]. The electronic and steric properties of the substituents hardly affect the enantioselection. Propiophenone, isobutyrophenone, cyclopropyl phenyl ketone, and 1′- and 2′-acetonaphthone are converted to the corresponding chiral alcohols in ex-



chiral catalyst:

trans-$RuCl_2$[(*S*)-tolbinap][(*S*)-daipen] + $(CH_3)_3COK$; (*S*,*S*)-**31A**
trans-$RuCl_2$[(*S*)-tolbinap][(*S*,*S*)-dpen] + $(CH_3)_3COK$; (*S*,*SS*)-**31B**
$RuCl_2$[(*S*)-tolbinap](pica) + $(CH_3)_3COK$; (*S*)-**31C**
trans-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] + $(CH_3)_3COK$; (*S*,*S*)-**31D**
trans-$RuCl_2$[(*S*)-xylbinap][(*S*,*S*)-dpen] + $(CH_3)_3COK$; (*S*,*SS*)-**31E**
trans-RuHCl[(*S*)-binap][(*S*,*S*)-cydn] + $(CH_3)_2CHOK$; (*S*,*SS*)-**31F**
trans-RuH(η^1-BH_4)[(*S*)-xylbinap][(*S*,*S*)-dpen]; (*S*,*SS*)-**31G**
trans-RuH(η^1-BH_4)[(*S*)-xylbinap][(*S*,*S*)-dpen] + $(CH_3)_3COK$; (*S*,*SS*)-**31H**
trans-$RuCl_2$[(*S*)-xyl-hexaphemp][(*S*)-daipen] + $(CH_3)_3COK$; (*S*,*S*)-**31I**
trans-$RuCl_2$[(*R*)-xyl-p-phos][(*R*,*R*)-dpen] + $(CH_3)_3COK$; (*R*,*RR*)-**31J**
trans-$RuCl_2$[(*R*)-xylyl-phanephos][(*S*,*S*)-dpen] + $(CH_3)_3COK$; (*R*,*SS*)-**31K**
trans-$RuCl_2$[(*R*)-**1Bb**][(*R*)-daipen] + $(CH_3)_3COK$; (*R*,*R*)-**31L**
trans-$RuCl_2$[(*S*)-xyl-sdp][(*R*,*R*)-dpen] + $(CH_3)_3COK$; (*S*,*RR*)-**31M**
trans-$RuCl_2$[(*S*)-**3A**]$_2$[(*S*,*S*)-dpen] + $(CH_3)_3COK$; (*S*,*SS*)-**31N**
$RuCl_2$[(*S*,*S*)-bdpp][(*S*,*S*)-dpen] + $(CH_3)_3COK$; (*SS*,*SS*)-**31O**
$RuBr_2$[(*R*,*R*)-bipnor]–(*S*,*S*)-DPEN + KOH; (*RR*,*SS*)-**31P**
$RuCl_2$[(*S*,*S*)-**1Aa**](dmf)$_n$–2-(*n*-propyl)aniline + $(CH_3)_3CONa$; (*SS*)-**31Q**
$[NH_2(C_2H_5)_2][\{RuCl[(S)\text{-tolbinap}]\}_2(\mu\text{-}Cl)_3]$; (*S*)-**31R**
RuClCp*(cod)–(*S*)-**4A** + KOH; (*S*)-**31S**
trans-RuHCl[(*S*)-binap][(*R*,*R*)-**2D**] + $(CH_3)_3COK$; (*S*,*RR*)-**31T**
$RuCl_2[P(C_6H_5)_3]_3$ + (*R*,*R*)-**4B** + $(CH_3)_3COK$; (*R*,*R*)-**31U**
$[RhCl(nbd)]_2$–(*S*,*S*)-DIOP + $(C_2H_5)_3N$; (*S*,*S*)-**31V**
$[RhCl(nbd)]_2$–(*S*,*S*)-BDPP + $(C_2H_5)_3N$; (*S*,*S*)-**31W**
$[RhCl(cod)]_2$–(*R*,*S*,*R*,*S*)-Me-PennPhos + 2,6-lutidine + KBr; (*R*,*S*,*R*,*S*)-**31X**
$[Ir\{(S)\text{-binap}\}(cod)]BF_4$–P[2-N$(CH_3)_2C_6H_4]_2C_6H_5$; (*S*)-**31Y**





trans-$RuCl_2$[(*S*)-tolbinap][(*S*)-daipen]: X = Y = Cl,
Ar = 4-$CH_3C_6H_4$, R^1 = R^2 = 4-$CH_3OC_6H_4$, R^3 = $(CH_3)_2CH$
trans-$RuCl_2$[(*S*)-tolbinap][(*S*,*S*)-dpen]: X = Y = Cl,
Ar = 4-$CH_3C_6H_4$, R^1 = H, R^2 = R^3 = C_6H_5
trans-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen]: X = Y = Cl,
Ar = 3,5-$(CH_3)_2C_6H_3$, R^1 = R^2 = 4-$CH_3OC_6H_4$, R^3 = $(CH_3)_2CH$
trans-$RuCl_2$[(*S*)-xylbinap][(*S*,*S*)-dpen]: X = Y = Cl,
Ar = 3,5-$(CH_3)_2C_6H_3$, R^1 = H, R^2 = R^3 = C_6H_5
trans-RuH(η^1-BH_4)[(*S*)-xylbinap][(*S*,*S*)-dpen]: X = H, Y = η^1-BH_4,
Ar = 3,5-$(CH_3)_2C_6H_3$, R^1 = H, R^2 = R^3 = C_6H_5

$RuCl_2$[(*S*)-tolbinap](pica): Ar = 4-CH_3(
diastereomeric mixture

Fig. 32.31 Hydrogenation of alkyl aryl ketones.

R	Ar	Catalyst	SCR[a]	H_2 [atm]	Temp. [°C]	Yield [%]	ee [%]	Config.	TON	TOF [h^{-1}]
CH_3	C_6H_5	(*S,S*)-**31E**	100 000	8	45	100	99	*R*	100 000	40 000
CH_3	C_6H_5	(*S,SS*)-**31F**	5000	3	20	100	88	*R*	5 000	>417
CH_3	C_6H_5	(*S,SS*)-**31G**	100 000	8	45	100	99	*R*	100 000	14 286
CH_3	C_6H_5	(*S,SS*)-**31H**	100 000	8	45	100	99	*R*	100 000	133 333
CH_3	C_6H_5	(*S,S*)-**31I**	3000	8	rt	>99	99	*R*	>2 970	>6 364
CH_3	C_6H_5	(*R,RR*)-**31J**	100 000	34	25–28	99.7	99	*S*	99 700	2 764
CH_3	C_6H_5	(*R,SS*)-**31K**	20 000	8	18–20	>99	99	*R*	>19 800	>13 200
CH_3	C_6H_5	(*R,R*)-**31L**	1 000 000	48	rt	100	98.6	*S*	1 000 000	20 000
CH_3	C_6H_5	(*S,RR*)-**31M**	100 000	50	40	98	98	*S*	98 000	1 361
CH_3	C_6H_5	(*S,SS*)-**31N**	2000	50	0	95	93	*R*	1900	475
CH_3	C_6H_5	(*SS,SS*)-**31O**	500	2	rt	100	84	*R*	500	10
CH_3	C_6H_5	(*S,RR*)-**31T**	2000	2	5	>99	71	*S*	>1 980	>495
CH_3	C_6H_5	(*R,R*)-**31U**	100	30	rt	100	76	*S*	100	6
CH_3	C_6H_5	(*S,S*)-**31V**	200	69	50	64	80	–	128	21
CH_3	C_6H_5	(*S,S*)-**31W**	100	69	50	72	82	*S*	72	3
CH_3	C_6H_5	(*R,S,R,S*)-**31X**	100[b]	30	rt	97	95	*S*	97	4
CH_3	C_6H_5	(*S*)-**31Y**	100	54–61	60	63	54	*S*	63	0.5
CH_3	2-$CH_3C_6H_4$	(*S,S*)-**31A**	100 000	10	28	94	99	*R*	94 000	1 958
CH_3	3-$CH_3C_6H_4$	(*S,S*)-**31D**	10 000	10	28	98	100	*R*	9 800	204
CH_3	3-$CH_3C_6H_4$	(*SS*)-**31Q**	500	7	rt	>99	93	*S*	>495	>33
CH_3	4-$CH_3C_6H_4$	(*R,RR*)-**31E**	2000	4	28	100	98	*S*	2 000	286
CH_3	4-*n*-$C_4H_9C_6H_4$	(*R,RR*)-**31E**	2000	4	28	100	98	*S*	2 000	400
CH_3	2,4-$(CH_3)_2C_6H_3$	(*R,R*)-**31D**	2000	4	28	99	99	*S*	1 980	248
CH_3	2-FC_6H_4	(*S,S*)-**31D**	2000	8	28	100	97	*R*	2 000	154
CH_3	2-FC_6H_4	(*S*)-**31R**	1300	85	35	21	>99	–	273	6
CH_3	3-FC_6H_4	(*R,RR*)-**31E**	2000	4	28	99	98	*S*	1 980	330
CH_3	4-FC_6H_4	(*R,R*)-**31D**	2000	4	28	100	97	*S*	2 000	333
CH_3	2-ClC_6H_4	(*R,RR*)-**31E**	2000	4	28	99.5	98	*S*	1 980	110
CH_3	2-BrC_6H_4	(*R,R*)-**31A**	10 000	10	28	100	98	*S*	10 000	1 667
CH_3	2-BrC_6H_4	(*R,R*)-**31D**	2000	4	28	99	96	*S*	1 980	660
CH_3	2-BrC_6H_4	(*S*)-**31R**	950	85	35	95	97	*S*	903	19
CH_3	3-BrC_6H_4	(*R,R*)-**31D**	2000	4	28	100	99.5	*S*	2 000	667
CH_3	4-BrC_6H_4	(*S,S*)-**31D**	20 000	8	28	99.9	99.6	*R*	19 980	3 996
CH_3	4-BrC_6H_4	(*S,S*)-**31D**	500	1	28	99.7	99.6	*R*	499	166
CH_3	4-BrC_6H_4	(*R,SS*)-**31K**	3000	8	18–20	>99	99	*R*	>2970	>2 970
CH_3	4-IC_6H_4	(*S,S*)-**31D**	2000	8	28	99.7	99	*R*	1 994	499
CH_3	2-$CF_3C_6H_4$	(*R,R*)-**31D**	2000	4	28	99	99	*S*	1 980	660
CH_3	3-$CF_3C_6H_4$	(*R,R*)-**31D**	2000	4	28	100	99	*S*	2 000	500
CH_3	3-$CF_3C_6H_4$	(*R,SS*)-**31K**	3000	8	18–20	>99	99	*R*	>2970	>5 940
CH_3	4-$CF_3C_6H_4$	(*S,S*)-**31D**	10 000	10	28	100	99.6	*R*	10 000	500
CH_3	2-$CH_3OC_6H_4$	(*R,R*)-**31D**	2 000	4	28	100	92	*S*	2 000	200
CH_3	3-$CH_3OC_6H_4$	(*R,R*)-**31D**	2 000	4	28	99	99	*S*	1 980	495
CH_3	4-$CH_3OC_6H_4$	(*S,S*)-**31D**	2 000	10	28	100	100	*R*	2 000	2 000
CH_3	4-$CH_3OC_6H_4$	(*R,S,R,S*)-**31X**	100	30	rt	83	94	*S*	83	2
CH_3	3-(*R*)-glycidyl-oxyphenyl	(*S,SS*)-**31G**	2 000	8	25	99	99	*R,R*	1 980	141
CH_3	4-(C_2H_5OCO)-C_6H_4	(*S,SS*)-**31G**	4 000	8	25	100	99	*R*	4 000	267

R	Ar	Catalyst	SCR[a]	H_2 [atm]	Temp. [°C]	Yield [%]	ee [%]	Con-fig.	TON	TOF [h^{-1}]
CH_3	4-[$(CH_3)_2CH$-OCO]C_6H_4	(*S,S*)-**31D**	2000	8	28	100	99	*R*	2000	667
CH_3	4-$NO_2C_6H_4$	(*S,S*)-**31D**	2000	8	28	100	99.8	*R*	2000	133
CH_3	4-$NH_2C_6H_4$	(*S,S*)-**31D**	2000	8	28	100	99	*R*	2000	500
CH_3	1-naphthyl	(*S,SS*)-**31B**	100000	10	28	99.5	98	*R*	99500	2488
CH_3	1-naphthyl	(*R,RR*)-**31E**	2000	4	28	99	99	*S*	1980	495
CH_3	1-naphthyl	(*S,S*)-**31V**	200	69	50	100	84	–	200	40
CH_3	2-naphthyl	(*R,RR*)-**31E**	2000	4	28	99	98	*S*	1980	495
CH_3	2-naphthyl	(*RR,SS*)-**31P**	500	5	28	65	81	*R*	325	33
C_2H_5	C_6H_5	(*R,RR*)-**31E**	2000	4	28	100	99	*S*	2000	133
C_2H_5	C_6H_5	(*S,RR*)-**31K**	3000	5.5	18–20	>99	98	*S*	>2970	>1980
C_2H_5	C_6H_5	(*R,S,R,S*)-**31X**	100	30	rt	95	93	*S*	95	1
C_2H_5	4-FC_6H_4	(*R,RR*)-**31E**	2000	4	28	99	99	*S*	1980	248
C_2H_5	4-ClC_6H_4	(*S,S*)-**31D**	20000	8	28	99.9	99	*R*	19980	1249
$(CH_3)_2CH$	C_6H_5	(*R,R*)-**31D**	10000	8	28	99.7	99	*S*	9970	712
$(CH_3)_2CH$	C_6H_5	(*S*)-**31Y**	200	54–61	90	78	84	*R*	156	1
cyclo-C_3H_5	C_6H_5	(*S,S*)-**31D**	2000	8	28	99.7	96	*R*	1994	142
$(CH_3)_2CH$-CH_2	C_6H_5	(*S*)-**31S**	100	10	30	98	95	*R*	98	<16
$(CH_3)_3C$	C_6H_5	(*S*)-**31C**	2000	5	25	100	97	*R*	2000	167
$(CH_3)_3C$	C_6H_5	(*S*)-**31S**	100	10	30	99	81	*R*	99	<17

a) SCR = substrate : catalyst molar ratio.
b) Without addition of KBr.

cellent ee. *trans*-RuHCl[(*S*)-binap][(*S,S*)-cydn] with $(CH_3)_3COK$ (**31F**) also exhibits high catalytic activity [88]. In a similar manner, Ru catalysts bearing biaryl diphosphines, Xyl-HexaPHEMP (**31I**) [89], Xyl-P-Phos (**31J**) [90], and **1Bb** (**31L**) [91], show high enantioselectivity. The use of planar-chiral Xylyl-Phanephos (**31K**) [92] or chiral spiro diphosphine Xyl-SDP (**31M**) [93] gives excellent results. A Ru complex with a chiral monodentate phosphinite **3A** and DPEN in a 2:1 ratio (**31N**) shows high selectivity [94]. BDPP/DPEN–Ru (**31O**) [14p] or BIPNOR/DPEN–Ru catalysts (**31P**) [95] results in a good enantioselectivity. An *in-situ*-prepared catalyst from $RuCl_2$(**1Aa**)$(dmf)_n$, achiral 2-(*n*-propylthio)aniline, and $(CH_3)_3CONa$ (**31Q**) shows high enantioselectivity in ethanol [96]. Selection of alcoholic solvent notably affects the stereoselection. Ru catalyst bearing BINAP and a chiral amino phosphine **2D** (**31T**) [97] or a nitrogen-based tetradentate ligand **4B** (**31U**) [98] are also usable. Sterically hindered pivalophenone is smoothly hydrogenated with $RuCl_2$[(*S*)-tolbinap](pica) (PICA = *a*-picolylamine) and $(CH_3)_3COK$ [(*S*)-**31C**] to yield the *R* alcohol in 97% ee [99]. The best enantioselectivity is achievable in ethanol. A ternary catalyst system consisting of RuClCp*(cod) (Cp* = pentamethylcyclopentadienyl), a chiral diamine **4A**, and KOH (**31S**) is also usable [100]. Halogen-substituted acetophenones at the C2′

position are hydrogenated in the presence of $[NH_2(C_2H_5)_2][\{RuCl(tolbinap)\}_2(\mu\text{-}Cl)_3]$ (**31R**) to afford the chiral alcohols in up to >99% ee [101].

The BINAP/1,2-diamine–$RuCl_2$ complexes require the addition of alkaline base to form reactive RuH_2 species for the hydrogenation of simple ketones to neutralize releasing HCl. *trans*-$RuH(\eta^1\text{-}BH_4)$(xylbinap)(dpen) (**31G**) produces the active species without an additional base, while an even higher rate is obtainable in the presence of an alkaline base (Fig. 32.31) [102]. The base-free procedure can be applied to the hydrogenation of several base-sensitive ketones. For example, the reaction of ethyl-4-acetylbenzoate catalyzed by (*S*,*SS*)-**31G** quantitatively yields ethyl (*R*)-4-(1-hydroxyethyl)benzoate in 99% ee [102]. No transesterification is observed.

Enantioselective hydrogenation of alkyl aryl ketones catalyzed by chiral diphosphine–Rh complexes has also been reported. A catalyst system consisting of $[RhCl(nbd)]_2$, DIOP, and $(C_2H_5)_3N$ (**31V**) promotes the hydrogenation of acetophenone and 1′-acetonaphthone with high enantioselectivity (Fig. 32.31) [103, 104]. Hydrogenation of acetophenone with a BDPP–Rh catalyst (**31W**) gives 82% optical yield [105]. A Me-PennPhos–Rh complex with 2,6-lutidine and KBr (**31X**) catalyzed the hydrogenation of several aromatic ketones in up to 95% ee [106]. A cationic BINAP–Ir(I) complex with an achiral aminophosphine (**31Y**) is also usable [107].

Figure 32.32 shows a proposed mechanism for the hydrogenation of simple ketones catalyzed by TolBINAP/DPEN–Ru complexes [2, 108–110]. Under the hydrogenation conditions, the precatalyst **32A** is converted to the cationic RuH species **32B**, which equilibrates with the neutral complex **32E**. The 16-electron species **32B** reacts reversibly with an H_2 molecule to form **32C**, followed by a base- or solvent-assisted deprotonation resulting in the active RuH_2 species **32D**. A ketone is immediately reduced by **32D** to give the alcohol product and the 16-electron species **32E**, which is spontaneously protonated by alcoholic solvent, generating **32B**. Under highly basic or aprotic conditions, **32D** is reproduced by the reaction of **32E** and H_2. The six-membered pericyclic transition state **32F**, in which carbonyl moiety of the ketone does not interact with the Ru center, results in a low energy barrier at the reducing step, **32D** → **32E** [2, 108, 109]. The H–Ru–N–H 1,4-dipole function fits well with the carbonyl dipole. The hydride on the Ru center migrates to the electrophilic carbonyl carbon, while the amino-proton is delivered to the carbonyl oxygen simultaneously. Therefore, the presence of the NH_2 (or NH) end is crucial to achieve high catalytic activity.

As shown in Figure 32.30, the hydrogenation of acetophenone catalyzed by the (*S*)-TolBINAP/(*S*,*S*)-DPEN–Ru complex gives (*R*)-1-phenylethanol. The sense of enantioselection is general for various simple aromatic ketones. According to the "metal–ligand bifunctional mechanism" described above, the absolute configuration of alcohol products is kinetically determined at the stage of **32D**→**32E** (Fig. 32.32) [2, 108, 109]. Both possible diastereomeric transition states, *Si*-**33A** and *Re*-**33A** (Fig. 32.33), utilize the NH_{ax} (not NH_{eq}) proton for formation of the pericyclic ring due to the smaller H–Ru–N–H_{ax} dihedral angle. The *R* alcohol is selectively produced through *Si*-**33A**, because the *Re*-**33A** lead-

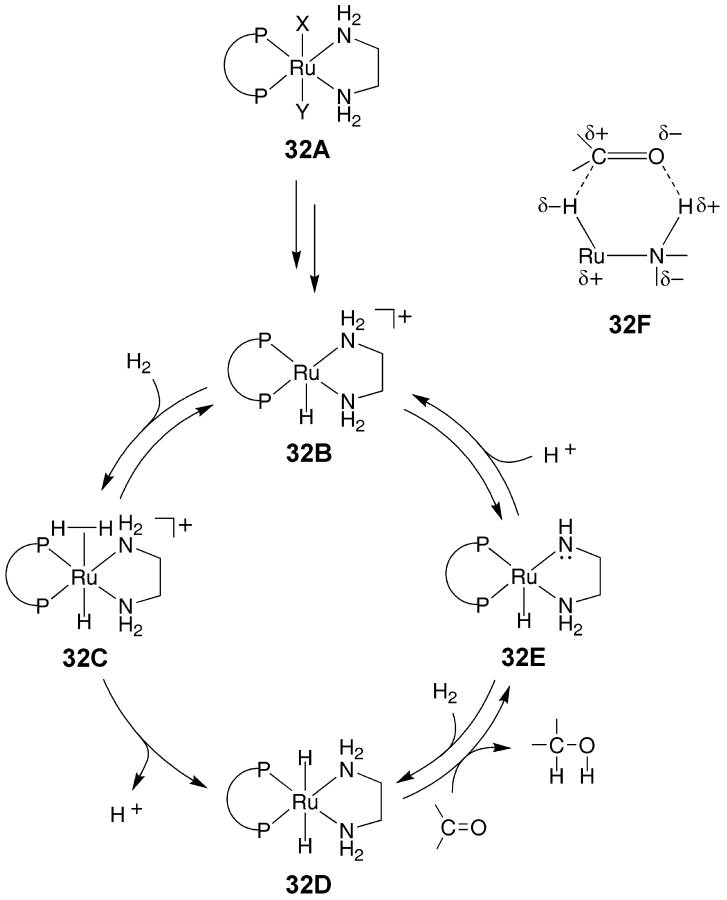


Fig. 32.32 Proposed catalytic cycle of hydrogenation of simple ketones with the TolBINAP/DPEN–Ru catalyst.

ing to the *S* alcohol suffers from significant nonbonded repulsion between the *P*-tolyl group and the phenyl ring of acetophenone. This explanation is consistent with the result that the use of the bulkier XylBINAP achieves higher optical yield (99% versus 80%).

The BINAP/1,2-diamine–Ru catalysts achieve rapid and enantioselective hydrogenation of simple aromatic ketones. However, enantioselective hydrogenation of 1-tetralones is difficult with these catalysts. This problem is solved by the use of IPHAN (Fig. 32.4), a chiral 1,4-diamine [111]. Hydrogenation of 1-tetralone with an (*S*)-XylBINAP/(*R*)-IPHAN–Ru complex and $(CH_3)_3COK$ [(*S*,*R*)-**34C**] in 2-propanol gives (*R*)-1-tetralol in 99% ee (Fig. 32.34). Tetralones substituted by CH_3O and F at the C7 position are reduced with **34C** in 99% and 98% optical yield, respectively. The use of an (*S*)-TolBINAP/(*R*)-IPHAN–Ru catalyst

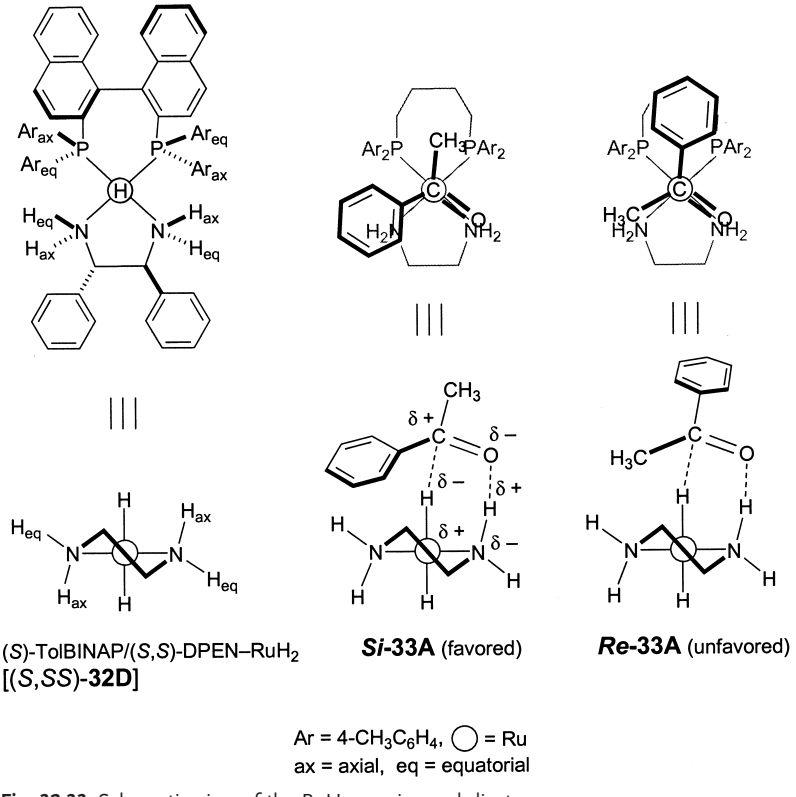
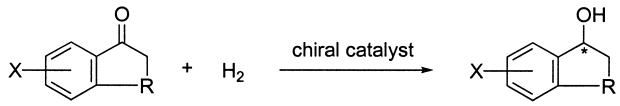


Fig. 32.33 Schematic view of the RuH_2 species and diastereomeric transition states in the hydrogenation of acetophenone. The equatorially oriented phenyl groups in the DPEN are omitted in **33A**.

[(*S*,*R*)-**34B**] or the *R*,*S* combination gives the best results for the hydrogenation of 4-, 5-, and 6-substituted ketones. 5,7-Disubstituted ketones are stereoselectively reduced with an (*S*)-BINAP/(*R*)-IPHAN catalyst. A cationic BINAP–Ir(I) complex with an addition of achiral aminophosphine (**31Y**) effects for hydrogenation of a series of cyclic aromatic ketones (Fig. 32.34) [112]. 1-Tetralones and their analogues are hydrogenated in up to 95% optical yield, while the reaction requires H_2 pressure up to 57 atm and temperature of 90 °C. The hydrogenation of 1-indanone under the same conditions gives 1-indanol in 86% ee [112].

Immobilized catalysts on solid supports inherently have benefits because of their easy separation from the products and the possibility of recycling. They are also expected to be useful for combinatorial chemistry and high-throughput experimentation. The polystyrene-bound BINAP/DPEN–Ru complex (beads) in the presence of $(CH_3)_3COK$ catalyzes the hydrogenation of 1′-acetonaphthone with an SCR of 12 300 in a 2-propanol–DMF mixture (1 : 1, v/v) to afford the chiral alcohol in 97% ee (Fig. 32.35) [113]. This supported complex is separable



chiral catalyst:

trans-$RuCl_2$[(*S*)-binap][(*R*)-iphan] + $(CH_3)_3COK$; (*S*,*R*)-**34A**
trans-$RuCl_2$[(*S*)-tolbinap][(*R*)-iphan] + $(CH_3)_3COK$; (*S*,*R*)-**34B**
trans-$RuCl_2$[(*S*)-xylbinap][(*R*)-iphan] + $(CH_3)_3COK$; (*S*,*R*)-**34C**

Fig. 32.34 Hydrogenation of cyclic aromatic ketones.

R	X	Catalyst	SCR[a]	H_2 [atm]	Temp. [°C]	Yield [%]	ee [%]	Config.	TON	TOF [h^{-1}]
CH_2	H	(*S*)-**31Y**	190–230	50–57	90	72	86	*S*	<166	<8
CH_2	5-Cl	(*R*)-**31Y**	190–230	50–57	90	81	84	–[b]	<186	<10
$(CH_2)_2$	H	(*R*)-**31Y**	190–230	50–57	90	88	95	*R*	<202	<3
$(CH_2)_2$	H	(*S*,*R*)-**34C**	3000	9	25	99.6	99	*R*	2988	374
$(CH_2)_2$	5-CH_3O	(*S*,*R*)-**34B**	55000	9	25	100	98	*R*	55000	3929
$(CH_2)_2$	6-CH_3O	(*S*,*R*)-**34B**	1000	9	25	98	92	*R*	980	75
$(CH_2)_2$	7-CH_3O	(*R*)-**31Y**	190–230	50–57	90	74	95	–[b]	<170	<3
$(CH_2)_2$	7-CH_3O	(*S*,*R*)-**34C**	3300	9	25	100	99	*R*	3300	413
$(CH_2)_2$	7-NO_2	(*R*)-**31Y**	190–230	50–57	90	64	94	–[b]	<147	<2
$(CH_2)_2$	7-F	(*S*,*R*)-**34C**	3000	9	25	100	98	*R*	3000	375
$(CH_2)_2$	5,7-$(CH_3)_2$	(*R*)-**31Y**	190–230	50–57	90	78	95	–[b]	<179	<3
$(CH_2)_2$	5,7-$(CH_3)_2$	(*S*,*R*)-**34A**	3300	9	25	99.9	95	*R*	3297	1648
$(CH_3)_2$-CCH_2	H	(*R*,*R*)-**34B**	12000	9	25	99.9	93	*R*	11988	666
OCH_2	H	(*R*)-**31Y**	190–230	50–57	90	89	93	*R*	<205	<3
SCH_2	H	(*S*)-**31Y**	190–230	50–57	90	87	84	*S*	<200	<5

a) SCR = substrate : catalyst molar ratio.
b) Not reported.

by a simple filtration, and is reusable as a catalyst. The reaction with SCR of 2470 per batch can be conducted 14 times without loss of enantioselectivity (total TON = 33000). Some heterogenized BINAP/DPEN–Ru catalysts have also been used for this purpose. Poly-NAP [114], poly(BINOL–BINAP) [115], poly(BINAP) [116], or dendritic BINAP **5A** [117] show a high performance. Ru catalysts with poly-NAP [114] or **5A** [117] can be reused four times, with SCR of 1000 per batch and 500 per batch, respectively.

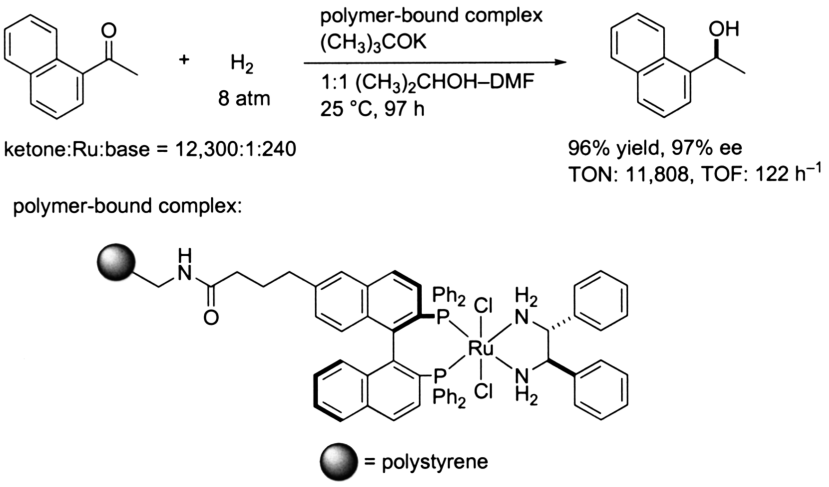


Fig. 32.35 Hydrogenation of 1′-acetonaphthone with the polymer-bound BINAP/DPEN–Ru catalyst.

32.3.2
Hetero-Substituted Aromatic Ketones

Enantioselective hydrogenation of *α*-, *β*-, and *γ*-amino-substituted ketones yields the corresponding chiral amino alcohols directly. Several chirally modified Rh and Ru catalysts have been applied in this reaction. Hydrogenation of 2-aminoacetophenone hydrochloride catalyzed by MOC-BIMOP–$[Rh(nbd)_2]ClO_4$ [118] or $[RhX(cy,cy\text{-}oxopronop)]_2$ (X = Cl, $OCOCF_3$) [119] provides the corresponding amino alcohol in 93% ee (Fig. 32.36). 2-(Dimethylamino)acetophenone hydrochloride is hydrogenated to the chiral amino alcohol in 96% ee with an MCCPM–Rh catalyst at an SCR of 100 000 [120, 121]. Epinephrine hydrochloride is produced in 95% ee by hydrogenation in the presence of $[Rh(nbd)(bppfoh)]ClO_4$ and $(C_2H_5)_3N$ [122]. 2-Dialkylamino ketones in their neutral form are reduced with BINAP–Ru [14n, 40] and DIOP–Rh [123] catalysts in high optical yield. The MCCPM–Rh-catalyzed hydrogenation of *β*- and *γ*-amino ketone hydrochlorides gives the corresponding chiral amino alcohols in up to 91% ee [124]. Hydrogenation of 2-(dimethylamino)acetophenones with Cy,Cy-oxoProNOP–Rh [125] and Cp,Cp-IndoNOP–Rh [126] catalysts affords the chiral alcohols in up to >99% ee. This reaction is applied to the synthesis of an atypical *β*-adrenergic phenylethanolaminotetraline agonist SR58611A [127].

A chiral catalyst consisting of *trans*-$RuCl_2$(xylbinap)(daipen) and $(CH_3)_3COK$ in 2-propanol effects asymmetric hydrogenation of *α*-, *β*-, and *γ*-amino aromatic ketones [128]. Hydrogenation of 2-(dimethylamino)acetophenone catalyzed by the (*R*)-XylBINAP/(*R*)-DAIPEN–Ru complex [(*R*,*R*)-**31D**] gives the *R* amino alcohol in 93% ee (Fig. 32.36). The optical yield is increased up to 99.8%, when

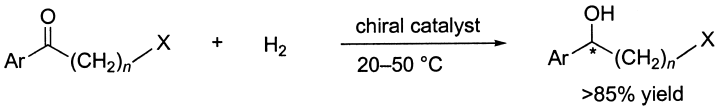
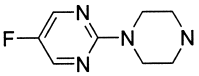


Fig. 32.36 Hydrogenation of α-, β-, or γ-heterosubstituted aromatic ketones.

Ar	*n*	X	Catalyst (SCR) [a]	H_2 [atm]	ee [%]	Config.	TON	TOF [h^{-1}]
C_6H_5	1	$ClNH_3$	$[Rh(nbd)_2]ClO_4$–(*R*)-MOC-BIMOP + $(C_2H_5)_3N$ (1000)	90	93	*R*	1000	6
C_6H_5	1	$ClNH_3$	[Rh{(*S*)-cy,cy-oxo-pronop}-(cod)]BF_4 (200)	50	93	*S*	200	100
C_6H_5	1	$ClC_6H_5CH_2NH_2$	$[RhCl(cod)]_2$–(2*S*,4*S*)-MCCPM + $(C_2H_5)_3N$ (1000)	20	93	*S*	1000	50
3,4-$(OH)_2C_6H_3$	1	$ClCH_3NH_2$	[Rh{(*R*)-(*S*)-bppfoh}(nbd)]-ClO_4 + $(C_2H_5)_3N$ (100)	50	95	*R*	100	0.6
C_6H_5	1	$(CH_3)_2N$	$RuBr_2$[(*S*)-binap] (500)	100	95	*S*	425	18
C_6H_5	1	$(CH_3)_2N$	(*R*,*R*)-**31D** (2000)	8	93	*R*	2000	167
2-naphthyl	1	$(C_2H_5)_2N$	$[RhCl(nbd)]_2$–(*S*,*S*)-DIOP (200)	70	95	+	186	9
C_6H_5	1	$Cl(CH_3)_2NH$	$[Rh(OCOCF_3)$[(*S*)-cp,cp-indonop}]$_2$ (200)	50	>99	*S*	200	11
3-ClC_6H_4	1	$Cl(CH_3)_2NH$	[Rh{(*R*)-cy,cy-oxo-pronop}-(cod)]BF_4 (200)	1	96	*R*	200	11
C_6H_5	1	$Cl(C_2H_5)_2NH$	$[RhCl(cod)]_2$–(2*S*,4*S*)-MCCPM + $(C_2H_5)_3N$ (100000)	20	97	*S*	100000	5000
3-ClC_6H_4	1	C_6H_5CONH	$RuCl_2$[(*S*,*S*)-**1Ab**](dmf)$_n$–$(CH_3)_3CSCH_2CH_2NH_2$ + $(CH_3)_3CONa$ (500)	7	93	*R*	>495	>33
C_6H_5	1	$C_6H_5CO(CH_3)N$	(*R*,*R*)-**31D** (2000)	8	99.8	*R*	2000	250
4-C_6H_5-$CH_2OC_6H_4$	1	C_6H_5CO[3,4-$(CH_3O)_2$-$C_6H_3(CH_2)_2$]N	(*R*,*R*)-**31D** (2000)	8	97	*R*	2000	83
C_6H_5	2	$ClCH_3NH_2$	$[RhCl(cod)]_2$–(2*S*,4*S*)-MCCPM + $(C_2H_5)_3N$ (1000)	30	79.8	*R*	1000	21
C_6H_5	2	$(CH_3)_2N$	(*S*,*S*)-**31D** (10,000) [b]	8	97.5	*R*	10000	2000
C_6H_5	2	$(CH_3)_2N$	(*S*,*SS*)-**31G** (4000)	8	97	*R*	4000	333
2-thienyl	2	$(CH_3)_2N$	(*R*,*R*)-**31D** (2000) [b]	8	92	*S*	2000	286
2-thienyl	2	$(CH_3)_2N$	$RuCl_2$[(*R*,*R*)-bicp](dmf)$_n$–$NH_2C(CH_3)_2CH_2NH_2$ + $(CH_3)_3CONa$ (2000)	7	96	*S*	1800	120
C_6H_5	2	$Cl(CH_3)_2NH$	[Rh{(*S*)-cy,cy-oxo-pronop}-(cod)]BF_4 (200)	50	93 [c]	*R*	180	4
C_6H_5	2	$ClC_6H_5CH_2(CH_3)$-NH_2	$[RhCl(cod)]_2$–(2*S*,4*S*)-MCCPM + $(C_2H_5)_3N$ (1000)	30	90.8	*R*	1000	21
4-FC_6H_4	3	R′ [d]	(*S*,*S*)-**31D** (10000)	8	99	*R*	10000	313

Ar	n	X	Catalyst (SCR) [a]	H_2 [atm]	ee [%]	Config.	TON	TOF [h^{-1}]
C_6H_5	3	$Cl(CH_3)_2NH$	[Rh{(*S*)-cy,cy-oxo-pronop}-(cod)]BF_4 (200)	50 [e]	92	*R*	192	5
C_6H_5	3	$ClC_6H_5CH_2(CH_3)$-NH_2	[RhCl(cod)]$_2$–(2*S*,4*S*)-MCCPM + $(C_2H_5)_3N$ (250)	50	88.4	*R*	250	4
C_6H_5	1	CH_3O	(*R*,*R*)-**31D** (2000)	8	95	*R*	2000	400
4-$CF_3C_6H_4$	1	CH_3O	$RuCl_2$[(*S*,*S*)-**1Ab**](dmf)$_n$–$(CH_3)_3CSCH_2CH_2NH_2$ + $(CH_3)_3CONa$ (500)	7 [f]	97	*R*	>495	>33

a) SCR = substrate : catalyst molar ratio.
b) *trans*-$RuCl_2$(xylbinap)(daipen) is treated with $(CH_3)_3COK$ in 2-propanol prior to hydrogenation.
c) Contaminated with 5% propiophenone.
d) R' = 
e) At 80 °C.
f) At –10 °C.

acetophenone derivatives with an amido group at the α position are hydrogenated with the same catalyst [128]. This method is applied to the synthesis of (*R*)-denopamine, a β_1-receptor agonist used for treating congestive heart failure (the structure is shown in Fig. 32.44) [128]. When 3-(dimethylamino)propiophenone, a base-labile β-amino ketone, is reduced under controlled conditions using an (*S*)-XylBINAP/(*S*)-DAIPEN–Ru catalyst prepared from the $RuCl_2$ complex and a minimum amount of $(CH_3)_3COK$, the *R* amino alcohol is obtained in 97.5% ee and in 96% yield, contaminated with 2% of 1-phenyl-1-propanol, a deamination-derived byproduct [128]. The desired product is obtained quantitatively by reaction with *trans*-RuH(η^1-BH_4)[(*S*)-xylbinap][(*S*,*S*)-dpen] [(*S*,*SS*)-**31G**] under base-free conditions [102]. Similarly, a 2-thienyl derivative is also reduced selectively [129]. The chiral β-amino alcohols are key intermediates for the synthesis of antidepressants (*R*)-fluoxetine and (*S*)-duloxetine (see Fig. 32.44). The γ-amino ketone shown in Figure 32.36 is hydrogenated with (*S*,*S*)-**31D** in basic 2-propanol, giving the *R* alcohol in 99% ee, which is a potent antipsychotic, BMS 181100 (see Fig. 32.44) [128]. Hydrogenation of 2-methoxyacetophenone catalyzed by (*R*,*R*)-**31D** affords the *R* α-methoxy alcohol in 95% ee (Fig. 32.36) [85a]. A Ru catalyst consisting of $RuCl_2$(**1Ab**)(dmf)$_n$, achiral $(CH_3)_3CSCH_2CH_2$-NH_2, and $(CH_3)_3CONa$ effects enantioselective hydrogenation of 2-benzyloxy-amino- and 2-methoxyacetophenone derivatives (Fig. 32.36) [96]. Hydrogenation of 3-dimethylamino-1-(2-thienyl)-1-propanone, a β-amino ketone, with a BICP/$NH_2C(CH_3)_2CH_2NH_2$–Ru catalyst gives the β-amino alcohol in 96% ee [96].

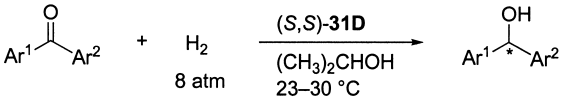


Fig. 32.37 Hydrogenation of diaryl ketones.

Ar^1	Ar^2	SCR[a)]	Yield [%]	ee [%]	Config.	TON	TOF [h^{-1}]
2-$CH_3C_6H_4$	C_6H_5	2000	99	93	*S*	1980	180
2-$CH_3OC_6H_4$	C_6H_5	2000	100	99	*S*	2000	133
2-FC_6H_4	C_6H_5	2000	99	97	*S*	1980	141
2-ClC_6H_4	C_6H_5	20000	99	97	*S*	19800	360
2-BrC_6H_4	C_6H_5	2000	99	96	*S*	1980	152
2-BrC_6H_4	4-$CH_3C_6H_4$	2000	99	98	*S*	1980	132
4-$CH_3OC_6H_4$	C_6H_5	2000	95	35	*R*	1900	146
4-$CF_3C_6H_4$	C_6H_5	2000	99	47	*S*	1980	165
4-$CH_3OC_6H_4$	4-$CF_3C_6H_4$	2000	97	61	–	1940	162
Ferrocenyl[b)]	C_6H_5	2000	100	95	*S*	2000	154

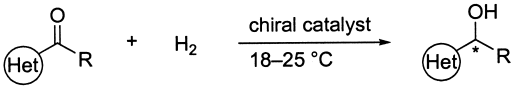
a) SCR = substrate : catalyst molar ratio.
b) (*S*,*S*)-**31A** is used as a catalyst.

32.3.3
Diaryl Ketones

Enantioselective hydrogenation of pro-chiral diaryl ketones requires the electronic or steric differentiation of two otherwise similar aromatic functions. Furthermore, hydrogenolysis of the produced diarylmethanols is to be avoided. Hydrogenation of 2-substituted benzophenones in the presence of an (*S*)-XylBINAP/(*S*)-DAIPEN–Ru complex and $(CH_3)_3COK$ [(*S*,*S*)-**31D**] in 2-propanol provides the diarylmethanol in up to 99% ee (Fig. 32.37) [130]. No detectable diarylmethane is produced under such basic conditions. 2-Substitution of electron-donating and -attracting groups such as CH_3, CH_3O, F, Cl, and Br has a minimal effect on enantioselectivity. Chiral alcohols obtained from 2-methyl- and 2-bromo-4′-methylbenzophenones are easily converted to antihistaminic (*S*)-orphenadrine and (*R*)-neobenodine, respectively (see Fig. 32.44) [130]. Substrates with a substituent at the C3 or C4 positions are hydrogenated with only moderate enantioselectivity. Benzoylferrocene is hydrogenated with an (*S*)-TolBINAP/(*S*)-DAIPEN–Ru catalyst [(*S*,*S*)-**31A**] to afford the *S* alcohol in 95% ee [130].

32.3.4
Heteroaromatic Ketones

General enantioselective hydrogenation of heteroaromatic ketones is achieved by means of the XylBINAP/DAIPEN–Ru complexes and $(CH_3)_3COK$ in 2-propanol. A variety of substrates with an electron-rich and -deficient heteroaromatic func-

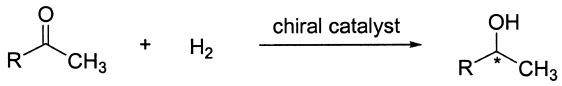


Het = hetero-aryl

Fig. 32.38 Hydrogenation of heteroaromatic ketones.

Het	R	Catalyst (SCR) [a]	H_2 [atm]	Yield [%]	ee [%]	Config.	TON	TOF [h^{-1}]
2-furyl	CH_3	(*R,R*)-**31D** (40 000)	50	96	99	*S*	38 400	3 200
2-furyl	CH_3	(*R,SS*)-**31K** (3000)	5.5	>99	96	*R*	>2 970	>1 188
2-furyl	CH_3	(*S,RR*)-**31M** (5000)	50	99	98	*S*	4 950	990
2-furyl	CH_3	(*R,S,R,S*)-**31X** (100)	30 [b]	83	96	*S*	99	10
2-furyl	n-C_5H_{11}	(*R,R*)-**31D** (2000)	8	100	98	*S*	2 000	167
2-furyl	$(CH_3)_3C$	(*S*)-**31C** (2400)	8	99	97	*R*	2 376	475
2-thienyl	CH_3	(*R,R*)-**31D** (5000)	8	100	99	*S*	5 000	417
2-thienyl	CH_3	(*S,S*)-**31D** (1000)	1	100	99	*R*	1 000	59
2-thienyl	CH_3	$RuCl_2$[(*R,R*)-bicp]-(tmeda)–(*R,R*)-DPEN + KOH (500)	4 [c]	100	93	*S*	500	10
2-thienyl	CH_3	(*S,RR*)-**31M** (5000)	50	98	98	*S*	4 900	980
2-thienyl	$(CH_3)_3C$	(*S*)-**31C** (2100)	8	100	98	*R*	2 100	420
2-(5-chloro)-thienyl	CH_3	$RuCl_2$[(*R,R*)-bicp](dmf)$_n$– $NH_2C(CH_3)_2CH_2NH_2$ + $(CH_3)_3CONa$ (500)	7	>99	94	*S*	>198	>13
3-thienyl	CH_3	(*R,R*)-**31D** (5000)	8	100	99.7	*S*	5 000	1 000
3-thienyl	CH_3	(*S,RR*)-**31K** (3000)	5.5	>99	98	*S*	22 970	2 990
2-(1-methyl)-pyrrolyl	CH_3	(*S,S*)-**31D** (1000)	8	61	97	–	610	31
2-[1-(4-toluene-sulfonyl)]-pyrrolyl	CH_3	(*R,R*)-**31D** (1000)	8 [d]	93	98	*S*	1 000	56
2-thiazolyl	CH_3	(*R,R*)-**31D** (2000) [e]	8	100	96	*S*	2 000	167
2-pyridyl	CH_3	(*R,R*)-**31D** (2000) [e]	8	99.7	96	*S*	1 994	665
2-pyridyl	$(CH_3)_2CH$	(*R,R*)-**31D** (2000)	8	100	94	*S*	2 000	167
3-pyridyl	CH_3	(*R,R*)-**31D** (5000)	8	100	99.6	*S*	5 000	417
3-pyridyl	CH_3	(*R,SS*)-**31K** (1500)	8	>99	99	*R*	>1485	>495
4-pyridyl	CH_3	(*R,R*)-**31D** (5000)	8	100	99.8	*S*	5 000	417
2,6-diacetyl-pyridine		(*R,R*)-**31D** (10 000)	8	99.9	100	*S,S*	9 990	588

a) SCR = substrate : catalyst molar ratio.
b) Reaction in methanol.
c) At –30 °C.
d) Reaction in 1 : 10 DMF : 2-propanol.
e) $B[OCH(CH_3)_2]_3$ is added. Ketone/B = 100.



catalyst:
$RuH(\eta^1\text{-}BH_4)$[(*S*)-tolbinap](pica); (*S*)-**39A**

Fig. 32.39 Hydrogenation of alkyl methyl ketones.

R	Catalyst	SCR[a]	Solvent	H_2 [atm]	Yield [%]	ee [%]	Con-fig.	TON	TOF [h^{-1}]
n-C_4H_9	(*R,S,R,S*)-**31X**	100	CH_3OH	30	96	75	*S*	96	2
$(CH_3)_2$-$CHCH_2$	(*R,S,R,S*)-**31X**	100	CH_3OH	30	66	85	*S*	66	0.9
$(CH_3)_2CH$	(*R,S,R,S*)-**31X**	100	CH_3OH	30	99	84	*S*	99	1
cyclo-C_3H_5	(*S,S*)-**31D**	11 000	$(CH_3)_2CHOH$	10	96	95	*R*	10 560	880
cyclo-C_6H_{11}	(*R,S,R,S*)-**31X**	100	CH_3OH	30	90	92	*S*	90	0.9
cyclo-C_6H_{11}	(*S,S*)-**31D**	10 000	$(CH_3)_2CHOH$	8	99	85	*R*	9 900	990
$(CH_3)_3C$	(*S*)-**31C**	100 000	C_2H_5OH	20	100	98	*S*	100 000	4 167
$(CH_3)_3C$	(*S*)-**39A**	2 000	C_2H_5OH	4	100	97	*S*	2 000	400
$(CH_3)_3C$[b]	(*R*)-**31C**	2 300	C_2H_5OH	5	100	97	*R*	2 300	460
$(CH_3)_3C$	(*R,S,R,S*)-**31X**	100	CH_3OH	30	51	94	*S*	51	0.5
$(CH_3)_3C$	[Rh{(*S,R,R,R*)-tmo-deguphos}-(cod)]BF_4	1 000	$(CH_3)_2CHOH$	73	30	84	*S*	300	288
1-methyl-cyclopropyl	(*S,S*)-**31D**	500	$(CH_3)_2CHOH$	4	96	98	–	480	160
1-adamantyl	(*S*)-**31C**	2 000	C_2H_5OH	5	100	98	*S*	2 000	400

a) SCR = substrate : catalyst molar ratio.
b) 2,2-Dimethyl-3-undecanone.

tion are converted to the chiral alcohols in high ee (Fig. 32.38) [129]. Hydrogenation of 2-acetylfuran with (*R,R*)-**31D** gives (*S*)-1-(2-furyl)ethanol in 99% ee, leaving the furan ring intact. With the same catalyst, 2- and 3-acetylthiophene are reduced in >99% optical yield. Sterically congested 2-pivaloylfuran and 2-pivaloylthiophene are enantioselectively reduced with the TolBINAP/PICA–Ru complex and $(CH_3)_3COK$ (**31C**) in ethanol [99]. Reaction of the substrates with 2-(1-methyl)pyrrolyl or 2-[1-(4-toluenesulfonyl)]pyrrolyl group also gives high enantioselectivity. Under the regular conditions, reaction of 2-acetylthiazol and 2-acetylpyridine do not go to completion, probably due to the high binding ability of the alcoholic products to the catalyst metal center. This problem is solved when $B[OCH(CH_3)_2]_3$ (ketone : Ru : borate = 2000 : 1 : 20) is added as a co-catalyst [129]. The hydrogenation of 3- and 4-acetylpyridine under standard conditions yields the pyridyl alcohols in excellent ee. Double hydrogenation of 2,6-diacetylpyridine in the presence of (*R,R*)-**31D** gives the *S,S* diol in 100% yield out of three possi-

ble stereoisomers. The (*R*)-Xylyl-Phanephos/(*S,S*)-DPEN–Ru catalyst [(*R,SS*)-**31K**] [92] and (*R*)-Xyl-SDP/(*R,R*)-DPEN–Ru catalyst [(*R,RR*)-**31M**] [93] also show excellent performance in this reaction. The *in-situ*-prepared catalyst from $RuCl_2$[(*R,R*)-bicp](tmeda), (*R,R*)-DPEN, and KOH is also usable [131]. A BICP/$NH_2C(CH_3)_2CH_2NH_2$–Ru catalyst promotes hydrogenation of 2-acetyl-5-chlorothiophene to afford the chiral alcohol in 94% ee [96]. Reaction of 2-acetylfuran with the Me-PennPhos–Rh catalyst (**31X**) gives 96% optical yield [106].

32.3.5 Dialkyl Ketones

The enantioselective hydrogenation of simple aliphatic ketones remains difficult because of the lack of general chemistry to differentiate two alkyl groups. The Me-PennPhos–Rh catalyst (**31X**) attains a good optical yield in the hydrogenation of *n*-alkyl methyl ketones (Fig. 32.39) [106]. 2-Hexanone is reduced with (*R,S,R,S*)-**31X** to afford (*S*)-2-hexanol in 75% ee. Sterically demanded pinacolone is reduced with 94% optical yield [106]. The (*S*)-XylBINAP/(*S*)-DAIPEN–Ru complex [(*S,S*)-**31D**] catalyzes the hydrogenation of cyclopropyl methyl ketone and cyclohexyl methyl ketone in basic 2-propanol to give the *R* alcohols in 95% and 85% ee, respectively (Fig. 32.39) [85a, 87]. Pinacolone is efficiently hydrogenated with the (*S*)-TolBINAP/PICA–Ru complex and $(CH_3)_3COK$ [(*S*)-**31C**] in ethanol to afford the *S* alcohol in 98% ee [99]. The reaction completes with an SCR of 100 000. 2,2-Dimethyl-3-undecanone and 1-adamantyl methyl ketone are also hydrogenated enantioselectively. RuH(η^1-BH_4)(tolbinap)(pica) (**39A**) reduces pinacolone under base-free conditions [99]. The TMO-DEGUPHOS–Rh catalyzes hydrogenation of pinacolone in 84% optical yield [132].

Heterogeneous Ni catalysts modified by tartaric acid and NaBr show relatively high enantioselectivity for the hydrogenation of simple aliphatic ketones (Fig. 32.40) [133]. In the presence of an excess amount of pivalic acid, 2-alka-

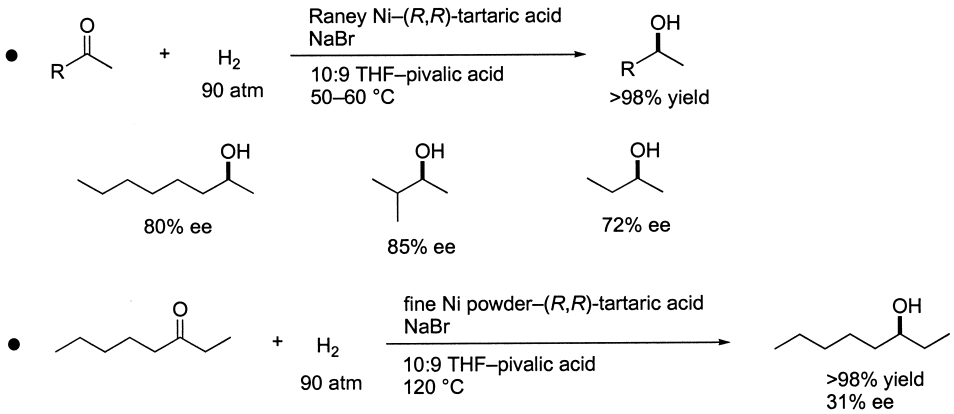


Fig. 32.40 Hydrogenation of aliphatic ketones with the modified Raney Ni.

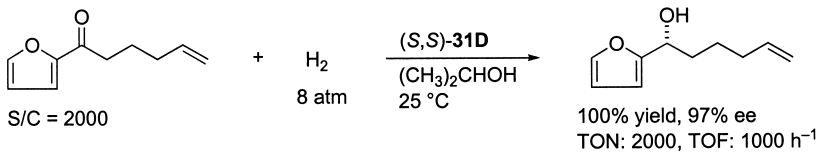


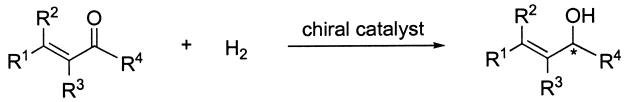
Fig. 32.41 Hydrogenation of an unconjugated enone to the chiral enol.

nones are reduced with the modified Raney Ni catalyst to give the 2-alkanols in up to 85% ee. Even 3-octanone is reduced with 31% optical yield, when the chirally modified fine Ni powder is used as a catalyst in place of a chiral Raney Ni [133 c].

32.3.6 Unsaturated Ketones

The enantioselective hydrogenation of unsaturated ketones to chiral unsaturated alcohols is a difficult subject, because most existing hydrogenation catalysts preferentially reduce olefinic bonds over carbonyl functions. This long-standing problem has been solved by the use of BINAP/chiral 1,2-diamine–Ru catalysts in base-containing 2-propanol [86, 87, 102, 129, 134–136]. As shown in Figure 32.41, 1-(2-furyl)-4-penten-1-one, an unconjugated enone, is hydrogenated with (*S*)-XylBINAP/(*S*)-DAIPEN–Ru and $(CH_3)_3COK$ [(*S,S*)-**31D**] in 2-propanol, yielding the *R* enol in 100% yield and in 97% ee [129]. The olefinic bond is left intact.

Enantioselective hydrogenation of *α,β*-unsaturated ketones affording chiral allylic alcohol is also achieved with the BINAP/1,2-diamine–Ru catalyst system. A variety of allylic alcohols in high optical purity are obtained by reaction with *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] (or the *R*/*R* combination) and K_2CO_3 (**42A**) in 2-propanol (Fig. 32.42) [87]. The use of a relatively weak base, K_2CO_3, effectively prevents the formation of undesired polymeric byproducts. Hydrogenation of benzalacetone (**a**) catalyzed by (*S,S*)-**42A** gives (*R*)-(*E*)-4-phenyl-3-buten-2-ol in 97% ee. No saturation of the olefinic bond was observed. Hydrogenation of (*E*)-6-methyl-2-hepten-4-one (**g**) with (*R,R*)-**42A** affords the *S* allylic alcohol in 90% ee [87], which is a synthetic intermediate of the *α*-tocopherol (vitamin E) side chain (see Fig. 32.44). Reaction of 1-acetylcycloalkenes (**i–k**) results in the allylic alcohols in >99% ee. Highly base-sensitive 3-nonene-2-one (**e**) is hydrogenated with (*S,S*)-**42A** in basic 2-propanol under high dilution conditions ([ketone]= 0.1 M) to give (*R*)-3-none-2-ol in high yield [87]. When the reaction is conducted with *trans*-$RuH(\eta^1\text{-}BH_4)$[(*S*)-xylbinap][(*S,S*)-dpen] [(*S,SS*)-**31G**] without addition of base, the desired *R* allylic alcohol is quantitatively obtained, even with a 2.0 M substrate concentration [102]. (*R*)-Xylyl-PhanePhos/(*S,S*)-DPEN–Ru catalyst [(*R,SS*)-**31K**] [92] and (*S*)-Xyl-SDP/(*R,R*)-DPEN–Ru catalyst [(*S,RR*)-**31M**] [93] are also useful for this reaction. The olefinic *t*-butyl ketones (**c** and **f**) are smoothly hydrogenated with the TolBINAP/PICA–Ru complex (**31C**) in basic ethanol [99].



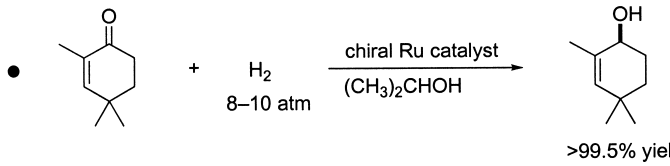
a: $R^1 = C_6H_5$; $R^2 = R^3 = H$; $R^4 = CH_3$
b: $R^1 = C_6H_5$; $R^2 = R^3 = H$; $R^4 = (CH_3)_2CH$
c: $R^1 = C_6H_5$; $R^2 = R^3 = H$; $R^4 = (CH_3)_3C$
d: R^1 = 2-thienyl; $R^2 = R^3 = H$; $R^4 = CH_3$
e: $R^1 = n\text{-}C_5H_{11}$; $R^2 = R^3 = H$; $R^4 = CH_3$
f: $R^1 = n\text{-}C_6H_{13}$; $R^2 = R^3 = H$; $R^4 = (CH_3)_3C$
g: $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = (CH_3)_2CHCH_2$
h: $R^1 = R^2 = R^4 = CH_3$; $R^3 = H$
i: R^1–$R^3 = (CH_2)_4$; $R^2 = H$; $R^4 = CH_3$
j: R^1–$R^3 = (CH_2)_5$; $R^2 = H$; $R^4 = CH_3$
k: R^1–$R^3 = (CH_2)_3$; $R^2 = R^4 = CH_3$
l: R^1 = 2,6,6-trimethylcyclohexenyl; $R^2 = R^3 = H$; $R^4 = CH_3$ (β-ionone)

catalyst:
trans-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] + K_2CO_3; (*S*,*S*)-**42A**
trans-$RuCl_2$[(*S*)-xylbinap][(*S*,*S*)-dpen] + K_2CO_3; (*S*,*SS*)-**42B**

Fig. 32.42 Hydrogenation of α,β-unsaturated ketones.

Substrate	Catalyst	SCR[a]	H_2 [atm]	Yield [%]	ee [%]	Config.	TON	TOF [h^{-1}]
a	(*S*,*S*)-**42A**	100000	80	100	97	*R*	100000	2500
a	(*S*,*S*)-**42A**	10000	10	100	96	*R*	10000	667
a	(*R*,*SS*)-**31K**	3000	5.5	>99	97	*R*	>2970	>2970
a	(*S*,*RR*)-**31M**	5000	50	100	96	*S*	5000	1667
b	(*S*,*S*)-**42A**	2000	8	100	86	*R*	2000	100
c	(*S*)-**31C**	2050	5	100	97	*S*	2050	410
d	(*R*,*R*)-**42A**	5000	8	100	91	*S*	5000	714
e	(*S*,*S*)-**31D**	2000	8	98	97	*R*	1960	131
e	(*S*,*SS*)-**31G**	4000	8	95	99	*R*	3800	238
f[b]	(*R*)-**31C**	2040	8	99.6[b)]	98[c)]	*R*[c)]	2032	406
g	(*R*,*R*)-**42A**	2000	10	100	90	*S*	2000	54
h	(*S*,*SS*)-**42B**	10000	8	100	93	*R*	10000	625
i	(*S*,*S*)-**31D**	10000	10	99	100	*R*	9900	619
j	(*S*,*S*)-**31D**	2000	8	99.9	99	*R*	1998	285
k	(*S*,*S*)-**31D**	13000	10	100	99	*R*	13000	867
l	(*S*,*S*)-**42A**	10000	8	99	94	*R*	9900	450

a) SCR = substrate : catalyst molar ratio.
b) A 5 : 1 *E*/*Z* mixture.
c) Data of the *E* alcohol.



Ru catalyst	S/C	temp, °C	% ee	confign	TON	TOF, h^{-1}
(*R*,*SS*)-**31B**	500	0	96	*S*	500	83
(*R*,*SS*)-**31B**	10,000	28	94	*S*	10,000	208
(*S*,*R*)-**34B**	10,000	25	96	*R*	9,950	1421

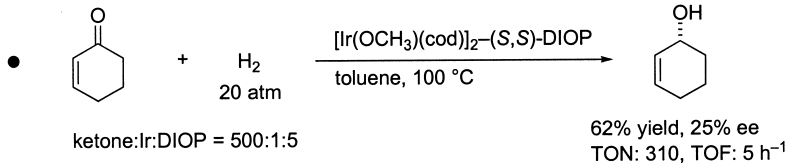


Fig. 32.43 Hydrogenation of 2-cyclohexenones.

Hydrogenation of 2,4,4-trimethyl-2-cyclohexenone, a cyclic enone, with (*R*)-TolBINAP/(*S*,*S*)-DPEN–Ru [(*R*,*SS*)-**31B**] (not (*R*,*RR*)-**31B**) in basic 2-propanol affords the *S* allylic alcohol in 96% ee (Fig. 32.43) [135, 136]. (*R*,*RR*)- or (*S*,*SS*)-**31B** gives lower reactivity and enantioselectivity. The (*S*)-TolBINAP/(*R*)-IPHAN–Ru complex and $(CH_3)_3COK$ [(*S*,*R*)-**34B**] is also an excellent catalyst for hydrogenation of the cyclic enone [111]. The allylic alcohol product is a useful intermediate for the synthesis of carotenoid-derived odorants and other bioactive terpenes. Hydrogenation of 2-cyclohexenone in the presence of the (*S*,*S*)-DIOP–Ir catalyst gives (*R*)-2-cyclohexenol in 25% ee (Fig. 32.43) [137].

Enantioselective hydrogenation of simple ketones catalyzed by BINAP/chiral diamine–Ru complexes is applied to the synthesis of biologically active compounds and a chiral phosphine ligand. Some examples are shown in Figure 32.44 [85a, 87, 102, 128, 130, 135].

32.3.7
Kinetic Resolution and Dynamic Kinetic Resolution

Hydrogenation of racemic 2-isopropylcyclohexanone with *trans*-RuH(η^1-BH_4)[(*S*)-xylbinap][(*R*,*R*)-dpen] [(*S*,*RR*)-**31G**] in 2-propanol selectively consumes the *R* ketone, resulting in the *S* substrate in 91% ee and (1*R*,2*R*)-2-isopropylcyclohexanol in 85% ee (*cis*:*trans*=100:0) at 53% conversion (Fig. 32.45) [102]. The k_{fast}/k_{slow} reaches 28. Similarly, racemic 2-methoxycyclohexanone is hydrogenated with (*S*,*SS*)-**31G** to give the unreacted *R* ketone in 94% ee and the 1*R*,2*S* alcohol in 91% ee (*cis*:*trans*=100:0) at 53% conversion [102]. The k_{fast}/k_{slow} is 38.

Enantiomers of 2-monosubstituted cycloalkanones equilibrate in base-containing alcoholic media. When one of the two isomers is preferably hydrogenated

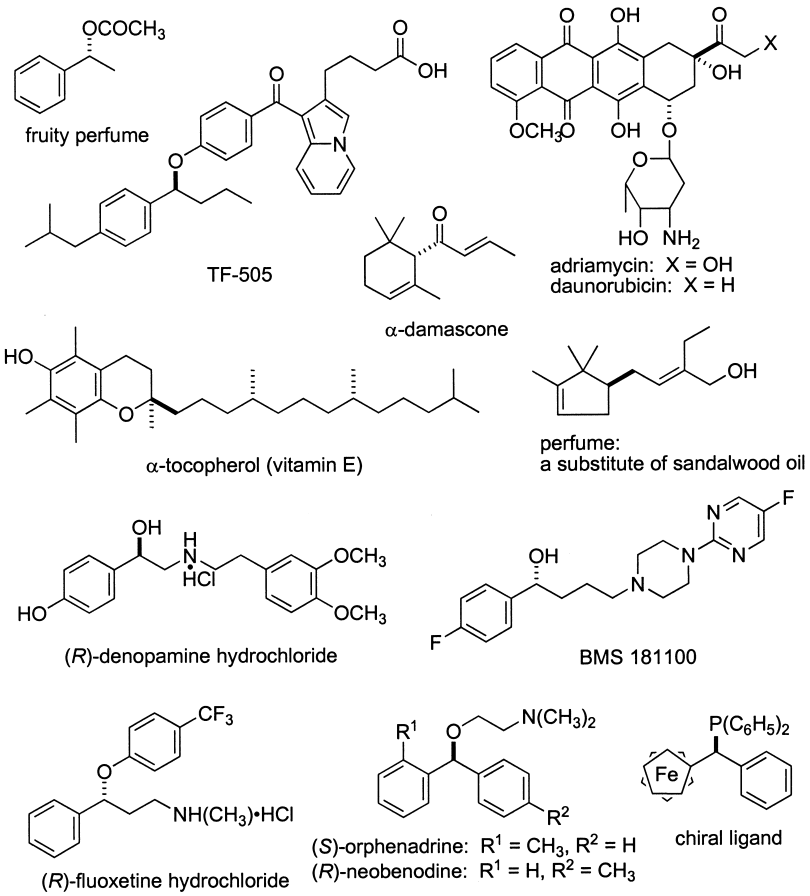


Fig. 32.44 Examples of biologically active compounds and a chiral ligand obtainable through hydrogenation of simple ketones catalyzed by BINAP/chiral diamine–Ru complexes.

over the other one with high diastereoselectivity, single isomeric alcohols among four possible stereoisomers are obtained through dynamic kinetic resolution (see Section 32.2.4). Indeed, hydrogenation of racemic 2-phenylcyclohexanone (**c**) with *trans*-$RuCl_2$[(*R*)-tolbinap][(*R*,*R*)-dpen] and $(CH_3)_3COK$ [(*R*,*RR*)-**31B**] ([$(CH_3)_3COK$] = 18 mM) in 2-propanol gives (1*S*,2*S*)-2-phenylcyclohexanol (*cis*:*trans* = 100:0) in 99.6% ee and in 100% yield (Fig. 32.46) [138]. The electronic property of aryl substituents has only a minimal effect on the stereoselectivity. With the same catalyst, 1-naphthyl- and 2-naphthyl-substituted cyclohexanones (**f** and **g**) are selectively converted to the 1*S*,2*S* alcohols. When (*S*)-BINAP/(*R*,*R*)-DPEN–Ru catalyst ([KOH] = 32 mM) is used for hydrogenation of 2-isopropylcyclohexanone (**b**), the 1*R*,2*R* alcohol (*cis*:*trans* = 99.8:0.2) with 93% ee is obtained [139]. Reaction of 2-methoxycyclohexanone (**h**) with (*S*)-XylBINAP/(*S*,*S*)-DPEN–Ru cata-

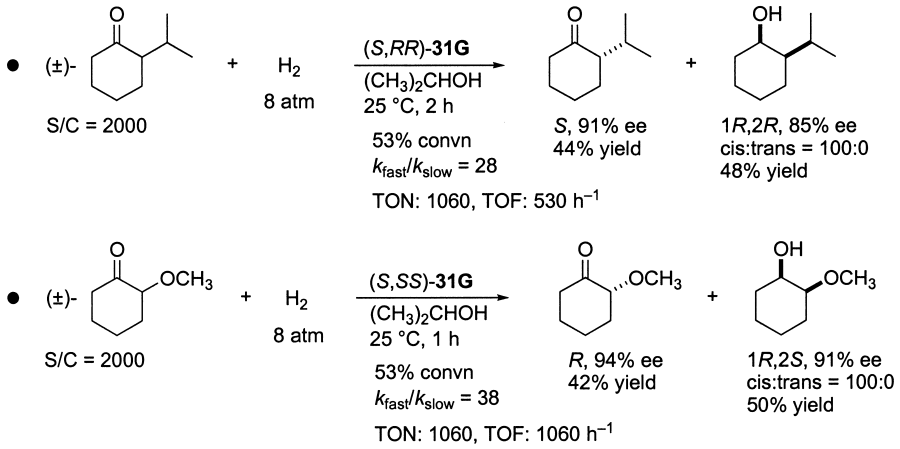
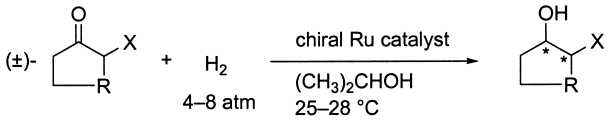


Fig. 32.45 Kinetic resolution of racemic 2-substituted cyclohexanones via hydrogenation with RuH(η^1-BH_4)(xylbinap)(d-pen).

lyst in basic 2-propanol at 5 °C gives the 1*R*,2*S* alcohol in 99% ee (*cis*:*trans* = 99.5 : 0.5) [140]. The chiral alcohol is a key intermediate for the synthesis of the potent antibacterial sanfetrinem and its analogues (Fig. 32.47) [140]. In the presence of (*S*)-XylBINAP/(*R*)-DAIPEN–Ru, 2-(*tert*-butoxycarbonylamino)cyclohexanone (**i**) is also converted to the 1*S*,2*R* amino alcohol in 82% ee (*cis*:*trans* = 99 : 1) (Fig. 32.46) [87]. Hydrogenation of 2-phenylcyclopentanone (**a**), a lower homologue, catalyzed by (*R*)-XylBINAP/(*R*)-DAIPEN–Ru complex and $(CH_3)_3COK$ [(*R*,*R*)-**31D**] ([$(CH_3)_3COK$] = 50 mM) affords (1*S*,2*S*)-2-phenylcyclopentanol (*cis*:*trans* = 100 : 0) in 98% ee [138]. Reaction of 2-phenylcycloheptanone (**j**) with the (*R*)-TolBINAP/(*S*,*S*)-DPEN combined catalyst (*R*,*SS*)-**31B** gives (1*S*,2*S*)-2-phenylcycloheptanol (*cis*:*trans* = 100 : 0) in 95% ee [138]. When (*R*,*RR*)-**31B** is used for this reaction, the 1*R*,2*S* alcohol is obtained in only 84% ee (*cis*:*trans* = 100 : 0). The hydrogenation catalyzed by **31B** is applicable to the azacyclohexanone derivatives, **k** and **l** (Fig. 32.46). Reaction of **k** with the *R*,*RR* catalyst gives the 2*S*,3*S* product (*cis*:*trans* = 96 : 4) in 96% ee. This chiral compound can be used for the synthesis of hNK_1 antagonist L-733,060 (Fig. 32.47) [138]. The 3-methoxyphenyl ketone **l** is reduced with the *S*,*SS* catalyst to yield the 3*S*,4*R* alcohol (*cis*:*trans* = > 99 : 1) in 97% ee. This product serves as a synthetic intermediate of (–)-precramol, a D_2/D_3-auto and sigma receptor agonist (Fig. 32.47) [138].

Hydrogenation of racemic 2-phenylpropiophenone, an acyclic chiral ketone, with the (*S*)-XylBINAP/(*S*)-DAIPEN–Ru complex and $(CH_3)_3COK$ [(*S*,*S*)-**31D**] ([$(CH_3)_3COK$] = 2 mM) in 2-propanol gives the 1*R*,2*R* alcohol (*syn*:*anti* = 99 : 1) in 96% ee (Fig. 32.48) [85 a].



a: R = CH_2; X = C_6H_5
b: R = $(CH_2)_2$; X = $(CH_3)_2CH$
c: R = $(CH_2)_2$; X = C_6H_5
d: R = $(CH_2)_2$; X = 4-$CH_3OC_6H_4$
e: R = $(CH_2)_2$; X = 4-$CF_3C_6H_4$
f: R = $(CH_2)_2$; X = 1-naphthyl
g: R = $(CH_2)_2$; X = 2-naphthyl
h: R = $(CH_2)_2$; X = CH_3O
i: R = $(CH_2)_2$; X = $(CH_3)_3COCONH$
j: R = $(CH_2)_3$; X = C_6H_5
k: R = $CH_2N(CH_2C_6H_5)$; X = C_6H_5
l: R = N(*n*-C_3H_7)CH_2; X = 3-$CH_3OC_6H_4$

Fig. 32.46 Hydrogenation of racemic 2-substituted cyclohexanones through dynamic kinetic resolution catalyzed by BINAP/chiral diamine–Ru complexes with base.

Ketone [M][a]	Catalyst (SCR)[b]	Base [mM]	Yield [%]	dr[c]	*cis* alcohol		TON	TOF [h^{-1}]
					ee [%]	Config.		
a (0.5)	(*R,R*)-**31D** (2000)	50	100	100:0	98	1*S*,2*S*	2000	21
b (0.8)	$RuCl_2$[(*S*)-binap](dmf)$_n$–(*R,R*)-DPEN + KOH (500)	32	100	99.8:0.2	93	1*R*,2*R*	500	45
c (0.5)	(*R,RR*)-**31B** (100000)	18	100	100:0	99.6	1*S*,2*S*	100000	2083
d (0.5)	(*R,RR*)-**31B** (2000)	5	100	100:0	99.5	1*S*,2*S*	2000	500
e (0.5)	(*R,RR*)-**31B** (2000)	6	99.9	99.9:0.1	98	1*S*,2*S*	1998	500
f (0.5)	(*R,RR*)-**31B** (2000)	9	>99	98:2	93	1*S*,2*S*	>1980	>124
g (0.5)	(*R,RR*)-**31B** (2000)	10	>99	>99:1	>99	1*S*,2*S*	>1980	>495
h (–[d])	$[NH_2(C_2H_5)_2][\{RuCl[(S)$-xylbinap$]_2(\mu$-Cl$)_3\}$–(*S,S*)-DPEN + KOH (1000)[e]	–[d]	>99.9	99.5:0.5	99	1*R*,2*S*	>999	50
i (0.2)	*trans*-$RuCl_2$[(*S*)-xylbinap]-[(*R*)-daipen] + KOH (300)	133	98	99:1	82	1*S*,2*R*	294	59
j (0.5)	(*R,SS*)-**31B** (2000)	25	100	100:0	95	1*S*,2*S*	2000	83
k (0.125)	(*R,RR*)-**31B** (500)	19	100	96:4	96	2*S*,3*S*	500	25
l (0.125)	(*S,SS*)-**31B** (500)	25	100	>99:1	97	3*S*,4*R*	500	21

a) Concentration of substrate.
b) SCR = substrate : catalyst molar ratio.
c) *Cis* : *trans* diastereomeric ratio.
d) Not reported.
e) Under 50 atm H_2 at 5 °C.

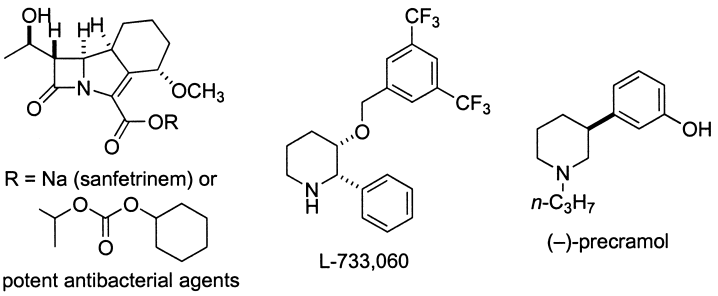


Fig. 32.47 Biologically active compounds achievable by BINAP/1,2-diamine–Ru-catalyzed hydrogenation of 2-substituted cyclohexanones through dynamic kinetic resolution.

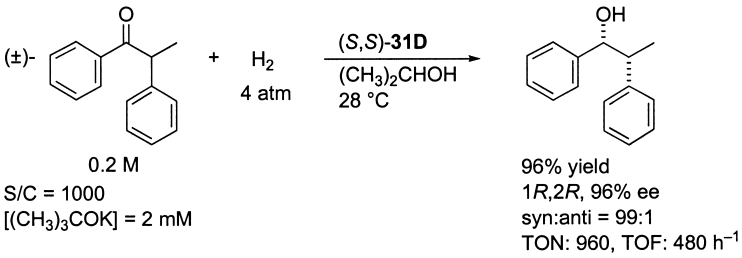


Fig. 32.48 Hydrogenation of racemic 2-phenylpropiophenone through dynamic kinetic resolution.

32.3.8
Enantioselective Activation and Deactivation

Although the hydrogenation of prochiral ketones with racemic catalysts gives racemic alcohols, the reactivity of two enantiomeric catalysts differs in a nonracemic environment. Thus, the addition of an appropriate chiral activator to a racemic metal complex can provide an enantioselective catalyst. A racemic $RuCl_2$(tolbinap)$(dmf)_n$ is a poor catalyst for the hydrogenation of 2,4,4-trimethyl-2-cyclohexenone. The addition of an equimolar amount of (*S,S*)-DPEN to the Ru complex promotes the reaction in a 7 : 1 2-propanol : toluene mixture containing KOH to give (*S*)-2,4,4-trimethyl-2-cyclohexenol in 95% ee (Fig. 32.49) [136]. This high ee-value, close to 96%, is obtainable in the hydrogenation catalyzed by an optically pure (*R*)-TolBINAP/(*S,S*)-DPEN–Ru complex under otherwise identical conditions [135, 136]. On the other hand, the *R,RR* combination gives the *R* alcohol in only 26% ee. The stereoselective outcome depends heavily on the structures of the diphosphine, diamine, and ketonic substrates. The (±)-TolBINAP/(*S,S*)-DPEN–Ru-catalyzed hydrogenation of 2′-methylacetophenone, an acyclic aromatic ketone, gives the *R* alcohol in 90% ee (Fig. 32.49) [136].

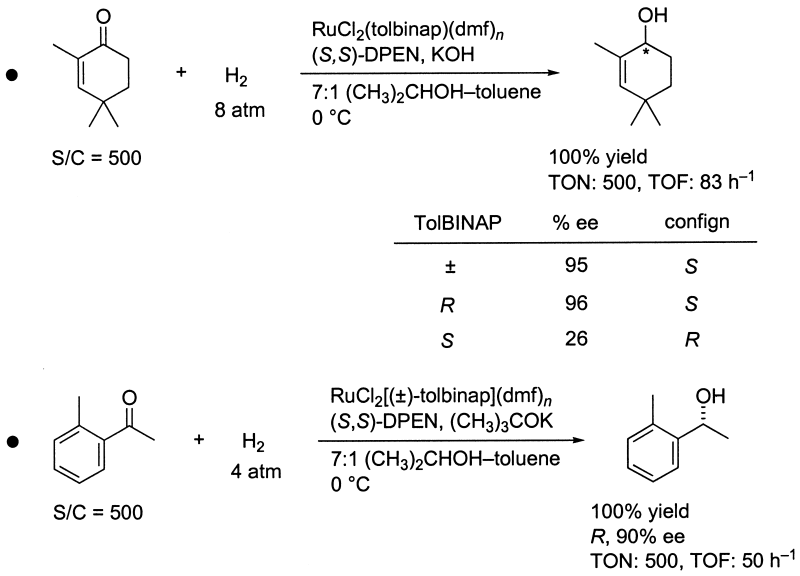


Fig. 32.49 Hydrogenation of ketones catalyzed by racemic BINAP–Ru complexes and (*S*,*S*)-DPEN: asymmetric activation.

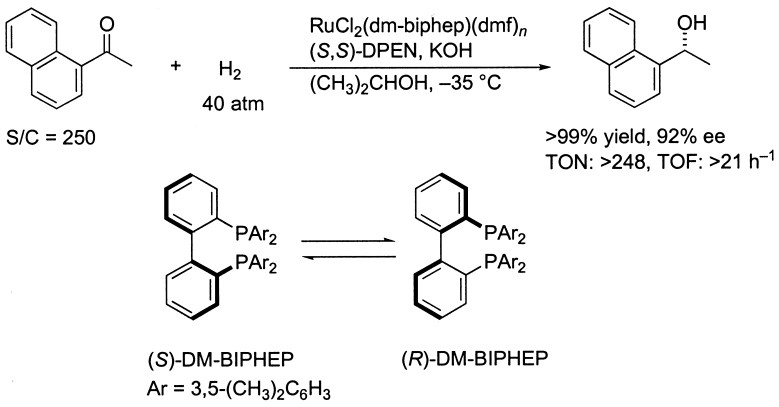


Fig. 32.50 Hydrogenation of 1-acetonaphthone with a DM-BIPHEP/(*S*,*S*)-DPEN–Ru catalyst.

DM-BIPHEP, a conformationally flexible diphosphine, exists as an equilibrium mixture of the *R* and *S* isomers (Fig. 32.50) [141]. Addition of an equimolar amount of (*S*,*S*)-DPEN to $RuCl_2$(dm-biphep)$(dmf)_n$ forms a 3:1 mixture of (*S*)-DM-BIPHEP/(*S*,*S*)-DPEN–$RuCl_2$ complex and the *R*,*SS* diastereoisomer. The major *S*,*SS* complex gives a more active and enantioselective catalyst for the hydro-

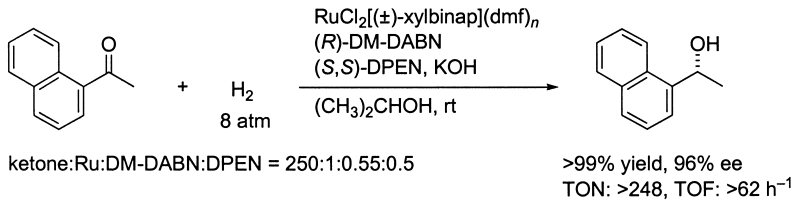


Fig. 32.51 Hydrogenation of 1-acetonaphthone with a (±)-Xyl-BINAP/(*R*)-DM-DABN/(*S*,*S*)-DPEN–Ru catalyst.

genation of acyclic aromatic ketones. Hydrogenation of 1-acetonaphthone with the DM-BIPHEP/(S,S)-DPEN–Ru complex and KOH in 2-propanol at –35 °C gives the *R* alcohol in 92% ee.

(*R*)-DM-DABN, a chiral aromatic diamine, interacts preferentially with $RuCl_2$[(*R*)-xylbinap](dmf)$_n$ over the *S* isomer affording the less-reactive $RuCl_2$[(*R*)-xylbinap][(*R*)-dm-dabn] for hydrogenation of aromatic ketones [142]. Combined use of the enantiomer-selective deactivation and the asymmetric activation described above (see Fig. 32.49) results in a highly enantioselective hydrogenation of aromatic ketones using a racemic XylBINAP–$RuCl_2$ complex. 1′-Acetonaphthone is hydrogenated with a catalyst consisting of $RuCl_2$[(±)-xylbinap](dmf)$_n$, (*R*)-DM-DABN, (*S*,*S*)-DPEN, and KOH in a 1:0.55:0.5:2 ratio to give the *R* alcohol in 96% ee.

Abbreviations

ee enantiomeric excess
TOF turnover frequency
TON turnover number

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