33
Rhodium-Catalyzed Enantioselective Hydrogenation of Functionalized Ketones

André Mortreux and Abdallah Karim

This chapter is dedicated to the memory of Professors Francis Petit and Hidemasa Takaya, two friends who have been pioneers in the field of homogeneous catalysis and enantioselective catalysis.

33.1
Introduction

Enantioselective hydrogenation, using molecular hydrogen to reduce prochiral olefins, ketones, and imines, has become one of the most efficient, practical, and atom-economical methods for the construction of chiral compounds [1–3]. Since the early 1970s, significant attention has been devoted to the discovery of new asymmetric catalysts, in which transition metal complexes modified by chiral phosphorous ligands have emerged as preferential catalysts for asymmetric hydrogenation. Thousands of efficient chiral phosphorous ligands with diverse structures have been developed for their application to asymmetric hydrogenation. Indeed, many represent the key step in industrial processes for the preparation of enantiomerically pure compounds. Consequently, numerous reviews have been devoted to the application of enantioselective catalysis in that context [4, 5].

In this chapter, we will focus on the rhodium-catalyzed hydrogenation of functionalized ketones and the development of chiral phosphorous ligands for this process. Although there are other chiral phosphorous ligands which are effective for ruthenium-, iridium-, platinum-, titanium-, zirconium-, and palladium-catalyzed hydrogenation, they will not be discussed here. For details of these chemistries, the reader should refer to other chapters of this book.

The Handbook of Homogeneous Hydrogenation.
Edited by J. G. de Vries and C. J. Elsevier

ISBN: 978-3-527-31161-3

33.2
Basic Principles of Ketone Hydrogenation on Rhodium Catalysts

In contrast to olefins, the hydrogenation of ketones on rhodium–phosphine complexes requires the presence of rather basic ligands, where either the classical aromatic groups in PPh_2 moieties have been changed or hydrogenated into PCy_2, or via synthesis involving the introduction of phosphorous–alkyl functions at some stage of the chiral ligand synthesis. This was first recognized by Schrock and Osborn, who found that the *cationic* catalytic precursors $[RhH_2\{P(C_6H_5)(CH_3)_2\}_2L_2]X$ (L = solvent, $X = PF_6^-$ or ClO_4^-) reduce acetone under 1 atm of H_2 in the presence of a small amount of water [6]. The same trend was observed later by Fujitsu, where the carbonyl group of *α,β*-unsaturated ketones was chemoselectively reduced on peralkyl-phosphine cationic rhodium system at 30 °C and atmospheric hydrogen pressure [7]. Tani and Otsuka achieved hydrogenation of ketonic substrates using a cationic rhodium complex with a fully alkylated bidentate diphosphane [8a]. In each of these cases, the high basicity of the ligands [9] increases the electron density of the rhodium center so that the overall reaction rate is accelerated [8a]. The same is true when using *covalent* catalytic precursors such as $HRh(PCy_3)_3$ [7].

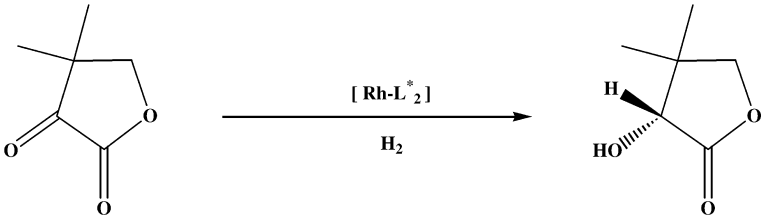
As a consequence of these preliminary results obtained with achiral ligands (and even when aryl-phosphorous chiral ligands were used in early studies), the objectives of many research groups have been to develop chiral ligands bearing alkyl substituents at phosphorus. In general, this allows the provision of a high reactivity at room temperature, which is often a prerequisite to obtaining and/or to improving enantioselectivities. In this chapter, an attempt will be made to describe most of the investigations conducted in this field, and the text will be devoted to ketoesters, -amides and -amines, most of which are suitable for the synthesis of chiral alcohols that can be used either directly as biologically active compounds or as chiral synthons valuable in the pharmaceutical industry.

33.3
Enantioselective Hydrogenation of Ketoesters

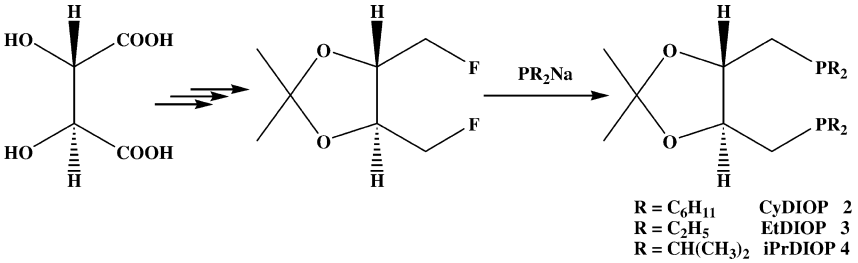
33.3.1
Enantioselective Hydrogenation of Ketopantoyllactone (KPL)

Among ketoesters, tremendous efforts have been devoted to the hydrogenation of dihydro-4,4-dimethyl-2,3-furandione (KPL), not only as a model reaction but also because the product *R*(–)-pantolactone is a key intermediate in the synthesis of vitamin B_5 and coenzyme A (Scheme 33.1).

One of the first investigations related to this chemistry reported the use of a ligand which was developed by Achiwa and Ojima during the late 1970s, and was derived from L-hydroxyproline, a natural amino acid, However, for hydrogenation using this diphenylphosphino-substituted bidentate ligand, BPPM (**1**),



Scheme 33.1 Hydrogenation of ketopantoyllactone.

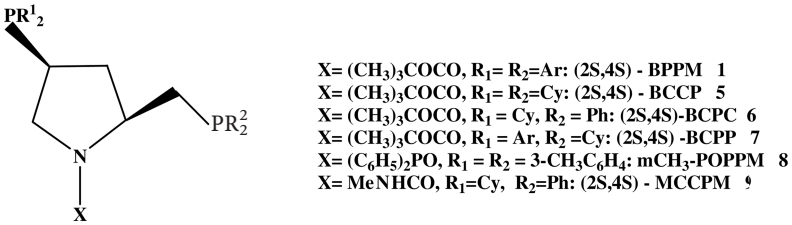


Scheme 33.2 DIOP-derived peralkyl ligands.

rather harsh reaction conditions (50 °C, 50 bar) were required, and the product was obtained with 87% ee [10].

Earlier studies conducted by Tani had confirmed the role of the basicity of the ligand in terms of activity, upon using dicyclohexyl, diethyl and diisopropyl modified DIOP **2**, **3**, and **4** (Scheme 33.2) for ketone hydrogenation [11]. Details of their use in KPL hydrogenation were published initially by Yamamoto, but the ee-values obtained were not very high (e.g., 45% with **2**) [12].

These investigations were followed by the synthesis of a series of new ligands derived again from L-hydroxyproline. Within this series, a fine tuning of electronic and steric effects was made by variation of the substituents on both phosphorus atoms, using the same ligand backbone (Scheme 33.3). BCCP **5** was synthesized and applied by Tani [11c], and also used by Achiwa, who prepared mixed alkyl-aryl diphosphine ligands, leading to highly dissymmetric bidentates giving rise either to highly suitable ligands in terms of activity *and* enantioselectivity, or to others which are clearly of minimal use for this reaction (e.g., compare BCPM and BCPP in Table 33.1) [13].



Scheme 33.3 L-Hydroxyproline-derived bidentate ligands.

Table 33.1 Catalytic results on rhodium-catalyzed ketopantoyllactone hydrogenation.[a)]

Catalyst/ligand	SCR[b)]	Reaction conditions [Solvent; temp., H_2 pressure, time]	ee [%] (config.)	Reference
[RhCl(2*S*,4*S*)-BPPM]$_2$/**1**	100	C_6H_6, 30 °C, 50 atm, 45 h	87 (*R*)	10b
[RhCl(*R*)-Cy-DIOP]$_2$/**2**	50	C_6H_6-EtOH(3/1), r.t., 15 atm, 15 h	45 (*R*)	12
[Rh(*R*)-*i*Pr-DIOP(NBD)]$^+$ClO4$^-$/**4**	200	EtOH, r.t., 1 atm, 1 h	7 (*S*)	11
[RhCl(*R*)-*i*Pr-DIOP]$_2$/**4**	200	C_6H_6, 35 °C, 1 atm, 1 h	54 (*R*)	11
[RhCl(2*S*,4*S*)-BCCP]$_2$/**5**	200	THF, 50 °C, 50 atm, 45 h	66 (*S*)	10
[RhCl(2*S*,4*S*)-BCCP]$_2$/**5**	10000	THF, 50 °C, 50 atm, 45 h	61 (*S*)	13
[RhCl(2*S*,4*S*)-BCPM]$_2$/**6**	10000	THF, 50 °C, 50 atm, 45 h	90 (*R*)	13
[RhCl(2*S*,4*S*)-BCPP]$_2$/**7**	1000	THF, 50 °C, 50 atm, 45 h	9 (*R*)	13
[RhCl(2*S*,4*S*)-*m*-MePOPPM]/**8**	150000	PhMe, 40 °C, 12 atm	95 (*R*)	14
[RhCl(*S*)-Ph,Ph-ProNOP]$_2$/**10**	200	PhMe, 50 °C, 50 atm, 18 h	60 (*R*)	15a
[RhCl(*S*)-Cy,Cy-ProNOP]$_2$/**11**	200	PhMe, 20 °C, 1 atm, 1 h,	47 (*R*)	15b
[RhCl(*S*)-Cp,Cp-ProNOP]$_2$/**12**	200	PhMe, 20 °C, 1 atm, 1 h	76 (*R*)	15b
[RhCl(*S*)-Cp,Cp-ProNOP]$_2$/**12**	10000	PhMe, 70 °C, 50 atm, 3 h	77 (*R*)	15b
[RhCl(*S*)-Cp,Cp-isoAlaNOP]$_2$/**13**	200	PhMe, 20 °C, 1 atm, 20 min	89 (*S*)	15e
[RhCl(*S*)-Ph,Cp-isoAlaNOP]$_2$/**14**	200	PhMe, 20 °C, 1 atm, 12 h	81 (*R*)	15e
[RhCl(*S*)-Cy,Cy-oxoProNOP]$_2$/**15**	200	PhMe, 20 °C, 1 atm, 2 h	96.6 (*R*)	15e
[Rh(CF_3CO_2)(*S*)Cy,Cy-oxoProNOP]$_2$/**15**	200	PhMe, 20 °C, 1 atm, 5 min	97.7 (*R*)	15e
[RhI(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	200	PhMe, 20 °C, 1 atm, 1 h	98 (*R*)	15e
[Rh(CF_3CO_2)(*S*)Cp,Cp-oxoProNOP]$_2$/**16**	200	PhMe, 20 °C, 1 atm, 5 min	98.7 (*R*)	15e
[Rh(CF_3CO_2)(*S*)Cp,Cp-oxoProNOP]$_2$/**16**	70000	PhMe, 40 °C, 40 atm, 24 h	96 (*R*)	15e
[Rh(CF_3CO_2)(*S*)-Cp,Cp-IndoNOP]$_2$/**18**	200	PhMe, 20 °C, 1 atm, 45 min	>99 (*R*)	15o
[Rh(CF_3CO_2)(*S*)-Cp,Cp-IndoNOP]$_2$/**18**	5000	PhMe, 20 °C, 1 atm, 5 h	97 (*R*)	15o
[Rh(CF_3CO_2)*syn*-(*S*,*S*)-Cr(CO)$_3$-Cp, Cp-IndoNOP]$_2$/**19**	200	PhMe, 20 °C, 1 atm, 1 h	>99 (*R*)	15o
[Rh(CF_3CO_2)*anti*-(*R*,*S*)-Cr(CO)$_3$-Cp, Cp-IndoNOP]$_2$/**20**	200	PhMe, 20 °C, 1 atm, 90 min	84 (*R*)	15o
[Rh(CF_3CO_2)(*S*)-Cp,Cp-QuinoNOP]$_2$/**21**	200	PhMe, 20 °C, 50 atm, 20 min	95 (*R*)	15p
[Rh(CF_3CO_2)*syn*-(*S*,*S*)-Cr(CO)$_3$-Cp, Cp-QuinoNOP]$_2$/**22**	200	PhMe, 20 °C, 50 atm, 30 min	85 (*R*)	15p
[Rh(CF_3CO_2)*anti*-(*R*,*S*)-Cr(CO)$_3$-Cp, Cp-QuinoNOP]$_2$/**23**	200	PhMe, 20 °C, 50 atm, 30 min	87 (*R*)	15p
[Rh(CF_3CO_2)Ph-MannOP]$_2$/**24**	200	PhMe, 50 °C, 50 atm, 19 h	44 (*S*)	18
[Rh(CF_3CO_2)Cp-MannOP]$_2$/**25**	200	PhMe, 20 °C, 50 atm, 4 h	80 (*R*)	18
[Rh(CF_3CO_2)Cy MannOP]$_2$/**26**	200	PhMe, 20 °C, 1 atm, 2 h	84 (*R*)	18
[RhCl(*S*)-Ph,Ph-ProNN′P]$_2$/**27**	200	PhMe, 50 °C, 50 atm, 18 h	33 (*R*)	15h
[RhCl(*S*)-Cp,Cp-ProNN′P]$_2$/**29**	200	PhMe, 20 °C, 1 atm, 12 min	70 (*S*)	15h
[RhCl(*S*)-Cy,Cy-ProNN′P]$_2$/**29**	200	PhMe, 20 °C, 1 atm, 7 h	69 (*S*)	15h
[RhCl(*S*)-Cp,Ph-ProNN′P]$_2$/**30**	200	PhMe, 20 °C, 1 atm, 8 h	80 (*S*)	15h
[RhCl(*S*)-Cp,Ph-ProNN′P]$_2$/**30**	200	PhMe, 20 °C, 1 atm, 24 min	83 (*S*)	15h
[Rh(CF_3CO_2)(*S*)-Cy,Ph-ProNN′P]$_2$/**31**	200	PhMe, 20 °C, 1 atm, 48 h	62 (*S*)	15h
[RhCl(*S*)-Cp,Ph-ProNN′P]$_2$/**30**	200	PhMe, 50 °C, 1 atm, 2 h	78 (*S*)	15h
[RhCl(*S*)-Cp,Ph-ProNN′P]$_2$/**30**	200	PhMe, 70 °C, 1 atm, 4 h	64 (*S*)	15h
[Rh(CF_3SO_3)BoPHOZ]$_2$/**32**	100	THF, 20 °C, 20 atm, 6 h	97.2 (*R*)	19

a) Catalysts were used either as isolated dimer complexes or, in the case of preformed *in situ* from addition of 2 equiv. bidentate ligand to the rhodium dimers [Rh(COD)X]$_2$ (X = Cl, $OCOCF_3$). Both techniques gave almost identical results, as exemplified by several authors.

b) SCR = substrate:catalyst ratio.

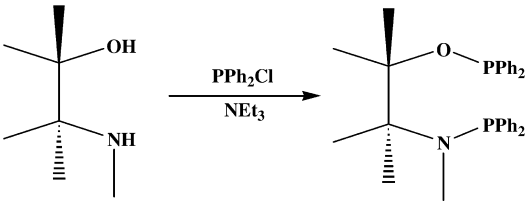
It must be recognized, however, that the preparation of such ligands requires synthetic schemes composed sometimes of 13 to 15 steps. This, from an industrial viewpoint, is an obvious drawback which would probably preclude any application.

The present authors began studying this reaction during the early 1980s, using chiral, natural amino acids and amino alcohols as starting materials to synthesize the so-called AMPP ligands (*AM*ino *P*hosphine *P*hosphinites) via a simple procedure by which the phosphino moieties are introduced via phosphinylation of the OH and NH functions of the amino alcohols using dialkylchlorophosphines (Scheme 33.4).

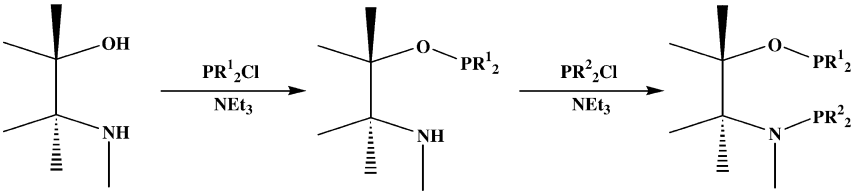
As expected, whereas hydrogenation using the previously reported ligand Ph,Ph-ProNOP **10** required higher temperatures and pressures to achieve conversion, the catalysts based on the peralkyl Cy,Cy-ProNOP **11** and Cp,Cp-ProNOP **12** ligands proved to be active and selective at room temperature and at 1 bar H_2. Furthermore, a one-pot, two-step procedure allowed the synthesis of mixed alkyl-aryl or alkyl-alkyl ligands via addition of 1 equiv. of chlorodialkylphosphine followed by 1 equiv. of another phosphinylating reagent (Scheme 33.5).

Using this procedure, a new series of AMPP ligands could be rapidly synthesized according to the starting amino alcohol and the phosphinylation reagents (Scheme 33.6) [15 a–h]. Of particular interest in the corresponding series of ligands arising from isoalaninol is the fact that changing the substituents at phosphorus could lead to a complete reversal of the asymmetric induction, using the same ligand backbone (see ligands **13** and **14**).

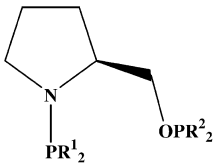
Following these early investigations, the major breakthrough in this field has been the change in both the structure of the ligand frame and that of the anion in the starting rhodium catalytic precursor. The [Rh(TFA){(S)-(Cp,Cp)oxoPro-



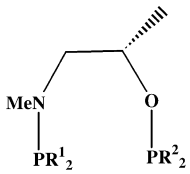
Scheme 33.4 One-step synthesis of aminophosphine phosphinite bidentate ligands.



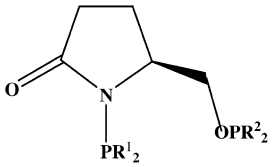
Scheme 33.5 One-pot, two-step procedure for the synthesis of mixed AMPP ligands.



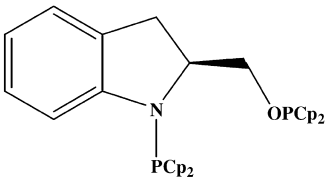
$R_1 = R_2 = Ph$ (S)-Ph,Ph-ProNOP 9
$R_1 = R_2 = Cy$ (S)-Cy,Cy-ProNOP 10
$R_1 = R_2 = Cp$ (S)-Cp,Cp-ProNOP 11



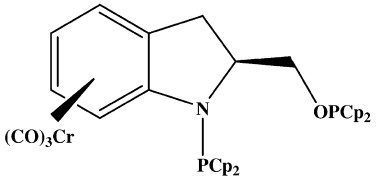
$R^1 = R^2 = Cp$ (S)-Cp,Cp-isoAlaNOP 13
$R^1 = Ph$, $R^2 = Cp$ (S)-Ph,Cp-isoAlaNOP 14



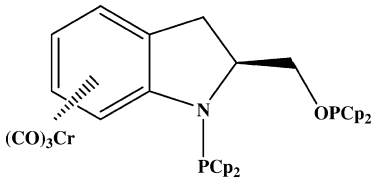
$R^1 = R^2 = Cy$ (S)-Cy,Cy-oxoProNOP 15
$R^1 = R^2 = Cp$ (S)-Cp,Cp-oxoProNOP 16
$R^1 = R^2 = i$Pr (S)-i-Pr,i-Pr-oxoProNOP 17



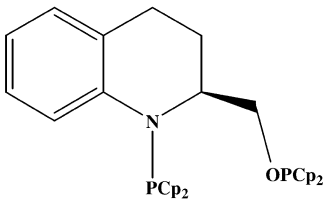
(S)-Cp,Cp-IndoNOP 18



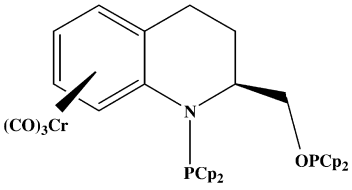
syn-(S,2S)-Cr(CO)$_3$-Cp,Cp-IndoNOP 19



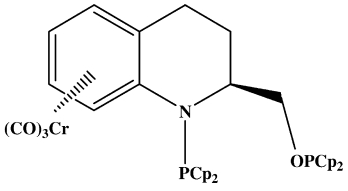
anti-(R,2S)-Cr(CO)$_3$-Cp,Cp-IndoNOP 20



(S)-Cp,Cp-QuinoNOP 21



syn-(S,2S)-Cr(CO)$_3$-Cp,Cp-QuinoNOP 22



anti-(R,2S)-Cr(CO)$_3$-Cp,Cp-QuinoNOP 23

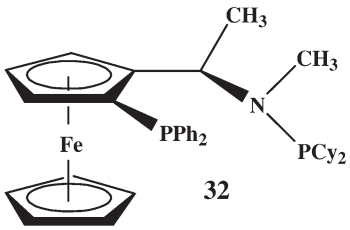
Scheme 33.6 AMPP ligands synthesized from amino alcohols.

NOP}]$_2$ amidophosphinite **15** complex catalyzes hydrogenation of the ketopantoyllactone, with ee-values up to 97% under very straightforward experimental conditions (20 °C, 1 bar H_2). The change of anion from chlorine to trifluoroacetate in the dimer complex allowed an enhancement of the reactivity of one order of magnitude, together with an increase in ee-values. In fact, ee-values of 96% have been obtained in a pilot plant using a substrate:catalyst ratio of 70 000 [15 e]. Other related ligands that fulfill these two key points – namely an increased rigidity of the ligand framework and electron-donating phosphorus atoms – have been synthesized from (*S*)-indoline carboxylic acid and (*S*)-1,2,3,4-tetrahydroisoquinoline carboxylic acid, and this led to similar (or even better) results in terms of enantioselectivity [15 o, p]. Ligands formed by chromium tricarbonyl complexation on the aromatic part of the ligand framework gave almost perfect enantioselectivity due to a beneficial effect of the matching chiralities in the *syn* form, even with the chloro dimer as the rhodium precursor.

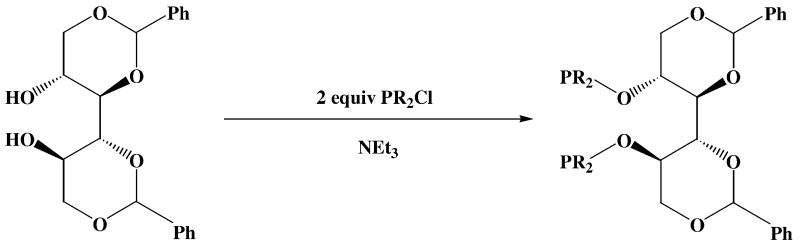
The use of sugars as the chiral source of the corresponding C2-symmetrical basic diphosphanes has been successfully explored. Aryldiphosphinites based on sugars have also been used successfully in the enantioselective hydrogenation of enamides [16, 17], and their behavior in the stereoselective hydrogenation of ketones has also been reported [17 c]. In this context, the 1,3–4,6-di-*O*-benzylidene-D-mannitol carbohydrate derivative can be readily prepared to provide, by further diphosphinylation, the C2-symmetric diphosphinites Ph,Ph-MannOP **24** Cp,Cp-MannOP **25** and Cy,Cy-MannOP **26** ligands, the latter being the more enantioselective (Scheme 33.7) [18].

Another series of bisaminophosphine (BAMP) ligands (Scheme 33.8) obtained by phosphinylation of diamines has also been synthesized and applied successfully, giving rise to better activities and selectivities using cyclohexyl-substituted phosphorus moieties [15 h].

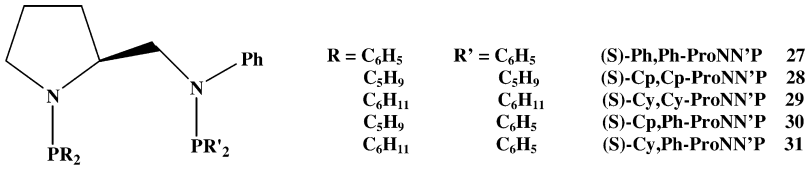
Interestingly, the use of phosphino-ferrocenylaminophosphine ligand **32** of the BOPHOZ series has also given good results for that reaction, indicating that dissymmetry of the ligand associated with the presence of a PN function may result in improved reactivities and selectivities, as observed with AMPP ligands.



32



Scheme 33.7 MannOP ligands synthesized from D-mannitol.



Scheme 33.8 BAMP ligands synthesized from diamines.

33.3.2
Hydrogenation of Ketoesters and Ketoamides

33.3.2.1 *α*-Ketoesters and Ketoamides

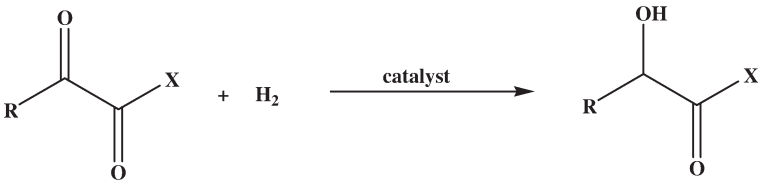
Some neutral rhodium catalysts with chiral ligands, such as MCCPM **9** (see Scheme 33.3**)** [20c], Cy,Cy-oxoProNOP **15**, and Cp,Cp-IndoNOP **18**, demonstrate excellent enantioselectivities and reactivities in the hydrogenation of *α*-ketoesters and ketoamides; indeed, they compare well with ruthenium-based catalysts (Table 33.2). Togni et al. have successfully used the Josiphos **47** ligand for the hydrogenation of ethyl acetoacetate [27], while the use of MannOPs has led to somewhat high enantioselectivities [18].

The enantioselective hydrogenation of isatine derivatives has also been performed with high ee-values (up to 94%) using the alkyl-substituted oxoProNOP ligands (15j).

Some developments have been carried out for the enantioselective synthesis of biologically active compounds. One such example is the synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutyrate, an important intermediate for the angiotensin-converting enzyme (ACE) inhibitor benazepril, or for coenzyme A, using the NORPHOS ligand (Scheme 33.9) [21].

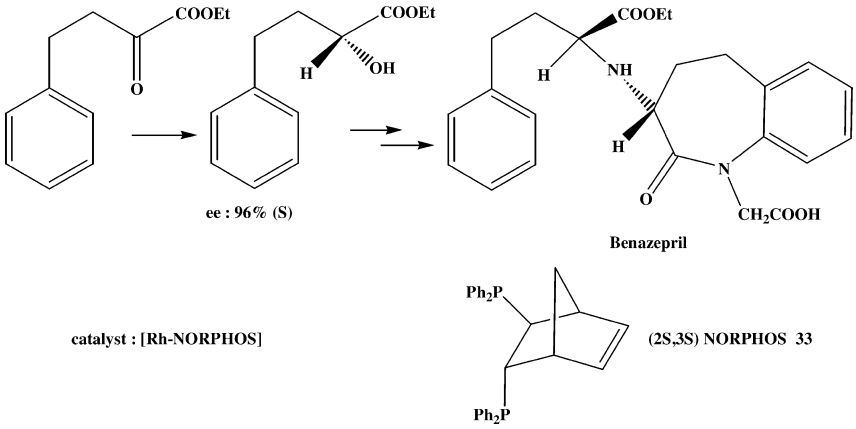
Substituted mandelamides such as **34** (Scheme 33.10) constitute a new class of agrochemical fungicides, acting specifically against the oomycetes family of phytopathogenic fungi such as *Phytophthora infestans* (potato late blight) and *Plasmopara viticola* (grape downy mildew) [34, 35]. Novel concise approaches to

Table 33.2 Enantioselective hydrogenation of α-ketoesters and ketoamides.

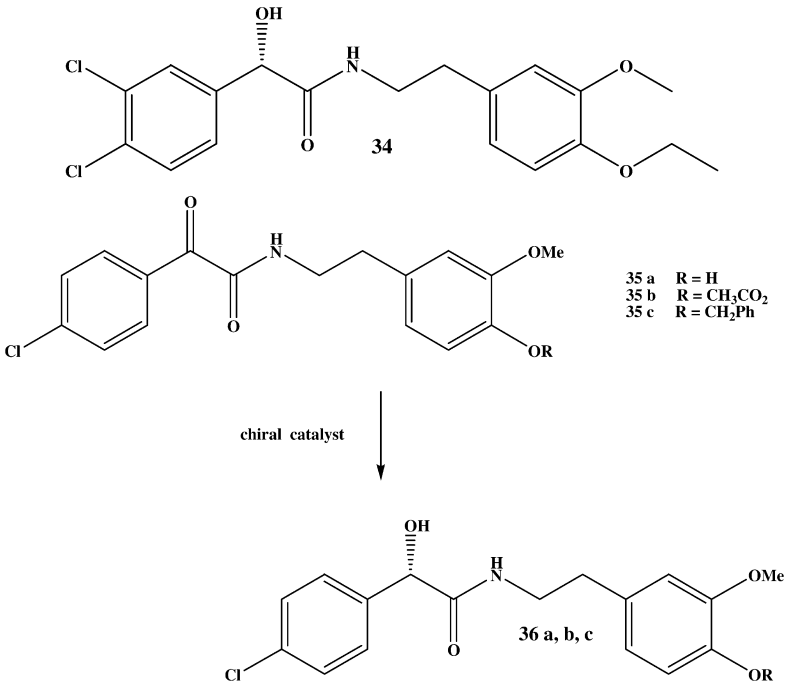


R	X	Catalyst	Reaction conditions [Solvent, temp, H_2 pressure, S:Rh, time][a)]	ee [%] (config.)	Reference
CH_3	CH_3O	[RhCl(2*S*,4*S*)-MCCPM]$_2$/**9**	THF, 20 °C, 20 atm, 1000, 24 h	87 (*R*)	20c–24
CH_3	CH_3O	[RhClPh-MannOP]$_2$/**24**	Toluene, 20 °C, 50 atm, 56 h	48 (*R*)	18
CH_3	CH_3O	[RhClCp-MannOP]$_2$/**25**	Toluene, 20 °C, 50 atm, 3 h	76 (*R*)	18
CH_3	CH_3O	[Rh(TFA)Cp-MannOP]$_2$/**25**	Toluene, 20 °C, 50 atm, 3 h	78 (*R*)	18
CH_3	CH_3O	[Rh(Cl)Cy-MannOP]$_2$/**26**	Toluene, 20 °C, 50 atm, 3 h	82 (*R*)	18
CH_3	CH_3O	[Rh(TFA)Cy-MannOP]$_2$/**26**	Toluene, 20 °C, 50 atm, 3 h	86 (*R*)	18
CH_3	CH_3O	[RhCl(*S*)-Cy,Cy-oxoProNOP]$_2$/**15**	Toluene, 20 °C, 20 atm, 3 h	95 (*R*)	15j
CH_3	CH_3O	[Rh(CF_3CO_2)(*S*,*S*)-Cr(CO)$_3$-Cp, Cp-IndoNOP]$_2$/**19**	MeOH, 20 °C, 50 atm, 6 h	95 (*R*)	15l
CH_3	C_2H_5O	[RhCl(2*S*,3*S*)-NORPHOS]$_2$/**33**	Toluene/MeOH, 25 °C, 20 atm, 50, 3 h	89 (*S*)	21
CH_3	C_2H_5O	[RhCl (2*S*,3*S*)-NORPHOS]$_2$/**33**	Toluene, 20 °C, 50 atm, 18 h	96 (*S*)	21
CH_3	C_2H_5O	[Rh(CF_3SO_3)BOPHOZ]$_2$/**32**	CH_3OH, 25 °C, 100 atm, 50, 3 h	92.4(*R*)	19
$Ph(CH_2)_2$	C_2H_5O	[RhClPh-MannNOP]$_2$/**24**	THF, 20 °C, 20 atm, 100, 6 h	43 (*S*)	18
$Ph(CH_2)_2$	C_2H_5O	[RhClCp-MannOP]$_2$/**25**	Toluene, 50 °C, 50 atm, 200, 48 h	65 (*S*)	18
Ph	$PhCH_2NH$	[Rh(TFA)Cp-MannOP]$_2$/**25**	Toluene, 20 °C, 1 atm, 18 h	50 (*S*)	18
Ph	$PhCH_2NH$	[Rh(Cl)Cy-MannOP]$_2$/**26**	Toluene, 20 °C, 50 atm, 18 h	76 (*S*)	18
Ph	$PhCH_2NH$	[Rh(TFA)Cy-MannOP]$_2$/**26**	Toluene, 20 °C, 50 atm, 18 h	65 (*S*)	18
Ph	$PhCH_2NH$	[RhCl(*S*)-Ph,Cp-isoAlaNOP]$_2$/**14**	Toluene, 20 °C, 50 atm, 18 h	88 (*S*)	15e
Ph	$PhCH_2NH$	[RhCl(*S*)-Cy,Cy-oxoProNOP]$_2$/**15**	Toluene, 20 °C, 1 atm, 24 h	95 (*S*)	15j
Ph	$PhCH_2NH$	[RhCl(*S*)-Cp,Cp-IndoNOP]$_2$/**18**	Toluene, 20 °C, 1 atm, 24 h	91 (*S*)	15o
Ph	$PhCH_2NH$	[RhCl(*S*,*S*)-Cr(CO)$_3$-Cp, Cp-IndoNOP]$_2$/**19**	Toluene, 20 °C, 1 atm, 24 h	97 (*S*)	15o
Ph	$PhCH_2NH$	[RhCl(*S*)-Cp,CpQuinoNOP]$_2$/**21**	Toluene, 20 °C, 1 atm, 3 h	99 (*S*)	15p
Ph	$PhCH_2NH$	[RhCl-*syn*-(*S*,*S*)-Cr(CO)$_3$Cp, Cp-QuinoNOP]$_2$/**22**	Toluene, 20 °C, 50 atm, 19 h	94 (*S*)	15p
Ph	$PhCH_2NH$	[RhCl-*anti*-(*S*,*S*)-Cr(CO)$_3$-Cp, Cp-QuinoNOP]$_2$/**23**	Toluene, 20 °C, 50 atm, 18 h	99 (*S*)	15p

a) S:Rh = substrate:catalyst ratio = 200, unless otherwise stated. Catalysts were generally prepared *in situ* by reacting [Rh(COD)Cl]$_2$ or[Rh(COD)(OCOCF$_3$)]$_2$ with 2 equiv. ligand in the solvent used for the catalytic reaction.



Scheme 33.9 Enantioselective hydrogenation with Rh–NORPHOS complex as a key step in the synthesis of the ACE inhibitor benazepril (see Table 33.2).

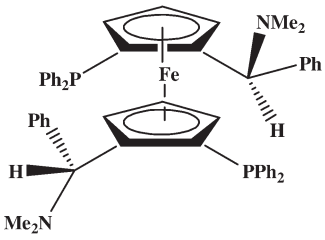


Scheme 33.10 Synthesis of substituted mandelic amides via enantioselective reduction of a phenylglyoxylic acid derivative.

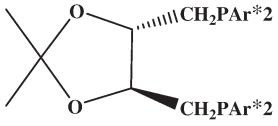
Table 33.3 Hydrogenation of phenylglyoxylic derivatives.

Substrate	Catalyst	Reaction conditions [a] [Solvent, temp, H_2 pressure]	TON/TOF [h^{-1}]	ee [%] (config.)
35a	[RhCl(*R*)-Cy,Cy-oxoProNOP]$_2$/**15**	CH_2Cl_2, 0 °C, 20 bar	100/5	87 (*R*)
35a	[RhCl(2*S*,4*S*)-BCPM]$_2$/**6**	THF, 20 °C, 10 bar	100/5	74 (*S*)
35a	[RhCl(*S*)-MeOBIPHEP]$_2$/**41**	CH_2Cl_2, 40 °C, 20 bar	100/5	65 (*S*)
35a	[RhCl(*R*)-BICHEP]$_2$/**40**	CH_2Cl_2, 40 °C, 20 bar	100/5	47 (*R*)
35a	[RhCl(2*S*,4*S*)-Ar*-BPPM]$_2$/**39**	THF, 20 °C,10 bar	89/5	47 (*S*)
35a	[RhCl(*R*,*R*)-Ar*-DIOP]$_2$/**38**	CH_2Cl_2, 40 °C, 20 bar	37/2	44 (*S*)
35b	[RhCl(*S*)-*i*-Pr-MeOBIPHEP]$_2$/**42**	CH_2Cl_2, 40 °C, 20 bar	96/5	62 (*S*)
35c	[RhCl(2*S*,4*S*)-BCPM]$_2$/**6**	THF, 20 °C, 10 bar	93/2	64 (*S*)
35c	[RhCl(*S*)-*i*-Pr-MeOBIPHEP]$_2$/**42**	CH_2Cl_2, 40 °C, 20 bar	95/2	54 (*S*)
35c	[RhCl(Mandyphos)]$_2$/**37**	THF, 25 °C, 60 bar	25/1	40 (*R*)

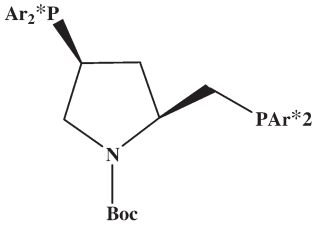
a) Substrate : Rh ratio = 100. Catalysts were prepared *in situ* by addition of the bidentate ligand to [Rh(norbornadiene)Cl]$_2$.



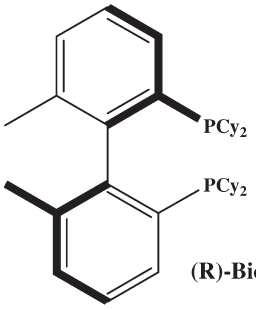
Mandiphos 37



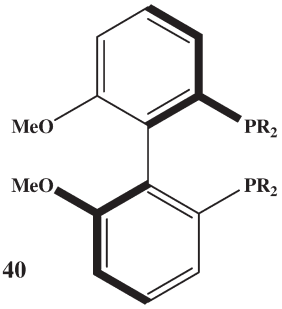
(R,R)-Ar*-DIOP 38
Ar = 3,5-*t*Bu$_2$-4-MeO-C$_6$H$_2$



(2S,4S)-Ar*-BPPM 39
Ar = 3,5-*t*Bu$_2$-4-MeO-C$_6$H$_2$



(R)-Bichep 40



R = Ph **MeOBiphep 41**

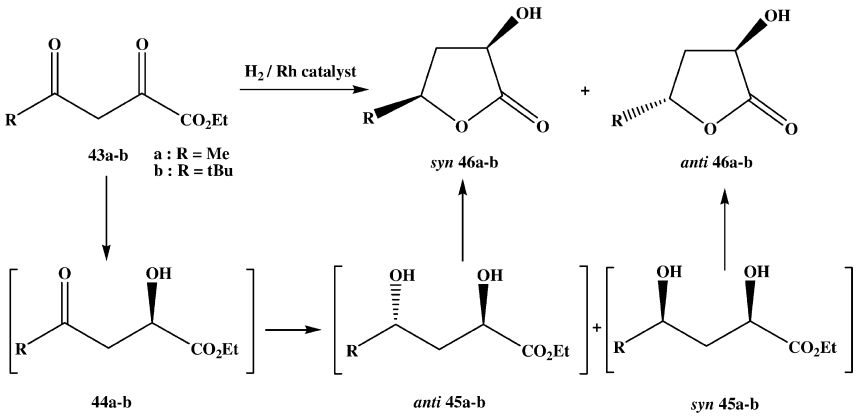
R = CH(CH$_3$)$_2$ ***i*Pr-MeOBiphep 42**

.

enantiopure mandelamides have been checked, and one of these involves the enantioselective reduction of a ketamide to produce directly the mandelamide, in which case the Cy,Cy-oxoProNOP ligand **15** was found to be the most efficient (Table 33.3) [28].

33.3.2.2 α,γ-Diketoesters

In recent years, much effort has been devoted to the enantioselective hydrogenation of β-ketoesters, essentially using ruthenium-based catalysts. The aim of these reactions is to produce selectively enantiopure *syn* diols which are the key building blocks for the synthesis of inhibitors of HMG-coenzyme A reductase. Due to the availability of the AMPP ligands, and the reactivity of the rhodium catalysts based on them (notably the alkyl-substituted ones) towards ketonic sub-



Scheme 33.11 Asymmetric hydrogenation of α,γ-diketoesters.

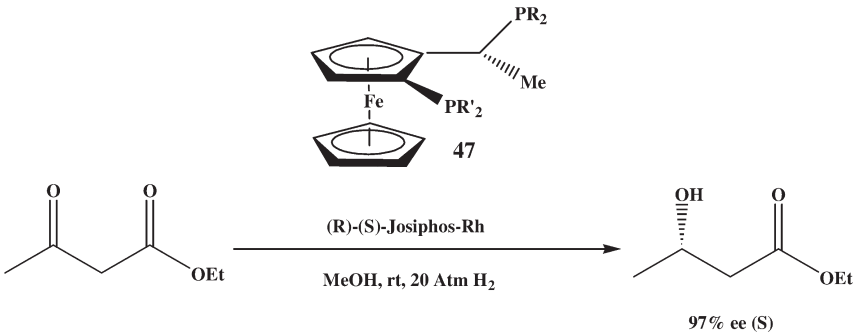
Table 33.4 Enantioselective hydrogenation of α,γ-diketoesters using rhodium catalysts [15m]. [a)]

Substrate	Catalyst	Time [h]	4 select.	6 select.	*syn:anti*	ee [*syn/anti*]
43a	[RhCl(2*S*,4*S*)-BPPM]$_2$/**1**	67	63	26	54:46	58/64
	[RhCl(*S*)-MeO-BIPHEP]$_2$/**36**	138	82	18	54/46	79/53
	[RhCl(*S*)-Cy,Cy-oxoProNOP]/**15**	84	81	18	65:35	80/60
	[Rh(TFA) (*S*)-Cy,Cy-oxoProNOP]$_2$/**15**	86	45	47	48:52	80/86
	[RhCl(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	19	64	23	42:58	73/86
	[RhCl(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	70	3	91	44:56	73/86
	[Rh(TFA) (*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	26	39	56	45:55	72/87
	[Rh((*R*)-MTPA)(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	44	42	49	49:51	73/81
43b	[RhCl(*S*)-Cy,Cy-oxoProNOP]$_2$/**15**	17	>99	0	–	88 (–)
	[RhCl(*R*)-Cp,Cp-oxoProNOP]$_2$/**16(R)**	25	78	22	31/69	97 (–)
	[RhCl(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	88	88	12	32:68	97 (+)
	[Rh(TFA)(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	38	>99	0	–	48 (+)
	[Rh((*R*)-MTPA)(*S*)-Cp,Cp-oxoProNOP]$_2$/**16**	140	4	92	49:51	73/81

a) Reaction conditions: for **43a** substrate: toluene, 60 °C, 50 atm H_2, [**43a**]/[P]/[Rh] = 200:2.2:1, [Rh] = 0.6–1.4 mmol L^{-1}; for **43b** substrate: toluene, 60 °C, 50 atm H_2, [**43b**]/[Rh] = 50:1, [Rh] = 0.5–4.0 mmol L^{-1}. Catalysts were prepared *in situ* from the appropriate precursor [Rh(COD)X]$_2$ (X = Cl, TFA or MTPA) and 2.2 equiv. ligand.

strates, some investigations have been made into the synthesis of 2-hydroxy-4-butyrolactones in a one-pot hydrogenation process (Scheme 33.11) [15m] (see also Table 33.4).

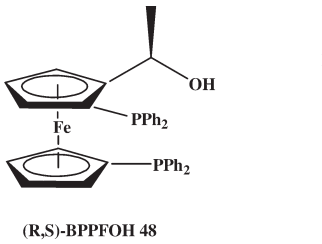
The Rh complex of the chiral C_1 symmetry Josiphos **47** is also effective for the enantioselective hydrogenation of ethyl 3-oxobutanoate [27].



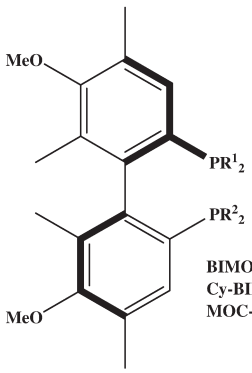
33.3.3 Hydrogenation of Amino Ketones

33.3.3.1 *α*-Amino Ketones

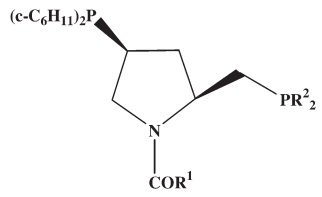
Amino ketones and their hydrochloride salts can be effectively hydrogenated with chiral rhodium catalysts (Table 33.5). The rhodium precatalysts, when combined with chiral phosphorus ligands such as BPPFOH **4** [20b], hydroxyproline derivatives ligands [20–24], Cy,Cy-oxo-ProNOP **15**, Cp,Cp-oxoProNOP **16**, and



(R,S)-BPPFOH 48

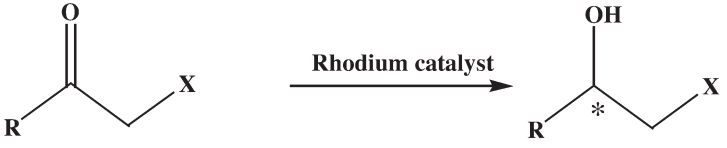


BIMOP 49 $R^1 = R^2 = Ph$
Cy-BIMOP 50 $R^1 = R^2 = C_6H_{11}$
MOC-BIMOP 51 $R^1 = C_6H_{11}$, $R^2 = Ph$



R^1	R^2		
NHPh	Ph	PCCPM	52
OMe	Ph	MCPM	53
OPh	Ph	PCPM	54
NHMe	3,5-Me_2-C_6H_3	MCCXM	55

Table 33.5 Enantioselective hydrogenation of α-amino ketones catalyzed by rhodium (I) complexes.[a)]



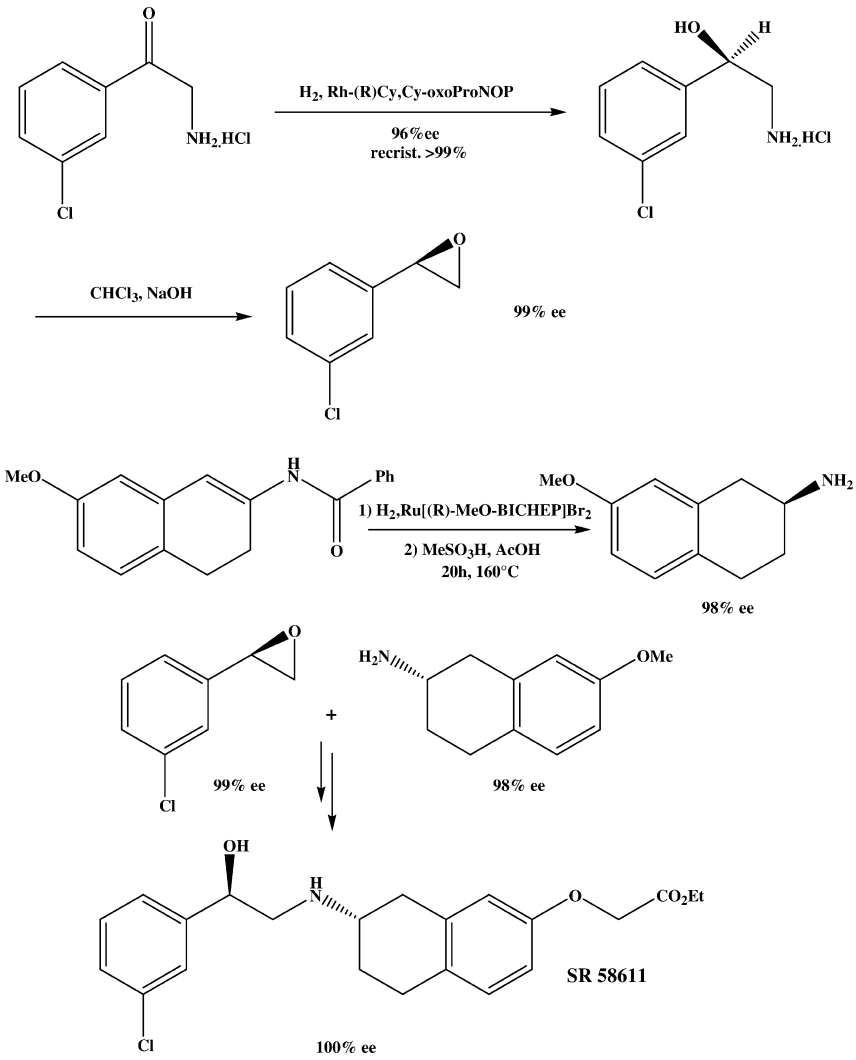
Chiral ligand	R	X	Reaction conditions [Solvent, temp., H_2 pressure, S:Rh]	ee [%] (config.)	Reference
(*R*,*S*)-BPPFOH/**48**	(3,4)$(OH)_2$Ph	NHMe.HCl	NEt_3, MeOH, r·t., 50 bar, 100	95 (*R*)	20b
(*S*)-Cy,Cy-oxoProNOP/**15**	Ph	$NH_2 \cdot HCl$	MeOH, 20 °C, 50 bar, 200	93 (*S*)	15i
(*S*)-Cy,Cy-oxoProNOP/**15**	Ph	$NMe_2 \cdot HCl$	MeOH, 20 °C, 50 bar, 200	96 (*S*)	15i
(*S*)-Cp,Cp-IndoNOP/**18**	Ph	$NMe_2 \cdot HCl$	Toluene, 20 °C, 50 bar, 200	99 (*S*)	15p
(*S*)-Cp,Cp-oxoProNOP/**16**	Ph	$NMe_2 \cdot HCl$	MeOH, 20 °C, 20 bar, 200	93 (*S*)	15i
(2*S*,4*S*)-MCCPM/**9**	Ph	$N(Me)CH_2Ph \cdot HCl$	MeOH, 50 °C, 30 bar, 1000	91 (*R*)	23a
(*S*)-Cp,Cp-oxoProNOP/**16**	Me	$NMe_2 \cdot HCl$	Toluene, 80 °C, 50 bar, 200	97 (*S*)	15p
(2*S*,4*S*)-MCCPM/**9**	Me	$NMe_2 \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	86 (*S*)	21
(2*S*,4*S*)-BCPM/**6**	CH_2Ph	$NEt_2 \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	91 (*S*)	20
(2*S*,4*S*)-BCPM/**6**	Ph	$NH_2 \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	81 (*R*)	23a
(2*S*,4*S*)-BCPM/**6**	Ph	$NHMe \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	81 (*R*)	23a
(2*S*,4*S*)-BCPM/**6**	Ph	$NHCH_2Ph \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	87 (*S*)	23a
(2*S*,4*S*)-MCCPM/**9**	Ph	$NHCH_2Ph \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	93 (*S*)	23a
(*R*,*R*)DIOP	Ph	NEt_2	Benzene, NEt_3, 50 °C, 70 bar, 200	93 (+)	25
(2*S*,4*S*)-MCCPM/**9**	Ph	$NEt_2 \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^5	97 (*S*)	23a
(2*S*,4*S*)-BCPM/**6**	Ph	$NEt_2 \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	93 (*S*)	23a
(2*S*,4*S*)-BCPM/**6**	Ph	$NHCH_2Ph \cdot HCl$	NEt_3, MeOH, 50 °C, 20 bar, 10^3	85 (*S*)	23a

(*R*,*S*)-BPPFOH/**48**	3,4-$(OH)_2$Ph	NHMe · HCl	MeOH, NEt_3, 40 °C, 50 bar, 100	95 (*R*)	20b
(2*S*,4*S*)-MCCPM/**9**	3-(OCH_2Ph)Ph	N(Me)CH_2Ph · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	85 (*S*)	23b
(2*S*,4*S*)-MCPM/**53**	3-(OCH_2Ph)Ph	N(Me)CH_2Ph · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	85 (*S*)	23b
(*R*,*R*)DIOP	2-Naphthyl	NEt_2	Benzene, NE_{t3}, 50 °C,70 bar, 200	95 (*S*)	25
(2*S*,4*S*)-MCCPM/**9**	CH_2OPh	$NHCHMe_2$ · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	87 (*S*)	21
(2*S*,4*S*)-MCCPM/**9**	CH_2OPh	$NHCH_2Ph$ · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	97 (*S*)	21
(2*S*,4*S*)-MCCPM/**9**	CH_2O-(C_6H_3-3,5-Me_2)	$NHCH_2Ph$ · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	95 (*S*)	21
(2*S*,4*S*)-MCCPM/**9**	$CH_2OC_6H_4(CH_2)OMe$	NH-*i*-Pr · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	93 (*S*)	21
(2*S*,4*S*)-MCCPM/**9**	CH_2O(1-Naphthyl)	NH-*i*-Pr · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	91 (*S*)	21
(2*S*,4*S*)-MCCXM/**55**	CH_2COOEt	NMe_2 · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	85 (*S*)	22a
(2*S*,4*S*)-MCCPM/**9**	CH_2COOEt	NMe_2 · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	83 (*S*)	22a
(2*S*,4*S*)-MCCPM/**9**	Ph	N(Me)CH_2Ph · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	91 (*R*)	22b
(2*S*,4*S*)-MCCXM/**55**	Ph	N(Me)CH_2Ph · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	82 (*R*)	22b
(2*S*,4*S*)-BCPM/**6**	Ph	N(Me)CH_2Ph · HCl	NEt_3, MeOH, 50 °C, 20 bar, 10^3	83 (*R*)	22b
MannNOP/**25**	Ph	NMe_2 · HCl	EtOH, 50 °C, 50 bar, 200	58 (*S*)	18
MannNOP/**26**	Ph	NMe_2 · HCl	EtOH, 50 °C, 50 bar, 200	78 (*S*)	18
BIMOP/**49**	Ph	NH_2 · HCl	NEt_3, MeOH, 50 °C, 50 bar, 500	8 (*S*)	31
CY-BIMOP/**50**	Ph	NH_2 · HCl	NEt_3, MeOH, 50 °C, 50 bar, 500	55 (*R*)	31
MOC-BIMOP/**51**	Ph	NH_2 · HCl	NEt_3, MeOH, 50 °C, 50 bar, 10^3	93 (*R*)	31

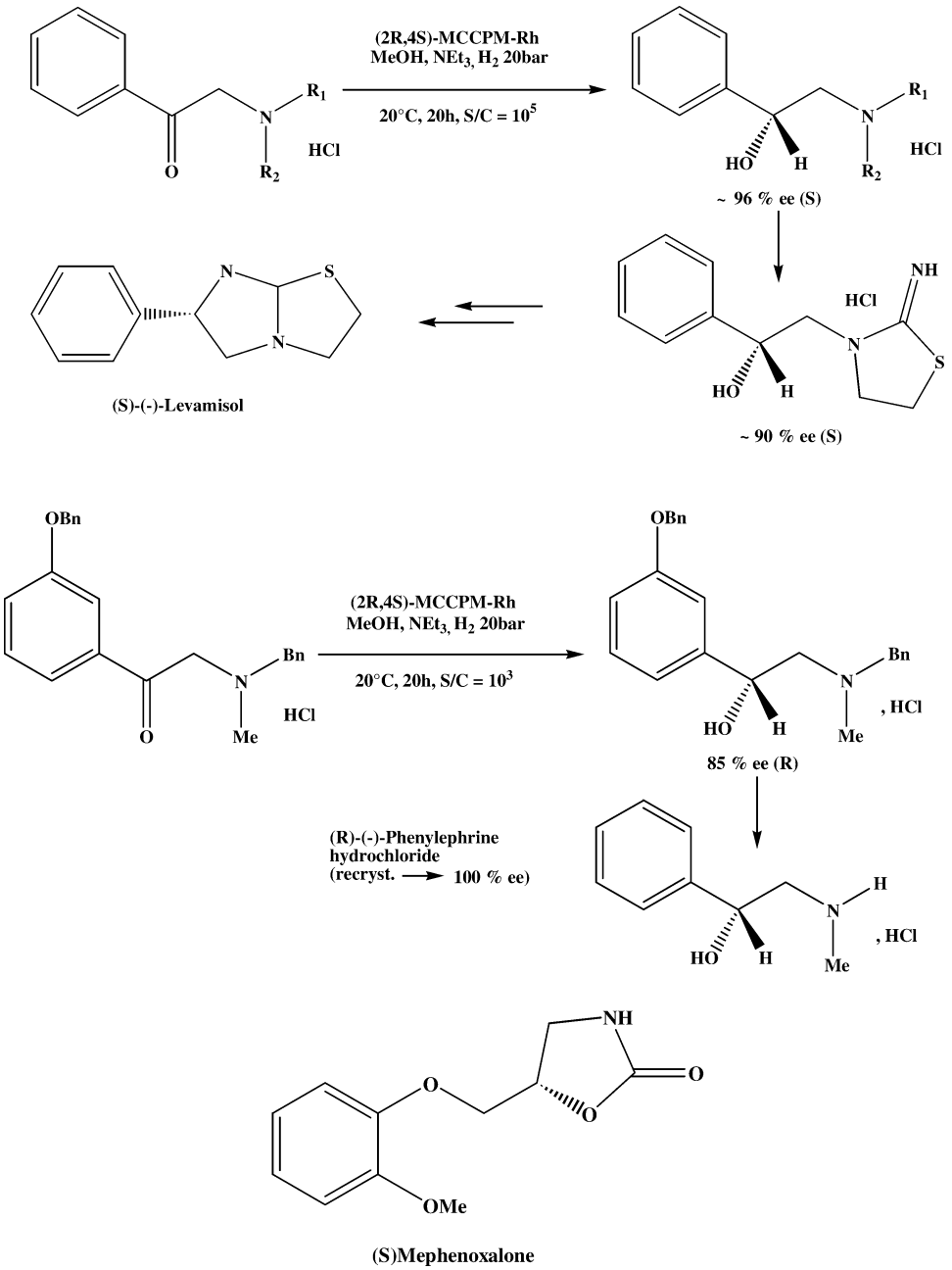
a) Catalysts were generally preformed *in situ* upon addition of the ligands to the $[Rh(COD)Cl]_2$ dimer, except for the reactions described in [15i], where the *in-situ* procedure used the mononuclear $Rh(COD)_2BF_4$ complex with 1.1 equiv. ligand. The reactions were conducted to completion after 5 to 24 h.

Cp,Cp-IndoNOP **18** [15p], have provided excellent enantioselectivity and reactivity for the enantioselective hydrogenation of α-, β-, and γ-alkyl amino ketone hydrochloride salts.

The enantioselective hydrogenation of α-amino ketones has been applied extensively to the synthesis of chiral drugs such as the β-agonist SR 58611 (Sanofi Cie). *m*-Chlorstyreneoxide was obtained via carbene-induced ring closure of the amino alcohol. Epoxide-opening by a chiral amine obtained via a ruthenium-catalyzed hydrogenation of an enamide has led to the desired compound where



Scheme 33.12 Enantioselective synthesis of the β-agonist SR 58611 using two enantioselective hydrogenations processes [15n].

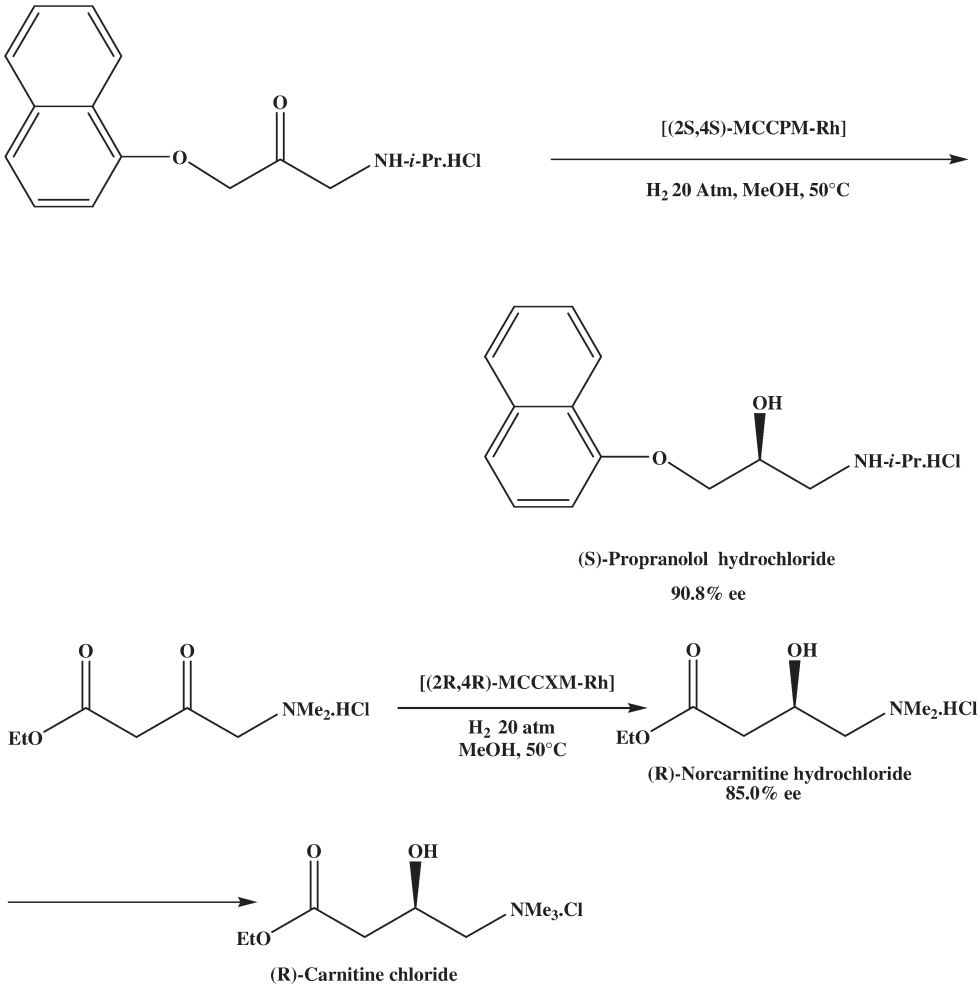


Scheme 33.13 Some applications of the enantioselective hydrogenation of α-amino ketones.

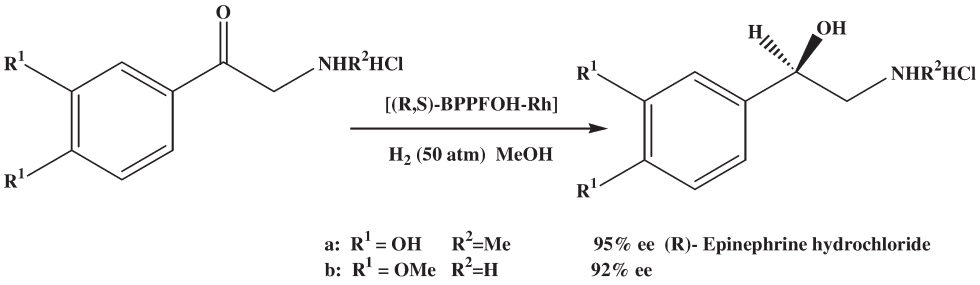
the two enantioselective centers have been obtained by asymmetric hydrogenation (Scheme 33.12) [15 n].

The neutral (2*S*,4*S*)-MCCPM **9**–rhodium complex was also found to be an efficient catalyst for the enantioselective hydrogenation of other α-aminoacetophenone derivatives. A practical enantioselective synthesis of (*S*)-(–)-levamisole [23 a], phenylephrine [23 b], and mephenoxalone [23] was realized by using this hydrogenation as a key reaction (Scheme 33.13).

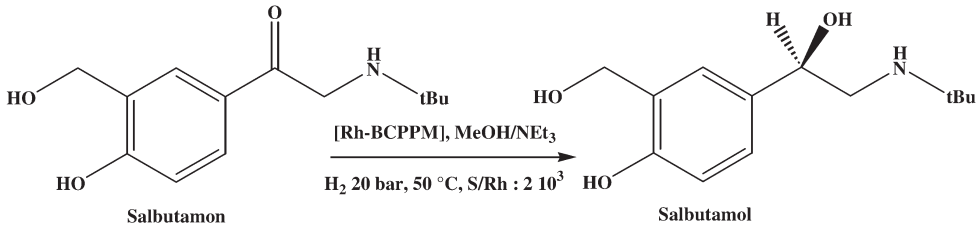
The enantioselective hydrogenation of 3-aryloxy-2-oxo-1-propylamine derivatives leads directly to 1-amino-3-aryloxy-2-propanol derivatives, which serve as α-adrenergic blocking agents. (*S*)-Propranolol is obtained in 90.8% ee from the corresponding α-amino ketone, using 0.01 mol.% of the neutral (*S*,*S*)-MCCPM **9**–Rh complex [21], and from norcarnitine using the MCCXM **54** ligand [22 a].



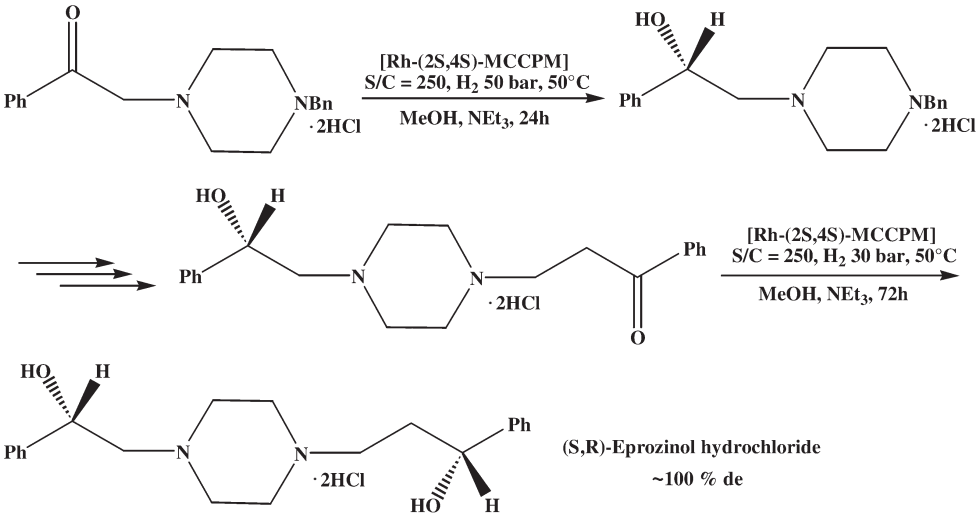
Epinephrine derivatives have also been synthesized using the (*R,S*)-BPPFOH ligand **48** [20a, b].



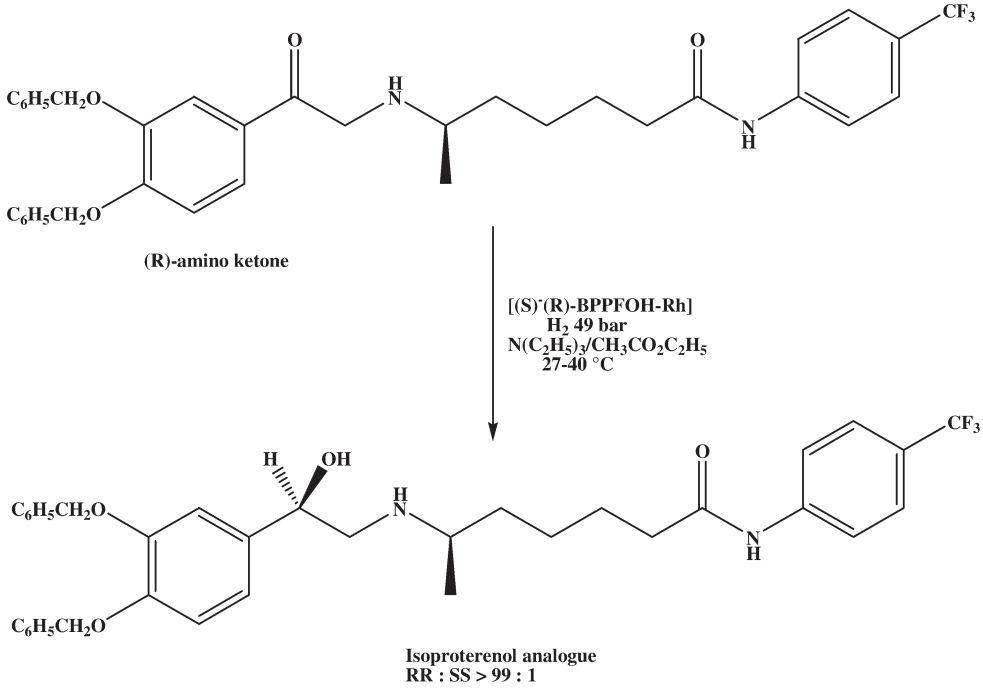
(*R*)-Salbutamol (levosalbutamol) was prepared in 90% yield and 70% ee by enantioselective hydrogenation of salbutamon using BCPPM **6** as ligand [29].



A synthetic route to optically active eprozinol, an anti-asthmatic compound, has been developed by efficient enantioselective hydrogenations of *α*- and *β*-amino ketone hydrochloride derivatives with a MCCPM–rhodium catalyst [30].



The (*R*)-amino ketone is hydrogenated enantioselectively by a neutral complex [{(*S*)-(*R*)-BPPFOH}RhCl]$_2$ to give the (*R*,*R*)-isoproterenol analogue, a compound which has been shown to possess very potent *β*-adrenoreceptor agonistic activity [33].

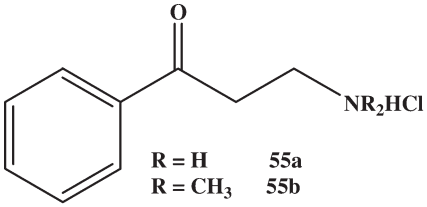


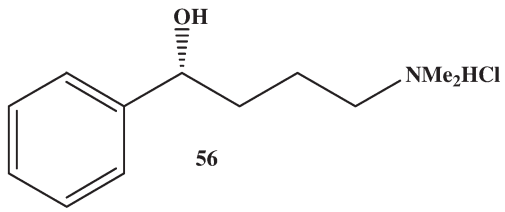
33.3.3.2 *β*- and *γ*-Amino Ketones

The (2*S*,4*S*)-MCCPM–Rh(I) complex was found previously by Achiwa and colleagues to be an efficient catalyst for the enantioselective hydrogenation of *β*-amino ketone derivatives, leading to a practical enantioselective synthesis of (*R*)-fluoxetine [*N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine] hydrochloride [22b]. Moreover, the use of AMPP ligands again proved to be efficient for these substrates, as exemplified in Table 33.6 [15i].

Zhang and colleagues [26] synthesized the Duanphos enantiomers **57** and **58**, and reported on the Rh–Duanphos-catalyzed highly efficient hydrogenation of a series of *β*-secondary-amino ketones with ee-values of up to >99%, and with turnover numbers (TONs) of more than 4500 (Table 33.7). This hydrogenation provides a potentially practical synthesis for key pharmaceutical intermediates. The *γ*-secondary amino alcohols are of particular interest to synthetic chemists as they are key intermediates for the synthesis of an important class of antidepressants, **59–62** [32].

Table 33.6 Hydrogenation of a series of aromatic β-and γ-amino ketones **55a–b** and **56** with [Rh–AMPP] catalysts.

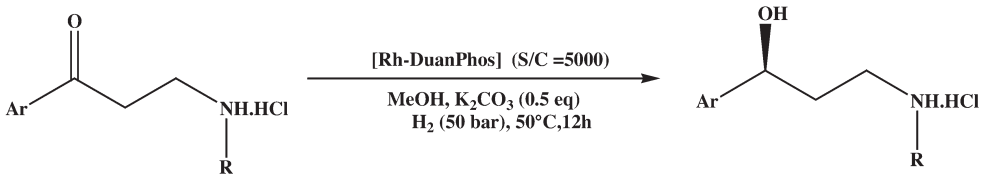




Substrate	Chiral ligand	Reaction conditions [temp, time (h)][a)]	ee [%] (config.)
55a	(*S*)-Cy,Cy-oxoProNOP/**15**	50 °C, 21	85 (*R*)
55b	(*S*)-Cy,Cy-oxoProNOP/**15**	20 °C, 45	93 (*R*)
55b	(*S*)-Cy,Cy-oxoProNOP/**15**	50 °C, 22	89 (*R*)
55b	(*S*)-Cy,Cy-oxoProNOP/**15**	50 °C, 18	87 (*R*)
55b	(*S*)-Cp,Cp-oxoProNOP/**16**	20 °C, 26	85 (*R*)
55b	(*S*)-Cy,Cy-ProNOP/**11**	20 °C, 44	77 (*R*)
55b	(*S*)-Cy,Cy-ProNOP/**11**	50 °C, 16	62 (*R*)
56	(*S*)-Cy,Cy-oxoProNOP/**15**	80 °C, 40	92 (*R*)

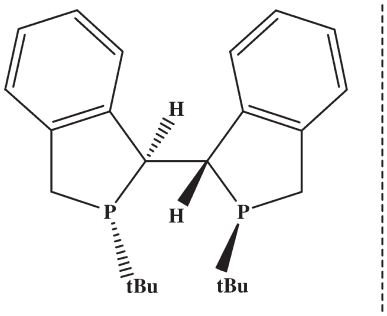
Solvent: MeOH; H_2 pressure: 50 atm., S:Rh ratio = 200; NEt_3:Rh = 5:1. TOFs are in the range 4.5 to 12.5 h^{-1}.
Catalysts were prepared *in situ* from the $[Rh(COD)_2]BF_4$ and 1.1 equiv. ligand.

Table 33.7 Hydrogenation of a series of β-secondary-amino ketones with Rh(Sc,Rp)-Duanphos catalyst.[a)]

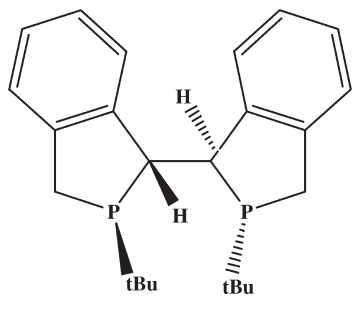


Substrate	Yield [%]	ee [%]	Configuration
Ar = 2-Me-Ph, R = Me	92	99	*S*
Ar = Ph, R = Me	90	98	*S*
Ar = 3-Br-Ph, R = Me	90	96	*S*
Ar = 4-Br-Ph, R = Me	93	99	*S*
Ar = 2-OMe-Ph, R = Me	93	93	*S*
Ar = 4-OMe-Ph, R = Me	93	99	*S*
Ar = 2-Naphthyl, R = Me	92	99	*S*
Ar = 2-Phenyl, R = CH_2-Ph	90	96	*S*
Ar = 2-Thienyl, R = Me	93	>99	*S*

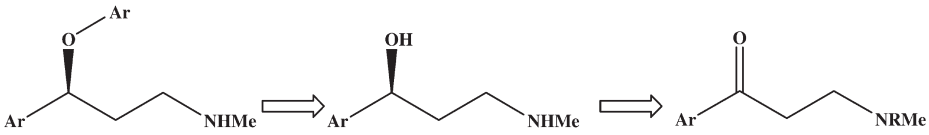
a) The catalyst was the isolated [Rh(Duanphos)(NBD)]SbF_6 complex.



(Sc,Rp)-Duanphos 57



(Rc,Sp)-Duanphos 58



59 Ar = Ph, Ar = 4-CF_3-Ph Fluoxetine
60 Ar = Ph, Ar = 2-CH_3-Ph Tomoxetine
61 Ar = Ph, Ar = 2-OMe-4-CF_3-Ph Nisoxetine
62 Ar = thiophenyl, Ar = 1-naphtyl Fluoxetine

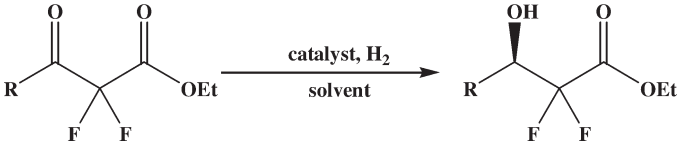
(93-99 % ee, up to >4500 TON)

R = CH_2Ph, Me or H

33.4
Enantioselective Hydrogenation of Fluoroketones

The catalytic enantioselective synthesis of chiral organofluorine compounds has played an important role in the development of medicines and materials based on the influence of fluorine's unique properties. Moreover, homochiral *R*-trifluoromethyl alcohols are versatile intermediates for the synthesis of anti-ferroelectric liquid crystalline molecules. Recently, Kuroki et al. found that chiral rhodium-(amidophosphinephosphinite) complexes, prepared from [Rh(COD)O-$COCF_3]_2$ and oxoProNOP ligands, catalyze the hydrogenation of 2,2-difluoro-3-oxocarboxylates and 4,4,4-trifluoroacetoacetate to give the corresponding β-hydroxy esters with good to excellent enantioselectivity (Table 33.8) [36, 37]. The stereochemical outcome from the latter β-ketoester indicated that the trifluoromethyl group has a significant influence on the enantiotopic face selection. An interesting feature that should be highlighted here is the fact that, although ruthenium-based catalysts are generally superior to rhodium, the results obtained with fluoroketones show that use of the latter catalysts, combined with the proper ligands (where the electronic properties have been tuned using alkyl substituents) are much more efficient, as when using ketopantoyllactone and ketoamide substrates.

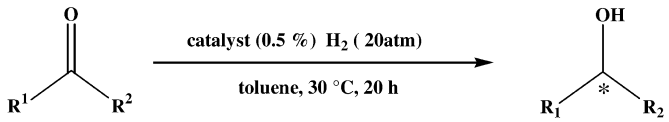
Table 33.8 Enantioselective hydrogenation of α-fluoro-substituted β-ketoesters.



R	Catalyst [a)]	Reaction conditions [Solvent, temp., H_2 pressure, t (h)]	Yield [%]	ee [%] (config.)
c-C_6H_{11}	[$RuBr_2$(*R*)BINAP]	EtOH, 100 °C, 100 atm, 24	96	77 (*R*)
$CH_3(CH_2)_8$	[RuCl((*R*)-Biphemp)(*p*-cymene)] Cl	EtOH, 100 °C, 100 atm, 24	100	81 (*R*)
CH_3	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 30 °C 20 atm, 20	93	96 (*R*)
$(CH_3)_2CHCH_2$	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 70 °C 20 atm, 20	95	92 (*R*)
Ph	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 30 °C 20 atm, 20	97	84 (*R*)
$PhCH_2$	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**51**	Toluene, 30 °C 20 atm, 20	63	94 (*R*)
$PhCH_2CH_2$	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 30 °C 20 atm, 20	100	96 (*R*)
$PhCH_2OCH_2$	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 30 °C 20 atm, 20	95	95 (*R*)
c-C_6H_{11}	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 70 °C 20 atm, 20	81	94 (*R*)
c-C_6H_{11}	[Rh((*S*)-Cp,Cp-oxoProNOP)$OCOCF_3]_2$/**16**	Toluene, 70 °C, 20 atm, 20	99	94 (*R*)
$CH_3(CH_2)_8$	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	Toluene, 30 °C, 20 atm, 20	98	97 (*R*)
$CH_3(CH_2)_8$	[Rh((*S*)-Cy,Cy-oxoProNOP)$Cl]_2$/**15**	Toluene, 30 °C, 50 atm, 18	43	90 (*R*)
$CH_3(CH_2)_8$	[Rh((*S*)-*i*-Pr,*i*-Pr-oxoProNOP)$OCOCF_3]_2$/**17**	Toluene, 30 °C, 10 atm, 20	99	97 (*R*)

a) Catalysts were prepared and isolated before use; 0.1–0.5 mol.% of catalyst was used.

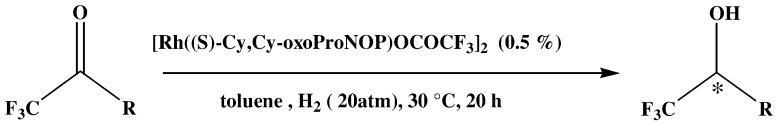
Table 33.9 Enantioselective hydrogenation of α-fluoroalkyl-substituted ketones.[a)]



R^1	R^2	Catalyst	Yield [%]	ee [%] (config.)
CF_3	C_8H_{17}	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	99	97 (*R*)
CF_3	C_8H_{17}	[Rh((*S*)-*i*-Pr,*i*-Pr-oxoProNOP)$OCOCF_3]_2$/**17**	100	97 (*S*)
CHF_2	C_8H_{17}	[Rh((*S*)-Cp,Cp-oxoProNOP)$OCOCF_3]_2$/**16**	100	27
CH_2F	C_8H_{17}	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	100	15
CH_3	C_8H_{17}	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	<1	–
CH_3	Ph	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	2	8
CF_3	Ph	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	93	73 (*R*)
C_2F_5	C_9H_{19}	[Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3]_2$/**15**	100	97 (*R*)

a) Catalysts were prepared and isolated before their use in catalysis.

Table 33.10 Enantioselective hydrogenation of α-trifluoromethyl-substituted ketones.[a)]



R	Yield [%]	ee [%] (config.)
C_6H_{13}	98	97 (*R*)
c-C_6H_{11}	90	97 (*S*)
c-$C_6H_{11}CH_2$	97	98 –
$PhCH_2$	97	97 –
$PhCH_2CH_2$	99	96 –
$PhCH_2OCH_2$	100	86 –
p-ClPh	8	38 –
p-CH_3OPh	100	83 –

a) The catalyst was prepared and isolated before use.

Another series of experiments has been performed using simple ketones substituted by fluoroalkyl groups. In this way it is clearly shown that the presence of a perfluorine group adjacent to the carbonyl to be hydrogenated is essential in order to provide both excellent activities and enantioselectivities (Table 33.9).

The direct substitution by a trifluoromethyl group led in most cases to excellent results, as detailed in Table 33.10.

33.5 Conclusions

Enantioselective catalytic hydrogenation is unquestionably one of the most significant transformations for use in both laboratory- and industrial-scale syntheses. The development of tunable chiral phosphorous ligands, and their ability to control enantioselectivity and reactivity, has allowed enantioselective catalytic hydrogenation to achieve unprecedented versatility and synthetic utility. This is exemplified in the preparation of enantiomerically enriched intermediates from prochiral ketones, notably in the synthesis of drugs and fine chemicals. Despite these excellent results, problems persist with regard to practical applications, notably the very high cost of some ligands, often in excess of that of the rhodium catalyst. In addition, TON values will also need to be increased. Whilst the nature of the chiral ligand is important, and fine tuning of the electronic properties may enhance the reaction's rate-limiting steps, reactivity and enantioselectivity may also be improved by changing the anion. Overall, rhodium-

based catalysts compare well with their ruthenium counterparts, while the use of chiral and/or highly dissymmetric mixed ligands has also proved successful. One major breakthrough in hydroformylation has been the use of a phosphine-phosphinite ligand [38] (also seen with the AMPP EPHOS ligand [39]), though future research must take into account the fact that asymmetric *and* dissymmetric ligands may lead to excellent enantioselectivities. It is essential that this point is considered in any future studies aimed at synthesizing new ligands from starting materials available in the chiral pool.

Abbreviations and Acronyms

AMPP *am*ino *p*hosphine *p*hosphinite
BAMP bisaminophosphine
KPL ketopantoyllactone
TON turnover number

References

1 (a) B. R. James, *Homogeneous Hydrogenation*, Wiley, New York, **1973**; (b) A. P. G. Kieboom, F. van Rantwijk, H. van Bekkum, *Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry*, Delft University Press, Rotterdam, **1977**; (c) A. J. Birch, D. H. Williamson, *Organic Reactions*, New York, **1976**, Vol. 24, p. 1; (d) B. R. James, *Adv. Organomet. Chem.* **1979**, *17*, 319; (e) R. Noyori, M. Kitamura, in: R. Scheffold (Ed.), *Modern Synthetic Methods*. Springer, Berlin **1989**, Vol. 5, p. 115; (f) H. Takaya, R. Noyori, in: B. M. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, Vol. 8. Pergamon, Oxford, **1991**, p. 443; (g) H. Takaya, T. Ohta, R. Noyori, in: I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*. VCH, New York, **1993**, Chapter 1; (h) P. A. Chaloner, M. A. Esteruelas, F. Joo , L. A. Oro, *Homogeneous Hydrogenation*, Kluwer, Dordrecht, **1994**; (i) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**, Chapter 2; (j) H. Brunner, in: G. Helmchen, R. W. Hoffman, J. Mulzer, E. Schaumann (Eds.), *Methods of Organic Chemistry* (Houben-Weyl), 4th edn. Thieme, Stuttgart, **1995**, Vol. E21d, p. 3945; (k) V. Fehring, R. Selke, *Angew. Chem. Int. Ed.*, **1998**, *37*, 1827.

2 (a) P. Rylander, *Catalytic Hydrogenation in Organic Syntheses*, Academic Press, New York, **1979**; (b) P. N. Rylander, *Hydrogenation Methods*, Academic Press, London, **1985**; (c) K. Harada, T. Munegumi, in: B. M. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, Vol. 8. Pergamon, Oxford, **1991**, p. 139; (d) S. Siegel, in: B. M. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, Vol. 8. Pergamon, Oxford, **1991**, p. 417.

3 (a) T. Ohkuma, R. Noyori, in: M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, Vol. 2. Wiley-VCH, Weinheim, **1998**, p. 25; (b) T. Ohkuma, R. Noyori, in: E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*. Springer, Berlin, **1999**, Vol. 1, p. 199; (c) T. Ohkuma, M. Kitamura, R. Noyori, in: I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*, 2nd edn. Wiley-VCH, New York, **2000**, p. 1.

4 (a) Y. Izumi, A. Tai, *Stereo-Differentiating Reactions: The Nature of Asymmetric Reactions*; Academic Press, New York, **1977**; (b) B. Bosnich (Ed.), *Asymmetric Catalys-*

sis. Martinus Nijhoff, New York, **1986**; (c) I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*. VCH, New York, **1993**; (d) H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis*. VCH, Weinheim, **1993**; (e) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*. Wiley, New York, **1994**; (f) G. Jannes, V. Dubois (Eds.), *Chiral Reactions in Heterogeneous Catalysis*; Plenum, New York, **1995**; (g) B. Cornils, W.A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*. VCH, Weinheim, **1996**; Vols. 1 and 2; (h) M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*. Wiley-VCH, Weinheim, **1998**; Vols. 1 and 2; (i) E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*. Springer, Berlin, **1999**; Vols. 1–3; (j) I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*. Wiley-VCH, New York, **2000**.

5 (a) G.M.R. Tombo, D. Bellus, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1193; (b) B. Cornils, W.A Herrmann, M. Rasch, *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 2144; (c) H.-U. Blaser, B. Pugin, in: G. Jannes, V. Dubois (Eds.), *Chiral Reactions in Heterogeneous Catalysis*. Plenum, New York, **1995**, p. 33; (d) R. Noyori, S. Hashiguchi, in: B. Cornils, W.A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds* VCH, Weinheim, **1996**; Vol. 1, p. 552; (e) H.-U. Blaser, B. Pugin, F. Spindler, in: B. Cornils, W.A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*. VCH, Weinheim, **1996**; Vol. 2, p. 992; (f), W.A. Herrmann, B. Cornils, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1049; (g) W. Keim, in: M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*. Wiley-VCH, Weinheim, **1998**; Vol. 1, p. 14; (h) H.-U. Blaser, F. Spindler, in: E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*. Springer, Berlin, **1999**; Vol. 3, p. 1427; (i) R. Schmid, M. Scalone, in: E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*. Springer, Berlin, **1999**, Vol. 3, p. 1440; (j) T. Aratani, in: E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*. Springer, Berlin, **1999**; Vol. 3, p. 1451; (k) S. Akutagawa, in: E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), *Comprehensive Asymmetric Catalysis*. Springer, Berlin, **1999**; Vol. 3, p. 1461; (l) H.U. Blaser, F. Spindler, M. Studer, *Applied Catalysis A: General* **2001**, *221*, 119; (m) G. Beck, *Synlett* **2002**, 837.

6 R.R. Schrock, J.A. Osborn, *J. Chem. Soc. Chem. Commun*. **1970**, 567.

7 H. Fujitsu, E.Matsumura, K. Takeshita, L. Mochida, *J. Chem. Soc. Perkin Trans I* **1981**, 2650.

8 (a) M.J. Burk, T.G.P. Harper, J.R. Lee, C. Kalberg, *Tetrahedron Lett*. **1994**, 35, 4963; (b) I.M. Lorkovic, R.R. Duff, Jr., M.S. Wrighton, *J. Am. Chem. Soc.* **1995**, *117*, 3617.

9 C.A. Tolman, *Chem. Rev.* **1977**, *77*, 313.

10 (a) K. Achiwa, T. Kogure, I. Ojima, *Chem. Lett*. **1977**, 4431; (b) I. Ojima, T. Kogure, T. Terasaki, K. Achiwa, *J. Org. Chem*. **1978**, *43*, 3444; (c) I. Ojima, T. Kogure, Y. Yoda *Org. Synth*. **1985**, *63*, 18.

11 (a) K. Tani, K. Suwa, E. Tanigawa, T. Yoshida, T. Okano, S. Otsuka, *Chem. Lett*. **1982**, 261; (b) K. Tani, K. Suwa, T. Yamagata, S. Otsuka, *Chem. Lett*. **1982**, 265; (c) K. Tani, T. Ise, Y. Tatsuno, T. Saito, *J. Chem. Soc. Chem. Commun*. **1984**, 1641; (d) K. Tani, E. Tanigawa, Y. Tatsuno, S. Otsuka, *J. Organomet. Chem*. **1985**, *279*, 87; (e) K. Tani, K. Suwa, E. Tanigawa, T. Ise, T. Yamagata, Y. Tatsuno, S. Otsuka, *J. Organomet. Chem*. **1989**, *370*, 203.

12 K. Yamamoto, Saeed-ur-Rehman, *Chem. Lett*. **1984**, 1603.

13 T. Morimoto, H. Takahashi, K. Fujii, M. Chiba, K. Achiwa, *Tetrahedron Lett*. **1986**, *27*, 4477; T. Morimoto, H. Takahashi, K. Fujii, M. Chiba, K. Achiwa, *Chem. Lett*. **1986**, 2061.

14 A. Broger, Y. Crameri, *EP 0218970* **1987**; R. Schmid, *Chimia* **1996**, 50, 110.

15 (a) A. Karim, A. Mortreux, F. Petit, G. Buono, G. Peiffer, C. Siv, *J. Organomet. Chem*. **1986**, *317*, 93; (b) C. Hatat, A. Karim, N. Kokel, A.Mortreux, F. Petit, *Tetrahedron Lett*. **1988**, 29, 3675; (c) C. Hatat, A. Karim, N. Kokel, A. Mor-

treux, F. Petit, *New J. Chem.* **1990**, *14*, 141; (d) A. Roucoux, F. Agbossou, A. Mortreux, F. Petit, *Tetrahedron: Asymm.* **1993**, *4*, 2279; (e) F. Agbossou, J.-F. Carpentier, C. Hatat, N. Kokel, A. Mortreux, P. Betz, R. Goddart, C. Krüger, *Organometallics* **1995**, *14*, 2480; (f) A. Roucoux, M. Devocelle, J.-F. Carpentier, F. Agbossou, A. Mortreux, *Synlett* **1995**, 358; (g) A. Roucoux, L. Thieffry, J.-F. Carpentier, M. Devocelle, C. Méliet, F. Agbossou, A. Mortreux, A. J. Welch, *Organometallics* **1996**, *15*, 2440; (h) A. Roucoux, I. Suisse, M. Devocelle, J.-F. Carpentier, F. Agbossou, A. Mortreux, *Tetrahedron: Asymm.* **1996**, *2*, 379; (i) M. Devocelle, F. Agbossou, A. Mortreux, *Synlett* **1997**, 1306; (j) J.-F. Carpentier, A. Mortreux, *Tetrahedron: Asymm.* **1997**, *8*, 1083; (k) C. Pasquier, S. Naili, L. Pelinski, J. Brocard, A. Mortreux, F. Agbossou, *Tetrahedron: Asymm.* **1998**, *9*, 193; (l) F. Agbossou, J.-F. Carpentier, F. Hapiot, I. Suisse, A. Mortreux, *Coord. Chem. Rev.* **1998**, *178*, 1615; (m) V. Blandin, J. F. Carpentier, A. Mortreux, *Eur. J. Org. Chem.* **1999**, 1787; (n) M. Devocelle, A. Mortreux, F. Agbossou, J.-R. Dormoy, *Tetrahedron Lett.*, **1999**, *40*, 4551; (o) C. Pasquier, S. Naili, A. Mortreux, F. Agbossou, L. Pélinski, J. Brocard, J. Eilers, I. Reiners, V. Peper, J. Martens, *Organometallics* **2000**, *19*, 5723; (p) C. Pasquier, S. Naili, L. Pelinski, J. Brocard, A. Mortreux, F. Agbossou, *Tetrahedron Lett.* **2001**, *42*, 2809.

16 Examples of carbohydrate diphosphinites: (a) R. Selke, H. Pracejus, *J. Mol. Catal.* **1986**, *37*, 213 and references cited therein; (b) R. Selke, *J. Mol. Catal.* **1986**, *37*, 227; (c) R. Selke, M. Schwarze, H. Baudish, I. Grassert, M. Michalik, G. Oehme, N. Stoll, B. Costisella, *J. Mol. Catal.* **1993**, *84*, 223; (d) R. J. Selke, *Organomet. Chem.* **1989**, *370*, 241; (e) W. R. Cullen, Y. Sugi, *Tetrahedron Lett.* **1978**, *19*, 1635; (f) H.-J. Kreutzfeld, C. Döbler, H. W. Krause, B. Facklam, *Tetrahedron: Asymm.* **1993**, *4*, 2047; (g) T. V. RajanBabu, T. A. Ayers, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1994**, *62*, 6012; (h) T. V. RajanBabu, B. Radetich, K. K. You, T. A. Ayers, A. L. Casalnuovo, J. C. Calabrese, *J. Org. Chem.* **1999**, *64*, 3429.

17 For examples of open-chain sugar-based diphosphanes: (a) M. Yamashita, M. Naoi, H. Imoto, T. Oshikawa, *Bull. Soc. Chem. Jpn.* **1989**, *62*, 942; (b) Y. Chen, Li, X., S. K. Tong, M. C. K. Choi, A. S. C. Chan, *Tetrahedron Lett.* **1999**, *40*, 957; (c) A. Bendaya, H. Masotti, G. Peiffer, C. Siv, A. Archalvis, *J. Organomet. Chem.* **1993**, *444*, 41; (d) B.M. Choudary, M. Ravichandra Sarma, A. Dyurga Prasad, N. Narender, *Indian J. Chem.* **1994**, *33B*, 152.

18 (a) S. Naili, I. Suisse A. Mortreux, F. Agbossou, M. Ait Ali, A. Karim, *Tetrahedron Lett.* **2000**, *41*, 2867.

19 N. W. Boaz, S. D. Debenham, E. B. Mackenzie, S. E. Large, *Org. Lett.* **2002**, *14*, 2421.

20 (a) T. Hayashi, M. Mise, M. Kumada, *Tetrahedron Lett.* **1976**, 4351; (b) T. Hayashi, A. Katsumura, M. Konishi, M. Kumada, *Tetrahedron Lett.* **1979**, 425; (c) K. Inoguchi, S. Sakuraba, K. Achiwa, *Synlett*, **1992**, 169.

21 H. Takahashi, S. Sakuraba, H. Takeda, K. Achiwa, *J. Am. Chem. Soc.* **1990**, *112*, 5876.

22 (a) H. Takeda, S. Hosokawa, M. Aburatani, K. Achiwa, *Synlett* **1991**, 193; (b) S. Sakuraba, K. Achiwa, *Synlett* **1991**, 689.

23 (a) H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Motimoto, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 363; (b) H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Motimoto, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 367.

24 H. Takahashi, T. Morimoto, K. Achiwa *Chem. Lett.* **1987**, 855.

25 S. Törös, B. Heil, L. Kollár, L. Markó *J. Organomet. Chem.* **1982**, *232*, C17.

26 D. Liu, W. Gao, C. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2005**, *44*, 1687.

27 A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062.

28 F. Cederbaum, C. Lamberth, C. Malan, F. Naud, F. Spindler, M. Studer, H. U. Blaser, *Adv. Synth. Catal.* **2004**, *346*, 842.

29 P. Kreye, A. Lehnhart, F. D. Klingler, Boehringer Ingelheim Pharma GmbH & Co. K.-G., (Germany). German Patent (2004), 6 pp. DE 10249576 B3 20040408.

30 S. Sakuraba, N. Nakajima, K. Achiwa *Tetrahedron: Asymm.* **1993**, (4), 1457.

31 T. Morimoto, K. Yoshikawa, M. Murata, N. Yamamoto, K. Achiwa. *Chem. Pharm. Bull.* **2004**, 52, 1445.

32 For enantioselective synthesis of compounds **55a**, **55b** and **56**, see: (a) V. Ratovelomanana-Vidal, C. Girard, R. Touati, J. P. Tranchier, B. B. Hassine, J. P. Genêt, *Adv. Synth. Catal.* **2003**, *345*, 261, and references therein. For enantioselective synthesis of **62**, see: (a); for **59**: J. Deeter, J. Frazier, G. Staten, M. Staszak, L. Weigel, *Tetrahedron Lett.* **1990**, *31*, 7101; **60**: H. Liu, B. H. Hoff, T. Anthonsen, *Chirality* **2000**, *12*, 26; **61**: A. Kamal, G. B. R. Khanna, R. Ramu, T. Krishnaji, *Tetrahedron Lett.* **2003**, *44*, 4783.

33 H. P. Märki, Y. Crameri, R. Eigenmann, A. Krasso, H. Ramuz, K. Bernauer, M. Goodman, K. L. Melmon, *Helv. Chim. Acta* **1988**, *71*, 320.

34 R. G. Griffiths, J. Dancer, E. O'Neill, J. L. Harwood, *New Phytologist* **2003**, *158*, 345.

35 O. Ort, U. Döller, W. Reissel, S. D. Lindell, T. L. Hough, D. J. Simpson, J. P. Chung, *Pesticide Sci.* **1997**, *50*, 331.

36 Y. Kuroki, Y. Sakamaki, K. Iseki, *Org. Lett.* **2001**, *3*, 457.

37 Y. Kuroki, D. Asada, K. Iseki, *Tetrahedron. Lett.* **2000**, *41*, 9853.

38 N. Sakai, S. Mano, K. Nozaki, H. Takaya, *J. Am. Chem. Soc.* **1993**, *115*, 7033.

39 Y. Pottier, A. Mortreux, F. Petit, *J. Organomet. Chem.* **1989**, *370*, 333.