Selective Hydrogenation for Fine Chemicals: Recent Trends and New Developments

Hans-Ulrich Blaser,* Christophe Malan, Benoît Pugin, Felix Spindler, Heinz Steiner, Martin Studer

Solvias AG, R 1055.628, P.O. Box, CH-4002 Basel, Switzerland
Fax: (+41)-61-686-6311, e-mail: hans-ulrich.blaser@solvias.com

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Abstract: In this overview, recent trends and developments for the selective hydrogenation of multifunctional molecules are discussed and assessed from the point of view of fine chemicals synthesis. In a first part, the design and preparation of catalysts and ligands with interesting properties are summarized, particularly meant for the catalysis specialist. The following topics are described in some detail: How enantioselective homogeneous catalysts are designed and tested; new effective chiral monodentate phosphines; successful bidentate phosphines ligand families (with axially chiral biaryl- and ferrocenyl-based backbones, new phospholanes and with stereogenic phosphorus); novel bidentate ligand families with P-O and P-N bonds; and oxazoline-based ligands. A short overview on immobilized chiral complexes and of the toolbox of heterogeneous catalysis (bimetallic, colloidal and modified catalysts) concludes this chapter. In a second part, progress for selected catalytic transformations and generic selectivity problems is described, intended mainly for the organic chemist who has to solve specific synthetic problems. Emphasis is on the following topics: The enantioselective hydrogenation of olefins with various substitution patterns; the chemo- and enantioselective hydrogenation of ketones; the diastereo- and enantioselective hydrogenation of C=N functions; the stereoselective hydrogenation of aromatic rings; chemoselectivity and hydroxylamine accumulation in the reduction of functionalized nitroarenes; chemoselectivity and new protecting groups for catalytic debenzylation; the mild hydrogenation of carboxylic acid derivatives; and the chemoselective hydrogenation of nitriles. In the last parts of the review, transfer hydrogenation and mechanistic issues are discussed, followed by a short conclusions and outlook paragraph.

Keywords: chiral diphosphines; enantioselective hydrogenation; fine chemicals; heterogeneous catalysts; homogeneous catalysts; hydrogenolysis; review; selective hydrogenation

From left to right: H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, and M. Studer.

Hans-Ulrich Blaser received the Diploma in Natural Sciences from the Federal Institute of Technology (ETH) Zürich in 1966. His doctoral research was carried out with A. Eschenmoser at the same institution, from which he received the PhD degree in 1971. Between 1971 and 1975 he held post-doctoral positions at the University of Chicago (J. Halpern), Harvard University (J. A. Osborn), and Monsanto (Zürich). During 24 years at Ciba-Geigy (1976–1996) and Novartis (1996–1999) he gained practical experience in R&D in the fine chemicals and pharmaceutical industry. At Solvias he is presently chief technology officer. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals and fine chemicals (both as project leader and section head). His main interests are the development and the industrial application of selective catalysts.

Christophe Malan studied chemistry in Toulon and Grenoble, as well as in Konstanz (Erasmus exchange student). He received the Diploma of Molecular Chemistry in 1994 and the PhD degree in 1997 from the University of Grenoble. His doctoral research was performed under the supervision of Dr. Ch. Morin. His first post-doctoral stay was at Marburg University with P. Knochel (1997–1998), followed by a second one at the University of Geneva with A. Alexakis (1998–1999). In both stays, he worked on asymmetric synthesis and catalysis with organometallics. He then joined the research group at Chirotech (1999–2001) and started his carrier in the field of industrial asymmetric synthesis and catalysis. Since 2001, he is a senior scientist at Solvias, where he is currently working on customer projects as well as doing research in asymmetric hydrogenation.

Benoît Pugin studied chemistry at the ETH in Zürich and stayed there to carry out his PhD thesis with Prof. Venanzi in the field of metal organic chemistry and homogeneous catalysis. In 1982 he moved to Ciba Geigy for a post-doctoral period where he acquired experience in molecular modeling and synthesis planning. Since 1983 he has been working in the catalysis research group of Ciba Geigy/Novartis and now as a leading scientist Solvias. He has always been attracted by interdisciplinary research and has been in charge of projects in the fields of sonochemistry, catalyst immobilization, enantioselective hydrogenation and catalytic oxidation. Today, his main activity is the development of new chiral ligands for enantioselective catalysis.

Felix Spindler graduated in chemistry at the Federal Institute of Technology (ETH) Zurich in 1976. His doctoral research on homogeneous catalysis was carried out with Prof. Piero Pino at the same institute, where he received the PhD degree in 1981. In 1982 he worked as scientific collaborator in the group of Pino. In 1983 he joined Ciba-Geigy in Basel and gained practical experience at R&D related to the application of homogeneous asymmetric catalysis in the fine chemicals and pharmaceutical industry, which were continued at Novartis (1996–1999) and at Solvias. He presently holds a position as leading scientist in the field of homogenous enantioselective hydrogenation. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals and fine chemicals.

Heinz Steiner received the chemistry technician diploma (Ciba-Geigy AG) in 1977 and the Masters Diploma in Chemistry from the Basel Institute of Technology, Muttenz in 1981. During 1976–1996 he gained broad experience in selective catalytic hydrogenation, high-pressure reactions and fluorine chemistry as a supervisor of Ciba-Geigy's Synthesis Services Group which continued at Novartis (1996–1999). At Solvias he presently is head of the business unit Hydrogenation and High-Pressure Services. During his industrial carrier, he has developed numerous hydrogenation processes for agrochemicals, pharmaceuticals and fine chemicals.

Martin Studer received the Diploma in Chemistry from the University of Basel in 1983. His doctoral research was started in 1984 with T. Kaden at the same institution, from which he received the PhD degree in 1988. Between 1988 and 1990 he held post-doctoral positions at the University Hospital in Basel (Prof. H. Mäcke) and the University of California, Davis (Prof. C. F. Meares). He started his industrial career at Ciba-Geigy (1991–1996) in the catalysis group, first in development, later in research. This continued at Novartis (1996–1999) and at Solvias where he presently is head of catalysis research. His main interests are in catalysis for fine chemical synthesis.

1 Introduction

There is no doubt that hydrogen is the cleanest reducing agent and hydrogenation is arguably the most important catalytic method in synthetic organic chemistry both on the laboratory and the production scale. In his now classical books on "Catalytic Hydrogenation in Organic Syntheses", P. N. Rylander[1a] gives several reasons for this conjecture: The scope is very broad, many functional groups can be hydrogenated with high selectivity, high conversions are usually obtained under relatively mild conditions in the liquid phase, due to the large pool of experience the predictability for solving a particular problem is high, and last but not least, the process technology is well established and scale-up is usually not problematic. Even though Rylander was talking about heterogeneous hydrogenation, the same holds true for homogeneous catalysis where progress in recent years was very spectacular, culminating in the 2001 Nobel Prize to W. S. Knowles and R. Noyori for enantioselective hydrogenation and to K. B. Sharpless for enantioselective oxidation catalysis.[2]

It would be outside the scope of any review to give a comprehensive survey on catalytic hydrogenation and its application to fine chemicals production. In this contribution, we will focus on recent trends and developments (up to June 2002) in areas we find interesting and consider to be important for solving complex synthetic problems on any scale. This does in no way mean that we are not interested in other aspects such as mechanistic or technological aspects, particularly when they help to find better catalysts (and if possible in a shorter time). We will approach the subject from two directions: For the catalysis specialist we describe recent trends and results concerning the design and preparation of novel catalysts and ligands with interesting properties. For the organic chemist we review the state of the art and recent progress for selected catalytic transformations and generic selectivity problems. Finally, we have added short chapters summarizing new results for transfer hydrogenation as well as current discussions on the mechanism of hydrogenation. A complementary review with emphasis on hydrogenation technology for the fine chemicals and pharmaceutical industry was recently published by Machado et al.[3] discussing aspects such as reactor and mixing technologies, high throughput screening, supercritical and sonochemical processing, or structured catalysts.

2 Design, Preparation and Catalytic Results of Homogeneous Catalysts

2.1 Designing Homogeneous Hydrogenation Catalysts

Most effective homogeneous hydrogenation catalysts are complexes consisting of a central metal ion, one or more (chiral) ligands and anions which are able to activate molecular hydrogen and to add the two H atoms to an acceptor substrate. The nature of the ligand and, to a somewhat lesser extent, of the anion control the catalytic properties of a particular metal for a specific transformation. Experience has shown that low-valent Ru, Rh and Ir complexes stabilized by tertiary (chiral) phosphorus ligands are the most active and the most versatile catalysts.[4] Not surprisingly, a majority of the past as well as of the current research is focused on this type of complexes. For particular applications, cyclopentadienyl complexes of early transition metals such as Ti or Zr show better selectivities,[4b] and very recently stabilized secondary phosphines[5a] and carbenes[5b] were also found to be suitable ligands for the Rh-catalyzed H_2 activation. Complexes which are active for transfer hydrogenation have different ligand requirements and are discussed in Section 5.

2.1.1 Synthetic Toolbox

As already pointed out, the choice of the ligand is decisive for the catalytic performance of a metal

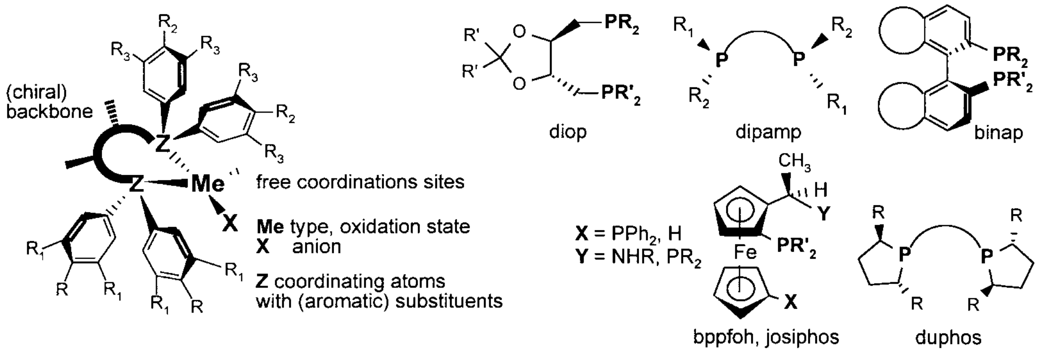


Figure 1. Design elements for chiral metal complexes and privileged ligand types for hydrogenation applications (with first examples).

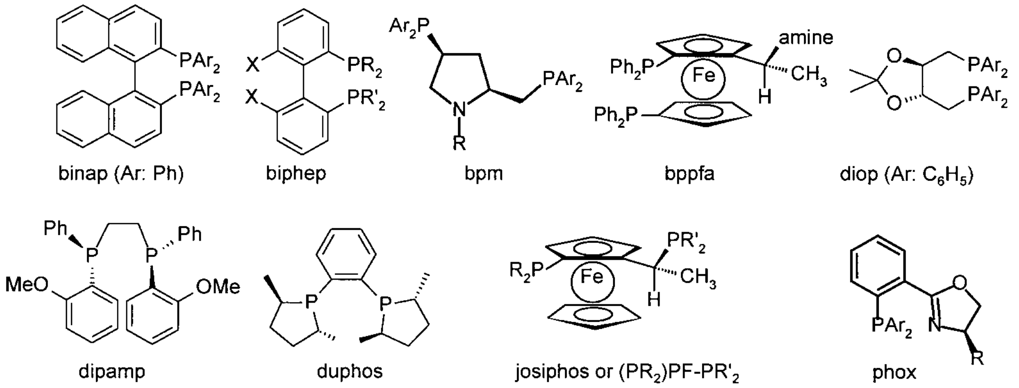


Figure 2. Structures and names or abbreviations of privileged ligands.

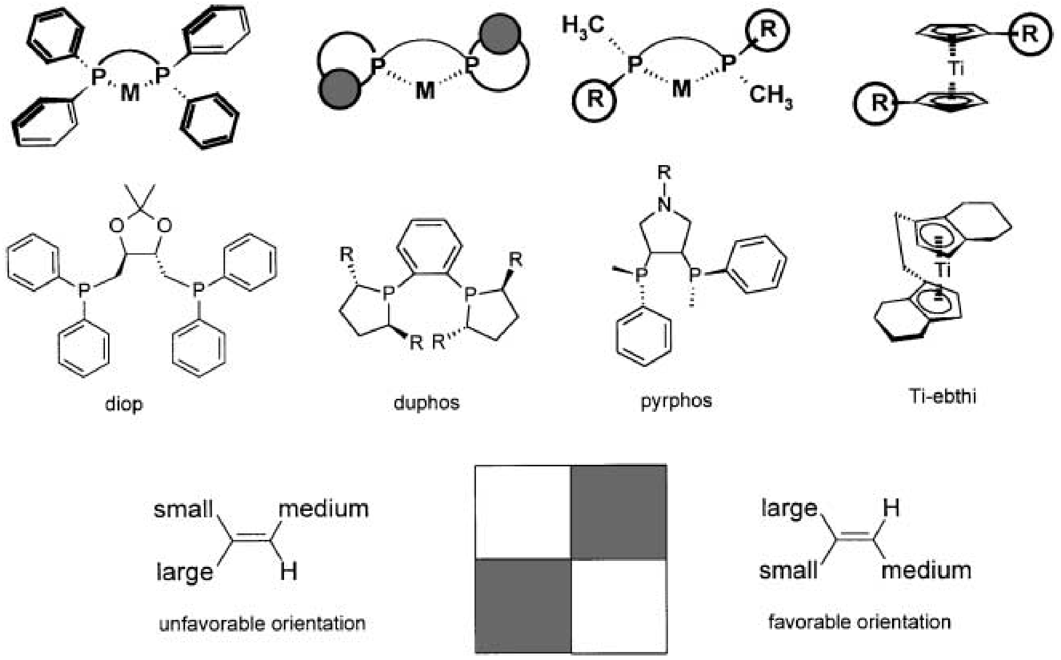


Figure 3. The quadrant model.

complex. The nature and structure of the ligand will influence how the metal center will react with H_2 and the substrate *via* a number of well understood elementary steps such as oxidative addition, insertion and reductive elimination (see also Section 6). During these transformations the ligand must be able to stabilize various oxidation states and coordination geometries. Very little ligand design has been reported for non-enantioselective applications and indeed Wilkinson's catalyst, $RhCl(PPh_3)_3$ is still the most widely applied complex in synthetic chemistry. The situation is very different for enantioselective hydrogenation where an impressively large number of chiral ligands is recorded in the literature which are able induce enantiocontrol and afford high enantioselectivities for a variety of catalytic reactions.[4a] However, if one has a closer look at the ligands really used by the synthetic organic chemist in academia, and even more so in industry, a very different picture emerges. Only very few chiral ligands are applied on a regular basis for the synthesis of commercially relevant target molecules[6] and Jacobsen has once coined the term "privileged ligands" for these selected few depicted in Figs. 1 and 2.

If one analyzes the structures of these ligands, several design principles can be identified which might lead to good enantiocontrol. Generally speaking, these measures create the necessary flexibility of the ligand to give high turnover rates and impart sufficient rigidity to control stereoselectivity. It has to be stressed though that there are always examples where just the opposite is true (giving a very good introduction to a publication). A ligand is more likely to induce high enantioselectivity if it

- is bidentate,[7a] usually *cis*-chelating for more rigidity (first example: diop), the optimal chelate size depend-

Ligand Glossary (abbreviation, type and Figure No.).

Abbreviation	Type	Fig.	Abbreviation	Type	Fig.
ambox	oxazoline – N	33	**L11 – L13**	one P-O/P-N	28
basphos	phospholane	24	**L14 – L18**	one P-O/P-N	30
bdpmi	miscellaneous	35	**L19 – L22**	two P-O/P-N	31
bicp	miscellaneous	35	**L23 – L26**	three P-O/P-N	32
bicpo	one P-O/P-N	28	L27 – L31	oxazoline – P	33
binap	biaryl	8	**L27 – L31**	oxazoline – P	33
binaphane	biaryl, ferrocenyl	11	**L34 – L38**	amino alcohol	57
binapo	one P-O/P-N	28	**L39**	oxazoline – P	57
biphep	biaryl	8	malphos	phospholane	24
bisbenzodioxanphos	biaryl	11	mandyphos	ferrocenyl	16
bisp*	P-chiral	26	Me-pennphos	phospholane	24
bophoz	ferrocenyl	16	miniphos	P-chiral	26
bppfa	ferrocenyl	15	monophos	monodentate	6
bppfoh	ferrocenyl	15	phanephos	miscellaneous	35
butiphane	phospholane	24	phox	oxazoline – P	3
Cat1 – Cat5	catalyst	58	p-phos	biaryl	11
daipen	diamine	14	ppm	miscellaneous	3
diop	miscellaneous	3	PR_2PF-PR'_2 (josiphos)	ferrocenyl	3
dipamp	P-chiral	3	pyrphos	P-chiral	26
dpen	diamine	14	R,S,S,R-diop (diop*)	miscellaneous	35
duphos	phospholane	24	rophos	phospholane	24
ebthi	miscellaneous	35	segphos	biaryl	11
eniphos	one P-O/P-N	28	siphos	monodentate	6
Et-bpe	phospholane	24	spirop	one P-O/P-N	28
f-binaphane	biaryl	11	tangphos	phospholane, P-chiral	24
ferrotane	phospholane	24	taniaphos	ferrocenyl	16
glup	one P-O/P-N	28	tataphos	miscellaneous	35
H_8-binap	biaryl	8	tlanop	one P-O/P-N	30
jm-phos	oxazoline – C	33	tmbtp	biaryl	11
josiphos (PR_2PF-PR'_2)	ferrocenyl	3	trap	ferrocenyl	16
L1 – L3	monodentate	6	ts-dach, ts-dpen	diamine	57
L4	sec. phosphine	7	tunaphos	biaryl	11
L5	biaryl	11	walphos	ferrocenyl	16
L6 – L8	phospholane	24	xylphanephos	miscellaneous	35
L9, L10	P-chiral	26			

ing on the backbone (miniphos forms 4-, dipamp 5-, bppfoh 6-, diop, binap 7- and walphos 8- membered metallocycles). The trap ligands (see Section 2.4.2.6) form 9-membered chelates for which the *trans* configuration is accessible for the first time;

- has C_2 symmetry[7a] (first example: diop) or is very strongly unsymmetrical[7b] (e.g., josiphos) in order to reduce the number of possible isomeric catalyst-substrate complexes;
- has two aryl or bulky alkyl groups at the P atom to "transfer" chirality from the more remote chiral backbone (first example: diop);
- has chiral elements as close as possible to the adsorbed substrate, e.g., the stereogenic P atom (first example: dipamp[8]);
- has the P atom included in a ring bearing stereogenic centers [7c] (first example: duphos);
- is modular, allowing ready tuning of steric and electronic properties[7d] (e.g., josiphos family).

In addition to these guidelines, adding an extra functional group to control the orientation of the reactant *via* secondary interactions[9] or restricting the conformational flexibility by additional substituents or bridges[10] has been successful. The first generation of chiral ligands had CH_2-PPh_2 or Ar-PPh_2 moieties. Later it was found that almost all types of three-coordinated phosphorus compounds with P-C, P-O or P-N bonds can give active complexes with high enantioselectivities. The first chiral ligands all had central chirality and were often prepared from chiral pool starting materials, e.g., diop from tartrate, prophos from lactic acid or glup from sugars.[11a] Later, backbones with axial (e.g., binap) as well as planar chirality (e.g., ferrocenylphosphines) proved to be just as effective.

2.1.2 Naming of Ligands

The naming of a new ligand does not follow any rules. Quite common are names with a connection to a company or university such as duphos (Dupont) or pennphos (Penn State) or to a person such as josiphos (Josephine Puleo) or tangphos. Also quite widespread are names related to a structural characteristic, e.g., binap or monophos and abbreviations of chemical names such as bppfa or PR_2PF-PR'_2. In order to help to find a particular ligand structure, the ligand glossary indicates which type a specific ligand represents and where the structure is depicted.

A number of privileged ligands will occur often in our review and their structures and names are listed in Figure 2. For new ligands, either the abbreviation or name used in the original paper or an **Lx** number will be used.

2.1.3 Explaining the Result: The Quadrant Rule

The question how the chiral ligand is able to control the sense of induction, i.e., the preferred addition of hydrogen either to the *re*- or *si*-face of a C=X bond has been addressed by many researchers. The most general concept which has evolved is the "quadrant rule":[12] upon coordination of the ligands to the metal atom, the substituents at the coordinating atoms are oriented in such a way that a chiral array is formed where two diagonal quadrants are blocked by bulky substituents. In Figure 3, four categories are depicted:

i) diphosphines, with two PAr_2 moieties attached to a chiral backbone, as for example binap or diop;
ii) diphosphines in which two chiral phosphacycloalkanes are connected to an achiral scaffold, as represented by duphos;
iii) diphosphines, in which the two chiral P atoms bear two sterically different substituents, as with dipamp, the pyrphos derivative or bis-P*;
iv) bis-cyclopentadienyl complexes of the ebthi type where the substituents of the cp rings occupy a defined space.

When the substrate coordinates to the metal atom, it will orient in such a way that steric repulsion is minimal. In many cases, this simple model is able to predict the sense of induction and also why certain substrate types are better suited than others (e.g., *E*- vs. *Z*-dehydroamino acids). While this model has indeed some merit, it has narrow limits and will not be able to explain more complex situations.[12b]

2.2 Catalytic Test Results

When assessing the results reported for new ligands, one has to keep in mind that the quality and relevance differ widely. For most new ligands only experiments under standard conditions with selected model test substrates were carried out (see Figure 4). The test substrates for olefins used most frequently are acetamidoacrylic acid (AAA) and acetamidocinnamic acid (ACA) derivatives or their methyl esters (MAA, MAC), itaconic acid or dimethyl itaconate (ITA, DMIT) and selected arylenamides. Test substrates for C=O are often acetoacetone and alkyl acetylacetates (AcAc, AcAcOR) and acetophenones, for C=N various derivatives of acetophenone (see Figure 4). These values are usually optimized for enantioselectivity, catalyst productivity (given as TON, turnover number or s/c, substrate/catalyst ratio) and catalyst activity (given as TOF, turnover frequency, h^{-1}, for high conversions) are only a first indication of the potential of a ligand. The decisive test, namely the application of a new ligand to "real world problems" will come later and tell about the scope and limitations of a given ligand (family) concerning tolerance to changes in the substrate structure and/or the presence of functional groups.

2.3 Chiral Monodentate Ligands

Even though monodentate phosphines were the first chiral ligands to be prepared and applied to enantioselective hydrogenations, with few exceptions (see Figure 5) they never matched the unparalleled enantioselectivities of bidentate ligands. In the last few years a

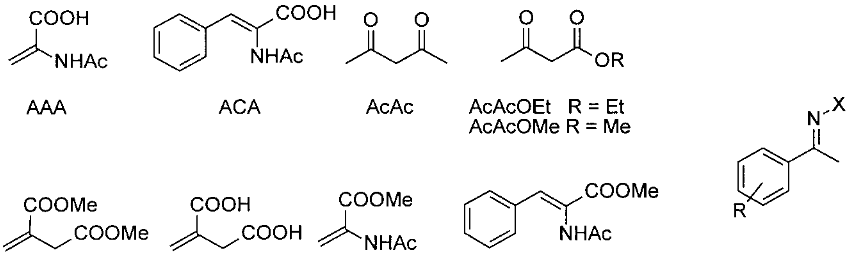


Figure 4. Structures and abbreviations of frequently used model test substrates.

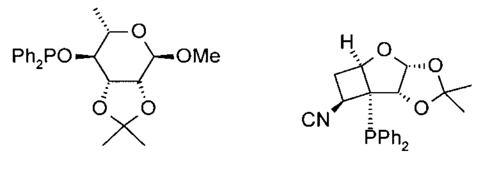


Figure 5. First generation monodentate ligands effective for the Rh-catalyzed hydrogenations.[11b]

revival has taken place and several novel ligand types show promising results in model test reactions.[13] The ligands are not yet available on a commercial bases but some are in the development stage.[14c]

2.3.1 Phosphonates, Phosphoramidites, Phosphites

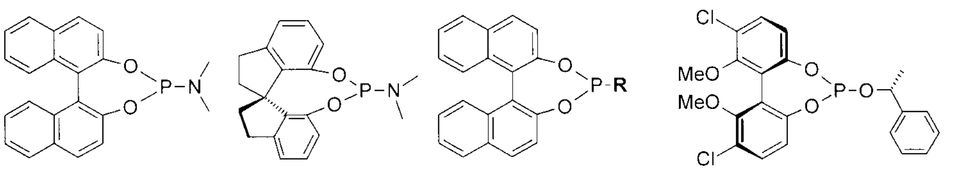
When reports appeared on the excellent catalytic properties of monodentate phosphoramidites[14] and phosphites[15] complexes for Rh-catalyzed hydrogenation reactions, this was surprising for two reasons. Firstly, that Rh complexes with this type of phosphorus ligand were active hydrogenation catalysts and, secondly, the fact that monodentate ligands achieved equal or even better enantioselectivities than the bidentate analogues. Both ligand families are modular and can be prepared from cheap, readily available starting materials. The ligands are not very air sensitive and have satisfactory hydrolysis stability. Combinations of several diols with P-O or P-N fragments have been prepared, but the most effective ligands have a binol (or closely related) backbone as depicted in Figure 6. In our view, some of these ligands have a good potential for industrial application but the scope and limitations are not yet established.

2.3.1.1 Phosphoramidites

Monophos and H_8-monophos, the simplest phosphoramidite ligands give the best results for the Rh^+-catalyzed hydrogenation of C=C bonds (Table 1, entries 1–3), routinely achieving ees for MAA, MAC and DMIT derivatives of > 90–99.9% with low to moderate TONs and TOFs, although these can be improved at 5–15 bar.[14c] Siphos, a spiro-phosphoramidite ligand, is very effective for α-arylenamides (entry 4) and is also able to hydrogenate MAC derivatives with ees > 99%. The Rh complexes can be used in a wide range of solvents with consistently good enantioselectivities. Other types of phosphoramidites are less effective.[16]

2.3.1.2 Phosphonites and Phosphites

The binol phosphonite derivatives (Figure 6, **R** = alkyl) give ees up to 92%;[15a] the results for the analogous phosphites both with small alcohols (R = O-alkyl)



L1 R = O-Alk
L2a R = *(R)*-O-CH(CH_3)Ph
L2b R = *(-)*-O-menthyl

Figure 6. Structures and abbreviations for ligands mentioned in Table 1.

Table 1. Selected results for the hydrogenation of C=C systems with cationic Rh-phosphoramidite and phosphite complexes (ligand structures and abbreviations see Figure 6).

Entry	Ligand (R)	Substrate	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	monophos	MAC	60	110	1650	97	at 1 bar 93%, TOF 1 h^{-1}	[14a]
2	monophos	MAA	1	20[a]	1[a]	99.6		[14a]
3	H_8-monophos	Cl-MAC[b]	20	500[a]	62[a]	99.9	ee 95.9% for Cl-ACA	[14b]
4	siphos	arylenamides	10–50	200[a]	20[a]	92–99.7[c]	ee 84% at s/c 1000	[14d]
5	**L1**	DMIT	1.3	1000	50	97.6 (*S*)	R = O-*i*-Pr	[15b]
6	**L2a**	DMIT	1.3	5000	250	99.4 (*S*)	**L2a′**[d] 98.4% (*S*)	[15b]
7	**L2b**	DMIT	50	10,000	830	94.4 (*S*)	90.5% (*R*) with (*R*)-binol	[15c]
8	**L3**	DMIT	0.5	10,000	5700	99		[15e]

[a] Standard test results, not optimized.
[b] 2- or 4-Cl substituted.
[c] At 5 °C.
[d] With *(S)*-O-CH(CH_3)Ph.

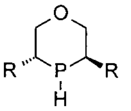

L4 R = *i*-Pr, cyclohexyl

Figure 7. Structures of effective secondary phosphines.

(Table 1, entry 5) and with more elaborate alcohols are quite impressive: MAC, MAA and DMIT can be hydrogenated with ees of 95–99%, TONs up to 10,000 and TOFs up to 1650 h^{-1} (entries 6 and 7). The absolute configuration of the binol part dictates the sense of induction, the alcohol part is useful for fine-tuning. The hydrogen pressure affects ees only slightly but has the expected positive effect on TOF. An interesting variant is the combination of conformationally flexible biphenol with menthol, resulting in up to 68% ee for the hydrogenation of DMIT.[15d] Phosphites **L3** with a substituted biphenyl backbone are also very effective ligands[15e] showing both very high ees as well as TOFs up to 6000 h^{-1} (entry 8).

Remarkably, the same enantioselectivities are observed for an Rh:L ratio of 1:1 and of 1:2. Since there are indications that an RhL_2 complex is the active species[15b] this suggests a complex solution behavior. The X-ray structure of a PtL_2Cl_2-complex[15a] shows that rotation of the ligand around the Pt-P bond is hindered thus reducing the number of rotamers, maybe one reason for the high enantioselectivities achieved with these monodentate ligands.

2.3.2 Secondary Phosphines

Maybe even more surprising than the effectiveness of phosphite ligands was the report by the Helmchen[5a] group that sterically hindered secondary phosphines as depicted in Figure 7 are suitable ligands for the Rh-catalyzed hydrogenation of itaconic, acetamidocinnamic and acetamidoacrylic acid with ees of 86–96%, and TONs of 100–500 albeit with rather low TOFs of *ca.* 4–20 h^{-1}. The secondary phosphines have to be stored as a borane adduct and deprotected before the preparation of the cationic Rh-$(R_2P\text{-}H)_2$ complex. These ligands represent a new type of cyclic phosphines (see Section 2.4.3).

2.4 Bidentate Phosphine Ligand Families

2.4.1 Axially Chiral Biaryl Ligands

2.4.1.1 Binap and Biphep

When binap hit the scene in 1980[17a] probably not even its inventors expected such an amazing success for a single ligand. Today, binap and a wide variety of axially chiral analogues are without any doubt the most versatile class of chiral ligands. Excellent enantioselectivities as well as good to very good activities have been achieved for a variety of synthetically important transformations.[4c,6a] In the area of hydrogenation the most successful applications are for various activated ketones, α,β-unsaturated acids, allylic alcohols and enamides usually with Ru complexes.

This success and the rather restricted licensing policy of Takasago led to a flurry of activities to find alternatives to binap and even today the search for new analogues is still going strong. The first success was achieved by Roche with the very versatile biphep ligand family which at least in part was successful because of its variability.[18] Binap and biphep derivatives which have been applied for solving industrial problems are depicted in Figure 8, selected application results are described in Figures 9 and 10. Since it would not be possible to review all successful ligands reported in the literature,

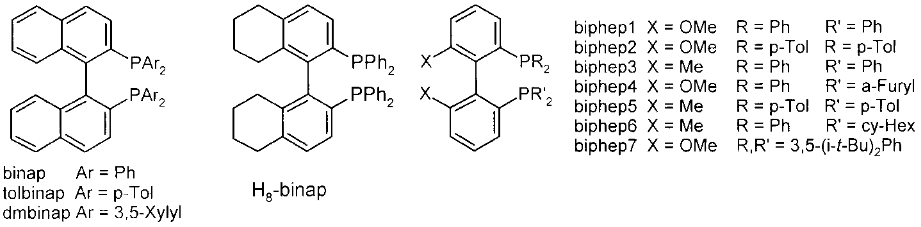
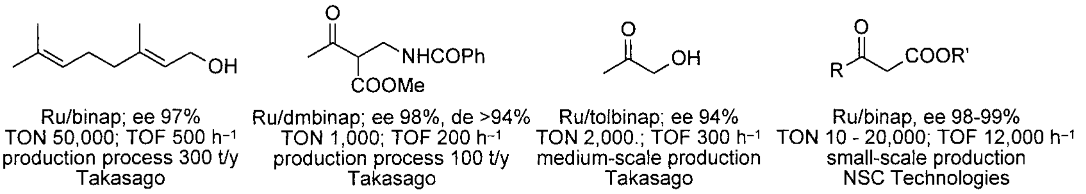


Figure 8. Structures and abbreviations of binap and biphep derivatives applied to industrial problems.[6,17b]



Ru/binap; ee 97%
TON 50,000; TOF 500 h^{-1}
production process 300 t/y
Takasago

Ru/dmbinap; ee 98%, de >94%
TON 1,000; TOF 200 h^{-1}
production process 100 t/y
Takasago

Ru/tolbinap; ee 94%
TON 2,000.; TOF 300 h^{-1}
medium-scale production
Takasago

Ru/binap, ee 98-99%
TON 10 - 20,000; TOF 12,000 h^{-1}
small-scale production
NSC Technologies

Figure 9. Industrial applications of Ru – binap catalysts (for details, see refs.[3b, 17b]).

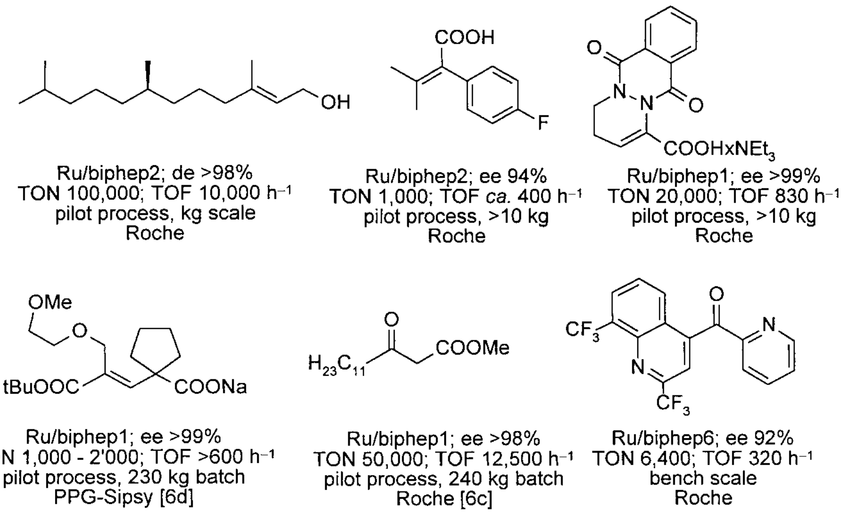


Figure 10. Industrial applications of Ru-biphep catalysts (for details, see refs.[6b, c,d]).

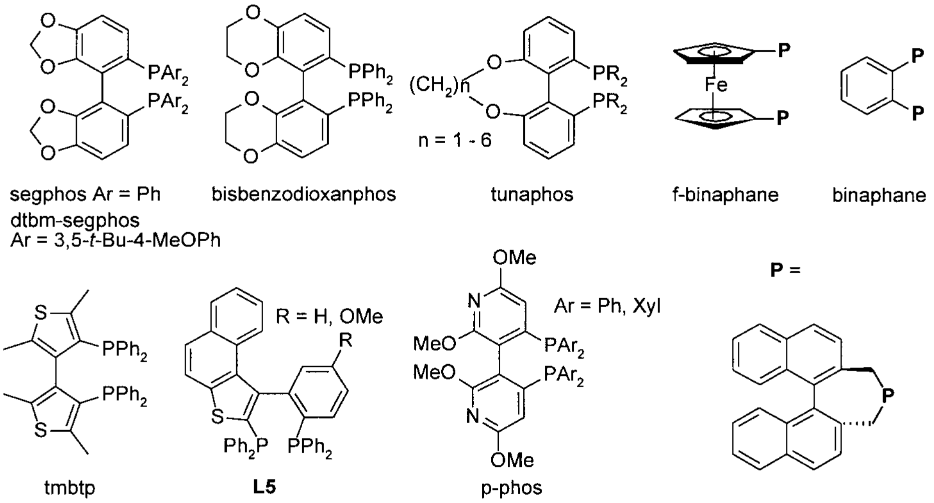


Figure 11. Structures and abbreviations of new axially chiral ligands.

we restrict ourselves to some recent original and/or successful new examples.

2.4.1.2 New Binap Analogues

Some relatively simple variations of the original binap have been exploited with good success. Replacing the PPh_2 group of binap by *p*-tolyl (tolbinap) or 3,5-xylyl (dmbinap) as well as the partial hydrogenation of the binaphthyl group (H_8-binap) generally improve both enantioselectivity and activity for a number of transformations (for selected examples see, Table 2, entries 1–5). Bisbenzodioxanphos showed comparable results to H_8-binap (entry 6).

An empirical correlation between enantioselectivity and the dihedral angle of the biaryl backbone[19] inspired attempts to design segphos and tunaphos. Both ligands indeed showed improved results relative to both binap and biphep1 (Table 2, entries 7–11 and 12). For tunaphos, ees for the hydrogenation of **4c** changed from around 90% for $n = 1$, to $> 99\%$ for $n = 3$ or 4 and then decreased to 96–97% for $n = 5$, 6, respectively.[19b] Whether similar tuning effects can be achieved for other transformations remains to be seen. An interesting new variant of an axially chiral ligand are the binaphanes designed by Zhang which are excellent ligands for Ir-catalyzed imine hydrogenations[20a] (see Table 24) and for the Rh-catalyzed hydrogenation of substituted α-arylenamides with ees of 95–99.7% (Table 2, entry 15).

A series of binap and biphep analogues with heteroaromatic backbone were developed by Sannicolo[21a, b] and by Chan,[21c] respectively. At least in principle, the heterocycles allow an effective tuning of the electronic without changing the steric properties of the ligand. Both the p-phos as well as Sannicolo's ligands show comparable properties to binap (entries 13, 14) but enantioselectivities and activities are lower than for

Table 2. Selected results for Ru-catalyzed hydrogenations using axially chiral ligands (ligand structures and abbreviations see Figures 8, 11, and 14, for substrates, see Figure 12).

Entry	Ligand	Substrate	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	dmbinap/daipen	**1**	50	500[a]	130	99	24% ee with binap/dpen	[17b]
2	dmbinap/dpen	**2**[a, c]	50	1000	50[c]	99	92% ee with binap	[17b]
3	H_8-binap	**3a**	1.5	200[b]	10[b]	97	91% ee with binap	[17b]
4	H_8-binap	**3b**	100	200[b]	25[b]	97	96% ee with binap	[17b]
5	H_8-binap	**3c**	50	5000	625	92	88% ee, TOF 50 h^{-1} with binap	[17b]
6	bisbenzodioxanphos	**4c**	4	~2000	~100	99.5	R′ = Me	[17c]
7	segphos	**4a**	30	3000	430	99.5		[19a]
8	segphos	**4b**	50	1000	60	98.6	94% for R′ = $PhCH_2CH_2$	[19a]
9	segphos	**4c**	10	10,000	2500	97->99	R′ = Ar, Alk, CH_2Cl, CH_2OBn	[19a]
10	segphos	**4d**	50	1000	50	99		[19a]
11	dtbm-segphos	**5**[a]	30	3000	n.a.	99.4	de 98.6%	[19a]
12	tuna-phos (n = 3, 4)	**4c**	70	200[b]	10[b]	>99	R′ = Me, various esters	[19b]
13	**L5**	**4c**	100	300[b]	60[b]	>99.9	R′ = Me	[21b]
14	p-phos (Ar = xylyl)	**4c**	25	7500	500	93	R′ = Ph	[21c]
15	Rh – binaphane	**6**	1	100[b]	4[b]	95–99.6	Rh complex	[20b]

[a] Dynamic kinetic resolution.
[b] Standard test results, not optimized.
[c] 5 °C, de 99%.

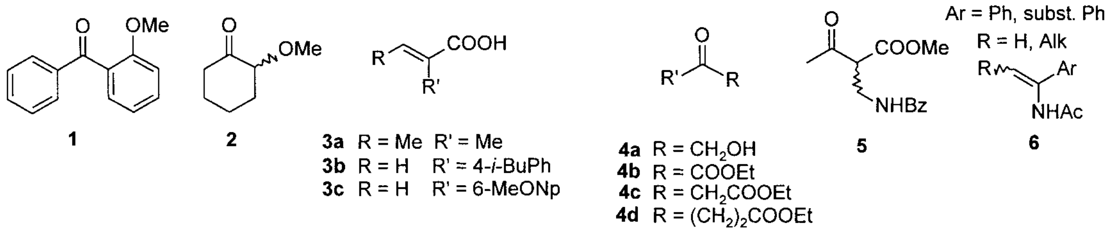


Figure 12. Substrate structures mentioned in Table 2.

segphos or dmbinap; an exception is the hydrogenation of **4c**. As shown in Figure 13, the Ru-tmbtp system has already been scaled-up to pilot scale.

2.4.1.3 Ru-Diphosphine/Diamine Catalysts

Recently, Noyori published the remarkable finding that Ru-binap/diamine complexes are exceptionally active catalysts for the hydrogenation of aryl ketones.[22] In contrast to classical hydrogenation complexes where two coordination sites are occupied by the diphosphine ligand, two additional sites are (and remain) complexed with the diamine.

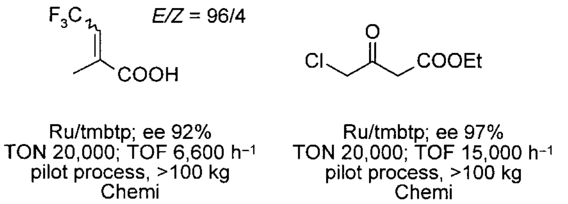


Figure 13. Industrial applications of Ru-tmbtp catalysts (for details, see ref.[6b]).

The new catalyst system has the following characteristics. Besides binap, other biaryl and related phosphines are suitable and while many diamines with at least one N-H group are effective, dpen and daipen often give the best performance (see Figure 14). With chiral diamines, a strong matched-mismatched effect is observed where the absolute configuration is controlled by the phosphine. The matched catalysts are up to 120 times more active than the mismatched ones, making asymmetric activation-deactivation strategies possible.[22f] The complexes are very stable and most active in presence of an inorganic base, usually *t*-BuOK, KOH or K_2CO_3 in an alcoholic solvent. Recently it was shown that both the basic anion [for abstraction of HCl from the RuCl(PP)(NN) precursor] as well as the metal cation are necessary for good activity.[23] It has been established that hydrogen is activated *via* a heterolytic mechanism and that no hydrogen transfer occurs from the alcoholic solvent. Remarkably, the transfer of the two H atoms to the ketone occurs without coordination of the C=O bond to the Ru center[23a, b] (see Section 6).

Significant results for the hydrogenation of acetophenones are compiled in Table 3. Entry 1 shows what is currently the TON world record for homogeneous

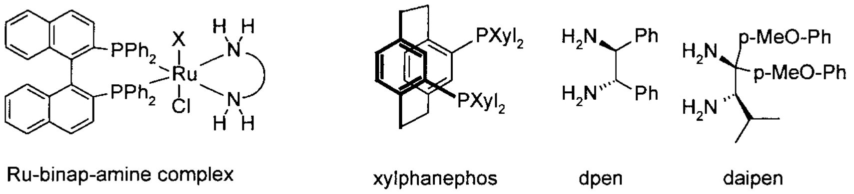


Figure 14. Structures and abbreviations for phosphines and amines mentioned in Table 3.

Table 3. Selected results for the hydrogenation of acetophenone with Ru-diphosphine-diamine complexes (ligand structures and abbreviations see Figure 14).

Entry	Complex	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	$RuCl_2$-(*S*)-tolbinap/(*S,S*)-dpen	45	2.4 Mio	50,000	80		[22b]
2	$RuCl_2$-(*S*)-dmbinap/(*S*)-daipen	8	97,000	1,620	99		[22c]
3	$RuH(BH_4)$-(*S*)-dmbinap/(*S,S*)-dpen	8	100,000	14,000	99	no base needed	[24d]
4	$RuCl_2$-(*R*)-phanephos/(*S,S*)-dpen	8	40,000	10,000	98.5		[22e]

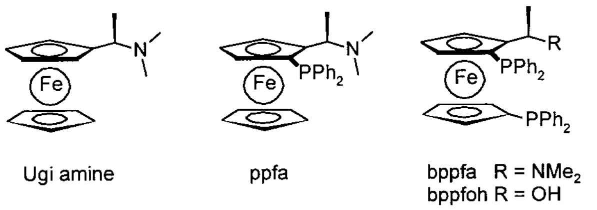


Figure 15. Structures of the first ferrocene-based chiral ligands.

catalysts, albeit with only 80% ee; entries 2–4 demonstrate that by the right combination of diphosphine and diamine very high ees and TONs are routinely obtained for acetophenone. The scope for other ketones is equally impressive. Acetophenones with a wide variety of ring substituents give consistently >97% ee with either the $RuCl_2$-dmbinap/daipen[22c] or $RuCl_2$-phanephos/dpen[22e] catalytic systems; steric bulk in α-position leads to decreased catalytic activity but still good enantioselectivities. Hydrogenation of furanyl, thienyl, pyridyl, pyrolyl and thiazolyl methyl ketones leads to the corresponding alcohols in >96–99.8% ee.[22e, g] Base-sensitive ketones can be hydrogenated without side reactions using the novel $RuH(BH_4)$-(*S*)-dmbinap/(*S,S*)-dpen catalyst.[24c] α-Amino ketones are also excellent substrates.[24c] *ortho*-Substituted benzophenones are hydrogenated to give unsymmetrical benzhydrols in ees of 93–99.4%.[24b] With the exception of *t*-butyl methyl ketone (ee up to 95%, TON 11,000, TOF 1000 h^{-1}), dialkyl ketones give enantioselectivities below 85%.[4c] Interestingly, only few reports describe the application for C=N hydrogenation and usually with low selectivity and activity.

Except for the production of (*R*)-1-phenylethanol as a fragrance,[17b] no applications of the Ru-diphosphine/diamine catalysts to "real world" synthetic problems have yet been published.

2.4.2 Ferrocenyl-Based Diphosphines

Ferrocene as a (rather exotic) backbone for diphosphine ligands was introduced by Kumada and Hayashi based on the pioneering work of Ugi related to the synthesis of enantiopure substituted ferrocenes[25] (see Figure 15). Ppfa as well as bppfa and bppfoh proved to be effective

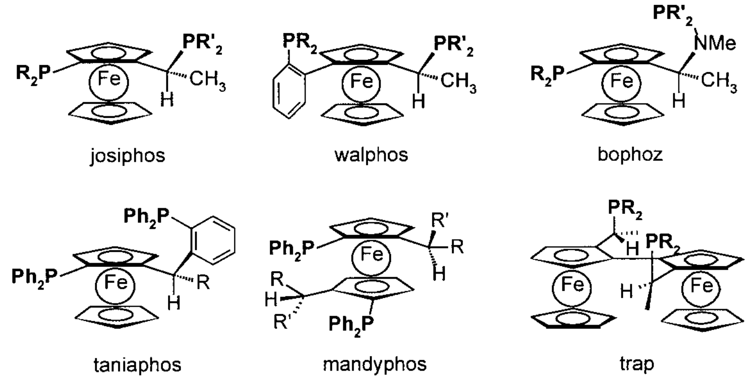
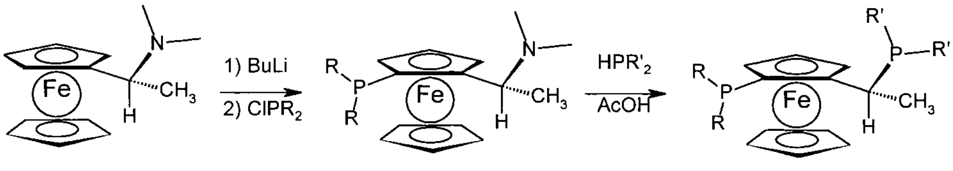
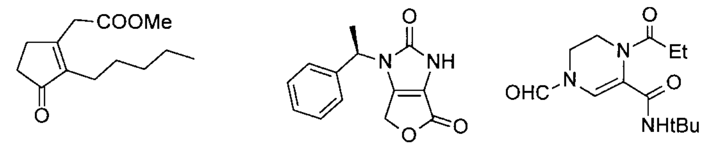


Figure 16. Structures and names of ferrocene-based ligand families.



R and R': substituted aryl, alkyl, cycloalkyl

Figure 17. Preparation of josiphos ligands starting from the Ugi amine.



Ru/josiphos or duphos; ee 90%
TON 2,000; TOF 200 h^{-1}
medium-scale production
Firmenich

Rh/josiphos; de 99%
TON 2,000; TOF n.a.
medium-scale production
Lonza

Rh/josiphos; ee 97%
TON 1,000; TOF 450 h^{-1}
pilot process, >200 kg
Lonza

Figure 18. Industrial applications of josiphos ligands (for details, see ref.[6b]).

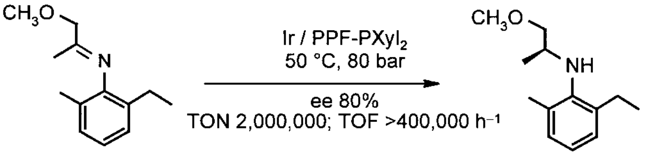


Figure 19. The industrial process for (*S*)-metolachlor of Ciba-Geigy/Syngenta.[27]

ligands for a variety of asymmetric transformations. From this starting point, several ligand families with various structural variations have been developed in the last few years (see Figure 16). In the following sections, we will briefly describe the various structures and compare the best catalytic results.

2.4.2.1 Josiphos

The first variation was carried out by Togni and Spindler by introducing the second phosphino group at the stereogenic center of the side chain of the Ugi amine. The resulting josiphos ligands of Solvias represent at the moment arguably the most versatile and successful ferrocenyl ligand family.[7c, d] Because the two phosphine groups are introduced in consecutive steps with very high yields (see Figure 17) a variety of ligands are available with widely differing steric and electronic properties. The ligands are technically developed, available in commercial quantities and have already been applied in 3 production processes, several pilot processes (see Figures 18 and 19) and many other syntheses. Major fields of application are the hydrogenation of C=N functions (see Table 4, entry 1), tetrasubstituted C=C bonds, itaconic acid derivatives and selected enamides (entries 2–4).

2.4.2.2 Walphos

The starting point for walphos is also the Ugi amine. Like josiphos, walphos is modular but forms 8-membered metallocycles due to the additional phenyl ring attached to the cyclopentadienyl ring.[28a] It shows promise for the enantioselective hydrogenation of olefins and ketones (Table 4, entries 5–7) with noticeable electronic effects but its scope is still under investigation. Several members of this ligand class are available on a technical scale.[7d] The first synthetic application for the hydrogenation of SPP100-SyA, an intermediate of the renin inhibitor SPP100 has just been realized (see Figure 20).

2.4.2.3 Bophoz

Bophoz is a combination of a phosphine and an aminophosphine and is prepared in 4 steps from ppfa with high overall yields. The ligand is air stable and effective for the hydrogenation of enamides, itaconates and α-keto acid derivatives (Table 4, entries 8 and 9). As observed

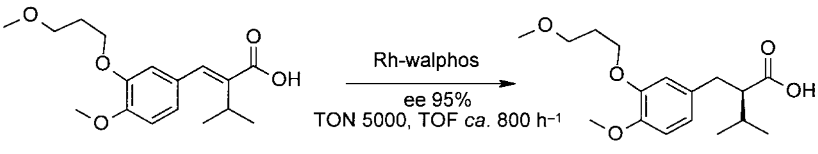


Figure 20. Bench-scale application of the walphos ligand.[26a]

Table 4. Selected results for Rh- and Ru-catalyzed hydrogenation using josiphos (**J**), walphos (**W**) and bophoz (**B**) ligands (ligand structures and abbreviations, see Figure 16, substrates, see Figure 21).

Entry	M-Ligand (R, R')[a)]	Substrate	$p(H_2)$	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	Rh-**J** (Ph, Xyl)	MEA imine	50	2 Mio	>400,000	80	production process (Fig. 19)	[27]
2	Rh-**J** (Ph, Cy or *t*-Bu)[a]	C=C tet[b]	–	2000	200	>90	production processes	[7d]
3	Rh-**J** (Ph, Cy)	MAA	1	100[c]	330[c]	97		[7d]
4	Rh-**J** (Ph, Cy)	DMIT	1	100[c]	200[c]	90–99.9		[7d]
5	Rh-**W** (Ph, Ar)	MAC	1	200[c]	≥10[c]	95	Ar = 3,5-Me_2-4-MeO-Ph	[28b]
6	Ru-**W** (Ar, Ar')	**7**	5	1000	≥60	95	Ar' = 3,5-CF_3-Ph	[28b]
7	Ru-**W** (Ph, Ar')	AcAc	20	1000	≥60	96	*dl:meso*: >99:1	[28b]
8	Rh-**B** (Ph, Ph)	MAC	1	100[c]	≥20[c]	99.1%	ee 98.5% for MAA	[29]
9	Rh-**B** (Ph, Cy)	**8**	20	100[c]	≥15[c]	97%	α-keto esters 90–92% ee	[29]

[a] Cy = cyclohexyl.
[b] See Figure 18.
[c] Standard test results, not optimized.

for several ligands forming seven-membered chelates high activities can be reached and TONs up to 10,000 have been claimed. The full scope of this modular ligand class has not yet been explored.

2.4.2.4 *Taniaphos*

Compared to the josiphos ligands, taniaphos has an additional phenyl ring inserted at the side chain of the Ugi amine.[30a] Whereas the effect of changing the two phosphine moieties has not yet been investigated much, the nature of the substituent R has a strong effect on the enantioselectivity for the hydrogenation of MAC and DMIT (Table 5, entries 1 and 2). Surprisingly, R = Me leads to the opposite absolute configuration of the product compared to R = NMe_2, *i*-Pr or H. β-Functionalized ketones are hydrogenated using Ru-taniaphos (R = dialkylamine) but catalytic activities are lower than for the state of the art Ru-binap catalysts. Again a dependence of the sense of induction on the nature of R is observed with $N(i\text{-}Bu)_2$ inducing opposite configuration (entry 3). Dynamic kinetic resolution of β-keto esters and β-diketones is achieved with des between 80–99% and ees of up to >99%, comparable to Ru-binap catalysts.

2.4.2.5 *Mandyphos*

Mandyphos is a bidentate version of ppfa with C_2 symmetry, where in addition to the PR_2 moieties, R and R' can be used for fine tuning purposes as well. The scope of this ligand family has not been yet explored but preliminary results indicate high enantioselectivities for the Rh-catalyzed hydrogenation of enamides, itaconates and enol acetates (Table 5, entries 4–6).

2.4.2.6 *Trap* (trans-*Chelating) Ligands*

The trap ligands developed by Ito et al.[31] form 9-membered metallocycles for which *trans*-chelation is possible for the first time. However, it is not clear whether the *cis*-isomer present in small amounts or the major *trans*-isomer is responsible for the catalytic activity. Up to now only few different PR_2 fragments have been tested, but it is clear that the choice of R strongly affects the catalytic performance. The Rh complexes work best at very low pressures of 0.5–1 bar and effectively reduce indole-derivatives **10** and **11** (Table 5, entries 7 and 8; the first example of a heteroaromatic substrate with high ees), enamides (entry 9; best ligand PEt_2-trap, unusual p and T effects) and itaconic acid derivatives (entry 10). β-Hydroxy-α-amino acids and α,β-diamino acids can be prepared *via* asymmetric hydrogenation of tetrasubstituted alkenes **13–15** with des of 99–100% and ees of 97% and 82%, respectively, but low catalyst activities (entry 11). Also described was the hydrogenation of an indinavir intermediate **12**[31d] (entry 12).

2.4.2.7 *Miscellaneous Ferrocenyl-Based Diphosphines*

A number of other diphosphines and related ligands with a ferrocene backbone have been described and tested with sometimes very good results. However,

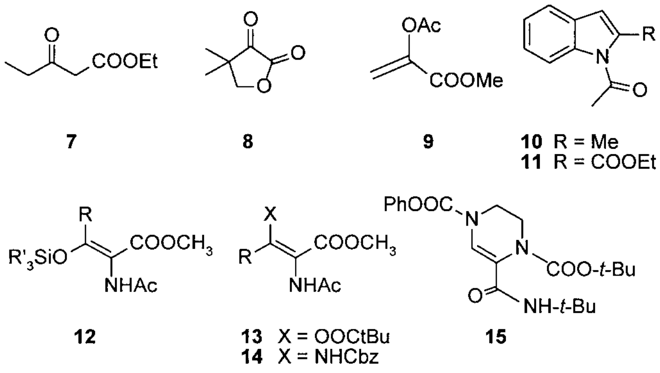


Figure 21. Substrate structures metnioned in Tables 4 and 5.

Table 5. Selected results for Rh- and Ru-catalyzed hydrogenation using mandyphos (**M**), taniaphos (**T**) and trap (**TR**) ligands (ligand structures and abbreviations, see Figure 16, substrate structures, see Figure 21).

Entry	M-Ligand (R)	Substrate	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	Rh-**T** (*i*-Pr)	MAC	1	100[a]	25[a]	96.6 (*R*)	52% (*S*) for R = Me!	[30a]
2	Rh-**T** (*i*-Pr)	DMIT	1	100[a]	25[a]	97.9 (*S*)	19% (*R*) for R = Me!	[30a]
3	Ru-**T** (N(*i*-Bu)$_2$)	AcAcOEt	100	200[a]	25[a]	98.6 (*S*)	95.5% (*R*) for R = NMe$_2$!	[30a]
4	Rh-**M** (Me)	MAC	1	100[a]	$\geq$600[a]	98.6	97.9% ee for MAA	[30b]
5	Rh-**M** (NMe$_2$)	*p*-Cl-MAC	1	100[a]	n.a.	>99	98% ee for MAC	[30d]
6	Rh-**M** (Me)	**9**	1	100[a]	8[a]	94.9		[30c]
7	Rh-**TR** (Ph)/Cs_2CO_3	**10**	50	100[a]	50[a]	94 (*R*)	ee 7% (*S*) without Cs_2CO_3	[31a]
8	Rh-**TR** (Ph)/Cs_2CO_3	**11**	50	100[a]	200[a]	95	ee 78% for Boc derivative	[31a]
9	Rh-**TR** (Et)	MAA	0.5	100[a]	50[a]	96	ee 70% at 1 bar	[31b]
10	Rh-**TR** (Et)	ITA	1	200[a]	30[a]	96	ee 68% for DMIT	[31c]
11	Rh-**TR** (Pr)	**12, 13**	1	100[a]	4[a]	97%	de 99:1; ee 82% for **14**	[31e, f]
12	Rh-**TR** (*i*-Bu)	**15**	1	100[a]	5[a]	97		[31d]

[a] Standard test results, not optimized.

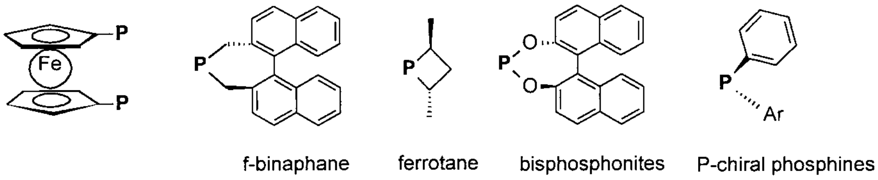
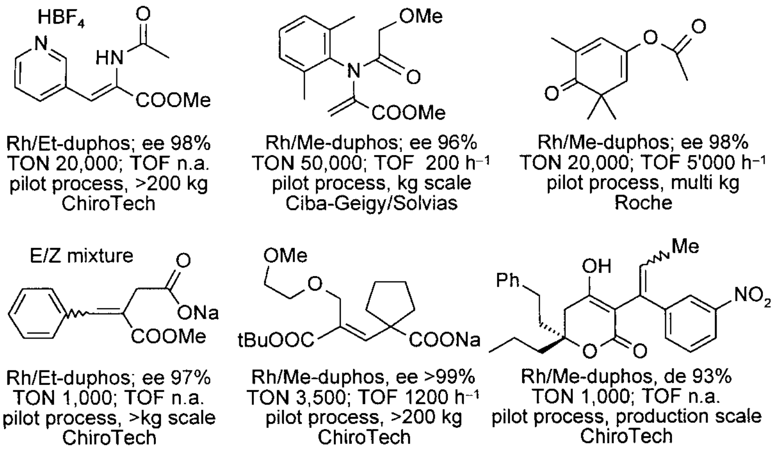


Figure 22. Selected C_2-symmetrical ferrocenyl-based ligands.

because the "character" of these ligands is dominated by another structural element they are described in other sections. Interesting examples are f-binaphane[20a] exhibiting very high ees for imine hydrogenation (see Section 2.4.1.2), ferrocenyl bisphosphonites[32a] (see Section 2.5.2), ferrotane[33] (see Section 2.4.3) and P-chiral phosphines[34] (see Section 2.4.4).

2.4.3 Phospholane Type Ligands

Duphos and its analogues were designed and introduced 1990 by Burk while at Dupont and are among the most versatile ligands available today.[7c] In principle, the ligands are modular because both the backbone as well as the R- groups (see Figure 1) can be adapted to the specific transformation. However, the synthesis of the individual species is not trivial and, indeed, only a limited number of the ligands are applied regularly. Rh-duphos and Rh-bpe complexes are often the catalysts of choice for the preparation of α- and β-amino acid derivatives, the hydrogenation of various *E*- and *Z*-arylenamides, itaconic acid derivatives, enol acetates (*E* and *Z*) and *N*-acylhydrazones. Ru-duphos catalysts are effective for the hydrogenation of α,β-unsaturated acids and β-ketoesters. For all these applications, ees of 95–



Rh/Et-duphos; ee 98%
TON 20,000; TOF n.a.
pilot process, >200 kg
ChiroTech

Rh/Me-duphos; ee 96%
TON 50,000; TOF 200 h-1
pilot process, kg scale
Ciba-Geigy/Solvias

Rh/Me-duphos; ee 98%
TON 20,000; TOF 5'000 h-1
pilot process, multi kg
Roche

Rh/Et-duphos; ee 97%
TON 1,000; TOF n.a.
pilot process, >kg scale
ChiroTech

Rh/Me-duphos, ee >99%
TON 3,500; TOF 1200 h-1
pilot process, >200 kg
ChiroTech

Rh/Me-duphos, de 93%
TON 1,000; TOF n.a.
pilot process, production scale
ChiroTech

Figure 23. Various industrial applications of Rh-duphos catalysts (for details, see ref.[6b]).

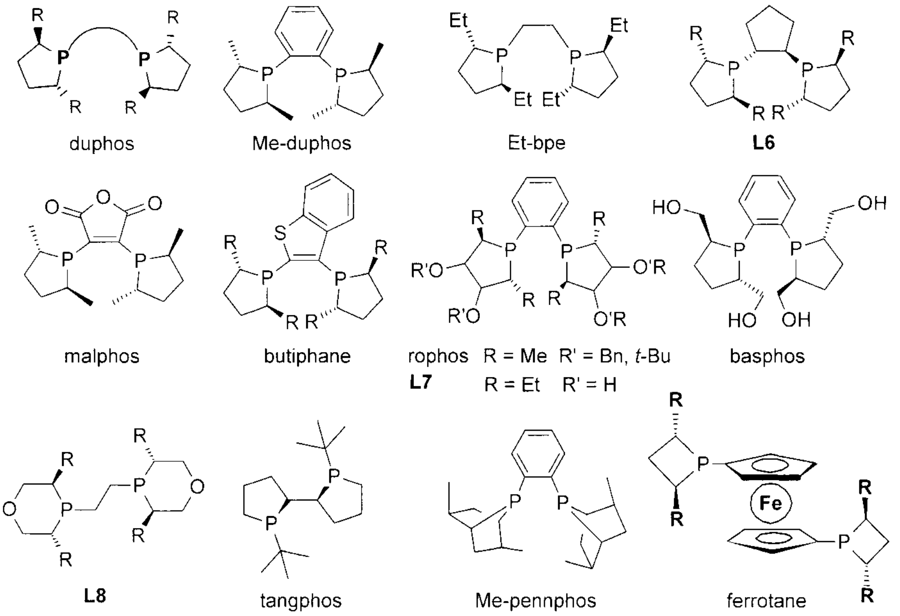


Figure 24. Structures and abbreviations of phospholane and related ligands.

Table 6. Selected results for Rh- and Ru-catalyzed hydrogenation reactions using phospholane ligands (ligand structures and abbreviations, see Figure 24, substrate structures, see Figure 25).

Entry	M-Ligand	Substrate	p(H$_2$)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	Rh-Et-duphos	**16**	1	100[a]	~200	98 – >99	ee 84 – 88% for *Z*-isomer	[35a, b]
2	Rh-malphos	**16**	1	100[a]	~100	95 – >99	ee 83 – 90% for *Z*-isomer	[35b]
3	Rh-butiphane	**16**	1	200[a]	≥20[a]	98	ee 99% for AAA	[26b]
4	Rh – **L6**	MAC	2	200[a]	~100[a]	98	ee 85% for Me-duphos	[36]
5	Rh-rophos	MAC	1	100[a]	<50[a]	97 – 98	ee 93 – 97% for ACA	[35c]
6	Rh-rophos	DMIT, ITA	1	100[a]	<300[a]	97 – 99		[35c]
7	Rh-basphos	AAA	1	100[a]	n.a.	99.6	reaction in water	[35d]
8	Rh-**L7**	AAA, MAA	3	100[a]	9[a]	>99		[10c]
9	Rh-**L7**	DMIT, ITA	10	100[a]	8[a]	>99	solvent MeOH or water	[10c]
10	Rh-**L7**	**17**	10	100[a]	4[a]	91 – >99	*E*/*Z*-mixtures	[10c]
11	Rh-tangphos	MAC, **17**	10	100[a]	8[a]	98 – >99	**17** *E*/*Z*-mixtures	[10d]
12	Rh-pennphos	**18, 19**	2 – 3	100[a]	5[a]	97 – >99		[10e, f]
13	Rh-pennphos[b]	AlkCOMe	2	100[a]	5[a]	73 – 94	ee 94% for R = *t*-Bu	[10g]
14	Rh-ferrotane[c]	**20**	5	1000[a]	1 – 6000[a]	92 – 99		[33a]
15	Ru-ferrotane[d]	β-diketone	70	50[a]	<1[a]	95 – 98	R = Me, de >95%	[33b]
16	Rh-**L8**	AAA, ACA, ITA	1	1000[a]	40[a]	94 – 97		[5a]

[a] Standard test results, not optimized.
[b] In the presence of KBr and 2,6-lutidine.
[c] Et-ferrotane.
[d] *i*-Pr- or cyhex-ferrotane.

>98% can be achieved and a high tolerance for other functional groups has been observed in many "real world" applications of duphos ligands (see Figure 23).

Not surprisingly, the success of the duphos ligands has created considerable activity in other laboratories and a number of interesting variants have been published in the last few years. The structures depicted in Figure 24 show modification of the backbone (butiphane,[26b] malphos[35b]), additional stereogenic centers (**L6**[36]) and/or functional groups (rophos,[35c] basphos[35d] and **L7**[10c]), direct connection of the phospholanes (tangphos,[10d] which is also P-chiral), the bicyclic phospholane pennphos[10e–g], the 4-membered ferrotanes[33] and a 6-membered phosphinane **L8**.[5a] Some of these analogues were obviously designed to circumvent the original patents, others to test mechanistic or design hypotheses. All of them induce similar catalytic characteristics like duphos when the corresponding Rh complexes are applied and notable results are collected in Table 6.

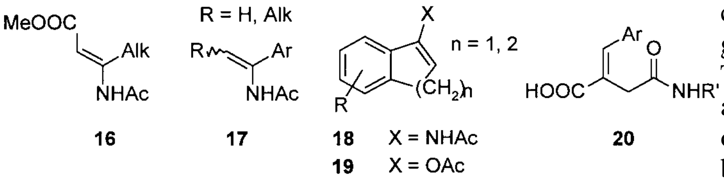


Figure 25. Structure of substrates mentioned in Table 6.

Most results presented in Table 6 do not need much of a comment. In addition to the transformations already described earlier,[7c] Rh-duphos is also an excellent catalyst for the preparation of β-amino acids (entry 1). The results described up to now for the relatively close analogues malphos (entry 2), butiphane (entry 3), rophos or basphos (entries 5–7) and **L7** (entries 8–10) show a similar profile as established for duphos. The introduction of additional stereogenic centers in the 3,4-position had only a marginal effect as demonstrated, e.g., for rophos; the diastereomer of **L6** depicted in Figure 24 achieved higher ees for MAC or MAA compared to Me-duphos (entry 4). Interestingly, this effect could not be rationalized using the quadrant model as applied by Burk[7c] for designing the duphos ligands.[36] Tangphos is certainly one of the smallest effective diphosphines known; it is rather air sensitive but gives high ees for enamides of type **17** (entry 11). The more rigid pennphos outperforms duphos in selected applications, e.g., for cyclic enamides **18** or enol acetates **19** or the hydrogenation of various methyl ketones (entries 12 and 13). The 4-ring ferrotanes show good performance with amidoitaconates and for the Ru-catalyzed hydrogenation of β-diketones with high des (entry 15). Interestingly, the bidentate 6-ring phosphinane **L8** (entry 16) has a similar performance as the monodentate secondary phosphine described in Section 2.3.

2.4.4 P-Chiral Ligands

P-Chiral ligands have seen a somewhat unexpected revival. Even though dipamp, the first ligand achieving not only high ees but also very good catalyst activities had stereogenic P atoms (Table 7, entry 1), diphosphines with chiral backbones proved to be just as effective and much easier to design and synthesize with a wide structural diversity. One reason for the revival was the progress in synthetic methodology for the preparation of P-chiral compounds.[34a] Two successful new structural variations deserve mention, i) the choice of different backbones,[34a, b,37] and ii) the choice of electron-rich phosphines[38] (see Figure 26). Like dipamp, the new ligands are most successful for the Rh-catalyzed hydrogenation of enamides and itaconates. Ligands **L9** and **L10** (entry 3) and particular stereoisomers of pyrphos reduce MAC analogues with ees > 96% (results

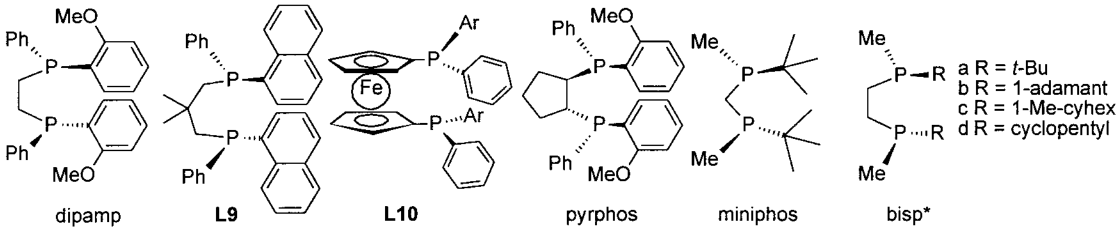


Figure 26. Structure of ligands mentioned in Table 7.

Table 7. Selected results for hydrogenation using cationic Rh complexes with P-chiral ligands (for ligand structures, see Figure 26, for substrate structures, see Figure 27).

Entry	Ligand	Substrate	p(H$_2$)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	dipamp	l-dopa	10	20,000	1000	95	production process	[8]
2	pyrphos	pinacoline	75	300[a]	20[a]	84	30% conversion	[37a]
3	**L9, L10**	**21**	1	200[a]	15[a]	96–98	Ar = Np, *o*-anisyl	[34c, d]
4	bisp* a	MAC	2	500[a]	500[a]	> 99	98% for ACA	[38a]
5	bisp* b	MAA	2	500[a]	500[a]	> 99		[38a]
6	bisp* d	**22b**	6	500[a]	500[a]	93	ee 91% for **22a**	[38a]
7	bisp* a	**23a**	3	100[a]	3–4[a]	99	substituted Ph with lower ee	[38b]
8	bisp* a	**23b**	3	100[a]	3–4[a]	99	inverted compared to R′ = Ph	[38b]
9	bisp* a	**23c**	3	100[a]	3–4[a]	99	ee 98% with miniphos	[38b]
10	bisp* c	DMIT	2	500[a]	500[a]	> 99	ee 98.6% with bisp* a	[38a]
11	miniphos	MAA, AAA	1	500[a]	20[a]	> 99		[38a]
12	miniphos	MIT	2	500[a]	20[a]	99.9	MIT methyl itaconate	[38a]

[a] Standard test results, not optimized.

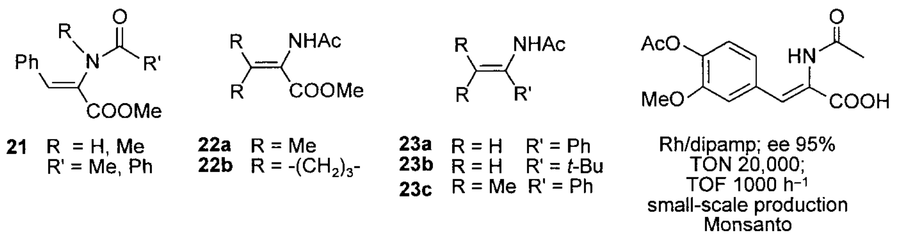


Figure 27. Structures of substrates mentioned in Table 7.

not shown). In contrast to many other ligands, **L9** and **L10** are quite tolerant towards changes in the structure of the amide moiety (such as N-methyl or benzoyl), Rh-pyrphos is also effective for bulky methyl ketones (entry 2). The two ligand families prepared by the group of Imamoto[38] show excellent enantioselectivity for many Rh-catalyzed hydrogenations of enamides (entries 4–12). Especially surprising was the effectiveness of miniphos which forms a 4-membered chelate with Rh. The bisp* ligand family is more effective and versatile compared to the miniphos and the enantioselectivities for enamides, itaconates and especially for tetrasubstituted olefins are equal or superior to the best available ligands known. Interestingly, the absolute configuration is inverted when bulky substrates **23b** are used compared to the phenyl analogues **23a**, explained by a different mode of adsorption when the R' group is very bulky.[38b] In contrast to other Rh-diphosphine complexes these electron-rich Rh catalysts hydrogenate the enamide substrates *via* the dihydride mechanism as discussed in Section 6. Both ligands are highly air sensitive and must be stored as a borane adduct or as the Rh complexes.

2.5 Bidentate Ligand Families with P-O and P-N Bonds

As already pointed out above, the first effective ligands have been phosphines with either alkyl or aryl groups. Later, P-O and P-N moieties were introduced with good success and in the last few years, a wide variety of such ligands has been prepared and tested with several model substrates. Up to now, few applications to more complex and functionalized substrates have been reported and most of the ligands described here are not (yet) available commercially or on a larger scale.

2.5.1 One P-O or P-N Bond: Phosphinites and Aminophosphines

2.5.1.1 Bisphosphinites and Bisaminophosphines

Bidentate phosphinites and aminophosphines with backbones derived from the chiral pool have a long and successful history[11] and for some time a Rh-glup-catalyzed l-dopa process was operated by Isis Pharmaceuticals[6b] (see Figure 29). In this area a number of interesting contributions concerning the hydrogenation of enamides and α-keto acid derivatives have appeared, whereas only poor to moderate ees have been observed for imines[39a] and enamines.[39b]

Rajanbabu[40] has extensively studied stereoelectronic effects using sugar-based phosphinites. Both the sugar backbone as well as the PAr_2 group allow the synthesis of a wide variety of modular ligands resulting in effective Rh complexes for the preparation of aromatic amino-acids (Table 8, entries 1 and 2). A potential problem can be the cost of the "unnatural" ligand enantiomer. Deprotected ligands can be applied in aqueous micellar

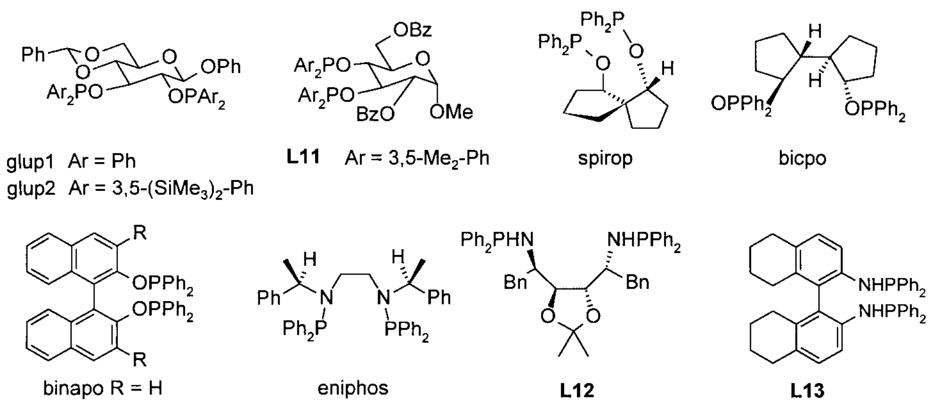


Figure 28. Structures and abbreviations for ligands mentioned in Table 8.

Table 8. Selected results for the hydrogenation of C=C systems with cationic Rh-phosphinite and aminophosphine complexes (ligand structures and abbreviations, see Figure 28).

Entry	Ligand	Substrate	$p(H_2)$	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	glup	MAC	2.5	1000	2000	99		[40a]
2	**L11**	ACA	2.5	1000	2000	97		[40a]
3	spirop	AAA	14	10,000	10,000	96.8	>99.9% ee at 1 bar	[42a]
4	bicpo	AAA	1	100[a]	4[a]	94.7		[42b]
5	binapo	MAA	3	100[a]	8[a]	99.9		[43a]
6	binapo[b]	$ArCOCH_2COOEt$	6	100[a]	5[a]	95–99	ee 96% for AcAcOMe	[43b]
7	binapo[b, c]	Ar(AcNH)C=CHCOOMe	6	25[a]	2[a]	96–99	*E/Z*-mixture	[43b]
8	**L12**	AAA	1	100[a]	5[a]	98		[43c]
9	**L13**	CH_2=C(NHAc)Ph	1	1000	6000	89.5	96.8% ee at 5 °C	[43d]

[a] Standard test results, not optimized.

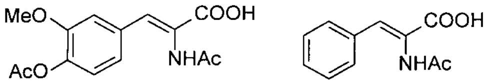
[b] Ru complex.

[c] R = 3,5-Xyl.

solutions with good results,[40b] bisphosphinites based on open-chain sugars are less effective.[41]

Bisphosphinites such as spirop with a spiro[42a], bicpo with a dicyclopentane[42b] or binapo[43a, b] with a binaphthyl backbone also demonstrate the potential of this ligand class for the hydrogenation of dehydroamino acids with ees ranging from >90–99.9% (Table 8, entries 3–5). Binapo also shows very high enantioselectivity for the hydrogenation of aryl substituted β-ketoesters and β-(acylamino)acrylates (entries 6 and 7). With the exception of spirop, TONs and TOFs are low. The cationic Rh complexes are not hydrolyzed in methanol.

Bisaminophosphines have a similar synthetic and catalytic potential and indeed eniphos was actually applied by Enichem to the technical synthesis of an intermediate for aspartame, albeit with only 83% ee[3b] (see Figure 29). New members with a chiral backbone instead of a chiral N-substituent show substantially better enantioselectivity for the more difficult hydrogenation of arylenamides as demonstrated by the performance of **L12** with 4 stereogenic centers and the binaphthyl derivative **L13** (Table 8, entries 8 and 9). Catalytic activities are low to moderate.



Rh/glup1; ee 91-92%
TON 2,000;
TOF *ca.* 330 h^{-1}
small scale production
VEB Isis-Chemie

Rh/eniphos; ee 83%
TON 15,000;
TOF 5,000 h^{-1}
production of 15 t
Enichem/Anic

Figure 29. Industrial applications of glup and eniphos Rh complexes (for details, see ref.[6b]).

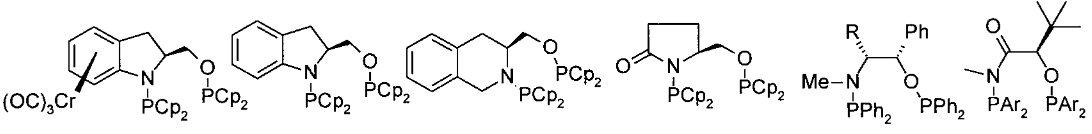
2.5.1.2 *Aminophosphine-Phosphinite Ligands*

Aminophosphine-phosphinite combinations (often abbreviated as NOP) have evolved to be effective ligands for the Rh-catalyzed hydrogenation of a number of α-keto acid derivatives with ees in the range of 95 – >99% and low to good TONs and TOFs[44a, b] (see Table 9, entries 1 – 5). As depicted in Figure 30, many backbones are derived from amino acids but hydroxyamides or other amino alcohols are also suitable starting materials. For the Rh-catalyzed hydrogenation of α-keto acid derivatives, the cyclopentyl derivatives often show the best enantioselectivities. Ir-tlanop yielded ees up to 89% for the hydrogenation of a cyclic iminium salt.[44c] In contrast to the analogous ephedrine-based ligand (R = Me), **L18** (R = Ph) was very effective for the hydrogenation of selected dehydroamino acids with high ees and in some cases high TONs[44d] (entry 6).

2.5.2 *Two P-O Bonds: Diphosphonites*

Diphosphonites based on a binol or related moiety achieve very high ees and respectable TONs for the hydrogenation of enamides and itaconates catalyzed by cationic Rh complexes (see Table 10). While the ferrocenyl backbone is easy to functionalize,[32a] the synthesis

Cp = cyclopentyl



L14 **L15** **L16** **L17** **L18** R = Ph tlanop

Figure 30. Structures and abbreviations for ligands listed in Table 9.

Table 9. Selected results for hydrogenation reactions with Rh-phosphinite-aminophosphine complexes (ligand structures and abbreviations see Figure 30).

Entry	Ligand	Substrate	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	**L14**	ketopantolactone	1	200[a]	1500[b]	>99		[44a]
2	**L14**	PhCOCONHBn	1	82[a]	27[a]	97		[44a]
3	**L15**	ketopantolactone	1	200[a]	2400[b]	>99		[44a]
4	**L16**	PhCOCONHBn	50	200[a]	11[a]	>99		[44a]
5	**L17**	ketopantolactone	1	200[a]	3330[b]	98.7		[44a]
6	**L18**	MAC	50	10,000	630	97	at s/c 100, ee 98.3%	[44c]

[a] Standard test results, not optimized.
[b] At 50% conversion.

Table 10. Selected results for the hydrogenation of C=C systems with cationic Rh-phosphonite complexes (ligand structures and abbreviations, see Figure 31).

Entry	Ligand	Substrate	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	**L19**	DMIT	1.3	5400	270	>99.5		[32a]
3	**L19**	DMIT	1.3	2000	100	99		[32a]
2	**L20**	MAA	1.3	1000	50	99.5		[32a]
4	**L21**	MAA	3.5	1000	2000	99 (*S*)	ee 95% (*S*) for MAC	[32b]
5	**L22**	MAA	3.5	1000	2000	99 (*S*)	ee 74% (*S*) for **L22'**[a]	[32b]
6	**L22**	MAC	5	5000	830	98.5 (*S*)		[32b]

[a] With (*S*)-binol-P.

of the cyclophane-based ligands[32b] is rather cumbersome. In this case, the planar chirality controls sense of selectivity (entries 4–6).

2.5.3 Three P-O Bonds: Phosphite Ligands

As already mentioned, monodentate phosphites have interesting ligand properties and the same holds true for the bidentate analogues as well as for bidentate ligands with one phosphite unit combined with another ligating group as depicted in Figure 32.[45] These ligands are highly modular and allow the tuning of the ligand in an exceptionally wide range; the sense of induction is controlled by the biaryl moiety (see Table 11, entry 3). The D-xylose backbone is cheap but not easy to modify, other sugar backbones give similar results.[45d] **L25** is easy to prepare, analogous phosphite-phosphine ligands

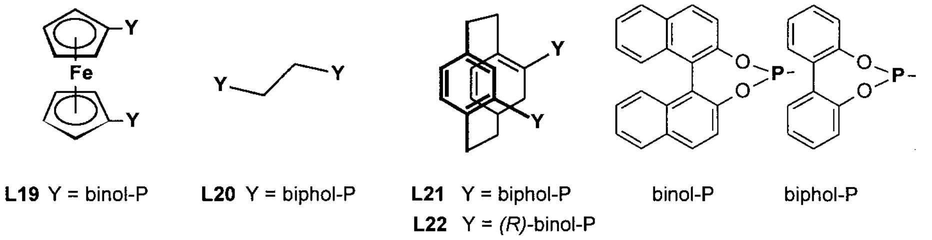


Figure 31. Structures and abbreviations for ligands mentioned in Table 10.

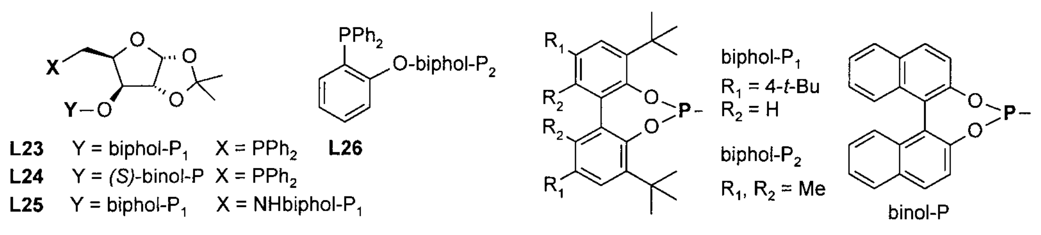


Figure 32. Structures and abbreviations for ligands mentioned in Table 11.

Table 11. Selected results for the hydrogenation of C=C systems with cationic Rh-phosphonite complexes (ligand structures and abbreviations, see Figure 32).

Entry	Ligand	Substrate	$p(H_2)$	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	**L23**	MAC	1	100[a]	30[a]	98.8		[45a]
2	**L23**	MAA	1	100[a]	40[a]	>99 (*R*)		[45a]
3	**L24**	MAA	1	100[a]	300[a]	98.3 (*S*)	with **L24′**[b] ee 97.6% (*R*)	[45a]
5	**L25**	DMIT	30	1000	100	97	at 2.5 bar TOF 6 h^{-1}	[45c]
4	**L26**	DMIT	5	10,000	420	99.6		[45b]

[a] Standard test results, not optimized.
[b] With (*R*)-binol-P.

Table 12. Selected results for Ir-catalyzed hydrogenation using oxazoline-based ligands (ligand structures and abbreviations, see Figure 33, substrate structures, see Figure 34).

Entry	Substrate	Ligand Family	$p(H_2)$	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	**24**	**L27**, **L28**, **L30, L31**	50	>5000[a]	1250[a]	>99[a]		[47a, e,c, d]
2	**24** (R' = H)	**L32**	50	500	250	98	ee 95% for jm-phos	[48a, 5b]
3	**25**	**L27**	100	100[b]	≥50[b]	81	tetrasubstituted C=C	[47a]
4	**26**	**L29**, **L30**	50	100[a]	≥50[b]	96–98		[47a]
5	**27**	**L27**, **L29**	50	100[b]	≥50[b]	95–97		[47a]
6	**28, 29**	**L27**, **L31**	50	100[b]	≥50[b]	97–>99		[47a]
7	**30**	**L27**	100	1000	≥50[b]	89	5 °C, see also Sect. 4.3.1	[47a, b, 73b]
8	**31**	Ru-ambox/PPh_3	5	100[b]	n.a.	96–99	ee 95–98%[c]	[49b]

[a] Optimized values for **L31** with R_1 = Bn, R_2 = Me, R_3 = Ph.
[b] Standard test results, not optimized.
[c] Transfer hydrogenation with *i*-PrOH/*i*-PrONa.[49a]

with an aliphatic instead of the aromatic spacer gave similar results.[45e] The corresponding cationic Rh complexes again are excellent catalysts for the hydrogenation of functionalized C=C bonds with ees of 95 – > 99% and in many cases medium to good TONs and TOFs (entries 1–5). An inherent disadvantage is the relative low stability in protic solvents. The full potential of these ligands has yet to be shown.

2.6 Bidentate Oxazoline-Phosphorus and Related Ligands

The application of chiral bidentate ligands with a phosphorus and a nitrogen as coordinating atoms for Ir-catalyzed hydrogenation reactions pioneered by Pfaltz is relatively recent. The motivation for trying such catalysts traces back to the extraordinary catalytic activities of (pyridine)(phosphine)iridium complexes described by Crabtree in the 1970s.[46] Several classes of ligands have been prepared by the group of Pfaltz[47] and others[48] combining an oxazoline *via* several type of

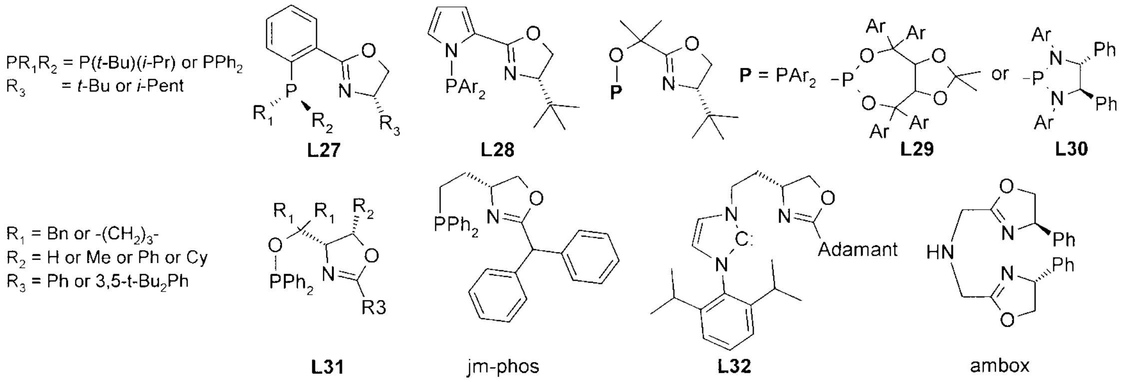


Figure 33. Structures of ligands mentioned in Table 12.

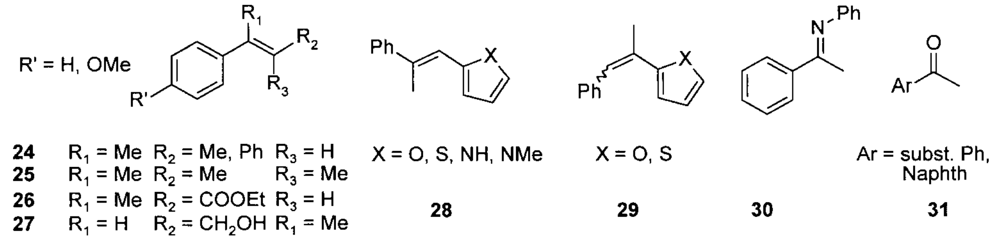


Figure 34. Structures of substrates mentioned in Table 12.

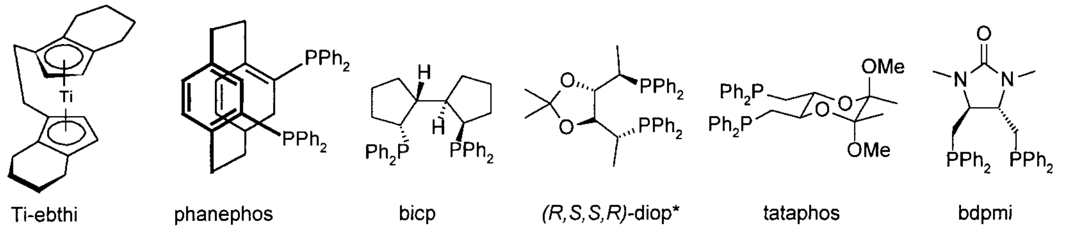


Figure 35. Ligand structures of Table 13.

Table 13. Selected results for hydrogenation reactions catalyzed by chiral catalysts (ligand structures and abbreviations, see Figure 35, substrates, see Figure 36).

Entry	Catalyst	Substrate	p(H_2)	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	*Ti-ebthi*	cyclic imines	$_5$5–30	20–100[a]	< 1–2[a]	98–99		[50c]
2	*Ti-ebthi*	**32**	1–5	20[a]	< 1[a]	90–99		[50b]
3	*Ti-ebthi*	**33**	140	20[a]	< 1[a]	95–> 99	ee 95% for R = CH_2NBn_2	[50a]
4	*Ru-phanephos*	β-keto esters	4	250[a]	15[a]	95–96	– 5 °C	[51a]
5	*Rh-phanephos*	MAA, MAC	1	100[a]	100[a]	98–> 99		[51b]
6	Rh-bicp	MAA	1	100[a]	< 4[a]	93–99	and subst. MAC analogues	[49b, c]
7	Rh-diop*	**34**	10	50[a]	~1[a]	97–> 99	(*R,R,R,R*) ligand: ee low	[49b, d]
8	Rh-tataphos	**34**	3	n.a.	n.a.	94–98		[49b]
9	Rh-bdpmi	**34**	1	100[a]	8[a]	> 99	also for *E/Z*-mixtures	[49e]

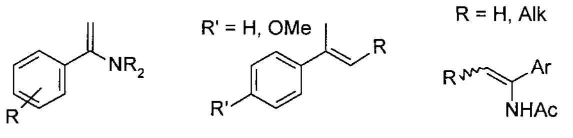
[a] Standard test results, not optimized.

bridges to a phosphine, aminophosphine, phosphinite, or phosphonite. In some cases not only the oxazoline but also the P moiety has one or more additional stereogenic centers (see Figure 33). All of these ligands are modular and can be prepared from readily available starting materials usually from the chiral pool.

Up to now, their major fields of application are two rather difficult selectivity problems, namely the hydrogenation of olefins without privileged functionalization (see Section 4.1) with ees often > 99% (Table 12, entries 1–6) and of imines (see Section 4.3.1) with ees up to 89% (entry 7). Somewhat of a drawback is a limited choice of solvents (chlorinated hydrocarbons or toluene are preferred) and the need for non-coordinating anions such PF_6 or BARF which is quite expensive. Ir-oxazoline-carbene BARF complexes were prepared by Burgess and tested for the hydrogenation of olefins with high enantioselectivities and moderate to good TON and TOF (entry 2). Somewhat different is the ambox ligand which is effective in the Ru-catalyzed (transfer) hydrogenation of aryl methyl ketones in the presence of PPh_3[49] (entry 9).

2.7 Miscellaneous Chiral Ligands

In this section we briefly describe new ligands which do not belong to any of the categories described above but show very interesting design concepts and/or give unusual catalytic performances. The Ti complex of Brintzinger's chiral bis-tetrahydroindan ligand is very effective for reducing cyclic imines, enamines and unfunctionalized C=C bonds, unfortunately with very low activities and little functional group tolerance (Table 13, entries 1–3). Phanephos is one of the few ligands with only planar chirality and has an activity profile similar to the biaryl ligands (entries 4 and 5). Bicp, diop*, tataphos and bdpmi form the same 7-



32 33 34

Figure 36. Substrates mentioned in Table 13.

membered chelate as diop but have restricted flexibility due to a more rigid backbone or additional substituents either in the ring or the side chain. With a similar substrate spectrum as diop, all four ligands exhibit far better enantioselectivities (entries 6–9). Rh-bicp is also effective for the synthesis of β-amino acid derivatives albeit with lower ees than Rh-duphos (97% vs. >99%, respectively).[10b]

2.8 Immobilized Chiral Complexes

After a period of stagnation, immobilization of (chiral) homogeneous catalysts has seen a renaissance in the last few years as, e.g., documented in a new monograph on catalyst separation.[52]

2.8.1 Why Immobilize Homogeneous Catalysts?

There are two major motivations for preparing and studying immobilized catalysts: Firstly and most important, improved separation and handling properties and secondly, the potential of creating active sites with improved catalytic performance. In this view, the ideal immobilized catalysts can easily be separated, re-used with constant activity and selectivity which are at least as good as or better than those of the homogeneous analogue. Needless to say that only few catalysts have reached this goal except when poorly performing homogeneous catalysts were immobilized.

In this section we concentrate on the aspects of catalyst separation and re-use. We will assess the different immobilization methods based on our personal experience in fine chemicals synthesis. Important criteria are the practicability of the catalyst preparation and separation methods, the generality of application and the availability of the catalysts. Before starting our discussion the following points should be noted:[6a]

- In the industrial practice, catalyst separation is seldom a problem since classical methods such as distillation, crystallization of the product or precipitation of the catalyst have proved to be quite successful.[6b]
- Immobilization makes the catalyst and thus the process more expensive; alternative non-catalytic processes might be cheaper.
- Sophisticated separation or catalyst preparation methods and also catalyst recycling (quality assurance!) add to the complexity of a catalytic system and make process development more demanding.
- Last but not least, the time frame for the development of a technical process is often < 6 months and does not allow a lengthy catalyst and/or separation method development.

2.8.2 Assessment of Separation Methods

Filtration and extraction (with cheap solvents) are the preferred separation methods. Ultrafiltration is more expensive and not yet state of the art for all solvents. However, it is likely that the future will see ultrafiltration membranes that allow the separation of homogeneous catalysts with molecular weights >500 from products without prior modification of the catalyst. Precipitation of the catalyst with (reasonable amounts of) an additional solvent is acceptable. Functionalization in order to attach a ligand to the support can double the cost of a catalyst but there are already a number of such ligands available. Due to the often high substrate specificity of most enantioselective catalysts, it is important that the immobilization methods are as

Table 14. Assessment of separation behavior of various catalyst types.

Catalyst Type	Method[a]	F[b]	S[c]	M[d]
A1. Solid; covalently attached to support	F	yes	b	m
A2. Solid; adsorbed *via* ligand-support interaction	F	yes	n	m
A3. Solid; entrapped in polymer matrix	F	no	n	l
A4. Solid; adsorbed *via* metal-support interactions	F	no	m	m
B1. Soluble; covalently bound to soluble polymer or dendrimer	UF, P/F	yes	m	h
B2. Soluble; covalently bound to 'smart' polymer	F	yes	n	h
C1. Soluble; water-soluble or perfluoro (one phase)	E	yes	n	h
C2. Soluble; water-soluble or perfluoro (two phases)	E	yes	n-m	l

[a] F filtration, UF ultrafiltration, P precipitation, E extraction.
[b] Additional functionalization of ligand necessary.
[c] Scope narrow/medium/broad (substrates, solvents, additives, reaction conditions).
[d] M mass transport (high/medium/low).

general as possible. Otherwise, each problem will require a tailor-made catalyst which is only economically feasible for established large scale products. Table 14 gives a summary assessment of the various immobilization approaches and their separation.

2.8.3 Successful Immobilization Methodologies

Interesting results were described mainly for four immobilization methodologies: i) Solid and soluble catalysts with covalently attached ligands (A1, B1), ii) catalysts entrapped or occluded in polymer matrices (A3), iii) catalysts adsorbed *via* metal-support interactions (A4), and iv) water soluble catalysts. A few of the most interesting immobilized catalysts described in the last few years are depicted in Fig. 37 together with a short summary of their catalytic performance, mostly in model test reactions.

2.8.3.1 Solid and Soluble Catalysts with Covalently Attached Ligands (A1, B1)

The binap ligand has been functionalized using several different methods and attached to supports such as polystyrene[53a] or polyethylenediol[53b] *via* grafting, rendered insoluble by oligomerization ($n = 8$)[53c] or co-polymerized with a chiral monomer.[53d] The resulting catalysts have catalytic performances which are comparable to the soluble analogues, under the test conditions (relatively low s/c ratio) most can be re-used without loss in activity and no apparent metal leaching. The catalyst prepared by Chan's group[53d] achieved even better performance than the parent Ru-binap, explained by a cooperation with the chiral backbone. Several josiphos ligands were functionalized at the lower cp ring and grafted to silica gel or a water-soluble group[54a] to give very active catalysts for the Ir-catalyzed MEA imine reduction ; an Rh-josiphos complex grafted to a dendrimer hydrogenated DMIT with ees up to 98.6%.[54b]

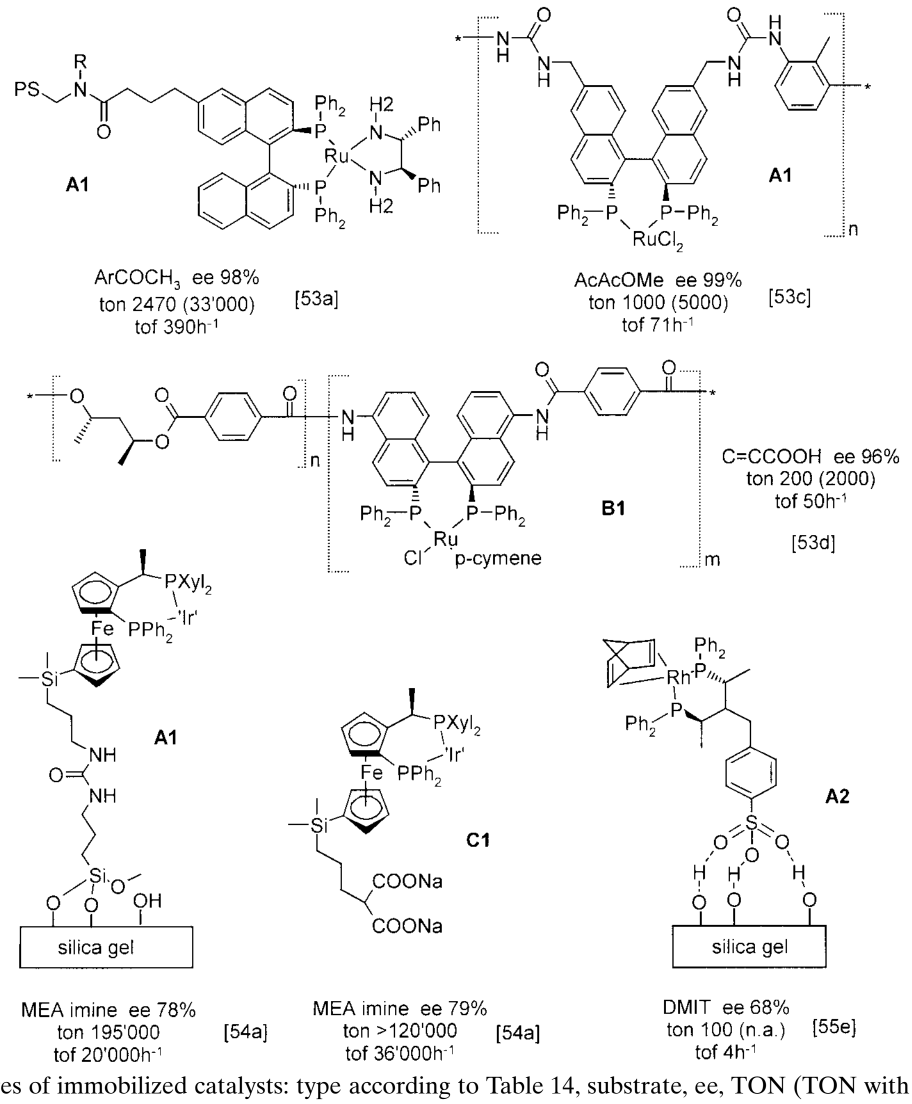


Figure 37. Structures of immobilized catalysts: type according to Table 14, substrate, ee, TON (TON with recycling) and TOF.

2.8.3.2 Catalysts Entrapped or Occluded in Polymer Matrices (A3)

While the entrapment in rigid inorganic matrices such as zeolites[52,54c] usually leads to a significant rate decrease, the occlusion in polyvinyl alcohol (PVA) or polydimethylsilane (PDMS) looks more promising but is still far from being practically useful. Rh-duphos occluded in PVA or PDMS hydrogenated MAA with $>96\%$ ee (TON 140, TOF *ca.* 15 h^{-1})[54d] and AcAcOMe with 90–93% ee (TON >1000, TOF 7–28 h^{-1}),[54e] significantly below the homogeneous analogue (ee 99%, TOF 480 h^{-1}). Leaching of the metal complex is often observed in solvents which swell the organic matrix; otherwise the catalysts can be re-used.

2.8.3.3 Catalysts Adsorbed **via** *Ionic Interactions with the Support (A4)*

This is an attractive method since it does not require the functionalization of the ligand. Augustine et al.[55a] developed heteropoly acids (PTA) as a “magic glue” to attach catalyst Rh and Ru complexes to various surfaces. The interaction of the PTA is thought to occur directly with the metal. Rh-dipamp attached to PTA-clay hydrogenated MAA with 97% ee (TON 270, TOF up to 400 h^{-1}) and TONs up to 12,000 were claimed for 1-hexene with an adsorbed Wilkinson catalyst.[55a] Rh-duphos on PTA-alumina achieved 96% ee (TON 55–1000, TOF 100–225 h^{-1}).[55a, b] Most catalysts have been tested at low substrate/catalyst ratios, a high recycling rate is therefore essential. Adsorption on MCM41 or specially prepared silica without “glue” either *via* the metal,[55c] the anion[55d] or a functionalized ligand[55e] (see Figure 37) is also possible but the catalytic performances reported in the open literature are not yet convincing. As with the occluded catalysts, the solvent and also ionic additives have to be chosen very carefully in order to have a stable, leach-free adsorbed catalyst

2.8.4 Interesting New Separation Approaches

To conduct the reaction homogeneously under optimal mass transport conditions and to induce phase separation by changing the temperature has been shown to work in principle.[56] In one approach, the ligand was covalently attached to a “smart” polymer soluble at reaction temperature which precipitates by cooling or heating the reaction mixture and can then be filtered off (B2). A second method is the use of solvent mixtures often with fluorous components which are homogeneous at reaction temperature but separate at lower temperature, allowing easy phase separation (C1,C2). It remains to be seen whether such systems have any chance of synthetic application because the “window of opportunity” is probably rather narrow.

3 Design and Preparation of Heterogeneous Catalysts

3.1 Toolbox of Heterogeneous Catalysts

The “classical” hydrogenation catalysts for preparative hydrogenation are supported noble metals, Raney nickel and supported Ni and Cu all of which are able to activate hydrogen under mild conditions.[1] Because only surface atoms are active, the metal is present as very small particles in order to give a high specific surface area (see Figure 38). It is important to realize that even today it is not possible to adequately characterize a preparative heterogeneous catalyst on an atomic level. From the study of defined model surfaces, one differentiates between terrace, edge, and corner atoms having 1, 2 or 3 free coordination sites, respectively, and exhibiting different reactivities. However, despite considerable efforts particularly by Augustine[57a] and Smith,[57b] it was not possible to reliably determine the number of these different sites. Catalysts are therefore still chosen on an empirical basis by trial and error and it is rarely understood why a given catalyst is superior to another one. Many problems can be solved adequately using standard catalyst types, more demanding processes often require tailored catalysts.

The catalytic performance of a heterogeneous hydrogenation catalyst can be influenced by the parameters listed below representing the “toolbox” of the heterogeneous catalysis:[58]

- *Type of metal*. Pd, Pt, Rh, Ru, Ni and Cu are used most often and each metal has its own activity and selectivity profile. Bimetallic catalysts are also applied (see Section 3.2).
- *Type of catalyst*. Noble metals are usually supported on a carrier, sometimes they are used as fine powders (Pd black and Pt black, PtO_2) or colloids (see Section 3.3), Ni is most often applied as skeletal catalyst (Raney nickel) or supported on silica, Cu as Cu-chromite. Recently, an effective Ni/C catalyst was described.[59]
- *Metal loading*. For supported noble metal catalysts 5% loading is standard; typical Ni concentrations are 20–50%.
- *Type of support*. Charcoal (also called active carbon) is most common in the production of fine chemicals; aluminas and silicas as well as $CaCO_3$ or $BaSO_4$ are used for special applications.
- *Active metal parameters* for the are surface area, dispersion (typically only 10–60% of the metal atoms are exposed), size of the crystallites (typically in the range 20–>200 Å), location in the pores of the support and oxidation state (reduced or unreduced).
- *Support parameters* are the particle size (for slurry catalysts typically 1–100 μm), the surface area (typ-

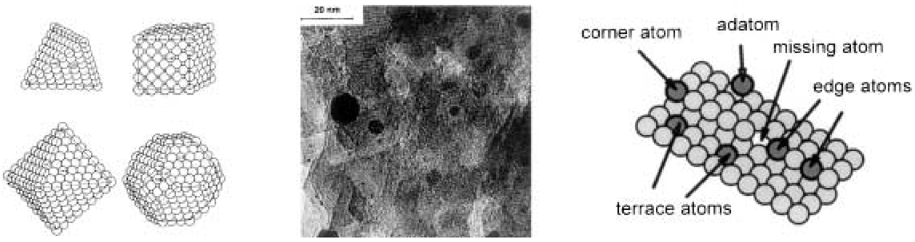


Figure 38. Different views of a metallic catalyst: Regular metal clusters with different geometries; transmission electron micrograph of a "real-life" Pt/Al_2O_3 catalyst; model surface with different atom types.

ically in the range of 100 – 1500 m^2/g), the pore structure (pore volume, pore size distribution) and acid-base properties.

– *Modifiers and promoters.* Compounds such as sulfides, amines or chiral entities are known to modify and promote the catalytic properties of a heterogeneous catalyst (see Section 3.4).

While research in heterogeneous hydrogenation was very active in the 1970's to 1980's culminating in the well known monographs by Rylander,[1a] Augustine[57a] or Smith,[57b] only the few selected topics discussed below received significant attention in the last years. It should be pointed out, however, that despite this "benign neglect" most catalytic hydrogenation reactions applied for fine chemical manufacture are carried out with classical heterogeneous catalysts and we are convinced that this will be remain true for the foreseeable future.

3.2 Bimetallic Catalysts

As expected, the addition of a second metal often significantly affects the properties of a catalyst. Classical examples are the Lindlar catalyst ($Pd-Pb/CaCO_3$), where the addition of lead allows the selective monohydrogenation of acetylenic bonds or the Nishimura catalyst (Rh-Pt oxide) for the mild hydrogenation of aromatic rings.[1c] Several interesting recent examples demonstrate the usefulness of this concept: For the hydrogenation of a pyridine-2-carboxylic acid derivative, a 4.5% Pd-0.5% Rh/C catalyst was shown to be twice as active as 5% Rh/C and, in addition, showed better *cis*-selectivity (see Section 4.4.1). The addition of Pb to $Pt/CaCO_3$ catalyst allows the selective hydrogenation of aromatic nitro groups in the presence of many other reducible groups (see Section 4.5.1). The Nishimura catalyst (Rh-Pt oxide) is able to reduce chiral α-amino and hydroxy acids to the corresponding amino alcohols and diols, respectively, at room temperature with high yields and no racemization (see Section 4.7). $Pt-Co/Al_2O_3$ catalyst hydrogenated 2-hexenal to the corresponding allylic alcohol with 92% selectivity at 90% conversion (see Section 4.2.1).

3.3 Colloidal Catalysts

Colloidal catalysts are of interest for two reasons: First, support effects can be eliminated and secondly, there is hope to better control the morphology (size and shape) of the metal particles compared to classical supported catalysts. On the other hand there are several drawbacks for colloidal catalysts such as their difficult preparation, a relatively low productivity and/or stability and separation problems. Indeed the danger is real to combine not the best properties of homogeneous and heterogeneous catalysts (as hoped) but their shortcomings. Nevertheless, there are some interesting leads which might eventually give technically useful catalysts, but probably only for special applications.

Pt, Rh and Ir colloids modified with cinchonidine were investigated by a number of groups for the enantioselective hydrogenation of α-functionalized ketones such as pyruvates, α-diketones and trifluoroacetophenone.[60] Most effective was polyvinylpyrrolidine (PVP) as stabilizer (ees for methyl pyruvate up to 98% with cinchona-modified Pt catalysts. It was demonstrated that the performance and reproducibility of the colloids depended strongly on the preparation procedure. Colloidal Ru[61a] and Rh[61b–d] catalysts were also shown to be active for the hydrogenation of various aromatic systems, in part under very mild conditions (see Table 26).

3.4 Modified Catalysts

The application of organic modifiers is an effective strategy to influence the catalytic properties, mainly the selectivity, of heterogeneous catalysts. This approach is especially attractive for the organic chemist since there is no need to prepare a new catalyst (which requires special know how). Freifelder[1b] gives a good overview on the effect of a wide variety of additives used in hydrogenation reactions. Classical examples are the use of sulfur or nitrogen compounds, e.g., for the selective hydrogenation of acid chlorides to give aldehydes (Rosenmund system) or for the selective hydrogenation of halogenated aromatic nitro groups.

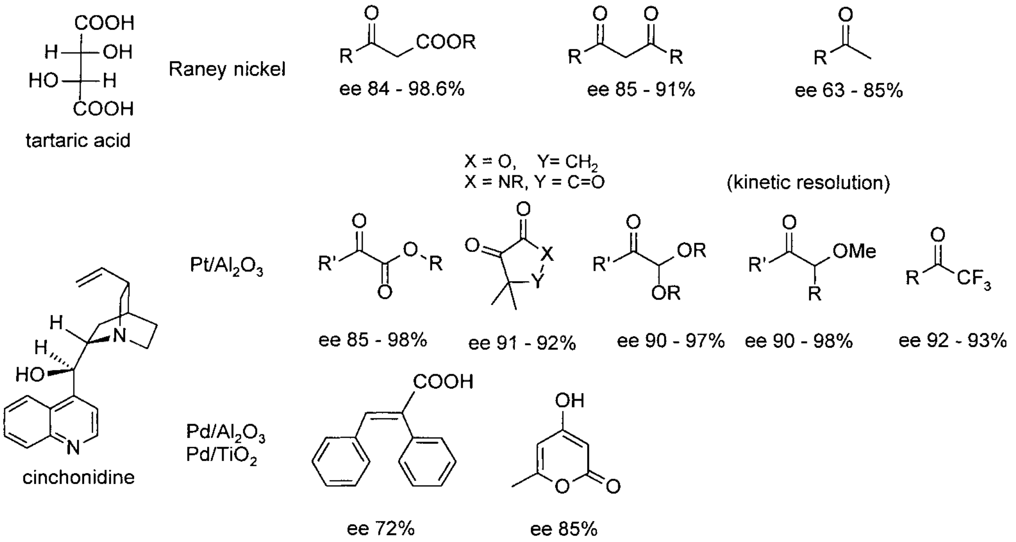


Figure 39. Best results reported for heterogeneous enantioselective catalysts (modifier, preferred catalyst and substrates).[60a]

3.4.1 Chemoselectivity

Recently it was shown that ethylenediamine is a good modifier for the Pd-catalyzed hydrogenolysis of benzyl ethers and hydrogenation of C≡C, C=C, nitro, azide and COOBn functions in the presence of an N-Cbz (N-COOBn) group.[62a] The classical Lindlar system gave also much higher selectivity for the semi-hydrogenation of aminoalkynes in presence of ethylenediamine.[62b] Similar modification effects were reported for certain pyridine derivatives as well.[62c, d] H_3PO_2 and other low-valent phosphorus additives in the presence of vanadium promoters were shown to be very effective modifiers for the Pt-catalyzed selective hydrogenation of aromatic nitro groups, tolerating many otherwise reducible functional groups.[63a, b] Vanadium compounds were shown to promote the decomposition of the unwanted arylhydroxylamine intermediates (see Section 4.5.2).

A generally accepted mode of action is the reversible or irreversible adsorption of sulfur-, phosphorus-, nitrogen- or halogen-containing modifiers occurring preferentially on the most reactive catalytic sites (which are thought to be the most unselective ones), thereby hindering adsorption and unselective hydrogenation. Other possible consequences of adsorption are the formation of isolated (smaller ensembles) or of electronically altered active sites with different selectivity.

3.4.2 Enantioselectivity

A metal surface can also be made chiral by the addition of suitable modifiers. The state of the art for the enantioselective hydrogenation applying chirally modified heterogeneous catalysts with emphasis on the developments up to 2002 has been reviewed.[60] The three most important asymmetric catalyst types are Raney nickel modified with tartaric acid, effective for β-functionalized ketones with ees up to 98.6%, platinum catalysts modified with cinchona alkaloids and related modifiers, successful for α-functionalized ketones with ees up to 98% and palladium catalysts modified with cinchona alkaloids which achieve ees up to 85% for selected activated C=C bonds. The best results for the three catalytic systems are depicted in Fig. 39. Mechanistic investigations comprising surface science and spectroscopic studies often combined with computational modeling as well as kinetic studies have led to the proposal of various mechanistic models (see Section 6).

4 Catalytic Transformations; Selectivity Problems

In this section transformations and generic selectivity problems of current interest and/or high scientific activity are discussed. This selection is by no means comprehensive but illustrates how we perceive the needs of the fine chemicals and life science industry.

4.1 Enantioselective Hydrogenation of Alkenes

Whilst the heterogeneous hydrogenation of olefins is a well established technology, current activities are centered on the enantioselective variant of these transformations, particularly using homogeneous catalysts. Indeed, the homogeneous hydrogenation of certain functionalized olefins is the best studied enantioselective catalytic reaction and it is also applied in industrial production.[4b, c,6b] The number of substituents at the

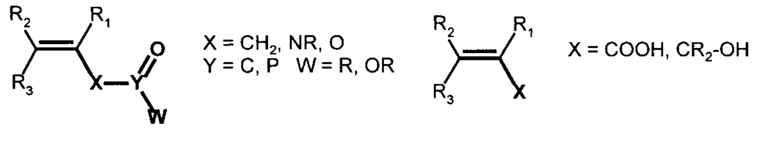


Figure 40. Olefins with privileged substitution patterns.

Table 15. State-of-the-art for the hydrogenation of olefins.[6a]

Substrate	ee [%][a]	TON[b]	TOF [h^{-1}][b]	Preferred Catalyst Types[c]
enamides, enol acetates, itaconates	90 – > 99	1,000 – 20,000	200 – 5,000	Rh-duphos, josiphos, ppm, bppfa
(C=C-C-OH)	80 – 95	10,000 – 50,000	1,000 – 5,000	Ru-binap, biphep
(C=C-COOH)	85 – 95	2,000 – 10,000	500 – 3,000	Ru-binap, biphep
C=C without privileged function	80 – 95	20 – 100	2 – 5	Ru-binap, Ir-phox, Rh-duphos

[a] Typical range for suitable substrate.

[b] After optimization.

[c] See glossary for guide to ligand structures.

C=C bond strongly affects the reaction rate both for heterogeneous and even more for homogeneous catalysts. As a general rule, the catalytic activity decreases in the series $RHC{=}CH_2 > R_2C{=}CH_2 >$ *cis*-$RHC{=}CRH >$ *trans*-$RHC{=}CHR > R_2C{=}CHR \gg R_2C{=}CR_2$. Over time, a few privileged substitution patterns have evolved that almost guarantee high ees with homogeneous catalysts. These structures are depicted in Figure 40, in most cases the C=C carries a second functional group able coordinate to the metal atom of the catalyst leading to better enantiocontrol. The state of the art of C=C hydrogenation is summarized in Table 15, new results are tabulated and briefly discussed in the following sections.

4.1.1 Dehydroamino and Itaconic Acid Derivatives

The hydrogenation of dehydroamino acid derivatives (Figure 40, X = NR, Y = C, W = R, R_1 = COOR) is not only the best known test reaction but has an obvious potential for the production of pesticides or pharmaceuticals.[6a, b] As is apparent from Table 16, most catalytic tests with new ligands are carried out with s/c ratios of 100 – 1,000, only entries 6 – 8 have TONs and TOFs useful for industrial applications. For the preparation of simple α-amino acids (entry 1), Rh complexes of almost all ligand classes of the new generation described in Section 2 give ees of 98 – > 99%. Such values were very rare for earlier ligand generations. For

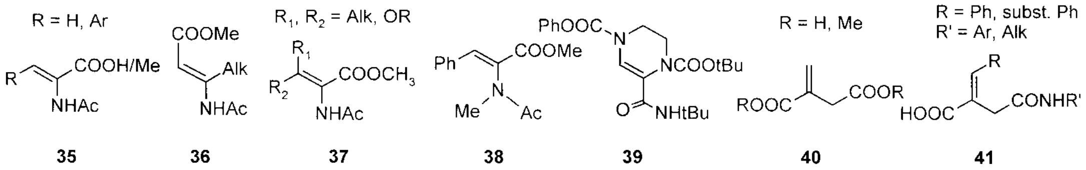
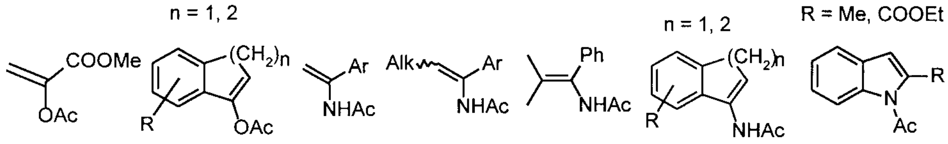


Figure 41. Structures of dehydroamino and itaconic acid derivatives listed in Table 16.

Table 16. Best new catalysts for the hydrogenation of dehydroamino and itaconic acid derivatives (substrates, see Figure 41, see glossary for a guide to ligand structures).

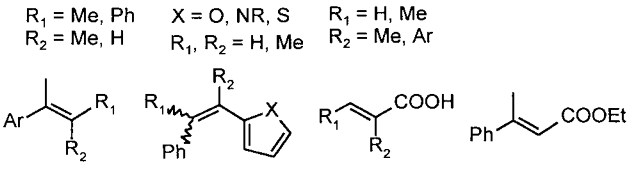
Entry	Substrate	Metal-Ligand	TON	TOF [h^{-1}]	ee [%]
1	**35**	**Rh**-H_8-monophos, mandyphos, bophoz, bisp*, miniphos, **L1**, **L7**, phanephos, tangphos, rophos, **L29**	100 – 500[a]	8 – 500[a]	98 – > 99
2	**36**	**Rh**-duphos, malphos	100[a]	100 – 200[a]	95 – > 99
3	**37**	**Rh**-trap	100[a]	4[a]	97
4	**38**	**Rh-L9, L10**	200[a]	15[a]	96 – 98
5	**39**	**Rh**-trap	100[a]	5[a]	97
6	**40**	**Rh**-josiphos, **L7**, **L26**, **L31**, miniphos	100[a] – 2000	8 – 200[a]	97 – 99.9
7	**40**	**Rh-L25**, **L32**	5 – 10,000	270 – 420	> 99.5
8	**41**	**Rh**-ferrotane	1000[a]	1 – 6,000[a]	92 – 99

[a] Standard test results, not optimized.



42 **43** **44** **45** **46** **47** **48**

Figure 42. Structures of enol acetates and enamides listed in Table 17.



49 **50** **51** **52**

Figure 43. Structures of unfunctionalized C=C and C=C-COOR listed in Table 18.

more difficult substrates such as β-dehydroamino acids (entry 2), tetrasubstituted analogues (entry 3) or *N*-methyl or cyclic derivatives (entries 4 and 5) only particular ligands were reported to achieve very high ees, usually with rather low catalyst activity. ITA and DMIT have been reduced again with several of the new ligands with high ees and in some cases with high TONs and acceptable TOFs as well (entries 6 and 7) while itaconic amides are effectively hydrogenated using Rh-ferrotane (entry 8).

4.1.2 Enol Acetates and Enamides

Especially cyclic enol acetates can be hydrogenated with good to excellent ees but low activity (Table 17, entries 1 and 2). α-Arylenamides **44** and **45** serve as standard test substrates and several ligands induce ees >99% albeit with low to medium activities (entries 3, 4, 6). Higher TONs and TOFs can be reached but usually with a loss in ee (entries 5 and 7). Tetrasubstituted and cyclic analogues can be reduced with good to very high ees but low to medium activity (entries 8–10).

4.1.3 Miscellaneous Olefins

The hydrogenation of alkenes without "privileged" functional groups (Figure 43, **49–51**) has made impressive progress. High ees with reasonable activities are now possible for several substitution patterns with the new Ir-oxazoline-phosphine catalysts of Pfaltz and

Table 17. Best new catalysts for the hydrogenation of enol acetates and enamides (substrates, see Figure 42, see glossary for a guide to ligand structures).

Entry	Substrate	Metal-Ligand	TON	TOF [h^{-1}]	ee [%]
1	**42**	**Rh**-mandyphos	100[a]	8[a]	94.9
2	**43**	**Rh**-pennphos	100[a]	5[a]	98–>99
3	**44**	**Rh** – binapo, basphos, **L25, L7**, miniphos, **L29**, bicp	100–1000[a]	<4–50[a]	>99
4	**44**	**Rh**-bisp*, **L27**, **L28**, **L30**, phanephos	100[a]–1000	100[a]–2000	98–>99
5	**44**	**Rh**-spirop	10,000	10,000	96.8
6	**45**	**Rh**-binaphane, **L7**, tangphos, bisp*, diop*	50–100[a]	~1–8[a]	97–>99
7	**45**	**Rh-L19**	1000	6000	89.5
8	**46**	**Rh**-bisp*	100[a]	3–4[a]	99
9	**47**	**Rh**-pennphos	100[a]	5[a]	97–>99
10	**48**	**Ru**-taniaphos, **Rh**-trap	100–200[a]	25–200[a]	94–95.5

[a] Standard test results, not optimized.

Table 18. Best new catalysts for the hydrogenation of unfunctionalized C=C and C=C-COOR (substrates, see Figure 43, see glossary for a guide to ligand structures).

Entry	Substrate	Metal-Ligand	TON	TOF [h^{-1}]	ee [%]
1	**49**	**Ir-L11**, **L24**, **L14, L16**	100[a] – >5000	>50[a]–1250	81–>99
2	**50**	**Ir-L11, L15**	100[a]	>50[a]	>99
3	**51**	**Ru**-H_8-binap	200[a]–5000	10[a]–625	92–97
4	**52**	**Ir-L13, L14**	100[a]	>50[a]	89–90

[a] Standard test results, not optimized.

others (Table 18, entries 1, 2, 4). The hydrogenation of α,β-unsaturated acids has been improved using H_8-binap (entry 3), while the hydrogenation of allylic alcohols has received little recent attention.

4.2 Chemo- and Enantioselective Hydrogenation of Ketones

Catalytic hydrogenation is the method of choice for reducing ketones on a larger scale, for the direct reduction of aromatic ketones to the corresponding methylene group and for selected chemo- and enantioselective reductions.[1a,57a, b] For the heterogeneous hydrogenation of carbonyl groups the preferred catalysts are Pd, Pt and Ni. The structure of the ketone has a strong effect on rate and selectivity; the chemo-, regio- and stereoselectivity can be controlled by catalyst, solvent, pH, modifiers and the reaction conditions. Homogeneous Rh, Ru and to a lesser degree Ir complexes are used for the enantioselective hydrogenation with both hydrogen and organic donors as reducing agent. In this Section we will concentrate on recent results for the chemoselective reduction of C=C-C=O compounds to the corresponding allylic alcohols and the enantioselective reduction of ketones.

4.2.1 *Chemoselective Reduction of C=C-C=O Compounds to Allylic Alcohols*

The selective hydrogenation of unsaturated aldehydes to allylic alcohols is a long-standing problem in heterogeneous catalysis, with numerous publications in the last few years.[57a, b] The state of the art has recently been reviewed by Gallezot[64a] and can briefly be summarized as follows. Best results are obtained when the C=C bond is substituted, using platinum group metals combined with a second more electropositive metal, a metal oxide and/or an organic modifier. Many parameters affect the selectivity of the transformation but their effect varies with the structure of the substrate. The degree of conversion strongly influences selectivity concerning overhydrogenation. Up to now, no catalytic system is available with satisfactory properties for synthetic applications. Somewhat arbitrarily, we report 4 recent publications with interesting approaches. The use of sCO_2 increased the selectivity for the hydrogenation of cinnamaldehyde (a standard test substrate).[64b] 2-Hexenal was hydrogenated with a new Pt-Co/Al_2O_3 catalyst with 92% selectivity (conversion 90%).[64c] The C=O group in the 1-position of 2,6,6-trimethylcyclohex-2-ene-1,4-dione was hydrogenated with 93% selectivity using a Pd/Al_2O_3 catalyst.[64d] This is interesting since heterogeneous catalysts usually are not able to hydrogenate a keto group in the presence of a C=C bond. Very recently Milone et al.[64e] demonstrated that Au/Fe_2O_3 is able to hydrogenate the aldehyde function in citral (3,7-dimethyl-2,6-octadienal) with >95% selectivity, remarkable both because of the high selectivity as well as the unusual catalyst.

In the last few years, homogeneous catalysts have been shown to be quite selective even for the hydrogenation of α,β-unsaturated ketones. A wide range of enones have been reduced with the Noyori catalysts Ru-binap-diamine complex (see Section 2.4.1.3) with high chemoselectivities as well as high ees.[4c,22a] Simple, but excellent examples are benzylideneacetone and acetylcyclohexenone, which are hydrogenated to the allylic alcohol selectively in up to 97 and 100% ee, respectively.[65] Quite good chemoselectivities were also described for phosphine-stabilized Cu hydride complexes[66a] and for transfer hydrogenation using Ni phosphite complexes.[66b]

4.2.2 *Enantioselective Hydrogenation of Ketones*

The hydrogenation of ketones using Rh and Ru diphosphine catalysts is the most versatile and efficient method for the synthesis of a large variety of chiral alcohols (see Table 19). Privileged substrate classes are ketones with O or N functions in α- or β-position. While Rh-diphosphine catalysts are often substrate specific, several Ru-binap and -biphep catalysts have a rather broad scope. These catalysts are effective for the hydrogenation of functionalized ketones such as β-keto esters, 2-amino- and 2-hydroxyketones with high ees and often reasonable TONs and TOFs. α-Keto esters are still preferentially hydrogenated with heterogeneous cinchona-modified Pt catalysts with nominal TOFs $>50,000\ h^{-1}$.[60]

Table 19. State-of-the-art for the reduction of ketones.[6a]

Substrate	ee [%][a]	TON[a]	TOF [h^{-1}][a]	Preferred Catalyst Types[b]
α-keto esters and diketones	90–97	1,000–5,000	100–500	Rh-nop, Ru-binap, biphep
α-OH/NH ketones	90–96	1,000–5,000	100–500	Ru-binap, Rh-bppfoh, nop, diop
β-functionalized	90–98	5,000–50,000	2,000–10,000	Ru-binap, biphep
ArCOR	90–98	5,000–20,000	500–10,000	Ru-binap-diamine

[a] Typical range for suitable substrate and optimized catalyst.

[b] See glossary for a guide to ligand structures.

Table 20. Best catalysts for the hydrogenation of α-functionalized ketones (substrates, see Figure 44, see glossary for a guide to ligand structures).

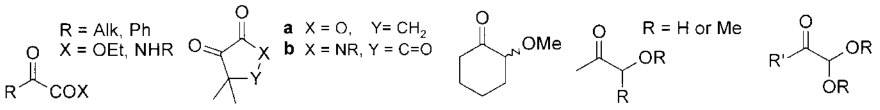
Entry	Substrate	Metal-Ligand (Modifier)	TON	TOF [h^{-1}]	ee [%]
1	**53**	**Ru**-segphos, **L14**, **L15**	80[b] – 1000	60	97 – > 99
2	**53**	**Pt**/Al_2O_3-cinchona	low – 100,000[d]	low – 50,000[d]	85 – 98
3	**54a**	**Rh**-bophoz, josiphos, **L14**, **L15**, **L17**	100 – 200[b]	1[b] – > 1000	97 – 99
4	**54a, b**	**Pt**/Al_2O_3-cinchona	1,000[d]	2,000[d]	91 – 92
5	**55**[a]	**Ru**-dmbinap/dpen	1000	50	99
6	**56**	**Ru**-segphos (R = H)	3000	430	99.5
7	**56**[c]	**Pt**/Al_2O_3-cinchona (R = Me)	low – 1,000[d]	low – 2,000	90 – 98
8	**57**	**Pt**/Al_2O_3-cinchona	low – 20,000[d]	low – < 20,000[d]	90 – 97

[a] Dynamic kinetic resolution.

[b] Standard test results, not optimized.

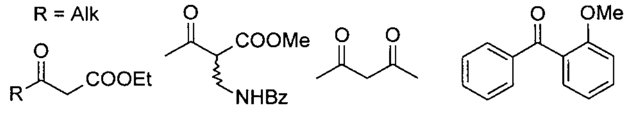
[c] Kinetic resolution.

[d] Rough estimates based on total metal content.



53 **54** **55** **56** **57**

Figure 44. Structures of α-functionalized ketones listed in Table 20.



58 **59** **60** **61**

Figure 45. Structures of β-functionalized ketones listed in Table 21.

4.2.2.1 *α*-Functionalized Ketones

While a few new homogeneous catalysts with high enantioselectivities for α-functionalized ketones were developed in the last few years (Table 20, entries 1, 3, 5, 6), additional applications and improvements were reported for the heterogeneous cinchona-modified Pt catalysts (entries 2, 4, 7, 8) with ees up to 98% and good to very high catalyst activities – one of the few exceptions where modified heterogeneous catalysts can compete with chiral metal complexes.

4.2.2.2 *β*-Functionalized Ketones

With few exceptions, catalyst activities and productivities for homogeneous and heterogeneous catalysts are low to satisfactory, while impressive progress concerning enantioselectivity with ees often > 98% has been achieved (Table 21). Catalysts of choice are clearly Ru-biaryl-diphosphine complexes, in the case of the aryl ketone **61** combined with a diamine. *ortho*-Substituted benzophenones are hydrogenated to give unsymmetrical benzhydrols in ees of 93 – 99.4%.[24b]

4.2.2.3 *Miscellaneous Ketones*

Ketones without an additional functional group can now also be reduced with very good ees. Especially impressive are the results for aryl methyl ketones (Table 22, entry 1) with the novel Ru-diphosphine/diamine system developed by Noyori exhibiting very high TONs and TOFs as well.[22] Hydrogenation of furanyl, thienyl, pyridyl, pyrolyl and thiazolyl methyl ketones leads to the corresponding alcohols in > 96 – 99.8% ee.[22e, g] Alkyl ketones are more difficult substrates and only bulky methyl ketones (Alk = *t*-Bu, *cyclo*-Pr) give ees > 80% (entries 3 and 4).

4.3 Diastereo- and Enantioselective Hydrogenation of C=N Functions

The catalytic hydrogenation of C=N functions is a well established technology for the synthesis of a variety of different amines. Pd, Pt and Ni are the catalysts of choice for the heterogeneous hydrogenation of both isolated and *in-situ* formed C=N systems (reductive amination or alkylation).[1a,57a, b] The homogeneous variant has rarely been described but is potentially of interest for asymmetric transformations.[67] Of special interest to us and a topic of current research is the stereoselective reduction to produce chiral amines. We will briefly describe some diastereoselective examples and summarize recent results for the enantioselective hydrogenation of C=N functions.

Table 21. Best catalysts for the hydrogenation of β-functionalized ketones (substrates, see Figure 45, see glossary for a guide to ligand structures).

Entry	Substrate	Metal-Ligand (Modifier)	TON	TOF [h^{-1}]	ee [%]
1	**58**	**Ru**-segphos, tuna-phos, **L5**, bisbenzodioxanphos	200[a] – 10,000	10[a] – 2500	97 – > 99.9
2	**58**	Raney-**Ni**-tartrate	2	< 1[c]	90 – 98.6
3	**59**[b]	**Ru**-dtbm-segphos	3000	n.a.	99.4
4	**60**	**Ru**-walphos, ferrotane	5 – 100[a]	< 1 – ≥ 6[a]	95 – 98
5	**61**	**Ru**-dmbinap/daipen	500[a]	n.a.	99

[a] Standard test results, not optimized.
[b] Kinetic resolution.
[c] Rough estimates based on total metal content.

Table 22. Best new catalysts for the hydrogenation of miscellaneous ketones (substrates, see Figure 46, ligand structures, see Section 2).

Entry	Substrate	Metal-Ligand (Modifier)	TON	TOF [h^{-1}]	ee [%]
1	**62**	**Ru**-(dmbinap, phanephos)/(daipen, dpen)	40 – 100,000	1 – 14,000	98 – 99
2	**62**	**Ru**-ambox/PPh$_3$	100[a]	200 – 600[a]	95 – 99
3	**63**	**Rh**-pennphos, **Ru**-dmbinap/daipen	100[a] – 10,000	5[a] – 500	73 – 95
4	**63**	**Cat5** (*i*-PrOH/*i*-PrONa) (Alk = *t*-Bu)	160[a]	10[a]	> 99
5	**64**	**Pt**/Al$_2$O$_3$-cinchona	150[b]	150[b]	93
6	**64**	**Ru**-dmbinap/daipen	2 – 10,000	150 – 2500	94 – 96
7	**65**	**Ru**-segphos	100[a]	50[a]	99

[a] Standard test results, not optimized.
[b] Rough estimates based on total metal content.

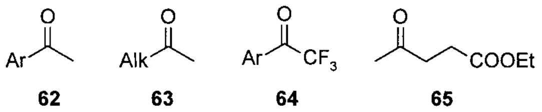


Figure 46. Structures of ketones listed in Table 22.

4.3.1 *Diastereoselective Hydrogenation of C=N Functions*

In most cases, heterogeneous Pd and Ni catalysts have been used for this purpose. Whereas cyclic imines can be hydrogenated with very high diastereoselectivities[68a, b] (Figure 47, left part), non-cyclic aryl ketimines usually give lower but still respectable des[68c] (Figure 47, right part). Two recent examples illustrate the potential to control the stereochemistry of cycloalkane derivatives. The first describes the hydrogenation of a tetralone derivative using a Ba-promoted Cu chromite catalyst to produce racemic intermediate for the antidepressant Sertralin with a very high *cis/trans* ratio.[68a] The high *cis* content allowed direct resolution and production of the desired polymorph *via* selective crystallization (see Figure 48). The synthesis of *cis*-aminocyclobutanols with ees up to 99% was achieved by the Raney Ni-catalyzed hydrogenation of the corresponding phenethylimine, dynamic kinetic resolution allowed yields > 50%[68b] (see Figure 49). It is interesting to note that the optimal catalyst was Cu chromite for the tetralone imine (rather unusual), Raney Ni for the cycloalkane derivatives and Pd/C for the non-cyclic imines. However, a recent publication demonstrates that Raney Ni in the presence of fluoride ions can also lead to des up to 90%.[68d]

4.3.2 *Enantioselective Hydrogenation* of C=N Functions

Even though the asymmetric hydrogenation of C=N functions has been investigated less systematically than that of C=C and C=O groups, significant progress has been made in the last decade as discussed in two recent reviews[6a,69] and summarized in Table 23. Several types of C=N functions can now be hydrogenated with good to very good enantioselectivities but moderate TONs and TOFs. An exception is the extraordinarily active and productive Ir-xyliphos catalyst used in the metolachlor process (see Figure 19) carried out by Syngenta. With a volume of > 10,000 ton/year it is the largest known production process with TONs up to 2,000,000 and TOFs > 400,000 h^{-1}.[27]

In the last few years several new complexes were developed achieving either very high ees or high activity/productivity. The most remarkable results are catalogued in Table 24. While Ir complexes, especially combined with the josiphos ligands R$_2$PF-PR'$_2$, still

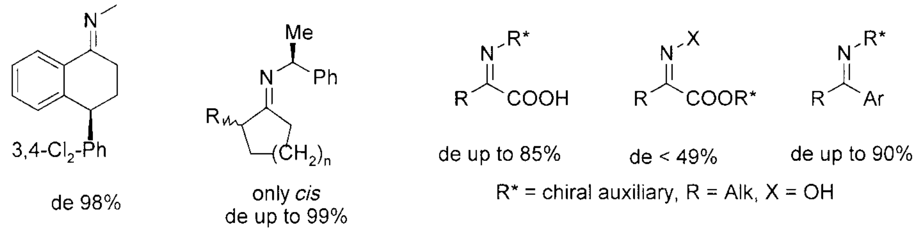


Figure 47. Diastereoselectivities for the hydrogenation C=N systems.

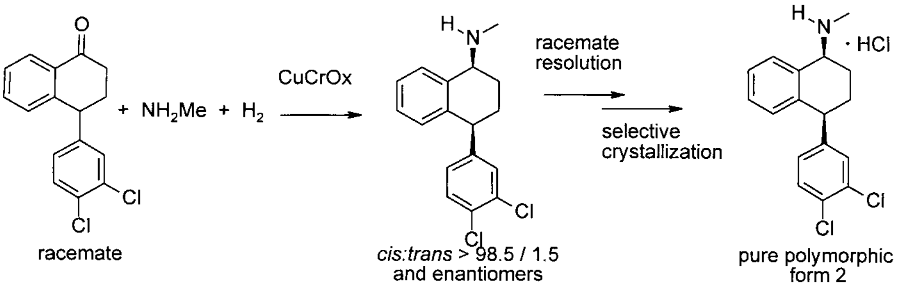


Figure 48. Diastereoselective reductive alkylation of a tetralone derivative.[68a]

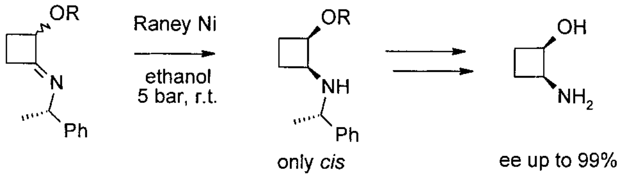


Figure 49. Diastereoselective hydrogenation of cyclobutanone imines.[68b]

seem to have the most potential, Ru and Rh complexes show very good ees particularly for transfer hydrogenations albeit with moderate TONs and TOFs (entries 7–9, 14, see also Section 5). Of special interest from an industrial point of view are the high TOFs claimed for the Ir-**L33a** system, unfortunately with low ee (entry 3), the high TONs achieved in supercritical CO_2 (entry 4) and the reductive alkylation reaction (entry 13).

Besides these results, we registered with interest the first example of a Pd-binap-catalyzed hydrogenation of a fluorinated α-imino ester in the presence of trifluoroacetic acid in fluorinated alcohols (ees up to 91%, but very low TON and TOF)[70a] and the claim by Magee and Norton[70b] that cpW-diphosphine complexes are able to hydrogenate imines *via* a novel ionic mechanism albeit with low ee and TOF. Also remarkable are the very high ees observed for the transfer hydrogenation using the cp*Rh-aminoindol **Cat4** (Section 5.2).

4.4 Stereoselective Hydrogenation of Aromatic Rings and the Application of Novel Catalysts

It is generally accepted that the hydrogenation of carbocyclic and heterocyclic aromatic rings is the domain of heterogeneous catalysts whereas few homogeneous complexes are active.[1a,57a, b,58,76] Preferred catalysts for the hydrogenation of substituted benzenes are Rh > Ru > Pt > Ni > Pd but the order of activity can change for other substrates or a particular substitution pattern and might depend on experimental conditions. Depending on the type of the aromatic ring system, the ease of reduction varies considerably. Most functional groups except carboxyl functions are usually hydrogenated prior to the aromatic rings, i.e., functional group tolerance is low. Major current issues are the stereo-

Table 23. State-of-the-art for the reduction of C=N groups.[6a]

Reaction	ee [%][a]	TON[a]	TOF [h^{-1}][a]	Preferred Catalyst Types[b]
N-Arylimines	80–90	500–10,000	50–100	Ir-josiphos, Rh-bdpp,[c] Ir-phox
Alkylimines	80–90	50–500	5–50	Rh-bdpp,[c] Ir-phox
Cyclic imines	90–98	50–1,000	1–50	Ti-ebthi, Ir-josiphos, Ir-binap
Various C=N-X	80–95	100–500	5–100	Rh-duphos, Ru-binap

[a] Typical range for suitable substrate and optimized catalyst.

[b] Structures, see Figures 2 and 3.

[c] 2,4-Bis-(diphenylphosphino)-pentane.

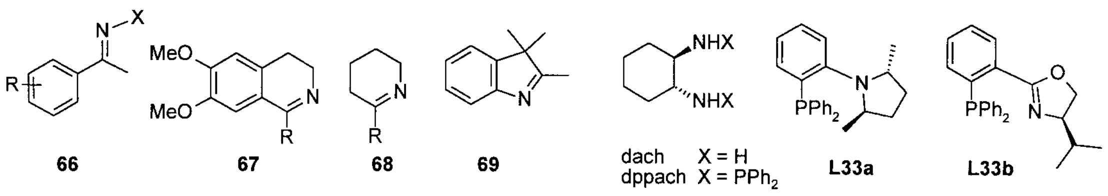


Figure 50. Structures of substrates and of selected ligands listed in Table 24.

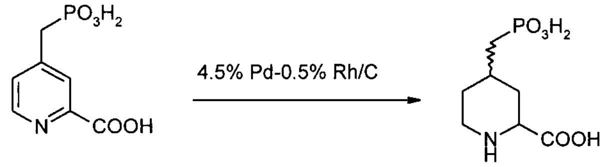


Figure 51. Stereoselective hydrogenation of a substituted pyridine.

selectivity of addition (*cis/trans*, enantio- and diastereoselectivity) and the development of novel catalysts. In this context we found the following results of interest.

4.4.1 Stereoselective Hydrogenation

The asymmetric hydrogenation of (hetero)aromatic rings would be an attractive way to chiral (hetero)-cyclohexanes. Several homogeneous catalytic systems have been found for the enantioselective hydrogenation of heteroaromatic systems[77] (see Table 25). Even though some catalysts were quite selective, catalytic activity and productivity were low. Diastereoselective hydrogenation of carbocyclic or heterocyclic systems coupled to chiral auxiliaries such as proline or related compounds gave des up to 95%[78] (selected examples, see Table 25). Usually, supported Rh catalysts show better performance than Ru catalysts but in all cases, laborious optimization and sometimes additives were necessary for good results. The issue of *cis*-selectivity in the hydrogenation of disubstituted heterocyclic[79a] and carbocyclic[79b–d] rings was addressed by several groups. Usually after extensive process optimization, classical catalysts such as Rh and Raney Nickel were able to give satisfactory *cis* selectivities but in some cases bimetallic systems [79a, b] proved to be superior.

A remarkable example for the synergism of bimetallic catalysts is the hydrogenation of pyridine-2-carboxylic acid derivatives as shown in Figure 51. Surprisingly, a 4.5% Pd-0.5% Rh/C catalyst is twice as active as 5% Rh/C and, in addition, shows better *cis* selectivity.[79a]

4.4.2 Novel Catalysts

Novel catalysts were described consisting of achiral homogeneous Ru[80a] and Rh complexes[80b] and a Ru

Table 24. Hydrogenation of C=N functions, substrate, catalyst (additives, reducing agent), best ee, TON and TOF (for structures of substrates and ligands, see Figures 3, 11, 35, 50, 56 and 57).

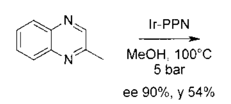
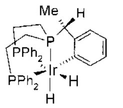
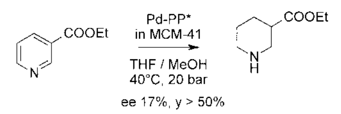
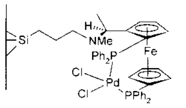
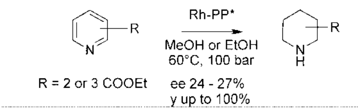
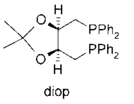
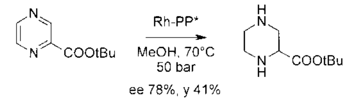
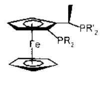
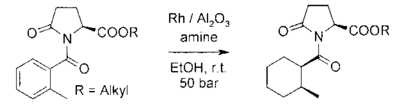
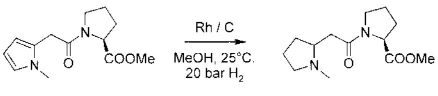
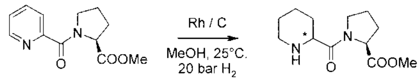
Entry	Substrate	R/X	Catalyst (Reducing Agent)	p(H_2)	ON	TOF [h^{-1}]	ee [%]	Ref.
1	**66**	H/Bn	**Ru**-dppach/dach	3	1500	23	92	[71a]
2	**66**	*o*-Me_2/Ph	**Ir**-PPF-P(4-CF_3Ph)$_2$/I^-/H^+	80	200[a]	n.a.	96	[72b]
3	**66**	H/Bn	**Ir-L33a**	100	100[a]	>36,000[a]	46	[73a]
4	**66**	H/Ph	**Ir-L33b** (scCO_2)	30	6,800	2,800	81	[73b]
5	**66**	var/*o*-Xyl	**Ir**-f-binaphane	70	100[a]	2[a]	>99	[20a]
6	**66**	var/$POPh_2$	**Rh**-Cy_2PF-PCy_2	70	500	500	99	[72a]
7	**66**	H/$POPh_2$	cp***Rh** (**Cat4**)	I[b]	n.a.	n.a.	>99	[74a]
8	**67**	*i*-Pr	cp***Rh**-Ts-dpen	F[b]	1000	1200	99	[74d]
9	**67**	Ar	**Rh**(C_6H_6)-Ts-dpen	F[b]	200[a]	100[a]	99	[71b]
10	**68**	cyclohexyl	**Ir**-binap	n.a.	n.a.	n.a.	>99	[75a]
11	**69**		**Ir**-bicp/phthalimide	70	200[a]	2[a]	95	[75b]
12	**69**		**Ir**-Xyl_2PF-$PXyl_2$/I^-/H^+	40	250[a]	56[a]	93	[72b]
13	MEA[c] + methoxyacetone		**Ir**-PPF-$PXyl_2$/I^-/H^+	80	10,000	>600	78	[72c]
14	2-(methylimino)-heptane		cp***Rh** (**Cat4**)	I[b]	500	500	95	[74]

[a] Standard test results, not optimized.

[b] Transfer hydrogenation, I: *i*-PrOH/*i*-PrONa, F: HCOOH/NEt_3.

[c] 2-Methyl-6-ethylaniline.

Table 25. Enantio- and diastereoselective hydrogenation of aromatic rings.

Reaction	Catalyst / Ligand	Ref.
		[77a]
		[77]
		[77c]
		[77d]
	de up to 96% yield > 90%	[78a]
	de up to 95%	[78c]
	de 27%	[78d,e]

cluster[80c] active for the hydrogenation of carbocyclic[80a, c] and heterocyclic rings.[80b] For the Ru cluster, Süss-Fink et al. proposed benzene hydrogenation without coordination to a metal[80c] (see also Section 6). A remarkable improvement of the productivity under mild conditions was noted for Rh complexes immobilized on MCM 41 supports[81a] or Pd-SiO$_2$[81b] (see Table 26). It was found that Nb and Ta alkoxide complexes are also able to hydrogenate unfunctionalized aromatic rings[82] (Table 26), but the catalysts proved to be very sensitive and the functional group tolerance was low. Colloidal Ru[61a] and Rh[61b–d] catalysts were shown to be active for the hydrogenation of various aromatic systems, in part under very mild conditions (see Table 26). However, major drawbacks of most of these novel catalysts is their often difficult preparation, low productivity and/or stability and/or functional group tolerance. Nevertheless, there are some interesting leads which might eventually give technically useful catalysts but probably only for special applications.

4.5 Aromatic Nitro Groups: Chemoselectivity and Hydroxylamine Accumulation

Hydrogenation with heterogeneous catalysts is the method of choice for the conversion of aromatic nitro compounds to the corresponding anilines. Whereas the hydrogenation of simple nitroarenes poses little selectivity problems and is indeed carried out on very large scale,[83] the situation is different if other reducible functional groups are present in the molecule. In addition to chemoselectivity, the accumulation of reaction intermediates can become a dominant issue. Here we will briefly discuss recent progress concerning chemoselectivity and hydroxylamine accumulation.[63a]

4.5.1 Chemoselectivity

Two novel catalyst systems were found to be selective for the selective hydrogenation of aromatic nitro groups tolerating functional groups such as C ≡ C, C=C, C ≡ N, C=N or C-Hal (see Figure 52):[63a, b]

Table 26. New catalytic systems for the hydrogenation of aromatic rings.

Catalysts	Substrates	TON	Conditions, Comments	Ref.
Ta(V) complexes with bulky ancillary alkoxide ligands	naphthalene	12 in 24 h	83 bar, 90 °C, s/c 1:20, 61%	[82]
Ru colloids	benzene	1000, reusable	20 bar, 80 °C, MeOH/THF	[61a]
Rh colloid	benzene, anisole, phenol, aniline, benzoate and others	2000	1 bar, 20 °C, aqueous biphasic with surfactant, reusable	[61b]
Rh colloid with anionic stabilizer	anisole	2600 in 144 h	3 bar, r.t., propylene carbonate	[61c]
Rh colloid in aqueous biphasic system (surfactant)	phenol, aromatic ester, 2-MeO-4-Pr-phenol	n.a.	10 bar H$_2$, 230 bar C$_2$H$_6$, (supercritical), 36 °C, high cis selectivity	[61d]
Rh-NN complex tethered to Pd on SiO$_2$	anisole	14,500 in 6 h	4 bar, 70 °C, heptane	[81b]

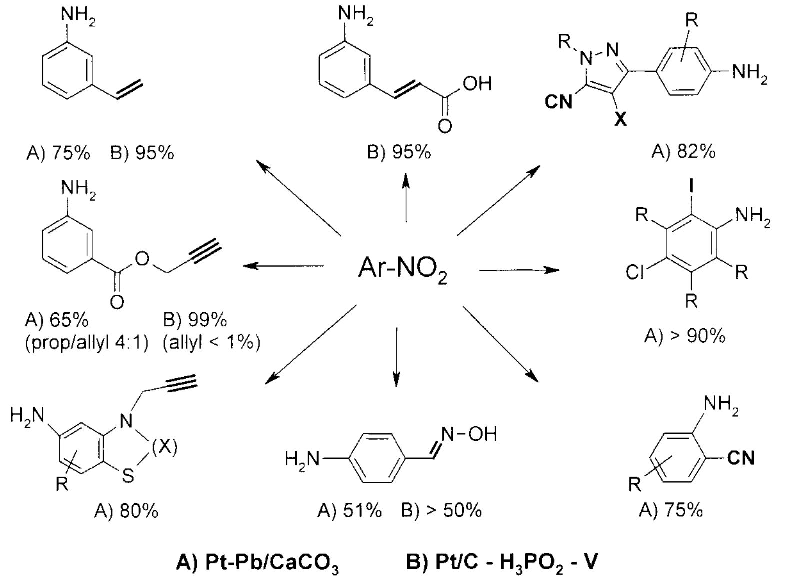


Figure 52. Scope of the modified Pt catalysts (yields non optimized).

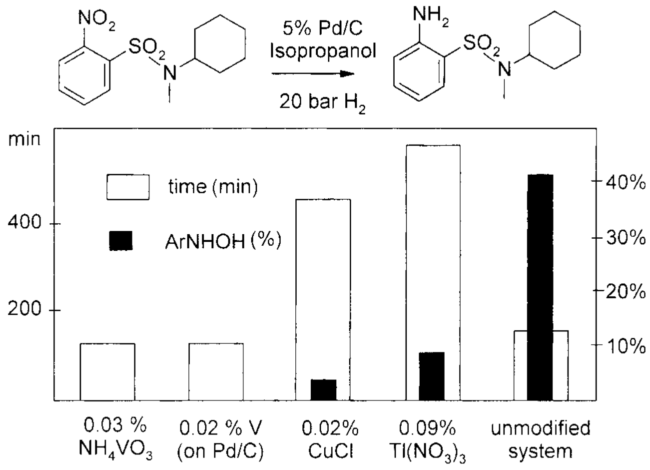


Figure 53. Effect of the addition of promoters to Pd/C on hydrogenation time and maximum hydroxylamine accumulation.

- Pt/C catalysts, modified by H_3PO_2 and other low-valent phosphorus additives and promoted by vanadium compounds highly effective in apolar solvents.
- Pt-Pb/$CaCO_3$ catalysts in presence of small amounts of $FeCl_2$ and tetramethylammonium chloride were shown to be suitable for polar solvents.

Both catalyst systems work with commercially available components, have a wide substrate scope as depicted in Figure 52 and are applied on a technical scale for several medium to large scale products.

4.5.2 Hydroxylamine Accumulation

Accumulation of hydroxylamines is problematic due their potential for exothermic decomposition, their toxicity and their ability to form colored condensation products leading to quality problems. The suppression of hydroxylamine accumulation is therefore a topic of industrial importance. Two recent publications described the addition of small amounts of metal, especially vanadium compounds to commercial Pt, Pd and Ni catalysts[63c, d] leading to a dramatic decrease of hydroxylamine accumulation often below 1% (for an example see Figure 53). In addition, for Pd and Pt catalysts, the over-all reaction with vanadium promoter was usually faster.[63c] For Ni catalysts the choice of the promoter is more difficult and in some cases, lower rates were observed.[63d] The reaction products obtained with efficient promoters were whiter (cleaner) than the ones without. A mechanism called 'catalytic by-pass' was proposed to explain the observed effects, whereby the vanadium promoters catalyze the disproportionation of the arylhydroxylamine to give aniline and the nitroso intermediate that re-enters the catalytic cycle. As a consequence, the hydroxylamine accumulation is avoided and the aniline formation is accelerated.

4.6 Catalytic Debenzylation: Chemoselectivity and New Protecting Groups

N- and O-benzyl groups are among the most useful protective groups in synthetic organic chemistry and the method of choice for their removal is catalytic hydrogenolysis.[1a,57a, b] In a recent review[58b] the most important factors were identified to be the choice of the

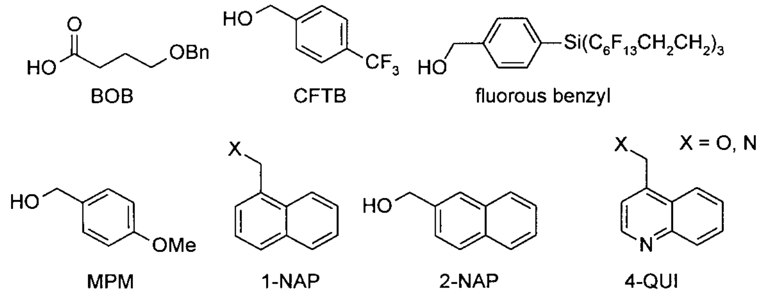


Figure 54. New protective groups which can be removed *via* selective hydrogenolysis.

catalyst, usually 5–20% Pd/C; the best solvents are alcoholic solvents or acetic acid, but water can have a significant effect; acids promote debenzylation, whereas amines can both promote and hinder hydrogenolysis. Here we discuss two areas of potential interest to the synthetic chemist: improvement of chemoselectivity and new protecting groups.

4.6.1 Improvement of Chemoselectivity

Chemoselectivity can mainly be influenced by modifying the classical Pd/C catalysts. The addition of ethylenediamine allowed the selective removal of benzyl ethers while the N-Cbz (N-COOBn) group survived the hydrogenation of a variety of functional groups.[62a] The addition of 2,2′-dipyridyl permitted the selective deprotection of N-Cbz and benzyl ethers in the presence of ArO-Bn groups[62c] and with a Pd/C-pyridine system an ArO-Bn bond was cleaved in presence of an ArO-*p*OMeBn group.[62d]

4.6.2 New Protecting Groups

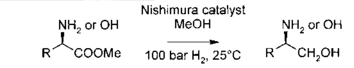
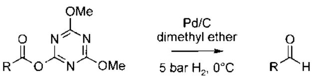
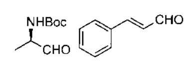
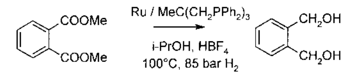
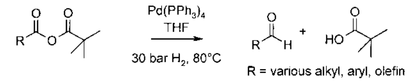
There is strong interest in protective groups which can be removed selectively and easily. Figure 54 depicts a series of recently published structures with interesting properties. 1-NAP and 4-QUI esters have been cleaved with a homogeneous Pd complex and a formate donor; benzyl esters, olefins, Ar-Br and other functional groups are tolerated.[84a] The highly selective removal of 1-NAP from N- and O-functions without affecting Bn and CFTB groups was reported for Pd/C-H_2.[84b] MPM-OAr groups survived the deprotection of Bn-OAr and CbzNH with Pd/C modified with pyridine but could easily be removed in absence of the pyridine modifier.[84c] Tagging with fluorous benzyl groups allowed a clever combination of protection and fluorous-phase chemistry with easy subsequent removal of the auxiliary group.[84d] BOB-protected hydroxy groups were deprotected *via* hydrogenolysis/lactonization compatible with a number of fatty acid esters.[84e]

4.7 Mild Hydrogenation of Carboxylic Acid Derivatives

Generally, the reduction of carboxylic acid derivatives to the corresponding alcohol is quite difficult with classical hydrogenation catalysts.[1] Stable aldehydes can be produced in good yields with high temperature processes using modified ZrO_2 or Cr_2O_3 catalysts.[85] The hydrogenation of functionalized carboxylic acid derivatives under mild conditions and with high chemoselectivity, and/or without racemization could be an attractive route to the corresponding alcohols but is very difficult. Two approaches have shown some success: novel homogeneous and heterogeneous catalysts and activated ester derivatives (see Table 27).

The Nishimura catalyst (mixed Rh/Pt oxide) is able to reduce chiral α-amino and hydroxy acids to the corresponding amino alcohols and diols, respectively, at room temperature with high yields and no racemization.[86a] A special RuO_2 catalyst was reported for the same reaction of the corresponding acids, albeit at higher temperature and pressure, with little but measurable racemization.[86b] The combination of a supported catalyst with $Mo(CO)_6$ increased the yields significantly in the hydrogenation of carboxylic acids; remarkably, ester functions present in the same molecule were not affected.[87a] A homogeneous Ru complex with a tripodal ligand was able to hydrogenate aromatic esters with good yields but

Table 27. Mild hydrogenation of carboxylic acid derivatives.

Reaction	Comments	Ref.
	high yield no racemization	86a
	 examples of product aldehydes	86c
	ton >100 78 % yield	87b
 R = various alkyl, aryl, olefin	high yield no reduction of ketones or olefins	87c

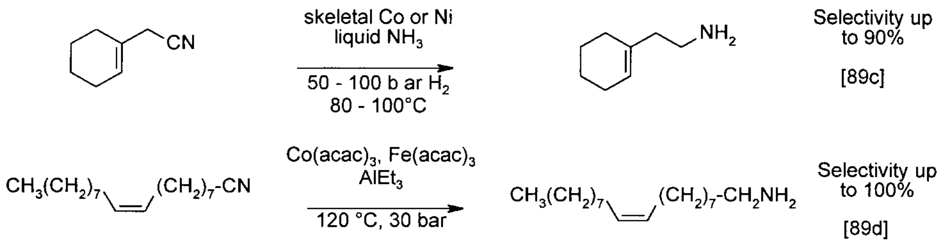


Figure 55. Chemoselective hydrogenation of nitriles in presence of a C=C bond.

needed relatively high pressure and temperature.[87b] Activated esters[86c] or mixed anhydrides[87c] can be hydrogenated to the corresponding aldehydes, and can be regarded as variants for the well known Rosenmund reaction. The reactions occur under remarkably mild conditions, often have high chemoselectivity (C=C, C=O), and no racemization is observed for protected amino acid derivatives.[86c] At the moment most of these catalyst systems are not yet technically mature but might be interesting alternatives on a small preparative scale.

4.8 Chemoselective Hydrogenation of Nitriles

The hydrogenation of nitriles is one of the basic methods to obtain primary amines, and especially diamines are of high industrial importance. Unfortunately, the literature is rather scattered and the most up-to-date review was written in 1994.[88a] We focus our summary of current results on selectivity to primary amines, catalyst deactivation, and functional group tolerance.

Besides primary amines, secondary and tertiary amines can be formed *via* condensation of reaction intermediates and control of this chemoselectivity problem is one of the main issues of nitrile hydrogenation. Addition of ammonia is most widely used to improve the selectivity for primary amines,[88a] but recently it was reported that less toxic strong bases such as NaOH[88b, c] and LiOH[88d] are also effective for Raney Ni and Co catalysts. The OH^- ions not only prevent catalyst deactivation by inhibiting polyamine formation on the catalyst surface for dinitrile hydrogenation,[88b] but also seem to block active sites responsible for by-product formation.[88c] Pre-treatment of Ni- and Co-catalysts with CO, CO_2, aldehydes or ketones also gave significantly less secondary amines.[88e]

For fine chemicals applications, functional group tolerance is an important issue. Substituents like aryl groups, benzylic functions or C-Hal are usually not reduced with skeletal Ni- or Co-catalysts. More difficult to conserve are heteroaromatic or heteroaryl-halogen functions, ketones, aldehydes or a second CN group, but with the proper catalyst, solvent and additives success is often possible.[89b] In contrast, the selective hydrogenation of CN groups in the presence of C=C bonds has long been an unsolved problem particularly if they are conjugated or in close proximity in the molecule.[89a, b] If the C=C bond is sterically hindered[89c] then high selectivity is possible in liquid ammonia which not only inhibits the formation of secondary amines, but also improves the selectivity to the unsaturated amine, probably by forcing its desorption. Another case of chemoselective nitrile hydrogenation has been described for fatty acid nitriles[89d] where the selective hydrogenation of remote CN-functions is possible with high selectivity applying a Ziegler-type Co-Fe catalyst even in the absence of NH_3 (see Figure 55).

5 Transfer Hydrogenation

By definition, molecular hydrogen is the hydrogen source in catalytic hydrogenations. However, the same reductions also occur *via* catalytic hydrogen transfer reactions where hydrogen is transferred from a donor molecule (DH_2) to the substrate to give reduced substrate and the oxidized donor D. Suitable DH_2 are cyclohexene, cyclohexadiene, ammonium formate or 2-propanol, often with very good selectivity.[90] A primary advantage of this technology is the avoidance of hydrogen gas and pressure equipment. A drawback is the often low catalyst activity and productivity. While many heterogeneous systems have been described,[90a] we focus here exclusively on homogeneous enantioselective catalysts since this is the area where most progress has been achieved in the last 5 years.

5.1 Ru, Rh and Ir Complexes for Enantioselective Transfer Hydrogenations

Whereas complexes containing chiral phosphine ligands are the catalysts of choice for hydrogenation reaction with H_2, Ru, Rh and Ir complexes with chiral NN or NO ligands (which are not able to activate H_2) have been shown to be very effective for asymmetric transfer hydrogenations. A comprehensive review presents the state of the art up to 1992,[90c] the reduction of ketones has recently been reviewed by Noyori and coworkers[4c,91a] and by Palmer and Wills.[91b] The mechanism of transfer hydrogenations is briefly discussed in Section 6. Generally, the transfer hydrogenation of C=C bonds

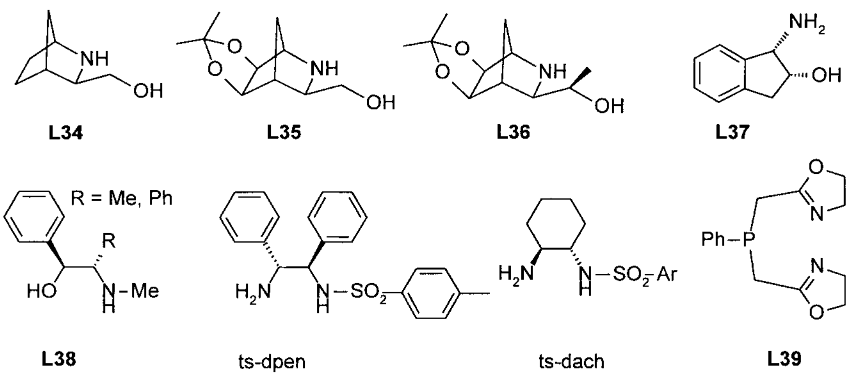


Figure 56. Structures of the most effective ligands for transfer hydrogenation of ketones.

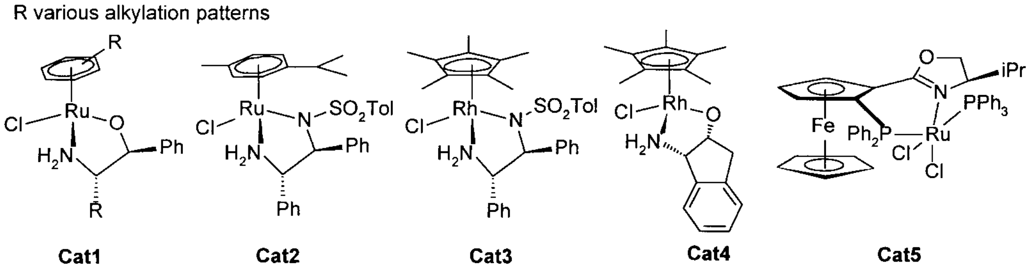


Figure 57. Structures of the most effective Ru, Rh catalyst precursors.

(preferred catalysts Rh and Ru diphosphine[91a]) is not competitive with hydrogenation. However, it can be a viable alternative for aryl ketones and ketimines which can be reduced with high ees but medium TONs and TOFs employing preferably Ru, sometimes Rh or Ir complexes. Here we will very briefly sketch the state of the art and discuss in some more detail interesting current results in this latter area.

Two versatile reducing systems have emerged, many others also work but are less practical:

1) Isopropanol in the presence of a strong base at 20–40 °C is environmentally friendly and easy to handle. A major drawback is reversibility, often leading to incomplete conversions and/or an erosion of ees at high conversion. Therefore the reaction is often run dilute, usually 0.1 M in substrate. This limitation can be overcome by distilling the acetone at reduced pressure.
2) Formic acid, usually as an azeotropic 5:2 mixture of HCOOH and NEt_3, in most common solvents, at 20–60 °C allows high substrate concentrations, is irreversible and allows high conversions without back-reaction and racemization. Due to evolution of CO_2, the process has to be run in an open system.

Of the plethora of ligands tested, only few are effective and also have a reasonable synthetic scope (see Figure 56). Most important are 1,2-amino alcohols, monotosylated diamines and selected phosphino-oxazoline ligands. The choice of the proper metal fragment is crucial and again, only few have proved to be useful (see Figure 57). The most active ones are half-sandwich π-complexes, Ru-arene and Rh (and also Ir)-cyclopentadiene complexes. It has been shown that the organometallic fragment stays intact in the catalytic

Table 28. Selected results for the transfer hydrogenation with HCOOH/NEt_3 (ligand structures and abbreviations see, Figure 57, substrates, see Figure 58).

Entry	Substrate	Catalyst	TON	TOF [h^{-1}]	ee [%]	Comments	Ref.
1	**70** (Y = CH_2NHBoc)	**Cat2**	200	n.a.	99		[93a]
2	**70** (Y = CH(NMeR)COOR)	**Cat2**	40	*ca.* 1	>99	kinetic resolution de 90%	[93b]
3	benzils	**Cat2**	1700	80	>99	de 97% for diol	[93c]
4	*t*-BuCOMe	**Cat5**	160	10	>99	*i*-PrOH/*i*-PrONa	[93d]
5	**73**	**Cat3**	200–1000	1200	99		[74d]
6	**74**	**Cat3**	5000	2000	95	yield 95%	[74a–c]

cycle (see Figure 65) and strongly influences the catalytic properties (for a discussion of mechanistic aspect see Section 6).

5.2 Catalytic Results

The catalysts described above have been developed with acetophenone as model substrate and standard reference. Many functionalized acetophenones **70** and analogous aryl ketones, acetylenic ketones **71** as well as cyclic aryl ketones **72** also give very good results.[4c,91d] All ketones depicted in Figure 58 can be reduced with ees of 95 – > 99% however, with still rather few exceptions, TONs are usually below 1000 and TOFs are also not very high. In other words: the major challenge in transfer hydrogenation today is no longer enantioselectivity but broadening the synthetic scope and increasing activity and productivity of the catalysts. In this respect, the strategy to improve ees of an insufficiently enriched alcohol *via* a subsequent dehydrogenation with the antipode of the original catalyst is ingenious but not practically useful.[92]

Recent extensions of scope have been reported for α-amidoaryl ketones and for the dynamic kinetic resolution of aryl β-ketoesters and benzils (Table 28, entries 1 – 3). The reduction of aliphatic ketones was improved by applying Ru phosphino-oxazoline **Cat5** with > 99% ee for *t*-butyl methyl ketone (entry 4) as well as for dimethyl cyclohexanone (ee > 99%) albeit with a moderate TONs and low TOFs. Finally, two very selective catalyst systems were recently described for the reduction of cyclic imines of type **73** as depicted in Figure 58 and closely related substrates. Mao and Baker[74d] prepared the cp*-Rh complex **Cat3** achieving ees up to 99%. In contrast, **Cat2**/formate yielded ees ≤ 97%, TONs up to 1200 h^{-1} and TOFs < 100 h^{-1} in the hands of the Noyori group[91a] and ees of 94 – 99% but very low TONs (5 – 100) and TOFs (< 4 h^{-1}) for imines with R = *ortho*-substituted aryl as described by Vedejs et al.[71c]

The catalysts **Cat3** and **Cat4** have been developed by Avecia for technical applications.[74a–c] **Cat4** was used for the transfer hydrogenation of ketones of type **70** and **72** on a 200-L scale (*i*-PrOH/*i*-PrOONa, s/c 1000, TOF 500 – 2500 h^{-1}, ee 87 – 97%, yield 95%), the hydrogenation of imine **74** is in development (entry 6). Also described were ees > 95% for the reduction of phosphinyl imines **75** (R = Naphth and C_4H_9) with TOFs of 1000 h^{-1}.[74b] These results demonstrate the industrial potential of the enantioselective transfer hydrogenation.

The question of catalyst activity was addressed by Andersson's group[94a] who optimized an azanorbornane-based ligand **L34** (see Fig. 56). As substantiated by the results in Table 29, the combined introduction of a dioxolane in the backbone and a methyl group in the α-position to the OH group (**L36**) resulted in significant

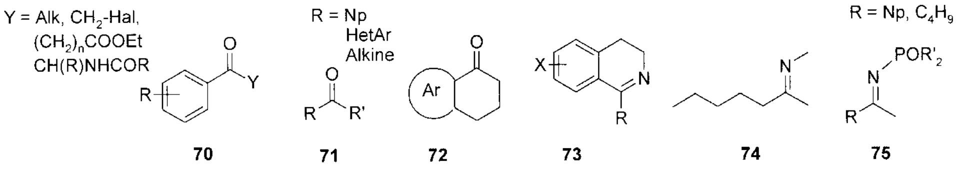


Figure 58. Suitable substrate types for enantioselective transfer hydrogenation.

Table 29. Transfer hydrogenation of aryl ketones with azanorbornane-based *p*-cymene Ru-**L** catalysts, s/c, ee, TON and TOF.[94a]

Ligand	Substrate	s/c	ee [%]	TON	TOF [h^{-1}]
L34	acetophenone	1000	94	900	300
L35	acetophenone	1000	96	920	920
L36	acetophenone	1000	96	970	3680
L36	acetophenone	5000	96	4800	3200
L36	acetophenone	7000[a]	96	5950	3250
L36	subst. acetophenones[b]	200 – 1000	90 – 98	180 – 1000	3000 – 6000
L36	3-aminoacetophenone	200	99	196	3000
L36	1-acetonaphthone	1000	> 99	980	4000
L36	acetylpyridines	200	89 – 91	180 – 196	800 – 4000

Reaction conditions: Ligand, [$RuCl_2$(p-cymene)]$_2$, 0.1 M ketone in *i*-PrOH, *i*-PrOK, r.t. Conversions > 90%.

[a] Stopped after 85% conversion.

[b] Me, MeO, Hal, Nitro in 2, 3 or 4 position.

improvement of catalyst activity and productivity. At the moment these are the most active and productive catalysts for the enantioselective transfer hydrogenation of a variety of aryl ketones. That even higher activities might be achievable has been shown with the achiral phosphino-oxazoline ligand **L39** depicted in Figure 56 which achieved TOFs of 70,000–$>$110,000 h^{-1} for the reduction of acetophenone and cyclohexanone.[94b]

6 Mechanistic Considerations

6.1 Activation of Hydrogen and Addition to Unsaturated Substrates

There is a consensus that the catalytic addition of hydrogen to an X=Y or the hydrogenolysis of an X-Y bond does not occur concerted but stepwise. This means that the H-H bond has to be cleaved first giving intermediate M-H species and in some cases protons which are then added stepwise to the X=Y or X-Y bond.

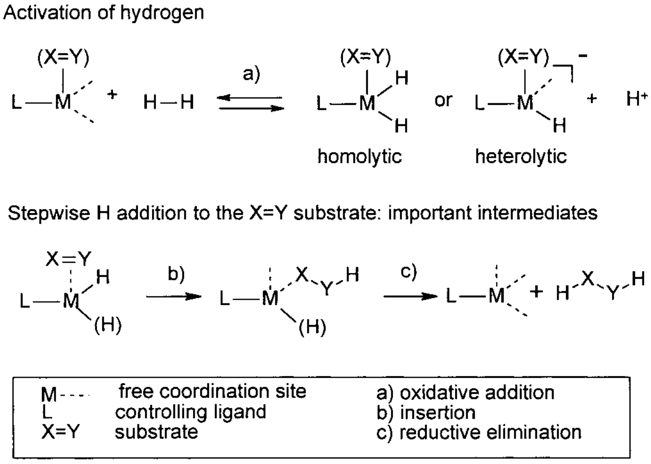


Figure 59. Schematic representation of the activation of a hydrogen molecule by a metal complex and addition to an X=Y bond.

This is schematically depicted in Figure 59 for a homogeneous metal complex where the cleavage step is called oxidative addition (because the formal oxidation state as well as the coordination number increase) giving either a metal dihydride (homolytic cleavage) or one M-H bond and a proton (heterolytic cleavage). The oxidative addition is known to occur both in the presence and in the absence of the substrate X=Y. In Figure 60 the analogous process is sketched for a metallic surface where the first step is called dissociative adsorption. In both cases the newly formed M-H bonds provide the energetic driving force for the cleavage of the strong H-H bond. A second function of the metal is the formation of complexes with the X=Y most probably *via* a π-bond thereby activating the second reactant and placing it close to the M-H fragments, allowing the addition to take place. There is ample evidence that some variant of the addition process depicted in the lower part of Figures 59 and 60 then leads to the saturated product. The complete catalytic cycle for the hydrogenation of alkenes using Wilkinson's complex was unraveled in a seminal study by Halpern[95] (see Figure 61). Recently Somorja[96] confirmed that the hydrogenation of ethylene on a Pt surface occurs *via* the same intermediates as schematically depicted in Figure 60.

The same pathways are also plausible and have been demonstrated in many cases for the hydrogenation of aromatic rings, and with less experimental evidence of C=O and C=N bonds. An example is the catalytic cycle proposed by Osborn[98] for the Ir-diphosphine-catalyzed hydrogenation of arylimines where the activation of hydrogen and the addition to the coordinated imine occurs in the last step maybe in a concerted fashion. However, several cases were recently discussed where hydrogenation seems to occur without coordination of the substrate to the metal (see Section 6.3).

There is also consensus that the H is added to the complexed or adsorbed X=Y from the metal side, leading to an over-all *cis* addition as depicted in Figures 60 and 61. This does not mean that the final result of the hydrogenation of a C=C bond or an aromatic ring is always and only *cis*, but trans products

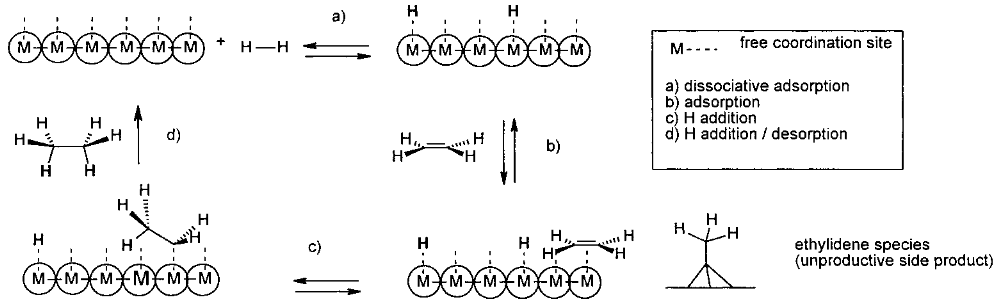


Figure 60. Schematic representation of the activation of a hydrogen molecule by a metal surface and addition to ethylene as presented by Somorja.[96]

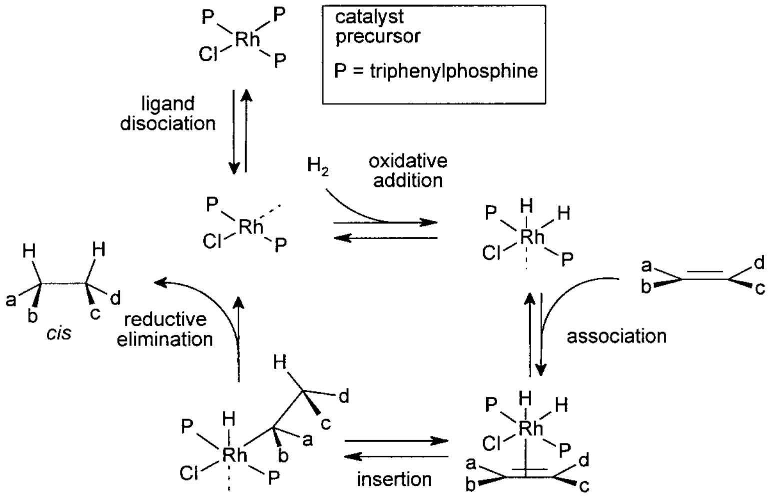


Figure 61. Halpern's catalytic cycle for the hydrogenation of an olefin with Wilkinson's catalyst *via* the hydride route.[95]

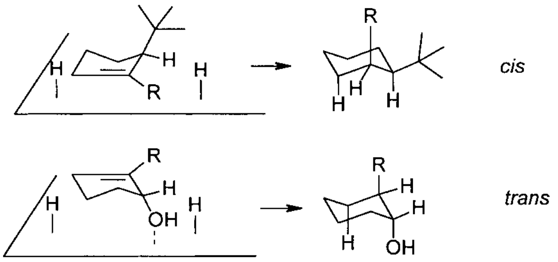


Figure 62. Diastereoselective hydrogenation of a cyclohexene derivative on a metal surface.

can be explained by isomerization equilibria even though the old question of direct *trans* addition on Pt surfaces was recently discussed again.[97] The outcome of a diastereoselective hydrogenation can also be rationalized with this mechanistic picture. Here, two cases can be distinguished. The first and more common case is the preferential adsorption of the less hindered face of the substrate due to repulsive interactions, the second the coordination *via* an anchoring group such as OH or an amine or sulfide, leading to the opposite stereoisomer. This is shown schematically for a cyclohexene derivative adsorbed on a metal surface in Figure 62 but similar arguments are valid for metal complexes as well.

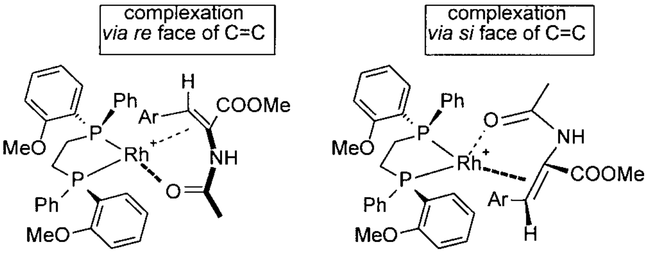
6.2 Enantioselective Hydrogenation

The mechanism of the Rh- and later Ru-catalyzed enantioselective hydrogenation has fascinated catalytic chemists since the first successful examples were published in the early 1970s. A recent review by Brown and Giernoth[99] gives an elegant account of the present state of understanding and of current research trends.

Halpern's[95] landmark investigation of the Rh-diphosphine-catalyzed hydrogenation of enamides showed that the reaction occurs *via* the unsaturated route, i.e., hydrogen reacts with the preformed Rh-substrate complex depicted in Figure 63 and not *via* the dihydride route as with the Wilkinson complex. Furthermore and at the time quite a sensation, Halpern demonstrated that the "lock-and-key" mechanism does not hold for this transformation. Indeed, the major adduct reacts much slower with hydrogen than the less stable complex, leading to just the opposite result than expected from the relative concentrations of the two Rh substrate complexes depicted in Figure 64. Obviously, the later step controls the stereochemistry, either the oxidative addition or the insertion into the Rh-H bond. Mechanistic investigations of the Rh-catalyzed hydrogenation using the electron rich miniphos and bisp* ligands showed that in contrast to most other Rh-diphosphine catalysts, the dihydride route is preferred, i.e., the enamide coordinates to the preformed dihydride and then the irreversible and stereocontrolling insertion occurs.[38a]

In contrast, Noyori[100b] demonstrated that for the Ru-binap-catalyzed enamide hydrogenation the relative stability of the two diastereomeric enamide adducts to an Ru-monohydride complex[100c] correlates with the observed enantioselectivity, i.e., this case, a "lock-and-key" mechanism operates. At least in hindsight this difference is not so surprising considering that the square planar Rh complex as depicted in Figure 63 has to rearrange to an octahedral complex upon oxidative addition whereas the corresponding Ru complex is already octahedral and therefor less drastic changes are needed. Since similar interactions control the stability of the two adducts as predicted by the quadrant rule (see Figure 3), this explains the fact that Ru-binap induces the opposite absolute configuration as the corresponding Rh complex.

The mechanism of the enantioselective hydrogenation using modified heterogeneous catalysts is less well understood.[60] As a basic reaction model, a stepwise



minor diastereomeric complex
fast reaction with H_2

major diastereomeric complex
slow reaction with H_2

Figure 63. Diastereomeric intermediates for the hydrogenation of enamides with an Rh-dipamp complex according to Halpern.[4b,95]

addition of dissociatively adsorbed hydrogen to the adsorbed C=O and C=C group, respectively, is the most plausible. A chiral active site is formed by strong adsorption of a modifier molecule on the metal surface. While the reaction on an unmodified metal site leads to racemic product, it is proposed that hydrogen bonds between the modifier and selected functional groups of the substrate molecule as depicted on Figure 64 not only control the adsorption mode (*via re-* or *si*-face) of the reacting molecule but also facilitate and control the addition of hydrogen. Computational studies indicate that the energy difference between the *pro-S* and *pro-R* activated complex determines the sense of induction and the enantioselectivity, i.e., that there is no kinetic preference for the less stable complex as found by Halpern for Rh-catalyzed homogeneous hydrogenation reactions.

6.3 Hydrogenation without Substrate Coordination

The questions whether the unsaturated substrate has to coordinate to and be activated by the metal has recently been addressed by Noyori[100a] for the transfer hydrogenation of ketones using Ru-amine complexes and somewhat surprisingly by Süss-Fink[80c] for the hydrogenation of benzene with a triruthenium cluster. The study of Noyori as well as of others[94a, c] accumulated convincing experimental and theoretical evidence that the transfer of the two H atoms occurs in a concerted

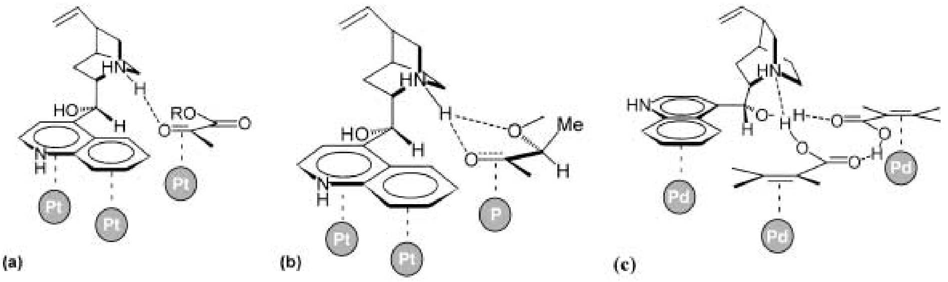


Figure 64. Schematic representation of proposed adsorbed substrate-modifier complexes. **a**) for Pt-cinchonidine-pyruvate (single H-bridge); **b**) Pt-cinchonidine-α-alkoxy ketone (bifurcated H-bridge); **c**) Pd-cinchonidine-α,β-unsaturated acid (acid dimer with two H-bridges).[60a]

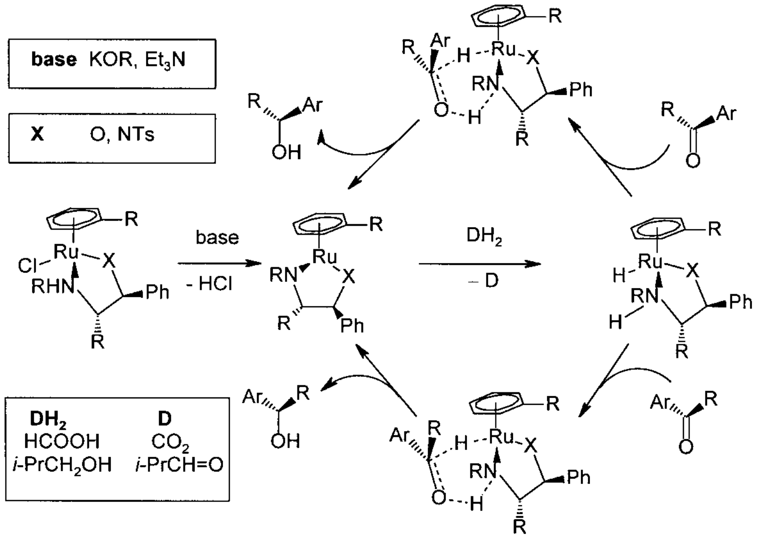


Figure 65. The two enantiomeric catalytic cycles proposed by Noyori for transfer hydrogenation with Ar-Ru catalysts *via* bifunctional catalysis without C=O – metal complexation.[100a]

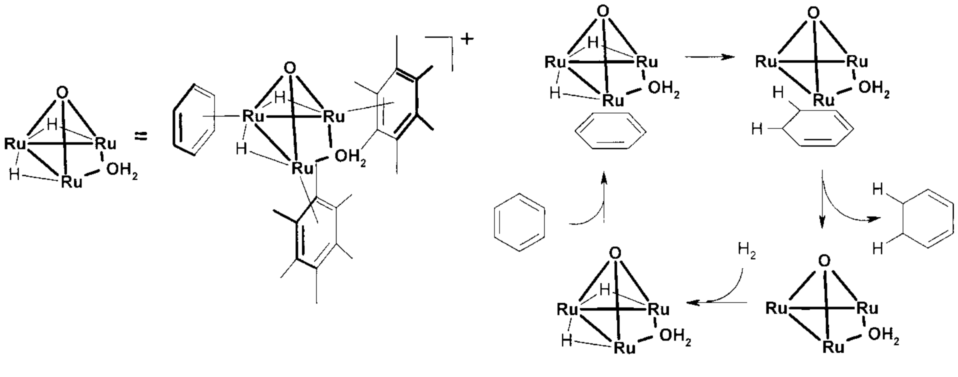


Figure 66. Structure of the active complex and proposed catalytic cycle for the hydrogenation of benzene with a triruthenium cluster.[80c]

manner as depicted in Figure 65 (upper and lower transition states). A similar transfer mechanism is also probable for the hydrogenation of ketones using Ru-binap/diamine complexes.[23] This hypothesis explains the need for an N-H moiety in the ligand and obviously, the protic nature of the N-H, coupled with the hydridic character of the Ru-H seems to be ideal to achieve very high reaction rates.

The case of the benzene hydrogenation described by Süss-Fink[80c] is not as well established. The cationic cluster is a surprisingly active catalyst for the hydrogenation of benzene and other arenes with small substituents. Since the coordinated arene ligands do not exchange with the substrate and the complex of the starting cluster with benzene was identified in a mass spectroscopic study, it is assumed that the hydrogenation occurs *via* adsorption of benzene in the hydrophobic pocket formed by the three arene ligands and direct H-transfer as depicted in Figure 66. While this is a plausible hypothesis, the opening of one of the Ru-Ru bonds and a direct benzene-Ru contact cannot be rigorously excluded.

7 Conclusions and Outlook

Selective catalytic hydrogenation is alive and well – both from the academic as well as industrial perspective. This is undoubtedly the major conclusion we can draw from our survey of the results published in the last few years. While progress has been made for all important selectivity issues, the most impressive results have unquestionably been achieved for the homogeneous enantioselective reduction of C=C, C=O and somewhat less of C=N functions. This progress was mostly due to the design of new chiral ligand types with unprecedented enantioselectivities. For the new generations of chiral complexes, ees $>99\%$ are quite common for the hydrogenation of several (model) substrates. Another area of notable progress was the development of heterogeneous catalysts with high chemo- and stereoselectivities for a number of industrially important transformations. Here, the most successful approach was the modification of technical catalysts with organic or inorganic compounds and to some extent the application of new catalyst types.

Where do we see the most pressing unsolved problems from the point of view of fine chemicals synthesis? In the area of enantioselective hydrogenation this is the lack of reliable information on the catalyst activity (TOF) and productivity (TON) for most homogeneous catalysts, and on their tolerance to changes in the structure of the substrate (specificity) and to the presence of other functional groups (chemoselectivity). Only partially solved is the question of effective reduction of many C=N groups and also for some sterically demanding C=C compounds. Still no solution exists for the enantioselective hydrogenation of aromatic rings. A major problem is also that only few of the most effective ligands are available for large-scale applications, either because of a restrictive license policy or (more frequently) because no technical synthesis for the ligands has been developed. For heterogeneous hydrogenation where there is less current research activity, we miss systematic studies for important selectivity problems as discussed above. For both homogeneous as well as heterogeneous catalysts the transfer of laboratory results to technical applications is often not trivial. For homogeneous (enantioselective) processes this is often due to the high purity requirements of the starting material and for heterogeneous reactions because modified catalysts are not (yet) commercially available in well defined and reproducible form.

In which directions will catalysis research head in the next period of time? There is no doubt that more new chiral ligands but also new heterogeneous catalysts will be prepared and tested, allowing progress in some of the major problem areas. We also see a minor trend to find active hydrogenation catalysts outside the established noble metal complexes, e.g., with Ni, Fe or W. We expect to see more applications of existing and new catalysts to "real world" synthetic problems and thus more insight into their synthetic scope and limitations. For this purpose, many companies (including Solvias) are assembling libraries of chiral ligands and developing higher through-put test methods in order to accelerate process development. It is also quite clear that the modern spectroscopic and computational tools will lead to a much better understanding of the mode of action particularly of homogeneous but to some extent also of heterogeneous catalysts. Whether we will ever be able to *ab-initio* design an effective catalyst for a specific transformation is very much an open question but who knows? One step in such a direction are attempts to design artificial catalytic antibodies, e.g., by imprinting methods[101] but except for some proof of principle results (very small effects), progress is slow and the goal still very far away. Other active areas of research with potential more on the technological side are the utilization of unconventional media such as water (biphasic),[102] ionic [103] or supercritical[104] liquids and the application of microwaves.[105] Last but not least, the ability to expedite process development by increasing the through-put in the screening as well as the optimization phase will be of growing importance.

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