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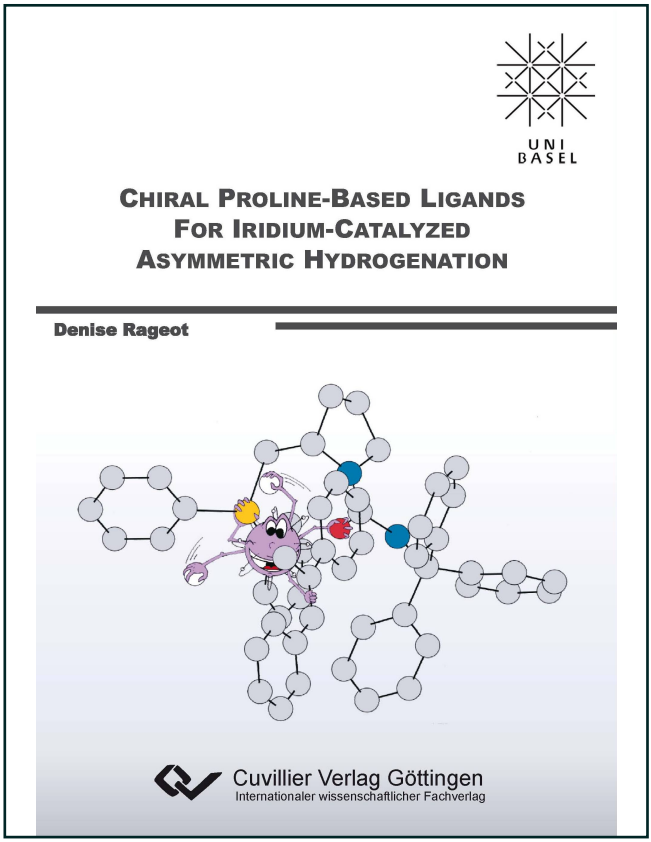
Chiral Proline-Based Ligands for Iridium-Catalyzed Asymmetric Hydrogenation



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CHAPTER 1

IRIDIUM-CATALYZED ASYMMETRIC HYDROGENATION AS A TOOL FOR ORGANIC SYNTHESIS

1.1 Introduction

Multiple pharmaceuticals, herbicides, fragrances and flavors manufactured on an industrial scale are known to involve a transition metal-catalyzed reaction in their synthesis.[1] Among these reactions, the most prominent reaction is the asymmetric hydrogenation catalyzed by a transition metal. The relevance of these products can be noticed by the fact that numerous non-specialists are familiar with their names (*e.g.* L-DOPA, ibuprofen and vitamin E). The metal-catalyzed hydrogenation is an attractive reaction for asymmetric synthesis, since it combines highly desirable advantages such as perfect atom economy, high conversions, low catalyst loadings and mild reaction conditions.[2] All these characteristics are well appreciated in modern organic synthesis and explain the various applications of metal-catalyzed asymmetric hydrogenation, not only in academic research but also in industrial synthesis. Although this reaction has been explored for many years and an impressive number of enantioselective catalysts have been developed it is still investigated today. The main goals in this field today are to find solutions to render this reaction more universal, meaning applicable to a wider range of substrates, or to discover more generally applicable, effective, inexpensive and readily available catalysts.[3]

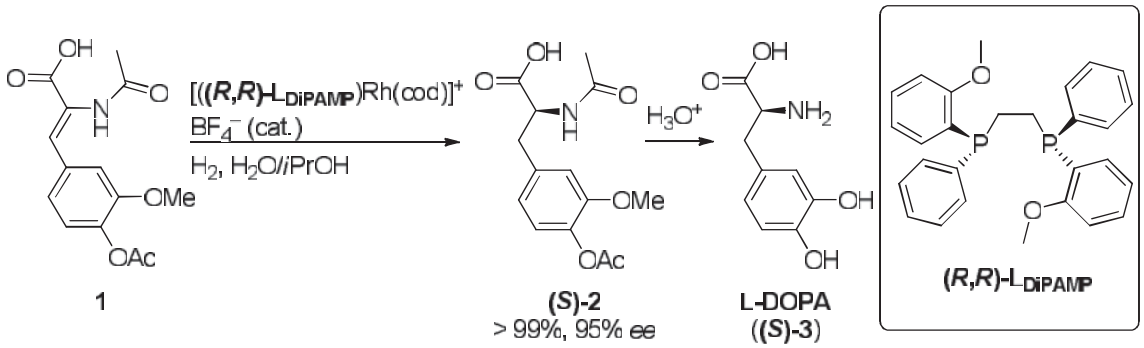
This first chapter of this thesis will show the ongoing need to design novel catalysts for iridium-catalyzed hydrogenation. First, the milestones set to reach today's knowledge in asymmetric hydrogenation reactions catalyzed by a transition metal will be summarized. The subsequent sections will then mainly focus on iridium catalysts for asymmetric hydrogenation, by showing their successful applications in industrial processes (see section 1.3.2) and in natural product synthesis (see section 1.4.2). This perspective will also allow to present many of the designed ligands for iridium-catalyzed asymmetric hydrogenations as well as the broad variety of the substrates they have been applied to (see section 1.4.1). Today's challenges in asymmetric metal-catalyzed hydrogenation,

[1] a) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (eds. H.-U. Blaser and H.-J. Federsel), Wiley, Verlag GmbH & Co. KGaA, Weinheim, **2010**; b) J. W. Scott, *Topics in Stereochem.* **1989**, *19*, 209-226; c) H.-U. Blaser, F. Spindler, M. Studer, *Applied Catalysis A: General* **2001**, *221*, 119-143.
[2] G Shang, W. Li, X. Zhang, *Transition Metal-Catalyzed Homogeneous Asymmetric Hydrogenation* in *Catalytic Asymmetric Synthesis* (ed. I. Ojima), Wiley, Hoboken, **2010**, 3rd Ed., pp. 343-436.
[3] a) H.-U. Blaser, B. Pugin, F. Spindler, *Chemistry Today* **2008**, *26*, 37-38; b) J. M. Hawkins, T. J. N. Watson, *Angew. Chem. Int. Ed.* **2004**, *43*, 3224-3228.

will then be discussed in section 1.5; prior to the presentation of the ligand scaffolds that have been investigated as part of the project described in this thesis (see section 1.6).

1.2 Transition Metal-Catalyzed Asymmetric Hydrogenation: a Historical Perspective

The first active catalyst for homogeneous hydrogenation was the rhodium complex discovered by WILKINSON (Nobel Prize 1973, $[(PPh_3)_3Rh]Cl$, Figure 1) and COFFEY.[4] Not much earlier, methods to prepare optically active phosphines were reported by HORNER *et al.* and MISLOW *et al*.[5] The remarkable idea to replace triphenylphosphine by chiral phosphines was obvious to many researchers, but it was first realized by HORNER and KNOWLES, who developed the first asymmetric hydrogenation using a rhodium complex.[6] The enantioselectivities were low, but promising. KNOWLES optimized this catalytic system until it led to the enantioselective synthesis of the rare amino acid L-DOPA (**(*S*)-3**), which was already known at that time to be active in the treatment of Parkinson's disease (Scheme 1).[7] This synthesis and the discovery in 1968 that a chiral rhodium catalyst can be used for catalytic and asymmetric hydrogenation earned KNOWLES the Nobel Prize in Chemistry in 2001 (shared with NOYORI and SHARPLESS).[8]



Scheme 1. Monsanto synthesis of L-DOPA: the process has been in operation since 1978 and was the first transition metal-catalyzed asymmetric synthesis of a commercialized product.[8]

[4] a) J. A. Osborn, F. H. Jardine, Y. F. Young, G. Wilkinson, *J. Chem. Soc. A* **1966**, 1711-1732; b) R. S. Coffey, *Imperial Chemical Industries, Brit. Pat.* **1965**, 1121642.
[5] a) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, P. Beck, *Tetrahedron Lett.* **1961**, *2*, 161-166; b) O. Korpiun, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784-4786.
[6] a) W. S. Knowles, *Chem. Commun.* **1968**, 1445-1446; b) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952; c) L. Horner, H. Büthe, H. Siegel, *Tetrahedron Lett.* **1968**, *37*, 4023-4026; d) L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942-942.
[7] a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc., Chem. Commun.* **1972**, 10-11; b) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106-112.
[8] W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998-2007.

Since the discovery that a metal complex can be used as a homogeneous catalyst for hydrogenations, many important achievements were reported, resulting in today's state-of-the-art in transition metal-catalyzed asymmetric hydrogenations. Figure 1 does not describe the chronological history of progresses accomplished in asymmetric hydrogenation, it is rather thought to give a figurative overview of how a discovery stimulated the next one to reach standards of reactivity. Nowadays countless combinations of ligands and transition metals have been reported to give good to high selectivities in the asymmetric hydrogenation of a myriad of substrates, but Figure 1 is only meant to show the most important compounds that represent landmarks in organometallic chemistry.

Shortly after KNOWLES'and HORNER's discovery, other researchers brought similar contributions and achieved the synthesis of various ligands for transition metals.[9] KAGAN *et al.* introduced C_2-symmetric diphosphines, such as DIOP (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, **(*R*,*S*)-L_{DIOP}**, Figure 1) as ligands and showed their synthesis to be practicable.[9a-b]

Another pioneer in this field, awarded with the Nobel Prize together with KNOWLES, is NOYORI.[10] He discovered the C_2-chiral diphosphine ligand BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, **(S_a)-L_{BINAP}**, Figure 1) as a versatile and efficient ligand for various metal-catalyzed transformations, including the asymmetric hydrogenation of α-(acylamino)acrylic acids or esters.[11] BINAP/ruthenium-complexes proved to be more efficient than their rhodium analogues for a broader range of substrates. Besides the C−C double bond reduction of functionalized alkenes, they also allow for the reduction of the C−O double bond in a wide range of ketones.[12] Important industrial syntheses, involving a transformation catalyzed by a BINAP/ruthenium or /rhodium catalyst as key step will be described in more detail in section 1.3.1.

[9] a) T. P. Dang, H. B. Kagan, *J. Chem. Soc. D* **1971**, 481-481; b) H. B. Kagan, T.-P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433; c) J. D. Morrison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, C. Phillips, *J. Am. Chem. Soc.* **1971**, *93*, 1301-1303.
[10] R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022.
[11] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934.
[12] a) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629-631; b) T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem.* **1988**, *27*, 566-569.

Ligand design for asymmetric hydrogenation catalyzed by a transition metal continued to be the main focus of research for several years and many modifications of the structural environment around the metal center were investigated. BURK *et al.* for instance, designed the bis(phospholane) ligand DuPhos for the rhodium-catalyzed hydrogenation of various olefins (**(*S*,*S*)-L_{DuPhos}**, Figure 1).[13] For a long time C_2-symmetric P,P ligands dominated in asymmetric transition metal catalysis. In the 90s, the planar chiral and non-symmetric ferrocene-based ligands Josiphos were discovered (**(*R*,S_{Fc})-$L_{Josiphos}$**, Figure 1).[14] After the discovery of sterically and electronically non-symmetric P,N ligands by PFALTZ, and independently by HELMCHEN and WILLIAMS, a change in the course of research in chiral ligands could be observed; many ligands that were introduced later on for asymmetric catalysis were non-symmetric.[15] Although the concept of C_2-symmetry has been very successful, the introduction of the non-symmetrical PHOX ligands proved that two electronically and sterically divergent coordinating units can be more effective than C_2-symmetric ligands. PHOX ligands, which were developed originally for palladium-catalyzed allylic substitutions, were also deployed to other transition metal-catalyzed reactions. Excellent enantiomeric excesses and turn over numbers were obtained in the iridium-catalyzed asymmetric hydrogenation of trisubstituted alkenes by the use of these P,N ligands. PHOX/iridium complexes were shown not require a polar coordinating group near to the C–C double bond that is reduced, contrarily to rhodium and ruthenium catalysts.

CRABTREE *et al.* reported already in 1979 that $[Ir(cod)(PCy_3)(Py)]PF_6$ was a highly active catalyst for the hydrogenation of alkenes (CRABTREE's catalyst, Figure 1).[16] This complex hydrogenated alkenes more rapidly than WILKINSON's catalyst. However, deactivation of the catalyst due to the formation of inactive hydride-bridged trinuclear complexes was observed.[16b] Such a trinuclear PHOX/iridium hydride complex was isolated and characterized.[17]

[13] a) M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519; b) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125-10138; c) M. J. Burk, *Acc. Chem. Res.* **2000**, *33*, 363-372.
[14] a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062-4066; b) H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* **2002**, *19*, 3-16.
[15] a) A. Pfaltz, W. J. Drury III., *PNAS* **2004**, *101*, 5723-5726; b) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336-345; c) J. M. J. Williams, *Synlett* **1996**, *8*, 705-710.
[16] a) R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1977**, *141*, 205-215; b) R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331-337.
[17] S. P. Smidt, A. Pfaltz, E. Martínez-Vivente, P. S. Pregosin, A. Albinati, *Organometallics* **2003**, *22*, 1000-1009.

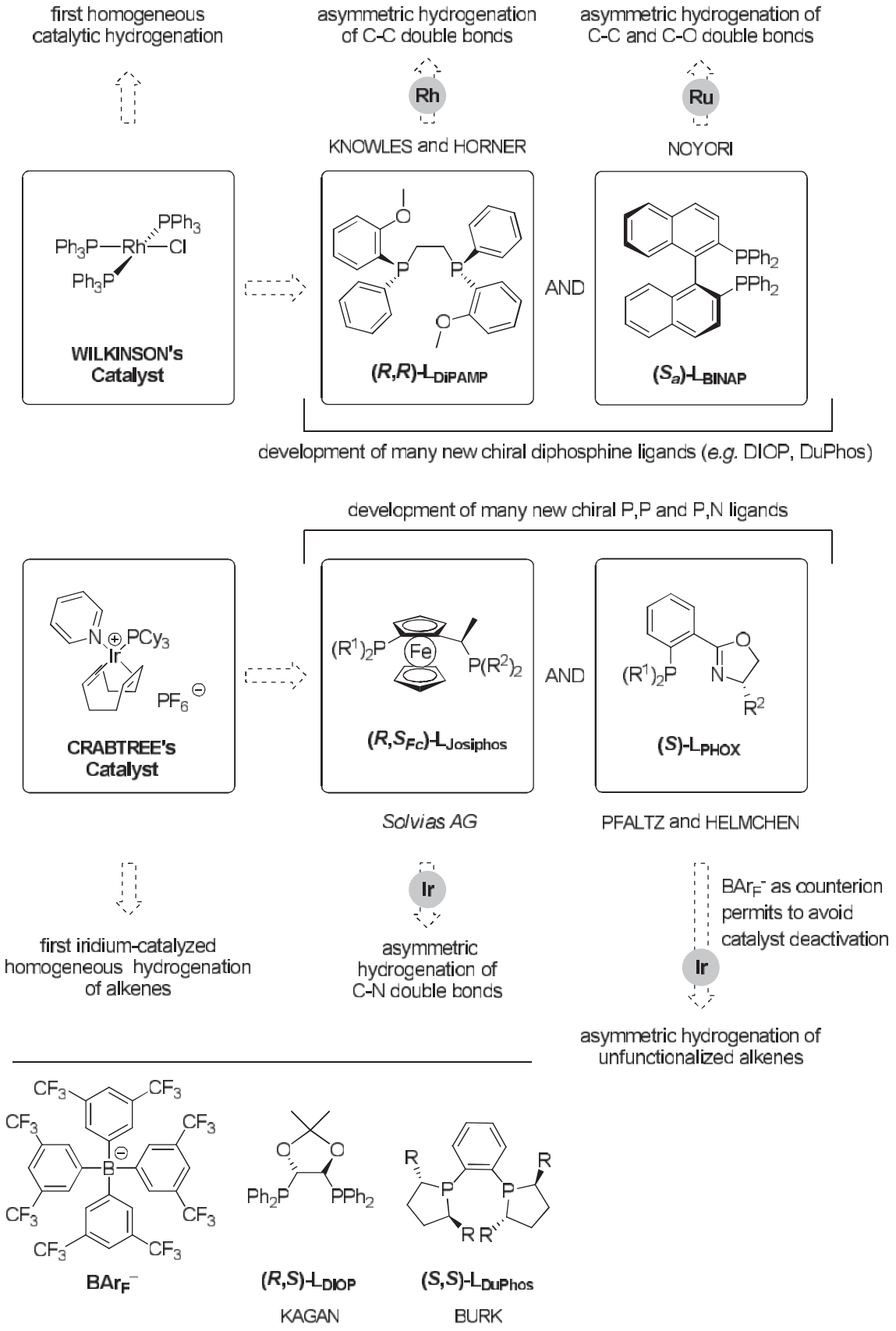


Figure 1. Figurative representation of milestones in metal-catalyzed asymmetric hydrogenation.

The catalyst deactivation was circumvented replacing the PF_6-anion with the weakly coordinating, bulky and apolar BAr_F-couteranion (tetrakis[3,5-bis(trifluoromethyl) phenyl]borate, Figure 1).[18] However, it seems that only this accumulation of different findings (non-symmetric ligands, solvent and counterion effects and the success of the Josiphos ligands in industry) permitted to show that iridium is an interesting alternative to rhodium and ruthenium for the catalytic enantioselective hydrogenation.

The mechanism of the rhodium/phosphine-complex catalyzed asymmetric hydrogenation has been elucidated. Detailed mechanistic studies of the DiPAMP/rhodium-catalyzed asymmetric hydrogenation of acetamidocinnamates were performed by HALPERN and BROWN *et al*.[19] The mechanism of the asymmetric hydrogenation of ketones using a BINAP/ruthenium complex was elucidated by NOYORI *et al*.[20] A definitive rationale of the mechanism of the iridium-catalyzed hydrogenation of C−C double bonds has not been proposed yet.[21] Although several studies have been undertaken, experimental evidence about each step of the catalytic cycle is still lacking and, according to computational studies, it seems that several pathways are possible.[21]

[18] a) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899; b) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402-1411; c) I. Krossing, I. Raabe, *Angew. Chem. Int. Ed.* **2004**, *43*, 2066-2090.
[19] a) J. Halpern, *Science* **1982**, *217*, 401-407; b) J. Halpern, *Asymmetric Catalytic Hydrogenation: Mechanism and Origin of Enantioselection*, in *Asymmetric Synthesis* (ed. J. D. Morrison), Academic Press, New York, **1985**, Vol. 5, pp. 41-69; c) J. M. Brown, P. A. Chaloner, *Tetrahedron Lett.* **1978**, *21*, 1877-1880; d) J. M. Brown, P. A. Chaloner, *J. Chem. Soc., Chem. Commun.* **1980**, 344-346; e) J. M. Brown, D. Parker, *Organometallics* **1982**, *1*, 950-956; f) J. M. Brown, L. R. Canning, A. J. Downs, A. M. Forster, *J. Organomet. Chem.* **1983**, *255*, 103-111; g) A. S. C. Chan, J. J. Pluth, J. Halpern, *Inorg. Chim. Acta* **1979**, *37*, 477-479; h) A. S. C. Chan, J. J. Pluth, J. Halpern, *J. Am. Chem. Soc.* **1980**, *102*, 5952-5954; i) A. S. C. Chan, J. Halpern, *J. Am. Chem. Soc.* **1980**, *102*, 838-840; j) C. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746-1754; k) I. D. Gridnev, T. Imamoto, *Acc. Chem. Res.* **2004**, 37, 633-644.
[20] C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490-13503.
[21] a) R. H. Crabtree, P. C. Demou, D. Eden, J. M. Mihelcic, C. A. Parnell, J. M. Quirk, G. E. Morris, *J. Am. Chem. Soc.* **1982**, *104*, 6994-7001; b) C. Mazet, S. P. Smidt, M. Meuwly, A. Pfaltz, *J. Am. Chem. Soc.* **2004**, *126*, 14176-14181; c) M. J. Burk, M. P. McGrath, R. Wheeler, R. H. Crabtree, J. Am. Chem. Soc. **1988**, *110*, 5034-5039; d) R. Dietiker, P. Chen, *Angew. Chem. Int. Ed.* **2004**, 43, 5513-516; e) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272-3296; f) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249-6253; g) Y. Fan, X. Cui, K. Burgess, M. B. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 16688-16689; h) J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit(Bee), Y. Zhu, K. Burgess, *Chem. Eur. J.* **2007**, *13*, 7162-7170; i) C. Hedberg, K. Källström, P. Brandt, L. K. Hansen, P. G. Andersson, *J. Am. Chem. Soc.* **2006**, *128*, 2995-3001; j) T. L. Church, T. Rasmussen, P. G. Andersson, *Organometallics* **2010**, *29*, 6769-6781; k) P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339-347; l) K. H. Hopmann, A. Bayer, *Organometallics* **2011**, *30*, 2483-2497; m) K. Källström, I. Munslow, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194-3200.

1.3
Metal-Catalyzed Asymmetric Hydrogenation in Industrial Processes

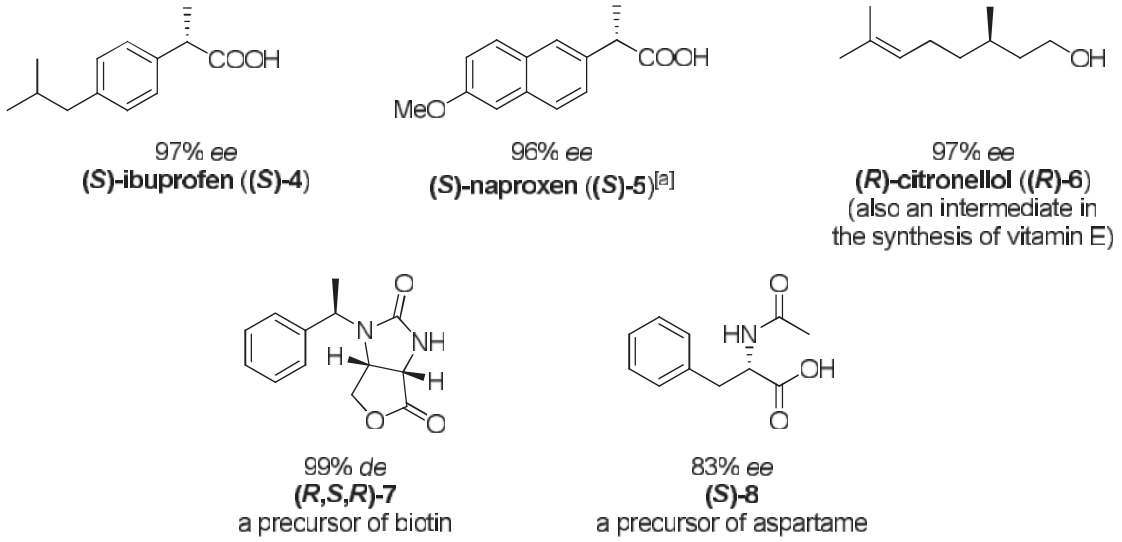
A major concern for chemical processes is efficiency. Catalysis can be highly productive and economical, as it reduces the waste deriving from racemate resolution in enantioselective synthesis. The asymmetric hydrogenation reaction is fundamental for the manufacturing of fine and industrial chemicals and has found application in the industrial synthesis of pharmaceuticals, agrochemicals, flavors and fragrances. Selected examples of transition metal-catalyzed asymmetric hydrogenation for industrial processes will be presented below.

1.3.1
Rhodium and Ruthenium Catalysts for Asymmetric Hydrogenation in Industrial Processes

Most of the asymmetric hydrogenations in industry involve chiral phosphorus ligands and are rhodium- or ruthenium-catalyzed. As described above, the first industrial application of a metal-catalyzed asymmetric hydrogenation was found in the synthesis of L-DOPA (Scheme 1). The catalyst developed by KNOWLES, not only proved to be efficient in the enantioselective synthesis of L-DOPA, but also led to the synthesis of several amino acids, such as phenylalanine, tryptophan and alanine with enantiomeric excess higher than 90%. This application of diphosphine/rhodium catalysts became a standard method for the production of enantiomerically pure amino acids. Although KNOWLES' DiPAMP ligand was efficient, the chiral phospholane DuPhos introduced later on replaced it since this ligand proved to be more convenient hydrogenation of (*E*)/(*Z*)-mixtures of olefins.[13c]

Another significant example of a pharmaceutically important compound that can be synthesized by asymmetric hydrogenation of a C–C double bond using this time a ruthenium-based BINAP catalyst is (*S*)-ibuprofen (**(*S*)-4**, Figure 2). This anti-inflammatory drug was obtained quantitatively from 2-(4-isobutylphenyl)propenoic

acid with 97% *ee*.[22] The synthesis of (*S*)-naproxen (**(*S*)-5**), a chiral anti-inflammatory drug) involves as well an enantioselective hydrogenation that can be catalyzed effectively by the BINAP/ruthenium catalysts developed by NOYORI *et al*.[23] Despite the good results obtained with several catalysts in terms of enantioselectivity, the asymmetric synthesis of (*S*)-naproxen (**(*S*)-5**) by asymmetric hydrogenation is still not valuable for industry. For economical reasons, (*S*)-naproxen is still produced on a large scale by the resolution of a racemate.[1c]



[a] (*S*)-Naproxen is still produced on a large scale by the resolution of a racemate.

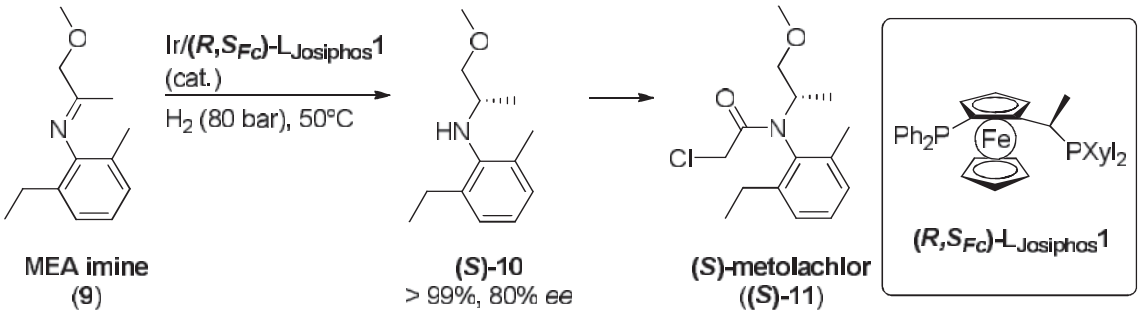
Figure 2. Asymmetric hydrogenation products produced in large scale by the use of chiral ruthenium and rhodium catalysts.[1c,23-26]

Some other compounds synthesized by asymmetric C–C double bond reduction are: citronellol (**(*R*)-6**) by *Takasago*;[1c,24] the intermediate **(*R*,*S*,*R*)-7** for biotin by *Lonza*;[1c,25] and the intermediate **(*S*)-8** in the synthesis of aspartame (sweetener) by *Enichem/Anic*[1c,26] (Figure 2). Whereas, the synthesis of citronellol involves as well a BINAP/ruthenium catalyst, the asymmetric hydrogenations affording **(*R*,*S*,*R*)-7** and **(*S*)-8** are rhodium-catalyzed.

[22] a) K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*, 3064-3076; b) H. Kumobayashi, T. Miura, N. Sayo, T. Saito, X. Zhang, *Synlett* **2001**, 1055-1064.
[23] a) T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem.* **1988**, *27*, 566-569; b) T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem*. **1987**, *52*, 3174-3176.
[24] S. Akutagawa, *Appl. Catal. A: General* **1995**, *128*, 171-207.
[25] R. Imwinkelried, *Chimia* **1997**, *51*, 300-302.
[26] a) I. Ojima, N. Clos, C. Bastos, *Tetrahedron* **1989**, *45*, 6901-6939; b) M. Fiorini, M. Riocci, M. Giongo, *Eur. Pat. Appl.* **1983**, EP 77099 A2.

1.3.2
Iridium Catalysts for Asymmetric Hydrogenation in Industrial Processes

Among all the production processes known to involve an asymmetric hydrogenation as the key step, only one of them employs an iridium catalyst (Scheme 2).[1c] In fact, iridium catalysts have found so far no commercially important application in the reduction of C–C double bonds, however the Josiphos 1/iridium complex has been applied successfully to the industrial synthesis of the herbicide (*S*)-metolachlor (**(*S*)-11**, Scheme 2). The active ingredient of the grass herbicide, commercialized as Dual®, was first sold as a racemate, until it was found in 1982 that only the (*S*)-enantiomer of metolachlor is bioactive. The iridium/ferrocenyl bisphosphine catalyst found its utility in the asymmetric reduction of the C–N double bond of the imine intermediate: 2-methyl-6-ethylphenyl-1'-methyl-2'-methoxyethylimine (MEA-imine, (**9**)). The Josiphos 1/iridium catalyst showed extremely high activities and high enantioselectivities in the presence of acid and iodine, compared to all the other rhodium/ or iridium/P,P ligand combinations previously tested.[27] *Solvias AG* (formerly *Ciba-Geigy*/*Novartis*) demonstrated that enantioselective hydrogenation can compete against other methods (such as classical resolution, chromatographic separation or biocatalysis) in the production of enantiomerically enriched chiral compounds.

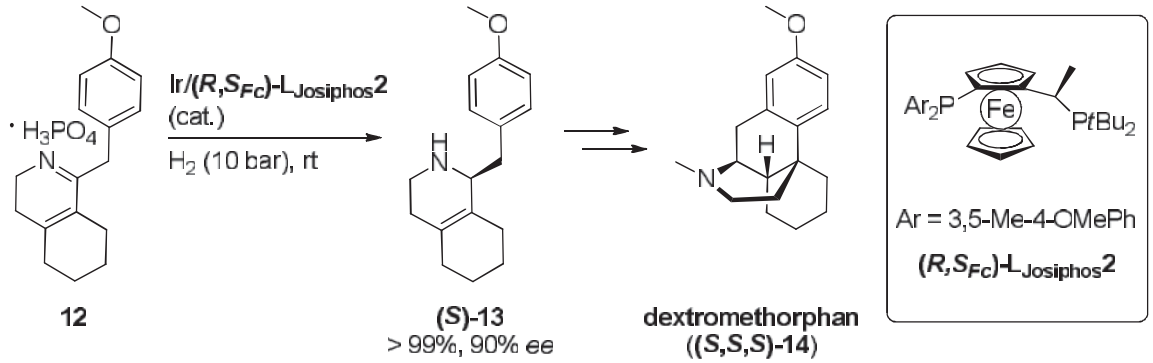


Scheme 2. (*S*)-Metolachlor process.[27]

The *Solvias* Josiphos ligand family is today almost as successful as the BINAP ligand family and has been reported to induce high enantioselectivities in a wide variety of transformations.[28]

[27] H.-U. Blaser, R. Hanreich, H.-D. Schneider, F. Spindler, B. Steinacher, *The Chiral Switch of Metolachlor: The Development of a Large-Scale Enantioselective Catalytic Process*, in *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (eds. H.-U. Blaser and E. Schmidt), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, **2004**.
[28] a) H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* **2002**, *19*, 3-16; b) H.-U. Blaser, B. Pugin, F. Spindler, M. Thommen, *Acc. Chem. Res.* **2007**, *40*, 1240-1250.

However, the enantioselective reduction of C−C double bonds in production is still dominated by rhodium and ruthenium catalysts, most likely due to their high efficiency, extensively reported in the literature. This observation is very surprising, considering the fact that iridium complexes can be more reactive than rhodium and ruthenium catalysts and, in contrast to rhodium and ruthenium complexes do not require an additional coordinating functional group close to the C−C double bond to promote its reduction.[19a,29] Further to these observations and considering the advantageous price of iridium compared to rhodium, efforts are being made to increase the number of industrial processes involving an iridium-catalyzed asymmetric hydrogenation. For instance, in a pilot process at *Lonza*, a Josiphos ligand has been used in combination with iridium in the reduction of the imine intermediate **12** for the preparation of dextromethorphan (**(*S*,*S*,*S*)-14**), an antitussive (Scheme 3).[1c,25] Unfortunately though, the catalyst efficiency was reported to be rather low (ton 1 500; compared to 2 000 000 in the hydrogenation of the (*S*)-metolachlor intermediate, Scheme 2).



Scheme 3. Pilot process at *Lonza*: asymmetric hydrogenation of imine **12** to amine **(*S*)-13**, an intermediate in the synthesis of dextromethorphan.

In order to encourage process chemists to consider asymmetric catalysis for the large scale manufacturing of low cost products, the chiral ligands need either to be available in large quantities or at least involve short synthesis. Today's challenges can be seen in two different ways, either researchers seek for the right substrate and catalyst combination using for example high-throughput methods, or go on seeking for more broadly applicable catalysts, that are readily available.

[29] A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33-43.