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ARTICLES

From a Chiral Switch to a Ligand Portfolio for Asymmetric Catalysis

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ABSTRACT

This Account is divided into two sections. In the first section, the development of an enantioselective manufacturing process for (*S*)-metolachlor, the active ingredient of the grass herbicide Dual Magnum, is described. This is today's largest application of asymmetric catalysis, and the Ir-Xyliphos hydrogenation catalyst achieves unprecedented 2 millions turnovers. The development started in 1982 and ended when the first production batch was run in November 1996. The strategies and approaches used for attaining the elusive goal are described, and the lessons learned are discussed. In the second section, the development and performance of a portfolio of chiral diphosphines for industrial asymmetric applications are described. Central to the portfolio is the idea of modular ligand families, i.e., diphosphines with the same backbone, where steric and electronic properties are easily tuned by the choice of the substituents at the phosphorous atoms.

1. The Chiral Switch of Metolachlor

Background. Metolachlor is the active ingredient of Dual, one of the most important grass herbicides for use in maize. It is a N-chloroacetylated, N-alkoxyalkylated *ortho*-disubstituted aniline. Metolachlor has two chiral elements: a chiral axis (because of hindered rotation around the C–N axis) and a stereogenic center, leading to four stereoisomers (Figure 1). Dual was introduced to the market in 1976 as a mixture of all four stereoisomers produced via the Pt/C-catalyzed reductive alkylation of 2-methyl-5-ethyl-aniline (MEA) with aqueous methoxyacetone in the presence of traces of sulfuric acid followed by chloroacetylation (Scheme 1).[1]

In 1982, it was found that about 95% of the herbicidal activity of metolachlor resides in the two (1′*S*) diastereomers, i.e., is mainly controlled by the absolute configuration of the stereogenic center of the side chain.[2] This means that with enriched material the same biological effect could be achieved with about 65% of the racemate, no small matter considering that >20 000 tons of this herbicide were produced, shipped, and applied every year! This finding initiated the search for a suitable catalyst to enantioselectively produce (*S*)-metolachlor, a search which lasted more than a decade and resulted in the largest enantioselective catalytic process. A list of important milestones is given in Table 1.

The story of the discovery of the Ir–Josiphos catalyst has already been described in some detail.[3–5] For this reason, we limit ourselves to a short summary of the most important milestones but will discuss the lessons learned because these affected our strategies concerning the development of both the process and ligand portfolio.

A Tough Start. In an extensive project study carried out in 1981, we came up with the four routes shown in Scheme 2, as assessed in Table 2. Three synthetic routes were tested experimentally: (i) enamide hydrogenation (inspired by the successful L-dopa process of Monsanto[6]), (ii) nucleophilic substitution of a (*R*)-methoxyisopropanol derivative with the enantioselective hydrogenation of methoxyacetone as a key step (by analogy to Pt–cinchona-catalyzed hydrogenation of α-ketoesters[7]), and (iii) hydrogenation of MEA imine. Because enantioselective reduction was considered to be the key step, the enamide and substitution routes were tested first.

After more than a year, we had to acknowledge complete failure: none of the three enamides showed any

Hans-Ulrich Blaser carried out his doctoral research with Prof. Eschenmoser at the ETH in Zürich, where he received his Ph.D. degree in 1971. Between 1971 and 1975, he held postdoctoral 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. His main interests are the study and industrial application of selective catalysts. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals, and fine chemicals (both as a project leader and section head).

Benoît Pugin studied chemistry at the ETH in Zürich and carried out his Ph.D. thesis with Prof. Venanzi in the field of metal organic chemistry and homogeneous catalysis. In 1982, he moved to Ciba-Geigy for a postdoctoral period, and since 1983, he has been working in the catalysis research group of Ciba-Geigy/Novartis and now as a leading scientist with Solvias. He has worked 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 did his doctoral research on homogeneous catalysis with Prof. Pino at the ETH in Zürich, where he received his Ph.D. degree in 1981. In 1983, he joined Ciba-Geigy in Basel and gained practical experience in R&D related to the application of homogeneous asymmetric catalysis in the fine chemicals and pharmaceutical industry, which continued at Novartis (1996–1999) and Solvias. During his industrial carrier, he has developed and implemented numerous catalytic routes for agrochemicals, pharmaceuticals, and fine chemicals. He presently holds a position as leading scientist in the field of homogenous enantioselective hydrogenation.

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Marc Thommen obtained his Ph.D. degree in 1995 from the University of Bern working with Prof. R. Keese. He spent 2 years as a postdoctoral researcher at Stanford University with Prof. B. M. Trost and joined the catalysis group of Novartis in 1998 as project leader for the development of catalytic processes. At Solvias, he was instrumental in the development of a comprehensive ligand portfolio. He was appointed product manager for chiral ligands and catalysis services. Presently, he holds the position of a senior project leader at DSM Nutritional Products, Switzerland.

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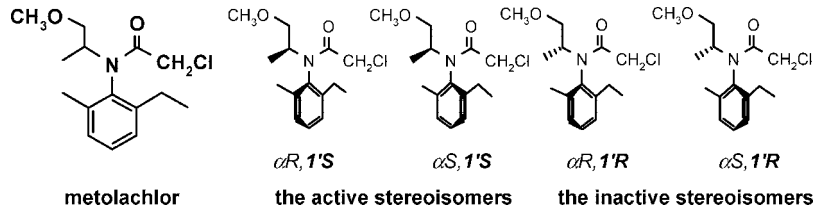


FIGURE 1. Structure of metolachlor and its individual stereoisomers.

Scheme 1

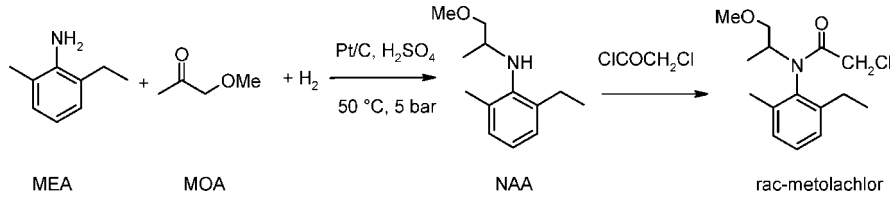


Table 1. Milestones in the History of Metolachlor

1970	discovery of the biological activity of metolachlor
1978	full-scale plant with a production capacity >10 000 tons/year in operation
1982	synthesis and biological tests of the four stereoisomers of metolachlor
1985	rhodium/cycphos catalyst gives 69% ee for the imine hydrogenation [University of British Columbia (UBC), Vancouver, Canada]
1987	new iridium diphosphine catalysts are more active and selective (up to 84% ee) than rhodium catalysts; catalyst deactivation is a problem
1992	novel ferrocenyl ligands are developed, leading to very active catalysts without deactivation problems
1993	the acid effect is discovered, and a laboratory process with Ir–Josiphos is established
1995/1996	pilot results for (*S*)-metolachlor: ee, 79%; turnover number, 1000000 turnover frequency, >200 000/h; first 300 tons produced
1996	full-scale plant for production of >10 000 tons/year of (*S*)-metolachlor starts operation

conversion with seven different Rh diphosphine catalysts at temperatures up to 50 °C and 1 bar. Methoxyacetone could be hydrogenated with a cinchonidine-modified Pt/C catalyst, but enantioselectivity never exceeded 12%. This left the hydrogenation of MEA imine as the only realistic possibility.

Imine Hydrogenation: Initial Success. First positive results were obtained by a UBC team, which adapted Rh diphosphine catalysts originally developed for alkene hydrogenation. The most effective catalyst, Rh–cycphos, achieved up to 69% enantiomeric excess (ee) at −25 °C (Figure 2).[8] Despite rather low activities, these results represented a breakthrough in enantioselective *N*-aryl imine hydrogenation.

Inspired by results of Crabtree,[9] who had described an extraordinarily active, albeit achiral Ir catalyst for the hydrogenation of tetrasubstituted C=C bonds, we focused on iridium instead of rhodium complexes. Very soon thereafter, impressive progress was forthcoming. For the MEA imine hydrogenation, an Ir–bdpp catalyst gave 84% ee at 0 °C, although with low turnover numbers (TONs). On the other hand, Ir–diop reached up to 10 000 TONs, but with lower ee values (Figure 2).[10] A major problem associated with these Ir catalysts was irreversible catalyst deactivation.

Even though these results were very promising and at that time represented by far the best catalyst performance for enantioselective imine hydrogenation, it was clear that the ambitious goals for a technical process (≥80% ee, >50000 TONs, <8 h reaction time) could probably not be reached using Ir complexed with "classical" diphosphine ligands. A new approach was clearly required.

The Final Breakthrough with a New Ligand and a Bit of Acid. As a consequence, a variety of new ligand types were synthesized and tested. The most promising were Josiphos ligands, novel ferrocenyl diphosphines developed by Togni and Spindler[11] (Scheme 3). Because to two phosphino groups are introduced sequentially in the last two steps, the electronic and steric properties can easily be varied, which is often difficult with other diphosphines. To our delight, several Ir–Josiphos catalysts proved to be very efficient.[3] Most notably, Xyliphos led to an exceptionally active catalyst, and even more importantly, it did not deactivate!

With Xyliphos as a ligand, a screen of solvents and additives as well as an optimization of the reaction conditions were carried out. Hans-Peter Jalett, an experience chief technician, observed an extraordinary effect: by adding 30% acetic acid to the reaction mixture in the presence of Ir–Xyliphos and NBu_4I, the maximum rate increased by a factor of 5. Even more exciting, the time needed for 100% conversion was more than 20 times shorter! It turned out that this was not a solvent but a general acid effect and that the same acceleration could be achieved with traces of strong acid. The reaction rate was approximately proportional to the hydrogen pressure and also increased with temperature. Enantioselectivities decreased from 81% at −10 °C to 76% at 60 °C but were not affected by changing the hydrogen pressure.

While these Ir–Xyliphos catalysts surpassed the required catalyst activity and productivity by far, the enantioselectivity just barely met the goal of 80% ee. Therefore, we tried to improve the enantioselectivity by changing both the electronic and steric properties of the Josiphos ligands. As shown in Table 3, this was indeed possible; however, as previously observed with other ligands, any gain in selectivity was offset by a loss in catalyst activity

Scheme 2

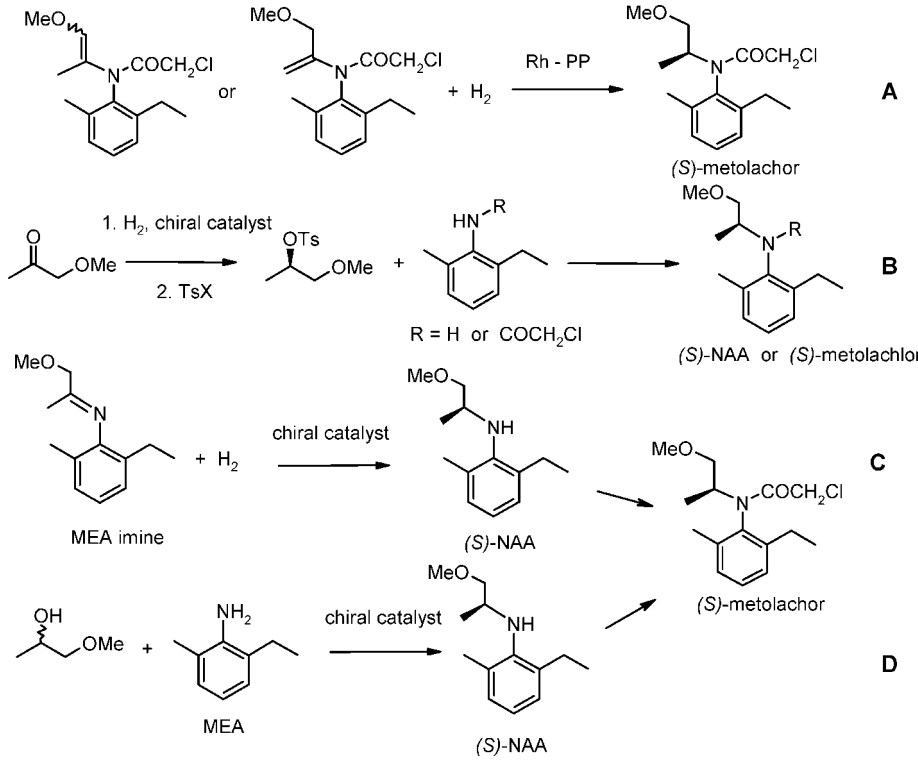


Table 2. Assessment of Possible Routes for the Synthesis of (*S*)-Metolachlor

route	catalytic step	other steps	cost (ecology)	priority
A, enamide	close analogy, ee > 90%	enamide synthesis difficult	high (medium)	1
B, substitution	weak analogy, ee > 80%	substitution very difficult	high (bad)	2
C, imine	weak analogy, ee < 30%	as in the current process	medium (good)	3
D, direct alkylation	no precedent	as in the current process	low (very good)	4

Table 3. MEA Imine Hydrogenation with Selected Ir–Josiphos Catalysts

R	R′	TON	TOF (h^{-1})	ee	comments
Ph	3,5-xylyl	1000000	>200 000	79	production process
p-$CF_3C_6H_4$	3,5-xylyl	800	400	82	ligand screening
Ph	4-^{t}Bu-C_6H_4	5000	80	87	low temperature
Ph	4-(^{n}Pr)$_2$N-3,5-xyl	100 000	28 000	83	optimized conditions

and/or productivity. In the end, Xyliphos was the best compromise for a technical process.

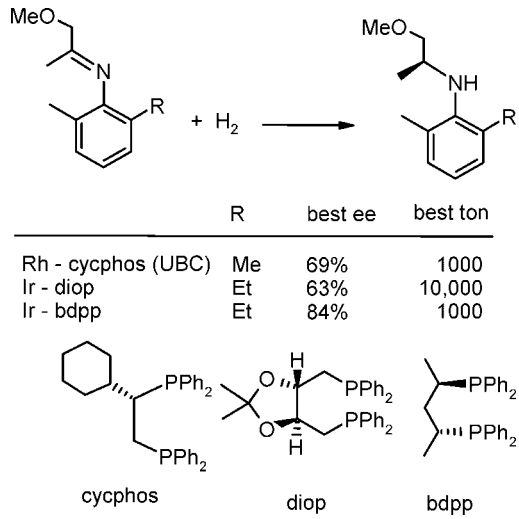


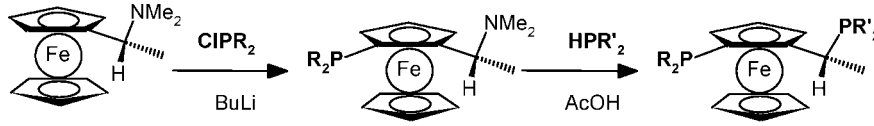
FIGURE 2. Rh- and Ir-catalyzed hydrogenation of 2,6-dimethylaniline (DMA) (R = Me) and MEA (R = Et) imine.

Developing a Technical Process. For this task, a large project team was set up consisting of process and analytical chemists, engineers, as well as specialists in catalysis. While the technical preparation of methoxyacetone and the chloroacetylation step were already established for producing racemic metolachlor, several facets of the new process required considerable development effort.[4]

Optimization of the Reaction Medium and Conditions. After optimization of acid and iodide and reaction conditions, MEA imine could be hydrogenated at 80 bar/50 °C with a substrate/catalyst ratio of $>1 \times 10^6$. Complete conversion is reached within 4 h with an enantioselectivity of 79–80%, with the initial turnover frequency (TOF) exceeding 1.8×10^6 h^{-1}.

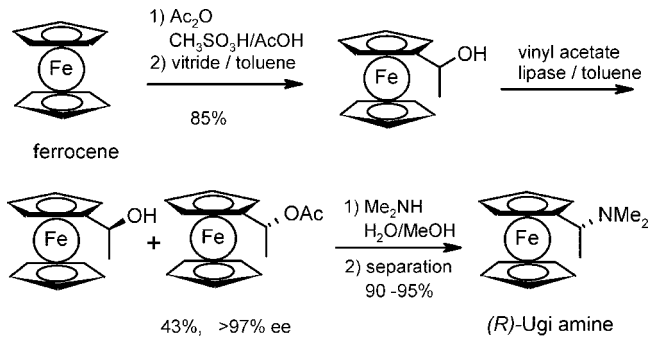
Ligand Synthesis. Because (*R*)-Ugi amine was not commercially available at the time, a scaleable synthesis had to be developed. The chemistry summarized in Schemes 3 and 4 allows for the preparation of a variety of Josiphos ligand with >99.5 % ee in multi-kilogram quantities. This expertise was decisive when we started our ligand business a few years later.

Scheme 3



Xyliphos: R = Ph, R′ = 3,5-Xyl

Scheme 4



Choice of Reactor Technology. Because the catalytic reaction was extraordinarily fast, optimal mass and heat transfer was required, and for this purpose, a loop reactor was the best choice. In this technology, the reaction mixture is pumped via a heat exchanger through a nozzle where hydrogen is fed into the reaction solution, allowing both very good cooling and mixing (Figure 3).

The first production batch was successfully run on November 16, 1996 and has been carried out without any major problems on a >10 000 tons/year scale ever since.[12]

Some Take Home Lessons. The metolachlor process is currently the largest enantioselective catalytic process, and Ir–Xyliphos is the most active and productive catalyst developed to date. There is no doubt that our achievement has laid to rest any doubts about the applicability of chiral homogeneous catalysis for the large-scale manufacture of relatively low-cost products. We learned of a few lessons that likely are of general interest and certainly had a strong influence on our strategy when we started to build up a commercial ligand portfolio, as described in the second part of this Account.

Lesson 1. Catalyst activity and productivity is a much more important issue than originally anticipated. Initially, we expected enantioselectivity to be critical; however, in reality, catalyst activity and productivity provided the greatest challenge in meeting the targets for an economical process.

FIGURE 3. Lower part of the 10 m^3 production loop reactor.

As a consequence, we now routinely monitor TON and TOF values in early stages of any process development.

Lesson 2. Know-how and expertise is decisive. This project caught us quite unprepared. While the catalysis section of Ciba-Geigy had a history dating back to the early 1930s,[13] its expertise was limited to the application of heterogeneous hydrogenation. We had no experience using chiral complexes, and our hydrogenation equipment was not well-suited for handling homogeneous catalysts. Thus, at the same time, while tackling the (*S*)-metolachlor project, we had to learn the basics of enantioselective catalysis (not a very comfortable position).

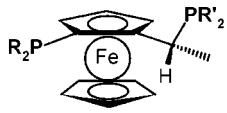
As a consequence, we initiated a strong research program first for the application of enantioselective catalysts and later in the area of chiral ligand synthesis.

Lesson 3. Availability of chiral ligands. At the beginning of our process development, less than 10 chiral diphosphines were commercially available and none in technical quantities. Most of these ligands had C_2 symmetry and diphenylphosphino groups, both elements considered to be essential for good performance in hydrogenation reactions. Josiphos, the first truly modular ligand family, clearly showed that this was not the case. On the contrary, we found that combining PR_2 moieties with bulky alkyl groups (even *tert*-Bu) with PAr_2 groups often led to the most effective ligands. When developing the Josiphos family, we also realized that the ferrocene backbone and its particular chemistry are ideally suited to obtain extraordinarily effective ligands. Furthermore, we also realized that the time and effort required for the scale-up of a ligand synthesis might discourage process chemists from considering asymmetric catalysis.

As a consequence, the concept of modularity and the availability of chiral ligands in technical quantities with short lead times were deemed key points for the future ligand portfolio of Solvias.

2. Building Up a Comprehensive Ligand Portfolio

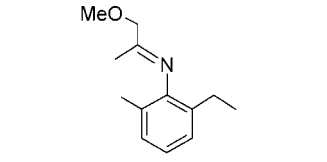
The Josiphos Ligand Family. Josiphos ligands that played such a decisive role in the (*S*)-metolachlor process were first synthesized in the context of a structure–activity study for the Au-aldol reaction. Two reviews[11,14] have described the background of their creation in detail. The Josiphos ligand family was an excellent basis for a



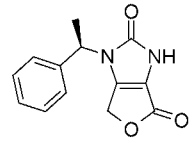
(R,S_{Fc})-Josiphos

number	R	R'	important applications
SL-J001	Ph	Cy	process for jasmonate; hydrogenation of enamides and itaconates; hydroboration; allylic alkylations; Michael additions; PMHS reduction of C=C; addition to meso anhydrides
SL-J002	Ph	t-Bu	opening of oxabicycles; biotin and MK-0431 processes
SL-J003	Cy	Cy	hydrogenation of phoshinylimines
SL-J004	Cy	Ph	Michael additions
SL-J005	Ph	3,5-Xyl	metolachlor process; methoxycarboxylation
SL-J009	Cy	t-Bu	hydrophosphination; C-X cross coupling
SL-J011	4-CF_3-Ph	t-Bu	hydrogenation of β-imino acid derivatives
SL-J013	4-MeO-Xyl	t-Bu	dextromethorphane process

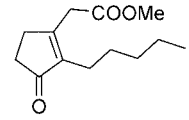
FIGURE 4. Structure, numbering, and applications for important Josiphos ligands.



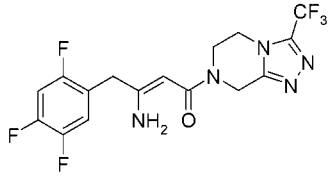
Ir / **SL-J005**; ee 80%
ton 2,000,000; tof > 400,000 h^{-1}
very large scale production
Ciba-Geigy/Solvias



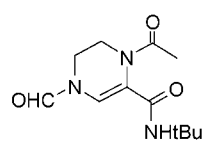
Rh / **SL-J002**; de 99%
ton 2,000; tof n.a.
medium scale production
Lonza



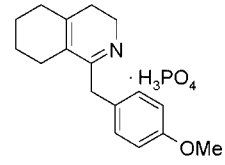
Ru / **SL-J001**; ee 90%
ton 2,000; tof 200 h^{-1}
medium scale production
Firmenich



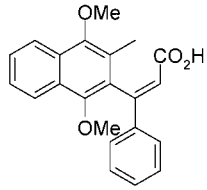
Rh / **SL-J002**, ee 94%
ton 350; tof ~50h^{-1}
multi tons/year
Merck



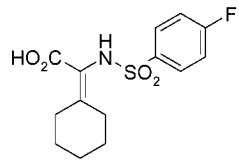
Rh / **SL-J002**; ee 97%
ton 1,000; tof 450 h^{-1}
pilot process, >200 kg
Lonza



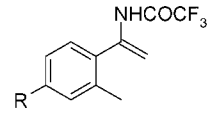
Ir / **SL-J013;** ee 90%
ton 1'500; tof n.a.
pilot process
Lonza



Rh / **SL-J001**; ee 93%
ton 100, tof 4 h^{-1}
feasibility study
Takeda Chemical Industries



Ru / **SL-J002**; ee 99%
ton 100, tof ~4 h^{-1}
feasibility study
Merck



Rh / **SL-J002**; ee 92-97%
ton 100, tof ~6 h^{-1}
feasibility study
Merck

FIGURE 5. Important industrial applications of Josiphos ligands.

comprehensive ligand portfolio when the former catalysis group of Ciba-Geigy was spun-off into Solvias in 1999.[15]

Today, the Josiphos ligands arguably constitute one of the most versatile and successful ligand families, second probably only to the Binap ligands. Rh–, Ir–, and Ru–Josiphos complexes are highly selective and active catalysts for the enantioselective hydrogenation of enamides, itaconic acid derivatives, acetoacetates, acrylic acids, and *N*-aryl imines, as well as for other transformations.[14] To date, only the (R,S_{Fc}) family (and its equally accessible enantiomers) but not the (R,R_{Fc}) diastereomers have led to high enantioselectivities. At present, about 150 different Josiphos ligands have been prepared and 40 derivatives are commercially available in a screening ligand kit and on a multi-kilogram scale for production purposes. The most successful ligands and their numbering and major applications are depicted in Figure 4, illustrating again the modular adaptability of the ligand properties to the requirements of different reactions.

Three aspects of the Josiphos ligands will be outlined in more detail: the application to industrial projects, the benefits of modularity, and the versatility of Josiphos **SL-J001** and **SL-J002** with bulky alkyl PR_2 substituents. Up to now, Josiphos ligands have been applied in four production and several pilot- and bench-scale processes involving Rh-, Ir-, and Ru-catalyzed hydrogenation reac-

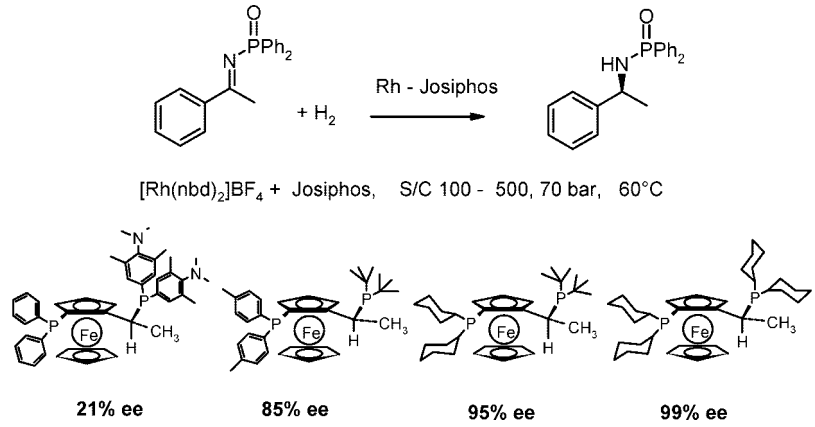
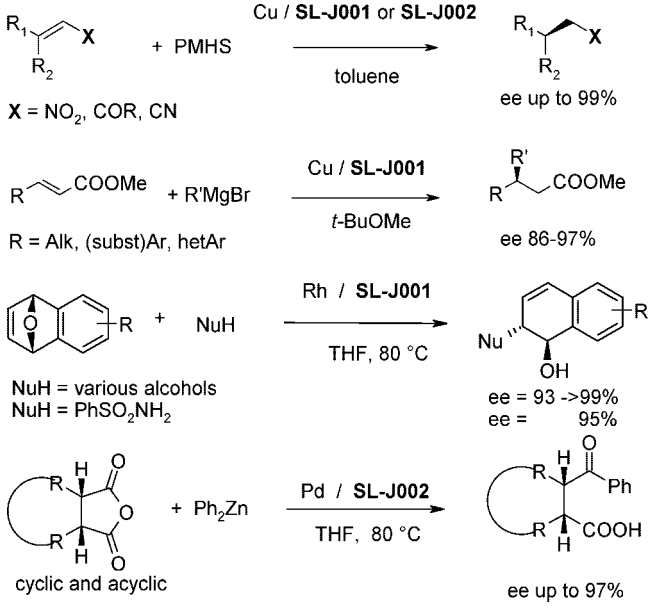


FIGURE 6. Tuning Josiphos ligands for the phosphinylimine hydrogenation.

Scheme 5



tions of C=C and C=N bonds[16] (Figure 5). While the most important application is the (*S*)-metolachlor process (Ciba-Geigy/Syngenta), production processes were reported for the synthesis of biotin (Lonza), methyl dihydrojasmonate (Firmenich), and MK-0431 (Merck). Pilot processes have been developed for precursors to crixivan and dextromethorphane (Lonza), and feasibility studies have been described for an α,β-unsaturated acid (Takeda), N-sulfonylated α-dehydroamino acids, and ene–trifluoroamides (Merck).

Note the large varieties of substrates depicted in Figure 5 that can be hydrogenated with very good catalyst performances by simply changing substituents at phosphorus. Another impressive example of the benefits of modularity is shown in Figure 6. When the P substituents are optimized, enantioselectivities >99% can be realized for the Rh-catalyzed hydrogenation of phosphinylimines[17] and many more such cases have been observed.

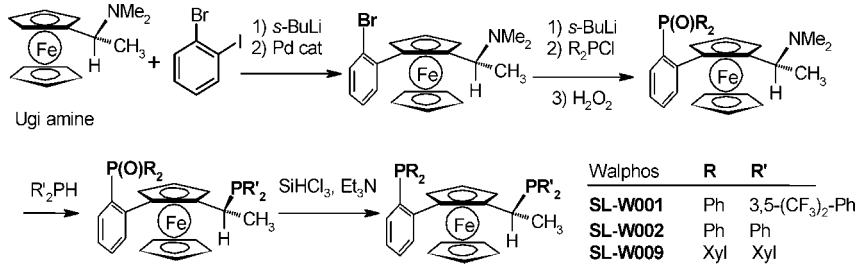
Josiphos **SL-J001** and **SL-J002** are ligands of choice for an amazing variety of reactions,[14] and several recent examples are shown in Scheme 5. Noteworthy are the highly enantioselective Cu-catalyzed reduction of nitro alkenes,[18] α,β-unsaturated ketones,[19] esters,[20] and nitriles[21] with polymethylhydrosiloxane (PMHS), as well as for the Michael addition of Grignard reagents to α,β-unsaturated esters.[22] The Rh-catalyzed nucleophilic ring opening of oxabicyclic substrates leads to interesting dihydronaphthalene derivatives[23] (scaled up to multikilogram). The Pd-catalyzed opening of cyclic anhydrides is also a new type of enantioselective transformation.[24]

Walphos, Mandyphos, and Taniaphos. The next addition to our ligand portfolio was Walphos. We had to focus on process research while still being part of Novartis, but on the other hand, it was possible to fund cooperative research. In this situation, we started a collaboration with Walter Weissensteiner of the University of Vienna, who proposed the synthesis of new ferrocene diphosphines. His concept was convincing because it met our criteria of modularity, tunability, and scalability; the resulting ligands were called Walphos.[25] Walphos ligands form eight-membered metallocycles and, similar to Josiphos, are air-stable and readily prepared in large quantities even though the synthesis requires two additional steps relative to that of Josiphos (Scheme 6).

Walphos ligands show promise for various enantioselective hydrogenations.[26] Rh–Walphos catalysts gave good results for dehydroamino and itaconic acid derivatives (92–95% ee), while Ru–Walphos complexes were highly selective for β-keto esters (91–95% ee) and acetyl acetone (>99.5% ee, S/C of 1000). Figure 7 depicts some specific applications. The hydrogenation of SPP100-SyA, a sterically demanding α,β-unsaturated acid intermediate of the renin inhibitor Aliskiren (Speedel/Novartis) is currently performed on a multiton scale. Lilly chemists developed a process for a peroxisome proliferator-activated receptor (PPAR) agonist using the Rh-catalyzed hydrogenation of a (*Z*)-cinnamic acid as a key step. A screen of over 250 catalysts and conditions revealed **SL-W001** as the most effective ligand, giving the product in 92% ee.[27] Recently, two novel transformations were reported to be catalyzed by Rh–Walphos complexes with high enantioselectivities: the [4 + 2] addition of 4-alkynals with an acrylamide by Tanaka and co-workers[28] and the reductive coupling of enynes with α-keto esters by Krische's group.[29]

Other groups also became involved in ferrocene-based ligands for hydrogenation.[30] In particular, the Knochel group has achieved remarkable success with Taniaphos[31]

Scheme 6



and Mandyphos,[32] two ligand families with similar modularity as Josiphos and Walphos but in many cases with complementary performance (Figure 8). Umicore (formerly dmc^2, a spin-off from Degussa), with IP rights to Knochel's patents, asked us to collaborate in the development of technical syntheses and to jointly market the two ligand families. Because of our experience with ferrocenyl ligands and with supply chain considerations suggestive of a high degree of synergy (because of the use of identical similar blocks and technologies), we agreed. Following the ligand development phase, extended screening tests confirmed that both ligands, indeed, had the expected modular behavior. Their performances as catalysts are in many respects complementary to the Josiphos and Walphos ligands.[33]

Taniaphos and Mandyphos are effective ligands for the enantioselective hydrogenation of a variety of C=C and C=O functions.[33] An impressive case of ligand specificity was described by Hashmi et al.[34] for the hydrogenation of furyl-substituted (*Z*)-dehydroamino esters. Of several ligands tested, only Mandyphos **SL-M004** with P(4-MeO-Xyl)$_2$ substituents gave satisfactory enantioselectivities (Scheme 7). After the ligands had been made available to research groups, several other interesting transformations were discovered, further documenting the potential of both Mandyphos and Taniaphos ligands. Two selected examples are depicted in Scheme 7: Rh–Taniaphos catalyzed ring opening of azabicycles[35] and cycloaddition

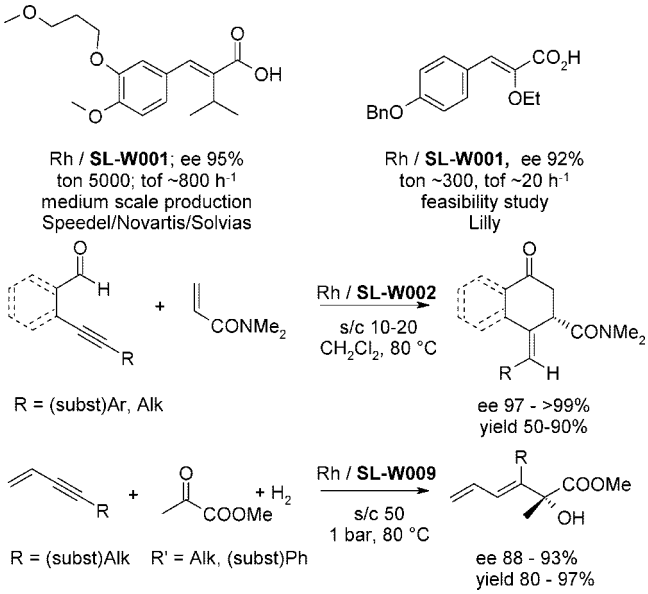
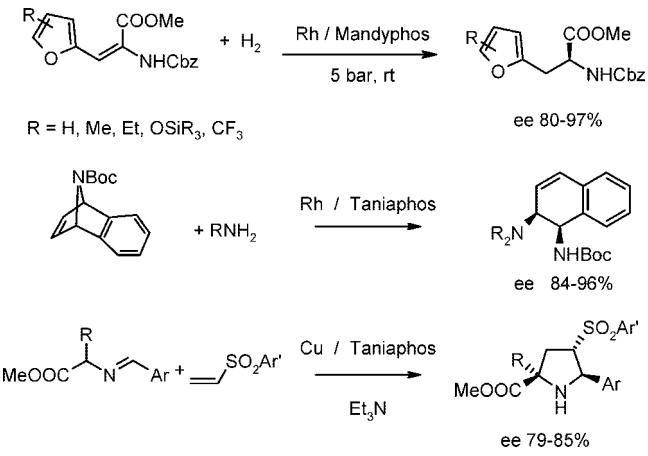


FIGURE 7. Industrial applications and novel transformations catalyzed by Rh–Walphos catalysts.

Scheme 7



of azomethine ylides to vinyl sulfones catalyzed by a Cu–Taniaphos catalyst.[36]

Phospholanes and Atropisomeric Ligands. Despite the power of modularity and the versatility of the ferrocene-

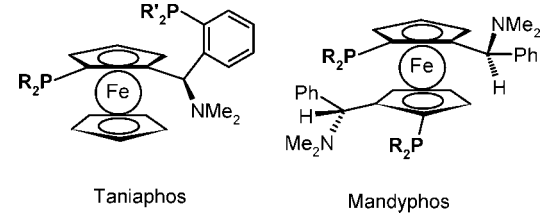


FIGURE 8. Commercialized Taniaphos and Mandyphos ligands.

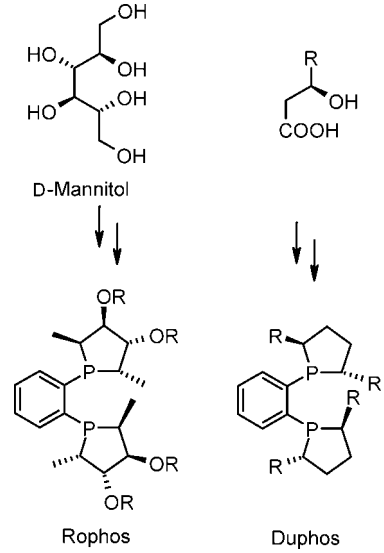
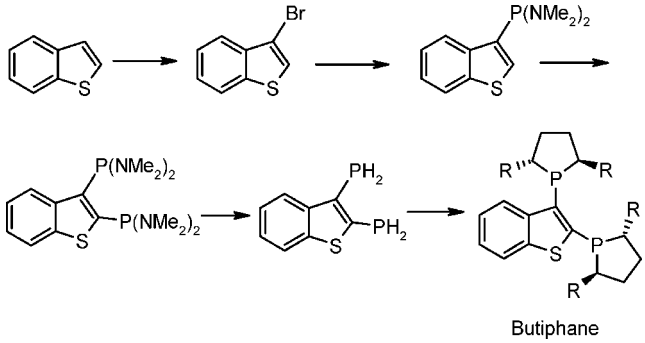


FIGURE 9. Starting materials and structures for Rophos and Duphos.

Scheme 8



based diphosphines, it was appreciated that we had to broaden our ligand portfolio further to make it truly comprehensive. We aimed at having a suitable ligand for hydrogenation of every important substrate type. Upon re-analysis of performance gaps in our portfolio, it became apparent that we were lacking the specific performance of a phospholane-type ligand, such as Duphos,[37] and an atropisomeric ligand,[38] such as Binap. However, in these areas, competition is fierce and it was not easy to devise novel ligands that would be competitive in performance and cost but not patent-protected. To achieve this goal, we not only initiated our own research program but also pursued collaboration and licensing strategies.

In 2001, we licensed Rophos from BASF. Rophos, an analogue of the Duphos[39] ligand, was designed and first prepared by the Börner group[40] in Rostock (Figure 9). Rophos contains a chiral phospholane ring that is created from mannitol and not from the synthetic chiral 1,4-diols, which at that time were prepared via a Kolbe reaction from the corresponding β-hydroxy acids. Despite the additional substituents in the 3 and 4 positions, these ligands have a very similar performance profile to that of Duphos. We succeeded in developing a scaleable synthesis starting from cheap natural D-mannitol. Although the ligand was performing nicely and also exhibited excellent stability as its bistriflate phosphonium salt,[41] its enantiomer could not be prepared in a cost-effective manner, despite significant effort. For this reason, the Rophos ligands are available in technical quantity upon request but are not part of the core portfolio of Solvias.

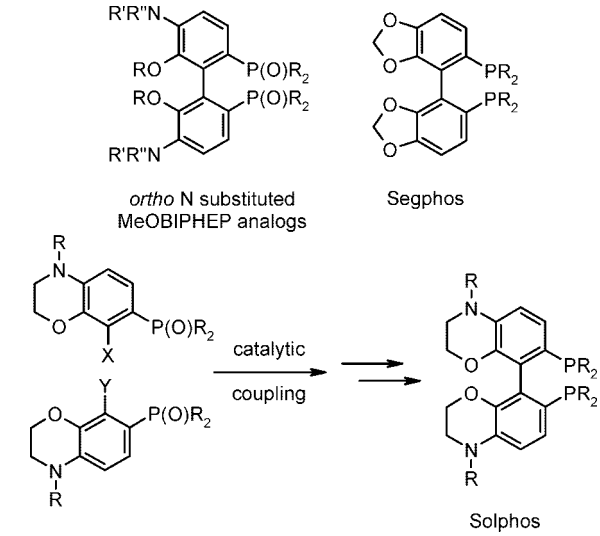
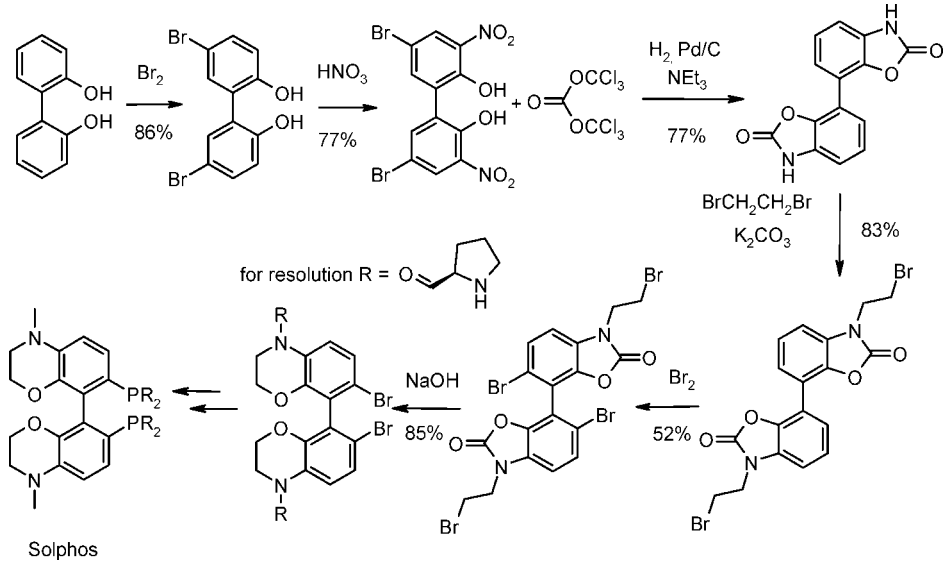


FIGURE 10. Coupling strategy for Solphos.

In a collaboration with our former colleagues from Ciba SC, in particula Ulrich Berens,[42] Butiphane was designed and developed. Unlike Duphos, the ligand backbone is not C_2 symmetrical; rather, it is based on a five-membered ring backbone, which results in a slightly different coordination sphere (sterics and electronics) around the metal when compared to Duphos. The synthesis depicted in Scheme 8 starts from benzothiophene and leads in five high yielding, scaleable steps to Butiphane ligands, which again show behavior akin to Duphos ligands, with high enantioselectivities for various activated C=C bonds.[42] The methyl derivative (R = Me) is included in our present ligand portfolio.

The quest for an atropisomeric diphosphine turned out to be equally difficult. When we started to create ideas, a large number of biaryl diphosphines was already known

Scheme 9



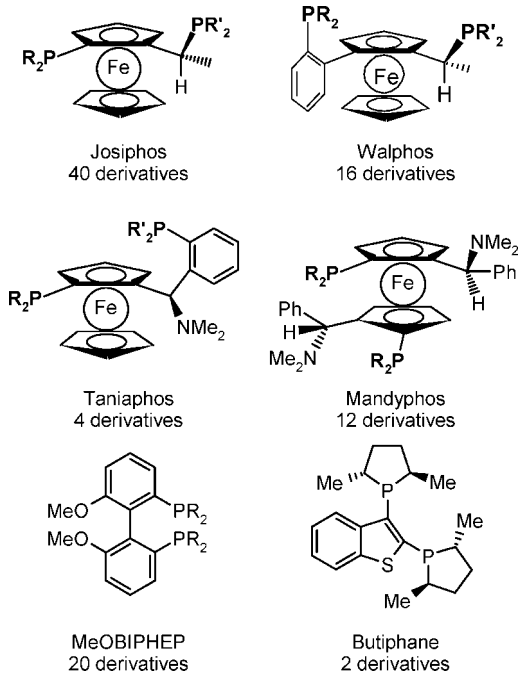


FIGURE 11. The Solvias ligand portfolio 2007.

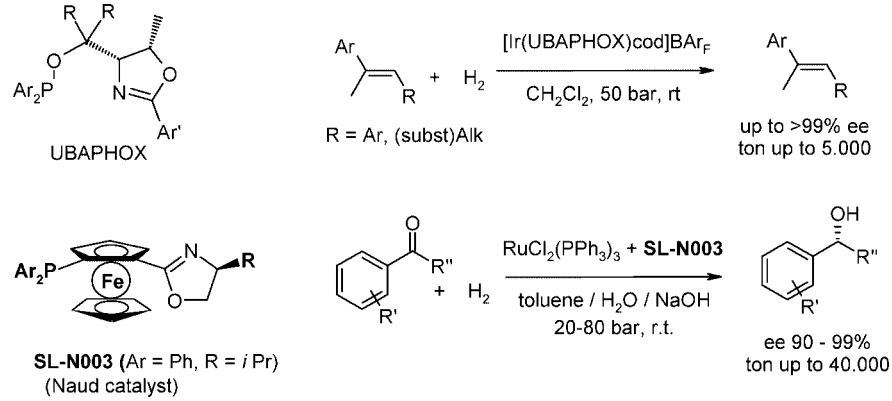
but only a few were commercially available. In our assessment, the MeO–BIPHEP ligands, created and owned by Roche,[43] had a very attractive performance profile, and a technical synthesis was available. We reasoned that additional N-based substituents *ortho* to the MeO group and *para* to the phosphorus atom would make the ligand slightly more electron-rich and should supply a handle to further tune and functionalize the ligand. Last but not least, this would provide ligands outside the numerous existing patents. When we analyzed a paper by Takasago[44] on the excellent results achieved with Segphos, another variation of the binap motif, we decided to concentrate on a benzoxazine structure. We assumed that a similar coupling and modular phosphine introduction strategy as developed for the MeO–BIPHEP ligands (Figure 10) would be applicable. Very soon, we found that things were not so simple. When we tried to couple the appropriate fragments with various X and Y substituents using a variety of catalysts, we found to our disappointment that only traces of the desired benzoxazine were formed. Because the few milligrams of the new ligand prepared via this route showed the expected excellent catalytic performance, we had to devise more promising approaches.

To make a very long and exhausting story short, the concerted efforts of several Solvias teams finally resulted in the technical synthesis depicted in Scheme 9.[45] To honor this concerted effort, we decided to name the new ligand family Solphos. A number of derivatives were prepared on a 10–100 g scale, although further scale-up proved difficult and not cost-effective. The excellent performance of the new ligands was confirmed for relevant model hydrogenation reactions as well as in several commercial projects. Nevertheless, we realized that despite this success the Solphos ligands still did not meet a key criteria for the Solvias ligand portfolio, namely, to be available in multi-kilogram quantities with short lead times.

A Comprehensive Ligand Portfolio for Asymmetric Catalysis. The solution to this problem was found when Roche agreed to give Solvias a license for the MeO–BIPHEP ligands (July 2006). Within a few months, we had validated the large-scale synthesis protocols provided by Roche in our own labs and had produced technical amounts of 12 different MeO–BIPHEP derivatives ready for commercial application. With this business success, the ligand portfolio depicted in Figure 11 fulfills all of our criteria for technical applications concerning tunability, established technical synthesis, stability to air and moisture, short-term availability for screening, scale-up, and manufacturing applications, consistent quality, and last but not least, commercial availability under customized licensing terms.

Besides these diphosphine ligands, we also have developed a number of P,N ligands for more specialized applications. Two catalytic systems are available on technical scale: Ir–UBAPHOX complexes for the hydrogenation of nonfunctionalized C=C bonds designed by Pfaltz[46] and developed in collaboration with him and the Ru phosphino oxazoline catalyst (Naud catalyst),[47] which is effective for aryl ketone hydrogenations (Scheme 10). Together with the ligands of the core portfolio, a wide variety of different substrate types can now be hydrogenated with a high chance of success (Figure 12).

Scheme 10



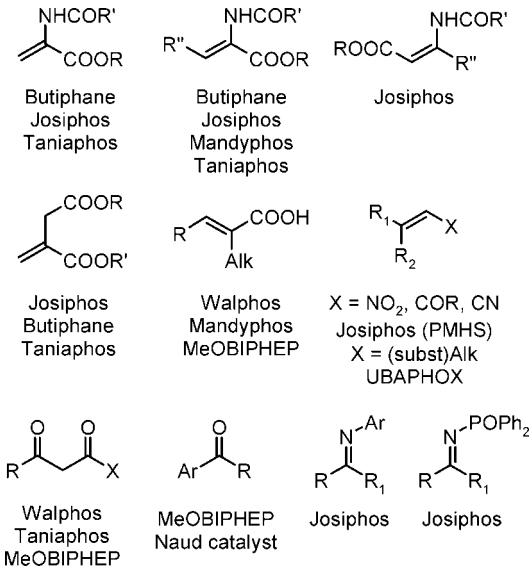


FIGURE 12. Scope of Solvias ligands for the reduction of C=X bonds.

Conclusions and Outlook

Industrial interest in the application of enantioselective catalysts was started in earnest only in the 1970s. However, after the first highly visible success of Knowles' L-dopa process, progress was rather slow. In this Account, we illustrate why this happened and describe the conclusions that we have drawn concerning the process development and ligand portfolio. The metolachlor process demonstrates that enantioselective catalysis is feasible even for very large-scale, relatively low-priced products. The availability of a variety of chiral ligands in technical quantities by Solvias as well as by other companies will be instrumental for the advancement in industrial applications of enantioselective catalysis. There is no doubt in our minds that asymmetric hydrogenation will develop into a mature technology within the next few years and will soon be considered a routine transformation with excellent predictability in process research. In the meantime, the quest for better ligands will continue because there is still ample room to expand the scope and effectiveness of this methodology.

We are indebted to all of our colleagues mentioned in the references but in particular to Rolf Bader for his support and Hans-Peter Jalett for his contributions in the metolachlor project. We thank Antonio Togni, Walter Weissensteiner, Pierre Martin, Paul Zbinden, Martin Kesselgruber, and Matthias Lotz for their invaluable experimental and intellectual contributions and Ulrich Berens and Andreas Pfaltz for their collaboration in the development of the Solvias ligand portfolio. Furthermore, we acknowledge all technicians who did an exceptional job, skillfully carrying out most of the practical work.

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