The Chiral Switch of (*S*)-Metolachlor: A Personal Account of an Industrial Odyssey in Asymmetric Catalysis

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Abstract: This account chronicles the various development phases of the Ir-catalyzed enantioselective hydrogenation for the production of (*S*)-metolachlor, the active ingredient of Dual Magnum® (one of the most important grass herbicides for use in maize). The final process is today's largest application of asymmetric catalysis and the Ir-xyliphos catalyst achieves unprecedented ton's of 2,000,000 and tof values around 600,000 h^{-1}. The development started in 1982 and ended when the first production batch was run in November 1996. On the one hand, the paper recounts the various breakthroughs and set-backs and how the final catalytic system slowly evolved, and discusses on the other hand the strategies and approaches used for attaining the elusive goal. The various actions and decision points are analyzed and commented, and the roles and the seminal contributions of three key team members, Felix Spindler, Benoit Pugin, and Hans-Peter Jalett are presented.

Keywords: chiral switch; development process; industrial application; homogeneous catalysis; Ir-catalyzed enantioselective hydrogenation; Ir-xyliphos catalyst; (*S*)-metolachlor process; personal account.

Abbreviations: MEA, DMA: 2-methyl-6-ethylaniline, 2,6-dimethaniline; MOA, MOIP: methoxyacetone, methoxyisopropanol; MEA-imine, DMA-imine: imine from MEA, DMA and MOA; NAA: *N*-alkylated aniline (hydrogenation product of MEA-imine); chiral diphosphine ligands: binap, diop, norphos, bppm, cycphos, bdpp, etc. (see Fig. 12); josiphos (Fig. 15); xyliphos (Fig. 18).

1 Motivation and Motto

At the urging of many friends both in academia and in industry but with somewhat mixed feelings I have agreed to write this personal account on how the chiral switch of metolachlor was accomplished. Mixed feelings, because we have described the approaches and results of this investigation quite extensively (and there are too many publications anyway). On the other hand, very few articles have been published offering a glimpse behind the scenes of a major industrial research project and even fewer commenting the decisions and actions that were taken to reach the elusive goal of a commercial enantioselective process.

Accordingly, this case history was written with the following goals in mind:

- to illustrate the often labyrinthine ways that have led to a significant industrial innovation;
- to discuss important aspects and prerequisites for successful research in an industrial setting;
- to portray a group of talented and dedicated scientists and explain their contributions to the discovery and development of today's largest enantioselective catalytic process;
- and, last but not least, to describe the changes that have occurred in the field of enantioselective catalysis both within Ciba-Geigy as well as outside.

The quest for finding a viable enantioselective catalyst can be compared to moving in a complicated labyrinth as described a few thousand years ago for Theseus hunting the Minotaur and depicted in the elegant drawing in Figure 1. In a labyrinth one has to decide at every turn whether to go right or left; most of the paths one can chose are probably dead ends or have some other nasty surprise ready and only one leads to the desired goal. In process development, the situation is even worse, because whereas Theseus at least knew that the Minotaur existed, one does not really know whether there is in fact a catalyst with the required properties. On the other hand, one can open up new paths by inventing new chemistry – something Theseus could not do (but he had at least some help from the beautiful princess). To illustrate our own situation, the search for a catalyst will be represented by the walk in a labyrinth that covers what I call the "ee-ton" space, i.e., we had to find a catalyst with a sufficient enantioselectivity (ee) as well as productivity (ton). Of course in addition, many other criteria such as reaction time (over all tof) or cost of ligands, etc. also

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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 institute, from which he received the PhD 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 20 years at Ciba-Geigy (1976–1996) he gained practical experience at R&D in the fine chemicals and pharmaceutical industry, which continued at Novartis (1996-1999) and now at Solvias. 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).

The Key Team: the author (second from left) with his colleagues of the catalytic team Benoit Pugin, Felix Spindler and Hans-Peter Jalett (from left to right).

Figure 1. Theseus finds the Minotaur after many hours of searching (with permission of Watts Publishing Ltd. and Jane Ray taken from The Orchard Book of Mythical Birds and Beasts).

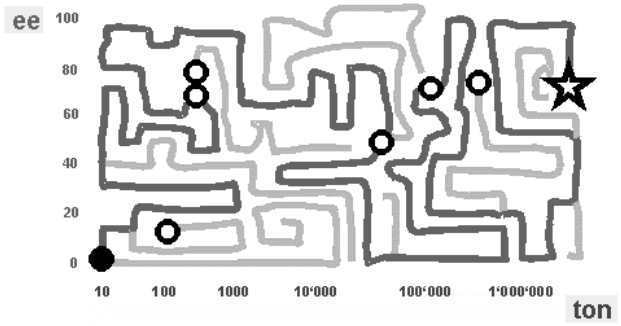

Figure 2. The ee-ton labyrinth (ton a logarithmic scale!) and the successful route.

play an important role but in the earlier phases of process development, ee and s/c (ton) are probably the dominant criteria.

To give the reader some orientation when reading this rather complicated account, a list of important milestones is given in Table 1. Most of them will be described in detail and commented in the text.

Table 1. Milestones in the history of metolachlor

1970	Discovery of the biological activity of metolachlor (patent for product and synthesis)
1973	Decision to develop a production process
1974	First 100 kg of racemic metolachlor produced
1975	Pilot plant in operation (4000-L reactor)
1978	Full-scale plant with a production capacity $>10{,}000$ t/y in operation
1981	Synthesis and biological tests of the four stereoisomers of metolachlor
1983	First unsuccessful attempts to synthesize *S*-metolachlor via enantioselective catalysis
1985	Rhodium/cycphos catalyst gives 69% ee for the imine hydrogenation (UBC Vancouver)
1987	Discovery of new iridium diphosphine catalysts that are more active and selective than Rh catalysts for MEA imine hydrogenation; the ee rises to 84% but the catalysts tend to deactivate.
1992	Novel ferrocenyl ligands are developed and tried for the MEA imine hydrogenation, the first catalyst without deactivation problems.
1993	The acid effect is discovered and laboratory process with Ir-xyliphos is established
1993/4	Patents for *rac*-metolachlor expire
1995/6	Pilot results for *S*-metolachlor: ee 79%, ton 1,000,000, tof $>200{,}000$/h, first 300 t produced
1996	Full-scale plant for production of $>10{,}000$ t/y *S*-metolachlor starts operation

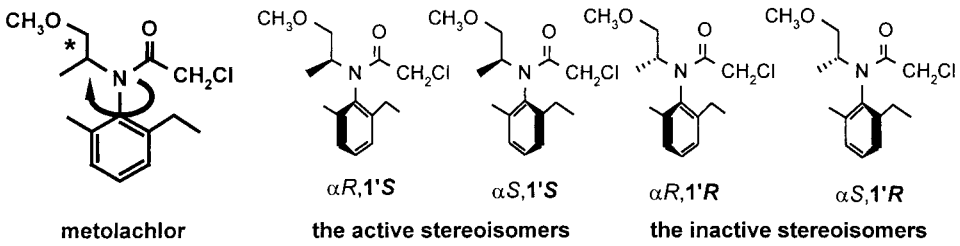

Figure 3. Structure of metolachlor and its individual stereoisomers.

2 Background

Metolachlor is the active ingredient of Dual®, one of the most important grass herbicides for use in maize and a number of other crops. It is an *N*-chloroacetylated, *N*-alkoxyalkylated *ortho*-disubstituted aniline. The unusual functionalization pattern renders the amino function extremely sterically hindered. Metolachlor has two chiral elements: a chiral axis (atropisomerism, due to hindered rotation around the C–N axis) and a stereogenic center, leading to four stereoisomers (Figure 3). Dual® was introduced to the market in 1976 containing a mixture of all four metolachlor stereoisomers produced via the Pt-catalyzed reductive alkylation of 2-methyl-5-ethylaniline (MEA) with aqueous methoxyacetone in the presence of traces of sulfuric acid followed by chloroacetylation (see Figure 4).[1]

Already in 1982 Ciba-Geigy published the finding that about 95% of the herbicidal activity of metolachlor resides in the two (1′*S*)-diastereomers as shown in Figure 5, e.g., it is only affected by the absolute configuration at the stereogenic center and not by the axial chirality.[2] One of the attractions of this finding was of course that the same biological effect could be produced at

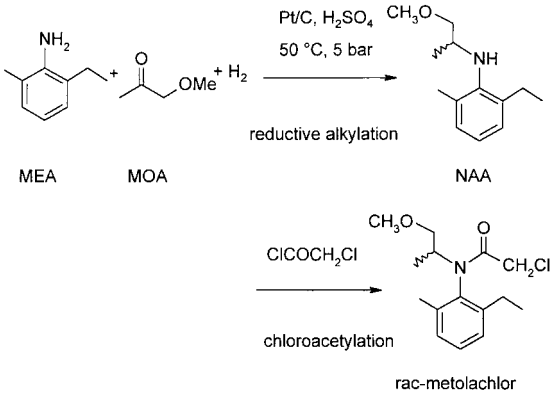

Figure 4. The process for the industrial production of racemic metolachlor.

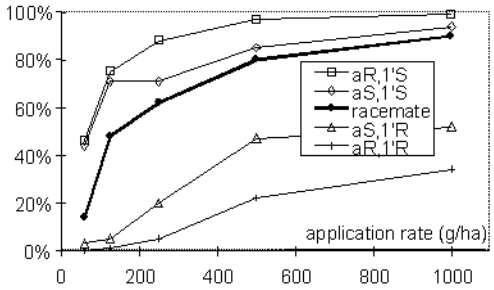

Figure 5. Effect of the application rate on the herbicidal activity for the 4 metolachlor isomers.

about 65% of the use rate of the racemic product, no small matter considering that >20,000 t/y of this herbicide were produced, shipped and applied! This very soon led to the question whether a commercially feasible process for the enantioselective manufacture of the (*S*)-enantiomers could be developed – the quest for a viable catalyst had started!

3 The Big Question and the First Assessment

It all started relatively innocently: In 1981 Beat Böhner (Head of Herbicide Research) came to Rolf Bader (at that time Head of the Catalysis Section of the Central Research Department) and asked whether there were any chances to find an enantioselective access to (*S*)-NAA. In an extensive project study Rolf and myself came up with four possible routes and we gave a short assessment of each variant.[3] The four routes are shown in Figures 6–9 and in Table 2, and are discussed below. Even though many possibilities exist for the enantioselective preparation of enriched (*S*)-metolachlor, it was clear from the beginning that because of the relatively low price and the large volume of the racemic product, only a catalytic route would be feasible.

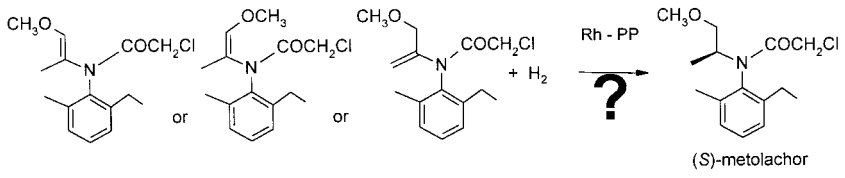

Figure 6. Enamide hydrogenation: Structures of tested enamides.

3.1 Enamide Hydrogenation (see Figure 6)

This idea clearly was inspired by the successful L-dopa process of Monsanto.[4] At that time, little was known on the effects of the substituents at the C=C bond and the amide nitrogen. A selective synthesis for one particular enamide isomers was judged to be difficult.

3.2 Nucleophilic Substitution of an (*R*)-Methoxyisopropanol Derivative (see Figure 7)

Here, the key step was the enantioselective hydrogenation of methoxyacetone in analogy to the Pt-cinchona-catalyzed hydrogenation of α-ketoesters[5] (the Ru-binap system was not yet known at that time). We had no idea how methoxyacetone would behave but the nucleophilic substitution with clean inversion was expected to be very difficult (weak nucleophile, no activation of the leaving group).

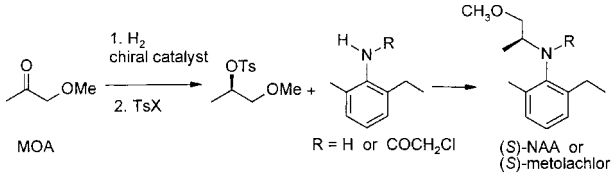

Figure 7. Enantioselective hydrogenation of methoxyacetone and nucleophilic substitution with a MEA derivative.

3.3 Hydrogenation of MEA Imine (see Figure 8)

Because the racemic metolachlor is commercially produced via a reductive alkylation, it was obvious to try to hydrogenate the imine intermediate, either isolated or formed *in situ*. However, at that time just one example for an imine hydrogenation was described in the literature with an ee of only 22%[6] and we predicted a lengthy development to achieve this goal.

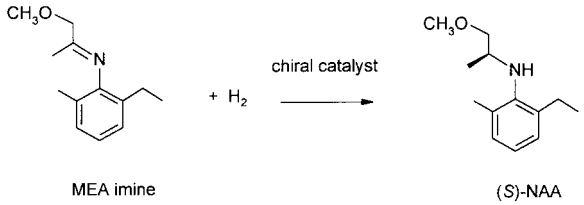

Figure 8. Imine hydrogenation: Structures of MEA imine and (*S*)-*N*-alkylated aniline.

3.4 Direct Catalytic Alkylation with Racemic Methoxyisopropanol (see Figure 9)

This idea was based on a gas-phase process for racemic NAA developed by one of our collaborators using a novel heterogeneous catalyst[7] and also on some results of the *N*-alkylation of aliphatic amines with primary alcohols using homogeneous Ru-phosphine catalysts.[8] This would be the shortest and most elegant variant but also the most difficult one.

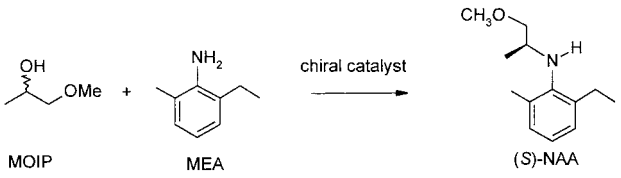

Figure 9. Direct alkylation of MEA with methoxyisopropanol.

3.5 Route Selection

In Table 2 the four proposed routes are classified according to 4 important criteria. The over-all ranking was used for setting priorities to carry out practical work. Because the enantioselective catalysis was considered to be the most difficult step, its chances of success dominated the decision and we recommended to Böhner to start experimental work with the enamide and the substitution route. Accordingly, a first project was agreed on with the following objectives: *"Evaluate the feasibility of enantioselectively hydrogenating NAA-precursors with ee's >70% (no goals were set for catalyst activity and productivity!). The enamide variant was to be investigated with first, the heterogeneous hydrogenation of MOA (substitution route) with second priority."* Because the Central Catalysis Section had to charge for its services to the operational divisions, Böhner also had to approve the quite respectable budget for the feasibility study. He did so without problems because he was not only convinced of the importance of the project but also because his department had already carried out several projects with the Catalysis Section, which had established a basis for mutual trust between the two units. In fact he was our first project champion in the Agro division, a key function for every project of this size.

Table 2. Comparison of possible routes for the synthesis of (*S*)-metolachlor.

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

A short description of the state of enantioselective catalysis in 1981 and a comment on the situation at Ciba-Geigy.

The first heterogeneous enantioselective hydrogenation was reported in 1940 by Nakamura[9] while the first homogeneous catalysts were described much later in 1968 by the groups of Knowles[10] and Horner.[11] Both areas were studied intensively in the late 1960's and during the 1970's and many publications appeared.[12,13] However, in 1981 only one asymmetric catalytic reaction was applied industrially, namely the production of L-Dopa *via* enantioselective hydrogenation of an enamide with a soluble Rh-dipamp complex by Monsanto.[4] This success was the major reason that during the next decade, the hydrogenation of ***enamides*** became the best studied catalytic reaction. Countless new ligands were synthesized and tested with different enamides (see Figure 10) and the basic reaction mechanism was unraveled. The most investigated model compound was $R_1 = R_4 = H$, $R_2 = Ph$, $R_3 = COOR'$, $R_5 = Me$; only one case was investigated where R_4 was not = H; none with an aryl group of any type. The best catalyst already gave 99% ee[14] but the highest ton's were a relatively modest 2300.[4]

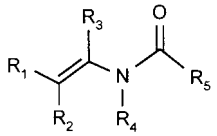

Figure 10. Structure of enamides used as model substrates for hydrogenation catalysts.

For the hydrogenation of ***C=O groups*** the most active catalysts were modified heterogeneous catalysts: Ni-tartrate for β-keto esters[15] and Pt-cinchona catalysts for α-keto esters[5] with best ee's up to 85%. Some soluble Rh diphosphine catalysts were also reported to give ee's up to 95% but without any data on activity.[16] In contrast, the enantioselective catalytic reduction of ***C=N functions*** was practically unknown. The best results were reported for the hydrosilylation of some *N*-alkylimines with ee's up to 65%[17] while the best ee for hydrogenation was only 22%.[6] The reduction of *N*-arylimines had never been described.

At that time less than 10 chiral ***diphosphine ligands*** were commercially available and of course only in small quantities. This made life very difficult for industrial groups because it severely hampered an efficient process development.

Concerning our own circumstances: This project caught us quite unprepared. While the Catalysis Section of Ciba-Geigy had a history dating back to the early 1930's, its expertise was concentrated on the application of heterogeneous hydrogenation. In the areas of homogeneous catalysis, the major fields of research were Ni- and Pd-catalyzed C-C bond formation, organometallic chemistry and a few preparative applications of Wilkinson's catalyst. However, we had never used a chiral metal complex and our hydrogenation equipment was not well suited for handling homogeneous catalysts. This meant that at the same time when we started the (*S*)-metolachlor project, we also launched our research activities in the field of enantioselective catalysis – certainly not an ideal situation!

4 1982 – 83: The First Steps in the Labyrinth – and the First Disappointment

The experimental work of the catalytic part was taken up by Hans-Peter Jalett, at that time a very experienced chief technician in the Catalysis Section, and in Agro Research by Hans Moser (he already had synthesized the 4 metolachlor isomers[2]) who agreed to synthesize the enamide isomers. Both the setting up and testing of suitable hydrogenation equipment for homogeneous systems as well as the synthesis of the enamide isomers (actually the acetyl analogs instead of the Cl-substituted "real thing") took a bit longer than anticipated. Nevertheless by the end of 1982 we could report the following progress:

- The three enamide isomers were prepared in gram quantities with > 95% purity
- The laboratory hydrogenation reactor was ready and worked quite well, even though only at atmospheric pressure
- The hydrogenation of acrylic esters with the Wilkinson catalyst and also with a Rh-diop complex worked according to literature descriptions but, somewhat ominously, were not always reproducible
- Several heterogeneous cinchona-modified Pt-catalyst systems were tested with methyl pyruvate as model substrate but the best literature values (80 – 85% ee) could not be reproduced. The best values were 75% – not a bad start here.

At the beginning of 1983 we were allowed to expand the Catalysis Research group. After some evaluation we decided to hire Felix Spindler who had done his Ph.D. work at the ETH in Zürich with Prof. Pino and had a lot of practical experience with homogeneous catalysis and indirectly with enantioselective hydroformylation. In addition, he was the first chemist in the Catalysis Section with personal computer experience! Felix took over the homogeneous part while Hans-Peter continued the quite successful heterogeneous investigations. Now, things accelerated significantly and the results with actual metolachlor precursors came in quick succession – ***and all of them were depressively negative***:

- None of the three enamides showed any(!) conversion with 7 different Rh-diphosphine catalysts at temperatures up to 50 °C and 1 bar.
- Methoxyacetone was hydrogenated successfully with a cinchonidine-modified Pt/C catalyst but the ee was never higher than 12% and the activity was also much lower than for methyl pyruvate. A very impressive case of substrate specificity (the difference of one C=O group!)

– MEA imine was also reducible with Pt-cinchona catalyst but the product was perfectly racemic – we did not even try the Rh-diphosphine catalysts under these circumstances.
– The *direct alkylation* was not tested experimentally, because chances for success were considered to be too low.

Almost at the same time, the Agro division made the decision to focus on other potentially interesting new herbicides and at least temporarily stop the (*S*)-metolachlor project. This meant that we had now time to digest our results (and disappointment) and to thoroughly analyze the situation.

Conclusions, Consequences and a Second Remark

In order to be able to be prepared for new development problems, the following research program was proposed (and accepted by Rolf Bader and supported by Beat Böhner). This program should enable us to react much faster to a new problem and to enhance the chances to find a solution within a reasonable period of time. For this purpose we made the following recommendations:

– Building up a collection of chiral ligands and metal precursors (chiral ligands were still hard to come by and we started to look for commercial and other sources).
– Because of lack of experience and resources, not to start our own ligand synthesis program. This was certainly the most problematic decision. It was probably right under those circumstances, but of course later on this decision was revised (see below).
– Start a program for the synthesis of enamides with a systematic variation of steric and electronic properties in order to understand why the enamide analogy failed so miserably. During the course of these investigations we learnt that this approach was very time- and resource-consuming and, except for invaluable experience, we got only very few concrete results.
– Construction of several vacuum lines and a very efficient hydrogenation setup with automatic data collection (here the IT know how of Felix came in handy), first for low pressure hydrogenations and later for higher pressures as well. The decision to install first low pressure equipment (based on the observation that high p gave lower ee's for the enamide hydrogenation) turned out be wrong: In many cases, high pressures were necessary to get reasonable tof's!
– To improve our analytic know how for the determination of ee's (something we underestimated at the start of the project).
– To continue with the systematic investigation of the heterogeneous systems. This led to a quite impressive series of new catalytic systems, processes and also papers and lectures. However, in the context of metolachlor this approach did not play a role anymore.

The failure to get any useable results taught us a few hard lessons that we were not likely to ever forget:

– *Catalyst activity* is a much more important issue than we thought. This means that in process development one cannot simply concentrate on enantioselectivity as was (and sometimes still is) done in academic research.
– Substrate specificity seems to be especially high for enantioselective catalysis (again much more than we expected) and this concerned not just selectivity but even more catalyst activity.
– In order to make structure-activity/selectivity predictions one needs a good basis because this can be done only empirically.

5 1985 – 1987: A Second Chance and a First Breakthrough

I will not describe our activities in the period 1983 – 85 but we acted on most of the conclusions described in the box. Our involvement with (*S*)-metolachlor began again in the fall of 1985 – and it started with somewhat of a shock to us. We knew that Hanspeter Fischer, a kind of scientific ambassador of the Agro division, had initiated a joint research project with a team headed by J. P. Kutney of the University of British Columbia in Vancouver funded by Ciba-Geigy and the NSERC of Canada Strategic Grants program. This group had investigated the hydrogenation of the MEA imine and the closely related 2,6-dimethylaniline (DMA) imine (Fig. 11). Kutney came to Basel and presented his remarkable results. The Vancouver team really had done a superb job: By screening a number of Rh-diphosphine complexes (see Fig. 12) they found several Rh

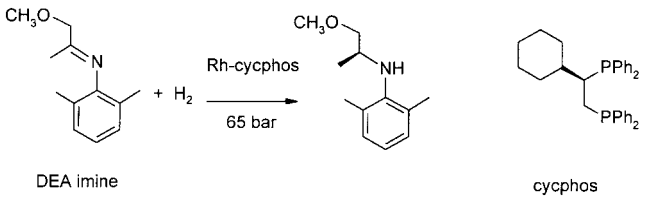

Figure 11. Hydrogenation of DMA imine.

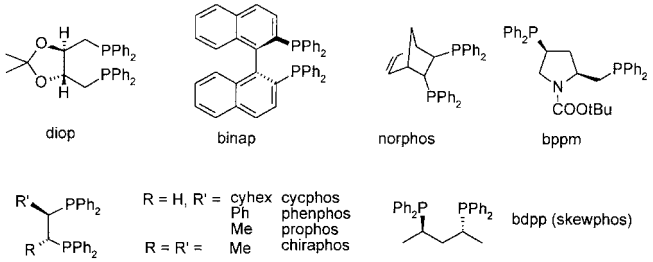

Figure 12. The most important ligands tested in the early phases of the project.

complexes able to hydrogenate DMA imine, the best catalyst, Rh-cycphos, gave an ee of about 40%! Even though catalyst activity was quite low and very high pressures were necessary for complete conversion, this was definitive proof that it was possible to homogeneously hydrogenate *N*-arylimines. By optimizing reaction conditions with Rh-cycphos the ee's could eventually be increased to 69% ($-25\,^{\circ}C$), the best tof (15 h^{-1}) and ton (1000) were obtained at 65 bar and room temperature.[18]

These results had of course significant consequences on the priorities of Agro division and with the request by Beat Böhner to formulate a new project proposal, the hunt for an imine hydrogenation catalyst was initiated in earnest. Felix started with reproducing the Vancouver results. Due to our decision to first install low pressure hydrogenation facilities, this took more time than we liked, but in the end he produced about 50 g enriched *N*-alkylated DMA for crystallization studies. For our research efforts we saw two alternative strategies: i) screen more Rh diphosphine complexes and/or find better reaction conditions, ii) try something else. Intuitively, Felix did not think that Rh-diphosphine complexes would ever be active enough and he proposed a program with Ir complexes. This was quite a risky decision. In contrast to Rh catalysts, very little was known on Ir-phosphine complexes and Ir-catalyzed reactions were very rare at that time and none was enantioselective. However, he remembered a paper by Crabtree who described extremely active Ir-tricyclohexylphosphine-pyridine complexes able to hydrogenate even tetrasubstituted C=C bonds with tof's of up to 4000 h^{-1}.[19] So he started to test Ir-diphosphine complexes with both MEA and DMA imine – and the success was spectacular.

Within one year, Felix and Benoit Pugin, a graduate student of Prof. Venanzi (ETH Zürich), who had recently joined the catalysis group, had demonstrated that Ir complexes were suitable catalysts for *N*-arylimine hydrogenation, which could be patent protected. In addition, they had elaborated a provisional laboratory process for the DMA imine and had made a first cost estimate. For an industrial company, these results were of the nature "good news – bad news":

Good news:

- Best ee's for DMA and MEA imine were 73% and 70%, respectively. The original goal of 70% had actually been reached.
- At 20 bar H_2 and 20 °C the reaction could be run at an imine/Ir ratio of 2000 with 68% ee but the reaction took 100 hours to go to completion (tof 20 h^{-1}). This was a new world record for imine hydrogenation with any homogeneous catalyst.

Bad news:

- While the catalysts were quite active at the beginning, deactivation was significant during reaction.
- Even worse: the estimate showed catalyst costs which were to high by a factor of >20 – in other words, we needed an s/c ratio of $\gg 40{,}000$ (and lower reaction times as well)!

For the first time, we now also had a goal for the productivity of the catalyst and a very ambitious one to be sure: At that time, there was no homogeneous catalyst known with a productivity of this order of magnitude (the very high ton's achieved by Takasago for the Ru-binap catalyst isomerization of allylic amines were reported much later). As a consequence, we undertook a tremendous effort to reach these elusive goals working in three different approaches. i) UBC was active in the field of the Rh-catalyzed reaction, ii) in a collaboration with Prof. J. A. Osborn (Université Louis Pasteur, Strasbourg) the chemistry of selected Ir-diphosphine complexes was studied in detail, and iii) Felix and Benoit ran a classical development program screening ligands, solvents and additives, reaction conditions, etc. For the enantioselectivity they were very successful, surpassing the original goal of 70% ee by 14%. However, whatever they tried to bring catalyst activity and productivity to the required level, ***it was all to no avail.*** While the productivity could be improved by a factor between 2 and 3, the big hit did not occur and by the end of 1987, we reluctantly agreed that it was time to stop the project. The results were patented[20] and published[18,21,22] and can be summarized as follows:

- For the MEA imine hydrogenation Felix and Benoit obtained very good ee's with an Ir-bdpp catalyst in presence of iodide ions (ee 84% at 0 °C). With this catalyst, the original goal of 70% ee was more than reached but productivity and activity were disappointing: tof <150 h^{-1} and s/c >100 led to a strong decrease in enantioselectivity.
- On the other hand, Ir-diop-iodide catalysts achieved ton's up to 10,000 (this was already quite close to the required 40,000) but reaction times between 40 and 50 h were needed even at 100 bar and 25 °C for full conversion and the ee under these conditions was 63% at best.
- Irreversible catalyst deactivation was a major problem of these new Ir-diphosphine catalysts; it could be somewhat

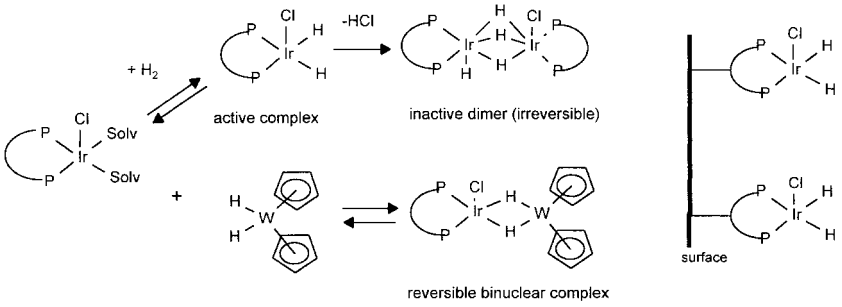

Figure 13. Stabilization of the active Ir species (drawing from a semester report).

controlled by a careful choice of Ir precursor complex, additional ions and the reaction conditions and the purity of the imine.
- These new Ir catalysts also worked for a variety of other *N*-arylimines with ee's between 22 and 84%.
- Osborn isolated several new Ir-diphosphine complexes with good stabilities and activities and contributed much to a better understanding of the mode of action of the Ir-catalyzed imine hydrogenation. In this collaboration we learnt to appreciate the sometimes decisive influence of the nature of the Ir precursor and also of the anions on catalyst performance.
- Two approaches to prevent deactivation were (partially) successful: i) Benoit Pugin immobilized Ir-bppm complexes on a solid support, ii) Felix Spindler prepared hydride bridged Ir-W complexes. The underlying idea was that deactivation was caused by the base-catalyzed, irreversible formation of hydride-bridged binuclear Ir complexes. Immobilization should give a local separation of the active species (site isolation) while the tungsten hydrides were thought to reversibly stabilize them (see Figure 13). Both methods showed positive results but only the immobilization was pursued further and later played quite an important role.

Ir catalysis around 1985 and a third personal comment

Compared to Pt, Pd, Ni or Rh, iridium did not play any role in preparative catalysis – neither homogeneous not heterogeneous. Of high interest to us were the Crabtree catalysts because of their ability to hydrogenate tetrasubstituted C=C bonds which was not possible with any of the known Rh complexes. As already mentioned, this led Felix to try Ir for the imine hydrogenation. This sounds trivial and obvious in retrospect. However, things were not so simple. First, these catalysts sometimes deactivated within minutes, not something you want for an industrial catalyst! Secondly, John Brown (Oxford University) had shown that replacing Rh for Ir for the enantioselective hydrogenation of enamides led to such a slow down of the reaction that made it possible to isolate the catalytic intermediates that were postulated by J. Halpern and others for the Rh-catalyzed process![23]

In 1984 Felix designed and synthesized a few chelating P,N ligands in the hope that these were less prone to deactivation and with the idea (unfortunately never realized) to later make chiral versions. However, in all cases the Ir-P,N catalysts were less active than Rh complexes.

Here, I would like to comment on three points:

i) I think that the decision of Felix to go for the Ir catalysts was not so much based on all these facts but on an intuitive feeling that Ir was "right". In addition, we all agreed that the gap between the actual results and the needed catalyst performance was so huge that the odds to reach the goals with a conservative approach were virtually nil – only a new approach had any chances of success. In addition, we always had a tradition of supporting calculated risk-taking in the Catalysis Group of Ciba-Geigy. The philosophy was (and still is) to rather try the impossible and succeed or fail with grandeur.

ii) We are quite convinced that the successful application of Ir complexes for an industrially important intermediate convinced other research groups to enter this field as well. As can be seen from Figure 14 after a certain lag time the number of publications on the chiral Ir complexes increased significantly.

iii) I remember how disappointed we were by the fact that we reached both goals regarding ee and ton (at least almost) *but with two different ligands*. Later we learnt that this is more the rule than the exception and that activity and selectivity often follow opposite trends.

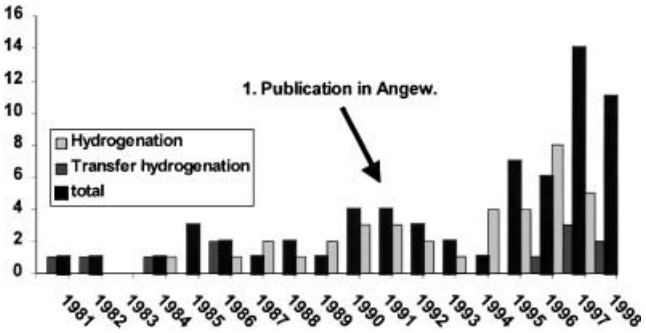

Figure 14. Statistics on the number of publications on chiral Ir complexes from 1981 to 1998.

6 Intermezzo 1988 – 1992

For a second time we could concentrate on less directed research and we also carried out other development projects. Here, I will briefly describe a few results which had a significant effect on the later phases of the (*S*)-metolachlor project.

6.1 Catalyst Deactivation and Separation

In 1988 Benoit Pugin started an exploratory project on separation methods for homogeneous catalysts. At first he focused on immobilization of diphosphine ligands via covalent linkages. He developed a modular system of supports (polymer, silica), linkers and appropriately functionalized ligands which allowed him to tailor the immobilized catalyst to a specific reaction. In 1990 he reported a first success with the MEA imine which (for obvious reasons) was chosen as one of the model test reactions. Supported Ir-bpm catalysts showed about 3 – 8 times higher activities compared to the homogeneous analogues; on second use, tof was higher by a factor of >20. The idea of preventing deactivation by immobilization worked!

6.2 New Ligands

Up to now we consciously had stayed out of ligand synthesis. This changed when in 1987 Antonio Togni and Steve Pastor of the homogeneous catalysis research group started to investigated the gold-catalyzed aldol reaction discovered by Hay-

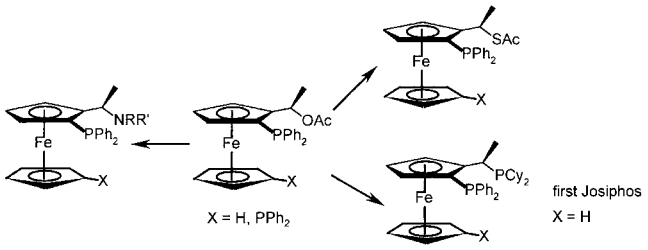

Figure 15. Substitution reactions at the stereogenic center of ethyl ferrocene derivatives.

ashi. In the course of systematic study they prepared several ferrocenyl ligands bearing different side chains. A key finding was that the acetate group at the stereogenic center could be smoothly substituted with complete retention of configuration by the nucleophilic thioacetate using KSAc in acetic acid solvent (right part of Figure 15, $X = PPh_2$). This finding led to the idea, developed together with Felix Spindler, to use secondary phosphines (e.g., $HPCy_2$) for the synthesis of novel chelating ligands bearing two different PR_2 groups (right part of Figure 15, $X = H$). This first example was named Josiphos after Josi Puleo, the technician who actually prepared it, but the name is now used for the whole family of ligands. Almost at the first try, the Josiphos was very highly selective for the Rh-catalyzed hydrogenation of enamides and itaconic acid derivatives and accordingly, this new class of ligands was developed further.[24,25]

6.3 Process Development

Several feasibility studies were carried out for the newly formed group "Asymmetric Synthesis" in the Agro division (B. Böhner, H. P. Buser, T. Früh, G. Ramos). While the results are not directly relevant for the (*S*)-metolachlor problem, this collaboration led to a high mutual trust between the catalyst specialists and the divisional chemists which proved very valuable later on.

6.4 Technical Synthesis of a Chiral Diphosphine

In collaboration with Pharma development we had developed a pilot process for the hydrogenation of (*R*)-levoprotiline (Figure 16). The best catalyst was a Rh-bppfoh catalyst and the ligand was not commercially available. For this reason, a technical synthesis was worked out and implemented on a multi-kg scale. At that time, we did not realize this of course, but it should prove invaluable later on.

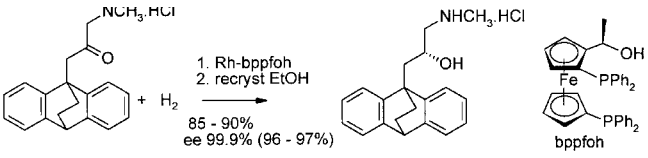

Figure 16. (*R*)-Levoprotiline synthesis with a Rh-ferrocenyl-diphosphine catalyst.

6.5 Enamide Hydrogenation

Our earlier systematic enamide investigations also had a late pay-off because we succeeded in finding suitable catalysts for the hydrogenation of highly hindered enamides with good to excellent enantioselectivities and respectable ton's and tof's as shown in Figure 17 (to be precise, the *R*-duphos-catalyzed process was developed only in the mid 1990's).[26] Interestingly, the discrepancy between ee and ton again showed up in one of the two cases: for the cyclic enamide, Rh-diop gave higher ee's whereas Ru-binap had good ton's.

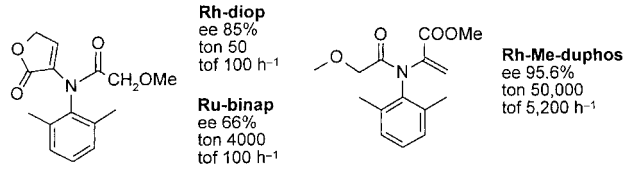

Figure 17. Hydrogenation of sterically hindered enamides (catalyst, ee, ton, tof).

In any case, these results show that it is indeed possible to get technically useful results for sterically demanding enamides, vindicating our decision to try this approach first. On the other hand it is also obvious that even the very impressive results with Rh-Me-duphos would not have been sufficient to solve the (*S*)-metolachlor problem.

A fourth comment

While we made not much progress in imine hydrogenation, I consider this period to be very important for the development and also self-confidence of our catalysis group. There is no doubt that the decision to stop the (*S*)-metolachlor project was conceived as defeat. The many successes in our research project(s) but also in the process development of enantioselective catalysts gave us self-confidence. In addition, the experience we gained was probably decisive in the next (and last) phases of the MEA imine hydrogenation that were to come. Also, parallel to our success, the whole field of enantioselective catalysis significantly grew in this period and many more chiral ligands became available to us either commercially or via our connections.

This is also an appropriate place to stress the importance of the continuity of our research efforts. Frequently, one can observe that research is either redirected (or even stopped) because a commercial application could not be realized. Thanks to the atmosphere prevailing at that time in Central Research of Ciba-Geigy and, perhaps even more important, thanks to the support we got from Rolf Bader, the head of the Catalysis Department, there was never any interference in our plans and project. In hindsight, this was probably one of the key factors for the later success.

7 May 1992 – June 1993: A Third Chance and a Second Breakthrough – Almost There!

Rather surprisingly, in May 1992 we got a third chance to find a commercially feasible catalyst to produce (*S*)-metolachlor. It turned out that the enriched (*S*)-metolachlor still played a major role in the post-patent strategy of the Dual herbicide. It was also clear that this would definitively be the last opportunity! In a short position paper Felix Spindler and myself assessed the probability of success and sketched a short project proposal. On this basis it was decided to form a project team headed by Gerardo Ramos (Agro) and myself and with Hanspeter Buser (Agro), Felix Spindler and Benoit Pugin and their teams.

In July 1992 John Dingwall (Head Herbicide Research, he proved to be an invaluable project champion in this critical phase) approved a substantial research project with the following objectives: *"Prepare the basis for a decision to develop a technical process until April 1993. Minimal requirements: ee ca. 80%, ton > 40,000, reaction time < 8 h"*. Our plan was to review again all the options, namely imine hydrogenation (both homogeneous and immobilized; 1st priority), enamide (2nd priority), reductive alkylation, transfer hydrogenation and heterogeneous catalysis (3rd priority, with a few experiments). We were quite optimistic to meet these goals because, as pointed out above, we had two very strong leads from the previous phase and we were also convinced to have learnt a lot in the last four years. What worried us were the lack of a good analytical method (it was still either optical rotation or NMR with a shift reagent), and also the synthetic effort needed to prepare all the ligands and Ir precursors we had in mind. Fortunately, Hanspeter Buser (an organic chemist by training) was well versed in chiral HPLC and indeed within a few weeks he had developed a very efficient and reliable method for NAA. In addition, he synthesized a number of special diphosphines. Benoit Pugin focused on preparation and testing of immobilized catalysts, Felix Spindler on the investigation of ligands, Ir precursors and reaction conditions.

The results of this huge effort shall be illustrated with the summaries of the reports for John Dingwall:

Status 23 September 1992: Analytical method (H. P. Buser); previous best experiments with DMA reproduced successfully with MEA; ligand screening started (new hit for Ir-bppm 79% ee); ligand and Ir precursor preparation started.

Status 2 November 1992: Ligand screening shows significant effect of the nature of R in the PR_2 group of various diphosphines; first comparisons homogeneous/immobilized confirm superior performance immobilized catalysts; the preparation of new Ir complexes is more difficult than expected; transfer hydrogenation and heterogeneous catalysis give only negative results and are abandoned.

Status 21 December 1992: Three new ligands prepared; otherwise no progress.

Summary Semester Report II/92, 15 February 1993: The results with soluble complexes are within expectation, best ee 79%; no breakthrough concerning ton and tof; ***at the moment the results with immobilized catalysts look most promising, in some cases activities are up to 10 times higher and ee's and stabilities are improved as well.***

Time was getting short and it looked as if immobilization was necessary to get catalysts with less tendency to deactivate. We decided to put more manpower in making functionalized ligands but this proved to be very difficult and time-consuming. With the homogeneous complexes, Felix Spindler focused on the best four ligands and tried whatever ideas he had to improve catalyst activity. On 30 April 1993 (practically in the last minute) a decisive experiment was carried out: one of the new ferrocenyldiphosphines with less basic PR_2 groups was tested and showed good initial activity ***and it did not deactivate at all!*** The ligand was xyliphos (see Figure 18, reaction with an

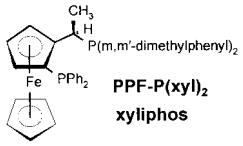

Figure 18. Xyliphos: The original drawing in the semester report

s/c ratio of 800 gave 73% ee in 6 h). We most certainly had a very promising lead.

The status report 1 June 1993 confirmed this in all respects (citation): *"We obtained a decisive breakthrough concerning catalyst productivity and activity: A novel Ir-PPFP(xyl)$_2$ catalyst achieved 35,000 turnovers with ee's around 70% (55 °C, 80 bar H_2, 48 h). The catalyst does not deactivate even at higher temperatures but ee's increase with lower T (best ee 81% at 0 °C)."*

"The immobilization of Ir complexes is feasible; immobilized catalysts show up to 50 times higher activities and 10 times higher ton's than the homogeneous analogs. Up to now best ton 12,500 but ee only 42%. There is no synthesis known for immobilizing ferrocenyldiphosphines."

The success of the new catalysts is shown in Figure 19. The success with the new ligands class of course guaranteed continuation of the project.

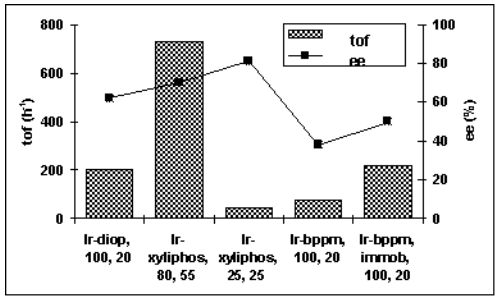

Figure 19. Comparison of ee and tof of the best Ir catalysts for the hydrogenation of MEA imine (bar, °C).

Before I end this chapter, I would like to give a verbatim citation from the "Minutes of the Weed Control Portfolio Meeting 2/93, June 10, 1993", which shows that our partner from the Crop Protection appreciated our efforts and good results: *"The Weed Control Portfolio Team congratulates Drs. Felix Spindler, Benoit Pugin, Hans-Peter Buser and their coworkers for the important scientific breakthrough in the preparation of CGA 77'102, which allows the Dual Post Patent Strategy Team to consider CGA 77'102 as a powerful weapon to defend our most important market into the 21st century."*

It goes without saying that this success was duly celebrated with an "*S*-DUAL Breakthrough Party" and a splendid dinner at Donati's, arguably the best Italian restaurant in Basel.

The amazing Josiphos ligand family and a fifth comment

Chiral ferrocenylphosphines were first described 1974 by Hayashi and Kumada.[27] First considered to be just a curiosity, it became clear quickly that these ligands have a great potential. As already described, Antonio Togni got interested in this ligands because of the gold-catalyzed aldol reaction. When he decided to try to introduce a PR_2 in the side chain, he asked Felix Spindler (at that time his lab mate) which R group to chose. Felix knew the sometimes unusual performance of diphosphines with two electronically different P-groups described by Kumada and advised to chose phenyl at the cp ring and cyclohexyl in the side chain – and the rest is history as they say. A good synthesis was developed and today there exist more than 70 Josiphos ligands with a wide combination of steric and electronic properties with already an impressive range of applications (see Figure 20).[25]

Here I would like to comment on three points. i) It was probably fortunate that we did not know the final requirements concerning ee, ton and tof in the earlier phases of the project; quite likely we would have given a very different (probably negative) assessment of the chances of success. ii) It might be surprising to the reader that we were so sure of success even though we had not really reached the goal. But catalyst deactivation was considered to be the major obstacle to a technical process and there was no doubt in our minds to have a solution for this problem. iii) I find the way the Josiphos ligands were invented highly fascinating. In hindsight several points were important: the interest of Togni and Pastor in structure-activity effects; the expertise of Spindler in asymmetric hydrogenation; the ability to quickly test new ligands; the need of the (*S*)-metolachlor project for new ligands. Maybe even more important however was the fact that two chemists working in the same lab on different projects with different approaches and goals communicated well and shared their successes as well as their failures.

8 July – December 1993: The Final Breakthrough

Despite our excitement we fully realized that there still were many hurdles to a technically feasible process and if we had any doubts the following excerpt from a protocol would bring us back to reality: *"Dr. Fäh (Head Agro Development) emphasizes that the weak point of the current process is the pressure*

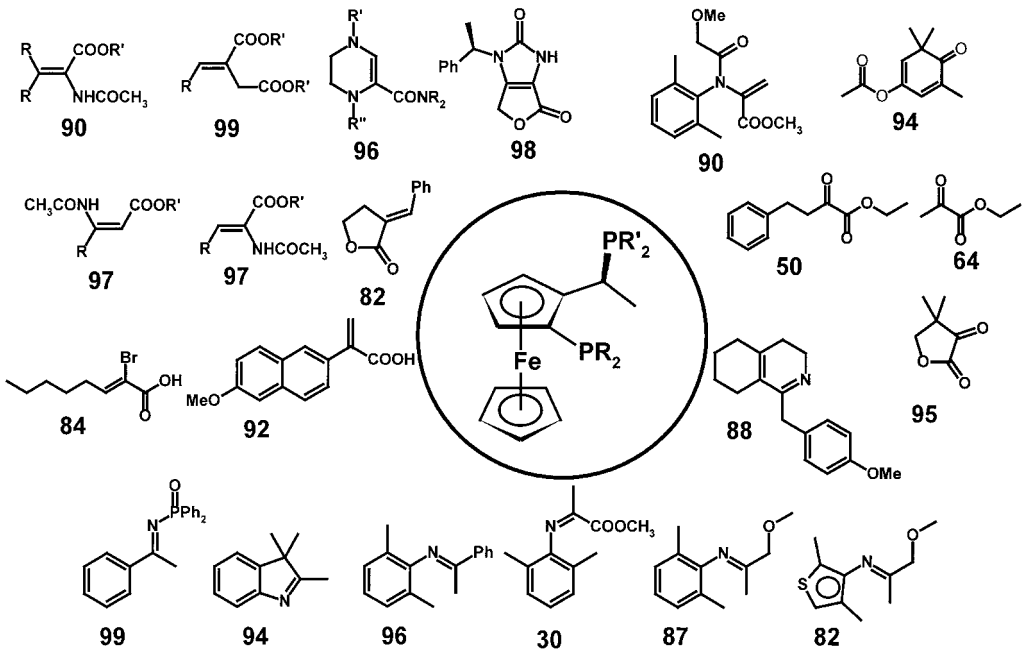

Figure 20. Enantioselectivities of Josiphos ligands for the hydrogenation of C=C, C=N and C=O functions.

which would require mammoth investments for production of 10,000 jatos" (J. Dingwall, Meeting on CG 77'102 Synthesis, June 15, 1993). Fortunately, this comment which certainly was correct at that time with tof's in the order of 800 h^{-1}, was taken care of when a much more active catalyst system was found (see below), leading to a much higher volume-time yield and thereby to fewer reactors.

Again an action plan containing the following elements was proposed and approved by the division:

- Optimizing ligand structure and reaction conditions.
- Elaboration of a first laboratory procedure.
- Immobilizing of ferrocenyl ligands.

The original team was enlarged and Hans-Peter Jalett joined the team again (almost 10 years after having made the first experiments!). In addition contacts were established with the teams of the development center of the Agro division, who would later be responsible for the further development.

As mentioned above, we were quite optimistic and expected our optimization strategy to result in a stepwise improvement of catalyst selectivity and activity. What really happened was completely unexpected and can be most effectively illustrated by the summary of Jalett's laboratory procedure of 22 November 1993: *"The laboratory procedure describes the homogeneously catalyzed hydrogenation of MEA imine. The process is well suited for technical application and is characterized by good reproducibility, high catalyst productivity (**max turnover number >200,000**) and good optical yield (**75 – 80% ee**). The procedure is a good basis for a production process."*

Obviously, something dramatic had happened. In the course of process development Hans-Peter Jalett also investigated the effect of the solvent. Instead of just using the conventional ones like toluene, alcohols or esters he also tried acetic acid – and with quite unexpected consequences: in AcOH the catalyst activity increased by a factor of 10 and even more surprisingly the ee increased by 5 – 6% at the same time! As can be seen in Figure 21, what was really needed was the addition of both acid and iodide, an additive which was necessary with all Ir complexes. This was the final breakthrough we had been looking for.

The experiment was immediately reproduced by others and confirmed. This gave a real energy boost to the project team and things now proceeded very fast. The reaction conditions were optimized, new Josiphos derivatives were synthesized and tested, an immobilizable version was designed and also the direct reductive alkylation was tried.

In the status report of 30 January 1994 (H. U. Blaser, G. Ramos) the results were summarized as follows:

- The original goals were reached or surpassed, in presence of acids ton > 600,000 could be obtained (reaction time 50 h, ee 76%), with s/c 50,000 reaction time is less than 4 h. A technical process can now be developed.
- Various acids and Ir precursor salts are suitable, the purity of the imine is very critical. The direct reductive alkylation is possible but with lower catalyst activities.
- The ligand screening (about 30 new derivatives) showed that xyliphos is the optimal ligand with the best combination of ee, ton and tof. Immobilized ligands (5 derivatives) achieved the same enantioselectivities but much lower ton and tof. Separation and re-use are possible but not trivial.

The improvements achieved in this relatively short period of time are best illustrated with the original diagram made for a presentation to Agro management (Figure 22).

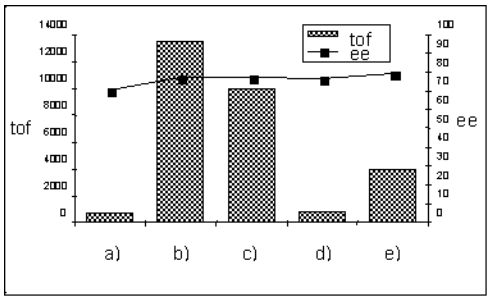

Figure 22. Comparison of catalyst activity and ee for Ir-xyliphos catalysts:
a) without acid
b) with AcOH, 80 bar, 50 °C
c) with AcOH , 20 bar, 50 °C
d) reductive alkylation
e) immobilized

Why acetic acid?

In order to understand why Hans-Peter Jalett used acetic acid, a small excursus into heterogeneous hydrogenation might help. In this field, acid and base effects are quite common and in his long career Hans-Peter had seen positive effects of acetic acid many times. The most important result in this context was undoubtedly the effect he observed for the hydrogenation of α-keto esters using cinchona-modified Pt-alumina catalysts which he studied extensively. In 1990 we found that when using acetic acid as solvent, ee's up to 95% could be obtained, for quite some time the world record for heterogeneous chiral catalysts. With this background and a very pragmatic mind, Hans-Peter decided to include acetic acid in his list "just to find out what it might do here". Fortunately, he had not asked anybody whether this might make sense or not – and I am quite sure that the homogeneous specialists would probably have dissuaded him from doing this. As a matter of fact, already in 1986 B. Pugin had used acetic acid as an additive with an Ir-diop complex with negative results.

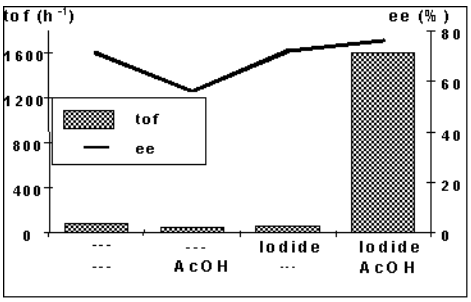

Figure 21. Effect of the addition of acetic acid and iodide to the Ir-xyliphos-catalyzed hydrogenation of MEA imine.

9 1994 – 16 November 1996: From Laboratory Procedure to the First Production Batch

With the laboratory procedure in place, the focus of the work shifted now to the technical aspects and also away from the catalysis team. For this reason I will cover this period of time only very briefly, because in this project phase, catalysis was only one of many aspects that had to be taken care of. For the catalysis team, this meant that they had to transfer as much of the know-how to the Agro Development Department – with the hope that our colleagues would take good care of our precious baby. Needless to say that the length of this part is almost inversely proportional to the number of people, of time and of money involved (for more details see ref.[28]). These teams did a very impressive job under an enormous time pressure: no matter how good our process was, without these efforts there would be no large-scale (*S*)-metolachlor process.

The following problems had to be solved, many of them in joint research/development teams:

Optimization of reaction medium and conditions. After the proper choice of the additives (acid and iodide) and of the reaction conditions, MEA imine can be now hydrogenated at a hydrogen pressure of 80 bar at 50 °C with a substrate to catalyst ratio (s/c) of >1,000,000. Complete conversion is reached within 4 h with an enantioselectivity of 79% with an initial tof exceeding 1,800,000 h^{-1}. These results set a new standard concerning catalyst activity and productivity for a homogeneous enantioselective hydrogenation.

MEA imine synthesis. The process for making MEA imine in the required quality turned out to be more difficult than expected. In the end, a complicated multi-step continuous distillation process was necessary for the purification of MEA imine involving recovery of solvent and non-reacted starting materials.

Scale-up of the ligand synthesis. Based on the experience with the bppfoh ligand mentioned, a synthesis was worked out which can be carried out in reactors up to 2500 liter. It is feasible for the preparation of xyliphos in quantities of hundreds of kilograms with >99.5% ee. In order to run an economical process it was crucial to define the most important parameters, to optimize these and to have them under good control on the production scale.

Choice and optimization of catalyst formulation. Because several requirements had to be met, this step turned out to quite complex. In the end, a liquid, highly active catalyst formulation was developed which was stable over several months and allowed us to feed the catalyst safely and easily to the hydrogenation reactor at any time of the reaction. After catalyst addition, full activity was available immediately so that cycle time and catalyst amount could be further optimized.

Choice of reactor technology. For optimal mass and heat transfer 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 mixing and the use of the appropriate exchange surface.

Scale-up of the process. The laboratory procedure was developed in a 300-mL reactor. The manufacture of 100 kg amounts of the enriched (*S*)-metolachlor, was carried out first in a stirred tank 50-L autoclave and then in a loop reactor of the same size. The actual piloting was carried out in a dedicated 1000-L loop reactor, which was also used to produce the first tons of product. All scale-up steps were carried out without changing the basic concept of the laboratory procedure and without major problems.

Figure 23. The Sandmeyer ceremony. From left to right: The catalysis team B. Pugin, H.-U. Blaser, H. P. Jalett, F. Spindler, H. P. Buser, the development and engineering team H. D. Schneider, K. Coers, A. Wegmann, R. Hanreich, E. Jelsch; H. L. Senti, President of the New Swiss Chemical Society.

Work-up, separation of the catalyst from the product. Three separation methods of product from the Ir-catalyst were evaluated: distillation, extraction and filtration. For the last two options the preparation of new modified extractable or immobilized xyliphos ligands was necessary. But as pointed out above, lower activity and selectivity of these xyliphos derivatives and the additional development work that would have been required led to the decision to stay with the already well-optimized soluble xyliphos system. After the hydrogenation step, a continuous aqueous extraction is performed to neutralize and eliminate the acid from the crude product. After flash distillation to remove residual water the catalyst is separated from (*S*)-NAA in a subsequent distillation on a thin film evaporator. From the organic distillation residue, iridium can be recovered whereas the chiral ligand is lost.

The design and construction of the production plant. Due to time constraints, this was started very early and partially in parallel to the later stages of process development. Luckily, no major changes occurred and the first production batch was run on 16 November 1996 with overwhelming success: about 10 t of NAA with an ee of 79% were produced using about 34 g of Ir complex, ca. 70 g of xyliphos ligand and some acid and iodide; reaction time was 2 hours and conversion 99.6%.

10 The Last Culmination Point: The Sandmeyer Prize 1999 of the New Swiss Chemical Society

The accomplishments of the metolachlor team were recognized by the New Swiss Chemical Society with the prestigious Sandmeyer Prize 1999 for achievements in the field of industrial chemistry. A paper in Chimia[28] also resulted from the price.

On March 23, 1999 we met a last time, first for the reception of the prize during the spring session of the NSCS as depicted in

Figure 23 and then for a dinner with our partners in the renowned restaurant Schützenhaus to celebrate the occasion. A very fitting ending of a fascinating story.

Some final comments on project management and the importance of long-term projects

The new metolachlor process is at the moment the largest scale application of an enantioselective catalytic process and the Ir-xyliphos catalyst is the most active and productive complex ever developed. There is no doubt that this achievement has laid to rest any doubts about the applicability of chiral homogeneous catalysts for large-scale processes for relatively low cost products. My account focused more on the strategies, approaches, contributions and decisions of the various players during the different phases of the project and not so much on the details of the chemistry, because those aspects have already been covered before. Projects of this magnitude obviously need good scientists and technicians but this is not sufficient. Good results can only be achieved when the technical team and the various management functions collaborate very well. There is no doubt that this was the case during all phases of the search for a suitable catalysts, when transferring the process to the divisional development and when designing and building the production plant.

A major role was played by the divisional project champions responsible for the metolachlor project. As pointed out above, catalysis in Ciba-Geigy was in the central R&D department while the development, production and sale of actual products was the responsibility of the operational division. This meant that the Agro division had to pay for the R&D work directly related to one of their products and the fun stops when a lot of money is involved. This was especially the case in the last phases during 1992 – 1993, when John Dingwall and Gerardo Ramos played this role. It was extremely important for the moral of the research teams that these two supported the work even during those phases when progress was slow and when it seemed almost impossible to reach the ambitious goals. Obviously, success defends itself but for quite some time it was by no means clear whether it was really justified to spend more money (and very much at that) for an approach that already had failed twice. John and Gerardo always backed us and left us the freedom to do what we thought best. I am very glad that their trust was rewarded so well.

A few remarks concerning my own role which changed significantly in the course of time. To describe this in sports terms: It changed from player to playing trainer to coach. In the later phases I was much more concerned with setting the overall strategy, to chose the right people for the various research teams and see that not everybody tried to run with the ball(s) at the same time. No project of this size is without tensions between the players or between project owners and researchers and it was my responsibility to recognize these and try to find solutions. The final success is certainly due to a terrific scientific team and very good management but there is no denying that luck also played a significant role.

Finally, a comment on the synergy between research and process development projects. In my account I have described how the focus of our efforts oscillated between the long-term research project on imine hydrogenation and ligand synthesis and the development of the metolachlor process. When it happened, this change in focus was by no means voluntary but due to the needs of the agro division. However, in hindsight I have to admit that our success would probably not have been possible without this switching back and forth between the two approaches with their very different requirements. The research phases allowed us to follow high-risk ideas and their long-term nature also gave us the necessary time to develop mature systems with technical potential. On the other hand, during the phases when we worked on the metolachlor project, we had the man-power to apply these concepts and results in a very concentrated fashion to the task at hand.

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Obviously, the success in finding and implementing a technically feasible process for the commercial production of (S)-metolachlor is due to many persons. In my account, I have tried to give a fair description of their contributions and their achievements and I would like to thank all of them for their commitment to the project. In addition, I would like to acknowledge the technicians who did most of the practical work for their invaluable contributions: B. Eng, Y. Fazis, M. Fischer, E. Gissinger, R. Häusel, M. Jörg, H. Landert, M. Luginbühl, M. Marro, S. Maurer, Th. Moser, U. Pittelkow, M. Parak, F. Riner, M. Rippstein, P. Ritter, A. Schwendemann, B. Soder, G. Thoma and N. Vostenka all did a great job.

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