CHIMIA 1999, 53, No. 6

Chimia 53 (1999) 275–280

ISSN 0009-4293

The Chiral Switch of Metolachlor: The Development of a Large-Scale Enantioselective Catalytic Process

Hans-Ulrich Blaser*, Hans-Peter Buser, Klaus Coers, Reinhard Hanreich, Hans-Peter Jalett, Eric Jelsch, Benoît Pugin, Hans-Dieter Schneider, Felix Spindler, and Arthur Wegmann

Sandmeyer Prize 1999 of the NSCS

Abstract. The development of an enantioselective catalytic process for the technical preparation of chiral agrochemicals is illustrated by the case history of the herbicide (*S*)-metolachlor (trade name *Dual Magnum*®). Four synthetic routes were investigated in some detail. The key step for the technical process of the enantiomerically enriched compound is the asymmetric hydrogenation of an imine intermediate made possible by a new iridium ferrocenyl diphosphine catalyst system. Using optimized conditions, the isolated imine can be hydrogenated at a hydrogen pressure of 80 bar and 50 °C with a substrate-to-catalyst ratio of >1'000'000. Complete conversion is reached within 4 h with an enantioselectivity of 79% with an initial turnover frequency (tof) exceeding 1'800'000 h^{-1}. This sets a new standard for the technical application of enantioselective catalysts. Important aspects and results for the different phases of the process development of the catalyst system as well as minimal prerequisites for the use of enantioselective catalysts for the production of agrochemicals are discussed.

1. Introduction and Problem Statement

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_{Ar}–N axis) and a stereogenic center, leading to four possible stereoisomers (*Fig. 1*). *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-ethyl-5-methylaniline (MEA) with aqueous methoxyacetone in the presence of traces of sulfuric acid followed by chloroacetylation (see *Scheme 1*) [1]. Already in 1982, it was found that about 95% of the herbicidal activity of metolachlor resides in the two (1'*S*)-diastereomers [2]. In 1997, after years of intensive research [3], *Dual*

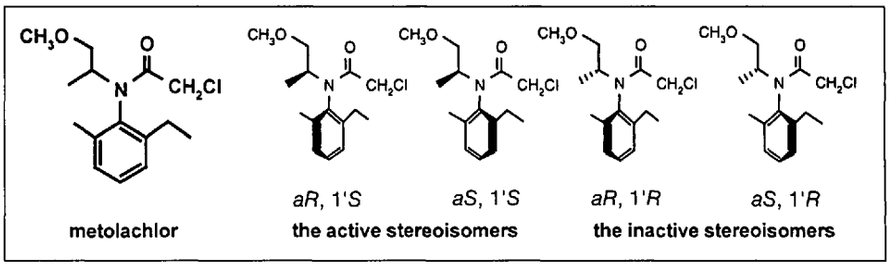
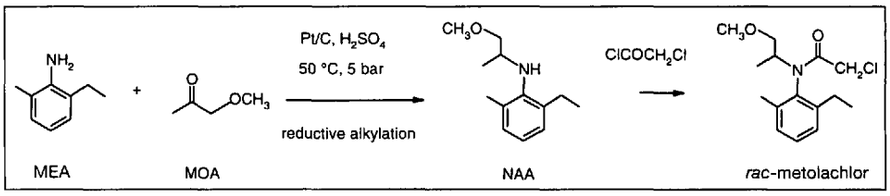


Fig. 1. *Structure of metolachlor and its individual stereoisomers*

Scheme 1. *The Process for the Industrial Production of Racemic Metolachlor*



Magnum® with a content of approximately 90% (1'*S*)-diastereomers and with the same biological effect at about 65% of the use rate of *Dual*® was introduced in the USA. To make this 'chiral switch' possible, a new technical process had to be found for the economical production of the enantiomerically enriched precursor of metolachlor. This account describes what problems were encountered and how these were solved in the course of the development work.

2. Route Selection

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 (>10000 t/y) of the racemic product, only a catalytic route would be feasible. The following four synthetic routes were studied in some detail.

*Correspondence: Dr. H.-U. Blaser
Novartis Crop Protection and *Novartis Services AG*
R-1055.6
CH-4002 Basel
E-Mail: hans-ulrich.blaser@sn.novartis.com

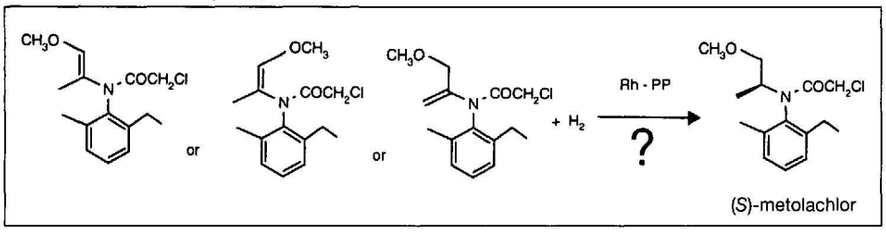
2.1. *Enamide Hydrogenation*

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 of one of the three possible enamide isomers depicted in *Scheme 2* looked difficult.

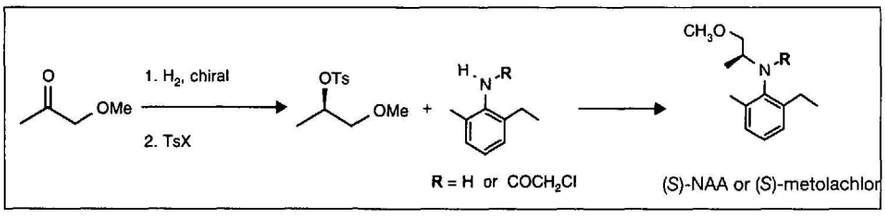
2.2. *Nucleophilic Substitution of an (R)-Methoxyisopropanol Derivative*

Here, the key step was the enantioselective hydrogenation of methoxyacetone (*Scheme 3*), in analogy to the Pt/cinchona-catalyzed hydrogenation of α-ketoesters [5] (the Ru/binap system was not yet known at that time). The nucleophilic substitution with clean inversion was expected to be difficult.

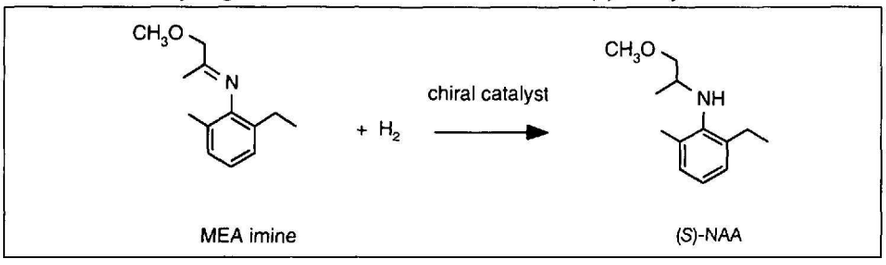
Scheme 2. *Enamide Hydrogenation: Structures of Tested Enamides*



Scheme 3. Enantioselective Hydrogenation of Methoxyacetone and Nucleophilic Substitution with a MEA Derivative



Scheme 4. *Imine Hydrogenation: Structures of MEA Imine and (S)-N-alkylated Aniline*



Scheme 5. *Alkylation of MEA with Methoxyisopropanol*

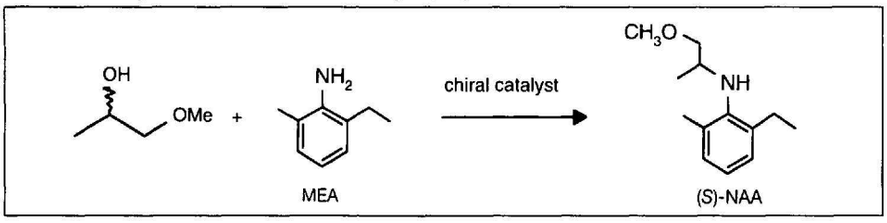


Table 1. *Comparison of Possible Routes for the Synthesis of (S)-metolachlor*

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 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

2.3. *Hydrogenation of MEA Imine*

Because the racemic metolachlor is produced *via* a reductive alkylation, it was obvious to try to hydrogenate the MEA imine intermediate (*Scheme 4*), either isolated or formed *in situ*. Unfortunately, at that time only one single imine hydrogenation was described in the literature with an *ee* of only 22% [6].

2.4. *Catalytic Alkylation with Racemic Methoxyisopropanol (Scheme 5)*

This idea was based on an alternative process developed for the racemic product with heterogeneous catalysts in the gas phase [7] and some results of the *N*-alkylation of aliphatic amines with primary alcohols using homogeneous Ru phosphine catalysts [8].

2.5. *Assessment and Screening of Proposed Routes*

For assessing the potential synthetic routes the following criteria were considered to be important:

- chances of success for the catalytic step according to precedents, *i.e.* closely related, efficient catalytic transformations
- number and perceived difficulty of the non-catalytic steps
- first approximations for costs and ecology of the overall synthesis
- In *Table 1*, the four proposed routes are classified according to these criteria. The overall ranking was used for setting priorities to carry out experimental work. Because the enantioselective catalysis is usually considered to be the most difficult step, its chances of success very often dominate the decision and accordingly, the enamide and the substitution route were tested first.

Enamide Route. The preparation of the three MEA enamides proved to be rather difficult. Disappointingly, we did not succeed to hydrogenate any of the three isomers using seven different Rh-diphosphine complexes at normal pressure and temperatures up to 50°.

Substitution Route. The hydrogenation of methoxyacetone was somewhat more successful: Using a Pt/C catalyst modified with cinchonidine as described by *Orito et al.* [5], (*R*)-methoxyisopropanol was obtained in good yields, but *ee*s were never higher than 12%.

Direct alkylation was not tested experimentally, because chances for success were considered to be too low.

Conclusion. The results of the route screening left the hydrogenation of the MEA imine as the only realistic possibility.

3. Imine Hydrogenation: Laboratory Process

3.1. *Finding the Right Metal/Ligand Combination*

The history of the development of a technically feasible catalyst for the enantioselective hydrogenation of MEA imine has been described [3]. Collaborations were very important, initially with a research team of the University of British Columbia at Vancouver, and later with the group of *J.A. Osborn* of the University of Strasbourg.

Screening of Rh Diphosphine Complexes

First positive results were obtained by trying to adapt Rh diphosphine catalysts originally developed for the hydrogenation of olefins. An extensive ligand screening led to $[Rh(nbd)Cl]_2$/cycphos (for ligand structures, see *Fig. 2)* as the best catalyst: 69% *ee* were achieved at –25°, the best turnover frequency (tof) being 15 h^{-1} at 65 bar and room temperature, far too low for any industrial application [9]. Nevertheless, these results represented a rMEArkable progress for the enantioselective hydrogenation of *N*-aryl imines.

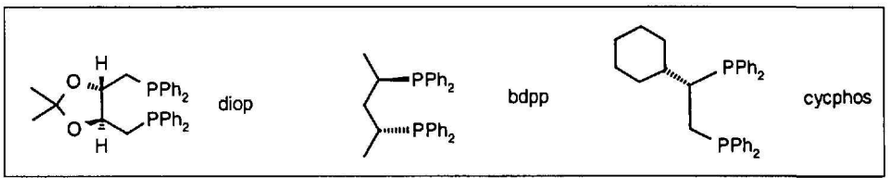


Fig. 2. Imine hydrogenation: Structure of important ligands

Scheme 6. *Preparation and Structure of Ferrocenyl Diphosphine Ligands*

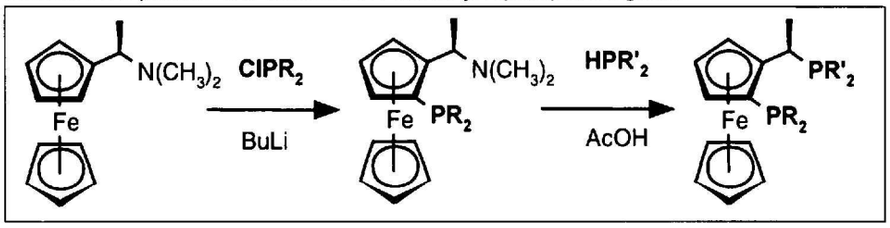


Table 2. *MEA Imine Hydrogenation with Selected Ir-ferrocenyldiphosphine Complexes* (Formulas, see *Scheme 6*)

R	R'	ton	tof (h^{-1})	*ee*	comments
Ph	3,5-xylyl	1'000'000	>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

Screening of Ir Diphosphine Complexes

The next breakthrough was obtained when iridium was used instead of rhodium. This idea was inspired by results of *Crabtree* who had described an extraordinarily active Ir/tricyclohexylphosphine/pyridine catalyst that was able to hydrogenate even tetrasubstituted C=C bonds. For the MEA imine hydrogenation very good *ee*s were obtained with an Ir-bdpp catalyst in presence of iodide ions (84% *ee* at 0°) but the activity was disappointing. Turnover numbers (ton) up to 10000 and tofs of 250 h^{-1} (100 bar and 25°) but somewhat lower *ee*s were obtained with Ir-diop-iodide catalysts [10][11]. A major problem of the new Ir diphosphine catalysts was an irreversible catalyst deactivation.

These results, especially the good enantioselectivities, were very promising and represented by far the best catalyst performance for the enantioselective hydrogenation of imines at that time. Nevertheless, it was also clear that the ambitious goals could probably not be reached using Ir complexes with 'classical' diphosphine ligands. Even though Ir/diop and Ir/bdpp catalysts showed much higher activities than the best Rh complexes for MEA imine, they were still far below the requirements: A new approach was clearly required.

Synthesis and Screening of a New Ligand Class

As a consequence, new ligand types were tested, among others novel ferrocenyldiphosphines (PPF) developed by *Togni* and *Spindler* [12]. Their mode of preparation (see *Scheme 6*) allows an efficient fine-tuning of the electronic and steric properties of the two phosphino groups, something that is often difficult with other ligand classes. Indeed, the Ir complexes of such diphosphines proved to be very efficient. Especially PPF-P(3,5-$(CH_3)_2C_6H_3)_2$ (R = Ph, R' = 3,5-xylyl), named xyliphos, turned out to give an exceptionally active catalyst and, even more important, it did not deactivate!

3.2. *Optimization of Reaction Medium and Conditions*

Using xyliphos as ligand, a screening of solvents and additives, as well as an optimization of the reaction conditions were carried out. Most remarkable was the effect observed when 30% of acetic acid were added to the reaction mixture of MEA imine and Ir-xyliphos-Bu_4NI: a rate increase by a factor of 5 was observed while the time for 100% conversion was more than 20 times shorter than without additives. The effect of pressure and temperature was investigated in presence of acid and iodide. The reaction rate was approximately proportional to the hydrogen pressure and also increased with temperature, *ee*s decreased from 81% at –10° to 76% at 60° but were not affected by changing the hydrogen pressure.

3.3. *Ligand Fine Tuning*

As described above, the Ir-xyliphos catalytic showed extremely high catalysts activities and productivities. On the other hand, the enantioselectivity to the desired (*S*)-enantiomer just barely met the requirements. Therefore, we tried to improve the *ee*s by tuning of the electronic and steric properties of the new ferrocenyl ligands. As shown in *Table* 2, it was indeed possible to increase the selectivity of the catalyst, however, as observed before with other ligands, any gain in selectivity was always set off by a loss in catalyst activity and often productivity. In the end, xyliphos was the best compromise regarding activity and selectivity for a technical process.

4. Imine Hydrogenation: Technical Process

Once a catalyst system with the required performance was found and confirmed, the attention turned to finding a technically feasible overall process. The

technical preparation of methoxyacetone and 2-ethyl-6-methylaniline as well as the chloroacetylation step were already established in the existing process for racemic metolachlor.

4.1. *Strategy for Process Development*

For the production of enriched (*S*)-NAA, the reductive alkylation step in the original process had to be replaced by a condensation reaction, followed by isolation and purification of the imine and a subsequent homogeneous asymmetric hydrogenation at high pressure (80 bar and 50°). As outlined above, a catalyst system was developed that was able to fulfill the minimal requirements to make a process commercially feasible: s/c >100000, reaction time < 8 h for >99% conversion and enantioselectivity ≥ 80%. The selected catalyst system was a mixture of four components: A dimeric iridium-cyclooctadiene complex $[Ir(COD)Cl]_2$, the xyliphos ligand, tetrabutyl ammonium iodide as iodide source, and acetic acid as the preferred acid at this stage. Because of the limited time available for the development of a definitive process, it was decided to change as few parameters as possible and to focus development activities on the following topics: purity requirements of starting materials, catalyst formulation, ligand synthesis, work-up procedure, separation of catalyst, and reactor design.

4.2. *The Production of the MEA Imine in the Required Quality*

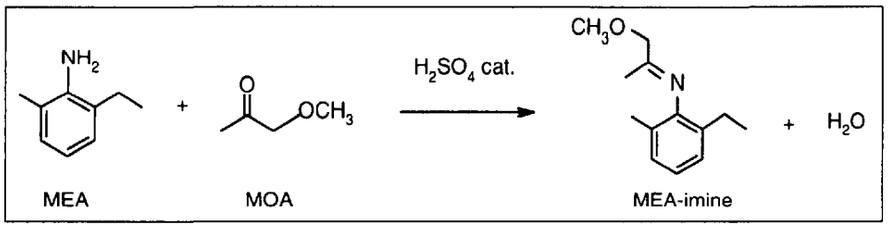
Surprisingly, the seemingly simple condensation of MEA with methoxy acetone (*Scheme 7*) turned out to be quite tricky: significant side-product formation was observed when trying to push the conversion of the reaction to 100%. When different MEA-imine qualities were tested, reproducibility of the results was very poor. Sometimes, some crude samples gave surprisingly good results when hydrogenated, while distillation not always led to an improvement of catalyst activity. In the end, it was concluded that depending on the composition of the side-product spectrum and as a result of the thermal instability of the imine and its sensitivity to air and moisture, a significant catalyst deactivation could result. With a complicated multi-step continuous distillation process for the purification of MEA imine, recovery of solvent and non-reacted starting materials an excellent imine quality was provided for the subsequent enantioselective hydrogenation step.

4.3. *Scale-Up of the Ligand Synthesis*

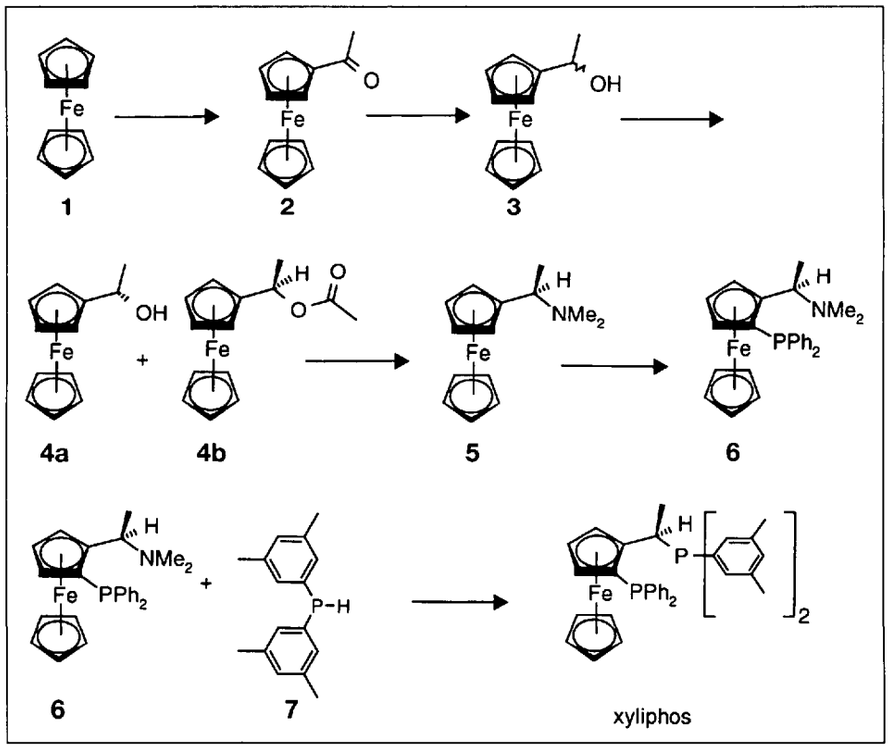
At the present stage of the application of enantioselective homogeneous catalysis, very few chiral ligands are commercially available on a kg scale or larger. This means that the development of a technical ligand synthesis must be part of the overall development process. In the case of the xyliphos ligand this meant that a 6-step synthesis (see *Scheme 8*) had to be scaled up from a laboratory process for making gram amounts to a commercial process producing hundreds of kilograms of ligand in a reproducible form and quality. Again, the starting point was the original synthesis and the experience that was gained a few years earlier for the synthesis of a similar ferrocenyldiphosphine, bppfoh, by a development team of the Pharma Division of *Ciba-Geigy* [13].

The challenge for the ligand-synthesis team was, on the one hand, to find an economical and technically feasible process giving a high quality of xyliphos, while at the same time providing xyliphos of a constant quality during all phases of the development of the MEA imine hydrogenation. The synthetic strategy was similar to one developed for the synthesis of the bppfoh ligand [13]. Acetylation of ferrocene (**1**) gave racemic acetylferrocene **2** which was reduced to the racemic alcohol **3**. This alcohol needed a careful work-up to get the appropriate quality for the subsequent enzymatic kinetic resolution *via* a lipase-catalyzed acetylation reaction [14]. For the conversion of **3** to **4b**, careful optimization of reaction temperature, quantity of enzyme, and reaction time was crucial to get the optimum selectivity. Lipases from different suppliers showed similar selectivities but had significant differences in activity. During work-up, special care had to be taken because of the thermal instability of **4b**. The enriched dimethylamino compound **5** was obtained by reacting a mixture of **4a** and **4b** with dimethylamine whereby the acetate group was replaced with retention of configuration. Compound **5** was converted to the intermediate **6** by reaction with butyllith-

Scheme 7. *Condensation of MOA with MEA*



Scheme 8. *The Technical 6-Step Synthesis of Xyliphos*



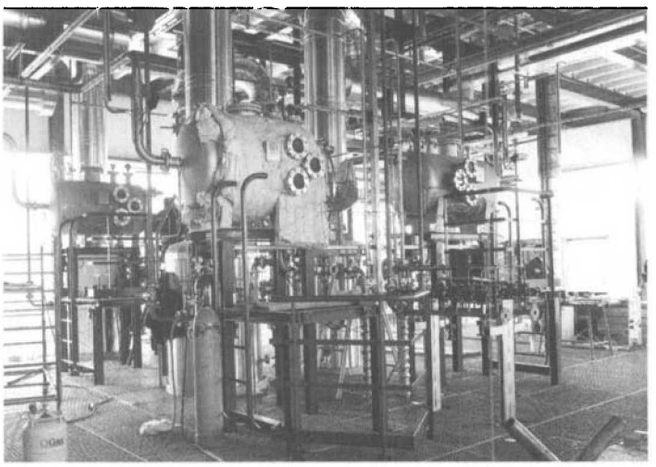


Fig. 3. *The two water separators for the removal of water during the condensation reaction*

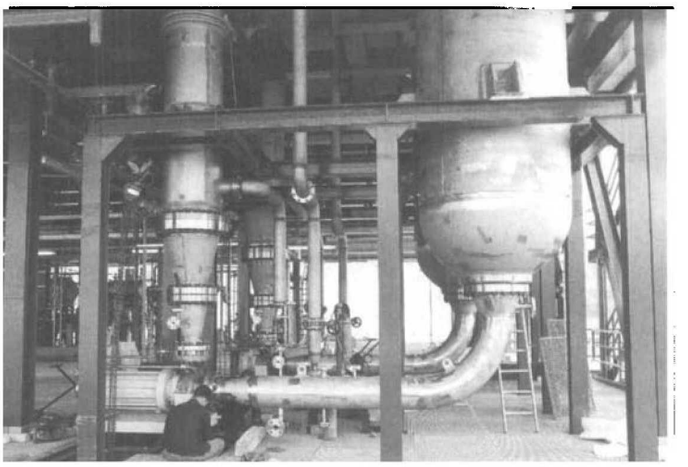


Fig. 4. *Close up of the loop reactor: On the left-hand side heat exchanger and pump, on the right the bottom part of the hold-up tank*

ium and chloro(diphenyl)phosphine. After crystallization of **6**, *ee*s of > 99.5% were obtained. Reaction of **6** with bis(3,5-dimethylphenyl)phosphine **7**, which is now commercially available, gave the final product xyliphos in high purity.

This synthesis was carried out in reactors up to 2'500 liters and is feasible for the preparation of xyliphos in quantities of hundreds of kilograms. 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.

4.4. *Optimization of Ir-Catalyst Formulation*

The use of a solid multi-component catalyst mixture was challenging especially because catalyst addition to a high pressure autoclave is usually time-consuming and increases the cycle time of the process. An advantage of the solid catalyst used at the beginning was the slow release of the catalyst activity due to the low dissolution rate of the components, and as a consequence, it was easy to control the exothermicity of the hydrogenation reaction. However, in cases of incomplete conversion, *e.g.*, because of catalyst deactivation, new catalyst had to be added, and this was difficult with a solid catalyst. Therefore, our attention was focused on the development of a liquid catalyst formulation, that would allow an easy addition to the reaction vessel whenever necessary. Many attempts to work with catalyst solutions failed due to the instability of the dissolved catalyst – only freshly prepared solutions could be used. In the end, a liquid, highly active catalyst formulation was developed which was stable over several months. Now it was possible 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.

4.5. *Choice of Reactor Technology*

Laboratory experiments had shown that the enantioselectivity in the hydrogenation of the MEA imine was mainly influenced by the temperature whereas hydrogen pressure had a significant effect only on the reaction rate. In the pilot trials it was confirmed that rate and selectivity of the reaction reach their optimum at 50° and 80 bar. Since under these conditions more than 70% of the reaction takes place within the first hour, control of reaction temperature could only be achieved using large external heat exchangers. For optimal mass and heat transfer, a loop reactor (see *Fig. 4*) 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.

4.6. *Scale-Up to the Production Autoclave*

The scale-up factor of the reaction from laboratory to production was >10000. Laboratory experiments for screening and optimization were run in 50 ml up to 1 liter high-pressure autoclaves. Due to the small amount of catalyst necessary and the high sensitivity of the hydrogenation to impurities in starting materials, reproducibility of experimental results was a critical factor and a big challenge for the experimental skills of the technicians. For the design of the new production unit, valuable experience was gained during the pilot trials. In some cases, results obtained in the pilot plant were much better than those from the laboratory; the discovery of the high-performing liquid catalyst system would have been very unlikely without these trials. Under optimized conditions, it was possible to significantly reduce the catalyst amount to a s/c ratio of 2'000'000. The new, ready-to-use catalyst solution proved its outstanding performance and pushed enantioselective hydrogenation into new dimensions. During these investigations, use of on-line NIR and polarimetry was very helpful for monitoring conversion and selectivity of the enantioselective reaction.

4.7. *Work-Up: Separation of the Catalyst from the Product*

The following three methods for the separation 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. However, 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 (see *Fig. 5*). From the organic distillation residue, iridium can be recovered whereas the chiral ligand is lost.

5. Summary and Conclusions

Table 3 gives an overview on the time table and the milestones for the development of a technical process for the produc-

Fig. 5. *Thin-film evaporator*

Fig. 6. *View of the production building* (imine preparation, hydrogenation, distillation). The small building in the foreground houses the hydrogen compressors.

tion of enriched (*S*)-metolachlor. It took so many years to reach the ambitious goal because the efforts to find a suitable catalyst system for the enantioselective imine hydrogenation basically had to start almost at point zero. The final 'result' of our efforts can be seen in *Fig. 6* which shows a partial view of the production building.

The case of (*S*)-metolachlor allows some generalized conclusions:

- The chiral switch from the racemate to an enriched form is attractive not only for pharmaceuticals but also for agrochemicals, and enantioselective hydrogenation is an especially suitable and commercially feasible technology to allow this.
- The activity of the catalyst, and not so much its enantioselectivity, was the major problem to be solved, and an appreciable amount of patience and intuition of the chemists involved as well as some luck were necessary to reach the challenging goal.
- The selection of the catalytic system was especially difficult because the required catalyst-performance goal was very ambitious and very little was known on enantioselective imine hydrogenation.

Table 3. *Milestones in the History of (S)-metolachlor*

1970	Discovery of the biological activity of *rac*-metolachlor (patent for product and synthesis)
1978	Full-scale plant for the production of *rac*-metolachlor in operation (capacity >10000 t/y)
1982	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)
1986	Discovery of new Iridium diphosphine catalysts that are more active and selective than Rh catalysts for the hydrogenation of MEA imine
1993	Ir/ferrocenyl diphosphine catalysts and acid effect are discovered. Process development starts.
1993/4	Patents for *rac*-metolachlor expire
1995/6	Pilot results for (*S*)-metolachlor: *ee* 79%, ton 1000000, tof >200000/h, first 300 t produced
1996	Full-scale plant for production of >10000 t/y (*S*)-metolachlor starts operation

We would like to thank *R. Bader, B. Böhner, J. Dingwall, H.J. Fäh, G.M. Ramos*, and *F. Weibel* for their encouragement and support during the various phases of this project, *P. Flatt, E. Schmidt*, and *A. Togni* for valuable advice and discussions, and *B. Eng, Y. Fazis, M. Fischer, E. Gissinger, R. Häusel, M. Jörg, H. Landert, M. Luginbühl, M. Marro, S. Maurer, T. Moser, U. Pittelkow, M. Parak, F. Riner, M. Rippstein, P. Ritter, A. Schwendemann, B. Soder, G. Thoma*, and *N. Vostenka* for their very careful experimental work.

Received: May 4, 1999

[1] R.R Bader, H.U. Blaser, *Stud. Surf. Sci. Catal.* **1997**, *108*, 17. R.R Bader P. Flatt, P. Radimerski, EP 605363-A1 (*Ciba-Geigy AG*, **1992**).
[2] H. Moser, G. Ryhs, H.P. Sauter, *Z. Naturforsch.* **1982**, *37b*, 451.
[3] For a case history of the discovery of the new catalyst system, see F. Spindler, B. Pugin, H.P. Jalett, H.P. Buser, U. Pittelkow, H.U. Blaser, *Chem. Ind. (Dekker)*, **1996**, *68*, 153.
[4] D. Vineyard, W. Knowles M. Sabacky, G. Bachmann, D. Weinkauf, *J. Am. Chem. Soc.* **1977**, *99*, 5946.
[5] Y. Orito, S. Ima, S. Niwa, *Bull. Chem. Soc. Jpn.* **1979**, 1118; **1980**, 670; and **1982**, 137.
[6] A. Levi, G. Modena, G. Scorrano, *J. Chem. Soc., Chem. Commun.* **1975**, 6.
[7] M. Rusek, *Stud. Surf. Sci. Catal.* **1991**, *59*, 359.
[8] Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi, T. Ohta, *J. Org. Chem.* **1984**, *49*, 3359, and references cited therein.
[9] W.R. Cullen, M.D. Fryzuk, B.R. James, J.P. Kutney, G-J. Kang, G. Herb, I.S. Thorburn, R. Spogliarich, *J. Mol. Catal.* **1990**, *62*, 243.
[10] Y. Ng Cheong Chan, J.A. Osborn, *J. Am. Chem. Soc.* **1990**, *112*, 9400.
[11] F. Spindler, B. Pugin, H.U. Blaser, *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558.
[12] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Amer. Chem. Soc.* **1994**, *116*, 4062.
[13] H.U. Blaser, R. Gamboni, G. Sedelmeier, B. Schaub, E. Schmidt, B. Schmitz, F. Spindler, Hj. Wetter, in 'Approaches to Pharmaceutical Process Development', Ed. K.G. Gadamasetti, 1999, p. 189.
[14] A. Wickli, E. Schmidt, J.R. Bourne, in 'Biocatalysis in Non-Conventional Media', Eds. J. Tramper, M. Vermüe, H. Beeftink, U. von Stockar, Elsevier, Amsterdam, 1992, p. 577.