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[28] F.N.M. Kühnle, Dissertation, ETH No. 11782, ETH-Zürich, 1996.

[29] B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 6117.

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[32] F. Toda, *Acc. Chem. Res.* **1995**, *28*, 480; F. Toda, H. Miyamoto, S. Kikuchi, R. Kuroda, F. Nagami, *J. Am. Chem. Soc.* **1996**, *118*, 11315, and ref. cit. therein.

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1. Introduction

Metolachlor is at the present time the most important herbicide of *Novartis*. It is produced since 1978 in volumes of > 20000 t per year and is sold under the trade name *DUAL MAGNUM*®. Starting in 1997, an enantiomerically enriched form will replace the racemic mixture, leading to a reduction of the environmental load by *ca.* 40%. The case history that is presented here might not be prototypical for an agrochemical. Nevertheless, it is an impressive example demonstrating the importance of enantioselective catalysis to the fine chemicals industry. Second, it illustrates that the development of a new catalytic system can sometimes take many years (see the *Table*).

**Correspondence*: Dr. H.-U. Blaser
Novartis Services AG
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When it became clear that the two (1*S*)-enantiomers of metolachlor were respon-

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

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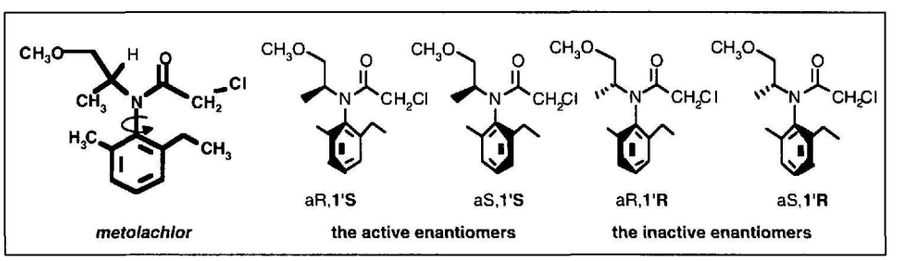

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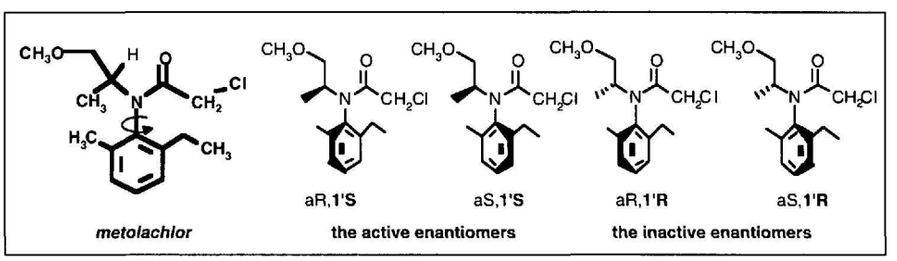

Fig. 1. *Structure and stereoisomers of metolachlor*

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sible for most of the biological activity, there was the obvious challenge of finding a chemically and economically feasible production process for the active stereoisomers. Many methods allow the enantioselective synthesis of chiral molecules (that is the preferential formation of one enantiomer instead of the usual racemate). However, the selective preparation of (*S*)-metolachlor was a formidable task, due to the very special structure and properties of this molecule and also because of the extremely efficient production process for the racemic product. During the course of the development efforts, the following minimal requirements evolved for a technically viable catalytic system: ee 80%, substrate to catalyst ratio (s/c) >50000, and turnover frequency (tof) >10000 h^{-1}.

Problem Analysis and a First Unsuccessful Approach via Enamide Hydrogenation

A careful analysis in 1982 led to the conclusion that only two approaches had some probability of success: First, the hydrogenation of an enamide precursor of metolachlor (*Fig. 2*) in analogy to the L-dopa process of *Monsanto* [3], and second, and more attractive from a practical point of view, the enantioselective hydrogenation of the imine intermediate that was produced *in situ* in the racemic reaction. However, enantioselective imine hydrogenation at that time was virtually unknown [4]. Accordingly, in 1982/3, we started to prepare all three isomers of the metolachlor-enamide shown in *Scheme 1*. This was by no means easy and to our huge disappointment none of the catalysts described in the literature was active for the hydrogenation of either isomer. Therefore, the feasibility study was terminated.

The First Successes: Imine Hydrogenation with Rh- and Ir-Diphosphine Complexes

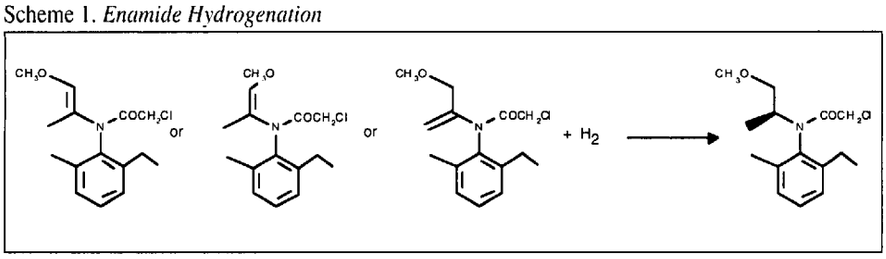
The next attempt at solving our problem was carried out in collaboration with a team at the University of British Columbia (UBC) who investigated the hydrogenation of both MEA- and DMA-imine with Rh-diphosphine complexes. They were indeed successful [5]: Under ambient conditions enantioselectivities in the range of 3–50% were obtained. The best optical yields of 69% ee were achieved using $[Rh(nbd)Cl]_2$/cycphos at –25° (for ligand structures see *Scheme 2*). The best activities were observed in methanol/toluene but the maximum tof was only 15 h^{-1} at 65 bar and r.t., far too low for an industrial application. Nevertheless, these results represented a remarkable progress for the enantioselective hydrogenation of *N*-aryl imines.

Based on these results, we realized that the **catalyst activity** would be the critical issue. Therefore, *F. Spindler*, who was responsible for the project, was very much attracted by the results of *Crabtree et al.* who described an extraordinarily active Ir/tricyclohexylphosphine/pyridine catalyst that was able to hydrogenate even tetrasubstituted C=C bonds [6]. He decided to give Ir catalysts a try even though he was aware of their fast deactivation and also of the very low activities of Ir-diphosphine catalysts for the hydrogenation of enamides described by *Brown* and coworkers [7]. The very first experiments with an *in situ* formed $[Ir(cod)Cl]_2$/diop catalyst were quite encouraging and an extensive screening of then available diphosphines, solvents, additives as well as an optimization of the reaction conditions was carried out. Here, we only summarize the best results [8], a more detailed report can be found in [9].

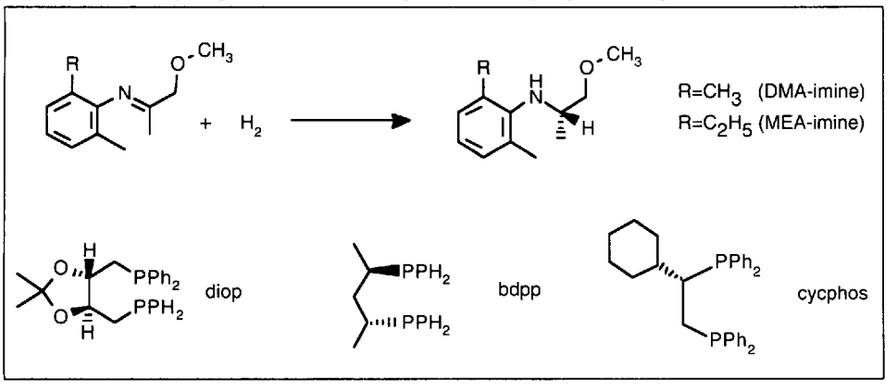
The highest optical yields were obtained with Ir-bdpp catalysts in presence of additional iodide (ee 84% at 0°) but the activity was disappointing. Better activities but with somewhat lower ee's were obtained for Ir-diop catalysts: Eventually, maximum turnover numbers of 10000 and higher, with an average tof of 250 h^{-1} could be achieved at 100 bar and 25°. When s/c ratios >10000 were applied, the reaction did no longer go to completion. A major problem of these 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 we could probably not reach our ambitious goals 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.

Scheme 1. *Enamide Hydrogenation*



Scheme 2. *Imine Hydrogenation: Structure of Imines and of Important Ligands*



3. A New Ligand Class Leads to a Production Process

Since we could not get stable catalysts with the known diphosphine ligands, we started to test new types. Among others, we screened novel ferrocenyl-diphosphines ($R_2PFPR'_2$) developed recently by *Togni* and *Spindler* [10]. Their mode of preparation (*Scheme 3*) allowed an efficient fine tuning of the electronic and steric properties of the two phosphino groups, something that is often very difficult with other ligand classes. When they were tested in the hydrogenation of MEA-imine, there was a pleasant surprise: While the *in situ* catalyst derived from $[Ir(cod)Cl]_2$ and the rather basic josiphos (R = Ph, R' = cyclohexyl) was not very active, the anal-

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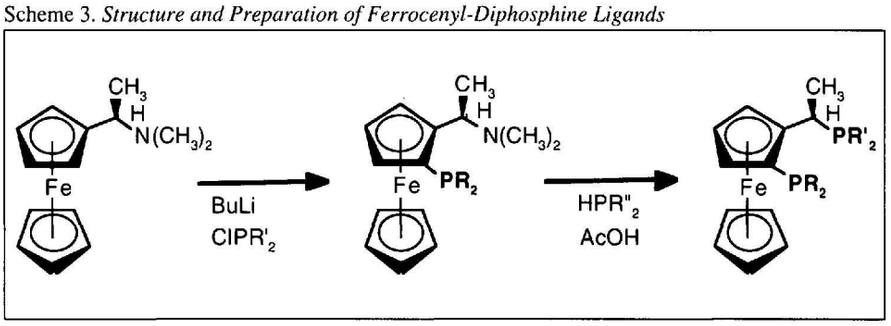
ogous catalysts with two diarylphosphino groups (R, R' = Ar) gave very promising results. Especially PPF-P(3,5-$(CH_3)_2$-$C_6H_3)_2$ (R = Ph, R' = 3,5-xylyl) turned out to give an exceptionally active catalyst and, even more important, it did not deactivate!

In collaboration with *H.P. Jalett* and *H.P. Buser*, *Spindler* again carried out an extensive screening of diphosphines, solvents, additives as well as an optimization of the reaction conditions. Most remarkable was the effect observed when 30% of acetic acid were added to the reaction mixture resulting in a rate increase by a factor of five, while the time for 100% conversion was more than 20 times shorter than without additives. Using optimized conditions, the isolated imine was hydrogenated at a hydrogen pressure of 80 bar and 50° using an s/c ratio of 750000. Complete conversion was reached within four h. The initial tof exceeded 1 800000 h^{-1} and optical yields were 80%. 1 000000 turnovers were achieved within six h. These results set a new standard for the enantioselective hydrogenation of imines (see *Fig. 2*). One molecule of the Ir catalyst can produce more than 500000 molecules of (*S*)-*N*-(2-ethyl-6-methylphen-1-yl)-1-(methoxymethyl)ethylamin within two to three hours. The selectivity to the desired (*S*)-enantiomer is not extremely high but fulfills the requirement for the production of enantiomerically enriched metolachlor. The technical handling of the organometallic catalyst precursor is rather easy, scale-up presented no problems, and at the moment, the production plant is being completed.

Scheme 3. *Structure and Preparation of Ferrocenyl-Diphosphine Ligands*



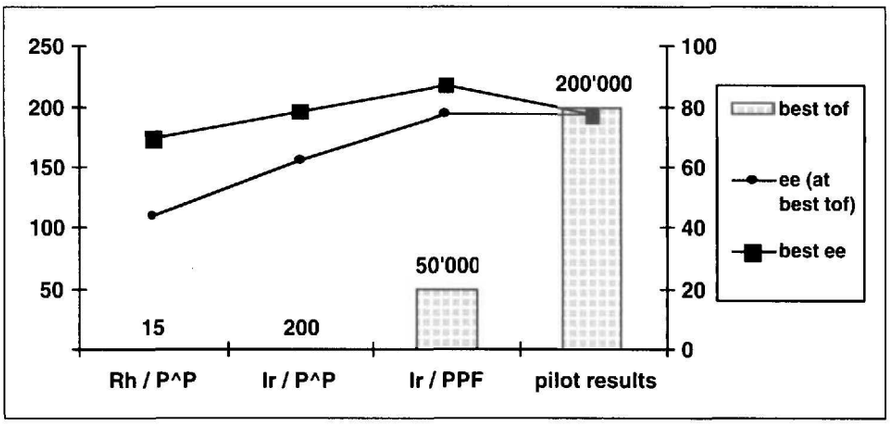


Fig. 2. *Milestones of progress for the enantioselective hydrogenation of MEA-imine* (requirements: ee 80%, tof > 10000 h^{-1}, s/c > 50000)

4. Conclusions

The case history of this large-volume chiral herbicide demonstrates that:

- Imine hydrogenation is a very powerful synthetic method to produce sterically hindered *N*-alkyl-anilines both chemo- and enantioselectively. The choice of the catalytic system is unusually important for getting the necessary high catalyst activities and selectivities.
- A chiral switch from the racemate to an enriched form is not only attractive for pharmaceuticals [11] but is also an important strategy for agrochemicals [12].
- The time for process development depends very much on the state of the art of a given catalytic technology. It was quite short for the reductive alkylation, a well-known method already in 1972, whereas it took more than 10 years to develop a suitable catalyst for the enantioselective imine hydrogenation.
- An empirical approach is the fastest way to find or develop a catalytic system for a problem that has no close precedent. Mechanistic information is especially helpful in later stages of process development or for trouble-shooting.

The results described in this case history are due to the efforts of several teams of very dedicated chemists, engineers, and technicians, and we would like to acknowledge the contributions of *H.P. Buser*, *R. Hanreich*, *H.P. Jalett*, *U. Pittelkow*, *B. Pugin*, *H.-D. Schneider*, *A. Togni*, *A. Wirth-Tijani*, *B. Eng*, *R. Häusel*, *S. Maurer*, *M. Parak*, *G. Thoma*, and *N. Vostenka*. We also thank *Rolf Bader*, *Beat Böhner*, *John Dingwall*, and *Gerardo Ramos* for their continuous encouragement and support during the course of this project.

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[1] C. Vogel, R. Aebi, DP 23 28 340 (*Ciba-Geigy AG*), 1972.
[2] H. Moser, G. Ryhs, H. Sauter, *Z. Naturforsch.* **1982**, *37b*, 451.
[3] D. Vineyard, W. Knowles, M. Sabacky, G. Bachmann, D. Weinkauf, *J. Am. Chem. Soc.* **1977**, *99*, 5946.
[4] For recent overviews on enantioselective imine hydrogenations, see H.-U. Blaser, F. Spindler, *Chim. Oggi* **1995**, June, 11; H.-U. Blaser, F. Spindler, 'Proceedings of Chiral Europe '94 Symposium', Spring Innovations, Stockport, UK, 1994, p. 69.
[5] W.R. Cullen, M.D. Fryzuk, B.R. James, G. Kang, J.P. Kutney, R. Spogliarich, I.S. Thorburn, US Pat. 4,996,361 (*Ciba-Geigy AG*), 1987; 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.
[6] R. Crabtree, H. Felkin, T. Fellebeen-Khan, G. Morris, *J. Organomet. Chem.* **1979**, *168*, 183.
[7] N. Alcock, J.M. Brown, A. Derome, A. Lucy, *J. Chem. Soc., Chem. Commun.* **1985**, 575.
[8] F. Spindler and B. Pugin, EP Pat. 0256982 (*Ciba-Geigy AG*), 1988; F. Spindler, B. Pugin, H.-U. Blaser, *Angew. Chem. Int. Ed.* **1990**, *29*, 558.
[9] F. Spindler, B. Pugin, H.P. Jalett, H.P. Buser, U. Pittelkow, H.-U. Blaser, in 'Catalysis of Organic Reactions', R.E. Malz, Ed., Marcel Dekker Inc., New York, 1996, p.153.
[10] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4061.
[11] S.C. Stinson, *C&EN* **1995**, October 9, 45.
[12] G. M. Ramos Tombo, D. Bellus, *Angew. Chem.* **1991**, *103*, 1219; H.P. Fischer, H.-P. Buser, P. Chemla, P. Huxley, W. Lutz, S. Mirza, G.M. Ramos Tombo, G. Van Lommen, V. Sipido, *Bull. Soc. Chim. Belg.* **1994**, *103*, 565.