Hans-Ulrich Blaser, Felix Spindler
Solvias AG - Basel (Switzerland).
hans-ulrich.blaser@solvias.com

DEVELOPING INDUSTRIAL PROCESSES FOR CHIRAL INTERMEDIATES

Strategies for the development of catalytic enantioselective processes for the manufacture of chiral intermediates are presented. After a general introduction, three specific examples from the catalysis group of Ciba-Geigy/Novartis/Solvias are discussed in some details.

The biological properties of chiral biologically active compounds are often strongly related to the absolute configuration (1). As a consequence, the technical synthesis of pure or enriched enantiomers is of growing importance in the modern life science industry. All general methods for the introduction of chirality are applied: separation of stereoisomers, the use of chiral building blocks, enzymatic and microbial transformations and asymmetric synthesis. A very promising technology for efficient asymmetric syntheses is the application of chiral organometallic complexes as catalysts. In this contribution, the development of industrially feasible stereoselective syntheses for three chiral compounds used in crop protection are discussed: (S)-metolachlor (2), (R)-metalaxyl (3) and (αS,3R)-clozylacon (4) (see Figure1). In all three cases, the depicted stereoisomer(s) are responsible for most of the biological activity. The main focus of this contribution will be on the approaches chosen for the various phases of the development process and on the problems related to the application of chiral catalysts and on the strategies used to find economical as well as ecological solutions.

Development strategies

The choice of a development strategy that promises the best answer in the shortest time is the first decision at the start of a process development. This strategy will depend on a number of considerations: the goal of the development, the know how of the investigators, the time frame, the available manpower and equipment, and so on. In process development, there is usually a hierarchy of goals (or criteria) to be met. It is simply not possible to reach all the requirements for a technically useful process in one step. Usually, the catalyst selectivity (combined of course with an acceptable activity) is the first criterion - just as in academic research. But when a reasonable selectivity has been obtained, other criteria will become important: catalyst activity, productivity and stability, catalyst separation (and maybe recycling).

Then, questions like e.g., the effect of substrate quality and last but not least the cost of the chiral catalyst and other materials have to be addressed. The final process is usually a compromise since quite often not all of these requirements can be fulfilled maximally. As already pointed out, it is not always possible to proceed in a linear fashion, i.e., very often one has to go back to an earlier phase and sometimes additional question turn up that have to be answered before it is possible to go on. It is useful to divide the development of a manufacturing process into different phases:

- Phase 1: Outlining and assessing possible synthetic routes on paper;
- Phase 2: Demonstrating the chemical feasibility of the key step, usually the enantioselective catalytic reaction;
- Phase 3: Optimizing the key catalytic reaction;
- Phase 4: Optimizing the over-all process.

In the following paragraphs, short case studies are given for the work carried out during the different phases of development for (S)-metolachlor, (R)-metalaxyl and (αS,3R)-clozylacon.

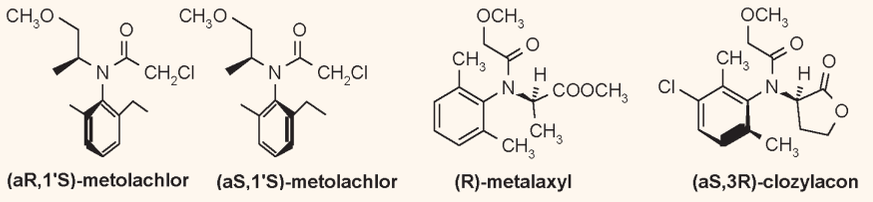


Figure 1 - Structures of the active stereoisomers of metolachlor, metalaxyl and clozylacon

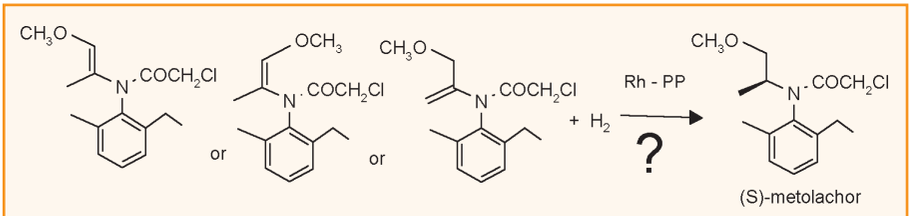


Figure 2 - Enamide hydrogenation: structures of tested enamides

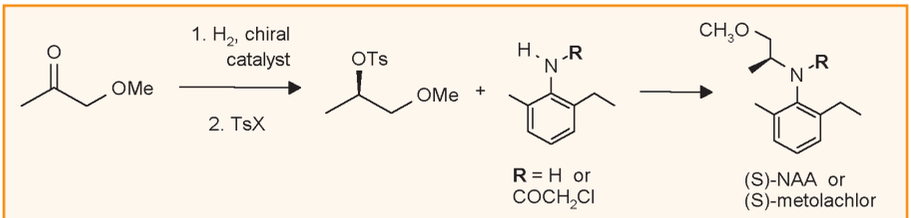


Figure 3 - Enantioselective hydrogenation of methoxyacetone and nucleophilic substitution with a MEA derivative

Phase 1: Outlining and assessing synthetic routes

This is of course the fundamental task of the development chemist and here is not the occasion to dwell on this subject. Sufficient to say that the goal is to find the most economical and ecological technical synthesis in the time frame dictated by the development schedule. When applying asymmetric catalysis, the overall synthesis is usually designed around the enantioselective catalytic transformations. The reason for this is that only a limited number of effective catalytic enantioselective transformations are available. In addition, it is quite difficult to transfer the results obtained for a particular substrate to even a close analogue due to the high substrate specificity (low tolerance for structure variation even within a class of substrates).

When assessing proposed routes with enantioselective catalytic steps the following criteria are important:

- chances of success for the key steps 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 over-all synthesis.

Routes to (S)-metolachlor

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 (>10,000 t/y) of the racemic product, only a catalytic route would be feasible. The following four synthetic routes were studied in some detail.

Enamide hydrogenation (Figure 2) - This idea clearly was inspired by the successful L-dopa process of Monsanto (5). 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 enamides looked difficult.

Nucleophilic substitution of a (R)-methoxyisopropanol derivative (Figure 3) - Here, the key step was the enantioselective hydrogenation of methoxyacetone in analogy to the Pt-cinchona catalyzed hydrogenation of α-ketoesters (6) (the Ru-binap system was not yet known at that time). The nucleophilic substitution with clean inversion was expected to be difficult.

Hydrogenation of MEA imine (Figure 4) - 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*. Unfortunately, at that time only one single imine hydrogenation was described in the literature with an enantiomeric excess (ee) of only 22% (7).

Direct catalytic alkylation with racemic methoxyisopropanol (Figure 5) - This idea was based on an alternative process developed for the racemic product with heterogeneous catalysts in

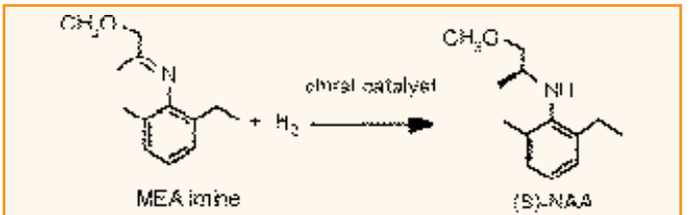


Figure 4 - Imine hydrogenation: structures of MEA imine and (S)-N-alkylated aniline

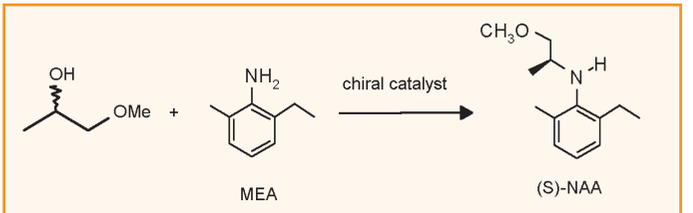


Figure 5 - Direct alkylation of MEA with methoxyisopropanol

the gas phase (8) and some results of the N-alkylation of aliphatic amines with primary alcohols using homogeneous Ru-phosphine catalysts (9).

Assessment of the four routes - In Table 1 the four proposed routes are classified according to these criteria. The over-all ranking was used for setting priorities to carry out practical 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 (see below).

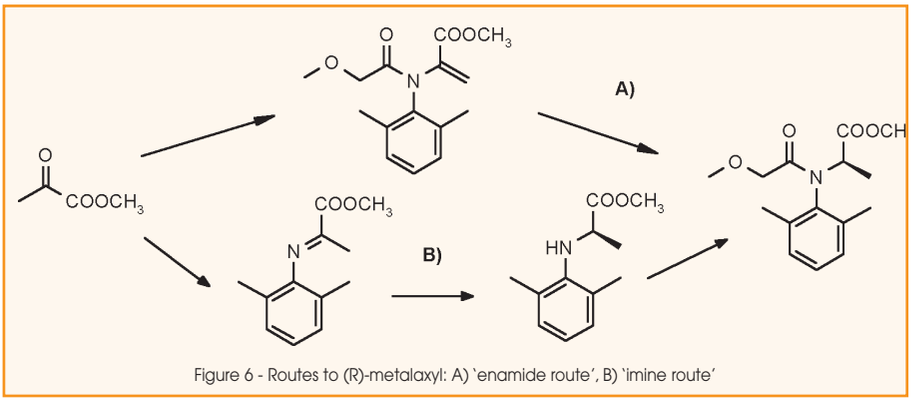


Figure 6 - Routes to (R)-metalaxyl: A) 'enamide route', B) 'imine route'

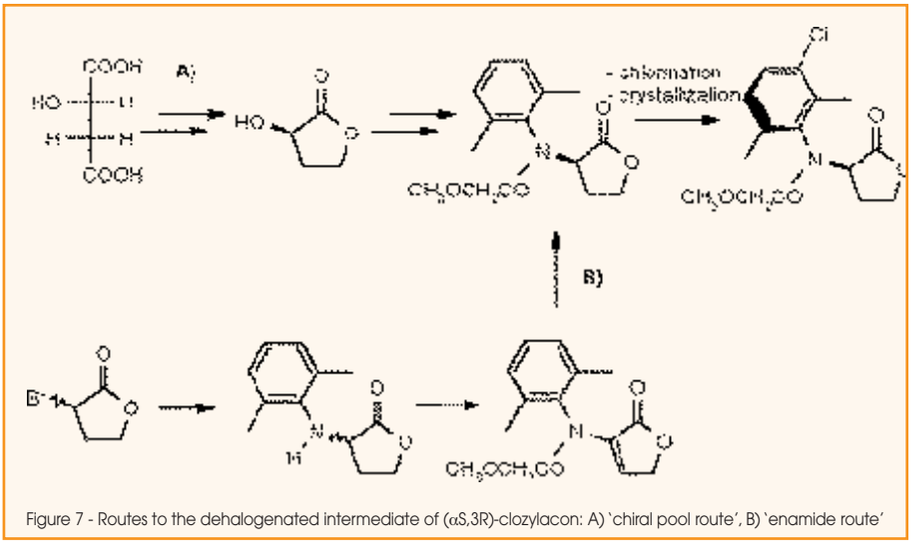


Figure 7 - Routes to the dehalogenated intermediate of (αS,3R)-clozylacon: A) 'chiral pool route', B) 'enamide route'

(R)-Metalaxyl (3)

Because of the success of the hydrogenation methodology for the synthesis of (S)-metolachlor and (αS,3R)-clozylacon (see below), two possibilities for introducing the stereogenic center were considered (see Figure 6): namely the hydrogenation of the corresponding enamide and imine, respectively.

(αS,3R)-Clozylacon (4)

Because a procedure for the final chlorination step followed by a separation of the two diastereomeric atropisomers was already established, the target was to find routes to the dehalogenated (3R)-precursor (see Figure 7). Due to the time pressure, only two synthetic routes with high probability of success were evaluated. The first started with L-malic acid from the chiral pool.

The second had as key step again an enamide hydrogenation, despite the fact that no precedence existed for cyclic, N-aryl substituted enamide substrate.

Nevertheless, the chances for success in this asymmetric hydrogenation were rated as medium to high.

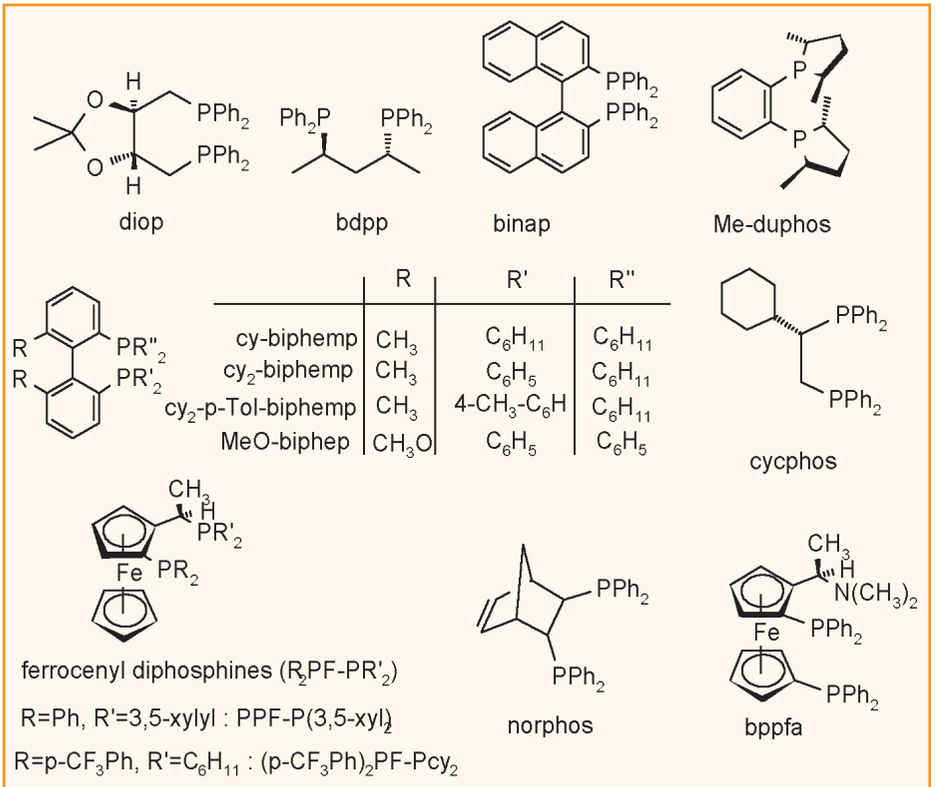
In addition, the amide precursor had already been used for making racemic clozylacon.

Phase 2: Demonstrating the chemical feasibility of the key (catalytic) step

Once possible routes have been designed, the critical step(s), of course most of the time the catalytic step, must be tested experimentally. Here the major question is whether it is possible to find a chiral catalyst and the right reaction conditions to catalyze the desired transformation with satisfactory efficiency. As a general rule, the *parameters of the catalytic system* will be chosen first (metal, support or ligands, chiral auxiliary, solvent and maybe some additive). Naturally, the first choice will rely on experience and on analogies in the literature. Depending on the results of this preliminary phase, one has to decide whether to find better catalysts by screening alternative structures or by optimizing the most promising catalytic system by small changes of the catalyst and the chiral auxiliary.

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



	R	R'	R''
cy-biphemp	CH_3	C_6H_{11}	C_6H_{11}
cy_2-biphemp	CH_3	C_6H_5	C_6H_{11}
cy_2-p-Tol-biphemp	CH_3	4-CH_3-C_6H	C_6H_{11}
MeO-biphep	CH_3O	C_6H_5	C_6H_5

Figure 8 - Imine hydrogenation: structure of important ligands

The following critical factors determine the technical feasibility of an enantioselective process (10):

- the *enantioselectivity* of a catalyst should be >99% for pharmaceuticals when further purification is not possible. Ee's >80% are often acceptable for agrochemicals or if further enrichment is easy (via recrystallization or at a later stage via diastereomer separation);
- the *catalyst productivity*, given as turnover number (ton) or as substrate/catalyst ratio (s/c), determines catalyst costs. Ton's ought to be >1,000 for high value products and >50,000 for large scale or less expensive products (catalyst re-use increases the productivity);
- the *catalyst activity* (turnover frequency, tof, h^{-1}), affects the production capacity. Tof's ought to be >500 h^{-1} for small and >10,000 h^{-1} for large scale products.

(S)-Metolachlor

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 °C.

Substitution route - The hydrogenation of methoxyacetone was somewhat more successful: Using a Pt/C catalyst modified with cinchonidine as described by Orito *et al.* (6), (R)-methoxyisopropanol was obtained in good yields, but ee's were never higher than 12%. The *direct alkylation* was not tested experimentally, because chances for success were considered to be too low.

Imine hydrogenation - The results of the route screening left the hydrogenation of the MEA imine as the only realistic possibility. This proved to be a very difficult task and took many years because at that time, the enantioselective catalytic hydrogenation of imines was virtually unknown. A detailed account on the development of a technically feasible catalyst for the enantioselective hydrogenation of MEA imine has appeared (2). Very important were collaborations, initially with a research team of the University of British Columbia at Vancouver (UBC) and later with the group of J.A. Osborn of the University of Strasbourg.

Screening of Rh diphosphine complexes - First positive results were obtained at UBC 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 (ligand structures see Figure 8) as the best catalyst: 69% *ee* were achieved at –25 °C, the best turnover frequency (tof) was 15 h^{-1} at 65 bar and room temperature, far too low for any industrial application (11). Nevertheless, these results represented a remarkable progress for the enantioselective hydrogenation of N-aryl imines.

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 tetra-substituted C=C bonds. For the MEA imine hydrogenation very good ee's were obtained with an Ir-bdpp catalyst in presence of iodide ions (ee 84% at 0 °C) but the activity

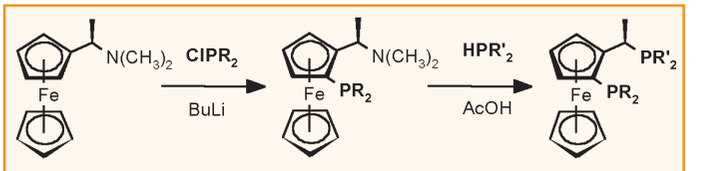


Figure 9 - Preparation and structure of ferrocenyldiphosphine ligands

was disappointing. Ton's up to 10,000 and tof's of 250 h^{-1} (100 bar and 25 °C) but somewhat lower *ee*'s were obtained with Ir-diop-iodide catalysts (12, 13). 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 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 (14). Their mode of preparation (see Figure 9) 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!

Table 2 - Selected screening results for the Rh-diphosphine catalyzed hydrogenation of the metalaxyl enamide precursor

Entry	Ligand	Ton	Tof (h^{-1})	Ee (%)
1	(R,R)-Me-duphos	1,000	4,600	98 (R)
2	(S)-MeO-biphep	1,000	55	97 (R)
3 [a)]	(S)-binap	100	6	97 (R)
4	(S)-cy-biphemp	1,000	333	97 (R)
5	(S)-cy_2-biphemp	1,000	4,000	99 (R)
6	(S)-cy_2-p-Tol-biphemp	1,000	4,000	99 (R)
7 [a)]	(2S,3S)-norphos	90	330	94 (R)
8 [a,b)]	(R)-(S)-bppfa	100	10	93 (S)
9 [a,c)]	(R)-(S)-(p-$CF_3Ph)_2$PF-Pcy_2	100	<10	91 (R)

Reaction conditions: catalysts prepared in situ from $(Rh(nbd)_2)BF_4$ and the ligand; s/c: 1,000 ([a)] 100); $p(H_2)$: 10 bar ([b)] 40 bar); T: 25°C ([c)] 40 °C)

Table 3 - Selected screening results for the clozylacon enamide hydrogenation

Entry	Ligand	Ton	Tof (h^{-1})	Ee (%)
1	Rh^+/(4S,5S)-diop	50	100	85
2	Rh^+/(2S,4S)-bdpp	50	2	75
3	Rh^+/(S)-binap	50	3	33
4 [b,c)]	$Ru(OAc)_2$(S)-binap	4000	93	66

a) Rh^+: $(Rh(nbd)_2)BF_4$. Reaction conditions: $p(H_2)$: 33 bar (b) 100 bar; T: 25 °C (c) 50 °C; Absolute configuration of product: (S)

(R)-Metalaxyl (3)

Both the 'imine route' and the 'enamide route' (see Figure 6) were tested experimentally. The following targets were set: enantiomeric purity ≥95% ee; ton ≥50,000; H_2-pressure ≤10 bar.

A) Imine route - The route via enantioselective hydrogenation of imine turned out to be not feasible. Only insufficient optical purities (≤30% ee) and catalyst activities (tof ≤5 h^{-1} at s/c 100) were achieved with Ir catalysts generated *in situ* from $(Ir(COD)Cl)_2$, a chiral diphosphine and iodide - the catalytic system that worked so well for the MEA-imine hydrogenation. Therefore, work on the imine route was stopped.

B) Enamide route - For the enantioselective hydrogenation of enamide, 34 chiral Rh diphosphine catalysts were tested in an extensive screening program. 12 of these complexes produced enantiomeric excesses >90% ee; representative results of these experiments are summarized in Table 2. Regarding activity as well as enantioselectivity, the best ligands were diphosphines with either a duphos or a biphemp framework and at least one basic phosphine group. The activity of the Rh/(R,R)-Me-duphos, Rh/(S)-cy_2-biphemp and Rh/(S)-cy_2-p-Tol-biphemp catalysts was very promising: tof's in the range of 4,000-4,600 h^{-1} (see Table 2).

(αS,3R)-Clozylacon (4)

Here, we only describe the hydrogenation results because the 'chiral pool route' turned out to be unsuitable. In contrast to the failure for the hydrogenation of the metolachlor enamides, promising preliminary results for the asymmetric hydrogenation of clozylacon enamide were obtained and an extensive parameter screening with various Rh- and Ru-catalysts was carried out (results see Table 3). Of all the Rh diphosphine catalysts tested, the catalysts prepared *in situ* from $(Rh(nbd)_2)BF_4$ and diop or bdpp afforded the highest enantioselectivities (30-85% ee and 75% ee, respectively). However, catalyst activities were low and in many cases irreproducible due to catalyst poisoning.

Slightly lower optical yields (66% ee at 100 bar, 50 °C) but no indication of a catalyst deactivation were observed with the precursor $(Ru(OAc)_2$(S)-binap). The optical yields were not affected by temperature and pressure in the ranges of 22-50 °C and 4-100 bar H_2, respectively. Preliminary scale up experiments showed that 4,000 turnovers could be achieved but the activity was relatively low (tof 93 h^{-1}). Enantiomerically pure intermediate could be obtained in 63% chemical yield by a single crystallization of the crude reaction product. At this stage, the project was stopped because undesired biological side-effects of (αS,3R)-clozylacon were observed in field tests. Despite the fact, that the results were

Table 4 - MEA imine hydrogenation with Ir-ferrocenyldiphosphine complexes: ligand fine tuning

R	R'	Ton	Tof (h^{-1})	Ee (%)	Comments
Ph	3,5-xylyl	>1,000,000	>600,000	79	production process
p-$CF_3C_6H_4$	3,5-xylyl	800	400	82	ligand screening
Ph	4-^{t}Bu-C_6H_4	5,000	80	87	low temperature
Ph	4-(^{n}Pr)$_2$N-3,5-xyl	100,000	28,000	83	optimized conditions

not (yet) technically useable, these results represented the first successful enantioselective hydrogenation of a cyclic, N-aryl substituted enamide. It is not unreasonable to believe that further organization of the Ru-binap system would eventually have led to a technically feasible process.

Technical feasibility and optimization of the catalytic system

When a preliminary choice of the catalytic system has been made, the reaction conditions (H_2 pressure, temperature and concentrations and ratios of reactants, catalyst and auxiliary) are optimized. The most important criteria in this phase are chemoselectivity and enantioselectivity, catalyst productivity and activity, sensitivity of the catalytic system to the quality of reagents and the synthetic fit of the catalytic step into the complete manufacturing process. If the minimal requirements are not reached, one has to go back to finding a more suitable catalyst/auxiliary. Then, the optimization has to be repeated. This means that very often, the development of a technical process does not proceed linearly.

(S)-Metolachlor (2, 14)

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-NBu_4I: we observed a rate increase by a factor of 5 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, ee's decreased from 81% at -10 °C to 76% at 60 °C. 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 (s/c) of 1,000,000. Complete conversion is reached within 4 h with an enantioselectivity of 79% and an initial tof exceeding 1,800,000 h^{-1} (21). These results set a new standard concerning catalyst activity and productivity for a homogeneous enantioselective hydrogenation.

Ligand fine tuning - As described above, the Ir-xyliphos catalysts showed extremely high catalysts activities and productivities. On the other hand, the enantioselectivity to the desired S-enantiomer just barely met the requirement. 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 4, the enantioselectivity of the catalyst was indeed improved (21). However, as observed before with other ligands, an increase in selectivity was always offset by a loss in activity and often productivity. In the end, xyliphos was the best compromise regarding activity and selectivity for a technical process.

Strategy for the development of the over-all process - Once a catalyst system with the required performance was found and confirmed, the attention turned to finding a feasible overall process. The technical preparation of methoxyacetone and 2-methyl-6-ethyl-aniline as well as the chloroacetylation step were already established in the existing process for racemic metolachlor. 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 °C). As outlined above, a catalyst system was developed that was able to fulfill the minimal requirements to make a process commercially feasible: s/c >100,000, 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, reactor design.

The production of the MEA imine in the required quality - Surprisingly, the seemingly simple condensation of MEA with methoxy acetone (Figure 9) 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. 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.

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 over-all development process.
In the case of the xyliphos ligand this meant that starting from ferrocene, a 6-step synthesis 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. In addition, the synthesis team had to provide xyliphos of a constant quality during all phases of the development of the MEA imine hydrogenation. This synthesis was optimized and is now carried out in reactors up to 2,500 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.

Fine 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 slows down 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 that 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.

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 °C and 80 bar. Because 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 was therefore the best choice. In this technology, the reaction mixture is

Sviluppo di processi industriali per la produzione di intermedi chirali

RIASSUNTO

Vengono presentate una serie di strategie per lo sviluppo di processi enantioselettivi nella manifattura di intermedi chirali. Dopo un'introduzione generale vengono discussi in dettaglio tre esempi specifici sviluppati dal gruppo di catalisi di Ciba-Geigy/Novartis/Solvias.

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 - The scale-up factor of the reaction from laboratory to production was >10,000. 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 molar 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.

Work-up, separation of the catalyst from the product - The following 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 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.

(R)-Metalaxyl (3)

Also for this case, some further efforts were carried out in order to improve the catalyst productivity. The effect of the H_2-pressure and the temperature on the enantioselectivity between 1-60 bar and 20-60 °C was strongly dependent on the nature of the ligand. It was negligible with (R,R)-Me-duphos but very pronounced when ferrocenyl ligands of the type (R)-(S)-R_2PF-PR'$_2$ were used. Optimization and scale up experiments with the catalyst (Rh(*nbd*)$_2$)BF_4/(R,R)-Me-duphos improved the turnover number to 50,000 at 10 bar H_2 and 60 °C. The enantioselectivity (95.6% ee) and the tof (5,200 h^{-1}) were above the specified minimum limits. In conclusion, the enamide hydrogenation is in principle feasible for a production process for highly enriched (R)-metalaxyl.

Conclusions and outlook

We have illustrated with three examples how enantioselective catalysis can be applied for the efficient synthesis of chiral intermediates for agrochemicals. These case histories allow 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 choice of the over-all route and the of the most promising enantioselective catalytic reaction requires a broad experience and success is still not easy to predict.
- Quite often, the activity of the catalyst and not so much its enantioselectivity is the major problem to be solved and an appreciable amount of patience and intuition of the chemists involved as well as some luck are necessary to reach the goal.
- Especially for the (S)-metolachlor the selection and development of the catalytic system took a very long time, first because the required catalyst performance was very ambitious and secondly because very little was known on enantioselective imine hydrogenation.

References

(1) For periodical updates on chiral pharmaceuticals see S.C. Stinson in *C&EN*: 1999, November 22, 57; 2001, May 14, 45. For agrochemicals see G.M. Ramos Tombo, H.U. Blaser, in Pesticide Chemistry and Bioscience, G.T. Brooks, T.R. Roberts (Eds.), Royal Society of Chemistry, Cambridge, 1999, p. 33 and references cited therein.

(2) For a more detailed case history see F. Spindlerm *et al., Chem. Ind. (Dekker),* 1996, **68,** 153; H.U. Blaser, *Adv. Synth. Catal.,* 2002, **344,** 17.

(3) F. Spindler, Th. Früh in Chirality in Agrochemicals, N. Kurihara, J. Miyamoto (Eds.), Wiley, New York, 1998, p. 141.

(4) H.P. Buser *et al., Tetrahedron,* 1991, **47,** 5709, and references therein.

(5) D. Vineyard *et al., J. Am. Chem. Soc.,* 1977, **99,** 5946.

(6) Y. Orito *et al., J. Chem. Soc. Jpn.,* 1979, 1118; 1980, 670 and 1982, 137.

(7) A. Levi *et al., Chem. Commun.,* 1975, 6.

(8) M. Rusek, *Stud. Surf. Sci. Catal.,* 1991, **59,** 359.

(9) Y. Watanabe *et al., J. Org. Chem.,* 1984, **49,** 3359 and references cited therein.

(10) H.U. Blaser *et al.,* in Applied Homogeneous Catalysis by Organometallic Complexes, B. Cornils, W.A. Herrmann (Eds.), VCH Weinheim, 1996, p. 992.

(11) W.R. Cullen *et al., J. Mol. Catal.,* 1990, **62,** 243.

(12) Y. Ng Cheong Chan, J.A. Osborn, *J. Am. Chem. Soc.,* 1990, **112,** 9400.

(13) F. Spindler *et al., Angew. Chem., Int. Ed.,* 1990, **29,** 558.

(14) H.U. Blaser *et al., Chimia,* 1999, **53,** 275.