doi:10.2533/chimia.2008.476 CHIMIA **2008**, *62*, No. 6

Chimia 62 (2008) 476–481

ISSN 0009–4293

Strategies for Accelerating the Development of Catalytic Enantioselective Reactions

Hans-Ulrich Blaser, Garrett Hoge*, Matthias Lotz, Ulrike Nettekoven, Anita Schnyder, and Felix Spindler

Abstract: The development of enantioselective catalytic processes for the manufacture of chiral intermediates is a very complex endeavor and can be very time consuming and expensive. In this contribution the major issues which might lead to long development times will be discussed and strategies to deal with these problems are described. The general part is illustrated with the approach Solvias has chosen for assisting and supporting the development of enantioselective homogeneous hydrogenation processes, at the moment the most important industrial application of asymmetric catalysis. Special emphasis is given to the application of high-throughput screening (HTS) using a Symyx HiP system and the description of the Solvias portfolio of chiral ligands which makes a broad variety of diphosphine ligands available for all phases of process development from the first screening experiments to the large-scale manufacturing phase. Four case histories serve to illustrate the generic description of the development process.

Keywords: Asymmetric hydrogenation · Chiral diphosphines · Enantioselective hydrogenation · Process development · Solvias ligands · Technical process

Introduction

For many applications of chiral compounds the racemic forms are no longer acceptable. Today, pharmaceuticals and vitamins, agrochemicals, flavors and fragrances but also functional materials are increasingly produced as enantiomerically pure compounds. The reason for this development is the often superior performance of the pure enantiomers and/or that regulations demand the evaluation of both enantiomers of a biologically active compound before its approval. This trend has made the economical enantioselective synthesis of chiral performance chemicals a very important topic. Among the approaches for producing enantiopure (*ee* >99%) or enantioenriched compounds enantioselective catalysis is one of the most attractive.[1] One drawback of this methodology is the more demanding process development (both in resources and in time) for a catalytic step as compared to the more classical stoichiometric reactions. For this reason it is important to continuously improve the efficiency of the development process in order to make and keep the catalytic approach competitive. In this contribution we will briefly discuss the major issues which might lead to long development times and will then describe the strategies available for improvement. In this part, special emphasis is given to the approach Solvias has chosen for assisting and supporting the development of enantioselective homogeneous hydrogenation processes, at the moment the most important industrial application of asymmetric catalysis.

For the purpose of this discussion it is useful to divide the development of a manufacturing process for a chiral intermediate or an active ingredient into different phases (it has to be stressed, however, that this is not a linear but an iterative activity!):

Phase 1: Route planning, *i.e.* outlining and assessing possible synthetic routes on paper. Here, the decision is made whether to apply catalytic steps for making the desired product (as a rule in a multi-step synthesis). Major factors which affect the time spent on this phase are the complexity of the target, technical limitations (*e.g.* high pressure equipment) and the experience and know how of the development chemist.

Phase 2: Demonstrating the chemical feasibility of the catalytic reaction (often the key step). In general, the most difficult problem is finding the right metal/ligand combination usually *via* screening. Major issues are know-how and the availability of a large variety of chiral ligands and testing equipment (including analytics).

Phase 3: Optimizing and scale-up to bench scale of the catalytic reaction (as well as the other steps) in order to show the technical feasibility (including catalyst separation, impurities *etc.*). Important is the timely availability of the selected catalyst in multi-gram amounts.

Phase 4: Further optimization and scale-up to the pilot and manufacturing scale. Decisive is again that ligand and metal precursors in up to multi kilogram quantities are at hand with very short lead times.

In our experience finding a suitable chiral catalyst in general and a chiral ligand in particular and its availability on various scales are frequently the major issue when

*Correspondence: Dr. G. Hoge
Solvias AG
P.O. Box
CH-4002 Basel
E-mail: garrett.hoge@solvias.com

Table. Activities and requirements for ligand selection

Stage of development	Activities	Performance criteria	Milestones	Ligand sourcing aspects
2 early phases of development	*screening, analytics*	*selectivity; (activity)*	*chemical feasibility*	*availability in screening amounts (ca. 100 mg)*
3 bench scale phase	*optimization, scale up, catalyst handling quality risk analysis*	*selectivity, activity, productivity*	*technical feasibility*	*Catalyst supply typically <1 kg, quality, lead times*
4 pilot and production process	*process adaptation of / to infrastructure*	*selectivity, activity, productivity, recycling/refining, metal removal*	*verification of production process*	*>kg quantities of ligand and metal precursor; lead times, quality, refining of metal*

developing an asymmetric process. This is summarized in the Table.

In Phases 2 and 3, not only the results of the catalyst tests (selectivity, activity, productivity, catalyst costs *etc*.) but the *total product costs* decide whether the catalytic route will be further developed or abandoned. In the final analysis, which synthetic variant is chosen depends on the answers to two questions:

– Can the costs for the over-all manufacturing process compete?
– Can a robust, economically feasible catalytic step be developed in the given time frame and with the given development resources?

Strategies to Meet the Needs of the Process Development Chemist

Before discussing the strategy adopted by Solvias to address the issues described above let us stress that a company involved in the development of catalytic processes has basically two possibilities: Either do it in-house or collaborate with a custom research organization (CRO) such as Solvias. Most CROs are willing to assist both in in-house development as well as to carry out process research for customers. This is not the place to discuss advantages and disadvantages of the two options, but it is clear that the optimal division of work strongly depends on the expertise and equipment of the development department. In our experience it is usually much faster to collaborate with specialists (internal or external) for the route scouting and to out-source the early phases of process development, unless there is significant internal expertise for the desired transformation.

Early Phases 1 and 2: Route Selection and Finding the Right Ligand via High-Throughput Screening (HTS)

In order to find the right ligand and catalyst, the development chemist will rely on his or her intuition, as well as personal experience and the literature. However, since many enantioselective catalysts are quite substrate-specific, analogies can prove to be fairly unreliable making both synthesis planning and ligand selection difficult. For this reason a broad ligand screening is still the approach of choice. However, it has to be pointed out that screening is most efficient when the scope and limitations of as many ligands as possible are known so that choice of ligand candidates as well as of the reaction is optimal. In addition, the ligand must be available to the development chemist *via* commercial or in-house sources otherwise it will take too much time for the experiment to be done.

To assist the development chemist in this early phase in carrying out an efficient screening, Solvias has developed a Ligand Kit with a wide variety of industrially proven chiral ligands (Fig. 1). At the moment, the kit encompasses both enantiomers of 40 different ligands and is available from Sigma-Aldrich. Additional ligands with other PR_2 moieties and therefore different steric and/or electronic properties are available from Strem and Solvias. For all families a technical synthetic route has been developed and selected ligands are being produced in multi-kilogram quantities. Investigations on scope and limitations have been published for all ligand classes and can be obtained on request from Solvias.[2–8]

In our experience, one of the most time-consuming steps is usually the search for and identification of the most effective catalyst. This is due to the fact that most chiral catalysts are rather substrate-specific. Despite the existence of a large body of experience for many substrate classes and a growing understanding of catalyst structure–activity relationships, it is still not possible to predict the optimal catalyst for a specific transformation. This means that screening of a (sometimes very large) number of different candidates is the most effective approach to find a suitable catalyst. In the following paragraphs we describe how HTS can help to accelerate process development, illustrated in some detail by the approach taken by the Solvias catalysis group.

In a recent review, Jäkel and Paciello[9] distinguish between two basically different HTS approaches: i) The preparation and screening of 'instant' ligand libraries, and ii) the screening of pre-existing ligand and catalyst libraries. In the first approach, the ligands are synthesized from scratch and tested without purification or isolation for catalytic activity. Proof of principle for this approach was provided by Nugent *et al*.[10] with the parallel synthesis of amino alcohols *via* ring opening of chiral epoxides with amines. These ligands were then applied in the Zr-catalyzed desymmetrization of epoxides with nucleophiles, albeit in a conventional manner. The same idea was implemented in an HTS format about a decade later by the de Vries group at DSM.[11] In this case, a broad variety of phosphoramidite ligands are prepared *via* the fully automated synthesis by coupling chloro-

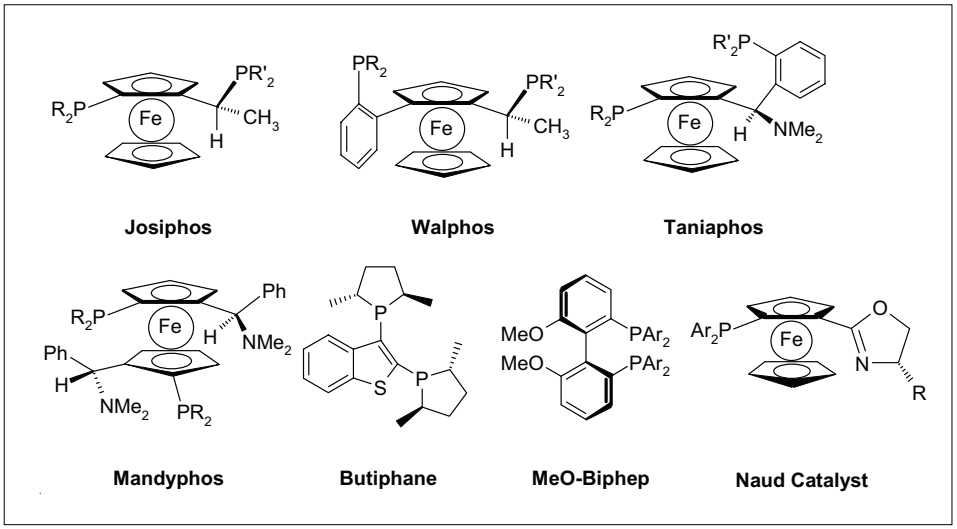


Fig. 1. 80-Member Solvias Ligand Kit

phosphites (prepared by reaction of PCl_3 with the appropriate diol) with amines in toluene, followed by filtration. The active catalysts are prepared *in situ* by mixing the ligands with an appropriate metal complex (usually $[Rh(cod)_2]BF_4$) and then tested in a HTS mode for enantioselectivity and activity in the desired hydrogenation reactions. According to de Vries, it is possible to prepare and test about 96 ligands in two days. This is a very elegant method that allows the testing of a wide structural variation of phosphoramidites. Currently, however, the approach is restricted to very few classes of ligands and it is certainly not feasible for more complex phosphines.

The second, more classical approach is the use of a pre-existing library of ligands and/or catalysts.[12] The effectiveness of this strategy depends directly on the number and structural diversity of the available ligands. At Solvias >600 chiral ligands are stored for testing, 65% of these with Solvias IP rights and 35% where the IP rights are with third parties or patent free systems. Furthermore, a large fraction of the Solvias ligands is available in technical quantities, allowing very fast further process development and scale up with successful candidates.

The actual screening is carried out using a Symyx HiP platform with 96-well plates equipped with 1 ml vials placed in the reactor block. The system allows operation of pressure reactions of up to 100 bar (Fig. 2). All ligands, catalysts and solvents are handled in a glove box to ensure inert conditions. In general, the catalysts are generated *in situ* using various metals, precursor types (neutral or cationic), counter ions, additives, solvents and reaction conditions. High-throughput analysis is carried out using the appropriate SFC, HPLC or GC method. A single software package is used for the experimental design of the plate, the dispensing robot, pressure shaker, analytics as well as reporting. Throughput is up to two plates, *i.e.* 192 reactions/day.

The following workflow was refined over the last 15 months:

1. Setup of HTS analytics (usually adapted from a regular HPLC or GC method).
2. Activity tests: 2–4 scouting experiments in single 50 ml autoclaves to define optimal pressure and temperature ranges for screening.
3. Software-assisted experimental design for the first 96 HTS experiments: Choice of ligands, metals, counter ions, additives, solvents, conditions. The reactions are carried out at a substrate to catalyst ratio (S/C) of 25 (4 mol% catalyst) in order to avoid potential catalyst poisoning by impure substrates and to deliver reproducible HTS leads.
4. HTS analysis and automated report generation.

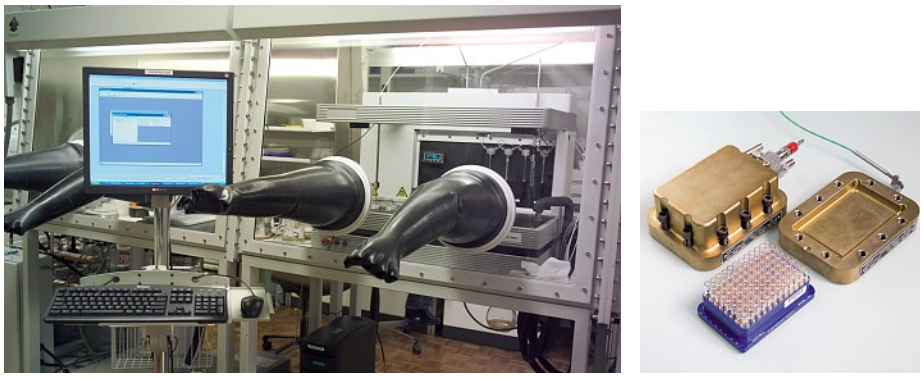


Fig. 2. Symyx HTS system: Inert glove box and 96-well plate

5. Validation: Best lead(s) are repeated at higher S/C (typically S/C 100) in single 50 ml autoclave.
6. Iterative optimization of leads in single or semi-automated autoclaves, further HTS plates to find additional leads or to investigate the experimental space around the previously obtained hits.
7. Optimization of reaction condition for the selected catalyst.
8. Scale-up to the desired size (from gram up to multi kilogram scale).

This generic scenario using the Symyx HiP technology has proved to be highly efficient and in the last two years more than 100 projects were carried out. The hit rate for finding solutions has increased from 50% to >90% since we started using the equipment. This is due to the ability to perform three times more experiments with the 96-well HiP reactor in approximately the same amount of time required to perform experimentation using more classical parallel reactors. Furthermore, the increased throughput often resulted in the discovery of multiple leads whereas in the past we would screen until a lead was found, which would then be developed further. Now we often find a variety of leads for development – the right choice often being based on the analysis of a collection of variables including catalytic turnover, chemo- and enantioselectivity, ligand price, ligand availability in bulk, and precious metal choice. As a consequence, the HTS approach described above can reduce the time required for the initial phases of the development of an asymmetric hydrogenation from up to one year to 2–4 months. Furthermore, the amount of starting material needed to investigate the feasibility of an asymmetric hydrogenation with HTS is only 2–4 grams compared to the 10–20 grams required for conventional methods. In our experience, selectivity results obtained in HTS studies are well reproducible on larger scale and in traditional autoclaves. However, there is no doubt that HTS does NOT replace conventional testing and optimization in 50–300 ml autoclaves. It is really the combination of the two approaches which lead to better processes in much shorter time. Case Histories 1–3 serve to illustrate our approach and the results obtained.

Phases 3 and 4: Scale-up to Pilot and Manufacturing

In the scale-up phase the technical feasibility of the catalytic system must be shown and questions such as catalyst handling, storability, process stability and reproducibility with technical grade solvents and starting materials but also costs and supply chain issues become important. An example how such problems can be approached is described in Case History 4. The separation and recycling/refining of the homogeneous catalyst, especially of the precious metal and the removal of trace metal impurities must be studied. In this phase, CROs can help in solving such problems due to their experience in the development of enantioselective processes and/or the availability of the necessary equipment. As an illustration, the equipment available at Solvias for carrying out catalytic reactions under pressure is depicted in Fig. 3 ranging from relatively simple 50 ml autoclaves for optimizing reaction conditions and raw material test all the way up to 50 l for producing 50 g to multi-kg quantities of product within a few weeks (examples are described in Case Histories 1–3). In cases where the nature of metal precursor, solvent or additives play an important role and as a consequence many combination must be tested, semi-quantitative results can also be obtained in the HTS mode (see Case History 3), again leading to significant time savings.

In the scale-up phase to the pilot stage multi-gram to kg amounts of ligand with defined quality will be required often with quite short lead times. Solvias guarantees to meet all these requirements for all ligands in the Solvias Ligand Kit depicted in Fig. 1.

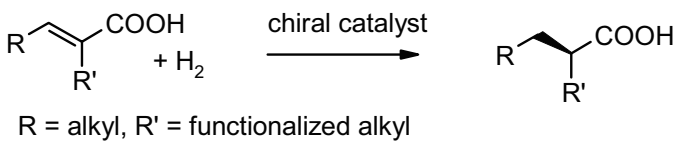
Fig. 3. Solvias scale-up facilities: 50 ml autoclaves, stirring bar (top left). Various autoclaves with hollow shaft impellers, pressure range 1–>100 bar: 100 ml to 1 l (top right), 8–16 l (bottom left) and 50 l (pressure up to 80 bar, bottom right).

In the manufacturing phase the supply of multi-kg amounts of chiral ligand on time and with the required quality must be guaranteed to ensure a reliable but also cost effective production. Solvias will deliver the ligand with an all-inclusive fixed kg price (IP and manufacturing cost incorporated in the price of the ligand or catalyst). Solvias also has experience in establishing a supply chain for large-scale ligand procurement for manufacturing purposes. These options allow to fit the ligand manufacturing into the general supply chain and manufacturing strategy for the target molecule (*i.e.* API) of interest.

Case Histories

Case History 1. Enantioselective Hydrogenation of an α,β-Disubstituted Unsaturated Acid: A Key Building Block for Several Drug Candidates (Scheme 1)

Customer goals: >95% *ee*; technically feasible solution; delivery of 3 kg product within three months.



Scheme 1.

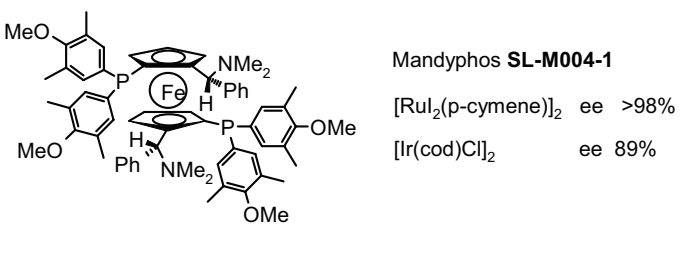


Fig. 4.

State of the art: ≤ 90% *ee* for related substrates with similar R groups using Rh-based catalysts at low to medium pressure.

Due to time restrictions and reasonable literature precedents, it was decided to restrict the first screening to Rh catalysts.

Design of 1st HTS plate: S/C 25, 1 bar H_2, MeOH, DCE, 25 °C, 3 Rh precursors (2 cationic, 1 neutral), 18 different ligands and 3 preformed chiral Rh-diphosphine catalysts, NEt_3 and DMAP as additives, 15 h reaction time.

Results: Two leads in MeOH with 90 and 92% *ee* were identified, thereby missing the target of 95%.

Decision: Expand screening to other metals and include more ligands.

Design of 2nd HTS plate: S/C 25, 10 bar, 40 °C, 2 Rh (1 cationic, 1 neutral), 1 Ir, 1 Ru precursor, 21 ligands, MeOH, THF, DCE, EtOH, 14h reaction time.

Results: Two unprecedented leads with Mandyphos **SL-M004-1** (Fig. 4) with Ru (98% *ee*) and Ir (89% *ee*) were identified. Since there was no time to further optimize the leads, the Ru-system was selected for validation.

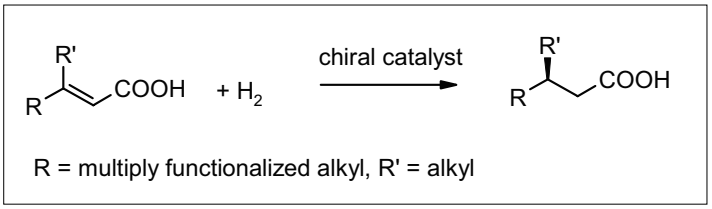
Validation of the HTS lead run with the Ru-system in a 50 ml autoclave on 0.5g scale gave 98.5% *ee* and full conversion in 10 h. After optimization and scale-up all of the customer's objectives have been met: $[RuI_2(p\text{-cymene})]_2$, **SL-M004-1**; S/C 1000; 40 °C; 10 bar, 15% w/w substrate in MeOH, 4 h cycle time, 100% conversion, 98.5 % *ee*. In a first campaign, 3 kg of product were manufactured. The total development time from start of the HTS program to the production of 3 kg was only five weeks. Subsequently, the process was transferred to the customer.

Case History 2. Enantioselective Hydrogenation of a β,β-Disubstituted Unsaturated Acid for a Pharmaceutical Target (Late Step of the cGMP Sequence) (Scheme 2)

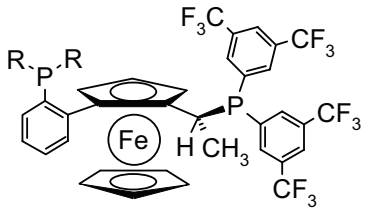
Customer goals: >98% *ee*, efficient metal removal to <5 ppm levels, no significant by-product formation; scalable and economical solution; ready for implementation on kg scale within eight weeks.

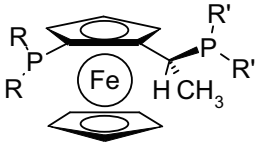
State of the art: No precedence for substrates having this specific *Z*-β-R'-substituent.

A total of 2 g were initially available for the HTS program. Scouting experiments in-



Scheme 2.





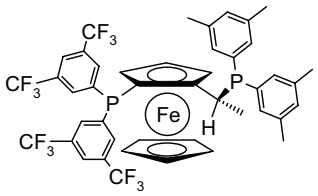
Walphos	R
SL-W001-1	Ph
SL-W005-1	4-MeOXyl

Josiphos	R	R'
SL-J002-1	Ph	*t*-Bu
SL-J504-1	Cy	2-Tol

1st HTS plate $[Rh(nbd)_2]BF_4$
SL-W001-1 91% ee
SL-J002-1 89% ee

2nd HTS plate $[Rh(nbd)_2]BF_4$
SL-W005-1 94% ee
SL-J504-1 94% ee

Fig. 5.



Josiphos **SL-J008-1**

precursor	$[Ir(cod)Cl]_2$
solvent, additive	toluene / AcOH 10 / 1, TBAI
conversion	100 %
de	98 %

Fig. 6.

dicated that higher pressure and temperature would be required to achieve reasonable conversions using Rh, Ru and Ir-based catalysts.

Design of 1st HTS plate: S/C 25, 50 bar H_2, THF, DCE, EtOH, TFE, 50 °C, 2 Rh precursors (1 cationic, 1 neutral), 1 Ir precursor, 1 Ru precursor, 13 different ligands and 4 preformed chiral Rh diphosphine complexes, no additives, 18h reaction time.

Results: Two leads with a Josiphos and Walphos ligand with 89 and 91% *ee*, respectively (Fig. 5).

Decision: Conduct 2nd plate and add more Josiphos and Walphos ligands with different steric and electronic properties.

Design of 2nd HTS plate: S/C 25, 50 bar, 25 °C, 3 Rh precursors (2 cationic, 1 neutral), 1 Ru precursor, 16 ligands, EtOH, THF, TFA as additive, 14 h reaction time.

Results: Two improved leads identified with almost identical performance at the HTS screening level of S/C 25.

Validation of both HTS leads in 50 ml autoclaves indicated that the more electron rich Josiphos-type ligand **SL-J504-1** outperformed the Walphos ligand **SL-W005-1** in activity. The optimized process using Josiphos was performed on a 100 g scale and finally transferred to the customer. Final conditions: S/C 1500, $[Rh(nbd)_2]BF_4$/**SL-J504-1**, EtOH/TFA 25:1, full conversion after 12 h with 98.8% *ee*. A simple and inexpensive charcoal treatment of the crude hydrogenation product lowered the metal contamination of the product to <1 ppm Rh.

Overall, the development time from the start of HTS screening to the transfer of the process required only six weeks. The process has subsequently been scaled to multi-kg quantities by the CMO.

Case History 3. Diastereoselective Hydrogenation of a Chiral Imine for a Building Block used in the Manufacture of a Pharmaceutical Product (Scheme 3)

Customer goals: >95% de; economical solution on scale; S/C > 5'000, pressure limitation < 25 bar; ready for implementation on >100 kg

State of the art: Feasibility of asymmetric hydrogenation of similar imines has been described, but not for the specific imine. All data published suggested that at the required low pressure a S/C of 1'000 would be the maximum achievable.

Scouting experiments with Ir / diphosphine systems indicated that conditions of 80 bar and 40 °C allowed for full conversion.

Design of 1st HTS plate: S/C 25, 80 bar H_2, toluene, DCE, EtOH, AcOH and mixtures thereof, 40 °C, 2 Ir precursors, 21 different ligands, acid and ammonium halide additives, 16 h reaction time.

Results: Only one sufficiently performing lead (**SL-J008-1** (Fig. 6)) was identified but with a very high *de* of 98%.

Decision: Continue with identified ligand and optimize reaction conditions in a second HTS plate.

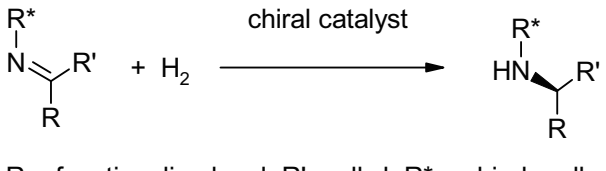
Design of 2nd HTS plate: S/C 25–10,000, 20 bar, toluene, AcOH and mixtures thereof, 25 °C, $[Ir(cod)Cl]_2$, **SL-J008-1**, TBAI (tetrabutylammonium idode), 16 h reaction time.

Results: Full conversion and 98% *de* with S/C 10,000 in toluene/AcOH = 5:1, 20 bar, 25 °C, TBAI as additive, 12%ww substrate.

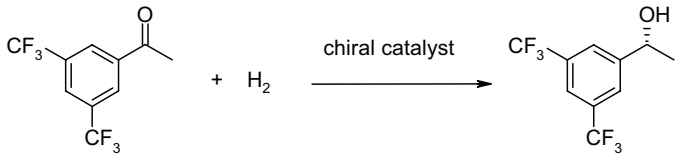
The result was confirmed in a 100 ml hollow-shaft turbine-stirred autoclave. Due to the better mixing the reaction times were reduced by a third and *de* improved to 98.5%. The overall development time from start of HTS to the successful 100ml validation experiment required less than three weeks. After a 'traditional' fine tuning of reaction parameters and a thorough substrate quality risk analysis of the starting material, a scale-up to a 16 l autoclave was performed and then the process was transferred to the customers' production plant.

Case History 4. Enantioselective Hydrogenation of an Aromatic Ketone: From R&D to Pilot Scale (Scheme 4)[8,13]

(*R*)-3,5-bistrifluoromethyl phenyl ethanol (BTMP) is an interesting chiral building block for a number of pharmaceutically interesting targets such as an NK-1 receptor antagonist.[14] The most attractive route to BTMP is the enantioselective hydroge-



Scheme 3.



Scheme 4.

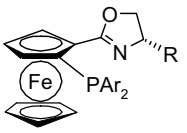
nation of 3,5-bistrifluoromethyl acetophenone (BTMA). Since many of the efficient catalytic systems are patent protected, a new catalyst had to be found and a technically feasible process had to be developed in order to produce >200 kg amounts of BTMP.

The key issues investigated during the course of the project were:

– To identify the best catalyst/ligand for a highly reproducible hydrogenation reaction that meets the defined specs: Conversion: >99%, enantioselectivity: >94% *ee*, substrate/catalyst ratio (S/C): ≥10,000, preferably ≥20,000.
– To carry out a quality risk analysis with emphasis on the hydrogenation reaction as basis for the up-scaling in the production reactor.
– The timeline set for this project (from screening to pilot plant) was very ambitious: Solvias and its scale-up partner Novasep Synthesis had a mere two months available to develop a pilot process and to manufacture the required amounts of BTMP.

Under these circumstances it was decided to restrict the investigations to the Ru-phosphine oxazoline catalyst developed by Naud *et al.*[8] The screening experiments with various ligands were carried out in 50 ml autoclaves under the standard reaction conditions established during the research phase. As the variations in enantioselectivity (*ee* 91–95%) were rather small, the ligand A (R = i-Pr, Ar = Ph, Fig. 7) was chosen for scale-up and further optimization and development since it is produced by Solvias on a kg scale and is also the cheapest of the tested ligands.

The optimization of the reaction conditions was carried out in 50 ml autoclaves and encompassed solvent and base (preferred toluene/aqueous NaOH), as well as pressure and temperature (20 bar, 25 °C). Experiments in a 2.5 l autoclave provided information the catalyst loading needed for a reaction time of <15 h (up to 20,000 standard laboratory material) substrate concentrations(between 0.4 and >3 mol/l can be employed).



R = *i*-Pr, *t*-Bu, Ph
Ar = Ph, 3,5-Xyl, 4-CF_3Ph
Preferred ligand A
R = *i*-Pr, Ar = Ph

Fig. 7.

Of particular importance was the effect of the BTMA quality, the most important factor affecting catalyst performance. BTMA of three different suppliers was tested in a 300 ml autoclave showing strongly different behavior. Without any further purification, material from suppliers 1 and 3 led to reaction times of <20 h for complete conversion whereas BTMA from supplier 2 did not react under the standard conditions! Unexpectedly, a simple distillation did not remediate the problem and an involved extraction procedure/distillation had to be applied to get satisfactory results. In the end, scale-up hydrogenations were performed with the BTMA from supplier 3 which could be used without any further purification.

In addition, analyses concerning other quality risks, health and safety issues as well as catalyst removal were carried out. Finally, to produce the required amounts of BTME, the optimized process was run twice with 140 kg of substrate in a 4 m^2 hydrogenation reactor with an S/C ratio of 20,000 at 20 bar and 25 °C. Full conversion was reached after 15 and 11.5 h, respectively. Standard multipurpose equipment was used for work up. The *ee*s after the reaction were 95.8 and 95.4% which improved to 98.6 and 97.7% after the crystallization of the BMTP, with an isolated yield of 70.1 and 70.7%. Overall the process scaled very predictably and no unforeseen issues appeared, allowing a timely delivery of product within the preset timeframe of only two months.

Received: February 21, 2008

[1] For an introduction and leading references see H. U. Blaser, E. Schmidt in 'Large Scale Asymmetric Catalysis', Ed. H. U. Blaser, E. Schmidt, Wiley-VCH, Weinheim, **2003**, p. 1.
[2] For ferrocene-based phosphines see W. Chen, H. U. Blaser in 'Trivalent Phosphorus Compounds in Asymmetric Catalysis: Synthesis and Applications', Ed. A. Börner, Wiley-VCH, **2008**, p. 359.
[3] Josiphos: H. U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Topics in Catalysis* **2002**, *19*, 3; H. U. Blaser, M. Lotz, 'eEROS, Encyclopedia of Reagents for Organic Synthesis', **2008**.
[4] Walphos: T. Sturm, L. Xiao, W. Weissensteiner, *Chimia* **2001**, *55*, 68; T. Sturm, W. Weissensteiner, F. Spindler, *Adv. Synth. Catal.* **2003**, *345*, 160.
[5] Taniaphos, Mandyphos: F. Spindler, C. Malan, M. Lotz, M. Kesselgruber, U. Pittelkow, A. Rivas-Nass, O. Briel, H. U. Blaser, *Tetrahedron: Asymmetry* **2004**, *15*, 2299.
[6] MeO-Biphep: H.U. Blaser, M. Lotz, M. Thommen, *Chimica Oggi,* **2007**, *25(2)*, Supplement Catalytic Applications, p. 8.
[7] Butiphane: U. Berens, U. Englert, S. Geyser, J. Runsink, A. Salzer, *Eur. J. Org. Chem.* **2006**, 2100.
[8] Naud catalyst: F. Naud, C. Malan, F. Spindler, C. Rüggeberg, A. T. Schmidt, H. U.; Blaser, *Adv. Synth. Catal.* **2006**, *348,* 47.
[9] C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912.
[10] W. A. Nugent, G. Licini, M. Bonchio, O. Bortolini, M. G. Finn, B. W. McCleland, *Pure Appl. Chem.* **1998**, *70*, 1041.
[11] J. G. de Vries, L. Lefort, *Chem. Eur. J.* **2006**, *12*, 4722.
[12] For an early example using this approach see R. Kadyrov, T. H. Riermeier, U. Dingerdissen, V. Tararov A. Börner, *J. Org. Chem*. **2003**, *68*, 4067.
[13] F. Naud, F. Spindler, C. Rüggeberg, A. T. Schmidt, H. U. Blaser, *Org. Process Res. Dev.* **2007**, *11*, 319.
[14] K. B. Hansen, J. R. Chilenski, R. Desmond, P. N. Devine, E. J. J. Grabowski, R. Heid, M. Kubryk, D. J. Mathre, R. Varsolona, *Tetrahedron: Asymmetry* **2003**, *14*, 3581.