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STRATEGIES FOR ACCELERATING THE DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE REACTIONS

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 remedy these problems are described.

In recent years, the economical enantioselective synthesis of chiral performance chemicals has gained in importance. Among the approaches for producing enantiopure (ee > 99%) or enantioenriched compounds enantioselective catalysis is one of the most attractive ones. 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 [1]. 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 ingredi-

ent 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 developing an asymmetric process. This is summarized in the following Tab. 1.

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.

Tab. 1 - Activities and requirements for ligand selection

Phase 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 phas	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 proces	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

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 step 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 catalysts 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 chlorophosphites (prepared by reaction of PCl_3 with the appropriate diol) with amines in toluene, followed by filtration. The active catalysts were prepared *in situ* by mixing the ligands with an appropriate metal complex (usually $[Rh(cod)_2]BF_4$) and then testing them 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 allowing 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 (see Fig. 2). All ligands, catalysts and solvents are handled in a glove box to ensure inert conditions. 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 2 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.
5) Validation: best lead(s) are repeated on a 0.5 g scale in 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 proved to be highly efficient and in the last few years >150 projects were carried out. The hit rate for finding either a lead for further development or directly a feasible solutions has increased from 50% to >90% since we started using the equipment. This is due to the ability to perform 3 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 develop 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 to from up to one year to 2-4 month. Furthermore, the amount of starting material

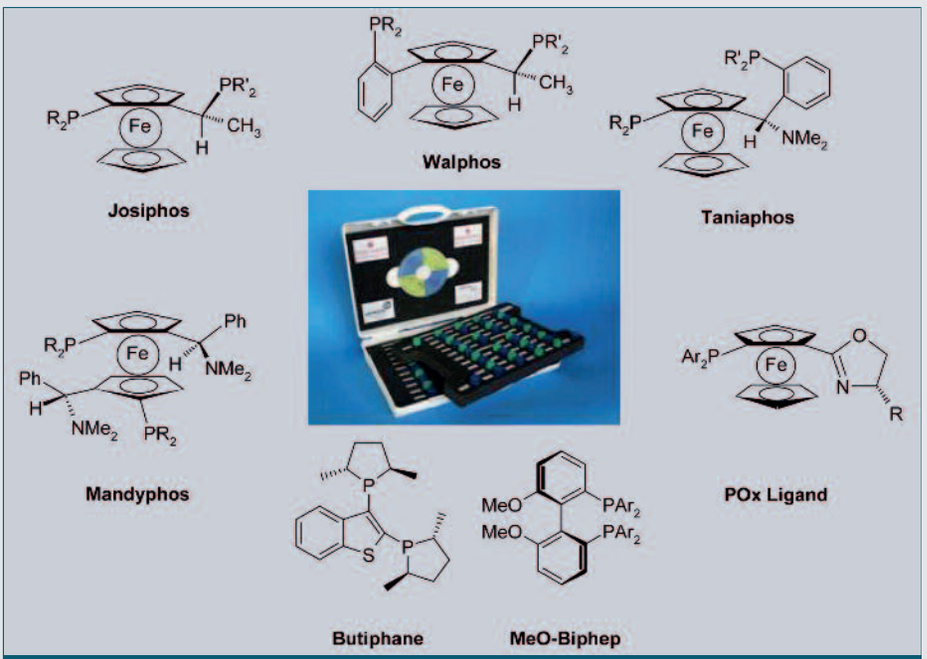

Fig. 1 - 80-Member Solvias Ligand Kit

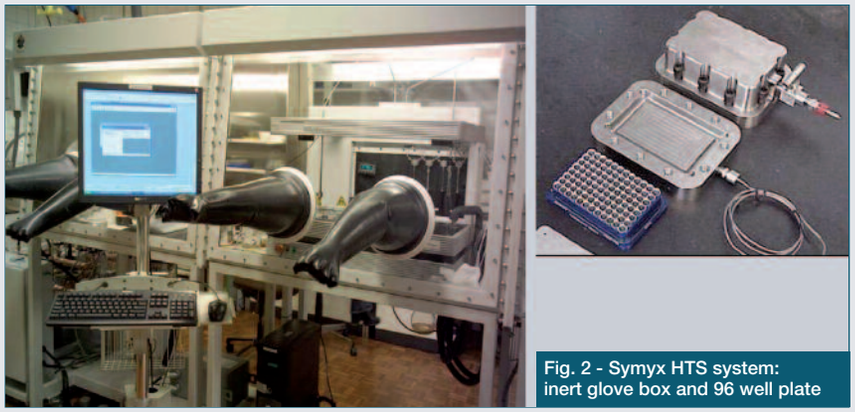

Fig. 2 - Symyx HTS system: inert glove box and 96 well plate

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.

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. 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 ranges from relatively simple 50 ml autoclaves for optimizing reaction conditions and raw material test all the way up to a 50 l autoclave for producing 50 g to multi kg quantities of product within a few weeks. 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, again leading to significant time savings.

In the scale-up phase to the pilot stage multi gram up 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. 2. 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 built 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.

Extension of HTS screening to other reactions

Standard CX-Coupling Reactions (Heck, Suzuki, Buchwald-Hartwig) and Carbonylation Reactions

For this very important class of reactions, Solvias has developed standard experimental designs with the following set of parameters (the actual choice will depend on the reaction type, the substrate as well as the goals of the customer):

Ligands: Various monophosphines such as P(*t*-Bu)$_3$, Buchwald phosphines or CatAXCium ligands as well as biphosphines such as binap or xanthphos

Pd-Precursors: $Pd_2(dba)_3$, $[Pd(allyl)Cl]_2$, $(Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$

Bases: K_2CO_3, NaOtBu, KOtBu, K_3PO_4, $CsCO_3$, or other base with powder density <150 mmole/mL

Solvents: Toluene, DME, dioxane, or other solvent with boiling point >10 °C above reaction temperature.

Reaction conditions: S/C ratio, base equivalents, temperature, concentrations and for carbonylations CO pressure) will be determined after preliminary test experiments.

Enzyme Screening

The enzyme collection contains ca. 200 proprietary wild type enzymes (mainly ketoreductases) from various established providers. Enzymes were selected on the basis of guaranteeing supplies of larger quantities within a short period of time to ensure a seamless scale-up to multi kg-scale.

Chemoselective Hydrogenation

Based on our extensive experience with heterogeneous hydrogenation reactions, a typical design will be testing 24 different catalysts (Pt, Pd,

RIASSUNTO

Strategie per accelerare lo sviluppo di reazioni catalitiche enantioselettive

Lo sviluppo di processi catalitici enantioselettivi per la produzione di intermedi chirali è un problema molto complesso e può essere molto impegnativo in termini di tempo ed economici. In questo articolo vengono trattate le principali difficoltà che potrebbero portare a lunghi tempi di sviluppo e le strategie per porvi rimedio.

and Ru metals on supports such active carbon, Al_2O_3, $CaCO_3$ as well as Raney nickel or other Ni catalysts) under 4 different reaction conditions.

Classical Resolution

This screening is generally performed using either 32 chiral acids or bases, respectively, depending on the substrate and pKa values. Experiments are usually conducted on a 0.4 ml scale and analysis and determination of enantiomeric excess (ee) using SFC-chromatography.

Conclusions

Based on our experience, we can state that the HTS approach described above can reduce the time required for the initial phases of the development of an asymmetric hydrogenation to 2-6 month. The amounts of starting material needed is only 2-4 grams compared to the 10-20 grams required for conventional methods. However, there is no doubt that HTS does NOT replace conventional testing and optimization in 50-300 ml autoclaves but it is the combination of the two approaches which lead to better processes in much shorter time.

In our experience, selectivity results obtained in HTS studies are well reproducible on larger scale and in traditional autoclaves even though fast reactions might be affected by limitations in mass transfer of the 96-well-plate shaker affecting conversion. In addition to lead-finding, HTS can also be used for catalysis process optimization. However, handling of the small amounts of catalyst when running reactions at an S/C ratio >5000 is not trivial and required special precautions.

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