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Discovery and Optimization of Catalysts and Solvents for Absorption Using High Throughput Experimentation

Découverte et optimisation de catalyseurs et d'absorbants par expérimentation haut débit

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Development of Asymmetric Hydrogenation Catalysts via High Throughput Experimentation

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Résumé — Développement de catalyseurs d'hydrogénation asymétrique par criblage haut débit —

La découverte de nouvelles molécules pharmaceutiques a sa propre dynamique qui impose des contraintes temporelles très strictes au chimiste en charge de développer la production du principe actif à large échelle. En conséquence, ce dernier va se tourner vers l'utilisation de technologies éprouvées et robustes quitte à rendre le procédé plus coûteux ou plus polluant. Afin de pouvoir faire face à des temps de développement très courts et d'introduire en production des technologies modernes et non polluantes comme l'hydrogénation asymétrique, nous avons développé une plateforme de criblage haut débit pour la découverte de nouveaux catalyseurs. Dans cet article, nous décrivons une des facettes de cette plateforme qui est la synthèse de bibliothèques de ligands chiraux et leur application au cas réel d'une molécule pharmaceutique.

Abstract — Development of Asymmetric Hydrogenation Catalysts via High Throughput Experimentation —

The dynamics of drugs discovery imposes severe time constraints on the development chemist in charge of implementing the large scale production of a new Active Pharmaceutical Ingredient (API). This results in the use of well-established and robust transformations at the expense of the cost-efficiency and the sustainability of the process. In order to cope with the short development time and allow the implementation of new more efficient production technologies such as asymmetric hydrogenation, we have turned towards the use of high throughput experimentation for the discovery of new catalysts. The protocol for the preparation of a library of chiral ligands and its application to real-life pharmaceutical molecules is described in this article.

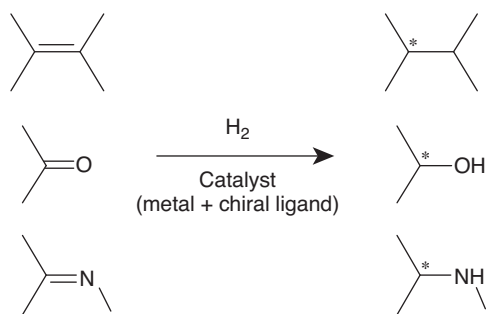


Figure 1

Schematic representation of enantioselective hydrogenation.

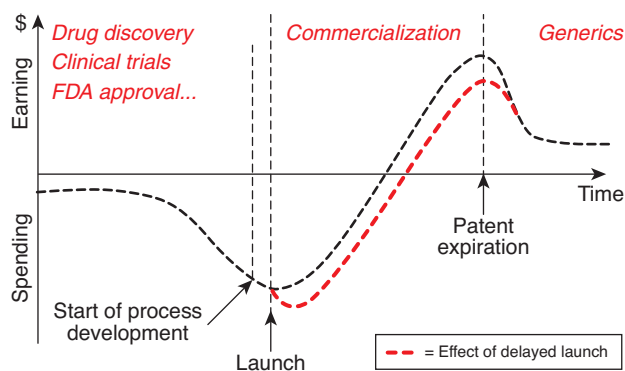


Figure 2

Dynamics of drug development.

INTRODUCTION: AN INDUSTRIAL PERSPECTIVE ON ASYMMETRIC HYDROGENATION

In 2001, the Nobel Prize for chemistry was awarded to W. Knowles and R. Noyori for their work on asymmetric hydrogenation¹. This technology consists of the metal-mediated enantioselective addition of H₂ onto an unsaturated bond (olefin: C=C; ketone: C=O and imine: C=N) of a prochiral substrate (*Fig. 1*) [1-3]. Discovered in the late 60's, asymmetric hydrogenation allows the synthesis of the desired enantiomer of a chiral molecule (*i.e.* in most cases, an intermediate/building block towards an API) with 100% theoretical yield and 100% atom-efficiency, thus generating no waste by-product. From an industrial point of view, it is consequently a very attractive methodology for large-scale production. However, nowadays, the majority of enantiopure molecules are still produced either by fermentation, *i.e.* with the use of the synthetic machinery of a microorganism or by classical resolution of the racemate, *i.e.* the separation of diastereomeric salts where the maximum yield is only 50%. In spite of its attractiveness asymmetric hydrogenation has found limited use in large-scale production. Probably no more than 20 processes were ever implemented [4].

The main reason for this paradoxical situation has to do with the dynamics of drug discovery and development [5-7]. The development of a new drug requires very large upfront investments from the pharmaceutical companies. Recovering those investments and further profits will come only when the drug is finally launched on the market – *i.e.* when all clinical trials have been passed successfully (*Fig. 2*). During the development phase, little effort and resources are dedicated to the design of a robust synthetic route fitted for large-scale production. This is due to the large attrition rate for drug candidates. The current average clinical success

rate is only 11% [8]. The majority of New Chemical Entities (NCE) are abandoned during the clinical trials because they can not be proven effective or appear to have significant side-effects. The quantities of Active Pharmaceutical Ingredients (API) needed for the clinical trials during the development phase are produced *via* a synthetic route identical or close to the one initially used by the medicinal chemists who discovered the new molecule, *i.e.* a synthetic route fitted to prepare a few grams of compounds without concern for cost, safety and sustainability. Once a new drug has finally been cleared to enter the market, there is a strong pressure to start production as soon as possible. This means that development times for these processes are measured in months rather than years. Since every month of delay in the launch of a new drug can mean a substantial loss of revenues (see *Fig. 2* for the effect of a delayed launch), most development chemists choose to fall back on well-established chemistry, *i.e.* classical resolution processes for the production of chiral building blocks, rather than embarking on a search for a new asymmetric hydrogenation catalyst that can be lengthy and without full guarantee of success.

Although asymmetric hydrogenation can be considered as a rather mature technology, finding the right catalyst allowing good conversion and high enantioselectivity for an entirely new prochiral substrate remains a difficult problem. The chiral ligand is the cornerstone of the catalyst assembly. It determines not only the level of enantioselectivity but also influences the activity of the catalyst. Since the pioneering work of Knowles and Sabacky in the 1960's [9], numerous chiral ligands² have been prepared but most of them were tested only with model substrates. Real-life substrates, *i.e.* the prochiral intermediates towards a pharmaceutical target molecule are certainly related to these model substrates (*Fig. 3*) but they also exhibit specific geometries/configurations or

¹ K.B. Sharpless was also a recipient of this Nobel Prize for his work in asymmetric oxidation.

² A few 1 000 chiral ligands have been reported in the literature and a few hundreds are commercially available.

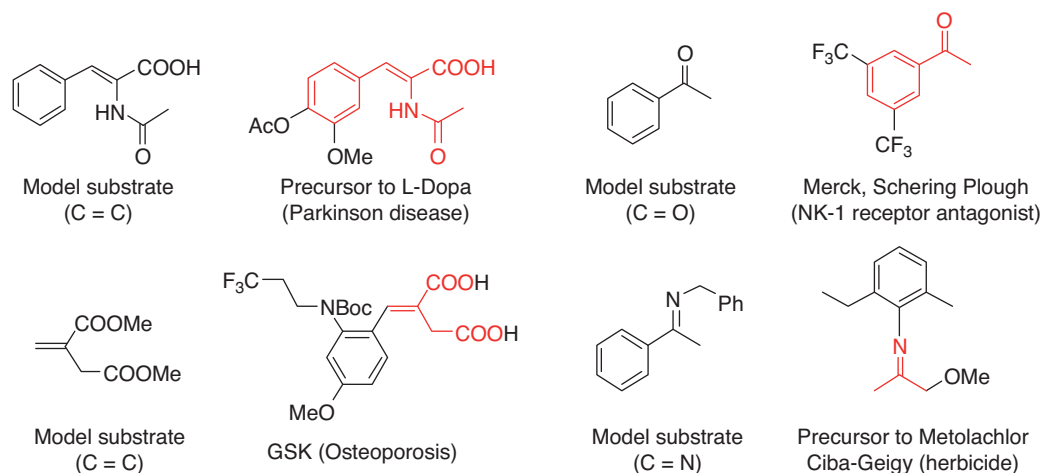


Figure 3

Model substrates and real-life substrates for asymmetric hydrogenation. (The owner of the molecule and its applications are given in parenthesis).

contain additional functional groups that hinders the direct application of a catalyst efficient for the model substrate to the real substrate.

In other words, there is no such a thing as a universal chiral catalyst that would work for every new substrate [10]. Consequently, for every new prochiral candidate for asymmetric hydrogenation, a search is needed to find the adequate catalyst. The parameters that can affect the outcome of an asymmetric hydrogenation experiment are numerous and all should be considered during the search for the optimal catalyst:

- metal: Ru, Rh, Ir are the most common metals used in asymmetric hydrogenation. Rh is preferred for C=C, Ru for C=O and Ir for C=N;
- chiral ligand: the chiral ligand determines *e.e.* (enantiomeric excess) and activity. It is selected among those commercially available or present in house. In some cases, existing chiral ligands will not induce a sufficiently high enantioselectivity for the substrate of interest, in which case the preparation of an entirely new ligand will be required. This is an extremely time consuming exercise with no guarantee of success as “there is no such thing as ligand design”³. An additional selection criterion that can be considered during the screening for a hydrogenation catalyst is the cost of the ligand. Not only the metals, such as rhodium, iridium and ruthenium but also the chiral ligands that are often

prepared using multi-step syntheses including racemate resolutions can be extremely expensive⁴. If the target cost for the process is set to very low, one can exclude the most expensive ligands from the start;

- ancillary ligands, counterions: the other achiral entities present around the metal centre can be of great importance not only for activity and stability of the catalyst but also for its enantioselectivity;
- method of catalyst preparation: depending on the reaction conditions used during the catalyst preparation, different metal complexes with different catalytic properties can be obtained;
- solvent used during the hydrogenation: in many cases, the solvent is not innocent and can play a crucial role with respect to activity and enantioselectivity;
- substrate to catalyst ratio: to be cost effective, a process based on asymmetric hydrogenation must use as little as possible of the expensive precious metal/chiral ligand. As a rule of thumb, we consider that catalysts exhibiting a T.O.N. (Turn Over Number). under 1 000 have little chance to be implemented in production;
- temperature: in asymmetric hydrogenation, the temperature rarely exceeds 100°C. Higher temperatures have a beneficial effect on the activity but are detrimental to the enantioselectivity;
- hydrogen pressure: increasing the hydrogen pressure usually improves the activity. The effect on enantioselectivity varies depending on the catalyst and substrate;

³ An interesting quote stemming from Manfred T. Reetz addressing a chemist involved in “ligand design”: “Can you tell me if you designed your ligand to give the (*R*)- or the (*S*)-isomer of the product?”. It is clear that no one can answer this question. Hence, there is no such thing as ligand design. At best one can copy features that are present in “privileged” ligands, *i.e.* ligands that have been successful in other cases [10].

⁴ Most bisphosphines, except BINAP will cost between 50 000-150 000 €/kg.

additives: acids, bases, phase-transfer catalysts used in various ratios relative to the catalyst or substrate can have a significant effect.

Considering the numerous parameters to be tested to find an efficient catalyst and the severe time constraints for process development, it is not very surprising that until recently, asymmetric hydrogenation was not part of the first-generation processes of drugs and agrochemicals but used mostly in case a second-generation processes was implemented.

It became clear to us that asymmetric hydrogenation could only break through as a major production technology for new drugs and agrochemicals if something could be done about timelines – *i.e.* if a robust and efficient catalyst could be discovered within the limited time allocated for process development. That's why, at DSM InnoSyn™, we decided to apply High Throughput Experimentation (HTE) as a means to cope with these severe time-constraints and to substantially shorten the time necessary for catalyst screening and process development [11-16].

1 HIGH THROUGHPUT EXPERIMENTATION AND ASYMMETRIC HYDROGENATION

HTE is a methodology where a large number of chemical entities are quickly synthesised and tested for a desired feature/performance, thus leading to an extensive exploration of the parameter space in a relatively short amount of time. In the search for a new or improved enantioselective hydrogenation catalyst, the HTE protocol consists of 3 steps: the preparation of a library of chiral ligands and catalysts, the testing of this library under different conditions, the analysis of the reaction to determine both activity and enantioselectivity. Therefore, high throughput screening cannot start without a library of chiral ligands. There are 3 ways to assemble such libraries:

- purchasing commercially available chiral ligands: a few hundred structurally diverse chiral ligands based on phosphorus or nitrogen can simply be purchased from various commercial sources [17-23];

- manually synthesizing a small set of ligands using a modular approach: using traditional synthetic methods, some groups prepared their own library of ligands from the same family. Each ligand is synthesized and purified individually, thus limiting the size of the library to, at the most, a few dozen members. Diversity is introduced along the way *via* divergent synthesis. In this approach, an optically pure advanced intermediate is prepared on a large scale and used to synthesize many different ligands [24-30];
- synthesizing a library of ligands in parallel using combinatorial chemistry techniques and automated equipment: drawing its inspirations from the techniques used in combinatorial chemistry for the automated synthesis of large libraries of small organic molecules, very few groups have developed protocols based on solid-phase synthesis [31-34] to prepare libraries of ligands attached on polymer beads. The ligands were not released from the beads and the catalytic test was performed with the supported catalyst directly. The main disadvantage of this method is that the polymeric support can have a significant effect on the catalyst performance. At DSM InnoSyn™, we were the first to report the parallel synthesis of a large library of chiral ligands in solution [35]. Our methodology, named “*Instant Ligand Library*” is described later in this article.

The second important prerequisite to perform HTE is hardware. For the preparation of the ligands and the catalyst, many useful liquid-dispensing robots and synthesizers have recently come on the market. We currently use two Zinsser Lissy liquid handling robots both equipped with 4 dispensing needles and many custom-designed trays and racks (*Fig. 4*) [36]. One of our robots is placed within a glovebox to allow the handling and the preparation of air-sensitive catalysts. For the parallel hydrogenation, we mostly rely on two parallel reactors, the Premex A96 (from the firm Premex, 96 high pressure reactors with a common headspace – thus the same pressure – and same temperature) [37] and the Endeavour™ (from the firm Biotage, 8 autoclaves with independent



Zinsser robot



Biotage Endeavour™



Premex A96

Figure 4

Pictures of our high throughput equipment.

temperature and pressure) [38]. The A96 parallel reactor was developed in collaboration with DSM and is now commercially available to the scientific community. Analysis turned out not to be a major bottleneck and conventional GC (Gas Chromatography) and HPLC (High-Performance Liquid Chromatography) could be used after some adaptation. In addition, we have set up a flow NMR (Nuclear Magnetic Resonance) system that can handle 1 sample per 3 minutes, which can be used for analysis of reaction mixtures.

2 INSTANT LIGAND LIBRARY OF CHIRAL PHOSPHORAMIDITES

Although we routinely include in our high throughput screenings for asymmetric hydrogenation a large number of commercially available ligands, we anticipated that the fast preparation of a library of chiral ligands specially tailored to the substrate of interest would be an even more powerful way to tackle the problem of finding the best catalyst for a new substrate. At the time we embarked into this endeavour, there were only three reports in the literature on automated synthesis of phosphorus ligands [31-34, 39]. The scarceness of reports describing ligand libraries is related to the difficulties associated with such an endeavour. One of the most important requirements is the ease of synthesis, which is a prerequisite for the development of automated procedures. The lengthy syntheses including chromatographic purification associated with the current state-of-the-art chiral ligands (*i.e.* bisphosphines) suggest that this class is not a viable target for a library approach. For this reason, we decided to focus on simple chiral ligands that can be prepared in 1-2 synthetic steps. Binol based phosphoramidites developed by De Vries, Feringa and Minnaard at the University of Groningen appeared to fulfil this requirement (*Fig. 5*) [40, 41].

Since these ligands are easily prepared, a protocol for their automated synthesis in solution became an attainable goal. The first step of the most common phosphoramidite synthesis, the formation of the phosphochloridite from the BINOL and PCl_3 , proceeds essentially quantitatively and purification is effected by distilling off excess PCl_3 . The robotic synthesis can thus start with stock solutions of the stable phosphochloridites

leaving only a single synthetic step. This last step usually yields the ligands in a purity with respect to phosphorus of 90-95%, the main contaminant being triethylammonium chloride. Thus, it is clear that the final purification is the only hurdle that needs to be taken in order to effect this robotic ligand synthesis. Although parallel column chromatography is feasible, this solution is not very appealing. To verify if purification is really necessary, a known phosphoramidite (derived from (*R*)-2,2'-binaphthol and diethylamine) was synthesized and tested without purification in a known asymmetric hydrogenation reaction. This led to very poor results: both conversion and enantioselectivity were substantially lower than with the purified ligand. Since the main culprit is the presence of soluble chloride, a known catalyst inhibitor, the solvent for the ligand synthesis was switched from DCM (DiChloroMethane) to toluene, allowing the complete removal of the chloride salt by filtration. Remarkably, the ligand purified in this manner had a very similar performance in the hydrogenation reaction as the purified ligand. This simple finding opened the door to automation. The coupling reactions between phosphochloridite and amine were performed in a 96 well microtiterplate equipped with an oleophobic filter. After 2 hours of reaction, the microplate was placed on a manifold, vacuum was applied and the filtered ligand solutions were collected in another 96 well plate. This protocol was initially tested on a set of 32 ligands, which were subsequently screened in the Rh-catalysed enantioselective hydrogenation of two model substrates (*Fig. 6*) [31-34].

Figure 7 shows the result of this library of 32 phosphoramidites used in the Rh-catalysed enantioselective hydrogenation of a model substrate, methyl *Z*-3-acetamido-2-butenate (**1**). As can be observed on the color-coded schemes depicting the activity and the enantioselectivity of the 32 members of the library, only a few catalyst shows good performance in this transformation (B1, C1, B2, D7). Although ligand D7 based on a primary amine was known to give good results with these substrates [42], the library shows that in general all BINOL-based phosphoramidites that contain a primary amine with branching in the α -position give excellent results (B1, C1, B2). This is one of the added advantages of high throughput screening where the large number of data collected under very similar conditions uncovers general trends.

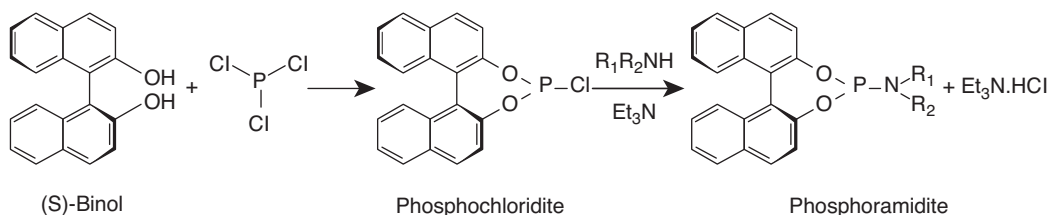


Figure 5

Two step synthesis of Binol-based phosphoramidites.

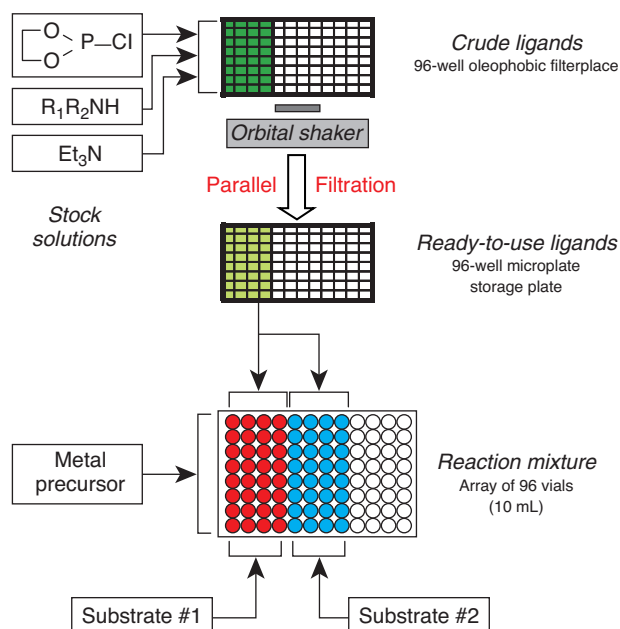


Figure 6

Phosphoramidite library synthesis and screening protocol (reprinted with permission from the American Chemical Society from Ref. [31-34]).

3 APPLICATION OF THE "INSTANT LIGAND LIBRARY" METHODOLOGY TO A REAL-LIFE SUBSTRATE [43]

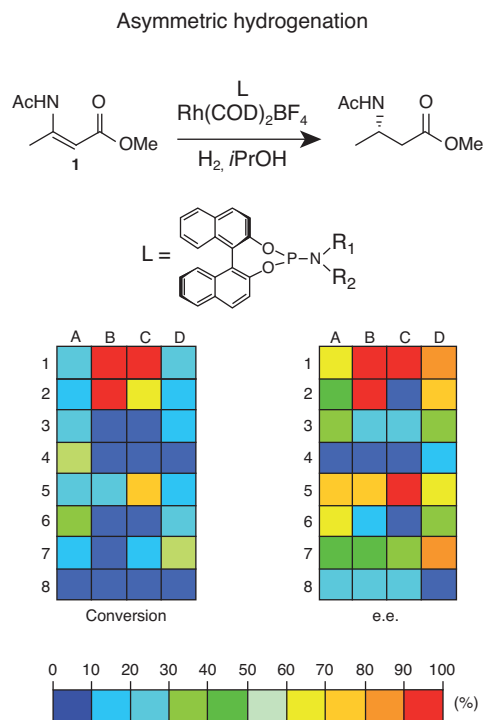
Compound **4** (Fig. 8) was discovered by Merck to be a potent melanocortin receptor agonist potentially useful in the treatment of obesity [44, 45]. The Merck scientists demonstrated that one of the chiral centers of **4** could be installed *via* asymmetric hydrogenation of the enamide, **2**. Numerous homogeneous catalysts have been developed for the hydrogenation of similar enamides with high enantiomeric excess [46, 47]. However, the prochiral substrate **2** was endowed with a very bulky ortho substituent, *i.e.* an N-Boc piperidyl group, thus belonging to a class of molecules unexplored in asymmetric hydrogenation. The catalyst used by the Merck scientists was (*S,S*)-Me-BPE-Rh(COD)BF₄ (Me-BPE = (-)-1,2-Bis((2*S*,5*S*)-2,5-dimethylphospholano)ethane) giving full conversion and an enantiomeric excess of 87-90% at S/C = 500 [48]. At such a substrate to catalyst ratio, the contribution of the catalyst price in the overall cost for production was too high to consider large scale production. Upon request from Merck, we applied our high throughput screening protocol to discover a more cost-effective hydrogenation catalyst for the production of **3**.

In an initial set of experiments using a single rhodium/phosphoramidite catalyst, we identified alcohols (MeOH,

	A	B	C	D
1				
2				
3				
4				
5				
6				
7				
8				

Figure 7

The set of 32 amines used to prepare the ligands and their performance in the Rh-catalyzed hydrogenation of a model substrate.



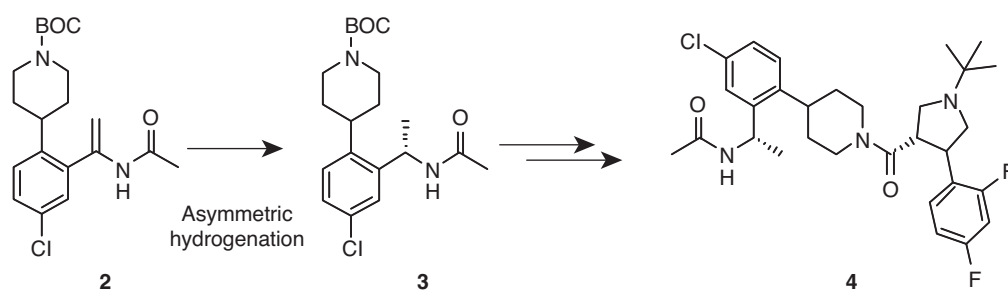


Figure 8

Asymmetric hydrogenation towards the Active Pharmaceutical Ingredient, 4.

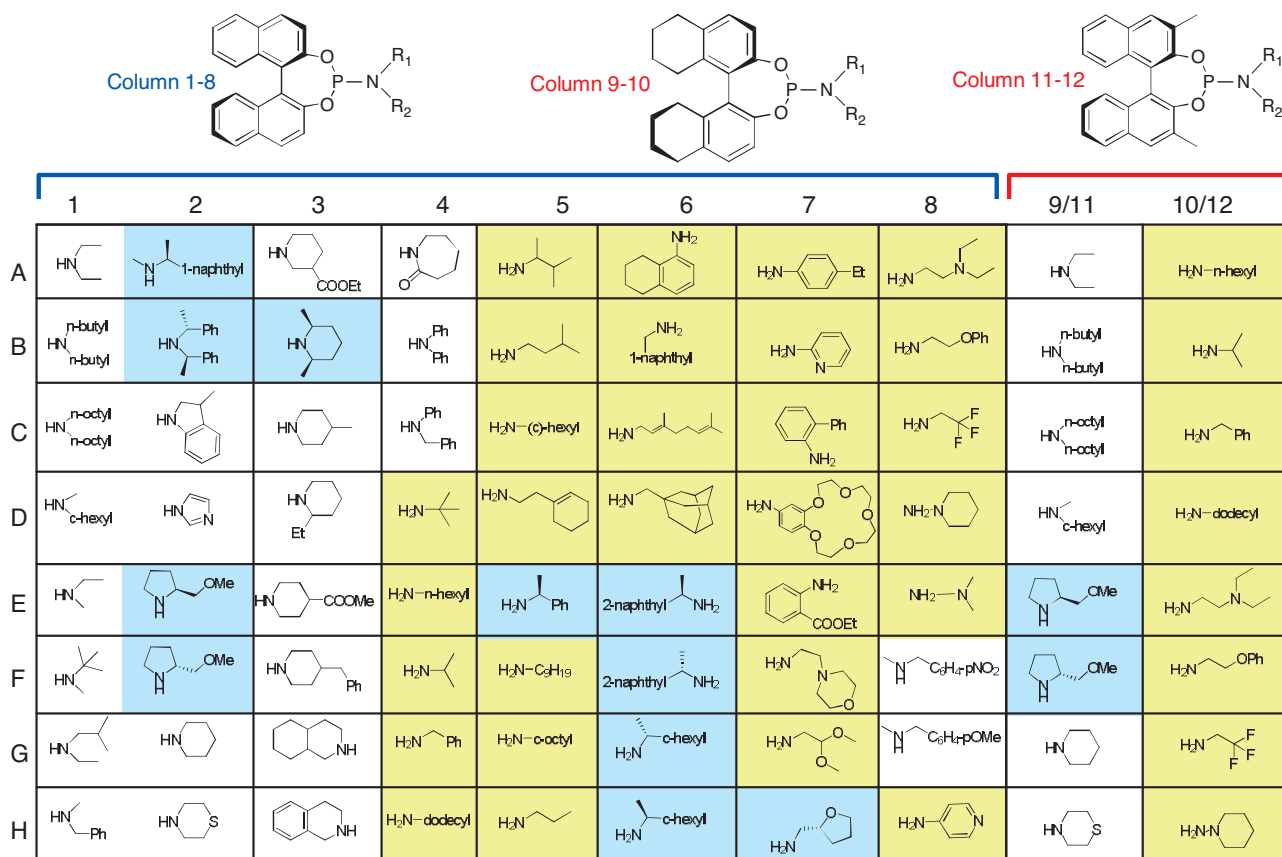


Figure 9

Set of amines (yellow: 1^{ary} amine, white: 2^{ary} amine, blue: chiral amine) used to prepare the first library of 96 phosphoramidite ligands.

EtOH, IPA) as the most suitable solvents and 25 bar of H₂ and room temperature as reaction conditions allowing the formation of sufficient product to measure the enantiomeric excess (substrate to catalyst ratio of 50). Next, we prepared a library of 96 phosphoramidite ligands (Fig. 9) composed of:

- 64 (*R*)-Binol-based ligands (column 1-8);
- 16 (*R*)-octahydro-Binol-based ligands (column 9-10);
- 16 (*R*)-3,3'-dimethyl Binol-based ligands (column 11-12).

The amines used in combination with these 3 different Binols were chosen as diverse structurally and electronically as possible to cover a large part of the parameter space.

Reaction of these 96 ligands with Rh(COD)₂BF₄ led to the formation of the catalysts, Rh(COD)₂L₂BF₄ (L = phosphoramidite ligand) which were tested in parallel in the asymmetric hydrogenation of **2**. Results are given in Figure 10, following the layout for the ligands as described in Figure 9.

At first sight, the library appears overall unsuccessful. The predominant colors are in blue/green tones indicating conversions and e.e.'s below 50%. Nevertheless, two red spots stand out in the last column. Indeed, two ligands based on 3,3'-dimethyl Binol and primary amines with α -branching

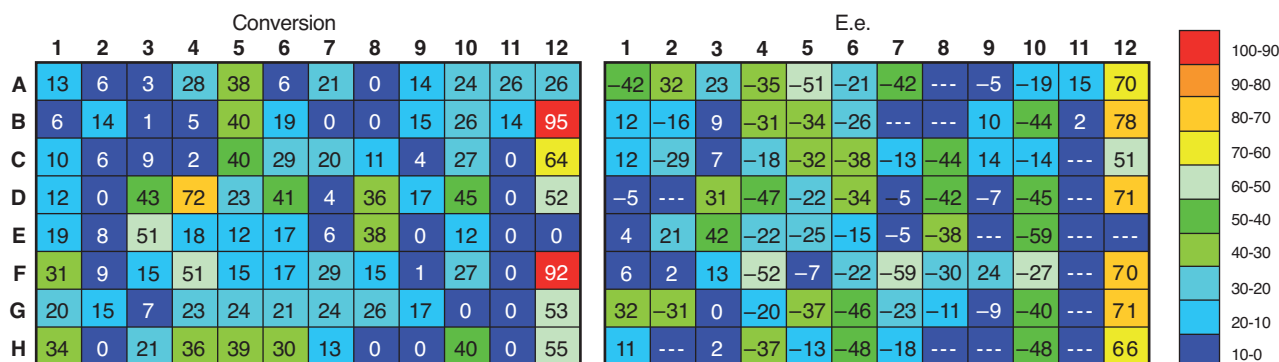


Figure 10

Results of the screening of the library of the 96 phosphoramidite ligands (reaction conditions: Rh(COD)₂BF₄, 25°C, 25 bar H₂, [2] = 0.073M in dry EtOH, 2/Rh = 50 mol/mol, reaction time = 3 h).

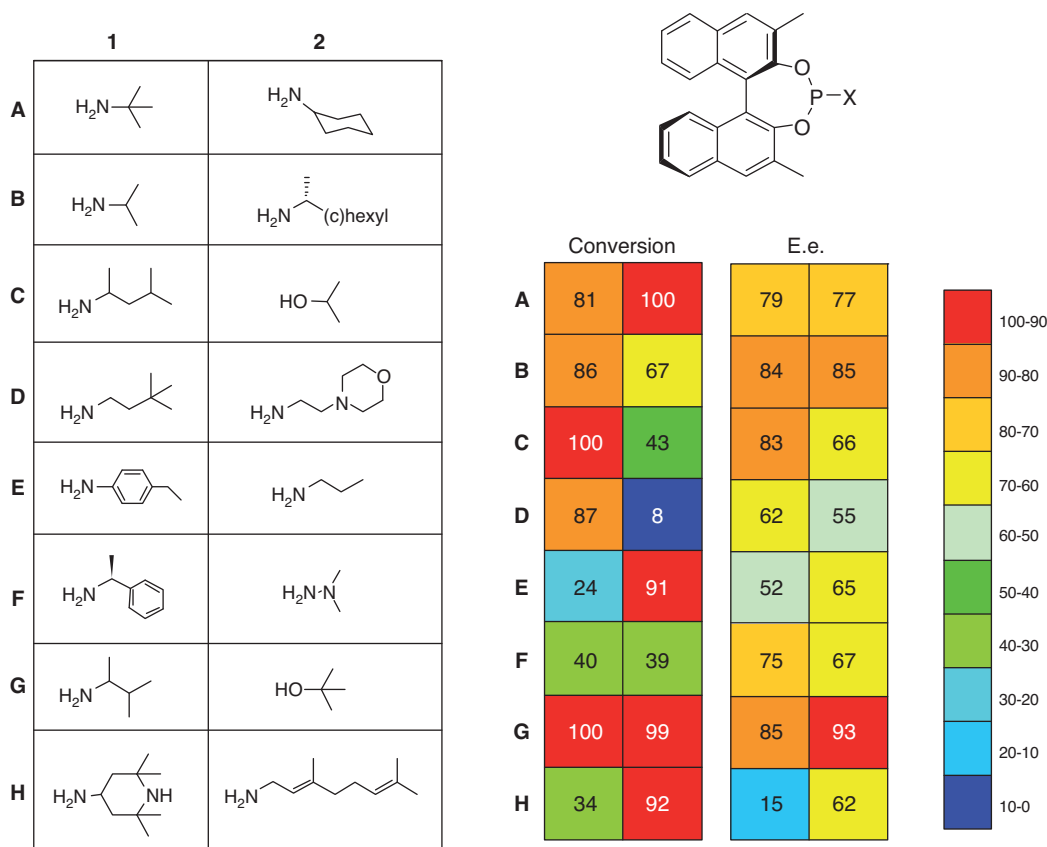


Figure 11

Set of amines and alcohols used to prepare the focused library and results of the screening of this library of the 16 ligands (reaction conditions: Rh(COD)₂BF₄, 25°C, 25 bar H₂, [2] = 0.073M in dry EtOH, 2/Rh = 50 mol/mol, reaction time = 3 h).

(column 12, row B and F) induced conversions above 90% associated with the highest e.e.'s of this library. The most active and enantioselective catalyst was the one based on **B12** with *i*-PrNH₂ as amine giving 95% conv., 78% e.e.). Quite surprisingly, catalysts based on the ligands derived

from 3,3'-dimethyl-Binol and secondary amines (column 11) hardly showed any activity.

These promising results led us to prepare a second smaller library of ligands focusing on the structural feature of the hits of the first one – 16 ligands derived from 3,3'-dimethyl-Binol

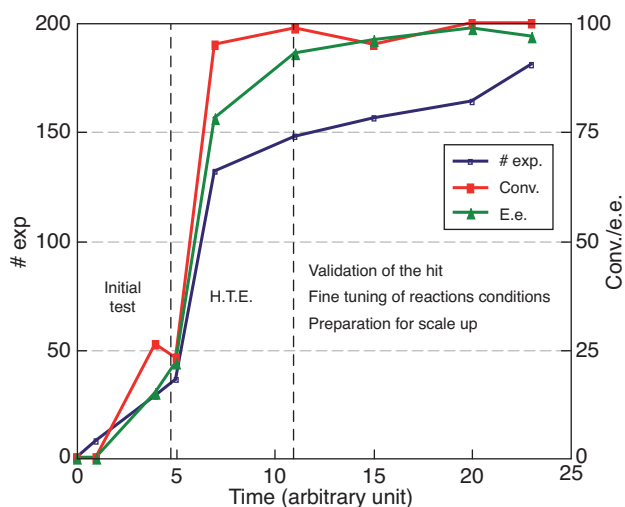


Figure 12

Progress of the project (activity and e.e. of the best catalytic system at the time; cumulated number of experiments performed) versus time (days).

in combination with primary amines (Fig. 11). Monodentate phosphites obtained from the reaction of the chlorophosphite with an alcohol instead of an amine are relatively similar to monodentate phosphoramidites [49]. Consequently, two alpha branched aliphatic alcohols (*i*-PrOH at **C2** and *t*-BuOH at **G2**) were included in this second focused library. The ligands of this secondary library were tested under the same conditions as before and the results are presented in Figure 11. The predominance of red and orange colored cells confirms that we were on the right track. Most of the ligands in this second library performed much better than the ones in the first screening. Several new phosphoramidite ligands (**C1**, **G1** and **A2**) led to full conversions and induced enantioselectivities of ~85%, but the best ligand was the phosphite based on *t*-BuOH (**G2**, 99% conv., 93% e.e.). Having a closer look at these results, it is apparent how sensitive the outcome of the hydrogenation is to small variations in the structure of the ligand. The phosphite ligand based on *i*-PrOH (**C2**) led to only 43% conv. and 85% e.e. demonstrating that the absence of a simple methyl group can have a tremendous effect.

Gram scale amounts of **G2** and of the precatalyst Rh(COD)(**G2**)₂BF₄ were easily prepared. The reaction conditions were further optimized in an additional set of small-scale experiments. For the kg production, the hydrogenation was performed in a 16L autoclave using the following conditions: 0.35 mol% catalyst, 9 wt% substrate, 7.5 L IPA, 6 bar H₂, 32°C. The reaction proceeded well, leading to complete conversion after 20 h. The enantiomeric excess was lower than the one obtained on lab scale: 89% e.e., possibly still due to impurities in the starting material. However, the enantiomeric excess was increased to 98.9% via recrystallization in the follow-up steps.

CONCLUSION

Since the implementation of our high throughput screening platform, we have applied it to numerous projects and in many cases, it appeared to be a key success factor for the discovery of an efficient catalyst within the short time frame available. Figure 12 shows the typical profile of a successful screening project. On this graph, the cumulated number of experiments and the performance of the best catalytic system at any given moment are plotted versus the time. In general, the project starts with a few experiments to get acquainted with the new substrate. At this stage, the performance of the catalyst is rather modest. A major improvement is achieved via the use of HTE. At the end of the project, the best results obtained using the parallel equipment are confirmed in a large scale autoclave that resembles the one used for ton scale production. In general, slightly better performances are observed due to easier handling of larger amounts of material and better gas-liquid mixing at higher scale. Not surprisingly, the improvement of the catalytic system is related to the number of experiments. Even today, as the world becomes more and more virtual, chemistry and more specifically asymmetric hydrogenation remain an experimental science.

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