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15 Years of Catalysis Research – A Journey through Time, Companies, and Research Projects

Benoît Pugin*

Abstract: This paper gives a personal and narrative account of three research projects in the fields of sonochemistry, catalytic oxidation, and the immobilization of homogeneous catalysts for enantioselective hydrogenation. The projects were started at different times and in different environments. The emphasis of this account is to describe the situations and factors that influenced the selection of the projects and the way in which we proceeded.

Keywords: Catalysis · Hydrogenation · Immobilization · Oxidation · Sonochemistry

Benoît Pugin, born in 1952, studied chemistry at the ETH in Zürich and stayed there to make his Ph.D. with Prof. L.M. Venanzi in the fields of metal organic chemistry and catalysis. In 1982 he moved to Ciba Geigy for a postdoctoral period where he acquired experience in molecular modeling and synthesis planning. Since 1983 he has working in the catalysis research group of the former Ciba Geigy / Novartis and now Solvias.

*Correspondence: Dr. B. Pugin
Solvias AG
Catalysis Research
WRO-1055.6.29
Klybeckstrasse 191
CH-4002 Basel
Tel.: +41 61 686 63 35
Fax: +41 61 686 63 11
E-Mail: benoit.pugin@solvias.com

Introduction

In 1983, when I started to work at the central research department of the former Ciba Geigy, fundamental research was the thing to do. Accordingly, my first research project in the field of sonochemistry dealt with fundamental questions such as whether ultrasound can produce extraordinary effects on heterogeneous reactions or whether it may be useful in heterogeneous catalysis. Still at the central research department in 1986, an applied problem, the enantioselective hydrogenation of imines with Ir for the manufacture of a herbicide initiated another quite fundamental research project. The goal was to learn how to immobilize enantioselective catalysts without affecting their catalytic performance in a negative way and to develop methods for the separation of homogeneous catalysts. A third project on catalytic chemoselective oxidation was started at Novartis in 1998, at a time when shareholders began to prefer companies that focused on their already available strengths and to call for the fast development of new market products. The objective of this project was to extend the toolbox of catalytic methods.

Today, in a small company like Solvias, our research has become clearly more applied and focuses on the development of new chiral ligands for hydrogenation catalysts that can be commercialized.

I feel that doing research is a privileged kind of work. Very much like play, it leaves a lot of room for creativity and the freedom to choose the way and the approach. In this account I will put some emphasis on describing the situations we encountered during our journey through different research projects and on showing how we decided which approach to take.

Sonochemistry

In 1983, when I started to work in the central research department of Ciba Geigy, the literature suggested that if you had a problem with a chemical reaction, ultrasound would solve it. As a consequence, a research project was started and my first task was to find out about the possible magic of ultrasound. Also, since I was working in the catalysis research group, we were interested to learn whether ultrasound may have beneficial effects on heterogeneous catalysis.

When ultrasound is applied in a liquid with sufficient power, small bubbles form. These resonate with the ultrasound and eventually implode to produce a short and very high temperature and pressure peak as well as a mechanical form of energy, a microjet. This so-called cavitation is made responsible for the effects of ultrasound on chemical reactions. Since

ultrasound is not uniformly distributed in a liquid, we first measured the local ultrasound energies in ultrasound devices and reactors and built up a basis that allowed us to apply ultrasound under very controlled conditions [1].

We then studied the influence of ultrasound on heterogeneous reactions. To answer the question whether ultrasound could produce some unexpected effects, we chose the Grignard reaction. Whitesides [2] had shown that the reaction of alkylbromides with an activated magnesium surface is mass-transport controlled, that is, the reaction is so fast that it is limited by the rate of supply of new starting material. He had also found that the reaction rate with alkyl- and aryl-chlorides is much lower and not limited by mass-transport but by the intrinsic reaction rate. In our opinion, ultrasound would have had magic power if it were able to substantially accelerate these lower, intrinsic reaction rates. However, our results clearly showed that ultrasound only accelerates already fast, mass-transport controlled reactions and has no significant effect on slower Grignard reactions [3].

Another series of experiments was then performed to get an idea whether ultrasound may have beneficial effects on heterogeneous catalysis. Most of our heterogeneous catalysts have supports with small pores (< 5 nm). In general, the catalytic sites are within these pores. We were therefore interested to know whether ultrasound may have an influence on mass-transport within such pores. To learn about this, Prof. P.B. Weisz, one of the pioneers in the field of zeolites who was our consultant at that time, suggested a simple experiment. A wet, porous support with a size of a few millimeters and with a known pore size distribution is placed into a solution with a dye. The solution is either stirred or treated with ultrasound. After a defined period of time the support is taken out of the solution, split in two halves and the penetration depth of the dye is compared. We found that ultrasound only accelerates mass-transport in supports with very large pores and does not affect mass-transport in supports with small pores. From these findings we concluded that there is little chance for ultrasound to accelerate heterogeneous catalysis.

Thanks to our efforts in the field of sonochemistry we today have the expertise and equipment to run reactions under controlled ultrasound conditions and we are able to predict potential effects of ultrasound for a large variety of reactions.

Catalytic Chemoselective Alcohol Oxidation

This work was started at Novartis in 1998, with the goal to extend our toolbox of catalytic methods. We wanted to be able to make feasibility studies and, if possible, also develop new catalytic systems. Oxidation is a vast field and we first had to decide on which reactions to concentrate. We interviewed a representative number of R&D and production chemists within the company and found that most interest was in alcohol oxidation, followed by benzylic oxidation. There was clearly less interest in dihydroxylation and epoxidation. We also learned about the attitude of the chemists towards oxidation: *'If you have an oxidation step in a synthesis that goes to production, then you have a severe problem. We prefer to use starting materials with a high oxidation state. Reductions are much simpler and more selective'.*

Catalytic oxidation with inexpensive oxidants such as oxygen/air or peroxides is well established in the bulk chemical industry. For the oxidation of fine chemicals there is an enormous number of methods described in the literature. Since most of these methods have only been tested with very few and simple substrates, their scope and limitations are usually not known. The main problems related with chemoselective oxidation of fine chemicals are chemoselectivity/overoxidation, functional group tolerance and safety (with cheap oxidants such as oxygen or peroxides).

For the oxidation of alcohols we chose several approaches. In a 'rational' approach we advanced a Ru-catalyzed transfer dehydrogenation reaction that had been described by Bäckvall [4]. We found that the commonly used acetone is a poor hydrogen acceptor and that alternative ketones such as 1,3-dialkoxy-propan-2-ones are much more powerful and allow a much wider range of alcohols to be oxidized. Transfer dehydrogenation proved to have many advantages such as no overoxidation, no safety problems, good chemoselectivity, and high functional group tolerance. Work on this promising but still too expensive approach is continuing in collaboration with Prof. J. Bäckvall with the goal to make it competitive.

In a 'screening' approach we determined scope and limitations of known oxidation methods. One method that caught our attention was the aerobic oxidation of primary and secondary alcohols with heterogeneous Pt or Pd catalysts [5] (Fig. 1). We screened a large number of catalysts and found that Ru can also give good results. We tested the functional group tolerance and found that most functional groups slow down the reaction but do not react.

Today, thanks to the experience that we have acquired in this relatively short-term project and thanks to our consultants we are able to assess oxidation problems and to offer feasibility studies in the field of oxidation of alcohols and benzylic functions.

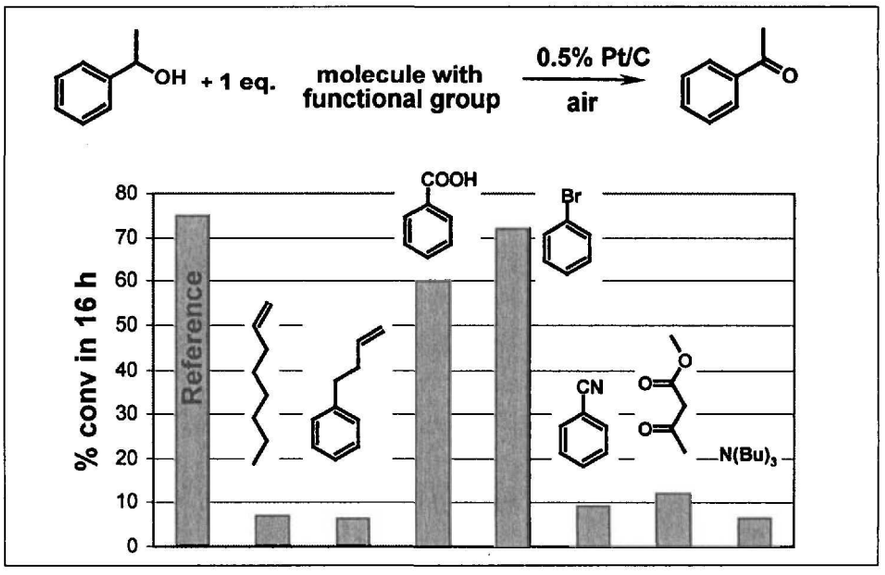


Fig. 1. Influence of functional groups on rate of aerobic oxidation.

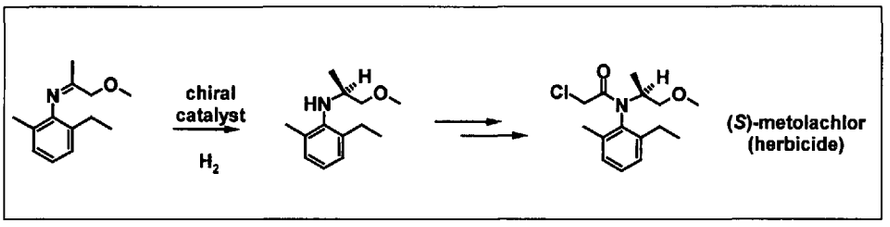
Immobilized and Water-soluble Catalysts for Enantioselective Hydrogenation

In 1986, just after the Sonochemistry project, I had the opportunity to substitute for my colleague Felix Spindler for one year, who was and still is the project leader in the field of enantioselective hydrogenation. The most important project he had been working on was a chiral switch – the enantioselective hydrogenation of an imine for the preparation of (*S*)-metolachlor [6] (Scheme 1). Metolachlor, Ciba Geigy's most important herbicide, was at that time produced as a racemic mixture in a volume of approx. 20,000 to/y.

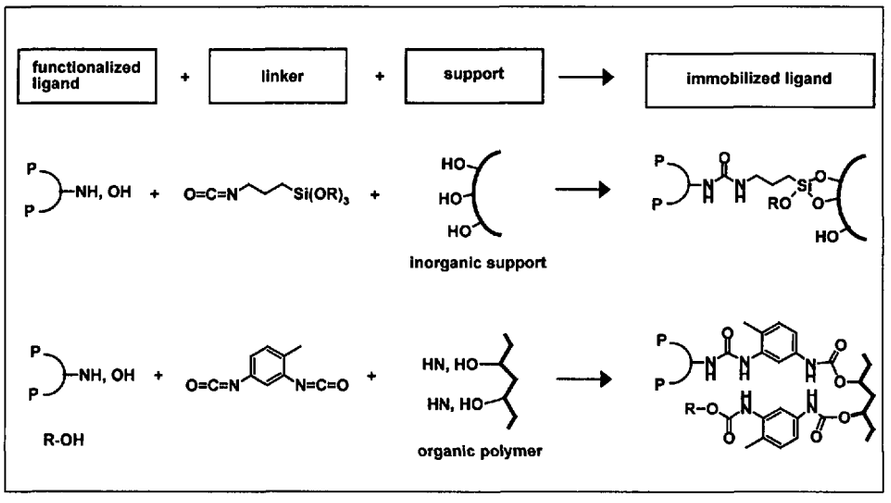
The patent for racemic metolachlor was to run out in 1994. Former investigations had shown that only the (*S*)-enantiomers are biologically active. A method that would allow the production of the (*S*)-enantiomers with 80% ee would result in approx. 40% reduction of environmental load and at the same time give rise to new patent protection for an additional 20 years. To be competitive, a very active and productive catalytic system had to be found. The minimum requirements were an ee of 80 %, a productivity of > 50,000 TON and an activity of > 10'000 TO/h.

When Felix Spindler started this project, the only state of the art was a paper from Marko (see [7]) who described the hydrogenation of imines with Rh-diphosphine catalysts with very low activities and productivities. Felix Spindler soon found that Ir was superior. When I took over this project, he had a young and still quite unexplored Ir system in hand that so far allowed 3000 TON to be achieved. My first activities were to investigate the scope and limitations of this new Ir system and to produce further examples for the patent that had been filed. We found that N-alkyl-imines can also be hydrogenated and that reductive amination is possible, both however only with low productivity. Therefore, I turned my attention to catalyst deactivation. We found that a gradual deactivation of the catalyst took place with all imine substrates and that this prevented high productivities. With N-aryl-imines, we could rule out inhibition or poisoning of the catalyst by the product formed. NMR measurements of the hydride region of spent Ir-catalysts indicated that the cause for deactivation maybe the irreversible formation of catalytically inactive hydride-bridged Ir clusters as described by Crabtree [8]. This indication made us for the first time think of catalyst immobilization, that is to attach Ir-diphosphine catalysts in such a way that they cannot interact with each other. In addition to the chance to produce more productive Ir catalysts for imine hydrogenation, immobilization offered also further opportunities such as easy catalyst separation and new possibilities in process engineering. At this point we started to make a survey of the literature on immobilized enantioselective catalysts for enantioselective hydrogenation. We found that with one exception, all catalysts that had been immobilized so far were by several orders of magnitude less active and productive than their homogeneous counterparts [9]. This clearly showed that it was not possible to obtain good immobilized catalysts without building up our own expertise in that field.

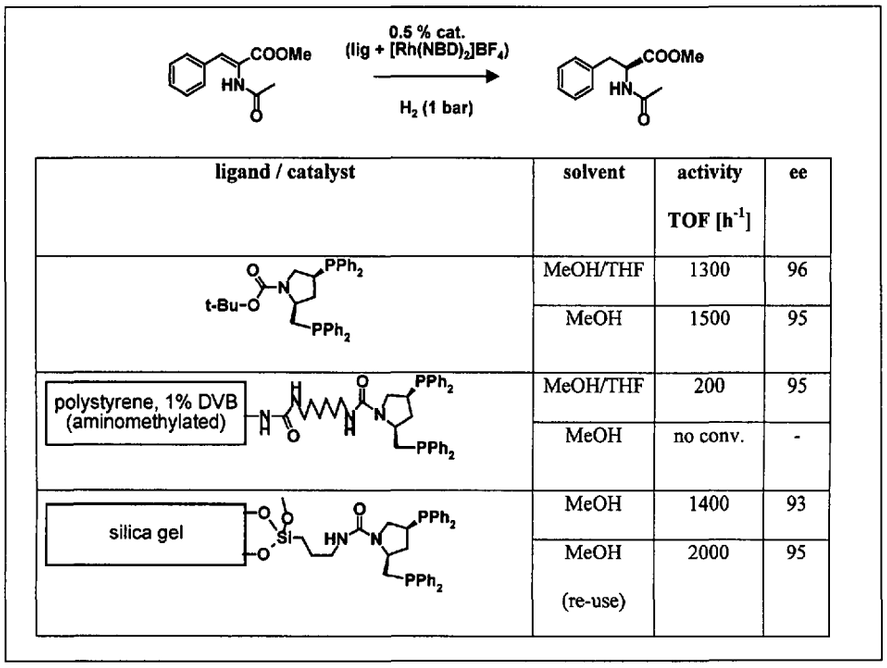
Before starting practical work, I thought about possible immobilization strategies. Enantioselective hydrogenation is used for the manufacturing of fine chemicals. Fine chemicals are very diverse and rather complex molecules with often many different functional groups. The fact that each substrate requires its own, optimized catalytic system (metal, chiral diphosphine ligand, anion, solvent, H_2-pressure, temperature, *etc.*) and that it cannot be predicted which catalytic system will be the best, called for an immobilization approach that allows a large variety of ligands to be attached to different supports. I therefore chose a modular approach, which is based on preparing and using diphosphine ligands with an additional OH or NH function that can react with commercial isocyanate linkers (Scheme 2).



Scheme 1. Enantioselective imine hydrogenation for (*S*)-metolachlor

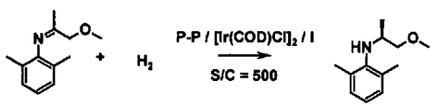


Scheme 2. Modular approach for the immobilization of ligands



ligand / catalyst	solvent	activity TOF [h^{-1}]	ee
	MeOH/THF	1300	96
	MeOH	1500	95
polystyrene, 1% DVB (aminomethylated)	MeOH/THF	200	95
	MeOH	no conv.	-
silica gel	MeOH	1400	93
	MeOH (re-use)	2000	95

Fig. 2. Typical performance of catalysts with different supports



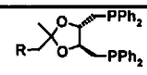
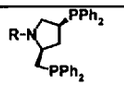
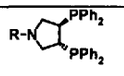
ligands	Immobilized catalysts		free catalysts	
	Productivity, activity	ee	productivity, activity	ee
	1000 TO in 40h catalyst still active	62	550 TO in 43 h catalyst dead	62
	1000 TO in 54 h catalyst still active	62	300 TO in 42 h catalyst dead	57
	500 TO in 6 h catalyst still active	29	200 TO in 20 h catalyst dead	29

Fig. 3. Imine hydrogenation with free and immobilized Ir-catalysts test reaction

To immobilize ligands on inorganic supports, trialkoxysilane-alkyl-isocyanate linkers are used. The isocyanate group is first reacted with the functionalized ligand, yielding a ligand with a trialkoxysilane function that will then react with the surface OH groups of *e.g.* silica gel and give an silica-supported ligand. In a similar way, the same ligands can be attached to organic polymers with OH or NH functions by the use of diisocyanate linkers. All catalysts were prepared '*in situ*' by addition of a solution of a suitable metal complex such as [Rh(norbornadiene)$_2$]BF_4, [Rh(cyclooctadiene)Cl]$_2$ or [Ir(cyclooctadiene)Cl]$_2$ to the immobilized ligands.

To identify suitable supports, we prepared a series of different immobilized ligands and tested these in the hydrogenation of methyl acetamido cinnamate with Rh, a standard test in enantioselective hydrogenation (Fig. 2).

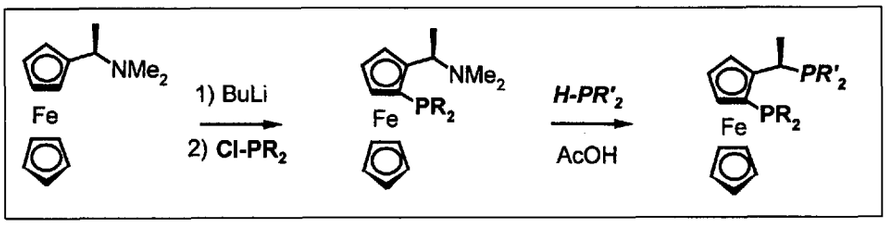
When aminomethylated polystyrene that is crosslinked with 1% of divinylbenzene is used as support, a solvent like THF that swells the polymer is required. The hydrogenation results show that the immobilized catalyst is significantly less active than its homogeneous counterpart. We attribute this to restricted mass-transport within the swollen polymer. Without THF, the polystyrene support does not swell and no significant mass-transport and reaction takes place. These results illustrate a limitation associated with swellable polymer supports: the polymer dictates the choice of solvent. We prefer supports that can be used with any solvent, since the choice of solvent will be dictated by the catalytic reaction. To circumvent this problem we also used highly crosslinked polystyrene supports. As expected, the results became more solvent independent, however the catalytic activities were all very low.

The best results were always obtained with silica gel. This porous inorganic solid does not change its properties with different organic solvents and a large variety of silica gels with different pore size distributions and specific surfaces are commercially available. In many cases the immobilized catalysts are at least as efficient as their homogeneous counterparts.

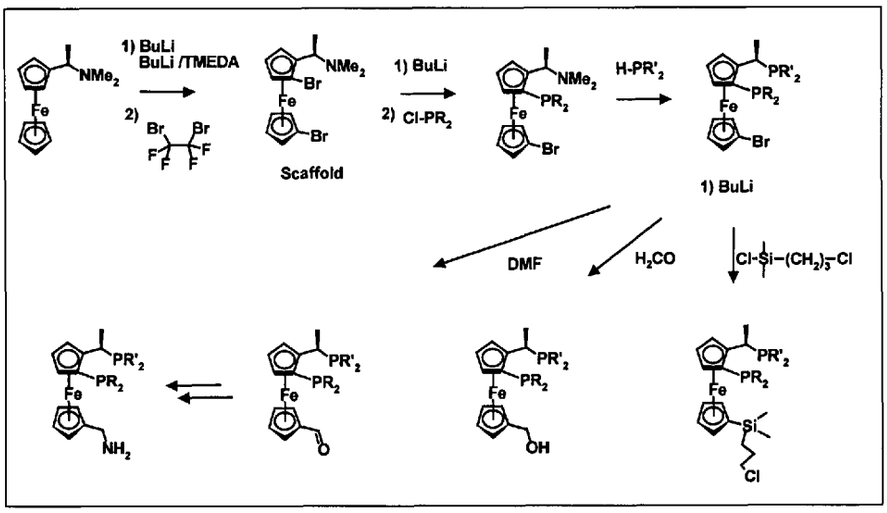
With these excellent silica gel bound diphosphine ligands in hand we set out to study potential effects of site isolation with different Rh and Ir catalysts [10]. We immobilized catalysts on silica gel with varying loading (mmol of ligand/m^2 support surface) and determined their catalytic activities. Our working hypothesis was confirmed for the imine hydrogenation with Ir catalysts: the catalytic activity dropped with increasing catalyst loading if the same amount of catalyst was used. A similar behavior was found with neutral Rh-Cl catalysts, which as described by Hetflejs [11] can form chloride-bridged dimers. Only the cationic Rh-BF_4 catalysts were not affected by different catalyst loading.

A comparison of free and immobilized Ir catalysts then clearly showed that in many cases the immobilized catalysts are superior with respect to catalytic activity and productivity (Fig. 3).

However, in spite of a lot of optimization work and further screening of alternative diphosphine ligands, it was not possible to achieve more than 10,000 to 15,000 TON with immobilized or free Ir catalysts. It became clear that to meet the requirements of an industrially relevant catalytic system, a new opportunity/tool was needed. Fortunately, another colleague, Antonio Togni, who had been working for a long time on new ferrocene-type ligands, and together with Felix Spindler developed a new class of



Scheme 3. Synthesis of Josiphos ligands



Scheme 4. Functionalization of Josiphos ligands

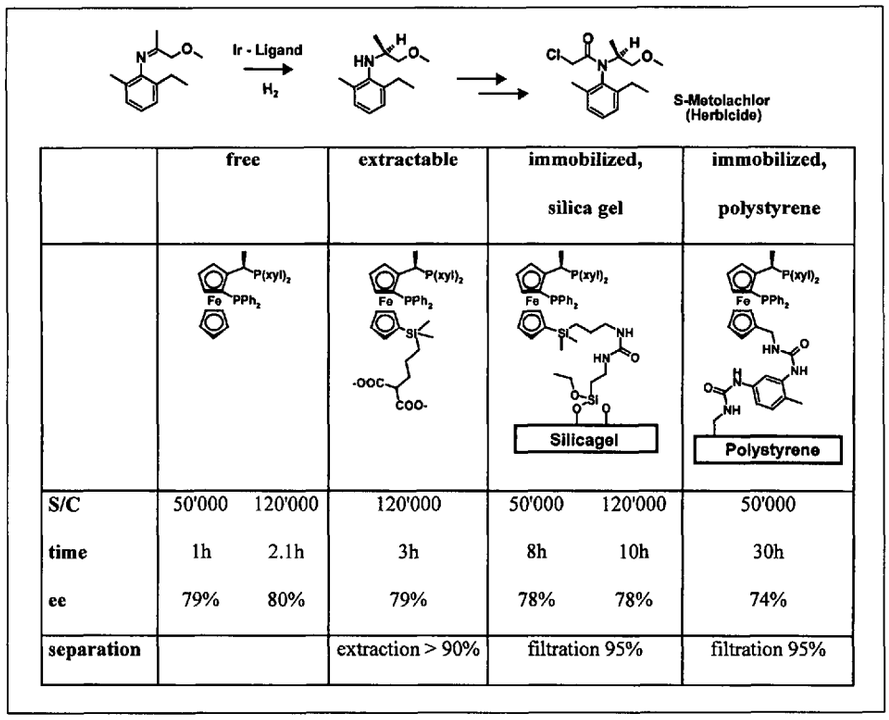


Fig. 4. (*S*)-Metolachlor. Hydrogenation with free, immobilized and extractable Xyliphos

ligands, the Josiphos ligand family that was named after the technician, Josi Puleo, who prepared the first compound [12]. These ligands proved to be very successful in many different types of catalytic reactions. It was soon found that with Ir they gave catalysts with unprecedented activity and productivity for the imine hydrogenation and yielded the desired chiral amine with ees around 80% [6] (Scheme 3).

There were several important reasons for us to try to functionalize the Josiphos ligands: (a) the ease and selectivity for the introduction of two different phosphine groups is unprecedented and makes it very easy to tune the electronic and steric properties of these ligands; (b) it was very probable that a Josiphos-type ligand would become the ligand of choice for the production of (*S*)-metolachlor and we wanted to have a solution for catalyst separation at hand if needed; (c) the limitation of our modular toolbox was the small number of available functionalized ligands.

We recognized that if we were able to introduce a functional group into the Josiphos ligand, then we would not only be able to immobilize one ligand but a whole family of ligands. The invention of the Josiphos ligands made us dream of an ultimate modular toolbox that would allow us on one hand to tune the chemical (electronic and steric properties) as well as the 'technical' (solubility, separation) properties of a ligand.

Our first attempts to functionalize Josiphos were not successful. It was known that that either the top cyclopentadienyl (cp) ring or both cp rings of N,N-dimethyl-1-ferrocenyl-ethylamine could be lithiated. However, we found no way to lithiate only the bottom cp ring. We eventually found a viable access to functionalized Josiphos ligands *via* dilithiation of N,N-dimethyl-1-ferrocenyl-ehtylamine and introduction of bromides. The chiral dibromo scaffold is highly versatile and allows the preparation of immobilized or water soluble [13] as well as new ligands [14] (Scheme 4).

In the mean time, the catalytic system that is now used for the production of (*S*)-metolachlor was developed. It is based on an Ir catalyst with Xyliphos, a ligand from the Josiphos family. We functionalized and immobilized this Xyliphos ligand and also prepared a first prototype of an extractable ligand. The results of the hydrogenation reactions are summarized in Fig. 4.

The silica gel bound catalyst holds the world record of 120,000 TON for an immobilized stereoselective catalyst. However, the immobilized catalyst is significantly less active than the free catalyst which has an unprecedented activity and productivity (in production, complete conversion is obtained in a few hours

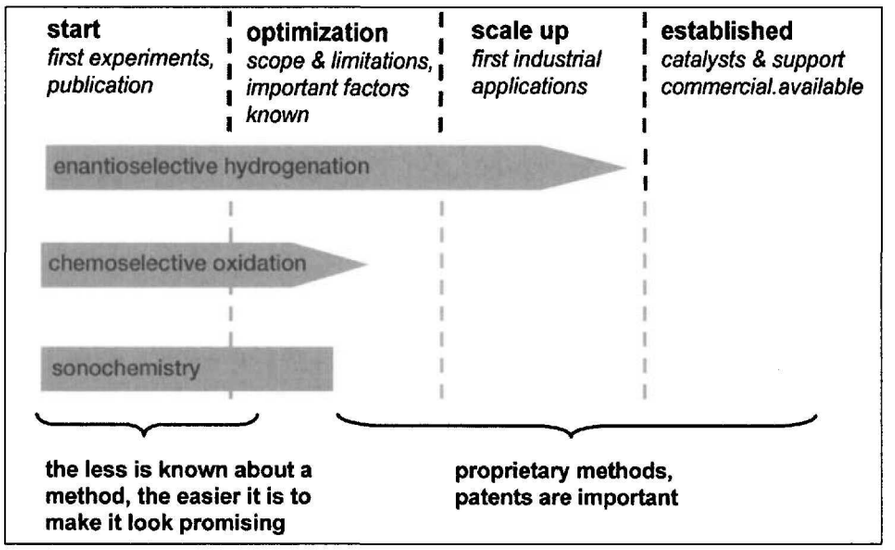


Fig. 5. The degree of maturity of methods

with a s/c of up to 2,000,000). As we had always observed, the polystyrene bound catalyst is less active than the silica gel bound analogue. Estimates based on models suggest that the lower activities may result from mass-transport problems within the supports.

The extractable catalyst showed excellent results. Its performance was similar to the free catalyst and catalyst separation was easy. However, in the technical process catalyst separation and purification is possible today by distillation of the product and therefore the unfunctionalized catalyst can be used.

With these functionalized ligands, we have a tool box in our hands that has proven to be very useful in several cases. One example is the diastereoselective hydrogenation of folic acid in water with water-soluble ligands. Our collaboration with Dr. Viola Groehn (Eprova AG) defined a new state of the art for this reaction [15]. Another example is the use of our immobilized Josiphos ligands by Firmenich SA for the Rh-catalyzed stereospecific isomerization of allylic amines to prepare citronellal from diethyl-geranylamine [16].

Conclusions and a Look into the Future

This contribution summarizes the story of three research projects in fields with very different maturities (see Fig. 5). Methods in an early stage of maturity often look very promising. It requires many efforts from the research community of academia and industry to make their real scope and limitations known. There is a risk that in the field of catalysis for fine chemicals, the duration between the finding of new catalytic systems and its application will become longer. 20 years ago, universities used to publish their inventions and industry was free to use them. Today, due to economic pressure, many universities are forced to file for patents. In the field of fine chemicals, where fast development is important and where alternative non-catalytic methods are often available, industry is reluctant to go into licensing negotiation and often refuses to take a potentially superior but patented catalytic method into consideration.

How will the fields I have been working in develop? While I do not expect major progress in the field of sonochemistry in the next decade, I believe that catalytic chemoselective oxidation is a still young field with an important potential. There are many unexplored opportunities and this field is an ideal playground for multiparallel/random screening. Chemoselective oxidation may therefore develop into one of the important research fields in catalysis in the near future.

Enantioselective hydrogenation is at the point of becoming an established method and Solvias is focusing on its commercialization. Solvias aims to become a leading producer of chiral diphosphines and related ligands as well as for the corresponding metal complexes. Since about one year, Solvias has been developing its ligand business to serve the LSM and fine chemical industry. The goal is to make ligands commercially available and accessible in kg quantities.

Accordingly, research today focuses on the development of new chiral ligands. This fascinating work is done in collaboration with the group of Prof. A. Pfaltz at the University of Basel in a project that is partly funded by the Swiss Government (KTI, Kommision für Technologie und Innovation). I'm looking forward to the suspense that goes along with the first tests of catalysts with newly designed and synthesized ligands.

Acknowledgements

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