The Power of High-Throughput Experimentation in Homogeneous Catalysis Research for Fine Chemicals

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The use of high-throughput experimentation (HTE) in homogeneous catalysis research for the production of fine chemicals is an important breakthrough. Whereas in the past stoichiometric chemistry was often preferred because of time-to-market constraints, HTE allows catalytic solutions to be found within a very short time frame. At the same time, a reliable process can be achieved because extensive imisation can be undertaken. We give examples of lead generation and optimisation, and of scope determination, based on our basic research program aimed at developing low-cost aromatic substitution reactions (C–H activation, Heck and Suzuki reactions). We also give an example of HTE in mechanistic research, which stems from our work on asymmetric hydrogenation with low-cost monodentate phosphoramidite ligands.

1. Homogeneous Catalysis for Fine Chemicals

The application of homogeneous catalysis for the production of bulk chemicals is well established.[1] Processes are known based on oxidation, hydroformylation, carbonylation, hydrocyanation, and metathesis. In fine chemical production, however, the use of homogeneous catalysis is still fairly limited, although the number of transformations applied in production is somewhat higher.[2,3] In addition to the above reaction types, processes are known based on aromatic substitutions, such as Heck, Suzuki, Sonogashira, Kumada and Negishi couplings, isomerisations, racemisa-

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Johannes (Hans) G. de Vries was born in Amsterdam (1951). He received his Ph.D. at the University of Groningen under the guidance of R. M. Kellogg, working on a bio-organic subject. After a postdoctoral appointment at Brandeis University, Waltham, USA, with J. B. Hendrickson and R. H. Abeles he returned to Europe to take up employment with Sandoz as a medicinal chemist, first in Vienna and then in London. More interested in developing new chemistry rather than drugs, he took up employment with DSM in Geleen, The Netherlands, where he works today as a principal scientist in homogeneous catalysis for fine chemicals. His main task is to introduce homogeneous catalysis in the plants of DSM's fine chemicals branch. He was also a member of the team at DSM that pioneered the use of HTE in catalysis. An important part of his job is dedicated to the interface between industry and academia. In 1999 he was appointed as a part-time professor at the University of Groningen. In 2001 he was appointed as a visiting industrial professor at the University of Bristol. He is married and has three children.

André H. M. de Vries, born in 1967, received a Ph.D. in organic chemistry in 1996 from the University of Groningen, the Netherlands, working with B. L. Feringa on asymmetric catalysis. During his Ph.D. studies he introduced the monodentate chiral phosphoramidites as highly successful ligands for conjugate addition reactions of dialkylzinc reagents to α,β-unsaturated ketones. After a postdoctoral position in the group of J. M. Brown (Oxford University) studying asymmetric hydrogenations he joined DSM in 1998. His research interests are homogeneous catalysed transformations, in particular palladium-catalysed coupling reactions and asymmetric hydrogenations, with a focus on applications in the fine chemicals industry. They are not related, but share their enthusiasm for homogenous catalysis.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

tions and enantioselective catalysis such as hydrogenation and cyclopropanation.

The fine chemical industry is highly diverse, comprising pharmaceuticals, agrochemicals, polymer additives, dyestuffs, food additives, flavours and fragrances, chemical intermediates, and many more. Particularly in the lower range of production size, there is a long tradition of simply scaling up from known stoichiometric laboratory procedures as this reduces the time necessary for development and usually leads to robust and reliable processes. The downside of this approach is that it generates rather large amounts of waste. Especially in high-value-added products, such as pharmaceuticals that are often produced by lengthy multistep syntheses, this approach can lead to quite excessive waste/product ratios of ca. 25−100.[4] There are many advantages to the use of homogeneous catalysis in fine chemical production, which may be summarised as follows:

− Reduction of waste
− High selectivity
− Production of a desired single enantiomer through asymmetric catalysis
− Shortcuts in lengthy total syntheses
− C−C bond formation under mild conditions obviating the use of protective groups

In view of all these advantages, it seems surprising that the percentage of fine chemical production processes making use of homogeneous catalysis is still below 10%.[5] There are a number of reasons for this.

Economics is often a decisive factor when there is a choice of production methods.[6] Obviously, many transition metals are very expensive and the same holds true for ligands that have to be prepared by lengthy total syntheses. A key success factor, therefore, is the rate of the reaction, usually expressed as its turnover frequency (TOF = moles of product/moles of catalyst × hour). Of equal importance is the stability of the catalyst, expressed as its turnover number (TON = moles of product/moles of catalyst).

A second factor is the scalability and robustness of the process. Many transition metal-catalysed reactions may work well on a laboratory scale, but, on scaling up, substrate and product inhibition may be an issue and sensitivity to impurities may become apparent. It is very important to keep the number of components of a reaction to a minimum, as extraction, crystallization, and distillation are the only economically viable means of purification. The presence of ligands can be a nuisance in this respect, particularly if they are used in amounts over 5 mol %. Reproducibility is also a necessity, which requires knowledge of possible inhibition mechanisms.

But by far the most important limiting factor is time. Particularly in the production of pharmaceutical intermediates, time-to-market is an absolute requirement. In stark contrast to bulk processes, development time for a new fine chemical process is measured in months rather than years. Obviously, this requirement is at odds with the desire to find a robust, low-cost process. In addition, extensive catalyst screening is often required to find the desired catalyst for a given transformation. Not surprisingly, early applications of homogeneous catalysis in fine chemicals production were limited to second-generation processes for compounds that were once produced using stoichiometric chemistry, but that have grown to a scale, often above 1000 tons/year, where catalytic chemistry becomes both profitable and environmentally superior. Prominent examples of this are the syntheses of intermediates for vitamins A and E,[7] menthol,[8] and the agrochemical Metolachlor.[9] Homogeneous catalysis in first-generation products was limited initially to those cases where it was already part of the synthetic route used by the discovery chemist.

In the past few years, this outlook has changed radically with the introduction of high-throughput experimentation (HTE). In this article, we will illustrate the basic concepts of HTE using examples from DSM's Homogeneous Catalysis for Fine Chemicals program. Emphasis in this program is currently on development of robust and economic procedures for aromatic substitution[10] and asymmetric hydrogenation.[11]

2. HTE for Homogeneous Catalysis Research in Fine Chemicals

The development and the success of parallel synthesis and screening methodologies in the combinatorial chemistry field[12] have triggered the use of HTE and parallel ligand libraries for homogeneous catalysis. Many groups have reported the synthesis of ligand libraries using a parallel approach, especially for the discovery of new chiral ligands for asymmetric catalysis.[13−18] The split-and-mix method, however, generally cannot be used for homogeneous catalysis.[19]

From the industrial perspective, the most important revolution that has emanated from these attempts to copy the successes of the combichem revolution in catalysis research has been the introduction of high-throughput experimentation. In retrospect, it seems odd that this approach took so long to evolve. The timing, however, was about right, as years of automation in solid-phase peptide synthesis, as well as analytical equipment and, above all, the development of the PC with user-friendly software, were critical to the success of this development. HTE has been embraced by a substantial part of the academic community as a means to increase the output, enlarge the scope, and improve the quality of its research. In industrial catalysis research, most companies have also recognised the method as the solution to the time-to-market problems mentioned above. The use of HTE in the entire R&D process is expected to lead to increased reliability of implemented processes, yet with lower development costs.

But there are more incentives than this that make HTE superbly suited to homogeneous catalysis research. One of the most maddening aspects of homogeneous catalysis is the almost complete lack of useful structure−activity relationships. One of the reasons for this lack of data is that most catalytic cycles consist of several consecutive discrete steps, and the chemical nature of each intermediate may be

quite different. Although there are many parameters that affect the outcome of the overall reaction, the effects that they have on each discrete step may differ widely and may even be opposing. This thwarts most attempts to direct an optimisation approach with a rational choice of parameters based on analogies, which is the common approach in synthetic research. Thus, a slow and painful step-by-step approach to lead finding and optimisation was common practice. A legendary example is the discovery of a catalyst for the asymmetric imine hydrogenation in the production of the agrochemical Metolachlor, which took 12 years.[9] HTE makes it possible to screen all parameters to their full extent, instead of a small selection, in a reasonable amount of time. Not only does this approach result in more rapid screening, but also it increases the chances of finding unexpected solutions. Several reviews have appeared concerning this approach, though synthesis and use of ligand libraries have been central in most of these.[13−18,20−25]

There is a large difference between an HTE approach to a bulk chemical versus a fine chemical process (Table 1). In bulk chemicals, the cost of the product is the overriding driving force for research aimed at new catalytic processes. Therefore, radical new approaches are often pursued to effect the large reductions in cost that are necessary to justify a huge investment in a new bulk chemical plant. Consequently, entirely new transformations or catalysts will often be the targets of this research. An HTE approach for bulk chemicals usually starts with a primary screen, aimed at testing large numbers of catalysts for activity in the desired transformation. A simple "yes/no" answer will do. Visual or spectroscopic means of analysis can be very valuable in this approach, although simple measurement of heat of reaction is not sufficient; product formation has to be proven. Once the lead has been found, the secondary screening will take place yielding more detailed information, in particular about rate and selectivity. In fine-chemical research, where the size and the rate of turnover of the product are much smaller, and its lifetime much shorter, there is neither time nor money available for radical new approaches, except as part of a basic research program. For this reason, HTE in fine chemical catalysis research has much more the character of a secondary screening. Delivering on time, within the cost price target, is the goal. The real cost price battle may start once the drug has come off patent and several generic companies start to compete with the originator company.

3. Requirements for HTE in Homogeneous Catalysis Research

So, what is needed for the successful application of HTE in homogeneous catalysis research? This is the list of essentials:

- Hardware: robots, parallel rigs
- Software and data handling
- The right mindset
- Libraries of ligands and catalysts
- Fast analysis

Though several companies have developed their own machines, currently there are several reasonably priced robots on the market for a variety of chemistries, even under high pressure.[26] The number of vessels may vary between 4 and 96, with their sizes ranging from a few mL up to 50 mL. Most machines come with user-friendly software running under Windows. We rely strongly on the two machines shown in Figure 1 for our HTE runs. Chemspeed's ASW 2000 can handle 16−96 reactions simultaneously (normally we use 32 vessels) at temperatures between −40 and 150 °C. The Endeavor is a device for eight parallel high-pressure reactions up to 30 bar. A poor man's approach is also possible and has been used by us and many others. It may take the form of 10 Schlenk tubes in an oil bath or several vials with their septa pierced with a small syringe needle in a single autoclave.

Because it is easy to conduct parallel experimentation using HTE, the explored parameter space can be much larger within a certain time frame than in ordinary research. The parameters listed in Table 2 need to be considered in HTE.

It is obvious that even with only two or three values for each parameter an excessive number of experiments may be necessary, and so, even in HTE research, there is a need to find ways to reduce the number of experiments. Although it is fraught with danger, most researchers will rely on their knowledge of a particular reaction type and on the availability of the chemicals as a basis for the choice of parameters to be screened. Unfortunately, Design of Experiments (DOE) is not very useful in the lead-finding phase for reasons outlined in Section 2 (lack of structure−activity relationships). On the other hand, it is very useful as part of process development for optimising a lead.

Unlike academic research, the desired output from industrial research is not limited to high yields and selectivities, but also includes minimum values for TOF and TON. Eco-

Table 1. Primary vs. secondary screening in homogeneous catalysis research

Process	Number of experiments per run	Catalyst	Output	Analysis	Used mainly for
Primary screening (high throughput)	100−1000	entirely new catalysts and/or ligands	yes/no answers	visual, spectroscopic	bulk chemical processes
Secondary screening (medium throughput)	5−100	commercially available or easy-to-synthesise ligands	information about rate and selectivity	LC, GC-MS, NMR	bulk and fine chemical processes

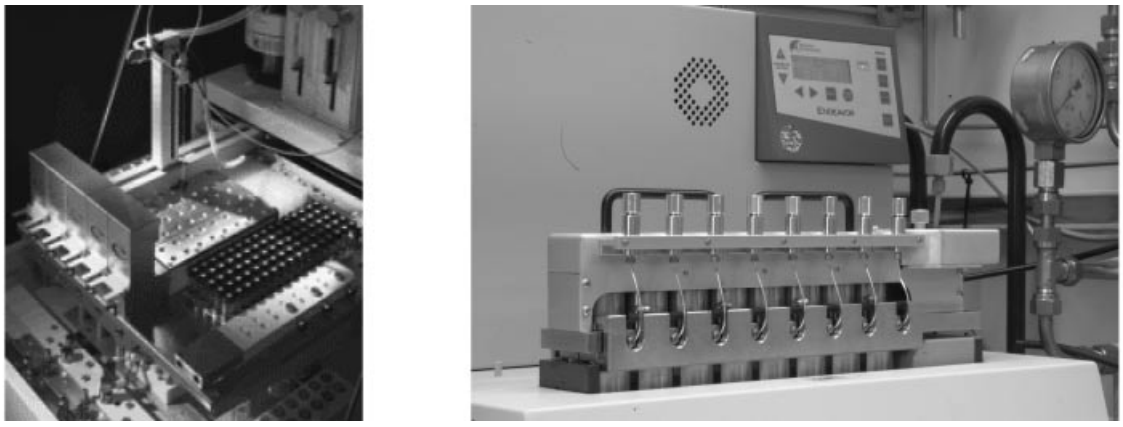


Figure 1. High-throughput equipment: left: Chemspeed's ASW 2000; right: Argonaut's Endeavor for high-pressure reactions

Table 2. Parameters for HTE screening of homogeneous transition-metal-catalysed reactions (random order)

1	Metal
2	Counterion
3	Ligand
4	Ancillary ligand
5	Metal/ligand ratio
6	Method of catalyst preparation
7	Substrate/catalyst ratio
8	Reactant
9	Solvent
10	Temperature
11	Pressure
12	Substrate/reactants ratio
13	Concentrations of catalyst, substrate, and reactants
14	Order of mixing catalyst and reactants
15	Rate of addition of one or more reactants
16	pH
17	Additives such as acids, bases, or tetraalkylammonium salts

nomics will dictate the lower limits of these values, in relation to the costs of the metal and ligand.

Basic requirements for industrial HTE in homogeneous catalysis are the availability of catalyst precursors and ligands. In practice, this will mean about two dozen of the most common catalyst precursors based on palladium, platinum, rhodium, ruthenium, nickel, cobalt, copper, manganese, and titanium. Many ligands are commercially available, but at some point it will be highly desirable to have available a library of proprietary ligands, particularly for asymmetric catalysis (vide infra). Once these basic ingredients are in place, the real bottleneck becomes the synthesis of the starting materials, which is usually not trivial.

The experiments need to be analysed. Although many papers have appeared that describe rapid screening using clever devices such as colour tests[27] or IR imaging,[25,28] we prefer to use the traditional analytical tools such as GC-MS,[29,30] HPLC, and NMR spectroscopy. At DSM, a high-throughput flow NMR spectrometer has been developed that can screen one sample every three minutes for the presence of a desired component. Since we never perform more than 96 experiments at one time, the analytical methods can easily keep up in pace. Determination of enantiomeric excess (*ee*) is a special issue. We still prefer the use of chiral HPLC and GC. In addition, the flow NMR system has led to a revival of interest in NMR spectroscopic methods using shift reagents or derivatising agents. Several interesting new approaches have been published for high-throughput *ee* determination.[16,31]

Data handling can be more of a problem. A cost-effective general program that links the data of the robots and the parallel rigs to the analysis data is not yet available.

In this article, we give some examples from our own practice of the application of HTE for lead finding and optimisation, scope determination, mechanistic research, and the creation of libraries of ligands, and show how this can be used in industrial research.

4. Lead Finding and Optimisation

We distinguish two different kinds of lead finding:

− Finding an entirely new catalyst for a reaction or finding a catalyst for an entirely new reaction. In the industrial context, this approach will either be part of a basic research program or it is related to a new process for a bulk chemical.

− Finding a catalyst and/or conditions that show the required TOF, TON, and selectivity, for a transformation aimed at the synthesis or production of a particular molecule.

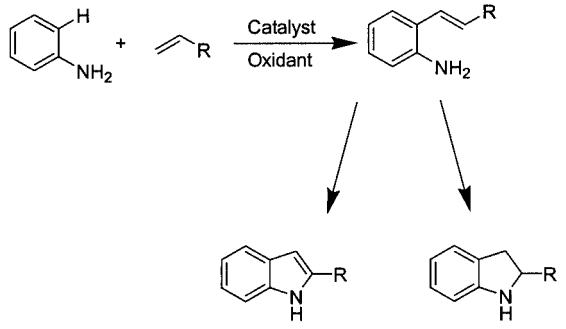
Many fine chemical companies practice the latter concept, often as a service to their clients. At DSM Pharmaceutical Products this is a routine activity that we perform both to find new routes to drugs and to reduce the cost of a catalytic transformation already developed by the client. Through the introduction of HTE, we have been able to reduce the time to solve a customer's request to find a catalyst and conditions down to three weeks.

Most of the academic efforts have been concentrated on finding improved ligands by combinatorial synthesis of ligand libraries (vide infra). A number of cases have been reported in which the metal also played an important role. One example stems from the work of Burgess et al. who developed a catalyst for the carbene insertion into a C−H

bond of a *meso* substrate by screening seven metal salts, five ligands, and four solvents.[32] Another celebrated example of lead discovery using a combinatorial/HTE approach reported by Jacobsen et al. led to the discovery of a new iron-based asymmetric epoxidation catalyst.[33] Morken et al. found a catalyst and conditions for a reductive aldol reaction by screening four metals, seven ligands and six hydride sources.[34]

4a. Discovery of a Catalyst and Reaction Conditions for Heck Arylation of Anilides by C−H Activation

Recently we had the opportunity to practice the first kind of lead finding in a collaboration with the Van Leeuwen group at the University of Amsterdam. At DSM we have a long-standing program aimed at finding clean, salt-free methods of carbon−carbon bond formation.[35] As an extension to this program, we were interested in developing new routes to indoles and indolines based on C−H activation of aniline-type derivatives (Scheme 1).



Scheme 1. Indoles and indolines by C−H activation

Arylation of olefins based on C−H activation is a known reaction that comes in two forms. The ruthenium-catalysed hydroarylation of aromatic compounds *ortho* to a carbonyl function has been developed by Murai.[36] The oxidative arylation of olefins can largely be credited to Fujiwara.[37] None of these systems, however, has been reported to work for aniline derivatives and, thus, a mild method for this transformation is highly desirable. It is obvious that there is a wide choice of starting materials to consider, as it seems unlikely that aniline itself will undergo this type of reaction. The diversity in this HTE attempt lies, thus, in the aromatic compound, as well as in the olefin, the catalyst, the solvent, and the oxidant (Figure 2). For the first two runs of 32 reactions, we chose to keep the temperature constant at 80 °C. As solvents, we chose NMP, HOAc and toluene. We tested one palladium and three ruthenium catalysts, and half the runs were performed with a stoichiometric amount of benzoquinone as the oxidant. In all but one vial, styrene was the olefin since it is the less reactive of the two we wanted to test. In addition to four aniline derivatives (**1**−**4**), we also tested benzonitrile.

In the first run using compounds **1**−**3**, we found only a single hit: the reaction catalysed by $Pd(OAc)_2$ on acetanilide (**1**) in AcOH using benzoquinone as oxidant. This hit was included in the next run where compounds **4** and **5** were

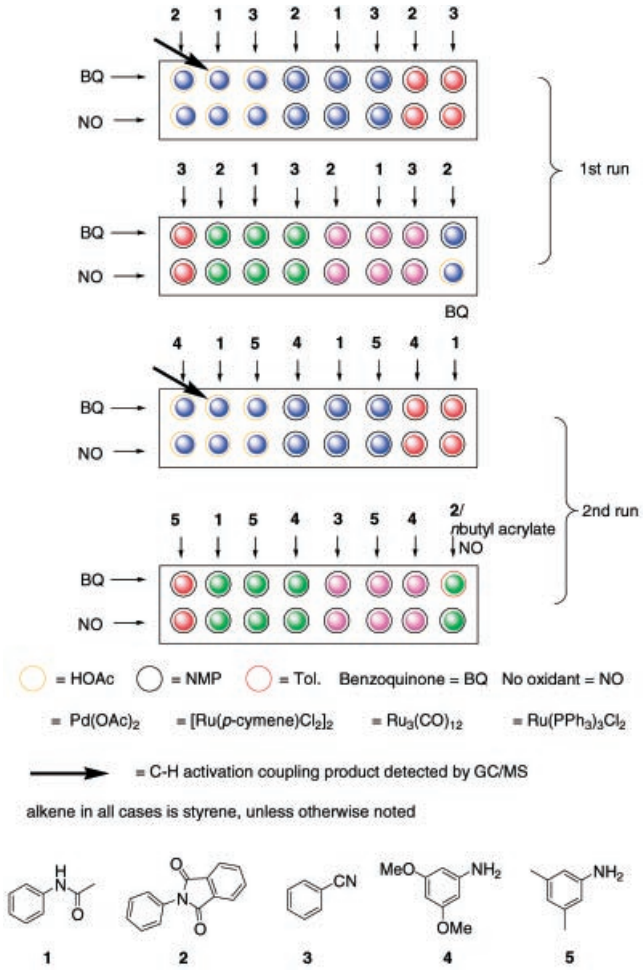
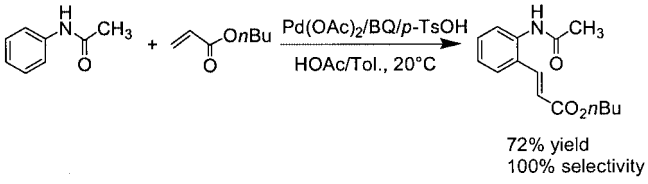


Figure 2. Discovery of C−H activation based arylation of olefins with aniline derivatives in two ASW 2000 runs (64 reactions at 80 °C)

screened. We were able to duplicate the initial lead, but no new hits were found in this run. As expected, butyl acrylate was more reactive than styrene, allowing the reaction to be performed at room temperature. The reaction has been optimised further, resulting in a 72% yield of coupling product between **1** and butyl acrylate using 2 mol % of $Pd(OAc)_2$ as catalyst, a stoichiometric amount of benzoquinone, and catalytic *p*-toluenesulfonic acid in an HOAc/toluene mixture (Scheme 2).[38]



Scheme 2

This approach clearly shows the power of the HTE method in finding not only a working catalyst, but also suitable reaction conditions. It is doubtful that this lead would

have been found if a classical single-reaction approach had been used.

4b. Discovery of an Easily Recyclable Ligand-Free Palladium Catalyst for Heck Reactions

The wide functional group tolerance in palladium-catalysed carbon−carbon bond formations, particularly those involving sp^2-carbon atoms[39] as in the Heck reaction, opens up new and important synthetic applications for fine chemicals.[3,40]

Recently, a lot of effort has been put into the development of new, more active and more stable palladium catalysts for the Heck reaction by the use of palladacycles, underligated single-phosphane systems, and carbene complexes.[41] The use of phosphorus ligands, however, is often undesirable in fine chemical processes. They are expensive, toxic, unrecoverable, and they frequently hamper the isolation and purification of the desired product as well as the performance of consecutive catalytic steps of the total synthesis.

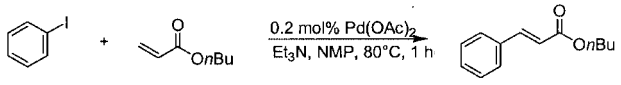
On the other hand, phosphane-free systems have shown excellent activities in Heck reactions,[41] especially when phase-transfer agents, aqueous systems, palladium nanoparticles, or less-usual leaving groups (diazonium salts, acid chlorides or anhydrides) are used. An additional advantage of ligand-free approaches is the potentially easy recovery of the palladium catalyst, which usually precipitates after the reaction has reached completion.

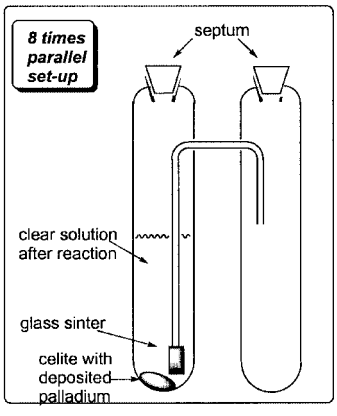
We have used this advantage to develop a "recyclable" palladium catalyst. We first measured the palladium content of the solution remaining after the Heck reaction between iodobenzene and *n*-butyl acrylate catalysed by $Pd(OAc)_2$ (Figure 3) by filtering off the deposited palladium through Celite. More than 99% of the palladium was precipitated and no more than 5.5 ppb of palladium was found in the filtrate. When the recovered palladium is reused for a second run, however, its activity is greatly diminished. Precipitation on carriers such as silica or Celite improved the activity somewhat by increasing the surface area, but the activity was still about tenfold lower than that of the virgin $Pd(OAc)_2$. We envisioned that the only way to restore the palladium to its original activity would be to oxidise it back to a "monomeric" species.

Several different additives were tested by using the ASW 2000 equipped with a filtration block (eight parallel vessels, see also Figure 3). In the first run, all vessels were filled with the same reagents, including $Pd(OAc)_2$ and Celite, and obviously all gave the same result: > 98% yield of the *trans* product after 60 min. The vessels were cooled, and the reaction mixtures were separated from the precipitated palladium on Celite by applying a small vacuum in the right-hand side vessel (Figure 3). The residues were washed with methyl *tert*-butyl ether (MTBE) and filtered by the same vacuum method to exclude any residual homogeneous palladium. The resulting grey materials were treated with different oxidants or additives dissolved in NMP before the next Heck reaction was performed (Run 2). Note that all handling was automated.

Remarkably, mild oxidants such as Br_2 or I_2 dissolve the precipitated palladium (on Celite) rapidly returning the original activity in successive runs of the ligand-free Heck reaction (Figure 3).[42]

Other additives, such as HOAc, LiI, and HI, did not restore catalytic activity to the same extent. When no reactivator or stronger oxidants (HNO_3, H_2O_2, $NaIO_4$) were used, hardly any Heck product was formed in the successive runs. This lead-finding HTE approach resulted in a protocol where we add just two equivalents of I_2 (or Br_2) to the recovered Pd on Celite in NMP prior to the next run, leading to fully restored activity in the Heck reaction. In this manner, we have performed up to eight consecutive runs without loss of activity.





run 1 yields	catalyst reactivation with:	run 2 yields	catalyst reactivation with:	run 3 yields
99	–	9	–	1
99	H_2O_2	2	H_2O_2	2
98	LiI	70	LiI	57
99	HOAc	41	HOAc	17
99	HI	81	HI	56
98	I_2	99	I_2	99
99	Br_2	99	Br_2	98
98	$NaIO_4$	10	$NaIO_4$	2

Figure 3. Schematic representation of a successful HTE approach to finding a suitable reactivator of precipitated catalyst in a ligand-free palladium-catalysed Heck reaction

In general these HTE approaches produce a considerable number of samples which must have their conversions, yields and selectivities determined. The need for faster analysis than the conventional GC method of ca. 30 min is obvious. By using fast GC, analysis on a narrow-bore CPSIL8CB column, the compounds *n*-butyl acrylate, iodobenzene, *n*-butylcinnamate, dihexyl ether (internal standard), NMP, and Et_3N are separated in 1.5 min (Figure 4).

Aryl bromides are less reactive than aryl iodides. Reactions that proceed smoothly can be achieved, however, when the conditions are chosen in such a way that the oxidative addition of the substrate to the palladium(0) species[43] − the start of the catalytic cycle leading to the product − is faster than precipitation of the catalyst as inactive palladium black crystals. With the same ligand-free catalytic system [$Pd(OAc)_2$, base (Et_3N or NaOAc), in NMP], this principle was demonstrated with 3-bromopyridine and 4-bromoacetophenone as substrates. Three successive runs, in which the palladium was recovered by Celite and reactivated with iodine prior to the next run, were performed with 3-bromopyridine at 130 °C, each time giving the product in > 80% yield within 4 h (0.3 mol % of palladium).[42]

5. Scope Determination by the HTE Approach

Once a new reaction has been discovered it is good practice, generally, to get an idea about its scope. Whereas in the past this has been a tedious affair, the HTE approach allows for rapid screening of substrates under a set of standard conditions. These reactions are followed over time to get an impression of their rates and possible inhibition of the catalyst. Although GC-MS is an ideal tool for these analyses, recently we have begun to use high throughput flow NMR spectroscopy as a means of analysing these reactions. Apart from exact data about conversion, yield, and selectivity, the method also supplies information about the structure of side products. In addition, no sample handling is necessary, which makes the method very rapid.

5a. Homeopathic Palladium Catalysis in the Heck Rreaction with Aryl Bromides

Spurred by the findings described in the last paragraph of Section 4b, we posed the seemingly contradictory thesis: "*the lower the palladium loading the higher the turnover frequencies (TOF).*" Lowering the concentration of palladium shifts the equilibrium between monomeric palladium and clusters to the monomeric side (Figure 5). At some concentration the point will be reached where all palladium stays in solution throughout the reaction.[44]

With this hypothesis of preventing the formation of less-active clusters and precipitated palladium in mind, the Heck reaction of iodobenzene and *n*-butyl acrylate was performed with a very low catalyst loading: 2 mg of $Pd(OAc)_2$ (0.01 mol %) was sufficient to couple 20 g of iodobenzene with *n*-butyl acrylate within 2 h at 85 °C. This process amounts to a TOF of about 7500 mol product/mol catalyst/h.

This low-loading ligand-free approach, dubbed *homeopathic palladium loading*, is also applicable to the less-react-

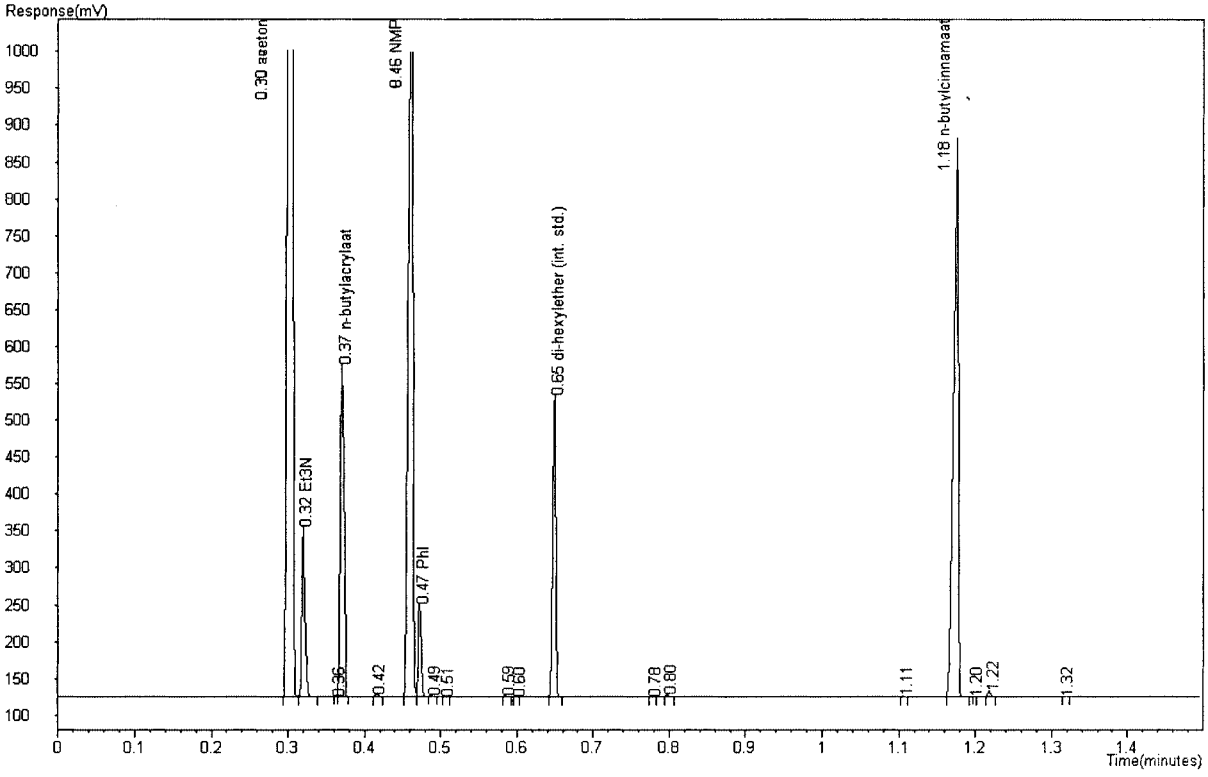


Figure 4. High-throughput GC for Heck chemistry

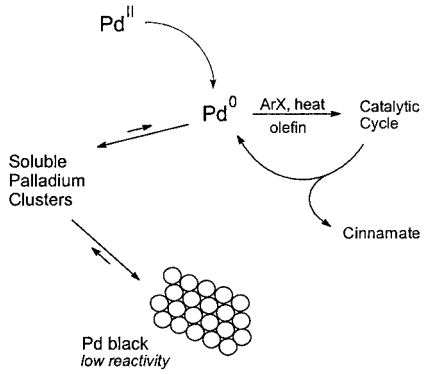


Figure 5. Low palladium concentrations suppress formation of palladium black and keep all the metal available for catalysis

ive bromides. Again 0.01 mol % of $Pd(OAc)_2$ converted both 4-bromoacetophenone and 3-bromopyridine to the Heck products with *n*-butyl acrylate (selectivity > 90%, GC analysis) within two and 20 h, respectively, at 130 °C and with NaOAc as base.[45]

By using the ASW 2000, the scope of this low-catalyst-loading procedure has been tested with respect to the aryl bromides used. Thus, a wide range of different aryl bromides were examined in the ligand-free Heck reaction by using 0.05 mol % $Pd(OAc)_2$, NaOAc, and *n*-butyl acrylate, in NMP at 130 °C (2 mmol scale). At set intervals, samples were taken from the reaction mixtures and conversions and selectivities were determined (off line) by GC. Most substrates studied (Figure 6) were converted successfully into the Heck product, (i.e., a yield of trans Heck product of > 80%, reaction times between one and 24 h).

The scope of the low-loading principle was further investigated by another ASW 2000 run. Several different olefins were treated with four aryl bromides (4-bromoacetophenone, bromobenzene, 4-bromochlorobenzene, and 2-bromo-6-methoxynaphthalene). Selectivities in these reactions were similar to those obtained using conventional phosphane-containing catalysts (Figure 6).

The invented catalyst system (ligand-free, low loading) is widely applicable and, relative to conventional systems, very cost effective. Furthermore, since the reaction mixture contains no phosphane ligands, isolation of the product is very easy.

5b. Homeopathic Palladium in the Suzuki Reaction

Biaryl compounds play an important role in industrial chemistry, appearing in commercial products ranging from performance materials to pharmaceuticals.[46] Much research has been published on synthetic routes towards *ortho*-tolylbenzonitrile, a common intermediate for a number of *Sartan*-type blood-pressure-lowering agents.[10] During the last three decades, there have been a number of significant advances in biaryl coupling technology that have really broadened the scope of previous methods (e.g., Ullmann coupling) used in multistep synthetic schemes.[47]

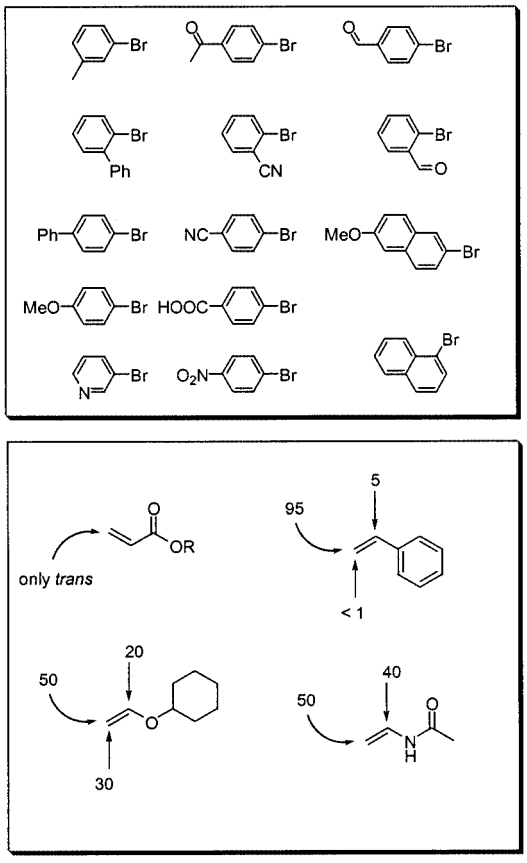


Figure 6. Scope of the "homeopathic" Heck reaction between aryl bromides and butyl acrylate (top) and between various aryl bromides and olefins (bottom) [conditions: 0.05 mol % $Pd(OAc)_2$, NaOAc, NMP, 130 °C, 2 mmol scale]

The characteristics of organoboron reagents (i.e., high selectivity in cross-coupling reactions, stability, nontoxic nature, and tolerance towards functional groups) often gives the Suzuki coupling a practical advantage over other cross-coupling processes.[48] Recently, highly efficient conversions have been reported for Suzuki couplings that are based on the use of bulky electron-rich ligands[49] or on two-phase catalysed processes using water-soluble phosphane ligands.[50]

We were particularly interested in the application of the ligand-free homeopathic palladium loading procedure in Suzuki reactions.[51–53] In view of the large number of parameters affecting the Suzuki reaction, we envisioned that an HTE approach would be an efficient way to approach optimisation.[54,55] Using the ASW 2000, we screened several different solvents, palladium sources, bases, additives, and reaction conditions, for a wide range of aryl bromides and arylboronic acids.

Preliminary experiments coupling 4-bromoacetophenone with phenylboronic acid using $Pd(OAc)_2$ (0.05 mol %) and K_2CO_3 in NMP revealed that this ligand-free approach is promising, but these unoptimised conditions caused precipitation of the palladium before full conversion was reached. An HTE screening of several different solvents and solvent combinations showed that NMP/water (19:1), toluene, and

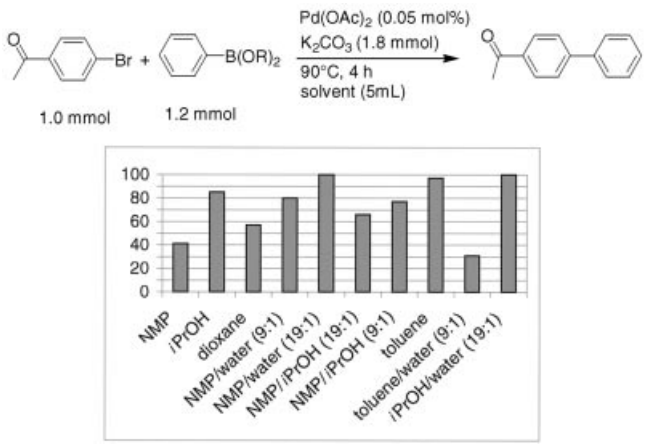


Figure 7. Solvent effects in Suzuki couplings of 4-bromoacetophenone and phenylboronic acid

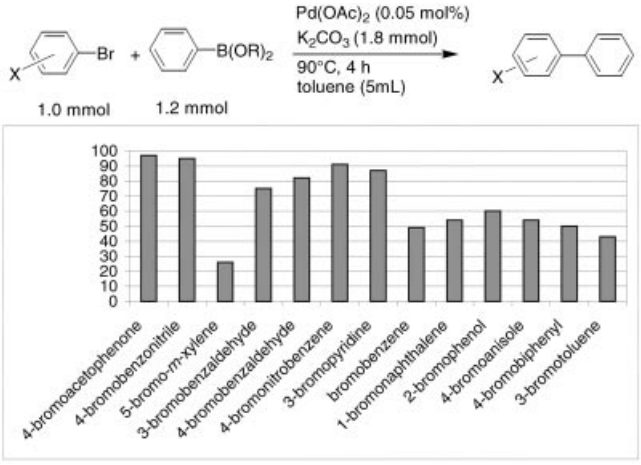


Figure 8. Scope of aryl bromides used in "homeopathic" palladium-catalysed Suzuki reactions with $PhB(OH)_2$

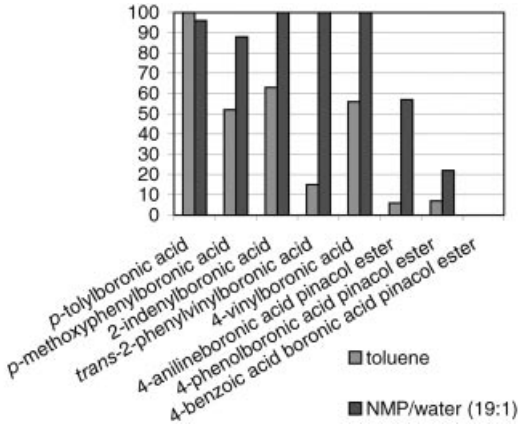


Figure 9. "Homeopathic" palladium catalyses Suzuki couplings of 4-bromoacetophenone with organoboron reagents in two different media [1 mmol scale, 0.05 mol % $Pd(OAc)_2$, K_2CO_3, 90 °C]

*i*PrOH/H_2O (19:1), are especially suitable media for the studied coupling (Figure 7).

It is interesting to note that next to protic media, well known from earlier studies,[48] toluene is also a highly effective solvent. In toluene/water (9:1), however, the conversion of the aryl bromide is remarkably low. Apparently the balance between highly active ligand-free palladium and less-active palladium clusters is a delicate one. However, we were very pleased to see that with these unoptimised conditions [$Pd(OAc)_2$ (0.05 mol %), K_2CO_3, toluene] a wide range of aryl bromides can be coupled with phenylboronic acid. Activated aryl bromides gave smooth conversions and high yields, and yields between 26 and 60% were obtained with nonactivated and deactivated aryl bromides (Figure 8).

Several different bases, such as K_2CO_3, DBU, K_3PO_4, KF, NaOAc, and NaOH, were tested in the Suzuki reaction of $PhB(OH)_2$ and 4-bromoacetophenone in two different media: toluene and NMP/water (19:1). K_3PO_4 and KF were less efficient than K_2CO_3 and DBU gave poor results in both toluene and NMP/water. In toluene, $NaOAc{\cdot}3H_2O$ and NaOH gave very poor results, but when NMP/water was the solvent, the latter two both resulted in complete conversion of the aryl bromide.

Next, we performed an HTE screening study of different organoboron reagents in the coupling with 4-bromoacetophenone using the ligand-free homeopathic palladium loading in two different media. As is shown in Figure 9, several functional groups are tolerated in the organoboron reagent.

In most cases, the couplings in NMP/water (19:1) are higher yielding than those in toluene. Pinacol esters of functionalised boronic acids were difficult to couple. It is unclear if this low reactivity is due to the ester functionality or the functionality (amine, phenol or acid group) in the organoboron reagent.

In an ASW 2000 run, several Pd catalysts were tested for the coupling of 4-bromoacetophenone with phenylboronic acid and 2-indenylboronic acid, respectively, in toluene and in NMP/water. During this test, the catalysts were 0.01 mol % $PdCl_2$, PdI_2 and $Pd(CF_3CO_2)_2$, which were added as suspensions in toluene. The results are summarised in Table 3.

Table 3. The conversion of 4-bromoacetophenone in the Suzuki coupling catalysed by different Pd species

Pd catalyst	Conversion in toluene (%)	Conversion in NMP/water (19:1) (%)
$Pd(acac)_2$	94	100
$Pd_2(dba)_3$	97	92
$PdCl_2$	32	100
PdI_2	79	90
$Pd(CF_3CO_2)_2$	81	99
$Pd(OAc)_{23}$	100	97

From these results it can be concluded that the Pd source is not very important for reactions carried out in NMP/water, but when toluene is the solvent, the results differ significantly. This observation might be due to the solubility of the catalyst.

To verify the effectiveness of the ligand-free homeopathic palladium loading in Suzuki couplings, we performed some

selected examples − including workup and product isolation − on a laboratory scale (10 mmol). Isolated yields of between 76 and 95% were obtained.

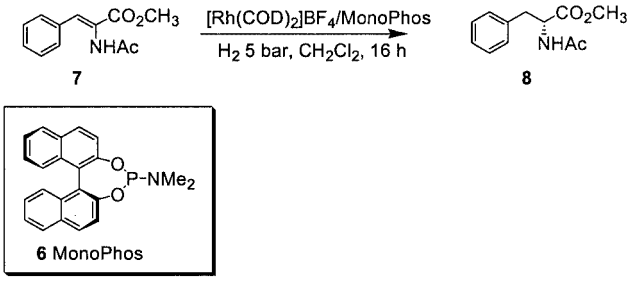
Using this HTE approach, we developed a widely applicable and very cost-effective catalyst for Heck and Suzuki couplings of aryl bromides in a very short period of time.

6. Mechanistic Research

Although the use of HTE makes it possible to find leads and optimise them with a limited knowledge of the underlying chemistry, a better understanding of the mechanism helps to reduce the number of variables (see Table 2) that must be screened. HTE can be a valuable tool in this analysis.

Not much work has appeared in the literature about the use of HTE techniques for mechanistic research. One prominent exception is the work of Chen and co-workers, who developed the concept of "mechanism-based high-throughput screening of catalysts". They have developed this concept mainly for screening of mixtures of transition metal catalysts for olefin polymerisation. The method is based on the detection of polymers using ES-MS. Using collision-induced dissociation they were capable of splitting the catalyst from the polymer. Out of mixture of eight palladium catalysts, a single one emerged successfully from this test.[19]

A recent example of a mechanistic use of HTE stems from our work in collaboration with Feringa's group on the application of monodentate phosphoramidites in the asymmetric hydrogenation of olefins.[11] MonoPhos (**6**), the simplest member of the class of BINOL-based phosphoramidites, shows excellent performance in the rhodium-catalysed hydrogenation of methyl 2-acetamidocinnamate (**7**). In initial screens aimed at optimising this reaction, we made the surprising discovery that at a ligand-to-rhodium ratio of less than two the hydrogenation of **7** became faster, yet the enantioselectivity of the product remained the same. These experiments were performed in Schlenk tubes with magnetic stir bars at 1 bar pressure at the relatively high catalyst/substrate ratio of 5 mol %. Under these conditions, mass transfer can become a limiting feature that may have a profound effect on the rate and selectivity of the reaction. For this reason, we performed a series of experiments in the Endeavor™, which has efficient overhead stirring. The hydrogenations of **7** using Rh/MonoPhos were performed with a substrate/catalyst ratio of 6500 mol/mol (0.015 mol %) at a pressure of 5 bar (Scheme 3). Figure 10 shows the results of 12 experiments that are the result of two Endeavor runs. The duration of the experiment was chosen such that no reaction went to 100% completion. This allows us to use the GC yield as a measure of the rate of the reaction.[56]



Scheme 3

The results confirm the earlier observation that the rate of the reaction increases at ligand/rhodium ratios of less than two. In this case, the optimal ratio seems to be around 1.5. If the ratio exceeds three, the catalysis stops. Assuming a reaction mechanism in which the substrate is bound to the rhodium in a bidentate fashion, the oxidative addition of H_2 to the rhodium complex would be impossible if more than two ligands are bound to the metal. These results also confirm that the *ee* of the product remains practically constant over the range of L/Rh of 0.62 to 3. This strongly suggests that the active catalyst species remains the same over this range. To obtain more information we have followed a 1 bar hydrogenation experiment (**6**/Rh = 2.1) by electrospray mass spectrometry. In addition to the expected peaks corresponding to [Rh(**6**)(substrate)]$^+$ and

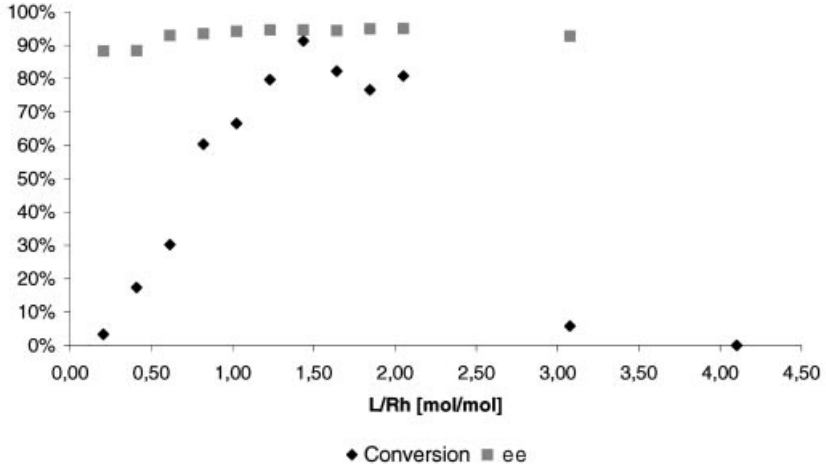
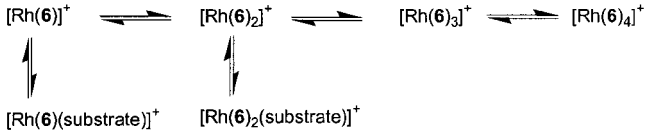


Figure 10. Dependence of the MonoPhos/Rh ratio on the conversion of **7** and the *ee* of **8**



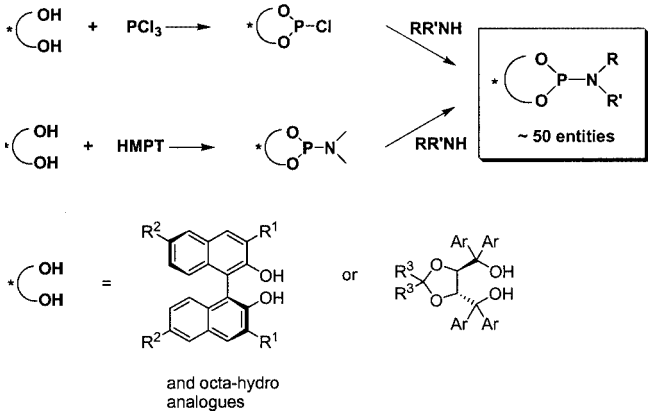
Scheme 4. Species observed by ES-MS in the asymmetric hydrogenation of **7** using Rh/MonoPhos.

$[Rh(\mathbf{6})_2(substrate)]^+$, we observed much larger peaks that can be assigned to $[Rh(\mathbf{6})_3]^+$ and $[Rh(\mathbf{6})_4]^+$ (Scheme 4). The latter species could be isolated in crystalline form, which allowed us to prove its structure by X-ray crystallography.[11d] The conclusion of these experiments is that the actual catalyst contains one or two ligands. The active catalyst is in equilibrium with more-highly ligated species that are inactive. Lowering the ligand concentration shifts the equilibrium to the lower-ligated species. We are currently studying methods to suppress the formation of the higher-ligated species.

7. Ligand Libraries

After the original work of Gilbertson,[57] who synthesised libraries of polypeptides in which phosphane-containing amino acids were incorporated for asymmetric hydrogenation, many publications and patents have appeared concerning the preparation of ligand libraries by parallel synthesis. Quite a number of review articles have appeared recently on this subject.[13−18] The library approach is particularly attractive for chiral ligands as the factors that cause induction of high levels of enantioselection are hard to predict. In addition, the enantioselectivity will always be dependent on the structure of the substrate. From the industrial point of view, one would thus like to have available medium- to large-sized libraries of chiral ligands; least one for each type of transformation. We believe that ligands that are produced by lengthy synthetic sequences do not suit this approach. Not only will it be hard to produce the desired library, but it will also be problematic to produce kg amounts within a short period of time for production purposes. Furthermore, the cost factor is very important. For example, chiral bis(phosphane) ligands will cost EUR 30000−100000/kg, which means that very high turnover numbers are needed for cost-effective production based on their use. Therefore, we have focused on non-phosphane ligand libraries for asymmetric hydrogenation reactions. This approach has led to the discovery of monodentate phosphoramidites for the asymmetric hydrogenation of olefins.[11] Other monodentate ligands such as phosphites[58] and phosphinites[59] are also highly amenable to a library approach, but publications have yet to appear describing their incorporation into libraries.

For other types of catalysis, the focus has been on modular approaches, using readily available components that can be combined in high yield in just a few steps.[60] Amino acids are major building blocks in these approaches.[61] Salen/amino acid-type catalysts developed by Hoveyda[62] and by Jacobsen[63] have been used for asymmetric hydrocyanation and the Strecker reaction. Ligands based on chiral β-amino sulfonic acids have been developed by Gennari[64] and by Liskamp.[65] The modular approach has been used by us for the synthesis of a library of monodentate phosphoramidite ligands (Scheme 5).

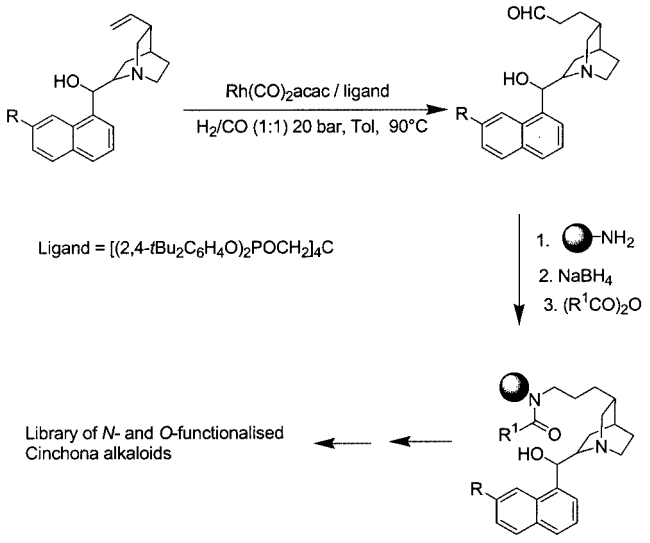


Scheme 5. Modular approach to a library of phosphoramidite ligands

Cinchona alkaloids have been used as ligands for several types of catalysis, such as asymmetric dihydroxylation and aminohydroxylation.[66] In addition, they have been used as organocatalysts for asymmetric alkylation and asymmetric Michael-type reactions.[67] They are superbly suited for a combinatorial approach; in particular, the hydroxy and tertiary amino moieties have been functionalised extensively. We were interested in the creation of a library of immobilised cinchona alkaloids. Although the amino function can be used for attachment to the solid support, doing so would seriously compromise the diversity of the libraries. We therefore turned our attention to a method that would allow the attachment of the alkaloids via their olefinic units. This process was accomplished by highly regioselective hydroformylation of the olefin using a catalyst based on rhodium and a tetradentate phosphite ligand. The resulting aldehydes were isolated in good yields.[68] The formyl group can be easily attached to a resin containing a primary amine by reductive amination. We are currently engaged in the synthesis of a library of *O*- and *N*-functionalised cinchona alkaloids, to be used in catalysis[69] and chiral recognition[70] (Scheme 6).

8. Conclusions

Through the introduction of HTE techniques in our technology development programs, as well as our process development, we have been able to increase both the output and the quality of our R&D. More importantly, we have been able to reduce the time necessary to find a catalyst and conditions for a given transformation to about three weeks, given availability of the starting materials. We have been able to reach this goal with catalyst precursors and ligands that are, for the most part, commercially available. The HTE approach works for lead discovery as well as for op-



Scheme 6. An approach to an immobilised library of cinchona alkaloids

timisation. For asymmetric catalysis, it is important to have sizeable libraries of chiral ligands that are easily prepared in no more than three synthetic steps. A modular approach may be the best method to do this. Ideally, at least one library should be available for each transformation. We are currently expanding our libraries of monodentate phosphoramidites and of immobilised cinchona alkaloids. Mechanistic insight remains very important, as it helps to guide us in the selection of suitable parameters. We have shown that it is possible to use HTE even for mechanistic research. Once a new reaction or catalyst system has been developed, HTE can be used for rapid determination of its scope. Use of GC-MS, HPLC, and flow NMR spectroscopy suffices to measure the outcome of these screens. As a result of the implementation of HTE, DSM Pharmaceutical Products expects to implement several processes based on homogeneous catalysis.

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[1] *Applied Homogeneous Catalysis with Organometallic Compounds*, vol. 1 and 2 (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**.
[2] J. G. de Vries, in *Encyclopedia of Catalysis* (Ed.: I. Horvath), Wiley, New York, **2002**, web-edition.
[3] *Transition Metals for Organic Synthesis; Building Blocks and Fine Chemicals*, vol. 1 and 2 (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**.
[4] R. A. Sheldon, *J. Mol. Catal. A: Chem.* **1996**, *107*, 75−83.
[5] This percentage is based on the personal observations of the authors.
[6] See also: H.-U. Blaser, B. Pugin, F. Spindler, in *Applied Homogeneous Catalysis with Organometallic Compounds*, vol. 2 (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, pp. 992−1009.
[7] C. Mercier, P. Chabardes, *Pure Appl. Chem.* **1994**, *66*, 1509−1518.
[8] H. Kumobayashi, *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 201−210.
[9] [9a] H.-U. Blaser, H.-P. Buser, K. Coers, R. Hanreich, H. P. Jalett, E. Jelsch, B. Pugin, H.-D. Schneider, F. Spiondler, A. Wegmann, *Chimia* **1999**, *53*, 275−280. [9b] H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 17−31.
[10] C. E. Tucker, J. G. de Vries, *Top. Catal.* **2002**, *19*, 111−118.
[11] [11a] M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539−11540. [11b] M. van den Berg, A. J. Minnaard, B. L. Feringa, J. G. de Vries, Catalyst for asymmetric (transfer) hydrogenation, WO 02 04466, January 17, **2002**. [11c] M. van den Berg, R. M. Haak, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Adv. Synth. Catal.* **2002**, *344*, 1003−1007. [11d] M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal.* **2003**, *345*, 308−323.
[12] *Combinatorial Chemistry. Synthesis, Analysis, Screening* (Ed.: G. Jung), Wiley-VCH, Weinheim, **1999**.
[13] K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885−1889.
[14] R. H. Crabtree, *Chem. Commun.* **1999**, 1611−1616.
[15] A. Hagemeyer, B. Jandeleit, Y. Liu, D. M. Poojary, H. W. Turner, A. F. Volpe, Jr., W. H. Weinberg, *Appl. Catal A: General* **2001**, *221*, 23−43.
[16] M. Reetz, *Angew. Chem. Int. Ed.* **2001**, *40*, 284−310.
[17] S. Dahmen, S. Bräse, *Synthesis* **2001**, 1431−1449.
[18] A. Hoveyda, in *Handbook of Combinatorial Chemistry*, vol. 2 (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 991−1016.
[19] There are exceptions. See: C. Hinderling, P. Chen, *Angew. Chem. Int. Ed.* **1999**, *38*, 2253−2256; *Angew. Chem.* **1999**, *111*, 2393−2396.
[20] J. M. Newsam, F. Schüth, *Biotechnol. Bioeng.* **1998/1999**, *61*, 203−216.
[21] B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem. Int. Ed.* **1999**, *38*, 2494−2532; *Angew. Chem.* **1999**, *111*, 2648−2689.
[22] M. Larhed, C. Moberg, A. Hallberg, *Acc. Chem. Res.* **2002**, *35*, 717−727.
[23] M. Eckert, U. Notheis, in *Handbook of Combinatorial Chemistry*, vol. 2 (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 831−863.
[24] O. Brümmer, B. Jandeleit, T. Uno, W. H. Weinberg, in *Handbook of Combinatorial Chemistry*, vol. 2 (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 864−884.
[25] B. Archibald, O. Brümmer, M. Devenney, S. Gorer, B. Jandeleit, T. Uno, W. H. Weinberg, T. Weskamp, in *Handbook of Combinatorial Chemistry*, vol. 2 (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 885−990.
[26] M. Bauser, H. Stakemeier, in *Handbook of Combinatorial Chemistry*, vol. 1 (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 190−224.
[27] [27a] A. C. Cooper, L. H. McAlexander, D.-H. Lee, M. T. Torres, R. H. Crabtree, *J. Am. Chem. Soc.* **1998**, *120*, 9971−9972. [27b]

G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 4306−4307. [27c] K. H. Shaughnessy, P. Kim, J. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 2123−2132. [27d] O. Lavastre, J. P. Morken, *Angew. Chem. Int. Ed.* **1999**, *38*, 3163−3165; *Angew. Chem.* **1999**, *111*, 3357−3359.

[28] [28a] A. Holzwarth, H.-W. Schmidt, W. F. Maier, *Angew. Chem. Int. Ed.* **1998**, *37*, 2644−2647; *Angew. Chem.* **1998**, *110*, 2788−2792. [28b] M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem. Int. Ed.* **1998**, *37*, 2647−2650; *Angew. Chem.* **1998**, *110*, 2792−2795.

[29] D. B. Kassel, *Chem. Rev.* **2001**, *101*, 255−267.

[30] S. Senkan, K. Krantz, S. Ozturk, V. Zerngin, I. Onal, *Angew. Chem. Int. Ed.* **1999**, *38*, 2794−2799; *Angew. Chem.* **1999**, *111*, 2965−2971.

[31] For a highlight summarising recent developments, see: M. T. Reetz, *Angew. Chem. Int. Ed.* **2002**, *41*, 1335−1338.

[32] K. Burgess, H.-J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220−222; *Angew. Chem.* **1996**, *108*, 192−194.

[33] M. B. Francis, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1999**, *38*, 937−941; *Angew. Chem.* **1999**, *111*, 987−991.

[34] S. J. Taylor, J. P. Morken, *J. Am. Chem. Soc.* **1999**, *121*, 12202−12203.

[35] M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, *Angew. Chem. Int. Ed.* **1998**, *37*, 662−664; *Angew. Chem.* **1998**, *110*, 688−690.

[36] F. Kakiuchi and S. Murai, in *Topics in Organometallic Chemistry*, vol. 3 (Ed.: S. Murai), Springer-Verlag, Berlin, **1999**, pp. 47−79.

[37] C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633−639.

[38] M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586−1587.

[39] F. Diederich, P. J. Stang, *Metal-catalysed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.

[40] J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086−1092.

[41] I. P. Beletskaya, A. V Cheprakov, *Chem. Rev.* **2000**, *100*, 3009−3066.

[42] [42a] F. J. Parlevliet, A. H. M. de Vries, J. G. de Vries, WO 02/00340. [42b] A. H. M. de Vries, F. J. Parlevliet, L. Schmieder-van de Vondervoort, J. H. M. Mommers, H. J. W. Henderickx, M. A. M. Walet, J. G. de Vries, *Adv. Synth. Catal.* **2002**, *344*, 996−1002.

[43] We assume that the resting state of the catalyst is an anionic PdX^-_3 species (X = Br, I). See ref.[42b] for details.

[44] A kinetic explanation is also possible: Formation of clusters will be higher order in palladium, whereas the Heck reaction will be first- or half-order in palladium, depending on if the resting state is monomeric or dimeric. For a Heck reaction half-order in palladium, see: G. P. F. van Strijdonck, M. D. K. Boele, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1999**, 1073−1076.

[45] A. H. M. de Vries, J. G. de Vries, WO 02/057199, **2002**, to DSM nv.

[46] H. Geissler, in *Transition Metals for Organic Synthesis*, vol. 1 (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp. 158−183.

[47] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359−1469. See also a special issue of *J. Organomet. Chem.* **2002**, *653*, no. 1−2.

[48] [48a] A. Suzuki, in *Metal-catalysed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 49−97. [48b] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457−2483. [48c] A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 83−90.

[49] Phosphanes: A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028, and references therein. Imidazolium salts: G. A. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell, S. P. Nolan, *Organometallics* **2002**, *21*, 2866−2873, and references therein.

[50] [50a] S. Haber, H. J. Kleiner, DE 19527118. [50b] M. Beller, J. G. E. Krauter, A. Zapf, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 772−774.

[51] For ligand-free Suzuki couplings in water or aqueous mixtures (at least 50% water), see: I. P. Beletskaya, *Pure Appl. Chem.* **1997**, *69*, 471−476, and references therein.

[52] T. I. Wallow, B. M. Novak, *J. Org. Chem.* **1994**, *59*, 5034−5037.

[53] D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170−7173.

[54] An earlier example of the use of HTE in the optimisation of a Suzuki raction: E. G. IJpeij, F. H. Beijer, H. J. Arts, C. Newton, J. G. de Vries, G. J. Gruter, *J. Org. Chem.* **2002**, *67*, 169−176.

[55] For a similar HTE approach using Ph_3P-based polymer-supported catalysts in Suzuki couplings, see: T. J. Colacot, E. S. Gore, A. Kuber, *Organometallics* **2002**, *21*, 3301−3304.

[56] This assumption is valid only when no catalyst deactivation occurs.

[57] S. R. Gilbertson, X. Wang, *Tetrahedron Lett.* **1996**, *37*, 6475−6478.

[58] M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889.

[59] C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* **2000**, 961.

[60] R. Kramer, K. Eis, O. Geis, S. Mühle, J. W. Bats, H.-G. Schmalz, *Chem. Eur. J.* **2000**, *6*, 2874−2894 and references cited therein.

[61] G. Liu, J. A. Ellmann, *J. Org. Chem.* **1995**, *60*, 7712−7713.

[62] [62a] B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668−1671; *Angew. Chem.* **1996**, *108*, 1776−1779. [62b] K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoeveyda, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704−1707; *Angew. Chem.* **1997**, *109*, 1781−1785.

[63] [63a] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902. [63b] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315−5316.

[64] [64a] C. Gennari, S. Ceccarelli, U. Piarulli, C. A. G. N. Montalbetti, R. F. W. Jackson, *J. Org. Chem.* **1998**, *63*, 5312−5313. [64b] I. Chataigner, C. Gennari, U. Piarulli, S. Ceccarelli, *Angew. Chem. Int. Ed.* **2000**, *39*, 916−918.

[65] A. J. Brouwer, H. J. van der Linden, R. M. J. Liskamp, *J. Org. Chem.* **2000**, *65*, 1750−1775.

[66] R. A. Johnson, K. B. Sharpless, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojina), 2nd ed., Wiley-VCH, New York, **2000**, p. 357−398.

[67] K. Kacprzak, J. Gawronsky, *Synthesis* **2001**, 961−998.

[68] M. Lambers, F. H. Beijer, J. M. Padron, I. Toth, J. G. de Vries, *J. Org. Chem.* **2002**, *67*, 5022−5024.

[69] European Union-funded RTN network, *The Discovery of New Molecular Catalysts through Combinatorial Chemistry. Activity and Selectivity from Diversity*, HPRN-CT-2000-00014. See: http://www.oc.uni-koeln.de/berkessel/CombiCat/index.shtml

[70] European Union-funded RTN network, *Enantioselective Recognition. Towards the Separation of Racemates*, HPRN-CT-2001-00182 See: http://www.soton.ac.uk/~jdk1/ecn/

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