Perspectives in Catalysis

Combinatorial chemistry, high-speed screening and catalysis

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Combinatorial and high-speed screening techniques, which have revolutionized the search for new drug molecules, are now finding broader application in the chemical and materials development areas. The ability to generate large "libraries" of samples and to evaluate their performance simultaneously reduces the time and cost per sample and enables multicomponent parameter spaces to be explored. In the area of catalyst development, the impact of this technology promises to be substantial, not only in synthesis and performance evaluation, but also for the optimization of operating parameters. In this review, the major experimental approaches are described; for heterogeneous catalysts, especially, the parallel approach proves the most useful, rather than the "split-and-mix" methods of drug screening. Novel techniques for the high-speed, parallel performance evaluation of catalyst arrays are reviewed with numerous recent examples. Indications are provided of expected future trends in this rapidly developing area.

Keywords: combinatorial chemistry, split-and-mix and parallel synthesis, high-speed screening techniques, catalysis

1. Introduction

Combinatorial chemistry and high-speed screening are complementary technologies for the simultaneous preparation of large numbers of chemical compounds or formulations and their subsequent performance testing. Since the end of the nineteen-eighties, combinatorial chemistry as a tool for the screening of large "libraries" of new drug molecules has shown unprecedentedly rapid development, to the point that combinatorial methods are becoming an industrial standard for the discovery of novel drugs [1]. The first new pharmaceutical products developed with its help are expected to reach the market shortly.

The incentive to adopt this technology is provided by the fact that, in contrast to traditional methods, in which product formulations or sets of processing conditions are tested sequentially, by using high-speed screening (HSS) techniques it is possible to synthesize and screen arrays of tens or hundreds of samples simultaneously. Clearly, this approach has the potential for substantial time-savings in research and development, reducing considerably the time-to-market of new industrial developments. Industrial interest in combinatorial and HSS technology is demonstrated by the mushrooming of small dedicated new companies and joint ventures as providers of the technology to the pharmaceutical and, to an increasing extent, other industries.

To illustrate the advantages of combinatorial chemistry, one may assume that, on average, a chemist is able to create one pharmaceutical compound per week at a cost of $7500, while in the same amount of time combinatorial equipment can generate, say, around 800 compounds at a total cost of $10000, that is $12 per single compound [2]. Automated equipment can perform operations more rapidly (and for 24 h a day) and can also cope with very small amounts of reactants with high precision. Besides being faster and cheaper, combinatorial methods are also safer and have a lower environmental impact, since they use only small quantities of reactants. A further advantage of combinatorial techniques is their high reproducibility; since the operations are largely performed by robotic equipment, the experimental errors due to different preparation conditions or different operators are reduced and the reproducibility of the experiments is notably increased.

The early successes in the area of drug-molecule screening have stimulated the application of these techniques to the development of other materials [3]. Areas in which interesting results have been obtained include: the discovery of high-temperature superconductors [4] and of magnetoresists [5] (materials which change in electrical resistance when a magnetic field is applied); synthesis of metal surfaces exhibiting a gradient in composition [6]; synthesis of organic host compounds [7] (crystals containing lattice inclusions); optimization and discovery of luminescent metal oxide materials [8–10]; development of biodegradable polymers [11]; molecular recognition [12–14] (particularly of compounds able to extract a specific molecule or ion from a mixture).

Catalysis is a field to which the application of combinatorial and HSS techniques is particularly suited and, in the following, an overview will be provided of the impact of combinatorial chemistry on catalysis [15–20]. All operations involved in the development of a catalyst lend themselves to the application of these techniques. The synthesis of both homogeneous and heterogeneous catalysts,

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their screening for activity and selectivity in test reactions, and also the determination of the optimal process parameters for a specific reaction, can all be conducted with much greater speed and efficiency employing the miniaturized, automated combinatorial/HSS procedures than by the use of conventional methods. In the area of catalysis research and development alone, it is estimated that industrial spending already exceeds $US 500 million annually.

2. Methods

In order better to understand what combinatorial chemistry is, it is instructive to consider as an example the reaction of a compound of class A (e.g., a Lewis acid) with a compound of class B (e.g., a Lewis base) in a solvent S to give a product P. Combining n different compounds of class A with m different compounds of class B and l different solvents S, $n \times m \times l$ different experiments would be defined, each of which could lead to a different product or to a different yield for a particular product. Such an approach can be useful if one were trying, e.g., to obtain product P with the highest yield.

Once such a collection of products (usually referred to as a *library*) has been synthesized, it is necessary to subject it to a screening test regarding their performance or physical properties. The mode of screening depends on the type of product and on its properties (e.g., catalyst selectivity or product yield).

When performing a synthetic combinatorial chemistry experiment, two basically different strategies may be followed to create a library of compounds: *split-and-mix* (or split and pool) and *parallel* synthesis.

2.1. Split-and-mix synthesis

Split-and-mix synthesis is generally related to the use of polymer resin beads as support for the reaction and used to synthesize bioactive compounds [1], typically polypeptides. In the first step of the synthesis, the resin is divided into n equal parts and each of them is treated with one of the n different reagents. After that the n portions of resin are washed, combined and mixed in one vessel, then divided again into n equal parts. In the second step each portion is again treated with one of the n reagents and then the washing, mixing and splitting steps are repeated. The procedure is iterated m times. At the end a library of n^m products is obtained in just m steps (figure 1).

Once such a library has been created, it has to be tested to determine, e.g., the bioactive compound(s). A problem that arises when the split-and-mix synthesis method is used, is how to identify the compound(s) among the components of the library giving positive results during that screening.

One way to overcome this problem is by a process known as *deconvolution* [1]. In the first step the elements of the library are divided into the n vessels and screened for activity: the active vessel is identified and the others are eliminated. The compounds of this vessel are resynthesized in smaller libraries and screened again for activity. The process of elimination goes on until the active compound is established (figure 2).

Although deconvolution has proved useful, it presents some drawbacks: it is quite a time-consuming process, besides, when the active vessel is identified, there is no certainty that the activity is due to the presence of a single active product but could result from the presence of many weakly active compounds.

Another technique used to identify the compounds that showed activity during screening is that of *encoding*. The

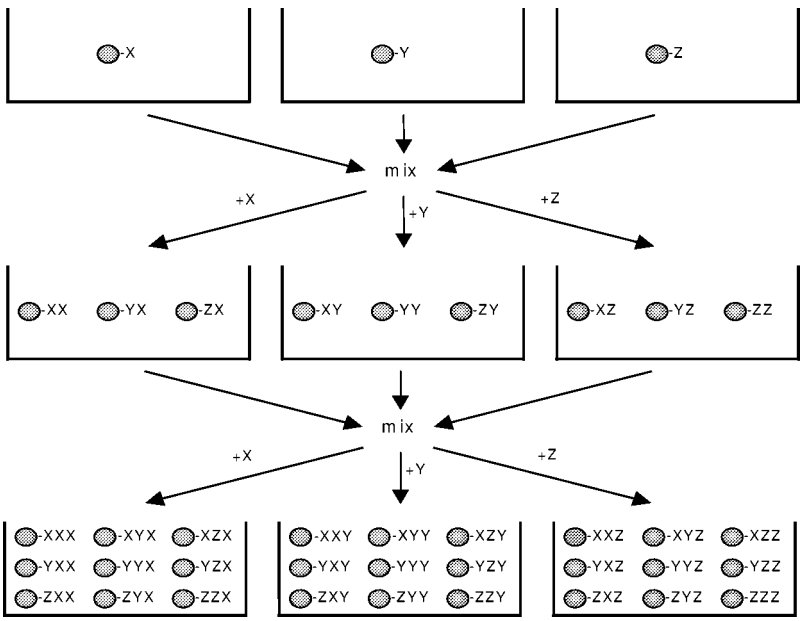

Figure 1. Split-and-mix synthesis; in this example, a library of 27 elements is generated in just three steps by combining three different reagents.

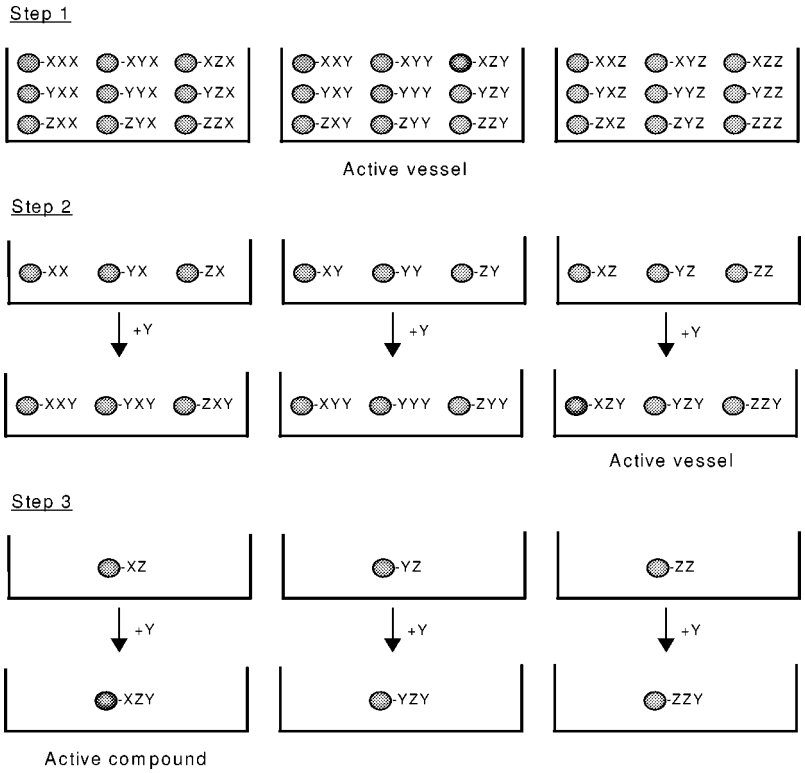

Figure 2. Example of deconvolution process for a library of 27 compounds.

method consists in tagging each compound of the library during the synthesis with a different tag; suitable tags show particular chemical or physical properties that can be easily detected [21,22].

2.2. Parallel synthesis

In parallel synthesis the various reactions take place in separate vessels; typically, robotic equipment is used to pick and mix the reactants in different miniature vessels or wells, so that an array of distinct products is obtained.

The library thus created, again, has to be screened to determine the active compound(s). In contrast to the split-and-mix approach, in this case the problem is not to identify the active product after screening, since they are arrayed in separate wells, but to find a suitable way to test all the isolated products at high throughput speeds.

If the screening process of the library is performed one well at a time it can be very expensive and time consuming and would negate some of the advantages of combinatorial synthesis. To avoid this, fast and affordable analytical methods, usually referred to as *high-speed screening* (HSS) techniques [23], are being developed by many groups [30,44]. Current HSS technology is based on the use of miniaturized, automated and parallel versions of tools conventionally employed to screen the compounds under study, such as chromatographic, spectroscopic or thermographic techniques, and in some cases of new specifically developed methods. The choice of the type of HSS is related to the particular feature that is to be detected and, therefore, has to be tailored for any system under investigation.

Comparing the two synthetic strategies, it is clear that the split-and-mix approach is more useful when it is necessary to evaluate numerous different compounds (diverse library). On the other hand, parallel synthesis could be preferable when some knowledge of the structure of the target compound is available or when just an optimization of the target is requested (focussed library).

Parallel synthesis is generally the choice for materials other than pharmaceuticals; even for the latter the complexity of the split-and-mix approach is causing its displacement by parallel synthesis, except in favourable cases. It may be noted that there is an increasing tendency to reserve the term “combinatorial” for library generation and screening of molecules such as drugs and to use “high-speed screening” for the parallel sample preparation and testing of other materials including catalysts.

3. Combinatorial and high-speed screening techniques in catalysis

The development of new catalysts is a challenging task. In many cases the correlation between their features (structural, electronic) and their performance (activity, selectivity, lifetime) is not easily established. Therefore an iterative process of “design”, synthesis and testing is usually followed to improve catalyst performance. Combinatorial chemistry and HSS technology can accelerate this process considerably, allowing for the simultaneous evaluation of

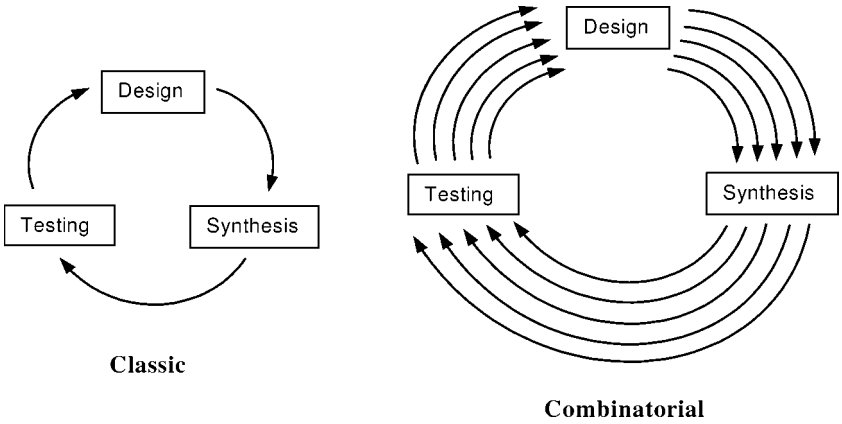

Figure 3. Comparison between classic and combinatorial methods.

a large number of candidates (figure 3). Although combinatorial chemistry can be considered as a powerful tool to increase the number of possible candidates to be examined, it is no alternative to rational methods for the development of catalysts: chemical intuition is needed to make the choices regarding the type of library needed and the kind of screening to be employed, depending on the target aimed at (e.g., discovery of new systems, optimization of known ones, reduction of side reactions, etc.)

Up to now, combinatorial chemistry has been applied mostly to the optimization of previously known catalytic systems [24–33] and only a few cases of the generation of new catalysts using that approach have been reported [34–36]. In the field of catalysis, the parallel approach is the one most commonly used.

3.1. Screening techniques and inorganic catalysts

To efficiently analyze the products obtained in a combinatorial experiment, high-speed screening techniques need to be applied. The choice of the screening method depends on the feature that has to be detected and on the availability of a suitable technology to perform that analysis. Up to now, many works dealing with the applications of combinatorial chemistry to catalysis, particularly heterogeneous, put the stress more on the development of the screening techniques used to follow the catalyzed reactions rather than on the improvement of the catalysts.

Infrared thermography has found some applications as a high-speed screening technique to identify the most active catalysts for a number of reactions [37–39]. As many chemical reactions are exothermic, the most active catalyst will lead to the highest yield in the reaction and therefore to the largest temperature change. An IR imaging camera can be used to measure the temperature simultaneously for all the vials involving the catalyzed reactions: so the most active catalyst can be identified. It has been demonstrated that temperature differences down to 0.1 K can be detected reliably and that the technique can be applied over a wide temperature range even if working with small catalyst amounts [37]. The main shortcoming of IR thermography is that it is not suitable to determine the selectivity of the catalyst.

Willson et al. created a combinatorial library of zerovalent metal elements supported on γ-alumina and screened them as catalysts for hydrogen oxidation by means of infrared thermography [37]. The samples were tested over a wide range of temperatures. The results confirmed the well-known activity of Pd, Pt, Ir and Rh and therefore proved the suitability of the screening technique for that system.

IR thermography was also used by Maier et al. to screen a library of binary alloys impregnated on amorphous microporous metal oxides as catalysts for the hydrogenation of hexyne and for the oxidation of isooctane and toluene [38]. The screening was performed at different temperatures and led to the identification of active catalysts for each reaction.

A highly sensitive and fully automated *scanning mass spectrometer* was developed by the Weinberg group [16,40] and employed in the screening of a triangular library of 120 different Pt, Pd and Rh alloys, representing a ternary phase diagram for the system. The alloys were prepared, using a parallel approach, in thin films (100 nm) and tested as catalysts for the oxidation of CO to CO_2, by either O_2 or NO. After the library was synthesized, it was placed in the scanning mass spectrometer, in which quartz capillaries permitted the reaction gases to reach the elements of the library, one at a time, and then let the product gas flow to the ionization zone of the spectrometer, allowing for separate analysis of catalysts activity. A CO_2 laser was used selectively to heat each sample. The oxidation reactions were screened at different temperatures and, for both oxidants, showed a trend in activity in agreement with literature data (Rh $>$ Pd $>$ Pt). Furthermore, new libraries were prepared replacing each of the noble metals with the less expensive Cu. The alloys were tested again for the two reactions: some positive results were obtained using O_2 as oxidant, particularly with Rh–Cu binary alloys, while catalyst deactivation was observed for the oxidation with NO.

Senkan developed the high-speed screening technique *resonance-enhanced multiphoton ionization* (REMPI) for testing libraries of heterogeneous catalysts for the dehydrogenation of cyclohexane to benzene ($C_6H_{12} \rightarrow C_6H_6 +$

$3H_2$) [41,42]. The technique is a combination of the selective photoionization of reaction products using UV lasers under resonance conditions, with the successive detection of the photoionized products by means of an electrode. Although very selective, the main drawback of this technique is that molecules must have different ionization potentials (IP) to be selectively identified; moreover, they should neither dissociate when ionized nor have too large IP values. These intrinsic requirements reduce the range of compounds to which this technique can be successfully applied. In the initial work [41a], it was found that samples with the highest loading of Pd or Pt catalyst showed the highest activity, demonstrating the consistency of the screening technique for that system. In a second experiment [42] a dehydrogenation catalyst was studied in more detail and optimized; ternary catalysts were prepared by impregnation of Pt, Pd and In on γ-Al_2O_3 in different ratios. The screening confirmed the suitability of the technique and lead to the identification of the most active ternary mixture ($Pt:Pd:In = 8:1:1$).

Akporiaye et al. used a combinatorial approach to synthesize zeolites by developing an autoclave able to carry out at least 100 parallel crystallizations at temperatures up to 200 °C [43]. First they studied the well-known ternary phase system Na_2O–Al_2O_3–SiO_2–H_2O and obtained a ternary phase diagram showing different zeolite types as a function of the composition rates of Na_2O, Al_2O_3 and SiO_2. Comparing this result with the published phase diagram for the same system, they were able to confirm, despite some variations in the results with respect to those obtained by traditional methods, the general validity of their approach. In a second step the Na_2O–Al_2O_3–SiO_2 system was modified by introducing Li, Na, Cs and tetramethylammonium cations, thus generating a quaternary phase diagram showing the presence of six different types of zeolites as a function of the composition rates of the four cations. It is worthy of note that the zeolites described in this work are obtained only from dilute aqueous solutions; different synthesis conditions should lead to different results, so that it is clear that the richness of this system has hardly begun to be explored. X-ray diffraction was used to assess the different zeolite structures. The authors claim that procedures for a fully automated powder X-ray diffraction analysis of the arrays of materials are under development [43]. However, equipment of this type has already been used by Maier and colleagues for the screening of a parallel library of 37 titanium silicalites TS-1 [44]. They employed a commercial microdiffractometer in which a high intensity X-ray beam can be focussed to a diameter of 50 μm, allowing individual analysis of each element of the library. They were able to determine the identities of the various crystalline or amorphous phases, using only small amounts (50–150 μg) of each of the 37 samples. In this way they proved that this technique may be used to identify the crystalline structure of libraries of solids obtained from synthesis in the liquid phase.

Hill and Gall, in the first reported account of the use of combinatorial techniques to synthesize a parallel library of 39 heterogeneous phosphorus-centered molybdenum and tungsten polyoxometalates (heteropoly acids having the Keggin structure) catalysts, tested them for the selective oxidation of tetrahydrothiophene to its corresponding sulphoxide (figure 4) [45]. Gas chromatography was used to determine the yields and selectivities of the reaction and to identify the most effective catalyst; however, almost all the tested compounds showed comparable catalytic activity for this oxidation. Traditional ^{51}V-NMR and IR spectroscopic techniques were used to characterize the polyoxometalates.

Mallouk, Smotkin and co-workers used a parallel combinatorial approach to synthesize metal alloys utilized as catalysts for direct methanol fuel cells [34]. A library of 645 binary, ternary and quaternary alloys containing Pt, Ru, Os, Ir, Rh was prepared and screened. The choice of the metals constituting the alloys was based on the knowledge of the reaction mechanism, which involves two metal centres: one to activate methanol and another one to activate water (figure 5). The library was synthesized using a modified ink-jet printer that allowed for dispensing of aqueous solutions of metal salts. The screening was performed by converting the hydrogen ions generated in the anode reaction into a fluorescent signal, by means of a fluorescent acid–base indicator; the strongest fluorescence indicates the most active catalyst. In this way it proved possible to identify the composition of a new high-performance catalyst ($Pt_{44}Ru_{41}Os_{10}Ir_5$). In subsequent work [46], these metal alloy catalysts have been thoroughly characterized using X-ray diffraction and X-ray photoelectron spectroscopy.

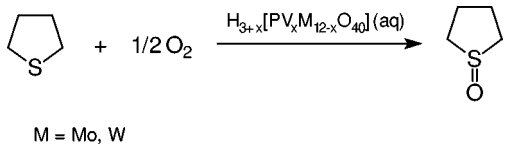

Figure 4. Oxidation of tetrahydrothiophene to the tetrahydrosulphoxide.

Anode reaction:

$$CH_3OH + H_2O \rightarrow CO_2 + 6H^+ + 6e^-$$

Mechanism (M^I = Pt, Ir; M^{II} = Ru, Os):

$$M^I + CH_3OH \rightarrow M^I\text{–}(CH_3OH)_{ads}$$
$$M^I\text{–}(CH_3OH)_{ads} \rightarrow M^I\text{–}(CH_3O)_{ads} + H^+ + e^-$$
$$M^I\text{–}(CH_3O)_{ads} \rightarrow M^I\text{–}(CH_2O)_{ads} + H^+ + e^-$$
$$M^I\text{–}(CH_2O)_{ads} \rightarrow M^I\text{–}(CHO)_{ads} + H^+ + e^-$$
$$M^I\text{–}(CHO)_{ads} \rightarrow M^I\text{–}(CO)_{ads} + H^+ + e^-$$
$$M^{II} + H_2O \rightarrow M^{II}\text{–}(H_2O)_{ads}$$
$$M^I\text{–}(CO)_{ads} + M^{II}\text{–}(H_2O)_{ads} \rightarrow M^I + M^{II} + CO_2 + 2H^+ + 2e^-$$

Figure 5. Anode reaction of a methanol fuel cell.

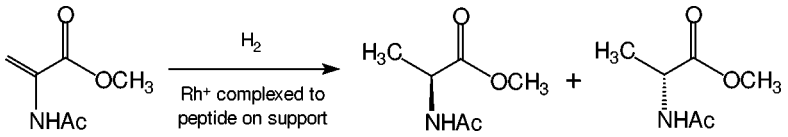

Figure 6. Hydrogenation of methyl 2-acetamidoacrylate.

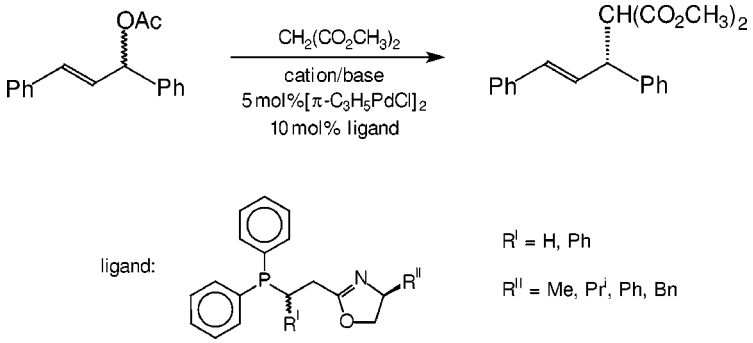

Figure 7. Asymmetric addition of malonate to 1,3-diphenylprop-2-enyl acetate.

Besides identifying a new catalyst, Mallouk and Smotkin also demonstrated that, in some cases, combinatorial libraries of catalysts can be screened by detecting a change in a chemical feature that takes place during the reaction. In an analogous way, Crabtree and co-workers are developing a screening method for catalytic reactions involving C=C or C=N functonalities, based on the colour variation of the reaction solution [47]. They attached an electron donor and an electron acceptor group to the compound containing the C=C or C=N, so that the two groups are conjugated through the double bond and the compound acts as a dye. When the reaction involving the double bond takes place, the electronic connection between donor and acceptor groups is interrupted and the colour of the dye changes; the most effective catalyst produces the largest rate of colour change. This technique has still to be optimized to find suitable acceptor and donor groups; furthermore, the usual caution in working with model compounds applies, since the presence of the two groups may change the reactivity of the substrate.

3.2. Organometallic catalysts

Combinatorial chemistry has been applied by various researchers to the development of organometallic catalysts for asymmetric synthesis. The main application in this field so far is the optimization of the ligands of known catalysts to obtain higher performance [24–32] but just a few cases in which different reaction conditions are optimized have been reported [35,36,48,49]. Frequently, the catalysts are supported on polymer beads to simplify their separation from the products of the reaction. Chromatographic methods have been widely used to screen the activity and selectivity of asymmetric catalyst libraries (GC [24,29,31,35], GLC [26,28] and HPLC [30,32,36,48,49]). This proved that, besides spectroscopic and diffractive techniques, also

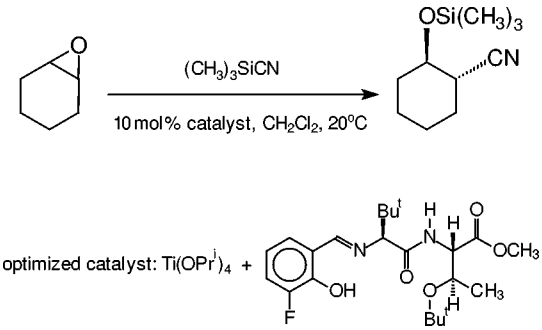

Figure 8. Enantioselective addition of trimethylsilyl cyanide to cyclohexane epoxide.

chromatography can be a viable and simple way to test catalyst libraries for selected reactions.

One of the first applications of combinatorial chemistry to asymmetric catalysis is that of Gilbertson and Wang [24]. They synthesized a library of 63 peptide-based phosphine ligands for a Rh(I) catalyst and tested it for the enantioselective hydrogenation of methyl 2-acetamidoacrylate (figure 6). Although the results did not lead to the identification of ligands leading to high stereoselectivity, this work demonstrated that combinatorial methods can be applied to the optimization of catalyst ligands. In more recent work Gilbertson and Chang used the same approach to optimize a palladium catalyst for the asymmetric addition of malonate to 1,3-diphenylprop-2-enyl acetate (figure 7) [25]; both the palladium ligands and the solvent were optimized. Two kinds of phosphinodihydroxyazole ligands were screened, with either one or two chiral centers. In both cases high enantiomeric excesses were observed.

Hoveyda, Snapper et al. have utilized parallel synthesis to optimize a chiral peptide Schiff-base ligand to prepare a titanium complex used as catalyst for the enantioselective addition of trimethylsilyl cyanide to cyclohexane epoxide, giving cyanohydrins (figure 8) [26,27]. The following strategy in the search of the most effective combination of three

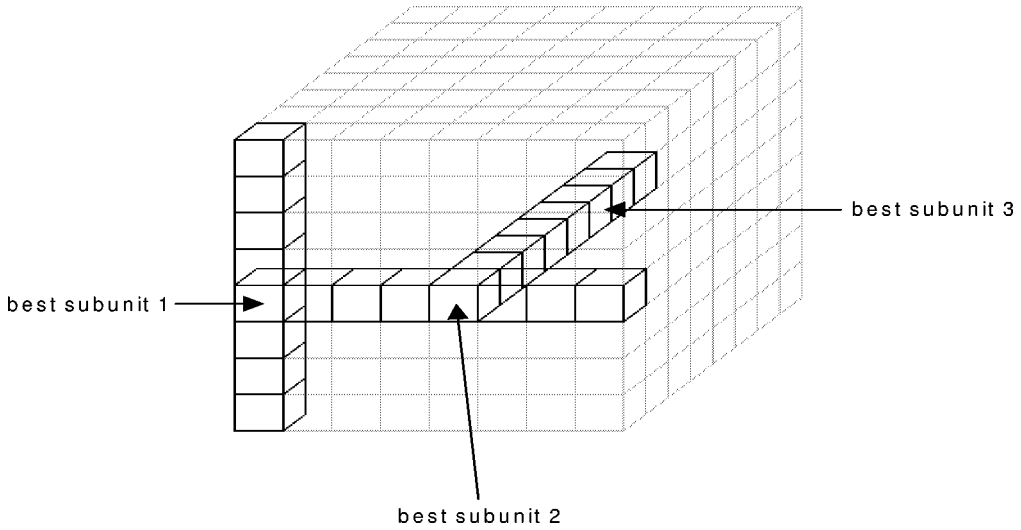

Figure 9. Schematic representation of the strategy assuming an additive and independent effect of each subunit.

subunits constituting the ligand was employed: each subunit was optimized separately by varying it, while keeping the other two constant. Hence, it was not necessary to consider all possible combinations of the three subunits, reducing the time requested to identify the most suitable ligand (assuming an additive and independent effect of each building block, cf. figure 9, however, such assumptions may only hold for selected systems). Using this approach, a catalyst with high selectivity was identified. Subsequently, the same optimization was performed successfully with different epoxide substrates [26,28]. It may be pointed out here that the matrix nature of parallel-synthesis arrays can be enlisted to detect interactions between components by employing experimental-design techniques.

Another example of a parallel combinatorial approach used for the optimization of catalyst ligands is reported in the work of Jacobsen and Sigman [29]. Polymer-supported tridentate Schiff-base complexes were used as catalysts for the asymmetric hydrocyanation of imines, known as the Strecker reaction (figure 10). A library of catalysts with different metal ions was first screened for enantioselectivity; from the results obtained a second library was created and tested. On the basis of the results achieved, a third library was built and screened; finally, the best catalyst was identified as a metal-free species.

In more recent work [35] Jacobsen and Francis used both split-and-mix and parallel approaches to identify a novel catalyst for the epoxidation of *trans*-β-methylstyrene, TBMS (figure 11). A library of 5760 elements was created by combining 30 different metal ions with 192 ligands constituted of various amino acids and imines supported on polystyrene. After having identified H_2O_2 as a viable oxidant and a 1 : 1 mixture of CH_2Cl_2 and Bu^tOH as best solvent for the whole library, 30 different pools, each containing a mixture of all 192 ligands and a metal-ion source, were synthesized and screened for the epoxidation of TBMS: the pool containing the complexes prepared from $FeCl_2$ was identified as the most active. Then a parallel

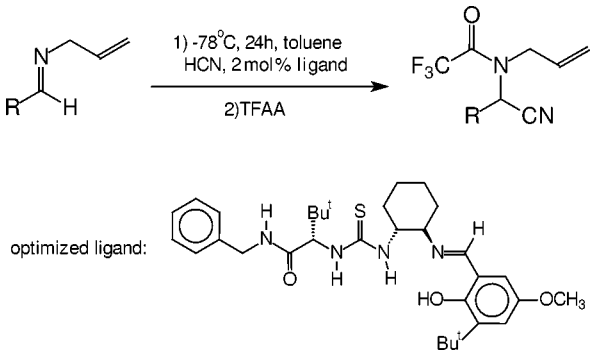

Figure 10. The Strecker reaction.

approach was used to resynthesize all 192 combinations of ligands with $FeCl_2$ in separate vessels; by screening this library the three ligands (all containing a pyridine group) that led to the highest catalytic activity were identified. Finally, these three ligands were modified to enhance the enantioselectivity of the catalysts, creating and screening a library of 96 elements. The best three catalysts obtained from this last optimization showed, however, only a slight increase in the enantioselectivity rates compared to those identified in the previous step.

Moody et al. highlighted some possible limitations of the use of ligands prepared as polymer-bound species, such as the introduction of a functional group on the ligand to attach it to the polymer resin or the potential steric variations between supported and free ligands. Therefore, they used a parallel approach to create a non-supported library of 80 carboxylic acid ligands for a Rh(II) catalyst for the enantioselective Si–H insertion reaction of diazoesters with silanes (figure 12) [30]. The majority (69) of the ligands gave chiral dirhodium(II) carboxylate complexes, the structure of which was confirmed by automated NMR and mass spectrometry. The dirhodium catalysts were then tested for the selected Si–H insertion and two complexes were identified as the most effective ones. Some derivatives of the two related chiral carboxylic acid ligands were used fur-

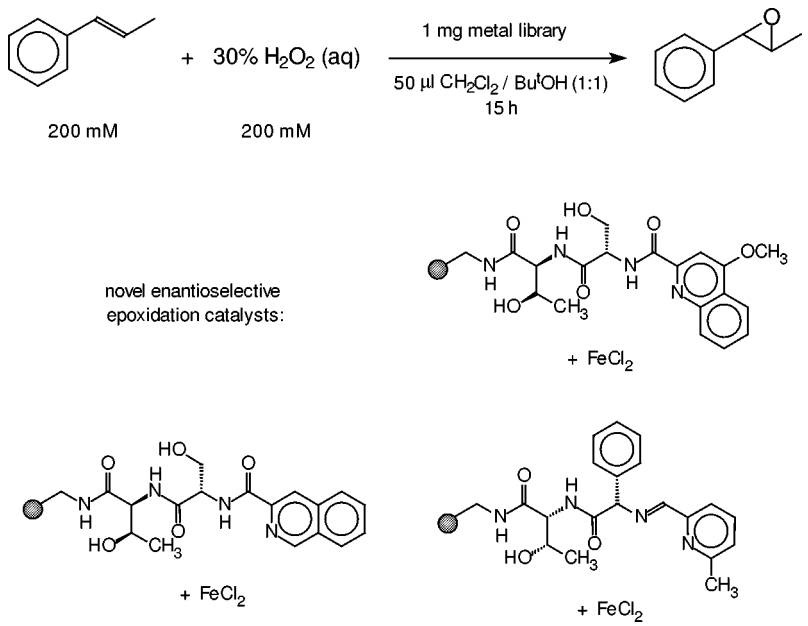

Figure 11. Epoxidation of TBMS.

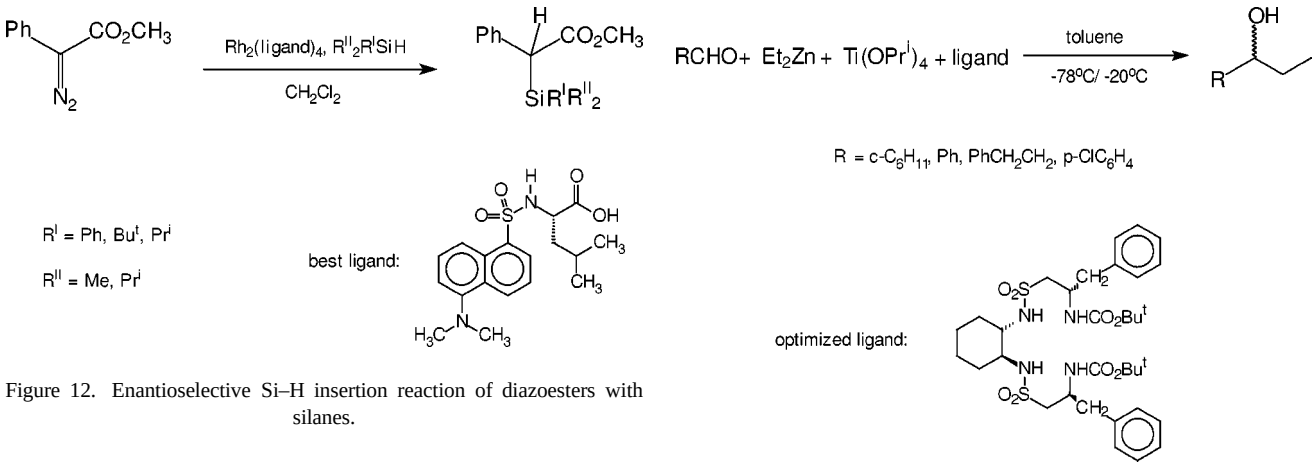

Figure 12. Enantioselective Si–H insertion reaction of diazoesters with silanes.

Figure 13. $Ti(OPr^i)_4$-mediated enantioselective catalytic addition of Et_2Zn to aldehydes.

ther to create another library of ligands. This new library was screened for the same reaction in order to identify the catalyst ligand that lead to the highest enantiomeric excess.

Gennari, Piarulli and co-workers created a library of 30 disulphonamide metal chelating chiral units by parallel synthesis [31]. These ligands were screened for the $Ti(OPr^i)_4$-mediated enantioselective catalytic addition of Et_2Zn to various aldehydes: the reaction was tested both with one disulphonamide ligand and a mixture of four aldehydes and with a mixture of five disulphonamide ligands and one aldehyde. In this way, the most selective catalyst ligand was identified (figure 13).

Mikami and co-workers used a parallel combinatorial strategy to optimize a different catalyst for the same enantioselective addition of Et_2Zn to aldehydes described above [32]. In a first step they prepared a library of chiral ligands and activators (chiral additives which can enhance the catalyst efficiency). On the basis of the results obtained after screening this library for the addition of Et_2Zn to aldehydes, they created another library of activators. The screening of this second library allowed the identification of a chiral ligand/activator couple that led to a very selective and active catalyst, superior to that found by Gennari and co-workers for the same reaction (figure 14).

Burgess and colleagues used parallel combinatorial methods to obtain better catalysts for selected reactions by varying a range of experimental parameters. In their initial work [36] they studied various organometallic catalysts for the intramolecular cyclization of diazo compounds involving asymmetric insertion of metallocarbenes into C–H bonds (figure 15). To obtain the most effective catalyst they tested different combinations of metal centers, ligands and solvents using 96-well plate equipment; the best results were obtained with a Cu(I) and an Ag(I) complex using THF as solvent. In a more recent investigation [48] they screened catalysts for the asymmetric allylation of 4-acyloxy-2-pentenes by coupling the variation of the phos-

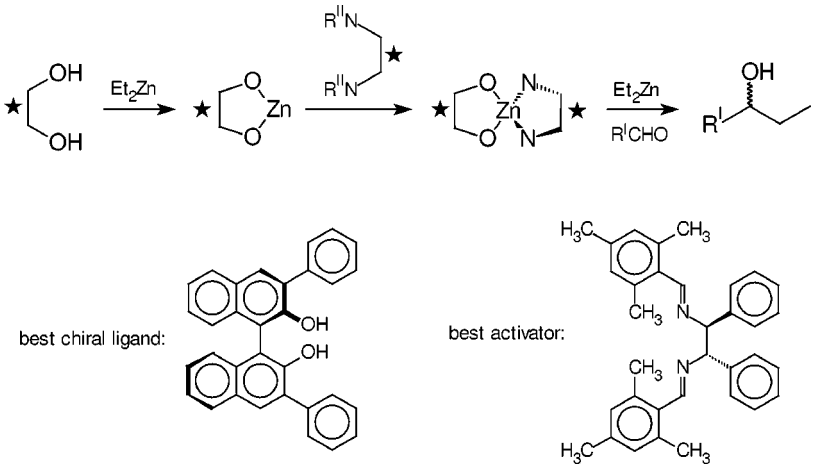

Figure 14. Enantioselective catalytic addition of Et_2Zn to aldehydes in presence of an activator.

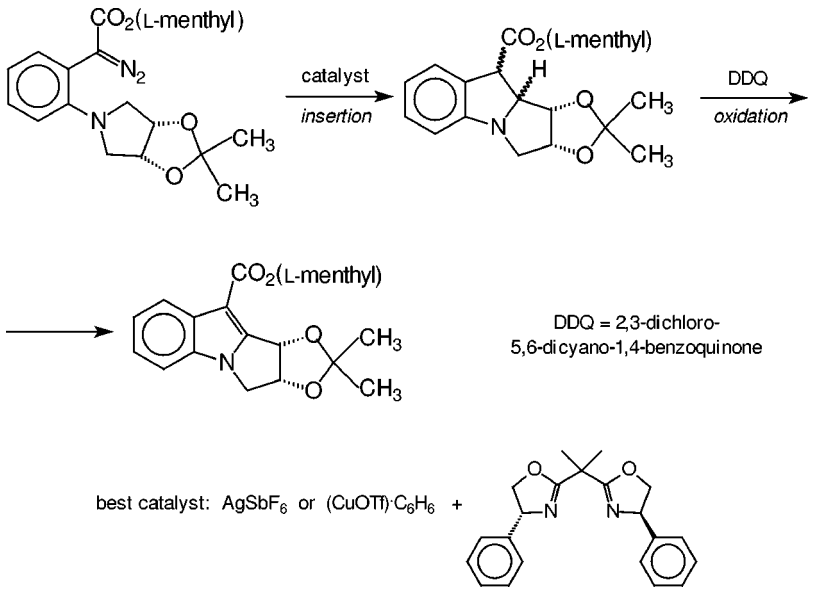

Figure 15. Intramolecular cyclization of diazo compounds involving asymmetric insertion of metallocarbenes into C–H bonds.

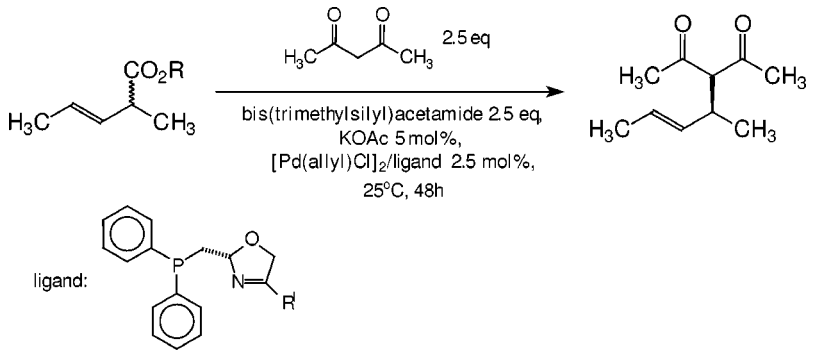

Figure 16. Asymmetric allylation of 4-acyloxy-2-pentenes.

phine ligands with that of the metal : ligand ratio (figure 16). The data obtained showed trends that lead to some general considerations about the most suitable features of the catalyst, i.e., larger substituents on the phosphine ligands and a lower ligand-to-metal ratio lead to higher enantioselectivity.

Using a similar approach to that of Burgess, Whiting and co-workers created a 144-member library of Lewis-acid catalysts for the asymmetric aza-Diels–Alder reaction of an imino dienophile (see figure 17) [49]. The library was produced by combining different metal salts, ligands,

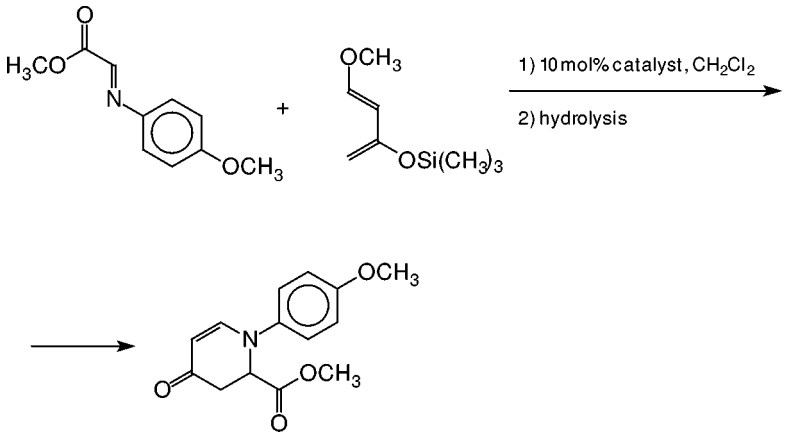

Figure 17. Asymmetric aza-Diels–Alder reaction of an N-aryl imine.

solvents and additives. Many of the tested catalysts showed a high enantioselectivity, but it was not possible to identify any specific trend in these results.

Additionally, the optimization of ligands for organometallic catalysts through combinatorial chemistry approaches has found applications in fields other than asymmetric synthesis: Murphy, Powers and colleagues studied ligands for Ni and Pd catalysts for olefin polymerization [33]. Employing parallel synthesis, they created a library of 96 aryl-substituted 1,2-diimine ligands and complexed them with Ni(II) and Pd(II) centers on a cross-linked polystyrene support. These catalysts were screened for their ethylene polymerization activity; while the polymer-supported nickel catalysts turned out to be less effective than the corresponding free species, the palladium catalysts showed an enhanced activity, compared with that of their free complex homologues.

3.3. Organic catalysts

Taylor and Morken created a library of 3150 polymer-bound nucleophilic catalysts for acylation reactions using the split-and-mix synthesis approach combined with encoding techniques [39a]. The catalysts were made by combining three building blocks: an amine, an amino acid and a carboxylic acid. The library was screened for the acetylation of ethanol (figure 18) by means of IR thermography; 23 catalysts were identified as the most active ones, separated and characterized.

Menger and co-workers used parallel synthesis to produce very large libraries of polymers that could mimic enzymes for selected reactions [50]. Screening of the libraries by means of UV absorbance allowed the identification of the most effective catalysts. Nevertheless, it has not been possible to separate and characterize the active polymer catalysts; the discovery of active catalysts is thus possible with this approach, but not an explanation of why they are active.

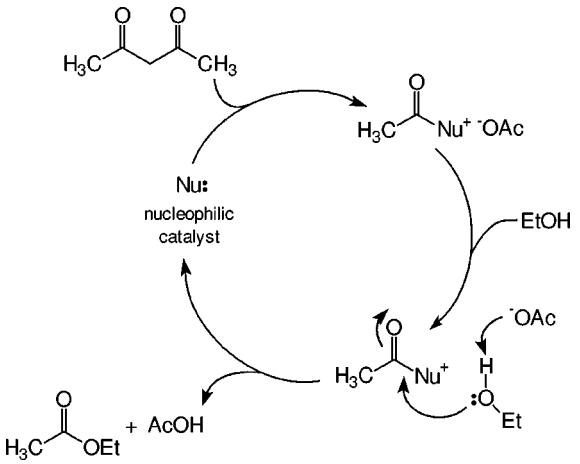

Figure 18. Catalytic acetylation of ethanol.

4. Conclusions

The widespread application of combinatorial and HSS technology to research and development in the field of catalysis and materials science is only very recent. Further developments are therefore to be expected in experimental techniques required to address specific problems, as outlined below:

(1) New strategies to minimize the number of experiments necessary to obtain satisfactory information about a combinatorial array. An example of such a strategy is the independent optimization of building blocks used by Hoveyda and Snapper [27], particularly if extended by the use of experimental-design methods for identifying interactions between components.

(2) Development of adequate synthetic methods and suitable automated equipment for the preparation of new materials, particularly inorganic solids such as heterogeneous catalysts. Current examples of these methods are thin-film deposition in solid-state synthesis [4,8] and ink-jet technology, that uses modified ink-jet printers to dispense samples, for liquid-phase synthesis [34].

(3) Novel high-speed screening techniques.

However, current research already shows much promise and, together with the further development of the various areas mentioned, combinatorial chemistry and HSS are likely to become very powerful tools for both the discovery and optimization of new catalysts and materials. In the case of catalysts, HSS techniques are also of value for the optimization of processing parameters.

References

[1] N.K. Terret, M. Gardner, D.W. Gordon, R.J. Kobylecki and J. Steele, Tetrahedron 30 (1995) 8135.
[2] A. Persidis, Chem. Ind. 19 (1998) 782.
[3] X.-D. Xiang, Chem. Ind. 19 (1998) 800.
[4] X.-D. Xiang, X. Sun, G. Briceño, Y. Lou, K.-A. Wang, H. Chang, W.G. Wallace-Freedman, S.-W. Chen and P.G. Schultz, Science 268 (1995) 1738.
[5] G. Briceño, H. Chang, X. Sun, P.G. Schultz and X.-D. Xiang, Science 270 (1995) 273.
[6] B.E. Baker, N.J. Kline, P.J. Teado and M.J. Natan, J. Am. Chem. Soc. 118 (1996) 8721.
[7] K. Sada, K. Yoshikawa and M. Miyata, J. Chem. Soc. Chem. Commun. (1998) 1763.
[8] E. Danielson, J.H. Golden, E.W. McFarland, C.M. Reaves, W.H. Weinberg and X.D. Wu, Nature 389 (1997) 944.
[9] E. Danielson, M. Devenney, D.M. Giaquinta, J.H. Golden, R.C. Haushalter, E.W. McFarland, D.M. Poojary, C.M. Reaves, W.H. Weinberg and X.D. Wu, Science 279 (1998) 837.
[10] J. Wang, Y. Yoo, C. Gao, I. Takeuchi, X. Sun, H. Chang, X.-D. Xiang and P.G. Schultz, Science 279 (1998) 1712.
[11] S. Brocchini, K. James, V. Tangapasuthadol and J. Kohn, J. Am. Chem. Soc. 117 (1995) 11610.
[12] M.T. Burger and W.C. Still, J. Org. Chem. 60 (1995) 7382.
[13] M.S. Goodmann, V. Jubian, B. Linton and A.D. Hamilton, J. Am. Chem. Soc. 117 (1995) 4553.
[14] W.C. Still, Acc. Chem. Res. 29 (1996) 155.
[15] B. Jandeleit and W.H. Weinberg, Chem. Ind. 19 (1998) 795.
[16] W.H. Weinberg, B. Jandeleit, K. Self and H. Turner, Curr. Opin. Solid State Mater. Sci. 3 (1998) 104.
[17] S. Borman, Chem. Eng. News 74 (1996) 37.
[18] T. Bein, Angew. Chem. Int. Ed. Engl. 38 (1999) 323.
[19] (a) R. Schlögl, Angew. Chem. Int. Ed. Engl. 37 (1998) 2333;
(b) W.F. Maier, Angew. Chem. Int. Ed. Engl. 38 (1999) 1216.
[20] J.M. Thomas, Angew. Chem. Int. Ed. Engl. 38 (1999), in press.
[21] J.J. Baldwin, J.J. Burbaum, I. Henderson and M.H.J. Ohlmeyer, J. Am. Chem. Soc. 117 (1995) 5588.
[22] E.J. Moran, S. Sarshar, J.F. Cargill, M.M. Shahbaz, A. Lio, A.M.M. Mjalli and W.W. Armstrong, J. Am. Chem. Soc. 117 (1995) 10787.
[23] M.F. Asaro and R.B. Wilson, Chem. Ind. 19 (1998) 777.
[24] S.R. Gilbertson and X. Wang, Tetrahedron Lett. 37 (1996) 6475.
[25] S.R. Gilbertson and C.-W.T. Chang, J. Chem. Soc. Chem. Commun. (1997) 975.
[26] B.M. Cole, K.D. Shimizu, C.A. Krueger, J.P.A. Harrity, M.L. Snapper and A.H. Hoveyda, Angew. Chem. Int. Ed. Engl. 35 (1996) 1668.
[27] K.D. Shimizu, M.L. Snapper and A.H. Hoveyda, Chem. Eur. J. 4 (1998) 1885.
[28] K.D. Shimizu, B.M. Cole, C.A. Krueger, K.W. Kuntz, M.L. Snapper and A.H. Hoveyda, Angew. Chem. Int. Ed. Engl. 36 (1997) 1704.
[29] M.S. Sigman and E.N. Jacobsen, J. Am. Chem. Soc. 120 (1998) 4901.
[30] R.T. Buck, D.M. Coe, M.J. Drysdale, C.J. Moody and N.D. Pearson, Tetrahedron Lett. 39 (1999) 7181.
[31] C. Gennari, S. Ceccarelli, U. Piarulli, C.A.G.N. Montalbetti and R.F.W. Jackson, J. Org. Chem. 63 (1998) 5312.
[32] K. Ding, A. Ishii and K. Mikami, Angew. Chem. Int. Ed. Engl. 38 (1999) 497.
[33] T.R. Boussie, C. Coutard, H. Turner, V. Murphy and T.S. Powers, Angew. Chem. Int. Ed. Engl. 37 (1998) 3272.
[34] E. Reddington, A. Sapienza, B. Gurau, R. Viswanathan, S. Sarangapani, E.S. Smotkin and T.E. Mallouk, Science 280 (1998) 1735.
[35] M.B. Francis and E.N. Jacobsen, Angew. Chem. Int. Ed. Engl. 38 (1999) 937.
[36] K. Burgess, H.-J. Lim, A.M. Porte and G.A. Sulikowski, Angew. Chem. Int. Ed. Engl. 35 (1996) 220.
[37] F.C. Moates, M. Somani, J. Annamalai, J.T. Richardson, D. Luss and R.C. Willson, Ind. Eng. Chem. Res. 35 (1996) 4801.
[38] A. Holzwarth, H.-W. Schmidt and W.F. Maier, Angew. Chem. Int. Ed. Engl. 37 (1998) 2644.
[39] (a) S.J. Taylor and J.P. Morken, Science 280 (1998) 267;
(b) M.T. Reetz, M.H. Becker, K.M. Kühling and A. Holzwarth, Angew. Chem. Int. Ed. Engl. 37 (1998) 2647.
[40] P. Cong, R.D. Doolen, Q. Fan, D.M. Giaquinta, S. Guan, E.W. McFarland, D.M. Poojary, K. Self, H.W. Turner and W.H. Weinberg, Angew. Chem. Int. Ed. Engl. 38 (1999) 488.
[41] (a) S.M. Senkan, Nature 394 (1998) 350;
(b) I.E. Maxwell, Nature 394 (1998) 325.
[42] S.M. Senkan and S. Ozturk, Angew. Chem. Int. Ed. Engl. 38 (1999) 791.
[43] D.E. Akporaye, I.M. Dahl, A. Karlsson and R. Wendelbo, Angew. Chem. Int. Ed. Engl. 37 (1998) 609.
[44] J. Klein, C.W. Lehmann, H.-W. Schmidt and W.F. Maier, Angew. Chem. Int. Ed. Engl. 37 (1998) 3369.
[45] C.L. Hill and R.D. Gall, J. Mol. Catal. A 114 (1996) 103.
[46] B. Gurau, R. Viswanathan, R. Liu, T.J. Lafrenz, K.L. Ley, E.S. Smotkin, E. Reddington, A. Sapienza, B.C. Chan, T.E. Mallouk and S. Sarangapani, J. Phys. Chem. B 102 (1998) 9997.
[47] A.C. Cooper, L.H. McAlexander, D.-H. Lee, M.T. Torres and R.H. Crabtree, J. Am. Chem. Soc. 120 (1998) 9971.
[48] K. Burgess and A.M. Porte, Tetrahedron: Asymm. 9 (1998) 2465.
[49] S. Bromidge, P.C. Wilson and A. Whiting, Tetrahedron Lett. 39 (1998) 8905.
[50] F.M. Menger, J. Ding and V.J. Barragan, Org. Chem. 63 (1998) 7578, and references 1, 2 reported there.