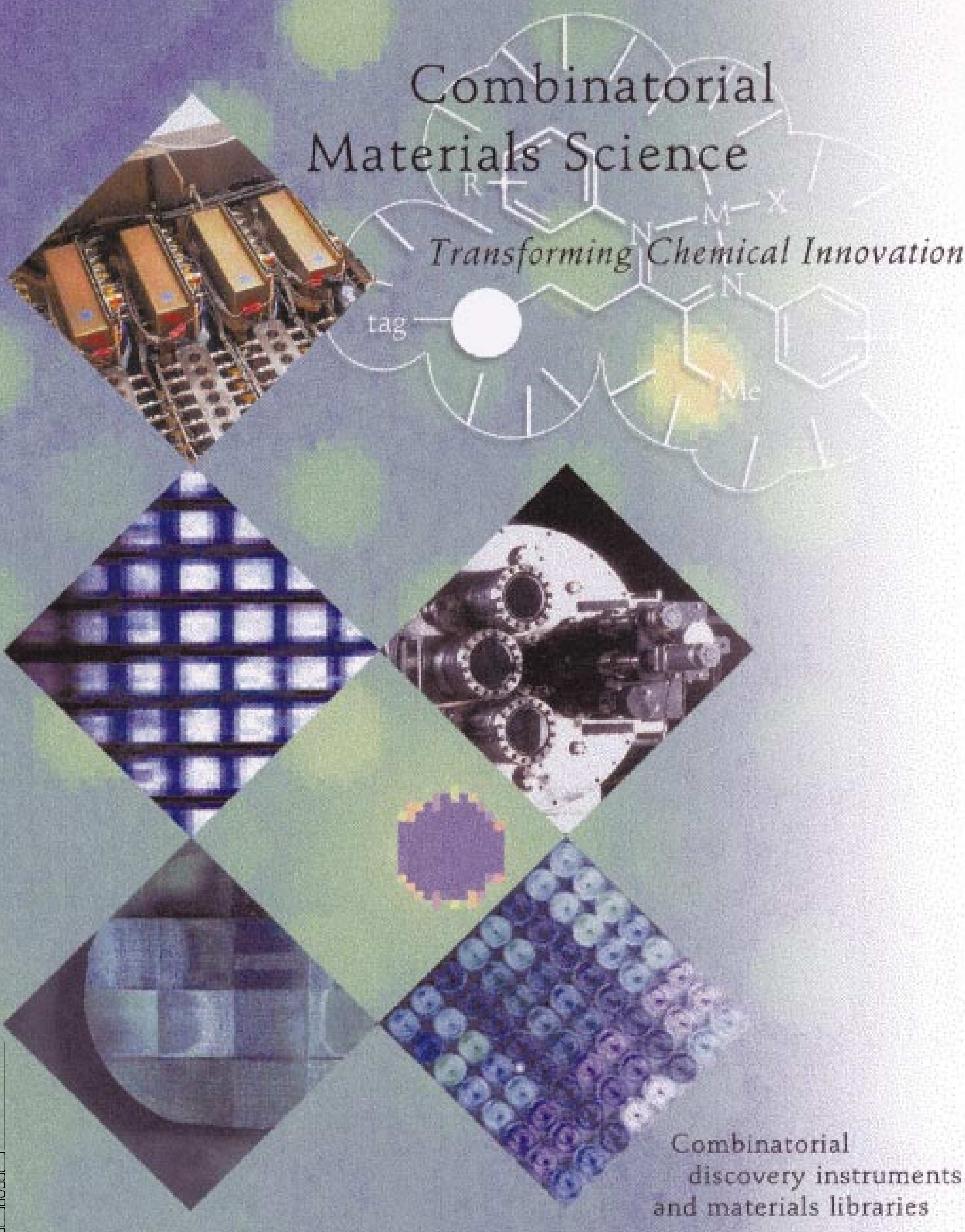
Combinatorial Materials Science

Transforming Chemical Innovation



Combinatorial
discovery instruments
and materials libraries

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Combinatorial Materials Science and Catalysis

Bernd Jandeleit,* Dieter J. Schaefer,* Timothy S. Powers, Howard W. Turner, and W. Henry Weinberg

Combinatorial chemistry has significantly changed the drug discovery process in the pharmaceutical industry, and promises to bring to the marketplace more drug entities per unit time than ever before. With rising economical demands to increase efficiency in other areas of research and development, it is not surprising that a similar paradigm is taking hold in the chemical industry as a whole. In particular, combinatorial synthesis and sophisticated screening technologies are now being applied to the discovery of more efficient catalysts and materials, and with these new technologies come the promise of faster commercialization rates and reduced research and development costs. The combinatorial process aims at efficiently exploring the large parameter space that controls the properties of a product through the combination of rapid parallel or combinatorial synthesis of vast numbers of compounds and subsequent high-throughput assaying of these compounds for any given application. Unlike in the pharmaceutical industry where screening variables such as solvent, temperature, and additives are held constant to eliminate assay variability, varying screening and processing conditions in the search for new materials becomes important if not essential. By combinatorially varying process and reaction conditions, combined with combinatorial synthesis, the total number of experiments one can screen rises exponentially, which drastically increases the chances of identifying a new material or catalyst. Since the inception of applying combinatorial methods and high-throughput screening to discovery research in materials science, tremendous advances in this rapidly growing field have been made in the academic, private, and public sectors over the past four years. The goal of this review is to examine the contributions made during this time period, to offer a critical analysis of the state-of-the-art methodologies being implemented, and to provide insight as to what the future holds for combinatorial catalysts and materials research.

Keywords: asymmetric synthesis · catalysts · combinatorial chemistry · high-throughput screening · materials science

1. Introduction

New products need to be brought to the market place rapidly as a result of the increasing competition in the chemical industry. Enormous pressure is put on research and development, as simultaneously more innovative ideas, higher success rates, shorter lead and development times, and lower research and production costs per product are required. This paradigm was first encountered in the pharmaceutical industry, where long development times and high research costs forced the development of new approaches to dramatically accelerate the drug discovery process. These approaches encompass combinatorial chemistry and high-throughput screening and represent a powerful research strategy when applied to problems where a large parameter space controls the properties of a product.[1–15]

The combinatorial process involves the design and synthesis of high-density discovery libraries aimed at efficiently exploring large numbers of structurally or compositionally diverse compounds thought to be of interest as a result of an understanding of their chemical, physical, and structural properties. Rapid, sensitive measurements of one or more relevant chemical or physical properties of each library member result in the identification of a family of lead compounds with a desired property. These compounds are then optimized by continuously varying the stoichiometries or structures of a more focused set of compounds in a focus library (Figure 1). Materials with the optimum compositions are then synthesized in quantities sufficient for their detailed characterization. Finally, with methods of combinatorial chemical synthesis evolving together with rapid analysis and high-throughput screening, high-capacity information process-

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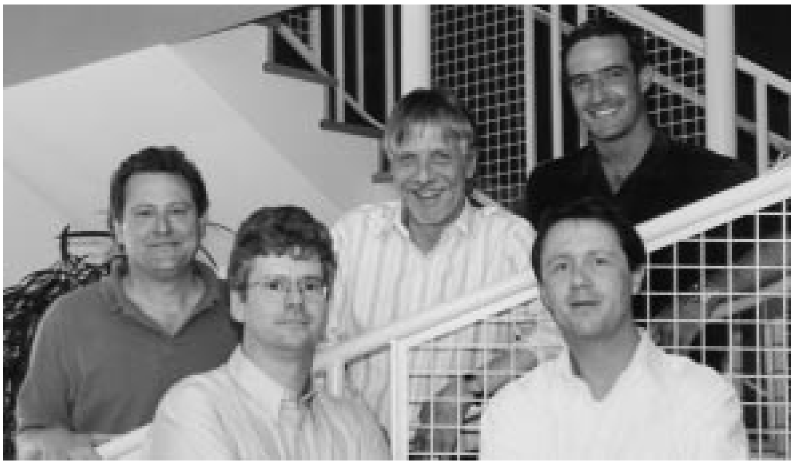
[*] Dr. B. Jandeleit, Dr. D. J. Schaefer, Dr. T. S. Powers, Dr. H. W. Turner,
Prof. Dr. W. H. Weinberg
Symyx Technologies
3100 Central Expressway, Santa Clara, CA 95051 (USA)
Fax: (+1)408-748-0175
E-mail: bjandeleit@symyx.com, dschaefer@symyx.com

1433-7851/99/3817-2495 $ 17.50+.50/0



back: H. W. Turner W. H. Weinberg T. S. Powers
front: D. J. Schaefer B. Jandeleit

Bernd Jandeleit, born in 1965 in Stolberg (Germany), completed his Ph D in chemistry in 1995 under the direction of Prof. D. Enders at the RWTH Aachen. His work focused on chirality transfer processes in iron-mediated allylic and dienylic substitution reactions. He was awarded a postdoctoral fellowship of the Studienstiftung des Deutschen Volkes and BASF AG and worked from 1995 to 1997 as a research associate with Prof. K. C. Nicolaou at The Scripps Research Institute, La Jolla on synthetic efforts toward farnesyl transferase and squalene synthase inhibitors and on the design of nonpeptidic integrin antagonists (angionesis inhibitors). Since 1998 he has been employed by Symyx Technologies, where he works on the combinatorial development and high-throughput screening of new organometallic catalysts.

Dieter J. Schaefer, born in 1962 in Bonn (Germany), studied chemistry at the University of Mainz and completed his Ph D with Prof. Dr. H. W. Spiess at the Max-Planck-Institut für Polymerforschung, Mainz in 1992. His doctoral work involved the study of slow molecular dynamics associated with the glass transition and relaxation phenomena in polymers and novel polyelectrolytes. As a Visiting Research Scientist with Dr. A. D. English in Central Research & Development at the DuPont Experimental Station in Wilmington, Delaware he studied the dynamics and morphology of high-tech fibers. In 1994 he joined Prof. B. F. Chmelka's group at the Department of Chemical Engineering at the University of California at Santa Barbara as a Research Associate, and investigated the molecular guest dynamics and diffusion in zeolite catalysts. Since 1997 he has been a Staff Scientist with Symyx Technologies working on high-throughput screening methods.

Timothy S. Powers, born in 1965 in San Francisco, California, obtained a BS degree in Chemistry from the University of California, Davis in 1987 and a Ph D in Organic Chemistry from the University of Chicago in 1993 under the direction of Prof. W. D. Wulff. His dissertation focused on asymmetric Aldol, Diels–Alder, and stereospecific intramolecular cycloaddition reactions using Fischer carbene complexes of Group VI metals. In 1993 he joined Sphinx Pharmaceuticals, a Division of Eli Lilly & Company, where he worked in the Combinatorial Drug Discovery Program, focusing predominantly in the Cancer and Endocrine Research Programs. He joined Symyx Technologies in 1997 where he works as a Staff Scientist in the Homogeneous Catalyst Group developing novel organometallic catalysts.

Howard W. Turner received a BS in chemistry at the University of California, Berkeley and a Ph D in Inorganic Chemistry from MIT. He joined Symyx Technologies from Exxon Chemical's Long Range Polymer Research group and currently holds a position as director, Catalyst Research at Symyx Technologies. His work (described in over 40 US patents and patent applications) includes the determination of the mechanism of alumoxane activation of metallocene catalysts and the development of alumoxane-free single-site olefin polymerization catalysts based on novel compatible noncoordinating anions. This catalyst technology was recently commercialized and is now part of Exxon's EXXPOL catalyst licensing package.

W. Henry Weinberg obtained a Ph D degree in Chemical Engineering from the University of California, Berkeley in 1971. He carried out postdoctoral studies at the University of Cambridge, and then joined the faculty of the California Institute of Technology, where he remained until 1989 when he joined the faculty of the University of California at Santa Barbara. He was Visiting Professor of Chemistry at Harvard University in 1980 and at the University of Munich in 1982, and Visiting Professor of Materials at the University of Oxford in 1991. Dr. Weinberg was appointed Chief Technology Officer and Vice President of Symyx Technologies in 1996. He has received numerous awards and honors, including the Allan P. Colburn Award of the American Institute of Chemical Engineers, an Alexander von Humboldt Foundation Senior US Scientist Award, and both the Colloid or Surface Chemistry Award and the Arthur W. Adamson Award of the American Chemical Society. He is a member of the National Academy of Engineering (USA) and has authored over 500 scientific papers.

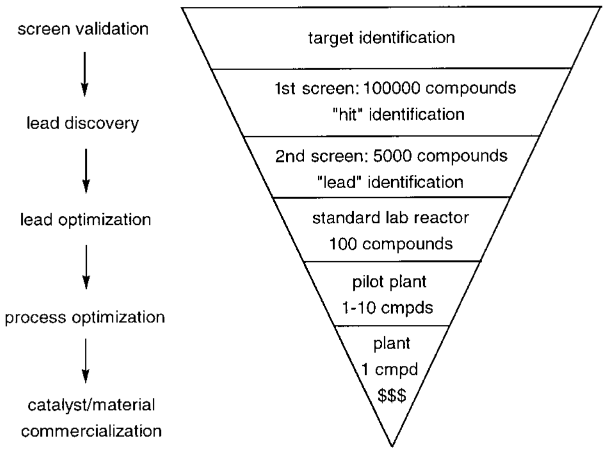


Figure 1. The process of catalyst/materials discovery and optimization. Large numbers of diverse compounds are rapidly synthesized and screened for desired properties, which dramatically speeds up catalyst/materials discovery and optimization.

ing and data management becomes challenging and requires appropriate database technology.

Combinatorial chemistry methodologies are increasingly being applied to the field of materials science including homogeneous and heterogeneous catalysis and will unquestionably influence and change the way research is carried out in the future. It is already apparent that catalyst discovery and optimization can be dramatically accelerated by coupling automated library synthesis with high-throughput screening methods and sophisticated high-capacity informatics systems. Combinatorial methodologies should equally facilitate the discovery and optimization of new and/or superior compounds with new and/or enhanced material properties, since such methodologies make it possible to rapidly synthesize, process, and evaluate large libraries of many inorganic and organic materials and devices, thereby dramatically accelerating the rate at which these entities can be designed, executed, and analyzed.

Combinatorially synthesized libraries of potential catalysts can comprise organic, organometallic, inorganic, or solid-state materials. In heterogeneous catalysis, where active sites exist on the exterior and/or interior surface of a solid-state inorganic material, library synthesis can be carried out by a variety of solution and vapor deposition methods. The same synthetic techniques can be used to prepare compositions consisting of three, four, five, or more elements to explore the universe of possible new materials with interesting physical and chemical properties. Efficiently searching for trends in the materials properties by using combinatorial approaches can significantly shorten the time required to probe the largely unexplored domain of possible chemical compositions. Work reported by Schultz and co-workers in 1995 has initiated tremendous efforts in this field,[16] although the concepts and their experimental realizations can be traced back to Hanak in the early 1970s.[17] In homogeneous catalysis, where the active site is most often a metal ion stabilized by a ligating organic moiety, library synthesis may be carried out using combinatorial organic synthesis followed by metal complexation. This approach allows combinatorial homogeneous catalysis to rapidly advance by taking advantage of, and extending, the numerous solid- and solution-phase combinatorial methodologies developed within the pharmaceutical industry to ligand synthesis.[18–26] Furthermore, polymer-supported reagents have emerged as useful combinatorial chemistry tools.[27–30]

Three different approaches to the task of preparing and testing libraries of compounds exist (Figure 2). Conventional research in a "one at a time" or serial fashion provide thorough quality control of the samples that enter the screening process to insure that accurate data are obtained. Combinatorial methods that involve, for example, "split-pool" synthesis are much faster and render the preparation of relatively large numbers of compounds feasible but often lack control over the purity of the compounds entering the assay screen. Methods intermediate between the two extremes outlined above are based on parallel or array syntheses in a spatially addressable format with usually one compound per well, coupled to automated screens. Thus, multidimensional problems in the discovery and in the optimization of catalysts or materials may be efficiently addressed by coupling parallel synthesis with automated or high-throughput screens.

A SciFinder reference search performed in July 1999 using the key word "combinatorial" resulted in more than 6000 "hits" since 1973. An analysis of the literature search clearly demonstrates tremendous growth of scientific publications and patent applications in the combinatorial field. While most references deal with combinatorial methodologies and technologies in pharmaceutical, biological, and medical disciplines, recent years have witnessed significant advances in the development of combinatorial approaches to the discovery and optimization of homogeneous and heterogeneous catalysts and new materials. This is clearly manifested in the increasing number of scientific publications and patent applications concerning these areas within the last few years. A few review articles on the application of combinatorial chemistry to catalyst discovery and optimization, a process

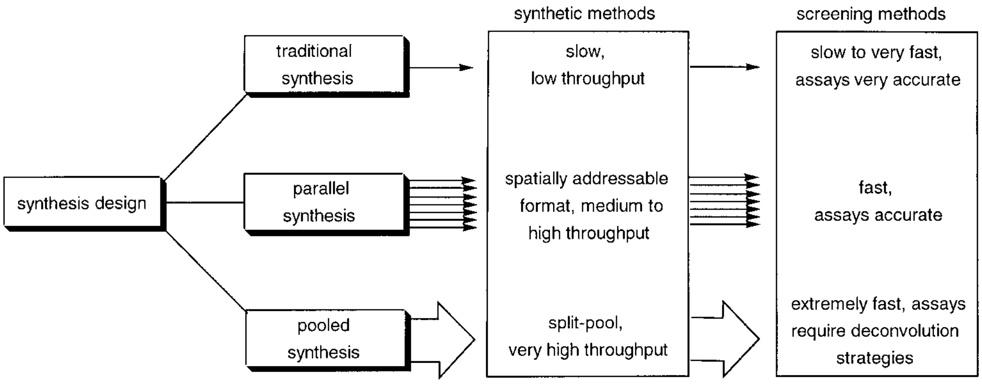


Figure 2. Conventional, parallel, and pooled approaches to synthesis and screening.

dubbed "combinatorial catalysis", have appeared in the literature.[31–44] Similarly, some reviews have been published that discuss the evolving area of combinatorial materials science.[36, 45–55]

Three new journals exclusively dedicated to combinatorial chemistry have been created to focus and channel the results of this exploding field: a) *Molecular Diversity* (Kluwer Academic Publisher, 1995), b) *Combinatorial Chemistry* (John Wiley & Sons, 1998), and c) *Journal of Combinatorial Chemistry* (American Chemical Society, 1999). Furthermore, a web site offers instant access to valuable information on combinatorial chemistry including an extensive and current list of papers and reviews (http://www.5z.com/divinfo/).

The Commission of the European Union has funded a network entitled "Combinatorial Approaches to Molecular Catalysts" under the Training and Mobility of Researchers Program to exploit the methods of combinatorial chemistry for the discovery of new catalysts (http://www.ncl.ac.uk/~nrfwj/d.html). Currently, eight participating laboratories will target both hydrolytic and carbon–carbon bond forming processes by using polymer-supported immobilized scaffolds with several attached side chains that will be able to act cooperatively on a centrally located substrate and that will be elaborated to yield libraries of structures with potential catalytic properties.

The present review, covering the years 1995 to 1998, summarizes and critically analyzes the latest developments in the application of combinatorial methodologies to the discovery of new homogeneous and heterogeneous catalysts and solid-state materials. The following section summarizes the efforts in solid-state combinatorial materials science and starts with a general overview of combinatorial materials synthesis techniques. Section 3 presents combinatorial approaches for the development of organic and organometallic catalysts. Section 4 discusses progress in the employment of libraries for the discovery and optimization of inorganic and heterogeneous catalysts. Section 5 presents some high-throughput screening technologies developed for this area of catalysis in particular. A summary and an outlook concerning the future of combinatorial materials science and catalysis are presented in Section 6.

2. Combinatorial Solid-State Materials Science

The properties of many functional solid-state materials arise from complex interactions involving the host structure, dopants, defects, and interfaces, and therefore they depend heavily on composition and processing conditions. Few general principles have emerged that allow the prediction of structure, reaction pathways for the synthesis, and resulting properties of such solid-state compounds. Conventional one-at-a-time synthesis and evaluation is generally a long and expensive process, and combinatorial materials science holds great promise in facilitating the materials discovery and optimization process.

Besides the tremendous interest in homogeneous and heterogeneous catalysts, which will be treated in the third and fourth parts of this review, combinatorial technology has been applied to the discovery and optimization of superconducting, magnetoresistive, ferroelectric, dielectric, and luminescent materials, as well as zeolites, organic materials, and polymers. The integrated application of rapid chemical synthesis, high-throughput screening, and large-scale data analysis is the essence of combinatorial materials science. Figure 3 shows schematically the combinatorial process in one manifestation as applied to materials deposited by vapor methods in two-dimensional arrays. A diverse library of different materials is created through automated synthesis. The libraries are then subjected to one or multiple screens for a variety of specific or general properties, and the data trends within the library are compared to previously created libraries to search for new materials or property relationships.

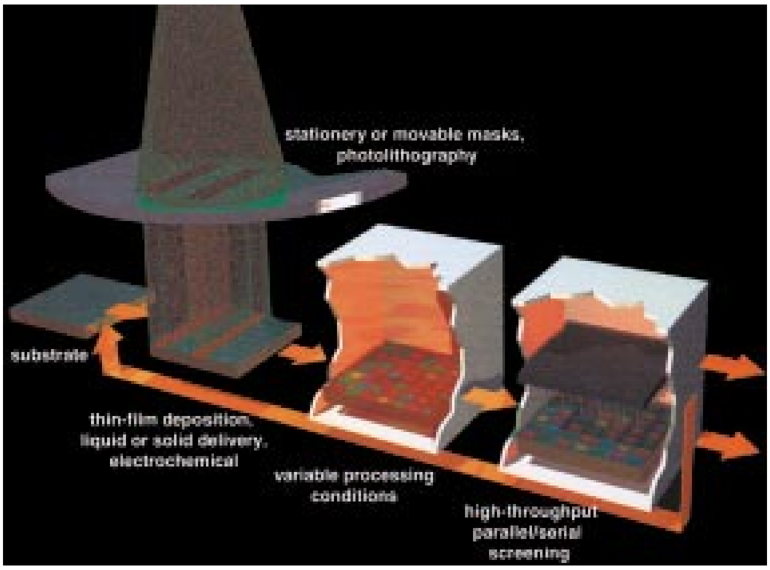


Figure 3. Combinatorial materials discovery: a diverse library containing large numbers of individual samples in a spatially addressable two-dimensional array format is deposited by one of several automated deposition methods. Each spatial location represents a different composition or processing history. Multiple high-throughput screening for a variety of specific or general properties identifies lead materials that can be used to guide the design of subsequent libraries to search for new materials or property relationships.

2.1. Synthesis of Materials Libraries

Unlike the case of drug discovery, where the use of solid-phase resins has proven important in combinatorial synthesis, solid-state materials synthesis often relies on sample preparation at temperatures in excess of 800 °C, and two-dimensional, spatially addressable arrays of samples have emerged as the standard library framework. By modifying technologies similar to those used to make integrated circuit (IC) chips, materials libraries or integrated materials (IM) chips were first developed and utilized by Schultz and co-workers.[16]

Several synthesis techniques have been developed for combinatorial materials library formation; some compounds can be made by solution methods, while others are more suited for thin-film deposition.[51, 54, 56–59] Thin-film vapor deposition is commonly used in the semiconductor industry to deposit thin films of material onto a substrate. Vapor deposition techniques include electron-beam and thermal evaporation, sputtering, and pulsed laser ablation.[60] A typical vacuum deposition system for combinatorial materials science has several source materials and is used in conjunction with masking techniques (physical or shadow masks, movable shutters, or photolithography) to sequentially or simultaneously deposit different materials in particular areas of the substrate. The design of the masks and the sequence in which they are used determine which materials are deposited at any given location of the substrate. By altering the sequence, time, and rate of deposition, it is possible to control the exact chemical composition of each element in the library.

The efficiency with which one can survey a particular materials landscape of interest is dictated by the masking strategy employed.[61] Simple binary and gradient masks are useful for optimizing the composition of a known material. In the binary masking strategy only half of the substrate area is exposed to thin-film deposition with different patterns (1,2,4,… strips oriented in two different directions) in each step (Figure 4). The number of different compositions after N steps is 2^N, which includes all possible combinations of N elements. Gradient or $x-y$ shutter masking utilizes movable masks that expose or shield certain areas of the substrate, which allows for controlled concentration and/or thickness variations of the deposited films.

Quaternary masking strategies have been developed that enable efficient generation of diverse libraries containing materials with very different compositions. In the quaternary masking scheme deposition is carried out using a series of N different masks that successively subdivide the substrate into a series of nested quadrant patterns (Figure 4). Each mask is used for up to four depositions, and each time the mask is rotated by 90°. With N different masks this process will generate up to 4^N different compositions in just $4N$ deposition steps. The rth ($1 \leq r \leq N$) mask contains 4^{r-1} windows where each window exposes one quarter of the area deposited using the preceding (r-1) mask. Within each window is an array of 4^{N-r} openings, which can be provided by means of an underlying contact mask or created directly on the substrate by photolithography techniques.[47, 50, 51, 54, 62] Each section of the substrate is thus exposed to a different combination of precursors by depositing each layer through a different mask.

Thin film deposition methods are synthetically quite versatile; they have progressed to enable atomic- and molecular-layer epitaxy and offer the ability to construct artificial lattices, epitaxial overlayers, and patterned films of a variety of materials.[60] Dopants are usually sandwiched between layers of the host material to avoid evaporation and to assure proper interdiffusion. Subsequent thermal processing provides a library of materials or devices, the physical properties of which can be screened with either contact or noncontact screening probes. The number of compounds that can be simultaneously synthesized by this technique is limited by the spatial resolution of the masks and detectors and by the degree to which synthesis can be carried out on a microscale.

One can use either physical shadow masks[16] or photolithographic lift-offs[62] to carry out masking. Photolithography, which is a standard process in the semiconductor industry to make integrated circuits, has a high level of spatial resolution and accuracy and can generate chips with a very high density of diverse compositions (up to 10^6 per square inch (25.4×25.4 mm)). A substrate is first coated with photoresist—a polymer that is sensitive to light—and the substrate is illuminated by light that has passed through a mask. In the combinatorial approach the exposed areas of photoresist are then removed, and one of the source materials is deposited over the whole substrate. Chemicals are used to wash away the remaining photoresist, including its coating of source material, so that only those areas originally exposed to light are covered with the source material. The whole process is repeated until the library has been produced.

At first glance this multilayer thin film deposition approach, with multiple layers of precursors deposited onto a small substrate sequentially seems straightforward; however, the problem is that generally homogeneous crystalline compounds are desired. Only by means of an effective two-step annealing process is it possible to develop the desired multi-element single phase instead of multiple binary phases.[51] The avoidance of early nucleation, and thus the creation of binary phases, is accomplished by deposition at relatively low temperatures, which effectively controls the thickness of the deposited layer to a critical value of typically 1 to 10 nm (material dependent), below which diffusion is dominant over nucleation for sequential precursor layers.

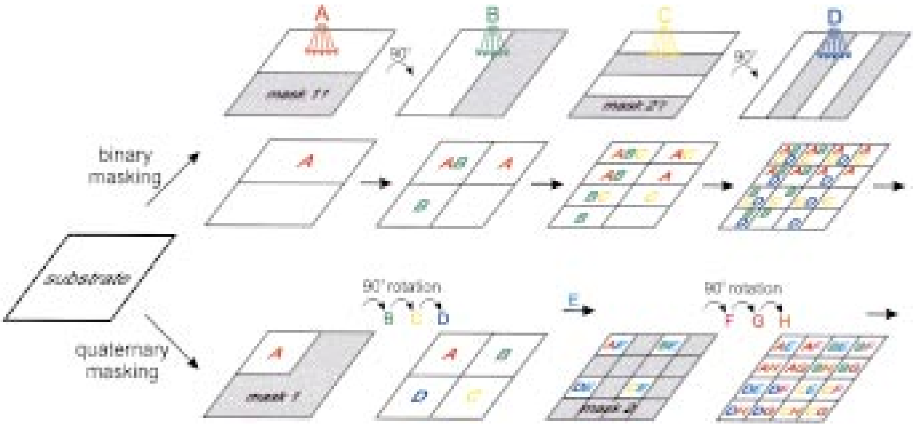


Figure 4. Binary and quaternary masking strategies for combinatorials materials library fabrication. See text for details.

Johnson et al. has advanced this elegant technique with the sequential controlled deposition of thin films.[63] First, an extended period of low temperature (100–400 °C) annealing is used for proper interdiffusion of thin film precursors. Subsequently, crystallization of the intermediate, uniformly amorphous material is induced by a high-temperature annealing process. This yields predominantly single-phase crystalline films, which allows the epitaxial growth of entire integrated materials chips.[64] Growing entire integrated materials chips in this way is important for many high-tech materials, where the material properties are closely tied to the crystalline quality of the films. Conventional X-ray diffraction is used to directly and nondestructively characterize individual films of as-grown combinatorial libraries, and synchrotron X-ray microbeam diagnostics has been developed for the same purpose.[65]

Reflection high-energy electron diffraction (RHEED) has been proposed for in situ monitoring of a laser molecular beam epitaxy (MBE) deposition.[56] In this context it should be noted that the main focus is not always the synthesis of optimized thin films on the library chip, but rather on the acquisition of information as quickly as possible regarding the trends of physical properties with material composition.

For many materials, for example, zeolites, polymers, and powder phosphors, synthesis is best accomplished by solution-phase methods. This allows mixing at the molecular level, which reduces the need for high temperature interdiffusion and also facilitates the isolation of metastable phases. As mentioned above, thin film vapor deposition must be followed by high-temperature annealing to interdiffuse the sequentially deposited layers, which generally results in the thermodynamically stable phase rather than the kinetically metastable products. Xiang and Schultz have demonstrated that a scanning multihead inkjet delivery system can be used to perform automated micro-synthesis of solid-state material libraries, which enables rapid delivery and accurate control of nanoliter deposition volumes that is critical in determining the final stoichiometry of solid-state materials.[54, 57] Droplets are delivered sequentially to single reaction wells; the droplet size is on the order of 500 picoliters with reproducibility better than 99 % and a maximum delivery speed of 2000 droplets per second. The system has been successfully used to generate libraries of 100 members inch^{-2}, and a system to generate 1000 members inch^{-2} is under development.

A solution-based combinatorial strategy has been described by Baker et al. for the synthesis of surfaces exhibiting nanometer-scale variation in mixed-metal compositions and architecture.[58] Continuous or stepped gradients in the size and number density of surface features can be generated simultaneously over different regions of a single substrate. They prepared a library of Ag-clad colloidal Au arrays, in which the coverage of colloidal Au and the extent of reductively deposited Ag coating were varied in an attempt to optimize the enhancement factor for surface enhanced Raman scattering (SERS).[58, 66] A sulfide-functionalized glass slide was immersed at a constant rate into an aqueous solution of colloidal gold, and the plate was then rotated by 90° and lowered at a fixed rate into a solution of Ag^{I} ions. As a result a library was generated containing approximately 10^8 colloids that differed in their particle size and Ag coverage. *p*-Nitrosodimethylaniline was adsorbed onto this surface and the enhancement factor of the Raman scattering of this compound by the surface was measured. The values spanned roughly three orders of magnitude across the library and allowed for the identification of a region of the library that gave the greatest enhancement. Atomic force microscopy was then used to determine the nanometer-scale morphologies of these regions of interest. The availability of dispersible metal-containing nanoparticles and the numerous routes to metal deposition from complexed metal cations should allow the extension of this method to a variety of other metals.

A scheme for generating complex, spatially separated patterns of multiple types of semiconducting and/or metallic nanocrystals has been presented by Vossmeyer et al.[59] Nanocrystals may play an important role in future technologies such as photovoltaics, switches, phosphors, light-emitting diodes, electronic data storage systems, and sensors. Most of the photonics and electronics applications will eventually require parallel schemes for the control of spatial positioning of the nanocrystals. Standard patterning techniques such as laser ablation of the material and depositing through a shadow mask do not work well for nanocrystals since most metal and semiconductor nanocrystals have covalently bound organic surfactants that tend to desorb at temperatures above 100 °C and consequently any patterning approach must be carried out at low temperatures. The stepwise preparation of multiple particle arrays is based on the lithographic patterning of amino-functionalized organic monolayers that contain a photolabile protection group covalently bound to SiO_2 surfaces. The photosensitive substrate is irradiated through a mask in the near-UV wavelength range, which removes the protection group in the areas exposed to the radiation.

To prepare binary micropatterns consisting of Pt or Au and highly luminescent CdSe/CdS core/shell nanocrystals, the substrate is treated with a solution of amine-stabilized metal-containing nanoparticles, which assemble in the area of deprotected amino groups. After changing the orientation of the mask, the deprotection step is repeated and the amine-stabilized CdSe/CdS nanoparticles are assembled onto areas of freshly deprotected amino groups, to yield a binary nanoparticle array. Nanocrystal assembly occurs with high selectivity on just one type of the spatially and chemically distinct sites. The production of binary, ternary, and quaternary patterns of nanocrystals is reported and the procedure appears applicable for the preparation of multicolored nanocrystal-based color pixels. Moreover, the technique should be compatible with other lithographic patterning steps, such as those involved in the formation of electrical contacts, capacitors, and other device components of the photonics and electronic technology, and has been demonstrated on a variety of substrates.

2.2. Applications of Combinatorial Materials Science

2.2.1. *Superconducting Materials*

The technique of using two-dimensional, spatially addressable arrays of samples for combinatorial materials synthesis was first demonstrated by Schultz and co-workers.[16] It involved the preparation of libraries of superconducting copper oxide thin films by radio-frequency (RF) sputtering several metal oxides in sequence onto an inert single-crystal support of either MgO or $LaAlO_3$.[67] In their initial experiments arrays containing different combinations, stoichiometries, and deposition sequences of $BaCO_3$, Bi_2O_3, CaO, CuO, PbO, $SrCO_3$, and Y_2O_3 were generated with a series of four and seven binary secondary masks and primary masks having either 16 or 128 openings, respectively, to yield a spatially addressable library of 16 (2^4) 2 × 2 mm and 128 (2^7) 1 mm × 2 mm samples distributed over a chip with a surface area of one square inch. After annealing the entire library at 840 °C in an oxidizing atmosphere, the superconductivity of each sample was evaluated by measuring its resistance as a function of temperature with an array of small four-point probes that analyze 64 samples at a time.[54] Superconducting films of $BiSrCaCuO_x$, $BiPbCaSrCuO_x$, and $YBa_2Cu_3O_x$ were identified that had critical temperatures in the range of 80–90 K. Subsequent libraries demonstrated that large effects in superconductivity result not only from the identity and stoichiometry of the metal oxides in each sample but also from deposition order and annealing conditions. Samples as small as 200 × 200 μm in size and spacings of 50 μm between sites were generated, which corresponded to library densities of 10000 sites per square inch. This first publication was geared more toward establishing the principle of combinatorial materials synthesis rather than producing novel materials since the reactants chosen were known constituents of superconducting materials.

2.2.2. Magnetoresistant Materials

The same preparative combination of thin-film deposition and physical masking techniques was subsequently used by Xiang and co-workers in the discovery of a new class of cobalt oxide magnetoresistance materials.[68, 69] Magnetoresistance is the variation of a compound's electrical resistance with the applied magnetic field, and materials with very large magnetoresistance properties are useful, for example, in high density magnetic storage technology such as read heads for computer hard drives.[70] Colossal magnetoresistance (CMR) was first discovered in Mn-based perovskite oxides $(La,R)_{1-x}A_xMnO_{3-\varepsilon}$, where R is a rare earth element, and A is Ca, Sr, or Ba. Magnetoresistance ratios $\Delta R/R(0) = R[(H=0) - R(H)]/R(H=0)$ as large as 99.0, 99.9, and 99.99% have been reported for polycrystalline samples of $La_{0.6}Y_{0.07}Ca_{0.33}MnO_3$ and epitaxial thin films of $La_{0.67}Ca_{0.33}MnO_3$ and $Nd_{0.7}Sr_{0.3}MnO_{3-\varepsilon}$, respectively. Two identical 128-member libraries of composition $Ln_xM_yCoO_z$ (1 × 2 mm) were synthesized on $LaAlO_3$ single crystals to examine the magnetoresistivity of materials that contain cobalt rather than manganese in simple perovskite $LnCoO_3$ and related Ln_2CoO_4 or $Ln_{n+1}Co_nO_{3n+1}$ structures, where $Ln = (La, Y)^{III}$, partially substituted with different stoichiometries of $M = (Ca, Sr, Ba, Pb)^{II}$. The two libraries were annealed and sintered under different conditions, and one showed an overall decrease in magnetoresistivity. This highlights that in combinatorial materials synthesis post-deposition processing conditions represent important variables.

Large magnetoresistance ($\Delta R/R(0) > 5\%$) was measured in $La_x(Ba,Sr,Ca)_yCoO_z$ samples by using a four-point probe method with a multichannel switching system in a liquid-helium cryostat with a superconducting 12 T magnet; Y-based samples exhibited much smaller magnetoresistive effects. The magnetoresistance of the Co-containing compounds was found to increase as the size of the alkaline earth metal increases, in sharp contrast to Mn-containing compounds, in which the magnetoresistance effect increases as the size of the alkaline earth metal decreases. The magnetoresistance ratio $\Delta R/R(0)$ of a subsequently synthesized bulk sample of the lead compound $La_{0.58}(Ba,Sr,Ca)_{0.41}CoO_z$ was significantly higher than that of the corresponding thin film sample in the combinatorial library ($\Delta R/R(0) = 60\%$ as compared to $\Delta R/(0) = 30\%$). This finding again illustrates that libraries are screened in the combinatorial approach to materials discovery to point the direction to a promising lead; synthesis and characterization of a bulk sample is then performed to determine the bulk properties which can considerably differ from the properties of the thin film compound. False positives (that is, where the bulk sample does not possess the positive behavior of the thin film sample), are not of major concern, which is in contrast to the case of false negatives, in which the bulk sample would possess positive behavior in spite of the thin film not showing such behavior.

2.2.3. Dielectric and Ferroelectric Materials

The combinatorial discovery approach has been successfully applied in the field of dielectric materials, which have a variety of potential applications in the information technologies industry.[71] Driven by the current trend of miniaturization of electronic devices, improved thin-film insulators are needed, for example, in dynamic random access memory (DRAM) computer chips. By using the composition spread technique,[17, 72] a gradient composition technique, van Dover and co-workers from Lucent Technologies have reported new dielectric thin film materials that have higher dielectric coefficients than amorphous silicon dioxide (α-SiO_x), the insulating material most commonly used today.[73] The formation of mixtures by the compositional spread technique involves co-depositing three different reagents simultaneously onto a substrate from a triangular arrangement of targets. As the reagents spread from the point of deposition they mix to form a continuous composition variation in which the relative concentration of each component decreases with the distance from its source and with the three two-component compounds along the three sides of the triangle.

This method is limited to ternary systems with two independent compositional variables. When this technique is applied without using movable shutters in the deposition a complete ternary phase diagram is not obtained, and compositions as a function of position on the substrate are difficult to infer. Van Dover and co-workers used off-axis RF magnetron sputtering guns positioned at 90° intervals around a rectangular TiN-coated Si wafer (66 × 63 mm) to codeposit a ternary continuous composition variation of Zr, Ti, and Sn. The three sputter guns operated simultaneously to create an intimate reactant mixing. A continuous thin film was obtained and the position-related composition was inferred with Rutherford backscattering spectroscopy.

To develop their optimum thin film transistor candidate ($Zr_{0.15}Sn_{0.3}Ti_{0.55}O_{2-\varepsilon}$), more than thirty combinatorial libraries were synthesized and evaluated at a rate of about one per day. The critical electrical properties, capacitance C (per unit area CA^{-1}) and breakdown voltage V_{br}, were evaluated with a scanning Hg-probe instrument as a function of position at approximately 4000 points in the 66 × 63 mm rectangle, and the figure of merit data ($CV_{br}A^{-1}$) was mapped onto a conventional ternary phase diagram. It was found that the properties of the $Zr_xSn_yTi_zO_{2-\varepsilon}$ thin films depend strongly on the deposition conditions, as does the region of composition that yields the highest values for the figure of merit. Full compositional scans for films prepared under various processing conditions thus proved essential. In their choice of elements, van Dover and co-workers have focused on deposition at substrate temperatures below 300 °C to maintain compatibility with back-end Si IC fabrication technology, and did not apply any annealing treatment. In contrast to the application of combinatorial materials synthesis for superconducting and magnetoresistant materials, in this application reproduction of the thin film results by bulk materials samples is not crucial, since in the final production process the materials will be manufactured by thin film deposition techniques.

Combinatorial approaches have also recently been applied by Xiang and co-workers to ferroelectric materials where the effects of transition metal dopants on the dielectric coefficient and tangent loss of a library of thin films of $(Ba_xSr_{1-x})TiO_3$ (BST) were determined.[64] Ferroelectric materials are being widely used in the development of new microwave devices such as frequency agile filters, phase shifters, and tunable high-Q resonators. $(Ba_xSr_{1-x})TiO_3$ compounds have been intensely studied for such applications because of their low loss and high dielectric coefficients. Four libraries of 256 differently doped thin films of $(Ba_xSr_{1-x})TiO_3$, where $x = 1$, 0.8, 0.7, and 0.5, were generated on a 2.54 × 2.54 mm $LaAlO_3$ substrate by using multistep thin film RF sputtering together with a quaternary masking strategy with four physical shadow masks. These four hosts were then doped with different combinations of up to three out of nine different metallic elements with each dopant added in excess of 1 mol % with respect to the BST host; the resultant dopant map for the $BaTiO_3$ (BTO) quadrant is shown in Figure 5 a.

The same map applies to the other three quadrants of the library with the three other host materials, $(Ba_{0.8}Sr_{0.2})TiO_3$, $(Ba_{0.7}Sr_{0.3})TiO_3$, and $(Ba_{0.5}Sr_{0.5})TiO_3$. Appropriate postannealing afforded high-quality epitaxial thin films, comparable to those made by conventional in situ methods from stoichiometric targets on hot substrates. The rapid, quantitative, and nondestructive characterization of the microwave dielectric properties—the dielectric coefficient and loss tangent—of samples in the library was achieved with a scanning-tip microwave near-field microscope[47, 51, 54, 74] at 1 GHz, and the results were found to be consistent with measurements made with interdigital electrodes.

In Figure 5 b the averaged dielectric coefficient and tangent loss data are displayed for the BTO quadrant; each square corresponds to a different thin-film sample site, and the darker shade represents the lower dielectric coefficient. Compared to sample 1, the pure $BaTiO_3$, all samples in the upper right hand quadrant containing 1 mol % W have a lower value for the dielectric coefficient, which is also observed in the films with different ratios of Ba and Sr in the other three quadrants. Specific dopants were found to significantly affect the dielectric coefficient and the tangent loss, with La (sample 2) and Ce (sample 3) increasing the dielectric coefficient, whereas most dopants result in decreased values relative to the undoped material. In the tangent loss data a

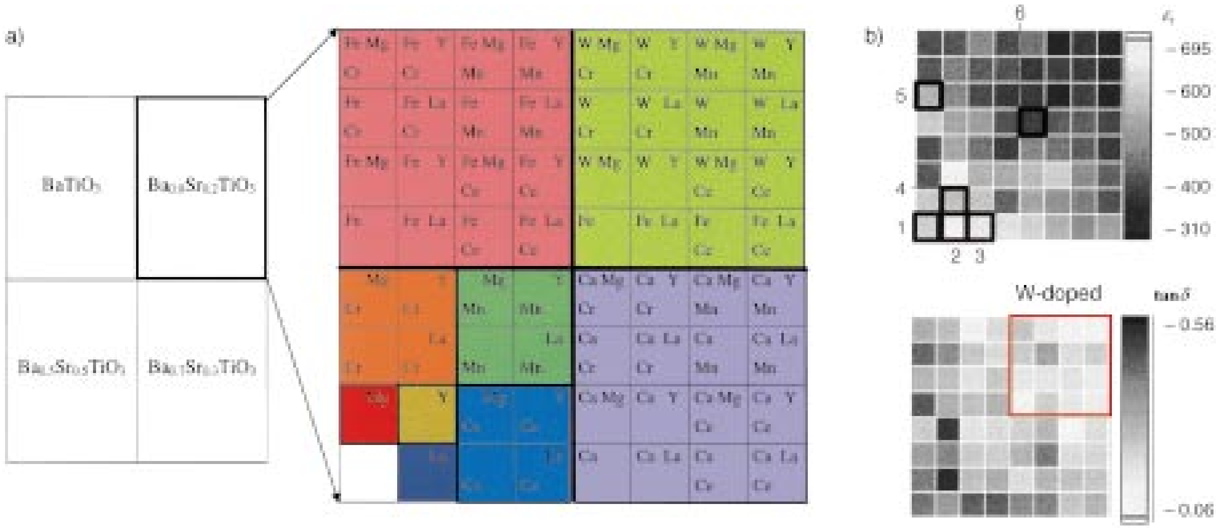


Figure 5. a) Dopant map for the $BaTiO_3$ quadrant of a ferroelectric thin film library; the same map applies to the other three quadrants containing different host materials. A quaternary masking scheme with four masks was used to deposit 256 differently doped thin films of $Ba_xSr_{1-x}TiO_3$ ($0.5 < x < 1$) on a 2.54 × 2.54 cm $LaAlO_3$ substrate. b) Representation of the dielectric coefficient (top) and loss tangent images (bottom) of doped $BaTiO_3$ films, measured using a scanning-tip microwave near-field microscope with submicron spatial resolution. Each square corresponds to a different thin film sample site as given in the composition map above. (Reprinted with permission from the author.[64] © 1999 American Institute of Physics.)

lighter shade implies a lower loss tangent, and thus all the W-doped samples have a lower loss tangent than the pure BTO; this reduction is also observed for the other host compositions. In the case of microwave applications, where the values of the dielectric coefficient are considered to be high, a minor reduction may be tolerable as long as there is a noticeable improvement in the tangent loss. This is especially important for the microwave application of these tunable dielectric materials and could lead to a radar that steers the beam and quickly locates objects electrically rather than mechanically, and cell phones that instantaneously tune into the incoming signals.

Subsequently, Xiang and co-workers evaluated the effects of dopants on device performance by incorporating a layer of the doped dielectric $(Ba_xSr_{1-x})TiO_3$ in a parallel-plate capacitor library between Pt and $La_{0.5}Sr_{0.5}CoO_3$ electrodes.[75] Like the work of van Dover et al. on thin film dielectrics, this investigation aims to aid in the identification of the optimum dielectric material, for example, for integrated capacitors in dynamic random access memory chips (DRAM). Multilayer device structure libraries of 240 different host/dopant combinations were epitaxially synthesized with sharp interfaces from amorphous layers on a 12.7 × 12.7 mm $LaAlO_3$ substrate. Addition of 1.5 mol% W was found to increase the figure of merit, the ratio of the effective dielectric current and the leakage current density, 220-fold and reduce the high-frequency tangent loss fourfold. The epitaxial growth of heterostructures in thin film device libraries is necessary in order to explore the intrinsic effects of compositional variations in the absence of polycrystalline microstructural effects, which can provide sites for charge traps and other defects.

Since the conventional techniques of high-temperature in situ epitaxial thin-film growth cannot be used for combinatorial library synthesis, Xiang and colleagues developed a synthesis method to form epitaxial multilayers from amorphous layers deposited at room temperature by pulsed laser deposition (PLD). The capacitor library consists of a 100–200 nm thick amorphous layer of $La_{0.5}Sr_{0.5}CoO_3$ (LSCO) on $LaAlO_3$; the substrate is then annealed at 850 °C for 1.5 h. By using two-dimensional shutters the three different hosts $BaTiO_3$, $Ba_{0.7}Sr_{0.3}TiO_3$, and $Ba_{0.5}Sr_{0.5}TiO_3$ are deposited from stoichiometric targets in the x direction of the substrate, whereas in the y direction typically up to four dopants are added as a gradient from 0 to 3 mol% to each host. The stoichiometry is controlled by moving the shutters at a controlled speed during deposition. With help from the automated multitarget carousel and shutters in the PLD system the host-dopant layers can be deposited in a single experiment, typically in less than 3 h. Two-step annealing then ensures uniform interdiffusion of dopants and epitaxial crystal growth with sharp interfaces between the BST and the LSCO layer. To complete the device structure individual Pt electrodes (50 nm) were deposited with a photolithographic mask. Approximately 5500 capacitors, each 50 × 50 μm in size were formed with 240 different host/dopant concentration combinations, which afforded about 23 capacitors for each host/dopant concentration and provided a test of the reproducibility of each device.

2.2.4. Luminescent Materials

The combinatorial methodology of thin-film deposition and masking techniques to create materials chip libraries has quickly found applications in the discovery and optimization of luminescent materials. Despite many years of intensive research fewer than 100 useful commercial phosphor materials have been discovered through conventional one-at-a-time synthesis and testing. Phosphor materials with high quantum efficiency find application in display technologies such as cathode ray tubes (CRTs) and are of great importance for developing improved plasma, field emission, and electroluminescent flat-panel displays, as well as lighting.[76] Phosphors are typically inorganic powders that consist of a polycrystalline host doped with ions of a rare earth and/or a transition metal.[77] The dopants may act as a center for luminescence that generates light when excited by ultraviolet light, or as a sensitizer that absorbs and transfers the ultraviolet energy to the luminescent center. Although the photophysical processes leading to luminescence are relatively well understood, the specific spectral properties, luminescence efficiencies, and operational lifetimes depend on complex interactions between the excitation source, host lattice, sensitizer, and luminescent center.

Two groups reported the application of combinatorial methods to the discovery and optimization of several phosphorescent compounds based on metal oxides. Oxides are attractive host materials for the development of advanced phosphors as a result of their ease of synthesis and stability. For example, the efficient refractive oxide phosphors, $Y_2O_3{:}Eu^{III}$ (red), $Y_3Al_5O_{12}{:}Tb^{III}$ (green), and $BaMgAl_{10}O_{17}{:}Eu^{II}$ (blue), have found applications in tricolor lamps, projection TVs, and plasma displays.

Symyx Technologies' red phosphor, a vanadate of yttrium, aluminium, lanthanum, and europium, $Y_{0.845}Al_{0.07}La_{0.06}VO_4{:}Eu_{0.025}$ that has a quantum efficiency approaching those of existing commercial red phosphors, was discovered in a library of 25000 different compositions produced by electron-beam evaporation to deposit thin films onto a 76.2 mm silicon wafer.[78] In a discovery library, four constant thickness columns consisting of SnO_2 (480 nm), V (160 nm), Al_2O_3 + V (150 nm+80 nm), or Al_2O_3 (300 nm) were first deposited. On top of these layers were deposited four rows of linearly varying thickness of La_2O_3, Y_2O_3, MgO, or Sr_2CO_3 to create 16 host lattice subregions. Finally, within each of the 16 subregions linearly varying thickness of the rare earths, Eu_2O_3, Tb_4O_7, Tm_2O_3, and CeO_2 were deposited, which resulted in approximately 600 different chemical compositions per square centimeter (Figure 6a).

A stainless steel primary mask consisting of 230 × 230 μm elements spaced 420 μm apart was attached to the substrate to separate individual library elements. The spatial variation of materials deposited on the library was created using stationary and movable physical masks to control the thickness of specific evaporants in selected regions of the substrate; two masks were used: one with a single 19.1 mm wide rectangular slit and the other with four 4.8 mm wide rectangular slits. Since the constituents of each library element were deposited in layers oxidative thermal processing at various temperatures

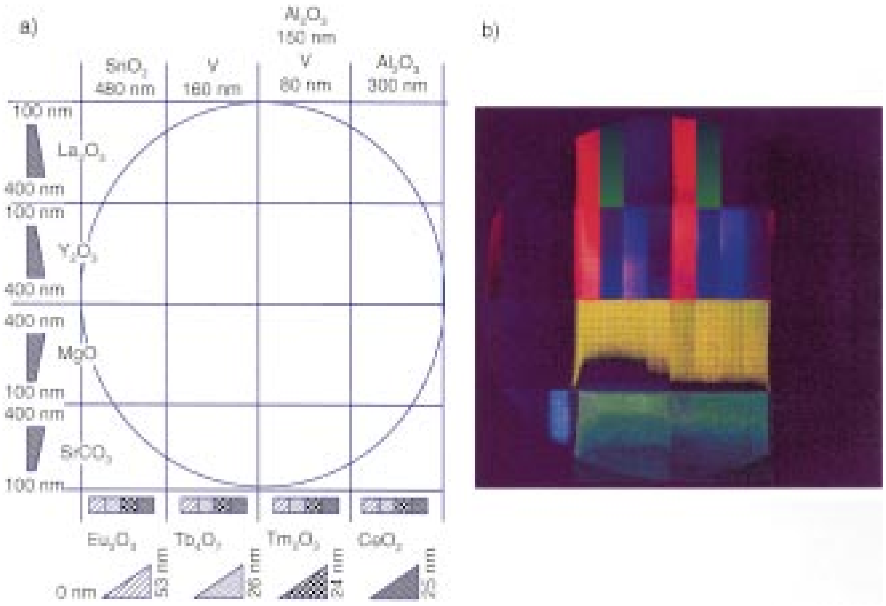


Figure 6. a) Deposition map of a diverse phosphor discovery library showing the thicknesses of the various materials deposited on a 7.62 cm silicon wafer. b) Photograph of the photoluminescence of the discovery library containing approximately 25 000 different compositions after excitment with UV light. In this library novel efficient red and blue phosphor compositions were identified and subsequently optimized in focus libraries. (Reprinted with permission from the author.[78] © 1999 Nature.)

was needed to mix the layers and create the desired chemical compounds. High-throughput screening for ultraviolet-excited photoluminescence (see Figure 6 b) was performed by photographing the visible emission of the library with a charge-coupled device (CCD) camera while exciting with a 254 nm broadband source. A quantitative measure of the chromaticity relative to calibration standards was calculated from three images obtained with red, green, and blue tristimulus emission filters, respectively.

To optimize the best host compositions of the Eu-doped red phosphors $Y_{1-m}Al_mVO_4$ materials identified in the initial high-density exploration library a second library was deposited on a triangular grid, including La as a third host component. First, Eu_2O_3 and V were deposited uniformly over the entire substrate, followed by linearly varying the amount of Y_2O_3, Al_2O_3, and La_2O_3 along three axes offset by a rotation of 120°, thereby exploring all possible $Y_{0.95-m-n}Al_nLa_mVO_4{:}Eu_{0.05}$ compounds. The maximum intensity with red chromaticity suitable for a commercial material corresponds to the phosphor composition $Y_{0.82}Al_{0.07}La_{0.06}VO_4{:}Eu_{0.05}$. The activator concentration in this lead host was subsequently optimized with a third library in which the Eu^{III} concentration was varied between 0 and 20 % by using a single movable mask, and probing the compositions $Y_{0.87-m}Al_{0.07}La_{0.06}VO_4{:}Eu_m$. Screening of this optimization library identified 2.5 % Eu as the most efficient dopant, which gave the final optimized composition $Y_{0.845}Al_{0.07}La_{0.06}VO_4{:}Eu_{0.025}$ with improved red chromaticity ($x = 0.67$, $y = 0.32$) compared to the more orange standard commercial red phosphor $Y_{1.95}O_3{:}Eu_{0.05}$ ($x = 0.64$, $y = 0.35$). Synthesis of bulk samples by conventional methods produced materials indistinguishable from the thin film library samples and confirmed the performance of the newly identified composition.

The group from Symyx Technologies followed this work with a report on a novel luminescent oxide, Sr_2CeO_4.[79] Whereas previous studies of luminescent materials had primarily focused on the synthesis of compositional variants within classes of materials with previously known structure types, the discovery of this fundamentally new blue–white phosphor in an unexpected region of composition space exemplifies and validates the combinatorial methodology of materials science and discovery. The new luminescent phase Sr_2CeO_4 was identified by automated high-throughput screening of the discovery library shown in (Figure 6 b), which suggested the possibility of a new phosphor with blue–white emission in the region of the combinatorial library containing Sr, Sn, and Ce. A subsequent ternary focus library containing combinations of these three elements revealed that Sn was not needed for the observed emissive properties, and that maximum luminescence was observed at Sr:Ce ratios greater than one. A bulk sample with a 2:1 ratio of Sr:Ce was prepared from the reaction of CeO_2 with $SrCO_3$ to study the optical and other physical properties. The excitation and emission spectra of Sr_2CeO_4 displayed broad maxima at 310 and 485 nm, respectively, with the emission appearing blue–white to the eye ($x = 0.198$, $y = 0.292$) and with a quantum yield of 0.48. The phosphor is effectively excited by X-rays and exhibits efficient cathodoluminescence. The structure, determined by powder X-ray diffraction is highly anisotropic and reveals one-dimensional chains of edge-sharing CeO_6 octahedra that are linked together by Sr^{II} ions (Figure 7).[80]

This unusual structure has not previously been found for rare earth based oxide phosphors, and it is believed that the structure is critical for the observation of luminescence in Sr_2CeO_4. Strong evidence suggests the mechanism of luminescence to be based on ligand-to-metal charge transfer ($O^{II-} \rightarrow Ce^{IV}$), and not from isolated valence transitions (d–f) from Ce^{III} defect centers as in all known cerium-based phosphors.

To determine if there were other luminescent phases within the M_2CeO_4 (M = Ba, Ca, Sr) composition space a triangular library was prepared with the M_2CeO_4 compositions at each corner. The library was prepared by robotically dispensing sol–gel precursors followed by heating to 900 °C. The Sr containing region was observed to have the brightest emission under 254 nm excitation, and there is no appreciable luminescence from the Ba and Ca regions. This work shows that the combinatorial materials synthesis approach can identify fundamentally new and unexpected structures with properties that arise from unusual mechanisms.

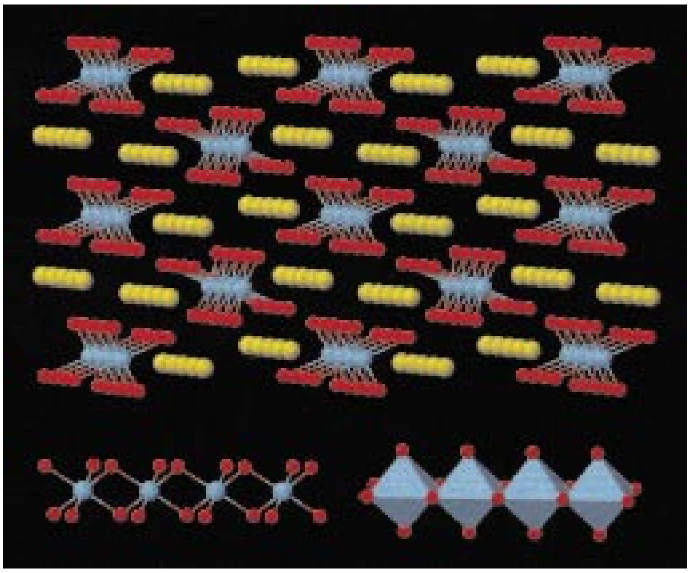


Figure 7. The crystal structure of the blue phosphor Sr_2CeO_4 consists of linear chains of *trans* edge-sharing CeO_6 octahedra with four equatorial O atoms and two terminal Ce–O bonds per octahedron, surrounded by interchain Sr^{2+} ions. The O atoms are red, Ce atoms blue, and Sr atoms yellow. (Reprinted with permission from the author.[79] © 1999 American Association for the Advancement of Science.)

Xiang et al. have used the binary masking approach already applied in the combinatorial synthesis of superconducting and magnetoresistant materials to prepare several 128-member libraries of perovskite aluminates of the form $Gd(La,Sr)AlO_x$ doped with rare earth activators and have evaluated the phosphorescence of all the samples simultaneously by photographing the entire library under broad-wavelength UV light (254 nm).[81] The resulting color photograph allowed for a convenient qualitative evaluation of the library, and the brightest red, green, and blue phosphors were resynthesized on a larger scale. Although bulk samples generally behaved similarly to their thin-film counterparts, exceptions were noted for blue phosphors where the good performance of the thin-film material in the library was not reproduced in the bulk sample. The combinatorial libraries were used to rapidly survey a wide range of compositions of oxides under a variety of processing conditions, which was facilitated because seven identical libraries could be deposited simultaneously on $LaAlO_3$, MgO, or Si single-crystalline substrates and then subjected to different annealing and sintering conditions.

Subsequently, Xiang and co-workers demonstrated that a scanning multi-inkjet delivery system can be used to accomplish the solution-phase synthesis of libraries of phosphors based on refractory metal oxides doped with rare earth metals, by focusing their efforts on the same class of rare earth activated $Gd(La,Sr)AlO_x$ materials already investigated with the combination of thin film deposition and binary masking techniques mentioned above.[57] $(La_mGd_{1-m})Al_nO_x{:}Eu_y^{3+}$ phosphors generated in the inkjet library afforded strong red photoluminescence, and the composition corresponding to the brightest phosphor in the library is reported to be almost identical to the one found in the libraries deposited by RF sputtering.

Multi-composition materials libraries of thin film phosphors $(Gd,La,Y)_m(Ta,Zr,W,Mo,Zn)_n(Al,Mg,Sr)_kO_x{:}(Tm,Eu,Tb,Ce)_y$ (with $0 \leq m,n,k \leq 1$, $0.005 \leq y \leq 0.1$) were generated by Sun and Xiang by sequential RF sputtering of thin-film precursors through combinatorial physical masks to create three identical libraries simultaneously on $LaAlO_3$ crystals with 128 different compositions each.[82] Different annealing conditions and atmospheres completed the synthesis of the phosphor materials libraries, and photoluminescence images were acquired under 254 nm-centered broad-wavelength UV radiation of a Hg lamp by using color photography. A new red phosphor with the structure $(Gd_{1.54}Zn_{0.46})O_{3-\delta}{:}Eu^{III}_{0.06}$ is claimed, and reported to have characteristics comparable to the state-of-the-art orange–red phosphor $Y_2O_3{:}Eu^{III}$ and also to possess excellent X-ray and cathodoluminescent properties.

By applying their refined quaternary masking strategy, and by using a photolithography lift-off technique rather than an actual physical mask, Schultz and co-workers generated by RF/DC sputtering three identical 1024-member libraries of compositionally diverse silicate and gallate host materials containing a number of different dopants on 2.54 × 2.54 mm thermally oxidized Si substrates.[62] The libraries were subsequently annealed under a variety of different conditions, and a parallel imaging system and scanning spectrophotometer were used to identify and characterize compositions in the library with interesting luminescent behavior. The emission and excitation of approximately 100 selected blue, green, and red photoluminescent silicates and gallates in the library were measured, with about 25 of the 1024 sites showing significant blue photoluminescence. However, for these compositions no blue luminescence was observed from bulk and thin film samples prepared on a $LaAlO_3$ substrate and it was suspected that SiO_2 diffusion from the substrate plays an important role. To test their assumption gradient libraries of $Gd_xGa_{1-x}O_z{:}(SiO_2)_y$ on $LaAlO_3$ substrates were generated, in which the stoichiometry of the materials was varied continuously by using pulsed laser deposition (PLD). Broadband blue emission was observed from this library, which was postulated to arise from interfacial electronic states of SiO_2 finely dispersed in the $Gd_3Ga_5O_{12}$ matrix and possibly coated on the surface of $Gd_3Ga_5O_{12}$ grains.

2.2.5. Zeolites

Multicomponent zeolite synthesis is another area of advanced solid-state materials for which combinatorial discovery and optimization can be applied fruitfully. A multiautoclave system capable of carrying out at least 100 crystallizations under the special conditions used in the synthesis of zeolites, such as temperatures above the normal boiling point (up to 200 °C) of the reaction mixture and elevated pressure, has been reported by Akporiaye et al.[83] In its simplest form the reactor consists of a Teflon block with cylindrical holes, designed to accommodate Teflon-coated septa, sandwiched between two steel plates. The ability to stack identical synthesis blocks allows the parallel synthesis of on the order of 1000 combinations in one experiment. The system was tested by reproducing in a single experiment under identical conditions the phase diagram of the ternary phase system Na_2O-Al_2O_3-SiO_2-H_2O, the perhaps most intensively studied of all zeolite syntheses and known to produce several different zeolite structures depending on conditions and composition.[84] With a total volume of each sample gel of not more than 0.5 mL the crystalline phases zeolite A, faujasite, and gmelinite were obtained, with the region of zeolite A coinciding almost perfectly with the earlier results and good agreement obtained in the faujasite region; the formation of sodalite, however, was only observed in the more recent investigation. The only partial agreement was attributed to a control of the water content in the parallel autoclave.

Although the authors mentioned that the ternary diagram could be extended by varying the water content, nothing is reported on the results of such an experiment to substantiate their claim. To increase the complexity of their system they introduced additional cations to replace Na and used the multiautoclave system to screen cation combinations of the two ternary combinations Li_2O-TMA_2O-Na_2O-Al_2O_3-SiO_2 and TMA_2O-Na_2O-Al_2O_3-SiO_2 and the quaternary combination TMA_2O-Cs_2O-Li_2O-Na_2O-Al_2O_3-SiO_2, which in effect spans the quaternary phase diagram in the range of molar ratios between 0 and 1 for Na_2O and 0 to 0.9 for TMA_2O,Cs_2O and Li_2O. The screening maps the six zeolite phases and approximate stability regions, and improves the efficiency by two orders of magnitude by applying combinatorial strategies.

The attractiveness of combinatorial methods for hydrothermal synthesis was also realized by Klein et al., who claim that the advantage of their reactor over the one described in the previous section is the direct preparation of a library of materials whose components can be identified automatically on the library substrate by X-ray microdiffraction, and their much smaller reaction volume of on the order of 2 μL.[85] The central part of their reactor is a Si wafer, which contains the sintered reaction products and represents the library after hydrothermal synthesis and calcination. The identification of the individual products can then directly be carried out with a GADDS microdiffractometer (GADDS = general area detector diffraction spectroscopy). Their results on the synthesis of titanium-containing TS-1 with variation of the template molecules and metal components, followed by screening for qualitative indication of the materials formed and the information "amorphous or crystalline", confirm that zeolite synthesis on a microgram scale is possible and justified.

2.2.6. Organic Materials and Polymers

The application of combinatorial chemistry holds great promise in the discovery of lattice inclusion compounds whose inclusion cavities are difficult to design from molecular structures.[86] When screened against one particular guest compound, seventeen new ammonium carboxylate host compounds were discovered in a combinatorial library of 100 salts formed by mixing ten commercially available amines and ten carboxylic acids. The application of this technique to chiral recognition by the proper choice of amines and carboxylic acids to form a variety of host compounds is under investigation.

Chiral recognition has also been the driving force behind another application of combinatorial synthesis and analysis methodology. A small model library of chiral stationary phases for HPLC was prepared on optimized polymer supports by reacting a mixture of three L-amino acids with 12 aromatic amines. On-column screening of the mixture for enantioselectivity, and deconvolution enabled the single best selector to be identified.[87] To determine which of the 36 selectors in the HPLC column is the most powerful a deconvolution process involving the preparation of beads with a progressively smaller number of selectors was used. In contrast to the "one column, one selector" approach, which would require the preparation and testing of 36 chiral stationary phases, this combinatorial scheme requires the preparation of only 11 columns for the discovery of the most selective material. The advantage of the mixed selector column approach becomes even more convincing with a larger set of selectors; for a library of 240 selectors the deconvolution can be completed with only 17 columns.

The same group then reported the preparation of a parallel 108-member library of 4-aryl-1,4-dihydropyrimidine enantiomers, which were screened by observing the enantioselectivity for resolution on a "brush-type" chiral stationary phase; the best candidates were then attached to monodisperse macroporous beads to prepare new polymer-based chiral stationary phases, which proved efficient for the resolution of several analytes.[88]

Chiral separations are also the focus of another application of combinatorial libraries. The binding performances of molecularly imprinted polymers (MIPs) give these materials great potential in combinatorial approaches as recognition matrices for the screening and rapid selection of ligands from a combinatorial library.[89] Molecular imprinting is a technology by which recognition sites can be generated within a macromolecular matrix by the use of a molecular template in a casting procedure.[90] The selected ligand (print molecule) is first allowed to interact through bond formation with one or more functional monomers in solution. The resulting adducts are subsequently copolymerized with a large excess of cross-linker to give a rigid, insoluble polymer. Following extraction of the print molecule, specific recognition sites are left in the polymer where the spatial arrangement of the complementary functional entities of the polymer network, together with the shape image, corresponds to the imprinted molecule.

The technique has been demonstrated in the screening of a combinatorial steroid library.[89a] A combinatorial library of molecularly imprinted polymers has also been tested in chiral separations.[89c] It normally takes several days to complete the tedious and time-consuming experimental steps involved in the preparation and evaluation of molecularly imprinted polymers, and a method involving combinatorial chemistry is desired that can readily perform the preparation and evaluation of MIPs to establish an optimal functional monomer system in a short time. Takeuchi et al. reported in 1999 a novel method for synthesizing and evaluating artificical receptors, by combining a molecular imprinting concept and a combinatorial chemistry strategy.[91] Combinatorial libraries of MIPs were prepared and screened for high affinity and selectivity to the original template by a newly developed semiautomatic system. The preparation of the MIPs was automatically performed by using programmed liquid handling equipment with a new in situ molecular imprinting protocol whereby MIP is prepared on the bottom surface of each glass vial, followed by an automated discrete binding test with the programmed liquid handler. Two assesments of the created 49-member libraries were carried out, namely "instant first screening" and "regular screening". The instant first screening is performed on the synthesized polymer films to roughly estimate the affinity of the template to the resultant polymer by quantifying the amount of template bound. Regular screenings are carried out later to make more precise evaluation of the affinities and selectivities of the MIP library.

Molecularly imprinted polymers were prepared as artificial receptors for the triazine herbicides ametryn and atrazine by the combinatorial molecular imprinting using a varied amount of two functional monomers, methacrylic acid and 2-(trifluoromethyl)acrylic acid. By examining the MIP libraries it appears that, depending on the functional monomer used, the imprinting efficiency is different for each triazine herbicide. The results suggest that the proposed high-throughput combinatorial molecularly imprinting technqiue is a promising method for finding optimal conditions of MIP preparations for given molecules.

Combinatorial approaches are also beginning to be applied to polymer chemistry. For example, a small library of polyarylates (0.2 g per sample) was prepared from 14 distinct tyrosine-derived diphenols and eight aliphatic diacids, which resulted in 112 structurally related strictly alternating copolymers.[92] These copolymers are biodegradable and potentially useful as medical implant materials. The structural variations provided incremental differences in polymer free volume, bulkiness, flexibility, and hydrophobicity. Up to 32 polymers were synthesized in parallel under identical reaction conditions. Physical measurements were carried out on a sample-by-sample basis by conventional methods: molecular weight by GPC, T_g by DSC, and the air–water contact angle (sessile drop), to provide several structure–property correlations. In vitro cell proliferation studies confirmed the fundamental hypothesis that the availability of the copolymer library facilitates more meaningful biological correlations and the selection of polymers for biomedical applications when the test materials exhibit systematic variations in structure while sharing a range of common features.

Finally, polymerization reactions between different combinations of two starting materials have been found to lead to many new, uniquely responding sensors with responses not simply related to the proportions of the starting materials.[93] Discrete polymer-sensing cone arrays or gradient sensors show broadly diverse shifts in the wavelength of the fluorescence emission in response to organic vapor pulses. Combinatorial polymer synthesis from a limited number of starting materials thus presents an attractive approach to rapidly generate large sets of unique and diverse polymer sensors for analyte detection.

Safir and colleagues at Symyx Technologies have focussed on combining rapid synthesis and rapid characterization techniques with full automation to reap the full benefit of combinatorial chemistry in the area of polymer science.[94] Living free radical polymerizations, which allow for molecular weight control, were studied to demonstrate this integration of synthesis and characterization.[95] In particular, the effects of different initiators (organo halides) and catalyst/control agents (low oxidation state organometallic reagents) on atom transfer radical polymerizations (ATRP), which have been shown to successfully polymerize a variety of monomers, were studied. A 45-member library comprising the combinations of five Cu^I initiators and nine organo halide control agents was screened for controlled styrene polymerization using 4,4′-di-(5-nonyl)-2,2′-bipyridine (dNbpy) as the ligand.[96] To produce molecular weight diversity in an 80-member styrene ATRP library the monomer–initiator ratio (M:I) was varied and the rate of propagation was slowed by diluting with solvent. Two initiators were used, each with either two concentrations and five M:I ratios (100 to 500 in steps of 100), or five solvents and six dilutions (ranging from 73% to 31% monomer); all elements in the library used CuCl+2 dNbpy as the catalyst/control agent.

Finally, structural and molecular weight diversity was introduced in a 55-member library by using one initiator with five M:I ratios (100 to 500 in steps of 100) in the copolymerization of styrene and butylacrylate, which created a gradient in the polymer composition from 0% to 100% butylacrylate with 10% increments. By utitilizing the standard microtiter plate format equipped with a teflon faced sealing mechanism a 96-well glass lined aluminum reactor was developed to conduct organic reactions above the boiling point of the reagents without loss of pressure.

Two methods of rapid molecular weight determination, specifically precipitation-redissolution chromatography (PRC)[97] and rapid fire light scattering (RFLS) were used to screen the resulting polystyrene samples. Precipitation-redissolution chromatography uses rapid solvent gradients (from a bad solvent to a good solvent) to separate polymers according to their solubility, which is related to size; molecular weight values can be obtained in as fast as eight seconds (one minute is more commonly used). To determine polymer molecular weights in as short as 6 seconds (25 seconds is more commonly used) rapid fire light scattering utilizes a flow-through static light scattering (SLS) detector followed by a mass detector (such as refractive index) in conjunction with a small PS-GPC guard column that separates monomer and catalyst from the polymer.

3. Combinatorial Organic and Organometallic Catalysis

In homogeneous catalysis[98] the catalytically active species is in most cases a metal ion stabilized by one or more ligating or chelating organic moieties. The relationship of ligand structure to chemical and physical properties of derived metal complexes is a central theme in numerous fields such as selective catalysis, sensor discovery, and bio-organic chemistry. In an extremely challenging rational approach, the identification of metal–ligand complexes with new physical or chemical properties such as well-designed structural, electronic, and/or stereochemical features typically involves the synthesis of a small number of appropriate ligand derivatives, and, subsequently, the individual analysis of their metal-binding properties. This "empirical approach" often proves to be very labor intensive and not economical since the potential for optimization is limited by resources and time. In this context, a systematic methodology for the expedient generation of new classes of coordination complexes would clearly be of great value. The synthesis of a library of ligands for the discovery of new or improved catalysts may be carried out by using combinatorial organic synthesis methodologies to overcome a limited ligand supply, and may subsequently be followed by metal complexation and screening for catalytic activity in a targeted chemical transformation.

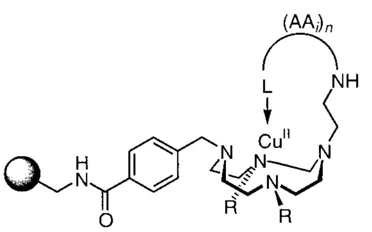
3.1. Metal-Binding Peptidic Ligands and Enzyme Mimetics

The application of combinatorial methodologies to the synthesis of metal-binding agents may be considered as one of the starting points in the development of organic and organometallic catalysts by combinatorial methods. Since combinatorial methods have their origin in the field of peptide library synthesis, it is not surprising that libraries of peptide-based compounds have been studied to identify new sequences with high affinity for transition metals. A traditional approach to new metal-binding agents is based on core receptors that already have established binding properties and the modification of their substitution patterns to induce changes in binding strength and selectivity.

3.1.1. Novel Metal-Binding Peptidic Ligands

The following section describes three examples of the combinatorial synthesis of new metal-binding peptidic ligands based on a lead structure, and two examples where such a lead structure did not previously exist. In 1995 Still and co-workers combined the aforementioned concepts and synthesized libraries of up to 10^5 peptide-modified macrocyclic cyclens.[99] The cyclic tetramine cyclen, its derivatives, and several related macrocylic ligands possess an affinity for metal ions such as Cu^{II} and Co^{II} and are widely investigated and used as synthetic transmembrane ionophores.[100] These researchers attached one of the ring nitrogen atoms of the cyclen core to a polyethylene glycol-grafted polystyrene resin (PEG-PS-resin). The remaining three secondary nitrogen atoms of the cyclen scaffold were then subsequently used for further substituent elaboration by using a "split-pool" protocol for library diversification. Peptidic side arms, derived from a pool of 19 side-chain protected amino acids (AA_n), were attached through aminoethyl spacers by employing established Fmoc solid-phase peptide synthesis methodology (Fmoc = fluoren-9-ylmethoxycarbonyl). Four different cyclen libraries were furnished, which differed in both length and nature of the peptidic side arms (Figure 8).

model of a cyclen-based metal binder:



library 1: R = $(CH_2)_2NHAA_1NH_2$ (19)

library 2: R = $(CH_2)_2NHAA_1AA_2NH_2$ (361)

library 3: R = $(CH_2)_2NHAA_1AA_2AA_3NH_2$ (6859)

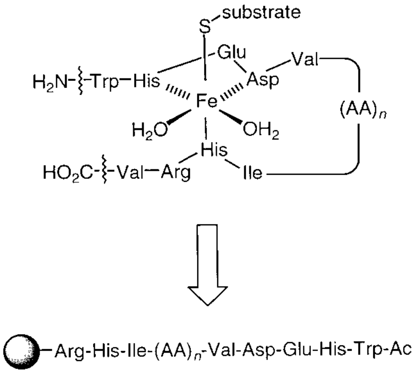
library 4: R = $(CH_2)_2NHAA_1AA_2AA_3AA_4NH_2$ (130321)

● = PEG-grafted polystyrene resin

Figure 8. Libraries of peptidic cyclen-based Cu^{II} binding agents synthesized on a solid support. The numbers in parenthesis represent the appropriate library size. AA_i = D-/L-Ala, Val, Pro, Ser, Gln, Asn, Lys, Glu, Asp, Gly.

The side-chain-protected and -deprotected resins were agitated with diluted aqueous Cu^{II} and Co^{II} solutions. Selective metal binding was screened by visual observation for the indicative bright blue and red colors upon complexation to Cu^{II} and Co^{II}, respectively. Subsequent deconvolution of the chemically encoded polymer beads with the encoding/deconvolution technique of Still et al.[101] allowed for the identification of ligand structures that were responsible for the selective binding of the targeted metal ions. The peptidic sequences generally differed for Cu^{II} and Co^{II} ions, and the length and chemical nature of the peptidic appendages in both protected and unprotected amino acid forms significantly influenced the affinity of the new peptidic functionalized tetraamines for Cu^{II} and Co^{II} ions relative to the corresponding unfunctionalized or alkylated cyclen core.

In a more recent example of a closely related approach the X-ray structure of metalloprotein recombinant isopenicillin *N*-synthase (IPNS) has served as a lead structure for library design. IPNS possesses two iron-binding peptides, Ile-His-Arg and Trp-His-Glu-Asp-Val, at its active site that are linked by a short peptidic sequence (Figure 9).[102] Baldwin, Wood, and their co-workers combinatorially explored various



● = PEG-grafted polystyrene resin

Figure 9. A peptide based on isopenicillin *N*-synthase. Top: Schematic diagram of the active site. The wavy lines represent the remainder of the protein. Bottom: A peptidic library designed to mimic the metal-binding region of the peptide. Library size: 7420 compounds, $n = 0-3$. AA = amino acid, Ac = acetyl.

versions of resin-bound peptide libraries of the general structure resin-Arg-His-Ile-$(AA_i)_n$-Val-Asp-Glu-His-Trp-Ac (AA_i = amino acid; $n = 1-3$), in the hope of discovering potentially new catalysts by examination of their metal-binding abilities (Figure 9).[103]

Three different peptide libraries with a total of 7240 individual oligomers, each differing in length and amino acid content, were synthesized using Fmoc peptide coupling chemistry on a TentaGel resin. The "divide, couple, and recombine" strategy was used to incorporate up to three variable proteinogenic amino acids between the conserved peptide sequences Ile-His-Arg and Val-Asp-Glu-His-AcTrp. By analogy to the protocol described above, selective ion binding was assayed by agitating the resin beads with aqueous solutions of Cu^{II}, Fe^{II}, and Co^{II} sources. Any significant metal binding was accompanied by a color change of the beads. Cobalt(II), for which the color of the beads changed to from the initial pale yellow to pink–purple, showed the most promising results in terms of selectivity. Unfortunately, no encoding/deconvolution strategy was implemented in order to characterize the ligand structure that gave rise to colored metal complexes from the pooled assay. Furthermore, the catalytic activity of the new metal complexes in the targeted desaturative ring closure of the Arnstein tripeptide (ACV) to isopenicilline *N* was not addressed.[102]

Another example for this strategy is represented by the well known amino terminal Cu^{II}- or Ni^{II}-binding (ATCUN) motif that is a structural feature of several naturally occuring proteins such as certain types of albumin (for example, HSA, BSA, and RSA), neuromedins C and K.[104] Characteristic for the ATCUN protein are 1) a free NH_2 terminus, 2) a His residue in the third position, and 3) two intervening peptide nitrogen atoms to reveal the general form, for example, $Ni^{II} \cdot AA_1$-AA_2-His, of this domain. These metalloproteins, especially synthetically or biosynthetically appended to proteins or other biomolecules, are finding increasing utility in the biochemical analysis of noncovalent protein–nucleic acid and protein–protein interactions such as protein–DNA cleavage, protein–protein interactions through oxidative cross-linking, or directed protein cleavage.

Long et al. employed a "positional scanning" combinatorial protocol to optimize the deoxyribose-based cleavage of B-form DNA by $Ni^{II} \cdot AA_1$-AA_2-His metallopeptides.[105] The procedure employed 18 naturally occuring L-α-amino acids (excluding Cys and Trp) to generate two libraries in which the first (AA_1) and the second position (AA_2) of the peptide ligand were varied within the basic AA_1-AA_2-His sequence. The synthetic combinatorial libraries were synthesized by using a standard Boc protecting group protocol (Boc = *tert*-butyloxycarbonyl) and "split-and-mix" technique on methylbenzhydrylamine (mBHA) resin to yield tripeptides having free amino termini and amidated carboxy termini.

Increased direct DNA cleavage for the cleaved tripeptides relative to Ni^{II} · Gly-Gly-His was observed after incubation with a Ni^{II} source and oxidative activation of the metal complex with $KHSO_5$ or MMPP (MMPP = magnesium monoperoxophthalate) when 1) the amino-terminal peptide position contained a hydrophobic amino acid such as Pro, Met, Arg, or Lys (five- to eightfold increase, with Pro exhibiting the greatest activity) and 2) the second peptide position contained an ionic or polar amino acid such as Lys, Arg, Met, Ser, or Thr (three- to fivefold increase, with Lys exhibiting the greatest activity).

The optimized and resynthesized metallotripeptide domain Ni^{II} · Pro-Lys-His was found to oxidatively cleave DNA an order of magnitude better than the reference Ni^{II} · Gly-Gly-His. While metal complexation and the A/T-rich site selectivity for DNA of the optimized metallopeptides were not altered, DNA binding affinity, determied by competitive binding with distamycin, was slightly increased relative to Ni^{II} · Gly-Gly-His. Molecular modeling experiments of the metal complex Ni^{II} · Pro-Lys-His resulted in a proposal for the mechanism of increased DNA cleavage activity that involved prior noncovalent interactions between the metallotripeptide domain and DNA.

Two research groups used a very similar combinatorial approach to discover selective metal-binding ligands. Unlike the two cases above, these approaches did not incorporate predefined metal-binding sites although the metal ion binding ability of the new ligands was again based on peptidic chains. In the first example, Jacobsen and his group reported the synthesis of a 12000-member library by using the "split-pool" methodology to discover highly selective metal-binding agents directly on a solid support.[106] In this case library members comprised four variable modules: 1) an amino acid, 2) a turn element (cyclic β-amino alcohol or an α-amino acid), 3) an amino acid, and 4) a capping agent (Figure 10). The ensemble of the stereochemically defined building blocks was introduced "with the notion that this conformational restriction would encourage the formation of a potential binding site in which both amino acid side chains might interact with metal".

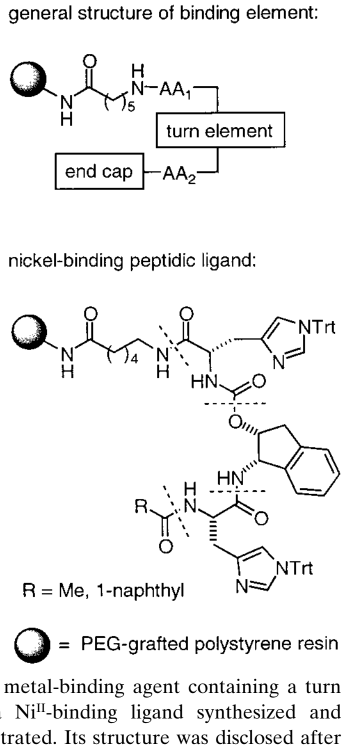


Figure 10. General structure of a metal-binding agent containing a turn element. Specific examples of a Ni^{II}-binding ligand synthesized and screened on solid support are illustrated. Its structure was disclosed after staining and deconvolution of its chemical history. AA_i = amino acid, Trt = trityl (= triphenylmethyl).

The new resin-bound ligands were screened in a "pooled" assay by agitation in methanolic solutions of Ni^{II} and Fe^{III} salts according to the protocol of Still et al.[101] After staining the beads with the appropriate indicators (dimethyglyoxime in the case of Ni^{II} or KSCN in the case of Fe^{III}), those containing high concentrations of Ni^{II} or Fe^{III} were visually identified by their red or orange–red color, respectively, using a light microscope. The chemical tags on the selected beads were cleaved from the solid support without any interference with the peptidic ligands, which allowed deconvolution of the chemical synthesis history of an individual selective metal-binding ligand. Several new ligand structures were disclosed that selectively bind Ni^{II} or Fe^{III}, each of which consisted of histidine residues, and in most cases, a set of two turning elements and/or terminating caps.

In a second example, Schneider-Mergener and his group synthesized and screened a cellulose-bound hexapeptide combinatorial library for the identification of ^{99m}Tc-binding peptides.[107] Technetium-99m complexed to organic compounds, proteins, peptides, or antibodies plays an important role in the radioimmunodetection (RAID) of organs and in tumor imaging because of its low cost, ideal physical properties, and broad availability. These researchers synthesized a combinatorial library of approximately 8000 hexapeptides of the general structure B_1-X-B_2-X-B_3-X, where the amino acids B_i ($i = 1-3$) were positioned on the defined positions 1, 3, and 5 within the hexapeptide sequence and each was one of the 20 naturally occurring L-amino acids. The amino acids X_i in positions 2, 4, and 6 were "systematically randomized". Automated synthesis on a cellulose platform ("spot synthesis") furnished the library of hexapeptides in a spatially addressable format. After incubation, the library was screened for ^{99m}Tc affinity by phosphorimaging by using an aqueous pertechnate solution as a ^{99m}Tc source. Besides a variety of cysteine-containing hexapeptides, known for their strong complexing capability towards ^{99m}Tc, peptidic ligands containing the amino acids His, Lys, Arg, and Met showed significant affinity towards the radioisotope. In a "positional scanning" of two additional libraries, three X-positions were defined and revealed the non-cysteine-containing primary sequences Lys-Gly-His-Ser-His-Val and Lys-Ala-Met-Tyr-His-Gly as superior ligands for ^{99m}Tc.

The aforementioned contributions exemplify the successful implementation of combinatorial methods such as parallel synthesis on solid supports and "spot synthesis", "split-mix" methodology, and encoding/deconvolution techniques for the identification of potential ligands and their metal–organic complexes. Although the screening tools were in most cases relatively simple, the high grade of parallelism and the simplicity of these approaches allowed efficient and rapid screening of literally thousands of ligands. In all cases, the new ligand structures created a range of potential coordinating environments through a diverse set of functional groups and conformational restrictions, a concept which, of course, has been applied frequently. Catalytic studies were not addressed in any of the studies.

A 625-member library of undecapeptides has recently been assayed for catalytic activity in phosphate hydrolysis by using test substances that form insoluble indigo dyes in the presence of oxygen. By using a split-mix approach Berkessel and Hérault synthesized on solid support sequences Phe-X-GlyGly-X-GlyGly-X-GlyGly-X, where X is one of Arg, His, Tyr, Trp, or Ser.[108] About 2500 beads were incubated with Cu^{II}, Zn^{II}, Fe^{III}, Co^{III}, Eu^{III}, Ce^{IV}, and Zr^{IV} solutions; only in the presence of Zr^{IV} did the observation of the blue indigo color indicate catalytic hydrolysis activity. The most promising candidates were isolated, identified, and synthesized on a solid support and in solution to confirm the library results.

3.1.2. Combinatorial Libraries of Polymeric Catalysts as Enzyme Mimetics

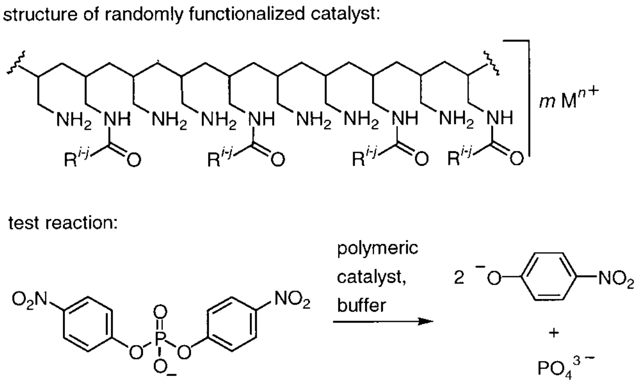
Biological enzymes are held up as the ideal in catalyst performance since they often exhibit perfect selectivities and possess high activities under relatively mild reaction conditions.[109] As a consequence enzymes have found widespread use in industry in a multitude of chemical reactions such as hydrolytic detergents, in fermentation processess, and even in organic synthesis for various functional group interconversions or resolutions of racemic mixtures.[110]

Costly enzyme supply and problems with performing and controlling the enzyme-catalyzed reactions, in addition to the prospect of improving the versatility, compatibility, and efficiency, stimulated chemists to rationally design and synthesize numerous classes of appropriate low molecular weight synthetic enzyme catalysts ("synzymes") that mimic a natural enzymatic function or structure. However, most of them have fallen short of the goal of efficiently reproducing enzymatic catalysis. Nonetheless, these studies have brought more insights into enzymatic reactions.[111]

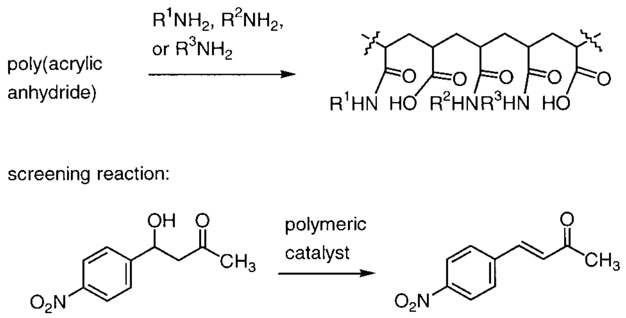
Menger and co-workers investigated a new approach to identify new organic catalysts by searching a multitude of randomly generated systems for their catalytic or reactive potential, in the hope of generating compounds with multiple functional groups in proper juxtaposition to effect catalysis of a targeted reaction.[112] This approach to catalyst discovery and development differs markedly from "empirical approaches" where a relatively small body of knowledge is available from previous work or from "rational approaches", where a more or less detailed understanding of fundamental reaction steps is available but bears the intrinsic problem of how to identify a specific catalyst in the reaction mixtures.

The discovery of catalysts with phosphatase activity for hydrolytic cleavage of phosphorus ester bonds, reported by the same group in 1995, was one of the first applications of this concept in combinatorial catalysis.[113] In their study commercially available polyallylamine was functionalized with various combinations and proportions of eight carboxylic acids to afford randomly functionalized polymers bearing amides ranging in concentration from 5 to 45% (Scheme 1). The polymeric mixtures were then screened for catalytic activity towards hydrolysis of bis(*p*-nitrophenyl)phosphate in the presence of various metal ions such as Mg^{II}, Zn^{II}, and Fe^{III}.

One-at-a-time spectrophotometric monitoring of the absorption of the generated *p*-nitrophenolate ion gave initial hydrolysis rates of the bis(*p*-nitrophenyl)phosphate. Neither the unfunctionalized polyallylamine nor those polymers derivatized with only one kind of carboxylic acid produced a



Scheme 1. Model of a hydrolytically active polyallylamine catalyst randomly functionalized by amide bonds of various carboxylic acid derivatives and used for the hydrolysis of activated phosphates. R^{i-j} = funtionalized organic residues.



Scheme 2. Representative example of a polymeric catalyst based on poly(acryl anhydride) and randomly functionalized with amide bonds, which catalyzes the dehydration of a β-hydroxy ketone.

catalytically active polymer. Significant rate accelerations (k_{cat}/k_{uncat}) of up to 3×10^4 (exceeding that of a catalytic antibody for the same reaction[114]) were observed for a polymer composition derived from 15% 4-imidazolacetic acid, 10% *p*-hydroxybenzoic acid, 7.5% octanoic acid, and 5% Fe^{III}. Other combinations proved to be far less active. The random nature of the synthesis of the polymeric catalysts leads to a lack of structural information about catalytically active sites but the researchers stated that they were concerned more with function than with structure.

A very similar but technically more sophisticated strategy resulted in the development of a polymeric catalyst for the reduction of keto esters to the corresponding α-hydroxy acids, for example, benzoylformic acid ($PhCOCO_2^-$) to mandelic acid.[115] Automated dispensing of all reagents neccessary for amide bond formation furnished the synthesis of a total of 8198 polymeric variations. The random functionalization of the amino or imino groups of polyallylamine (PAA) or polyethylenimine (PEI) catalyst supports, respectively, in the range of 20 to 60%, were obtained with sets of three to four functionalized carboxylic acids. Additionally, a 5–10% content of 1,4-dihydropyridine (DHP), known from NADH-models to reduce activated ketones to alcohols, was incorporated as a reducing agent. In the subsequent parallel spectrophotometric screening for the disappearance of the dihydopyridine chromophore, carried out in the presence of divalent Cu^{II}, Mg^{II}, and Zn^{II} ions, about 92% of the combinatorial variations were found to be catalytically inactive. The two most active polymer compositions were determined, and the active PEI-based polymer had a functional composition of 5% dihydropyridine, 2.5% 2-imidazolacetic acid, 15% 2-naphthylcarboxylic acid, 2.5% 3-mercaptopropionic acid, and 5% Zn^{II}.

A recent objective was to develop a combinatorial polymer capable of catalyzing the biologically relevant dehydration of β-hydroxy ketones. On the assumption that polymeric catalysts possessing both acid and basic functional groups in proper spatial orientation would likely catalyze this reaction (Scheme 2),[116] polymers were formed from poly(acrylic anhydride) by aminolysis with sets of mixtures of three to four amines taken from a library of 11 amines. A total of 1344 polymer variations, each functionalized with amide bonds to an extent of up to 20%, were obtained from 14 combinations of amines in 96 different ratios by using instrumentation similar to that described above. In parallel spectrophotometric monitoring of the appearance of the α,β-unsaturated β-aryl ketone, about 1% of the polymeric catalysts revealed a significant rate enhancement (920 at pH = 7.0 and 23°C) over the background reaction. For comparison, an antibody-catalyzed dehydration of the test substrate (pH = 7.0 and 37°C) afforded a catalysis rate enhancement of 1200 above the background.[117] An interesting feature was the observation of a "nonbiological induced fit", that is, a substrate-induced transformation into a catalytically active conformation upon variation of the reaction parameters such as temperature and pH.

Ion-exchange latexes, especially those bearing quaternary ammonium anion exchange sites, significantly increase the hydrolysis rate of activated esters such as *p*-nitrophenyldiphenylphosphate.[118] In 1998 Ford and Miller reported the parallel synthesis of a library of 32 anion exchange alkyl methacrylate latexes.[119] Latexes based on 25 mass% vinylbenzyl chloride, 73 mass% aliphatic methacrylates, 1 mass% of divinylbenzene for cross-linking and 1 mass% of (*m*/*p*-vinylbenzyl)trimethylammonium chloride for stabilizing purposes were prepared by radical polymerization. The latexes differed in the number and combination of the aliphatic monomers present. Anion exchange sites were introduced by quaternization of the benzyl chloride residues with either trimethylamine or tributylamine to afford anion exchange particles containing 19–20% of quaternary ammonium units (Figure 11).

Pseudo-first-order reaction rate coefficients were calculated over the first 20% of conversion from the spectrophotometrically recorded formation of the *p*-nitrophenoxide anion. Relative rate enhancements ranged from 2.3 for a polystyrene–trimethyl ammonium (TMA) latex to 16.5 for a 2-ethyl-

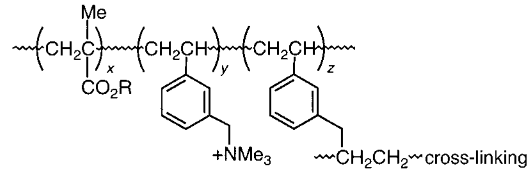
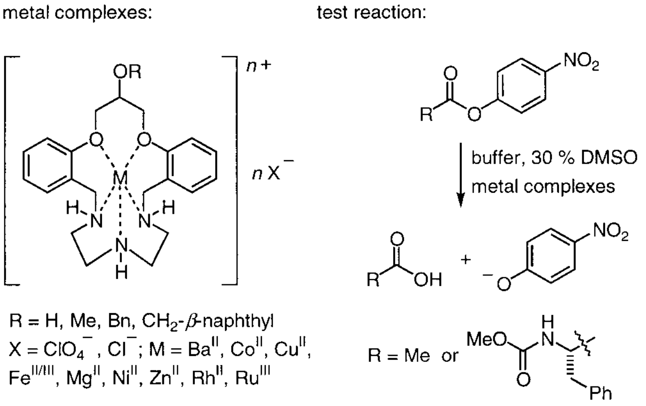


Figure 11. Representative structure of a trimethylammonium (TMA) functionalized latex.

hexyl methacrylate–tributyl ammonium (TBA) latex. Generally, latexes containing a 2-ethylhexyl methacrylate unit proved to be the most active catalysts, and several additional performance trends were rationalized from the molecular structure. This parallel synthesis approach has enabled the rapid evolution of latex catalysts and can be used to identify active polymeric catalysts for many other important chemical reactions.

3.1.3. Combinatorial Metal Complexes as Enzyme Mimetics

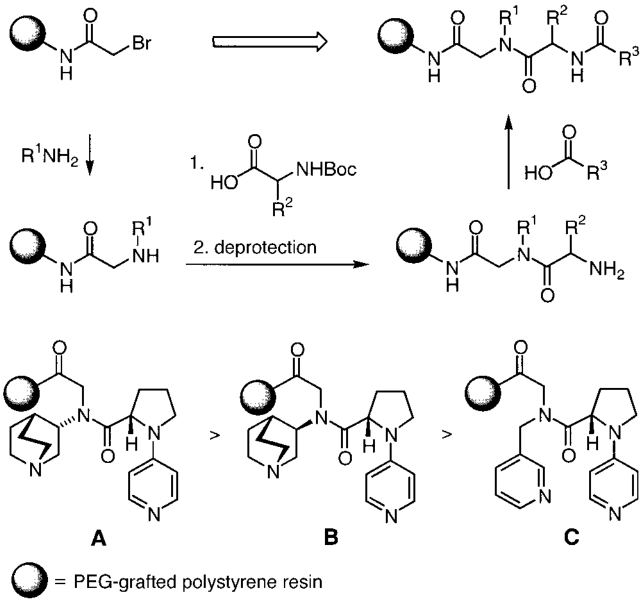
Enzyme mimics for activated ester or phosphate hydrolysis remain at the center of interest. By using a concept similar to the approach of Still et al. for tailoring ligand-binding properties[99] Janda and his group synthesized and screened novel transition metal complexes as enzyme mimics that catalyze the hydrolysis of carboxylic esters.[120] Based on a hydroxyazacrown ether with known affinity to several transition metal ions, a conventional three-step O-alkylation sequence afforded three additional macrocylic ligands (Scheme 3). These four ligands were then complexed with ten transition metal ion sources. The 40-member transition metal complex library was screened in parallel, without prior purification or isolation of the intermediates, for hydrolytic activity towards the well-established model substrates *p*-nitrophenyl acetate and *N*-methoxycarbonyl-L-phenylalanine-*p*-nitrophenyl ester. Initial reaction rates were determined by repetitive scanning of the absorption of the *p*-nitrophenolate ion. Zinc and cobalt complexes gave only moderate rate enhancements ($k_{obs}/k_0 \approx 3$), and the kinetic data implied that the systems do not behave like hydrolytic enzymes because a linear dependence on both substrate and metal complex concentration was observed.



Scheme 3. General structure of transition metal complexes of hydroxy- or alkoxyazacrown ethers that are efficient for the hydrolysis of activated carboxylic acid esters.

Meanwhile, the researchers extended this methodology towards the synthesis of the corresponding azacrown ether–lanthanide complexes that are capable of hydrolyzing phosphate esters, which is a crucial chemical transformation in nucleic acid chemistry.[121] The lanthanide complexes synthesized catalyzed the cleavage of phospho di- and triesters and double-stranded DNA as well, which opens the possibility of using this class of chemicals as therapeutics. Furthermore, another important potential application is the hydrolytic decontamination of toxic organophosphates, phosphonates, and fluorophosphates that are widely used as insecticides and are stockpiled as chemical warfare agents.

Mimicking the hydrolysis of activated ester bonds is not the only enzyme-catalyzed reaction that chemists focus on. By assuming that mimics for acyl transferases require a concerted interplay between tethered functional groups (the catalyst should possess a suitable base that is covalently tethered in close proximity and in the correct orientation relative to a nucleophilic center), Taylor, Morken, and their co-workers reported in 1998 the preparation of a library of 3150 distinct nucleophilic acylation catalysts on approximately 7000 encoded polymer beads prepared by "split-pool" methods.[122] Their trimeric catalysts, synthesized on a special tentagel S–NH_2, consisted of three modules: 1) a primary amine, 2) a protected amino acid including the capping agent *N*-4-pyridylproline, and 3) functionalized carboxylic acids (Scheme 4). Temperature changes that arise from the exothermic catalytic acetylation of ethanol were monitored directly on the floating polymeric supports by IR thermography (see Section 5.1). The "hottest" 23 beads were then manually selected, and their decoding revealed the catalyst structures (Figure 12). Most of them incorporated *N*-4-pyridylproline as the capping agent and contained either (*R*)- or (*S*)-3-aminoquinuclidine as the primary amine component (Scheme 4, structures A–C). This paper is exciting in that the authors successfully implemented IR thermography as a sophisticated parallel screening tool. The authors also stated that the evaluation of organometallic libraries or ligand-accelerated metal catalysis in reactions of current interest should reveal novel catalyst structures with potentially new modes of catalysis.



Scheme 4. Solid-phase synthesis of a nucleophilic acylation catalyst library. The structures of the most catalytically active compounds (**A**–**C**) contain the *N*-4-pyridylproline moiety. R^1, R^2, R^3 = functionalized organic residues; Boc = *tert*-butoxycarbonyl.

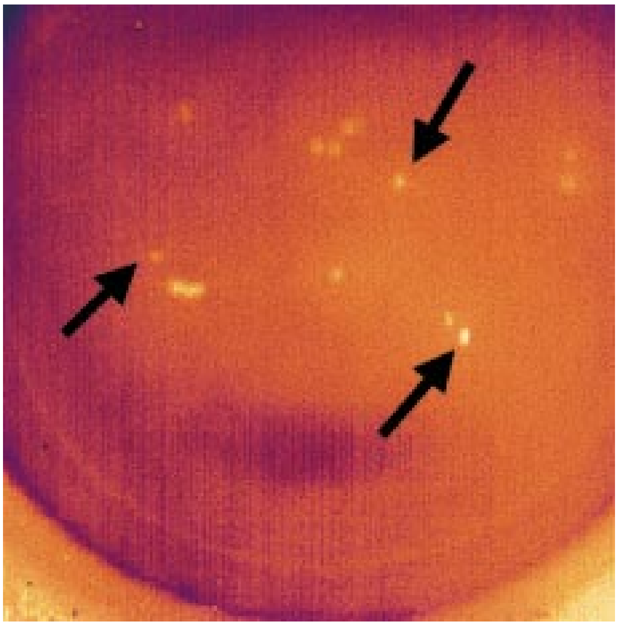


Figure 12. Infrared thermographic image of about 20 catalyst beads in the presence of approximately 3000 noncatalyst beads. Arrows indicate two of the visible "hot" beads. (Reprinted with permission from the author.[122] © 1998 American Association for the Advancement of Science).

3.2. Combinatorial Catalysis in Asymmetric Synthesis

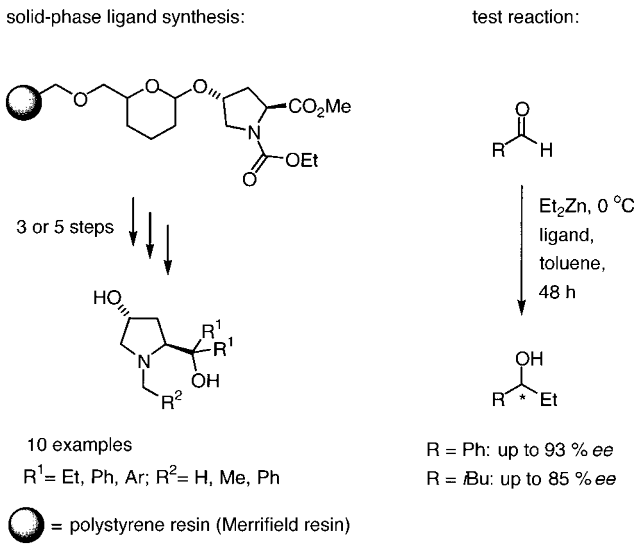
The importance and practicality of asymmetric synthesis as a tool to obtain optically pure or enantiomerically enriched compounds have been fully acknowledged by chemists in the areas of synthetic organic, medicinal, agricultural, and natural products chemistry and their related industries.[123] The most desirable and also the most challenging of the asymmetric transformations is catalytic asymmetric synthesis, where one chiral catalyst molecule can create millions of targeted chiral product molecules in a process that has been termed "chirality multiplication". Thus, asymmetric catalysis represents a significant economic advantage over stoichiometric asymmetric synthesis, and, consequently, the development of new methods for discovering asymmetric catalytic transformations stands as an important and emerging objective in chemistry.

Divergent ligand synthesis strategies, where the transformation of an advanced ligand intermediate into a series of different chiral ligands is performed, appear to be especially fruitful in this area. In most cases, the ligand bears the chiral information and, therefore, creates a discriminating chiral environment in close proximity to the active metal site of the catalyst. Asymmetric synthesis is an especially suitable area for combinatorial catalyst discovery since asymmetric catalysis is often mechanistically very complex and critical variables in the parameter space to be evaluated for catalyst development and optimization are mutually dependent. Thus, by rapid parallel synthesis and metal complexation of chiral ligand libraries, coupled with automated or high-throughput screening, multidimensional problems in the discovery and in the optimization of catalysts may be efficiently addressed.

3.2.1. *Combinatorial Catalyst Libraries in Enantioselective Additions of Dialkylzinc Reagents to Aldehydes*

The enantioselective addition of dialkylzinc reagents to aldehydes can be catalyzed by enantiopure amino alcohols, and this class of reaction has rapidly developed since the observations by Oguni and Omi in 1984 and by Noyori and co-workers in 1986.[124] This ligand class as well as other proline-based ligands have also been used extensively to prepare asymmetric catalysts for enantioselective reductions of ketones and asymmetric Diels–Alder reactions.[125] Furthermore, chiral 1,2-amino alcohols attached to polymers have been used to catalyze the enantioselective addition of organozinc derivatives to aldehydes.[126]

In 1995 Ellman and co-workers reported the parallel solid-phase synthesis of a small library of substituted 2-pyrrolidinemethanol ligands.[127] A parallel solid-phase synthesis approach involving a cleavable tetrahydropyranol linker was used to anchor *trans*-4-hydroxy-L-proline methyl ester as a ligand scaffold to Merrifield resin.[128] Subsequent nucleophilic addition of various Grignard reagents, followed by reductive N-alkylations, gave the desired amino alcohols (Scheme 5). On-bead screening of the asymmetric addition of diethylzinc to a variety of aromatic (up to 94% *ee*) and aliphatic aldehydes (up to 85% *ee*) yielded slightly inferior enantioselectivity relative to that of the corresponding free ligand in solution (Scheme 5). Further studies revealed that the purification of the ligands was not necessary to yield catalysts of comparable performance with both aromatic and aliphatic aldehydes. This early effort is significant in that it represents a general solid-phase synthesis strategy for the development of 2-pyrrolidinemethanol ligand classes. An efficient catalyst was discovered that performs the title reaction for aliphatic aldehydes, which are known to give generally inferior results relative to appropriate aromatic aldehydes.

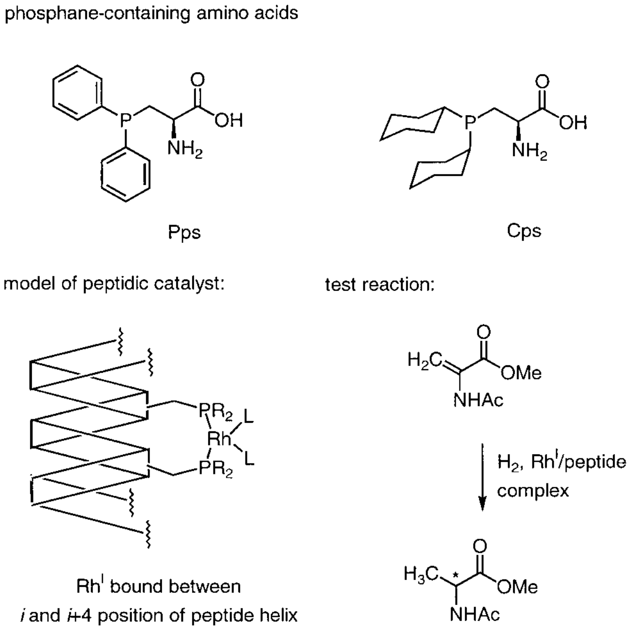


Scheme 5. Parallel solid-phase synthesis of pyrrolidine-type catalysts and their screening in the enantioselective addition of diethylzinc to aldehydes.

3.2.2. Chiral Phosphane Ligands for Asymmetric Hydrogenation

In homogeneous catalysis phosphanes are extremely important ligands in late-transition metal catalyzed processes such as hydrosilylation, hydroformylation, carbonylation, olefin dimerization and, last but not least, hydrogenation.[129] For example, the synthesis of Monsanto's drug L-Dopa, a phenylalanine derivative used for the treatment of Parkinson's disease, was one of the first significant commercial successes of chiral catalytic processes. The reaction involves an asymmetric catalytic hydrogenation of an *N*-(acyl)didehydro amino acid to an *N*-(acyl)amino acid using a Rh^I catalyst with chelating tertiary phosphane ligands.[130] Another important example can be found in the synthesis of Merck's novel HIV-protease inhibitor Indinavir, marketed currently as *Crixivan*.[130]

Phosphane-containing amino acids were originally synthesized to effect conformational states of peptides and to stabilize and control peptide structures upon metal binding.[131] Their application in catalytic asymmetric hydrogenation was reported in 1996 by Gilbertson and Wang.[132] Geysen's polyethylene pin technique was used to synthesize a 63-member library of peptidomimetic ligands for the Rh^I-catalyzed hydrogenation of methyl 2-acetamidoacrylate to the corresponding amino acid derivative *N*-acetylalanin. The general primary structure of the ligands, best described as Ac-Ala-Aib-Ala-[P-containing, internal peptide]-Ala-Aib-Ala-NH_2, shared terminal Ala-Aib-Ala sequences to force an overall α-helical secondary structure and to bring the phosphane groups of the internal peptide sequence in close proximity to each other (Scheme 6). Three classes of structurally unique chiral tetra- or pentapeptides were synthesized for the internal sequence by combining the novel amino acids dicyclohexyl- and diphenylphosphane serine (Cps and Pps, respectively) with two or three hydrophobic amino acids. Each ligand was screened directly on-bead in a parallel 24-vial reactor that was coupled to a GC equipped with a chiral stationary phase to determine the enantioselectivity and overall conversion. Unfortunately, only modest enantiomeric excesses (up to 18.3%) were observed but some trends and correlations between peptide sequence and selectivity were established.



Scheme 6. Screening of a library of support-bound α-helical peptide/phosphane-Rh^I catalysts in enantioselective hydrogenation reactions of prochiral methyl 2-acetamidoacrylate to *N*-acetylalanine methyl ester.

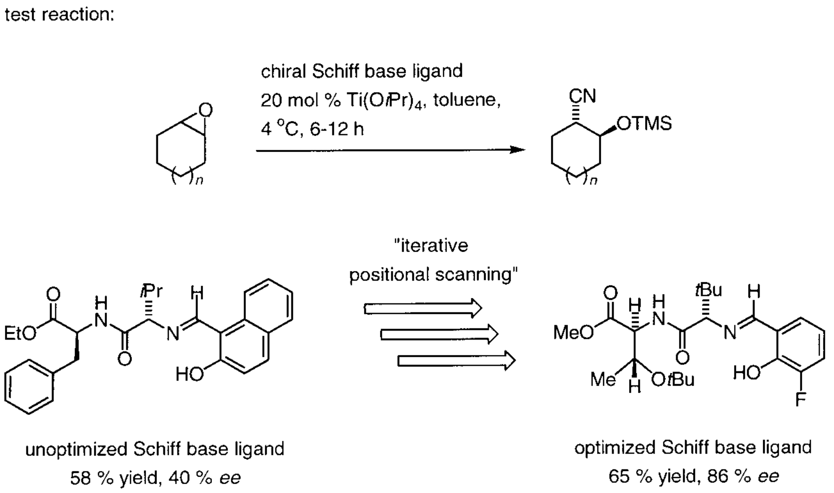
3.2.3. Asymmetric Reactions Catalyzed by Schiff Base Type Ligands

The following examples of Snapper, Hoyveda, and coworkers,[133] as well as those of Jacobsen and co-workers[134] describe the successful application of a modular approach based on well-established functional building blocks to the rapid discovery of novel catalysts. In both cases, ligand backbones consisting of chiral Schiff bases modified with amino acids were evaluated. Imines or Schiff bases of the salen or hemisalen type are of continuing interest and widely explored because they are easily accessible and possess well-established binding modes. Thus, they represent important classes of ligands in various fields of chemistry, but especially in asymmetric catalysis.[135]

Asymmetric ring-opening reactions of (achiral) *meso*-epoxides fall into a class of chemical operations termed as "desymmetrizations",[136] and encompass a synthetic strategy in which chiral target molecules are prepared by "off-mirror" reactions of *meso* compounds catalyzed by chiral catalysts or mediated by chiral auxiliaries.[137] First, a symmetrical building block is prepared from easily accessible starting materials, for example, the conversion of cyclohexene to *meso*-cyclohexenoxide, and the subsequent asymmetric desymmetrization opens access to important chiral, nonracemic intermediates for the synthesis of enantio- and diastereomerically enriched pharmaceuticals and agrochemicals.[137]

In 1992 Oguni and co-workers reported the addition of trimethylsilyl cyanide (TMSCN) to epoxides catalyzed by titanium Schiff base complexes to yield racemic β-cyanohydrins.[138] On the basis of this work Snapper, Hoyveda, and coworkers disclosed a diastereo- and enantioselective version of this reaction in 1996 (Scheme 7).[133] Nonracemic β-cyanohydrins were obtained in good chemical and optical yields with combinatorially optimized chiral titanium/Schiff base complexes. Chiral dipeptidic hemisalen ligands of the general structure SB-AA_2-AA_1-GlyOMe (SB = Schiff base or hemisalen, AA_i = amino acid) were synthesized in a modular fashion from various amino acid and aldehyde building blocks by using parallel solid-phase synthesis techniques. After cleavage from the solid support, complexation with a titanium alkoxide source, and parallel screening of the chiral Lewis acids for efficiency and enantioselectivity, a potent catalyst system for the ring opening of cyclohexene oxide in 89% *ee* was discovered (Scheme 7). Subsequent work by the same group demonstrated that screening did not require cleaving the Schiff base ligand from the solid support, which significantly accelerated the optimization process.[139]

By using a closely related approach for their ligand synthesis, in 1998 Sigman and Jacobsen disclosed polymer-



Scheme 7. Discovery of a new Schiff base catalyst for the Ti-catalyzed enantioselective addition of trimethylsilyl cyanide (TMSCN) to *meso*-epoxides by an iterative optimization approach that uses "positional scanning".

supported Schiff base catalysts of the general structure linker(1)-amino acid-linker(2)-complex (Scheme 8).[134] They explored the on-bead iterative optimization of ligands for the asymmetric hydrocyanation of imines (Strecker reaction). The Strecker reaction constitutes one of the most direct and viable strategies for the asymmetric synthesis of α-amino acid derivatives.[140] Ligand synthesis was made amenable to solid-phase synthesis techniques by choosing readily accessible building blocks and reaction conditions (Scheme 8).

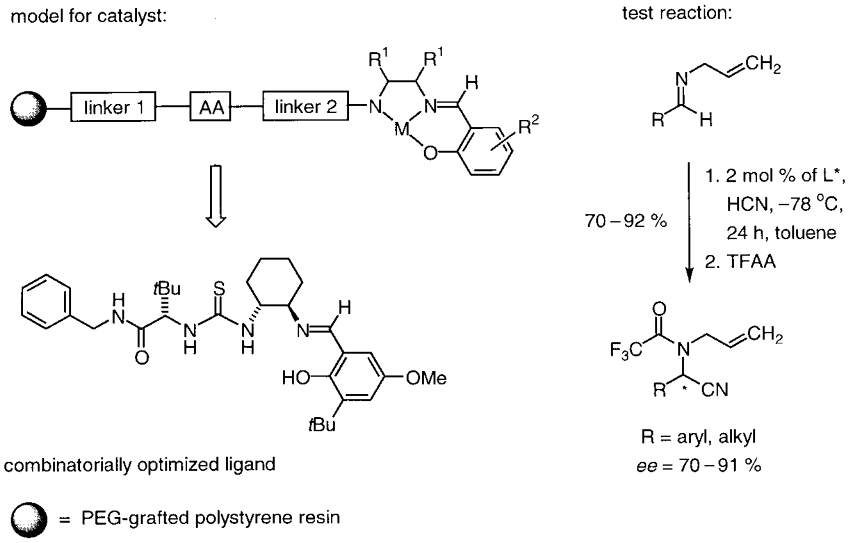
Systematic but nonobvious permutation cycles of their building blocks ("iterative optimization"), such as sequential variation of the amino acid components, the nature of the linker, or the diamino bridging moiety, revealed a transition metal-free catalyst after the synthesis of only three ligand generations that mediated the reaction of both aromatic and aliphatic aldimines in more than 70 % and 83 % enantiomeric excess, respectively. Screening was performed sequentially by gas chromatography on a chiral stationary phase. The best catalyst was resynthesized in solution and in an individually performed experiment showed a further improved enantioselectivity of 91 % *ee* for an aromatic aldimine. Meanwhile, independent investigations by the same group disclosed a very active chiral salen–Al$^{\mathrm{III}}$ complex for the same reaction, which resulted in imine hydrocyanation products of enantiomeric excesses as high as 95 %.[141]

Common to the iterative optimization approach ("positional scanning approach") of the modules comprising the ligand structure are the two assumptions: 1) there is an independent and additive influence of each of the building blocks, and 2) there is an absence of negative cooperative effects during their systematic variation. In addition, the "positional scanning" approach, especially when coupled with automated screening, not only offers unique opportunities for the identification of substrate-specific catalysts (fine tuning), but also permits the discovery of ligands that possess unusual properties and which might otherwise elude detection.

Jacobsen's group disclosed in 1999 the discovery of a novel catalyst for alkene epoxidation.[142] By using a solid-phase synthesis protocol on an aminomethyl polystyrene resin, ligands bearing potential metal-binding moieties were prepared. The ligands comprised five amino acids with donor side arms (Asp, Cys, His, Met, and Ser), three different chiral linking elements each differing in rigidity (1-amino-2-indanol, *trans*-1,2-diaminocyclohexane, and Ser), and 12 different capping agents with functionalities such as heterocycles, phosphanes, and salicylimines, which in turn were attached through imine and amide bonds. Initially, the metal-binding ability of the resulting 192 ligands was determined in a pooled assay with 30 different metal ion sources comprising Ti$^{\mathrm{IV}}$, V$^{\mathrm{IV/V}}$, Cr$^{\mathrm{II}}$, Mn$^{\mathrm{II/III}}$, Fe$^{\mathrm{II/III}}$, Co$^{\mathrm{II}}$, Ni$^{\mathrm{II}}$, Cu$^{\mathrm{II}}$, Zn$^{\mathrm{II}}$, Zr$^{\mathrm{IV}}$, Mo^{0}, Pt$^{\mathrm{IV}}$, Ru$^{\mathrm{II/III}}$, Rh$^{\mathrm{II}}$, Pd$^{\mathrm{II}}$, Ag$^{\mathrm{I}}$, W$^{0/\mathrm{VI}}$, R eV$^{\mathrm{II}}$, Ir$^{\mathrm{IV}}$, Yb$^{\mathrm{III}}$ to yield 5760 possible metal–ligand combinations. Metal binding was visually detected with selective inorganic staining reagents in a similar fashion as in their previous studies.[106]

The entire pooled catalyst library was first screened for the epoxidation of *trans*-β-methylstyrene (TBMS) to determine suitable reaction conditions. In a second screening process, 30 batches of catalyst sublibraries containing mixtures of 1) all 192 ligands plus each individual metal source 2) the 30 individual metal sources alone, and 3) a metal free control were assayed for epoxidation activity by analysis of the product by gas chromatography. Those catalysts prepared from VOSO$_4$ and FeCl$_2$ were most active, although VOSO$_4$ and MeReO$_3$ displayed significant epoxidation activity in the absence of the ligand library too.

Subsequently, 12 FeCl$_2$-derived libraries each containing a mixture of the 16 basic

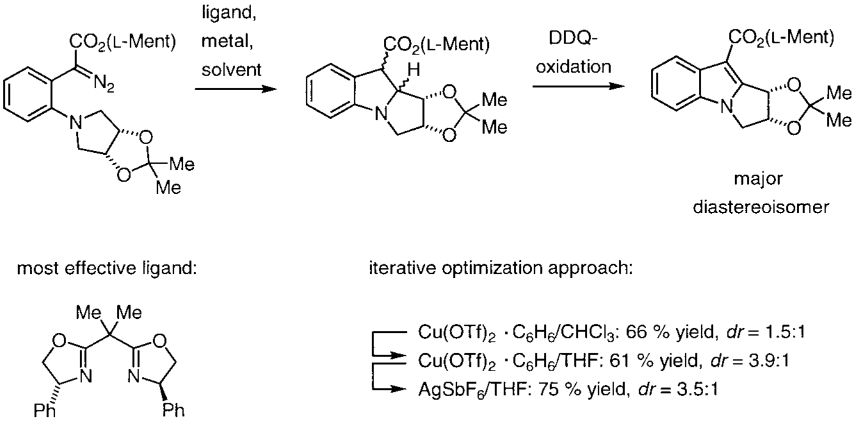


Scheme 8. Combinatorially optimized Schiff base ligand for the asymmetric Strecker reaction (hydrocyanation of imines). AA = amino acid; TFAA = trifluoroacetic anhydride.

structures and a different end cap were further screened. Eventually ligands comprised of pyridine-containing end caps were identified as the most active epoxidation catalysts. Further deconvolution together with the results of additional experiments showed that the most active catalyst compositions were comprised of $FeCl_2$ and ligand structures exhibiting an ensemble of a pyridine-containing end cap, a serine as linking element, and serine or cysteine as the amino acid bound to the solid support, but only low enantioselectivity for the epoxidation of TBMS ($ee = 4-7\%$) was observed. An initial 96-member optimization library based on the identified epoxidation catalyst produced moderately enantioselctive variants ($ee = 15-20\%$) for the target reaction. It is noteworthy that the researchers applied combinatorial strategies for initial catalyst lead discovery and did not obtain these novel catalysts through the synthesis and analysis of parallel libraries of structural analogues based on a previously identified design motif.

3.2.4. Diastereo- and Enantioselective Metallocarbene C–H Insertions

Intramolecular C–H insertion of metal carbenes generated by catalytic decomposition of diazocarbonyl compounds is a facile methodology for C–C bond formation. The reaction proceeds with diazo compounds having suitably oriented substituents and involves presumably the insertion of in situ generated metallocarbenes into C–H bonds. These reactions are often catalyzed by rhodium complexes typically bearing optically pure ligands derived from amino acids.[143] In 1995 Sulikowski and his co-workers disclosed active copper catalysts for this type of reaction and used them in the synthesis of chiral indolyl derivatives from diazoesters.[144] Subsequently, Burgess and colleagues elegantly expanded this work using a highly parallel screening approach for the optimization of ligand/metal/solvent combinations for the same reaction (Scheme 9).[145] In this case, the instrumental set-up for parallel high-throughput catalyst screening encouraged the researchers to investigate a wide variety of systems, some of which would have been regarded as too unusual to warrant testing in a sequential fashion.



Scheme 9. Discovery and optimization of a new catalyst for the intramolecular C–H insertion reaction of Rh–carbenes from α-diazo esters for the synthesis of indolyl derivatives by high-throughput catalyst screening. L-Menth = L-menthyl; *dr* = diastereomeric ratio; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

A library of 96 catalytic systems was created in a standard microtiter/filtration plate in order to accommodate incremental variation of the reaction parameters. Combinations of five different natural or synthetic chiral ligands, seven metal precursors, and four solvents were evaluated in a high-throughput fashion by using a HPLC device equipped with an autosampler. Subsequent data analysis not only identified two superior catalyst systems based on a bis(oxazoline) ligand but also led to the identification of a novel and unexpected Ag^I-based catalytic system with an overall increased diastereoselectivity ($dr = 3.9{:}1$, THF, 10 °C) relative to the original system ($dr = 2.3{:}1$, CH_2Cl_2, 25 °C).

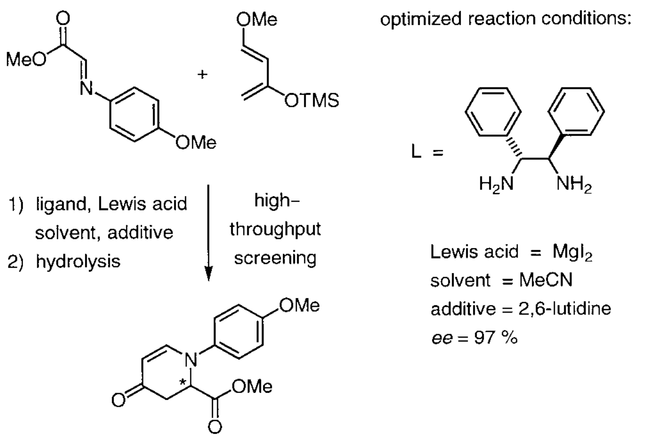
3.2.5. Homochiral Lewis Acid Catalysts for the Asymmetric Aza-Diels–Alder Reaction

Despite the striking advances asymmetric catalysis has experienced in the past two decades many important classes of synthetic transformations lack useful enantioselective catalysts.[146] Although Lewis acid catalysts are widely used to accelerate a variety of C–C bond formations the development of chiral Lewis acid catalysts appears to be an unexplored area compared to that of chiral transition metal catalysts and is becoming the subject of intense research.

The asymmetric aza-Diels–Alder reaction provides an effective route to optically active nitrogen-containing heterocycles, as well as to other compounds of fundamental importance.[147] Asymmetric catalysis of imine dienophiles has remained elusive, and the successful asymmetric induction in the aza-Diels–Alder reaction heavily relied on auxiliary-based methodology. However Yamamoto and Hattori's stoichiometric enantiopure triarylborate Lewis acids[148] and ytterbium-based Lewis acid for azadienes of Kobayashi et al. represent recent exceptions.[149] Furthermore, aza-Diels–Alder reactions of α-imino ester dienophiles with activated dienes by Johannsen and Jørgensen et al. merit closer attention. [150] In 1999 Jnoff and Ghosez disclosed asymmetric Diels–Alder reactions of 2-azadienes that were catalyzed by chiral copper(II) complexes to give enantiomerically pure piperidones.[151]

In 1998 Whiting and his colleagues reported a parallel synthetic and screening approach to chiral catalyst discovery in the Lewis acid catalyzed aza-Diels–Alder reaction of an *N*-arylimine with Danishefsky's diene,[152] a reaction known not to proceed under normal thermal cycloaddition conditions (Scheme 10).[153]

Discrete homochiral Lewis acid complexes were individually generated in solution on multiple-well plates from four different metal salts, three different common enantiopure ligands, three different solvents, and two different additives (Scheme 10). Screening was performed sequentially in about one week by measuring the enantiomeric excesses and conversions by means of an automated HPLC



Scheme 10. Parallel screening of an asymmetric induction in Lewis acid catalyzed aza-Diels–Alder reaction of a *N*-arylimino dienophile with Danishefsky's diene. TMS = trimethylsilyl.

equipped with a chiral stationary phase to result in 144 sets of approximate yields and enantiomeric excesses. Reproducibility was confirmed and the most efficient chiral Lewis acid was a combination of MgI_2 and (*R*,*R*)-1,2-diphenylethylenediamine in acetonitrile in the presence of 2,6-lutidine, which afforded the *N*-arylpiperidinone in 97 % enantiomeric excess.

3.2.6. Divergent Ligand Synthesis and Parallel Assay in Palladium-Catalyzed Allylic Alkylations

In 1998 Burgess et al. highlighted with several examples the value of divergent ligand synthesis strategies for the preparation of focused ligand libraries and the use of automated ligand screening.[154, 155] By definition, divergent syntheses of chiral ligands are characterized by the production of an optically pure material, which is then subsequently used to prepare many ligands of a structurally similar class of ligands.[156]

A chiral building block ("chiral synthon = chiron") based on L-serine was prepared as a key intermediate that was then converted into a family of 13 novel chiral phosphanyloxazoline ligands through several different routes by employing conventional organic synthesis in solution.[154] It was shown that the divergent ligand synthesis approach was very suitable for efficiently accessing this ligand class with a good diversity in terms of steric bulk and/or electronic pertubation (Figure 13).

Correlations of various influential reaction parameters, such as the ligand substitution pattern, presence or absence of ions, ligand:metal ratios, and solvent effects on the enantiomeric excess and absolute configuration in the asymmetric alkylation of 1,3-diphenylpropenyl acetate with malonate as a classical test reaction[157] was evaluated with a customized parallel reaction block in a 27- or 34-well format. Product evaluation and analysis was performed in an automated serial fashion by means of a conventional HPLC equipped with a chiral stationary phase (Scheme 11).

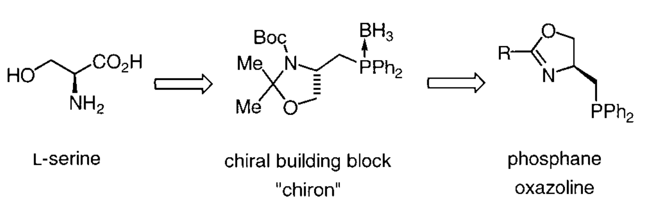
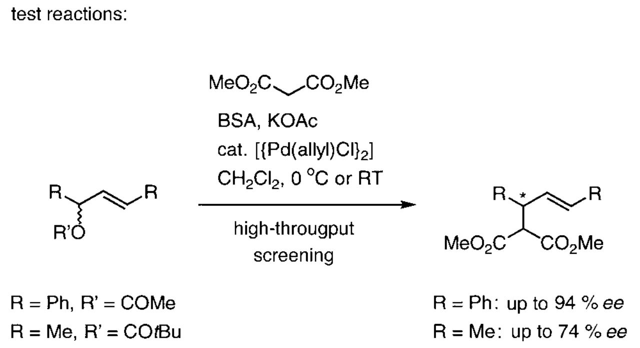


Figure 13. Synthesis of phosphanyloxazoline ligands. Boc = *tert*-butoxycarbonyl; R = various alkyl and aryl residues, 13 examples.



Scheme 11. High-throughput screening of phosphanyloxazoline ligands in Pd-catalyzed asymmetric allylic alkylation reactions. BSA = *O*,*N*-bis(trimethylsilyl)acetamide. Parameters screened: solvent effects, influence of ligands, substitution pattern, presence of chloride ions, ligand:metal ratios.

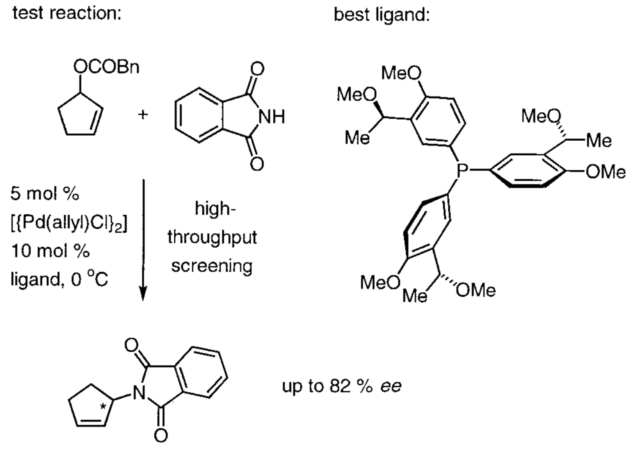
Although loading the array with the reactants was performed manually, parallel screening under an inert gas atmosphere and eventually in two-dimensional assays rapidly established several trends for solvent effects, electronic pertubations, and substituent topographies of the phosphanyloxazoline ligands, the presence or absence of chloride ions, and ligand:metal ratios on the overall stereochemical outcome of the reaction products for each ligand family and each reaction system tested. Besides an essential ligand:metal ratio of 1:1, electron-rich oxazoline ligands and ligands tailored by substituent topography, such as the pseudospherical adamantyl group, resulted in alkylation products with an enantiomeric excess as high as 94%. In a closely related experiment, the best enantiomeric excess observed for a dimethyl-substituted allyl system was found to be 74%.[155]

The same divergent ligand synthesis strategy and an identical instrumental set-up for the high-throughput catalyst screening as described above recently revealed novel "propeller-shaped", C_3-symmetric triarylphosphanes as chiral ligands.[158, 159] They were screened in a related allylic amination reaction yielding N-substituted phthalimine derivatives with up to 82% *ee* (Scheme 12).

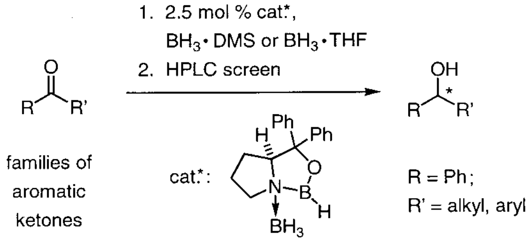
The work described above unambiguously demonstrates that parallel synthesis and automated screens facilitate rapid accumulation of large amounts of useful data, in this case for the targeted asymmetric allylic substitution reaction.

3.2.7. One-Pot, Multisubstrate Screening in Asymmetric Catalysis

Kagan and co-workers investigated an interesting alternative approach to combinatorial catalysis.[160] A library of prochiral substrates may be used in the screening of a chiral catalyst to rapidly gain the maximum information about the performance profile of a new asymmetric catalyst, preferably



Scheme 12. High-throughput screening of "propeller-shaped" C_3-symmetric phosphane ligands in Pd-catalyzed asymmetric allylic amination.



Scheme 13. One-pot, multisubstrate screening of a chiral oxazaborolidine catalyst in the enantioselective reduction of a family of aromatic ketones. DMS = dimethylsulfide.

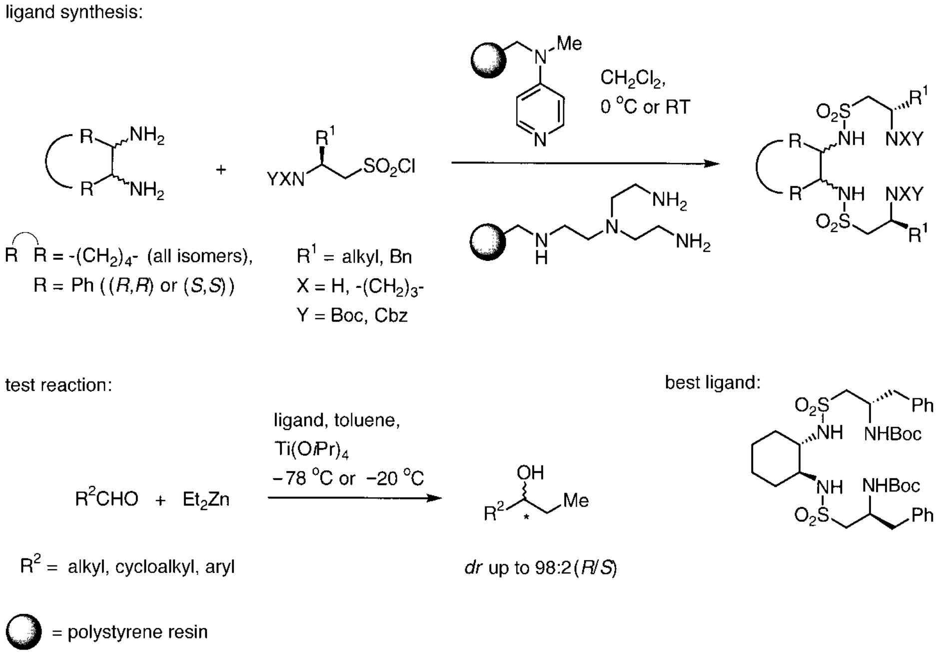
by performing only one experiment. Kagan's group checked the validity of their novel approach ("one asymmetric catalyst/a set of prochiral substrates") in the asymmetric reduction of mixtures of prochiral aromatic ketones to their corresponding alcohols using Corey's chiral oxazaborolidine catalyst (Scheme 13).[161]

The conversion and enantiomeric excesses of the resulting mixture of alcohols was monitored by HPLC equipped with a chiral stationary phase. The careful calibration of the screening conditions was crucial, including baseline separation of the starting ketones, alcohols, and, in addition, a sufficient resolution of the enantiomers of the resulting alcohols. All ketone reductions were repeated in solution, with most of the discrepancies between the individual asymmetric reductions and the multisubstrate approach ranging within 1–7%. For example, the asymmetric reduction of acetophenone resulted in the formation of (*R*)-1-phenylethanol with 97% *ee* under screening conditions (ketone mixture) and in the isolated ketone reduction.

In a recent example of an application of a one-pot multisubstrate screening approach, Gennari et al. disclosed a new family of chiral ligands for the enantioselective catalysis of the $Ti(OiPr)_4$-mediated addition of diethylzinc to various aliphatic and aromatic aldehydes.[162] The novel ligands were based on a modular building block strategy to enable the incorporation of disulfonamide moieties as metal chelating units (Scheme 14). Related disulfonamide ligands have previously been shown to facilitate the title reaction as well as asymmetric cyclopropanation reactions.[163]

The 30-compound ligand library was synthesized by coupling the commercially available vicinal diamine scaffolds 1,2-diphenylethylenediamine ((*R,R*) and (*S,S*) isomers) and 1,2-diaminocyclohexane (*trans*-(*R,R*), *trans*-(*S,S*), *cis*-(*R,S*), and *rac-trans* isomers) in the presence of the polymer-bound nucleophilic DMAP derivatives with five N-protected β-aminosulfonyl chlorides derived from the L-amino acids Ala, Val, Ile, Phe, and Pro.[164] To avoid the classical aqueous work-up and purification of the ligands, solid-phase extraction (SPE)[165] was utilized; excess reagents were scavenged by the solid-phase-bound tris(2-aminoethyl)amine (Scheme 14). This methodology also eliminated the need for additional handles on the scaffolds for attachment to a solid support and avoided any interplay of a solid matrix on the yields and enantiomeric ratios of the catalyzed reactions.

In analogy to Kagan's protocol the individual ligands were assayed in parallel and in spatially addressable format on a mixture of four aldehydes. After optimization of the conditions, product analysis was performed sequentially with a capillary GC equipped with a chiral stationary phase. Excellent enantiomeric ratios for aromatic and aliphatic aldehydes in favor of the *R* enantiomer (*R*/*S*: 97–98:3–2)



Scheme 14. a) Synthesis of bis(sulfonamide) ligands with a polymer-supported DMAP catalyst and solid-phase extraction technology. b) One-pot screening of bis(sulfonamide) ligands in the enantioselective addition of diethylzinc to aldehydes. DMAP = 4-*N*,*N*-dimethylaminopyridine; Boc = *tert*-butoxycarbonyl; Cbz = benzyloxycarbonyl; *dr* = diastereomeric ratio.

were obtained, with the ligand derived from *trans*-(*S*,*S*)-diaminocyclohexane and the N-protected β-aminosulfonyl chloride derived from L-Phe (Scheme 14). The purified ligand was subjected to characterization, and the screening results were confirmed by reaction with the four separate aldehydes.

A conceptionally related combinatorial or family approach to the resolution of racemates was reported by Vries et al.[166] The simultaneous addition of a family of resolving agents to a solution of a given racemate caused a very rapid precipitation of crystalline diasteriomeric salts in good to high enantiomeric purity and yield.

Whether this approach holds promise for future applications will remain in question. The novel "one-pot multi-substrate screening in asymmetric catalysis" concept may suffer from some intrinsic drawbacks and limitations such as peak overlaps in the HPLC screen or cooperative/noncooperative interactions between the chiral catalyst and chiral reaction product (autoinduction, nonlinear behavior of catalytic activity, etc.). However, the simplicity of this method makes it convenient for a preliminary evaluation of many different chiral reagents or catalysts in a targeted reaction once the substrate mixture is standardized. Looking forward, this method might be supplementary to parallel screening of chiral catalysts or auxiliaries prepared by combinatorial chemistry, as described in the previous paragraphs.

3.3. Parallel Synthesis of Substituted Aminomethylphosphanes

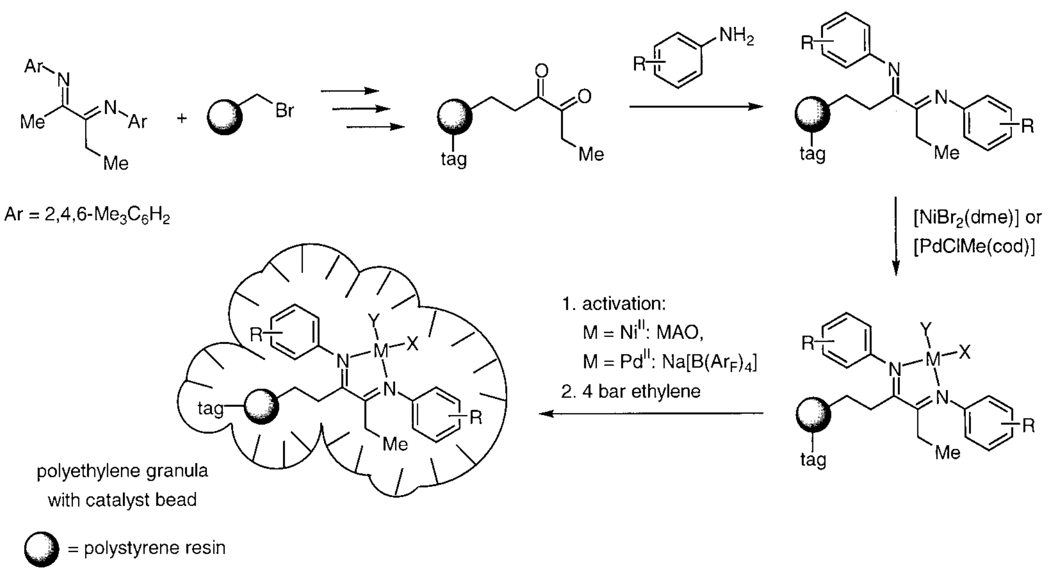
Besides the potential utility of a particular class of ligands for a particular catalytic application, several features must be considered in the selection of ligand libraries. Reactions that use more than two different starting materials are called multicomponent reactions (MCRs).[167] In the light of chemical productivity and generation of molecular diversity an ideal MCR should be comprised of more than two components. High atomic economy (idealy the incorporation of all of the atoms building the starting materials into the final product) is an asset[168] and, furthermore, ligand synthesis and purification procedures must be readily amenable to parallel synthesis techniques. Multicomponent reactions occupy an outstanding position among other reactions with respect to their productivity, yield, conversion, and facile execution, which makes them especially intersting for the concept of combinatorial chemistry. Attemps are now being made to even discover new multicomponent reactions by means of combinatorial technology.[167]

In this context LaPointe reported in 1999 the parallel synthesis of substituted aminomethylphosphanes of the general structure $R_aR_bPCHR_cNR_dR_e$.[169] A 96-member library of substituted aminomethylphosphanes, which were termed PCN ligands in reference to their backbone building atoms, was synthesized by combining two secondary phosphanes (R_aR_bPH), a subset of six substituted aldehydes (R_cCHO), and eight secondary amines (HNR_dR_e) in a facile Mannich-type three-component condensation reaction. The relatively mild reaction conditions (THF, room temperature), the large number of substructures available, and the lack of protection/deprotection steps for the phosphane functional group made this one-step phosphane synthesis an attractive target for parallel synthesis. Reagent delivery and mixing was performed by an automated liquid dispenser. The crude condensation products were of sufficient purity (ca. 95% by ^1H and ^{31}P NMR spectroscopy) for their use as ligands. The parallel synthesis of libraries of metal complexes of the PCN ligands and their use as ethylene polymerzation catalysts, for example, is currently being investigated.[170] This is one of the first reported parallel syntheses of organophosphanes, and as a consequence of the broad accessibility of appropriate building blocks, large numbers of diverse, functionalized, and/or polydentate PCN ligands could potentially be synthesized.

3.4. Combinatorial Approaches to Olefin-Polymerization Catalysts

An annual production of approximately 46 million metric tons exemplifies the industrial importance of polyolefins.[171] Recent reports have shown that certain catalyst systems based on late transition metal diimines exhibit olefin polymerization activities comparable to those reported for commercially employed systems based on early transition metal single-site metallocenes.[172–174] These new systems have sparked considerable interest in the polyolefin industry because of their high activity, ease of synthesis and handling, and tolerance toward functionalized olefins such as methacrylate and vinyl acetate. Over the past few years an increasing effort has been developed, both in academic and industrial research laboratories, for the discovery of new olefin polymerization catalysts that differ dramatically from the forefront Group 4 metallocenes and half-sandwich titanium amide catalysts.[175] Most commercial-scale polyolefin processes employ high surface area supports for immobilizing olefin polymerization catalysts, and only few reports have appeared examining the use of polystyrene as a catalyst support.[176]

Powers, Murphy, and their colleagues from Symyx Technologies developed a parallel synthesis and screening protocol for a polymer-bound 96-membered library of 1,2-diimine–transition metal complexes (Scheme 15).[177, 178] A key resin-bound diketone intermediate was converted in a titanium-mediated condensation with 48 commercially available aminoarenes with varying steric and electronic substituents to furnish a 48-member 1,2-diimine library. In these catalytic systems both substituent topography and electronic pertubation have been reported to play a dramatic role in catalyst activity, and the molecular weight and yield of the polymer.[179] The splitting of the ligand library followed by conversion into the corresponding 48 Ni^{II} or Pd^{II} complexes with $[NiBr_2(dme)]$ or $[PdClMe(cod)]$, respectively, afforded a polymer-bound 96-membered library of 1,2-diimine–transition metal complexes. A corresponding 1,2-diimine solution-phase library based on a related diketone framework was synthesized in order to compare the performance of the resin-bound catalysts with those of the corresponding catalysts in solution.[177] The researchers used metal delivery agents (MDAs), a novel class of polymeric reagents, as metal ion



Scheme 15. Synthesis of Brookhart-type polymer-bound Ni^{II} or Pd^{II} 1,2-diimine complexes and their use in the polymerization of ethylene. $M = Ni^{II}$, $X = Y = Br$; $M = Pd^{II}$, $X = Me$, $Y = Cl$; R = alkyl, aryl, heteroaryl, halogen, functional groups; tag = chemical code; MAO = methylalumoxane, $Ar_F = 3,5\text{-}(F_3C)_2C_6H_3$; dme = 1,2-dimethoxyethane; cod = 1,5-cyclooctadiene.

sources to efficiently complex the solution phase 1,2-diimine library with Ni^{II} and Pd^{II} ions.[30, 180] After activation of the Ni^{II} or Pd^{II} catalyst precursors (1,2-diimine complexes) with MAO (MAO = methylalumoxane) or sodium tetrakis(3,5-bistrifluoromethyl)phenyl borate, respectively, a custom high-pressure parallel polymerization reactor with a modular series of 48 reaction chambers was used to screen for ethylene polymerization. The device was equipped with individual ethylene pressure controls, and reactants were loaded by a three-axis liquid handling robot (Figure 14).[177]

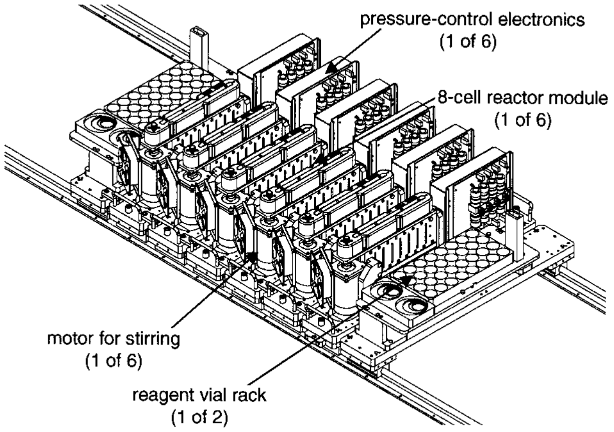


Figure 14. Custom-built parallel polymerization reactor. (Reprinted with permission from the author.[178] © 1999 Elsevier.)

Compared to the corresponding free complexes screened under identical conditions in solution, catalyst performance consistently proved to be decreased for the on-bead Ni^{II} catalysts and increased for the polymer-bound Pd^{II} complexes. For example, molecular weights (M_W) up to 59000 $g\,mol^{-1}$ for resin-bound Ni catalysts and up to 213000 $g\,mol^{-1}$ for the corresponding diimine–Ni catalysts in solution were found by assaying the isolated discrete polyethylene granules by rapid high-temperature gel permeation chromatography. By assuming that catalyst performance is proportional to the "growth" of the polystyrene support beads (2–10 times from the initial diameter of 70 μm), visual inspection of the beads allowed a distinction between Ni^{II}- and Pd^{II}-derived catalysts in mixed assays (Figure 15). The application of a chemical encoding/deconvolution strategy with cleavable tertiary amine tags, followed by HPLC analysis, confirmed these results.

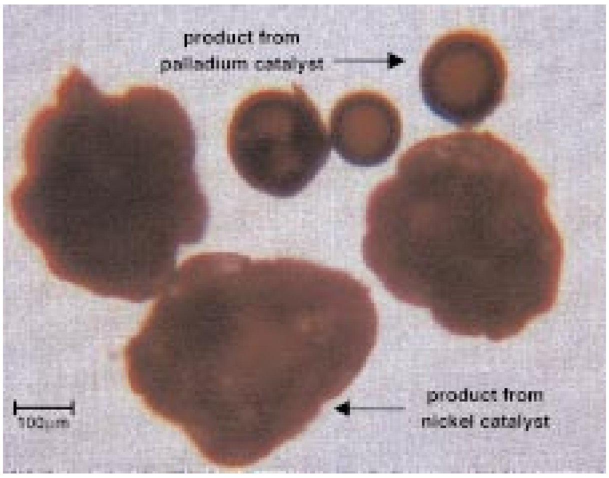


Figure 15. Representative samples of polymeric products obtained from a pooled polymerization of ethylene with polymer-supported Ni^{II} and Pd^{II} 1,2-diimine catalysts. (Reprinted with permission from the author.[177] © 1999 WILEY-VCH.)

The present work demonstrates the feasibility of applying a multitude of combinatorial techniques, including solid-phase synthesis, on-bead screening, and the encoding/deconvolution of pooled libraries of catalysts, for the discovery and optimization of new olefin-polymerization catalysts. Moreover, the technology appears suitable for catalytic processes other than ethylene polymerization.

4. Combinatorial Inorganic Catalysis

Recently, the question was posed as to whether combinatorial heterogeneous catalysis presents a new scientific approach to catalyst discovery or is just “the King’s new clothes”.[45, 181] In contrast to well-known “empirical” and “rational” approaches, the combinatorial approach seems to be well suited to tackle problems where a large parameter space controls the properties of a product. Such is the case in heterogeneous catalysis, where complex ternary and higher order inorganic materials often offer superior performance characteristics.[182] The combinatorial chemistry approach as a “novel concept” enables a larger body of possible materials to be examined than does conventional synthesis, which results in a significant reduction in the development time for a new or improved catalyst system.[181] In this context it is clearly important that the catalytic properties of the rapidly synthesized new materials can be measured in a similarly rapid high-throughput fashion, which often requires, especially in heterogenous catalysis, the development of conceptionally novel high-throughput screening tools.

4.1. Combinatorial Alloys as Electrooxidation Catalysts

Direct methanol–air fuel cells (DMFCs) utilize the electrooxidation of methanol to carbon dioxide and water to create electricity. As a consequence of their high energy density and the low cost of methanol as a fuel they represent an attractive, safe, efficient, and environmentally friendly alternative to hydrogen fuel cells. In order for DMFCs to become commercially viable, better electrocatalysts for the anode reaction need to be developed. In this context, the following paragraph examplifies a fruitful cooperation between the power of combinatorial chemistry and a rational approach for the evaluation of methanol electrooxidation catalysts.[183]

Smotkin, Mallouk, and their co-workers developed a rapid combinatorial screening method for ternary and quaternary alloy catalysts for the electrooxidation of methanol (Scheme 16).[184] Ley et al. had previously suggested that the use of oxophilic additives such as molybdenum, rhenium, osmium, ruthenium, and tin as alloying components with platinum would be beneficial to the overall reaction rates.[183] Nine exploratory library arrays with 15 amorphous ternary compositions of five transition metals (Pt, Ru, Os, Rh, and Pd) each were created, which resulted in a total of 135 unique ternary compositions. The libraries were synthesized by manually dispensing spatially addressable combinations of metal precursor aliquots (spotlike) onto triangular shaped conducting Toray carbon fiber paper, followed by reduction of the metal salts with a borohydride reagent. The libraries were submerged in an aqueous methanolic sodium sulfate electrolyte containing a fluorescent pH indicator such as quinine. Screening was performed with a typical three electrode cell (electrode array as working electrode, Pt-counter cell and a saturated calomel reference electrode) by conducting a single potential sweep from cathodic to anodic potentials against a Pt/Ru (50/50 atom %) reference electrode. Visual inspection under a UV lamp of the highest fluorescent intensities arising from local proton release (pH drop) upon the electrooxidation of methanol determined the catalytically most active spots on a given library. A composition of Pt/Os/Rh (60/25/15 atom %) effectively catalyzed the reaction at low overpotentials.

$$\mathrm{H_3COH\,(aq) + H_2O\,(l) \xrightarrow{anode} CO_2\,(g) + 6\,H^+\,(aq) + 6\,e^-}$$

$$E^0 = +\,0.04\ \mathrm{V\ vs.\ NHE}$$

Scheme 16. Half-cell reaction for the anodic oxidation of methanol to carbon dioxide in direct methanol fuel cells (DMFC). NHE = normal hydrogen electrode ($E^0 = 0.000$ V).

In 1998 the same group reported new and improved results as well as an automated method for generating larger libraries of metal catalysts by using a modified inkjet printer to print metal salt “inks” on conducting Toray carbon paper (Figure 16).[185]

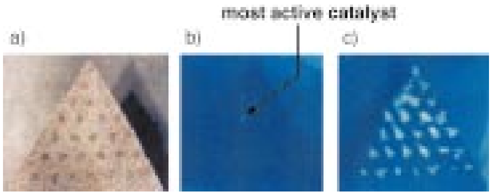


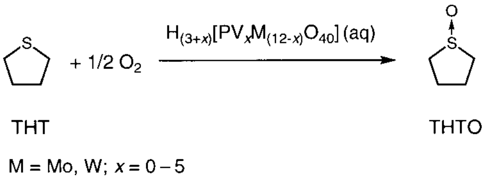
Figure 16. A ternary Pt-Rh-Os array in 6 M aqueous methanol (pH 6) with a quinine indicator. a) Image in white light. b) Fluorescence image at low overpotential, which identifies the most catalytically active region. c) Fluorescence image at high overpotential, where methanol oxidation occurs at every spot in the array. (Reprinted with permission from the author.[185] © 1998 American Association for the Advancement of Science.)

A 645-member electrode array of the five elements Pt, Ru, Os, Ir, and Rh (80 binary, 280 ternary, and 280 quarternary metal combinations) was created in an automated fashion and then screened as described above to identify the most active regions of the composition space. “Zoom screens” were then used to pinpoint several catalytically active hits from ternary and quarternary regions on the Toray carbon paper, some of them surrounded by rather inactive binaries. The most active catalyst possesses a quaternary composition of Pt/Ru/Os/Ir (44/41/10/5 atom %) and showed an approximately 40 % higher current density at a working temperature of 60 °C and at an overpotential of 400 mV compared to the best commercially available alloy Pt/Ru (50/50 atom %). The new catalyst is close in composition to the known binary and ternary alloys in composition but shows a much higher performance profile.[186]

4.2. Combinatorial Libraries of Polyoxometalates as Homogeneous Inorganic Oxidation Catalysts

Early transition metal oxygen anion clusters or polyoxometalates (POMs) have a significant impact in the research fields of self-assembly, supramolecular and cluster chemistry, magnetic properties, materials and surface chemistry, and photo- and electrochromism. Major subsets of polyoxometalate chemistry address catalysis by heteropolyacids, electrochemistry and electrocatalysis, and, most importantly, selective hetero- and homogeneous oxidation processes.[187] Of extraordinary interest are POMs of the Keggin type that possess the general formula $H_{(3+x)}[PV_xM_{(12-x)}O_{40}](aq)$ ($M = Mo, W$; $x = 0$ to 5).

Inspired by this remarkable diversity and versatility of the polyoxometalates, Hill and Gall published in 1996 the combinatorial synthesis of phosphorous-centered molybdenum and tungsten polyoxometalates of the Keggin structure and their consequent evaluation in the selective aerobic oxidation of tetrahydrothiophene (THT) to its corresponding sulfoxide (THTO) (Scheme 17).[188]



Scheme 17. Aerobic oxidation of tetrahydrothiophene (THT) to tetrahydrothiophene sulfoxide (THTO) by combinatorially prepared polyoxometalates.

The oxidation catalysts were synthesized by combinatorially mixing aliquots of stock solutions of appropriate tungsten, molydenum, and vanadium sources under a constant phosphate concentration. Completion of catalyst formation was achieved by equilibration at room temperature and was determined by ^{51}V NMR spectroscopy. By using gas chromatography to quantify product (THTO) yields and selectivities promising catalysts were selected and subsequently identified with the aid of ^{51}V NMR and IR spectroscopy, and revealed the complex $[\alpha\text{-}1,4\text{-}PV_2W_{10}O_{40}]^{5-}$ as the most effective among them.

Unfortunately, all the samples evaluated, including the starting materials, exhibited catalytic efficiency in the selective conversion of THT to THTO, which suggested that Keggin-type polymolybdato- or tungstophosphates have the ability to selectively oxidize THT to THTO regardless of their vanadium content. The authors stated that the results were consistent with the catalytically active species being primarily Keggin polyoxometalates rather than isopolyoxometalates, monomeric metalate species, or lower nuclearity polyoxometalates, but did not prove it. Several other combinatorial libraries containing boron, silicon, and arsenic were evaluated under a variety of conditions, but the results were not quantified.

5. Novel High-Throughput Screening Tools

The process of discovering catalysts or materials for a given set of properties from a large pool of potential candidates requires a reliable and robust screening process. Traditionally, this process often presents itself as a bottleneck in the discovery effort, especially if large libraries of potential catalysts or materials have already been synthesized or prepared. With the advent of combinatorial chemistry, high-throughput screening (HTS), robotics, and data management capabilities in the pharmaceutical industry, the rate of discovering new pharmacologically active compounds appears to be the future of the drug discovery process. Methods currently being developed for applications in the chemical industry, whether it be the discovery of new catalysts or materials, can be seen to follow a similar pathway in terms of the overall screening process. For example, in the field of catalysis the first step involves the identification of a specific chemical transformation of interest. A collection of potential catalysts, prepared from a set of chemically diverse ligand sets and metal precursors, are then combined in a parallel or combinatorial fashion and screened for activity in a primary high-throughput screen. The goal at this earliest stage of discovery is to identify promising lead catalysts worthy of further investigation and follow-up. Relative activity is usually established because of the large volume of potential catalysts examined in a primary screen, however, absolute activity can be established in some instances. Lead materials are then examined in a secondary screen which usually involves a lower throughput relative to a primary screen, however, the absolute performance trends are generally established as well as possibly other considerations such as product selectivity and catalyst lifetime. The information obtained from the secondary screen is then used to prepare further generation catalysts with the ultimate goal of identifying a catalyst that possesses characteristics worthy of commercialization.

5.1. Infrared Thermography as a Tool for Parallel Screening

Infrared thermography detects the infrared radiation emitted by all objects; modern photovoltaic IR cameras with focal plane array (FPA) detectors made out of, for example, InSb, HgCdTe, or PtSi, deliver a high-resolution two-dimensional thermal image, that is, a spatial map directly related to the temperature and emissivity distribution of the objects in the picture.[189] The IR image of an object is composed of emitted and reflected radiation, and the relative ratio is different for each surface. Different colors in thermal IR images visualize different photon intensities of the detected IR radiation. Photon intensities can be converted into (blackbody) temperatures of the object either by knowing the emissivity of a material or through a temperature calibration. Originally developed for military applications and surveillance, present-day applications include a variety of civilian applications in the aircraft and electronics industry, medicine, engineering, quality control, environment protection, building inspection, law enforcement, and science. Since IR thermography is a noncontact technique it is thus not surprising that it has also found application in the study of local spatial temperatures and reaction rates of exothermic reactions. Moreover, the technique promises to become a widely applied screening method for the evaluation of activity in combinatorial libraries of catalysts.

In this emerging field IR sensors are primarily used to detect, image, and measure patterns of thermal radiation that catalysts emit as a by-product of their activity. Pawlicki and Schmitz first reported using IR thermography to monitor the dynamics of reactions on solid surfaces in 1987,[190] and Sermon and co-workers applied this technology for the analysis of temperature profiles of exothermic reactions on platinum catalysts supported on silicon oxide.[191] Time-resolved IR thermographic detection and IR emission analysis of temperature profiles enable virtually any exothermic reaction to be monitored in a truly parallel fashion.[192, 193] The following sections highlight recent applications of this technology in combinatorial catalysis.

5.1.1. Infrared Thermography in the Heterogeneously Catalyzed Oxidation of Hydrogen to Water

Willson and his co-workers employed IR thermographic imaging to identify possible formulations of heterogeneous catalysts for the oxidation of hydrogen to water.[194] The catalyst entities on the array were prepared in a conventional manner by impregnating pellets of γ-aluminum oxide (catalyst support) with aqueous stock solutions of 16 metal salt precursors (Figure 17). Between 80 to 98 % of the metals were thus deposited onto the pellets of approximately 0.2 mm thickness so that they contained 0.5 wt % of metal. After reduction to zero valent metals by exposure to pure hydrogen, the pellets were manually placed in a aluminum reactor and then assayed in a parallel manner and in a spatially addressable format. The reactor was equipped with a sensitive infrared imaging camera and devices to control reaction conditions such as gas flow, heating rates, and data collection/analysis.

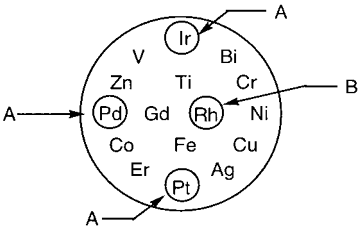


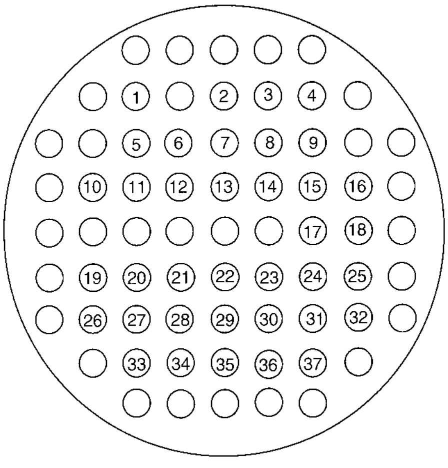
Figure 17. Schematic illustration of a catalyst library of 16 γ-aluminum oxide pellets impregnated with the metals indicated. Circled metals catalyze the oxidation of hydrogen with oxygen and "ignite" upon exposure to a mixed oxygen/hydrogen gas flow. The catalytic activity was recorded qualitatively and directly by IR thermography. A: ignition starts at 35 °C; B: ignition starts at 82 °C.

After calibrating the IR camera and equilibrating the reactor at 35 °C with hydrogen, a gas stream containing 5 vol % of oxygen was introduced into the hydrogen feed stream. Catalytic activity for the hydrogen oxidation was found for pure Pd, Pt, and Ir within 10 s of oxygen introduction (Figure 17). Heating the reaction chamber up to 300 °C "ignited" the Rh-loaded pellet at about 82 °C and the activity was followed with the infrared imaging camera as an increase in temperature against background while the reaction chamber was continuously heated. Several additional experiments to identify other possible catalyst candidates failed, and no combinatorial catalyst libraries were screened. The report is basically a proof of concept, but, nevertheless, the experimental procedure could be useful for parallel screening of new catalyst formulations or evaluating operational issues such as catalyst lifetime, resistance to poisoning, and regenerability.[195]

5.1.2. Emissivity Corrected Infrared Thermography in Heterogeneously Catalyzed Reductions and Oxidations

In 1998 Maier and co-workers applied emissivity corrected IR thermography to detect activity in heterogeneously catalyzed gas phase reactions on a model library.[196] The researchers chose transition metal impregnated, amorphous microporous mixed oxide (AMM) supports, a class of materials previously having shown to possess unusual properties as bulk catalysts or as catalytic membranes in selective oxidation, hydrocracking, hydrogenation, etherification, and esterification reactions.[197] Catalytic AMMs are a promising target for combinatorial searches of catalytic activities since a large variety of catalytically active elements can be atomically dispersed in the shape selective environment of micropores.

The researchers chose the catalytic hydrogenation of hexyne and the oxidation of isooctane and toluene as their test reactions. With established and automated sol–gel procedures, less then 200 µg of each catalyst was deposited on a low reflection slate substrate. The controlled drying, calcination, and reduction afforded a catalyst array in the format and composition displayed in Figure 18.



No.	Ti cat.	No.	Si cat.
1	Ir_1Ti	18	Cu_5Si
2	Pt_1Ti	19	Pd_1Si
3	Pt_2Ti	20	Pd_5Si
4	Pt_5Ti	21	Cr_5Si
5	Zn_5Ti	22	Co_5Si
6	V_5Ti	23	Ni_5Si
7	Mn_3Ti	24	Rh_5Si
8	Mn_5Ti	25	Ru_5Si
9	Fe_5Ti	26	Ti_5Si
10	Pd_1Ti	27	Zn_5Si
11	Pd_5Ti	28	V_5Si
12	Cr_5Ti	29	Mn_3Si
13	Co_5Ti	30	Mn_5Si
14	Ni_5Ti	31	Fe_5Si
15	Rh_5Ti	32	$Fe_{10}Si$
16	Ru_5Ti	33	Ir_2Si
17	Cu_5Ti	34	Ir_5Si
-	-	35	Pt_1Si
-	-	36	Pt_2Si
-	-	37	Pt_5Si

Figure 18. Schematical representation of the composition of the oxide catalyst spots of the library according to the AMM notation (molecular percentages of active metal and base metal oxide are given, for example, AMM-Ti_3Si stands for 3 mol % titanium oxide in 97 mol % silica).

A common high-sensitivity FPA IR camera with a platinum silicide (PtSi) detector was used for monitoring the heat evolution upon catalytic conversion and allowed rapid and parallel catalyst screening. The same catalyst array was screened in a customized parallel reactor and on a catalyst microgram scale under appropriate conditions for three test reactions. Several effective catalysts for each of the targeted conversions were identified. For example, catalytic activity for the hydrogenation of hexyne at 100°C was observed for AMM-Pd/Si catalysts 19 and 20 and the AMM-Pt/Si catalysts 35 and 37 (Figure 18). The Ti-containing catalysts (2, 3, 6, 10, 16, and 17) showed catalytic activity for the oxidation of isooctane, and, furthermore, catalyst 37 among others (2, 3, 4, 6, and 17) was one of the most active materials for the oxidation of toluene (Figure 18).

Thus, an IR-sensitive camera appears to be an attractive tool for the simultaneous display of catalytic activities of a catalyst library after careful removal of the artefacts by emissivity correction.

5.1.3. Time-Resolved IR Thermography of Enantioselective Catalytic Reactions

In 1998 Reetz and his team stressed the general usefulness of IR thermography by applying of this technique to the time-resolved thermographic screening of liquid-phase catalytic reactions such as enantioselective hydrolytic ring opening of epoxides to nonracemic diols and a lipase-catalyzed acetylation of a secondary alcohol.[192] For their reactions they used a modified microtiter plate consisting of a commercial Eppendorf Thermomixer with the top replaced by an aluminum plate, in which holes were drilled and cylindrical glass reaction vessels of 8 mm diameter and 35 mm height placed. As a model reaction the enantioselective lipase-catalyzed acylation of (*R*)-, (*S*)-, and *rac*-1-phenylethanol with vinyl acetate was followed with the IR camera, whereby 250 images (5 s) of the library array were periodically acquired and then averaged and visually inspected. Subsequently, they turned their attention to enantioselective transition metal catalysis and studied the ring opening of epoxides with salen catalysts (see above). In order to demonstrate the screening capability of the IR camera under these homogeneous conditions the activity and selectivity of three metal catalysts were tested thermogaphically in the hydrolysis of epichlorhydrin. Finally, relative substrate activity was screened by studying the hydrolysis of three different chiral epoxides with the cobalt catalyst that was found to be the most active in the previous screening of epichlorhydrin hydrolysis. In all cases, relative trends in the activity and selectivity of the catalytic reactions already known from the literature were reproduced.

These applications of IR thermography hold promise for more extensive application of this technology in homogeneous and heterogeneous, organic and inorganic catalysis research. However, the thermal IR imaging screen does not possess the ability to resolve the product composition of the catalyst, which is an important issue in chemical catalysis, and for which methodologies are currently being developed.

5.2. Resonance-Enhanced Multiphoton Ionization (REMPI) as a Tool for High-Throughput Parallel Screening

In an initial proof of concept experiment, Senkan has described a high-throughput screening technology for combinatorial catalyst libraries that may supply data on both activity and selectivity for a dehydrogenation reaction.[198] His approach was based on in situ photoionization of the reaction products by using tunable UV lasers. Under resonance-enhanced multiphoton ionization (REMPI) conditions the resulting photoelectrons or photoions were detected by an array of microelectrodes in close proximity to the photoion or photoelectron generating beam. The test reaction was the catalytic dehydrogenation of cyclohexane to benzene.

The initial instrumental set-up contained 72 sites (8 × 9 array), but the technical feasibility of the screening method was demonstrated initially only on a part of the array. Four sites out of eight in one row of the array were filled with commercially available catalysts containing either 0.5 or 1.0% of Pt or Pd (Figure 19). The screening of the catalyst site at 300°C by a gas flow (argon containing 13% cyclohexane) showed the generation of benzene in the four wells filled with the appropriate known catalysts, but there was some "cross-talk" among the wells as evidenced by benzene signals even from empty wells.

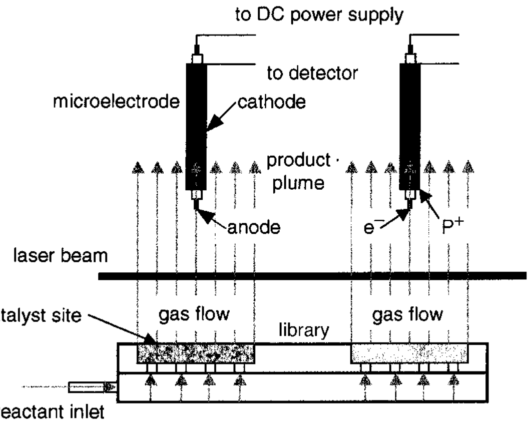


Figure 19. Illustration of high-throughput screening of combinatorial catalyst libraries by resonance-enhanced multiphoton ionization (REMPI). The library consists of a square ceramic substrate (7.62 × 7.62 cm) containing 72 (8 × 9) sites 5 × 5 mm wide and separated 2 mm from each other. The reactant gases are forced through individual sites on the library to generate product plumes if the sites are catalytic. The beam of a tunable UV laser is then passed above the sites, and intercepts the plumes and generates the product photoions and photoelectrons from benzene. Microelectrodes placed above the sites in close vicinity to the laser beam simultaneously collect either the photoions or photoelectrons depending on the bias voltage applied. (Reprinted with permission from the author.[198] © 1999 Nature.)

In this first approach only the benzene product was measured, and selectivity measurements were not carried out although they were described as being possible by using different laser frequencies to generate REMPI signals for different products. Since the most likely side products for this reaction are cyclohexene and cyclohexadienes, which require UV wavelengths shorter than the 259.7 nm used for their REMPI detection, it remains to be seen how they can be detected, given the current status of laser technology. In addition, issues such as sensitivity, laser-power stability, and demonstration of the parallel assay with combinatorially synthesized catalysts were not addressed.

In 1999 the same group reported the application of the REMPI technology together with novel array microreactors for the discovery of an optimal composition in the ternary Pt/Pd/In metal catalyst system for the same reaction.[199] The novel design for the microreactor was comprised of a customized two-slab micromachined ceramic reactor block containing 17 cylindrical wells for insertion of catalyst pellets. Isolated channels, connecting reactant gas inlets and outlets, were designed to allow unobstructed uniform gas flow over the catalyst entities. The full assembly was furthermore equipped with devices for individual pre-heating of reactant gas or reactor block, a laser beam, and a REMPI signal detection microelectrodes array. The multimetallic catalyst formulations were prepared by means of a computer-controlled high-accuracy liquid delivery system in conjunction with a *x*,*y*,*z* translation table by conventional co-impregnation under standardized conditions. The preformed cylindrical γ-Al$_2$O$_3$ supports (30 mg) were treated with aqueous metal precursor stock solutions of H$_2$[PtCl$_6$], PdCl$_2$, and InCl$_2$, dried, and calcinated. The catalyst library consisted of 66 ternary combinations of Pt, Pd, and In in 0.1 % wt increments of each with 1 % total metal loading on the alumnia support.

Catalyst screening was performed after conditioning the reactor unit and reduction of the metal precursors to metalic form with hydrogen. Contrary to their previous report,[198] the researchers confirmed by time of flight mass spectroscopy (TOF-MS) and using the same 259.7 nm laser that only benzene ($M^{\bullet+}$: $m/z = 78$), and not cyclohexane, hydrogen, helium, or other potential reaction side products, contributed to the signals measured by the microelectrodes. Indium proved to be catalytically inactive in the dehydrogenation and Pt and Pd individually exhibited catalytic activities, with Pt being more active than Pd. Most importantly, a ternary mixture (0.8 % Pt, 0.1 % Pd, 0.1 % In) exhibited the best benzene productivity of all the 66 ternary metal combinations tested. The screen for the entire catalyst library (66 catalysts) required five cycles in a time window of approximately 23 h and the total time for discovery (library preparation and screening) took 2.5 days, and included additional checks for reproducability of the results. The researchers demonstrated that the improved instrumental set-up for the array microreactor, coupled with the REMPI screening and in conjunction with the combinatorial catalyst library preparation, hold promise for use as a useful screening tool for the discovery and optimization of heterogeneous catalysts.

5.3. Rapid Parallel Screening of Heterogeneous Catalysts by Scanning Mass Spectrometry

Cong, Guan, and co-workers at Symyx Technologies have developed a new and useful instrument for the rapid screening of heterogeneous catalysts by using a scanning mass spectrometer (Figure 20).[200, 201] The instrument is divided into two parts: a reaction chamber where each library element is examined for catalytic activity and an analysis chamber where the products from the catalytic process are "sniffed" from the reaction chamber and analyzed by a mass spectrometer. In addition to the two chambers, ancillary equipment is used to control the positioning of the library and to maintain variables such as the flow rate of reactant gases, temperature, and reaction pressures. The catalyst libraries, which are prepared on 3 inch diameter (7.62 cm) quartz substrates, can be prepared as binary, ternary, and quaternary mixtures of elements and oxides through deposition techniques that include both chemical and physical deposition methods.

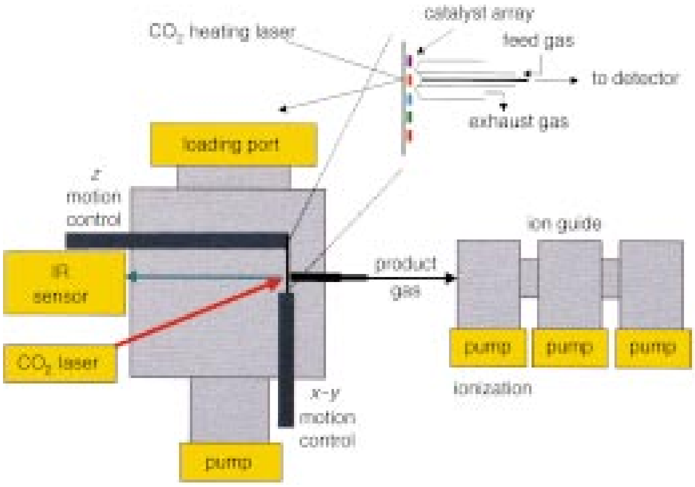


Figure 20. Schematic representation of the scanning mass spectrometer for screening catalyst libraries for catalytic activity. See text for details.

In a typical experiment the library is placed onto a platform capable of translation in three orthogonal directions. Gas flows to and from the library through a cylindrical delivery tube containing a second concentric internal tube. A reactant gas flows down the annular region of the tube onto the quartz substrate. Product gas flows from a single element in the library into the analysis chamber through the inner tube by a capillary connection between the two chambers. Product gas exits the capillary in the ionization zone of the quadrupole mass spectrometer. The temperature of the individual library elements is controlled using a CO$_2$ laser, an IR sensor, and a feedback control loop.

By analyzing the data collected from the entire library (approximately one library element per minute), the relevant kinetic parameters associated with the reaction such as catalyst activity and selectivity are determined for each element in the library. This provides the research scientist with a powerful tool for understanding the trends that can be used in the future generation catalyst libraries.

The oxidation of CO by O$_2$ is one of the most thoroughly studied heterogeneous catalytic reactions with investigations ranging from single-crystalline surfaces under ultra-high vacuum conditions to supported metal catalysts in microreactors. In addition, this reaction is also important in air polution control and is used in threeway catalytic converters of automobile exhaust.[202]

Cong and his colleagues disclosed in 1998 a combinatorial approach to catalyst discovery for the oxidation of carbon monoxide to carbon dioxide.[203] They prepared catalyst precursor solutions with automated liquid dispensing. The resulting solutions were dispensed onto a quartz plate containing 144 etched wells arranged in a 12 × 12 square grid and calcined at various temperatures in a reducing atmosphere (6 % H$_2$ in argon). The (1,2) element is pure Rh, the (1,12) element is pure Pt, and the (11,12) element is pure Pd.

The design of the library allowed the deposition of two identical ternary arrays on the wafer (mirrored about the diagonal), leaving the diagonal elements vacant to provide a baseline calibration. The catalyst array resembled therefore an equilateral triangular 66-element ternary composition diagram, so that mixtures with compositions ranging from 0 to 100% in increments of 10% of each of the components could be tested (Figure 21).

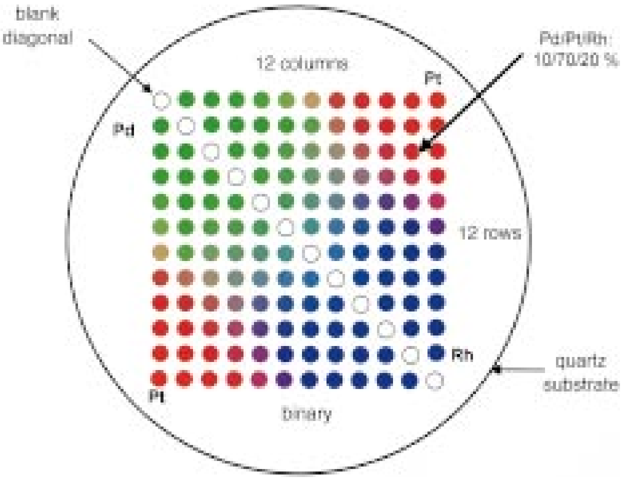


Figure 21. Two identical ternary arrays of 66 Pd/Pt/Rh catalyst compositions for CO oxidation.

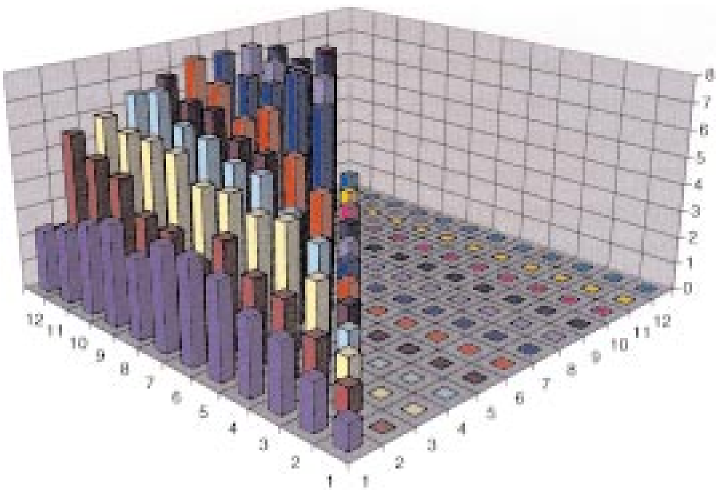


Figure 22. Representation of the signal intensity of CO_2 ($M^{\bullet +}$: m/z 44) at 350 °C as a function of the library element for the library shown in Figure 21. For clarity, the redundant data are omitted and only one-half of the library is shown. (Reprinted with permission from the author.[33] © 1998 Current Biology.)

By using the sensitive and fully automated scanning mass spectrometer (Figure 20) differences in the performance of each library entity in the conversion of carbon moxide to carbon dioxide were screened. For illustration Figure 22 displays the intensity of the CO_2 signal at mass 44 as a function of the element number of the library at 350 °C. The conversion increased with the concentration of Pd in the mixture, and the blank diagonal elements exhibited no significant activity. Along the Pt–Rh binary line (row 1) the conversion goes through a maximum with increasing Pt content, and along the Pd–Rh binary line the conversion increases with increasing Pd content.

A systematic combinatorial approach to heterogenous catalyst discovery has been developed as an extension of this methodology.[204] Cong et al. reported a systematic and integrated approach for the synthesis and screening of libraries of mixed metal alloys containing rhodium, palladium, platinum, and copper. Fully automated gas phase thin film deposition techniques (RF sputtering) were used to synthesize three unique 120-member libraries of Rh/Pt/Cu, Rh/Pd/Cu, and Rh/Pt/Pd alloys by repeatingly overlaying superlattices of the corresponding metals with the help of physical masks. For comparison, a redundant Rh/Pt/Pd library was synthesized by solution-phase techniques (sol–gel techniques). The library entity at the apex of the typical two-dimensional 15 × 15 × 15 triangular array format was the pure metal, with its concentration decreasing linearly when going away from the apex and reaching zero at the adjected side of the triangle; the adjected side is composed of binary mixtures of the two other metals, and a row of 16 blank elements was added to one side of the triangle as a control to provide backgroud calibration (Figure 23; similar to Figure 21).

The total deposition time for such a library was only about one hour. Each element of the array contained approximately 2–4 μg of catalyst material with a unique composition of the elemental metals after annealing the library in a reductive atmosphere. Homogeneity of the metal mixtures was confirmed by an automated but serial powder X-ray diffractometer. The metal alloy combinatorial libraries were screened in the scanning mass spectrometer as described before for the gas-phase oxidation of carbon monoxide and the reduction of nitric oxide. In accordance with the literature, and despite some discontinuities, rhodium-rich regions in the Rh/Pt/Pd ternary generally showed enhanced activity for carbon mon-

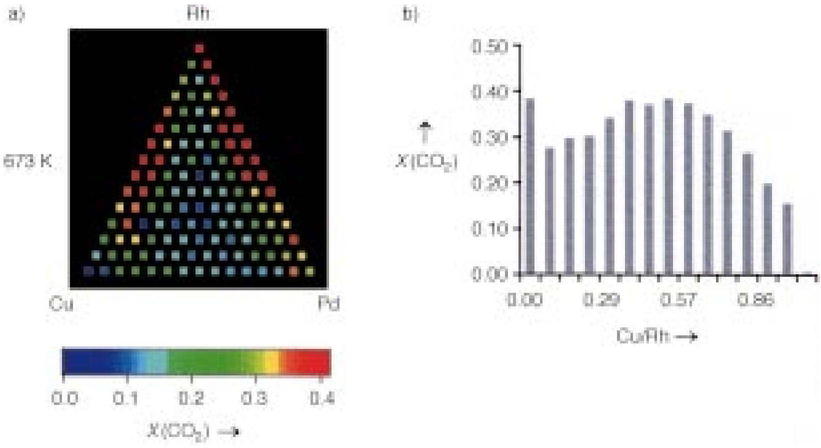


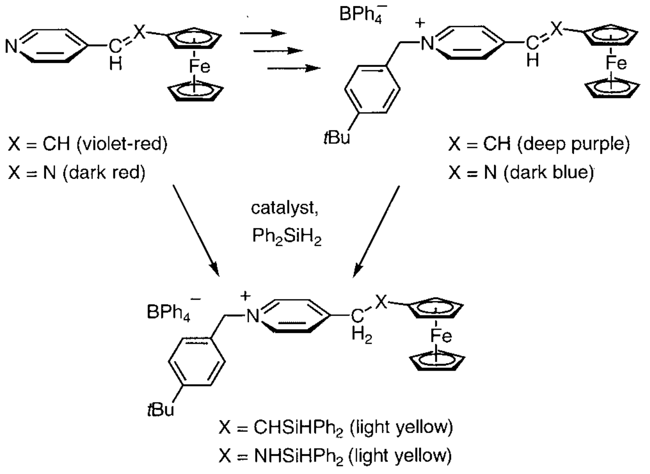
Figure 23. a) Ternary Cu/Rh/Pd library in a 15 × 15 × 15 triangular array format. The library was screened for CO oxidation and NO reduction. The colored diagram shows the CO_2 production as a function of the ternary catalyst composition. b) Plot of the same data along the Rh/Cu binary. (Reprinted with permission from the author.[204] © 1999 WILEY-VCH.)

oxide oxidation with oxygen and, interestingly, Rh/Cu binaries such as Rh/Cu (50/50 atom%) showed promising oxidation activity. For the more challenging and complex oxidation of carbon monoxide with nitric oxide to carbon dioxide and nitrogen it was clearly established that rhodium and rhodium-rich catalyts from the Rh/Pt/Pd library favored the nitrogen production channel at elevated temperatures; on the other hand the N_2O channel became relatively more important at high temperatures for palladium and palladium-rich catalyts.

These experiments clearly demonstrated the applicability of combinatorial chemistry to heterogeneous catalysis. The high sensitivity of the mass spectrometric assay, in conjunction with the miniaturization of the catalyst arrays, allows rapid screening; that is, the scanning mass spectrometer should be considered to be a sophisticated combinatorial screening tool for a broad variety of heterogeneously catalyzed reactions.

5.4. Methods for the Rapid Screening of Homogeneous Catalysts with Reactive Dyes

Crabtree et. al. reported the use of dyes as visual probes to dectect catalytic activity in the hydrosilation of alkenes and imines.[205] Visual dectection remains one of the most simple and practical methods for measuring catalyst activity since it allows for a very rapid determination of activity. In the above example, four ferrocenyl-substituted dyes were prepared which contained electron-donor and -acceptor groups linked together through a reactive functionality (Scheme 18). When the reactive functionality is saturated upon reaction with a catalytic species the electronic connection between the donor and acceptor groups is diminished, which gives rise to a loss of the parent dye color.



Scheme 18. Reactive dyes used to assay hydrosilation catalyst activities in a parallel screening strategy.

A small discovery library on a 60-well plate was then assayed in parallel using a digital camera to record visual images over time. Of the twelve hydrosilation catalysts examined by the authors, Wilkinson's catalyst, which is a known hydrosilation catalyst, was among the most active of the catalysts screened. However, a cyclic palladium Heck reaction catalyst was also quite active, a compound not previously reported as a hydrosilation catalyst.

These initial results certainly prove the concept of using dyes as visual probes in catalytic reactions. However, it is worth pointing out that the use of such dyes does not come without possible constraints. For example, one would anticipate that the performance of any catalyst is certainly going to depend upon the structural and electronic features of any given substrate. Even though the concept has been proven successful, the generality of using such probes must be further established by examining a broader range of substrates.

5.5. High-Throughput Screening Methods for the Rapid Determination of Enantiomeric Excess by Circular Dichroism

Recently, a number of reports have appeared that utilize combinatorial strategies to facilitate the discovery and optimization of chiral catalysts (see above). Even though these reports have successfully addressed the synthetic combinatorial aspects of chiral catalyst discovery, they still rely solely on conventional means for determining the enantioselectivity, for example, high performance liquid chromatography (HPLC) or gas chromatography (GC) methods equipped with chiral columns, a time-consuming process that creates a potential bottleneck in any combinatorial discovery effort.[206] As a possible alternative to address this issue, Mikami and co-workers have developed a new screening strategy that employs circular dichroism (CD) detection in conjunction with HPLC on nonchiral stationary phases for the rapid determination of enantiomeric excesses of a reaction product without having to perform the tedious separation of the chiral products.[207] The CD signal $\Delta\varepsilon$ and the molar absorption coefficient ε provide a dissymmetry factor g ($\Delta\varepsilon\,\varepsilon^{-1}$), which is independent of product concentration and is linearly related to the *ee* value. In order to validate this approach, the researchers examined the solution-phase addition of diethylzinc to prochiral aldehydes in the presence of chiral diol ligands (L1*, L2*, ...) and chiral nitrogen-based activators (A1*, A2*, ...). Reactions were screened in 1 mL polypropylene (PP) microtubes and the crude reaction products were then autosampled into a HPLC instrument equipped with CD detection. Through the course of combining diethylzinc with an assortment of chiral ligands and activators the researchers identified an extremely effective ligand/activator combination that gave excellent *ee* values in high overall yield with a variety of aldehydes. Although the authors dubbed the above technique as "super high throughput screening" (SHTS), the technique may still be somewhat limiting in terms of it's overall throughput (ca. three minutes per sample) and is probably best described as a rapid serial screening technique and may not be suitable for screening large catalyst libraries in a time-efficient manner.

6. Summary and Outlook

It is virtually certain that we find ourselves at the dawn of a new age of applying combinatorial methodologies to materials discovery and optimization. As this review demonstrates, significant first steps in that direction have been taken in the area of materials science, and a multitude of tools are now available by using combinatorial technologies to appropriately accommodate the new tasks and requirements for combinatorially accelerated materials and catalyst research. A common underlying theme associated with these technologies is miniaturization, parallelization, and automation so that large numbers of samples can be synthesized and screened efficiently.

Rapid serial and parallelized adaptations of conventional analytical techniques will become increasingly important in the assay of materials properties, as will the development and implementation of new and unconventional high-throughput screening tools. Software development and engineering support in the construction and design of synthesis and screening tools are as crucial as are further advances in chemistry, even when appropriate tools or robots for synthesis and screening automation are commercially available. Finally, the combinatorial methodology generates data much faster than the conventional research that employs empirical and rational approaches to materials discovery, and, inevitably, the proper data handling and storage should accompany the high-throughput synthesis and screening to maintain the integrity of research and development efforts.

Full realization of the combinatorial methodology will require the integration of chemistry, physics, engineering, and informatics to greatly enhance the probability of finding a global reaction optimum of a catalyst for a targeted reaction or materials with desired properties. In the future, the scientist's intuition may be shifted, at least to some degree, towards optimally programming and setting up appropriate experiments and screens, as well as for the analysis of the obtained data and materials. All these efforts will require an enormous initial investment in all of these areas.

The authors wish to thank A.-M. Stoll and M. Hardy for administrative support, R. Krasnow, P. Cohan, and P. A. Stone for checking the manuscript, Drs. T. J. Crevier, D. Giaquinta, M. Devenney, A. Safir, P. Cong, R. Nielsen, and T. Uno for helpful discussions, and Drs. X.-D. Xiang, S. M. Senkan, J. P. Morken, T. E. Mallouk, S. C. Kuebler, R. C. Haushalter, P. Cong, K. Self, and C. Goh for providing figures.

Received: February 10, 1998 [A323IE]
German version: *Angew. Chem.* **1999**, *111*, 2648–2689

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