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Combinatorial Heterogeneous Catalysis—A New Path in an Old Field

Selim Senkan*

Combinatorial catalysis is the systematic preparation, processing, and testing of large diversities of chemically and physically different materials libraries in a high-throughput fashion. It also embodies microfabrication, robotics, automation, instrumentation, computational chemistry, and large-scale information management (informatics), and as such carries the promise of a renaissance in catalytic reaction engineering. Significant progress has already been made in demonstrating the speed and economic advantage of

combinatorial approaches by the discovery of superior catalytic materials in a matter of hours and days, as opposed to the months and years required using traditional methods. Combinatorial methods can also significantly contribute to our understanding of catalytic function by increasing our chances of discovering totally new and unexpected catalytic materials, and by expediting the recognition of trends and patterns of structure–activity relations, from which new catalytic materials can be

designed more efficiently. Combinatorial catalysis undoubtedly will be the new paradigm of catalysis research as the industry faces increasing global competition and pressure for the development of environmentally friendly processes at a time when resources for research are diminishing.

Keywords: combinatorial chemistry · heterogeneous catalysis · high-throughput screening · catalysts

1. Combinatorial Catalyst Research

1.1. A New Route

Solid catalysts are used in the manufacture of a vast array of chemicals and fuels, and as such significantly contribute to our economy and high living standards.^[1, 2] Catalysts are used in the production of over 7000 compounds worth over \$3 trillion globally. Catalyst-based manufacturing accounts for about 60% of chemicals production and 90% of processes.^[1] These figures will likely increase in the future as a result of increasing pressures for the development of environmentally friendly manufacturing processes (see Table 1). The economic benefits of an efficient catalyst are enormous: catalytic processes are less capital intensive, have lower operating costs, produce higher purity products and fewer by-products. In addition, catalysts provide important environmental benefits, such as catalytic converters for automobiles. However, in spite of their significance and broad utility, the discovery of new catalysts continues to be an arduous and rather unpredictable trial-and-error process.^[3]

Table 1. Role of catalysis in the economy.^[a]

Catalysts are used globally in the manufacture of over 7,000 products worth over \$3 trillion per year	
Catalysts are used in 60% of chemicals production and 90% of processes	
Globally catalyst manufacturing is about an \$8.5 billion per year industry	
Globally there are about 100 catalyst manufacturing companies	
Catalyst usage	Annual turnover
Petroleum Refining	\$2.2 billion
Polymerization	\$2.2 billion
Chemicals Production	\$2.1 billion
Environmental Protection	\$2.1 billion

[a] Sources: "Catalysts", *Chem. Week*, September 1999 and *Chem. Eng. News* September 20, 1999; CMA, U.S. Chemical Industry Statistical Handbook, 1996.

Catalysts traditionally are developed using a variety of tedious and time consuming recipes, characterized and tested for performance repeatedly until no further improvements are justified. In addition, the time scales for success often are measured in months and years. This level of productivity can no longer be justified by the industry because of increasing pressures to remain profitable in an environmentally responsible manner while facing increasing global competition. The industry needs innovative ideas, shorter lead and development times for lower-cost products all at a time when significantly less resources are available for research and development. Such pressure was previously encountered by the pharmaceutical industry about a decade ago which

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subsequently led to the explosive growth of combinatorial chemistry as the new paradigm of doing business.^[4, 5] The field of catalysis is poised for a similar transformation as evidenced by the increase in the number of conferences and workshops held on combinatorial catalysis since 1999, whereas there were none a few years ago. Notable examples of such meetings, where issues pertaining to combinatorial catalysis were discussed, are presented in Table 2. In addition, the subject of combinatorial catalysis is also receiving attention from both academic and industrial research communities as evidenced by the increased number of papers presented and sessions organized in scientific and technical meetings around the world (see for example the recent National Meetings of the American Chemical Society (ACS) and the American Institute of Chemical Engineers (AIChE)).

Table 2. Recent meetings where combinatorial catalysis was covered.

<i>Combinatorial Approaches for Materials Discovery 1999 (San Jose, USA) and 2000 (San Diego, USA) and CombiEurope (Frankfurt, Germany)</i> organized by the Knowledge Foundation, Brookline, MA
<i>Combinatorial Catalysis and Catalyst Optimization 1999 (Philadelphia, USA)</i> , organized by the Catalyst Group, Springhouse, PA
<i>Combinatorial Chemistry: Beyond Pharmaceuticals 1998 and Microscale Characterization for Materials Discovery 1999 (Newark, USA)</i> , organized by the University of Delaware, Newark, DE
<i>Engineered Catalysis 1999 (New Orleans)</i> , organized by the Cambridge Healthtech Institute, Newton Upper Falls, MA
<i>Analytical Techniques in Combinatorial Chemistry 1999 (New Orleans, USA)</i> , organized by the American Chemical Society
<i>Combinatorial Methods for High Throughput Catalyst Design and Testing 1999 (Vilamoura, Portugal)</i> , organized by the University of Liverpool as a NATO Advanced Study Institute
<i>Advanced Technology Program 1999 (San Jose, USA)</i> , organized by the National Institute for Standards and Technology
<i>Combinatorial Catalysis and High Throughput and Combinatorial Methods in Catalyst Preparation and Testing 2000 (Los Angeles, USA)</i> organized by the American Institute of Chemical Engineers

1.2. Combinatorial Approaches

Combinatorial catalysis is a methodology or a set of tools^[6] where large diversities of solid-state materials libraries are prepared, processed, and tested for activity and selectivity in a high-throughput fashion.^[7] Since the data and information

generated are vast, the development and use of sophisticated high-capacity information-management systems (informatics) is also an essential component of this methodology. In fact, the successful implementation of combinatorial approaches will require that all of the components shown in Figure 1 must be in place and function smoothly, otherwise “bottlenecks” will limit the throughput.

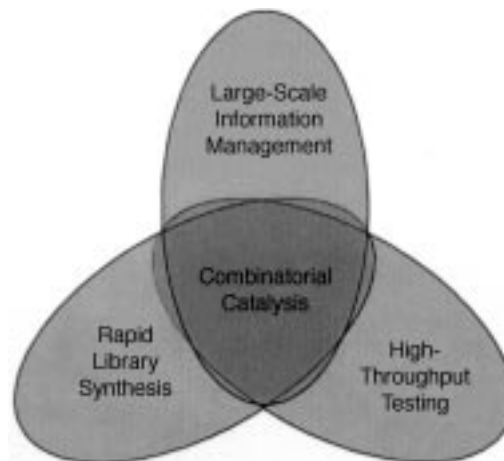


Figure 1. Essential components of combinatorial catalysis.

The integration of all the components of combinatorial catalysis is the ultimate goal of this field, enabling the intelligent planning and execution of highly parallel experiments with minimal human intervention. Initial integration of library synthesis and high-throughput screening is nearly realized as evidenced by numerous publications in these fields, which are summarized below. However, the development of software to organize and analyze the data and then provide an automatic feedback to library design is in its infancy. In this review, the status of each of the components of combinatorial catalysis as shown in Figure 1 will be summarized with examples.

It is important to note that combinatorial approaches can also contribute to our understanding of catalysis in a number of ways. First, by speeding up the pace of research, the chances of discovery of totally new and unexpected catalytic materials are increased. New discoveries should lead to a quantum leap



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in our understanding of catalysis, analogous to the impact that the discovery of high-temperature superconductors had in physics. Second, through the use of systematically acquired data and data-mining technologies, combinatorial catalysis should expedite the discovery of trends and patterns of structure–activity relations from large databases, which will be useful to develop practical catalysts. The issues related to data management are covered in Section 1.5. In addition, since surface characterization techniques can also be miniaturized, automated, and coupled with combinatorial tools, a closer link between traditional and combinatorial catalysis research can be made.

Interestingly, the idea of applying combinatorial approaches to heterogeneous catalysts is not new. In the early part of the 20th century Alwin Mittasch implemented an impressive program preparing and testing a large number of combinations of metals to catalyze the synthesis of NH_3 from H_2 and N_2 . These and related efforts subsequently were summarized in a review article in *Advances in Catalysis*.^[8] Consequently, the genesis of combinatorial inorganic chemistry should rightfully be attributed to heterogeneous catalysis and not to materials research,^[9] as is often done in the literature. However, the Mittasch approach for catalyst discovery and optimization was not pursued much further due, in part, to the high labor costs involved. Instead, the field evolved into its present form, which emphasizes step by step surface science approach fueled by the availability of extensive surface characterization equipment. In fact, according to a recent survey, nearly 50% of all the papers published in heterogeneous catalysis today are devoted to the surface characterization of these materials.^[10] However, recent advances in automation, robotics, microfabrication, and instrumentation should propel combinatorial approaches as the new paradigm in catalytic reaction–engineering research.

The implementation of combinatorial techniques to heterogeneous catalysis is a significantly more challenging problem than in other application areas of materials science.^[11] Additional challenges arise from the complex and dynamic nature of catalysts.^[12] First, real heterogeneous catalysts generally are extended solids with multiple discontinuities in structure and composition allowing very limited systematic variation in these properties with the overall composition. This is illustrated in the scanning tunneling microscope picture of a typical heterogeneous catalyst (Figure 2), where sharp changes in composition and structure are evident. In addition, these structures are strongly dependent on the methods of preparation and change with time under reaction conditions, with better catalysts being more resilient to change. All of these issues render heterogeneous catalysis research a difficult subject. In addition, the absence of markers or descriptors of diversity in solid-state mixtures impede the undertaking of systematic studies.^[13]

Second, heterogeneous catalysts must bind the reactants, induce them to bonding interactions, and allow the products to depart so that the catalytic cycle progresses. These requirements demand that no catalyst intermediate be too stable or the product too strongly adsorbed, otherwise the turnover number can not be high enough to be practically useful. In other words, heterogeneous catalysts must expedite the

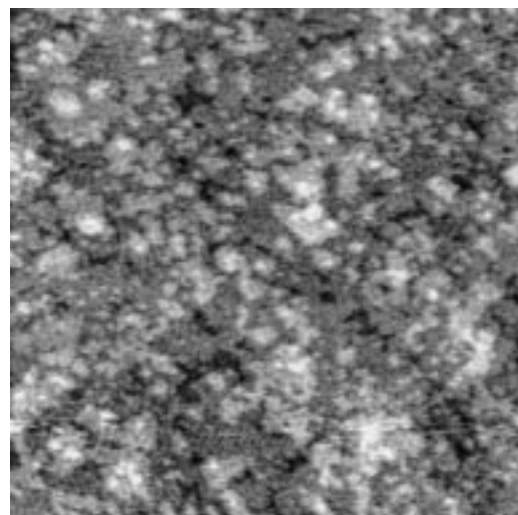


Figure 2. Scanning tunneling microscope picture of a real catalyst showing discontinuities in composition and structure.

formation of a suitable and energetically favorable transition state. Transition states are induced by the three-dimensional active sites on catalyst surfaces, both of which are poorly understood. It is likely that a multitude of active sites exist on solid surfaces and their distribution changes with time. The rates of change or shift of these sites is influenced by the rates of solid-state diffusion and gas–solid interactions both of which are influenced by temperature and local composition. Typically, catalysts deactivate with time as a consequence of events such as, surface reconstruction, sintering, poisoning, coke formation, and volatilization.^[14] Conversely, the activities of some catalysts peak only after a period “on stream”,^[15] again suggesting the involvement of events such as reconstruction. These considerations clearly call for the development of methodologies that will allow the undertaking of a large number of systematic, parallel experiments to unravel the underlying elementary events.

1.3. The Parameter Space

Before recent progress in combinatorial catalysis is summarized, it is useful to establish the magnitude of the parameter space that needs to be dealt with. For this purpose let us assume first that there are 50 useful, stable elements in the periodic table that are suitable candidates for heterogeneous catalysis. Based on this premise and the combinatorial formula [Eq. (1)], it can be shown that there will be 1225 binary, 19600 ternary, 230000 quaternary, and 10^{10} decanary combinations of these elements.

$$N(n_E/n_T) = n_E!/[n_T!(n_E - n_T)!] \quad (1)$$

N is the total number of combinations, n_E and n_T are the number of elements and their specific groups (binary, ternary etc.), respectively. It must be recognized that this parameter space becomes significantly larger if compositional and structural diversities are also considered. For example, if n_C compositional increments are used, the total number of

possible combinations can be shown to be given by the recursion formula [Eq. (2)].

$$N(n_{E+1}, n_C) = N(n_E, n_C) + N(n_{E+1}, n_{C-1}) \quad (2)$$

In Table 3 the number of multielement compositional combinations possible are presented for a variety of n_E and n_C values. For example, for a ternary mixture ($n_E = 3$) the use of 11 discrete concentrations on the binary axes would require the consideration of a total of 66 combinations. Similarly, for a quaternary system, the total number of combinations that must be evaluated would be 286. As evident from Table 3, the number of combinations increase geometrically with the increase in number of elements and the number of different compositions to be considered. For example, the consideration of a library having 10 elements from the periodic table and 25 composition increments in the binary axes require the evaluation of 38 567 100 discrete combinations! It must be recognized that the numbers presented in Table 3 are on the low side as they do not account for the physical or structural diversity induced by the methods of preparation.

Parameters describing the methods of preparation, for example, the temperature, the chemical composition of the atmosphere, and duration of calcination, must also be considered as independent variables that influence the parameter space in catalysis research. These considerations easily increase the number of parameter combinations to billions (Table 3). In view of this large parameter space, combinatorial techniques represent the most rational approach for the discovery and optimization of new catalytic materials. However, even with the development of high-throughput experimentation tools, we will be able to search only a small fraction of this large parameter space. Thus, one of the most important goals of combinatorial catalysis research should be to build representative libraries that ensure the greater probability of obtaining leads for a given reaction, by exploiting the accumulated know-how in traditional catalysis research, as well as chemical intuition and numerical simulation techniques.

Challenges imposed by large parameter space are also compounded because there are no well understood systematic variations of catalytic properties with composition and structure, that is, structure–activity relationships are still primitive and no markers for diversity exist. These issues render the application of conventional design of experiments impractical because of the difficulties associated in constructing response surfaces.^[16] The initial successes in combinatorial catalysis will probably be accomplished by the application of a variety of search strategies that will be investigator specific,

until sufficient experience accumulates. Nevertheless, possible search strategies can be categorized into two major groups:

1. Heuristic or stochastic formulation of initial catalyst libraries followed by steepest-gradient optimization search around the hits found in the library.
2. Totally stochastic methods of library preparation and modification.

The former approach appears most suitable for catalyst optimization problems where improvements of existing formulations are the goal. Indeed, a number of superior catalytic materials have already been discovered as variants of existing ones. Examples include the development of amorphous microporous mixed oxides (AMM) containing metals for the hydrogenation of 1-hexyne^[17] and the oxidation of propylene,^[18] the discovery of a superior quaternary Pt-Ru-Os-Ir catalyst for the reforming of methanol,^[19] the discovery of a superior ternary Rh-Pd-Pt catalyst for the oxidation of CO,^[20] a ternary Pt-Pd-In catalyst for the dehydrogenation of cyclohexane to benzene,^[21] and a ternary Mo-V-Nb catalyst for the oxidative dehydrogenation of ethane.^[22]

1.4. Stochastic Methods

Stochastic methods of library preparation include genetic algorithms (GA), Monte Carlo methods such as simulated annealing and tempering, branch and bound, and tabu search. These techniques are most suitable for the discovery and optimization of new catalytic materials. They rely on the implementation of some ad hoc rules to make progress in the search process and can be applied for the planning of combinatorial catalysis experiments.

1.4.1. Genetic Algorithms

Genetic algorithms are based on the concepts in natural evolution and the survival of the fittest.^[23, 24]

The GA approach involves the iterative preparations of libraries, which are screened for catalytic function, for example, conversion and selectivity, and the experimentally determined responses are then used as input to the GA to find better leads. The GA generally result in a set of very good, but not necessarily the best, solutions in a very large parameter space. The elements used in the creation of first generation catalysts can be selected from a subset of elements in the periodic table either heuristically or randomly, together with their corresponding concentration levels and methods of preparation. First generation catalysts that exhibit an acceptable performance level are then selected as parents for the creation of next-generation catalysts through crossover and

Table 3. Total number of compositional combinations of multielement mixtures.

n_C	$n_E = 2$	$n_E = 3$	$n_E = 4$	$n_E = 5$	$n_E = 6$	$n_E = 7$	$n_E = 8$	$n_E = 9$	$n_E = 10$
6	6	21	56	126	252	462	792	1287	2002
11	11	66	286	1001	3003	8008	19448	43758	92378
15	15	120	680	3060	11628	38760	116280	319770	817190
21	21	231	1771	10626	53130	230230	888030	3108105	10015005
25	25	325	2925	20475	118755	593575	2629575	10518300	38567100
31	31	496	5456	46376	324632	1947792	10295472	48903492	211915132
41	41	861	12341	135751	1221759	9366819	62891499	377348994	2054455634

mutations. In crossover, the elements and preparation methods from a “fit” parent are exchanged to some extent with another material. This operation enables the evolutionary process to move forward toward promising regions of the search space. The mutation processes are intended to prevent premature convergence to a local optimum by randomly introducing new elements or removing existing ones, or by changing the concentration of elements.

Genetic algorithms have been applied to the synthesis of combinatorial chemical libraries,^[25–28] for the design of heterogeneous catalysts,^[29] and the preparation and optimization of combinatorial libraries of heterogeneous catalysts.^[30, 31] Recently GA were also combined with high-throughput synthesis and screening methods for the discovery of new catalytic materials for the low-temperature oxidation of low concentrations of propane.^[32] This work is significant because it demonstrates for the first time how all of the essential components of combinatorial methodologies can be integrated for the discovery of totally new catalysts, see Section 5.

1.4.2. Monte Carlo Methods

Simulated annealing is a Monte Carlo approach in which one of the variables of the catalyst preparation process is subjected to a random change. If the new catalyst formulation performs better than the previous one, for example, provides higher yields (Y), the new catalyst is accepted unconditionally. If the performance of the new catalyst is inferior, then the new configuration is accepted with the Metropolis probability $p_M = \exp(-\alpha(Y_{\text{new}} - Y_{\text{old}}))$, where α is a weighting factor.^[33] Simulated tempering is an adaptation of simulated annealing, in which the weighing factor α is also treated stochastically. Recently simulated annealing has been used to design combinatorial libraries.^[34–36] Modifications of these methods, such as parallel tempering^[37] can also be used in the search for heterogeneous catalysts.

1.4.3. Other Methods

Tabu search is another iterative method to solve discrete combinatorial optimization problems.^[38] The basic idea behind the tabu search is to explore the parameter space by a sequence of moves, where each move represents the best course of action based on both the short-term and long-term history of the earlier moves. The tabu search intends to prohibit moves which take the solution to points previously visited, thereby forcing the exploration of a larger solution space. Tabu search is also finding application in combinatorial chemistry.^[39] Other optimization techniques such as branch and bound have also been applied to combinatorial materials research.^[40, 41] Undoubtedly we will see intensified activities both on the application of these stochastic optimization methods and the development of new techniques for the design of libraries of catalytic materials in the near future.

1.5. Data Mining

As evident from the foregoing discussion, although the number of experiments in combinatorial catalysis is large, the amount of data generated will be even larger. Consequently the development and implementation of large-scale information management tools will be crucial for the success of combinatorial catalysis (Figure 1). While the initial efforts in combinatorial catalysis will be directed towards answering specific short-term questions, the accumulated data will be of significant strategic value to discover patterns relating catalyst formulation (composition and methods of preparation) to catalytic function (activity, selectivity, and lifetime). In other words, the accumulated data, stored in data warehouses, can be a source of significant new knowledge. “Data mining”, also called “knowledge discovery” in data bases, is a rapidly emerging software technology that can be employed to accomplish this goal. Data mining can broadly be defined as the efficient and automatic discovery of previously unknown patterns in large databases, rather than to verify that a pattern exists.^[42, 43]

Data mining already has been used in a host of applications from commercial retail business decision support,^[44] to the estimation of the potential toxicity of chemicals from their molecular structure,^[45] from gene mapping,^[46] to aircraft component replacement.^[47] In addition, data mining can be used to determine the time evolution of patterns, which is important in time-on-stream testing of catalysts. Parallel data-mining algorithms are also being developed to speed up the analysis of very large databases.^[44] In summary, recent developments in data warehousing and data mining, in conjunction with advances made in discrete optimization methods provide a strong impetus for the application of combinatorial methods for the discovery and optimization of new catalytic materials.

2. Library Synthesis

The preparation of solid-state libraries of catalytic materials can be accomplished using techniques that can basically be grouped into two primary categories *thin film deposition based* methods of synthesis, and *solution-based* methods of synthesis of combinatorial libraries. In Table 4 recent studies involving combinatorial heterogeneous-catalyst library synthesis methods are presented. This table clearly illustrates the infancy of the field and shows that abundant research and development opportunities exist for the discovery and optimization of new and improved heterogeneous catalysts through the application of combinatorial approaches.

An important practical issue in library synthesis is scale-up. Since the ultimate goal of catalysis research is to develop industrial catalysts, it is desirable that each step of the combinatorial effort lends itself to large-scale production. This requirement places a lower limit on the number of milligrams for each site in combinatorial libraries to enable characterization and seamless transition to bulk production. Clearly, as the cluster dimensions are reduced, the substrate surface chemistry will play an increasingly important role in

Table 4. Recent research on combinatorial heterogeneous catalysis.

Catalyst library	Site size	Reaction investigated	Preparation method	Screening method	Major conclusion	Reference
0.5% Ag, Bi, Co, Cr, Cu, Er, Fe, Gd, Ir, Ni, Pd, Pt, Rh, Ti, V, Zn, on γ -Al ₂ O ₃ pellets	100 mg	H ₂ + O ₂	Solution based: Impregnation	Infra-red thermography	Relative activities observed	[65]
37, 1–10% Co, Cr, Cu, Fe, Ir, Mn, Ni, Pd, Pt, Rh, Ru, V, Zn on Si, Ti oxides	200 μ g	Hydrogenation of 1-Hexyne	Sol-gel method	Infra-red thermography	Relative activities observed	[17]
100 Na ₂ O-Al ₂ O ₃ -SiO ₂ Zeolites with Li and Cs	1–10 mg	–	Solution based hydrothermal zeolite synthesis	–	Parallel synthesis of mg zeolites demonstrated	[63]
37 TiO ₂ -Al ₂ O ₃ -SiO ₂ -TiO ₂ -ZrO ₂ zeolites	50–150 μ g	–	Solution based hydrothermal zeolite synthesis	–	Parallel synthesis of μ g zeolites demonstrated	[64]
645 clusters of Pt, Ru, Os, Ir on carbon	50–200 μ g	Methanol reforming	Solution based: Co-precipitation	Fluorescence-acid-base indicator	Superior catalyst discovered	[19]
120 ternary thin film clusters of Pt, Pd, Rh, and Pd, Rh, Cu	2–4 μ g	CO oxidation, CO + NO	Thin film based: Sputtering	Scanning quadrupole mass spectrometry	Reactivity trends observed	[20]
72 commercial 0.5–1% Pt and Pd pellets	40 mg	Cyclohexane dehydrogenation to benzene	Commercial vendor	Resonance enhanced multiphoton ionization, REMPI	Application of REMPI technique demonstrated	[71]
66 ternary combinations of 1% Pt, Pd and In on γ -Al ₂ O ₃	30 mg	Cyclohexane dehydrogenation to benzene	Solution based: Impregnation	REMPI	Superior ternary composition discovered	[21]
16 Au/Co ₃ O ₄ and Au/TiO ₂ powders	46 mg	CO oxidation	Solution based: Co-precipitation	Quadrupole mass spectrometry	Parallel synthesis and automatic testing of conventional microreactors demonstrated	[61]
33 1–6% Ag, Au, Bi, Co, In, Cr, Cu, Fe, Mo, Ni, Re, Rh, Sb, Ta, Te, V, Y on Si, Ti, Zr oxides	2 mg	Propylene oxidation	Solution based: Sol-gel method	Quadrupole mass spectrometry	Spatially resolved analysis of an array of batch microreactors	[18]
50 ternary and quaternary oxides of Co, Cd, Fe, Ga, Ge, In, Mn, Mo, Ni, Nb, V, W, Zn	300 mg	Ethane and propane dehydrogenation	Solution based: Co-precipitation	Gas chromatography	Evolutionary method for catalyst discovery demonstrated	[30]
30 binary combinations of Na ₂ WO ₄ and Mn on SiO ₂ ; Au and In on ZrO ₂ , TiO ₂ , SiO ₂ , MgO, ZnO, Nd ₂ O ₃ , Y ₂ O ₃ , CeO ₂ , Mn ₂ O ₃	300 mg	Oxidative coupling of methane and CO oxidation	Solution based: Impregnation and deposition, precipitation	Quadrupole mass spectrometry	Parallel synthesis and automatic testing of conventional microreactors demonstrated	[76]
66 ternary combinations of oxides of Mo, V and Nb	150 μ g and 50 mg	Ethane oxidative dehydrogenation	Solution based: Sol-gel deposition	Quadrupole mass spectrometry, photothermal deflection, gas chromatography	Superior selectivity ternary composition discovered	[22]
144 ternary combinations of oxides of V-Al-Nb, and Cr-Al-Nb	150 μ g	Ethane oxidative dehydrogenation	Solution based: Sol-gel deposition	Quadrupole mass spectrometry, photothermal deflection	Superior selectivity ternary composition discovered	[62]
66 ternary combinations of 1% Pt, Pd and In on γ -Al ₂ O ₃	30 mg	Cyclohexane dehydrogenation to benzene	Solution based: Impregnation	Quadrupole mass spectrometry	Higher activity ternary composition discovered	[72]
45 3–5 element combinations of Pt, Pd, Rh, Ru, Au, Cu, Ag, and Mn on TiO ₂ and α -Fe ₂ O ₃	200 mg powder and 23 mg pellets	C ₃ H ₈ total oxidation	Solution based: Impregnation	Quadrupole mass spectrometry	Higher activity compositions discovered after 3 generations using the GA	[32]
56 quaternary combinations of Pt, Pd, In, Na on γ -Al ₂ O ₃	23 mg	NO reduction by C ₃ H ₆	Solution based: Impregnation	Quadrupole mass spectrometry	Higher activity quaternary composition discovered	[73]
V ₂ O ₅ –TiO ₂ mixtures	1 to 60 μ g	Oxidation on naphthalene to naphthoquinone	Solution based: Co-precipitation	Laser induced fluorescence imaging (LIFI)	Feasibility of LIFI demonstrated	[70]

influencing both the chemical and physical structure of the final catalyst product. For example, substrate surfaces can selectively adsorb trace additives from the solution, thereby limiting their incorporation into the crystal structure of the catalyst.

2.1. The Thin Film Deposition Based Method

The so called sputtering with physical masking has recently been used to deposit solid-state libraries for the discovery and optimization of CO oxidation catalysts.^[20] The techniques used by these investigators are based on the pioneering work of Hanak^[9] and more recently by Xiang et al.^[48] where the methodologies for parallel synthesis of spatially addressable solid-state materials libraries were reported. The thin-film library of Cong et al.^[20] contained 120 ternary combinations of Rh-Pd-Pt, and was prepared by sequentially depositing films of the individual elements onto a quartz substrate (7.5 cm diameter and 1.5 mm thick) as 1.5 mm diameter spots using masks. The deposition process was accomplished in 10 sequential steps, with 10 nm of material being deposited in each step. The total library synthesis took about 1 h. Following the deposition of the films, the library was annealed at 773 K under an H₂/Ar atmosphere for 2 h to induce interfilm diffusion and to form alloys. A sketch of the ternary library prepared is shown in Figure 3.

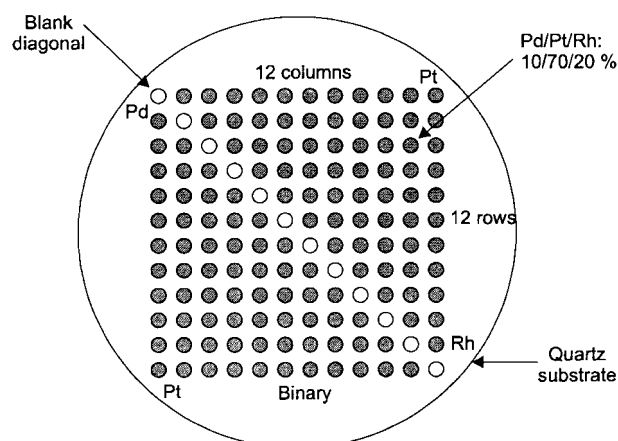


Figure 3. Catalyst library prepared by sequential sputtering.^[20]

Even greater speeds of synthesis of solid-state materials libraries can be accomplished by the simultaneous or co-sputtering of multiple-target materials, an idea originally proposed by Hanak.^[9] In the example shown in Figure 4, four targets are used to simultaneously create a quaternary library where a continuum of compositions can be generated. With the use of a mask, which is also indicated in Figure 4, a discrete and spatially addressable library can be created. Because with sputtering a large number of sites can be prepared simultaneously with very high speed, this technique can be a useful tool for the creation of very large discovery libraries. Thin films, once deposited, can then be processed, for example, calcined and reduced to produce catalytic

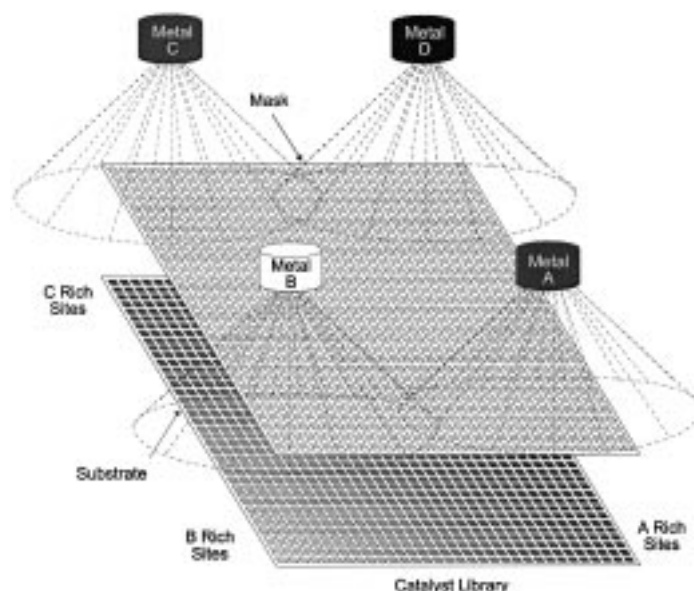


Figure 4. Preparation of libraries of catalytic materials by co-sputtering.

materials. In addition, other thin-film deposition methods, such as thermal^[49, 50] and plasma chemical-vapor deposition,^[51, 52] molecular beam epitaxy,^[53] and pulsed-laser deposition^[54, 55] can be used to create solid-state catalyst libraries.

Thin film deposition based catalyst preparation techniques are particularly promising for use in conjunction with micro-electro-mechanical systems (MEMS) that are created by using semiconductor device manufacturing techniques.^[56] In fact, the recently developed sub-millimeter size reactor systems with flow and temperature sensors would be an ideal platform for testing microgram quantity catalysts.^[57] For example, thin films of catalytic materials can be introduced into these microreactors during the MEMS fabrication process, and can then be tested readily without the need to transfer any solid-state materials. When developed, this should be an efficient mechanism for the creation of libraries of catalytic materials.

There are significant technical challenges that need to be resolved before utilizing MEMS technology in catalysis research. First, these reactor systems must allow for the pre-processing of catalytic materials under realistic conditions, that is, similar to those encountered in high-temperature calcination processes. At present, temperature limitations of MEMS devices restrict their utility in catalysis. The Second, and equally important concern, is the issue of scale-up of the leads obtained in MEMS reactors to produce gram quantities of catalytic materials for bench-top testing. Nevertheless, the MEMS technology promises to be an exciting tool in combinatorial catalysis.

2.2. Solution-Based Synthesis of Libraries

Most commercial catalysts are prepared today using highly refined, solution-based techniques that were developed over decades of trial and error experiments. Solution-based methods can be divided into two primary groups: coprecipi-

tation and impregnation.^[58–60] There are also a number of other techniques that can be considered as variants of these two primary methods; they include complexation, gelation, crystallization, ion exchange, grafting, adsorption, and deposition.^[60]

Coprecipitation involves the mixing of two or more solutions or suspensions, followed by precipitation, filtration, washing, drying, forming, and activation. Consequently, the surface area and mechanical properties of the catalytic materials have to be considered as an integral part of the preparation process. Impregnation involves the contact of a porous carrier with a solution containing the catalytic components, followed by drying and activation. In this case, the carrier primarily determines the surface area and mechanical properties of the final catalyst. Since most commercial catalysts are prepared by techniques that are variations of these two techniques, the miniaturization and automation of coprecipitation and impregnation methods is likely to be the route to exploit combinatorial techniques in the near future.

Efforts in this direction have already met with success as shown in Table 4. For example, solution-based ink-jet print-head technology has successfully been used to prepare a 645 combination Pt-Ru-Os-Ir library for the reforming of methanol.^[19] This study led to the discovery of a superior catalyst with composition 44 % Pt/41 % Ru/10 % Os/5 % Ir. A larger-scale (quantity) automation of the coprecipitation technique was also recently developed and used for the synthesis of a 16 combination library of Au-Co₃O₄ and Au-TiO₂ for the oxidation of CO.^[61]

In related studies, the sol–gel method was applied for the preparation of 37 combinations of 1–10 % Co, Cr, Cu, Fe, Ir, Mn, Ni, Pd, Pt, Rh, Ru, V, Zn on AMM of Si and Ti as catalysts for the hydrogenation of 1-hexyne.^[17] The same group also reported the preparation of 33 combinations of 1–6 % Ag, Au, Bi, Co, In, Cr, Cu, Fe, Mo, Ni, Re, Rh, Sb, Ta, Te, V, Y on Si, Ti, and Zr AMM as catalysts for the oxidation of propylene.^[18] A group at Symyx reported a 66 combination ternary Mo-V-Nb catalyst library for the oxidative dehydrogenation of ethane also prepared using a miniaturized and automated sol–gel method.^[22] Recently, the Symyx group prepared V-Al-Nb and Cr-Al-Nb oxide libraries for the oxidative dehydrogenation of ethane.^[62] In related efforts, solution-based crystallization techniques were miniaturized for the parallel synthesis of libraries of zeolites.^[63, 64]

Impregnation techniques were also successfully miniaturized and used for the preparation of libraries of catalytic materials. Moates et al. reported in 1996 the preparation of a 16 site library by the manual impregnation of commercial γ -Al₂O₃ pellets with up to 0.5 % Ag, Bi, Co, Cr, Cu, Er, Fe, Gd, Ir, Ni, Pd, Pt, Rh, Ti, V, and Zn using aqueous precursor solutions.^[65] Previously, we reported on the development of an automated, multinozzle liquid-dispensing system to rapidly and precisely prepare micro-liter level solution libraries.^[21] This system was used for the impregnation synthesis of a 66 combination catalyst library of Pt-Pd-In on γ -Al₂O₃ which subsequently was used to study the dehydrogenation of cyclohexane to benzene. This library preparation system developed is shown in Figure 5. In the resulting library, the 0.8 % Pt/0.1 % Pd/0.1 % In composition was determined to give best benzene productivity in the range of conditions investigated.

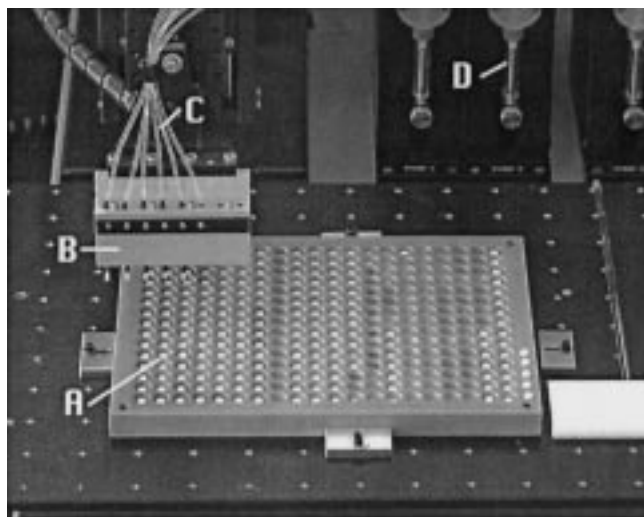


Figure 5. Micro-jet liquid-dispensation system for the preparation of solution libraries. A) Wells to hold solution libraries and catalyst carrier pellets, B) liquid injector nozzles, C) solution delivery lines, D) syringe pumps.

This catalyst preparation system was also used for the preparation of quaternary libraries of Pt-Pd-In-Na and Ag-Cu-Co-Ga for the selective catalytic reduction of NO using propene.^[66]

Recently a similar, single-nozzle liquid-dispensation system was also developed and used to prepare supported multimetal catalysts for the low-temperature oxidation of propane.^[32] In this work TiO₂ and α -Fe₂O₃ powders were impregnated with the aqueous precursor solutions of Pt, Pd, Rh, Ru, Au, Ag, Cu, and Mn in groups of 3–5 elements under incipient wetness conditions. Catalyst libraries containing 45 discrete combinations were prepared using the GA approach, and resulted in the discovery of a number of superior catalytic materials after three iterations; further details will be provided in the case study in Section 5.

In summary, a number of techniques are emerging for the systematic and automatic synthesis of large combinatorial libraries of catalytic materials. These techniques or their variants will probably be the way of the future in catalysis research and development because of their superior accuracy and reliability compared to traditional methods. Fully automated thin-film deposition methods based on sputtering are now available for the synthesis of libraries of multimetal catalysts. Similarly, solution-based impregnation systems are rapidly developing as useful tools for the preparation of supported multimetal catalyst libraries. On the other hand methods to prepare metal oxide catalysts and zeolites by techniques such as coprecipitation and sol–gel synthesis have yet to reach a similar level of miniaturization and automation.

3. Library Screening

The screening of libraries of catalytic materials continues to be a challenging task because of the dynamic, that is, the time-dependent nature of catalytic function. As noted in Section 1.2, the activities of most catalytic materials change with time on stream. Most catalysts deactivate with time, although some catalysts have significant induction periods before they become active. Consequently, to truly assess the practical

value of the new catalytic materials developed, their reaction performance must be tested for extended reaction times. This is likely to remain the primary bottleneck in combinatorial catalysis research and development. However, the development and application of miniaturized and highly parallel reactor systems coupled to suitable high-speed screening systems promises to ease this bottleneck. This is being researched by a number of groups worldwide.^[17, 18, 21, 61]

To date a number of complementary techniques have been developed to screen and/or test libraries of solid-state materials for catalytic activity. Table 4 also summarizes the variety of screening methods developed. Although each specific application must be evaluated to identify the most suitable screening tool, optical methods and mass spectrometry have been the most commonly used methods in catalyst screening because of their broad applicability and relative speed compared to other techniques, such as chromatography. The most significant advantage of optical techniques is that they are *in situ* methods, and as such do not require the withdrawal of samples.

3.1. Optical Methods

Perhaps the simplest optical screening is the color indicator method, which is applicable to liquid-phase reactions. This technique was applied first to determine the relative activity of a series of conventional hydrosilation catalysts.^[67] For this, a dye was chosen in which an electron-donor ferrocenyl group and an acceptor pyridinium functional group were separated by a reactive C=C or C=N group. When the hydrosilation reaction saturated these links, the intensity and hue of the color changed signaling a hit.

A related technique was developed to screen ternary and quaternary alloy catalysts for the electrooxidation of methanol.^[19] In the latter case, the libraries were evaluated for their hydrogen ion generation by monitoring the color change of the fluorescent pH-indicator quinine under UV light. Visual inspection of the library allowed these investigators to pick a superior quaternary alloy of 44% Pt/41% Ru/10% Os/5% Ir for the oxidation of methanol. An important challenge and limitation of these color-based screening methods is that they provide information only on products for which specific indicator molecules are available or can be developed.

3.1.1. Infrared (IR) Techniques

Among the optical methods, infrared (IR) thermography is most widely used to screen the activities of libraries of catalytic materials because of its ease of applicability. Willson and co-workers were the first to demonstrate the utility of IR thermography as a heterogeneous catalyst screening tool using hydrogen oxidation as the model reaction.^[65] Subsequently, Maier and co-workers refined the IR thermography method by taking into account the different emissivities of catalyst clusters, and made it a more quantitative tool.^[17] In IR thermography, radiation energy is emitted from surfaces according to the modified Stefan–Boltzmann law [Eq. (3)].

$$q = e\sigma T^4 \quad (3)$$

T is the absolute temperature, e is the temperature- and composition-dependent emissivity of the surface and σ is the

Stefan–Boltzmann constant. As evident from Eq. (3), energy radiation is extremely sensitive to surface temperature, allowing the detection of very small differences in temperature by the IR technique. IR thermography was also applied as a time-resolved screening tool for catalytic reactions^[68] and in the selection of encoded polymer-bead catalysts in solution.^[69] However, although IR thermography is an extremely fast and nonintrusive screening technique, it clearly does not provide information on the chemical identity of the products formed in a reaction. Nevertheless, IR thermography can be a useful preliminary activity screening tool to explore very large discovery libraries.

Fourier transform infrared (FTIR) spectrometry can also be used to screen libraries of solid-state catalytic materials.^[83, 84] The FTIR approach provides a significant improvement over IR thermography as it provides chemically specific information. However, the detection of gas-phase species at low concentrations creates a challenge that must be addressed for the effective use of FTIR to screen large libraries of catalytic materials.

Recently, the use of thermistor arrays were also proposed to screen libraries of catalytic materials,^[85] as an alternate method to IR thermography. In spite of their intrusive nature, thermistors provide a greater sensitivity to temperature, allowing the measurement of temperature changes of the order 100 μ K, as opposed to 10 mK in IR thermography.

3.1.2. Laser Induced Fluorescence Imaging (LIFI)

An improved optical screening technique based on laser induced fluorescence imaging (LIFI) has been reported recently by Su and Yeung.^[70] This technique exploits the alteration of fluorescence properties of molecules as a consequence of the breakage and formation of chemical bonds. However, as evident from its name, LIFI is only for the detection of fluorescent species, and this limits the use of this technique.

3.1.3. Resonance-Enhanced Multiphoton Ionization (REMPI)

A broadly applicable optical screening technique that provides specific product information on gas-phase species has been reported by Senkan.^[71] The approach is based on the *in situ* ionization of reaction products by UV lasers, followed by the detection of the photoions or electrons by spatially addressable microelectrodes placed in the vicinity of the laser beam. When the laser frequency is tuned to a real intermediate electronic state of a molecule, the cross section for ionization is significantly enhanced, resulting in resonance-enhanced multiphoton ionization (REMPI).^[71] On the other hand, when the laser wavelength is not tuned to a real electronic state, the probability for photoionization is much smaller. There are several means by which REMPI can be induced. The most common method is the resonant 2-photon ionization (R2PI or 1+1), in which one photon ($h\nu_1$) energizes the molecule to an excited electronic state (this is the step where selectivity is introduced) and the second photon ionizes the molecule. The two photons used can have the same or different frequencies.

There are several advantages as well as some limitations of the REMPI approach. First, REMPI can be used for the

detection of a wide variety of polyatomic molecules and radicals *in situ*.^[71] This is in contrast to other optical techniques such as laser induced fluorescence (LIF; which is essentially applicable to monatomic and diatomic species, and LIFI for fluorescent species (see Section 3.1.2)). Second, molecules are ionized from a selected vibrational level of an electronically excited state, thereby allowing for the specific photoionization of target molecules. This can be used to distinguish between isomers. Third, the REMPI process can be used repeatedly to detect different products using different laser frequencies, and thus can allow the rapid determination of selectivities. Finally, REMPI is a highly sensitive technique with real-time detection limits at low parts per billion values readily achievable.^[71]

Unfortunately, the REMPI features of many molecules are not known, and thus must be determined first before the technique can be applied for catalyst screening. That is, considerable research still needs to be done to establish appropriate REMPI strategies and libraries. It is also possible that some molecules may simply not exhibit REMPI features or that these features occur at photon energies that are not accessible using commercial lasers. The implementation of REMPI also requires a considerably more investment of capital than other optical techniques, although this is rapidly changing by the availability of less expensive, tunable solid-state lasers.

Recently the REMPI technique was combined with array microreactors as an effective catalyst-screening tool.^[21] Array microreactors consist of isolated channels that are micromachined on a flat nonporous substrate (Figure 6). Each channel possesses a cylindrical well to hold the pellets of catalytic materials. This system was used to screen the activities and selectivities of a ternary Pt-Pd-In library for the dehydrogenation of cyclohexane to benzene.^[21] The screening protocol demands the unambiguous detection of benzene at the exit of each microreactor against a background of cyclohexane, hydrogen, helium, and other reaction byproducts, under the reaction conditions. To accomplish this goal, the REMPI spectra of the reactants and products were explored to identify a suitable UV-laser wavelength that selectively produces benzene REMPI ions. In Figure 7, the atmospheric pressure REMPI spectra of benzene at various temperatures are presented over a wavelength range of 248 to 265 nm. Based on this and related information, a 259.6 nm laser light was chosen to detect benzene *in situ* in the reactor exhaust gases. This screening process led to the discovery of 0.8% Pt/0.1% Pd/0.1% In on γ -Al₂O₃ as a catalyst superior to other combinations considered (see Figure 5).

3.1.4. Photothermal Deflection (PTD)

Additional optical techniques will probably be developed and applied to screen libraries of catalytic materials on a case-

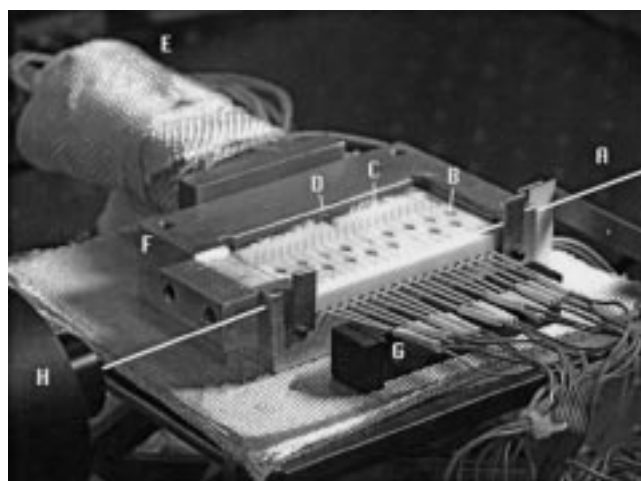


Figure 6. Array microreactor equipped with REMPI-screening components. A) Laser beam, B) catalyst pellets in wells, C) flow distribution baffles, D) feed-gas line, E) feed-gas preheater, F) metal heating block, G) electrodes, H) laser-power meter.

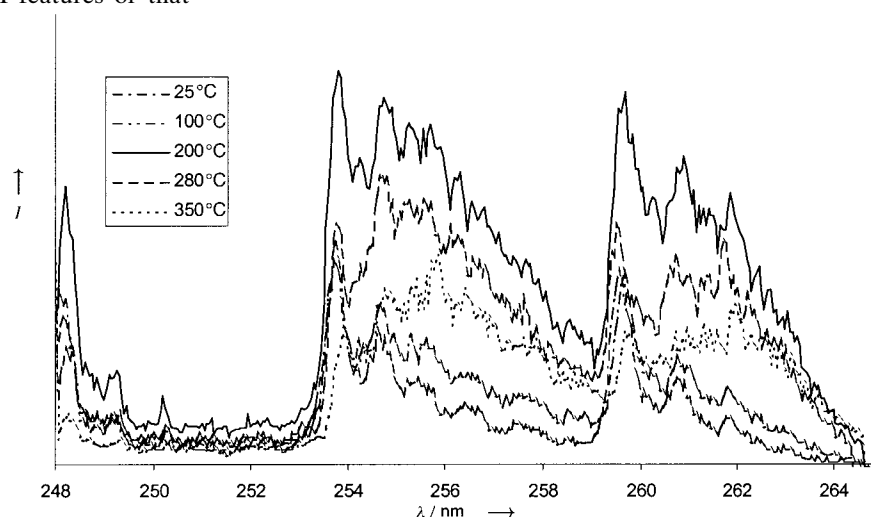


Figure 7. Effect of temperature on the atmospheric-pressure REMPI spectra of benzene.

by-case basis. For example, a photothermal deflection (PTD) method has recently been reported to provide a highly sensitive and selective detection of ethylene in an ethane background.^[22] The PTD method was developed to overcome the problem of ethylene signal contamination caused by the fragmentation of ethane in electron impact ionization mass spectrometry. In PTD, ethylene was excited at 10530 nm by a tunable CO₂ laser, followed by the measurement of changes in refractive index caused by hot C₂H₄, detected by using a HeNe probe laser beam. The authors report a discrimination factor of about 10⁶ against C₂H₆, thereby providing an effective means to detect trace C₂H₄ in an ethane background. As with other optical techniques, the further utility of PTD will depend on the identification of suitable IR laser wavelengths that will selectively excite specific molecules of interest.

3.2. Mass Spectrometry Methods

Mass spectrometry is a mature and widely used detection technology and can readily be applied to analyze complex

gaseous mixtures. However, it requires sample withdrawal, and application to combinatorial catalysis needs the development and implementation of new strategies.

Recently, Cong et al.^[20] reported a quadrupole mass spectrometer (QMS) based system to screen heterogeneous catalyst libraries in a sequential fashion. The catalyst library consisted of small circular patches of films deposited on a nonporous silicon wafer using sputtering with masks (see Figure 3). Each catalyst site on the library was sequentially heated to the desired reaction temperature by a CO₂ laser beam. The reactant gases were then transported to the catalyst site through the annular section of a double concentric probe in a stagnation-flow manner. The gases deflected from the catalyst site also contain the reaction products, and were then withdrawn through the innermost tubing of the probe and analyzed by on-line quadrupole mass spectrometry (Figure 8). After the completion of the screening of a particular site, the library was physically moved to facilitate the testing of the next site. The total time to heat and screen one catalyst site was reported to be about 1 min. With this technique these investigators were able to evaluate a large number of catalysts for the oxidation of CO (see Table 4).

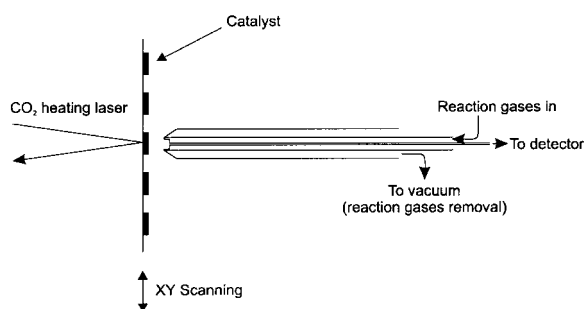


Figure 8. Scanning mass spectrometer system to screen catalysts.^[20]

A similar mass spectrometer based screening technique was also reported by Maier and co-workers.^[18] In this case the library consisted of an open structure where catalyst powders, prepared for example by the sol-gel method, were placed in a spatially addressable configuration on a heated substrate. Library screening was achieved again by sequentially flowing the feed gas onto the surface of a particular site through a capillary feed line and by withdrawing the products through another capillary (Figure 9). The capillary bundle, containing both the feed and sampling lines, was then moved from site to

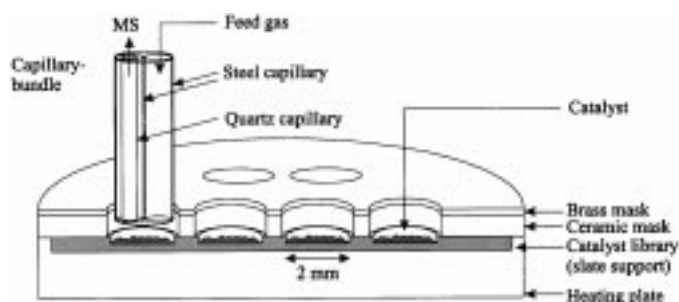


Figure 9. Spatially resolved mass spectrometer system to screen catalysts.^[18]

site by using a robotic movement mechanism. The time to screen each site was reported to be around 1 min. The utility of this system as a viable catalyst-screening tool was then demonstrated by determining the identities of different products in the partial oxidation of propylene as a function of catalyst formulation. It should be noted that the screening systems developed by Cong et al.^[20] and Orschel et al.^[18] cannot efficiently address issues related to the time-dependent behavior of catalytic materials because they were designed to provide reactant-catalyst contact only for a short period of time, about 1 min.

3.3. Array Microreactors

One approach to evaluate the time on-stream performance of catalytic materials is the use of array microreactors,^[72] as shown in Figure 10. In this approach, it is possible to test a large number of catalysts in parallel and for extended periods

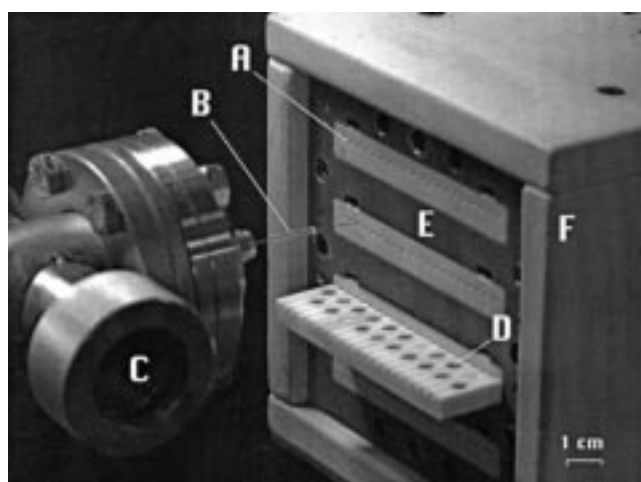


Figure 10. Array microreactor block details: A) ceramic microreactor array, B) capillary sampling line, C) mass spectrometer, D) catalyst pellets in wells, E) aluminum heating block, F) insulation.

of time, thereby identifying leads that have greater chances of becoming practical catalysts. Catalyst screening can be accomplished by analyzing the reaction products by QMS, REMPI, or any other suitable technique. Array microreactors and QMS were recently used to screen the activities and selectivities of an entire 66 combination Pt-Pd-In ternary catalyst library for the dehydrogenation of cyclohexane to benzene in 24 h.^[72] In Figure 11 the benzene levels in the exhausts (indicating conversion) of all the microreactor channels are presented as a function of time-on-stream.

As can be seen from Figure 11, the activities of all the catalysts decreased significantly during the 24 h testing period, demonstrating the need to evaluate the time-on-stream performance of libraries for the discovery and optimization of practical heterogeneous catalysts. Of particular significance is that the activity profiles of some catalysts cross one another over time, suggesting that initial activity measurements are not sufficient for catalyst screening.

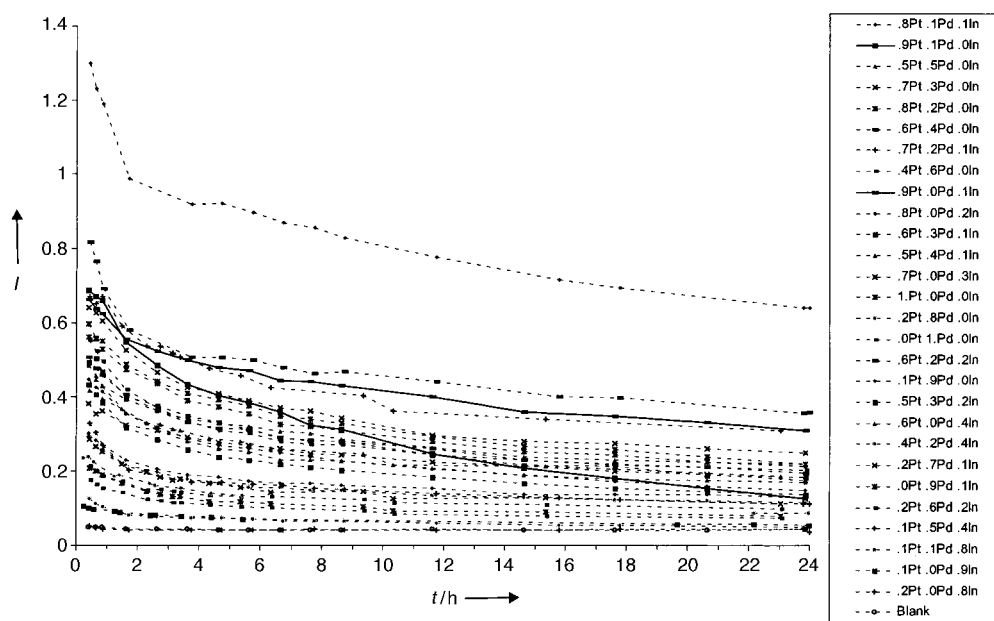


Figure 11. Time-on-stream dependence of the activity (I) of the ternary Pt-Pd-In catalysts in the dehydrogenation of cyclohexane to benzene.

Recently array channel microreactors and mass spectrometry were used for the discovery and the optimization of catalysts for NO reduction,^[73] and low-temperature oxidation of propane.^[32] In the former work, a quaternary library of Pt-Pd-In-Na was prepared by the impregnation of γ -Al₂O₃ pellets. Using a feed-gas composition of about 3500 ppm NO, 3500 ppm C₃H₆, 1.5% O₂, and the rest helium, a 56 combination quaternary library was screened for NO reduction activity at a space-time velocity of 50000 h⁻¹ and over a temperature range of 200–550 °C.

In Figure 12 the actual results of one particular screening test are presented at a temperature of 350 °C. The mass abundances are presented in terms of arbitrary units as a function of microreactor channel number. Signal peaks correspond to levels present in the reactor effluent and sharp increases and/or decreases represent signals acquired during the transit of the capillary probe from one channel to another.

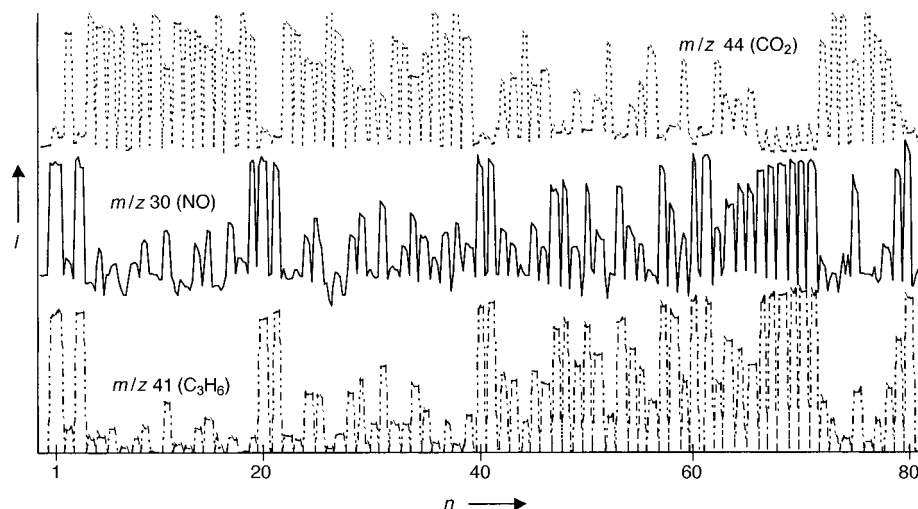


Figure 12. Channel microreactor exit concentrations of NO, C₃H₆, and CO₂ during an experiment. n = Channel number.

As evident from Figure 12, decreases in NO signals are always associated with decreases in the C₃H₆ signal, clearly suggesting the close coupling of these species in the NO-reduction process. On the other hand, for some catalysts while the C₃H₆ signals were significantly decreased, no reduction in the NO signals was observed. An example of this behavior can be seen in the microchannel reactor 19. Evidently, some catalysts were efficient at oxidizing C₃H₆, thereby depriving the NO-reduction process of the necessary hydrocarbon species. The CO₂ mass signals (mass 44), that are also presented in Figure 12 clearly support this picture.

In Figure 13, the microreactor exit concentrations of NO are presented for the quaternary Pt-Pd-In-Na catalyst library at different reaction temperatures. The different library compositions are represented as discrete coordinates on the equilateral tetrahedron. Each corner of the tetrahedron corresponds to pure metal on alumina as indicated. Exit NO concentrations are represented as variations in gray scale and size and the conversion by the size of the circles, as indicated in Figure 13. Consequently, catalysts that exhibit increasingly darker and larger circles (Figure 13) are better performers as far as the NO-reduction process is concerned. An examination of Figure 13 indicates several significant features. First, the NO reduction activities of the catalyst formulations, when present, increase first and then decrease with the increase in temperature. This feature is evident in Figure 13 by the appearance and then disappearance of black circles upon increase in temperature. This trend is in complete agreement with the literature and our current understanding of the interplay that exists between the reactions with NO and the combustion of hydrocarbons.^[74]

Second, and most significantly, multicomponent formulations provided superior NO reduction performances compared to single-component Pt and Pd catalysts under these conditions. A closer examination of Figure 13 also reveals that the catalyst formulation of 0.6% Pt, 0.2% Pd, and 2% Na had the best NO conversion performance, resulting in nearly 75% reduction at 350 °C. Noteworthy is that while Pt-rich mixtures

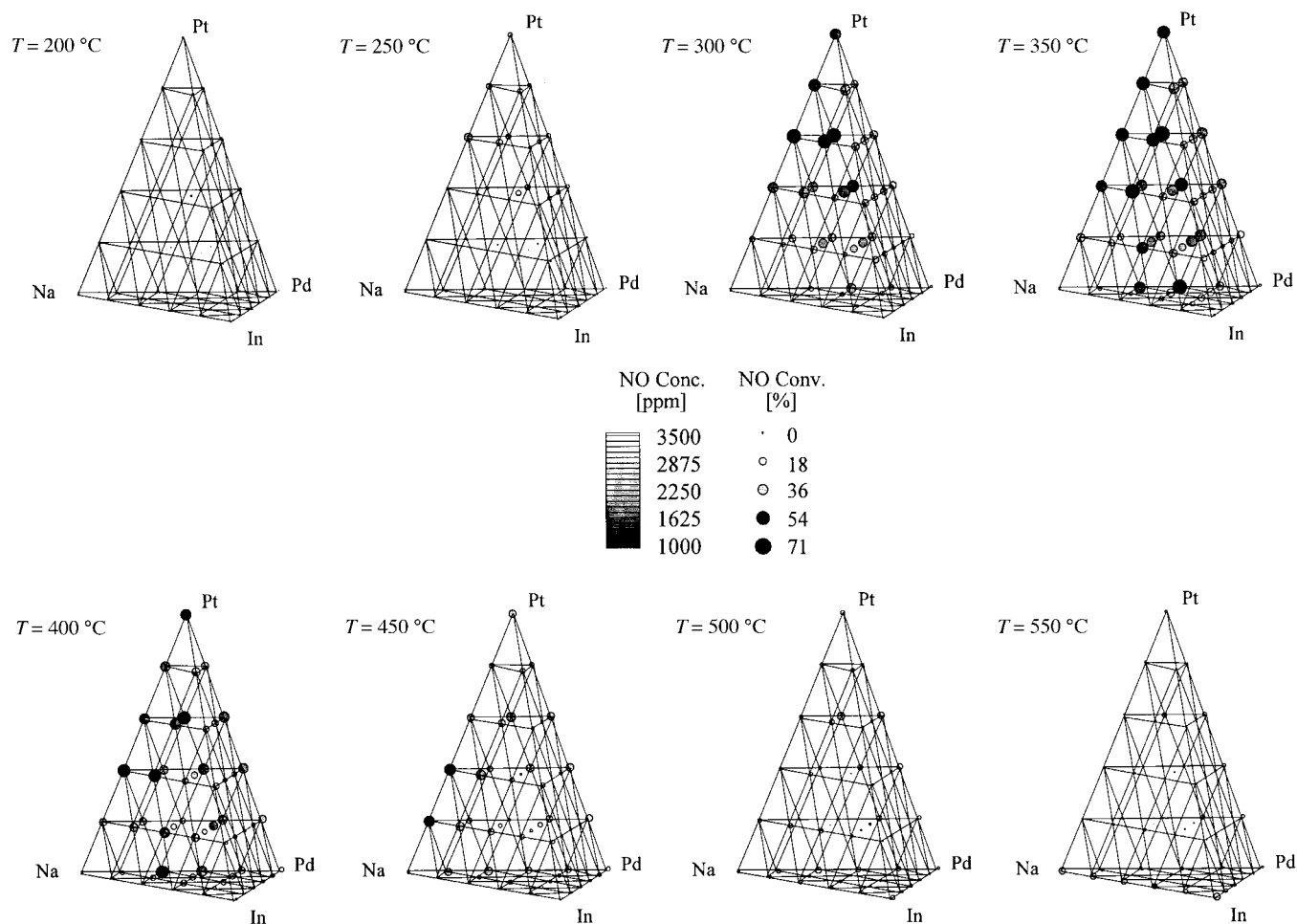


Figure 13. NO-reduction activities (exit concentration and conversion) of the quaternary Pt-Pd-Na-In catalysts as a function of temperature.

generally exhibited superior NO reduction activities over a limited temperature range of 300–450 °C, multielement catalyst formulations were effective over a broader temperature range. The former result is consistent with reported Pt-based, selective, NO-reduction catalysts.^[74, 75]

To better illustrate the speed advantage of combinatorial approaches relative to traditional methods, the time elements associated with each step in our combinatorial approach leading to the results shown in Figure 13 are presented in Table 5. As can be seen from this Table, it was possible to prepare, process, and then screen 56 quaternary catalysts over

Table 5. Time associated with the preparation, processing, and screening of 56 catalysts.

Operation	<i>t</i> [h]
<i>Library preparation</i>	
Preparation of precursor solutions	0.5
Preparation of solution library	0.25
Incipient wetness impregnation	0.25
Drying	2.0
Calcining	2.0
Reduction	2.0
<i>Library screening</i>	
One time mass spectrometric screening	0.50
<i>Total time for discovery and optimization</i>	7.5

the entire 200–500 °C range, in less than 10 h. Clearly, traditional methods would have taken much longer to arrive at the same set of results.

As can be ascertained from the foregoing discussion, the implementation of combinatorial techniques to heterogeneous catalysis is being pursued in two parallel paths. In the first approach, a large number of potential solid-state materials are screened for catalytic properties in short-term tests.^[18, 20] The initial hits identified in the primary screening must then be followed-up by secondary or bench-scale testing studies for the determination of the time-on-stream performance of the catalytic materials. In the second approach the primary and secondary screening methods are essentially combined through the use of array channel microreactors.^[21, 72] Clearly, to successfully implement the former approach, conventional bench-top reactor systems must also be automated. This is indeed being pursued by a number of research groups around the world. For example, the development of an automated high-pressure system containing 16 parallel multitube reactors (each 1 cm diameter) was recently reported by Schüth and co-workers.^[61] A similar block-reactor system containing 15 packed-bed reactors was developed by the Baerns group,^[32, 76] and in a related study, a catalyst screening system consisting of 6 parallel reactors was also reported.^[77]

4. Numerical Simulations

Numerical simulation codes are gaining wide spread use in catalysis research as evidenced by the increasing number of papers published in this area and special issues of journals devoted to this subject.^[78] Computational methods to date have been used primarily to unravel the mechanisms of elementary steps of known catalytic reactions. However, they can also serve as valuable tools for the discovery and optimization of new catalytic materials. That quantum chemistry as well as molecular simulation programs have already proven to be useful tools to complement experiments is most encouraging.^[78, 79] Some areas where computational methods could contribute to combinatorial catalysis include the building of structural models and pre-screening of catalytic materials before undertaking experiments, the determination of structure–activity relationships from which the activities of new catalytic materials can be rapidly ascertained.

The successful application of computational tools to combinatorial catalysis will probably involve the implementation of a two-step approach, as in the case with experiments. In the first stage, approximate but fast simulation methods, such as semi-empirical quantum chemistry, can be employed to establish qualitative trends in reactivity. If these initial efforts prove promising, then the undertaking of more rigorous and time consuming computational methods, such as *ab initio* and/or density functional theory (DFT) calculations, can be justified. For example, the utility of semi-empirical quantum chemistry as a rapid catalyst-screening tool has recently been demonstrated in the oxidative coupling of methane (OCM) reaction.^[80] This investigation showed that lithium doping significantly reduces the activation energy barrier for the dissociative adsorption of methane on MgO from 40 to 15 kcal mol⁻¹, suggesting that Li/MgO should be a better catalyst for the OCM reaction than MgO alone. This conclusion is in complete harmony with earlier experimental results,^[81] demonstrating the potential utility of semi-empirical quantum chemistry as a fast pre-screening tool in combinatorial catalysis.

In another, but more detailed study molecular dynamics and DFT calculations were utilized to evaluate and design more effective (i.e. water resistive) ion-exchanged ZSM-5 catalysts for the selective reduction of NO.^[82] These investigators determined that the differences in calculated enthalpies of adsorption of NO and H₂O correlated well with the available experimental data regarding the water stability of ion-exchanged ZSM-5. Based on this observed correlation, Cr³⁺-, Ir³⁺-, and Ti³⁺-exchanged ZSM-5 zeolites were proposed as new and potentially superior catalysts.

It should be recognized, however, that although computational methods have the promise to make important contributions to combinatorial catalysis, there are several difficulties that need to be recognized. First and foremost is the experimental synthesis of new materials that have been identified by the simulation studies. It is very simple to create new materials with well-defined structures on a computer screen. However, the laboratory syntheses of these materials

are seldom straight forward and in some cases synthesis may be impossible. Second, the simulation of realistic surfaces and catalytic function is likely to remain a demanding computational problem. As noted earlier, catalysts provide three-dimensional active sites that enhance the formation of suitable transition states, and the realistic simulation of such sites requires the use of a very large numbers of atoms, many of which are elements with d- and f-orbital electrons. Consequently, numerical simulations can take as much time as the experiments, diminishing their value to direct experiments. In addition, some catalytic centers can exhibit dynamic behavior during the reactions, rendering molecular simulations significantly more difficult to implement and connect with the experiments. Nevertheless, computational chemistry holds promise as a useful tool to complement and, in the future, to direct experiments in combinatorial catalysis.

5. A Case Study

It is important to end this review with a case study demonstrating how high-throughput synthesis and screening methods can be integrated with discrete optimization methods for the *automatic discovery* of new catalytic materials. Recently the impregnation method of catalyst preparation was coupled with multitube packed-bed reactors^[76] and array microchannel reactors^[71] within the framework of genetic algorithms^[31] to find catalysts for the low-temperature oxidation of propane at low concentrations.^[32] The catalytic materials libraries were prepared by use of an automatic liquid-dispensation system applying the incipient wetness method. A total of 8 active components (Pt, Pd, Rh, Ru, Mn, Cu, Au, Ag) were selected as candidates for incorporation into TiO₂ or α -Fe₂O₃ as carrier materials. The selection of these materials was based, in part, on the accumulated know-how in related studies. The following procedure was used in the discovery process:

1st Step: Initialization of the 1st generation of catalytic materials based on the predefined primary components. For this a library containing of 45 supported catalytic materials consisting of mixtures of active elements at different quantitative and qualitative compositions were prepared in a stochastic manner in such a way that each catalytic material consisted of up to five of eight primary components.

2nd Step: Parallel testing of catalytic materials and evaluation of catalyst quality. The libraries were tested for their catalytic performance (conversion of C₃H₈ to CO₂) in both the multitube packed-bed reactors^[76] and in array channel microreactors.^[71] Catalysts were used as powders (200 mg) in multitube packed-bed reactors and as pellets (23 mg) in the array microreactors. Feed-gas composition was kept at about 0.1% propane and 20% O₂ with the rest He. The operating conditions were atmospheric pressure, temperature range 50 to 250 °C, and residence times were of the order of 10 ms in the array microreactor experiments and 100 ms in the multitube reactors.

3rd Step: Creation of the next generation library based on the catalytic results of the previous generation. This was accom-

plished using mutation and cross-over operators of the genetic algorithm approach^[31] as applied to the previous generation catalysts. This led to the creation of another library also containing 45 supported catalytic materials.

Steps 2 and 3 can be repeated until satisfactory results are obtained. In Figure 14, the array microreactor screening results of the 1st and 3rd generation catalyst libraries are compared with one another at 250 °C. As is evident from Figure 14, the application of GA successfully steered the catalyst development process and led to a substantial improvement in activity in only two generations using a modest library size of 45 catalytic materials.

In Table 6 the compositions of all the 3rd generation catalysts prepared and tested are presented. This table also shows the propane conversions obtained using both the multitube packed-bed and array microreactors. As a consequence of the differences in contact times, array microreactors had to be operated at higher temperatures to achieve levels of conversion similar to those of the packed-bed reactors. As can be seen in Table 6 significant propane conversions could be achieved even at 50 °C with few catalytic materials even in the 3rd generation. Catalysts providing propane conversions of the order 90% were also achievable at higher temperatures. The best catalytic materials, indicated in bold characters, were found to be rich in ruthenium; multimetal combinations were significantly superior.^[32] These results clearly show the benefits of exploring large parameter spaces to make progress in the discovery of superior catalysts. Noteworthy is that the ordering of the activities of the catalysts obtained by the multitube and array microreactors were the same, albeit at different temperatures, thus supporting the suitability of array microreactors as a practical discovery tool. This case study is important in demonstrating, for the first time, how all the components of combinatorial catalysis can be integrated and used for the discovery and optimization of totally new catalytic materials. Therefore, it represents an important milestone in establishing combinatorial catalysis as an effective new tool catalyst research.

6. Summary

With recent advances in experimental methods (both library preparation and screening) together with data management and numerical optimization tools, combinatorial catalysis is poised to make a significant impact on the pace of research leading to the discovery and optimization of new generations of superior heterogeneous catalysts. By a suitable combination of methods, it is now feasible to prepare, process, and test thousands of potentially catalytic materials in a day. New catalyst discoveries are routinely occurring now in a number of laboratories in time scales of the order of days and weeks as opposed to the months and years required by traditional methods. In the next few years we should see intensified activities in all aspects of combinatorial catalysis as well as the commercialization of new discoveries. All of this should spur further interest in combinatorial catalysis as the new paradigm in catalyst research and development.

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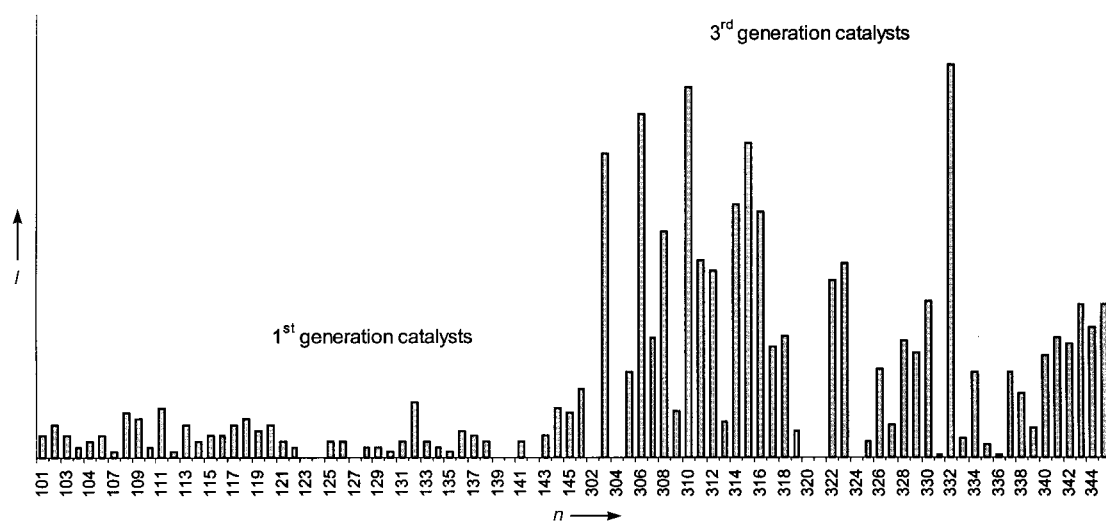


Figure 14. Comparison of the performance of the 1st and 3rd generation catalysts for the oxidation of propane. Feed-gas composition: about 1000 ppm C_3H_8 , 19.6% O_2 , rest He, $T=150^\circ C$. n = Catalyst numbers (1st generation 101–145, 3rd generation 301–345), I = intensity of the signal for $m/z=44$.

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Table 6. Metal contents (wt %) and catalytic results (propane conversion percent) of the TiO₂-supported catalysts of the 3rd generation (from ref. [32]).^[a]

Cat. No.	Pt	Pd	Rh	Ru	Au	Cu	Ag	Mn	Multitube reactor			Array microreactor				
									50 °C	100 °C	150 °C	150 °C	175 °C	200 °C	225 °C	250 °C
301	0.55	–	–	0.98	–	1.47	–	–	6	14	50	7	16	10	44	67
302	–	0.59	0.71	0.04	0.65	1.00	–	–	0	2	9	4	8	0	5	9
303	–	–	0.88	2.12	–	–	–	–	12	18	57	24	28	51	76	85
304	–	–	–	–	–	3.00	–	–	0	0	0	5	12	0	1	0
305	0.59	–	–	1.22	–	0.57	0.62	–	2	14	47	11	20	25	57	75
306	–	–	–	3.00	–	–	–	–	12	30	75	19	26	64	85	90
307	0.51	–	0.80	0.91	–	–	0.78	–	2	16	51	9	15	24	55	72
308	–	–	1.57	1.43	–	–	–	0.00	2	25	72	12	23	33	71	83
309	–	0.79	0.68	0.58	0.95	–	–	–	3	22	66	3	7	12	45	64
310	–	0.59	–	2.41	–	–	–	–	4	32	81	17	27	52	73	85
311	–	–	0.43	0.75	1.44	–	–	0.38	1	20	58	7	12	32	57	76
312	0.20	–	1.15	1.17	0.47	–	–	–	4	30	67	6	13	31	74	84
313	–	2.55	–	–	–	–	0.45	–	0	1	5	0	0	0	0	3
314	0.26	–	–	0.91	–	–	0.78	1.06	1	13	49	6	12	34	57	73
315	0.65	–	–	2.35	–	–	–	–	7	34	84	6	16	50	77	89
316	1.07	–	–	1.93	–	–	–	–	9	32	83	12	24	47	71	84
317	0.15	–	0.84	0.86	0.69	0.47	–	–	1	20	55	10	7	22	44	66
318	–	–	1.10	1.00	0.91	–	–	–	12	33	68	7	12	29	60	76
319	–	–	0.77	0.71	0.64	0.47	0.41	–	5	13	38	3	6	10	31	58
320	–	–	1.91	0.13	0.18	–	0.78	–	4	14	26	1	4	0	8	28
321	1.52	–	–	–	–	1.49	–	–	4	2	3	2	2	8	0	10
322	0.24	–	0.76	1.33	–	–	–	0.67	9	30	60	8	11	30	65	82
323	–	–	–	1.66	1.34	–	–	–	10	31	80	14	9	43	74	88
324	–	1.08	0.65	0.07	1.19	–	–	–	3	7	21	0	0	0	0	1
325	0.32	0.68	–	–	–	1.05	–	0.95	0	1	3	0	0	0	1	1
326	0.21	–	1.19	0.61	0.99	–	–	–	12	29	67	4	3	14	46	69
327	–	–	2.14	0.15	0.20	–	–	0.52	5	13	20	0	-3	7	7	24
328	–	0.01	0.72	1.00	–	–	1.27	–	5	18	43	1	8	26	50	70
329	0.70	0.01	–	1.01	–	–	1.29	–	5	11	43	2	3	23	54	74
330	–	–	1.60	1.40	–	–	–	–	12	33	68	0	0	25	58	77
331	1.19	–	–	–	–	–	1.82	–	1	1	1	0	0	0	0	7
332	–	–	–	1.72	–	–	–	1.28	11	37	84	11	30	55	76	85
333	–	0.05	–	–	1.27	0.90	0.78	–	1	2	1	0	1	0	6	8
334	–	1.49	–	1.52	–	–	–	–	9	28	58	1	7	15	48	72
335	1.46	–	–	–	–	–	1.55	–	1	0	0	0	0	3	5	5
336	–	–	–	–	1.22	0.73	0.55	0.49	1	0	1	0	3	0	5	7
337	0.10	–	–	0.56	0.45	–	0.39	1.49	4	15	43	0	9	12	33	55
338	–	1.29	–	0.98	0.72	0.02	–	–	7	22	51	3	10	14	42	61
339	–	–	1.60	–	–	–	–	1.40	4	3	7	0	5	1	13	17
340	0.49	–	–	1.76	–	–	0.75	–	7	14	67	5	9	26	61	78
341	–	0.01	–	0.82	–	–	1.04	1.13	8	13	50	7	13	18	41	60
342	–	–	–	1.52	–	–	1.48	–	8	18	59	8	10	27	63	77
343	0.20	–	1.15	1.17	0.47	–	–	–	16	30	70	1	12	24	57	80
344	0.24	–	1.36	1.39	–	–	–	–	13	28	59	2	8	21	60	82
345	0.65	–	–	2.35	–	–	–	–	15	29	78	7	17	38	75	90

[a] The materials with the best catalytic activity are indicated in bold.

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