High-Throughput Screening in Heterogeneous Catalysis

Edited by
Alfred Hagemeyer, Peter Strasser,
Anthony F. Volpe, Jr.

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Foreword

Nature has utilized catalysis by employing enzymes since time immemorial. For example, the enzyme urease is one of the most effective catalysts nature has designed. It is capable to catalyze the decomposition of urea 10^{14} times faster than what is possible in the uncatalyzed elimination reaction. In this highly efficient reaction, nature (bacteria) decomposes the urea produced (in the Krebs Cycle) by mammals to ammonia and carbon dioxide for future uptake by plants, which is one of the requirements for their growth and ultimate ingestion by man; thus completing the life cycle. Nature has had time in its favor to ingeniously design its catalytic systems. Man has had a much shorter time span to discover desired catalysts for the production of useful intermediates and products and thereby influencing the course of modern life.

It was Berzelius, who in 1835 first coined the word catalyst, describing it as a substance capable of accelerating reactions without itself being destroyed in the process. Some fifty years later, in 1891 Oswald developed his theory of catalysis putting it on a thermodynamic basis and proposing the concept of microscopic reversibility. Then in the 1920's Mittasch became one of the first to promote the idea of a rational scientific approach to the design of catalytic materials. This noble goal is some eighty years later still a subject of much debate and want.

While nature had time in its favor, it had to work with only a limited number of elements from which to design its key catalytic functionalities (e.g. nickel in urease), and being limited by temperature constraints, man on the other hand has the whole periodic table at his disposal from which to select key catalytic elements and is not bound by any significant temperature constraints. Thus, even in the absence of any unified catalysis theory, the ingenuity of man and his persistence to succeed, and by utilizing working hypotheses and refining them through experimental feed back, has discovered over the past one hundred years several major industrial processes based on heterogeneous catalysis. Among these are: the IG Farben Haber-Bosch process for the synthesis of ammonia utilizing Fe-Al-oxide based catalysts; the Houdry catalytic cracking process using Si-Al-oxides; the UOP Platforming process using Pt-Al-oxides; the SOHIO acrylonitrile process using Bi-Mo-oxides; and the Mobil aromatics isomerization process using ZSM-5 zeolites, to name but a few.

All of these mentioned commercial processes have had a major impact on the industrial world and hence indirectly also on man's improved lifestyle over the years. Currently and for the foreseeable future, the majority of industrial processes for the manufacture of petrochemical intermediates and organic chemicals are based on heterogeneous catalysis.

The proverbial question remains, how can we accelerate the process of catalyst discovery? Looking back, it is obvious that a great amount of ingenuity and chemical intuition, combined with hard work has gone into the discovery process. It is very unlikely that purely empirical research would have led to the important catalytic process discoveries of the past one hundred years. This is particularly true because many of the tools available to the researcher today were not available to him or her some fifty years ago. For example, in the 1950's GC and NMR were not routinely available and product analysis became one of the major bottlenecks in catalytic research. For these reasons it was common then to experiment with 100 g catalyst charges in order to collect sufficient material for product analysis, which consisted often of making appropriate organic derivatives so that they could be analyzed and quantized by chemical and IR analyses. Indeed a tedious and time consuming process that often only allowed one experiment to be performed per week! By the 1960's the analytical methods had improved to the point that many exploratory experiments could be performed on 5 g samples, which decreased to milligram samples by the 1970's and thereafter. Nonetheless, most of the exploratory catalytic research was performed in 1 to 5 g microreactors. Some two or three tube microreactors were used in industrial laboratories by the 1980's, but those were rather rare and single tube microreactors much more common.

Now with the advent of high throughput screening techniques, also known as combinatorial methodologies, pioneered by Symyx Technologies and the subject of this book, the catalyst researcher is provided with an entirely new tool which allows for experimentation to be accelerated by a factor of 10^2 to 10^4. This indeed is remarkable as is amply described and dissected in the different contributions of this book, for it is now possible to combine chemical know-how, experience, intuition and fast experimentation all at once.

It is believed that modern catalytic research has been altered by the advent of combinatorial methodology permanently and that it will behoove the researcher to employ these methods to enhance the process of discovery, thus shortening significantly the time from inception, confirmation and ultimate commercialization of promising catalytic systems. Combinatorial methodology is a tool that all catalyst researchers should avail themselves of in order to enhance their discovery process. It is a tool and in itself not exclusively sufficient for the discovery process, as several contributors to this book attest. Combinatorial methodology needs to be combined with sound chemical knowledge, structural and surface analyses, well thought out working hypotheses, experience, intuition and theory, to achieve optimum results.

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Preface

Rising economic demands for higher efficiency and productivity in Research and Development in the chemical and refining industries have led to the implementation of high throughput, or combinatorial, methods in heterogeneous catalysis. The key drivers have included the desire to reduce the time-to-market for new and optimized catalysts and processes, increased probability of success and better intellectual property protection from the ability to perform many more experiments than in the past, shorter/more projects possible per unit time, and the increased organizational efficiency resulting from improved data storage, access, analysis, and sharing. The number of experiments that can now be screened can be orders of magnitude higher than using traditional methods.

The combinatorial process in catalysis allows the exploration of large and diverse compositional and parameter spaces by utilizing integrated workflows that include software-assisted design of diverse, high-density assemblies, or arrays, of potential catalytic materials (known as "libraries"), and high-throughput synthesis, characterization, and screening techniques that are characterized by the use of robotics and advanced software. The integrated synthesis and screening of a plurality of catalysts in library format has been recognized as an essential factor. Equipment miniaturization and integrated data management systems are also key aspects of successful workflows. The development and implementation of these methods requires the involvement of unconventional engineering and software resources not commonly available at chemical, refining and petrochemical companies where heterogeneous and homogeneous catalysis is practiced.

This book will describe the current state of the art synthesis and screening techniques for high throughput experimentation in chemical catalysis with a focus on technology developed over the last 2–3 years. It will provide an up-to-date overview of the current status and advances that have been made in this rapidly growing field in both academia and industry. The targeted readership is the advanced-level student, the catalytic or solid-state chemist in industrial and academic R&D and engineers specializing in reactor technology, detection schemes and automation.

It has been a great pleasure and distinction for us to assemble a diverse group of distinguished international authors from both academia and industry, each contributing the most up-to-date results and status in their application of high throughput methodologies. The book covers reactor technology and integrated synthesis and screening workflows, experiment design and search strategies, detection schemes, and applications to liquid and gas phase heterogeneous catalysis, fuel cell electrocatalysis and homogeneous catalysis. Diverse catalyst systems, such as mixed metal oxides, supported metals, microporous systems/zeolites, mesoporous sieves, as well as diverse chemical transformations (oxidations, dehydrogenations, C1 chemistry, emissions control, petrochemical transformations, hydrogenations, fuel processors) are discussed. We hope that this book will clearly demonstrate the applicability, utility and advantage of combinatorial and high throughput methodologies in chemical catalysis and that the reader will benefit from this snapshot of a rapidly developing field in applied materials science.

We would like to thank all the authors for their contributions. We are thankful to Silvia Lee for her help in putting the book together.

Santa Clara, May 2004

Alfred Hagemeyer
Peter Strasser
Anthony F. Volpe, Jr.

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1
Impact of High-Throughput Screening Technologies on Chemical Catalysis

W. Henry Weinberg and Howard W. Turner

1.1
Introduction

Traditional methods of catalyst synthesis and testing are slow and inefficient. Whether one considers either homogeneous or heterogeneous catalyst systems, the root causes for this problem are the same: the ability to predict theoretically the optimal catalyst structure, composition, and synthesis conditions is poor to non-existent, and the catalyst and catalyst formulations are prepared and tested one at a time in a manually intensive fashion. While chemical principles and knowledge of the literature guide the chemist in designing targets and experiments, even in the most well understood areas of catalysis the parameter space that one needs to explore is huge. The result is that the chemist using traditional methods must navigate a complex and unpredictable diversity space with a limited data set to make discoveries, a situation that is perhaps acceptable for the optimization of known systems where the synthesis–structure–property surface is smooth, but unacceptably inefficient for the optimization of systems where this surface is jagged or for the discovery of unprecedented catalytic systems. The reliance on traditional methods of catalyst research leads to a bottleneck in the supply of fundamentally new classes of catalytic materials (which we refer to as "hits") and enormous competition in industrial and academic laboratories during the optimization of the precious few new systems that are discovered and published. Given the inefficiency of traditional optimization of new homogeneous and heterogeneous catalytic systems, the competition in recent decades is not surprising, such as for metallocene olefin polymerization catalysts and the MoVNb-oxide partial oxidation catalysts discussed below.

Until the publication of Schultz [1] in 1995 describing broadly "combinatorial" or "high-throughput" methods for materials discovery, including homogeneous and heterogeneous catalysts, and the creation of Symyx Technologies, the first company dedicated to developing and applying these methods, efforts to improve the efficiency of R&D were largely limited to enhancing analytical techniques to better understand catalyst structure, computational approaches for the prediction of structure–property relationships, improving the precision of laboratory reactor data and its correlation to the commercial process, and the use of statistically designed experiments to minimize the number of experiments necessary to advance a target. Miniaturization of reactor screening technologies existed before 1995, but efforts to create highly automated and massively parallel workflows did not. Combinatorial methods were developed in the 1980s to improve the efficiency of drug discovery, and these involve various high-dimensional experimental techniques including the use of "split-pool" synthetic procedures where mixtures of thousands of compounds are created on beads, parallel synthesis to produce a collection of related organic compounds known as a "library", and new property-screening technologies that allow the scientist to sort through large collections of potential leads in an efficient and increasingly precise fashion. Philosophically related to these methods, but differing substantially in application, Symyx developed a hierarchical approach to create entire workflows for the synthesis and screening of homogeneous and heterogeneous catalyst libraries. The hierarchical screening philosophies are similar but the physical embodiments of high-throughput drug discovery and high-throughput catalyst discovery and optimization are utterly different. These catalyst discovery workflows can be considered as assembly lines, which allow one to methodically and efficiently generate arrays of new classes of materials in a specific format (a library) designed to maximize the ease of screening for various catalytic transformations, and, then, upon the discovery of "hits" to optimize them efficiently to create "leads" which become commercial development candidates for the targeted process and product. In the following we refer to the use of these workflows as "high-throughput research and development" (HT-R&D) and define this term to include both the synthesis and property evaluation of the catalyst libraries.

The hierarchical workflow shown in Fig. 1.1 illustrates three distinct phases of research leading to commercialization.

The first phase, known as "primary screening", is designed for broadly and efficiently screening a large and diverse set of *families* of materials that logically *could* perform the desired catalytic transformation. It is during this phase that "hits",

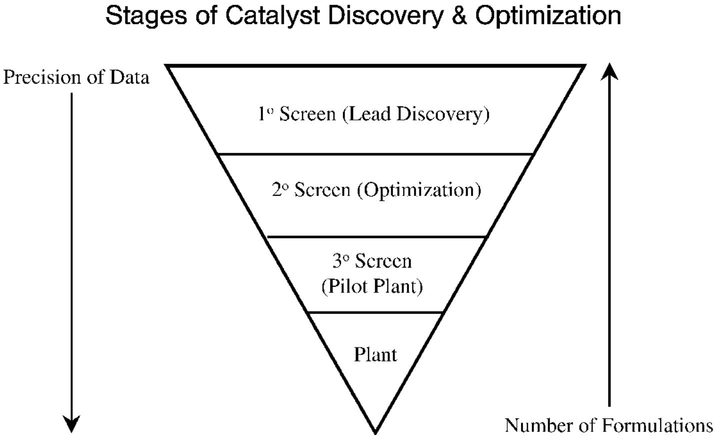

Fig. 1.1 Hierarchical high-throughput R&D workflow.

truly new classes of materials that show promise for a specific catalytic transformation, can be efficiently discovered, and a key bottleneck in the R&D process can be eliminated. Predictably, it is this phase with which the traditional catalytic chemist is the most uncomfortable. All well trained chemists have been taught rigor in the synthesis and characterization of the materials they produce before testing for the desired application. They have also been taught to maximize the quality and precision of the catalytic testing data by using reactors that have a high level of process control and that are as close as possible to the "real" process in which the material will be commercialized. These are all good things and are necessary, but only at a later stage of the hierarchical workflow where optimization and commercial development occur. While we seek to maximize the quality of data and mimic the "real" process conditions during primary screening, the sheer volume of experiments, often thousands per day, makes it extremely difficult to obtain conventional laboratory quality data. Fortunately, this does not pose a problem. In some cases, to get the throughput necessary for a program, we do not screen for the exact property that we seek, but rather screen for an easier and faster observable that represents a necessary but not sufficient property of the targeted material [2]. We trade precision for throughput in a rational way that increases the probability of success and shortens time to commercialization. The key in this enterprise is to create a validated primary screen (i.e., a screen where we have proven that we can "rediscover" state-of-art catalysts and observe known trends). In a primary screen we seek qualitative trends in the data to eliminate families of materials from diverse libraries and to identify hits that have the *potential* to become a lead, i.e., materials that warrant testing in a secondary screen. We design our primary screening technologies to minimize both false negatives and false positives, the latter of which waste time and money in the slower and more precise hit validation phase. To the uninitiated the issue of false negatives is usually the biggest concern; methods of minimizing the risk of "missing a hit" have been well described for homogeneous catalyst workflows [2] and Chapter 3 discusses this issue as it relates to primary screening for heterogeneous catalysts.

Secondary screening plays two roles. First, it validates or eliminates hits generated from the primary screen. As mentioned above, often the primary screen seeks to identify a property that is easy to measure in a high-throughput fashion that is a necessary but not sufficient condition for the hit to be active and/or selective for the targeted chemical transformation. Here, the secondary screen is the first test for the "real" property, and often hits fall out of the program at this stage. In a second role for secondary screening, once a hit, identified by primary screening or identified in the literature, has been validated, secondary screening tools are used to optimize the hit to create a "lead" material. In secondary screening, rigorous catalyst synthesis procedures are important, and, since most optimizations require multiple modifications with small improvements in performance at each successful step, the data quality and precision need to be on a par with a typical laboratory reactor. Therefore, automated laboratory-scale synthetic techniques and highly parallel reactor systems for various processes have been developed. Some of the systems invented at Symyx Technologies are described in Chapter 3. This technology has evolved to the point that the quality of the data obtained during the secondary screening stage allows for the synthesis and screening of hundreds of catalytic materials per week with data quality that is equivalent or superior to that obtained using conventional laboratory technologies.

Optimized leads identified in the secondary screening phase of a HT-R&D program are then taken to the tertiary screening phase to generate commercial development candidates. This usually takes the form of a conventional mini- or pilot-plant.

Finally, the workflow must include advanced experimental design, library design, data management, database, and data mining software. When taken together and executed properly, HT-R&D programs generate vast data sets with concomitant knowledge derived therefrom, shorten time scales for completing a program, increase the probability of success of the program, and increase the strength of an intellectual property portfolio. The talented synthetic chemists should not fear that HT-R&D technologies will render them less important because robots do the chemistry. The opposite is true for several reasons. First, in a HT-R&D environment the number of variables in diversity space that one is able to address is so large that insightful and creative thinking based on sound chemical knowledge and principles is necessary to reduce the number of experiments to a realistic level. This is no different than in traditional laboratories; it is just that one can explore one's concepts more rapidly and more thoroughly. Secondly, since the number of projects one can initiate and conclude in one's career is substantially larger, the chemist will be constantly challenged to create new concepts for new problems. Finally, the increase in R&D efficiency due to HT-R&D technologies will result in a lower unit cost for research and increase the desire for industry to invest in the development of advanced technologies.

To illustrate the power of integrated workflows consisting of primary and secondary screening technologies we briefly describe two examples from our own laboratories.

1.2
Application of HT-R&D Methods in Heterogeneous Catalysis

The discovery of catalytic systems and processes that selectively convert unsaturated hydrocarbons such as ethane and propane into higher value chemicals, such as ethylene, acrylic acid, and acrylonitrile, is a key R&D goal within the chemical and petrochemical industries. The dominant process targeted for these advances involves the use of heterogeneous catalysis in either fixed bed or fluidized bed processes. The chemical challenge is great due to the difficulty of selectively activating saturated hydrocarbons at low temperature, the dominance of inherently unselective free radical pathways at high temperatures, and the fact that the desired products are often more easily oxidized than the saturated hydrocarbon starting material, leading to low selectivity at commercially viable conversions.

In 1978 Union Carbide scientists reported the discovery and optimization of oxidative dehydrogenation catalysts for converting ethane into ethylene that were based on mixed metal oxides consisting of Mo, V, and Nb [3]. This study described a systematic evaluation of the effect of composition (i.e., the ratio of the three metals in the tertiary composition) on performance as measured by space–time yield. The composition $Mo_{0.72}V_{0.26}Nb_{0.02}O_x$ was reported to be optimum.

More than a decade after the publication of the MoVNb catalyst system, scientists at Mitsubishi Chemical reported that modifying this family of mixed metal oxides with Te produced a catalyst for the amoxidation of propane to acrylonitrile [4] and the oxidation of propane to acrylic acid [5]. Modification of the Union Carbide catalyst system with Te was probably not a random choice as it is a known propylene activator [5 b] and the molybdate phase $TeMoO_x$ oxidizes propylene into acrolein and ammoxidizes propylene to acrylonitrile [6], a key intermediate in the commercial production of acrylic acid using Mo-based oxides. Significant efforts to optimize this and related mixed metal oxides continues for the production of both acrylic acid and acrylonitrile, with the main participants being Asahi, Rohm & Hass, BASF, and BP.

In 1998 scientists at Hoechst reported that the addition of Pd to the MoVNb ethane dehydrogenation catalyst enabled the efficient production of acetic acid from ethane [7]. Doping of this known ethane dehydrogenation catalyst with Pd was probably not random, but predicted on the basis of the classical Wacker catalysis.

Fig. 1.2 summarizes the lineage of discoveries based on the MoVNb "hit" published in 1978 and is included to emphasize the importance of the discovery of new starting points in chemical catalysis.

Symyx entered this competition in 1997 in collaboration with Hoechst with the goal of creating and validating primary and secondary synthesis and screening technologies and the use of this workflow to broadly explore mixed metal oxide compositions so as to discover and optimize new "hits". The initial goal was a 10-fold increase in the space–time yield relative to the state-of-the-art MoVNb system for the ethane oxidative dehydrogenation reaction to ethylene.

In the workflow used in this program (Fig. 1.3) *primary* screening is carried out in "wafer" format. The libraries are synthesized from soluble metal precursors using specialized library design software [8] and liquid-dispensing robots in a ter-

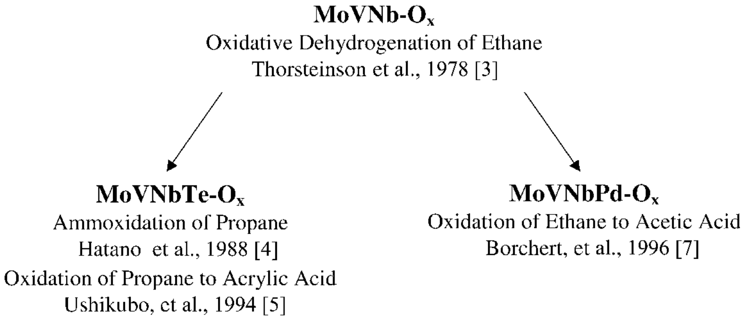

Fig. 1.2 Lineage of discoveries based on the MoVNb partial oxidation catalyst.

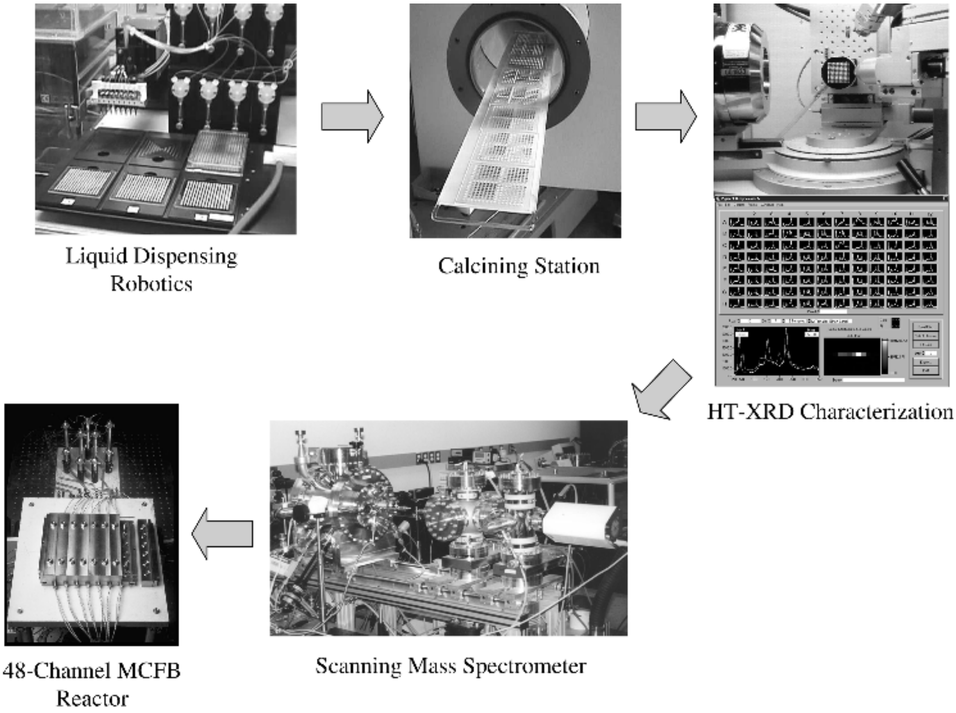

Fig. 1.3 HT-R&D workflow used in the oxidative dehydrogenation of the ethane program at Symyx Technologies.

tiary phase diagram format. The automated process involves creating arrays of mixtures of metal precursors under conditions where the mixtures remain in solution and then depositing 1–2 μl aliquots onto a quartz wafer that has been etched to create an ordered array of micro-wells. Multiple "daughter" wafers are prepared and then calcined under various conditions to minimize the chances of false negatives and/or to help identify optimal processing conditions for bulk catalyst synthesis. Variable space for primary screening includes elemental composition, choice of support (starting material wafers with microgram quantities of powders derived from any commercial or proprietary supports can be produced using similar robotics), choice of metal precursor, and calcining conditions. The wafer-based libraries can be characterized by scanning XRD using commercially available equipment and proprietary methods [9] when appropriate.

The performance of each library member can be screened by several proprietary primary screening technologies [10], including the scanning mass spectrometer (SMS) technology shown in Fig. 1.3. The wafer is placed on a motion control stage capable of positioning a single library element approximately 100 microns below a probe that flows the feed of the starting material over the catalyst surface and removes reaction products to a mass spectrometer and/or other detector technologies. The individual catalyst elements are heated to a preset reaction temperature using an IR laser from the backside of the quartz wafer and an IR camera is used to monitor temperature. The power of the laser is adjusted to control temperature. This is a rapid serial method requiring approximately 2–3 min per sample. The system is fully automated and, after the library is placed on the motion control stage and the experiment initiated, the entire library can be screened unattended.

Several proprietary *secondary* screening technologies for fixed bed processes have been described [11], one of which is depicted in Fig. 1.3. The 48-channel reactor includes a single feed system that supplies reactants to a set of flow restrictors. The flow restrictors divide the flows evenly among the reactors. The back pressure created by the flow restrictors is designed to be large compared with any pressure drop caused by the catalyst bed or downstream plumbing to ensure that an even flow occurs through each reactor. The multichannel fixed bed reactor (MCFB) shown in Fig. 1.3 and used in the ethane oxidative dehydrogenation program is in a 6×8 rectangular array format and can accommodate up to 100 mg of solid catalyst in each reactor.

A more detailed description of heterogeneous catalyst library synthesis (primary and secondary), primary screening, and secondary screening technologies is given in Chapter 3 and references therein.

The first step in this or any new HT-R&D program is to validate the workflow. In the oxidative dehydrogenation of ethane program, primary screening validation was accomplished by "rediscovering" the trends and optimum composition for the MoVNb catalyst system described in 1978 by Union Carbide. Duplicate 66-member libraries (11 members on each diagonal of the phase diagram) were synthesized using soluble Mo, V, and Nb precursors. The libraries were calcined and then characterized by scanning XRD, confirming that the thick film library elements had similar phase composition to bulk samples prepared using traditional methods. The libraries were placed on the SMS motion control stage and screened in a rapid serial mode using a mass spectrometer to quantify CO_x and a laser pump–probe measurement to quantify ethylene. These detectors were calibrated and together allowed the ranking of both activity and selectivity at low conversion.

Fig. 1.4 compares, in topological format, the space–time yield versus composition for the data presented in the 1978 Union Carbide publication and the activity rankings observed in the SMS in an experiment that took less than 4 h, most of which was unattended. The correlation is remarkable. The primary synthesis and screening components of the workflow were thus validated. "Hit" criteria were established that involved ranking the yield of the reaction over the various catalysts (the activity figure of merit multiplied by selectivity). The "hit" criteria performance bar increased as the discovery program evolved and improved systems were discovered.

The 48-channel MCFB reactor and the catalyst synthesis workflow components were similarly validated in experiments where bulk samples were prepared in library format, screened in the array format, and the data compared with known examples. This part of the workflow was used for initial hit validation and to opti-

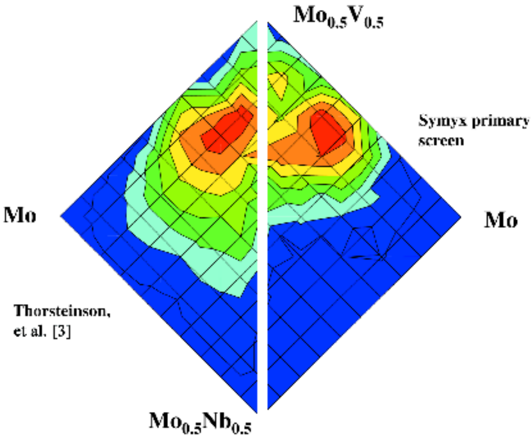

Fig. 1.4 Comparison of STY with the composition as measured by Thorsteinson et al. [3] using traditional methods and by Symyx scientists using wafer-based primary screening technologies where the innermost enclosed areas represent the highest STY.

mize those systems that exhibited acceptable performance under commercially realistic conditions.

The discovery program began by broadly screening ternary mixed-metal oxide compositions. Although many catalyst compositions can be prepared and screened using this workflow, testing of all possible ternary mixed-metal oxide compositions is impractical. The combination of all possible ternary combinations (assuming 70 metal oxides) with 10% gradient steps results in millions of unique compositions. This number increases by many factors as one explores multiple library processing conditions and alternate metal precursor options. Thus, priority decisions based on sound chemical knowledge were made. Since the focus of the research was the low temperature partial oxidation of ethane to ethylene the scope of the search could be reduced by the assumption that the ternary mixed-metal oxides should contain at least two different metal oxides that can be reduced by hydrocarbons and their reduced forms oxidized by molecular oxygen at low temperature. The third metal oxide component was generally designed to act as a matrix or stabilizer and was not required to be redox-active under catalytic conditions. In this way, synergy between different redox-active metals could be explored. With these assumptions the diversity space was narrowed to about 100000 composition and processing experiments.

Nickel-based systems containing certain other metals such as Ta, Nb and Ce emerged as lead candidates. The best Ni-based catalysts showed activities as measured by SMS that were 50–100× that of the best MoVNb systems. In secondary screening the Ni-based systems distinguished themselves from the Mo-based systems in terms of both space–time yield and the unique and highly desired property of having a flat selectivity versus conversion (i.e., selectivity vs. temperature) relationship relative to the state-of-the-art MoNbV systems. Fig. 1.5 shows a timeline of how the performance characteristics of the best Ni-based systems evolved in terms of activity measured in the primary screen, space–time yield measured in the MCFB secondary screen, and in a ternary screen carried out in pilot plant