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High-Throughput Approaches for the Discovery and Optimization of New Olefin Polymerization Catalysts

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ABSTRACT: The discovery of new olefin polymerization catalysts is currently a time-intensive trial-and-error process with no guarantee of success. A fully integrated high-throughput screening workflow for the discovery of new catalysts for polyolefin production has been implemented at Symyx Technologies. The workflow includes the design of the metal–ligand libraries using custom-made computer software, automated delivery of metal precursors and ligands into the reactors using a liquid-handling robot, and a rapid primary screen that serves to assess the potential of each metalligand-activator combination as an olefin polymerization catalyst. “Hits” from the primary screen are subjected to secondary screens using a 48-cell parallel polymerization reactor. Individual polymerization reactions are monitored in real time under conditions that provide meaningful information about the performance capabilities of each catalyst. Rapid polymer characterization techniques support the primary and secondary screens. We have discovered many new and interesting catalyst classes using this technology. © 2002 The Japan Chemical Journal Forum and Wiley Periodicals, Inc., Chem Rec 2: 278–289; 2002: Published online in Wiley InterScience (www.interscience.wiley.com) DOI 10.1002/tcr.10025

Key words: high-throughput; olefin polymerization; catalyst; primary screen; secondary screen

Introduction

High-throughput synthesis and screening approaches were originally developed within the pharmaceutical industry, where long development times and high research costs forced the establishment of techniques to accelerate the discovery process. The basic concept of the high-throughput approach is the creation of large libraries of structurally or compositionally diverse components that can be rapidly processed and screened for a desired property. Such an approach represents a powerful research strategy that is best suited to problems where a large parameter space influences the key properties of a desirable compound or formulation. In the last few years, high-throughput approaches have been extended to materials

science for the rapid discovery and optimization of catalysts, polymers, and electronic materials.¹

Within the polyolefins industry, new single-site catalysts with improved performance features are the subject of intense research activities. Improvements in catalyst performance features such as temperature stability, productivity, comonomer incorporation capability, high molecular weight capability, comonomer sequence distribution control, and the ability to copolymerize new monomer combinations are currently

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being sought through design and modification of catalyst structures. Indeed, structural changes to the ligand frameworks of single-site catalysts have led to impressive advances in catalyst technologies over the past 20 years. Such advances have led to the emergence of commercial processes employing metallocene complexes for the preparation of commodity polyolefins.²⁻⁴ More recent advances include single-site catalyst classes based upon new noncyclopentadienyl ligands, and mid- and late-transition metals, including the discovery of 1,2-diimine based palladium catalysts capable of copolymerizing ethylene with previously incompatible monomers such as acrylates.⁵⁻⁷ Further discoveries of new classes of single-site catalysts will undoubtedly lead to improved and more versatile performance features, in addition to unique polymer product families with interesting properties.

The discovery of new olefin polymerization catalysts is currently a time-intensive trial-and-error process with no guarantee of success. For example, it is currently not possible

to predict which new metal-ligand combinations will lead to active catalyst classes and which metal-ligand combinations will have low or no activity. Even for a well-studied catalyst, small changes to the ligand structure can have dramatic and unpredictable effects upon catalyst performance. Thus, even upon discovering a novel catalytically active metal-ligand combination, it is extremely difficult to predict the structural features necessary to optimize the catalyst performance. Because catalyst performance can be influenced profoundly through choices in ligand, metal, activator and polymerization conditions, olefin polymerization catalysts represent good candidates for the application of high-throughput approaches.

High-throughput approaches offer significant advantages over conventional methods of catalyst discovery. Firstly, high-throughput screen can rapidly identify catalytically active systems and, importantly, identify and reject inactive systems. Additionally, the ability to generate sufficient quantities of meaningful catalyst performance data can provide compre-

► The Homogeneous Catalysis Group at Symyx

During the past five years, the homogeneous catalysis research group at Symyx Technologies has implemented a fully integrated high-throughput synthesis and screening infrastructure for the accelerated discovery and optimization of new catalyst technologies and polymer products. The high-throughput infrastructure has been designed for the discovery and optimization of both solution-phase and solid-supported catalysts. Research is currently focused on the discovery of next-generation catalysts for the production of polyolefins and specialty polymers.

Symyx, founded in 1994, is a pioneer in the development and application of high-speed combinatorial technologies to discover novel materials for life science, chemical, and electronics applications and is revolutionizing the way new materials are discovered. Symyx provides research services to its partners through its Industry Collaborations business, seeks to license discovered materials through its Proprietary Materials programs, and offers selective access to its proprietary technologies, including instruments, software, and intellectual property, through its Discovery Tools business. Approximately 25 leading life sciences, chemical, and electronic companies are among Symyx' increasing base of worldwide partners and customers. ■



► Vince Murphy obtained a B.Sc. degree in chemistry from the University of Manchester, Institute of Science and Technology U.K., and a D.Phil degree from the University of Oxford, U.K. in 1993, where his research under Professor Dermot O'Hare centered upon the synthesis and characterization of novel organometallic molecular magnetic materials. After postdoctoral research on synthetic and structural inorganic chemistry with Professor Gerard Parkin at Columbia University, and polyolefin catalysis with Dr. Howard Turner at Exxon Chemical, he joined Symyx Technologies in 1997, where he is currently the Director of Homogeneous Catalysis. ■

hensive structure-property relationships. In our view, the key for the efficient screening of thousands of metal-ligand combinations for their potential as olefin polymerization catalysts is a fully integrated high-throughput workflow which takes into consideration all of the critical disciplines. In this regard, ligand synthesis, organometallic chemistry, activation chemistry, the high-throughput screening workflow, polymer characterization, engineering, instrument software, data management, and data mining all play a critical role in the implementation of the high-throughput program at Symyx (Fig. 1). Herein we review the infrastructure developed at Symyx for the high-throughput discovery and optimization of new olefin polymerization catalysts.⁸

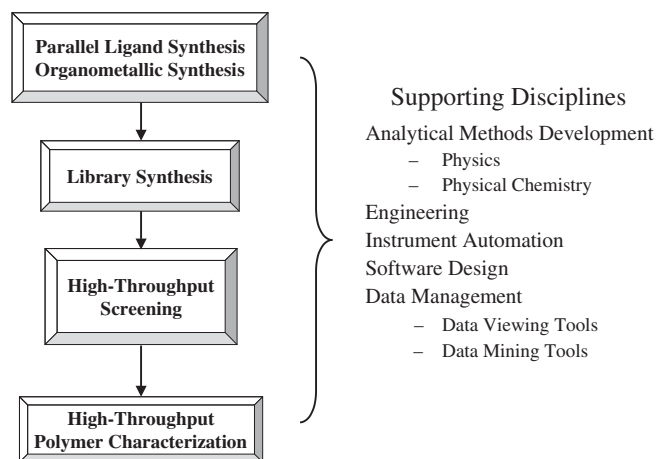
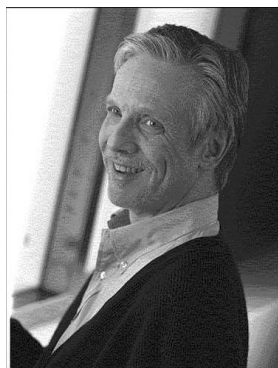


Fig. 1. Workflow and supporting disciplines for a high-throughput polyolefin catalyst discovery program.

The High-Throughput Approach

To ensure a smooth and progressive workflow, and an efficient discovery and optimization process for catalyst candidates amongst very large numbers of metal-ligand combina-

tions, we have adopted a three-tiered approach employing primary, secondary, and tertiary screening methodologies (Fig. 2).



► W. Henry Weinberg obtained a B.S. degree in Chemical Engineering from the University of South Carolina, and a Ph.D. degree in Chemical Engineering from the University of California, Berkeley, in 1971. After a postdoctoral year at the University of Cambridge, he joined the faculty of the California Institute of Technology in 1972. He was promoted to Associate Professor with tenure in 1974, and to Professor Chemical Engineering and Chemical Physics in 1977. He was the first Chevron Professor of Chemical Engineering from 1981 to 1986. He was a Visiting Professor of Chemistry at Harvard University in 1980, a Visiting Professor of Chemistry at the University of Munich in 1982, a Visiting Professor of Chemistry at the University of Pittsburgh in 1987–88, and a Visiting Professor of Materials at the University of Oxford in 1991. He assumed the position of Professor of Chemical Engineering, Materials Engineering, and Chemistry at the University of California, Santa Barbara, in 1989. He was appointed CTO of Symyx Technologies of Santa Clara, California, in 1996 and remains an Adjunct Professor at UCSB.

Professor Weinberg has presented over 350 invited lectures or seminars at various academic, industrial, and governmental organizations around the world during the past 25 years. During that same period of time, he has presented over 200 invited or contributed talks at various national and international conferences. He has authored or coauthored over 550 scientific papers that have appeared in refereed journals, as well as the book *Low-Energy Electron Diffraction: Experiment, Theory, and Surface Structural Determination* (Springer-Verlag, Heidelberg, 1986 with M.A. van Hove and C.M. Chan). All of these publications are related to various aspects of surface chemistry and physics, heterogeneous catalysis, or combinatorial materials science. He has served on numerous review panels for industrial and academic organizations, and for various governmental agencies (particularly, the Department of Energy and the National Science Foundation). Currently, he is on the Advisory Editorial Board of *Applied Surface Science* and *Journal of Combinatorial Chemistry*. In addition, he is the General Editor of the prestigious review journal *Surface Science Reports*. ■

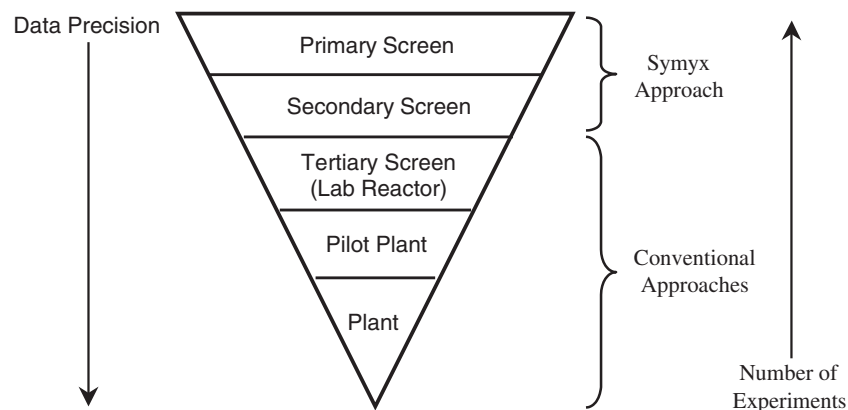


Fig. 2. Stages of catalyst discovery and optimization.

The Primary Screen

The purpose of a primary screen is an assessment of many thousands of metal-ligand-activator combinations for their potential to perform as olefin polymerization catalysts. Hundreds of polymerization reactions are performed each day at the microliter scale. The primary screen provides information to quickly identify “hits” (those candidates meeting a predetermined figure of merit from the screen) and serves as a filter to rule out metal-ligand combinations that perform poorly. In order to accommodate hundreds of polymerization reactions each day, it is often necessary to tolerate certain compromises regarding the quality of the data obtained from such a screen. One example of a primary screen currently used at Symyx is a 1-octene polymerization screen designed to discover new catalysts with potential for the production of ethylene- α -olefin copolymers. Insertion barriers for α -olefins are higher than for ethylene, and catalysts capable of polymerizing α -olefins would be predicted to copolymerize ethylene with the α -olefin. We therefore rationalized that an assessment of activated metal-ligand complexes for their ability to homopolymerize bulky α -olefins would serve as a meaningful primary screen for new catalyst discovery.⁹ We are aware that ethylene- α -olefin copolymerization catalysts that are incapable of successive α -olefin insertions will not be detected using this primary screen. Such a limitation is representative of a compromise for the sake of throughput. We adopted this approach believing that a rapid primary screen in which multiple arrays of metal-ligand combinations were assessed for their ability to polymerize 1-octene would provide sufficient numbers of new catalyst discoveries to offset such a limitation. Additionally, the use of a liquid α -olefin such as 1-octene in a primary screening format is convenient, as this allows liquid handling robots to rapidly deliver reagents and monomer to an array of reaction vessels. Furthermore, catalytically active metal-ligand combinations will produce soluble poly-1-octene products that

can be conveniently and rapidly manipulated at room temperature using a liquid handling robot. The 1-octene primary screen can be performed using real-time or post-reaction screening methods. Primary screening hits can then be investigated for their ability to copolymerize ethylene with 1-octene under more controlled and commercially relevant conditions in our secondary screen (*vide infra*).

The Preparation of Metal-Ligand Complexes for a Primary Screen

Inevitably, an archive of ligands and metal precursors is required for the preparation of metal-ligand complexes in high-throughput. At Symyx we have developed a substantial archive of diverse ligands specifically targeted for the preparation of diverse arrays of organometallic compounds. It is important to note that an archive of metal precursors that can readily react with a diverse ligand set is of equal importance to the ligand archive. Scoping studies, in which selected ligands are treated with a variety of metal precursors, are typically carried out in order to establish high-yielding routes to the targeted classes of metal-ligand complexes. Additionally, in order to offset any limitations in complexation chemistry across a diverse ligand library, our primary screens incorporate multiple metal precursors that encompass a variety of synthetic routes to each metal-ligand combination. Finally, multiple activation conditions offer additional opportunities for metal-ligand complexation to occur. Once again, we adopted this approach believing that a rapid primary screen in which multiple arrays of metal-ligand combinations were screened using multiple activation conditions would provide sufficient numbers of new catalyst discoveries to offset any limitations in complexation efficiency.

Our protocol for screening selected metal-ligand combinations starts with the layout of a 96-element ligand set that is

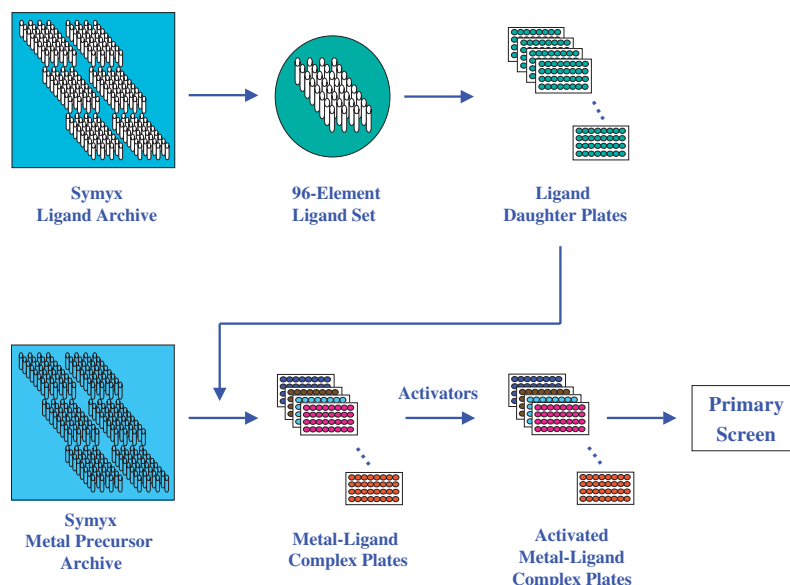


Fig. 3. The preparation of metal-ligand complexes for a primary screen.

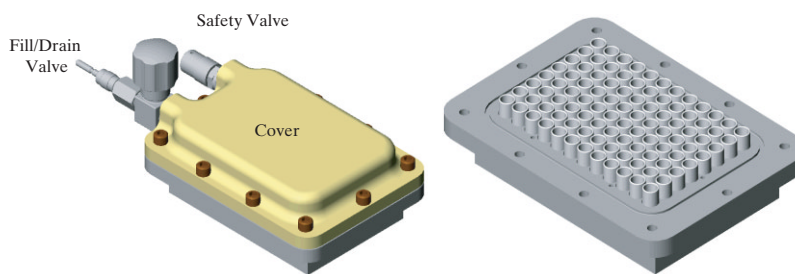


Fig. 4. Equipment for a postreaction primary screen.

replicated to create ligand daughter plates (Fig. 3). Addition of various metal precursors to each of these daughter plates creates the metal-ligand combinations that are ready for primary screening. The addition of multiple activation combinations in the presence of the monomer(s) initiates the screen. The layout of the 96-element library is designed using specially developed computer software Symyx Library Studio™ that generates a recipe file for automated execution of the library through the use of liquid-handling robots controlled using another custom software package (Symyx Impressionist™). All reagents and protocols are registered in a searchable database.

The Use of Postreaction Primary Screening

Postreaction primary screening employs high-throughput analysis of the resultant polymer products produced in a

primary screen (e.g., weighing for product yields or performing GPC or FTIR analysis). A typical format for a postreaction primary screen is shown in Figure 4, and comprises a metal plate housing an [8 × 12] array of 1 mL vials fitted with miniature stir-bars. The apparatus shown in Figure 4 can additionally be pressurized with monomer gases and heated to the desired screening temperature. Thus, simple and effective (co)polymerizations can be conducted to rapidly survey each metal-ligand combination for its potential as an olefin polymerization catalyst. For example, Figure 5 illustrates the results of a postreaction primary screen for 1-octene polymerization performance for an array of 24 ligands combined with $\text{Hf}(\text{CH}_2\text{Ph})_4$ and activated under four different conditions. The figure of merit in this screen is the conversion of 1-octene to poly(1-octene). The results demonstrate that this is a highly efficient method of identifying new catalyst classes.

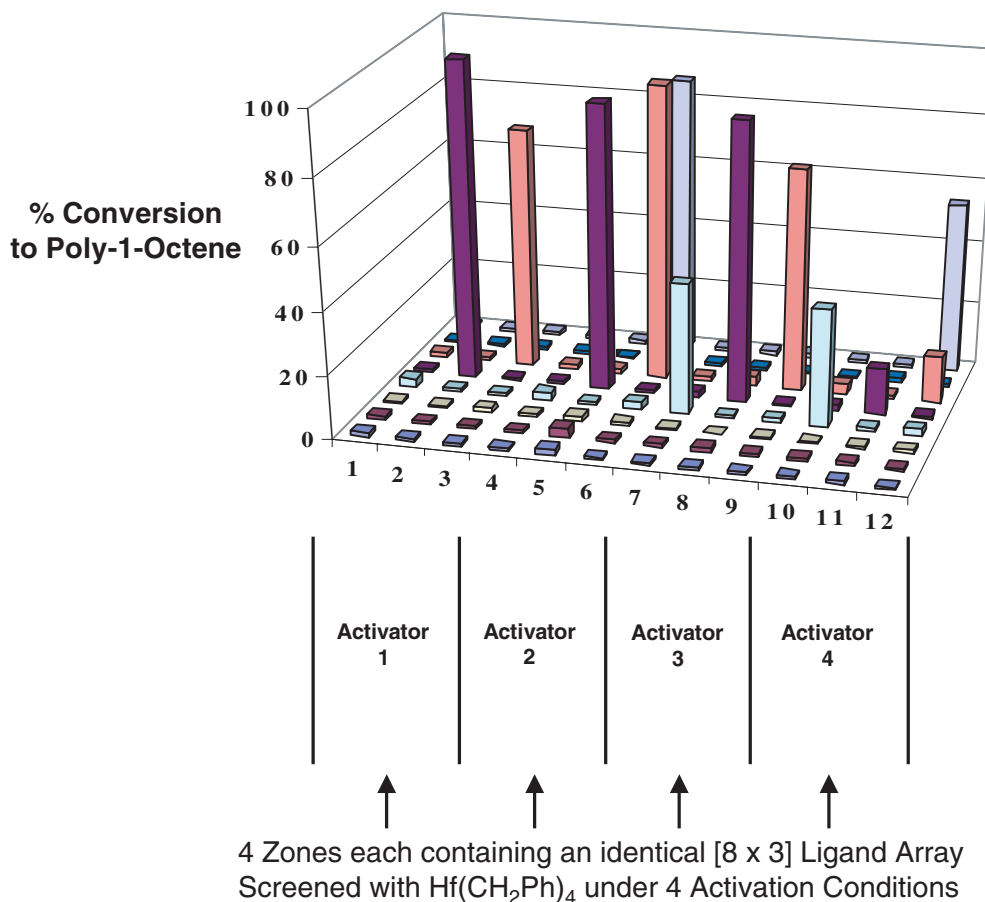


Fig. 5. Poly-1-octene conversion data from a postreaction primary screen.

The Use of Infrared Thermography as a Real-Time Primary Screen

Digital imaging using infrared thermography (IRT) represents a powerful and rapid method of primary screening to assess the relative activities of catalyst arrays in real time. The application of IRT techniques have been previously reported¹⁰ and can be used to monitor nearly any chemical reaction in which heat transfer takes place. In a typical experiment using IRT, an array containing the catalyst mixtures to be studied is placed inside a reactor and is situated so as to be in optical contact with an IR transparent window mounted in the top of the reactor and a digital infrared camera located above the window. At the commencement of the experiment the infrared camera begins to record digital images of the array at a prescribed rate and period of time. The IR camera records temperature changes associated with heat evolution and, by inference, catalyst activity for the entire array simultaneously. Figure 6 shows representative data from a screening experiment in which a 96-element library containing a $[8 \times 3]$ metal-ligand array (repeated in four zones) was activated

using four distinct activation conditions and exposed to ethylene gas for a one-hour time period. The digitally enhanced image on the left side of Figure 6 shows thermal changes that occurred in the wells of the array where the temperature had risen above background (shown in green) at 50 minutes into the experiment. The collection of such digital images (frames) can be viewed sequentially in the form of a movie where active catalysts can be easily identified from those that are inactive. Alternatively, the data contained in each image can be processed by subtracting the temperature profile of a nominally room temperature control well from each well in the array to yield the change in temperature for each well as a function of time. Such ΔT versus time relationships can be plotted and integrated to obtain a figure of merit for catalyst activity (notwithstanding the nature of the material produced) and also provide valuable kinetic information about the evolution of catalyst activity during the course of the experiment. The right side of Figure 6 shows a plot of the relative activity (in arbitrary units of integrated emission per hour) for each well in an array over the entire experiment. The plot was constructed from processing a series of digital images such as the

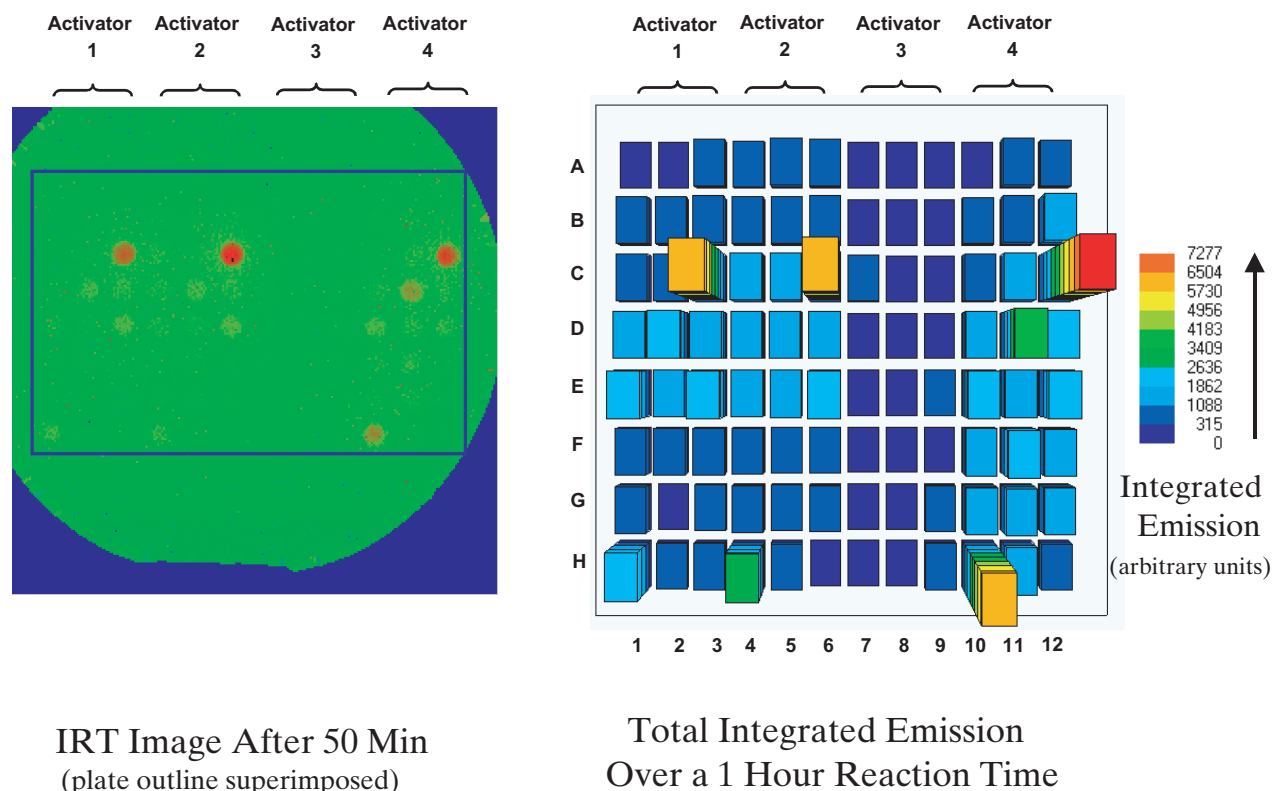


Fig. 6. Data from a primary screen using infrared thermography.

one shown on the left side of Figure 6. This method of data analysis provides a convenient and accurate means of determining catalyst activities obviating the need to sequentially view all the frames captured and can be readily automated.

A more sophisticated apparatus for IRT-based primary screening has been recently described.¹¹ The device shown in Figure 7 employs a high-pressure reactor that houses up to six 96-element catalyst arrays nested in a rotary carousel with an IR viewing window. A unique feature of this design is a series of injectors that allow reagents (such as catalyst activators) to be added *in situ* to the wells of the arrays while under pressure. In a typical screening experiment for an assessment of metal-ligand-activator combinations for ethylene polymerization/oligomerization activity, the catalyst arrays are loaded onto the carousel, the door to the apparatus (which is shown open in Fig. 7) is then sealed, and the reactor is pressurized with ethylene. When the system has reached temperature and pressure equilibrium the arrays can be selectively disengaged from the carousel and moved underneath the injector banks where additional chemical components such as activators can then be added. The arrays are then returned to the carousel and are rotated in sequence into a position directly underneath an opening that is in optical contact with a digital IR camera mounted above the reactor. As each array comes into optical

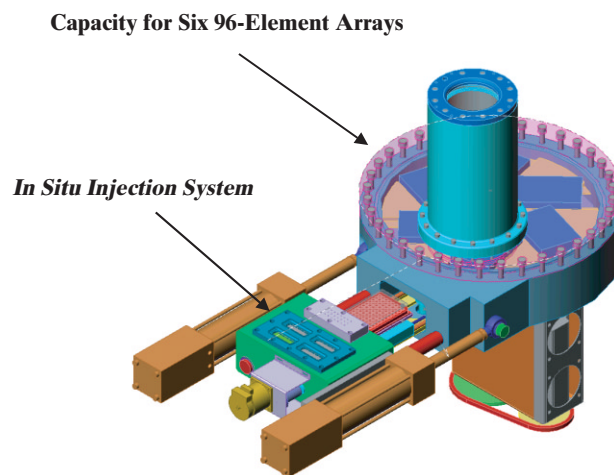


Fig. 7. Infrared screening carousel with *in situ* reagent addition capabilities.

view of the IR camera, the rotation is paused briefly to allow the IR camera to record a digital image and is then resumed to allow the next array to be digitally photographed. The cycle of rotation/pause/photograph is repeated a predetermined number of times over the course of the experiment and results in the generation of a data stream of digital images at differ-

ent points in time for each the arrays. This stream of images is then deconvolved to produce individual time-resolved image streams for each array, which can then be viewed in the form of a movie or subjected to data analysis as described above. The entire system is fully automated to screen close to 600 metal-ligand-activator combinations per hour.

The Secondary Screen

The most promising metal-ligand combinations identified using either of the aforementioned primary screening formats are then subjected to our secondary screen in which the catalyst performance properties for the targeted application are assessed using more commercially relevant conditions. Metal-ligand combinations that meet predetermined performance criteria in these initial secondary screens are then subjected to iterative rounds of secondary screening aimed at rapid

optimization through the structural elaboration of the newly discovered ligand class. Secondary screens are therefore intended to improve upon the catalyst performance and, importantly, to establish relationships between catalyst structure and catalyst performance.

As previously discussed, the rationale for the 1-octene polymerization primary screen is that catalysts capable of polymerizing bulky α -olefins would be predicted to copolymerize ethylene with the α -olefin to produce a copolymer. However, because commercial solution processes for the production of ethylene- α -olefin copolymers operate at temperatures in excess of 100°C, high temperature stability is an additional requirement for new catalysts. Therefore, in our secondary screen we performed ethylene-1-octene copolymerization experiments at 130°C. In order to meet the throughput required to perform secondary screening on primary screening discoveries within our program, we have built and developed our own 48-cell parallel polymerization reactor (Fig. 8).¹² Although this parallel

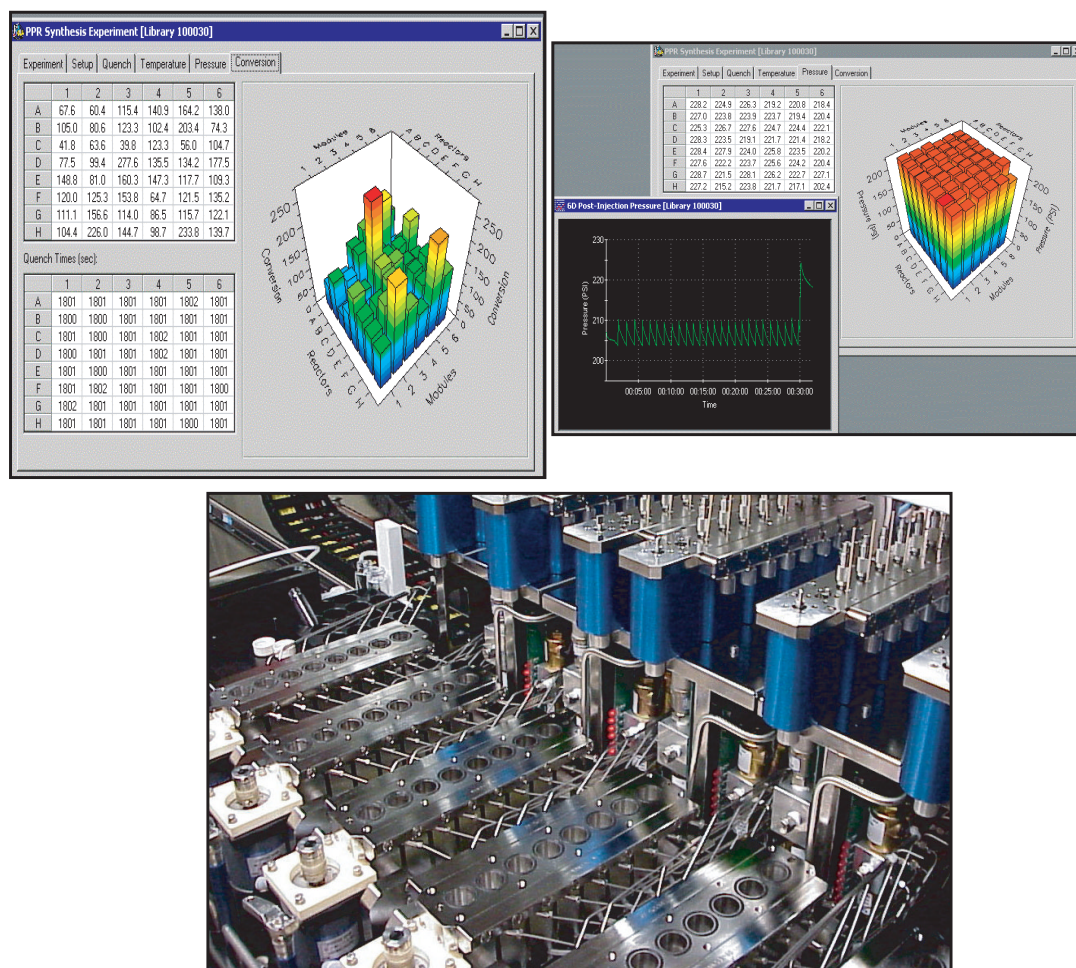


Fig. 8. Forty-eight-cell parallel pressure reactor and associated software for secondary screening.

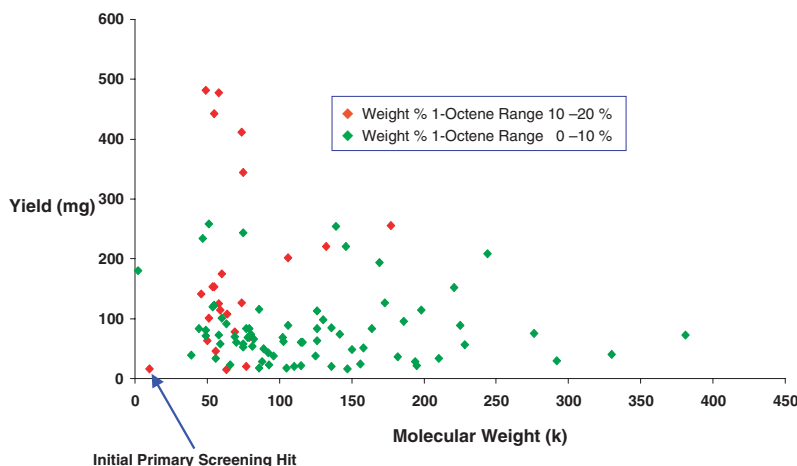


Fig. 9. Results from a secondary screen. Ethylene-1-octene copolymerizations using 96 ligand/ $\text{Hf}(\text{CH}_2\text{Ph})_4$ combinations (performed at 130°C).

reactor has been described elsewhere, the important features of this instrument are worth mentioning. The instrument consists of 48×15 mL individually controlled high-pressure batch reactors with magnetically coupled mechanical overhead stirring. Each reactor cell possesses its own pressure and temperature control, and gaseous monomer and quench gas feed lines. Reagent stations with liquid dispensing robots are situated alongside the reactors (and are used to mix reagents where necessary) and add reagents to each cell of the reactor. Because reagents can be added to the reactor cells at high pressures and high temperatures, metal-ligand combinations can be prepared, activated, and quickly injected into each cell at the equilibrated temperature and pressure of the copolymerization. Moreover, upon catalyst injection, real-time temperature, pressure, and ethylene uptake measurements can be made on each of the 48 cells simultaneously. Thus 48 individual polymerization reactions can be monitored in real-time under conditions that provide meaningful information about the performance capabilities of each catalyst at high temperatures. Typically, 100–250 mg of copolymer product is targeted from our secondary screening studies. Such a quantity allows a comprehensive analysis of the polymer properties but will not foul the reactor or prevent the passage of the monomer to the catalyst sites during the polymerization experiment. Figure 9 shows the results of an ethylene-1-octene secondary screen performed on a focused 96-member ligand library containing significant structural variations on a primary screening hit. The copolymerizations were carried out at 130°C . The data displayed in Figure 9 illustrates that for this class of catalyst there is a strong dependence of polymer yield, molecular weight, and 1-octene incorporation on the ligand structure, with many of the catalysts demonstrating significant perfor-

mance improvements over the initial primary screening discovery. Promising candidates or “leads” that pass this additional filter are screened in conventional laboratory batch reactors (tertiary screen), the stage where the conventional catalyst research begins.¹³

Rapid Analytical Techniques

Ideally, the analytical technique should not represent the limiting step of a high-throughput program. The analytical techniques chosen must therefore possess a throughput that is commensurate with the throughput of the given primary or secondary screen. The analyses of products from a primary screen therefore represent the most challenging task, as hundreds of products will be generated each day. The nature of the primary screen and the associated analytical screen should be considered very carefully because they will certainly govern the throughput of the program. The primary screen and associated analytical technique should work together to provide the *minimum* number of critical parameters necessary to ascertain the potential of each candidate. For example, infrared thermography provides a simultaneous (or parallel) measurement of the catalyst activity in real-time for each metal-ligand-activator combination. In contrast, for postreaction screening we have developed a Rapid \diamond GPCTM technique that can provide molecular weight and conversion data at a rate of 90 seconds per sample polymer.¹⁴ The resolution of this technique is compromised somewhat with such a high throughput, but the quality of the data obtained is sufficiently accurate for a primary screen. Figure 10 shows the Rapid \diamond GPCTM instrument developed at Symyx. Additionally, in order to ascertain

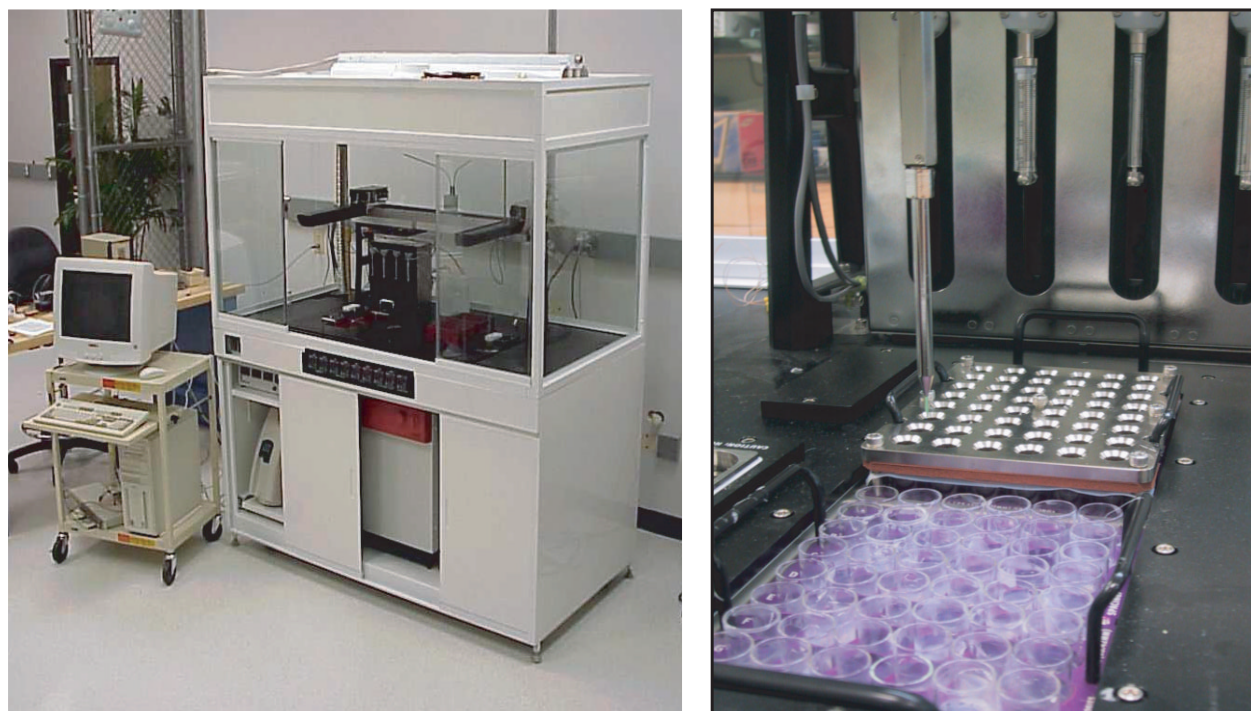


Fig. 10. The Rapid GPC™ developed by Symyx Technologies.

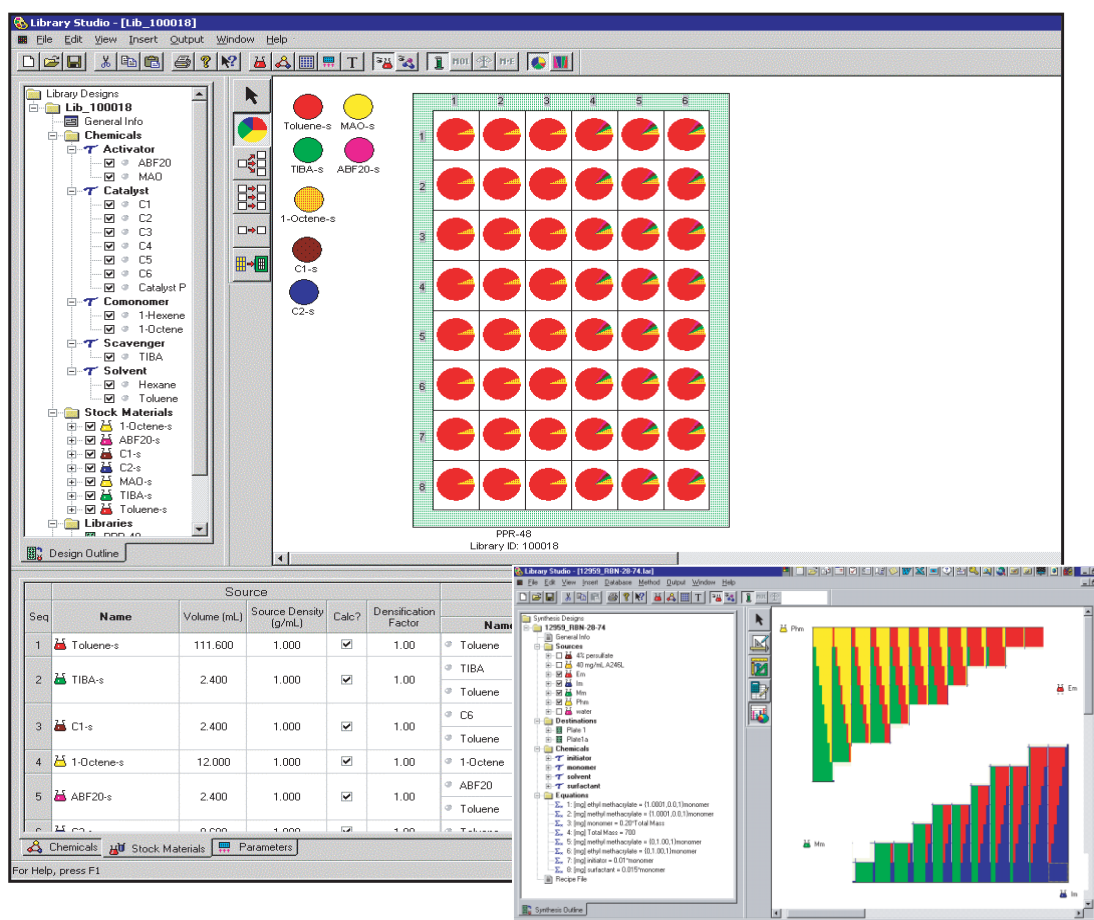


Fig. 11. Screenshot of Library Studio™, the Symyx tool for designing and visualizing libraries.

the 1-octene content of the copolymers produced in the secondary screen, we have developed a Rapid \diamond FTIRTM technique that operates with a throughput of two minutes per sample.¹⁵ Polymer samples from primary and secondary screens are prepared for analysis using liquid handling robots driven by Symyx software (ImpressionistTM).

Data Management and Software

The successful implementation of a high-throughput synthesis and screening program requires the development of sophisticated software tools. The process begins at the library design phase, where the amounts of each reagent used in the formulation of the 96-well array have to be calculated based on information that is stored in a database (such as molecular weight, concentrations, and density). Ideally, this tool will allow the chemist to visualize the amounts of each reagent to be added to the vials in order to readily visualize the design of the library (Fig. 11).¹⁶ The software must allow the chemist to vary the process variables used in the chemical synthesis (e.g., the orders, rates, and temperature of addition) and to convert these instructions into machine language to control the robots

used for reagent dispensing. For executing the screen, additional tools are necessary to control and record the high-throughput screening experiments and the performance characteristics of each catalyst formulation. Finally, a database and database interfaces must be created to record information related to library synthesis and screening experiments in such a way as to allow for high-level data mining. The development of this software capability is one of the more complicated and expensive aspects of creating a useful high-throughput infrastructure.

Conclusion

A fully integrated high-throughput screening workflow for the discovery of new polyolefins catalysts has been implemented at Symyx. The workflow (Fig. 12) employs many of the principles discussed in this section: design of the libraries on a computer, automated delivery of metal precursors and ligands into the reactors by a robot, primary screening at a level of more than 1000 reactions per day, secondary screening with online monitoring of reaction rates, all supported by rapid and highly automated polymer characterization tools. We have used this

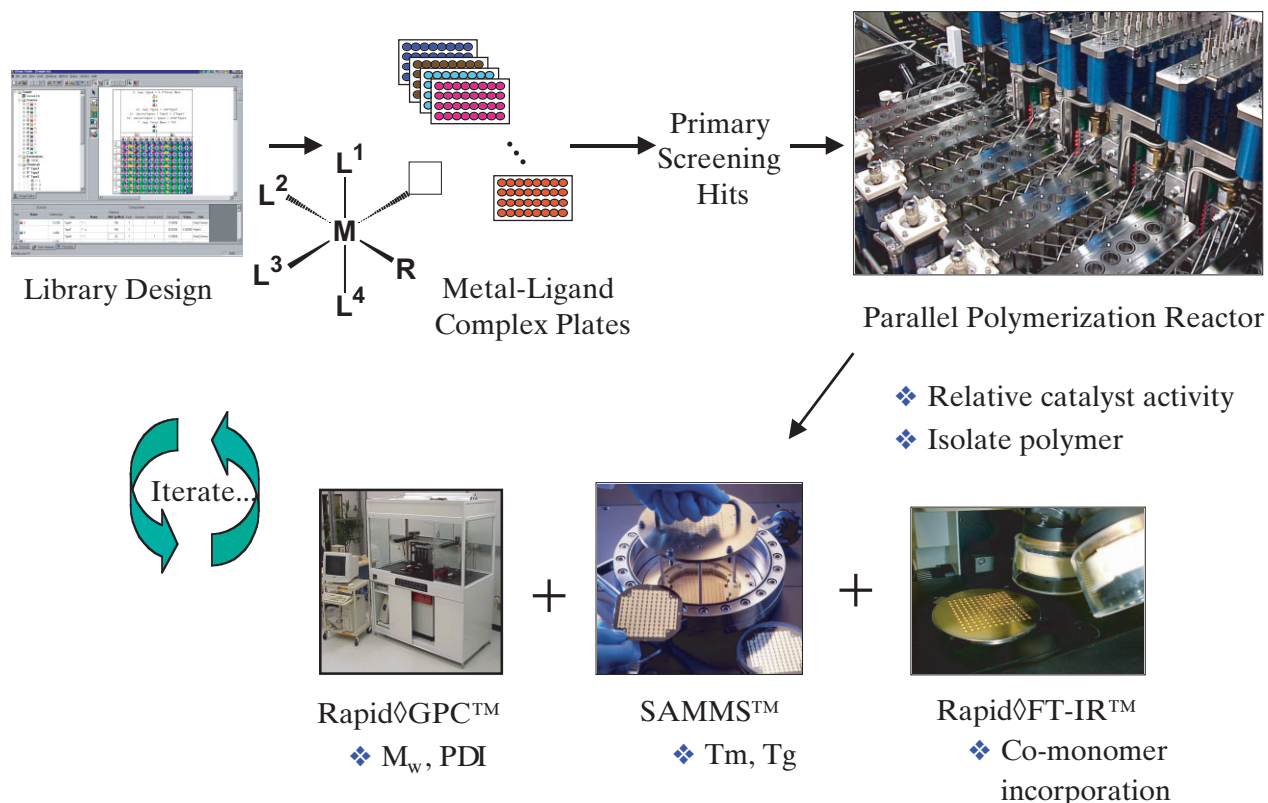


Fig. 12. Discovery and optimization screening workflow for new olefin polymerization catalysts.

high-throughput infrastructure to screen many thousands of metal-ligand combinations for a variety of targeted catalyst applications. Many interesting new catalyst classes have been discovered using this technology.

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