Efficient Assays for Combinatorial Methods for the Discovery of Catalysts

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The activities associated with chemical research and development often involve a significant manual component and specialized skills. Thus, the typical organic synthesis in the laboratory requires many operations such as weighing, setup of equipment, filtration, and distillation. Similarly, assessing the properties of interest, such as the pharmacological activity of organic compounds or the superconductivity of metal oxides, is a complex endeavor. This high level of manual human involvement has been maintained even in the computer age, at a time when many mental processes such as complex calculations as well as control of equipment are highly automated. The discovery of new compounds with useful properties has therefore been fairly slow and expensive.

The desire to change all this has led, first in the area of pharmaceutical research, to the development of combinatorial methods in chemistry.[1] These methods target two interdependent aspects of the discovery process: synthesis and characterization. By learning from the powerful paradigm of the immune system chemists initially targeted the automated synthetic combination of appropriate organic building blocks such as amino acids. Even random combinations of just 20 amino acids can produce large numbers of different oligopeptides; for example, one can prepare 64 million different hexapeptides. One can distinguish the generation of building-block combinations on mixtures of beads as well as in rapid parallel synthesis in miniature reactors such as on 96-well plates. The former allow the formation of vast numbers of different compounds, but active beads must be identified by some tracking method. Parallel synthesis in discrete reactors usually limits the number of possible products, but the products are identified by position. The characterization of the resulting thousands or millions of new products poses enormous challenges for creative assays. Some of the earliest assays involve binding studies; for example, beads bearing the products of solid-phase organic synthesis can be exposed to receptors attached to fluorescent or colored chromophores. Strong binding is detected by the optical change of the active beads. The promise and excitement associated with the combinatorial approach has led to explosive growth in this field; nearly every major drug company now has an active effort in combinatorial organic chemistry.

In comparison to the developments in molecular organic chemistry, other fields of chemistry and materials science have not yet experienced such a broad effort to accelerate the scientific discovery process.[2] There is, however, one notable exception: the American company Symyx, which has recently become a combinatorial pioneer in many areas of materials synthesis and catalysis. There are interesting differences between the synthesis of organic compounds by the permutation of molecular building blocks (in linear, cyclic, starlike, or other arrangements) and the preparation of materials such as oxide superconductors or X-ray phosphors. The latter are made by mixing different quantities of starting materials; diversity can be generated by gradual changes in composition as well as processing conditions. Symyx's now famous "library" of thousands of luminescent spots on a single wafer demonstrates the power of parallel synthesis and array-based assays; the optical properties of all spots can be assessed simultaneously, even with the human eye.[3] Two major synthetic methods have been developed so far: 1) gas-phase deposition on wafers with control of deposition time and masking to build the array (see above), and 2) liquid dosing into miniature wells,[4] followed by some thermal and/or reactive processing.

Will it be possible to create new catalysts with combinatorial approaches? Nature teaches us that the answer is clearly "yes": The powerful natural catalysts, enzymes, are basically combinations of the natural amino acids in different sequences and sizes. Recent work has been focused on the design of combinatorial enzyme libraries that aim to improve features such as temperature or chemical stability.[5] In a very creative use of natural systems, Schultz and Lerner have recently demonstrated that antibodies can be made catalytically active when they are raised against molecular models of the presumed shape of the transition state of a chemical reaction.[6] Catalytic antibodies can have chemoselectivity and enantioselectivity, with high activity. In an extention of this approach, powerful chemical selection tools can be applied to antibody catalysis to find active systems.[7]

In homogeneous molecular chemistry, where discrete building blocks can be assembled, several recent examples of automated or semiautomated catalyst discovery have been reported.[8, 9] Different core structures have been assembled on beads, and diversity was introduced by the attachment of

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combinations of building blocks to the cores. Several of these systems were then metalated and resulted in a set of catalyst candidates. In an early example, Ellman reported the solid-phase synthesis of 2-pyrrolidinemethanol ligands that were examined in enantioselective addition reactions after cleavage from the support.[10] The high-throughput screening of metal catalysts for an asymmetric C–H insertion that involved diazo compounds was achieved by Burgess and co-workers,[11] and disulfonamide-based chelating ligands were prepared in a parallel synthesis and screened in solution for the enantioselective addition of diethylzinc to aldehydes.[12]

Hoveyda and co-workers showed that ligand diversity can be developed without the need to synthesize all possible permutations of building blocks, which thus reduces dramatically the synthetic efforts for catalyst development.[13] In this example of the titanium-catalyzed enantioselective addition of trimethylsilylcyanide to epoxides, various dipeptide Schiff base ligands were synthesized. It was possible to vary the building blocks at just one position at a time on the core structure in order to improve catalytic activity and selectivity. The final catalyst was the combination of all the optimized ligands at the various positions. This counterintuitive result suggests that there may be other examples where cooperativity in metal coordination spheres may be less important for catalytic behavior. It was also shown that this ligand discovery process can also be performed in a very efficient way on a solid support.[14] Sigman and Jacobsen found synergistic effects between components of Schiff base catalysts for the highly enantioselective asymmetric Strecker reaction.[15]

In another peptide-based assembly method a library of phosphane-containing peptides was used to complex rhodium and was shown to give moderate enantiomeric excess in the asymmetric hydrogenation of enamide.[16] Alternative approaches include the one-pot screening of a library of prochiral substrates with a chiral catalyst.[17] The first examples of combinatorially prepared inorganic catalysts have also been reported. Hill and Gall synthesized various polyoxometalates for the aerobic oxidation of the mustard analogue tetrahydrothiophene from stock solutions that contained precursors such as Na_2WO_4, Na_2MoO_4, and Na_2HPO_4.[18]

As demonstrated in the above example,[13] the creative design of the catalytic assay is a key element in the development of effective "algorithms" for the discovery of new homogeneous catalysts. It would be intriguing to create truly parallel means to detect catalytic activity in arrays. The enthalpy changes associated with many chemical reactions have been observed with infrared cameras to achieve this feat. The advent of sensitive thermal imagers (infrared cameras) with array detectors also allows the arrays of reactive solutions to be monitored. Reetz and co-workers[19] applied this concept in the study of the homogeneous enantioselective acylation of a chiral alcohol (1-phenylethanol) that was catalyzed by immobilized lipase (from *candida antarctica*), as well as in the enantioselective ring opening of chiral epoxides with transition metal salen catalysts (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion). The reactants were placed in arrays of small vials, and the PtSi-based thermal imager (staring into the vials from above) could clearly distinguish active from nonactive vials. An extra twist was provided for the detection of enantioselectivity of the catalysts: The array of reactants included the two different enantiomers of substrate, for which the catalysts showed drastically different activities. Crabtree and co-workers recognized the attractive features of color changes for parallel assay purposes and developed reactive dyes that contain an electron donor and acceptor linked by a reactive functionality such as C=C.[20] When this functionality is changed during the catalytic reaction, for example, by hydrosilation, the electronic connection between the donor and acceptor groups is interrrupted, and the color of the dye fades (Figure 1). This elegant approach promises to be amenable to many other catalytic reactions.[27]

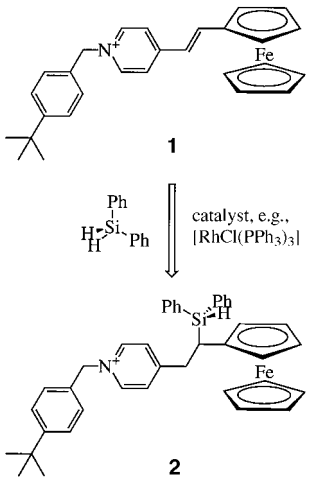

Figure 1. The use of a reactive dye **1** for the detection of hydrosilation activity. The dye changes its color from deep purple to light yellow following hydrosilation with a homogeneous catalyst within a few minutes.[20]

Very different types of challenges await the practitioner of heterogeneous catalysis. While arrays of heterogeneous catalysts such as metal alloys or mixed oxides could be automatically constructed along the lines developed by Symyx and others (gas-phase deposition or liquid dosing), the assay of catalytic activity is nontrivial. Even if one accepts the presence of different surface areas and dispersions of active material, which can lead to significant errors in the determination of "intrinsic" activity such as turnover frequency, an efficient determination of activity and selectivity under realistic conditions might require different solutions for every different catalytic system under study.[21] Several promising developments in this area have recently been reported. Recent work by Morken and co-workers has extended the earlier work of Willson[22] with heated catalyst pellets (metals on alumina were used to oxidize hydrogen), and focused on the heat evolved from several thousand encoded beads that were partially immersed in a reactive solution for an acylation reaction.[23]

In a recent interesting development Maier and co-workers showed that thermal imaging can be a very sensitive means of detecting activity in positional catalytic libraries that contain only about 200 μg of catalyst on each position.[24] Tiny wells in slate (chosen for its low thermal reflectivity to avoid

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interference) were filled with sol–gel precursor solutions for amorphous microporous mixed-metal oxides of different compositions, which were processed to yield an array of catalyst candidates (Figure 2). A thermal image of the whole

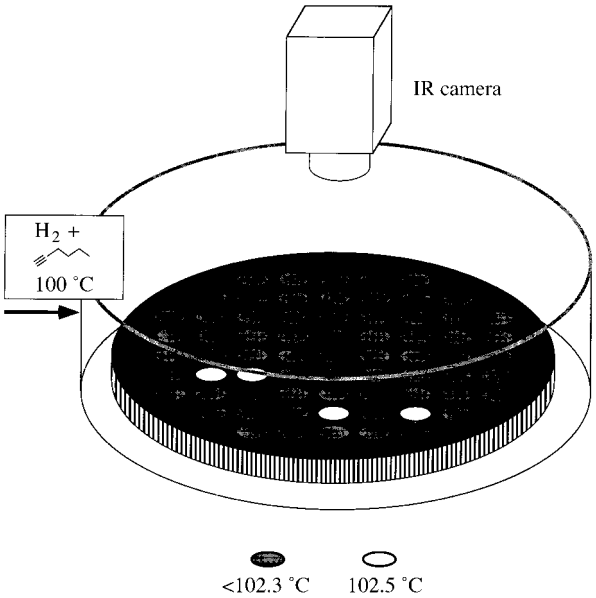

Figure 2. The arrangement used for thermal imaging of the hydrogenation activity of catalyst spots (ca. 200 μg per spot) on a slate substrate. The catalysts were prepared by the combination of titania or silica sols with solutions of metal salts in the slate wells, followed by heating to 250 °C. The IR camera detects temperature differences as small as 0.1 °C.[24]

array without substrate was stored and subsequently subtracted from the images of the array under operation. This technique allowed Maier et al. to minimize the effect of different thermal emissivities of the catalyst wells, such that they could detect very small temperature differences associated with catalytic activity. Thermal imaging was shown to offer convenient and fast parallel assays of whole catalyst libraries, in this case for the hydrogenation of 1-hexyne at 100 °C and the oxidation of isooctane and toluene at 350 °C. An obvious limitation of thermal imaging is the absence of chemical information about the products generated by the catalysts. However, it might be possible to use the emission or absorption of IR radiation by the reaction products to achieve this goal.

Other strategies have been shown to provide information on chemical selectivity together with information on catalytic activity. Mallouk and co-workers demonstrated that metal alloy electrocatalysts could be optimized by using the production of protons during the electrochemical oxidation of methanol in a fuel cell.[25] An elegant technique based on a fluorescent pH indicator allowed the researchers to identify active catalyst spots (Figure 3). These spots were generated by deposition of different metal salt solutions at various ratios with a commercial ink jet printer, followed by reduction with $NaBH_4$. Another important recent development is the detection of catalytic reaction products that evolve from an array of solid catalysts on a porous support in a pseudo-parallel fashion by using laser ionization techniques (Figure 4).[26] This approach addresses in an effective way the

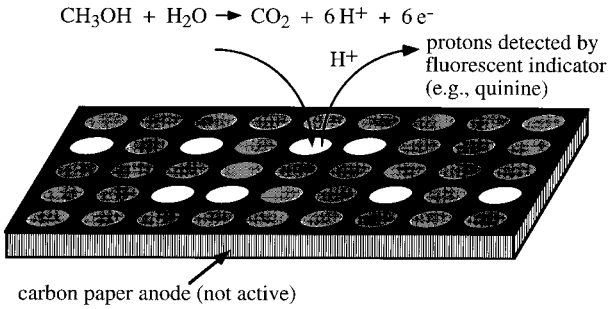

Figure 3. Ternary and quaternary arrays are used for the anodic oxidation of methanol in an aqueous indicator solution. A fluorescence indicator such as quinine shows the evolution of protons near the anode over the most active catalyts spots.[25]

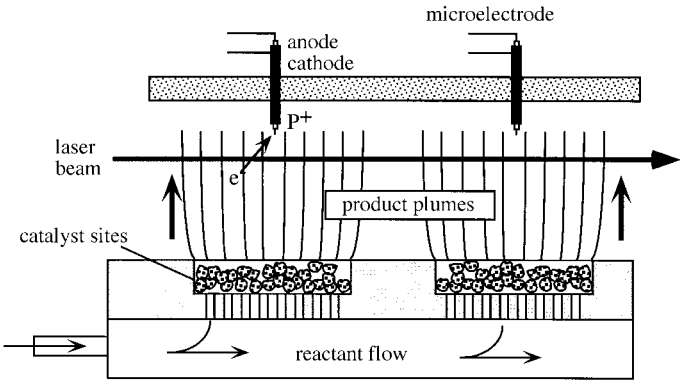

Figure 4. High-throughput screening of catalyst libraries with laser-induced resonance-enhanced multiphoton ionization for selective detection of reaction products. In this case, dehydrogenation of cyclohexane to benzene was detected. The latter was selectively photoionized by pulsed, tunable ultraviolet light in the vicinity of the catalytic sites (5 × 5 mm) of the array. The laser generates photoions P^+ and photoelectrons depending on the bias voltage.[26]

great need for the identification of reaction products that emanate from positional catalyst libraries.

In summary, following the revolutionary developments in pharmaceutical science, combinatorial approaches are now being explored in such diverse areas as materials design and homogeneous and heterogeneous catalysis. The issues associated with the parallel synthesis of many materials, as well as their structural and physical characterization in an efficient manner will continue to challenge the creativity of scientists and engineers involved in this exciting field.

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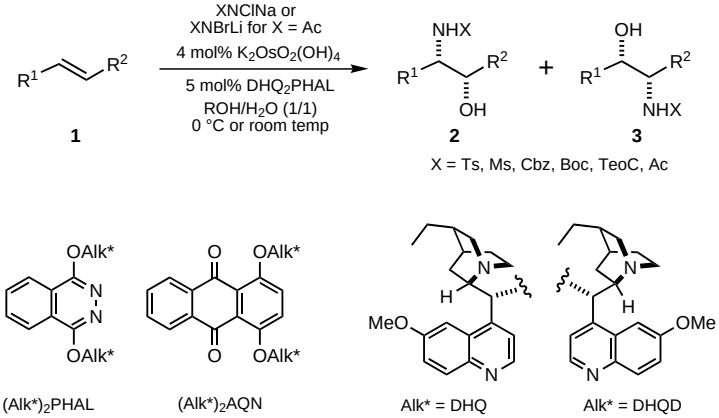
Sharpless Asymmetric Aminohydroxylation: Scope, Limitations, and Use in Synthesis

Peter O'Brien*

Since Sharpless' seminal contribution in 1996,[1] the catalytic and asymmetric conversion of alkenes into enantiomerically enriched N-protected amino alcohols [asymmetric aminohydroxylation (AA)] has rapidly become an extremely useful process. Using a reaction that is a close cousin of asymmetric dihydroxylation,[2] it is now possible to prepare amino alcohols (with different N-protecting groups) in good yields and high enantiomeric excesses from a range of alkene types. This is important since the β-amino alcohol functionality is found in many biologically active compounds and is therefore considered an important pharmacophore. Indeed, a large proportion of the recent papers on asymmetric aminohydroxylation have focussed on its application for the synthesis of biologically active compounds; these are summarized at the end of this article. The main purpose of this highlight is however to compare the yields, regioselectivities, and enantioselectivities obtained by using the different types of AA reactions. In addition, it is hoped that the present discussion will provide useful guidelines for those using Sharpless AA in synthesis.

Currently, there are six different methods available for carrying out asymmetric aminohydroxylations. All of the methods have originated from the Sharpless group and they differ only in the N-protecting group (*p*-toluenesulfonyl (Ts),[1] methanesulfonyl (Ms),[3] benzyloxycarbonyl (Cbz),[4] *tert*-butoxycarbonyl (Boc),[5, 6] 2-trimethylsilylethoxycarbonyl (TeoC),[7] or Ac[8]) that is introduced (Scheme 1). Each



Scheme 1. Overview of Sharpless asymmetric aminohydroxylation (AA).

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