Catalyst discovery through combinatorial chemistry

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Combinatorial chemistry and high-throughput strategies can be used to identify effective small-molecule chiral catalysts. Infrared thermography has been used recently as the means to identify the most active catalyst.

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Chemists have always been in awe of biological catalysts. This is not a surprise — enzymes are impressively efficient and selective, and, as would be expected from any discriminating catalyst, enzymes are remarkably specific as well. What happens if we want to catalyze a reaction that nature has not developed an enzyme for? A significant problem in modern chemistry is to identify small-molecule catalysts that emulate enzymes in their ability to facilitate chemical transformations. Finding such catalysts, however, has not been easy. The main reason for this difficulty is that small energy differences typically separate an inactive or nonselective catalyst from one that is potent and selective (~1–2 kcal/mol variance in transition state energy). Such differences often arise unpredictably and from subtle variations in the catalyst structure, reaction conditions, substrate structure or any combination of these reasons. Although a mechanistic knowledge is useful in allowing chemists to appreciate the general contours of a reaction course, we do not know enough (and we might never know enough) to fully 'design' catalysts that can reliably initiate a particular reaction efficiently and selectively. Once we do discover an attractive catalyst, it is not effective for a very wide range of substrates. This is not surprising, as a selective catalyst that recognizes a certain structural type with great fidelity cannot, by nature, recognize and associate with a broad range of substrates.

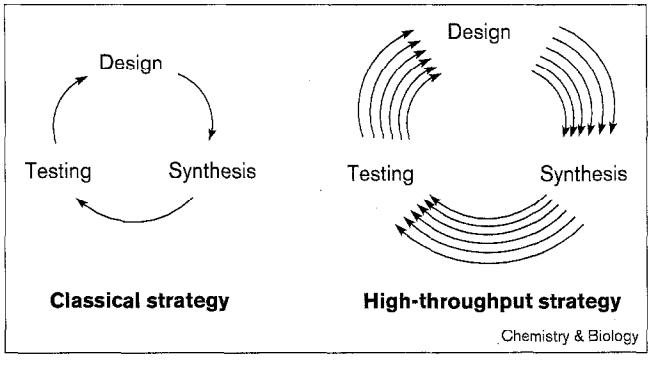
To address the above questions, chemists in search of better ways to identify catalysts have turned their attention to recent advances in combinatorial and high-throughput strategies. This shift in focus arises from the realization that if it is often the screening of a large number of potential catalysts that leads to a discovery then why not do it systematically and more efficiently, and cover a broader range of catalyst candidates? The other important reason for the adoption of diversity-based approaches is that screening a large number of compounds will allow chemists to identify optimal catalysts for a particular substrate and thus overcome the problem of generality that is usually posed when a limited number of candidate catalysts is available. Combinatorial and related strategies have therefore been utilized recently in investigations in catalyst discovery and development [1].

The search for therapeutic agents and asymmetric catalysts share a number of facets. Traditionally, both fields have relied on iterative approaches in which a single entity is designed, synthesized and tested. The cycle is repeated until a compound is obtained that has the desirable levels of enantioselectivity or activity. In contrast, as illustrated in Figure 1, a high-throughput strategy enables one to generate and test simultaneously notably larger numbers of candidates, potentially reducing the entire search cycle to one or two iterations. Furthermore, the discovery of catalysts through combinatorial libraries poses problems that are absent in a search for a biologically active molecule. Selection of effective catalysts requires an assay that measures kinetics and turnover, whereas identification of effective drugs entails selection on the basis of the thermodynamics of binding [2]. For drugs, the binding event provides a record of an interaction: in a bead-based library, use of a labeled substrate results in a labeled bead. A requirement for active catalysts is that the reaction product dissociates itself from the catalyst, thereby precluding a similar reporting event and raising a difficulty in screening large split-pool combinatorial libraries.

Catalyst screening by parallel synthesis

Such difficulties have caused researchers to shy away, at least initially, from screening large collections of molecules available from split-pool synthesis. Instead, many have employed focused libraries prepared through parallel synthesis. Research in our laboratories indicates that if

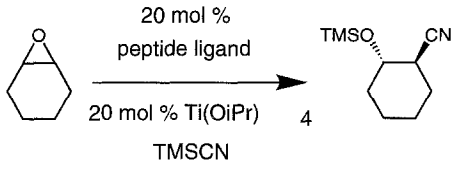
Figure 1

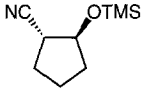
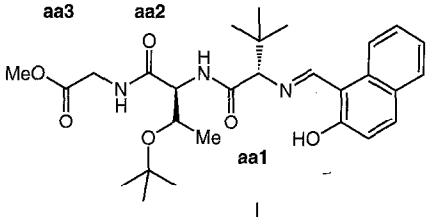
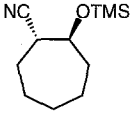
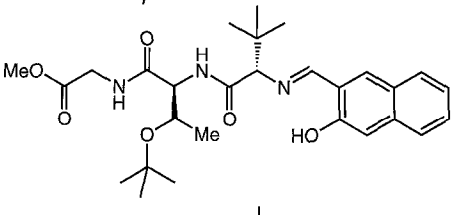
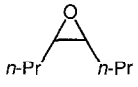
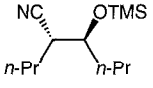
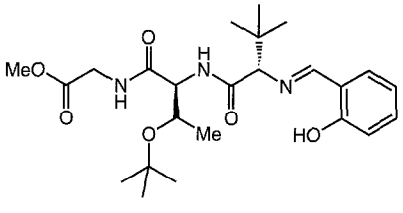


The classical strategy versus high-throughput strategy for the identification of therapeutic agents and catalysts.

Table 1

Optimized ligands for Ti-catalyzed asymmetric addition of TMSCN to epoxides.

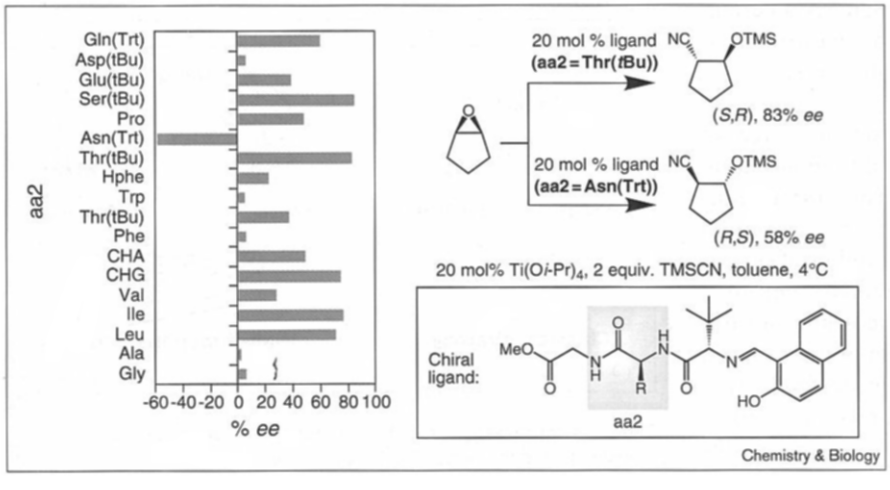


Entry	Substrate	Product	*ee* [%]	Yield [%]	Optimized ligand
1			83	72	
2			84	68	
3			78	69	

ee, enantiomeric excess.

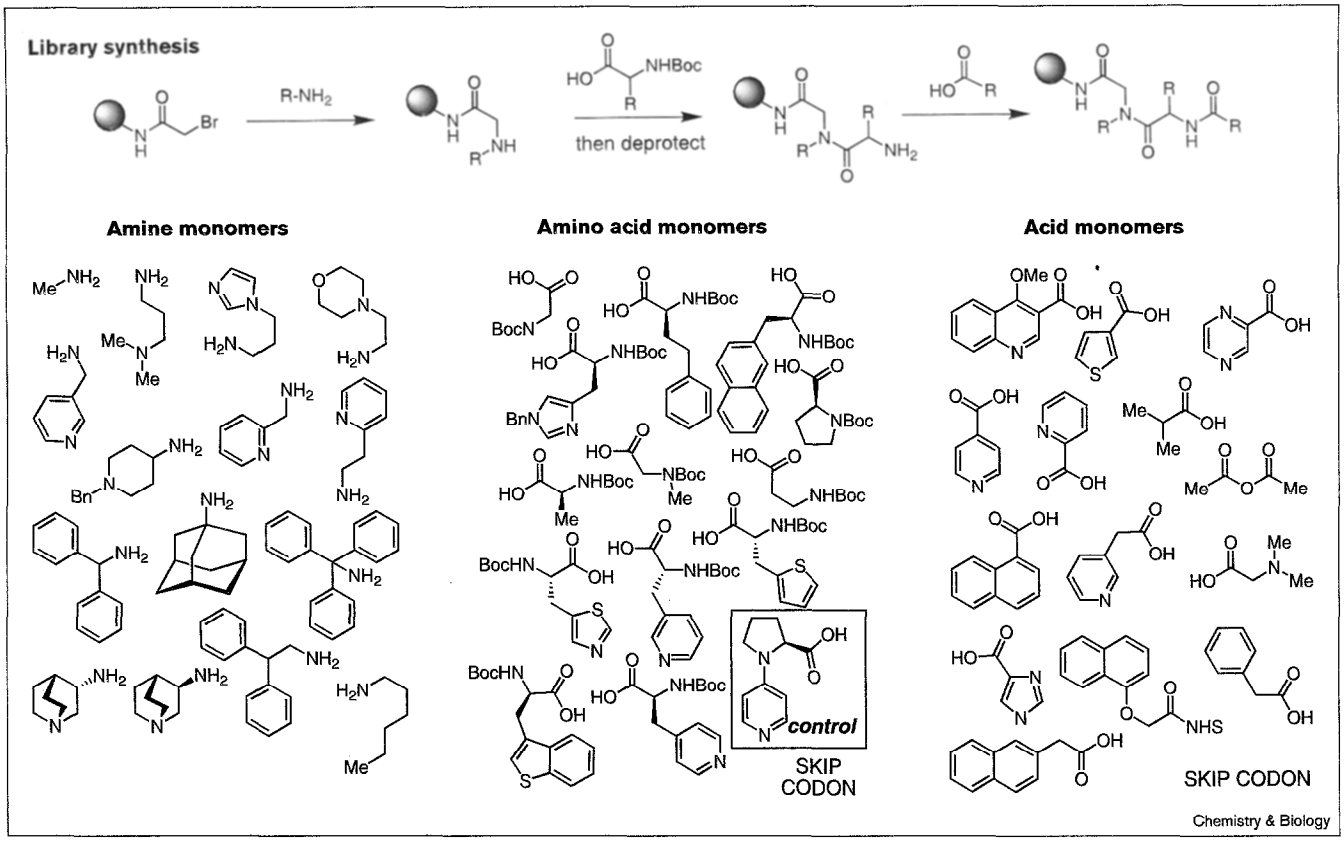
screening can be carried out easily, even substrates of similar structure might prove to have different optimal catalysts [3–5]. For example, as illustrated in Table 1, different epoxide substrates react with trimethylsilyl cyanide (TMSCN) with the highest selectivity in the presence of a similar but structurally unique chiral catalyst. In each instance, approximately 50–80 ligands were screened rapidly. As mentioned before, the high levels of

Figure 2



Subtle structural modifications within the catalyst structure can lead to significant variations in selectivity.

Figure 3



Synthesis scheme and monomers used in the preparation of the nucleophilic catalyst library.

selectivity observed with enzymatic reactions are also often accompanied by a lack of substrate generality. In this case, because ligand modification is relatively straightforward, substrate specificity does not necessarily imply an absence of generality.

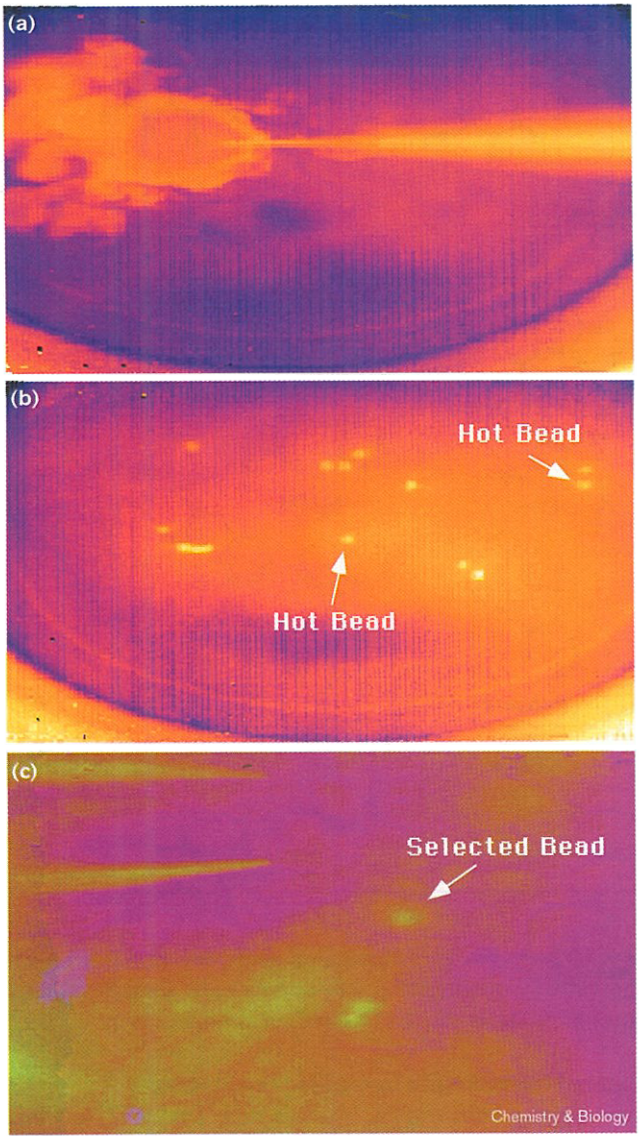
An advantage of the present method in catalyst identification is that it can lead to the discovery of the unexpected. An example was found in our search for the most enantioselective Ti ligand complex for cyclopentene oxide. We observed that use of a ligand complex containing an Asn(Trt) (Trt = trityl) as amino acid 2 (aa2; compare with entry 1, Table 1) results in the reversal of reaction selectivity without alteration of the absolute stereochemistry of ligand stereogenic centers. A subtle modification in the constitution — not stereochemical identity — of one amino acid in the peptide framework can, therefore, give rise to a reversal in selectivity. As illustrated in Figure 2, in contrast to the chiral peptide ligand with aa2 as Thr(tBu), which affords the (*S*,*R*) product in 84% enantiomeric excess (*ee*), the ligand with aa2 as Asn(Trt) leads to the formation of the (*R*,*S*) product in 58% *ee*. A subtle modification of the aa2 structure restores the original mode of selectivity: the homologous Gln(Trt) as aa2 affords the originally expected enantiomer in ~ 60% *ee*. These observations point out an advantage of individually synthesizing and testing each catalyst, as mixtures of catalysts can lead to racemic products [6].

Catalyst identification by infrared thermography

In a more recent report, Morken and Taylor [7] disclose the first solution that should allow chemists to examine large polymer-bound catalyst libraries that result from split-pool synthesis. These researchers argued that because most catalytic reactions involve a change in enthalpy, the temperature changes might serve as a signature of a chemical process. Because all catalysts, in a library assay, are evaluated for their ability to facilitate the same transformation, and because the temperature change is dependent on the turnover rate and the change in enthalpy (ΔH_r) by definition, the catalyst with the highest turnover rate should lead to the largest temperature variation. Such changes can be monitored by using infrared thermography [8]. Through this technique, Morken and Taylor [7] have been able to visualize the temperature of every bead and hence the activity of the attached catalyst simultaneously.

For proof-of-principle experiments, a library of potential acyl transfer catalysts was prepared by solid-phase split-pool

Figure 4

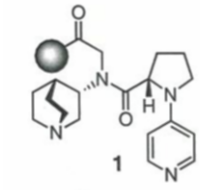
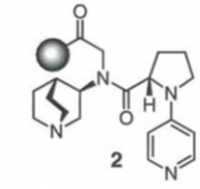
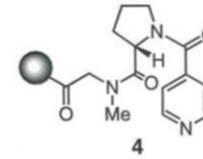
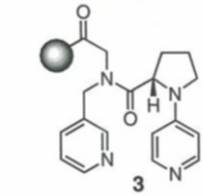


(a) Addition of acetic anhydride to a chloroform solution of triethylamine, ethanol and catalyst beads. **(b)** Thermographic image of ~ 20 catalyst beads in the presence of ~ 3000 noncatalyst beads after the addition of acetic anhydride. **(c)** Selection of a 'hot' library bead prior to decoding (tweezers in upper left-hand corner). Figure courtesy of Jim Morken.

synthesis [9] and binary encoding reported by Still [10]. A library synthesis similar to the synthesis of 'peptoids' [11] was used, where a collection of 3150 polymer-supported catalysts was produced (Figure 3). In each position of the library, monomers with varying nucleophilic, basic and hydrophobic functional groups in their monomer sidechain were included. As both nucleophilic and basic functional groups facilitate acyl transfer [12], it was hoped that an efficient catalyst might be identified through

Table 2

Occurences of the structures in the library corresponding to the hottest beads.

Predicted compound	Occurences
 1	11
 2	10
 4	1
 3	1

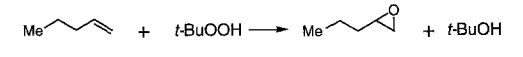
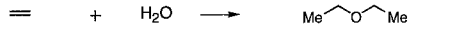
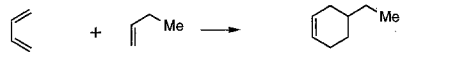
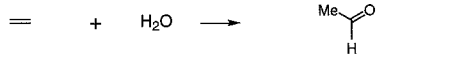
proper combination of the two groups to attain multifunctional catalysis. As the control, a known catalytic element [13] was included so that, at the very least, some compounds were guaranteed to have catalytic activity.

To assay for catalytic activity, the library of potential catalysts was added to a solution containing the reagents for the acyl-transfer process (Figure 4). At this stage, it was important that a high-density solvent be employed to ensure that the beads would float near the surface of the solution. Because the infrared radiation measured by the camera was absorbed by the reaction solvent, such interference had to be minimized. Morken and Taylor [7] indeed established that when the beads sank, they became invisible to the infrared camera and precluded visualization of catalysis.

The structures corresponding to the hottest beads in the library, as predicted by post-isolation library decoding, are shown in Table 2. The library consistently selected compounds bearing the 4-aminopyridine nucleus, these results bear testimony to the reproducibility of the library assay. A second notable result is that 21 of 23 beads bear a quinuclidine attached to the control element (compounds **1** and **2**; Table 2), indicating that a quinuclidine may be

Table 3

Calculated enthalpy change for selected transformations.

Reaction	ΔH_r° (kcal/mol)
	−51.1
	−28.3
	−25.5
	−27.6
	−40.4
	−31.9
	−57.8

responsible for enhanced catalytic activity. Kinetic experiments confirm that **1** and **2** are more active than other nonselected entities in the library and that they are more active than other 'control' catalyst species. Although the mechanism by which quinuclidine may promote catalysis is not clear, the result once again underscores one of the attractive features of combinatorial chemistry and high-throughput screening: performing a large number of experiments can lead to unexpected observations.

In regards to applying thermographic techniques to the analysis of other transformations, it is noteworthy that the acyl transfer examined by Taylor and Morken [7] has a −14.9 kcal/mol enthalpy of reaction, which is significantly lower than that of many other chemical processes currently of interest to synthetic chemists (Table 3) [14]. Thermoneutral reactions, such as those catalyzed by olefin metathases [15] and reactions with low turnover rates, would be difficult to screen by thermographic techniques, but there certainly will be processes for which the protocols described here should prove useful.

The above studies represent efforts based on the principle that, even within a single class of substrates, the identity of the 'optimum catalyst' may change. Perhaps this area of research has its deepest roots in the history of scientific inquiry: it is often the unanticipated 'hit' that becomes the key result that fuels a successful investigation. This line of research does not advocate that we abandon rational investigations of mechanisms of important processes. Elements of design and *a priori* decisions are still required to determine the collection of catalysts that need to be prepared; the framework is simply broader and thus initial bias that might be based on few initial observations has less of a chance to lead us in the wrong direction.

Acknowledgements

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