High-Throughput Strategies for the Discovery of Catalysts

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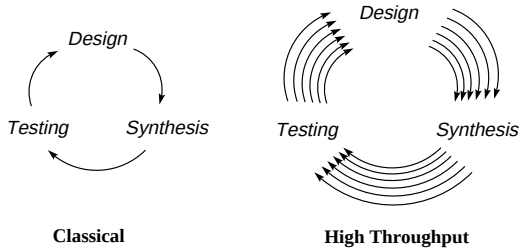
Abstract: This paper provides a brief survey of the first attempts made to use principles of combinatorial chemistry and high-throughput strategies to identify effective organometallic chiral catalysts. The scope and limitations of each advance and its relevance to future investigations are discussed.

Keywords: asymmetric catalysis · asymmetric synthesis · combinatorial chemistry · enantioselective synthesis · high-throughput strategies

Introduction

The major application of combinatorial chemistry remains the search for biologically active molecules.[1] Diversity-based strategies, however, might be effective in the identification of compounds that have attractive properties. Combinatorial and related strategies have indeed been utilized recently in investigations involving materials science,[2] molecular recognition,[3, 4] polymer chemistry,[5] and asymmetric catalysis.[6] This article is a brief overview of the recently developed diversity-based approaches in the screening and identification of effective metal-based catalysts for enantioselective synthesis. In a few instances, it is likely that the more traditional design and screening approaches, often based on a priori mechanistic bias, would have been less successful, at least within the same time span.

The searches for therapeutic agents and asymmetric catalysts share a number of facets. Traditionally, both fields have relied on iterative approaches wherein a single compound is designed, synthesized, and tested (Scheme 1). The cycle is repeated until a compound is obtained with the desired levels of enantioselectivity or activity. In contrast, as illustrated in Scheme 1, a high-throughput strategy enables one to generate and test simultaneously considerably larger numbers of candidates, potentially reducing the entire search cycle to one or two iterations.



Scheme 1. The diversity-based approach can provide a wealth of data on reactivity and selectivity in an efficient manner.

Combinatorial chemistry brings together rational design and high-throughput evaluation; it is rooted in empirical observations and logical deduction. Structure–selectivity observations remain the basis for propagating molecular features from one generation of catalysts to the next. Such strategies therefore permit more initial guesses and a greater allowance for failure. Combinatorial chemistry is particularly well-suited to optimizing novel and previously unexamined reactions for which little mechanistic data is available. Such strategies can be viewed as the chemist's attempt to address the notion that mechanistic subtleties that often differentiate the selectivity and reactivity of one substrate or catalyst from another may not be generalized. Such a broad-based approach relieves the chemist of the risk of following a relatively narrow path selected on the basis of fickle mechanistic parameters. It is perhaps fair to state that the development of almost all successful asymmetric catalysts has benefited, at some point, from serendipitous observations. Combinatorial chemistry integrates this aspect of catalyst discovery into the overall search process, increasing the rate at which advantageous mutations can occur. Nevertheless, a combinatorial approach can significantly promote the mechanistic studies of new asymmetric processes, as it can put forth a large structure–selectivity database from which mechanistic paradigms can be generated.

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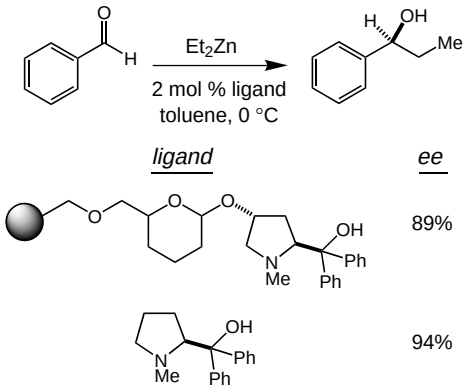
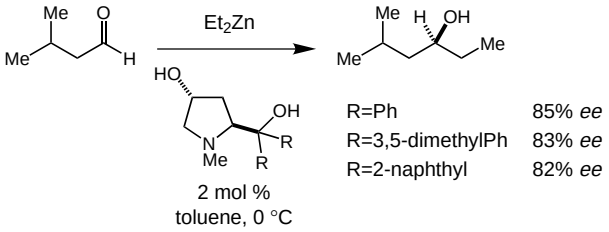
Discussion

Asymmetric aldehyde alkylation: In 1995, Ellman selected the dialkylzinc addition to aldehydes (Scheme 2) to gauge the potential utility of a combinatorial approach.[7] Thirteen ligands were synthesized on a solid support from a 4-hydroxyproline precursor and attached to the support (Merrifield resin) through the 4-hydroxy unit. The ligands were initially screened while still covalently anchored to the support. The levels of enantioselectivity for reactions initiated by the resin-bound ligands proved to be high, but slightly lower than those obtained with the free ligands in solution (e.g., 89% vs 94% *ee*).



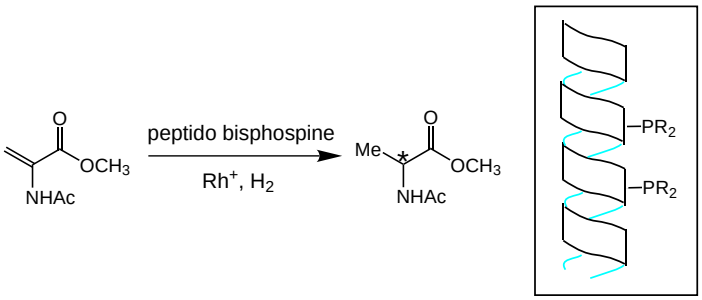
Scheme 2. In catalytic alkylation of aldehydes, similar but slightly lower enantioselectivity is attained when the chiral ligand is anchored to a solid support.

Screening was carried out with unbound chiral ligands synthesized on a solid support and subsequently freed from the resin. Representative data are shown in Scheme 3. It is important to note that, subsequent to cleavage from the solid support, little or no purification of the ligands was required to maintain excellent enantioselectivity. This is a tribute to the efficient multistep synthesis carried out on the Merrifield resin and to the benefits of ligand-accelerated catalysis.[8] The effects of the chiral pyrrolidinone ligand are sufficiently dominant so as not to allow adventitious side products from ligand synthesis to catalyze product formation and lower selectivity.



Scheme 3. Influence of various chiral ligands on the enantioselective addition of Et_2Zn to an aliphatic aldehyde.

Asymmetric hydrogenation: As with many other metal-catalyzed asymmetric reactions, it is often difficult to predict which phosphine ligands or metal centers will lead to the most efficient and selective hydrogenation. Gilbertson and coworkers therefore set out to prepare a sixty-three member library of chiral phosphines, built within a helical peptide scaffold, that could be screened for catalytic and enantioselective olefin hydrogenation. A variable sequence of four to five amino acids was inserted into the peptide Ac-Ala-Aib-Ala-[ ]-Ala-Aib-Ala-NH_2 to yield a range of chiral ligands. Folding of the polypeptide backbone was expected to bring together two different donor phosphine units to present effectively a bisphosphine system and an appropriate chiral environment to the transition metal (Scheme 4).[9] The terminal Ala-Aib-Ala sequences were designed to promote helix formation by bringing the two synthetic amino acids with phosphine side chains into close proximity when they are positioned at spacings of $(i, i+1)$ and $(i, i+4)$.



Scheme 4. Phosphine units attached to helical peptide scaffolds have been screened as catalysts for enantioselective hydrogenation.

Sixty-three different peptides were synthesized in parallel on pins and tested for asymmetric induction while still attached to the solid phase. As depicted in Scheme 4, Rh^I was selected as the metal center (based on ample precedence) and the enantioselective hydrogenation of an α-amino acid was examined. Although relatively low levels of enantioselectivity were observed ($\leq 19\%$ *ee*), this study demonstrated that a combinatorial protocol can efficiently provide the chemist with a wealth of data. It is not clear whether any reliable mechanistic information can be gleaned from these initial results because of the low levels of stereodifferentiation.

Asymmetric addition of TMSCN to *meso* epoxides: We have utilized diversity-based protocols to introduce variations within a modular peptide-based ligand to identify chiral ligands for enantioselective TMSCN addition to *meso* epoxides (Scheme 5). These peptides are expected to be excellent metal ligands[10] and are composed of three independently variable subunits: Schiff base (SB), amino acid 1 (AA1), and amino acid 2 (AA2).[11] Such peptide-based systems are attractive, since chiral amino acids are available in the nonracemic form. Moreover, peptidic systems can be prepared efficiently, in parallel, by established solid-phase protocols.

In principle, 8000 (20^3) different chiral catalysts could be made from the 20 natural amino acids and 20 different aldehydes with the catalyst shown in Scheme 5. However, to control the numbers of compounds synthesized and screened, a representational search strategy was employed (Figure 1).

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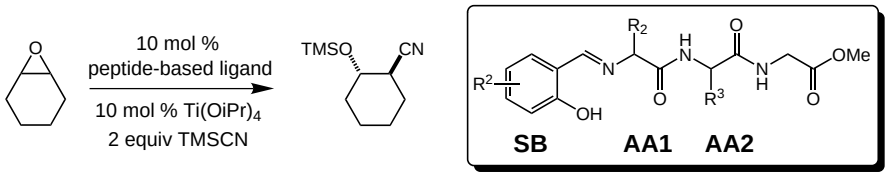


Scheme 5. Peptidic Schiff bases may be screened for identification of an effective chiral ligand for catalytic enantioselective addition of TMSCN to *meso* epoxides.

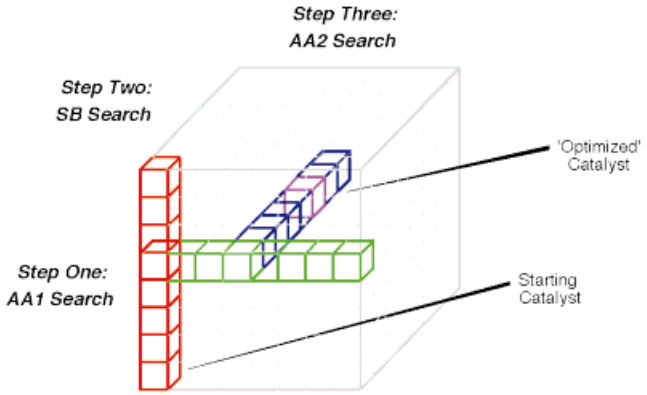


Figure 1. Representational search strategy adopted for catalyst screening allows identification of effective ligands without examination of all possibilities.

Each of the three subunits in the modular ligand was successively optimized, such that the first amino acid 1 (AA1, shown in gray) was varied and the other two subunits were kept constant. *Tert*-leucine was found to be optimal at position AA1 and this structural element was retained in successive generations. The second position (AA2) was then altered, and *O-tert*-butylthreonine was identified as the best AA2. Finally, from a pool of salicylic aldehydes, 3-fluorosalicylaldehyde was selected as the best Schiff base (SB). In the end, only a representative sampling of sixty (20×3) catalysts was necessary to identify one that affords nearly a 95:5 ratio of enantiomers (89 % *ee*). The initial randomly selected catalyst provided the addition product with only 26 % *ee* (cyclohexene oxide as substrate); successive modifications of the ligand structure enhanced selectivity in three steps to afford eventually a synthetically attractive level of enantioselectivity (with 3-fluorosalicylaldehyde-*tert*-leucine-*O-tert*-butylthreonine-glycine-OMe as the catalyst).

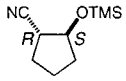
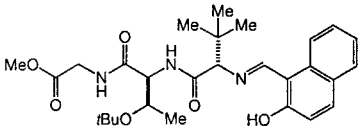
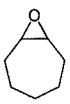
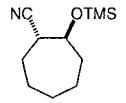
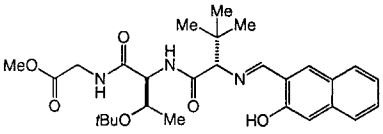
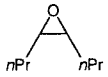
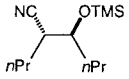
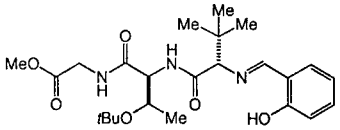
In the approach described above, we have made certain assumptions about the additivity and absence of cooperativity between the three subunits. At least for this small sample, these assumptions seem to hold true, but without testing every combination we cannot definitively answer this important question. Examination of every possibility would tax and detract from the efficiency of the general screening method. An advantage of the above approach is that, in a relatively short amount of time, we could identify a selective catalyst for an entirely new asymmetric process.

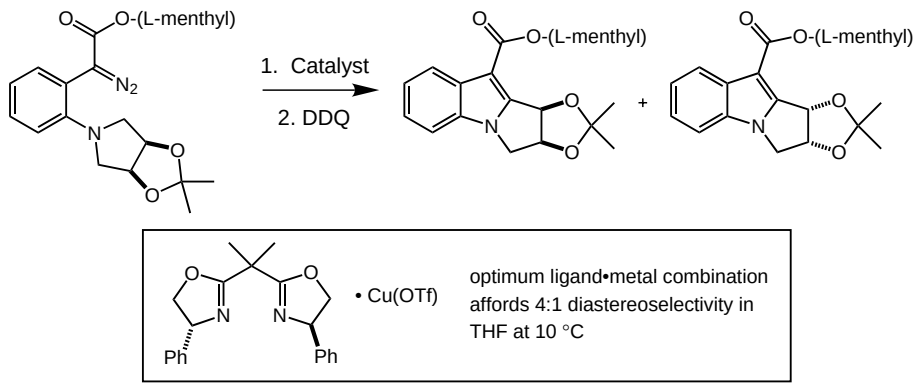
We subsequently applied the above search strategy to various other *meso* epoxide substrates.[12] These studies indicated that for each epoxide substrate a similar but unique chiral catalyst was identified (Table 1). The high levels of selectivity observed with enzymatic reactions are also often accompanied by the lack of substrate generality. In this instance, because ligand modification is relatively straightforward, substrate specificity does not necessarily imply absence of generality.

Catalytic asymmetric carbene insertion: Burgess and Sulikowski adopted an alternative approach by matching an array of chiral ligands with a range of metal centers.[13] A third dimension of diversity was introduced by changing the reaction conditions through variation of the solvent systems. All told, five chiral ligands coupled with six different metal salts were examined in four different solvents. Ninety-six of the possible one hundred and twenty different combinations were examined in less than a week for their ability to direct the asymmetric carbene C–H insertion (Scheme 6). The most effective catalyst was found to be a $Cu^{I} \cdot$(bis)oxazoline ligand complex which was optimized to give a 3.9:1 diastereomeric ratio, compared to the previously reported 2.3:1 selectivity. The unprecedented catalysis of carbene insertion by Ag^{I} was also observed, underlining an additional strength of the high-throughput approach.

Identification of catalysts by infrared thermography: Modern combinatorial synthesis techniques give chemists the ability to produce millions of unique polymer-bead-bound compounds in a simple and reliable manner. Further, with new encoding technology, the chemical structure attached to any given polymer bead may be determined in a relatively straightfor-

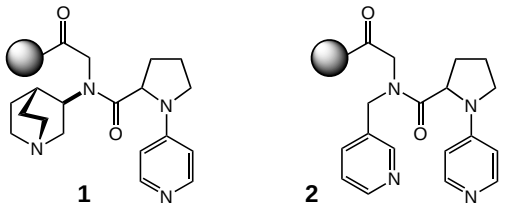
Table 1. Optimized ligands for catalytic enantioselective addition of TMSCN to *meso* epoxides. Conditions: 20 mol % Ti(O*i*Pr)$_4$, 20 mol % ligand, 4 °C, toluene, 6–20 h.

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



Scheme 6.

ward operation. However, screening all prospective catalysts in such a library has presented a significant obstacle as it requires an assay that can be carried out in parallel rather than in series. For instance, if the assay of each catalyst in a one-million-membered library includes a 30 second GC analysis, approximately one year would be required to perform a serial analysis of the entire collection. One solution to this problem was recently reported by Morken and Taylor,[14] who describe a novel parallel assay of an encoded polymer-bead-bound catalyst library for a solution phase catalytic transformation. In situ infrared thermal imaging was used to monitor temperature differences amongst the beads, and therefore the activity of each catalyst, in the presence of reagents undergoing an exothermic reaction. Screening an encoded library of 3150 unique catalysts, followed by selection of hot beads, led to identification of compounds **1** and **2** as effective nucleophilic acylation catalysts.



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IR imaging is an attractive tool, as it should be applicable to a wide range of size and type of catalyst libraries. While screening reactions with small enthalpy changes will be a challenge, with sufficiently large library size and diversity it is reasonable to expect high-turnover-number catalysts to be present and thus detectable. Similar to the results of Taylor and Morken, screening large catalyst libraries is likely to reveal new structures with potentially novel modes of activity and thus open new avenues of catalysis research.

Conclusion

The above studies represent some initial attempts to establish general protocols for the identification and discovery of new catalysts.[15] These efforts are based on the realization 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 asymmetric catalysis: it is often the unanticipated hit that becomes the key data that fuel a successful investigation. If so, why not carry out research in a manner that enhances the probability of making positive chance observations?

In recommending this line of research we are not advocating that rational investigations of mechanisms of important processes be abandoned. Elements of design and a priori decisions are still required in determining which collection of catalysts need be prepared; the framework is simply broader and thus initial bias that may be based on few initial observations has less of a chance to direct us in the wrong direction. Diversity-based strategies will allow us to base our mechanistic hypotheses on a much wider pool of data points.

The above investigations are the first steps on the exciting road that lies ahead. It is likely that we will soon be able to screen significantly larger catalyst collections. A recent report by Jacobsen[16] in connection with an impressive library of chiral metal complexes represents an important first step in this direction. The high-throughput approach to enantioselective reaction discovery should present us with a more complete picture, where the hidden subtleties are highlighted, where the exciting exceptions, as well as the more useful generalities, become more apparent.

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[1] For recent reviews and discussions on combinatorial chemistry, see: a) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337; b) S. Borman, *Chem. Eng. News* **1998**, *76*(14), 47–67.

[2] G. Briceño, H. Change, X. Sun, P. G. Schultz, X.-D. Xiang, *Science* **1995**, *270*, 273–275.

[3] Y. Cheng, T. Suenaga, W. C. Still, *J. Am. Chem. Soc.* **1996**, *118*, 1813–1814.

[4] M. S. Goodman, B. Jubian, B. Linton, A. D. Hamilton, *J. Am. Chem. Soc.* **1995**, *117*, 11610–11611.

[5] S. Brocchini, J. V. Tangpasuthadol, J. Kohn, *J. Am. Chem. Soc.* **1997**, *119*, 4553–4554.

[6] S. Borman, *Chem. Eng. News* **1996**, November 4, 37–39.

[7] G. Liu, J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 7712–7713.

[8] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159–1170; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1070.

[9] S. R. Gilbertson, X. Wang, *Tetrahedron Lett.* **1996**, *37*, 6475–6478.
[10] H. Nitta, D. Yu, M. Kudo, A. Mori, S. Inoue, *J. Am. Chem. Soc.* **1992**, *114*, 7969–7975.
[11] B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1671. A similar approach was recently used to identify Schiff base catalysts for an asymmetric Strecker reaction. M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.
[12] K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1781–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707.
[13] K. Burgess, H.-L. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem.* **1996**, *108*, 192–194; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220–222.
[14] S. J. Taylor, J. P. Morken, *Science*, **1998**, *280*, 267–270. Also see: F. C. Moates, M. Somani, J. Annamalai, J. T. Richardson, D. Luss, R. C. Willson, *Ind. Eng. Chem. Res.* **1996**, *35*, 4801–4803.
[15] For additional recent examples, see: a) F. M. Menger, A. V. Eliseev, V. A. Migulin, *J. Org. Chem.* **1995**, *60*, 6666–6667; b) X. Gao, H. B. Kagan, *Chirality* **1998**, *10*, 120–124; c) M. T. Reetz, A. Zonta, K. Schimossek, K. Liebeton, K.-E. Jaeger, *Angew. Chem.* **1997**, *109*, 2961–2963; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2830–2831.
[16] M. B. Francis, N. S. Finney, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 8983–8984.

  0947-6539/98/0410-1889 $ 17.50+.25/0