Combinatorial Methods for the Discovery and Optimisation of Homogeneous Catalysts

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Dedicated to Professor Henri Kagan for his achievements in asymmetric catalysis

Abstract: The use of combinatorial methods to discover new catalysts is one of the youngest fields of combinatorial chemistry. The main focus of this review is the application of combinatorial liquid- and solid-phase methods for the discovery and optimisation of homogeneous catalysts. In addition, high-throughput screening techniques for fast detection of activity and selectivity in catalytic reactions are discussed. The literature from 1995 to December 2000 is covered.

1 Introduction

The ability to screen hundreds of thousands of compounds for their biological activity within a few days together with the need for new potent pharmaceuticals rendered the chemical development of new compounds into the bottleneck of pharmaceutical research. The implementation of automation as well as solid-phase synthetic procedures initially developed for peptide synthesis has ultimately led to the invention of high-throughput techniques usually referred to as combinatorial chemistry. Within less than one decade, combinatorial chemistry established itself as an attractive approach to prepare libraries of compounds able to be tested for their biological activities.1–3

Initially the term combinatorial chemistry was derived from the split-and-mix method, invented by Furka in 1988, and was therefore limited to a particular solid-phase peptide synthesis protocol. The invention of liquid- and solid-phase high-throughput techniques accessible through the rise of automation led to confusion about the term combinatorial chemistry. However, in a modern definition, combinatorial chemistry is nowadays referred to as "the applied use of technology and automation for the rapid chemical syntheses of relatively large numbers of compounds".5

Diversity-based strategies, however, might also be effective in the identification of compounds that have attractive properties other than their biological activity. Combinatorial and related strategies have indeed been utilised recently in investigations involving material science,6,7 molecular recognition,8 polymer chemistry,9 and asymmetric catalysis (various single immobilised ligands and catalysts reviewed by Shuttleworth10).

Owing to our interest in this field, and of its growing literature coverage,11–16 this article was written covering work published between 1995 and December 2000. Functionised polymers, supported reagents and catalysts have recently been reviewed and are therefore not included in this overview.10 In addition, high-throughput strategies for the development and screening of heterogeneous catalysts are presently given a great deal of attention.17,18 In this review, we will therefore concentrate on truly combinatorial approaches towards the development of homogeneous catalysts either in liquid phase or on solid support.

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Serendipity is one factor that combinatorial chemistry has brought about to the search for biologically active compounds and which has had a significant impact in finding lead structures. The more traditional design and screening approaches, which are often based on a priori mechanistic bias, can only lead to structures that were somehow expected by the chemist. The same applies even more to the search for (asymmetric) catalysts where the mechanistic understanding of a catalytic reaction drastically limits the number of reasonable metal/ligand combinations that one would usually screen for a given reaction. As already pointed out by Snapper and Hoveyda,19 combinatorial chemistry brings together both rational design and high-throughput evaluation; it is routed in empirical observations and logical deduction. However, the ability to produce and screen a large number of compounds permits a greater allowance for failure or unreasonable metal/ligand combinations. This serendipity has already led to the discovery of some new catalysts. In addition, it will perhaps give rise to completely unexpected classes of catalysts and catalytic reactions, as fast analytical methods for the high-throughput screening of enantiomerically enriched compounds steadily emerge.

2 Methods in Combinatorial Catalysis

In contrast to the traditional approach of catalyst design and optimisation wherein a single system is designed, synthesised and tested, repeating this circle until a system is obtained with the desired levels of activity and selectivity, combinatorial catalysis allows for the generation and testing of considerably larger numbers of candidates, potentially reducing the entire research cycle to one or two iterations (Figure 1). This does not imply that combinatorial catalysis eliminates the need for the mechanistic understanding of a given catalytic reaction by simply varying all possible parameters in an automated reaction set-up. The chemical design is still very important because it determines how fast and efficient new catalytic systems can be found. In contrast to traditional catalysis, already at the beginning of a combinatorial screening (e.g. the synthesis of a library of metal complexes) the chemist usually has to decide on a whole variety of ligands or ligand building blocks, metal precursors and additives he wants to employ in the reaction. A careful choice and an intelligent screening set-up can lead to the discovery of highly potent catalytic systems carrying out only a small fraction of all possible reactions, as some of the examples will show (vide infra).

Apart from being able to access a broad range of catalyst precursors, the automation of catalyst synthesis and screening is most important. Automation starts from being able to perform multiple reactions simultaneously, for instance in microtiter plates (MTP) handled in a glove box, or an array of vials simultaneously heated and stirred by a standard laboratory stirrer (Figure 2).

Biographical Sketches

Stefan Bräse (left) and Stefan Dahmen have been working together for two years in the fascinating areas of solid-phase chemistry and combinatorial catalysis. Stefan Dahmen was born in Rheydt, Germany in 1971 and studied chemistry at the RWTH Aachen, Germany and University of York, UK.

Stefan Bräse was born in Kiel, Germany in 1967. He studied at the Universities of Göttingen, Bangor (UK) and Marseille and received his PhD in 1995, after working with Armin de Meijere in Göttingen. After post-doctoral appointments at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou) as DAAD fellow, he began his independent research career at the RWTH Aachen in 1997 (associated to Dieter Enders). In June 2001, he finished his habilitation and moved to the University of Bonn as a Professor of Chemistry. His research interests include asymmetric metal-catalysed processes and combinatorial chemistry towards the synthesis of biologically active compounds.

In 1999, he obtained his Diploma in chemistry in the group of Dieter Enders under the supervision of Stefan Bräse. He is currently a PhD student with Stefan Bräse and is interested in the development of combinatorial methods for solid-phase synthesis and asymmetric catalysis.
Automation can be carried further using rather compact synthesisers like the Anachem SK 233 WorkstationTM or Chemspeed Workstations for process screening (temperature, reagents, solvents, stoichiometry, reaction times, additives can be varied) with relatively small reaction volumes (1 to 10 mL). Finally, process development workstations like the Argonaut SurveyorTM or Bohdan PDW200 (Figure 3) are capable of carrying out complex reaction runs (e.g. independent temperature control for each reaction vessel, automated workup, online analytics) and handling larger volumes.

Analytical methods for the determination of activity and selectivity of catalysts are equally essential. These may be rather simple like thin layer chromatography (TLC) or fluorescence assays, but also very elaborated methods like IR-thermography, MS techniques, and screening of mixtures of substrates, ligands and metals have emerged (vide infra).

Automation can be applied equally to solution-phase techniques as well as solid-phase techniques. Solid-phase methods have been used for the production of ligands either by solid-phase syntheses, or by the application of supported reagents or scavengers. Ligands prepared by solid-phase synthesis have been tested either on support or have been cleaved from the support prior to testing.

3 Combinatorial Liquid-Phase Methods

3.1 Reaction Examples

3.1.1 Carbene Insertion

One of the first studies dealing with liquid-phase high-throughput screening was the intramolecular carbene insertion into C-H bonds, which was published by Burgess et al. in 1996.20 The insertion reaction was carried out in a 96-well microtiter plate format in a glove box followed by DDQ oxidation to simplify the determination of the chiral products while evaluating the stereoselectivity of the tricycle formation.

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1** Diastereoselective C-H insertion by Burgess et al.,

DDQ = 2,3-dichloro-5,6-dicyano-p-benzoquinone
Three different bis(oxazoline) ligands (5–7), a salen-type ligand (9), and sparteine (8) were used in combination with seven different metal salts \{AgSF₆, Sc(OTf)₃, [Rh(nbd)]BPPh₃, (CuOTf)₂C₆H₅, La(OTf)₃, Yb(OTf)₃, AuCl(SMe₂); Tf = F₃CSO₂, nbd = norbonadiene\}, and four different solvents (THF, acetonitrile, chloroform, toluene) (Figure 4). The observed stereochemical outcome varied from 1:2.4 \((\text{uene})\) (Figure 4). The transition metal-catalyzed reaction of enamines 15 derived from \(\beta\)-oxoesters 13 and \(\alpha\)-amino acid amides 14 with Michael acceptors, such as methylvinylketone 16, was examined by Christoffers et al. \(^{25}\) (Scheme 3). In the first screening step, the enaminoketones 15 were reacted with methylvinylketone in the presence of catalytic amounts of 14 metal salts 17 in dichloromethane. The auxiliaries based on valine, leucine, iso- and tert-leucine already gave rise to selectivities of up to 78\% ee in the absence of a metal salt which could be improved by 20\% (up to 98\% ee) by the addition of Cu(OAc)₂·H₂O as catalyst. Variation of solvent and catalyst loading finally led to the catalytic system depicted in Scheme 3. Although stoichiometric amounts of auxiliary had to be employed, this paper demonstrated the application of combinatorial techniques in auxiliary-controlled catalytic reactions.

3.1.2 Reductive Aldol Reaction

The reductive aldol reaction represents a valuable process for the mild, diastereoselective synthesis of polypropionates (Scheme 2). The advantage of this reaction is that a stoichiometric preformation of an activated enolate as a nucleophile is not required when late transition metal catalysts are used. In 1999, Morken et al. reported the optimization of independent reaction variables by an arrayed catalyst evaluation attempt in which 192 independent catalytic systems were screened.\(^ {23}\)

In the initial array, four transition metal salts \{Co(acac)₂, [(allyl)PdCl]₂, [(cod)IrCl]₂, [(cod)RhCl]₂\}, seven ligands \((i\text{-Pr}-\text{pybox}, \text{r}-\text{Bu}-\text{box}, \text{Ph}-\text{semicorrin}, \text{MOP}, \text{BINAP}, \text{DuPhos}, \text{quinal}\)\(^ {24}\) and six hydride sources \((\text{Cl}_2\text{MeSiH}, \text{PhSiH}_3, \text{Ph}_2\text{SiH}_2, \text{catechol borane}, \text{Cl}_2\text{SiH})\) were employed in glass 96-well plates and the products examined by GC analysis versus an internal standard. The authors pointed out a number of relationships between reaction conditions and yield and also found strong interdependencies between catalyst and hydride source. On the other hand, reactivity and selectivity have no correlation: the three most active catalyst systems \([(\text{cod})\text{RhCl}]_2\text{-BI-NAP-catechol-borane} (100\% \text{ relative yield}), \text{Co}(\text{acac})_2\text{-MOP-PhSiH}_3 (94\% \text{ relative yield}), \text{and} [(\text{cod})\text{RhCl}]_2\text{-DuPhos-Cl}_2\text{MeSiH} (94\% \text{ relative yield})\) show \(\text{syn}\)anti selectivity of 7:1, 2:1, and 23:1, respectively. The latter catalyst system was further explored in the reductive aldol reaction with aliphatic and unsaturated aliphatic aldehydes, which were shown to participate in the reaction without interference from competitive conjugate reduction. However, enantioselective transformation was observed with a few catalyst systems and was not discussed further because all ee values were lower than 30\%.

3.1.3 Michael Addition

The transition metal-catalysed reaction of enamines 15 with Michael acceptors, such as methylvinylketone 16, was examined by Christoffers et al.\(^ {25}\) (Scheme 3). In the first screening step, the enaminoketones 15 were reacted with methylvinylketone in the presence of catalytic amounts of 14 metal salts 17 in dichloromethane. The auxiliaries based on valine, leucine, iso- and tert-leucine already gave rise to selectivities of up to 78\% ee in the absence of a metal salt which could be improved by 20\% (up to 98\% ee) by the addition of Cu(OAc)₂·H₂O as catalyst. Variation of solvent and catalyst loading finally led to the catalytic system depicted in Scheme 3. Although stoichiometric amounts of auxiliary had to be employed, this paper demonstrated the application of combinatorial techniques in auxiliary-controlled catalytic reactions.

3.1.4 Diethyl Zinc Addition to Aldehydes

Diethyl zinc addition to aldehydes has been investigated extensively\(^ {26}\) since this reaction is catalysed by a great variety of metal complexes and ligands and its mechanism exhibits interesting features like chiral amplification in the amino alcohol-promoted variant.\(^ {27}\) Mikami et al.\(^ {28}\) studied the possibilities to optimise catalytic systems consisting of a chiral diol \(L‘\) in Scheme 4 or \(L_1‘\)–\(L_5‘\) in Figure 5 and a chiral activator \(A‘\) in Scheme 4 or \(A_1‘\)–

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The active catalyst in the addition reaction is presumably a monomeric zinc alkoxide \( \text{ZnL}^* \). The cleavage of aggregates \( (\text{ZnL}^*)_n \) which is accomplished by an additional \( N \)-ligand \( \text{A}^* \) activates the system efficiently by forming monomeric zinc species like \( \text{ZnL}^* \text{A}^* \) (Scheme 4).

First, a library of chiral ligands (\( L_1^* - L_5^* \)) and chiral activators (\( A_1^* - A_5^* \)) was screened and the combination of sterically hindered BINOL derivative \( L_5^* \) and diimine \( A_4^* \) or \( A_5^* \) was found to deliver the best results (quantitative conversion with up to 65\% ee) (Figure 5). Based on these results, twelve diimine ligands derived from enantiomerically pure 1,2-diphenylethylamine or 1,2-diaminocyclohexane were synthesised and applied in a second generation library together with diol \( L_5^* \). Reactivity and selectivity of the thus formed catalysts were found to increase dramatically, the relative configuration of the product obviously only being influenced by the relative configuration of the diol and not the diimine. However, the steric hindrance of the diimines was shown to be important for the reaction as the best results were obtained with the sterically most crowded diimine (quantitative conversion, 90\% ee). Using lower reaction temperatures (\(-78°C\)), 99\% ee and quantitative conversion were reached for benzaldehyde as well as very good results for a variety of other aldehydes.

One further aspect of Mikami’s work is, that the ee’s were determined using a combination of HPLC and circu-
lardichroism avoiding the time consuming separation of enantiomers by HPLC or GC.

3.1.5 Aza-Diels–Alder Reaction

Until the mid 90s, successful approaches towards asymmetric aza-Diels–Alder reactions have relied almost entirely upon auxiliary-based methodology, with the exception of Yamamoto’s stoichiometric homochiral triarylborate Lewis acids.29,30 Stoichiometric and catalytic hetero-Diels–Alder reactions including aza-Diels–Alder reactions have recently been reviewed by Jørgensen.31 In 1998, Whiting et al.32 reported on a parallel combinatorial approach towards a Lewis acid-catalysed asymmetric Diels–Alder reaction using imino dienophile 20 and Danishefsky’s diene (19) (Scheme 5).

The parallel screening approach involved library generation using discrete homochiral Lewis acid complexes generated from four different metal salts [Yb(OTf)3, MgI2, Cu(OTf)2 and FeCl3] and three different homochiral ligands (22–24). Three different solvents (dichloromethane, toluene, and acetonitrile) and two additives (2,6-lutidine and 4 Å molecular sieves) were also screened resulting in an overall set of 144 reactions carried out in multiple well plates. The yields and enantiomeric excesses were measured using HPLC with a chiral stationary phase and an autosampler. In the initial screening step, 70% of the combinations showed some level of asymmetric induction and catalysis. Repetition of selected experiments on a 1 mmol scale and 10% catalyst loading lead to a system based on MgI2 and chiral diamine 24 giving 97% ee and 64% yield.

3.2 Modular Ligand Systems for Homogeneous Metal Catalysis

In order to speed up the process of catalyst development, modular ligand architectures are highly desirable, because they facilitate the systematic variation and optimisation of the ligand structure. Important classes of chiral catalysts based on modular ligands are, for instance, ferrocenyl systems of type 25,33–35 chiral oxazolines of type 26,36–40 and binaphthyl derived complexes of type 2741–45 (Figure 6). However, combinatorial accesses to most modular ligand systems have not been elaborated yet.

The concept of divergent ligand syntheses is usually not emphasised, though it frequently emerges as a factor in well-designed approaches to asymmetric catalysts. For instance, Jacobsen’s ligands for asymmetric epoxidation46–49 as well as other processes50–53 were developed combining relatively expensive or less accessible optically active diamines and a variety of readily available salicylaldehyde derivatives. It would be wrong to claim that divergent ligand synthesis is the best strategy for every situation; in fact, it is preferable to obtain ligands directly from commercially available sources, as in the Sharpless epoxidation,54,55 or in a few synthetic steps, as for bisoxazolines.56 However, such straightforward access to good molecular architectures for asymmetric coordinating groups is relatively rare. In cases where there is no convenient strategy, divergent routes to well-designed systems are an attractive option.

Burgess et al. demonstrated the synthesis of a library of phosphine oxazoline ligands 29 and its application in the allylic substitution reaction.57 Compound 28 was chosen as a key intermediate which was prepared from serine.

Several methods to prepare oxazolines from amino alcohols were used in this work. For instance, ligand 30a was formed from 29 by reaction with triethyl orthoacetate (method A, Scheme 6). Acylation/cyclisation sequences were used for the preparation of some other phosphine oxazolines. Thus, reaction of pivaloyl chloride with 29, protection of the phosphine as a phosphoryl borane, mesylation in the presence of DABCO, then slight elevation of temperature gave the tert-butyl-substituted ligand 30b (method B). Other ligands were obtained via reaction of the amino alcohols with imidate esters, e.g. the phenyl-substituted ligand 30i (method C).
Ligands 30 were employed in the palladium-catalysed asymmetric allylic substitution reaction using 1,3-diphenylpropenyl acetate (31, Scheme 7) and dimethyl malonate (32) as a nucleophile. Reactions were carried out in parallel in a cooled aluminium block carrying 34 1.1-mL polypropylene microtubes as reaction vessels. Different solvent, electronic, steric and salt effects were discussed. Comparison of the enantioselectivities observed for the different R substituents (Scheme 6) indicated that aryl rings with electron-releasing \textit{para} substituents (Me or OMe) tend to give higher enantioselectivities than similar groups with electron-withdrawing substituents (4-NO\textsubscript{2} and C\textsubscript{6}F\textsubscript{3}). Highest enantiodiscrimination in this work was observed for the adamantyl ligand 30e (94% ee). Some ligands with smaller or larger R substituents gave much lower enantioselectivities; for instance, the methyl ligand 30a gave a product of only 53% ee and for the triphenylmethyl system 30d the ee was reversed to –6%.

A modular approach to structurally diverse bidentate ligands was described by Schmalz et al.\textsuperscript{58} The ligand backbone exhibits three points of variation and can be synthesised starting from hydroquinone via a protection and (in some cases) bromination strategy (Scheme 8). Variation point L\textsuperscript{1} was established by \textit{ortho}-metallation or metal-halogen exchange, and successive quenching with a variety of electrophiles, including disulfides, dienamides, chlorophosphines, and carbamoyl chlorides.

Cross-coupling under Suzuki conditions of boronic acids generated from 34 with various heteroaryl bromides was also used to establish L\textsuperscript{1}. A third possibility for the introduction of L\textsuperscript{1} was the Pd-catalysed amination allowing the incorporation of diverse, including chiral, amino side chains. Variation at point L\textsuperscript{2} was carried out by cleavage of the protecting group R\textsuperscript{2} and O-phosphorylation of the thus formed phenols with the electrophiles L\textsuperscript{2}X shown in Scheme 8.

Overall, 23 ligands are described, 13 of which are trans- and for the triphenylmethyl system 30d the ee was reversed to –6%.

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of two on-bead catalysts for activity, it is not necessary to know exactly how many of the supported active sites are in fact active, but the beads in the study must have approximately the same proportion of active sites.

Direct comparison of immobilised catalysts with solution analogues will not necessarily give reliable information, because it is not exactly known whether to ascribe any deviation to improper synthesis of the active catalyst, to catalyst-polymer or catalyst-linker interactions or to the favoured formation of monodentate or mononuclear complexes on the solid support.

4.1 Screening for Metal Binders

Ligand synthesis on solid support brings about the advantages of solid-phase chemistry like automation of repetitive steps (peptide synthesis) and ease of workup by washing the resin. If it is intended to employ the ligands in metal-catalysed reaction while still bound to the polymeric support, the coordination of metal ions to the ligand has to be studied in the first place. In 1996 Jacobsen et al.59 published results about the search for new coordination complexes by solid-phase techniques (Figure 7).

Figure 7 Constitution of the Jacobsen system59

The ligand library comprised four variable components: two amino acids, linked by a turn element and terminated by various capping reagents. The library of ligands was synthesised by split-and-mix techniques and theoretically consisted of 12,000 different ligands and was encoded using established tagging methods. The beads were exposed to selected metal salt solutions [Ni(II), Fe(III), Cu(II), Pt(IV), Sn(IV), and Pd(II)] and stained with metal stains to determine the active members (Figure 8). Tag photolysis and GC-ECD analysis allowed the identification of hits and revealed several structural motives which could specifically bind one metal ion.

4.2 Catalysts in C-C Bond Formation

4.2.1 Diethyl Zinc Addition to Aldehydes

The first example of ligand tuning by a combinatorial approach was reported by the Ellman group in 1995, with the synthesis of a library of prolinol derivatives to be used as ligands in the enantioselective addition of diethyl zinc to aldehydes60 (Scheme 9). The variable step was the addition of several Grignard reagents to polymer-bound proline methyl ester. The secondary nitrogen of proline was protected as a methoxycarbonyl derivative which after the Grignard addition was either reduced with Red-Al to yield methylamino derivatives, or removed to acylate the resin-bound ligands prior to Red-Al reduction. Overall, 21 ligands were generated and screened in the diethyl zinc addition. In one case (R1 = Ph, R2 = H) the conversion was quantitative and the ee was 89%, which could even be improved to 94% when carried out in liquid phase.

Scheme 9 Diethyl zinc addition catalysed by a solid-phase-bound catalyst by Ellman et al.60
The major drawback of the above methodology is the inherent lack of variable steps, the creation of molecular diversity being confined to the use of different reagents in a single step of the ligand synthesis sequence. In this case, the parallel ligand synthesis does not differ significantly from the traditional approach of catalyst development by sequential optimisation. However, as already mentioned, it was the first example of a combinatorial approach to ligand tuning.

Gennari et al. made a further approach in 1998 using both solid-phase and liquid-phase techniques. Starting from commercially available vicinal diamines $47a-f$, which were coupled with $N$-protected $\beta$-amino sulfonyl chlorides $48g-k$, obtained in high yield from $\alpha$-amino acids, disulfonamides $49ag-fk$ were synthesised and purified using solid-phase extraction (SPE) (Scheme 10).

The ligands were tested in the diethyl zinc addition mediated by $\text{Ti(O\text{t}-\text{Pr})}_4$ using a mixture of four aldehydes (Scheme 11). The ee values were determined by GC analysis. The screening revealed that the ligand consisting of 15,25-diaminocyclohexane ($47b$) and sulfonyl chloride $48j$ derived from $L$-phenylalanine was best for this reaction, giving up to 96% ee for aromatic aldehydes.

Supported peptidosulfonamide tweezers $52$, synthesised by a combinatorial solid-phase approach, were shown to catalyse the diethyl zinc addition to aldehydes in the presence of $\text{Ti(\text{O\text{t}-\text{Pr})}_4}$ by Liskamp et al. (Figure 9).

The tweezers were constructed on a pyrrolidine backbone attached to poly(ethylene glycol)-polystyrene resin (Argonaut resin) because preliminary results had shown that tweezers synthesised on Merrifield resin were completely devoid of catalytic activity. Using a multi-substrate screening approach as suggested by Kagan et al. (vide infra), moderate ee's (< 32%) were observed on solid phase, which in some cases could be improved to around 60% ee when carried out in liquid phase with re-synthesised ligands.

4.2.2 Addition of Trimethylsilylcyanide to meso-Epoxides

Also one of the early publications in the field of combinatorial catalysis dealt with the optimisation of peptide-based ligands for the enantioselective ring-opening of meso-epoxides by means of trimethylsilylcyanide (TMSCN). Snapper and Hoveyda et al. chose a solid-phase approach to construct a modular ligand system ($53$) consisting of two amino acids (AA1 and AA2 in Scheme 12) and a Schiff base (SB).

The Ti-mediated addition of trimethylsilylcyanide to epoxides is further enhanced with an alkoxide-Schiff base. Preliminary results on the comparison of selectivity of supported ligands and ligands in solution indicated that...
polymer-bound ligands can indeed show higher selectivity than the corresponding free ligand. However, as the type of linker used also influenced the outcome of the reaction dramatically, the authors decided to first screen the free ligands. In a first generation library the amino acid AA1 (10 amino acids) was varied while AA2 and the Schiff base (SB) were kept unchanged. t-Leucine was found to be the best candidate for AA1. With t-leucine as AA1 and 2-hydroxy naphthaldehyde as Schiff base, AA2 was varied in a second-generation library (using 16 amino acids for AA2). With O-tert-butyl threonine found to be best for AA2, 13 aldehydes were screened for the position SB in a third-generation library. Finally 3-fluoro salicylaldehyde gave the best results leading to a ligand catalysing the epoxide-opening reaction of 54 with 86% ee.

Snapper and Hoveyda used a strategy of optimising all three subunits successively and keeping the other two subunits constant. In this way only 60 ligands had to be synthesised to obtain enantioselectivities of 86%. However, this strategy is based on the assumption that all three subunits do not behave cooperatively although this could not be proved by the experiments carried out. This approach has already been shown to be valuable in a number of publications that followed.65–67

Later on, a similar approach with support-bound ligands was published by the same group.66 The authors correlated the results of support-bound and free ligands and found that the best ligands in liquid-phase experiments were usually also the best ligands on solid support although the differences in the obtained ee’s could be quite large (for some examples the selectivities were 40% ee on solid phase compared to 20% ee in solution; the best ligand however gave 78% ee on solid phase and 89% ee in solution). A positive nonlinear effect in the enantioselective epoxide-opening with free ligands was also observed contributing to the assumption that an equilibrium of monomeric catalytic species and higher agglomerates exists (the authors assume that the active species is a monomeric Ti-complex).

4.2.3 Asymmetric Strecker Reaction

A similar approach as the one by Snapper and Hoveyda was chosen by Jacobsen et al. for the optimisation of catalysts for the asymmetric Strecker reaction.66 Initially one ligand of type 57 (Scheme 13) was prepared and evaluated for the catalysis of addition of TBSCN to N-allyl-benzaldehyde in the presence of different metal ions (Library 1). Whereas comparable reactivity was observed in each case, the ligand proved to be most enantioselective (up to 95% conversion, up to 19% ee) in absence of any added metal. In a second library, 48 different ligands were prepared on solid support varying the amino acid, the diamine and the salicylaldehyde at the same time. Also at this stage, the linker moieties (Linker1 and Linker2 in Scheme 13) were optimised in a classical approach. Within this library, ligands giving rise to selectivities of up to 55% ee were found. In a third library consisting of 132 thiourea derivatives (at the position of Linker0 of only nonpolar amino acids and 3-tert-butyl-substituted salicylaldehyde derivatives, selectivities of up to 80% ee were observed. The amino acid component was found to be crucial, the bulkiest derivatives (t-Leu, cyclohexylglycine, and isoleucine) providing the best results. The best catalyst identified from library 3 (57a in Figure 10) was synthesised independently in solution and was tested in the asymmetric Strecker reaction using aromatic as well as aliphatic substrates. Enantioselectivities ranging from 70% to 91% were obtained.

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A soluble analogue of 57b was prepared (57c) and evaluated against 21 different aromatic and aliphatic imines giving selectivities of 77% up to 97% ee in 65–99% yield. Also, the authors were able to show that the polymer-bound derivative 57b could be repeatedly used in the Strecker reaction without loss of activity or selectivity (10 cycles).

4.2.4 Allylic Substitution Reactions

Gilbertson et al. used their system that allows for the incorporation of amino acids possessing protected phosphine groups into peptide structures (vide infra) to produce peptide β-turn forming motives capable of binding palladium. The basic ligand design consists of the turn-forming sequence Pro-D-Yyy with the metal binding phosphine-containing amino acid flanking this element. The ligands were synthesised on I-series MD-SynPhase Crowns from Chiron Technologies and tested in the palladium-catalysed allylic substitution reaction on solid support (Scheme 14).

The structural features that were varied in the initial library were adding and then varying amino acids at the N-terminus, the substitution of amino acids other than Gly at the C-terminus end of the peptide and substitution of D-amino acids other than D-Ala next to the proline. The basic sequence examined in the library was Ac-Xxx-Pps-Pro-D-Yyy-Pps-Zzz-Rink (Scheme 14). The selectivities obtained with this library ranged from 34% to 80% ee. 77 members of this 96-membered library gave 60% or greater selectivity. The best ligand (D-Phg-Pps-Pro-D-Val-Pps-D-Leu) was removed from solid support, purified by HPLC and tested again in solution to give the same selectivity as observed on solid support (96%, 74% ee). Further optimisations and screening of three other allylic acetates as substrates for the substitution reaction were also reported.

4.3 Catalytic Oxidation and Reduction Reactions

4.3.1 Alkene Epoxidation

Jacobsen et al. studied the epoxidation of alkenes with polymer-bound ligands capable of metal binding in 1999. 69 192 potential ligands were synthesised by solid-phase methods consisting of amino acid fragments attached to an aminomethyl polystyrene resin, which were functionalised with chiral diamine, amino acid or aminoalcohol derivatives. Finally, endcapping with functionalised (hetero)cyclic end groups furnished the chelating ligands (Scheme 15). A structure similar to known epoxidation catalysts was also added as a potential control for screening. The pooled ligand library was incubated with 30 different metal salts leading to a library of 5760 possible complexes (Figure 11), 80% of which were actually obtained as estimated by the authors (colour change and use of metal staining agents).
and FeCl₂ showed the highest epoxidation activity in the present libraries. Ferrous chloride (FeCl₂) was chosen as the metal source for the third screening step, which consisted of a deconvolution strategy because the vanadium species showed high activity even in the absence of a ligand. Finally, all 192 ligands were separately incubated with FeCl₂ and tested again.

The best results were achieved with the complexes depicted in Figure 12. These represent active but not very enantioselective catalysts. Nevertheless, the found ligands have no structural relationship to already known systems.

### 4.3.2 Catalytic Hydrogenation

The concept of using modified peptidic structures as ligands for metal catalysis was also used by Gilbertson et al.⁷⁰ The authors employed amino acid derivatives carrying a phosphine sulfide group in the synthesis of peptides. They used the Chiron Multipin™ Multiple Peptide Synthesis system to prepare the supported phosphine ligands (Scheme 16) by mix-and-split methods and to test them in the rhodium-catalysed hydrogenation of acetamidoacrylates ⁷³ (Scheme 17).

The phosphine sulfide groups incorporated in the supported peptides could be transformed into phosphines by means of alkylation and subsequent desulfurylation with HMPT. The first 27 peptides had phosphine containing amino acids in $i, i+4$ relationship, because the authors assumed that even on solid support the peptides would adopt the helical structure necessary for metal coordination. 36 other peptides had the phosphine groups in $i, i+1$ relationship. Screening this first-generation library resulted in very moderate $ee$’s ranging from 18% for the $S$-enantiomer to 17% for the $R$-enantiomer. In a second-generation library also the $i, i+3$ position was examined (a D-phosphine containing amino acid in the $i$ position and an L-phosphine containing amino acid in the $i+3$ position). With this library selectivities of up to 37% $ee$ ($S$-enantiomer, 2.2% conversion) were achieved.

![Image](image-url)
One speciality of this paper is the reaction set-up for the hydrogenation reaction. The crowns with the metal complexes attached were disconnected from the stems and placed in individual vials to which the acrylate was added. The vials were then stacked in a Parr pressure reactor, which was charged with hydrogen and agitated on an orbital shaker for 48 hours.

4.4 Catalytic Phosphate Hydrolysis

The hydrolysis of phosphates is a reaction usually catalysed by antibodies or enzymes containing a metal ion in the active site. In addition, multiple coordination sites are necessary to bind the substrate and activate it for the hydrolysis. Usually chromogenic test substrates like p-nitrophenyl esters (76) are employed because the liberated p-nitrophenol 77 can easily be determined by UV/Vis spectroscopy (Scheme 18).

In 1995, Menger et al. were the first to introduce modified polymers capable of binding metal ions to catalyse the hydrolysis of phosphodiesters.72 Poly(allylamine) 86 was grafted with different mixtures of carboxylic acids using the EDC protocol. Depending upon the proportions used, 5% to 45% of the polymer’s amine groups were derivatised. Since the arrangement of the functionalities was not controlled, a huge family of different polymers was formed (Scheme 19).

Catalytic activity towards bis(p-nitrophenyl) phosphate was determined by mixing a buffered solution of the polymer, an aliquot of metal chloride solution (Mg2+, Zn2+ and Fe3+ salts were used) and a phosphodiester solution. Initial hydrolysis rates were obtained by periodic monitoring of the p-nitrophenolate absorption at 400 nm. The following conclusions have drawn by the authors: (a) Derivatisation with only a single functional group never produced a catalytically active polymer. As with enzymes, catalysis is predicated upon multiple interactions. (b) Comparison of these combinatorially based catalysts with antibody-catalysed hydrolyses 73 indicate that the best polymers [containing 10% Oxa (78), 10% Imi (81), 10% salicylic acid, 10% Thi-1 (83), and 10% Zn2+] hydrolyse a phosphomonooester about five times faster than the antibody systems.

Menger et al. used the same type of polymers in the catalytic dehydration of β-hydroxy ketones to α,β-unsaturated ketones.74

The approach of producing hydrolytically active polymers was taken up by Berkessel et al. in 1999.75 Using the split-mix synthesis, a library of 625 solid-phase-bound undecapeptides was synthesised on Tentagel S-NH2 by using PyBOP as the coupling reagent (Figure 13).

The amino acids L-Arg, L-His, L-Tyr, L-Trp, L-Ser were introduced at the positions X which were separated by two glycine (Gly) moieties as spacer units. The beads were incubated with different metal salts (Cu2+, Zn2+, Fe3+, Co3+, Eu3+, Ce4+, Zr4+) and subjected to hydrolysis experiments with the 3-hydroxyindolyl derivatives 89 (Scheme 20).

When the ester function of the substrate is hydrolysed, the resulting indoxyl derivative 90 is air-oxidised in solution to afford the turquoise and insoluble indigo dye 91 staining the active beads. Activity was found in the presence of Zr4+ salts. The most intensely coloured beads were collected and the peptide sequence was determined by Edman degradation. Using control experiments and re-synthesis of active and inactive sequences, the authors could establish a motif containing L-Ser at the N-termi-
nus and L-His at the C-terminus of the undecapeptide. In two of the three active sequences a combination of L-His and L-Arg was found in the two middle positions of the peptide strand. Although no structural data for the peptide-zirconium complex can be derived from the experiments carried out, this study clearly delivers more information about active substructures within the catalyst than in the random experiment by Menger et al. (vide supra).

Recently, Berkessel et al. reported on an extension of their approach. The ligand library synthesised (containing a total of 1458 ligands) consisted of three sublibraries. In all three sublibraries, the linear ligand strand starts with a tripeptide zone (AAS1-AAS2-AAS3), composed of L-Arg, L-Lys, and L-His in a combinatorial manner (Figure 14). The peptide zone was followed by an unsaturated mono-or dicarboxylic acid (R1), the dicarboxylic acid again being capped by the methyl ester of L-Arg, L-Lys or L-His. The mono- and dicarboxylic acids all carried a C=C double bond, which was subjected to the Sharpless asymmetric dihydroxylation, using either AD-mix α or β generating a diol substructure intended to serve as a phosphoryl group acceptor. As the thus functionalised peptide segments were no longer susceptible for Edman degradation, 10% of the resins loading capacity was used for the attachment of a coding strand consisting of nonfunctional amino acids. The resin-bound ligands were again incubated with different metal salts and subjected to the phosphodiesterase experiments. Active beads were identified using either a staining reaction producing insoluble Prussian blue from K3[Fe(CN)6] and Fe3+ or by ion pairing of the negatively charged phosphate groups remaining on the active beads with the cationic dye cresyl violet. The most intensely coloured beads were collected, analysed by Edman degradation and re-synthesised on solid support.

Berkessel et al. also carried out studies towards the activity of only parts of the ligand structures found active in the essays. He found out that for some ligands (e.g. 93) all structural elements were necessary in combination with the right metal ion to obtain activity, while in the case of other peptides, variation (92) (or truncation of the structure) lead to the discovery that polymer-bound histidine in combination with Eu3+ was the active substructure. Furthermore, neither histidine itself nor histidine bound to poly(ethylene glycol) (PEG) showed activity in the presence of Eu3+. In other words, the assay responded only to the substructure whereby the polymeric support (TentaGel S-NH2) was crucial for activity.

5 High-Throughput Screening in Catalysis

High-throughput screening in the pharmaceutical industry became so efficient by the early 1990s that it made the synthesis of drug candidates the rate-determining step in the drug discovery process and encouraged the adoption of combinatorial techniques. In the area of catalysis, neither high-throughput screening methods nor combinatorial synthesis has been applied until very recently. In most of the examples described above, standard GC or HPLC analysis for the separation of enantiomers or determination of conversion was used (in the combination with autosampler-equipped machines one or two hundred samples can be analysed within a reasonable time). However, if the analysis of hundreds or thousands of reactions is required or mixtures of catalysts are screened, special techniques have to be employed.

5.1 IR-Thermography

The idea to use IR-thermography for the detection of the active members in mixtures of supported acylation catalysts was first described by Taylor and Morken in 1998. In their reaction set-up, the beads carrying the catalysts swam on the surface of a solution containing both the alcohol and the acylation reagent. It was the objective of
this study to visualise temperature differences, which arise from the catalytic activity of a catalyst.

Reetz et al. were first to report on the application of IR-thermographic techniques for the screening of enantioselective catalytic reactions in liquid phase. Using already known highly enantioselective catalytic systems like the lipase-catalysed acylation of 1-phenylethanol with vinyl acetate as acyl donor or the transition metal-catalysed ring-opening hydrolysis of epoxides, they were able to show that the most active catalyst could be found by time-resolved IR-thermography. However, the systems used (e.g. the Jacobsen catalysts for epoxide-opening) were all known to be highly enantioselective. Therefore, the authors correlated the observed activity of the complexes with the well-known selectivity and called their method IR-thermographic screening for enantioselectivity. This, however, can only be deduced for well-known reactions but the method is surely not suitable for the screening of enantioselectivity of unknown catalytic systems.

The IR-thermographic screening approach was extended to endothermic reactions by Reetz et al. in 2000. They chose the ruthenium-catalysed ring-closure metathesis reaction (RCM) of substrates like 1,7-octadiene. The reactions were carried out in microtiter plates (MTP) using the catalyst precursors and were followed by time-resolved IR-thermography (Scheme 21).

For the active catalysts “cold spots” were observed on the MTP, which were attributed to an endothermic effect in the reaction of 94 to 95 and 96. Thermodynamic calculations indicated that the reaction was slightly endothermic (4.8 kJ mol⁻¹), however, the evolution of ethylene during the reaction might also contribute to the cooling of the solution. The authors stated that the catalysts precursors were examined for all substrates as the most active ones. Although the authors claimed to be able to examine even thermoneutral reactions using the cooling effect of evaporating ethylene, no example for a really thermoneutral reaction was given. As indicated by the authors themselves, for a better understanding of the observed endothermic effect, the enthalpies of solvation and mixing would also have to be considered.

5.2 Isotope Labelling/Pseudo Enantiomers

Concentrating on assays capable of screening hundreds to thousands of catalytic reactions per day, Reetz et al. reported on an ESI-MS (electron spray ionisation mass spectrometry) based method using pseudo enantiomers as substrates. Pseudo enantiomers are chiral compounds, which differ only in the absolute configuration and in isotope labelling. The use of pseudo enantiomers for ee determination goes back to a publication of Horeau et al., in which the MS detection of isotope-labelled diastereomers was described. Reetz et al. envisaged this technique for two stereochemical processes: kinetic racemate resolution and asymmetric conversion of prochiral substrates with enantiotopic groups. The outcome of the catalytic reaction (relative amounts of reactants and products) is directly determined by ESI-MS as the pseudo enantiomers have different molecular weights (Scheme 22).

Correlation of ee’s determined by chiral GC and ESI-MS measurement, indicated that the ESI-MS method with pseudo enantiomers delivers usable results. However, the method requires access to the substrate in both enantiomERICally pure and isotope-labelled forms.

Techniques for the diastereoselective acylation of chiral amines or alcohols with mass-tagged acids leading to diastereomers separable by ESI-MS have also been described.

5.3 Fluorescence Assays

Hartwig and co-workers have reported an interesting discontinuous fluorescence screen in which a series of forty conventional homogeneous Pd(dba)₂ + L (L = phosphine or diphosphine) catalysts were assayed for activity for coupling of an aryl halide with an alkene (Heck reaction, Scheme 23). The aryl halide component was grafted onto cross-linked polystyrene and catalytically coupled with a soluble alkene bearing a powerfully fluorescent coumarin group.
Scheme 23  Fluorescence assay for the Heck reaction by Hartwig et al.\textsuperscript{87}

At the end of the catalytic reaction the polymer beads were isolated by filtration and their fluorescence assayed visually as low, moderate or high. Greater catalyst activity for a conventional homogeneous reaction using the same catalyst was shown to correlate quite well with the catalyst that gave the strongest fluorescence in the rapid assay. For example, the L = t-Bu₅P catalyst was identified as one of the most active ones.

In 1999, Copeland and Miller\textsuperscript{88} proposed a method in which the catalytic O-acylation of N-acetylated amino alcohol\textsuperscript{109} was followed by fluorescence: the acid released in the acyl transfer step protonates the dye precursor\textsuperscript{112} and turns on the fluorescence response (Scheme 24). The use of an automated fluorescence plate reader allowed quantitative, parallel intensity data to be obtained in solution on a 96-well plate, making the comparison in triplicate of seven catalysts at three different loadings possible. The data were good enough to allow the kinetics to be followed.

5.4 Reactive Dyes

The formation of coloured products has long been used for monitoring enzyme reactions. Visual selection of the most active catalyst was first shown to be applicable by Crabtree et al. in 1998.\textsuperscript{89} They synthesised the reactive alkene (114a,b) and imine dyes (115a,b) and tested them in hydrosilylation reactions using Ph₂SiH₂ and twelve catalysts, some of which were already known to be active in the hydrosilylation reaction (Figure 15).

When the reactive C=C or C=N bond is hydrosilylated, the electronic connection between donor and acceptor is broken and the absorption coefficient drops by a factor of ca. 100. A colour change of the dyes was observed and the time for bleaching recorded. The bleaching times for the catalysts showed that Wilkinson’s catalyst was, as expected by the authors, among the most highly active. The palladacyclic Heck reaction catalyst \{[Pd(Ar₂PC₆H₄CH₂)OAc]₂\} \textsuperscript{90} of Herrmann, Beller et al.\textsuperscript{90} a compound not previously considered for hydrosilylation, was also among the most active. However, comparison of the dyes with conventional hydrosilylation substrates showed that the dyes were much more reactive, which on one hand is helpful for rapid screening, on the other hand it prevents a direct transformation of the found catalytic systems to standard olefins. Crabtree also described the preparation of a monophosphine library\textsuperscript{14} and its application in the hydrosilylation of the above-mentioned dyes 114a,b and 115a,b.

5.5 One-pot Multi Substrate Screening

An interesting approach for combinatorial catalyst screening using a defined mixture of substrates has been reported by Kagan et al.\textsuperscript{13,63} They used a given catalyst in the presence of a set of different substrates. The reaction may in principle be valid if the products do not interfere with the catalyst and if the resulting product mixtures can be

Scheme 24  Assay system for acylation reactions by Copeland and Miller\textsuperscript{88}

Figure 15  Assay system for hydrosilylation reactivity by Crabtree et al.\textsuperscript{89}
analysed without overlaps in the elution of the various compounds. In fact, Kagan et al. were able to show that the CBS reduction of ketones could be carried out on a set of seven ketones and that results correctly reproduced the enantioselectivities of reduction (in parentheses) performed on individual ketones (Scheme 25). If there is no interference of the formed products with the catalytic system, this approach can be used for a preliminary evaluation of chiral reagents or catalysts.

5.6 Screening of Mixtures of Catalysts

As already pointed out in the introduction to this chapter, parallel or nonparallelled assays are to date the most effective ways to determine the outcome of catalytic reactions. The screening of mixtures of catalysts as described by Morken et al. 77 and Berkessel et al. 75, 76 usually relies on techniques developed for the mix-and-split synthesis of peptides or derivatives thereof. These techniques allow for the production of large ligand libraries (several thousand) due to the possibilities of peptide chemistry, but are also drastically limited because small peptide derivatives can only be reasonably applied in a fairly small number of metal-catalysed reactions. A second drawback is the low amount of information that can be obtained from IR-thermographic or colour assays, which are intrinsically necessary for mixtures of catalysts. Nevertheless, these techniques can perhaps be seen as a first step in a screening cascade.

5.7 Miscellaneous Chromatographic Methods

Usually HPLC or GC methods are not suitable for high-throughput determination of enantioselectivities because the separation of enantiomers on chiral modified columns is a time consuming process. If, however, usual columns can be used to separate starting materials or side products from enantiomeric products, the process is sped up drastically. The enantiomeric excess of the products can then be determined by methods like circular dichroism (CD) as shown in the already mentioned publication of Mikami et al. 26 for the diethyl zinc addition using diols and chiral activators. Here a HPLC detector was used which could measure the circular dichroism (Δε) and the UV absorption (ε) at a certain wavelength simultaneously. The ee of a given probe shows a linear dependency of the g factor, which can be derived from the CD and the UV data (g = Δε/ε). In a very recent full paper Mikami et al. stated that the ee determination of each sample required less than 1.5 minutes. 92

Reetz et al. reported the use of capillary electrophoresis for the high-throughput ee determination of chiral amines. 93 They used a commercially available capillary array electrophoresis unit called MegaBASE consisting of 96 capillaries and were thus able to determine more than 7000 ee’s per day. The authors also estimated that by optimisation of the separation conditions 15000 to 30000 ee determinations per day could be performed.

6 Conclusion

The field of combinatorial catalysis has seen considerable progress within the last few years. Reliable methods for the parallel synthesis of ligands in liquid phase as well as on solid support have emerged and techniques for the high-throughput determination of activities and selectivities have been developed and are still improved. However, the most promising aspect of combinatorial catalysis lies within the application of modular ligand systems. But the access to chiral nonracemic building blocks is still limited which causes most authors to rely on peptidic structures modified by suitable metal binding groups or turn elements as seen for instance in the work of Jacobsen, Gilbertson, Snapper and Hoveyda. 64 Until now, the creation of chiral ligands in a combinatorial fashion is limited to only a few systems like, e.g., the examples by Burgess and Schmalz. 3 The ligand systems consisting of variable building blocks and therefore representing ideal platforms for combinatorial variations like ferrocenyl systems of type 25, 33–35 chiral oxazolines of type 26, 36–40 and binaphthyl-derived complexes of type 27, 41–43 (Figure 6), have, until now, not even found an application in combinatorial catalysis.

Asymmetric catalysis, especially for systems prepared in situ or using additives, is mechanically complex. Researchers attempting to discover and optimise catalytic systems may be aware of the degree of complexity, but they are often forced to assume that all of the variables are independent because they do not have the capacity to proceed any other way. Consequently, a typical experimental approach is to hold all but one parameter constant, find the optimal condition for this variable and retain it, then pro-
ceed to the next variable. However, critical parameters for catalysis are often mutually dependent.

The real opportunity that combinatorial catalysis offers is to gain a whole lot of information about a given catalytic reaction in a relatively short period of time. Interdependencies of variable parameters may be discovered by two- (or even higher) dimensional high-throughput reaction screens. Design and chemical intuition are only valuable for setting boundary conditions. In fact, it is impossible to reliably select a complete set of ideal experimental parameters using design and chemical intuition alone, especially if some show high degrees of mutual variability. Additionally, in a classical approach in catalysis, catalytic systems are often optimised for certain substrates, which in most cases proved very suitable rather than being interesting from a chemical or economical point of view. These highly optimised systems frequently suffer from a very small substrate specificity leading to the consequence that only very few ligands find broad applications and are usable in different reactions. In a combinatorial approach, a broad spectrum of substrates and catalysts can be examined in a relatively short period of time giving rise to more structural activity (or selectivity) relationship data and therefore perhaps a better understanding of catalytic processes.

References
