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Combinatorial Chemistry: A Tool for the Discovery of New Catalysts

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Abstract: The discovery of new reactions and catalysts has always presented an intriguing challenge to scientists. With the rise of combinatorial chemistry, a new method has emerged that holds considerable promise to facilitate the task since it allows for the simultaneous generation and testing of a large number of compounds. The crucial difficulty lies in establishing general technologies for rapid and reliable screening of libraries to determine the catalytic activity of their members. Several recent publications have addressed this question by using infrared thermography, colorimetric assays and fluorescence spectroscopy. These techniques have not only been applied successfully to the high-throughput screening of parallel compound arrays but also to the screening of one-bead-one-compound libraries. This demonstrates that combinatorial chemistry possesses indeed the potential to establish itself as a powerful tool for the discovery of new catalysts. This review describes the methodologies used so far for the detection of catalytic events and will place particular emphasis on the on-bead screening of one-bead-one-compound libraries.

1. INTRODUCTION

Using the principles of random mutation and selection of the fittest, nature has evolved enzymes with unique efficiencies as well as specificities for catalytic transformations. In organic chemistry, the permanent quest to produce compounds in ever better yields and higher enantiomeric purities has driven the development of new and more effective catalytic reactions. However, despite this strong interest and numerous efforts, the number of rationally designed synthetic catalysts with performances comparable to their natural counterparts is small. This underlines the subtle mechanistic aspects that govern catalytic reactions and make the rational design of a catalyst an extremely challenging task. As a result, considerable time is consumed during the development of a new catalyst by the sequential testing of series of ligands with different yet similar substituents as well as by trials for the best reaction conditions such as stoichiometries and concentration of the reactants, or the choice of the metal. Given the subtle mechanistic factors that control the reactivity and selectivity of a catalyst and the tedious stepwise conventional catalyst development, there is a strong need for a more empirical approach to make the catalyst discovery process more efficient.

Combinatorial chemistry holds the potential to fill this gap since it allows for the simultaneous generation and rapid testing for a desired property of large numbers of chemically related compounds. Thus, one might regard combinatorial chemistry as the scientist's attempt to mimic the natural principles of random mutation and selection of the fittest. However, in comparison to the areas of molecular recognition [1], material science [2] as well as drug discovery and optimization [3] where combinatorial chemistry has already established itself as an invaluable tool, current combinatorial approaches to the development of catalysts are not as widespread and less mature [4,5]. The challenge is posed by the need for general and reliable screening methodologies that allow for the facile identification of catalytically active library members within a large library of potential catalysts. Recent advances demonstrate that

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combinatorial chemistry is in the course of becoming a powerful tool for catalyst development.

This review will discuss those screening technologies that allow for the simultaneous testing of many potential catalysts. The testing of compound arrays that rely on the offline analysis of a catalytic event by conventional analytical methods (HPLC, GC, etc.) is not truly combinatorial and will be neglected in this review.

2. SPATIALLY ADDRESSABLE LIBRARIES VERSUS "ONE-BEAD-ONE-COMPOUND" LIBRARIES

Two conceptually different approaches for the generation of molecular diversity must be distinguished: The parallel or array synthesis of spatially addressable libraries and the "split-and-mix" protocol for the generation of "one-bead-one-compound" libraries.

2.1. Spatially Addressable Libraries

In spatially addressable or parallel libraries, the individual members are prepared in predetermined separate reaction containers, typically the wells of 96-well microtiter plates [6]. The compounds are synthesized in solution or on a solid support in a stepwise manner. The generated molecular diversity is therefore somewhat limited, but each library member has a clearly defined location and can be synthesized in amounts large enough to allow for the analysis of its purity by conventional HPLC, GC, NMR-spectroscopy, etc. Screenings of the library members for a desired activity are performed individually in the separate compartments of the microtiter plate. Thus, the synthesis as well as the screening of a parallel library can be performed in an automated high throughput fashion. The efficiency of high throughput screenings relies highly on efficient synthesis and screening robots as well as on a powerful data management.

Parallel libraries have served well for the discovery of novel drugs and in enzyme activity studies where a crucial minimal amount of test compound is needed [3]. Furthermore, parallel arrays of novel materials have been successfully employed for the discovery of new materials with hard to design properties (superconductivity [7], magnetoresistance [8], luminescence [9], among others [2, 4]).

Given the relative ease of product identification in parallel libraries, it is not surprising that the first approaches for the discovery of novel catalysts by combinatorial means took advantage of this methodology. The catalytic activity of each library member was determined by individual HPLC or GC analysis of the products formed in each reaction compartment. In a pioneering work, Hoveyda *et al.* demonstrated the usefulness of the methodology by systematically screening the members of a parallel library of different Schiff bases for their influence on the Ti(O*i*Pr)$_4$ catalyzed addition of TMSCN to *meso*-epoxides [10, 11].

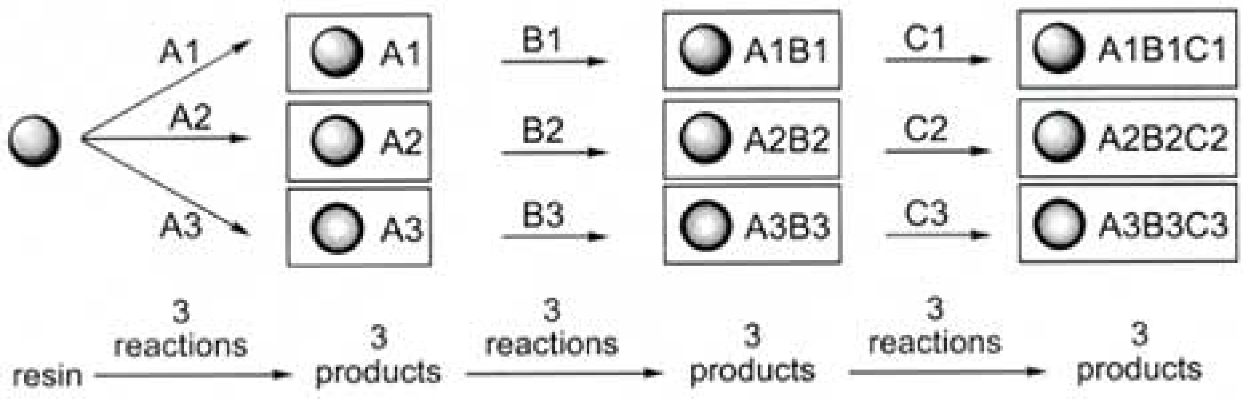

Fig. (1). The basic concept of parallel synthesis.

Product yields and enantiomeric excess were determined by using HPLC. A formerly unknown ligand that would have been difficult to design rationally surfaced as the most active and the most selective catalyst.

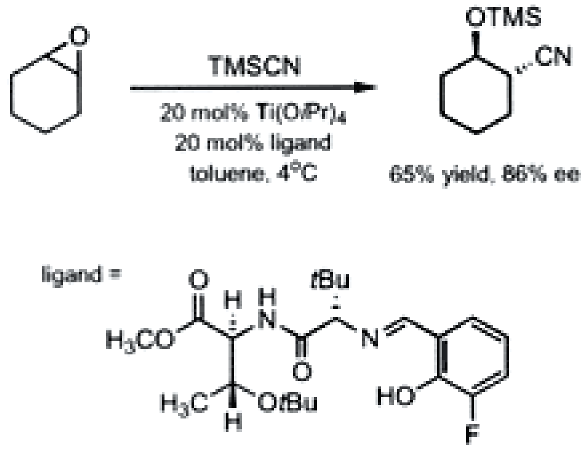

Fig. (2). Schiff-base ligands for the Ti(O*i*Pr)$_4$ catalyzed addition of TMSCN to meso-epoxides from a HTS of a parallel library.

Similar approaches led to the discovery of efficient catalysts for the addition of diethylzinc to aldehydes [12, 13], intramolecular metal-carbene insertions [14], Pd-catalyzed allylic alkylations [15], aza-Diels Alder reactions [16] and Strecker synthesis of amino acids [17, 18], among others [4, 19]. While some of these screenings tested several catalysts simultaneously for their efficiency, the assays ultimately rely on the time consuming step by step analysis of each catalytic reaction by HPLC or GC and will not be discussed any further in this review.

2.2. One-Bead-One-Compound Libraries

While the high throughput screening of spatially addressable libraries might be considered as an extension of the conventional “one at a time“ synthesis and testing of compounds, one-bead-one-compound libraries are truly combinatorial assemblies of large numbers of different compounds. Molecular diversity is generated by the split-and-mix protocol which involves splitting of the resin into equal portions, subjecting each portion to a different reaction and finally mixing of the resin [20, 21]. Successive cycles of distributing, reacting and mixing of the beads lead to an exponentially increasing number of compounds relative to the number of reactions used. Since each bead reacts with only one set of reagents in each cycle, each bead carries only a single library member. As a result, the split-and-mix protocol allows for the simultaneous generation of many more compounds than parallel synthesis.

However, the analysis of the compound on a single bead is more difficult since each bead carries typically only ~100 pmol of compound. Recent advances in modern analysis techniques [22-24]

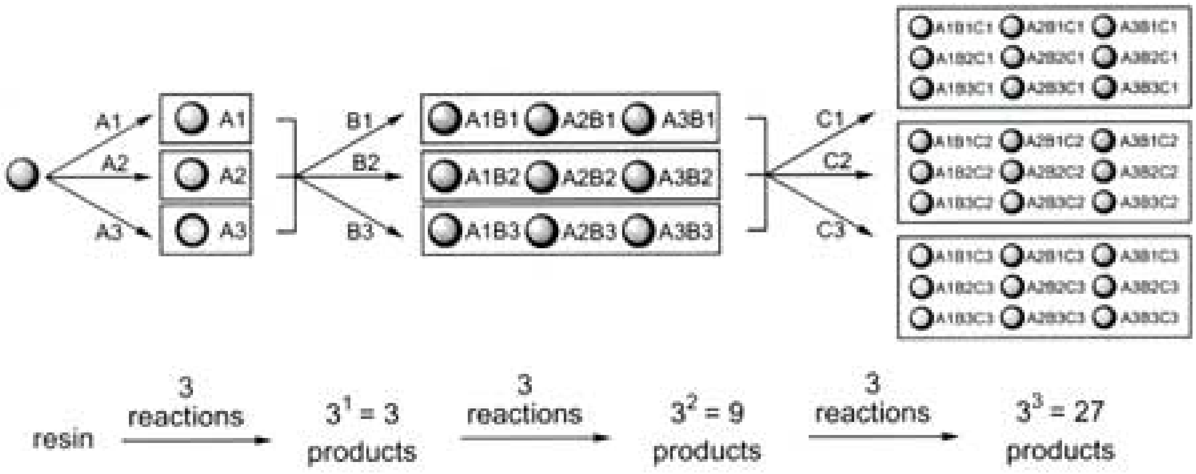

Fig. (3). The basic concept of split synthesis.

have surmounted the problem to a large extent, but the true breakthrough was accomplished by the introduction of encoding techniques [25]. Molecular tags that uniquely encode each step of the library synthesis are attached to the solid support and record the reaction history of each individual bead. The cleavage and the analysis of the molecular tags of the beads carrying library members of interest reveal the structure of the active compound.

The most important encoding methods employ either microsequenceable oligonucleotides [26], oligopeptides [27-30] or small molecules that can be analyzed by using gas chromatography [31, 32], high-performance liquid chromatography [33, 34] or mass spectrometry [35].

One-bead-one-compound libraries allow for the simultaneous screening of a large number of chemically related compounds for a desired activity. The screening is typically performed with the compounds attached to the solid support since the encoding information would be lost otherwise. On-bead screenings have been employed especially successfully for the identification of novel metal complexes [36-39] and in studies of molecular recognition where it has been possible to detect selective intermolecular interactions that would have not been possible to predict by conventional means [40-45]. Furthermore, Jacobsen *et al.* demonstrated that several of the identified metal complexes are efficient catalysts for epoxidation reactions [37].

The on-bead binding assay simply encompasses mixing of the solution of a receptor whose binding properties are of interest with a one-bead-one-compound library of potential guest molecules. An interaction between the two binding partners can be detected directly at the bead if the binding partner in solution carries a marker that allows for visual detection. Such markers can be simple dyes or fluorescent molecules that allow for visual detection [1, 40-45], enzymes or antibodies that allow for their detection by a color reaction [21, 31] or radioactivity that can be detected by phosphoimaging techniques [46] or microradiography [47].

The on-bead screening of a library of potential catalysts presents a larger challenge since the reactants and the reaction products usually diffuse into the surrounding solution and leave the catalyst – naturally – unchanged. Thus, smart and reliable assay systems are needed to surmount the intrinsic difficulties of the combinatorial screen for catalytic activity. The question has been addressed by colorimetric and fluorescence spectroscopy, visual detection of the on-bead polymer growth and infrared thermography.

3. COMBINATORIAL SCREENING METHODOLOGIES FOR THE IDENTIFICATION OF CATALYSTS

3.1. Colorimetric and Fluorescence Assays

3.1.1. Hydrosilation of Alkenes or Imines

Crabtree *et al.* have used the bleaching of a reactive dye as a method for detecting the catalytic activity of potential hydrosilation catalysts [48]. The group prepared four ferrocenyl-substituted dyes with electron-donor and –acceptor groups at each end of either an alkene or imine and tested

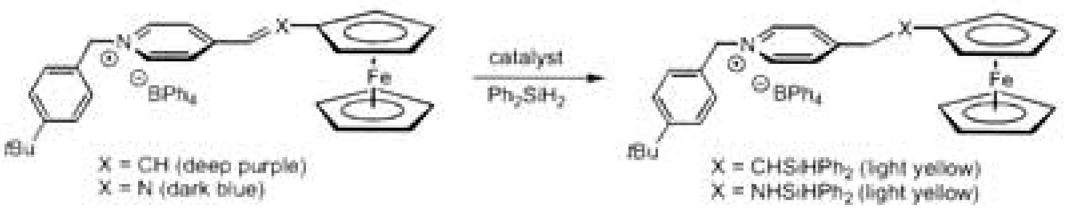

Fig. (4). Reactive dyes to select for hydrosilation catalysts in a parallel screening.

twelve metal complexes for their hydrosilation properties in a parallel screening. When the reactive functionality, the alkene or the imine, is saturated upon reaction with a catalytic species, the color of the dye bleaches since the electronic connection between the electron donor and acceptor is diminished.

The bleaching can be observed qualitatively by eye and is recorded quantitatively by a digital camera. Using this facile visual screen, the authors found the known Wilkinson catalyst to be the most active, but also discovered that a palladacycle, [Pd{(*o*-tolyl)$_2$PC$_6$H$_4$}OAc]$_2$, usually applied for Heck reactions but never considered as a hydrosilation catalyst, was among the most active catalysts. Control reactions proved that the relative order of reactivity of the hydrosilation catalysts is identical when conventional unsaturated systems instead of the reactive dyes are employed.

3.1.2. Allylic Alkylations

While the screening for the hydrosilation of an unsaturated compound relies on the disappearance of color, Lavastre and Morken used the generation of color for the identification of catalysts [49]. Combinations of eight different ligands and twelve different metal salts where screened in a 96-well plate for their efficiency to catalyze the allylation of ß-dicarbonyl compounds. The researchers used 1-naphthyl allyl carbonate as an allyl source and the diazonium salt of Fast Red as an indicator. Formation of the active π-allyl complex furnishes CO$_2$ along with 1-naphthoxide which deprotonates the 1,3-dicarbonyl compounds that can in turn react with the π-allyl metal complex. Since 1-naphthol is the only species in the reaction mixture that can react with the diazonium salt to generate the bright red azo dye Fast Red, the red color is indicative of the successful formation of the active π-allyl complex.

The assay identified not only the well known catalyst system Pd(OAc)$_2$ combined with a phosphine ligand but also the combination of [{IrCl(cod)}$_2$] and *i*Pr-pybox or 1,10-phenanthroline as efficient catalysts. The later present the first examples for non-phosphane iridium catalysts capable of allylic alkylations.

3.1.3. Heck Reactions

Hartwig and coworkers have used fluorescence detection for the parallel screening of 45 different phosphine and diphosphine ligands for their ability to form an active catalyst with Pd(dba)$_2$ for the coupling of an aryl halide with an alkene [50]. A polymer supported aryl halide was coupled

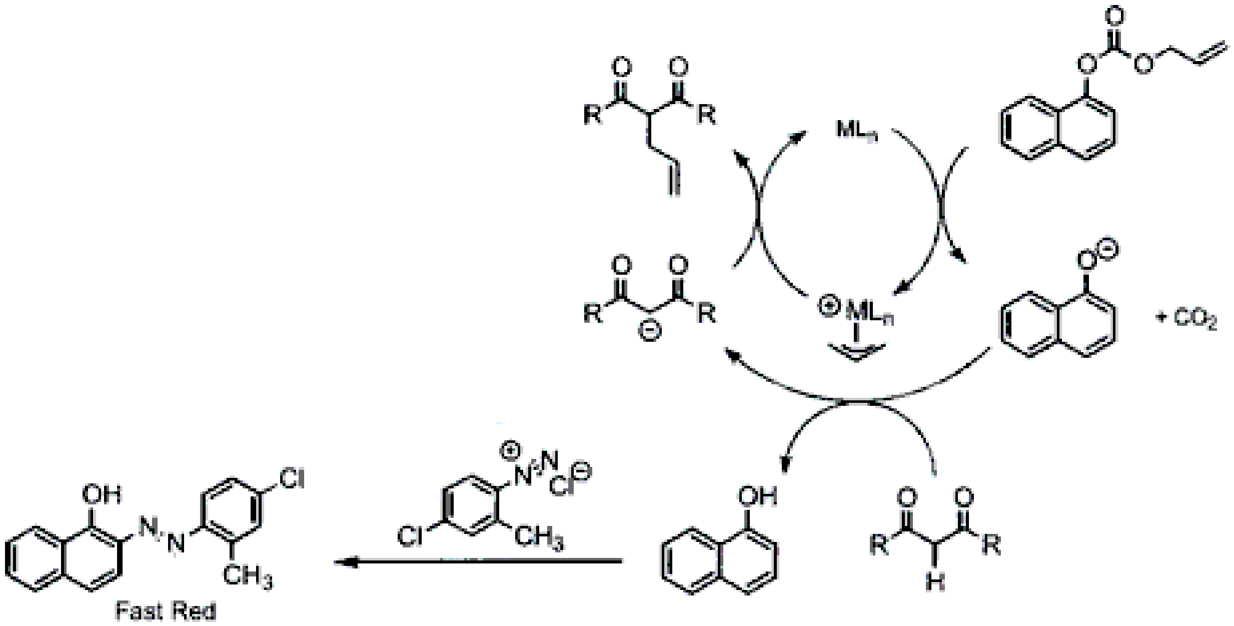

Fig. (5). Colorimetric assay for the detection of allylic alkylations.

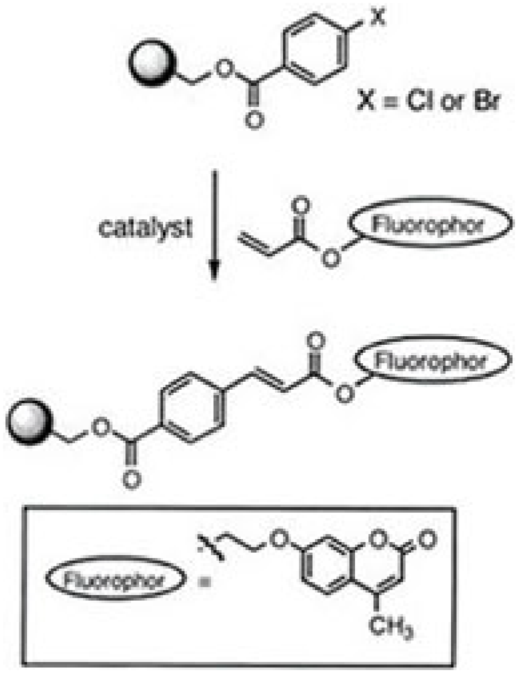

Fig. (6). Heck reaction between a polymer bound aryl halide and a fluorescently marked alkene.

with an alkene bearing a coumarin group as a fluorescent marker. Thus, a successful coupling is signalled by the fluorescence of the solid support.

The screenings resulted in the identification of di(*tert*-butylphosphino)ferrocene and tri(*tert*-butyl)phosphine as highly effective ligands for the Heck coupling of both aryl chlorides and bromides.

3.1.4. Hydrolysis Reactions

While all of the above-described assay methods are specific for a single reaction, Berkessel and Herault established a screening system that allows for the detection of catalysts with hydrolytic or cleavage activity in general among the members of a one-bead-one-compound library [51]. The colorimetric assay relies on the formation of a brightly colored insoluble indigo dye which forms upon hydrolysis of the substrate and precipitates on the bead carrying the active catalyst Fig. (**7**).

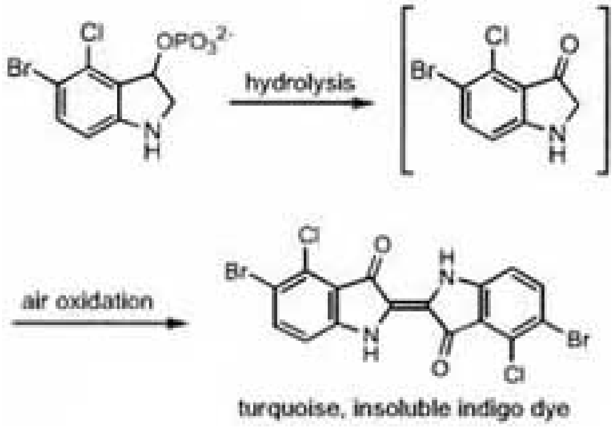

Fig. (7). Colorimetric assay for the screening of hydrolytic activity.

3-Hydroxyindolyl derivatives served as substrates to discover novel artificial hydrolases in the screening of a one-bead-one-compound library of metallated undecapeptides. A 625-membered library of undecapeptides was synthesized by the usual split-and-mix protocol with seven fixed and four randomized positions and was mixed with various metal salts to generate the metal complexes. Mixing of the metallated peptides with the phosphate derivative showed that certain Zr^{IV}-peptide-complexes possess hydrolyzing activity as indicated by a few beads that were deeply stained.

Analysis of the peptide sequences of the active beads by Edman degradation revealed the active sequences. Their activity was further proven and quantitated in solution phase experiments not only with the examined indigo derivative but also with the corresponding *para*-nitrophenylphosphate. While the authors were not able to detect any compounds with ester- or amide-hydrolytic activity, the screening approach is generally suitable for the detection of any hydrolysis event by any class of potential hydrolyzing agent.

Earlier, Still and coworkers had demonstrated that cleavage activity is not limited to metal complexes of peptides [52]. In on-bead screenings

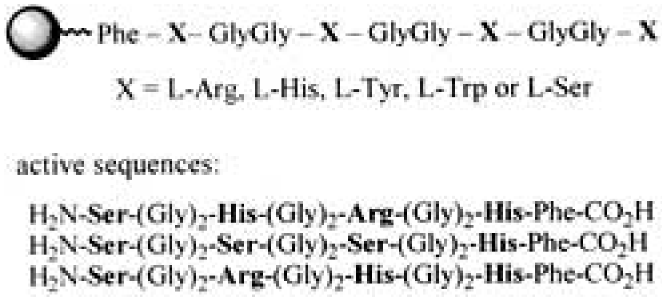

Fig. (8). Undecapeptide library containing hydrolytically active sequences.

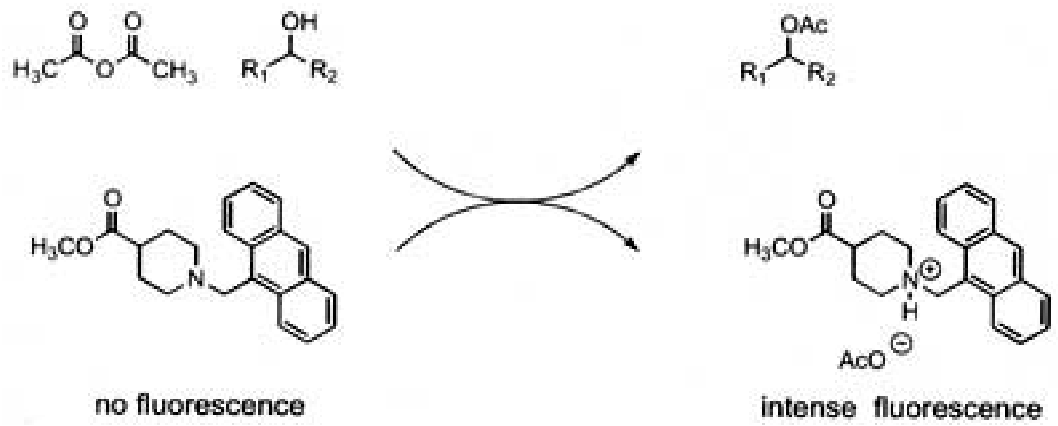

Fig. (9). pH-sensitive fluorescence indicators.

the group was able to select macrocyclic receptors capable of cleaving active esters of amino acids. While the experiments were not designed to observe catalytic turn-over, macrocyclic receptors discriminating between L- or D-amino acid-esters were identified. De Clercq and coworkers adapted this stoichiometric appoach and identified in a deconvolutive study members of a steroidal two-armed library with hydrolyzing activity against a para-nitrophenylester [53].

3.1.5. Acetylation Reactions

Miller and Copeland have used pH-sensitive molecular sensors for the discovery of novel acylation catalysts [54]. Aminomethylanthracene is utilized as an acid sensor since neutral aminomethylanthracene undergoes photoinduced electron transfer (PET) but fluoresces once it is protonated. With this fluorescence read-out system in hand, the acylation reaction of alcohols with acetic anhydride can be monitored since acetic acid is released in the acyl transfer reaction and triggers the fluorescence response.

Initially, the authors used this fluorescence-based assay in a solution phase high-throughput format for the parallel screening of the activity of seven known acylation catalysts. The fluorescence intensities of each reaction were monitored by a fluorescence plate reader and could be correlated to the overall catalytic activity of each catalyst. The obtained results were in good agreement with the known acylation activities of the examined catalysts [55].

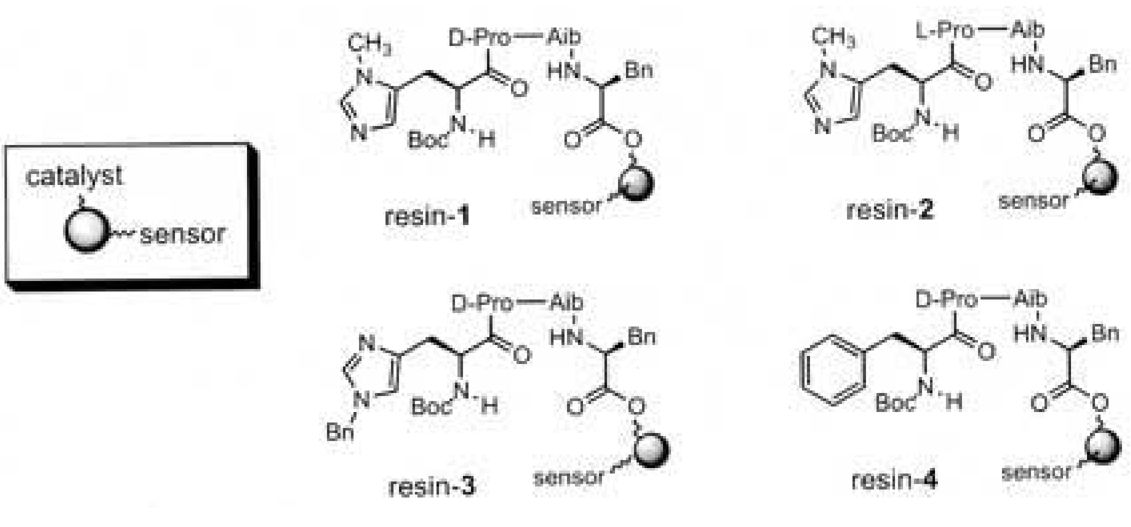

Fig. (10). On-bead fluorescence assay for acetylation catalysts.

Subsequently, Miller and Copeland proved that the fluorescence-assay can be adapted to on-bead screenings of one-bead-one-compound libraries [54]. The sensor was covalently attached to Wang resin which was simultaneously functionalized with potential catalysts. In a model experiment, four different resins with peptidic acylation catalysts of known activity were tested for their acylation activity.

When the four types of beads were exposed to identical reaction conditions in segregated reaction vessels, fluorescence micrographs indicated that the fluorescence intensity was homogeneous among the beads of the same kind and that the relative fluorescence intensity of the beads paralleled the reactivity trends of the catalysts observed in solution studies. Mixing of all resins and subjecting them to the reaction conditions showed beads with four different fluorescence intensities (resin-**1** >> resin-**2** > resin-**3** ≈ resin-**4**). This experiment indicates that the diffusion of acetic acid between the beads is a slow process relative to the reaction monitoring. Thus, the experiments should open the way to the screening of large one-bead-one-compound libraries for their acylation activities.

3.2. Polymer Growth

The ever-increasing need for polyolefins is constantly sparking the interest in novel olefin polymerization catalysts. While most commercial-scale polyolefin processes employ high surface area supports for immobilizing the catalysts, Powers, Murphy and colleagues have examined the use of polystyrene as a solid support [56]. The team developed a parallel synthesis and screening protocol for a polymer-bound 96-membered library of 1,2-diimine-transition metal complexes. Catalysts of this kind are easily synthesized and exhibit high activity and high tolerance towards functionalized olefins such as methacrylates and vinyl acetates [57]. The researchers set out to explore the steric and electronic influence of different substituents at the 1,2-diimine as well as the influence of the metal center on the catalytic performance. Thus, they used 48 commercially available anilines with varying steric and electronic substituents to synthesize the corresponding diimines. The polymer-bound diimines were converted into their Ni^{II} and Pd^{II} complexes, respectively, and were analyzed individually for their polymerization activity in a parallel screening.

Activation of the catalysts with either methylamuloxan, MAO, or tetrakis(3,5-bistrifluoromethyl)phenyl borate, $Na[B(Ar_F)_4]$, and exposure to ethylene in a high-pressure parallel polymerization reactor led to polymer growth around the polystyrene support. In comparison to the initial polystyrene beads, their size had increased from 2 to 10-fold depending on the catalyst on the bead. The size increase correlated to molecular weights of the produced polymer granules of up to 59,000 g/mol. While the influence of the substitution pattern of the ligand could not be analyzed, the Ni^{II} catalysts generally displayed higher activity than the corresponding

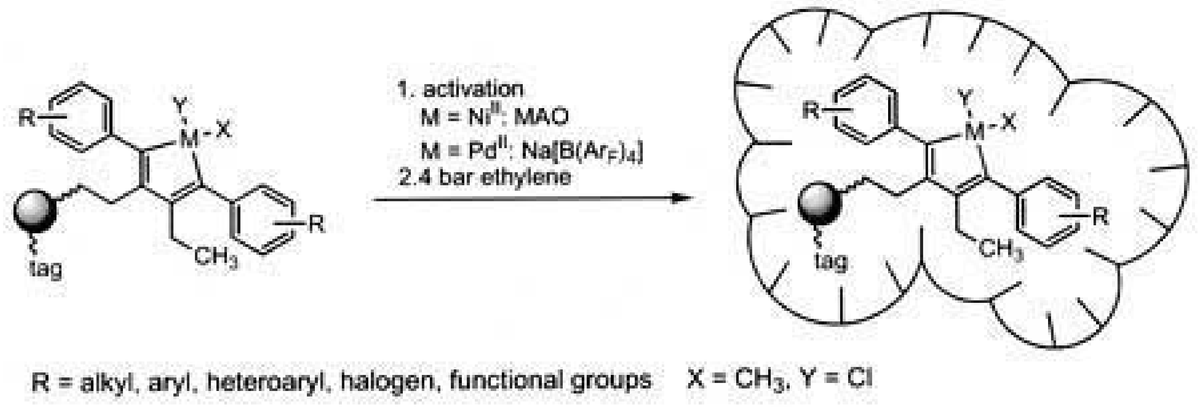

Fig. (11). Screening for polymerization catalysts by the size of the beads.

Pd^{II} catalysts. Interestingly, the polymer bound Pd^{II} catalysts were more active, the Ni^{II} catalysts less active than their solution-phase counterparts when screened under identical conditions.

In a proof of principle, the authors extended this high throughput screening of a spatially addressable library to the on-bead screening of a one-bead-one-compound “library consisting of only two different catalysts". A Ni^{II} as well as a Pd^{II} complex were synthesized separately on differently tagged beads, mixed and subjected to the polymerization conditions. Inspection under a microscope showed two distinct sizes of polymer products. The analysis of the tags from several beads revealed that in accordance with the previous results the larger polymer granules derived from the Ni^{II} catalyst, the smaller ones from the Pd^{II} catalysts. While the on-bead screening was performed with an unrealistically small one-bead-one-compound library, the experiments show that on-bead screenings can serve as a valuable tool for the detection of the catalytic activity of a polymerization catalyst.

3.3. IR-Thermography

Infrared thermography detects infrared radiation and has found numerous applications for recording local spatial temperature changes over time. Modern infrared cameras with focal plane array detectors made of InSb, HgCdTe or PtSi alloys deliver two-dimensional high resolution thermal images which are composed of emitted and reflected radiation. The ratio of emission and reflection varies for each surface. The different colors in thermal IR images visualize different photon intensities of the IR radiation. The photon intensities can be converted into blackbody temperatures of the object either by knowing the emissivity of a material or through a temperature calibration.

Since most chemical reactions have a measurable heat of reaction, ΔH_r°, IR-thermography presents a rather general tool to monitor the progress of a catalytic reaction. Catalysts with the highest activity will evoke the largest temperature change since the temperature change is proportional to the turnover number of the catalyst and the heat of the reaction.

3.3.1. IR-Thermography in Heterogeneous Systems

In a proof of concept report, Willson and coworkers employed IR-thermography to identify possible formulations of heterogeneous catalysts for the oxidation of hydrogen to water [58]. The ignition temperatures of an array of 16 different metal-doped aluminum pellets were IR thermographically monitored by heating the pellets in a special reaction container in a gas stream of hydrogen and 0.5% oxygen. Large thermographic changes (up to 82 °C) were observed and showed the palladium, platinum and iridium doped pellets to be the most active catalysts followed by the rhodium-loaded pellet.

Maier and coworkers showed that larger arrays of potential solid supported catalysts with smaller thermal changes could be successfully screened for their catalytic performance by IR-thermography [59]. The group applied emissivity corrected IR-thermography to detect the activity of various transition metal impregnated, amorphous microporous mixed oxides (AMM) in heterogeneously catalyzed gas phase reactions. Using automated sol-gel procedures the researchers deposited less then 200 μg of each potential catalyst in the tiny wells of a low reflection slate substrate. In order to monitor exclusively the temperature differences caused by the catalytic activity of each potential catalyst, a thermal picture of the array was taken prior to the addition of substrates and subsequently subtracted from the pictures taken during the isothermal catalytic experiment. This technique allows to minimize the effect of emissivity differences of the different catalyst wells. As a result, the researchers were able to reliably detect temperature differences as small as 0.1K. The setup also allowed for the consecutive screening of the same array of potential catalyst for their activity in different gas phase reactions.

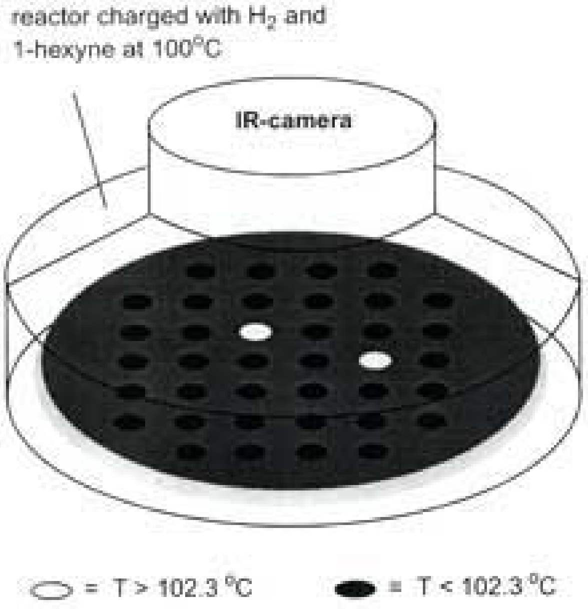

Fig. (12). IR-thermographic detection of catalytic activity.

For the hydrogenation of hexyne at 100°C, silicon doped AMM-Pd/Si and AMM-Pt/Si were found to be the most active. Two different titanium containing catalysts were best suited for the oxidation of toluene and isooctane, respectively, at 350°C. Recent advances show that the catalytic activity of such parallel arrays of potential metal catalysts in gas phase reactions can also be simultaneously analyzed by resonance-enhanced multiphoton ionization [60] or scanning mass spectrometry [61].

Taylor and Morken demonstrated that the tool of IR-thermography is not limited to the screening of parallel compound arrays but can be successfully applied to the on-bead screening of one-bead-one-compound libraries [62]. In a search for novel acylation catalysts, an encoded library of 3,150 different potential nucleophilic catalysts was prepared by the split and mix protocol and tested for their acylation and oxidation properties against a variety of substrates. The library beads were spread out in a reaction solution of chloroform/ethanol/triethylamine/acetic anhydride (40:6:6:3; v/v/v/v) and monitored with an IR camera. While most of the beads did not show a detectable thermal change, a few beads showed up as “hot spots”. Separation and decoding of the sequences of the “hottest beads” revealed a diastereomeric pair of *N*-4-pyridylprolines as the compounds on these beads. Kinetic experiments of the compounds underlined their high activity in comparison to other compounds that were present in the library but did not show activity in the thermal screening.

3.3.2. IR-Thermography in Homogeneous Solution

IR-thermographic screens are not limited to heterogeneous systems but can be applied to the solution phase. Reetz and coworkers have used time resolved IR-thermography for the liquid phase screening of catalytic reactions such as the enantioselective acylations of a chiral secondary alcohol by a lipase and the enantioselective ring opening of epoxides to non-racemic diols [63,64]. A modified microtiter plate was used for carrying out the reactions which were followed by periodically monitoring the temperature changes in the reaction wells. Recordings (250 within 5 s) of the library array were then averaged and visually inspected. The screenings showed that time resolved IR-thermography can clearly distinguish between active and inactive catalysts: In the two case studies, the relative trends in the activity and selectivity of the catalytic reactions already known from the literature were reproduced.

In a more recent study, Reetz and coworkers were also able to prove that IR-thermographic screenings are not limited to exothermic reactions [65]. The initiation rates of four known precatalysts for the metathesis reaction of 1,7-octadiene were examined using the method described above. The IR-thermographic pictures taken after 1-2 min of three of the four reactions revealed “cold spots”, while the reaction compartment of the fourth (least active) precatalyst remained unchanged. The observation of cold spots implies the uptake of heat indicating an endothermic effect. While it has not been possible to quantify the different catalyst activities, since the decrease of temperature is partially also due to the evaporation of one of the reaction products (ethylene), the measured relative catalytic activities were in good agreement with the corresponding laboratory scale reactions.

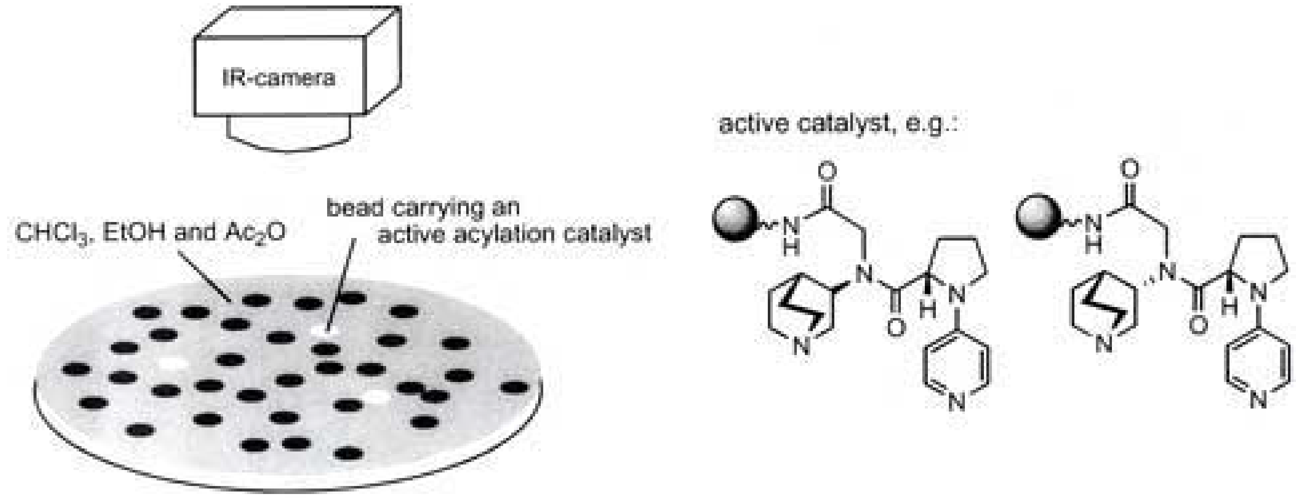

Fig. (13). On-bead IR thermographic screening for acetylation catalysts.

Since IR-thermography can be applied to the screening of large arrays of potential catalysts in homogeneous and heterogeneous phase as well as to on-bead screenings of one-bead-one-compound library, and since most reactions exhibit a measurable heat of reaction, IR-thermography offers the most general screening protocol to date for the catalytic activity of a combinatorial library. However, a limitation is posed by the lack of information on the structure of the generated reaction products.

4. OUTLOOK

Considering that the development of catalysts by combinatorial means is still in its infancy, significant breakthroughs have already been accomplished. Improvements in the synthesis and the high throughput screening of parallel libraries will go in hand with technological advances in miniaturization, parallelization and automation. The efficiency of on-bead screenings of one-bead-one-compound libraries strongly relies on the establishment of smart screening methodologies that allow for the rapid, simultaneous and general testing for catalytic activity.

Furthermore, assay systems are needed that allow for the determination of the enantiomeric excess of the generated products. So far all combinatorial assays have solely addressed the question of catalytic activity while the enantiomeric purity of the generated products remains to be determined in subsequent studies by time-consuming conventional chiral HPLC or GC analysis [66].

Thus, while many challenges remain to be solved, combinatorial chemistry is becoming an important tool for the optimization of existing catalytic systems and for the discovery of yet unknown catalytically active compounds.

REFERENCES

[1] a) Still, W.C. *Acc. Chem. Res.* **1996**, *29*, 155; b) Gennari, C.; Nestler, H.P.; Piarulli, U.; Salom, B. *Liebigs Ann./Recueil* **1997**, 637; c) de Miguel, Y.R.; Sanders, J.K.M. *Curr. Opin. Chem. Biol.* **1998**, *2*, 417; d) Nestler, H.P.; Liu, R. *Comb. Chem. High Throughput Screen.* **1998**, *1*, 113.

[2] a) Liu, D.R.; Schultz, P.G. *Angew. Chem. Int. Ed.* **1999**, *111*, 36; b) Maier, W.F. *Angew. Chem. Int. Ed.* **1999**, *38*, 1216.

[3] a) Gallop, M.A.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E.M. *J. Med. Chem.* **1994**, *37*, 1233; b) Gallop, M.A.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E.M. *J. Med. Chem.* **1994**, *37*, 1385; c) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2288; d) Thompson, L.A.; Ellmann, J.A. *Chem. Rev.* **1996**, *96*, 555.

[4] Jandeleit, B.; Schaefer, D.J.; Powers, T.S.; Turner, H.W.; Weinberg, W.H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2495.

[5] Crabtree, R.H. *Chem. Commun.* **1999**, 1611.

[6] Geysen, M.H.; Meloen, R.H.; Barteling, S.J. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3998.

[7] Xiang, X.-D.; Sun, X.-D.; Briceno, G.; Lou, Y.; Wang, K.A.; Chang, H.; Wallace-Freedman, W.G.; Chen, S.-W.; Schultz, P.G. *Science* **1995**, *268*, 1738.

[8] Briceno, G.; Chang, H.; Sun, X.-D.; Schultz, P.G.; Xiang, X.-D. *Science* **1995**, *270*, 273.

[9] a) Danielson, E.; Golden, J.H.; McFarland, E.W.; Reaves, C.M.; Weinberg, W.H.; Wu, X.D. *Nature* **1997**, *389*, 844; b) Danielson, E.; Devenney, M.; Giaquinta, D.M.; Golden, J.H.; Haushalter, R. C.; McFarland, E.W.; Poojary, D.M.; Reaves, C.M.; Weinberg, W.H.; Wu, X.D. *Science* **1998**, *279*, 837.

[10] Cole, B.M.; Shimizu, K.D.; Krueger, C.A.; Harrity, J.P.A.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **1996**, *35*, 1668.

[11] Shimizu, K.D.; Cole, B.M.; Krueger, C.A.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1704.

[12] Liu, G.; Ellman, J.A. *J. Org. Chem.* **1995**, *60*, 7712.

[13] a) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C.A.G.N.; Jackson, R.F.W. *J. Org. Chem.* **1998**, *63*, 5312; b) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 916.

[14] Burgess, K.; Lim, H.-J.; Porte, A.M.; Sulikowski, G.A.; *Angew. Chem. Int. Ed.* **1996**, *35*, 220.

[15] Porte, A.M.; Reibenspiess, J.; Burgess, K. *J. Am. Chem. Soc*. **1998**, *120*, 9810.

[16] Bromidge, S.; Wilson, P.C.; Whiting, A. *Tetrahedron Lett*. **1998**, *39*, 8905.

[17] a) Sigman, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) Sigman, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc*. **1998**, *120*, 5315.

[18] Porter, J.R.; Wirschun, W.G.; Kuntz, K.W.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2000**, *122*, 2657.

[19] Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.

[20] Furka, Á.; Sebestyén, F.; Asgedom, M.; Dibô, G.; *Int. J. Pept. Protein Res*. **1991**, *37*, 487.

[21] Lam, K.S.; Salmon, S.E.; Hersh, E.M.; Hruby, V.J.; Kazmierski, W.M.; Knapp, R.J. *Nature,* **1991**, *354*, 82.

[22] for NMR-spectroscopic one-bead analysis see for example a) Pursch, M.; Schlotterbeck, G.; Tseng, L.-H.; Albrecht, K.; Rapp, W. *Angew. Chem. Int. Ed.* **1996**, *35*, 2867; b) Sarkar, S.K.; Garigipati, R.S.; Adams, J.L.; Keifer, P.A. *J. Am. Chem. Soc.* **1996**, *118*, 2305.

[23] for IR-spectroscopic one-bead analysis see for example a) Yan, B.; Sun, Q.; Wareing, J.R.; Jewell, C.F. *J. Org. Chem.* **1996**, *61*, 8765; b) Sun, Q.; Yan, B.; *Bioorgan. Med. Chem. Lett.* **1998**, *8*, 361; Haap, W.J.; Walk, T.B.; Jung, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 3311; c) Yan, B.*Acc. Chem. Res.* **1998**, *31*, 621.

[24] for MS one-bead analysis see for example: Egner, B.J.; Langley, G.J.; Bradley, M.J. *J. Org. Chem.* **1995**, *60*, 2652.

[25] Brenner, S.; Lerner, R.A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 5381.

[26] Needles, M.C.; Jones, D.G.; Tate, E.H.; Heinkel, G.L.; Kochersberger, L.M.; Dower, W.J.; Barrett, R.W.; Gallop, M.A. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10700.

[27] Nikolaiev, V.; Stierandová, A.; Krchňák, V.; Seligmann, B.; Lam, K.S.; Salmon, S.E.; Lebl, M. *Pept. Res.* **1993**, *6*, 161.

[28] Vágner, J.; Barany, G.; Lam, K.S.; Krchňák, V.; Sepetov, N.F.; Ostrem, J.A.; Strop, P.; Lebl, M. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 8194.

[29] Kerr, J.M.; Banville, S.C.; Zuckermann, R.N. *J. Am. Chem. Soc*. **1993**, *115*, 2529.

[30] Camarero, J.A.; Ayers, B.; Muir, T.W. *Biochemistry* **1998**, *37*, 7487.

[31] Ohlmeyer, M.H.J.; Swanson, R.N.; Dillard, L.W.; Reader, J.C.; Asouline, G.; Kobayashi, R.; Wigler, M.H.; Still, W.C. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10922.

[32] Nestler, H.P.; Bartlett, P.; Still, W.C. *J. Org. Chem.* **1994**, *59*, 4723.

[33] a) Ni, Z.-J.; Maclean, D.; Holmes, C.P.; Murphy, M.M.; Ruhland, B.; Jacobs, J.W.; Gordon, E.M.; Gallop,M.A. *J. Med. Chem.* **1996**, *39*, 1601; b) Ni, Z.-J.; Maclean, D.; Holmes, C.P.; Gallop, M.A.; *Methods Enzymol.* **1997**, *267*, 261.

[34] Fitch, W.L.; Baer, T.A.; Chen, W.; Holden, F.; Holmes, C.P.; MacLean, D.; Shah, N.; Sullivan, E.; Tang, M.; Waybourn, P.; Fischer, S.M.; Miller, C.A.; Snyder, L.R. *J. Comb. Chem.* **1999**, *1*, 188.

[35] Geysen, H.M.; Wagner, C.D.; Bodnar, W.M.; Markworth, C.J.; Parke, G.J.; Schoenen, F.J.; Wagner, D.S.; Kinder, D.S. *Chem. Biol.* **1996**, *3*, 679.

[36] Burger, M.T.; Still, W.C.; *J. Org. Chem.* **1995**, *60*, 7382.

[37] a) Francis, M.B.; Finney, N.S.; Jacobsen, E.N. *J. Am. Chem. Soc*. **1996**, *118*, 8983; b) Francis, M.B.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* **1999**, *38*, 937.

[38] Malin, R.; Steinbrecher, R.; Jannsen, J.; Semmler, W.; Noll, B.; Johannsen, B.; Frömmel, C.; Höhne, W.; Schneider-Mergener, J. *J. Am. Chem. Soc.* **1995**, *117*, 11821.

[39] Shibata, N.; Baldwin, J.E.; Woods, M.E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 413.)

[40] Wennemers, H.; Still, W.C. *Tetrahedron Lett.* **1994**, *35*, 6413.

[41] Maletic, M.; Wennemers, H.; McDonald, D.Q.; Breslow, R.; Still, W.C. *Angew. Chem. Int. Ed.* **1996**, *35*, 1490.

[42] a) Wennemers, H.; Yoon, S.S.; Still, W.C. *J. Org. Chem.* **1995**, *60*, 1108; b) Yoon, S.S.; Still, W.C.; *Tetrahedron* **1995**, *51*, 567; c) Borchardt, A.; Still, W.C. *J. Am. Chem. Soc*. **1994**, *112*, 373.

[43] a) Boyce, R.C.; Li, G.; Nestler, H.P.; Suenaga, T.; Still, W.C. *J. Am. Chem. Soc*. **1994**, *116*, 7955; b) Gennari, C.; Nestler, H.P.; Salom, B.; Still, W.C. *Angew. Chem. Int. Ed*. **1995**, *34*, 1765; c) Löwik, D.W.P.M.; Weingarten, M.D.; Broekema, M.; Brouwet, A.J.; Still, W.C.; Liskamp, R.M.J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1846; d) Davies, M.; Bonnat, M.; Guillier, F.; Kilburn, J.D.; Bradley, M. *J. Org. Chem*. **1998**, *63*, 8696.

[44] Patterson, S.; Smith, B.D.; Taylor, R.E. *Tetrahedron Lett.* **1998**, *39*, 3111.

[45] Liang, R.; Yan, L.; Loebach, L.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W.C.; Kahne, D. *Science* **1996**, *274*, 1520.

[46] a) Wu, J.; Ma, Q.N.; Lam, K.S. *Biochemistry* **1994**, *33*, 14825; b) Kassarijian, A.; Schellenberger, V.; Turck, C.W. *Pept. Res.* **1993**, *6*, 129.

[47] Nestler, H.P.; Wennemers, H.; Sherlock, R.; Dong, D.L.-Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1327.

[48] Cooper, A.C.; McAlexander, L.H.; Lee, D.-H.; Torres, M.T.; Crabtree, R.H. *J. Am. Chem. Soc.* **1998**, *120*, 9971.

[49] Lavastre, O.; Morken, J.P. *Angew. Chem. Int. Ed.* **1999**, *38*, 3163.

[50] Shaughnessy, K.H.; Kim, P.; Hartwig, J.F. *J. Am. Chem. Soc*. **1999**, *121*, 2123.

[51] Berkessel, A.; Hérault, D.A. *Angew. Chem. Int. Ed.* **1999**, *38*, 102.

[52] Weingarten, M.D.; Sekanina, K.; Still, W.C. *J. Am. Chem. Soc*. **1998**, *120*, 9112.

[53] De Muynch, H.; Madder, A.; Farcy, N.; De Clercq, P.J.; Pérez-Payán, M.N.; Öhberg, L.M.; Davis, A.P. *Angew. Chem. Int. Ed.* **2000**, *39*, 145.

[54] Copeland, G.T.; Miller, S.J. *J. Am. Chem. Soc*. **1999**, *121*, 4306.

[55] a) Miller, S.J.; Copeland, G.T.; Papaioannou, N.; Horstmann, T.E.; Ruel, E.M. *J. Am. Chem. Soc*. **1998**, *120*, 1629; b) Copeland, G.T.; Jarvo, G.T.; Miller, S.J. *J. Org. Chem.*. **1998**, *63*, 6784.

[56] a) Boussie, T.R.; Murphy, V.; Hall, K.A.; Coutard, C.; Dales, C.; Petro, M.; Carlson, E.; Turner, H.W.; Powers, T.S. *Tetrahedron* **1999**, *55*, 11699; b) Boussie, T.R.; Coutard, C.; Turner, H.; Murphy, V.; Powers, T.S. *Angew. Chem. Int. Ed*. **1998**, *37*, 3272.

[57] a) Johnson, L.K.; Killian, C.M.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 6414; b) Tempel, D.J.; Johnson, L.K.; Huff, R.L.; White, P.S.; Brookhart, M. *J. Am. Chem. Soc*. **2000**, *122*, 6686.

[58] Moates, F.C.; Somani, M.; Annamalai, J.; Richardson, J.T.; Luss, D.; Willson, R.C. *Ind. Eng. Chem. Res*. **1996**, *35*, 4801.

[59] Holzwarth, A.; Schmidt, H.-W.; Maier, W.F.; *Angew. Chem. Int. Ed*. **1998**, *37*, 2644.

[60] a) Senkan, S.M. *Nature* **1998**, *394*, 350; b) Senkan, S.M.; Ozturk, S. *Angew. Chem. Int. Ed.* **1999**, *38*, 791.

[61] a) Cong, P.; Doolen, R.D.; Fan, Q.; Giaquinta, D.M.; Guan, S.; McFarland, E.W.; Poojary, D.M.; Self, K.; Turner, H.W.; Weinberg, W.H. *Angew. Chem. Int. Ed*. **1999**, *38*, 484; b) Orschel, M.; Klein, J.; Schmidt, H.-W.; Maier, W.F. *Angew. Chem. Int. Ed.* **1999**, *38*, 2791; c) Senkan, S.; Krantz, K.; Ozturk, S.; Zengin, V.; Onal, I. *Angew. Chem. Int. Ed.* **1999**, *38*, 2794.

[62] Taylor, S.J.; Morken, J.P. *Science* **1998**, *280*, 267.

[63] Reetz, M.T.; Becker, M.H.; Kühling, K.H.; Holzwarth, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2647.

[64] Reetz, M.T.; Becker, M.H.; Klein, H.-W.; Stöckigt, D. *Angew. Chem. Int. Ed*. **1999**, *38*, 1758.

[65] Reetz, M.T.; Becker, M.H.; Liebl, M.; Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1236.

[66] for a HTS approach see: Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 497.

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