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Reviews

Breaking the New Bottleneck: Automated Synthesis in Chemical Process Research and Development

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Abstract:

An overview of the current methods, available systems, and applications of laboratory automation in chemical process research and development is given. Examples of the successful implementation of automated synthesis into reaction optimisation and process development are discussed.

Introduction

Laboratory automation in chemical process research and development is currently a rapidly growing field of interest in the life sciences as well as the fine chemicals and catalysts industry. Many reasons for this development are obvious. The idea of using automated methods for the optimisation of chemical processes was triggered by the extensive implementation of combinatorial techniques[1] into lead finding and optimisation, e.g., in medicinal chemistry. Today there is not only a huge variety of different synthesisers for combinatorial chemistry commercially available, but also as a second effect of combinatorial chemistry many process research departments are now facing capacity problems with the strong increase in the efflux of new development products from the drug discovery departments. To secure fast development of new drug or agrochemical candidates it is essential to automate as much as possible of the optimisation process, given the fact that the human resources for most chemical development departments are limited and that a shorter time to market has become crucial.

Another good reason for the installation of automated systems for chemical process optimisation is the fact that many processes cannot be perfectly optimised by manual work because of insufficient work capacities and strict time limits. It is well-known that processes which are not well optimised are expensive if they cause trouble in the manufacturing plants. Better optimised reactions will therefore help to save a lot of money and resources. Small increases of the chemical yield of a single step have a tremendous effect on the overall yield of a synthesis and therefore on the production costs. In a model calculation T. Laird[2] brought the example, for a pharmaceutical product involving 10 synthetic steps (assuming 80% yield in each step) manufactured at 100 tonnes per annum and costing $1000/kg to make, an increase in yield of each step by only 1% would save $14 million per annum and reduce the cost to $860/kg. This simple calculation is of course common knowledge to industrial chemists. If the goal of cost reduction can be reached by automated optimisation, the necessary investment into technical equipment will pay off in a very short period of time. The drivers for automation in process research and development were summarised by D. Emiabata-Smith and M. Owen[3] recently as follows: compress timelines to market, increase throughput of projects, accelerate process screening, accelerate process optimisation, significant benefits already realized in drug research, respond to the high number of compounds entering development.

As outlined above, the recent successes in the high throughput screening and testing of new chemical compounds and in combinatorial chemistry have shifted the bottleneck of the drug discovery and development process once again further down the line to the chemical development departments who are now facing the task to open this new bottleneck by extensive use of automation in chemical process research and development.

The purpose of this review is to give an overview on the literature which was published on this issue up to early 1999 with the primary focus not only on the first successes but also on the problems of applying automated synthesis in process research and development.

Implementation of Automated Systems into the Different Phases of the Chemical Process Development

The development of a new chemical process can be divided into three phases. When the synthesis for a new compound with interesting biological or material properties is handed over from the research department to the chemical development department, usually the *process screening* is the first activity. In a large number of reactions with small reaction volumes (1−5 mL) many variables and reaction

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(1) (a) Persidis, A. *Chem. Ind.* **1998**, 782. (b) Czarnick, A. W.; Wilson, S. R. *Combinatorial Chemistry: Synthesis and Applications*; Wiley: New York, 1997. (c) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem.* **1996**, *108*, 2436; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (d) Früchtel, J. S.; Jung, G. *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

(2) Laird, T *Org. Process Res. Dev.* **1998**, *2*, 339.

(3) Emiabata-Smith, D.; Owen, M. *Symposium presentation at The First International Conference on Process Research and Development*, San Francisco, 1997, Abstract Book.

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Table 1. **Automated systems for chemical process research and development**

system/ manufacturer	number of simultaneous reactions	size of reaction vessels (mL)	independent temperature control for each reaction vessel	development phase
Advanced ChemTech 496 MOS and Omega[4]	depends on the vessel size, 8−96	2.5−20	no −70 to +150 °C	process screening
Anachem SK233[5]	10−20 online HPLC analysis	4−15	no stem cooling rack: −30 to +50 °C stem heating rack: ambient temp −150 °C	process screening, process optimization
Argonaut Nautilus[6,7]	24	8 or 15	yes −40 to +150 °C	process screening, process optimization
Bohdan Process Development Workstation[8]	12 online HPLC analysis	20	yes −20 to + 140 °C lower temperature possible/ custom tailored	process screening, process optimization
Chemspeed rlx I[9]	depends on the vessel size, 40−112 online TLC analysis	0.5−10 or up to 100	no, same temperature for all reactions in one reaction block −70 to +160 °C	process screening
HEL autoMATE[10]	2−16	25−250	yes −80 to +350 °C (range = 50 °C between reaction vessels)	process optimization, process characterization and validation, calorimetry
ISRA Robot Systems[11]	40, depends on the system	depends on the system, 5−30 larger volumes possible	no, same temperature for all reactions in one reaction block, temperature range depends on the system −60 to +150 °C	process screening
Mettler-Toledo[12]				process characterization and validation, calorimetry
LabMax	1	0.6−21	yes −50 to +200 °C	
RC1	1	0.1−21	yes −70 to +230 °C	
Myriad[13] process developer	2 × 12 in-process liquid sampling for HPLC/TLC	3−10	no −70 to +150 °C	process screening, process optimization
Zymark[14]	depends, up to 50 online HPLC analysis	depends on the system, 5−30 larger volumes possible	no, same temperature for all the reactions in one reaction block, temperature range depends on system −60 to +150 °C	process screening, process optimization

parameters (e.g., temperature, time, reagents, solvents, stoichiometry) at wide ranges in batches are tested. Factorial design of experiments is an especially useful tool in this phase. The analysis of the reactions is usually restricted to the end-point. This early development phase is one of the more profitable for automation, saving time and capacity in the screening of a large number of reaction conditions.

When an initial process was defined in these first studies, the second phase of *process optimisation* begins. In a moderate number of reactions with larger reaction volumes (10−25 mL) a focused set of variables is investigated. Important issues in this phase are the individual and exact control of the temperature of each reaction as well as real-time analysis of the reaction mixtures. For these reasons more sophisticated and reliable automated systems are needed to ensure reproducibility of the obtained results. One of the central parts of process optimisation is reaction work-up and isolation of the product; therefore, it is important for a rapid development to be able to study these parts (e.g., extraction, crystallisation) by using automated systems.

Before a process finally can be transferred to the pilot plant and from there to the manufacturing, the *process characterization and validation* has to be accomplished successfully. This means that only a few reactions in larger scale (>11) are performed in reaction vessels that should mimic the real pilot plant conditions. This development phase is used for the final optimisation of the reaction and for the thorough chemical and thermodynamic characterization of a process. Of course these three phases are not separated from each other, and the borderlines between them are fluid; however, as there are different important issues during each phase, it is clear that the construction of automated systems also has to take this into account and that not every synthesiser will adapt equally well to each development phase.

Table 1 gives an overview of some of the most important automated systems for chemical process development. No claim of completeness is taken but this table can give some hints which devices could be most useful for the application for each development phase. The evaluation of the systems only reflects our personal view and no testing of these systems was performed.

Besides these and other commercially available systems several in-house solutions for automated chemical synthesis

and reaction optimisation were developed, e.g., those at Takeda Chemical Industries[15,16] and Sumitomo.[17]

The automation of laboratory synthetic chemistry was reviewed extensively by J. S. Lindsey (North Carolina State University).[18] The different design and construction of workstations and automated reactors for various purposes and a large variety of different synthetic problems is described in detail in this article. Lately, laboratory automation in chemical development was reviewed by S. Dewitt and M. Owen.[19] They discuss the challenges and fundamental questions connected with automation in chemical development. A practical approach to the questions why and how to automate operations in a chemical laboratory can be found in an interesting paper of J. P. Guette et al. (Rhone-Poulenc).[20] Another article on the topic of automation of unit operations in the chemical laboratory was authored by W. Rellstab. He described an approach to reaction optimisation with the automated Contalab laboratory reactor.[21]

There are also some special periphery devices for automated synthesisers already on the market. The handling and exact dispensing of solids is a difficult task in automated systems due to the challenging characteristics of solids (steady or uncontrolled powder flow, bridging and segregation of particles). Nevertheless there are clear-cut business benefits of automating this task because manual weighing is time-consuming and can be the source of errors. If the solids are poisonous or otherwise dangerous, the exposure to the operator becomes another problem. M. Owen (Glaxo Wellcome)[22] showed in a first proof-of-concept study that it is possible to overcome the special problems of solid-dispensing in most cases with the commercially available system Autodose L1000.[23] This system works in principle like a pepper mill in which the flow rate is controlled by the opening and closing of a valve and the speed at which the valve is rotated. The system is controlled by a dispense/weigh feedback loop from a balance where the reaction vessel is placed.

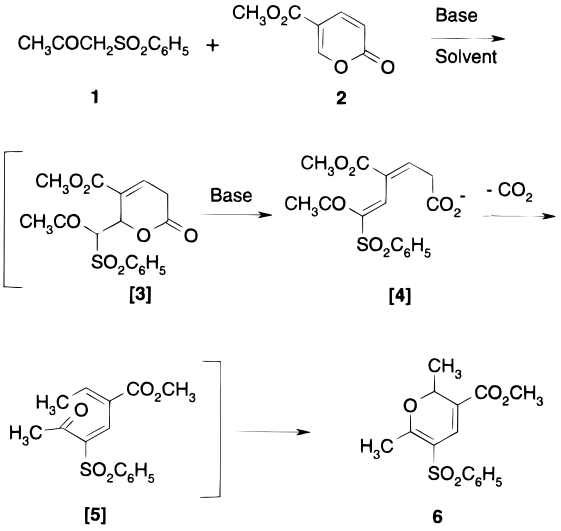
The handling of solids was also one issue for future development of automated workstations which was stated recently by J. S. Lindsey in an overview of automated reaction optimisation.[24] Following his statements other important subjects of further improvement are the integration of diverse analytical instruments and enhancement of the flexibility of synthesis workstations without sacrificing the efficiency, safety, and handling of the produced data by the implementation of factorial design experiments. The prospects for automated chemistry in the 21st century with a special focus on automated approaches toward reaction optimisation were also described recently by J. S. Lindsey.[25]

Overview of Automated Chemistry in Organic Process Research and Development

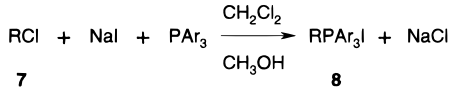
1. Pioneering Work. Most of the published work on automated synthesis deals with applications in the combinatorial chemistry, e.g., lead finding and lead optimisation. In a recently published review on automated synthesis S. H. DeWitt[26] besides summarizing other applications also summarised some of the first steps into the field of automated chemistry for process optimisation. In one of the first papers which appeared on this subject P. L. Fuchs et al. (Purdue University) already in 1984 described the yield optimisation through an automated system with operator-specified reaction sequences.[27] The system was developed around a Zymark robot and was capable of automated HPLC analysis. The synthesis of the trifunctional vinyl sulfone **6** was investigated. Initially, product yields varied widely between 5 and 30%, and it appeared that the reaction is very sensitive to the exact nature of the basic catalyst as well as to that of the solvent employed. In the first optimisation the synthesis of vinyl sulfone **6** was screened with eight different bases (DBU, $(n\text{-Bu})_4$NF, dimethylaniline, triethylamine, tetramethylethylendiamine, 1,8-bis(dimethylamino)-naphthalene, diisopropylethylamine, and DMAP) using acetonitrile as solvent. From these initial results DBU and $(n\text{-Bu})_4$NF were selected for further evaluation in four different solvents (tetrahydrofuran, acetonitrile, diethyl ether, and dichloromethane). Finally, the

(4) Contact adress: Advanced ChemTech, 5609 Fern Valley Road, Louisville, KY 40228-1075, U.S.A. Fax: +502/969-0000. Web address: http://www.peptide.com.
(5) Contact adress: Gilson/Anachem Ltd., Anachem House, 20 Charles Street, Luton Bedfordshire LU2-OEB, U.K. Fax: +44 1 582 391 768.
(6) Contact adress: Argonaut Technologies, 887 Industrial Rd., Suite G, San Carlos, CA 94070, U.S.A. Fax: +415/598-1359. Web address: http://www.argotech.com.
(7) Gooding, O.; Hoeprich, P.D.; Labadie, J. W.; Porco, J. A.; van Eikeren, P.; Wright, P. In *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*; Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996; p 199.
(8) Contact adress: Bohdan Automation, 562 Bunker Court, Vernon Hills, IL 60061-1831, U.S.A. Fax: +847/680-1199. Web address: http://www.bohdan.com.
(9) Contact adress: Chemspeed Ltd., Rheinstrasse 32, CH-4302 Augst (BL), Switzerland. Fax: +4161/816-9509. Web address: http://www.chemspeed-.com.
(10) Contact adress: Hazard Evaluation Laboratories, 50 Moxon Street, Barnet, Hertfordshire EN5 5TS, U.K.
(11) Contact adress: ISRA Robot Systems GmbH, Industriestrasse 14, D-64297 Darmstadt, Germany. Fax: +49/6151 948-140.
(12) Contact adress: Mettler-Toledo GmbH, Ockerweg 3, Postfach 110840, D-35353 Giessen, Germany. Fax: +49/641 52 951. Web address: http://www.mt.com.
(13) Contact adress: Mettler-Toledo Myriad, 2 Saxon Way, Melbourn, Royston, Herts SG8 6DN, U.K. Fax: +44/1763 261465. Web address: http://www.ttpmyriad.co.uk.
(14) Contact address: Zymark Corporation, Zymark Center, Hopkinton, MA 01748-1668, U.S.A. Fax: +508/4353439, http://www.zymark.com.
(15) Sugawara, T.; Kato, S. Eur. Pat. Appl. EP-510487, 1992.
(16) Sugawara, T.; Kato, S. U.S. Patent, US-0870426, 1992.
(17) Okamoto, H. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, **1998**, Abstract Book.
(18) Lindsey, J. S. *Chemom. Intell. Lab. Syst.* **1992**, *17*, 15.
(19) DeWitt, S. H.; Owen, M. In *Process Chemistry in the Pharmaceutical* Industry; Gadamesetti, K., Ed.; Marcel Dekker Inc.: New York, 1999; Chapter 23, p 429.
(20) Guette, J.-P.; Crenne, N.; Bulliot, H.; Desmurs, J.-R.; Igersheim, F. *Pure a. Appl. Chem.* **1988**, *60*, 1669.
(21) Rellstab, W. *Chem.-Technol. (Heidelberg)* **1991**, *20*, 204.
(22) Owen, M. *Symposium presentation at The Evolution of a Revolution − Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.
(23) Supplier: D. Riatsch, Copley Instruments Ltd., Colwick Industrial Estate, Nottingham NG4 2ER, UK.
(24) Lindsey, J. S. In *A Practical Guide to Combinatorial Chemistry*, Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997, p 309.
(25) Lindsey, J. S. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*; Leeds, 1997, Abstract Book.
(26) DeWitt, S. H. *Annu. Rep. Comb. Chem. Mol. Diversity* **1997**, *1*, 69.
(27) Fuchs, P. L.; Frisbee, A. R.; Nantz, M. H.; Kramer, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 7143.

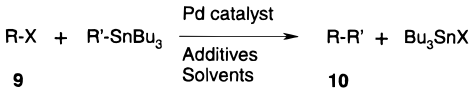
Scheme 1. **Preparation of vinyl sulfone 6**



Scheme 2. **Phosphine reaction**



Scheme 3. **Stille coupling reaction**



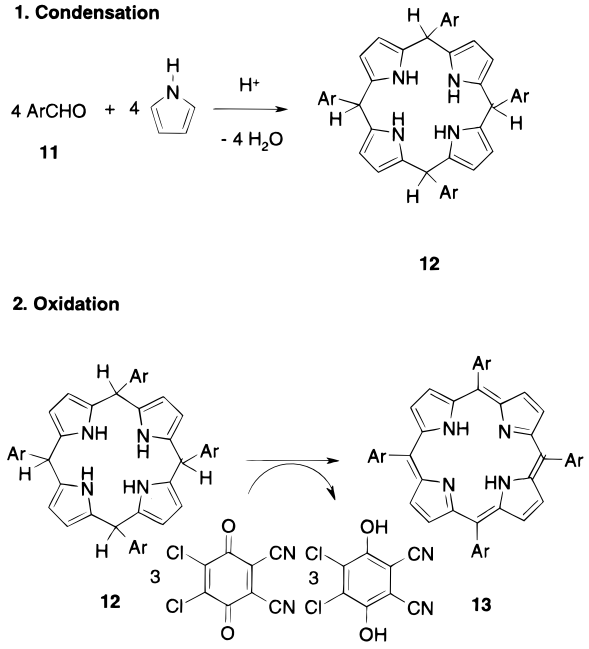
best conditions with DBU and dichloromethane were reproduced on a 50 mmol scale with a 67% isolated yield of sulfone **6** (Scheme 1).

In another pioneering paper S. Boettger described the development of a Zymark Py Technology automated system for process optimisation.[28] After having established the robotics system their first test reaction was a room-temperature reaction which is used in the synthesis of a wide variety of oral cephalosporin antibiotics[29] (Scheme 2).

The palladium-catalysed coupling of alkyl halides with alkyltributylstannanes is another reaction which is also of interest in the synthesis of new antibiotics.[30] This reaction was optimised by S. Boettger successfully with this Zymark system (Scheme 3).

A total of 52 palladium-catalysed coupling reactions was run, with systematic variation in the concentration, temperature, type of catalyst and additive, and amounts of stannane and zinc chloride. The reactions were followed by online HPLC analysis. The capacity of the robot to monitor multiple reactions simultaneously allowed evaluation of these variations in only 13 experimental runs. The good correlation between the robotic in situ yields and manually isolated yields made it possible to select the best candidates for scale-up experiments with the expenditure of only 17 g of starting material. This is an impressing example of using automated chemistry that is not only highly efficient in terms of development time but also very economic in terms of resources and substance demand.

Scheme 4. **Porphyrin reaction scheme**



Another Zymark system which was established at Rhône-Poulenc for carrying out multiple organic reactions was described by P. Josses et al.[31,32] At Dow Chemical Company T. E. Weglarz and S. C. Atkin developed an automated reaction optimisation system based also on a Zymark roboter.[33]

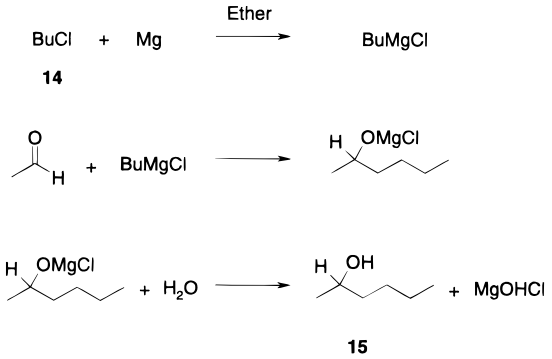
In a series of papers L. A. Corkan and J. S. Lindsey described the design concepts for synthetic chemistry workstations[34] as well as for the experiment manager software[35] for an automated chemistry workstation. With the sample reaction of porphyrinogen self-assembly and oxidation they showed the usefulness of combining an automated synthesis workstation with the statistical design of experiments.[36] An update on these interesting studies was given recently by J. S. Lindsey et al.[37] (Scheme 4).

A. Delacroix and colleagues designed several test reactors for the automation of organic reactions, e.g., Grignard reaction,[38] Diels−Alder-reaction[39] and the preparation of benzaldehyde ethylene acetal[40] (Scheme 5).

Very important pioneering contributions to the field of automation in chemical development were provided by D.

(28) Boettger, S. H. *Lab. Robotics Autom.* **1992**, *4*, 169.
(29) Naito, T.; Hoshi, H.; Aburaki, S.; Abe, Y.; Okumura, J.; Tomatsu, K.; Kawaguchi, H. *J. Antibiot.* **1987**, *40*, 991.
(30) (a) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H.; Munroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828. (b) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833.
(31) Josses, P.; Joux, B.; Barrier, R.; Desmurs, J. R.; Bulliot, H. *Adv. Lab. Autom. Robot.* **1990**, *6*, 463.
(32) Métivier, P.; Josses, P.; Bulliot, H.; Corbet, J.-P.; Joux B. *Chemom. Intell. Lab. Syst.* **1992**, *17*, 137.
(33) Weglarz, T. E.; Atkin, S. C. *Adv. Lab. Autom. Robot.* **1990**, *6*, 435.
(34) Corkan, A.; Lindsey, J. S. *Adv. Lab. Autom. Robot.* **1990**, *6*, 477.
(35) Corkan, L. A.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.* **1992**, *17*, 47.
(36) Corkan, L. A.; Plouvier, J. C.; Lindsey, J. S. *Chemom. Intell. Lab. Syst.* **1992**, *17*, 95.
(37) Wagner, R. W.; Li, F.; Du, H.; Lindsey, J. S. *Org. Process Res. Dev.* **1999**, *3*, 28.
(38) Porte, C.; Kouz, E. M.; Delacroix, A. *Lab. Robot. Autom.* **1994**, *6*, 119.
(39) Porte, C.; Desmoineaux, V.; Guette, J. P.; Petit, J.; Delacroix, A. *Lab. Robot. Autom.* **1993**, *5*, 3.
(40) Porte, C.; Canatas, A.; Delacroix, A. *Lab. Robotics Autom.* **1995**, *7*, 197.

Scheme 5. **Grignard reaction**



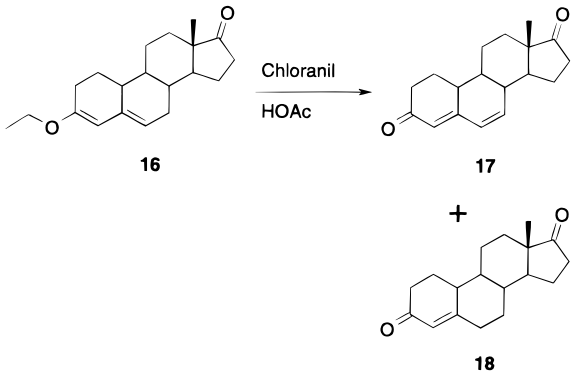
Emiabata-Smith and M. Owen[41] (Glaxo Wellcome) who described the in-house development of the DART (Development Automated Reaction Toolkit) system which consists of a Gilson 233XL autosampler, Stem Reaction stations, and an analytical system for the quantification of the reaction compounds. The DART system was developed at Glaxo Wellcome during 1995/1996 in collaboration with Anachem and Stem. The software of the DART system was also developed at Glaxo Wellcome. During the next two years the system evolved into the commercially available SK233 system (Anachem). This collaboration is an impressive example of a successful collaboration between pharmaceutical and automation hardware companies.

Further pioneering work was contributed by P. Hilberink et al. who also entered the field of automated organic process research and development very early and reported already in 1996 about the successful use of a Zymark system for the reaction optimisation at Organon.[42]

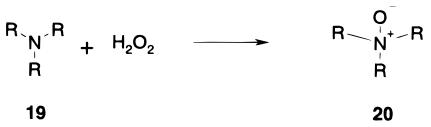
2. Modern Examples of Automated Optimisation of Organic Reactions. 2a. Oxidations. Automated optimisation with a Zymark system was used at Organon by P. Hilberink in the study of an oxidative de-enolization of the steroid derivative **16** for the introduction of a Δ-6,7 unsaturation.[43] In 42 reactions which were performed in 4 days the amount of the oxidizing reagent chloranil and the acetic acid was optimised, and a good ratio of main product **17** to byproduct **18** was achieved. This example shows that major improvements of product quality and yield of difficult chemical transformations can be achieved in a very efficient way and short time by using automated systems (Scheme 6).

J. Mills (R. W. Johnson Pharmaceutical Research Inst.)[44] used a Bohdan Process Development Workstation for the study of an oxidation reaction of a tertiary amine with hydrogen peroxide to the corresponding *N*-oxide. The reaction parameters which have been studied were temperature and the amount of hydrogen peroxide. The maximum yield was achieved at 50 °C with 2.25 equiv of hydrogen peroxide (Scheme 7).

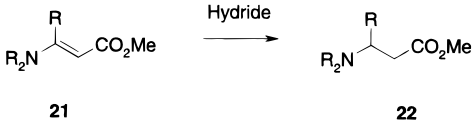
Scheme 6. **Chloranil oxidation**



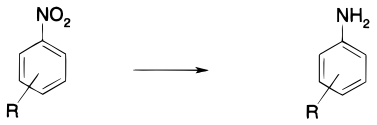
Scheme 7. **Oxidation of tertiary amines**



Scheme 8. **Hydride reduction in the preparation of *β*-amino acids**



Scheme 9. **Reduction of aromatic nitro compounds**



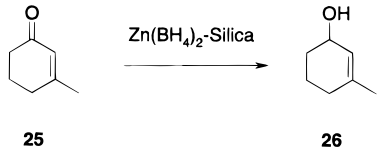
2b. Reductions. Until now only a few studies on reductions were reported. In a series of experiments performed by N. Evens at Zeneca a HEL AutoMate was used to get more information on the heat flow of the reactions.[45] The calorimetry in the hydride reduction during the preparation of a *β*-amino acid showed a severe exotherm spike after the reaction was complete (Scheme 8).

The reduction of aromatic nitro compounds to the corresponding anilines was studied with the same system. An initial endotherm was detected and a severe and variable accumulation through the addition was found. As a result of these experiments, a major but manageable hazard was identified by N. Evens[45] during the first run of reactions. This example shows that the HEL AutoMate system is a valuable tool not only for reaction characterization but also for the safety evaluation (Scheme 9).

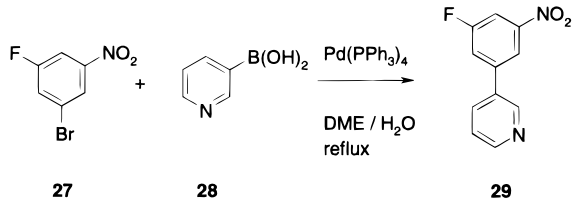
D. Cork (Takeda Chemical Industries) reported the automated reduction of 3-methyl-2-cyclohexen-1-one to the corresponding allylic alcohol with $Zn(BH_4)_2$ supported on silica gel by using the ASRA System (automated supported reagent apparatus) which was developed at Takeda.[46] The yield achieved in the automated reaction (92%) was even

(41) Emiabata-Smith, D.; Owen, M. *Symposium presentation at The Organic Process Research & Development Symposium*, Manchester, 1996.
(42) Hilberink, P.; Aelst, S. V.; Vink, T. Q.; Gool, E. V.; Kasperson, F. *ISLAR Proc. (Boston)* **1996**, 93.
(43) Hilberink, P. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1988, Abstract Book.
(44) Mills, J. *Symposium presentation at The Evolution of a Revolution − Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.
(45) Evens, N. *Symposium presentation at The Evolution of a Revolution − Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.

Scheme 10. **Zinc borohydride reduction of 3-methyl-2-cyclohexen-1-one**



Scheme 11. **Suzuki coupling reaction**



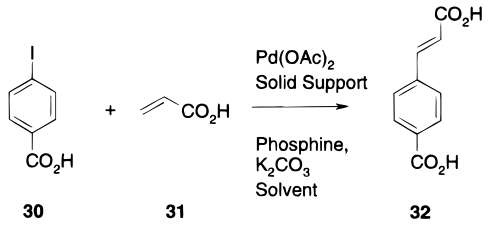
slightly superior to the manual experiment (86%) (Scheme 10).

2c. Reactions Catalysed by Metal Complexes. G. Smith and M. Armitage[47] from SmithKline Beecham described a palladium-catalysed Suzuki-coupling reaction which was automated with an Anachem SK233 and the REACTarray reaction block (Scheme 11).

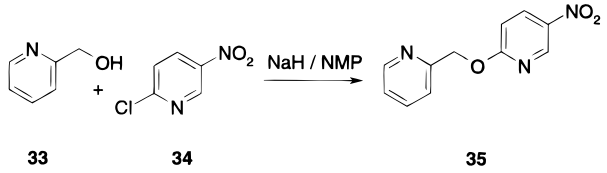
This reaction requires both reflux conditions and a good inert atmosphere due to the air sensitivity of the catalyst. Despite the difficult reaction conditions excellent reproducible results were obtained with the REACTarray reaction block, which was designed at SmithKline Beecham.[48] The REACTarray consists of a STEM reaction block with a set of reaction vessels (test tubes) and a coldfinger condensing system. The advantages of the REACTarray system are that it has outstanding condensing capacity so that only a very small amount of the solvent is lost during the reaction and that it allows the user to reflux a reaction, under an inert atmosphere, and simultaneously take an analytical sample via an XYZ robotic arm using an automated syringe. The system is made out of glass, and therefore it is easy to control visually what is going on in the reactions. Using the Design Expert software the effects of concentration, water level, catalyst loading, and boronic acid stoichiometry on the outcome of the Suzuki coupling reaction were investigated. The analysis of the experimental results showed that at high concentration (desirable for scale-up) a robust and reliable process can be achieved if the water level and catalyst loading are both high.

Another Suzuki coupling reaction was studied by L. C. Hsu et al. (SmithKline Beecham) with a Zymark BenchMate workstation.[49] The reactions were done in a Stem reaction block and the samples were transferred to the Zymark robot for further sample preparation, including dilution and filtration. The treated samples were then analysed by a HPLC system that was directly connected to the BenchMate workstation.

Scheme 12. **Heterogeneous Heck reaction**



Scheme 13. **Nucleophilic aromatic substitution of a nitropyridine**



D. Emiabata-Smith and M. Owen at Glaxo Wellcome[50] studied a heterogeneous Heck reaction with the DART system (Scheme 12).

2d. Aromatic Substitution Reactions. Another impressive example of what can be achieved by using automated optimisation methods especially for the rapid screening of conditions was also described by G. Smith and M. Armitage.[47] They studied the nucleophilic aromatic substitution reaction of a pyridine derivative. In the beginning the process was not particularly robust to scale-up and yielded only about 70% after recrystallisation from ethanol. The use of weaker bases as catalysts to minimize side reactions was studied. In a series of experiments the SK233 was used to rapidly screen a large number of combinations of bases and catalysts in toluene at 80 °C, and the reactions were followed by HPLC analysis. The whole study was performed in less than 1 week, and the yield was optimised to 91−93% which was reproducible on a large scale. The plant process was established 3 weeks after the first experiments were initiated, and 10 kg product was prepared in 6 weeks. This study was highly effective, and it shows that it is indeed possible to accelerate the drug development process by the application of automated optimisation techniques (Scheme 13).

From the point of view of automating chemical reactions heterogeneous reactions are always a challenge because reaction kinetics are complex and the reactions tend to be difficult to follow by analytical techniques. In the bromination of hydroxy-dihydro-indole derivative **36** with *N*-bromo succinimide in acetic acid G. Smith and M. Armitage[47,48] encountered the problem that the starting material slowly dissolved during the reaction and that the product **37** slowly began to crystallise. Two sets of three identical reactions (0.5 and 1.0 equiv NBS) were studied with a SK233. Samples were taken automatically at three time points (5 min, 45 min, 1.5 h), and the analytical results were compared. The authors found that a quantitative sampling was not possible, but

(46) Cork, D. G. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, **1998**, Abstract Book.

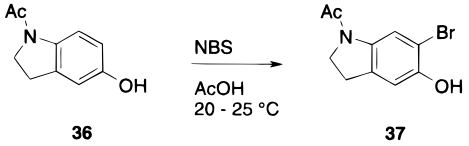
(47) Armitage, M.; Smith, G. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.

(48) Armitage, M. A.; Smith, G. E.; Veal, K. T. *Org. Process Res. Dev.* **1999**, *3*, 189.

(49) Hsu, L. C.; Webb, E.; Pin, L. *Symposium presentation at the International Symposium on Laboratory Automation & Robotics*, 1998, Abstract.

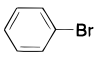
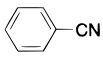
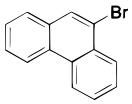
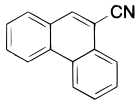
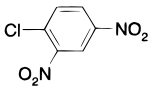
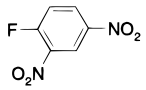
(50) Emiabata-Smith, D.; Owen, M. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Leeds, 1997, Abstract Book.

Scheme 14. **Electrophilic aromatic substitution**



36 **37**

Table 2. **Heterogeneous synthetic reactions performed manually and with ASRA**

Reagent	Substrate	Product	Manual %	ASRA %
CuCN / C			14	52
	38	**39**		
CuCN / C			65	84
	40	**41**		
KF / CaF_2			62	85
	42	**43**		
KI / CuI / Al_2O_3			62	74
	44	**45**		

nevertheless a qualitatively good agreement between the three identical reaction vessels was stated (Scheme 14).

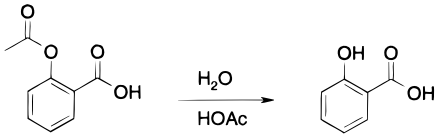
D. Cork (Takeda Chemical Industries)[46] reported a series of heterogeneous aromatic substitution reactions with the ASRA System. In a comparison between experiments performed manually or by the robotic system he showed that the results of the robot are at least comparable or in some cases have even better yields than the human work (Table 2).

2e. Protecting Group Chemistry. As chemical syntheses in the pharmaceutical and agriculturural industry are becoming more and more sophisticated, the chemistry of protecting and deprotecting special moieties of complex molecules is also increasing its importance in the development of large-scale chemical processes. Such steps in a synthesis usually do not contribute to the structure of the molecule. Therefore, it is quite interesting to automate such reactions to achieve yields as high as possible.

A relatively simple reaction which is used by J. Mills as a training reaction for chemists at R. W. Johnson Pharmaceutical Research Institute[44] to get acquainted with the Bohdan Process Development Workstation is the hydrolysis of *O*-acetyl salicylic acid in acetic acid. The chemistry of this reaction is well-known,[51] and therefore the chemists can concentrate on learning the options in programming the equipment. The reaction provides a feedback on both

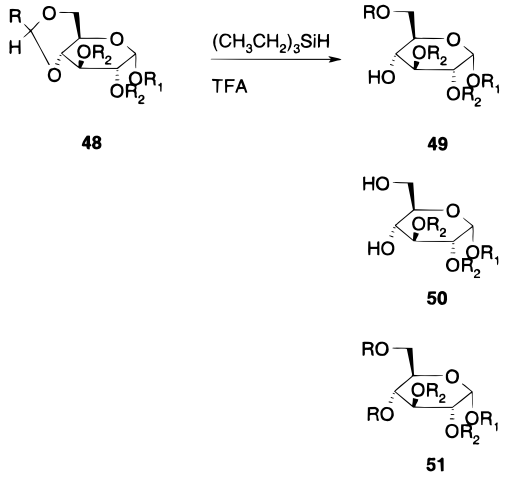
(51) Carstensen, J. T.; Attarchi, F. *J. Pharm. Sci.* **1988**, *77*, 314.

Scheme 15. **Hydrolysis of aspirin**



46 **47**

Scheme 16. **Reductive deprotection of an acetal**



48 **49** **50** **51**

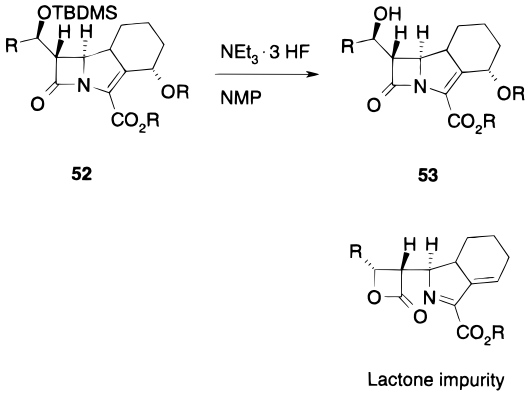
synthetic and analytical chemistry as it can be followed by online HPLC analytics. For this reason this reaction could also be of interest to other groups moving into the field as a simple training reaction for automated process development workstations (Scheme 15).

P. Hilberink at Organon reported the reductive deprotection of the acetal **48** in glycoside chemistry with triethylsilane and trifluoro acetic acid.[43] The reaction which produces besides the main product **49** the two impurities **50** and **51** was optimised by using factorial design methods. In 3 days three series of 10 reactions were successfully run on a Zymark system (Scheme 16).

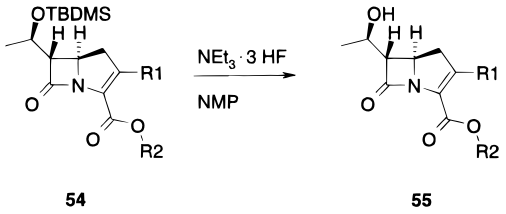
An example from the silyl protection group chemistry was studied in 1995/1996 by D. Emiabata-Smith and M. Owen at Glaxo Wellcome[19,50] with the DART system. Although many methods are known, conditions for deprotection of silyl ethers are often harsh, and when this methods were applied to the trinem antibiotic, **52** complete degradation was the result. In manual process screening experiments it was found that triethylamine trihydrogen fluoride in *N*-methylpyrrolidone was the most promising reagent. However, under these reaction conditions, a β-lactone impurity gradually forms, and therefore a careful on-line monitoring by HPLC was crucial for the successful optimisation. Automated screening of temperature (10−30 °C), reaction time (19−31 h), amount of solvent NMP (3−7 vols) and amount of reagent triethylamine hydrogen fluoride complex (1.0−1.68 equiv) showed robust conditions for the pilot plant with yields of more than 92%. This superb pioneering work demonstrated the value of applying both statistical design of experiments and automation techniques in the process research and development environment (Scheme 17).

A similar deprotection of a *tert*-butyl dimethyl silyl ether also in the field of β-lactam antibiotics was studied by G.Smith and M. Armitage (SmithKline Beecham)[47,48] with

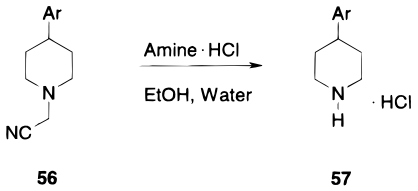
Scheme 17. **Deprotection of a *tert*-butyl dimethylsilyl ether**



Scheme 18. **Deprotection of a silyl ether**



Scheme 19. **Cyanomethylene deprotection**



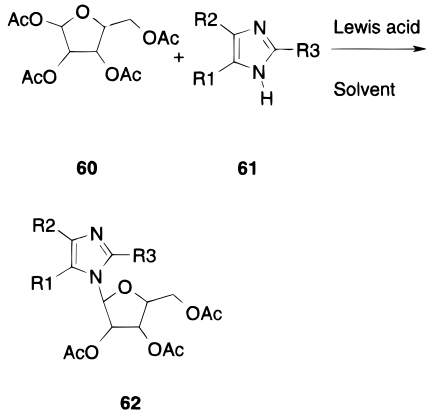
their Anachem system. The *tert*-butyl dimethyl silyl group of the β-lactam derivative **54** was removed and the alcoholic moiety released with the triethylamine hydrogen fluoride complex in NMP. The manual laboratory optimisation work had indicated that 1.1 equiv of the fluoride reagent in 10 vols NMP at 50 °C gave a solution yield of 69% of **55**, while higher temperatures and less reagent gave poorer yield. Design of experiment approach was used to optimise the reaction. Temperature, concentration, and the amount of reagent were the 3 factors which were considered to be important. A 3-factor 2-level full factorial design was drawn up resulting in 12 experiments in total. The 12 reactions were run in a 3 day period and monitored by hourly HPLC analysis. In total 360 HPLC runs were done. Analysis of the results indicated that a yield of 83% could be expected at 30 °C with 1.25 equiv fluoride reagent in four to seven vols NMP. This was also verified by a manual experiment in a round-bottom flask (Scheme 18).

The cyanomethylene deprotection of a piperidine derivative is another example studied by D. Emiabata-Smith and M. Owen with the DART System.[50] The product of this heterogeneous autochemistry reaction is isolated as the hydrochloride (Scheme 19).

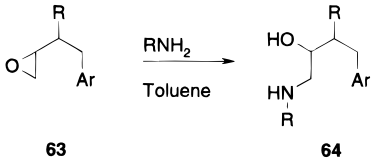
The introduction of a methanesulfonic protection group on a primary alcohol was studied by N. Evens at Zeneca with a HEL AutoMate.[45] Following this reaction by common analytical methods was difficult because the molecule contained no chromophore and was not volatile. Therefore,

Scheme 20. **Formation of a primary mesylate**

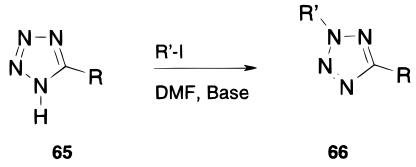
Scheme 21. **Nucleoside coupling reaction**



Scheme 22. **Epoxide opening reaction**



Scheme 23. **Tetrazole alkylation**



the power output of the calorimetric equipment was used for the determination of the endpoint of the reaction (Scheme 20).

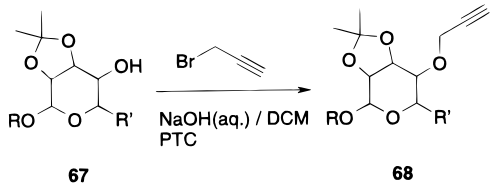
2f. Other Nucleophilic Substitution Reactions. Nucleoside coupling reactions were studied by D. Emiabata-Smith and M. Owen at Glaxo Wellcome with the DART System.[50] The influence of different solvents was screened in this early study. One of the important conclusions derived from this study was that automation gives the process research and development chemist the opportunity to investigate a greater number of options when carrying out screening studies and therefore to cover a greater diversity of reaction conditions leading to an increased chance of success (Scheme 21).

The opening of epoxides with amines in toluene to amino alcohols is another example of homogeneous autochemistry performed by D. Emiabata-Smith and M. Owen[50] (Scheme 22).

The alkylation of a tetrazole derivative with an alkyl iodide in DMF and the addition of a base was achieved under heterogeneous reaction conditions using the DART System (D. Emiabata-Smith and M. Owen, Glaxo-Wellcome)[50] (Scheme 23).

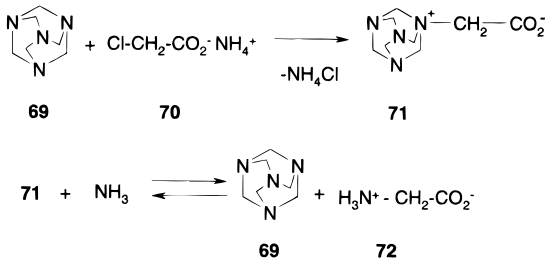
Phase transfer catalysis is a very important field in process research because it is often possible to perform reactions under milder conditions with higher yields and selectivities. For these reasons the contribution of D. Emiabata-Smith and

Scheme 24. **Biphasic alkylation of a pyranose derivative**



67 **68**

Scheme 25. **Glycine synthesis**



69 **70** **71**

71 + NH$_3$ ⇌ **69** + H_3N^+ - CH_2-CO_2^- **72**

M. Owen (DART System)[50] to the PTC research with their study of the biphasic alkylation of a pyranose derivative with propargyl bromide in dichloromethane/aqueous sodium hydroxide is of major interest (Scheme 24).

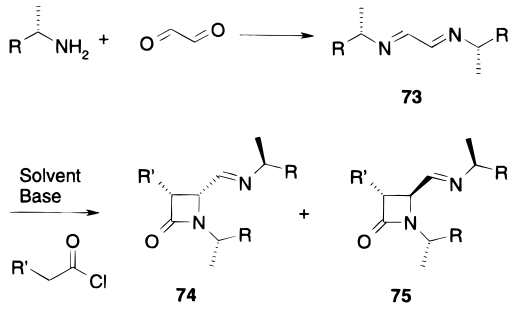
Glycine is an important amino acid from an industrial point of view, but its production is carried out generally with dangerous reagents under drastic conditions. However, reaction of monochloroacetic acid with ammonia in an aqueous medium with hexamethylenetetramine as catalyst gives glycine in good yields. H. Fauduet et al. automated this glycine synthesis with the modular Logilab system to find the optimum conditions for the process.[52] Experimental design method was used extensively. They found that yields higher than 93% can be obtained when the synthesis is carried out at a temperature of 73−78 °C and a pH of 5.1−5.6 (Scheme 25).

2g. Cycloaddition Reactions. The [2 + 2]-cycloaddition of imines with ketenes is a classical reaction for the preparation of β-lactams. The ketenes are prepared in situ by the addition of base to acid chlorides. The aim of this study by D. Emiabata-Smith and M. Owen (Glaxo Wellcome)[50] was to maximises the yield of β-lactam (**74** + **75**) in solution, to optimise the diastereomeric ratio in favor of **74** and to find robust reaction conditions. Therefore, the order of addition of the single components to the reaction mixture as well as the influence of eight different solvents and six different bases was studied (Scheme 26).

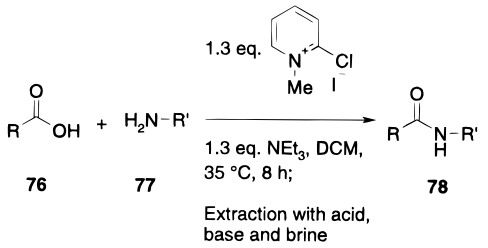
2h. Amide Synthesis. In a series of experiments described by B. Kutscher[53] (Asta Medica) the Mukayama amide synthesis was adapted to the automated ZymateTM XP system. It was possible to carry out the reaction in suspension (Scheme 27).

Automated synthesis and purification of amides in solution was also studied by R. M. Lawrence et al. (Bristol-Myers Squibb)[54] with a Zymark Benchmate Robotic Workstation. The separation of the product from starting material, reagents,

Scheme 26. **[2 + 2]-Cycloaddition**

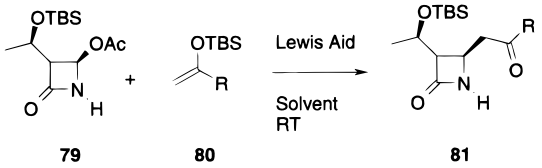


Scheme 27. **Mukayama amide synthesis**



76 **77** **78**

Scheme 28. **Lewis acid-catalysed reaction of acetoxy β-lactams with silyl enolethers**



79 **80** **81**

Lewis Acids	NEt_3·3HF	BF_3·Et_2O	$ZnCl_2$	$TiCl_4$	$SbCl_5$	CuI
	$FeCl_3$	$B(OMe)_3$	$SnCl_4$	BBr_3	K-10 Clay	$HgCl_2$
	$Yb(OTf)_3$	$La(OTf)_3$	$ZrCl_2$	$AlCl_3$	$Cu(BF)_4$	BCl_3
	TBAF on silica gel	$MgBr_2$				
Solvents	THF	Toluene	CH_2Cl_2	MeCN	Hexane	TBME
	DME					

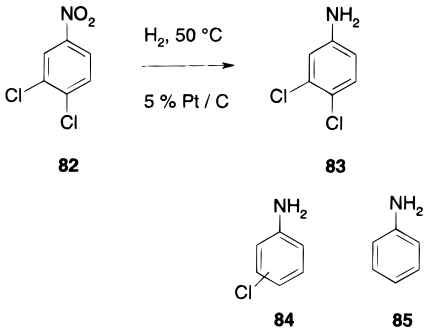
and byproducts was achieved by automated solid-phase extraction. Cation- and anion-exchange sorbents were used in a tailored process. Good to excellent yields of amides with very high purities of 95% and higher were achieved.

2i. Reagents and Solvent Screening. In the Lewis Acid-catalysed reaction of acetoxy β-lactams **79** with silyl enolethers **80** it was found in preliminary work that BF_3·Et_2O in DME gives reasonable yield (∼50%) of product **81**. The SK233 was used by G. Smith and M. Armitage[47,48] to screen a wide variety of Lewis acids and solvents (Scheme 28).

One hundred and forty combinations of eighteen Lewis Acids and seven solvents were screened in a 3-week period. A large number of unusual combinations was investigated that using conventional techniques probably would not have been attempted. The reactions were performed in blocks of seven reactions. They were monitored at 5 min, 30 min, and 6 h by HPLC. A total of 420 analyses was performed. The large amount of data was easily handled with Excel. A number of good catalysts was identified by the screening: BF_3·Et_2O in all solvents (especially in THF), $ZnCl_2$ in all solvents (except toluene), $MgBr_2$ in dichloromethane, CuI in dichloromethane. Air- and moisture-sensitive Lewis Acids, e.g., were easily handled by the SK233 with REACTarray.

(52) Fauduet, H.; Nikravech, M.; Porte, C. *Process Control Qual.* **1996**, *8*, 41.
(53) Kutscher, B. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Leeds, 1997, Abstract Book.
(54) Lawrence, R. M.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553.

Scheme 29. **Screening of Pt/C catalysts**



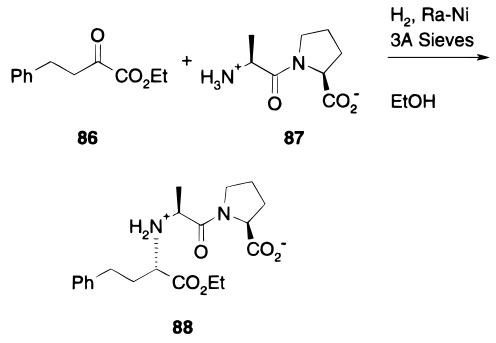
Comparable results were obtained using conventional glassware.

Although the work which was published by D. A. Rudge (Zeneca) about the automation of solution-phase synthetic chemistry using a Zymark laboratory robotic system[55] is not a typical example of process optimisation in the field of chemical development, it nevertheless shows that there are only few limitations concerning the types of chemistry that can be automated. Reactions that were undertaken in order to produce 8000 new compounds for biological testing include alcohol oxidation, aldol condensation, amide coupling, amination of chloro heterocycles, epoxidation, ester hydrolysis, formation of esters and ethers, Knoevenagel condensation, N-alkylation, N-oxidation, palladium-catalysed coupling reactions, amination of penta fluoro benzene, reductive amination, synthesis of sulphonamides, sulphonamido ureas, ureas, thioethers, transesterifications, and Wittig reactions.

3. Automation in Catalyst Research. Rapid screening and reaction optimisation by using automated synthesis techniques can be applied advantageously in homogeneous and heterogeneous catalysis. Catalyst preparation as well as catalyst screening are important potential applications in catalyst research. K. Simons[56] described the experience of Johnson Matthey with the automated catalyst preparation of 5% Pt/C catalysts with the Technology Partnership (TTP) personal synthesiser.[57] Previously up to three catalysts were made per person per day but now there is potential for over 48 catalysts per day and the rate-determining step becomes chemistry. As a test reaction for the efficiency of these heterogeneous catalysts, the catalytic hydrogenation of dichloronitrobenzene **82** to dichloroaniline **83** was chosen. Special focus was on the selectivity of the prepared catalysts concerning the two impurities **84** and **85** (Scheme 29).

A recent study which was not accomplished by automated methods but nevertheless shows the great importance of multidimensional screening of catalysts and additives from an industrial point of view was done by M. A. Huffman and P. Reider (Merck Research Laboratories).[58] The large-scale synthesis of the ACE inhibitor enalapril **88** involves a key

Scheme 30. **Reductive amination in the synthesis of enalapril**

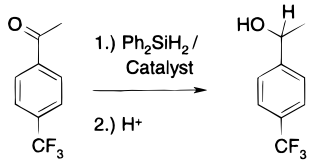


diastereoselective reductive amination reaction between α-ketoester **86** and the dipeptide alanyl proline **87** catalysed by Raney nickel (Scheme 30). Over the past decade the diastereomer ratio has been improved from initially 6.7:1 to 11:1 by traditional optimisation. Because of the extensive study that had already gone into this reaction, this was a challenging case to improve upon and thus a good test case for a novel approach. Different heterogeneous catalysts and potentially modifying additives were combined and evaluated in a multivariate fashion. The result of several hundred screening reactions is a unique set of reaction parameters (addition of 25% acetic acid and 4.0 equiv of KF) which gives improved stereoselectivity (17:1) and yield over the previous, highly optimised reaction conditions. The authors are of the opinion that neither of the additives alone is effective, and this leads to the conclusion that only experiments that simultaneously vary more than one factor would have discovered these improved reaction conditions for this high-volume, high-value drug, as it is highly improbable that these conditions would have been discovered by traditional methods. They also suggest that the impact of this type of experimental plan would be multiplied by the use of automation in reaction setup and assay.

Some ideas and studies concerning combinatorial approaches in the field of heterogeneous catalysis were critically reviewed recently by R. Schlögl.[59] Although there are special problems connected with the combinatorial synthesis and automated screening of heterogeneous catalysts, R. Schlögl sees an advantage in a scientifically better preselection of materials with interesting properties than what would be possible by conventional methods of synthesis. Connected with this there can be a great reduction of the time which is necessary for the development of a new process, and therefore it is especially important from the technical and economic point of view to implement combinatorial methods into the heterogeneous catalysts research. As with detection of the activity in the combinatorial synthesis of bioactive molecules in the life sciences there is a similar problem in detecting the catalytic activity in combinatorial libraries of heterogeneous catalysts. An innovative solution to this problem has now been described by W. F. Maier et al.[60] They found that it is possible to use

(55) Rudge, D. A. *Lab. Autom. Inf. Manage.* **1997**, *33*, 81.
(56) Simons, K. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.
(57) Contact adress: The Technology Partnership plc, Melbourn Science Park, Melbourn/Royston, Herts, SG8 6EE, U.K., Fax: +1763/261582.
(58) Huffman, M. A.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 831.
(59) Schlögl, R. *Angew. Chem.* **1998**, *110*, 2467.
(60) Maier, W. F.; Holzwart, A.; Schmidt, H.-W. *Angew. Chem.* **1998**, *110*, 2788.

Scheme 31. **Reduction of trifluoromethyl acetophenone by hydrosilation**



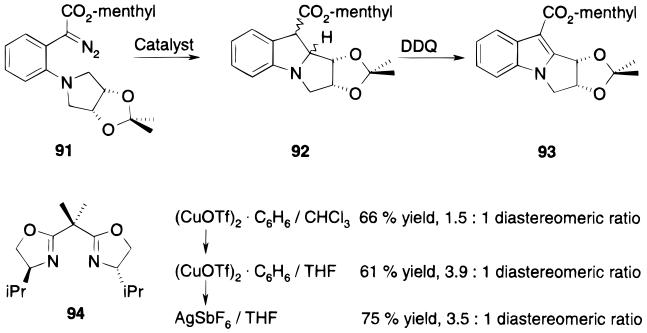
89 **90**

sensitive IR thermographic methods for the detection of the small differences in the heat flow which develop if the catalyst is transforming certain substrates in a chemical reaction or not. This method enables the rapid detection of catalytic activity in test reactions of combinatorial libraries of heterogeneous catalysts. M. T. Reetz et al.[61] showed that it is also possible to use this method in the screening of enantioselective catalytic reactions. As examples of test reactions they studied the kinetic resolution of rac-1-phenyl ethanol by lipase-catalysed esterification with vinyl acetate[62] and the Jacobsen method for the enantioselective opening of epoxides by water with chiral salene complex catalysts.[63]

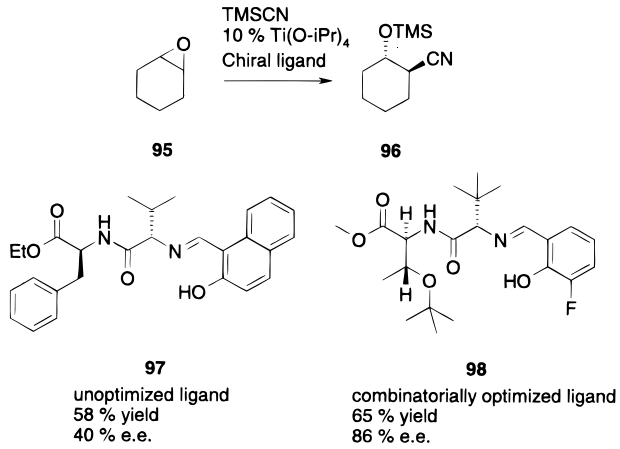
That a rapid parallel screening of homogeneous catalysts is also practical and worthwhile for the selection and optimisation of reaction conditions was shown by C. Barnard (Johnson Matthey Technology Centre).[64] He studied the influence of different metal and ligand combinations as catalysts on the hydrosilylation of 4-triflouromethyl-acetophenone. With this method it is possible to detect the best fitted metal−ligand combination for different substrates very rapidly. Other examples for homogeneous catalysis which were studied by C. Barnard are the reduction of amides to amines by hydrosilation, the palladium-catalysed amination of aromatic bromides (Buchwald Reaction) and the palladium-catalysed carbonylation of aromatic iodides (Scheme 31).

Combinatorial screening of catalyst libraries has been used by K. Burgess et al.[65,66] for the identification of an effective catalyst system for the formation of indolyl derivatives by cyclization reactions comprising intramolecular metallocarbene C−H-insertion of α-diazo esters. They created a library of 96 catalytic systems consisting of metals, ligands, and reaction conditions such as solvents, stoichiometries, etc. in a microtitre plate equipped with short-plug silica gel filtration devices to allow reaction parameters to be varied. Various combinations of five chiral ligands, seven metal precursors, and four solvents were evaluated. The screening confirmed the superiority of the previously characterized copper complex with ligand **94** but revealed an unexpected higher

Scheme 32. **Catalyst screening and optimization in the formation of indolyl derivatives**



Scheme 33. **$Ti(OiPr)_4$ catalysed addition of TMSCN to *meso*-epoxides**



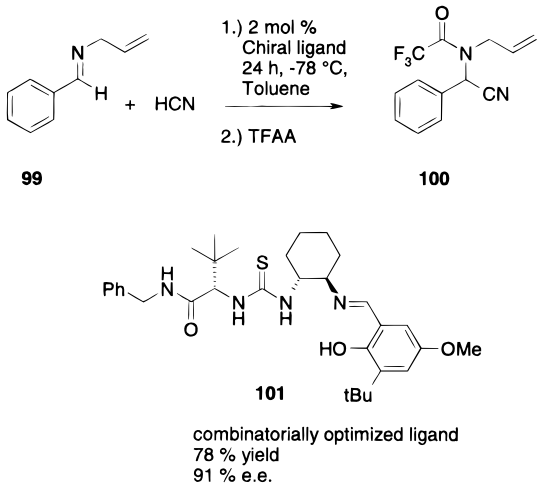
de when the reaction was carried out in THF rather than in chloroform. In addition, a powerful catalyst was obtained with the same ligand and silver hexafluoroantimonate, which is rarely used in this kind of chemistry. The yields were even higher than in the copper case (Scheme 32).

Chiral titanium Schiff base complexes have been used to catalyse the diastereo- and enantioselective addition of trimethylsilyl cyanide to achiral *meso*-epoxides to give cyanohydrins. Using parallel solid-phase synthesis techniques A. Hoyveda, M. L. Snapper, et al. (Boston College)[67] have produced a number of chiral dipeptidic hemisalen ligands. These ligands were complexed with a titanium source and screened as chiral Lewis acids for catalytic efficiency and selectivity. The researchers identified a potent catalyst system for the ring opening of cyclohexene epoxide in 86% enantiomeric excess. They also screened the ligands on the solid support,[68] which significantly accelerated the optimisation process and gives a convenient possibility to recover the ligand from the reaction mixture (Scheme 33).

Polymer-supported Schiff base catalysts for the asymmetric hydrocyanation of imines were produced by E. Jacobsen and M. Sigman (Harvard University).[69] This hydrocyanation, known as the Strecker reaction, is one of

(61) Reetz, M. T.; Becker, M. H.; Kühling, K. M.; Holzwarth, A. *Angew. Chem.* **1998**, *110*, 2792.
(62) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem.* **1997**, *109*, 1256; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1211.
(63) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
(64) Barnard, C. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.
(65) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem.* **1996**, *108*, 192; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220.
(66) Burgess, K.; Moye-Sherman, D.; Porte, A. M. In *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996, p 128.
(67) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoyveda, A. H. *Angew. Chem.* **1996**, *108*, 1776; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668.
(68) Shimizu, K. D.; Cole, B. M.; Kruger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem.* **1997**, *109*, 1782; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1700.
(69) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

Scheme 34. **Hydrocyanation reaction with transition metal-free catalyst**



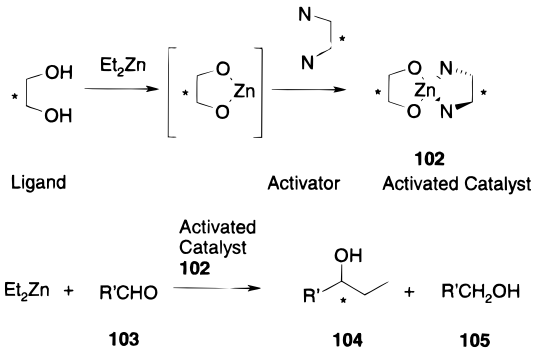
the most direct and useful routes for the asymmetric synthesis of α-amino acid derivatives. Systematic permutation cycles of building blocks for the ligand structure produced a transition metal-free catalyst that mediated the reaction of aromatic and aliphatic aldimines in more than 70% yield and more than 83% enantiomeric excess. The polymer-supported ligands were evaluated and optimised for the hydrocyanation reactions by carrying out the transformations in parallel with the polymer supported catalysts in individual reaction vessels (1 mL glass test tubes) and assaying the product mixtures with a commercial autosampler by chiral GC analysis. The best catalyst was resynthesised in solution and showed a further improved enantioselectivity of 91% for the aromatic aldimine **99** (Scheme 34).

K. Mikami et al. used the combination of an automated synthesiser (combinatorial chemistry (CC) factory, Dainippon Seiki, DNC) and a HPLC-CD system for the super-high-throughput-screening of chiral ligands and activators for the asymmetric activation of chiral dialcohol−zinc catalysts for the enantioselective addition of diethylzinc to aldehydes.[70] The combination of C_2-symmetric chiral dialcohols as ligands with chiral amines as further activators was shown to give very active catalyst systems with ee values in the range of 92−99% and very high yields. The optimum combination was found rapidly by this automated approach (Scheme 35).

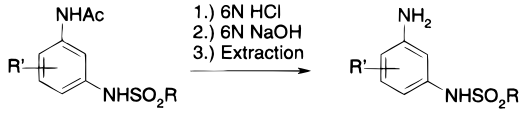
More examples of the application of combinatorial methods for the synthesis of new catalysts and the screening of their activities can be found in the reviews of A. H. Hoveyda et al.,[71] H. Weinberg et al.,[72−74] C. Gennari et al.,[75] and S. Borman.[76]

4. Work-up Studies, Crystallisations, and Separation of Racemates. Chemists in process research and development have to set their focus not only on the optimisation of

Scheme 35. **Asymmetric activation of dialcohol zinc catalysts by chiral N-ligands**



Scheme 36. **Hydrolysis of acetanilide 106**



reaction conditions but also on the work-up procedures of chemical reactions, the isolation of the wanted product, and the purification from side products. This task is sometimes even more tedious than the reaction itself, and not seldom many experiments with variations of the parameters are necessary to find the best work-up protocol. Therefore, it is not surprising that with the establishment of the new automated techniques this part is also studied very intensively.

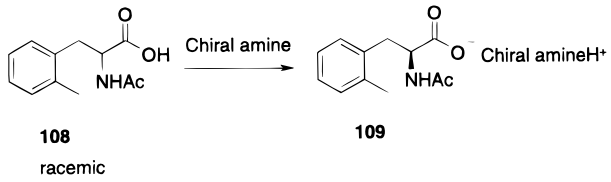
Liquid/liquid extraction is a common method for the isolation of organic compounds. The sulfonamide **107** is obtained by hydrolysis of the corresponding acetanilide **106** with 6 N hydrochloric acid (Scheme 36).

Instead of isolating the intermediate by neutralisation and subsequent filtration and drying of the precipitate K. Paulini et al. (Asta Medica)[77] investigated how the isolation by liquid/liquid extraction depends on pH, temperature, and different solvents. Ideally the extraction should be carried out with an inert solvent required for the following reaction step. This investigation was set up with a Zymark XP workstation. Within 3 days more than 220 extractions were performed largely unattended. A similar time was needed for the programming and preliminary test runs. It was found that at pH 1 an optimum is reached in the product distribution between the phases. Further neutralisation up to pH 6 does not improve the result and only leads to unwanted salt load. Presumably due to deprotonation of the sulfonamide moiety the product distribution worsens with further increase in pH. The investigation showed no significant influence of temperature and therefore no need for elevated temperatures. MiBK was found to be superior to toluene, extracting at least 5% more product under the optimum conditions.

Another important method for the large-scale purification of organic compounds is crystallisation from the reaction

(70) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem.* **1999**, *111*, 519.
(71) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885.
(72) Jandeleit, B.; Weinberg, H. *Chem. Ind.* **1998**, 795.
(73) Weinberg, W. H.; Jandeleit, B.; Self, K.; Turner, H. *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 104.
(74) Jandeleit, B.; Turner, H. W.; Uno, T.; Van Beek, J. A.; Weinberg, W. H. *CATTECH* **1998**, *2*, 101.
(75) Gennari, C.; Nestler, H. P.; Piarulli, U.; Salom, B. *Liebigs Ann./Recueil* **1997**, 637.
(76) Borman, S. *Chem. Eng. News* **1996**, *74*, 37.
(77) Paulini, K.; Dzieia, I.; Günther, E.; Kutscher, B.; Peter, G.; Reichert, D.; Laban, G.; Vogt, A.; Weckbecker, C.; Drauz, K. *Poster presentation on the 15th International Symposium on Medicinal Chemistry*, Edinburgh, 1998.

Scheme 37. **Resolution of racemic *N*-Acetyl-phenylalanine derivative 108**



108
racemic

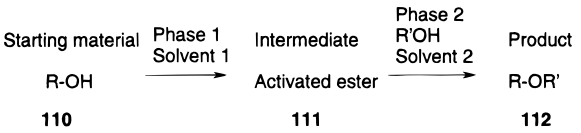
109

mixture. Crystallisations are also very popular methods for the optical resolution of racemates. These processes are usually robust and easily transferred to a pilot plant environment. The development of such a process is often rapid compared to the time and effort needed to develop an asymmetric synthesis. The high demand of optically active intermediates, the short development time frames, and the significant cost savings that can be achieved by companies reducing the time on critical path puts more pressure on the fast development of a large number of different resolution processes. However, until now the main limitation of diastereomeric salt crystallisation has been the time taken in screening for the appropriate salt. U. C. Dyer, D. Henderson, and M. B. Mitchell (Roche Discovery)[78,79] showed the application of thermal analysis and automation to resolving agent selection. Two libraries of 27 chiral bases and of over 70 chiral acids have been created. Both libraries are stored as 0.09 M ethanol solutions. This gave the opportunity to fully automate the initial screening by using an advanced ChemTech synthesis robot. A trial example is the resolution of the racemic *N*-acetyl-phenyl-alanine derivative **108** with chiral amines e.g., (+)-2-phenyl-ethylamine (Scheme 37).

Combining the simplified analysis of differential scanning calorimetry data by use of a computer program for phase-diagram construction with the advantage of high throughput by automated systems gives a powerful tool for the rapid screening of potential resolving agents. The resolution companion software package for the construction of phase diagrams and rapid analysis of DSC-data was developed in-house at Roche. This new application will probably be triggered further by the innovative approach of combinatorial resolution with substance groups of structurally related chiral acids and bases which was found recently by T. Vries, H. Wynberg, Q. B. Broxterman, S. v. d. Sluis et al.[80] This new method for the separation of racemates was already reviewed by A. Collet.[81]

5. Calorimetric Studies and Validation of Processes. How automated methods can be used successfully for the identification of critical reaction parameters and the validation of production steps was demonstrated by C. Killen (SmithKline Beecham).[82] He studied a process which already had produced 158 batches in a plant special area, but several batches (500 kg in total) were lost due to insufficient quality. The production cost loss had summarised up to approximately £1 m. To increase the understanding of the process which should lead to the elimination of plant failure and to the identification of future process improvements a study in an RC 1 automatic laboratory reactor with associated control systems was performed. In this reaction vessel the plant simulation is possible as well as the precise and repeatable control of process parameters. An ReactIR 1000 FTIR for nonintrusive in-process analysis was used to follow the reaction and to reduce the requirement for analytical input. With the help of design of experiments (DoE) the experimental information was maximised, and the handling of experimental data and the statistical evaluation was achieved with the Design-Ease software. The causes of process failure of this two-step reaction were detected, and with the gathered knowledge of the key parameters it was possible to define safe levels. Out-of-specification levels can now be detected by FTIR, and appropriate remedial action was defined (Scheme 38).

Scheme 38. **Two-step ether formation**



Adding calorimetry capability into the design of automated reactors gives a valuable tool for scale-up experiments as well as for the thorough investigation of processes and the identification of key reaction parameters. J. Singh (Hazards Evaluation Laboratory) demonstrated that important data on the progress of reactions can be gathered in the scale of 25 to 100 mL by using the HEL auto-mate mini-reactor.[83] Especially useful is the information about the heat flow of a reaction in view of a potential accumulation of dangerous reagents and also for the calculation of the necessary cooling capacity in large-scale batches. Reaction calorimetry with the auto-mate is available using the so-called power compensation method. The changes in the electrical heater power essentially mirror the thermal variations inside the reactor.

6. Manufacturing. Although the scope of this review is not spread to the automated process operating and controlling systems in the pilot and production plants the manufacturing of fine chemicals by using automated systems is briefly discussed here.

The automated synthesis of peptides[84,85] and oligonucleotides[86] is now a routine process, and automated synthesisers dedicated to solid-phase synthesis are commercially available. Most of these systems are restricted to a production scale of milligrams or grams of these highly active biomolecules. A

(78) Henderson, D. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.
(79) Dyer, U. C.; Henderson, D. A.; Mitchell, M. B. *Org. Process Res. Dev.* **1999**, *3*, 161.
(80) Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A. J.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem.* **1998**, *110*, 2491; *Angew. Chem., Int. Ed.* **1998**, *37*, 2349.
(81) Collet, A. *Angew. Chem.* **1998**, *110*, 3429.
(82) Killen, C.; *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Leeds, 1997, Abstract Book.
(83) Singh, J.; *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Leeds, 1997, Abstract Book.
(84) Andrews, R. P.; Summers, C. *Am. Biotechnol. Lab.* **1986**, *4*, 28.
(85) Newton, R.; Fox, J. E. *Adv. Biotechnol. Processes* **1988**, *10*, 1.

recent highlight in this field was presented by Y. S. Sanghvi (Isis Pharmaceuticals) on the automated manufacture of antisense oligonucleotides on a large scale.[87] The demand for a new phosphorothioate antisense drug under development with the indications of Crohn's disease, rheumatoid arthritis, and cancer could require approximately 1 metric ton of drug annually to satisfy peak market demand. When the drug development program was started in 1991 oligonucleotides were prepared at microgram or milligram scales, gram- or kilogram-scale syntheses were totally unknown. During the last years great progress was made in the design of the synthesisers and in the solid-supported synthesis methods, and today Isis Pharmaceuticals is the world's largest oligonucleotide manufacturer with further capacity expansion to a multi-ton scale being planned.

7. High Throughput Analysis and Purification in Support of Automated Synthesis. The development of new analytical methods for the rapid characterization of reaction samples taken from automated syntheses is currently a rapidly growing field. Most of this work was triggered originally by the need for analysing the purity of substances prepared in combinatorial libraries. However, hand in hand with the implementation of automated systems into the process research and development work the adaptation of analytical methods to automated systems is ongoing.

Traditionally HPLC systems are a very reliable and important tool for the process development chemist and are therefore often the method of first choice. Reverse phase HPLC is easily adaptable to automation, and it has a proven track record for performing separations of a wide variety of structural types. H. N. Weller et al. (Bristol-Myers Squibb)[88] described the use of short reversed phase columns in high throughput analysis in support of automated parallel synthesis. They were able to shorten the time per run for the analytical separation of a test mixture of four compounds from 30 min to 2−5 min. After having demonstrated that short columns operated at high flow rates can give a rapid and efficient analytical separation, they also extended the method to preparative HPLC purification in the scale of 200 mg per run (run time 10 min).

Another powerful analytical tool which can be used advantageously in the control of automated reactions is the combination of HPLC-MS with short reversed phase columns. This method gives additional information about the mass of the detected peak and can therefore be helpful in the rapid structure elucidation of impurities and reaction intermediates. This knowledge about the different components of the reaction mixture is crucial for a fast process development because it gives an insight into the mechanistic pathways of the reaction. The use of HPLC-MS and other analytical tools for solution-phase synthesis were reviewed recently by C. E. Kibbey with special focus on combinatorial chemistry and automated synthesis.[89]

A noninvasive method that also provides insight into reaction pathways as well as data for kinetic studies is FT-IR. It is especially useful for the monitoring of unstable or nonisolated intermediates and is compatible with a wide range of reaction conditions. A prerequisite for this method is that a detectable change in the characteristic vibrations of the molecule takes place during the reaction. C. P. Mak and W. Prikoszovich (Novartis) showed that FT-IR can be used for the monitoring of the deprotonation of pentan-3-one and silylation, for the study of the temperature effect on the transformation of esters to hydrazide, and for the detection of unstable lithium aryl intermediates during organometallic reactions.[90]

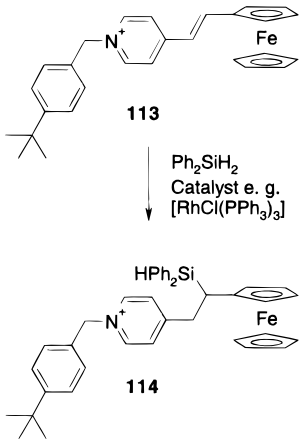
New approaches to the testing of the catalytic activity of combinatorial libraries of catalysts and ligands are currently under development. An easy usable assay for the detection of catalytic activity is necessary to have a high throughput of potential catalysts and to find the best fitted catalyst for a special synthetic problem. R. H. Crabtree et al.[91] followed an approach similar to high-throughput-screening of biological activity of compound libraries in enzyme and receptor tests using a color change to find the active catalysts. They used the pyridinium olefin derivative **113** for the detection of hydrosilylation activity of catalysts. With diphenylsilane and a catalyst (e.g., $RhCl(PPh_3)_3$) this reactive compound is transformed during a few minutes into **114**, and the color changes from dark violet to light yellow. With this simple optical assay a quick answer is possible if the prepared catalyst is active in the hydrosilylation of olefins or not. Therefore, the development of other special assays for different catalytic reactions will be becoming more and more important in the future. The current status of efficient analytical assays in support of combinatorial approaches to the discovery of new catalysts was reviewed recently by T. Bein[92] (Scheme 39).

Summary and Perspectives

As this review shows, automated chemistry in chemical process research and development is currently a rapidly growing field. The implementation of automated systems into the development process of drugs, agrochemicals, and fine chemicals as well as catalysts is getting more and more important as a response to the increasing pressure of reducing the times to market of a strongly increasing number of development compounds due to the first successes in combinatorial chemistry. This demand can be met by the chemical development departments by adding highly automated systems for the optimisation of reactions and for the high throughput analysis of complex reaction mixtures as

(86) Caruthers, M. H. *Science* **1985**, *230*, 281.
(87) Sanghvi, Y. S. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.
(88) Weller, H. N.; Young, M. G.; Michalczyk, S. J.; Reitnauer, G. H.; Cooley, R. S.; Rahn, P. C.; Loyd, D. L.; Fiore, D.; Fischman, S. J. *Mol. Diversity* **1997**, *3*, 61.
(89) Kibbey, C. E. In *A Practical Guide to Combinatorial Chemistry*, Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997, p 199.
(90) Mak, C. P.; Prikoszovich, W. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Leeds, 1997, Abstract Book.
(91) Crabtree, R. H.; Cooper, A. C.; McAlexander, L. H.; Lee, D.-H.; Torres, M. T. *J. Am. Chem. Soc.* **1998**, *120*, 9971.
(92) Bein, T. *Angew. Chem.* **1999**, *111*, 335.

Scheme 39. **Reactive dye for rapid screening of catalytic activity**



new working tools. Many major players in the pharmaceutical and fine chemicals industry are already deeply involved in automated chemical process research and development, whereas others are currently heavily investing in automated systems to keep track. The manufacturers of automated workstations for chemical synthesis are reacting to this trend by constructing new devices that meet the special demands of process development chemists (vide supra) while in the beginning there were only systems for combinatorial chemistry[93,94] available. This process is ongoing, and the design of new systems is planned.[95] The combination of the statistical design of experiments with the high throughput synthesis of automated systems gives a new powerful tool to the development chemists for the selection of the best reagents and reaction conditions. These new technologies will enable the process research and development departments to break the "new bottleneck" and to develop even better processes by a more rational approach than previously. A success story similar to that combinatorial chemistry is viable. However these goals can only be reached by a large input of "chemical intellect" because a synthesis robot will only produce results that are as good as the person who programmed it. Therefore, automation in chemical development will not be a danger to the jobs of process chemists, but it will create a big demand for new highly motivated and creative specialists in automated process research and development.

(93) Harness, J. R. In *Molecular Diversity and Combinatorial Chemistry*, Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996, 188.
(94) Hardin, J. H.; Smietana, F. R. In *High Throughput Screening; Discovery of Bioactive Substances*, Devlin, J. P., Ed.; New York, 1997.
(95) Hughes, J. *Symposium presentation at The Evolution of a Revolution - Laboratory Automation in Chemical Process R & D*, Chester, 1998, Abstract Book.

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