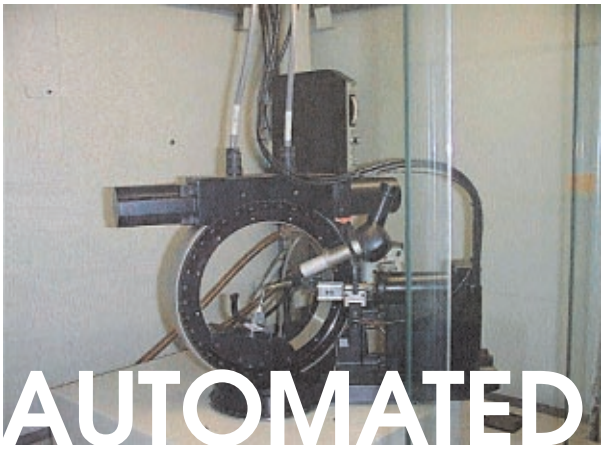


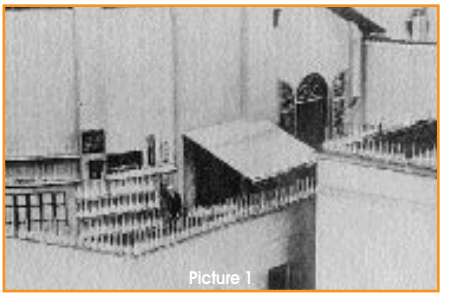
Jérôme Giovannoni, Amira Abou-Hamdan,
Christof Brändli, Josef Schröer
Chemspeed Ltd.
Augst (CH)
Chemspeed@chemspeed.com
www.chemspeed.com

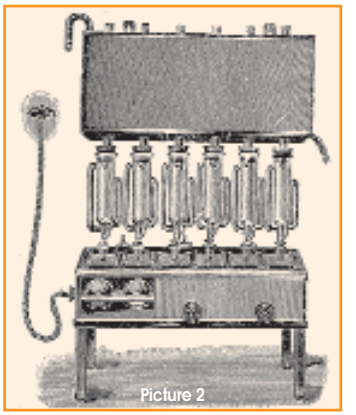
AUTOMATED EQUIPMENT FOR HIGH THROUGHPUT EXPERIMENTATION

Material science is one of the growing user field of automation and parallel equipment.
Areas like sample preparation, fragrances and flavours, crop science, healthcare, and so on are more and more aware of accelerating their discovery process and general workflow using non-traditional methods. Applying combinatorial methods in the discovery process, the outputs of molecules and materials are increased tremendously.

The field of combinatorial and parallel chemistry has recently emerged as a promising technology to accelerate research in biotechnology, pharmaceutical industry as well as in the chemical industry and materials science. Contrary to its view as modern topic, the first examples date back more then a hundred years; the first scientist to apply parallel methods was Thomas A. Edison (1, 2). On his efforts to find a suitable filament for electric bulbs, he tested more then 1,600 different materials until finding carbonized cotton threads as the material of choice. His scientific work is written down in more than 3,000 notebooks with 280 pages each and provided results for almost 2,500 granted patents. In 1912 Italian chemist Giacomo Ciamician placed hundreds of flasks on the roof of the university of Bologna in search of a photoactive substance for a photochemical process (3) (see Picture 1).

A contemporary catalogue supplying chemical laboratory equipment among parallel extractors (Picture 2), shakers (Picture 3) even offered an autoclave suitable for twelve parallel pressurized reactions with up to 10 bar (4). For a very similar idea of parallel reactions under the same pressure-atmosphere a patent was granted almost a 100 years later (5). Though representing an impressive commitment, these first approaches towards parallel and combinatorial experimentation naturally were lacking any automation, so that the analysis of the results was an extremely time consuming task. Consequently, these new ideas were not taken up by other chemists. After first initiatory works in the 1960s (6, 7), Joseph J. Hanak is now seen as the pioneer of the modern combinatorial research. He was the first author to report on the automated preparation and analysis/screening of libraries of inorganic materials in search of new superconductors (8, 9). Nevertheless, this new methodology became not popular among the scientific community because of the general lack of computers, which were essential for automated testing and data processing at that time (10). This changed in the end of the 1980s, when impressive progress in laboratory automation equipment was achieved together with the common availability of computers. Today, every step of a specific workflow starting from sample preparation, control of reaction conditions, purification, analysis and finally screening can be automated with suitable robotic equipment. In the following sections


Picture 1


Picture 2

applications of such automation equipment in organic synthesis, materials science and catalysis are described.

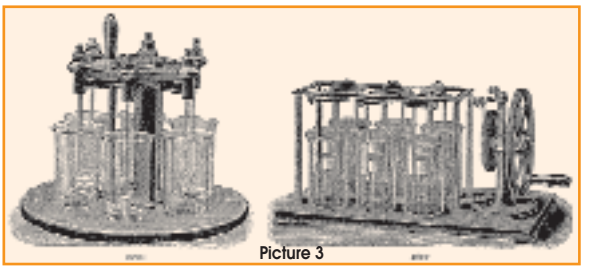
Materials science

Combinatorial research in materials science already is a well-elaborated field, successful applications range from new phosphors to luminescent materials and high-temperature superconductors (10).

Metal bipyridine complexes of the general type **2** are a promising class of compounds with non-linear optical properties. They combine advantages like ease of synthesis with a high thermal stability up to more than 300 °C and a high N(on) L(inear) O(ptics) efficiency. Synthesis of a library of complexes **2** was performed under inert conditions on our fully automated synthesis workstation ASW1000 (11) (Scheme 1).

Execution of the reaction involved slow addition of a solution of 4,4´-diethylaminostyryl-2,2´-bipyridine **1** ("DEASbpy") into the reactors that were previously charged with different metal salts. After stirring the suspensions at 30 °C, the solutions were filtered from insoluble material and subsequently evaporated in parallel. The remainder was taken up in CH_2Cl_2 and aliquots were transferred to a sample plate for UV-Vis-analysis. The spectra of the derived complexes showed a bathochromic shift that correlates well with Lewis acidity of the metal salt and the NLO activity of the complex (Table 1).

The optimization of reaction conditions is another field of application for automated parallel synthesizers, since variations of all parameters as reaction temperature and temperature, reactant ratios, solvents, catalysts etc. can be performed in parallel and subsequently analyzed on-line and/or off-line. A recent example is the optimisation of the living cationic polymerisation of 2-ethyl-2-oxazoline **3** and the determination of its activation energy (12) (Scheme 2). After (parallel) evaluation of the solvent of choice, sixteen polymerization reactions were screened in parallel at different temperatures. The temperature in each reactor is set and recorded individually. Aliquots for on-line GPC as well as off-line GC were taken automatically at specific times during the reaction. From the different reaction rates at specific reaction temperatures the activation energy of the polymerization was determined (Picture 4). The result was in good accordance with the previously reported activation energy of the polymerization of the closely related 2-methyl-2-oxazoline (68.7 and 72.9 kj/ mol resp.) (13). The authors mentioned that parallel experimentation reduced the time for solvent and temperature optimizing and evaluation of the activation energy from 6 to 7 weeks down to 2-3 days.



Picture 3

Metal salt	λ_{max} (nm)
free ligand	397
$Zn(OAc)_2$	444
$FeCl_2$	466÷595
$FeCl_3$	466÷595
$AlCl_3$	488
$NdCl_3$ x 6 H_2O	No complexation
VCl_3	No complexation
YCl_3	No complexation

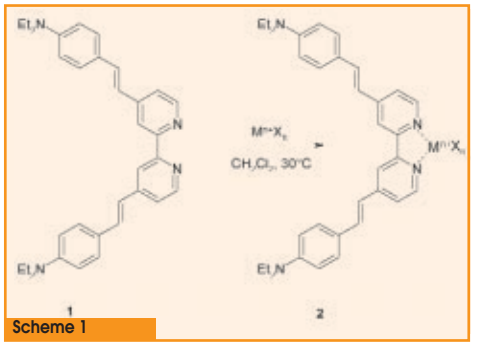
Table 1

Catalysis

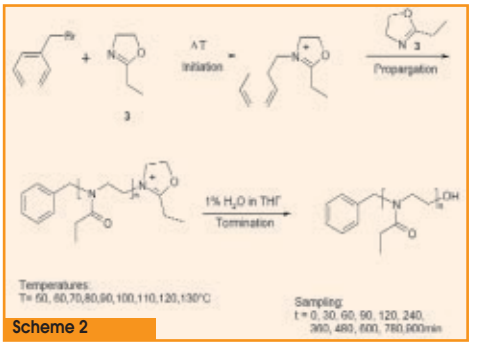
Optimization of a catalyzed reaction often is a difficult task, since minor modifications often have major impacts on conversion and/ or selectivity (14). Therefore, all parameters of catalytic reactions have to be optimized carefully; often the (repeated) robotic/automated dispensing of the reagents proves to be more accurate than manual handling of reagents.

The enantioselective hydrogenation of methyl 2-acetamido cinnamate **4** to N-acetyl phenylalanin methyl ester **5** was chosen as a test reaction to evaluate the transferability of this reaction from classical to an ASW2000P as automated equipment (15) (Scheme 3).

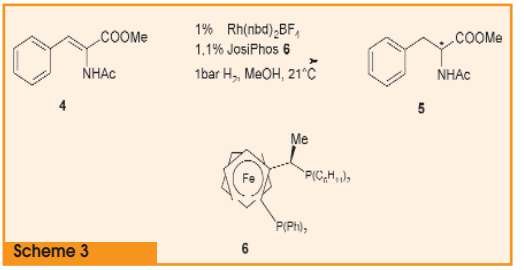
As catalyst, 1 mol-% of a *in-situ*-formed catalyst from $Rh(nbd)_2BF_4$ and a the chiral biphosphine JosiPhos **6** was employed. As was found for the classical as well as the automated experimentation, scaling effects had to be taken



Scheme 1



Scheme 2

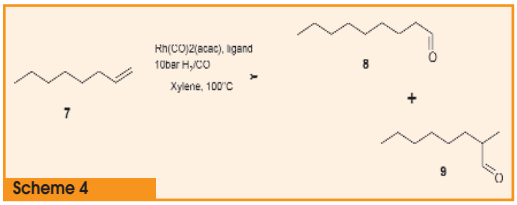


Scheme 3

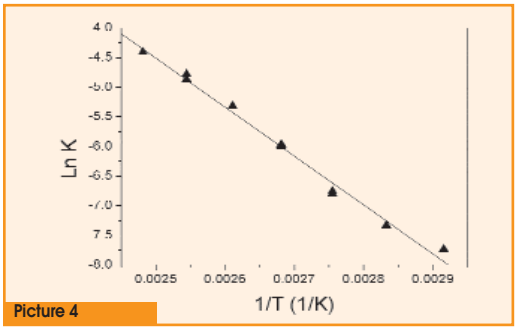
Sistemi automatizzati per la ricerca

ABSTRACT

L'approccio combinatoriale o parallelo è recentemente emerso come una promettente tecnologia in grado di accelerare la ricerca nell'industria farmaceutica, biotecnologica, così come nell'industria chimica e nello studio di nuovi materiali. Oggi, ogni stadio di un qualunque processo sia esso per la preparazione del campione, di controllo delle condizioni di reazione, purificazione, analisi e screening finale, può essere automatizzato usando sistemi robotizzati. Nell'articolo vengono descritte alcune applicazioni di sistemi automatici in sintesi organica, scienza dei materiali, e nello studio di catalizzatori.



Scheme 4



Picture 4

Entry	Phosphine ligand	Reaction time (min)	Experimental set-up	Agitation mode/ reactor type	Ratio (8:9)
1	1	60	ASW 2000P	Vortex/ steel reactor + glas inserts	90:10
2	1	60	Classical	Aeration stirrer/ glass reactor	85:15
3	2	60	ASW 2000P	Vortex/ steel reactor + glas inserts	75:25
4	2	60	Classical	Aeration stirrer/ glass reactor	72:28

Table 3

into account. The results are shown in Table 2. All hydrogenations were carried out under 1 bar of hydrogen and repeated seven times. The results between classical and automated experimentation are in complete alignment and show the accuracy of control of reaction conditions, which may influence especially the enantiomeric access, on our workstations.

In contrast to classical batch experiments, where shaking of the reaction solution is accomplished by magnetic or overhead stirring, agitation of the reactors on our automated workstations is accomplished by an inbuilt vortex shaker.

To assure the comparability of the results of automated parallel experimentation with classical experiments; the rhodium-catalyzed hydroformylation of 1-octene **7** to the linear *n*-nonanal **8** and the branched *iso*-nonanal **9** was chosen (Scheme 4). This reaction involves a gas-liquid phase-transfer and consequently is prone to differences in shaking efficiency. The results, which were gained in collaboration with BASF, Ludwigshafen, together with results from classical set-up, are shown in Table 3 (16).

Entry	Set-up	Reaction volume (ml)	Time (h)	Enantiomeric excess (%)	Standard deviation (%)
1	Classical	2,5	2	79,6	-
2[a]	ASW2000P	2,5	2	78,1	1.3
3	Classical	5	2	87,2	-
4[a]	ASW2000P	5	2	87,0	1.2
5	Classical	10	2	90,7	-
6[a]	ASW2000P	10	2	91,1	1.4

[a]*The results are averaged over eight reactions*

Table 2

All reactions showed quantitative conversion of the starting material after the stated. reaction time.

Comparison of the parallel vs. classical results (entry 1 vs. 2 and 3 vs. 4) show good correspondence between the classical and parallel set-up with a slightly enhanced n : iso ratio in the case of automated experimentation.

Summary and outlook

As shown in the previous sections, parallel synthesis has not only been applied to medicinal and pharmaceutical chemistry. Material science is one of the growing user field of automation and parallel equipment. Areas like sample preparation, fragrances and flavours, crop science, healthcare, and so on are more and more aware of accelerating their discovery process and general workflow using non-traditional methods. Applying combinatorial methods in the discovery process, the output of molecules and materials are increased tremendously. Regardless of in which area these tools are applied, they are generating a new bottleneck: optimisation, process development, and scale-up are still performed in a traditional way using the one-at-a-time approach. The future of automation in chemistry lies in the inclusion of all steps of the R&D process. Companies can no longer afford the costs of and time delays associated with traditional pilot-plant and scale-up developments. A new product from Chemspeed will face exactly this target: the process development reactor module will focus on the parallel implementation of optimisation and pilot-plant applications. This will allow any lab to execute the full transition from single flask chemistry to multiple synthesis within any step of the discovery and optimisation process.

References

(1) G.S. Bryan, Edison, the man and his work, Knopf, London, 1930.
(2) R. Hoogenboom *et al., Macromol. Rapid. Commun.*, 2003, **24**, 15.
(3) M. Freemantle, *Chem. Eng. News*, 1998, **76**, 37.
(4) http://www.neolab.de/museum/
(5) Symyx
(6) K. Kennedy *et al., J. Appl. Phys.*, 1965, **36**, 3808.
(7) N.C. Miller, G.A. Shirn, *Appl. Phys. Lett.*, 1967, **10**, 86.
(8) J. J. Hanak, *J. Mater. Sci.*, 1970, **5**, 964.
(9) E. J. Amis *et al., MRS Bull.*, 2002, **27**, 295.
(10) R. Dagani, *Chem. Eng. News*, 1999, **77**(10), 51.
(11) J.-P. Guégan *et al.*, Chemspeed Application Note No. 8.
(12) R. Hoogenboom *et al., Macromol. Rapid. Commun.*, 2003, **24**, 98.
(13) T. Saegusa, H. Ikeda, *Macromolecules*, 1973, **6**, 808.
(14) E.M. Vogl *et al., Angew. Chem. Int. Ed.*, 1999, **38**, 1570.
(15) C. Jablonski-Lorin, ICPSSP, 17.01.2003, Basel, Switzerland.
(16) J. Schröer, C. Munch, Chemspeed Application Note No. 3.