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From Green Chemistry to Green Engineering – Fostered by Novel Process Windows Explored in Micro-Process Engineering/Flow Chemistry

1.1

Prelude – Potential for Green Chemistry and Engineering

Green Chemistry is since about 20 years an approach which is meanwhile quite established in chemical research and education [1]. Experts predict a fast-paced growth of the market for Green Chemistry-type processing, from \$2.8 billion in 2011 to \$98.5 billion in 2020 (Pike Research study [2]). Finally – yet probably not before the next 20 years – experts expect this to eliminate the need for Green Chemistry as an own approach, since it will be identical to the chemistry in the future. Anastas and Kirchhoff [3] bring this to the point in “Origins, Current Status, and Future Challenges of Green Chemistry” as follows.

The revolution of one day becomes the new orthodoxy of the next.

Green Engineering followed somewhat later and just recently came out the shadow of “its big brother.” The implementation of that idea in the chemical industry proceeds now steadily, yet for reasons of complexity of the chemical processes, unavoidably at a slow rate. Today, only 10% of the current process technologies employed on industrial scale can be considered environmentally benign. It is estimated that another 25% could be made so. That leaves room for exploring and discovering the residual 65% of industrial process technology and to render them sustainable [4].

That means that there is still a considerable need to improve the enabling technologies which render chemical synthesis and chemical processes green. Under the umbrella of process intensification, microreaction technology and flow chemistry are prime enablers on the reactor and process side (see later in this chapter for citations). They help to improve current Green Chemistry approaches and in addition even give opportunities to develop new Green Chemistry concepts, which are not possible with conventional equipment. On top of that, micro- and milli-continuous processing provides a more straightforward way to upscale new green ideas. Seeing the last paragraph and the achieved 10% penetration, this is obviously still an open issue.

In continuation of the above given aphorism, this book shall open a window from Green Chemistry to Green Engineering as follows.

The revolution in the chemical laboratory needs to stimulate and bridge to the sustainability evolution on the full-production scale. [5]

1.2

Green Chemistry

Driven by political as well as societal demands, sustainability aspects gain increasing importance in all areas of human beings. Chemical production of compounds, for example, textiles, construction, ingredients in food and cosmetics, packaging, pharmaceuticals, and so on, covers more or less all aspects of human needs. The resulting extensive impact on our environment and consumption of depletable resources distinctly demands for the most efficient use of raw materials and energy. Pollution has to be prevented or at least minimized at the source to avoid end-of-pipe treatments.

New concepts have to come off with significant benefits, for example, in yield, selectivity, heat management, waste reduction, to become an environmentally benign alternative to the state of the art. Also, the environmental burdens of any reaction component, auxiliaries, and energies, obtained during upstream processes, as well as all downstream processes involved have to be taken into account.

All this has stimulated an on-going and total rethinking how to change the elemental pathways of chemical synthesis design, which has become a large movement and created an own scientific field and society known as *Green Chemistry*. While processes in the past were guided by economic, technical, and safety criteria, it is now becoming increasingly obvious and a to-do-must to have considered environmental criteria from the very beginning of the process development – which is the creative intuition of the organic chemist how to conceptually approach synthetic chemistry.

1.2.1

12 Principles in Green Chemistry

In one sentence, Green Chemistry was defined as follows [2].

Green chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products.

In kind of tabellaric goal definition, Green Chemistry was defined as follows [1b, p. 30].

- 1) Prevention
- 2) Atom economy
- 3) Less hazardous chemical syntheses
- 4) Designing safer chemicals

- 5) Safer solvents and auxiliaries
- 6) Design for energy efficiency
- 7) Use of renewable feedstocks
- 8) Reduce derivatives
- 9) Catalysis
- 10) Design for degradation
- 11) Real-time analysis for pollution prevention
- 12) Inherently safer chemistry for accident prevention.

Essentially, one can reduce that to three major incentives which are to optimize the type of feedstock, its efficiency in conversion, and the safety while doing so (derived from own thoughts and [2]).

- 1) *Feedstock*: A shift to renewable (non-petroleum) feedstocks
- 2) *Efficiency*: (i) make maximal use of starting materials (reactants) and minimize waste; (ii) minimize solvent load; and (iii) minimize energy efficiency
- 3) *Safety*: have maximal process safety and minimize toxicity (to human).

Ideally, supposed-to-be nongreen reagents just vanish from the chemical protocol by using a new chemical route such as given for GSK (Glaxo-Smith-Kline)'s green Friedel–Crafts alkylations [6]. Manifold applications have been demonstrated with respect to modern synthetic strategies, alternative solvents, renewable resources, catalysis, and environmental-friendly enzymatic catalysis in flow [1c-e, 7].

1.3

Green Engineering

1.3.1

10 Key Research Areas in Green Engineering

In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI) and global pharmaceutical companies established the ACS GCI Pharmaceutical Round-table to motivate for integration of Green Chemistry and Engineering into the pharmaceutical industry [8]. This Roundtable developed a list of key research areas in green chemistry in 2007. In 2010, the Roundtable companies have identified a list of the key green engineering research areas that is intended to be the required companion of the first list. The companies involved were Boehringer Ingelheim Pharmaceuticals, Pfizer, Eli Lilly, GlaxoSmithKline, Dutch State Mines/De Staats Mijnen (DSM), Johnson & Johnson, AstraZeneca, and Merck (US).

Ten key green engineering research areas were ranked in relevance (see Table 1.1). The issues 6–10 match with what is understood under process-design intensification in this book – (6) life-cycle analysis, (7) integration of chemistry and engineering, (8) scale-up, (9) process energy intensity, and (10) mass and energy integration. The key areas 1–5 in Table 1.1 refer partly to chemical intensification.

Table 1.1 Ten prime green engineering research areas as identified by ACS GCI Pharmaceutical Round Table (reproduced with permission).

Rank	Main key areas	Sub-areas/aspects
1	Continuous processing	Primary, secondary, Semi-continuous, and so on
2	Bioprocesses	Biotechnology, fermentation, biocatalysis, GMOs
3	Separation and reaction technologies	Membranes, crystallizations, and so on
4	Solvent selection, recycle, and optimization	Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects, and so on
5	Process intensification	Technology, process, hybrid systems, and so on
6	Integration of life cycle assessment (LCA)	Life cycle thinking, total cost assessment, carbon/eco-foot printing, social LCA, stream lines tools
7	Integration of chemistry and engineering	Business strategy, links with education, and so on
8	Scale-up aspects	Mass and energy transfer, kinetics, and others
9	Process energy intensity	Baseline for pharmaceuticals, estimation, energy optimization
10	Mass and energy integration	Process integration, process synthesis, combined heat and power, and so on

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1.3.2

12 Principles in Chemical Product Design

A product-design view is provided by the 12 Principles of Green Engineering which were proposed by Anastas and Zimmerman [9]. Sustainability is here approached in a hierarchical crossover between the molecular, product, process, and system levels.

1) *Inherent rather than circumstantial*

Designs of chemical processes shall be so much efficient and nonhazardous as possible. Example is a process to synthesize organic solvents from sugars, which has replaced many more hazardous solvents such as methylene chloride (Argonne National Laboratory). The very low energy input, high efficiency, elimination of large volumes of salt waste allows to reduce pollution and emissions.

2) *Prevention instead of treatment*

The production of waste shall be prevented rather than planning process including waste treatment.

- 3) *Design for separation*
The quest of energy and material efficiency is not only to be put on reaction but rather on separation and purification processes as well. Example is the use of supercritical CO₂, nearcritical water, and CO₂-expanded liquids, which in addition comprise nontoxic substitutes for conventional solvents.
- 4) *Maximize efficiency*
It shall be aimed at maximum efficiency in terms of mass, energy, space, and time. Example is a highly efficient family of catalysts to synthesize high-performance polymers from CO and CO₂.
- 5) *Output-pulled versus input-pushed*
Outputs (“pull”) should be removed from the system, rather than adding more input stresses (“push”) to minimize the energy and material consumption.
- 6) *Conserve complexity*
Different from the system design issue given in (5), the product design shall be complex. Idea is that the products then can have longer reuse times through better recycling than given for less complex products.
- 7) *Durability rather than immortality*
Product design shall guarantee for the product lifetime, but no longer to avoid environmental problems. Example is cellulose acetate, which is used for the filters of cigarettes. Their decomposition after use took years in the past. This could be substantially improved by incorporation of weak organic acids in the material. These are released with rain water and degrade the cellulose acetate much quicker.
- 8) *Meet need, minimize excess*
The production amount should be set just to meet the needs and not to result in over-production that creates wastes and is costly.
- 9) *Minimize material diversity*
Recycling and reusing is much facilitated when fewer materials compose a product. Example is a “unibody” piece of aluminum laptop frame that considerably reduced the product’s weight and allowed for easy recycling (Apple Inc).
- 10) *Integrate material and energy flows*
The utilization of waste energy and material flows can be used to improve the efficiency of another part of the production process. Example is the use of CO₂ to replace traditional blowing agents for the production of polystyrene foam sheets. The CO₂ used came from existing commercial processes as a waste by-product or from natural sources (Dow Chemical Company).
- 11) *Design for commercial “afterlife”*
Selection of materials or components of a process, product, or system should head for reusability and keeping high value after fulfilling their initial product function.

12) *Renewable rather than depleting*

With a similar intention, renewable sources should be used for energy, materials, or reagents, wherever possible. Example is a water-based, catalytic process for producing gasoline, jet fuel, or diesel from biomass with little external energy consumption (Virent Energy Systems Inc).

1.4

Micro- and Milli-Process Technologies

Micro- and milli-process technologies refer to (chemical) processing with reactors and other equipment with open internals in the micro (<1 mm) or milli (a few millimeters) range [10–12]. These devices provide the following functions:

- guide and structure flows;
- predetermine mass and heat transfer in single and multiple phase;
- define and reduce the volume;
- carry functional coatings and elements such as catalyst layers or membranes.

1.4.1

Microreactors

Microreactors typically comprise one or (many) more microchannels, and may also encase chambers, column/fin arrays, foams, nets, and fibers, and so on [10–12]. It is for most of these microstructures characteristic that they are artificial and engineering-made, typically by means of precision engineering or microfabrication, as opposed to nano- or microsized reaction compartments mimicking nature's cells or other organizational units such as supramolecular assemblies (micelles, vesicles, etc.). In expansion of this fabrication-related definition, also formerly existing reactor concepts, for example, monoliths, foams, and mini fixed beds as well as even capillaries, are subsumed under the umbrella of the new technology.

Microreactors are defined as check card, thin sized reactors with small outer dimensions, not exceeding a few centimeters (see Figure 1.1) [13]. These are typically made by classical microfabrication techniques based on photolithography, thin-film coating, and etching steps so that the preferred materials are glass, silicon, and polymers. Characteristic internal dimensions are typically in the range of 50–1000 μm .

1.4.2

Microstructured Reactors

Microstructured reactors have larger outer dimensions, especially concerning their length and width, while the internals are miniaturized (see Figure 1.2) [13]. These are typically made in stainless steel, but also in glass. For both, etching technologies can be used for microstructuring. Steel microstructured reactors are

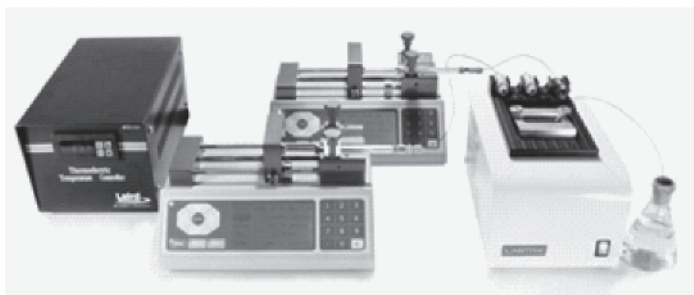
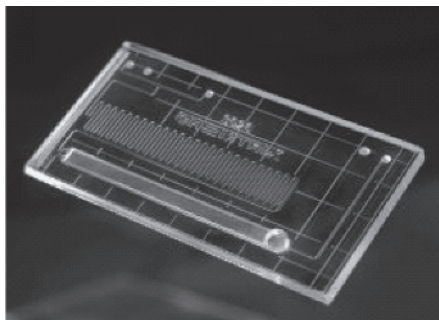


Figure 1.1 Glass chip microreactor with mixer and elongated serpentine channel for reaction; from Chemtrix (a). Such chip reactors are embedded in a flow chemistry environment consisting of pumps, a

microreactor holder with heating function and feed/collecting reservoirs, if needed, also a back-pressure valve for high-p experimentation; from Chemtrix (b). (Reproduced with permission from Chemtrix).

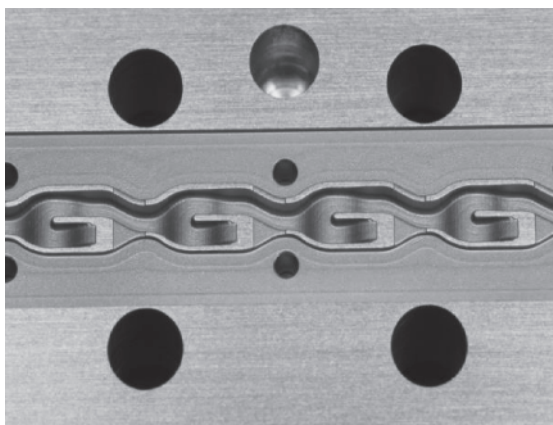


Figure 1.2 Split-recombine micromixers have dedicated microchannel structures due to their mixing principle based on repeated flow splitting – caterpillar micromixer from ICT-IMM

with smooth (“3D”) upwards and downwards sloping (left). Typically, such mixers are assembled as (screwed) two-plate structures. (Reproduced with permission from ICT-IMM).

also accessible through precision engineering (micromilling, cutting, embossing, and more), laser machining, and micro-electro discharge machining (μ EDM). Laboratory microstructured reactors are typically fist-size and below. Pilot- and production-scale reactors may be shoebox size or even approach extensions in the meter range.

The same classification can be applied to milli-reactors and millistructured reactors, which are the dimensional extension of the devices given above. Such reactors that are designed for larger throughput and are less prone to failure, for example, by clogging, but certainly also with lower performance potential. Milli-process technologies often use commercial capillaries and tubes with millimeter internal measurements, sometimes being filled with foams or fibers as structured packings.

Microreactors and microstructured reactors (as well as their milli counterparts) are typically scaled-up by two means:

- *Numbering-up*: internally via parallel channels in plates and via parallel plates with channels (see Figure 1.3); externally via parallel devices;
- *Smart scale-out*: moderate increase in channel dimensions.

The first concept has the charm of equaling-up the geometries and finally reaction conditions (mixing, hydrodynamics, heat transfer) from lab to production scale. It is especially applied towards gas-phase and multi-phase reactions. Gas-phase reactions benefit from comparatively easy means (diffuser/pressure barrier) for flow distribution. In case of multi-phase reactions, the maintenance of the flow pattern from lab- to production-scale is crucial; thus, the concept of smart scale-out will most often not be applicable. In case of liquid reactions, both the numbering-up and smart scale-out approaches are applied. Concerning the latter, Lonza Company has developed an extreme, but effective, version by making the whole flow development from lab to production scale within one

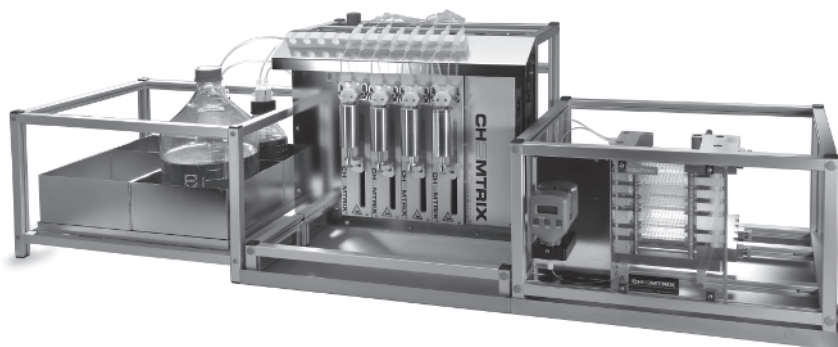


Figure 1.3 Flow production unit with internally numbered-up microreactor, at the right lower side of the plant; Plantrix system from Chemtrix. (Reproduced with permission from Chemtrix).

reactor or even one channel passage and having that in three steps (lab, pilot, production) smartly increased [14]. The latter also reduces the fouling sensitivity.

1.5

Flow Chemistry

1.5.1

10 Key Research Areas in Flow Chemistry

Ten key research areas of synthetic flow chemistry were identified and provided a deeper understanding into current and future issues in the field [10c]. Comparing these flow essentials with the three intensification fields, as discussed in this book, shows that both views have overlapping contents (see Table 1.2). This clearly shows that issues on chemical intensification have a major role currently in the overall development.

1.6

Two Missing Links – Cross-Related

There is a missing link between Green Chemistry and Green Engineering. Different approaches for green improvements of chemical syntheses pathways and process technologies have been followed by chemists and engineers during the last two decades, but often independently from each other. Whereas “Green Chemistry” approaches have been primarily apprehended as new chemical synthesis strategies [1] applying alternative solvents [2], chemistry based on renewable resources [3] or yield and selectivity improvements by catalysis [4], Green Engineering approaches have been put on a level with the design of novel

Table 1.2 Ten key research areas in flow chemistry [10c], which match with the three intensification fields, introduced in the next chapter.

Issue	Key characteristics	Intensification field
1	Size matters – micro versus minifluidic (or mesofluidic) reactors	Transport
2	Residence time, flow rate, and reactor volume – key factors in flow chemistry	Transport
3	Flow, heat, and pressure – a crucial relationship	Transport
4	Flow and reactive intermediates – a classical application	Chemical
5	Flow and supported reagents	Chemical
6	Flow and supported catalysts – an ideal match	Chemical
7	Flow and multicomponent reactions	Chemical
8	Flow and photochemistry – new options	Chemical
9	Flow and multistep synthesis – mimicking nature	Process-design
10	Flow, scale up and industrial application – think big	Process-design

equipment and new processing methods [5], using multifunctional reactors, new operating modes, or micro-process technology for process improvement and intensification [6]. Since environmental issues affect many disciplines, cross-disciplinary interaction is essential for success. Otherwise, undesired impacts are shifted from one domain to another, and well-intentioned green developments result in unexpected surprises. In the past, a lot of false decisions already emerged by concentrating only on the optimization of the chemical synthesis itself or by focusing on single principles of green process design, neglecting inconvenient aspects and missing broader implications.

One solution for this missing link was already been assigned to micro-process engineering and flow chemistry. Certainly, this is not the only solution and other solutions may be at hand as well. The citation and exploitation numbers show clearly that this is a prime concept (see Chapter 14).

Yet, there is a second missing link and this has been addressed already in the Motivation statement, placed directly before this first chapter. Microreactors as mostly used about 5 years ago had (and often still have) one prime disadvantage which is their short contact time given as an intrinsic feature. Organic reactions as we know are typically processed on much longer times. One the one side, there is seconds scale, on the other side often hours and days scale – seemingly a misfit.

In this context, this book aims to show how the novel equipment – micro-/flow reactors – allows to reach new operating modes – Novel Process Windows – which open novel opportunities in chemistry and overcome the above-mentioned dilemma (see Figure 1.4).

Novel Process Windows can then result in a much improved sustainability footprint via a full-chain oriented and multifunctional process design. Such technology innovation is expected to improve the cost structure of chemical industry and has many other advantages concerning product flexibility, product quality, process development time, and more. It is thus important to point out that Novel Process Windows combines chemical and engineering perspectives.

The book is organized as given in Figure 1.5 which provides a hierarchic approach to implement green ideas on all development stages in chemical process development (from top to down in the said figure) and names also their evaluation method counterparts and the achieved process intensification result (from left to right).

This results then in the following five-leveled hierarchy and interrelation of chapter packages and is the backbone of the book structure.

- *Chapters 1–3*: Here, the industrial and society needs are translated into the knowledge-based design approaches for synthesis and processing (Chapter 1). Then, it is shown how this can be used for door-opening functions in chemistry in an entirely new way (Chapter 3). A theoretical assessment is done in Chapter 3 to have the foundation for the knowledge-based design.
- *Chapters 4–8*: Here, the fundamental challenges and chances of the new door-opening concept are given to reach in praxis-intensified flow chemistry which relates to green metrics

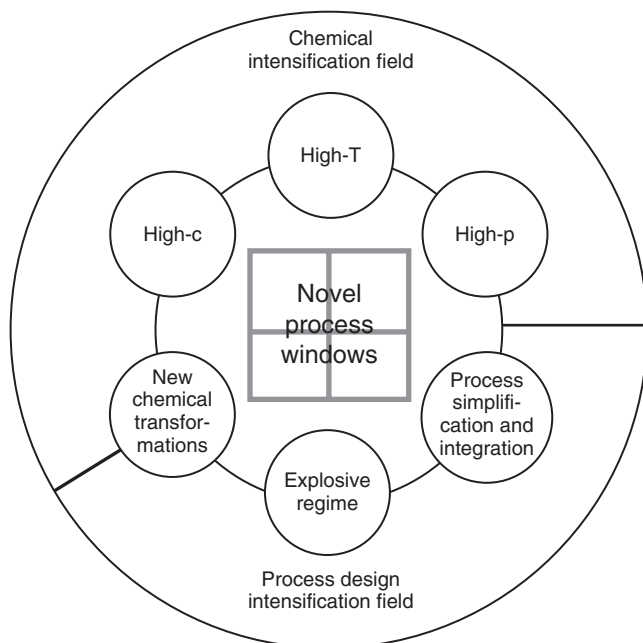


Figure 1.4 Schematic representation of Novel Process Windows. A more detailed description is provided in the coming chapters. (Hessel *et al.* [15]; reproduced with permission from Wiley-VCH).

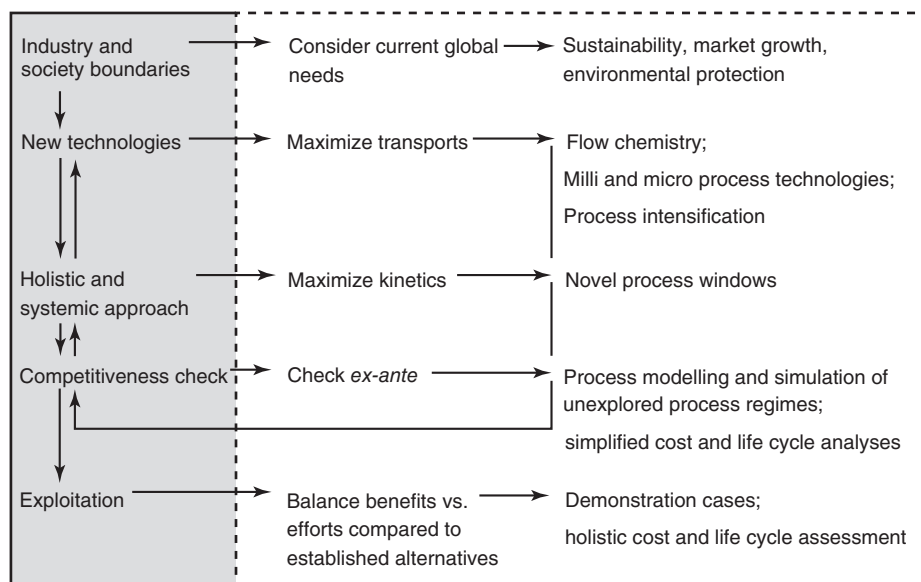


Figure 1.5 Combined approach of Novel Process Windows process design and accompanying life cycle assessment (LCA) and life cycle costing (LCC). (Kralisch *et al.* [15]; reproduced with permission from Wiley-VCH).

- *Chapters 9–10*: On a higher-complexity (holistic) process level, it will be demonstrated how these process windows change the chemical plant as a whole. Herein, process chemistry, engineering, and chemistry will merge.
- *Chapters 11–12*: This ends in a demonstration that the technique is beneficial for society through sustainability benefits and mature for chemical industry.
- *Chapter 13*: While the demonstration of the superiority of the concept of Novel Process Windows remains the task of the future, some first summary of 5-years achievement in terms of scientific dissemination and project exploitation is given here as a kind of concluding chapter and outlook.

References

- (a) Anastas, P.T. (2010) *Tetrahedron*, **66**, 1026–1027; (b) Anastas, P.T. and Warner, J.C. (1998) *Green Chemistry: Theory and Practice*, Oxford University Press, New York. Green Chemistry – catalysis:(c) Kidwai, M. (2010) in *Handbook of Green Chemistry, Set 1: Green Catalysis* (ed R.H. Crabtree), Wiley-VCH Verlag GmbH & Co. KGaA, pp. 81–92; (d) Hintermair, U., Francio, G., and Leitner, W. (2011) *Chem. Commun.*, **47**, 3691–3701; (e) Bandgar, B.P., Gawande, S.S., and Muley, D.B. (2010) *Green Chem. Lett. Rev.*, **3**, 49–54.
- Navigant Pike Research Study, www.navigantresearch.com/research/green-chemistry (accessed 13 May 2014).
- Anastas, P.T. and Kirchoff, M.M. (2002) *Acc. Chem. Res.*, **35** (2), 686–694.
- Warner Babcock Institute for Green Chemistry www.warnerbabcock.com/green_chemistry/about_green_chemistry.asp (accessed 13 May 2014).
- Ecochem http://ecochemex.com/10-business-reports-sustainability/?utm_campaign=newsletter&utm_source=hs_email&utm_medium=email&utm_content=10063171&_hsenc=p2ANqtz-VsH7jL_2lajp5XBWx7Aa6IFPsa8pHdxuvG7zKtmFStXYXVa9i_7itsILNiGtN-cjeYRjXrXoMegm_t9EwHc00YCj7w&_hsmi=10063171 (accessed 13 May 2014).
- Wilkinson, M.C. (2011) *Org. Lett.*, **13**, 2232–2235.
- Green Chemistry – new chemical synthesis strategies: (a) Fischmeister, C. and Doucet, H. (2011) *Green Chem.*, **13**, 741–753; (b) Savage, P.E. and Rebacz, N.A. (2010), *Water Under Extreme Conditions for Green Chemistry*. vol. 5, Wiley-VCH Verlag GmbH & Co. KGaA, pp. 331–361; (c) Reinhardt, D., Ilgen, F., Kralisch, D., Koenig, B., and Kreisel, G. (2008) *Green Chem.*, **10**, 1170–1181; Green Chemistry – renewable resources(d) Le, R.V., Dupe, A., Fischmeister, C., and Bruneau, C. (2010) *ChemSusChem*, **3**, 1291–1297; (e) Jones, M.D. (2010) *Catal. Met. Complexes*, **33**, 385–412; (f) Ilgen, F., Ott, D., Kralisch, D., Reil, C., Palmberger, A., and Koenig, B. (2009) *Green Chem.*, **11**, 1948–1954; Green Chemistry – environmental friendly enzymatic catalysis in flow:(g) Urban, P.L., Goodall, D.M., and Bruce, N.C. (2006) *Biotechnol. Adv.*, **24**, 42–57; (h) Asanomi, Y., Yamaguchi, H., Miyazaki, M., and Maeda, H. (2011) *Molecules*, **16**, 6041–6059; (i) Bolivar, J.M., Wiesbauer, J., and Nidetzky, B. (2011) *Trends Biotechnol.*, **29**, 7. (j) Fornera, S., Kuhn, P., Lombardi, D., Schliter, A.D., Dittrich, P.S., and Walde, P. (2012) *ChemPlusChem*, **77**, 98–101; (k) Pohar, A., Plazl, I., and Žnidaršič Plazl, P. (2009) *Lab Chip*, **9**, 3385–3390; (l) Kundu, S., Bhangale, A., Wallace, W.E., Flynn, K.M. *et al.* (2011) *J. Am. Chem. Soc.*, **133**, 6006–6611.
- Constable, D.J.C., Jimenez-Gonzalez, C., and Henderson, R.K. (2007) *Org. Process Res. Dev.*, **11**, 133–137.
- (a) Anastas, P.T. and Zimmerman, J.B. (2003) *Environ. Sci. Technol.*, **37** (5), 94A–101A; (b) Mulvihill, M.J., Beach, E.S., Zimmerman, J.B., and Anastas, P.T. (2011) *Annu. Rev. Environ. Resour.*, **36**, 271–293.

10. For a selection of reviews which deal with micro process technologies and flow chemistry: (a) Noel, T. and Buchwald, S.L. (2011) *Chem. Soc. Rev.*, **40**, 5010–5029; (b) Hartman, R.L., McMullen, J.P., and Jensen, K.F. (2011) *Angew. Chem. Int. Ed.*, **50**, 7502–7519; (c) Wegner, J., Ceylan, S., and Kirschning, A. (2011) *Chem. Commun.*, **47**, 4583–4592; (d) Glasnov, T.N. and Kappe, C.O. (2011) *J. Heterocycl. Chem.*, **48**, 11–30; (e) Webb, D. and Jamison, T.F. (2010) *Chem. Sci.*, **1**, 675–680; (f) Cukulovic, A., Monbaliu, J.-C.M.R., and Stevens, C.V. (2010) *Top. Heterocycl. Chem.*, **23**, 161–198; (g) Frost, C.G. and Mutton, L. (2010) *Green Chem.*, **12**, 1687–1703; (h) Hartman, R.L. and Jensen, K.F. (2009) *Lab Chip*, **9**, 2495–2507; (i) Geyer, K., Gustafsson, T., and Seeberger, P.H. (2009) *Synlett*, 2382–2391; (j) Fukuyama, T., Rahman, M.T., Sato, M., and Ryu, I. (2008) *Synlett*, **2**, 151–163; (k) Ley, S.V. and Baxendale, I.R. (2008) *Chimia*, **62**, 162–168; (l) Wiles, C. and Watts, P. (2008) *Eur. J. Org. Chem.*, **2008**, 1655–1671; (m) Mason, B.P., Price, K.E., Steinbacher, J.L., Bogdan, A.R., and McQuade, D.T. (2007) *Chem. Rev.*, **107**, 2300–2318; (n) Geyer, K., Codee, J.D.C., and Seeberger, P.H. (2006) *Chem. Eur. J.*, **12**, 8434–8442; (o) Kirschning, A., Solodenko, W., and Mennecke, K. (2006) *Chem. Eur. J.*, **12**, 5972–5990; (p) Jaehnisch, K., Hessel, V., Löwe, H., and Baerns, M. (2004) *Angew. Chem. Int. Ed.*, **43**, 406–446; (q) Hessel, V. and Löwe, H. (2003) *Chem. Eng. Technol.*, **26**, 13–24; (r) Hessel, V. and Löwe, H. (2003) *Chem. Eng. Technol.*, **26**, 391–408; (s) Hessel, V. and Löwe, H. (2003) *Chem. Eng. Technol.*, **26**, 531–544; (t) Jensen, K.F. (2001) *Chem. Eng. Sci.*, **56**, 293–303; (u) Jensen, K.F. (1999) *AIChE J.*, **45**, 2051–2054.
11. For some recent books pertaining flow chemistry: (a) Watts, P. and Wiles, C. (2011) *Microreactor Technology in Organic Synthesis*, CRC Press. (b) Wirth, T. (2008) *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH Verlag GmbH, Weinheim. (c) Yoshida, J.-I. (2008) *Flash Chemistry: Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, Hoboken, NJ. (d) Seeberger, P.H. and Blume, T. (2007) *New Avenues to Efficient Chemical Synthesis – Emerging Technologies*, Springer-Verlag, Berlin.
12. For books about micro-process technologies: (a) Ehrfeld, W., Hessel, V., and Löwe, H. (2000) *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH Verlag GmbH, Weinheim. (b) Hessel, V., Hardt, S., and Löwe, H. (2004) *Chemical Micro Process Engineering – Fundamentals, Modelling and Reactions*, Wiley-VCH Verlag GmbH, Weinheim. (c) Hessel, V., Löwe, H., Müller, A., and Kolb, G. (2005) *Chemical Micro Process Engineering – Processing and Plants*, Wiley-VCH Verlag GmbH, Weinheim. (d) Hessel, V., Renken, A., Schouten, J.C., and Yoshida, J.-I. (2009) *Handbook of Micro Process Engineering*, Wiley-VCH Verlag GmbH, Weinheim.
13. Hessel, V. and Noël, T. (2013) Micro process technology, 2. Processing, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH. doi: 10.1002/14356007.b16_b37.pub2
14. Kockmann, N., Gottsponer, M., and Roberge, D.M. (2011) *Chem. Eng. J.*, **167** (2–3), 718–726.
15. Kralisch, D., Streckmann, I., Ott, D., Krtschil, U., Santacesaria, E., Di Serio, M., Russo, V., De Carlo, L., Linhart, W., Christian, E., Cortese, B., de Croon, M. H. J. M., and Hessel, V. (2012) *ChemSusChem*, **5**, 300–311.

