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Conference Report

13. Freiburger Symposium 2017: Green Chemistry – from Concept to Industrial Reality

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Keywords: Freiburger Symposium · Green chemistry

Introduction

Am 11. und 12. Mai 2017 fand das 13. Freiburger Symposium – organisiert von der Division für Industrielle und Angewandte Chemie – an der Hochschule für Technik und Architektur in Freiburg statt. Unter dem Thema «Green Chemistry – from Concept to Industrial Reality» wurden industrielle Beispiele für Nachhaltigkeit in der chemischen Produktion und Entwicklung in insgesamt 14 Vorträgen präsentiert. Besondere Highlights im Rahmen des Programms bildeten die Key Note Lecture von Dottikon Exclusive Synthesis CEO Dr. Markus Blocher sowie die Sandmeyer Award Lectures der Preisträger von 2016 und 2017. Erstmalig wurde während des Symposiums die offizielle Vergabe des Sandmeyer-Preises an die Preisträger von 2017 durchgeführt. Die Übergabe fand im feierlichen Rahmen des Symposiumsdinners am Abend des 11. Mai in Anwesenheit von SCG-Präsident Dr. Alain De Mesmaeker und SCG-Geschäftsführer David Spichiger statt. Viele angeregte Diskussionen und das grosse Interesse der Teilnehmer zeigten die hohe Aktualität und Relevanz des Themas «Green Chemistry» für die schweizerische Chemieindustrie. Insgesamt war die Veranstaltung ein voller Erfolg und wir bedanken uns ganz herzlich bei allen Referenten und präsentieren Ihnen hiermit die Abstracts der Vorträge des diesjährigen Symposiums.

The 13th Freiburger Symposium – organized by the Division of Industrial and Applied Chemistry – took place at the College of Engineering and Architecture in Fribourg (CH) on May 11th and 12th 2017. On the topic 'Green Chemistry – from Concept to Industrial Reality' a total of 14 lectures with industrial examples for sustainability in the chemical industry were presented during the two days of the symposium. Within the diverse program the keynote lecture of Dottikon Exclusive Synthesis CEO Dr. Markus Blocher and the Sandmeyer Award lectures of 2016 and 2017 represented particular highlights. For the first time, the official Sandmeyer Award Ceremony with the award winners of 2017 was celebrated at the symposium dinner by SCG's president Dr. Alain De Mesmaeker and executive director David Spichiger. Many lively discussions and the high interest of the audience proved the actuality and relevance of the topic 'Green Chemistry'. Overall, the event was a great success and we would like to express our sincerest thanks once again to all the speakers who made this possible. We are now presenting the abstracts of the different lectures in this conference report.

Impressions of the Freiburger Symposium 2017

1. Synthetic Design with the *Chematica* Program – The Importance of Accurate Rules and of Higher-order Logic

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Keywords: Chematica · Computers · Retrosynthesis

The Chematica program for fully automated design of synthetic pathways leading to arbitrary targets has been under vigorous development for over a decade now.[1-3] Most recently, the Chematica GSI company was acquired by Millipore-Sigma/Merck and the software will soon become widely available. As the first examples of syntheses of nontrivial targets are rolled out for publication, it is timely to summarize some of the 'philosophical' assumptions that went into Chematica's design.

As in chess, organic-synthetic planning requires the knowledge both of one-step basic moves (*i.e.* reaction 'rules' describing various classes of reactions from simple S_N2 to complex rearrangements) and of 'strategies' prescribing how these moves can be used to construct entire games (*i.e.* complete synthetic pathways).

Teaching a computer the reaction rules is quite a daunting task in itself, since there are thousands of them and each has to prescribe very accurately the scope of permissible substituents, the stereo- and regiochemical considerations, electronic effects, protection requirements, as well as molecule-wide 'context' (*e.g.* whether there are other conflicting groups, is there steric hindrance from a distant part of the same molecule, *etc*.). Historically, there have been many attempts to extract this reaction information automatically from repositories such as Reaxys or SciFinder and then use various statistical or machine-learning (ML) methods to group specific, literature-reported precedents into generalized rules. The problems with such an approach, however, are manifold and range from the manual entry mistakes in the said repositories to much more severe limitations of available statistics being insufficient for meaningful learning. For example, in the nowadays popular and powerful deep-learning methods, the computer needs millions of data points to learn tasks such as image recognition. In contrast, in chemistry, all but the simplest types of reactions have only few to hundreds of literature precedents,[3] which cannot possibly capture the full scope of these methodologies. In one illustrative exercise, we have attempted to machine-learn the nuances of Diels-Alder chemistry, for which some of the most abundant statistics are available (~10,000 literature precedents in Reaxys). Even with the most sophisticated ML tools (support vector machines, random forests, convolution networks), the accuracy of the ML models in predicting proper regioselectivity was no better than a toss of a coin (50%). Such accuracy is a far cry from what is needed in any serious synthetic design. Moreover, even if the rules were captured with 90% accuracy (as in some state-of-the-art ML methods[4,5]), it should be remembered that the success of an entire pathway requires *all* steps to be correct – with 90% for each step, the likelihood of a ten-step pathway being flawless would be only $0.9^{10} \approx 35\%$ and decreasing sharply for longer routes.

Given the above limitations of available training sets and accuracy, it becomes clear that there is no simple, automated way to teach the computer organic-synthetic rules and, instead, they must be meticulously coded and generalized by expert chemists (see ref. [3] for details). That is one of the reasons why coding 40,000+ of Chematica's rules (vs. ~10 in chess!) took such a long time.

But even having all the reaction guidelines in place is just the beginning. Akin to an expert chemist, the computer must be taught the 'higher-order logic' of concatenating individual transformations into meaningful *sequences* and of planning ahead. There are many aspects of such strategic planning and the development of what we called 'strategic synthetic heuristics' (SSH) is at the forefront of current Chematica research. As one simple example, the machine needs to be told not to drag highly reactive intermediates (organomagnesium compounds, acyl chlorides, isocyanates, *etc*.) along many steps – such species should be made and then used in the very next step. The program needs to recognize intermediates that are unstable or structurally more complex (even if of smaller MW) than the target – it then does not waste time venturing into the 'branches' of synthetic possibilities that are unpromising. However, one must be careful here as there are also cases in which increasing structural complexity in the retrosynthetic direction is actually beneficial. For example, transforming a cyclohexane moiety into cyclohexene might seem futile as it does not simplify the structure – yet, any organic chemist will recognize that the purpose of such a move is to enable a subsequent Diels-Alder reaction. From an algorithmic point of view, the program needs to be taught such strategic sequences which allow it to overcome local complexity maxima and then dive into elegant solutions. There are currently 50,000+ of strategic sequences in Chematica and their number keeps growing.

As might be imagined, there is also a nontrivial problem of developing search algorithms using the rules and heuristics to navigate over enormous 'trees' of synthetic possibilities. The image on the left shows one very simple tree Chematica constructed in the early seconds of designing a synthesis of a small-molecule drug. By the time the machine was done with the design (after ~15 min), the tree grew by several hundreds of times and was significantly larger than a human metabolic network. Storing such graphs in computer's dynamic memory and analyzing them on-the-fly to report to the user currently-best pathways requires deep knowledge of graph theory as well as some advanced software engineering over parallelized, multiprocessor systems.

Notwithstanding the above challenges, Chematica has reached its maturity, or at least puberty. To be sure, there are some aspects of the program that require further work – these include a more streamlined graphical user interface, addition of some reaction rules and heuristics, further acceleration of the search algorithms, and few more. But there is no longer a question whether computers can offer any valuable help to practicing organic chemists – the question is rather how to overcome the skepticism of this being at all possible. The upcoming dissemination of Chematica under the auspices of Merck will, hopefully, allow the organic-synthetic community to test-drive its immense computer horsepower at full capacity.

Acknowledgements

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2. New Dimensions in Process Innovation as Enabler for Green Chemistry

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Keywords: Bio-based chemistry · Biofuels · Flexible operation · Robust design · Tolerant processes

Against the backdrop of global changes regarding the energy and raw material situation, chemical industry is presently facing challenges in existing and emerging markets. Shorter product lifecycles through commoditization and reduction of feedstock and energy dependency risks are only some examples along the value chain. Cradle-to-cradle production concepts and circular economy are in serious discussion and implementation. The commitment to sustainable products and processes necessitates new dimensions in process innovation.

Bio-based chemistry is an answer to change the raw material situation and market pull for green solutions. However, the overall process design challenges like flexibility towards *e.g.* seasonal dependent variables, renewable fluctuating energies and novel downstream scenarios (*e.g.* water-stable catalysts) require answers. Robust process design calls for comprehensive end-to-end approaches that balance between high performance and process reliability in an overall optimum. Enablers such as high throughput experimentation, big data analysis and innovation project management are key success factors.

The Clariant sunliquid® process is a second-generation biofuel production process as well as an ideal platform for bio-based chemicals (see Fig. 1). Biofuel production is known for its variety of chemical and bioprocess engineering disciplines involved in the complex chain from solid feed pre-treatment over fermentation of rheological challenging broths to alcohol purification. The process design successfully addresses these known technical challenges through co-development of all unit operations towards a fully integrated solution. Therefore, it demonstrates how innovations in an interdisciplinary environment and tolerant process design enable sustainable and green chemistry.

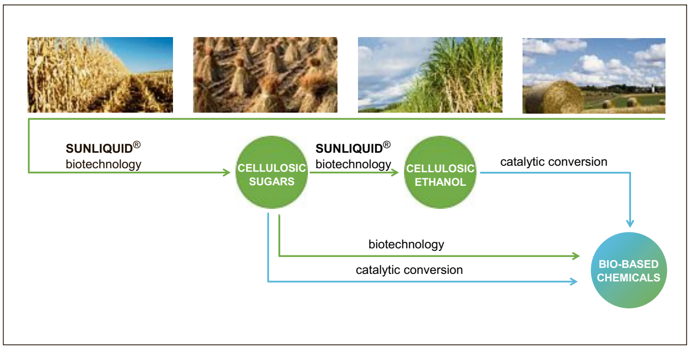

Fig. 1: Clariant sunliquid® process scheme.

Tolerant processes are realized through both robust design and flexible operation possibility, and are a major pillar of the new dimensions in process innovation (see Fig. 2). Robust design on the one hand requires layout tools considering uncertain boundary conditions and fluctuating input parameters as well as robust optimization tools for data and model driven design. Flexible operation on the other hand is guaranteed through the respective unit operation layout including novel catalysts and catalytic concepts as well as hybrid, multifunctional and modular equipment in an overall harmonized process.

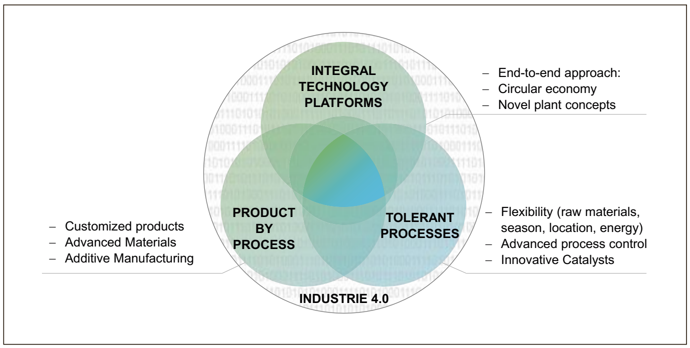

Fig. 2: The new dimensions in process innovation.

Consequently, a paradigm shift in the way we design and operate processes requires new approaches in process design, mobilization of funding opportunities as well as aligning education for the next generation of chemical engineers.

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3. Ways to Efficiently Develop Green Crystallization Processes

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Keywords: COSMO-RS · PAT · Supersaturation control

Batch crystallization is still the most widely used purification and form-giving method in the specialty and pharmaceutical industry. Typical green crystallization process development targets are: minimization of solvent volume, off-spec batches (with regard to polymorphic form, crystal purity and size), product characteristics variability, active substance loss and batch time reduction.

Efficient Thermodynamic Property Estimation

Solvent selection is a first and fundamental step during the design of a crystallization process in order to reach the desired solid property such as polymorphic form, analytical purity, color specification and solvent content in the crystal. The target of the solvent selection task under discussion is to find a replacement to the current solvent system, which has high price, is corrosive and poses safety issues during recycling.

The first step of the solvent selection method is to generate the solubility database of the main and by-product. The solubility of a solid in a given solvent or solvent mixture can be estimated using the COnductor like Screening MOdel for Real Solvents (COSMO-RS) method, which performs quantum chemical calculations for the surface charge density estimation. Other solubility estimation methods such as the Universal Functional Group Activity Coefficients (UNIFAC) can be used as well. The solubility database generated with COSMO-RS contains the solubilities of 3300 binary solvent pairs at several temperatures and is used to perform the solvent screening.

The first step of the procedure is to filter out all solubility curves, which do meet 'best practice' industrial crystallization process development criteria, *e.g.* solubility of the main component should be in a certain range, *e.g.* 20–40% at the crystallization start temperature and 3–5% at filtration temperature. Another important screening criteria, which was considered is that the solubility of the by-product at the filtration temperature should be above a threshold. The list of successful hits can be further filtered by imposing vapor pressure, corrosion and EHS related constraints. This screening was implemented by compiling a list of preferred solvents, which served as an additional filter.

PAT-based Feedback Control as Process Design Method

The Process Analytical Technology (PAT) initiative[1] published by the U.S. Department of Food and Drug Administration (FDA) has been a turning point in the way crystallization processes are investigated, designed and controlled. The guidance encourages the use of on-line measurements to efficiently gain process understanding and manage R&D risks. Since then, PAT has become a 'must have' tool in several industrial process R&D divisions.[2,3] An overview of the newly established 'Crystbench' PAT platform at BASF Schweiz AG is presented in Fig. 1.

As demonstrated by the 'Crystbench' project, the power of PAT can be leveraged by highly automated auxiliary laboratory equipment, which ensures the implementation of pre-programmed experiments and safe 24/7 operation. Another important 'Crystbench' feature is the implementation of advanced crystallization feedback control loops such as supersaturation and direct nucleation control.

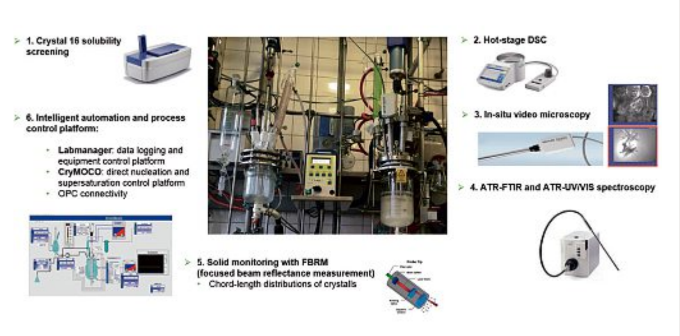

Fig. 1. The 'Crystbench' PAT laboratory at BASF Schweiz AG.

Supersaturation control is the most widely spread crystallization feedback control method and aims to adjust the supersaturation generation rate to the crystal nucleation and growth rates. This control method ensures that events that occur at rather high supersaturations are minimized (*e.g.* nucleation, agglomeration) and crystal growth is favored. The outputs of the controller are the holding time and temperature profile; thus, this crystallization control scheme can be regarded as an *automated process design method*. The resulting holding time and cooling profile can be approximated by linear segments for the off-line implementation in production plants. Fig. 2 shows the phase diagram of a supersaturation controlled process.

The People: Relevant Skills

Efficient green crystallization development requires that the relevant skills and experience are available to routinely perform thermodynamic property estimation and to operate complex laboratory PAT platforms. Ideally, these aspects of process development should be routinely represented in all process R&D project teams. The PAT-related challenges lie in the design and customization of complex laboratory hardware and software solutions, as well as in the implementation of data integration and evaluation platforms.

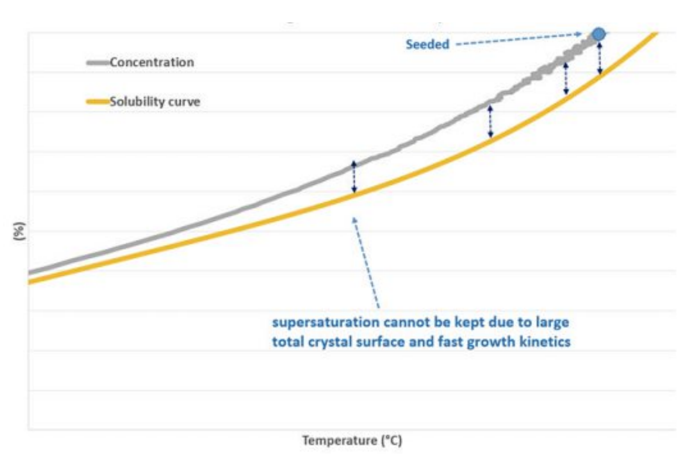

Fig. 2. Phase diagram of a supersaturation controlled process using the CryMOCO advanced crystallization control platform developed by Prof. Z. K. Nagy at Purdue University, U.S.A.

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4. Homogeneous Catalytic Hydrogenation Reactions towards Fragrance and Flavor. Industrial Applications

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Keywords: Homogeneous hydrogenation · Ruthenium · Rhodium · Ester hydrogenation · Dienal hydrogenation

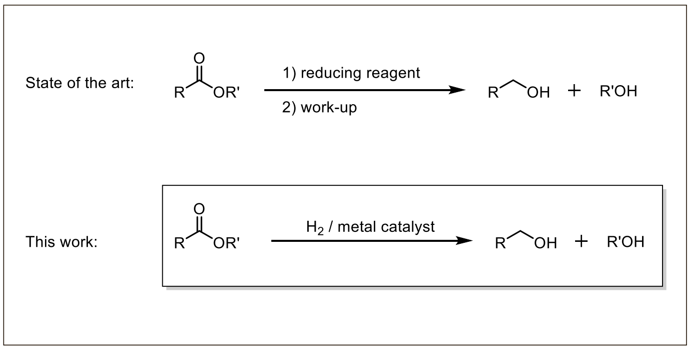
The research of new industrial catalytic processes is at the forefront of Firmenich R&D and it is one of our strategic pillars to realize our sustainability targets.[1]

The development of homogeneous catalytic hydrogenation processes was pioneered almost 20 years ago with the launch of *Paradisone* and it is now a well-established and recognized domain of research at Firmenich.[2,3] In this presentation two case studies will be highlighted to show how the development of new homogeneous catalytic hydrogenation has allowed the replacement of hazardous and waste generating processes.

Hydrogenation of Esters

Alcohols are important ingredients and building blocks in the synthesis of perfumery ingredients. The reduction of carboxylic esters to alcohols by hydrogenation with heterogeneous catalysts is currently the most common industrial alternative to the hazardous use of stoichiometric metal hydride (*e.g.* $LiAlH_4$). Despite the harsh conditions (T>100 °C), this process is used for the large scale synthesis of fatty alcohols, important components of fabric softeners. The development of milder conditions and selective catalysts is highly desirable as it will provide a more atom economical and environmentally benign process for the reduction of a wider class of carboxylic esters to alcohols. Unlike the homogeneous catalyzed hydrogenation of olefins, the homogeneous catalyzed hydrogenation of esters has been quite overlooked until recently where, with the need for more environmentally-friendly processes, the field has gained a new bloom with the discovery of new catalysts based on ruthenium, iron, cobalt, and manganese.[4]

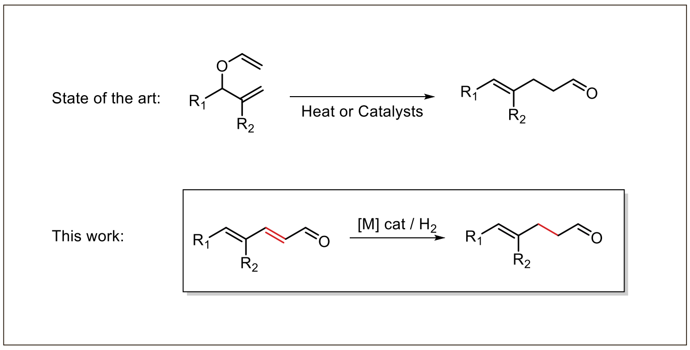
Herein, we present our own results concerning the use of readily prepared, and robust ruthenium complexes that allows the clean and selective hydrogenation of esters under mild conditions.[5] This catalytic process was successfully applied to lactones especially in the context of the synthesis of Cetalox®/Ambrox® Super; important perfumery ingredients with amber notes. Moreover, this process was successfully extended to esters containing C=C double bonds with the clean and selective formation of the corresponding unsaturated alcohol in high yield.



Scheme 1. Hydrogenation of esters.

Gamma-delta Unsaturated Aldehydes

Aldehydes are another important ingredient of the perfumery palette with examples such as Lilial and Citronellal.[2] Herein we describe the development of new rhodium complexes for the chemo- and regioseletive hydrogenation of conjugated dienals[6] into their corresponding gamma-delta unsaturated aldehydes.[7] This technology provides a new direct and complementary method for the synthesis of gamma-delta unsaturated aldehydes which were up to now accessible industrially only through the classical Claisen-rearrangement of allyl-vinyl ethers.



Scheme 2. Synthesis of gamma-delta unsaturated aldehydes.

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5. Chlorination and Sulfonation Chemistry – More Sustainable Approaches

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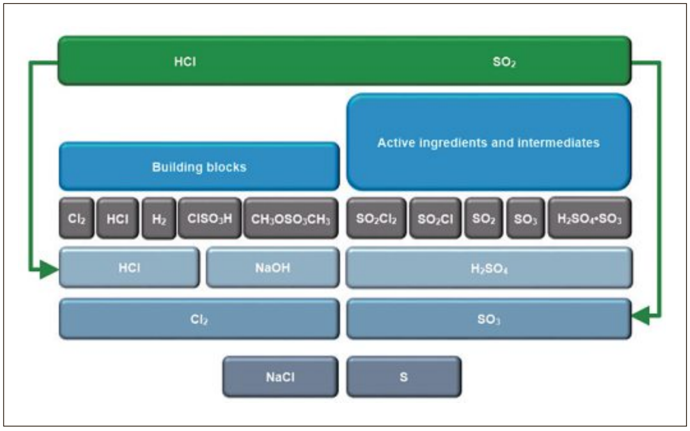
Keywords: Chlorination · Sulfonation · Sustainability

In the aim of designing 'greener' products and processes, nature is supposed to serve as a model for green chemistry: all reactions take place at ambient temperature, bio-based raw materials are used and enzymes catalyze the reaction to a product, which is biodegradable. However, nature does not have storage tanks and often has to carry out a multi-step synthesis to get to a target molecule because certain reagents or reactions are not possible. Especially regarding energy efficiency, natural processes might not be as straightforward as synthetic ones, therefore consume in total more energy, and create more waste to reach the final compound.

Chlorinations and sulfonations are not – or practically never – performed in nature. The use of hazardous reagents in many manufacturing processes allows a shortcut in the synthesis, saving energy and materials and creating less waste. Hazardous substances, however, should be avoided, according to the 12 Principles of Green Chemistry.[1]

Which Way Is 'Greener'?

CABB operates a chlorine electrolysis and sulfuric acid plant at its Pratteln/Switzerland site. Starting with salt and sulfur, in a first step chlorine and sulfur trioxide are produced as primary starting materials, which generates caustic soda, hydrogen and sulfuric acid as side products. Based on chlorine and sulfur trioxide, reagents like thionyl chloride, sulfuryl chloride, chlorosulfonic acid, dimethyl sulfate and oleum can be generated.



CABB's Verbund and Recycling System

These reagents are used for the manufacture of further downstream products: either building blocks, which are mostly single-step chlorinated or sulfonated products, or exclusive intermediates and active ingredients, which are mainly multi-step syntheses and which generally include a chlorination or sulfonation step.

The chlorination and sulfonation reactions release hydrochloride gas and/or sulfur dioxide. These gases are separated and purified and the HCl gas is absorbed in water and sold as hydrochloric acid. The SO_2 is completely fed back into the sulfur oxidation system and reused as SO_3 – without creating any waste.

Sustainable Chlorination

In a case study, a typical chlorination reaction of a carboxylic acid with thionyl chloride is examined. A scrubber generally absorbs the HCl and SO_2 off-gases, which are released. This requires additional use of caustic soda and results in waste water containing salt load.

In comparison, at CABB the off-gases are separated and purified in the Verbund and Recycling System and converted into commercial hydrochloric acid and SO_3, respectively. The comparison shows that the conventional scrubber method requires more energy and additionally caustic soda as input material, resulting in the formation of waste water, whereas no caustic is needed at CABB and no waste water is generated. This higher material efficiency is clearly seen in the PMI (process mass intensity) value of 2.1 for the Verbund process and 6.3 for the scrubber process.

The comparison of the E-factors, which describe the waste formation, is even more pronounced: the Verbund system shows a value of 0.04 whereas it is 5.3 for the scrubber system.

Sustainable Sulfonation

Sulfonation reactions are frequently carried out in synthetic chemistry and most reagents are cheap and easily available. Sulfonation reactions generally create a lot of waste and reagents have to be used in large excess.

Alternative reagents include sulfur trioxide amine complexes, in which the SO_3 is bound to give a transportable compound of moderated reactivity. These complexes are limited in their applications and the high price prevents the use for every sulfonation reaction.

The CABB Verbund system allows sulfonation reactions for fine chemical manufacturing using SO_3 to be carried out in a most sustainable and unique way.[2] The direct use of SO_3 does not create any waste like chlorosulfonic acid, sulfuric acid or other sulfonation reagents do. As it is an insertion of the SO_3 into a bond, no by-products are formed which could reduce the reactivity of the reagent. Liquid SO_2 is used as a solvent at low temperature (–20 °C) and moderates the high reactivity of the SO_3. After completion of the reaction, the SO_2 is evaporated and fed back into the Verbund system. This sulfonation reaction only creates a minimum of waste.

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6. Alternative Solvents: From a Compliance-driven Activity to a Trigger for Innovation

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Keywords: Surfactant · Sustainability · Water

During our evaluation of the potential of surfactant technology in collaboration with Prof. Lipshutz,[1] we have developed a variety of straightforward and highly advantageous transformations. We were fortunate to identify in our laboratories some key enabling process techniques that allowed us to apply the technology successfully on-scale in a large number of those transformations.[2] Benefits of the technology can be encountered across our entire portfolio, not just from an environmental standpoint but also from an economic and productivity perspective. To name a few: Reduction of organic solvent consumption, water use and cycle time, milder reaction conditions, improved yields and selectivities, which all contribute to improved process performance and lower manufacturing costs.[3]

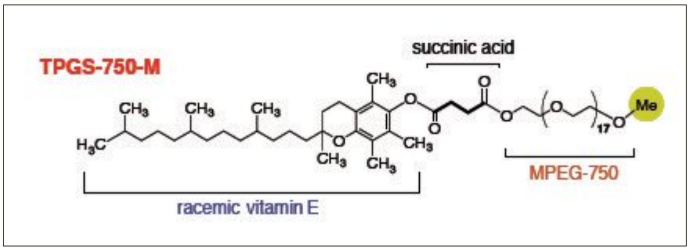

Fig. 1. Privileged designer surfactant TPGS-750-M.

These surfactant-mediated reactions can be up-scaled in the already existing multi-purpose facilities of pharmaceutical or chemical organizations, using a catalytic amount of a combination of a non-ionic designer surfactant (*e.g.* TPGS-750-M generally recognized as the surfactant of choice) in water, and a well-chosen organic co-solvent instead of traditional and undesirable organic solvents.[4]

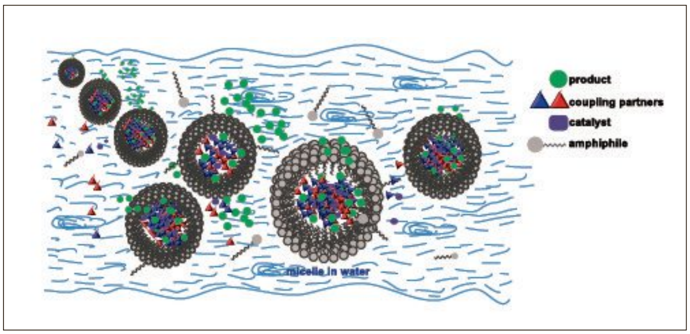

Fig. 2. Modern non-ionic surfactants for micellar catalysis in water.

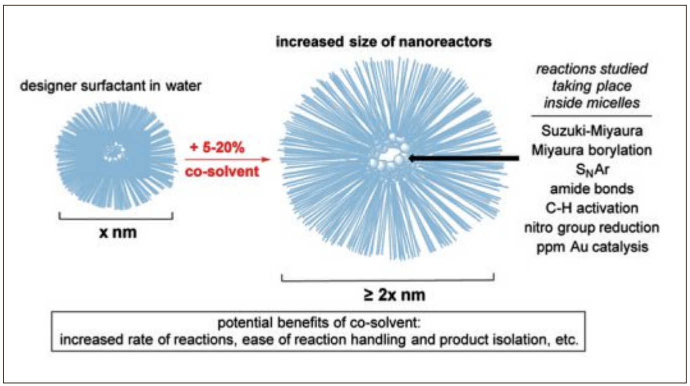

Fig. 3. Critical role of the co-solvent.

Further driven by the need for sustainability and reduction of usage of precious and endangered metal species, we targeted tailor-made catalytic systems and developed the concept of a double-nano effect to circumvent the use of high amount of catalyst by using iron nanoparticles (Fe-NPs) containing parts-

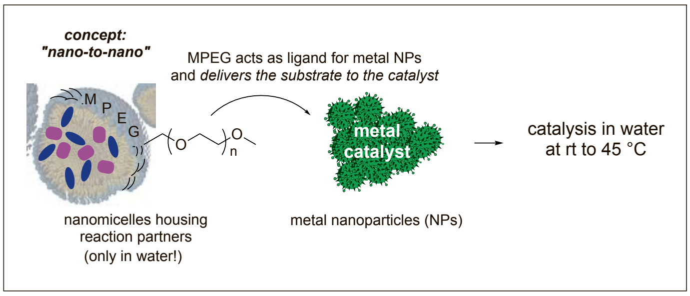

Fig. 4. Nano-to-nano concept.

per-million (ppm) levels of various metals.[5] Together with the surfactant in water as medium, this technology has been applied to cross-coupling reactions or other functional group manipulations and proved its efficacy and can be applied to a wide range of substrates.

Our experience in the field combined with new technologies available such as Fe-NPs allowed for the development of innovative and sustainable processes with a minimum of precious metal used. This field is opening great new perspectives and significant prospects in sustainable chemistry. Tailor-made reagents are in development to further take advantage of this medium with an increase selectivity and efficiency on established chemistry. We expect that the technology will find in the near future further useful applications in a broad range of reactions.

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7. Be Greener by Using Hazardous Reactions – Interests, Not Principles

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Keywords: Green chemistry · Hazardous reactions · Sustainability

It is common practice to base green chemistry on a set of principles. The claim is that when such principles are used in the design, process development and implementation of chemical products and manufacturing, they enable scientists to protect and benefit the economy, the people, and the planet. One of the principles is 'less hazardous synthesis'.

The promoted antithesis is that green chemistry is not about principles; it is about balanced basic values and interests within the social, environmental, and economic spheres. If the regulatory framework sets the right incentives regarding the conflicts of interest between those spheres, cost improvement as the only driver will lead to green chemistry. The antithesis will be supported by the notion that the use of hazardous reactions might indeed lead to greener chemistry. An adequate new definition of green chemistry is proposed.

Thesis I: Stand up for more interest-balanced regulation, not interest-based principles

Sustainability is defined as the development that meets the needs of the present without compromising the ability of future generations to meet their own needs. This means sufficient yield at minimum cost of resources, *i.e.* energy and raw materials.[1] The compromise for the adequate sustainability level requires a political process that starts with defining basic values, deriving common interests therefrom, and finally setting corresponding regulations. It is about defining what is fair, viable, and bearable, and therefore sustainable, in the conflicts of interest between society and economy, economy and environment, and environment and society (Fig. 1). Too often, regulations are derived from individual interests and only thereafter covered by fig leaves of pseudo basic values stated as principles, making it a question of political correctness rather than fundamental beliefs.

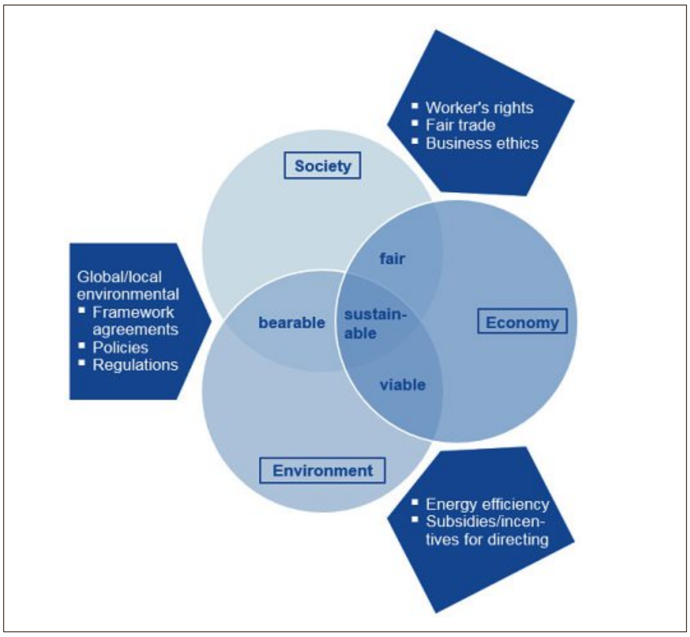

Fig. 1.

Thesis II: Production cost reduction is sustainable – be effective, not low-cost

In the current world of fast-track chemical development, the sequential process steps from route-finding, feasibility, process design and development, pilotation, optimization, and final scale-up to production levels, with the target to get robust and reproducible manufacturing, are heavily overlapping. In the search for the design space, critical process parameters are set in a function to the quality attributes by the quality-by-design approach so that the product meets the desired specification. The chemist's dilemma in green chemistry is the search for useful sustainability attributes. However, it is clear that the 12 principles of green chemistry[2] will not do it.

In principle, the second law of thermodynamics stipulates the minimum entropy change as an adequate sustainability attribute in theory.[3] In other words, the criterion for green chemistry and therefore sustainable development is the loss of energy to perform work should be minimal, *i.e.* production yielding minimal entropy increase. This approach also fails due to its non-practicality. Taking the basic rule of business into account: a dollar is a dollar, one can easily see that in developed economies, a lower cost structure with its main levers (yield, raw materials, and energy) often correlates with lower entropy increase (sufficient yield at minimum cost of resources, *i.e.* raw materials and energy). Smart regulation, *e.g.* by combining interest-balanced regulation with the basic rule of business, might set further cost reduction incentives by command-and-control or other economic directives. With an average of 90 new pages of regulation added per working day in new decrees in Switzerland from 2008–2016, adding huge complexity and therefore increasing entropy, this practice cannot be considered sustainable.

Thesis III: Be greener by safe use of hazardous reactions

The Haber-Bosch ammonia synthesis is responsible for 150 million deaths by its derived explosives in the past 100 years. Nevertheless, it is also responsible for feeding 50% of the world population today thanks to its derived fertilizers.[4] Of 1'994 drugs approved by the FDA in the USA until 2012, 1'086 were small molecules and 84% of them contain nitrogen, on average 2.3 nitrogen per active pharmaceutical ingredient (API).[5] The introduction of nitrogen into such APIs mainly occurs through hazardous reactions and reagents derived from ammonia, *e.g.* nitration, azide chemistry, cyanation, nitrosation, *etc*. Needless to say that the introduction of nitrogen into organic molecules is of great importance for healthcare. Safe use of such hazardous reactions is a prerequisite under a long-term view and thesis II, as incidents have considerable material and reputational costs.

In summary, green chemistry is performed by adhering to the following: (i) Standing up for more interest-balanced regulation, not interest-based principles; (ii) reducing production costs to be sustainable – being effective, not low-cost; and (iii) being greener by safe use of hazardous reactions.

The following new definition for green chemistry is proposed:

> **Green chemistry** is the design of chemical products and processes that reduces production costs under a value-based, interest-balanced regulatory regime.
>
> **Green chemistry** applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate waste treatment.
>
> **Green chemistry** is sustainable chemistry.

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8. Efficient Industrial Synthesis of Idasanutlin *via* a Cu(I)-catalyzed [3+2] Asymmetric Cycloaddition

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Sandmeyer Award 2017. A full article describing this award winning research will appear in CHIMIA in due course.

A concise asymmetric synthesis has been developed to prepare idasanutlin (**1,** Fig. 1), a small molecule MDM2 antagonist currently being investigated as a potential treatment for various solid tumors and hematologic malignancies. The highly congested pyrrolidine core, containing four contiguous stereocenters, was constructed *via* a Cu(I)/BINAP catalyzed [3+2]-cycloaddition reaction. This optimized copper(I) catalyzed process has been used to produce more than 1500 kg of idasanutlin.

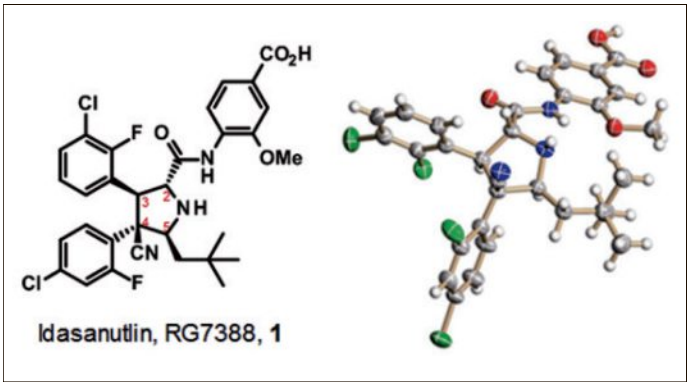

Fig. 1. Structure of idasanutlin.

The evolution of this synthetic route from the laboratory to commercial-scale manufacturing will be described, highlighting the exceptionally selective and consistent cycloaddition/isomerization/hydrolysis sequence. The excellent yields, short cycle times and reduction in waste streams result in a sustainable production process with low environmental impact.

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9. Development of Commercial Organic Additives for the Grinding of Inorganic Solids

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Sandmeyer Award 2016. A full article describing this award winning research is published in this issue: CHIMIA ***2017****, 71,* 451.

Grinding aids have been used successfully for decades in the production of many materials, such as cements, ceramics, pigments, *etc*. These products reduce the energy needed for grinding, which in the case of cement has major environmental implications worldwide. This is primarily due to the tremendous amounts of cement produced and also 30% of the associated electricity energy consumption is used for grinding. For example, yearly global savings of electrical energy achieved thanks to grinding aids are on the order of the energy generated by 2–3 nuclear power plants. However, even more importantly, these compounds make it possible to change cement compositions to produce materials of equivalent performance with much lower environmental impact. To give a scale of the environmental impact of cement production and the gains that can be made by reducing it, we point out that about 30–40% of the CO_2 reductions targeted by Switzerland in the Kyoto protocol have been achieved by the cement industry alone.

In this lecture, we examine the question of how to optimize these grinding aids linking molecular insight into their working mechanism. For this, we start by recognizing that surface and interfacial properties play an important role during the comminution process of inorganic minerals.[1–5] We focus on the clinker phases of ordinary Portland cement onto which grinding aids can adsorb during clinker grinding. For this, we apply molecular dynamics simulations using validated molecular models to study the interactions of various types of chemical additives with clinker minerals. A key role is hereby played by the quantitative representation of ionic versus covalent contributions to bonding in cement minerals *via* atomic charges. We establish the validity of molecular models and associated force field parameterization by precise atomistic simulation of structural, dynamic, surface, mechanical and thermal properties of minerals in agreement with available X-ray data, IR spectra, cleavage energies, and measured elastic constants.[6] This has led us to an understanding breakthrough of the molecular interactions of grinding aids on inorganic mineral surfaces at an atomistic level. Very importantly our molecular modeling results properly rank the performance of grinding aids as reported from full-scale cement production. Computed agglomeration energies of cement particles with various adsorbed organic compounds correlate with the reduction in surface forces in the form of experimental data on grinding efficiencies. Such knowledge paves the way to molecular design of chemical additives of improved performance. Finally, we will discuss the implications for industrial development of having research changing the conceptual thinking on how specific products function. We will finish by expanding these thoughts to the question of how to put a value on an 'invaluable contribution'.

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10. Project Clean-Cow: Reducing Methane Emissions from Ruminants

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Keywords: Climate change · Enteric methane · Greenhouse gas · Methanogenesis


Fig. 1. Cows.

The world's population is growing constantly and in parallel both the overall industrial production and the demand for food are increasing, including milk and beef products. According to the *FAO,* this is leading to substantially more green-house gas emissions over time.[1] The Paris COP-21 conference in 2015 prominently addressed this issue and the international community agreed on climate change targets for every country to keep the global temperature raise below 2 °C until the end of the century. However, after careful analysis (UNFCCC) it became clear that, for several regions in the world, these targets will not be reachable without taking the agricultural sector into account.[2] Billions of animals raised by men such as ruminants (dairy cows and beef-cattle) are now the main anthropogenic source of methane, one of the most potent greenhouse gases. Due to its high global warming potential (GWP, factor 28 compared to CO_2), methane is the second largest contributor to climate change. On the other hand, it possesses a short half-life (~12 years compared to hundreds of years for CO_2). Thus all efforts to reduce methane present attractive opportunities to quickly accomplish meaningful impact in fighting global warming.[3]

Rumen Methanogenesis and 3-NOP

Rumen methanogens has been a prevalent subject of research for at least 40 years. Reasons for this are a) the formation of methane by methanogenic archaea in the gastrointestinal tract of domestic ruminants is responsible for a loss of up to 12% of the gross energy ingested, and b) the CH_4 emission contributes to greenhouse gas emissions and climate change. The complex rumen ecosystem relies upon symbiotic communities, in which specialized microorganisms (archaea) utilize H_2 – a waste product of the fermentation process – and convert it, together with CO_2, into methane. Eructation and breathing of the animal will eventually expel it into the atmosphere. All methane mitigation strategies will therefore seek to understand the response of dietary interventions in a complex rumen microbiome with regard to the feed efficiency and CH_4 formation.[4]

In recent years, results on the efficacy of the feed additive 3-nitrooxypropanol (3-NOP) were published. It demonstrated persistent reductions in methane formation in ruminants (sheep,[5] dairy cows[6] and beef cattle[7]), reaching inhibition levels between 30–60% over prolonged periods of time and without negative side effects. For example, when 3-NOP was added to the feed of high-producing dairy cows at a dose level of 60 ppm (60 mg/kg feed), not only was methane emission decreased by 30%, but an increase in body weight gain was also observed without negative effect on feed intake, milk yield and milk composition.[6]

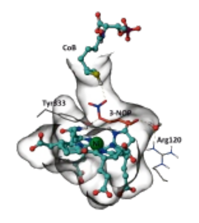

Fig. 2. Position of 3-NOP in the active site of MCR suggested by docking studies.

In silico, *in vitro* and *in vivo* studies revealed that 3-NOP specifically targets the methanogenic archaea. While designed to target the protein methyl-CoM reductase (MCR), this hypothesis has recently been validated by EPR measurements of the nickel-containing cofactor F_{430}, which is part of the active site of MCR and must be in the EPR active Ni(I) oxidation state to be catalytically active. MCR is responsible for the final step in the methane forming pathway utilizing methyl-coenzyme M and coenzyme B as substrates.[8]

The stereoelectronic properties of 3-NOP were found to be very similar to the natural substrate methyl-coenzyme M. It was demonstrated that the inhibitor is also able to effectively bind to the active site of MCR, resulting in a one-electron oxidation of the cofactor F_{430} from Ni(I) to Ni(II), rendering the enzyme temporarily inactive for methane formation. As a consequence of this inhibition event, nitrate, nitrite and most likely 1,3-propanediol were formed, of which nitrite was also shown to be able to inhibit MCR inside the methanogenic archaea. 3-NOP was therefore found to be a unique double acting inhibitor. Methanogens have a repair system in place to reduce Ni(II) in inactivated MCR back to Ni(I) and therefore facilitate reactivation, which in turn explains why inhibition of methanogenesis by 3-NOP is reversible *in vivo*.[8]

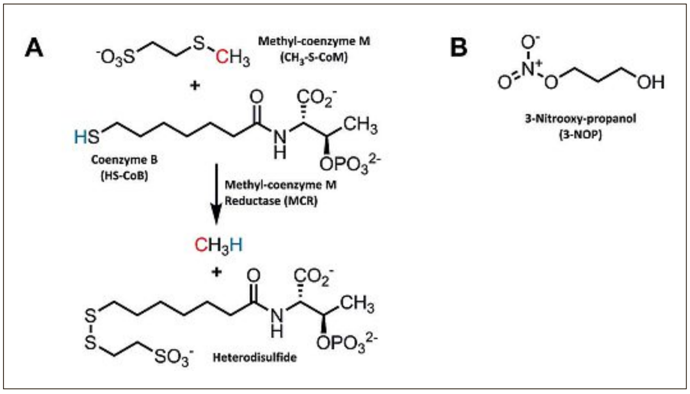

Fig. 3. (A) Reaction catalyzed by MCR. (B) Structure of the inhibitor 3-nitrooxypropanol (3-NOP).

In vivo Results and Conclusions

3-NOP was demonstrated to affect methanogenic archaea only. The understanding of the mode of action in combination with 3-NOP's high specificity corroborates 3-NOP as an attractive feed-supplement to address the environmental footprint associated with an increasing number of ruminants on the planet. Recent feeding studies showed a consistent methane reduction effect in sheep, dairy-cows, and beef cattle. Further studies are currently being carried out to investigate the effect of a reduced methane formation on the overall energy status of the respective animals, and first results in this direction look very promising for applications in dairy cows and beef cattle.

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11. Synthetic Biology – Terpenes Production *via* Microbial Fermentation

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Keywords: Flavors & Fragrances · Synthetic Biology · Terpenes

Terpenes and, more generally, plant-derived secondary metabolites are of great economic importance and are widely used for applications such as flavors and fragrances (F&F). Terpenes have unique olfactory properties but they are found in low concentrations in their native host and are often produced in a non-sustainable way. Because of this, the supply of a number of F&F terpenes is unstable, resulting in shortages and price fluctuations. Organic chemistry can be used to overcome the problems encountered with these plant-derived products by developing processes for the production of the target compounds independently of their native host. In fact, synthetic routes have been developed for many natural compounds including terpenes but, given their often complex structures, they represent very challenging targets for the synthetic chemist.

Microbial Production of Terpenes

Synthetic Biology could be defined as the re-design of living organisms for useful purposes such as the manufacturing of a particular substance. Recently, Synthetic Biology has allowed the engineering of various microbial cells to produce plant-derived compounds including terpenes. This has been made possible by the concomitant discovery and development of key enabling technologies. In particular, the recent development of rapid and cost-effective DNA sequencing technologies (collectively referred as Next Generation Sequencing or NGS) has provided genomic data for thousands of living organisms including aromatic plants. Newly discovered genome editing technologies (such as CRISPR/Cas9) combined with increasingly affordable synthetic DNA have also greatly contributed to facilitate and speed up microbial strain development. Genetic engineering of microbial cells for the biosynthesis of terpenes usually combines the regulated expression of one or more plant genes, together with genetic alteration of the host metabolism (usually *Escherichia coli* or *Saccharomyces cerevisiae)*. The production of complex terpene molecules such as sesquiterpenes ($C_{15}H_{24}$) and diterpenes ($C_{20}H_{32}$) in a microbial host offers several advantages over traditional extraction methods in scalability, consumption of natural resources and process sustainability. It also has the potential to provide these molecules at a lower cost through large-scale fermentation processes from inexpensive sugar–carbon sources. So far, this strategy has been mostly applied to the production of high-value therapeutic compounds, such as the sesquiterpene lactone and anti-malaria drug artemisinin.[1] However, recent progress in our understanding of terpene biosynthetic pathways and in the genetic engineering of microbial cells combined with fermentation optimization has led to the successful industrial production of F&F ingredients such as Clearwood® and Ambrox® that have been launched by Firmenich in 2014 and 2016, respectively.[2,3]

Ambrox® & Ambergris

Ambergris, a waxy substance produced by the intestinal tract of the sperm whale, has been a highly prized fragrance ingredient for millennia. Ambergris was known by ancient Egyptian and Chinese for its pleasant sweet and earthy scent. Because of supply shortage and price inflation, the chemical synthesis of ambergris constituents and molecules with ambergris character has been the focus of extensive research in the flavor and fragrance industry. One of the key olfactory components and most appreciated substitutes of ambergris, Ambrox® is produced industrially by semi-synthesis from sclareol, a naturally occurring diterpene alcohol (Fig. 1). Currently, the main sources of sclareol are the flowers and leaves of *Salvia sclarea* (Clary sage), a biennial herb native of Southern Europe and belonging to the Lamiaceae family. Of interest, sclareol has also been reported to have anticancer effects, inducing apoptotic death in several human cancer cell lines.

Sclareol is however an expensive material subjected to supply shortage. Recently, we have cloned and functionally characterized the two key enzymes, known as terpene synthases, responsible for the biosynthesis of sclareol in a commercially exploited species of sage. In addition, we have reconstructed and transplanted the entire sclareol biosynthetic pathway in engineered *Escherichia coli* and reached commercially relevant sclareol titers in high-cell-density fermentation.[4] This work coupled with a proprietary green chemistry technology led to the development of an alternative, sustainable, and cost-efficient industrial route to Ambrox®.[3]

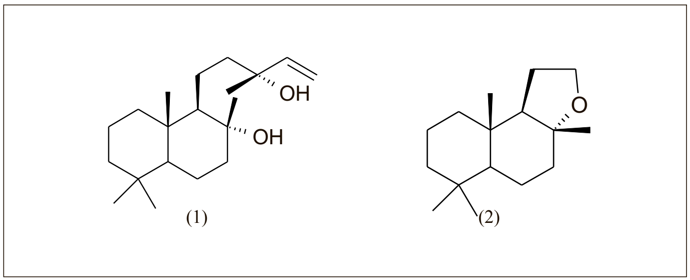

Fig. 1.Chemical structures of the diterpene alcohol sclareol (**1**) and the perfumary ingredient Ambrox® (**2**).

More to come…

Using genomics and transcriptomics, we are systematically investigating the biosynthetic pathways of strategic F&F terpene ingredients in various aromatic plants. Recently, we have successfully isolated and characterized the terpene synthases and cytochrome monooxygenases that control the structural diversity of the sesquiterpene backbones and their subsequent oxy-functionalization in Sandalwood.[5] The essential oil extracted from the heartwood and roots of this tropical tree is one of the most precious nature-derived fragrance material but it is currently facing dramatic shortage and price inflation due mostly to over-exploitation. An alternative route to access this economically important F&F ingredient is urgently needed.

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12. Avoid, Reduce, Recycle – Efficiency and Recovery of Energy from Waste

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Keywords: Efficiency · Incinerator

Lonza is one of the leading suppliers to the pharmaceutical, biotech and specialty ingredients markets. In the canton Valais is Lonza's origin and there is still the largest production site of Lonza in Visp.

Energy supply has always played an important role in the production, since the start of the company in 1897. Today the production site in Visp demands per year approx. 500 GWh of electricity (0.8% of the total Swiss electricity consumption) and as well approx. 500 GWh of natural gas (1.5% of the total Swiss natural gas consumption).

Things that need to be considered regarding energy use in the production are availability and cost efficiency. For the waste apply further regulations like the clean air act (Luftreinhalteverordnung) or the soil and water protection which needs to be fulfilled. In order to deal with these constrains, the leading waste and energy management concept implemented in the plant can be summarized by the action title 'Avoid - Reduce - Recycle' the amount of waste and the use of energy.

Avoid

In the first place the aim is to avoid the production of waste and the use of energy. For the waste production the choice of the procedure can be relevant. The same applies to the use of energy. The process design as well as the component selection is important. An example is a life cycle assessment of components. For this approach investment costs, operational costs as well as disposal costs are considered. For a more energy efficient component the investment costs might be higher, however, due to the lower energy consumption the operational costs are lower.

Reduce

For the reduction of waste a solvent processing plant is operated in Visp where solvents can be distilled, mixed and stored, solvent mixtures can be separated and intermediate products can be produced.

In order to reduce the energy consumption, energy efficiency projects are carried out, for example a program funded by the Swiss Department of Energy called ProEPA, which supports the analysis of the efficiency of pumps and encourages the replacement of inefficient ones. On the production site in Visp, 44% of the electricity is used to drive pumps. Out of almost 6000 installed pumps, eight were selected (selection criteria were f. e. the driving power and operational hours per year) for analyses. The results showed a significant amount of electricity that can be saved by replacing inefficient pumps and by optimizing the current process. These two options, analysis and optimization of current processes and the replacement of inefficient equipment with efficient and adapted components are the main strategies for the reduction in the use of energy.

Recycle

Two waste incinerators are in use in Visp, to generate steam from the waste generated in the production. The Residue Incineration Plant was launched in 1984 and has a capacity of 27'500 t/a of liquid and solid waste. The 1998 launched Liquid and Exhaust Gas Incineration Plant has a capacity 40'000 t/a of liquid waste and 6'000 Nm^3/h of exhaust gases. Typical waste that is used for the generation of up to 65 t/h of 80 bar steam are high caloric liquids, like process solvents and extractions, aqueous liquids, like cleaning water or waste water from chemical processes, solids, like single use material, chemical residues and out-of-spec batches, as well as reactive process exhaust gases.

In addition several heat recovery units are in place to ensure the further use of waste heat which is used for decentralized steam production and the district heating network. Latter was established in 1989. Today 23 GWh/a of heat is provided to 130 public and private buildings in Visp. Feed flow temperatures are 80 °C for the high temperature cycle, respectively 40°C for the low temperature cycle, which is fed by the return flow of the high temperature cycle.

In order to further decrease the use of fossil-based natural gas in the steam production, a 4.7 km long steam line was built between the municipal waste incinerator and Lonza in 2010. 37'000 t/a of municipal waste are incinerated and 86 GWh/a of steam generated. In addition to the reduction of 20'000 t/a in CO_2 emissions, the efficiency of the incinerator increased due to the constant steam generation from 25% to 70%.

Conclusions

The production site in Visp combines waste generating and energy intensive plants. This symbiosis led to an energy network where three waste incinerators (two operated by Lonza and one municipal) provide steam and electricity to the production and a district heating network.

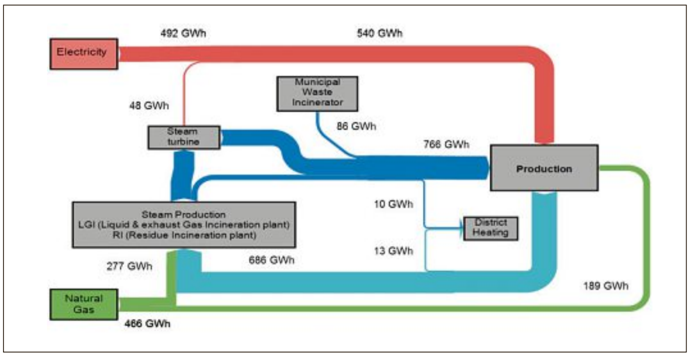

Fig. 1. Overview energy network.

71% percent of the required thermal energy can be recovered from the processes or produced by the incineration of waste. This ensures that the cost of energy on the products is low as well as emissions to the environment.

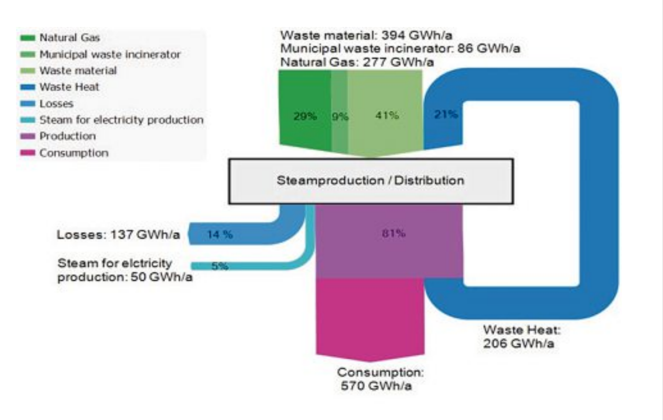

Fig. 2. Steam production and distribution.

13. Continuous Improvement and Capacity Expansion for Fungicide production: Improvement of an Existing Process in Terms of Wastes, Energy, and Tons

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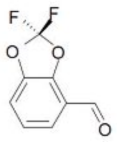
Keywords: Energy recovery · Waste valorization

Syngenta provides products and solutions to help farmers achieve global food security for a growing population, sustainably. The company employees more than 28'000 persons across 90 countries.

Syngenta Monthey is a production site for active substances, intermediates and formulated products. Its main activities are related to crop protection and, to a lesser degree, to the professional products division.

DFA (DF-Aldehyde) is a key intermediate in the synthesis of one of Syngenta's most important fungicide. This product is a broad spectrum fungicide that provides unmatched reliability against botrytis on grapes, fruits and vegetables.



DFA

DFA synthesis is based on the reaction between lithium (supplied as n-butyllithium 20% in toluene) and DFBD (2,2-di-fluoro-1,3-benzodioxole), activated by a ligand, TMEDA (tetramethylethylene-diamine).

Toluene Recovery

The production process involves large amount of toluene (as the nBuLi is supplied in toluene). The final step of the production process is the concentration of DFA in a evaporator. The toluene recovery takes then place by distillation. The recovered toluene can then be separated into two flows: one goes back into the process itself and the other flow is fed to another process in the building that requires toluene. The distillation residues (wastes) are sent to a concrete plan for revalorization by incineration (34% of the total toluene flow).

As the nBuLi is supplied in toluene, the reuse of toluene allows the production process to be almost independent on the toluene use, thanks to the recovery.

TMEDA Recovery

The TMEDA can also be recovered. As the production process involves a decantation, the TMEDA is found after decantation in the mother liquors. These mother liquors firstly go through the degassing of DMA. After that, a distillation is done and the TMEDA is fed back into the process. The yield of the recovery is about 97%. As TMEDA is a toxic compound, the recovery avoids the need to unload TMEDA often (unload of only 4 drums every 3 weeks).

Butane Valorization

The synthesis reaction produces butane that then needs to be retreated. As it is a hazardous gas, this flow needs to be treated in a dedicated installation. Butane is fed to gas burners that produces steam, which is then injected into the steam network of the building. In 2016, with 48 weeks of production, 778 m^3 of vapor were produced.

Environmental Care

Other vent gases are treated in a catalytic oxidizer. The presence of the catalyst allows the process to run at lower temperature than without (370–450 °C). Measuring tubes constantly check the LIE of entrant gases in order to protect the thermal catalyst from compounds that are not compatible. If the availability of the catalytic oxidizer decreases, the DFA production line is slowed down or stopped as the respect of the OPair norms are a priority.

Lithium Recovery and TOC Decrease

Recovery of lithium can be very interesting but the recovered lithium needs to be very pure in order to be taken back by a supplier. The recovery process needs also not to become a bottleneck in the production line. Studies on the carbonatation of the lithium have been done and gives good results. Studies are still ongoing for the moment.

TOC need also to be decreased in the process waters that are sent to water plant treatment. A work directly on the process has allowed to decrease the TOC from 50% but work is still needed for the remaining TOC. Photo-oxydation studies have been done and the TOC can be decreased from 30% but not very much more. Studies are also still ongoing for the moment.

Conclusion

DFA production is a typical case where the recycling and recovery of different solvents and raw materials are pushed to the edge. Despite this, several investigations are still continuing mainly regarding the lithium recovery and the TOC decrease.

With all this work, the AI production cost could be kept at very competitive costs. Green chemistry saves costs and then could be used as a locational advantage.

14. Green Solid-phase Peptide Synthesis (GSPPS)

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Keywords: COMU · *N*-Formylmorpholine · Green solvents · 2-Methyltetrahydrofuran · γ-Valerolactone

The drug arsenal can be classified into three groups: the so-called small molecules (molecular weight <500 D); biologics (isolated from natural sources or produced by biotechnology); and falling between these, peptides and oligonucleotides (TIDES). In recent years, the numbers of peptides of more than 20 residues approved by the Food and Drug Administration Agency has increased significantly. This has been possible thanks to the solid-phase peptide synthesis (SPPS) strategy used in two key steps of the process: Hit to Lead to Candidate and production of the Active Pharmaceutical Ingredient (API). SPPS was first reported by the Nobel Prize Laureate Bruce Merrifield in 1963[1] and is considered the method of choice for the synthesis of peptides from mg to multi Kg scale. Briefly, the strategy consists of protecting the C-terminal amino acid with a polymeric solid support and then elongating the peptide chain by the repetitive introduction of the *N*-protected amino acid and removal of the protecting group. At the end of the synthesis, the peptide is released from the solid support with concomitant removal of the protecting group of the side-chains of the amino acids, which were incorporated protected. The advantage of this method is that it allows for the use of an excess of reagents to facilitate completion of reactions. The excess reagents and soluble byproducts can be easily removed by filtration, followed by several washings steps of the resin.

In terms of greenability or sustainability, SPSS has *pros* and *contras*. With regard to the former, SPPS is highly in terms of labor required: shorter times for workups and automatization. Furthermore, as all reactions are carried out in the same reactor, there are no significant mechanical losses. However, with respect to environmental issues, the sustainability of SPSS is not optimum and calls for improvements in atom economy,[2] coupling reagents, and solvents.

If atom economy is defined as the molecular mass of the desired product divided by the molecular mass of all reactants multiplied by 100, the introduction of an amino acid protected as Fmoc is associated with an atom economy of approximately 0.15, depending on the coupling reagent used. This figure is far from being considered green (closer to 1 is a greener process).

Until a few years ago, 1-hydrooxybenzotriazole (HOBt) or a related compound was present in all peptide couplings. After September 11, HOBt was declared explosive and its use was banned.[3] Our group has recently proposed OxymaPure as a non-dangerous substitute for HOBt.[4] More recently, a joint study undertaken by the University of Strathclyde, Sigma-Aldrich, and GlaxoSmithKline reported 1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) to be the coupling reagent of choice.[5] COMU is a stand-alone coupling reagent based on OxymaPure.[6]

While SPPS boasts ease of work-up through washing and filtration, the large amount of solvents used pose the main drawback. Furthermore, *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidine (NMP), which are the most used solvents, have been classified as hazardous materials by several agencies.[7]

Using polystyrene (PS) and a ChemMatrix (a total polyethylenglycol) resins, we have undertaken a program to substitute DMF and NMP for greener or friendlier solvents. As model peptides, the coupling of Z-Phg-OH onto H-Pro-NH_2 in solution was used to study the racemization and syntheses of Aib[2,3] enkephalin (pentapeptide) and Aib[6,7] ACP (decapeptide). These two peptides contain two consecutive hindered 2-aminoisobutyric acids (Aib), thus facilitating study of performance during elongation.

For a solvent to be used in SPPS, it must show the capacity to swell the resin. ChemMatrix resins swell better than PS in all kinds of solvents. Regarding swelling, ChemMatrix resin is compatible with CH_3CN and THF (which are not considered full green solvents), 2-mehyltetrahydrofuran (MeTHF), cyclopentylmethylether (CPME), EtOAc, isosorbidedimethyl ether, dimethylcarbonate, γ-valerolactone (GVL), *N*-formylmorpholine (NFM), and α,α,α-trifluorotoluene. In contrast, THF, MeTHF, isosorbidedimethyl ether, and GVL appear to be promising for PS resin.

In terms of racemization, all the solvents tested (CH_3CN, THF, MeTHF, and CPME) gave less racemization than DMF when using a coupling reagent based on OxymaPure.

Using CH_3CN, THF, MeTHF, and CPME only for the coupling step, the pentapeptide and the decapeptide were obtained with better purity when compared with DMF when CH_3CN, THF, and MeTHF were used in combination with ChemMatrix. On the other hand, CPME showed poorer performance, presumably because it did not dissolve the protected amino acids properly.

MeTHF, which showed the best properties, was also used as solvent for the removal of the Fmoc (20% piperidine). Excellent purity of the decapeptide was obtained when both deprotection and coupling were carried in MeTHF at 40 °C. However, although the synthesis of the pentapeptide was successful in PS using MeTHF, the quality of the decapeptide was clearly inferior to that obtained in the ChemMatrix resin.

As in the synthesis of the decapeptide using MeTHF and PS, the LC-MS chromatogram showed peaks corresponding to hydrophobic Fmoc-terminated peptides, thus the removal of the Fmoc was studied using various solvents in PS. Satisfactory results were obtained using GVL and NFM. The use of these two solvents for both deprotection and coupling yielded the decapeptide in acceptable purity, which was clearly superior to that achieved with MeTHF.

In conclusion, the use of green solvents should not be detrimental to the quality of the final product when compared with more hazardous solvents. In fact, in terms of racemization and coupling, some of the solvents used gave better results than DMF. On the other hand, the removal of the Fmoc group proved more difficult than expected and will require further fine tuning.

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