

# Cost Analysis for a Continuously Operated Fine Chemicals Production Plant at 10 Kg/Day Using a Combination of Microprocessing and Microwave Heating

F. Benaskar<sup>1</sup>, A. Ben-Abdelmoumen<sup>1</sup>, N.G. Patil<sup>1</sup>, E.V. Rebrov<sup>2</sup>, J. Meuldijk<sup>1</sup>, L.A. Hulshof<sup>3</sup>, V. Hessel<sup>1\*</sup>, U. Krtschil<sup>4</sup> and J.C. Schouten<sup>1</sup>

<sup>1</sup>Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, P. O. Box 513, 5600 MB, Eindhoven, The Netherlands

<sup>2</sup>School of Chemistry and Chemical Engineering, Queen's University Belfast, Stranmillis Road, Belfast, BT9 5AG, UK

<sup>3</sup>Applied Organic Chemistry, Eindhoven University of Technology, P. O. Box 513, 5600 MB, Eindhoven, The Netherlands

<sup>4</sup>Institut für Mikrotechnik Mainz GmbH, Chemical Micro and Milli Process Technologies, Carl-Zeiss-Strasse 18–20, 55129 Mainz, Germany

An extended cost study consisting of 14 process scenarios was carried out to envisage the cost impact of microprocessing and microwaves separately or in combination for two liquid-phase model reactions in fine-chemicals synthesis: (1) Ullmann C–O cross-coupling reaction and (2) the aspirin synthesis. The former, a Cu-catalyzed substitution reaction, was based on an experimental investigation, whereas the latter, a noncatalyzed aromatic esterification reaction, was based on literature data. The cost of 4-phenoxy pyridine production, as a pharmaceutical intermediate in the synthesis of vancomycin or vancocin, was compared with that of the synthesis of aspirin, a key example of large-scale fine-chemical production plants. The operating costs in the Ullmann synthesis were found to be related to material-based process (reactant excess, pretreatment, and catalyst synthesis), whereas those in the aspirin synthesis appeared to be related to downstream-based process (workup, waste treatment). The impact of an integrated microwave heating and microprocessing system on profitability was demonstrated with respect to operational cost and chemical productivity. Different modes of microwave heating and catalyst supply were studied and compared with conventional oil-bath-heated systems in batch and continuous processes. The overall costs including profitability breakthrough for a competitive market price of product were obtained from various combinations of heating and processing. In case of the Ullmann synthesis, the CAPEX (capital expenditure) was negligible compared to the OPEX (operational expenditure), whereas in the aspirin synthesis, the CAPEX was found around 40%, both at a production scales of 1–10 kg/day using proposed upscale methods. The source of the catalyst strongly determined the profitability of a continuously operated Ullmann process due to its effect on the chemical performance. Higher energy efficiencies could be attained using single-mode microwave irradiation; however, the energy contribution to the overall cost was found to be negligible. Different scenarios provided a cost-feasible and profitable process; nevertheless, an integrated microwave heating and microflow processing led to a cost-efficient system using a micropacked-bed reactor in comparison to wall-coated microreactor, showing a profit margin of 20%.

**Keywords:** cost analysis, microwave technology, microprocessing, flow chemistry, catalyzed systems, Ullmann-type C–O coupling, aspirin synthesis

## 1. Introduction

**1.1. Microwave-assisted Flow Chemistry.** Currently, microwave irradiation is mostly applied to small-scale synthesis of complex molecules for pharmaceutical purposes [1]. Nevertheless, microwave process applications at larger scales are presently gaining more interest in the synthesis of fine-chemical intermediates [2]. Upscaling microwave technology to higher production scales, from multi-gram to kilogram scale, has become a major topic for industrial chemists [3]. As one of the few industrial examples, Novartis designed and built a microwave workstation that is equipped with four single-mode microwave reactors, capping and decapping stations, robotic arm, transport and rack storage system, pipetting robot and feed stations, and drying and gassing stations. Process control is made via an ethernet connection; the throughput is maximized by parallel multitasking [4]. In another study, Novartis reports about their scaling attempts and procedures that end with the installation of a batch microwave reactor in their kilo lab, having a reaction volume of approximately 1.1 L and being scaled up from a 15-mL scale. Several reactions were carried out successfully on a 50- to 100-g scale [5].

Presently, the challenge in this area is to establish a reliable and safe process design, where typical scale-up issues, such as the

limited penetration depth, energy efficiency, and temperature control, are addressed [3e, 3g, 6]. Conventional lab-scale organic syntheses, typically below volumes of 100 mL, are conducted in classical batch processes, where commercial microwave cavities are designed for these limited volumes. However, owing to the limited penetration depth of the microwave field, uniform heating at larger scales cannot be achieved without internal mixing. Depending on the dielectric properties of the liquid reaction mixture, the penetration depth is on the order of  $10^{-2}$ – $10^{-3}$  m and, therefore, heating is dominated by convective heat-transfer at larger liquid volumes. The maximum size of a batch reactor that can be heated homogeneously using microwave irradiation in standard ovens, thus, is limited to approximately 1 L.\* As a result, effective and fast heating can only be achieved in combination with a high power input and vigorous mixing, making use of microwave heating less energy efficient. Although the power-to-reactor volume ratio can still be upscaled linearly for most microwave reactors, fast heating and cooling profiles cannot be achieved as for small-scale reactors. In order to overcome these problems, stop-flow and continuous-flow reactors [7] have been developed to maintain the productivity in terms of space–time yield and retain efficient heating by properly fitting the reactor size to the penetration depth [8].

\* Author for correspondence: v.hessel@tue.nl

\* Assuming a cylindrical reactor with a diameter twice the penetration depth in a homogeneously irradiated cavity

### 1.2. Continuous Processing for Fine-chemicals Synthesis.

Similar to most of the continuous micro- and millioptions, process incompatibilities such as solid precipitation and capillary clogging accompanying heterogeneous mixtures are a major drawback for these microwave systems, especially when heterogeneous catalysts are required. The use of microwave-transparent thin-film-coated reactors or packed-bed reactors provides options to conduct continuous chemical processes for heterogeneous systems as described by Shore et al. [9]. The change from batch toward continuous processing requires dedicated modifications in the process conditions, which also explains the limited number of publications describing continuous processing in fine chemistry exceeding kilogram scales. Benaskar et al. used glass and Teflon-coiled flow cells, which were placed in a multimode microwave cavity to investigate the Kolbe–Schmidt carboxylation reaction as precursors for the aspirin synthesis [10]. The Suzuki coupling was investigated by Wilson et al. on 10-g scale; however, product crystallization and formation of solid particles resulted in tube clogging and limited its usability [8c]. Similar obstacles were found when Bowman et al. aimed to scale up a series of organic reactions from gram to multi-gram scale using a commercially available continuous-flow microwave reactor [11]. Further studies using stop-flow microwave reactors also revealed the same limitation of clogging, and optimal operations could only be attained when converting homogeneous solutions in a batch-loop system [7b]. Therefore, the chemical composition of a flow mixture in continuous processes often requires modifications such as increase in the reactants solubility and use of supported catalyst. Engels et al. published the modified Ullmann C–O coupling reaction, substituting solid bases by a homogeneous reaction mixture for continuous processing in homo- and cross-coupling reactions [12]. This development, however, has shown that the first step toward continuous processing in slurry systems requires several modifications to the chemistry. Illg et al. provided additional examples of the benefits of microprocessing in organic reactions, where guidelines with requirements and restrictions of milli- and microstructured reactors are proposed regarding safety and energy consumption in process intensification [13]. Similarly, studies on scaleup and multifunctional microreactors in real-case applications have been reported, underlining the scaleup strategy for industrial implementation [14]. An increasing number of reviews and reports on the chemical and technological feasibility of microprocessing and microwave heating have been published, also by

companies such as Merck [15] and Lonza [16], highlighting the scope and limitations of both novel technologies at small scales [17]. Krtschil et al. demonstrated that generally the cost division at 1-kg-scale process-intensified production plants using microprocessing can be visualized as shown in Figure 1. The proposed scenarios were based on an existing process for the production of 4-cyanophenylboronic acid at AzurChem GmbH, providing general applicability of the best scenario for noncatalyzed single-phase liquid systems [17f].

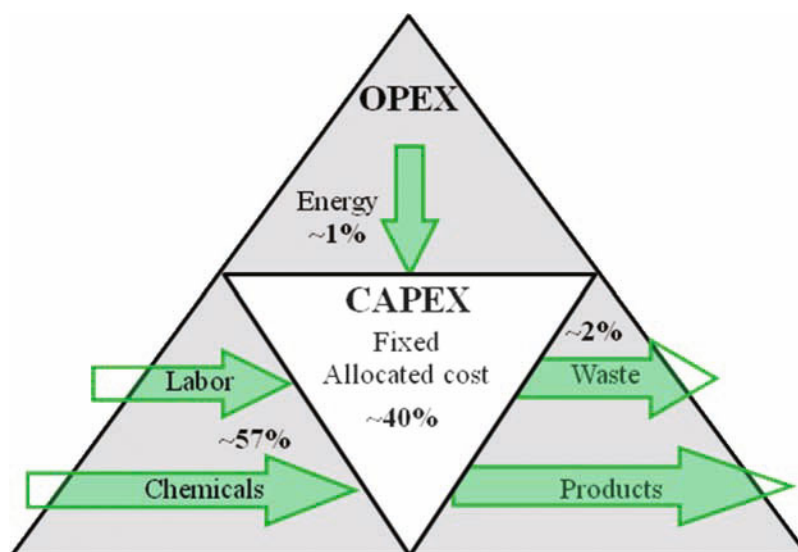
Although the first insights in cost–environmental analysis have been reported [17d], a thorough cost–technological evaluation of an integrated concept of microprocessing and microwave heating has not yet been reported and is explored in this study in a so-called “techno-enviro-economic” analysis. The cost and technological feasibility of implementing microwave heating and microprocessing in fine-chemicals processing at 1-kg production scale are demonstrated. The main aspects, highlighted in this study, concern the cost share of capital investment and operational costs. Microwave equipment and conventional heating systems were compared in both batch and continuous processes. In addition, a sensitivity analysis for larger production scales is carried out.

## 2. Experimental and Methodological Approach

The presented cost analysis is based on a fine-chemicals production plant for different liquid-phase flow syntheses at a production scale varying from 1 to 10 kg/day. In this case, the plant has been designed for two pharmaceutically relevant processes, that is, heterogeneously Cu-catalyzed homo- and cross-coupling reactions and the homogeneously acid-catalyzed aspirin synthesis. Wall-coated, micropacked bed and nano-slurry reactors that operated in either a batch or continuous process are compared in the Ullmann-type C–O cross-coupling reaction. The reaction rate constants over the Cu catalyst in the Ullmann-type C–O cross-coupling reaction of phenol and 4-chloropyridine-HCl and those of the liquid-phase aspirin synthesis from salicylic acid and acetic anhydride are taken from our earlier study [18].

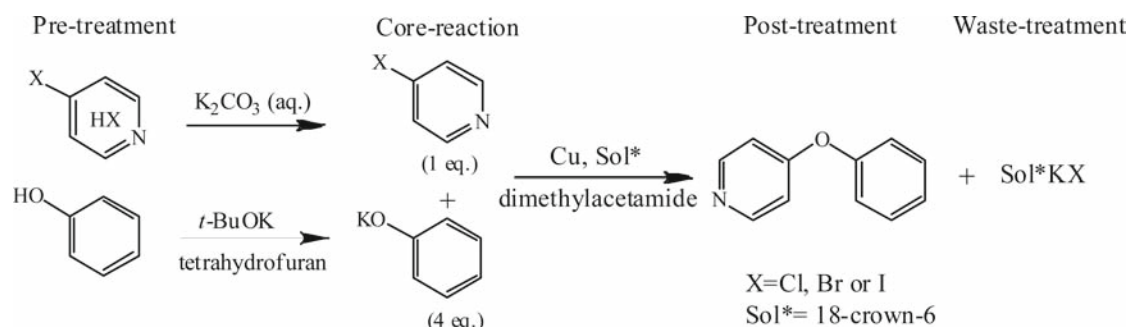
**2.1. Chemistry.** In this case study, the heterogeneous reaction was based on the liquid-phase Ullmann-type C–O coupling of phenol and 4-chloropyridine-HCl as shown in Scheme 1.

Since the original Ullmann reaction requires an excess of carbonate to deprotonate phenol and neutralize 4-chloropyridine-HCl, a novel chemical protocol was developed, allowing safe



**Figure 1.** Overall cost division in a microprocess plant in a nonmetal-catalyzed homogeneous system

**Scheme 1.** Liquid-phase Cu-catalyzed Ullmann C–O coupling. Starting material was subjected to separate pretreatment steps to avoid solids in the downstream chemistry. Different Cu-based catalysts were applied in this study



and sustainable continuous processing while increasing the productivity [12].

The acid-catalyzed liquid-phase aspirin synthesis from salicylic acid and acetic anhydride (see Scheme 2) differs from the Ullmann reaction since instead of pretreatment and catalyst synthesis, a more demanding product workup and waste treatment are required because of an acidic waste stream. The well-studied chemical protocol has previously been carried out in a microwave-assisted continuous process, allowing reliable use of kinetic data [19].

**2.2. Design Criteria and Methodology.** The studied process scenarios were designed according to process criteria as annotated below:

- A maximum capacity of the production plant of 10 kg/day isolated aspirin and 4-phenoxy pyridine was achieved by means of microwave cavity parallelization and chemical process intensification (see section “Chemical process intensification”).
- Production capacity was fixed at 80% of the maximum capacity.
- The microwave-assisted aspirin synthesis has been proposed for single-mode microwave cavities due to the higher energy efficiency.
- Market prices of products and raw materials were based on existing sources of large-scale suppliers (see ESI; Appendix A).
- The price of raw materials was based on purchases for 50–100 kg product and storage in designated buffer vessels. Purchase at smaller volumes led to unprofitable raw material prices (see ESI; Appendix A).
- Capital investments were based on existing suppliers of equipment or estimated using existing software. Allocated costs related to equipment installations were fixed at 400% (see ESI; Appendix B).
- Energy and waste costs were taken from earlier studies [17f].
- Lifetime, depreciation time, and investment rate of return were typically fixed and calculated at 12, 8, and 2 years, respectively [17f].
- Operational load was covered by one man-power at one shift/day, while the production capacity was set at 2000 working hours/year for 8 h/shift.

**2.3. Process Flow Diagram.** For a consistent approach, a structured design of the overall process has been proposed consisting of essentially four sections, where the equipment was mainly characterized by the size of operations and degree of utilization, which are

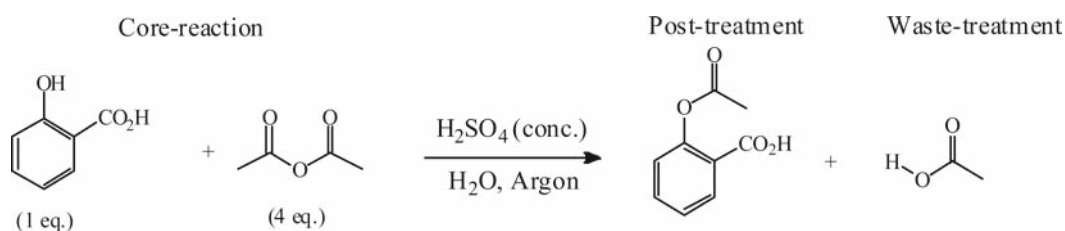
1. reactant storage for 100-kg production scale,
2. pre- and posttreatments at 25-kg scale,
3. production site at 10 kg/day scale, and
4. catalyst preparation at 1-kg scale.

Sections 1 and 3 are continuously operated at a utilization degree of 100%, whereas sections 2 and 4 are based on a batch-wise production with a utilization degree of 20% (i.e., 1 day/week). Therefore, these sections can be utilized by various on-site processes. Scheme 3 provides the areal division of an on-site production plant for fine chemicals starting from raw material storage to product purification and waste treatment. The ESI (Appendix C) provides a more detailed process flow diagram of the site, whereupon the various scenarios and the required equipment and utilities are based. It is clarified throughout this report that the capital investment can be minimized by combining several utilities in each section.

The storage (grey), pretreatment, and posttreatment (product workup and waste treatment) units (blue) are essentially the same for all subsequently presented scenarios and can be utilized in a synchronized manner, whereas the catalyst preparation and the production sites are varied for each scenario. The latter units also strongly influence the productivity and operational cost and, hence, have the highest impact on cost effectiveness. Therefore, the catalyst and production sections are of major importance and have been explored in much more detail to reveal the most economically feasible scenario for the production of fine chemicals using microprocessing, microwave heating, or a combination thereof.

**2.4. Scenario Studies.** In this section, several scenarios are proposed to investigate the economic feasibility of a process-intensified production plant from a combination of various catalysts, heating methods, and process operations applied for the Ullmann C–O coupling and the aspirin synthesis.

**Scheme 2.** The aspirin synthesis from salicylic acid and acetic anhydride under highly acidic conditions



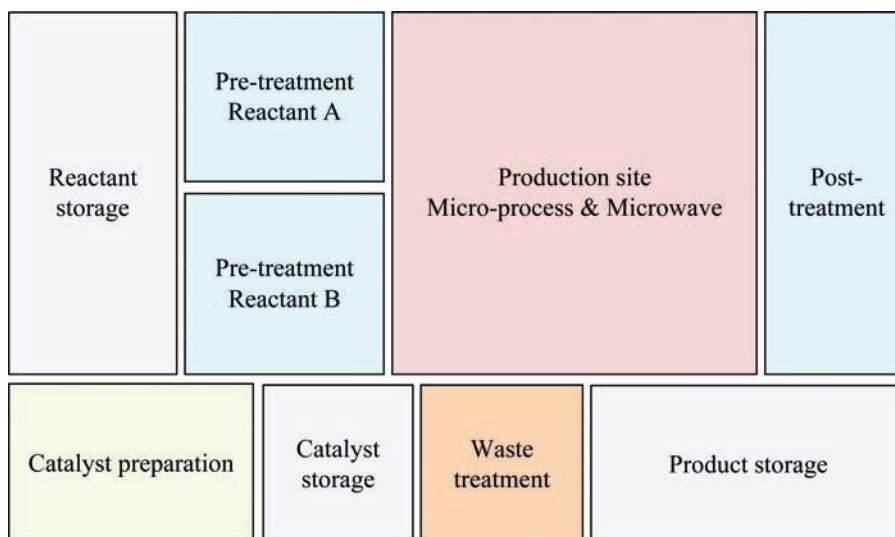
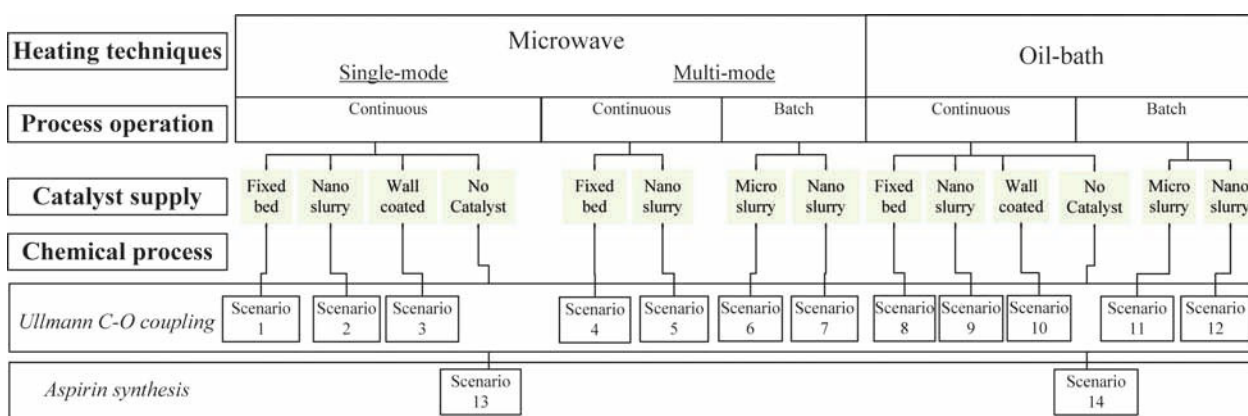
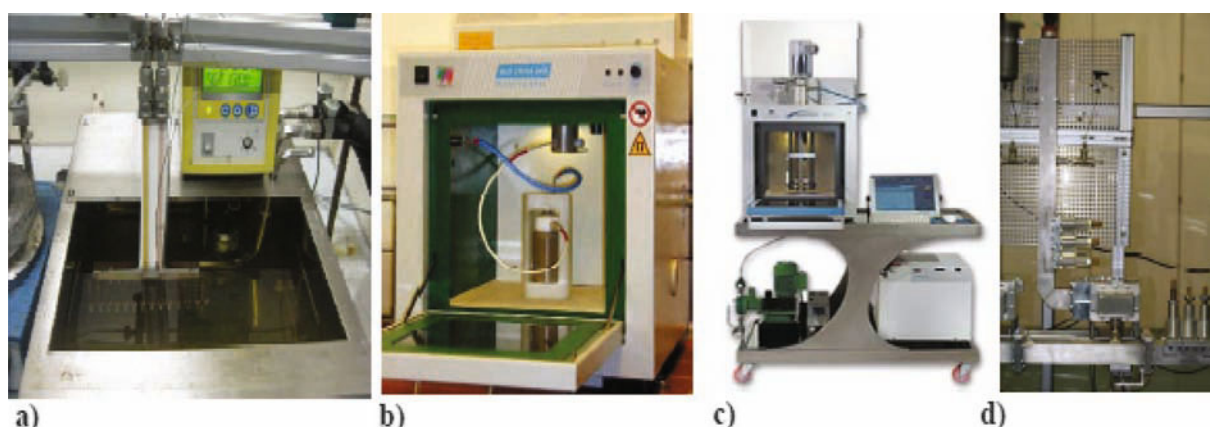
**Scheme 3.** Container concept of a production plant for the synthesis of fine chemicals using microprocessing and microwave equipment

Figure 2 shows a schematic overview of these combinations resulting in 14 different scenarios, each highlighting a different system for fine-chemicals synthesis. Scenarios 1–12 deal with the Ullmann C–O coupling reaction, whereas the aspirin synthesis is covered in scenarios 13 and 14. In the aspirin synthesis, single-mode microwave heating, being highly energy efficient, was compared with oil-bath heating [20].

In sections 2.5–2.9, the separate process units are explored in more detail.

**2.5. Heating Techniques.** During this study, three types of heating techniques have been applied, that is, oil bath, multi-mode microwave, and single-mode microwave heating, as shown in Figure 3. The oil-bath size was chosen to provide enough capacity for both fine-chemicals processes, and the related

**Figure 2.** Schematic overview of the scenarios divided over various sections applied for the Cu-catalyzed Ullmann C–O coupling and the nonmetal-catalyzed aspirin synthesis**Figure 3.** Three different heating methods: (a) oil-bath setup for batch and continuous processing; (b) multimode microwave cavity for batch processes; (c) multimode microwave cavity for continuous processes; (d) single-mode microwave cavity for continuous processing



productivity requirements were provided using a LAUDA Proline P 50 C thermostat. For multimode microwave heating, two different cavities were considered with a maximum power output of 1 kW, that is, a batch operated Milestones BatchSynth system and a continuously operated Milestones FlowSynth system. These multimode cavities provide enough power capacity for the productivity criteria. The single-mode microwave system consists of four cavities. It was designed and built by Fricke und Mallah GmbH and TU/e. Owing to application of single-mode cavities, the power output in each cavity was fully utilized without internal losses, thus providing the highest energy efficiency.

**2.6. Processes and Equipment for Chemical Syntheses.** In view of microprocessing and process intensification, all continuously operated systems have been explored in detail after the chemistry was developed in batch systems. The batch reactors were designed and manufactured for 100-mL liquid volumes and could easily be upscaled to 1-L processing. The continuously stirred batch reactors were heated using a jacket heating via an oil bath or direct insertion in the microwave cavity. Different tubular reactors ( $d_i = 1\text{--}5$  mm) were made to fit the microwave cavity dimensions and the catalyst loading techniques for the continuous processes. For the oil-bath and multimode microwave systems, a tubular glass reactor was coiled to fit the vessel/cavity size, whereas a straight tubular reactor was used in the single-mode microwave cavity (Figure 4).

**2.7. Cu Catalysts Used in the Ullmann C–O Coupling Reactions.** Different Cu-based supported and unsupported catalysts were developed for the Ullmann C–O coupling reactions [12].

**2.7.1. Micro-slurry Catalysts (scenarios 6 and 11).** Initially, the Ullmann reaction was carried out using metallic Cu powder of 30–50  $\mu\text{m}$  and required excessive use of solid bases (cesium carbonate) and has, therefore, been referred to the micro-slurry catalyst cases. Obviously, scenarios 6 and 11 could not be carried out in a continuous process because of clogging in the tubular milli-reactors and the pump parts and have, therefore, been considered only in the batch processes.

**2.7.2. Nano-slurry Catalysts (scenarios 2, 5, 7, and 9).** Once the modified Ullmann C–O coupling and the synthesis of copper nano-particles were developed, the difficulties with large solid particles were overcome through the introduction of the nano-slurry catalyst (Figure 2). This catalyst supply method, however, was subjected to highly expensive and inefficient catalyst separation and recovery and is, therefore, the least suitable for continuous operations.

**2.7.3. Structured Catalytic Films (scenarios 1, 3, 4, 8, and 10).** The fixed-bed system was further developed to provide titania or zinc-oxide thin-film-supported Cu catalysts. The films were dip-coated on 200- $\mu\text{m}$  glass beads as shown in Figure 4 (a) and (b). The wall-coated catalytic films were synthesized using

the same protocol as that for the glass beads or via the direct impregnation of the wall with a copper precursor [21].

**2.8. Reaction Processing.** Since both the unsupported and supported catalysts were studied, a different approach in reaction processing was required for the unsupported catalysts, resulting in two additional case studies. In the cases of the micro-slurry Ullmann C–O coupling, a one-pot synthesis was performed without separate pretreatment; however, excessive use of 3 molar equivalents of a highly expensive base was required. Alternatively, separate pretreatment steps were performed, where both reactants were individually treated using less expensive materials, prior to reaction over supported catalysts in continuous synthesis.

**2.9. Aspirin Synthesis Reaction (scenarios 13 and 14).** The aspirin synthesis did not require a metal catalyst. The premixed reactant mixture was heated using either oil-bath or single-mode microwave heating that represent two alternative scenarios.

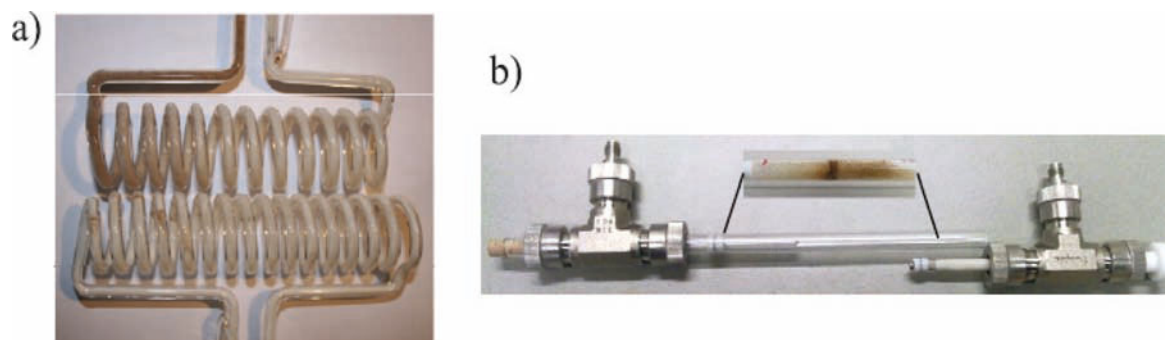
### 3. Results and Discussion

This cost study has been conducted in four major process units, which are presented in this section as a reagents' treatment unit, a catalyst preparation unit, a chemical reaction unit, and a product workup unit. Firstly, the capital and operating cost of each unit is determined, reflecting the overall production costs, and secondly, the profitability is calculated on the basis of the current market price of the target products.

**3.1. Capital Expenditure (CAPEX).** On the basis of the process flow diagram (see ESI for detailed version), the required equipment units in each system have been used to determine the capital expenditure (CAPEX) figures for each scenario as given in Figure 2. Table 1 summarizes the facility and equipment-related expenses in the CAPEX calculations.

The above-mentioned facility- and equipment-related fixed costs are equal for each scenario study and are based on realistic values for container-concept production plants [17f]. The equipment cost related to the production site is given in Figure 5. Cost contributions from chemical processing, catalyst synthesis, heating technique, and processing technique are shown separately as proposed for the different scenarios. The process-related units are referred to as setup housing, safety sensors, software-related equipment, and additional-analysis-related equipment (see ESI; Appendix B).

In the chemicals' processing part, the catalyst preparation done by different catalyst-preparation techniques according to the previously presented scenario proposals, while the remaining part of the process was unchanged in each scenario. Figure 5 shows a clear influence of the choice of catalyst and heating technique, where especially the production cost of the supported catalyst and the use of multimode microwave heating appeared to be dominant (Appendix E summarizes in detail



**Figure 4.** Two types of continuously operated tubular reactors were used: (a) a coiled tubular reactor for the multimode microwave cavity and (b) a straight tubular reactor for the single-mode microwave cavity

**Table 1.** Fixed-cost assumptions and characteristics related to process equipment and facility

Capital costs		
Lifetime core process	10	a
Annual output of the product	250	kg/a
Depreciation period core process	8	a
Depreciation period catalyst process	8	a
Annual depreciation	linear	Equipment cost/depreciation period
Equipment-related fixed cost	3.8	Factor of equipment cost
Facility cost		Annual total costs of building inclusive of heating, lighting, etc.
Specific facility costs	300	EUR/(m <sup>2</sup> a)
Storage	300	EUR/(m <sup>2</sup> a)
Floor space required	10	m <sup>2</sup>
Storage	15	m <sup>2</sup>
Maintenance costs	1000	EUR/a
Annual facility costs	3000	EUR/a
Storage	4500	EUR/a
<b>Total</b>	<b>8500</b>	<b>EUR/a</b>

a = annual.

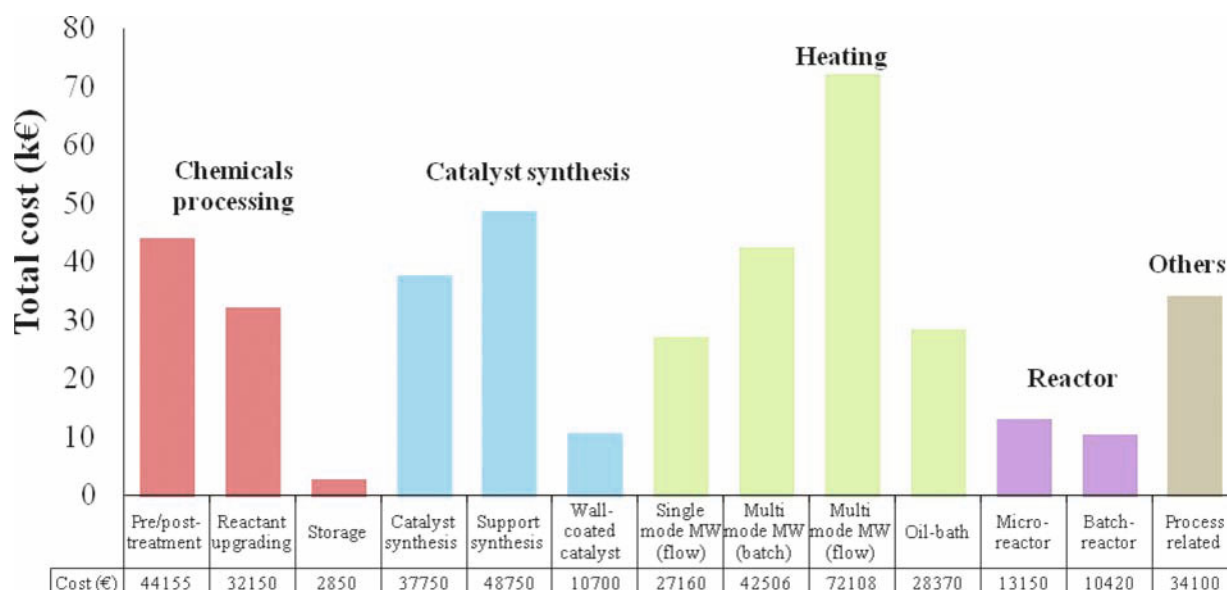
the equipment costs for the given process flow diagram in Appendix C). In section “Case studies,” the equipment costs of different heating techniques and catalyst systems are combined with either continuous microprocessing or batch-processing to obtain the overall equipment cost for a fine-chemicals production site. It was concluded that when microwaves were applied, a realistic cost-competitive process could be attained using single-mode microwave heating in combination with a fixed-bed catalyst. The costs related to microprocessing were found to be slightly higher than those of the conventional batch systems, where a profitable microprocess plant scenario could, however, only be reached at moderate benefits in the operational costs. Figure 6 shows the equipment-related CAPEX for each operation unit using different catalyst supply methods and heating techniques. The dominating costs using a fixed-bed catalyst are shown once more for all heating methods (orange) with respect to the wall-coated and slurry catalysts scenarios. However, the comparison of the CAPEX contributions from the different heating techniques reveals that the multimode microwave cavity for flow systems is more expensive than all other heating techniques.

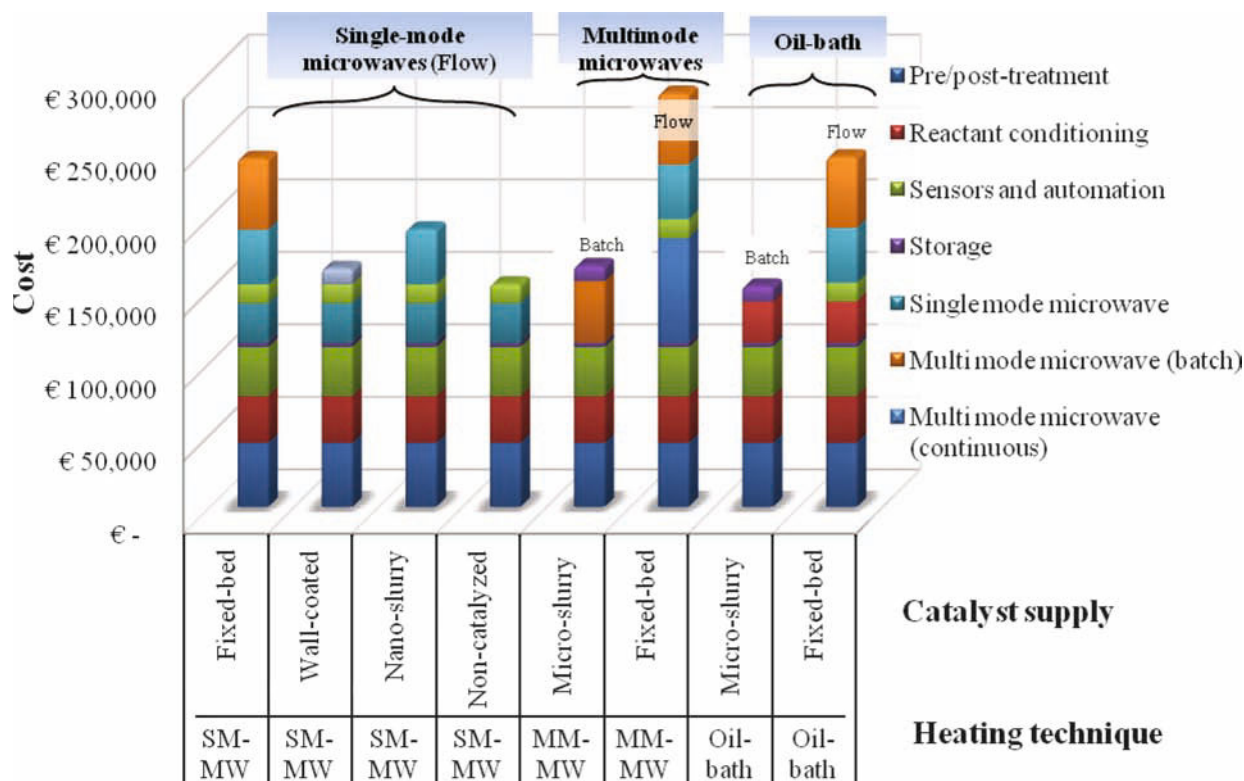
Both the wall-coated continuous and the micro-slurry batch systems appear to be very attractive regarding the equipment-related CAPEX costs. However, as seen later, this catalyst does not provide satisfying chemical conversions and results in a nonprofitable scenario. Obviously, for the nonmetal-catalyzed

aspirin process, the catalyst-related costs vanish completely and are, therefore, 33% lower than those of the fixed-bed scenario. In the following sections, case studies on the different scenarios are demonstrated, where both the CAPEX and OPEX (operational expenditure) costs are screened on profitability and cost feasibility of implementation in a real process. A cost-feasible scenario is defined as a scenario where the profitability (i.e., sales price minus production costs) exceeds 5% of the production costs and retains 5% margin with respect to the competitor’s sales price. Simultaneously, this criterion must also hold for a CAPEX-ROR (rate of return) of less than 2 years.

**3.2. Operational Expenditure (OPEX).** In this study, the operating costs have been mainly divided among raw and waste materials, energy, and personnel (operator), which are discussed separately in the subsequent section.

**3.2.1. Raw Materials Costs.** The raw materials’ costs are calculated for three different chemical systems, that is, the slurry-type Ullmann C–O coupling reaction (scenarios 6 and 11), the liquid-type Ullmann C–O coupling reaction (scenarios 1–5, 7–10, and 12), and the aspirin synthesis (scenarios 13 and 14). The raw materials’ costs can be divided into reagent, solvent, and catalyst costs and have been explored as such. As shown in Scheme 1, in the Ullmann reaction, halopyridines and phenol were applied as so-called electrophile and nucleophile, respectively. The halopyridine reactivity strongly depends on the halogen used, that is, 4-bromopyridine or 4-iodopyridine

**Figure 5.** Total cost based on the major process units; chemicals processing, catalyst synthesis, heating, and reactor design

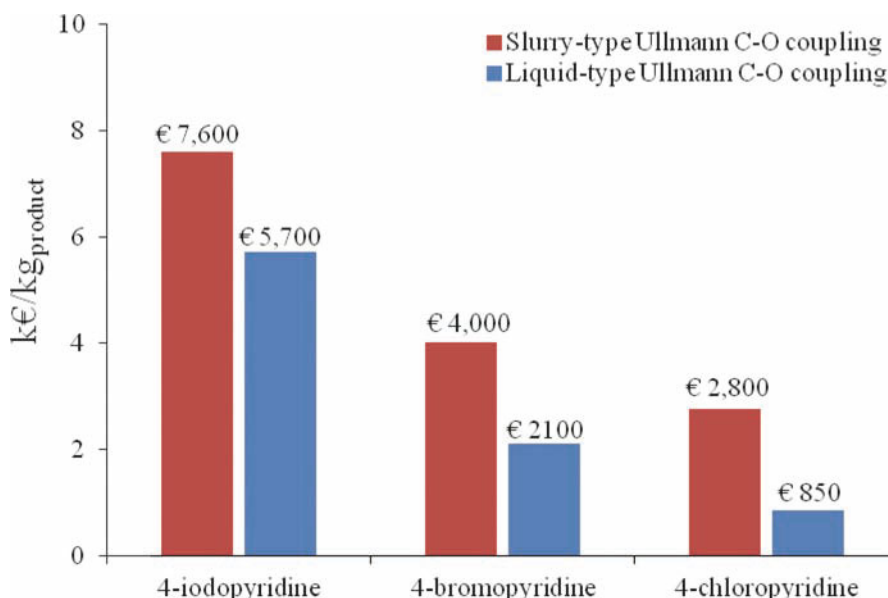


**Figure 6.** Overall cost and the contributions for all different heating systems, reactors, and catalyst options

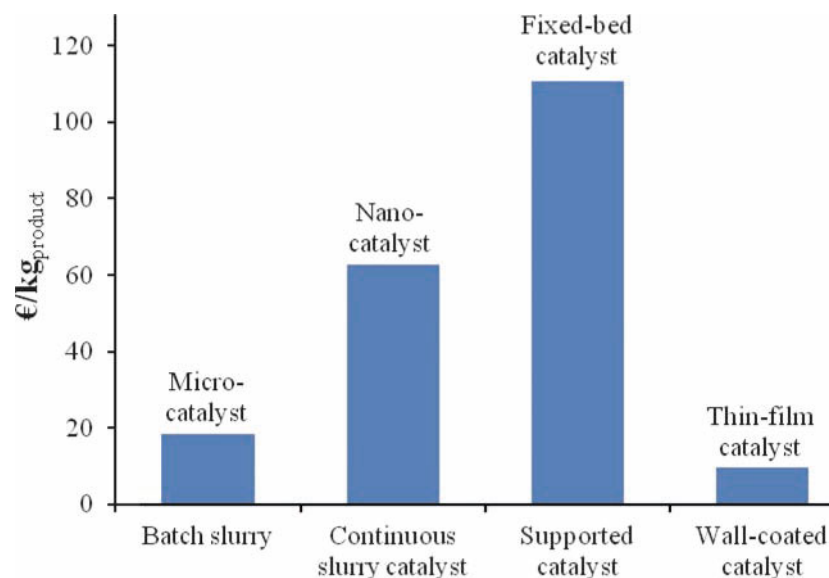
results in about 1.3 or 1.6 times faster reaction kinetics than 4-chloropyridine [22]. However, regarding the atom efficiency, iodo- and bromopyridine are much heavier than chloropyridine (and end up as waste), and regarding storage, iodo- and bromopyridine are relatively unstable. Figure 7 demonstrates the overall reagent costs for both liquid-type (blue) and slurry-type (red) Ullmann C–O coupling reactions using different halopyridines.

In general, it can be seen that the reagent expenses for the liquid-type Ullmann C–O coupling are a factor of 2 lower than those of the slurry-type reaction. The two main reasons for this difference can be, first, the additional costs of raw materials in

the one-pot synthesis applied in the slurry-type reaction and, second, the poor chemical performance of this system due to the rate-limiting in situ deprotonation of phenol and neutralization step of the halopyridine salts. Consequently, it was concluded that the use of bromo- or iodopyridine would not lead to a profitable production process, and both were, therefore, not considered as potential reactants in this study. Figure 8 provides an overview and comparison of the chemicals expenses related to the different catalysts used in this study. The straightforward way of synthesizing Cu coatings onto the reactor wall results in the lowest manufacture cost related to this catalyst system. Alternatively, the relatively complex fixed-bed system,



**Figure 7.** Reagent expenses in €/kg product in the traditional slurry-type and the modified liquid-type Ullmann C–O coupling reaction using chloro-, bromo-, or iodo-pyridine as the key reactant



**Figure 8.** Catalyst expenses for the slurry-type Ullmann C–O coupling reaction (micro-slurry catalyst) and three liquid-type Ullmann C–O couplings (wall-coated, nano-slurry, and fixed-bed catalysts)

impregnated with Cu nanoparticles onto a thin-film support [23], led to the highest catalyst expenses and appeared, therefore, economically least attractive. However, compared to the reagent expenses, the catalyst cost is relatively low but still has a strong influence on the effective use of chemicals and on cost due to an enhanced conversion. Consequently, the type of applied catalyst is not related to the catalyst expenses, but to the resulting conversion performance.

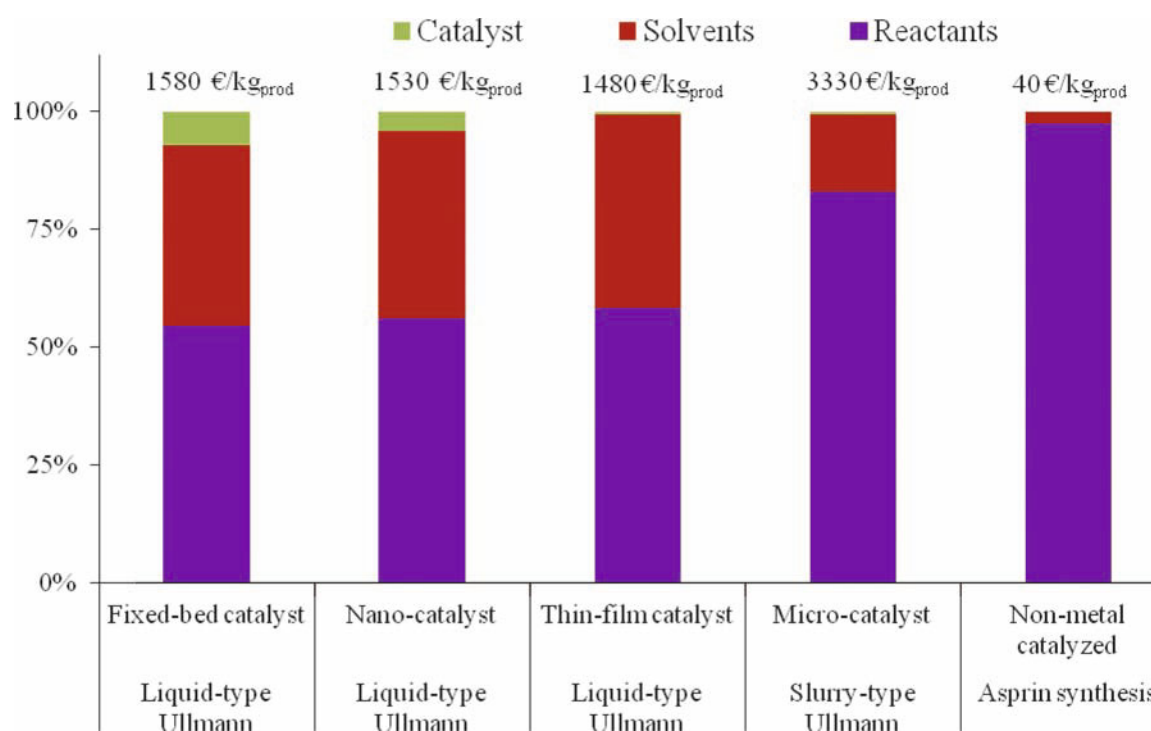
Figure 9 shows a comparison diagram of chemical expenses related to the overall raw materials' cost of the five different processes.

Figure 9 clearly demonstrates a major difference in overall raw materials' cost for the nonmetal-catalyzed aspirin synthesis and the Cu-catalyzed Ullmann C–O coupling reactions due to the price of raw materials and the origin of solvents, that is,

organic versus aqueous conditions. It is clarified that this difference causes a process to be either OPEX- or CAPEX-dominated and, consequently, determines the sales price and profitability of the target fine-chemicals product.

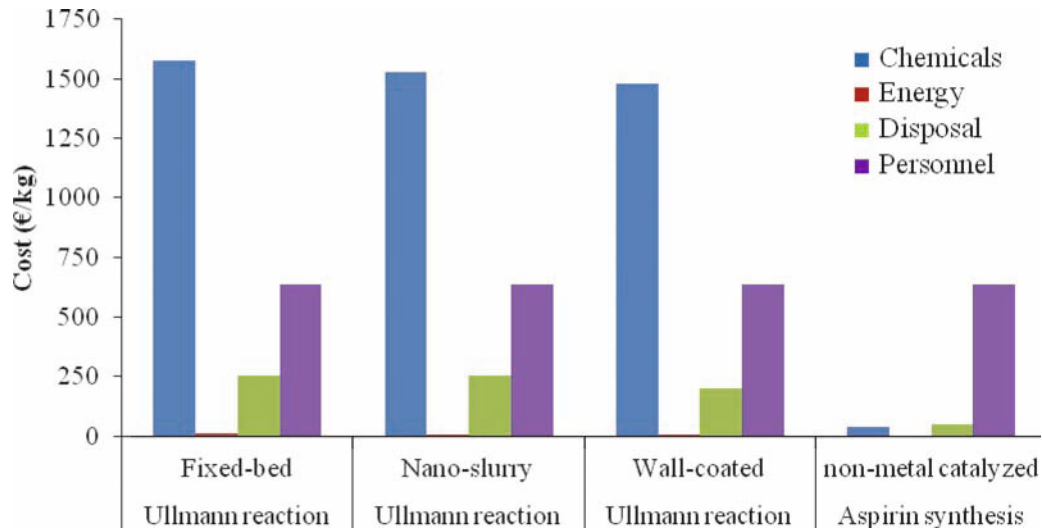
**3.2.2. Personnel and Disposal Costs.** As explained in the introductory part, the proposed production plant is operated at one shift/day and, therefore, requires a single operator cost-load. It has been assumed that the pre- and posttreatments, stock loading, and catalyst preparation can be done simultaneously in a fully automated production plant. However, the time spent, at which all different processes are spread, differs for each process based on five shifts/week:

- Pre/posttreatment 2 times ½ shifts/week, that is, 1 shift/week
- Catalyst synthesis 1 time 1 shift/week, that is, 1 shift/week



**Figure 9.** Source of the chemical expenses based on the raw materials' cost of the five different chemical systems





**Figure 10.** OPEX share for four different chemical processes using single-mode microwave heating

- Production plan 5 times  $1/3$ ; shift/week, that is,  $1^{2/3}$ ; shift/week
- Monthly storage 1 time  $1/3$ ; shift/week, that is,  $1/3$ ; shift/week
- Reporting and office work 5 times  $1/5$ ; shift/week, that is, 1 shift/week.

The disposal costs depend on waste source and have been divided into two categories for this study; for example, organic (halogen-rich) for the Ullmann reaction and aqueous (acidic) for the aspirin synthesis. Figure 10 shows the general cost division for both chemical systems, where microwave heating has been applied as the heating technique. It is shown that for the catalyzed systems, the operational costs are clearly dominated by the raw materials' share, whereas in case of the nonmetal-catalyzed aspirin synthesis, the personnel costs determine the profitability in operational costs. More interesting is the fact that energy hardly affects the costs in both cases and, therefore, the heating technique does not influence the operational costs.

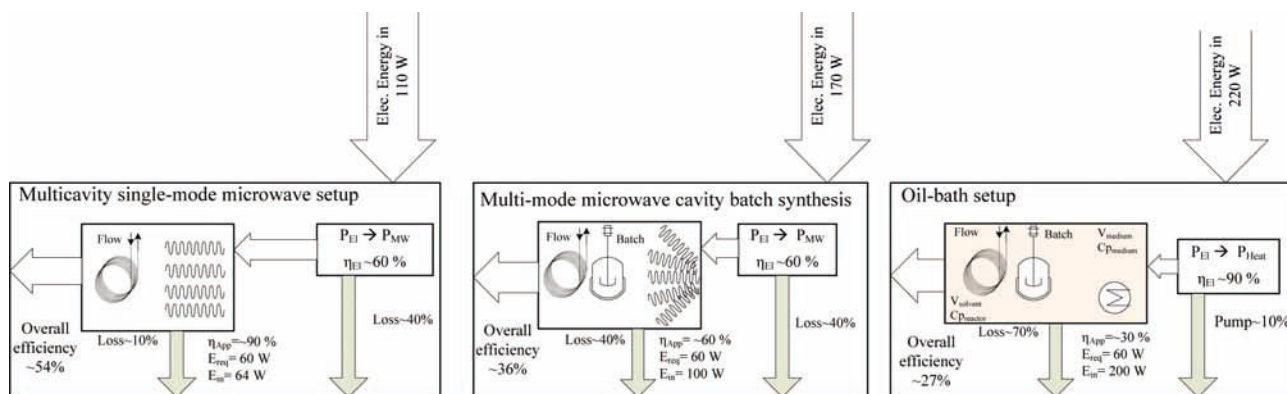
**3.2.3. Energy Cost.** In general, energy consumption is considered to be of less importance in the synthesis of fine chemicals at the kg-scale production [24]. However, compar-

ing conventional heating with microwave heating techniques, the most important operational cost parameter is energy. The energy efficiency of both technologies is demonstrated in this section, although at the chosen scale its contribution is only 6%. The energy conversion efficiencies in microwave systems are mainly dependent on the internal microwave generator and cavity losses, whereas for electric heating, the losses are dominated by losses of the medium to the environment, as found in earlier studies [25]. In this section, the energy required to heat the reaction medium was based on the Ullmann reaction conditions, which are described in Table 2.

Figure 11 shows the energy flow diagrams of a single-mode microwave system with four cavities, a multimode microwave system, and an oil-bath system, with the given energy conversion efficiencies for each [17j, 18b]. The thermal efficiency using electrical heating depending on the energy boundaries can be assumed to be 100%. However, commercially available electric heaters using a liquid medium for this production scale are equipped with internal pumping devices, which require roughly 10% of the electric energy [26]. Electric heating requires a higher heating medium volume than the reaction mixture, which leads to an additional loss in the overall energy

**Table 2.** Energy balance based on the process conditions

Process requirements				
$m_{\text{solvent}} = \frac{m_{\text{product}}}{C_{\text{product}} \cdot M_{\text{wproduct}}}$	Eq. 1	$m_{\text{product}} = 1$	kg/day	$m_{\text{RM}} \approx m_{\text{solvent}} = \text{energy absorbing fluid}$
		$C_{\text{product}} = 0.75$	mol/L <sub>sol</sub>	$C_{\text{p, RM}} \approx C_{\text{p, solvent}}$
		$M_{\text{wproduct}} = 0.172$	kg/mol	Solvent: dimethylacetamide
Microwave energy balance				
$Q_{\text{req}} = m_{\text{RM}} C_{\text{p, RM}} (T_{\text{R}} - T_{\text{Env}})$	Eq. 2	$\rho_{\text{solvent}} = 0.93$	kg/L	$T_{\text{R}} = \text{reaction temperature}$
$Q_{\text{MW}} = Q_{\text{loss}} + Q_{\text{abs}}$	Eq. 3	$m_{\text{solvent}} = 0.25$	g/s	$T_{\text{Env}} = \text{environment temperature}$
$Q_{\text{loss}} = \frac{Q_{\text{abs}}}{\eta_{\text{gen}}}$	Eq. 4	$C_{\text{p, solvent}} = 2^a$	kJ/kg/°C	$Q_{\text{MW}} = \text{microwave energy in}$
		$T_{\text{R}} = 140$	°C	$Q_{\text{req}} = \text{energy required for fluid heating}$
		$T_{\text{Env}} = 25$	°C	$Q_{\text{loss}} = \text{reflected microwaves}$
		$Q_{\text{req}} = 58$	W	$W = \text{absorbed microwaves}$
$Q_{\text{abs}} = \frac{Q_{\text{req}}}{\eta_{\text{app}}}$	Eq. 5	$\eta_{\text{gen}} = 55\text{--}60$	%	$\eta_{\text{gen}} = \text{efficiency of microwave generator}$
		$\eta_{\text{app}} = 35\text{--}90$	%	$\eta_{\text{app}} = \text{efficiency of microwave heating}$
Oil-bath energy balance				
$Q_{\text{RM}} = Q_{\text{req}} = V_{\text{RM}} C_{\text{p, RM}} (T_{\text{R}} - T_{\text{Env}})$	Eq. 6	$V_{\text{RM}} = 1\text{--}10$	L	$Q_{\text{HM}} = \text{energy of heating medium}$
$Q_{\text{HM}} = V_{\text{HM}} C_{\text{p, HM}} (T_{\text{R}} - T_{\text{Env}})$	Eq. 7	$V_{\text{HM}} = 4V_{\text{RM}}$	L	$V_{\text{HM}} = \text{volume of heating medium}$
$\eta_{\text{app}} = \frac{Q_{\text{RM}}}{Q_{\text{HM}}} = \frac{V_{\text{RM}} C_{\text{p, RM}}}{V_{\text{HM}} C_{\text{p, HM}}}$	Eq. 8	$C_{\text{p, HM}} = 1.48^a$	kJ/kg/°C	$V_{\text{HM}} = \text{volume of reaction mixture}$
		$\eta_{\text{app}} = 30$	%	$\eta_{\text{app}} = \text{efficiency of oil-bath heating}$
a = $C_{\text{p}}$ values at reaction temperature $T_{\text{R}} = 140$ °C p = specific heat capacity at constant (operating) pressure.				



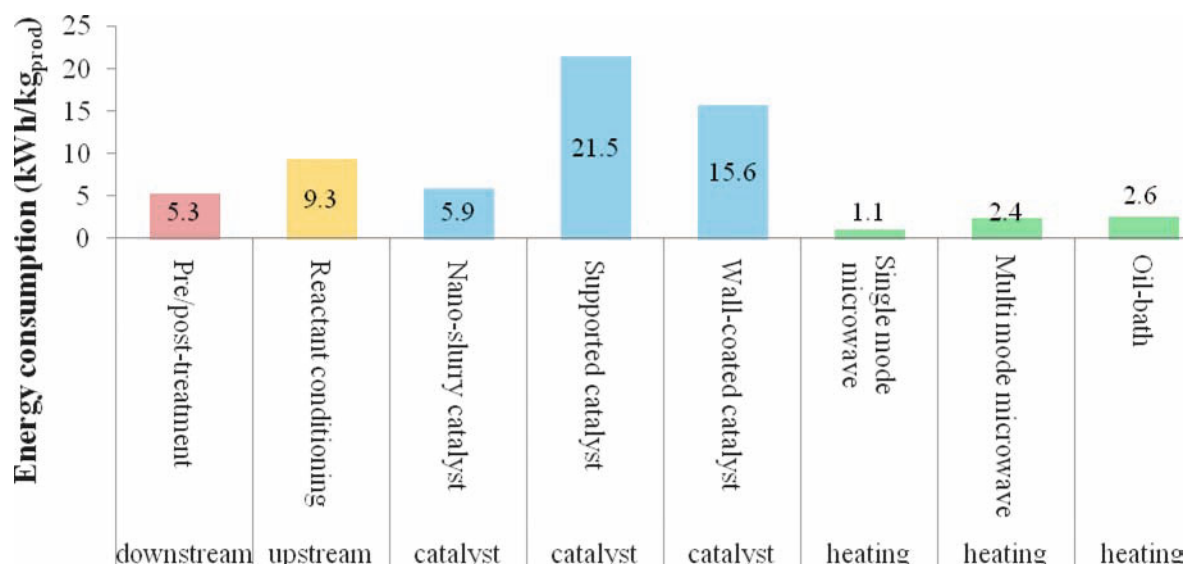
**Figure 11.** Energy flow diagrams for three heating systems studied; that is, single-mode (left), multimode (middle) microwaves, and oil-bath heating

efficiency in addition to heat losses to the environment [27]. Although a fair comparison of microwave heating with oil-bath heating is not straightforward and could even lead to contradicting results [28], it is mandatory to assign the energy boundaries to deduce overall energy efficiency and consumption [29].

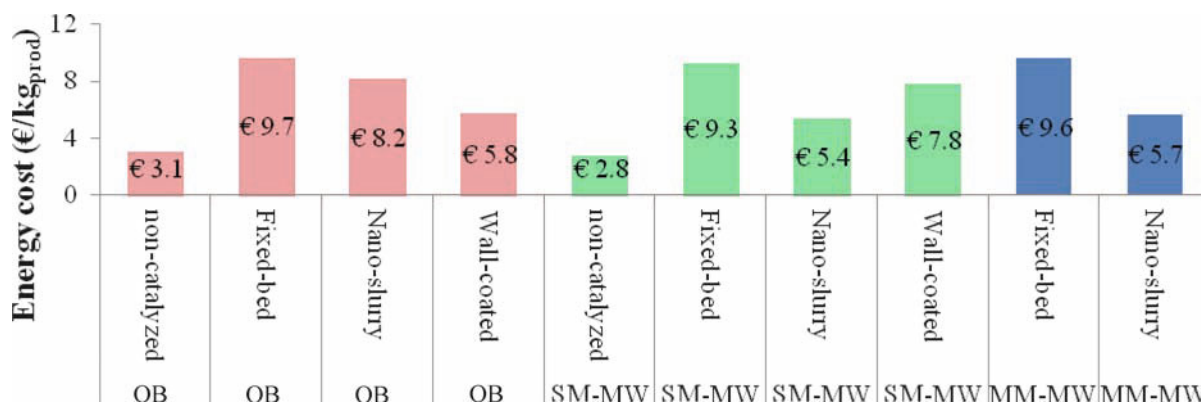
Similar to the comparison of oil-bath heating to microwave heating efficiencies, the microwave modes, single mode or multimode, require a thorough energy comparison study as given by

Nüchter et al. and, for upscaled microwave-heated processes, by Strauss et al. [17], 30] However, the given efficiencies clearly show 50% reduction in energy consumption for single-mode microwave systems [31]. Only a fraction of the overall process energy originates from reactor heating in fine-chemicals synthesis as shown in Figure 12.

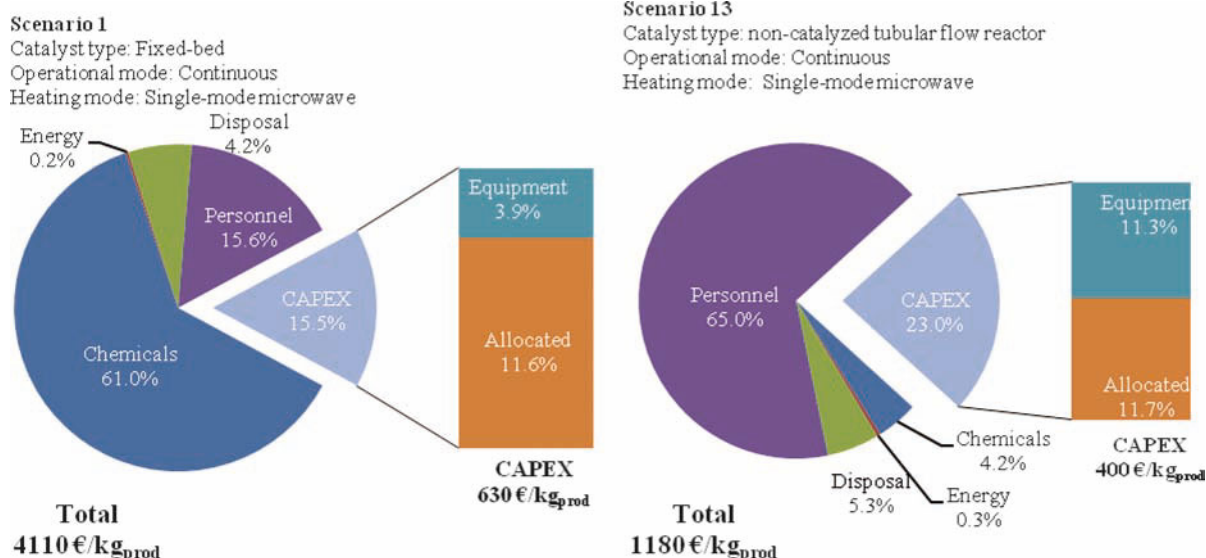
Figure 13 shows the cost share related to the overall process energy cost for the catalyzed and noncatalyzed systems using



**Figure 12.** Energy consumption in the overall process showing a major consumption in the catalyst synthesis part with heating as a minor contributor



**Figure 13.** Overall energy costs for the study of different scenarios in the noncatalyzed aspirin synthesis and the Cu-catalyzed Ullmann C–O coupling using single-mode microwave (SM-MW) and multimode (MM-MW) microwave heating, and oil-bath heating (OB)



**Figure 14.** Comparison of two chemical systems, that is, Cu-catalyzed Ullmann C–O coupling (scenario 1) and the nonmetal-catalyzed aspirin synthesis (scenario 13)

all different heating techniques. It is clearly shown that a significant cost contribution originates from the catalyst synthesis section for the metal-catalyzed systems.

Most studies that refer to energy efficiency in microwave applications mainly target noncatalyzed or homogeneously catalyzed processes, where rapid heating is required [32]. Therefore, a beneficial application of microwave heating in large-scale continuous processing could only be achieved at relatively short residence times. In the case of longer residence times, the benefits of microwave heating could be maintained using a loop reactor with short microwave irradiation times [33]. For catalyzed systems, the preparation and regeneration of the catalyst require energy-intensive processes (vacuum processing, calcination, centrifugation, etc.), and for the overall energy consumption, these contributions are most dominating (see ESI; Appendix D).

**3.3. Case Studies.** In this part, the overall costs of the different scenarios as proposed in Figure 2 are clarified and compared. Finally, an overall evaluation on profitability of each scenario is given, providing information on cost-feasible implementation in practice (see ESI; Appendix G provides detailed datasheet whereupon the scenario studies were based).

**3.3.1. Cost Effect of the Chemical Systems.** Most interesting for this study is the type of chemistry performed in an integrated microwave heating and microprocessing concept. Figure 14 shows the overall costs related to the heterogeneously Cu-catalyzed Ullmann C–O coupling and the nonmetal-catalyzed aspirin synthesis using the same setup.

The main cost aspects for cost feasibility in a microwave-assisted catalyzed and nonmetal-catalyzed system are highlighted from a process and heating point of view. Figure 14 shows that in the case of the aspirin process, the personnel cost becomes OPEX dominating, whereas the CAPEX/OPEX ratio increases tremendously compared to that of the Ullmann process. However, the comparable cheap synthesis of aspirin is strongly reflected in the final sales price and, therefore, the profitability (vide infra). For this study, it can be concluded that the cost effects between scenarios 1 and 13 are to a large extent governed by the prices of the raw materials. At these scales, the Ullmann process can be defined as a raw materials-priced process, whereas the aspirin process can be defined as an equipment-priced process. It should also be noted that as a result of these much smaller production scales combined with microprocess

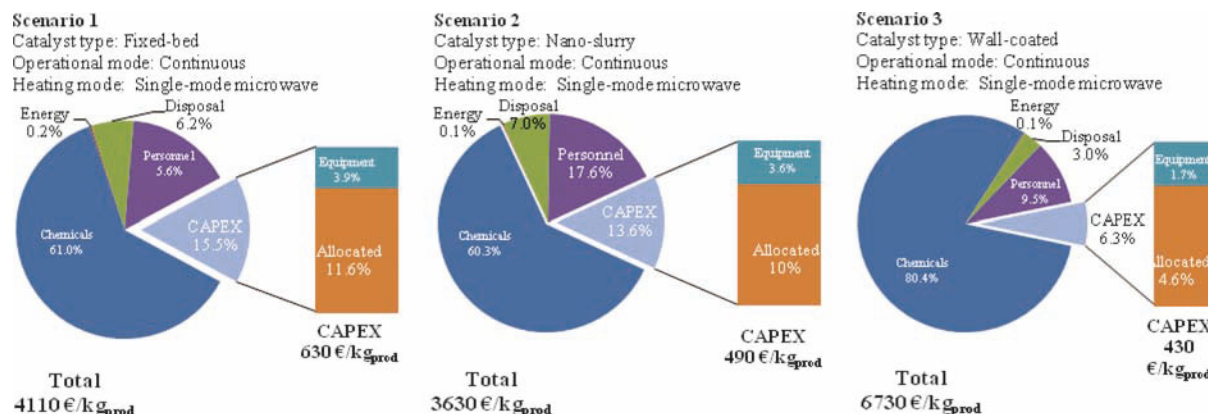
technology, the variable costs consisting of raw chemical and energy costs are much higher than those in case of conventional scale fine-chemicals production plants, where usually the fixed-to-variable cost ratio is found to be 1.5 (60% CAPEX and 40% OPEX) [34]. Moreover, the sales prices of 4-phenoxy pyridine were compared with those of Tokyo Chemical Industry (TCI-America) as a commercial producer and found to be 4500 /kg in 2011.†

**3.3.2. Cost Effect of Catalyst System.** As concluded from the earlier CAPEX study in section “Capital expenditure (CAPEX),” a large difference in equipment costs would result on using different catalyst synthesis options. This can be explained by a cost evaluation of the site utilities related to the catalyst preparation, which was found to be much higher than that of any other unit in the production site. The effect on the operational costs due to the catalyst precursors was negligible, since the amounts used in the chemical process were at trace level. However, the catalyst preparation section contributed significantly to the overall energy consumption (Figure 12, 21.5 kWh<sub>cat</sub> for the supported catalyst) though the overall energy consumption played a minor role in the operational cost. Figure 15 shows the CAPEX and OPEX contributions to the overall cost related to different catalyst systems. Major contributions from the CAPEX side are given again for the fixed-bed catalyst system (scenario 1) as compared to the nano-slurry and wall-coated catalysts (scenarios 2 and 3).

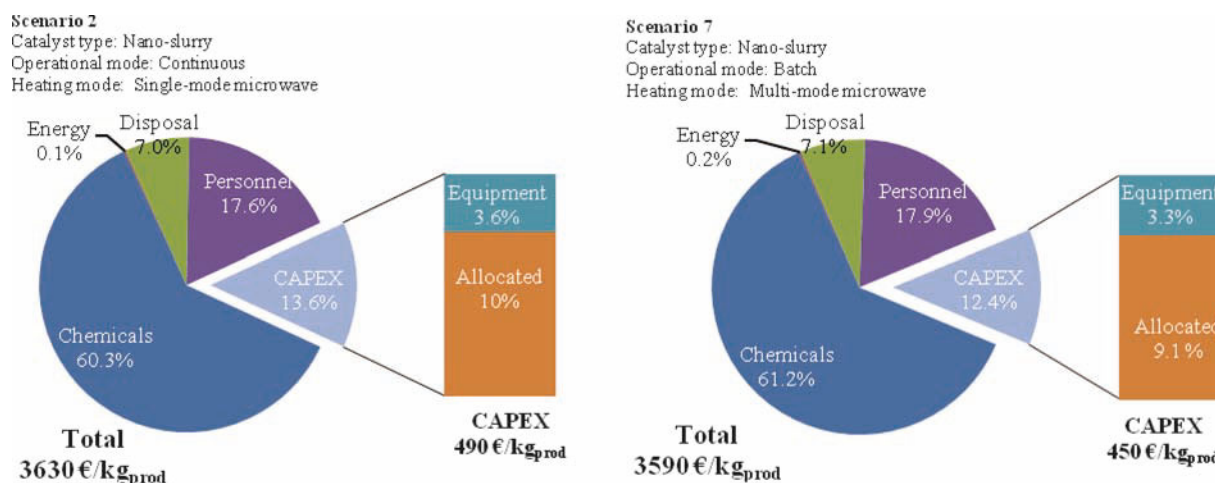
Regarding the overall costs given per kg product, the wall-coated catalyst appeared to be the least attractive due to a low chemical conversion and, therefore, high operational costs, whereas the fixed-bed and nano-slurry catalysts showed a much lower cost. In addition, it is shown in Figure 9 that the large difference in the chemical cost of nano-catalysts resulted from the enhanced chemical performance using nano-slurry catalysts when compared to that of the micro-slurry catalyst.

**3.3.3. Cost Effect of the Operational Microwave Mode.** The cost effects of employing a continuously operated process or a batch operated process are shown in Figure 16, where a micro-process plant is compared with a 1-L scale stirred batch reactor in a microwave cavity. To keep reactor dimensions at these space–time yields within reasonable limits, a single-mode cavity

† The profitability, as defined in section “Capital expenditure (CAPEX),” and the cost price was based on the existing market sales price.



**Figure 15.** Cost comparison of scenarios 1, 2, and 3 of the different supported catalyst systems in the Ullmann C–O coupling; that is, fixed-bed, nano-slurry, and wall-coated catalysts

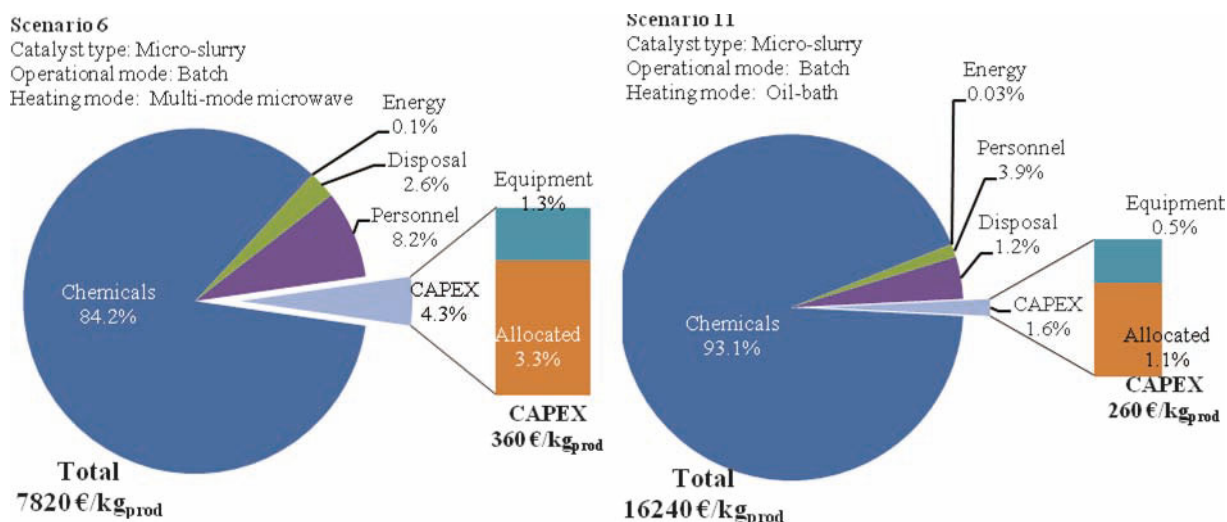


**Figure 16.** Comparison of scenarios 2 and 7 emphasizing the cost benefits of using continuous processing

is applied in microprocessing, while for the batch process, a multimode cavity is used. This comparison is justifiable since energy contributes only moderately to the costs and, therefore, the large difference in energy efficiency for the two microwave modes would not be reflected significantly in the overall cost. Therefore, no major cost difference is observed between

the single- and multimode microwaves when chemicals cost dominate.

**3.3.4. Microwave Cost Effect.** Figure 17 shows the overall cost related to the micro-slurry catalyst case using microwave (scenario 6) and oil-bath (scenario 11) heating. It was previously [35] shown that the use of a slurry reaction mixture



**Figure 17.** Comparison of scenarios 6 and 11 demonstrating the cost-related benefits of using microwaves



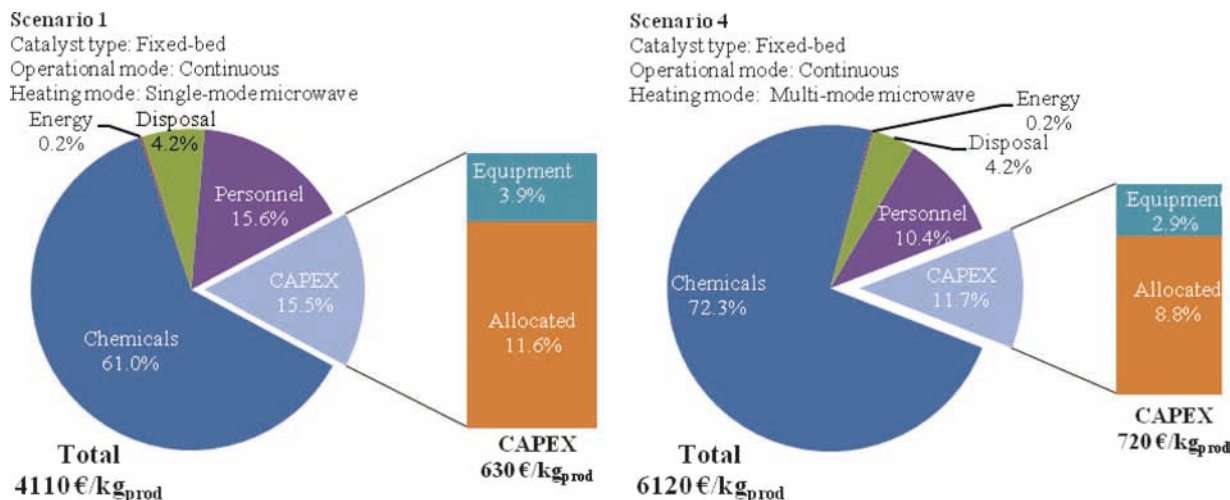


Figure 18. Comparison of scenarios 4 and 1 providing the benefits of using single-mode compared to multimode microwave cavities

enhances the heating efficiency and reaction rate because of the presence of salts and their rapid heating effect in combination with microwaves. For this reason, a microwave-assisted process finally turned out to be cheaper and favorable when compared to oil-bath-heated systems.

**3.3.5. Cost Effect of Single- and Multimode Microwave Cavities.** In continuation of the above given conclusions, the use of microwaves provided a beneficial cost effect compared to oil-bath heating. In this section, two different microwave modes are screened and compared, that is, single-mode and multimode microwaves. Figure 18 shows the cost diagrams related to both multimode (scenario 4) and single-mode microwave cavities (scenario 1) for a fixed-bed microprocess system.

The total costs of the multimode microwave technique appear to be 30% higher than those in the case of single-mode microwave applications. However, the costs related to the energy consumption are hardly reflected in the operational costs, even at higher energy efficiency, from the single-mode microwave cavities.

**3.4. Sensitivity Analysis of Production Scale and Catalyst Cost Contributions.** In this section, the previously presented

case studies are investigated in more detail using a one parameter at a time sensitivity analysis. On the basis of the total permanent investments ( $C_{TP}$ ) and the total capital investment ( $C_{TCI}$ ) of the processes, three parameters and their influences on the ROR and the payback period (PBP) are investigated as the major indicators of the venture profit (VP). Firstly, the influence of increased catalyst activity in terms of turnover frequency (TOF) and number (TON) is shown, which is followed up by the influence of chemical process intensification and process upscale. Figure 19 shows schematically the techno-economically feasible scenarios in green, which are related to the costs and profits of the studied scenarios (in /kg product) shown in Table 3.

On the basis of results shown in Table 3, a sensitivity analysis was carried out to envisage the potential to still bring unprofitable scenarios to profitability by extending the process window.

**3.4.1. Increasing Catalyst Activity.** The influence and the effects of increased catalyst activity on the overall cost, the profitability, and, eventually, the ROR and PBP have been investigated by comparing increased TOF and TON of the catalyst to current catalyst activities.

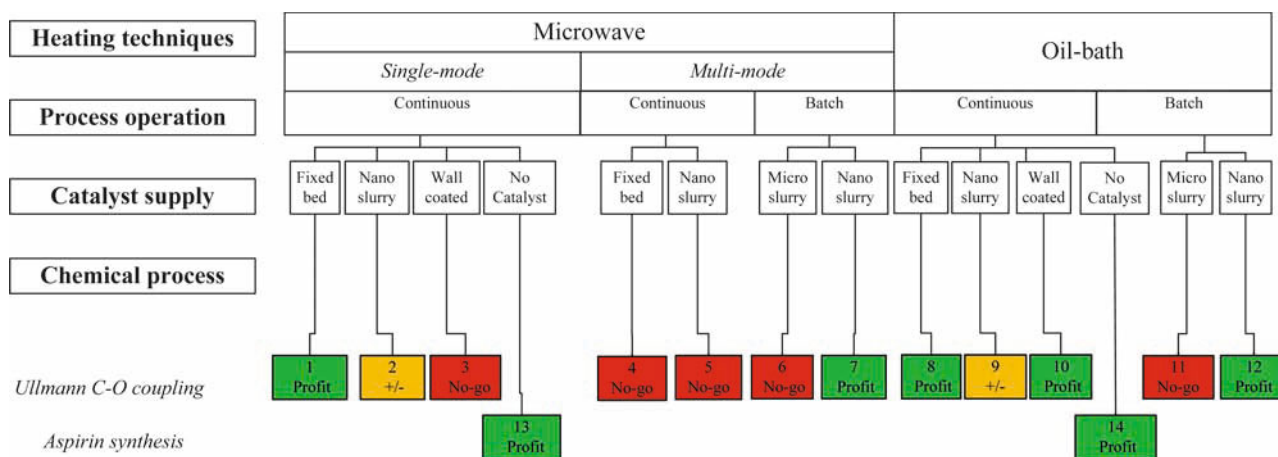
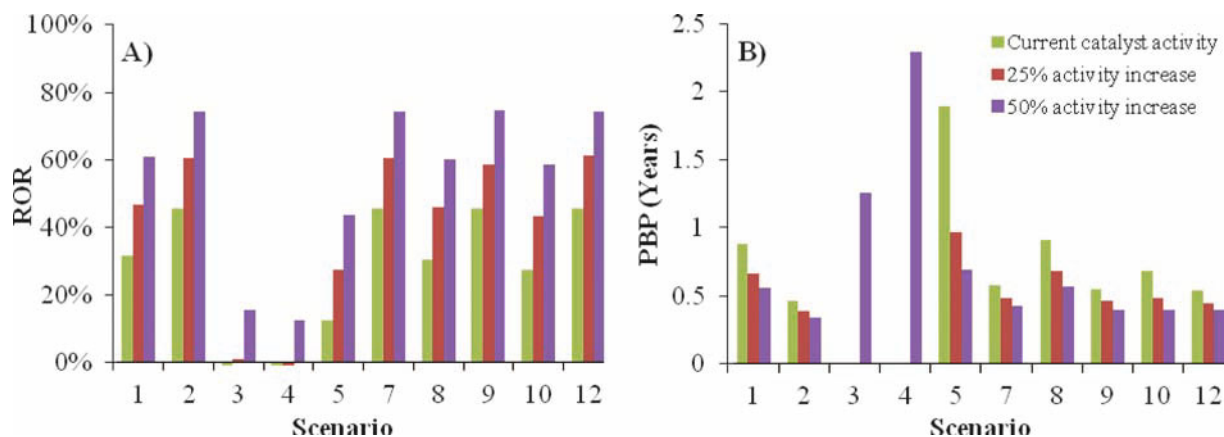


Figure 19. Profitability for each scenario study proposed in this study. The profitable, potential profitable, and non-profitable scenarios are shown in green, orange, and red, respectively

Table 3. Capital and operating costs used to derive profit for the different scenarios

Scenarios	1	2	3	13	4	5	6	7	8	9	10	14	11	12
OPEX ( /kg <sub>prod</sub> )	3416	3093	6258	736	5335	4001	7431	3093	3448	2841	3530	737	15,953	3094
CAPEX ( /kg <sub>prod</sub> )	699	542	471	249	790	661	391	491	601	401	472	212	281	380
Operating profit ( /kg <sub>prod</sub> )	385	865	-2229	515	-1625	-162	-3322	916	451	1258	498	551	-11,734	1026



**Figure 20.** Influence of catalyst activity on the rate of return (A) and payback period (B)

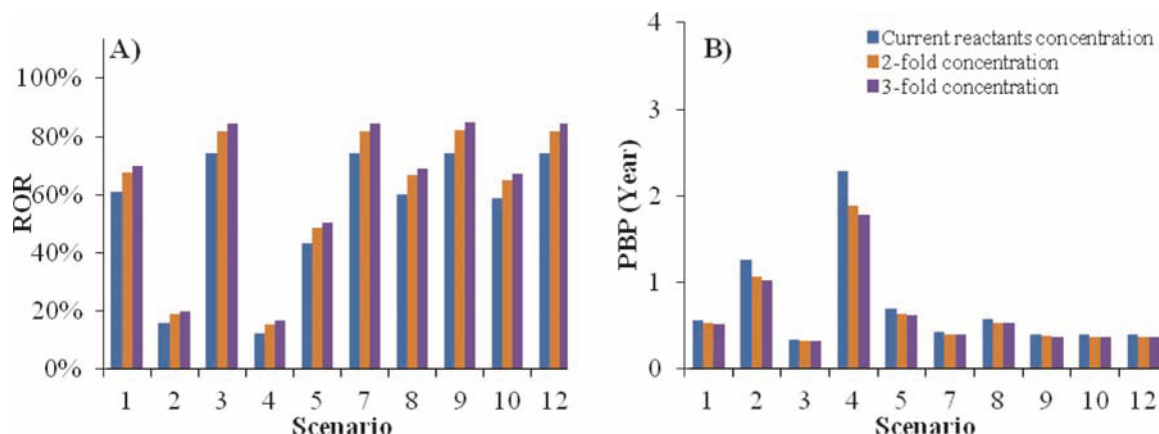
Figure 20 (a) shows the ROR for the different scenarios and the related PBP for different catalyst activities. Most noticeably for the catalyzed systems, ROR showed the linear dependency on catalyst activity, while a more asymptotic dependence was observed in case of PBP (see Figure 20b). The highest impact of activity increase on PBP was observed for scenario 5 (nanoslurry-catalyzed multimode microwave setup) due to relatively low ROR at the current catalyst activities. Moreover, scenarios 3 and 4 (wall-coated single-mode microwave and fixed-bed multimode microwave setup) can even reach a positive ROR and feasible PBP at just 50% increase in catalyst activity. Therefore, in these scenarios, both microwaves and microreactors are clearly not the cost drivers. They rather appear to be governed by the catalyst activity.

**3.4.2. Chemical Process Intensification.** In addition to the increased catalyst activity, the reactant concentration in the chemical process could also lead to decreased solvent costs and increased productivity in terms of space–time yield. However, increasing the reactant concentrations in the reaction solvent might consequently lead to increased reaction mixture viscosity, risk of crystallization, and modified liquid polarity and, therefore, microwave absorption properties. The pressure drop profiles based on the Ergun equation as a function of increased viscosities are supplied in the ESI (see appendix G). A sensitivity analysis on process intensification by increasing reactant concentration is required to justifiably assess its effect on ROR and PBP. Figure 21 (a) shows the ROR for all the scenarios at doubled and tripled reactant concentration with respect to the current experimental conditions. In contrast to the linear effect of catalyst activity on ROR, the effect of reactant concentration

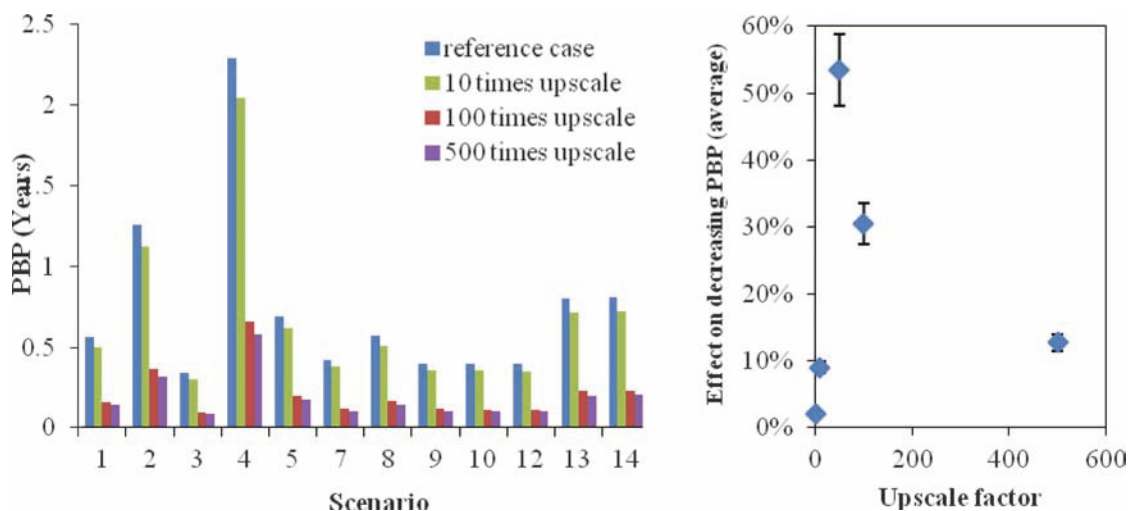
appears in most cases to behave logarithmically. This means an optimum can be attained by doubled concentrations, where threefold increase demonstrates less benefit. Besides the benefits of increasing catalyst activity, the wall-coated microreactor in a single-mode microwave system would be economically even more favorable at increased reactant concentration, resulting in a PBP being even less than 2 years (see Figure 21b).

**3.4.3. Process scale. Upscale by Numbering up or Numbering out?** The scale-up of the given processes has also been surveyed as a method to monitor the profitability window for different scenarios. The scale-up for the current process was based on a maximum production scale of 10 kg/day/unit, and as can be expected the expansion of the production capacity will lead to decreased operating cost and therefore decreased PBP for all scenarios. Figure 22 (left) shows the effect of 10-, 100- and 500-fold process scale-up on the PBP, which demonstrates only a minor decrease in the PBP at 10-fold upscale factor. However, a 100-fold process upscale demonstrated a much larger decrease in the PBP, resulting in a decrease of 58% in the best case for the wall-coated microreactor in a single-mode microwave cavity. Figure 22 (right) shows that at much larger upscale factor, the cost benefits, with respect to decrease in the PBP, decrease and provide no added value. It also shows that the optimal upscale factor of this process is found to be around 50-fold upscale in the capacity.

However, for higher production capacities, it is more beneficial to have a number of delocalized production plants at an optimum capacity of 500 kg/day (i.e., 10 times 50 kg/day; equivalent to 50-fold upscale plant). This way of scaling up by “numbering out” optimized production facilities provides



**Figure 21.** Influence of reaction mixture concentration on the rate on return (A) and payback period (B)



**Figure 22.** Influence of operating scale on the payback period (PBP, left) and the optimum upscale factor for minimizing the PBP (right)

an efficient way for production scale-up to 5 tons/day at 10 delocalized sites for 0.5 tons/day (equivalent to a total 50-fold upscale plant regarding the base case) and would lead to an economically more efficient production plant.

#### 4. Conclusions

In this study the impact of various chemical process parameters has been investigated on the overall production costs when implementing each of them in a microwave-assisted microprocess plant for the synthesis of fine chemicals. Two existing chemical production lines were considered, 2-acetoxybenzoic acid as aspirin and 4-phenoxy pyridine as antibiotic precursor in Vancocin production. The sales price of these products has been derived on this scale, based on the current market value, at 4500 €/kg and 1500 €/kg for 4-phenoxy pyridine and aspirin, respectively. Figure 19 shows that the use of single-mode microwave heating with microprocessing as a replacement for conventional heating and processing can be beneficial in heterogeneously catalyzed process when using a micro-fixed reactor (scenario 1). This combination resulted in an operating profit of 400 €/kg phenoxy pyridine and exceeded the techno-economic benefits for supported systems among all microwave-related scenarios. An alternative method to carry out catalytic reactions can be achieved profitably using catalyst nano-slurries (scenario 2 and 9); however, owing to insufficient profit margins relative to the large technical risk and catalyst cost, these processes are not advisable. For nonmetal-catalyzed homogenous liquid systems, the use of microwave heating in a microprocess plant (scenario 13) can in all cases be made feasible as compared to conventional heating (scenario 14), resulting in an operating profit of 500 €/kg aspirin. The use of wall-coated reactors (scenario 3) can provide a profitable scenario, however only if the chemical performance could be improved, for example, by increasing the catalyst surface by using either small (reactor) channel diameters (<50 μm) or highly porous wall material. This conclusion was confirmed by the sensitivity analysis performed, where catalyst activity appeared to be more influential on the ROR and the PBP and then chemistry intensification. However, the most influential parameter on profitability (in terms of ROR and PBP) appeared to be the production scale, at an optimum capacity of 500 kg/day using an optimum upscale unit as described in the sensitivity analysis. Larger production scales could attain even more profitability at decentralized production sites by means of “numbering-out” and providing the added value of flexible and transportable production of fine chemicals.

#### 5. Outlook

The results obtained for the Ullmann ether synthesis allow us to derive some general conclusions on the profitability of fine-chemicals processes when carried out in continuous flow (as compared to batch technology) – and the dominating and game-changing role of the right choice of heating and catalyst concept. In general, microprocessing costs and microwave-related equipment costs consist of given cost shares comparable to other fixed costs in the overall scenario and are by no means dominant over the alternative, more classical, processing (e.g., stirred batch reactors) and heating (e.g., electric heating). An economic benefit from these novel technologies is reflected in the operating costs caused by, for example, increased reaction rate and product selectivity, increased p-T window, and improved residence time control rather than costs related to the equipment purchase. Thus, when referring to a new, innovative, but yet unfamiliar, type of processing, the equipment costs are by no means necessary cost drivers rather than apparent cost drivers and require justified scaling regarding the overall profitability obtained from their process technological benefits. Microprocessing and microwave heating most importantly change the process protocol, and, thus, their secondary effects, derived from the changed protocol, as, for example, the catalyst supply (microwave-transparent support such as titania), reaction mixture homogeneity (addition of solubilizing agents such as crown ethers), and controlled heat input (presence of a metal catalyst in the microwave field), are much more relevant and are here the actual cost drivers as compared to the appropriate reactor or heat input. The most relevant general message from this paper is that the process-design needs in a holistic manner have to be taken into account rather than focusing only on the reaction. It can be concluded that microreactor technology (i.e., channel coated) typically combines better with oil-bath heating, by comparing scenarios 3 and 10, while flow-chemistry-type fixed-bed reactors combine with microwave technology; this is a result of areal heating and volumetric heating, respectively. In general, microprocessing was found to be most advantageous for non-catalyzed systems, i.e. which refers to and demands for process simplification as one means of the Novel Process Windows concept to develop noncatalyst systems. Catalyzed operations in microsystems increase the process complexity, as most of the technical investment shifts to the catalyst design rather than the reactor design. In any case, from the cost side, a pre-study, specific to the chemistry of interest, is always required before implementation.

**Acknowledgments** The authors acknowledge the Technology Foundation STW (MEMFiCS GSPT-07974), DSM Research, FrieslandCampina, IMM, LioniX, and Milestone s.r.l. (Italy) for financial support.

**Supporting Information available:** Supplementary data associated with this article can be found on the journal's homepage at [www.akademai.com](http://www.akademai.com).

## References and Notes

- Kappe, C. O.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH Verlag GmbH & Co KGaA: Weinheim, 2006; pp 9–28.
- Bogdal, D.; Prociak, A. *Chimica Oggi* **2007**, *25*(3), 30–33.
- (a) Dallinger, D.; Lehmann, H. r.; Moseley, J. D.; Stadler, A.; Kappe, C. O. *Org. Process Res. Dev.* **2011**, *15*(4), 841–854; (b) Lehmann, H.; LaVecchia, L. *Org. Process Res. Dev.* **2010**, *14*(3), 650–656; (c) Moseley, J. D. *Chimica Oggi* **2009**, *27*(2), 6–10; (d) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J.-P.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2007**, *12*(1), 30–40; (e) Wolkenberg, S. E.; Shipe, W. D.; Lindsley, C. W.; Guare, J. P.; Pawluczyk, J. M. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*(6), 701–708; (f) Loupy, A. *Microwaves in Organic Synthesis*; Wiley: Weinheim, 2006; Vol. 2; (g) Kremsner, J.; Stadler, A.; Kappe, C. O. *Top. Curr. Chem.* **2006**, *266*, 233–278.
- Chamoin, S. In *Advances in Microwave-Assisted Organic Synthesis: MAOS Conference and Exhibition*, Budapest, Hungary, 2006.
- Lehmann, H. In *Ernst Schering Foundation Symposium Proceedings*, Berlin–Heidelberg, Germany, 2007, Vol. 3, pp 133–149.
- Kappe, C. O.; Stadler, A., In *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006; pp 57–90.
- (a) Marafie, J. A.; Moseley, J. D. *Org. Biomol. Chem.* **2010**, *8*(9), 2219–2227; (b) Moseley, J. D.; Woodman, E. K. *Org. Process Res. Dev.* **2008**, *12*(5), 967–981; (c) Arvela, R. K.; Leadbeater, N. E.; Collins Jr, M. J. *Tetrahedron* **2005**, *61*(39), 9349–9355.
- (a) Kelly, C. B.; Lee, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2011**, *52*(2), 263–265; (b) Pipus, G.; Plazl, I.; Koloini, T., *Chem. Eng. J.* **2000**, *76*(3), 239–245; (c) Wilson, N. S.; Sarko, C. R.; Roth, G. P. *Org. Process Res. Dev.* **2004**, *8*(3), 535–538.
- Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem. Int. Ed.* **2006**, *45*(17), 2761–2766.
- Benaskar, F.; Hessel, V.; Krtschil, U.; Löb, P.; Stark, A. *Org. Process Res. Dev.* **2009**, *13*(5), 970–982.
- Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process Res. Dev.* **2007**, *12*(1), 41–57.
- Engels, V.; Benaskar, F.; Patil, N.; Rebrov, E. V.; Hessel, V.; Hulshof, L. A.; Jefferson, D. A.; Vekemans, J. A. J. M.; Karwal, S.; Schouten, J. C.; Wheatley, A. E. H. *Org. Process Res. Dev.* **2010**, *14*(3), 644–649.
- Illg, T.; Loeb, P.; Hessel, V. *Bioorg. Med. Chem.* **2010**, *18*(11), 3707–3719.
- (a) Hartman, R. L.; Naber, J. R.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2010**, *49*(5), 899–903; (b) Roberge, D. M.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. *Chim. Oggi* **2009**, *27*(4), 4.
- Schmalz, D.; Oldenburg, M. H.; Grund, M.; Muntermann, H.; Kunz U. *Chem. Ing. Tech.* **2005**, *77*(7), 859–866.
- Kockmann, N. In *Micro Process Engineering*; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 1–45.
- (a) Schmink, J. R.; Kormos, C. M.; Devine, W. G.; Leadbeater, N. E. *Org. Process Res. Dev.* **2010**, *14*(1), 205–214; (b) Nakamura, T.; Nagahata, R.; Kunii, K.; Soga, H.; Sugimoto, S.; Takeuchi, K. *Org. Process Res. Dev.* **2010**, *14*(4), 781–786; (c) Moseley, J. D.; Woodman, E. K. *Energy Fuels* **2009**, *23*(11), 5438–5447; (d) Hessel, V.; Kralisch, D.; Krtschil, U. *Energy Environ. Sci.* **2008**, *1*(4), 467–478; (e) Glasnov, T. N.; Kappe, C. O. *Macromol. Rapid Commun.* **2007**, *28*(4), 395–410; (f) Krtschil, U.; Hessel, V.; Kralisch, D.; Kreisel, G.; Kuepper, M.; Schenk, R. *Chimia* **2006**, *60*(9), 6; (g) Comer, E.; Organ, M. G. *Chem. Eur. J.* **2005**, *11*(24), 7223–7227; (h) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*(22), 8160–8167; (i) Roberge, D. M.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, B. *Chem. Eng. Technol.* **2005**, *28*(3), 318–323; (j) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*(3), 128–141.
- (a) Benaskar, F.; Engels, V.; Patil, N. G.; Chaibi, M.; Rebrov, E. V.; Meuldijk, J.; Hessel, V.; Hulshof, L. A.; Wheatley, A. E. H.; Schouten, J. C. **2011**, (Unpublished results); (b) Dressen, M. H. C. L.; van de Kruijs, B. H. P.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process Res. Dev.* **2010**, *14*(2), 351–361; (c) Drevina, V. M.; Markitanova, L. I.; Nesterov, V. M. *Khimiko-Farmatsevticheskii Zhurnal* **1976**, *10*(10), 53–55; (d) Drevina, V. M.; Nesterov, V. M.; Markitanova, L. I. *Khimiko-Farmatsevticheskii Zhurnal* **1976**, *10*(11), 120–122; (e) Markitanova, L. I.; Drevina, V. M.; Nesterov, V. M. *Khimiko-Farmatsevticheskii Zhurnal* **1976**, *10*(12), 85–88.
- (a) Dressen, M. H. C. L. 2009; (b) Wang, L.-D.; Cui, P. *Liaoning Huagong* **2009**, *38*(9), 623.
- Patil, N. G.; Hermans, A. I. G.; Benaskar, F.; Rebrov, E. V.; Meuldijk, J.; Hessel, V.; Hulshof, L. A.; Schouten, J. C. *AICHE Journal: Chemical Engineering Research and Development* **2011**, (Unpublished results).
- (a) Protasova, L. N.; Rebrov, E. V.; Glazneva, T. S.; Berenguer-Murcia, A.; Ismagilov, Z. R.; Schouten, J. C. *J. Catal.* **2010**, *271*(2), 161–169; (b) Shore, G.; Tsimmerman, M.; Organ, M. G. *Beilstein J. Org. Chem.* **2009**, *5*, 35; (c) Glazneva, T.; Rebrov, E.; Schouten, J.; Paukshtis, E.; Ismagilov, Z. *Thin Solid Films* **2007**, *515*(16), 6391–6394.
- D'Angelo, N. D.; Peterson, J. J.; Booker, S. K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P. J.; Kim, T.-S. *Tetrahedron Lett.* **2006**, *47*(29), 5045–5048.
- Benaskar, F.; Engels, V.; Rebrov, E. V.; Patil, N. G.; Meuldijk, J.; Magusin, P. C. M. M.; Mezzari, B.; Hessel, V.; Hulshof, L. A.; Thüne, P. C.; Hensen, E. J. M.; Wheatley, A. E. H.; Schouten, J. C. *Chem. Eur. J.* **2010**, in press.
- Stankiewicz, A. *Chem. Eng. Res. Des.* **2006**, *84*(7), 511–521.
- (a) Hoogenboom, R.; Wilms, T. F. A.; Schubert, U. S. *Polymer Preprints* **2008**, *49*(2), 930–931; (b) Graus, W. H. J.; Voogt, M.; Worrell, E. *Energy Policy* **2007**, *35*(7), 3936–3951.
- After personal discussion with Lauda Company, pump energy for internal circulation of heating medium was determined.
- In this study, the minimum heating medium volume required for uniform and stable heating was experimentally found to be around fourfold heating medium volume regarding the reaction mixture. At lower heat medium volumes, temperature fluctuations and high temperature gradients result. In conventional lab-scale systems, a much higher volume ratio of medium and reaction mixture is used.
- (a) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2005**, *9*(4), 516–518; (b) Simmons, H. E.; Smith, R. D., *J. Am. Chem. Soc.* **1958**, *80*(19), 5323–5324.
- (a) Moseley, J. D.; Kappe, C. O. *Green Chem.* **2011**, *13*(4), 794–806; (b) Nuchter, M.; Müller, U.; Ondruschka, B.; Tied, A.; Lautenschläger, W. *Chem. Eng. Technol.* **2003**, *26*(12), 1207–1216.
- Strauss, C. R. *Org. Process Res. Dev.* **2009**, *13*(5), 915–923.
- Hoogenboom, R.; Wilms, T. F. A.; Erdmenger, T.; Schubert, U. S. *Aust. J. Chem.* **2009**, *62*(3), 236–243.
- Razzaq, T.; Kappe, C. O. *ChemSusChem* **2008**, *1*(1–2), 123–132.
- Godwin, D. R.; Lawton, S. J.; Moseley, J. D.; Welham, M. J.; Weston, N. P. *Energy Fuels* **2010**, *24*(10), 5446–5453.
- (a) Bruggink, A. *Chim. Oggi* **1998**, *16*, 44–47; (b) Bruggink, A. In *CphI Conference Proceedings* **1993**, 38–47; (c) Berkoff, C. E.; Kamholz, K.; Rivard, D. E.; Wellman, G.; Winicov, H. *Chemtech* **1986**, *1986*, 552–559.
- Benaskar, F.; Engels, V.; Patil, N.; Rebrov, E. V.; Meuldijk, J.; Hessel, V.; Hulshof, L. A.; Jefferson, D. A.; Schouten, J. C.; Wheatley, A. E. H. *Tetrahedron Lett.* **2010**, *51*(2), 248–251.