Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.
[Link to publication](#)

The Claisen Rearrangement – Part 2: Impact Factor Analysis of the Claisen Rearrangement, in Batch and in Flow

Volker Hessel[1],*, Elnaz Shahbazali[1], Timothy Noël[1], Sergei Zelentsov[2]

Abstract

In Part 2, the factors impacting the Claisen rearrangement both in batch and flow processing are analyzed, including the choice of substituent, catalyst, temperature, pressure, concentration, flow rates, and solvent. Part 1 of this review series discussed the potential of using short-time spectroscopy and quantum mechanical calculations to elucidate the mechanism and transition state of the Claisen rearrangement. Flow processing offers profound opportunities for studying these factors known to impact the Claisen rearrangement done in batch. It is shown that the same impact factors also rule flow processing, yet now superposed by the very different residence and reaction time settings and by novel process windows which go beyond conventional processing. As a result, massive intensification can be reached and a mechanistic analysis can be done in entirely unpaved processing fields. This links to the analysis given in part 1: it is likely that flow processing can further promote the understanding of the mechanism and transition state of the Claisen rearrangement and, thereby, promote the achievement of better reaction performance.

Keywords: Claisen rearrangement, Flow chemistry, Microreactors, Novel process windows, Process intensification

1 Introduction

This review constitutes the second part of a two-review compilation. The first part focused on the mechanisms and transition states of the Claisen rearrangement using quantum mechanical calculations and ultrashort pulse spectroscopy. The conclusions of the first review shall serve as an introduction to this second review.

Beyond its synthetic power, the Claisen rearrangement is among the best fundamentally investigated reactions [1–6]. This was done over decades by means of classical reaction engineering/kinetic investigations and physical chemistry. This provided with time considerable insight into reaction mechanisms and revealed structures of their transition states; yet often on heuristic basis and with (many) differing and even conflicting statements in literature which cannot further be resolved and elucidated. Since recently, modern analytical techniques and theoretical/quantum-mechanical chemistry add more detailed and firm evidence of the proposed mechanism. Here, a basis has been laid to resolve conflicting assumptions. Direct proofs of existence of intermediates, and thus finally proposed respective transition states, are nowadays possible both by advanced experimental and theoretical methods [5, 7–8].

Ultra-short pulse laser spectroscopy gives very detailed and individual information about all major species on the reaction trajectory, including the transition state, through vibration analysis of many groups within a molecule [5, 7–18]. This equals the comprehensive functional-group analysis known from Raman spectra of molecules in their ground state; yet now on a femto-second time scale allowing to catch even the most-short lived species. In this way, massive evidence is provided on the major bond changes and which are the supposed critical structures on a reaction path, most notably which is the transition state (TS). Complementary to that, quantum-mechanical calculations can yield bond distances and other geometric information which give more direct answer, since it mirrors the key characteristic of the critical species involved, rather than arguing over the boundary conditions [19–21]. The

[1] Prof. Dr. Volker Hessel (corresponding author), Elnaz Shahbazali, Dr. Timothy Noël
Laboratory of Chemical Reactor Engineering/Micro Flow Chemistry and Process Technology, Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands.
E-Mail: v.hessel@tue.nl

[2] Prof. Sergei Zelentsov
Chemical Department, Lobachevsky State University of Nizhni Novgorod – National Research University, Prospect Gagarina 23, Nizhni Novgorod 603950, Russia.

usage of the modern quantum chemistry methods can not only provide geometrical parameters being close to experimental ones but they can correctly forecast the activation parameters of a chemical reaction such as activation energy and reaction enthalpy [22–28]. Both the new experimental and theoretical approaches allow to break down the multiple interpretations options to one mechanism and one transition state for a given reaction under given conditions.

The main question of this review is what flow processing with its much better defined process conditions and faster characteristic times can add hereto. Flow chemistry considerably widens the processing window of organic reactions. Unknown regions can be explored now. High pressure and high temperature, for example, can be easily realized. Solvent-free processing is common. This review will try to compile the chances and challenges of such processing options and will show what it can add in addition to batch processing.

Starting with an impact-factor analysis for the batch-processed Claisen rearrangement, this is mirrored to what the same and other new impact factor can do for the flow processing of the same reaction.

2 Factors Impacting the Rearrangement – for Batch Processing

Different means are known to control the Claisen rearrangement [29]. A key to such a control of the reaction is a special stabilization or destabilization of the TS.

2.1 Substituent effects

Castro [1] has compiled literature data to investigate the substituent influence on the Claisen rearrangement of allyl vinyl ether (AVE).

$$\text{(1)}$$
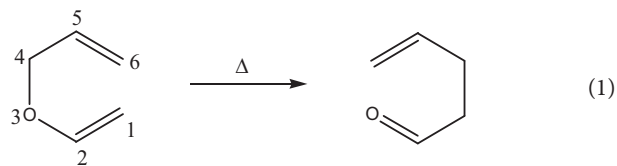
An acceleration of the rearrangement was given by (i) electron donating groups O, $-NH_2$, $-F$, $-CH_3$ in position 1 or $-OSi(CH_3)_3$, $-CH_3$, $-F$ in position 2 or $-CH_3$, $-OCH_3$ in positions 4 or 6, or if there were (ii) electron withdrawing groups $-CN$, $-CO_2^-$, $-CO_2CH_3$, $-CF_3$ in position 2 or $-CN$, $-CF_3$ in position 4 or $-CN$ in position 5 [1]. On the other hand, a slowing down of the rearrangement is given for (i) electron donating groups $-CH_3$, $-OCH_3$ in positions 5 or (ii) electron withdrawing groups $-CN$, $-CO_2CF_3$ in position 1 or $-CN$ group in position 6.

White and Wolfarth [30] showed that electron-donating groups and polar solvents increase the rate of the reaction. The rates of rearrangement of four allyl *p*-X-phenyl ethers in three solvents were compared. The rate constants were correlated by using the Hammet equation and σ^+ values. The ρ values in different solvents were negative and have quite low values, from -0.5 to -0.7. The correlations obtained mean that the substituents and solvents overall have not much influence onto the chemical reactivity in the *ortho*-Claisen reactions.

Gajewski [31] assumes that the structure of the TS adopts the features of the substrate or products depending on exothermic properties of the reaction. It will have an associative or dissociative character according to the way that the substituent can stabilize such TS.

In order to determine the impact of the substitution in *para*-position for the Claisen rearrangement of allyl phenyl ether (APE), kinetic and thermodynamic parameters of substituted allyl aryl ethers were calculated at the B3LYP/6-311G** level [32]. The results obtained in [32] are shown in Tab. 1.

Table 1. Thermal Gibbs free energies ($\Delta G°$), thermal enthalpies ($\Delta H°$), entropies ($\Delta S°$), activation energies (E_a), thermal Gibbs free energies for TS ($\Delta G^{\neq}$), entropies for TS ($\Delta S^{\neq}$), and pre-exponential multiplier (A) calculated at B3LYP/6-311G** level of theory for the Claisen rearrangement of allyl phenyl ethers having substituent in the *para*-position [32].

Substituent	$\Delta G°$ [kcal mol^{-1}]	$\Delta H°$ [kcal mol^{-1}]	$\Delta S°$ [cal mol^{-1}K^{-1}]	E_a [kcal mol^{-1}]	$\Delta G^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [cal mol^{-1}K^{-1}]	$\log A$
H	10.93	11.39	1.55	34.03	34.80	−4.57	12.23
NO$_2$	13.51	14.16	2.19	34.64	35.28	−4.13	12.32
CN	13.46	14.01	1.86	34.54	35.08	−3.82	12.39
CHO	11.89	12.45	1.88	34.16	34.80	−4.13	12.32
F	10.96	11.43	1.60	33.58	34.35	−4.55	12.23
Cl	11.46	11.96	1.67	33.86	34.53	−4.23	12.30
NH$_2$	9.96	10.30	1.16	32.28	33.01	−4.45	12.25
NHCH$_3$	8.78	9.10	1.08	31.46	32.07	−4.04	12.34
OH	9.61	9.94	1.11	32.57	33.43	−4.85	12.17
OCH$_3$	8.57	8.91	1.14	32.08	32.88	−4.67	12.21
CH$_3$	10.74	10.35	−1.32	33.43	34.90	−6.90	11.72

The calculated activation energies for the rearrangement and following proton shift reactions are 33.33 and 52.16 kcal mol^{-1}, respectively. Negative values for the activation entropy confirm existence of the concerted mechanism for the Claisen rearrangement and proton shift reaction. The Hammett ρ value of -1.34 was obtained in the first step. A negative ρ value indicates that the electron donating groups slightly increase the rate of the first step. A positive Hammett ρ value of 2.51 for proton shift reaction indicates that electron withdrawing groups increase the rate of reaction.

A kinetic study led to the proposal of two manifolds to rationalize differences in E/Z-product selectivity: reaction through a chair- or a boat-like TS, or reaction via a distorted (early) TS, where the scissile C–O bond started to elongate while the new C–C bond starts to form [33]. It is proposed that the differences in *E/Z*-product selectivity arise via reaction through different chair-like TS.

$$(2)$$

$$(3)$$

$$(4)$$

$$(5)$$
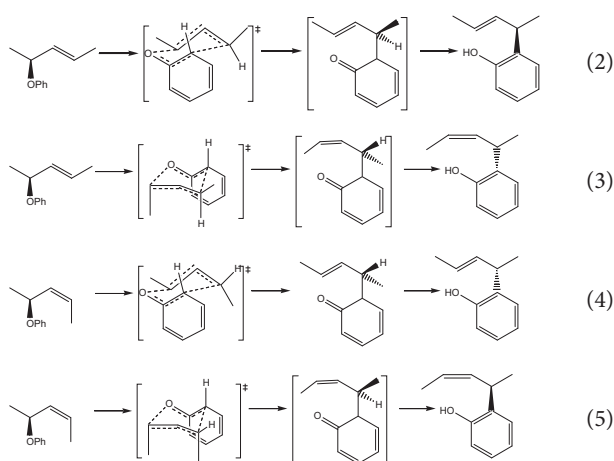
Quantum chemical calculations of the TS structures in the *ortho*-aryl-Claisen rearrangement through the chair and boat models were performed [34]. TS structures as shown in Fig. 1 resulted.

From the ΔG values, calculated for rearrangement through the respective chair/ boat TS pairs, it is evident that the chair-like TS is lower in energy than its respective boat-like counterpart indicating that reaction through the chair-like TS structure is more favorable. For TS structure pairs 1/2, 3/4, 5/6, and 7/8 the ΔΔG values are 2.4, 1.6, 2.2, and 2.5 kcal mol^{-1}, respectively [33, 34]. The absolute and relative computed ΔG values are in good agreement with experimental values (see Tab. 2).

Taking into account the TS structures given in Fig. 8 (see Sect. 3.5) it can be concluded [34] that there is only a small difference in the distances between the scissile and forming bonds of all calculated TS structures, with 2a, 5a, and 5b being nearly synchronous, 2, 3, 4, and 7 being the later

Table 2. Comparison of calculated free energy of activation (Δ*G*) using B3LYP/6-31G* for reaction occurring through chair-like or boat-like transition state. [a] Ref. [32], solvent: octane, 437.15 K. Calculated using rate constants and product ratios.

Calculated ΔG [kcal mol^{-1}]		Experimental [a] ΔG [kcal mol^{-1}]
TS chair	TS boat	
1/34.0	2/36.4	35.6
3/36.6	4/61.2	37.7
5/34.8	6/37.0	36.0
7/39.2	8/41.7	39.2

TS structures, and 8 being the early TS structure. It is likely that 2c is higher in energy than 2a due to the developing *cis*-alkene character forming within the TS. The destabilizing effect of the developing *cis*-alkene, relative to the lower energy *trans*-alkene, would be especially pronounced if the reaction proceeds through a synchronous or later TS and has progressed more towards formation of the nonaromatic Claisen intermediate, as it is apparent by observation of the lengths of the scissile and forming bonds for 3. The ΔG for reaction involving 5 is expected to be lower than for 3 due to the release of strain associated with converting a *cis*-alkene into a *trans*-alkene. Since there will be residual 1,3-diaxial interactions involving the *pseudo*-axial methyl group, the ΔG for reaction involving 5a will be higher than for 2. The free energy of activation barrier involving TS structure 7 is the highest in energy compared to the barriers involving the other aforementioned chair-like TS due to the formation of a *cis*-alkene along with many unfavorable 1,3-diaxial interactions that arise from the presence of two *pseudo*-axial methyl groups.

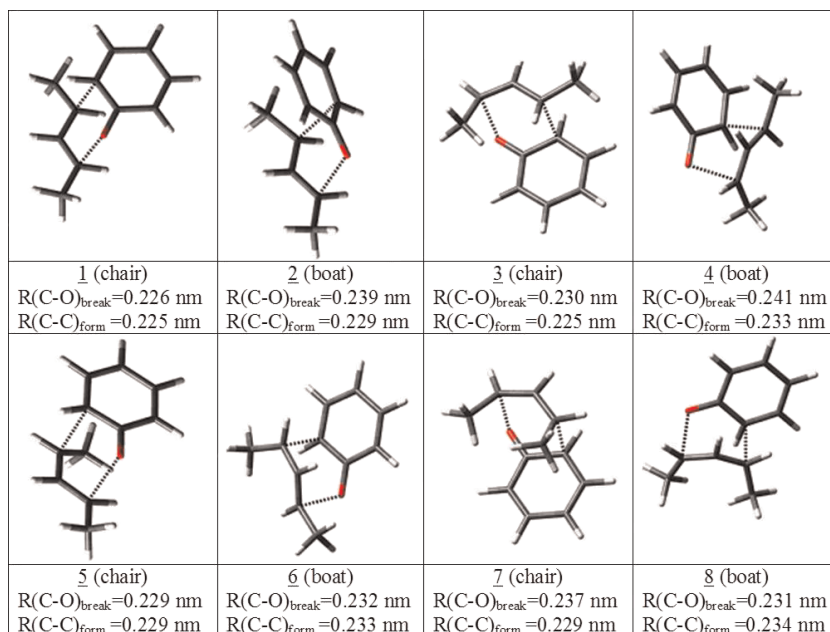|			
1 (chair)	2 (boat)	3 (chair)	4 (boat)
R(C-O)$_{break}$=0.226 nm	R(C-O)$_{break}$=0.239 nm	R(C-O)$_{break}$=0.230 nm	R(C-O)$_{break}$=0.241 nm
R(C-C)$_{form}$ =0.225 nm	R(C-C)$_{form}$ =0.229 nm	R(C-C)$_{form}$ =0.225 nm	R(C-C)$_{form}$ =0.233 nm
5 (chair)	6 (boat)	7 (chair)	8 (boat)
R(C-O)$_{break}$=0.229 nm	R(C-O)$_{break}$=0.232 nm	R(C-O)$_{break}$=0.237 nm	R(C-O)$_{break}$=0.231 nm
R(C-C)$_{form}$ =0.229 nm	R(C-C)$_{form}$ =0.233 nm	R(C-C)$_{form}$ =0.229 nm	R(C-C)$_{form}$ =0.234 nm

Figure 1. Transition state structures obtained by a kinetic study [34] (reproduced by permission of Elsevier).

2.2 Solvent Effects

A solvent used for a chemical reaction takes an important role in both mechanism and kinetics [35, 36]. An excellent review describing solvent effects on the Claisen rearrangement was published by Gajewski [36]. General comprehensive discussion of the solvent influence can be found in work written by Schmid [37].

Hughes and Ingold [38] seem to be the first who presented satisfactory qualitative explanation of solvent effects on reactivity by concept of an activated complex solvation. In other words [39], solvent effects on the rate constant depend on the relative stabilization of the reactant molecule and corresponding TS causing the activated complex solvation. For example, in protic (alcoholic) solvents the principle products of the photo-Claisen rearrangement are 2- and 4-allyl phenol and 3-allyl phenol is formed in very small amount [39]. However, in aromatic hydrocarbons or cyclohexane 3-allyl phenol is obtained in significant amount. But more profound effects lie in the field of kinetics. Hughes and Ingold stated that an increase in polarity causes an increase in reaction rate when the TS is more polar than the initial reagent and causes a decrease when it is less polar. There is more evidence that polar solvents accelerate the Claisen rearrangement [39–41]. The acceleration of the Claisen reaction with polarity increasing is evident on the base of data shown in Tab. 3 [40]. The data were obtained for the reaction
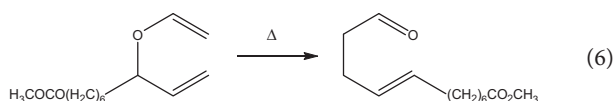

$$(6)$$

Table 3. Influence of solvents on rate constants for the Claisen rearrangement [40].

Solvent	$k \times 10^{-5}$ [s^{-1}]
CF_3CH_2OH	4.7
50 % H_2O-MeOH	3.6
25 % H_2O-MeOH	1.4
MeOH	0.72
25 % H_2O-DMSO	0.82
10 % H_2O-DMSO	0.50
C_2H_5OH	0.51
i-PrOH	0.42
MeCN	0.25
CH_3COCH_3	0.18
Benzene	0.17
Cyclohexane	0.084

For example, analysis of the experimental data suggests a rate enhancement at 75 °C in di-n-butyl ether of 9 and in water of ca. 1000 compared to the gas phase, leading to a barrier lowering of 1.5 and 4.7 kcal mol^{-1}, respectively, if the classical TS theory is used [41]. The effect of polar solvents on the rates of the Claisen rearrangements with special attention to assessment of ionic character was studied in [39]. A factor of 100 is given when going from the least polar (tetradecane) to the most polar (p-chlorophenol) for the *ortho*-Claisen rearrangement [42].

Not only polarity is responsible for the acceleration. It has been found long ago that the Claisen rearrangement acceleration can be caused by hydrogen bond formation [43–45]. Using quantum mechanical computational methods, Jorgensen [40] has developed a model to explain the aqueous acceleration of the Claisen rearrangement involving hydrogen bond interactions between two water molecules and the core heteroatom of the AVE in the optimized TS structure. It is worth to cite here in original wording of Rawal [45], stating that "hydrogen bonding by a simple chiral alcohol to a carbonyl group can accomplish what has previously been considered to be the domain of enzymes, catalytic antibodies and metal-based Lewis acids. These studies indicate the broad potential for hydrogen-bond catalysis in asymmetric synthesis".

Water is the most effective among hydrogen-bond forming solvents [46]. It was shown that the nonenzymatic rearrangement of chorismate to prephenate occurs 100 times faster in water than in methanol [47]. The rate acceleration in water comes from the hydrophobic effects and the hydrogen bond donating ability of water, increased hydrogen bonding of water to the TS [36].
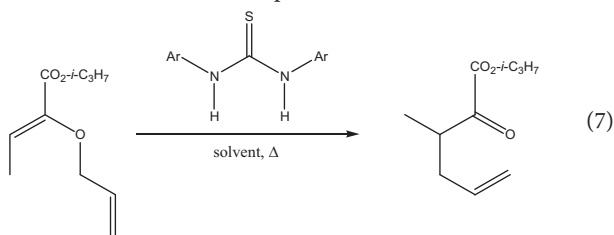
The simulations, Monte Carlo calculations and free-energy perturbation theory, have shown [48] that in the case of water, the rate enhancement is derived from the ability of the interfacial water molecules to stabilize a polar TS via enhanced hydrogen bonding at the oil/water interface. The position and orientation of the aromatic ethers at the interface are crucial factors affecting solvent accessibility during the reaction pathway. Computed solute-solvent energy pair and radial distribution functions show that the hydrophobic substituent of the solute provided more polar solvent environment than the hydrophilic substituent by tilting the reacting oxygen toward the water surface. Hydrophobic effects did not provide a substantial contribution in the lowering of the free energy activation barrier, less than 0.5 kcal mol^{-1}. Solvent polarizability via a polarizable force field was also found to be negligible in the observed rate accelerations. It was reported that an on-water environment, defined by the absence of water solubility of reactants, provide an increased rate acceleration, yield, and specificity compared to the case of organic solvents [48].

2.3 Catalytic Effects

The most important drawback of the Claisen rearrangement is the need for the relatively high temperature that is necessary to perform the reaction effectively. General way to overcome the drawback is to use a catalyst. An excellent review on catalysis in the Claisen rearrangement has been published [6]. Numerous substances such as transition-metal complexes, Lewis acids, Brønsted acids, bases, and water have been developed to catalyze the Claisen rearrangement and accelerate it [6].

Maruoka et al. [27, 49] have shown that the reaction rates of the AVE derivatives are increased in the presence of aluminum complexes. The catalyst on the basis of copper (II) complexes was also described [50]. A catalyst containing palladium metal has also been developed [51, 52]. The last reaction was found to proceed with involvement of the boat-like TS due to the coordination of palladium atom to both olefins. Metal-containing catalysts are generally able to enhance the rate of the Claisen rearrangement. However there are other very effective catalysts of organic nature.

Using quantum mechanical computational methods, Jorgensen has developed a model explaining the aqueous acceleration of the Claisen rearrangement involving hydrogen bond interactions between two water molecules and the core heteroatom of the AVE in the TS structure and used the obtained results to create new catalysts. Consistent with his hypothesis, compounds capable of dual hydrogen bonding such as ureas and thioureas were tested in Claisen rearrangement reactions and demonstrated modest rate accelerations when used in stoichiometric or super-stoichiometric amounts [53].
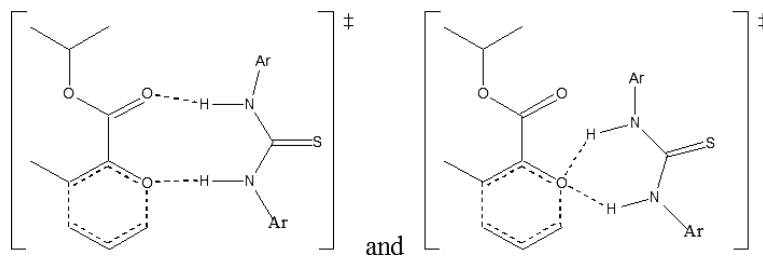

Figure 2. Calculated geometries of the thiourea-TS complex in the Claisen rearrangement [44b]. Reprinted with permission from [44b]. Copyright (2007) American Chemical Society.

A greater catalytic effect can be found for other complex forming compounds. The *N,N'*-diphenylguanidinium ion associated with the noncoordinating BArF⁻ counterion [54] is an effective catalyst for the Claisen rearrangement of a variety of substituted AVEs.
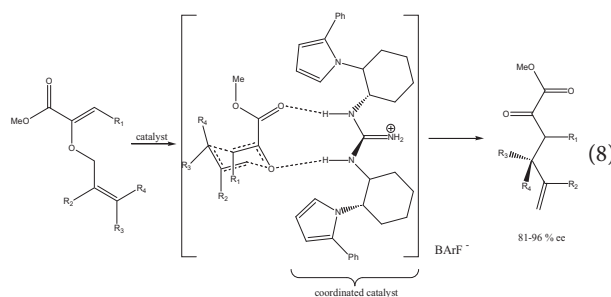
In this case it is possible to form quaternary *stereo*-centers having excellent diastereoselectivity and enantioselectivity. Catalytic Claisen rearrangements with high enantioselectivity of ester-substituted AVEs are found to take place when using the new C_2-symmetric guanidinium ion catalyst.

The promotion of the Claisen rearrangement of *ortho*-allyl α-ketoesters and induction of enantioselectivity through chiral arylpyrrole-substituted guanidinium ions was investigated by experimental and computational methods [55]. In addition to the stabilization of the developing negative charge on the oxallyl fragment of the TS by hydrogen-bond donation, evidence was obtained for a secondary attractive interaction between the π-system of the catalyst aromatic substituent and the cationic allyl fragment. The enantioselectivity across a series of substituted arylpyrrole derivatives varied as expected from the above. This mechanistic analysis led to the development of a new *para*-dimethylaminophenyl substituted catalyst which afforded improvements in enantioselectivity relative to the parent phenyl catalyst for a representative set of substrates.

where Ar = 2,5-$(CF_3)_2C_6H_3$.

Severance and Jorgensen [40] have described the Claisen rearrangement in the presence of thiourea supposed on the basis of DFT (density functional theory) calculation to be a potential organic catalyst. They observed slight reproducible rate accelerating effects shown in Tab. 4.

The authors have calculated the TS structures (shown in Fig. 2) with quantum chemistry methods [40].

2.4 Temperature Effects

The activation energies of the great majority of the classical Claisen rearrangements are in the range of 27.0–32.0 kcal mol⁻¹ [57a, 57b – 57e]. Some values are shown in Tabs. 1, 2, and 5. In addition, the activation energy of the classical Claisen rearrange-

Table 4. Influence of thiourea addition on the Claisen rearrangement effectiveness [40].

Solvent	thiourea concentration [mol %]	T [°C]	Time [h]	conversion [%]
CHCl₃	–	25	120	10
CHCl₃	20	25	120	17
CHCl₃	20	45	6	15
CF₃CH₂OH	–	25	120	41
CF₃CH₂OH	20	25	120	44
CF₃CH₂OH	–	45	6	41
CF₃CH₂OH	20	45	6	44
1,2-dichloroethane	–	25	5	7
1,2-dichloroethane	20	25	5	14

Table 5. Activation parameters of the Claisen rearrangement.

Ether name	Activation energy E_a [kcal mol^{-1}]	Pre-exponential multiplier A [s^{-1}]	Gibbs' free energy $\Delta G^{\neq}_{453.15K}$ [kcal mol^{-1}]	Reference
Allyl vinyl ether	30.6	5×10^{11}	33.3	[57a]
Allyl isopropenyl ether	29.3	5.4×10^{11}	31.9 ± 0.3	[57b]
1-Methylallyl vinyl ether	27.87	$1.0 \times 10^{11.32 \pm 0.03}$	31.0 ± 0.1	[57c]
2-Methylallyl vinyl ether	29.10 ± 0.17	$1.0 \times 10^{11.12 \pm 0.2}$	32.9 ± 0.2	[57d]
Allyl phenyl ether	31.6			[57e]

ment of APE was calculated by B3LYP/6-311 + G** calculation to be 35 kcal mol^{-1}, which is in good agreement with earlier reports [57f]. The activation energy values imply that elevated temperatures of up to 300 °C are crucial to achieve full conversion of APE in the Claisen rearrangement.

The use of high temperatures in the Claisen rearrangement allows to decrease reaction durability significantly. However, such processing is rather difficult to attain under conventional batch conditions and may deteriorate selectivity.

2.5 Pressure Effects

Another important physical parameter that can affect the reaction rate of the Claisen rearrangement is the pressure [58–62]. Typically, transformations that are accompanied by a decrease in volume (activation volume) are accelerated when pressure is increased.

It can be shown [58–62] that

$$RT \left(\frac{\delta \ln k}{\delta P} \right)_T = -\Delta V^{\neq} \tag{9}$$

Here, k is the reaction constant, P is the pressure, R is the Boltzmann's constant, T is the temperature, and $\Delta V^{\neq}$ is activation volume.

The Claisen rearrangements display a negative activation volume ranging from −13 to −6 cm^{3}mol^{-1} [60]. In the case of the Claisen rearrangement $\Delta V^{\neq}$ of AVE and allyl *para*-cresol ether in nonpolar solvents is −18 cm^{3}mol^{-1} and of allyl *meta*-methoxyphenyl ether in alcohol/water is −15 cm^{3}mol^{-1}. The Claisen rearrangement can be accelerated by elevated pressures since high pressure favors the cyclic TS [61].

3 Learning Lessons with the Same Impact Factors for Flow Chemistry

3.1 Beyond the Batch Process – Improvement Opportunities through Flow Processing

In the last decade, microreactor technology was much further developed and even applied on industrial scale [63], including the Claisen rearrangement [64–67]. It became almost a routine part of chemical reactor engineering. More and more chemists were attracted by the new synthesis tool since they discovered that it opens doors to new chemistries, in particular under harsh conditions. Novel process windows widened the synthetic possibilities and toolbox of the chemists [68–71]; adding chemical intensification to the prior developed transfer intensification. The term flow chemistry emerged.

A detailed benefit and potential analysis of microreactors and flow chemistry can be found in many reviews, see [63, 72–74]. For the purpose of this paper, it is useful to recall the main benefits in the following. High surface-to-volume ratios up to 10 000–50 000 m^{2}m^{-3} enable excellent heat and mass transfer rates [72] which constitute the transfer intensification. The heat exchange in microchannels is very efficient. Heat transfer coefficients reach values in the order of 10 kW m^{-2}K^{-1} [63, 67, 72]. The temperature of most reactions in flow has thus an even distribution avoiding local overheating. Yet there is a tendency to operate even quite exothermic reactions at highest concentration or solvent-free so that inevitably small hot spots are formed, yet in process windows inaccessible with conventional technology. Micromixers can mix on pilot- and industrial-scale level in some 100 ms and on laboratory-scale reach down to a few ms, if needed. This gives completely new opportunities to reactions which proceed on a time scale below one second such as ultrafast organometallic reactions like BuLi chemistry, Grignard, etc.

Enhanced heat and mass transfer can essentially inhibit side and diminish follow-up reactions, respectively [72, 75]. The substrate reaches the energy threshold of the reaction quickly after it flows into the heated part of the microchannel and quickly moves out from the part. Through very fast mixing, mixing and concentration masking, commonly known for ultrafast reactions, are absent. In this way, transient reactant excess environments are avoided which are known to foster multiple reactions. As a result, compared to traditional reaction systems, products contain fewer impurities and have higher yields and/or higher selectivity in flow [76–79]. The high reaction selectivity is often the result of precise residence and reaction time setting combined with the excellent heat exchange in flow. Most often, reaction and contact time are shortened in flow; often by several orders of magnitude.

A microreactor is also a closed system with small inventory. This leads to better handling of short-lived, sensitive species and intermediates which cannot tolerate at all effects of moisture and oxygen. Moreover, safe operation in process windows is possible which are not possible with conventional equipment. There are several industrial reports about further scaling-up of reactions in flow which were formerly stopped due to safety concerns [63].

With such background, the flow synthesis results are analyzed in the light of the same impact factors as done above for the batch syntheses, namely grouped into choice of substituent, solvent to carry out the reaction, catalyst added to activate the

reaction, imposed temperature, and pressure regime. These define novel process windows for the Claisen rearrangement [68–71].

Since flow processes have to be done at much shorter residence times than batch syntheses, the question of proper activation is to be addressed; in particular concerning relatively high values of the Claisen rearrangement activation energy. Yet, the new process windows are more than just a need to realize, they may provide new opportunities not seen before with batch technology. The temperature used should be quite high, up to 300 °C and more. Yet, other means of smart activation at lower processing temperature provides certainly an alternative to the use of high temperatures.

Such alternatives include

(i) use of a suitable catalyst;

(ii) noninertial ways to activate the process, such as microwave heating, photochemical initiating, vigorous mixing, localization of heating into a zone where the reaction really takes place;

(iii) use of elevated pressure taking into account negative value of activation volume.

Microreactors commonly facilitate the use of such alternative activation for a number of reasons and indeed such novel process windows were tested in flow [68–71]. The use of the microreactor or microfluidics concept might be considered as the simplest way to solve the shortcomings of the existing industrial realization of the Claisen-like processes [64–67, 80, 81].

While offering thus unique chances for reaction control, so far less effort has been made to couple microreactors to modern inline and online analytical tools, and to use them accordingly as dedicated tool to confirm theoretical chemistry considerations. This forced us to include descriptions of some ideas from chemical kinetics which seem to be useful to describe peculiarities of the Claisen rearrangement when applied in flow. The overall idea of using batch information to optimize flow chemistry and finally to find novel process windows in flow is given in Fig. 10 (see Sect.- 3.7). This is just following routine practice in our laboratories and all over the world. After such general discussion, now a summary about impacts on the Claisen rearrangement performed in flow as given above will be provided.

3.2 Substituent Effects

The yield of 2-allyl-4-chlorophenol in flow increases along with residence time to reach 37 % for 30 min at 200 °C [66]. The conventional batch mode of the Claisen rearrangement reaction gave only a yield of 14 %. Even comparatively small temperature increases have notable effect on the yield. The results obtained for other *para*-substituted phenyl allyl ethers are dependent on substituents and shown in Tab. 6.

It is evident from data shown in Tab. 8 (see Sect.- 3.4) that the yields in the flow mode are substantially larger than from the batch one and seem not
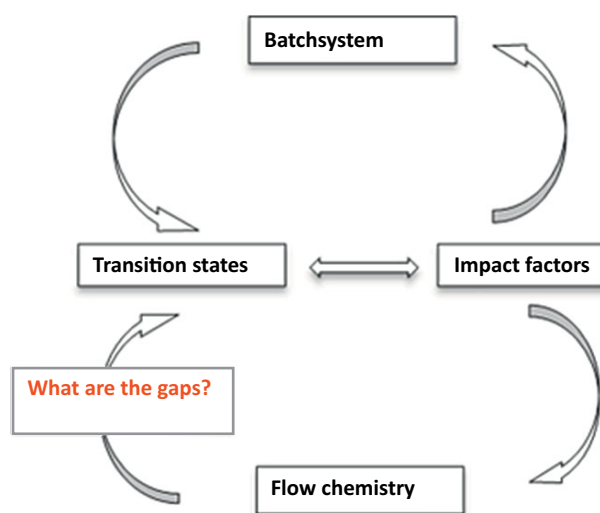

Figure 3. Links between the batch and flow chemistry for mutual optimisation and to widen the process window by flow operation.

to alter for different substituents as much as given in batch mode.

3.3 Catalyst Effects

As outlined earlier, various catalysts have shown great influence on the yield and selectivity in the case of batch reactor.

Table 6. Comparison of the microreactor and batch mode of the Claisen rearrangement in the case of *para*-substituted phenyl allyl ethers [66]. [a]For each substrate or solution of the solid substrate (5 mmol) the conventional reaction was performed in a reflux device at the same temperature for the reaction time of 3 h.

Substrate	Residence time [min]	T [°C]	Yield/ (%) Microreactor	conventional reaction[a]
p-chlorophenyl allyl ether	24	220	82	78
	36	220	83	–
p-methylphenyl allyl ether	24	200	69	34
	36	200	73	–
p-t.-butylphenyl allyl ether	24	225	94	83
	36	225	97	–
p-methoxyphenyl allyl ether	20	220	100	80
	24	220	100	–
p-phenylphenyl allyl ether	24	230	77	–
	24	240	90	71
p-cyanophenyl allyl ether	24	235	80	–
	24	245	93	69

Yet, the speeding-up effect of the desired reaction through using the catalyst may go along with making faster as well follow-up products as follows. It is known from batch synthesis that the primary Claisen product allyl phenol (from APE) can react further to the corresponding furan by cyclization when the reaction is carried out in an inert solvent such as 1,1,2,2-tetrachloroethane (TCE) or phenyl rings, from decomposition of the Claisen reactant, added to the double bond when it was carried out in a reactive solvent such as benzene or toluene, as given below [82], see also [83].

(10)
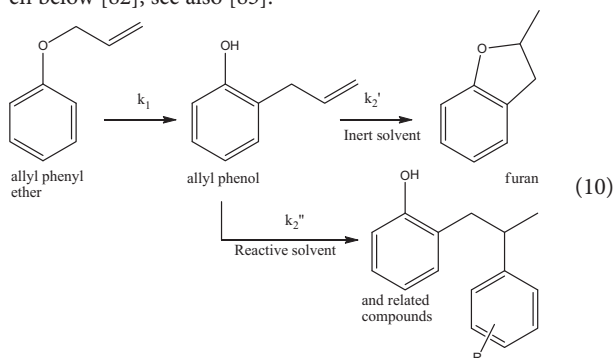
The kinetic constants for these three reactions were determined in toluene and terachloroethane (see Tab. 7) [82]. Despite the solvent, they vary considerably with increasing temperature leading to the advantage of obtaining the allyl phenol as the desired product. Indeed, at high temperatures in flow, there is much profitable situation compared to the batch study [82], and hardly any furan cyclization or other follow-up product was found [64]. This is probably partly due to the strong reduction in residence time which allows (partly) cutting off the follow-up products formation which emerge on a later time scale than the desired (intermediate) product.

With such motivation, it was aimed to investigate the effect of Lewis acids on the overall and individual kinetic rates as given above for the same reaction [84]. APE, 0.5 M in ethanol, was converted using a microcapillary (ID: 500 µm; length: 10 m) operated at temperature of 240 °C and pressure of 125 bar. BF$_3$ was the Lewis catalyst used at 10 % concentration. The results are given in Fig. 4.

Indeed, a considerable activation boost is given when increasing the residence time which achieves almost 60 % and 100 % conversion in less than 4 and 20 min, respectively [84]. Yet, the furan is the main product and virtually no allyl phenol was formed (not shown here). Even variation of the solvent to butanol, benzonitrile, or acetonitrile did not change the situation. Thus, it can be concluded that the use of the BF$_3$ Lewis catalyst led to reaction acceleration towards allyl phenol, but
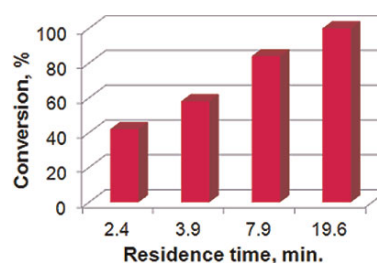

Figure 4. Conversion vs. residence time for the Claisen rearrangement of phenyl allyl ether to allyl phenol in flow at 240 °C and 125 bar using BF$_3$ Lewis catalyst (10 % in ethanol) [84].

even to more promoted conversion of the product to furan by subsequent cyclization. Albeit processing was made at high temperature, a product pathway preference just opposite to the noncatalytic high-temperature processing was found.

3.4 Solvent Effects (Including Reaction Environment)

Due to their small internal volumes, flow reactors do not need the presence of a solvent for filling reasons or as dilution media to control potential exothermic heat releases. Thus, solvent-free or high-concentration operation is quite common. New tailored, innovative solvents such as ionic liquids, supercritical fluids, and fluorous solvents offer many new possibilities for enhancing the reaction environment influence, especially when combined with the process control provided by flow reactors. A particular important point is that solvent selection for high temperature windows is not restricted anymore by the solvent's boiling point and low-boiling solvents can be used at the desired high temperature [64].

Following these lines, the Claisen rearrangement of APE to *ortho*-allyl phenol (*o*-AP) was performed in subcritical water (SCW) [65, 85]. In a solvent-free conventional method, *o*-AP was produced with 85 % yield at 220 °C, ambient pressure, and at a reaction time of 6 h. While in a similar batch process, but using SCW, the yield of *o*-AP was 84 % in addition to shorter reaction time of 10 min at 240 °C and 3.4 MPa. The comparison of these two methods with the microreactor case is shown in Tab. 8 [65].

The reaction time in the flow reactor is further decreased to about 2.5 min, while the yield is still notably further increasing. This example shows clearly how the combination of tailored solvent and flow reactor can lead to the opening of a new process window with increased intensification. This approach is

Table 7. Comparison of activation energies (AE) und kinetic constants (k) for the Claisen rearrangement of phenyl allyl ether to allyl phenol in two different solvents and for different temperatures; TCE: trichloroethylene [82].

Solvent	AE of k_1 [kcal mol^{-1}]	AE of k_2' [kcal mol^{-1}]	AE of k_2'' [kcal mol^{-1}]	k_1 [h^{-1}] at			k_2' [h^{-1}] at		
				70 °C	90 °C	110 °C	70 °C	90 °C	110 °C
Toluene	30	12.9	20.8	0.11	5.65	11.43	0.08	0.37	0.94
TCE	18.2	14.1	–	0.19	0.74	3.69	0.24	0.33	0.89

Table 8. The Claisen rearrangement in subcritical water (microreactor mode) [65].

Solvent	Concentration [mol kg⁻¹]	Temperature [°C]	Pressure [MPa]	Reaction time [s]	Selectivity [%]	Yield [%]
None	6.90	265	5	360	68	37
Subcritical water	0.77	265	5	81	74	73
Subcritical water	0.27	265	5	149	98	98

tored in flow reactors over the full range of temperatures studied. Solvent-free reaction conditions were feasible for the Claisen rearrangement and provided quantitative yields of the target product at 280 °C and 100 bar. The use of high pressure enables the superheated processing giving the base for the use at high temperature. Pressure gives also its own intensification when temperature is kept constant. Yet, it has to be questioned if thermal expansion and pres-
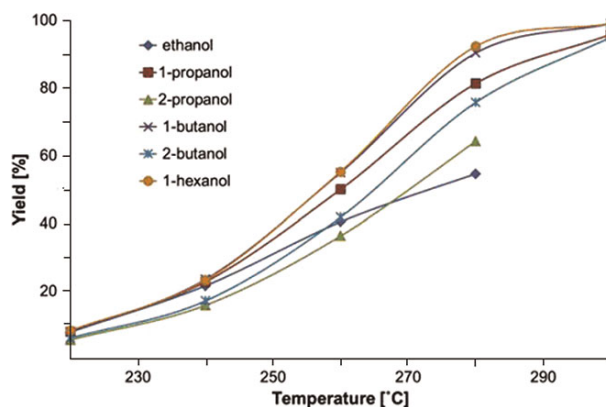
considered environmentally benign and is useful for the green organic synthesis [65].

Additionally, Kawanami et al. [85] used high-pressure, high-temperature (HPHT) water as a solvent in microreactor to produce *ortho-* and *para-*allyl phenol (Fig. 5). The study shows that HTHP water plays a significant role as a catalyst to speed up the reaction by transferring a proton with locally created hydrogen bond with substrate. In this study, the same results as the ones mentioned under the same conditions [65] were produced. Moreover, by substituting an electron donating group like a methyl group at *ortho-* and *para-*position of APE, the conversion over > 95 %, compare to only APE with no substituent, were achieved in lower reaction temperature (210 °C).

A comprehensive investigation of process windows in flow was done, comprising the investigation of high temperature, high pressure, high concentration, and solvent effects on the Claisen rearrangement and the Johnson-Claisen rearrangement [64]. The use of high temperature enabled in all experiments to have a sufficiently fast reaction rate. In a solvent screening study, 1-butanol was the optimal reaction solvent for this transformation in flow (Fig. 6). The study shows also how even smart differences in the solvents used, as, for example, in the case of different isomers (1- and 2-propanol), can be moni-

Figure 6. Influence of solvent and temperature on Claisen rearrangement of APE. Reaction conditions: 0.1 M allyl phenyl ether in solvent, 100 bar, 4 min residence time, benzonitrile as internal standard. [64] (reproduced with permission of Elsevier).

sure-related compression phenomena at such harsh reaction conditions are not partly or completely to be the cause of the effect found. These phenomena can lead to deviations of the desired residence time. Indeed in [64], a clear impact of the observed reaction trends is achieved. High-temperature operation in flow was also feasible for the Johnson-Claisen rearrangement of cinnamyl alcohol. Quantitative yields were obtained at 200 °C and at 100 bar.

In view of what has been presented above, it should be noted that there is a nonconsistency between the close match of dielectric constants, polarities, and hydrogen bond formation ability of ethanol and *n*-butanol and shown large difference in reactivity. The point is that the new windows opened by flow chemistry influence still upon other properties which may control the Claisen rearrangement effectiveness, see Sect. 3.1. Firestone and others [86] have observed an increase of the reactivity in solvents of different viscosity. At 130 °C, the relative rates of the Claisen rearrangement of APE are 1.00, 0.98, 1.13, and 1.36 in *n*-octane, iso-octane, *n*-octacosane, and Nujol, whose
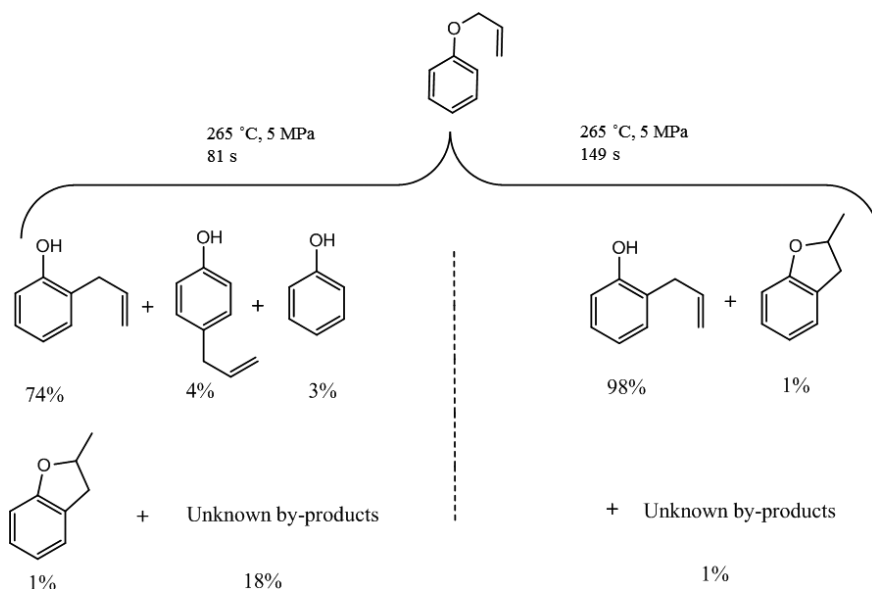

Figure 5. The Claisen rearrangement products of APE in HTHP water [85] (reproduced with permission of Elsevier).

relative viscosities at 100 °C are 1.00, 0.94, 4.92, and 11.8, respectively. Addition of polyethylene to the Nujol raises the relative viscosity to 48.5 and relative rate to 1.70. The latter means that there is a marked influence of the reagent molecules mobilities on their reactivities in the Claisen rearrangement.

Complexing and chelating agents can provide anisotropic reaction environments (microcavity) within solvents and consequently can (significantly) alter the product distribution. The photo-Claisen rearrangement of APE in water solutions containing β-cyclodextrin leads to *para-* and *ortho*-allyl phenols and phenol as main products [87]. The quantum yield for the APE forming a complex with β-cyclodextrin is different for free APE, being higher for *ortho*-product, almost the same for the *para*- product and lower for phenol. The *ortho*-selectivity remained the same in the photolysis of APE-β-cyclodextrin complex in the solid state.

Yet, even in the presence of a microcavity agent, the solvent itself still can play a role. In the presence of zeolite NaY, the *ortho*-to-*para* ratio in the photochemical Claisen-like rearrangement was different in the case of nonpolar (hexane) and polar (methanol) solvent and in hexane. In all cases, the *ortho*-isomer prevailing over *para*-isomer.

3.5 Temperature Effects

The use of high temperatures in the Claisen rearrangement allows to reduce the reaction times significantly. Such processing is rather difficult to attain under batch conditions. In contrast, the combination of sealed microreactor technology and back pressure regulators provides opportunities to heat the reaction

mixture far above the boiling point of the solvent. Consequently, solvent selection for high temperature novel process windows is not restricted anymore by the solvent's boiling point [64, 88].

Razzaq et al. applied the high-temperature/pressure flow system to perform the Claisen rearrangement of APE [88]. In addition, the high-temperature/pressure flow system allowed them to study this rearrangement in low boiling point solvents in or near their supercritical state (Fig. 7).

In contrast to observations under batch conditions, the best results are obtained in flow mode with longer chain alcohols. Based on experimental data, Kobayashi et al. [64] have calculated the activation energies for the Claisen rearrangement and these values follow the same reaction order as observed in batch: ethanol > 1-butanol > 1-hexanol. Yet, the sequence could reflect also the different thermal expansion of the solvents [66].

Microwave (MW) heating provides an alternative to the fluidic microreactor heating [89, 90]. Damm et al. [91] made a comparison between batch MW and conventionally heated flow scale-up protocols for three selected model reactions. Compared to a standard MW batch reactor, higher temperatures and pressures can be attained in a microreactor, therefore allowing further significant process intensification [91]. Conventional processing at the reflux temperature of the solvent requires reaction times of ca. 2–3 days for the Diels-Alder reaction in toluene at 110 °C. Using sealed vessel MW heating on a small scale (2 mL) at up to 270 °C, these reaction times could be reduced to a few seconds or minutes [91].

The space-time yields obtained with the continuous flow reaction system were significantly higher, up to a factor of 80, than those resulting for the batch experiments. Therefore,
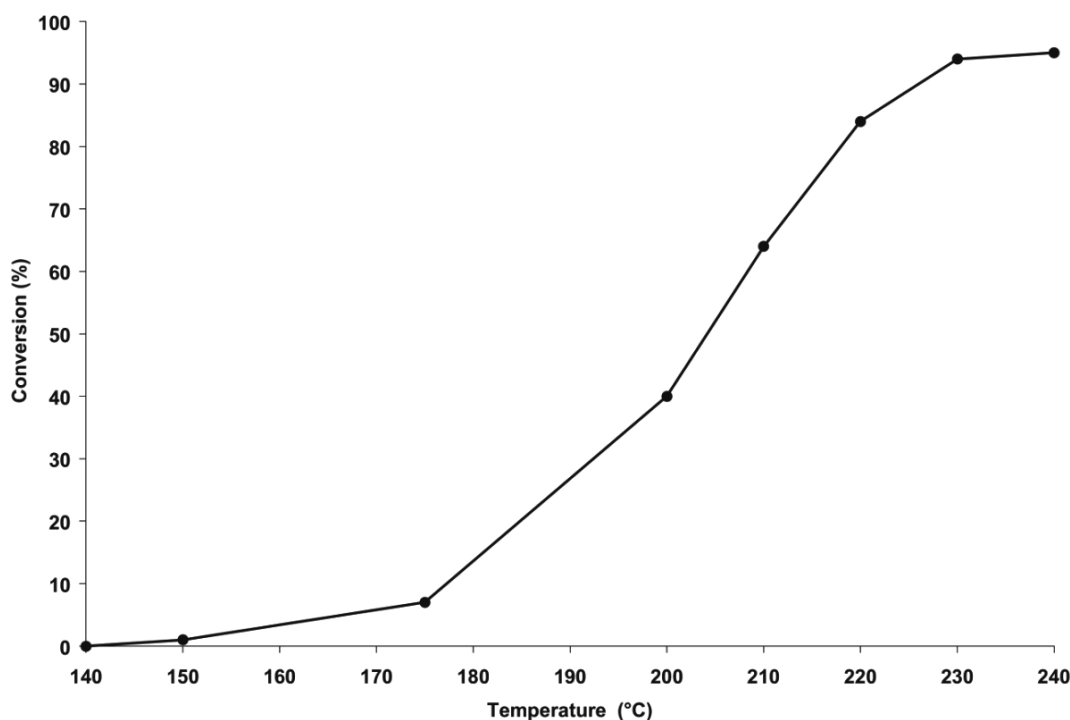

Figure 7. Temperature effect on the Claisen rearrangement of allyl phenyl ether under continuous flow conditions: 100 bar, 1.0 mL min^{-1} flow rate, 4 mL coil, 4 min residence time [88] (reproduced with permission of Elsevier).

high-temperature/pressure flow processing has significant potential for the manufacturing industry. At the same time, it needs to be emphasized that not all chemical transformations can be executed at these extreme conditions [91].

Scaling in the MW-assisted protocols require a reasonably strongly MW absorbing reaction medium in order to allow efficient heating by dielectric mechanisms [92]. When the absorption of the solvent/reaction mixture is low, scaling of the MW processing becomes difficult.

Moseley et al. [92] applied an automated stop-flow microwave to six pharmaceutically relevant-reactions. One of the chosen reactions is *ortho*-Claisen rearrangement of 1-(2-methylallyloxy)naphthalene and thereafter closure subsequent ring to the benzofuran (Fig. 8). Accordingly, the Voyager stop-flow microwave could reach 95 % conversion and throughput of 60 g h^{-1} after 12 min holding time and cycle time of 21 min. By scaling up, and performing 48 batches in the same cycle time, 1.44 kg of product could be gained on a daily basis.

Figure 8. Photograph of the stop-flow Voyager [92] (reprinted with permission from [92]). Copyright (2008) American Chemical Society.

Moreover, in another work, Moseley et al. [93] presented results of the same above mentioned reactions in a continuous flow microwave reactor. Results are shown in Tab. 9.

There is a less dangerous and often higher efficient alternative to the MW heating, using a changing magnetic field. Kirschning et al. have used a microreactor packed with iron oxide magnetic nanoparticles [94]. These nanoparticles generate heat when they are exposed to a constantly changing magnetic field (25 kHz). The nanoparticles are coated with silica to prevent degradation and to enable easy chemical derivatization of the nanoparticle surfaces for their enhanced reaction capabilities. One of their model reactions was the Claisen rearrangement. The flow synthesis was performed at 170 °C by the nanoparticles and gave 85 % yield of the product. Only 62 % yield was obtained by conventional heating.

3.6 Nonthermal Activation Effects: Photochemistry

Maeda et al. compared the batch and flow variant of the Photo-Claisen rearrangement [67]. In the batch process, irradiation of a benzene solution containing 2-[(2,4,6-trimethylphenoxy)-methyl]-1-(methoxycarbonyl)naphthalene carried out for 8 h, led to the formation of the cyclohexa-2,4-dienone derivative (22 %) as the photo-Claisen-type rearrangement product along with the *meta*-rearrangement product (19 %), 1-methoxycarbonyl-2-methylnaphthalene (9 %), and the dimeric product 1,2-bis[1-(methoxycarbonyl)naphthalen-2-yl]ethane (12 %). When the same photoreaction was carried out using a flow reactor (0.03 mL h^{-1}), 75 % conversion of the initial compound was achieved in 2.2 min residence time. The quantum yield in photochemical flow reactors is generally much higher than in batch owing to the small illuminated dimensions. No deeper penetration can be achieved in a batch reactor despite its large volume which means that the major part of the volume is unaffected feed tank which needs to be continuously transported to the outer shell by stirring where activation is possible. In addition, the products formed include cyclohexa-2,4-dienone derivative (33 %), the *meta*-rearrangement product (25 %), and 1,2-bis[1-(methoxy-carbonyl)naphthalene-2-yl]ethane (3 %). The reaction time was dramatically shortened in comparison with that using the batch system and the yield of the cyclohexa-2,4-dienone derivative increased, while the formation of 1-methoxycarbonyl-2-methylnaphthalene and 1,2-bis[1-(methoxycarbonyl)naphthalene-2-yl] ethane was suppressed. A further increase in the cyclohexa-2,4-dienone derivative/*meta*-rearrangement product ratio was brought by increasing the flow rate to 0.04–0.05 mL h^{-1}.
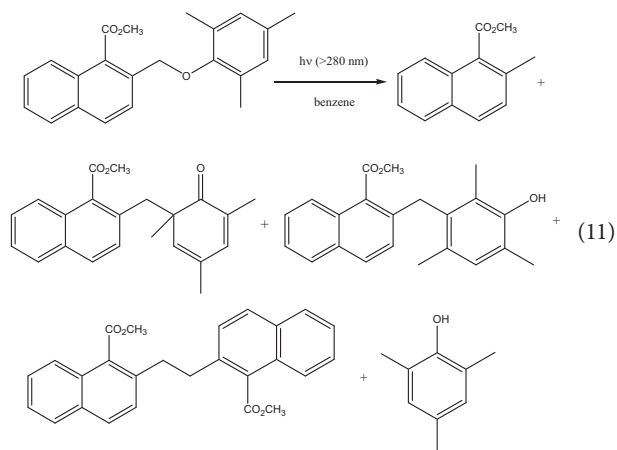

(11)

Table 9. Summary of the reaction data [93].

Reaction	Temperature [°C]	Residence time [min]	Flow rate [mL min^{-1}]	Concentration [L kg^{-1}]	Productivity [mol h^{-1}]
Claisen rearrangement	195	13.3	15	0.5	3.0

Maeda et al. proposed that a radical pair plays the key role in the mechanism of the flow photo-Claisen rearrangement [67]. Both in-cage and out-of-cage radical reactions contribute much to the final mixture of products. A *meta*-rearrangement product is formed by a secondary reaction. The high conversion and selectivity obtained are attributed to more efficient light absorption in thin layers [67] and the suppression of the secondary reactions. Fig. 9 explains the last hypothesis: the primary photoproduct formed in the flow system is quickly removed from the irradiated area, and as a result, the formation of a secondary product is diminished.

3.7 Pressure Effects

As mentioned in Sect. 3.5, the Claisen rearrangement was performed at high temperature/pressure, very close to the critical conditions for the solvent. With EtOH as a solvent and at a reaction temperature of 280°C, the Claisen rearrangement was executed at varying pressures between 75 and 200 bar [88]. Essentially, no significant dependence of the conversion on the pressure was observed (Fig. 10).

However, using another solvent and at still higher pressure, some slight pressure effects were observed by Kobayashi et al., as the reaction time was reduced [64, 95]. In the pressure range from 50 to 300 bar, the yield for the Claisen rearrangement was enhanced from 52 to 67 % (Fig. 11) and further increase could be expected once high pressures can be achieved in a micro-reactor. In addition, it was observed that the reaction is enhanced by the use of protic solvents, probably due to the catalyzing effect of hydrogen bonding.

In Sect. 2.5 an equation is given which describes the pressure dependence of the reaction rate to be related to the partial molar volumes in the standard state between the transition state and the reactants. Thus, reactions with volume compression are enhanced under higher pressure, while dissociative processes are restricted by increasing pressure. In the Claisen rearrangement reaction cyclic intermediates are proposed where atoms of the reactant are more closely packed. The volume difference between the partial molar volumes of reactants and products is usually determined experimentally from the pressure dependence of the rate constants. Most association reactions and bond cleavage mechanisms account for –10 and 10 cm^{3}mol^{-1} in volume change, respectively [96].

In general, the activation volume is the basic piece of information to identify the structure of the transition state and to clarify the reaction mechanism. This knowledge can be of great practical importance. Whenever a reaction can develop along different pathways associated to transition states with distinct activation volumes, the pressure variable offers the opportunity to control the selectivity of the reaction. This is also the case, when the reaction proceeds as a multistep process and the pressure has a different effect on the various intermediates. Pressure increase will favor reaction pathways corresponding to more negative activation volumes.

A further material- and nonreaction engineering-based explanation of the pressure influence is provided by the dependence of viscosity on pressure. Pressure increases the viscosity of liquids in an exponential manner [97].

$$\eta = \eta_0 \exp(\gamma p) \tag{12}$$

where, γ is the pressure coefficient, for the majority of organic solvents at 25 °C the pressure coefficient is 3–6$\times 10^{-4}$ bar^{-1}; p is the pressure in bar, and η and η_0 are the viscosity at pressure p and $p_0 = 1$ bar. The Claisen rearrangement shows a viscosity-related acceleration at elevated pressures [97].

A third explanation is based on the volume compression of liquids under pressure. Although liquids are generally considered as incompressible fluids, at the elevated pressures and temperatures employed in this study, this simplification is no longer valid (Fig. 12). It is therefore difficult to attribute the increase in yield exclusively to pressure effects and one must take into account that part of the yield increase is due to prolonged reaction times. There exists a significant difference in residence time of almost 30 s between the experiments performed at 50 and 300 bar (Fig. 12) [64].

3.8 Concentration Effects

Being a unimolecular reaction, it is not surprising not to observe strong concentration effects on the Claisen rearrangement yield (Fig. 13) [64]. Yet, solvent-free processing can make considerable difference to high-concentration solvent processing which is likely to be caused by the difference in the reaction medium parameters such as dielectric constant and viscosity. For solvent-free processing, reactant and product provide the reaction medium.

Figure 9. Schematic explanation of the difference in product selectivity observed between batch and flow reactors [67] (reproduced with permission of Springer).

3.9 Reaction Time Effects

Long exposure times of reaction mixtures at high temperatures in batch reactions are problematic and may cause the formation of many impurities. Shortening of re-
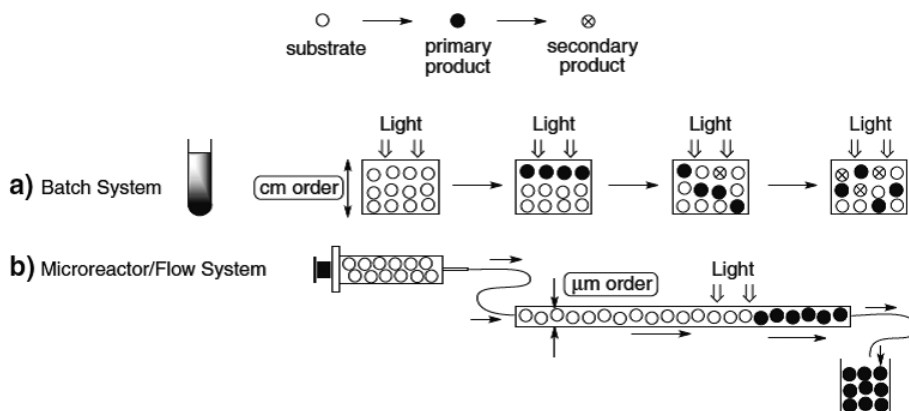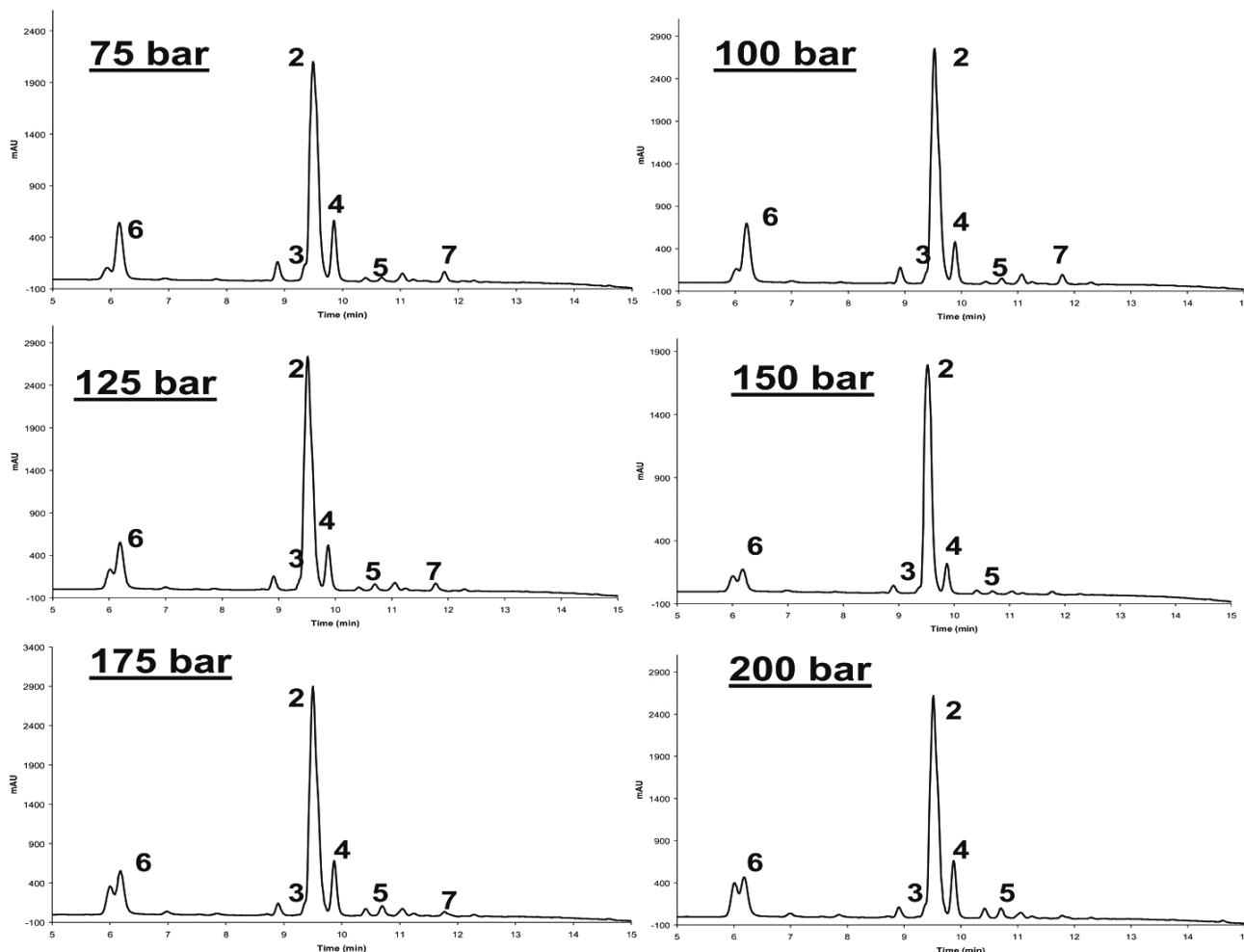
Figure 10. HPLC-UV results of the Claisen rearrangements of allyl phenyl ether (1) in EtOH (0.1 M) at different pressures, 280 °C, 1 mL min⁻¹ flow rate [88] (reproduced with permission of Wiley-VCH).
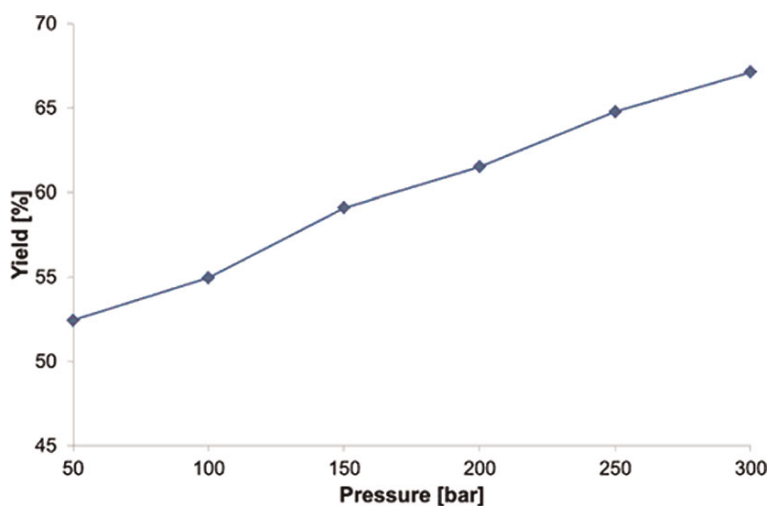

Figure 11. Influence of pressure on the Claisen rearrangement of allyl phenyl ether. Reaction conditions: 0.1 M allyl phenyl ether in 1-butanol, 260 °C, 4 min residence time, benzonitrile as internal standard [64] (reproduced with permission of Elsevier).

action time through using high reaction temperatures is a way to achieve high selectivity, while not comprising the conversion. Often, flow processing is mandatory for this [66]. To find the minimal needed kinetic reaction time, simple flow rate variations give the first idea. Kong et al., however, varied the residence time at fixed flow rate by processing at different reactor lengths and found that the yield of the Claisen rearrangement in a microreactor is affected by the flow rate (see Fig. 14) [66].

For the lower flow rate higher yields at all fixed residence times were found [63]. The difference in yield between the two flow-rate settings decreased, while the residence time increased.
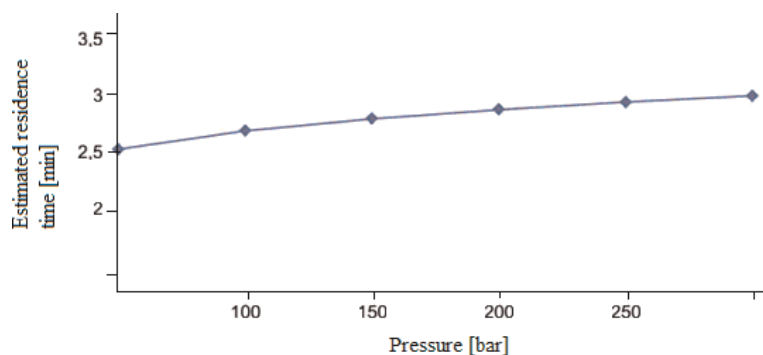
Figure 12. Estimated residence time at elevated pressures for 1-butanol [64] (reproduced with permission of Elsevier).
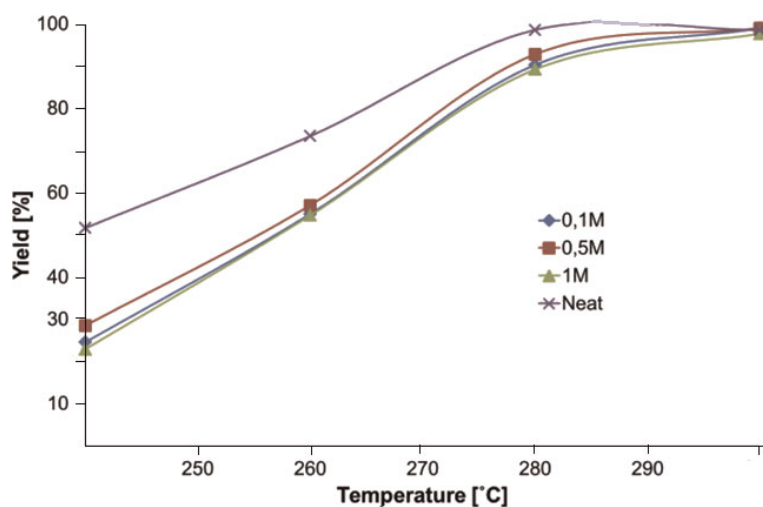

Figure 13. Influence of reactant concentration on the Claisen rearrangement of allyl phenyl ether. Reaction conditions: 1-butanol or solvent-free, 100 bar, 4 min residence time [64] (reproduced with permission of Elsevier).
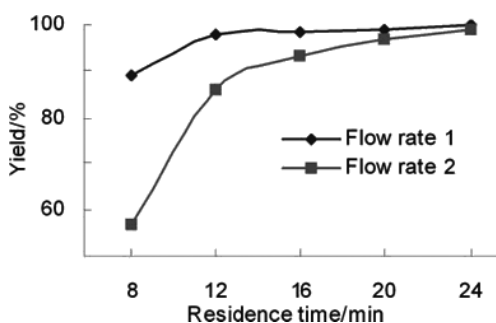

Figure 14. Effect of flow rate on the yield of reaction of allyl 4-methoxyphenyl ether at 220 °C (flow rate 1 = 0.06 mL min^{-1}; flow rate 2 = 0.12 mL min^{-1}) [66] (reproduced with permission of Royal Society of Chemistry).

4   Conclusions and Outlook

During more than 100 years development of the Claisen rearrangement, it became a well-known synthetic method with several applications. Among other causes, an even wider applica-

tion in industry is certainly somewhat hindered by the need to process at elevated temperature, while still needing very long residence time. In flow processing, such high-temperature processing is standard and the reaction times are much shorter. The match between synthesis and processing seems to be better in flow processing. Further, flow processing offers additional unique chances through reaction integration – a first flow reaction can synthesize a product which then can be directly used as reactant for a second flow-based Claisen rearrangement. This flow coupling leads to a widening of the synthetic space. A separate report on this issue will follow soon.

Beyond its synthetic power, the Claisen rearrangement is among the best fundamentally investigated reactions. This was done over decades with the means of classical reaction engineering/kinetic investigations and physical chemistry. This provided with time considerable insight into reaction mechanisms and revealed their transition states; yet often on heuristic basis and with (many) differing and even conflicting statements in literature which cannot further be resolved and elucidated. Since recently, theoretical/quantum-mechanical chemistry and modern analytical techniques add more detailed and firm evidence of the proposed mechanism. Here, a basis is laid to resolve conflicting assumptions. Direct proofs of existence of intermediates (and thus finally proposed respective transition states) are now possible.

Thus, the Claisen rearrangement shows nicely how far theoretical investigations are possible and also what cannot be resolved even today. Such deep knowledge is not available throughout many organic reactions done in batch; even for those generally used. Opposite to that, there is, to our best knowledge, no use of theoretical/quantum chemistry and physical chemistry approaches in flow chemistry. This seems to leave significant unreleased potential since small flow reactors have many advantages which allow to gather more and more reliable and previously not accessible data which can validate or further develop theories and assumptions in reaction mechanisms. This is, among others, due to fast response times, fast processing times, coupling with fast (real-time), on-line analytics.

While this has not been exerted so far for the Claisen rearrangement in flow processing, the authors are working towards reporting on this in the future, a simple juxtaposition of impact factors known from batch and flow processing can give first insight on how sensitive and predictable the flow process reacts on process settings and which process windows it opens for future mechanistic investigations. The power of the latter have been reported in detail in the first review [98] of this two-part compilation. To summarize what has been presented throughout this review, the latter were grouped with regard to the mechanistic and transition-state analysis. Tab. 10 contains a comparison of process windows for old and novel processing of the Claisen rearrangement (modified variant of the table shown in [43]).

Table 10. Comparison of known and novel process windows for the Claisen rearrangement.

Process Window	Batch-based (known) results	Flow-based (novel) results
High temperature	Medium conversion at 300 °C	Full conversion at 300 °C
High pressure	Invariant and kept at ambient pressure (1 atm)	15 % yield increase by increasing pressure from 50 to 300 bar
Increased concentration/Solvents	1. Selectivity losses for high-concentration and solvent-free processing 2. Solvents are commonly processed up to boiling point and at ambient pressure	1. High selectivity for high-concentration and solvent-free processing 2. New solvation properties accessible, e.g., for 1-butanol at high-temperature 3. Solvent-free conditions result in full conversion at 280 °C
Safety	Limits in usage of high temperatures and pressures	Safe high-pressure and high-temperature processing
Process integration	Claisen rearrangements make use of the (limited range) of commercially available products	Coupled two-step flow syntheses in an easy manner and without intermediate production isolation = increased chemical diversity

Acknowledgment

The authors have declared no conflict of interests.
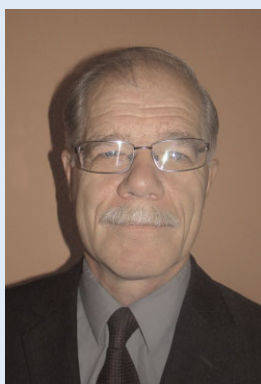
Sergei V. Zelentsov graduated from Gorky State University and received his Ph.D. (1990) and Dr. of Sci. (1999) under the supervision of Prof. Olei-nik. His works and dissertations were devoted to experimental and theoretical researches of photochemical reactivity in systems with low mobility of reagents, quantum chemical studies of photochemical reactions, photolithography, and azide and nitrocompound photochemistry. He is a Professor at the Lobachevsky University in Nizhny Novgorod and Head of the Photochemistry and Spectroscopy Chair. His current research interests include the development of novel methodologies of photochemical oxidations, quantum chemical modeling of chemical reactivity, photolithography, and studying the reactivity in the flow chemistry conditions.

Volker Hessel studied chemistry at Mainz University (Ph.D. in organic chemistry, 1993). In 1994 he entered the Institut für Mikrotechnik Mainz GmbH (1996: group leader microreaction technology). In 2002, Prof. Hessel was appointed Vice Director R&D at IMM and in 2007 as Director R&D. In 2005 and 2011, he was appointed as part-time and full professor at Eindhoven University of Technology, respectively, for the chair of Micro Flow Chemistry and Process Technology. Prof. Dr. Hessel is (co-)author of more than 270 peer-reviewed publications, with 18 book chapters and 8 books. He received the AIChE award Excellence in Process Development Research in 2007 and in 2010 the ERC Advanced Grant Novel Process Windows.

Elnaz Shahbazali studied chemical engineering at the University of Tehran from 2000–2005 and received her M.Sc. in Chemical Engineering from the Sharif University of Technology in 2008. She then moved to Eindhoven University of Technology and performed PDEng. (Professional Doctorate Eng.) program for two years. Next, in 2012, she started her Ph.D. at Eindhoven University of Technology in the research group of Prof. Volker Hessel in Chemical Engineering. Her research interest is mostly focused on organic synthesis in flow chemistry.

Timothy Noël received his M.Sc. degree (Industrial Chemical Engineering) in 2004 and his Ph.D. from the University of Ghent in 2009. After moving to the Massachusetts Institute of Technology as a Fulbright Postdoctoral Fellow, where he worked at the Novartis Center for Continuous Manufacturing, he accepted a position as an Assistant Professor at Eindhoven University of Technology in 2012. He received an Incentive Award for Young Researchers from the Comité de Gestion du Bulletin des Sociétés Chimiques Belges in 2011 and a Veni grant from the Dutch Government (NWO) in 2012. He was nominated for the European Young Chemist Award in 2012. His research interests are focused on the combination of flow chemistry, organic synthetic chemistry and catalysis.

References

[1] A. M. M. Castro, *Chem. Rev.* **2004**, *104*, 2939–3002.

[2] J. Rehbein, M. Hiersemann, *Synthesis* **2013**, *45 (9)*, 1121–1159.

[3] F. Galindo, *J. Photochem. Photobiol.*, C **2005**, *6 (2–3)*, 123–161.

[4] B. Ganem, *Angew. Chem., Int. Ed. Eng.* **1996**, *35 (9)*, 936–945.

[5] I. Iwakura, Y. Kaneko, S. Hayashi, A. Yabushita, T. Kobayashi, *Molecules* **2013**, *18*, 1995–2004.

[6] K. C. Majumdar, S. Alam, B. Chattopadhyay, *Tetrahedron* **2008**, *64*, 597–643.

[7] S. J. Harris, D. Murdock, Y. Zhang, T. A. A. Oliver, M. P. Grubb, A. J. Orr-Ewing, G. M. Greetham, I. P. Clark, M. Towrie, S. E. Bradforth, M. N. R. Ashfold, *Phys. Chem. Chem. Phys.* **2013**, *15*, 6567–6582.

[8] I. Iwakura, *Phys. Chem. Chem. Phys.* **2011**, *13*, 5546–5555.

[9] P. C. Becker, R. L. Fork, C. H. Brito-Cruz, J. P. Gordon, V. Shank, *Phys. Rev. Lett.* **1988**, *60*, 2462–2464.

[10] R. A. Mathies, C. H. B. Cruz, W. T. Pollard, C. V. Shank, *Science* **1988**, *240 (4853)*, 777–779.

[11] A. Stingl, R. Szipöcs, C. Spielmann, F. Krausz, *Opt. Lett.* **1994**, *19 (3)*, 204–206.

[12] J. Zhou, C.-P. Huang, C. Shi, M. M. Murnane, H. C. Kapteyn, *Opt. Lett.* **1994**, *19 (2)*, 126–28.

[13] A. Baltuska, Z. Wei, M. S. Pshenichnikov, D. A. Wiersma, *Opt. Lett.* **1997**, *22*, 102–104.

[14] T. Kobayashi, T. Saito, H. Ohtani, *Nature* **2001**, *414*, 531–534.

[15] T. Saito, T. Kobayashi, *J. Phys. Chem. A* **2002**, *106 (41)*, 9436–9441.

[16] S. J. Schmidtke, D. F. Underwood, D. A. Blank, *J. Am. Chem. Soc.* **2004**, *126*, 8620–8621.

[17] T. Kobayashi, Y. Kida, *Phys. Chem. Chem. Phys.* **2012**, *14 (18)*, 6200–6210.

[18] A. Baltuška, T. Fuji, T. Kobayashi, *Opt. Lett.* **2002**, *27 (5)*, 306–308.

[19] J. Jung, S. Re, Y. Sugita, S. Ten-no, *J. Chem. Phys.* **2013**, *138 (4)*, 044106-1–044106-10.

[20] F. Neese, A. Hansen, F. Wennmohs, S. Grimme, *Acc. Chem. Res.* **2009**, *42 (5)*, 641–648.

[21] H. B. Schlegel, *J. Comput. Chem.* **2003**, *24*, 1514–1527.

[22] M. R. A. Blomberg, P. E. M. Siegbahn, *Biochim. Biophys. Acta* **2010**, *1797*, 129–142.

[23] N. Moghadam, S. Liu, S. Srinivasan, M. C. Grady, M. Soroush, A. M. Rappe, *J. Phys. Chem. A* **2013**, *117*, 2605–2618.

[24] P. J. Silva, M. J. Ramos, *Int. J. Quant. Chem.* **2011**, *111 (7–8)*, 1472–1479.

[25] J. H. Jensen, *Molecular Modeling Basics*, CRC Press, Boca Raton, FL **2010**, 189.

[26] M. Saeys, M.-F. Reyniers, J. W. Thybaut, M. Neurock, G. B. Marin, *J. Catal.* **2005**, *236*, 129–138.

[27] A. F. Shamsutdinov, T. F. Shamsutdinov, D. V. Chachkov, A. G. Shamov, G. M. Khrapkovskii, *Int. J. Quant. Chem.* **2007**, *107*, 2343–2352.

[28] E. Lewars, *Computational Chemistry: Introduction to the Theory and Applications of Molecular and Quantum Mechanics*, Kluwer, Dordrecht **2004**.

[29] D. S. Karanewsky, Y. Kishi, *J. Org. Chem.* **1976**, *41 (18)*, 3026–3027.

[30] W. N. White, E. F. Wolfarth, *J. Org. Chem.* **1970**, *35 (10)*, 3585.

[31] J. J. Gajewski, K. E. Gilbert, *J. Org. Chem.* **1984**, *49 (1)*, 11–17.

[32] S. R. Emamian, M. R. Zardoost, K. Zare, E. Zahedi, H. Aghaie, *J. Phys. Theor. Chem.* **2009**, *6 (3)*, 183–190.

[33] E. N. Marvell, J. Stephenson, J. Ong, *J. Am. Chem. Soc.* **1965**, *87*, 1267–1274.

[34] T. R. Ramadhar, R. A. Batey, *Comput. Theor. Chem.* **2011**, *974*, 76–78.

[35] C. Reinchardt, *Pure Appl. Chem.* **1982**, *54 (10)*, 1867–1884.

[36] J. J. Gajewski, *Acc. Chem. Res.* **1997**, *30*, 219–225.

[37] R. Schmid, in *Handbook of Solvents*, (Ed: G. Wypych), ChemTec Publishing, Toronto **2001**, Ch. 13, 737–846.

[38] E. D. Hughes, C. R. Ingold, *J. Chem. Soc.* **1935**, 244–255.

[39] E. B. Brandes, P. A. Grieco, J. J. Gajewski, *J. Org. Chem.* **1989**, *54 (3)*, 515–516.

[40] D. L. Severance, W. L. Jorgensen, *J. Am. Chem. Soc.* **1992**, *114 (27)*, 10966–10968.

[41] M. M. Davidson, I. H. Hillier, R. J. Hall, N. A. Burtons, *J. Am. Chem. Soc.* **1994**, *116*, 9294–9297.

[42] W. N. White, E. F. Wolfarth, *J. Org. Chem.* **1970**, *35 (7)*, 2196–2199.

[43] A. Y. Lee, J. D. Stewartm, J. Clardy, B. Ganem, *Chem. Biol.* **1995**, *2 (4)*, 195–203.

[44] (a) C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130 (29)*, 9228–9229; (b) M. Kirsten, J. Rehbein, M. Hiersemann, T. Strassner, *J. Org. Chem.* **2007**, *72*, 4001–4011.

[45] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146–146.

[46] A. Lubineau, J. Auge, *Top. Curr. Chem.* **1999**, *206*, 1–39.

[47] S. D. Copley, J. R. Knowles, *J. Am. Chem. Soc.* **1987**, *109*, 5008–5013.

[48] O. Acevedo, K. Armacost, *J. Am. Chem. Soc.* **2010**, *132 (6)*, 1966–1975.

[49] K. Maruoka, H. Banno, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112 (21)*, 7791–7793.

[50] K. Maruoka, S. Saito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117 (3)*, 1165–1166.

[51] A. C. Varas, T. Noel, Q. Wang, V. Hessel, *ChemSusChem.* **2012**, *5 (9)*, 1703–1707.

[52] M. P. Watson, L. E. Overman, R. G. Bergman, *J. Am. Chem. Soc.* **2007**, *129*, 5031–5044.

[53] D. P. Curran, L. H. Kuo, *Tetrahedron Lett.* **1995**, *36*, 6647–6650.

[54] C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133 (13)*, 5062–5075.

[55] R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107 (48)*, 20678–20685.

[56] B. Gomez, P. K. Chattaraj, E. Chamorro, R. Contreras, P. Fuentealba, *J. Phys. Chem. A* **2002**, *106*, 11227–11233.

[57] (a) F. V. Schuster, G. W. Murphy, *J. Am. Chem. Soc.* **1950**, *72*, 3155–3159; (b) L. Stein, G. W. Murphy, *J. Am. Chem. Soc.* **1952**, *74*, 1041–1043; (c) H. M. Frey, D. C. Montage, *Trans. Faraday Soc.* **1968**, *64*, 2370–2374; (d) H. M. Frey, B. M. Pope, *J. Chem. Soc. B* **1966**, 209–210; (e) L. Kupczyk-Subotkowska, H. Saunders, H. J. Shine, *J. Am. Chem. Soc.* **1988**, *110 (21)*, 7153–7159; (f) S. Yamabe, S. Okumoto, T. Hayashi, *J. Org. Chem.* **1996**, *61 (18)*, 6218–6224.

[58] A. Drljaca, C. D. Hubbard, R. van Eldik, T. Asano, M. V. Basilevsky, W. J. le Noble, *Chem. Rev.* **1998**, *98 (6)*, 2167–2290.

[59] R. Van Eldik, T. Asano, W. J. Le Noble, *Chem. Rev.* **1989**, *89 (3)*, 549–688.

[60] K. R. Brower, *J. Am. Chem. Soc.* **1961**, *83*, 4370–4372.

[61] W. Verboon, *Chem. Eng. Technol.* **2009**, *32 (11)*, 1695–1701.

[62] C. Walling, M. Naiman, *J. Am. Chem. Soc.* **1962**, *84 (13)*, 2628–2632.

[63] For a selection of reviews which deal with micro process technologies and flow chemistry: (a) T. Noel, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010–5029; (b) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem., Int. Ed.* **2011**, *50*, 7502–7519; (c) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583–4592; (d) T. N. Glasnov, C. O. Kappe, *J. Heterocycl. Chem.* **2011**, *48*, 11–30; (e) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680; (f) A. Cukalovic, J.-C. M. R. Monbaliu, C. V. Stevens, *Top. Heterocycl. Chem.* **2010**, *23*, 161–198; (g) C. G. Frost, L. Mutton, *Green Chem.* **2010**, *12*, 1687–1703; (h) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495–2507; (i) K. Geyer, T. Gustafsson, P. H. Seeberger, *Synlett* **2009**, *2009 (15)*, 2382–2391; (j) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, *2*, 151–163; (k) S. V. Ley, I. R. Baxendale, *Chimia* **2008**, *62*, 162–168; (l) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, *10*, 1655–1671; (m) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; (n) K. Geyer, J. D. C. Codee, P. H. Seeberger, *Chem.-Eur. J.* **2006**, *12*, 8434–8442; (o) A. Kirschning, W. Solodenko, K. Mennecke, *Chem.-Eur. J.* **2006**, *12*, 5972–5990; (p) K. Jaehnisch, V. Hessel, H. Loewe, M. Baerns, *Angew. Chem., Int. Ed.* **2004**, *43*, 406–446; (q) V. Hessel, H. Loewe, *Chem. Eng.*

Technol. **2003**, *26*, 13–24; (r) V. Hessel, H. Loewe, *Chem. Eng. Technol.* **2003**, *26*, 391–408; (s) V. Hessel, H. Loewe, *Chem. Eng. Technol.* **2003**, *26 (1)*, 13–24; (t) K. F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293–303; (u) K. F. Jensen, *AIChE J.* **1999**, *45*, 2051–2054; For recent books pertaining flow chemistry: (v) C. Wiles, P. Watts, *Microreactor Technology in Organic Synthesis*, CRC Press, Boca Raton, FL **2011**; (w) *Microreactors in Organic Synthesis and Catalysis* (Ed: T. Wirth), Wiley-VCH, Weinheim **2008**; (x) J.-i. Yoshida, *Flash Chemistry: Fast Organic synthesis in Microsystems*, Wiley-VCH, Weinheim **2008**; (y) P. H. Seeberger, T. Blume, *New Avenues to Efficient Chemical Synthesis – Emerging Technologies*, Springer-Verlag, Berlin **2007**; For books about microprocess technologies: (z) W. Ehrfeld, V. Hessel, H. Loewe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim **2000**; (za) V. Hessel, S. Hardt, H. Loewe, *Chemical Micro Process Engineering – Fundamentals, Modelling and Reactions*, Wiley-VCH, Weinheim **2004**; (zb) V. Hessel, H. Loewe, A. Mueller, G. Kolb, *Chemical Micro Process Engineering – Processing and Plants*, Wiley-VCH, Weinheim **2005**; (zc) V. Hessel, A. Renken, J. C. Schouten, J.-i. Yoshida, *Handbook of Micro Process Engineering*, Wiley-VCH, Weinheim **2009**.

[64] H. Kobayashi, B. Driessen, D. J. G. P. van Osch, A. Talla, S. Ookawara, T. Noel, V. Hessel, *Tetrahedron* **2013**, *69*, 2885–2890.

[65] M. Sato, N. Otabe, T. Tuji, K. Matsushima, H. Kawanami, M. Chatterjee, T. Yokoyama, Y. Ikushima, T. M. Suzuki, *Green Chem.* **2009**, *11*, 763–766.

[66] L. Kong, Q. Lin, X. Lv, Y. Yang, Y. Jia, Y. Zhou, *Green Chem.* **2009**, *11*, 1108–1111.

[67] H. Maeda, S. Nashihara, H. Mukae, Y. Yoshimi, K. Mizuno, *Res. Chem. Intermed.* **2013**, *39 (1)*, 301–310.

[68] V. Hessel, I. Vural-Gursel, Q. Wang, T. Noel, J. Lang, *Chem. Eng. Technol.* **2012**, *35 (7)*, 1184–1204.

[69] V. Hessel, *Chem. Eng. Technol.* **2009**, *32 (11)*, 1655–1681.

[70] V. Hessel, B. Cortese, M. H. J. M. de Croon, *Chem. Eng. Sci.* **2011**, *66 (7)*, 1426–1448.

[71] V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746–789.

[72] K. Jaehnisch, V. Hessel, H. Loewe, M. Baerns, *Angew. Chem., Int. Ed.* **2004**, *43*, 406–446.

[73] P. Watts, S. J. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235–246.

[74] G. W. Whitesides, *Nature* **2006**, *442*, 368–373.

[75] X. Zhang, S. Stefanick, F. J. Villani, *Org. Process Res. Dev.* **2004**, *8*, 455–460.

[76] D. A. Waterkamp, M. Engelbert, J. Thorning, *Chem. Eng. Techn.* **2009**, *32 (11)*, 1717–1723.

[77] A. Hartung, M. A. Keane, A. Kraft, *J. Org. Chem.* **2007**, *72*, 10235–10238.

[78] H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046–3047.

[79] P. J. Nieuwland, K. Koch, J. C. M. van Hest, F. P. J. T. Rutjes, *Open Chem. Eng. J.* **2010**, *4*, 61–67.

[80] J. A. Rincón, M. Barberis, M. González-Esguevillas, M. D. Johnson, J. K. Niemeier, W. M. Sun, *Org. Process Res. Dev.* **2011**, *15 (6)*, 1428–1432.

[81] X. P. Ma, Z. M. Li, Q. R. Wang, *Chin. Chem. Lett.* **2011**, *22 (2)*, 167–170.

[82] S. G. Wagholikar, S. Mayadevi, N. E. Jacob, S. Sivasanker, *Microporous Mesoporous Mater.* **2006**, *95 (1–3)*, 8–16.

[83] N. T. Mathew, S. Khaire, S. Mayadevi, R. Jha, S. Sivasanker, *J. Catal.* **2005**, *229 (1)*, 105–113.

[84] A. Indrianingsih, T. Noel, Q. Wang, V. Hessel, unpublished results, TU Eindhoven, **2011**.

[85] H. Kawanami, M. Sato, M. Chatterjee, N. Otabe, T. Tuji, Y. Ikushima, T. Ishizaka, T. Yokoyama, T. M. Suzuki, *Chem. Eng. J.* **2011**, *167*, 572–577.

[86] R. A. Firestone, M. F. Vitale, *J. Org. Chem.* **1981**, *46 (10)*, 2160–2164.

[87] A. M. Sanchez, A. V. Veglia, R. H. de Rossi, *Can. J. Chem.* **1997**, *75 (8)*, 1151–1155.

[88] T. Razzaq, T. N. Glasnov, C. O. Kappe, *Chem. Eng. Technol.* **2009**, *32 (11)*, 1702–1716.

[89] C. R. Strauss, *Org. Process Res. Dev.* **2009**, *13*, 915–923.

[90] J. M. Kremsner, A. Stadler, C. O. Kappe, *Top. Curr. Chem.* **2006**, *266*, 233–278.

[91] M. Damm, T. N. Glasnov, C. O. Kappe, *Org. Proc. Res. Dev.* **2010**, *14*, 215–224.

[92] J. D. Moseley, E. K. Woodman, *Org. Process Res. Dev.*, **2008**, *12 (5)*, 967–981.

[93] F. Bergamelli, M. Iannelli, J. A. Marafie, J. D. Moseley, *Org. Process Res. Dev.* **2010**, *14*, 926–930.

[94] S. Ceylan, C. Friese, C. Lammel, K. Mazac, A. Kirschning, *Angew. Chem., Int. Ed.* **2008**, *47*, 8950–8953.

[95] S. C. Stouten, T. Noël, Q. Wang, V. Hessel, *Austr. J. Chem.* **2013**, *66 (2)*, 121–130.

[96] W. Wu, G. Qian, X.-G. Zhou, W.-K. Yuan, *Chem. Eng. Sci.* **2007**, *62*, 5127–5132.

[97] K. A. Swiss, R. A. Firestone, *J. Phys. Chem. A* **2000**, *104 (13)*, 3057–3063.

[98] S. Zelentsov, V. Hessel, E. Shahbazali, T. Noël, *ChemBioEng Rev.* **2014**, *1 (5)*, 230. DOI: 10.1002/cben.201400021