Strategic Application of Residence-Time Control in Continuous-Flow Reactors

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As a sustainable alternative for conventional batch-based synthetic techniques, the concept of continuous-flow processing has emerged in the synthesis of fine chemicals. Systematic tuning of the residence time, a key parameter of continuous-reaction technology, can govern the outcome of a chemical reaction by determining the reaction rate and the conversion and by influencing the product selectivity. This review furnishes a brief insight into flow reactions in which high chemo- and/or stereoselectivity can be attained by strategic residence-time control and illustrates the importance of the residence time as a crucial parameter in sustainable method development. Such a fine reaction control cannot be performed in conventional batch reaction set-ups.

1 Introduction

Continuous-flow (CF) transformations are of considerable current interest, as they offer a substantial number of advantages over conventional batch procedures, such as inherently safer and greener chemistry, outstanding mass and heat transfer, increased parameter space with an unprecedented level of control over the most important reaction conditions, and higher reaction rates.[1] Many of these advantages stem from the size of CF reactors, where the diameters of the pores and capillaries are mainly in the micro- or nanometer range. With such short distances, the mass transfer is faster and results in more effective mixing of the substrates.[1k, 2] The small internal dimensions are accompanied by high surface to volume ratios, which results in effective heat transfer, thereby allowing exact temperature control. The major consequence of these advantages is that the reaction times can be decreased relative to those in conventional batch procedures.

There are numerous fundamental differences between classical batch experiments and CF reaction technology. In a segmented operatively reaction vessel, the definition of reaction time is obvious,[20] whereas the concept of reaction time in a continuous process is not so clear, and the term residence time is therefore preferred, that is, the interval spent by a given molecule in the active reactor zone. The reaction rate, conversion, and product selectivity are influenced directly by this specific parameter; the residence time therefore being a crucial determining factor in flow chemistry.

One benefit of CF procedures is the time-resolved scale of the syntheses. In conventional batch reactors, the output depends on the batch size, and the synthesis can become appreciably complicated when unstable reactants are to be handled on a relatively larger scale. In contrast, the scalability of CF reactions is a straightforward function of time: the longer the reactor operates, the larger the scale of the production. Accordingly, CF transformations are time-resolved, and facile industrial scale-up is therefore warranted. The residence time is clearly determined by the flow rate and the volume of the CF reactor and can be fine-tuned precisely via the instrumentation.[26] The residence-time distribution of some packed-bed mini-flow reactors has been demonstrated to be influenced crucially by the properties of the filling material.[4e] Such an extraordinary control is not possible in traditional batch reactions, and flow chemistry therefore allows unprecedented selectivities and reaction rates, and even the development of completely new reaction routes.

Excellent recent reviews have focused on various aspects and applications of CF devices and syntheses in organic chemistry,[1a, l, 5] and there are numerous important papers in which conversions and reaction rates have been optimized via residence-time control in CF reactors.[8] There are many parameters concerning CF reactors, with which the reaction outcome can be fine-tuned. However, this review focuses on the role of the residence time as a unique tool in the optimization of reaction selectivity. We therefore survey the recent advances in the CF chemistry where high chemo- and/or stereoselectivity is ensured through precise control of the residence time.
2 Residence-Time-Controlled Selectivity

2.1 Selective flash transformations

Yoshida and co-workers have recently introduced the concept of ‘flash chemistry’, for flow reactions involving 1) fast consecutive transformations and reactive intermediates, 2) competing reaction pathways, 3) highly exothermic transformations, 4) undesired byproduct formation, and 5) transformations leading to labile products which readily decompose. These reactions are difficult (or sometimes impossible) to accomplish in traditional segmented unit operations, and selectivity issues often reduce their practical applicability. Flash chemical synthesis relies on high-resolution control of the residence time within a flow microreactor. For precise control over the reaction outcome, mixing should take place in a much shorter time than the residence time in the active reactor zone, which necessitates the use of micromixers that allow extremely fast mixing (Figure 1). In the last few years, there have been a huge number of outstanding contributions to the flash chemistry concept in various fields of organic synthesis (such as organolithium chemistry, cross-coupling reactions, and organo fluorine chemistry), and they have recently been reviewed extensively. Thus, only several selected examples will be detailed in the present manuscript.

The synthesis of multisubstituted pyridines has received particular attention in the field of drug discovery. The reaction of an electrophile with a pyridyllithium species generated from a bromopyridine via bromine–lithium exchange is a popular method for the introduction of substituents into the pyridine ring. However, such transformations need cryogenic conditions (e.g. –78 °C) in order to moderate side reactions (e.g. deprotonation or addition to the pyridine ring), which can lead to undesired byproduct formation and insufficient chemoselectivity. From aspects of sustainability and industrial-scale production, the avoidance of cryogenic conditions would be highly beneficial. With CF technology and precise residence-time control, the bromine–lithium exchange becomes readily regulated. The reaction of 2,3-dibromopyridine with n-butyllithium (nBuLi), followed by reaction with an electrophile, was carried out in a flow system consisting of two T-shaped micromixers and two microtube reactors (Figure 2).

In an elaborate optimization study, iodomethane (MeI) was applied as electrophile. 2-Bromo-3-methylpyridine was obtained in high yields even at 0 °C if an adequately low residence time (e.g. 0.06 s) was chosen. Increase of the residence time and/or the temperature enhanced the protonation of 2-bromo-3-pyridyllithium, leading to the formation of 2-bromopyridine as byproduct (Figure 3). The methodology was extended to the sequential introduction of two electrophiles by using dibromopyridines as starting materials to obtain disubstituted pyridines without isolation of the monobromopyridine intermediates.

In the context of ideal synthesis and green sustainable chemistry, protecting-group-free approaches have attracted considerable attention. The next example gives an insight into protecting-group-free CF iodine–lithium exchange reactions. Organolithiums react with ketones rapidly, and carbonyl groups are therefore traditionally protected prior to an organolithium reaction. Nevertheless, free ketone carbonyls can...
It has been demonstrated that, with very accurate control over short residence times, the reaction can be accomplished without protecting group chemistry in a low microreactor.

Iodine–lithium exchange reactions of acyliodobenzenes have been investigated (Scheme 1, Figure 4). Mesityllithium (MesLi) was generated in-line through the reaction of mesityl bromide and nBuLi at 0 °C. In the same flow, the resulting MesLi was then combined with the acyliodobenzene at −70 °C, and the resulting short-lived acylphenyllithium species was trapped with a quenching electrophile before undesired dimerization could take place (Scheme 1). It was shown that higher reaction times favored byproduct formation, and the residence time of the iodine–lithium exchange step was therefore progressively decreased to as low as 0.003 s so as to obtain the desired compound in high yield without significant formation of the byproduct (Figure 4).

The nitro group reacts vigorously with aryllithiums, and accordingly, the generation of nitro-substituted organolithium compounds in batch macroreactors is difficult; very low temperature is usually needed to gain sufficient control over the reaction selectivity. However, with flash chemistry, this problem can be overcome and nitro-substituted aryllithium reagents can easily be obtained via halogen–lithium exchange reactions in very short residence times. Accurate control over the residence time permits the selective use of either the kinetically or the thermodynamically preferred organolithium intermediate in the reaction of 1-bromo-2,5-dimethoxy-3-nitrobenzene with phenyllithium (PhLi) at −48 °C (Scheme 2).

Isobutyraldehyde as quenching electrophile is introduced through a mixing unit to give the desired product. The results reveal that, with a residence time of 0.055 s, the Kc product is
formed via the kinetically preferred organolithium reagent (Table 1, entry 2). An increase in residence time leads to the formation of the isomeric product derived from isomerization of the aryllithium reagent. With a residence time of 63 s, the thermodynamically controlled product \( \text{Kc} \) was obtained exclusively (Table 1, entry 6). The switch between kinetic and thermodynamic control proved to be an elegant way to fine-tune the reaction outcome.

Kappe and co-workers recently reported the highly controlled thermolysis of various substrates in a high-pressure/high-temperature microreactor environment, employing near-or supercritical fluids as reaction media.\(^{12}\) The method relies on exact control of the temperature and the flow rate, and hence, the residence time for the fine-tuning of the chemoselectivity. In the case of 5-benzoyl Meldrum’s acid, for example, differential scanning calorimetry studies revealed that the thermolysis largely depends on the reaction conditions. At \(-150\, {}^\circ\text{C}\), a 1,3-dioxin-4-one intermediate is formed, which decomposes to an \( \alpha \)-oxoketene dimer at higher temperatures (Scheme 3).

With precise residence-time control, the thermal decomposition of 5-benzoyl Meldrum’s acid could be nicely tuned to provide both products selectively at 150 °C. With longer residence times (>20 min), the dimer form was obtained with high selectivity, while as the residence time was reduced, the 1,3-dioxin-4-one intermediate became the favored product. As an example, complete conversion of the starting material was observed after 7 s, providing a selectivity of almost 90% for the 1,3-dioxin-4-one product.

### 2.2 Photocatalytic peptide fragment coupling

CF operation is highly beneficial for photochemical processes, as the narrow reaction channels and increased surface-to-volume ratio greatly improve light absorption as compared with conventional reaction vessels, and the irradiation-related side reactions and decomposition pathways are minimized as the irradiation period can easily be controlled via the residence time. Conventional methods for the generation of amide bonds suffer from a number of drawbacks (e.g. the need for stoichiometric amounts of activating agents, possible epimerization, high costs, and waste generation), which suggests a need for alternative approaches. For this reason, Jamison et al. developed a versatile CF approach for the construction of amide bonds by means of the photochemical rearrangement of nitrones.\(^{13}\) After verification of the capabilities of the CF method with transformations of simple alkyl-aryl nitrones, its potential concerning dipeptide formation was evaluated. Control of the residence time proved crucial in the fine-tuning of the proportions of the dipeptide product \( \text{C} \), the oxaziridine intermediate \( \text{B} \), and the starting nitrone \( \text{A} \) in the resulting mixture (Table 2). A quick scan revealed that a 10 min residence time was necessary for quantitative conversion of both the starting nitrone and the oxaziridine intermediates with an initial substrate concentration of 0.05 m (entries 1—4 in Table 2). At the expense of a slight residence time increase (12.5 min), the nitrone concentration could be increased to 0.1 m, thereby achieving higher productivity (entry 6). The scope and applicability of the CF method proved to be wide, but the irradiation time had to be extended by means of a residence-time increase in order to...
obtain dipeptides in good yields from sterically hindered nitro-
nes.

2.3 Stereoselective synthesis of γ-nitroaldehydes

The synthesis of γ-nitroaldehydes is of considerable current in-
terest as they are useful synths in organic chemistry and
drug discovery. The stereoselective CF synthesis of γ-nitroal-
dehydes has been performed with immobilized peptides as
catalysts, as outlined in Scheme 4.

In this reaction, two stereocenters are generated, and conse-
quently, the formation of four enantiomers is possible. Accord-
ingly, the syn/anti selectivity and the enantioselectivity within
an enantiomeric pair can be investigated. One of the major ad-
vantages of this methodology in addition to the good selectiv-
ities and yields is the simultaneous synthesis and immobiliza-
tion of the catalyst. The reaction parameters, including the
structure of the catalyst, the type of the solid support, the pro-
portions of the reactants, the pressure, the temperature, and the
residence time have been optimized. The effects of the res-
didence time on the yield and the diastereoselectivity are depicted
in Figure 5.

Increase of the residence time led to higher yields, but lower
diastereoselectivities. The latter effect is explained by the epime-
rization of the secondary amine functional group of the N-termi-
nal proline of the immobilized catalyst. This was highlighted by
recirculation of the γ-nitroaldehyde product on the catalyst,
which resulted in a lower syn/anti ratio. CF aldol reactions
have also been carried out in the same flow system, but no residence-time dependence of
the stereoselectivity was then observed. Such a high resolu-
tion control between syn/anti selectivity and conversion
cannot be achieved in a batch reaction.

2.4 Selective nitration

The nitration of benzene derivatives in conventional batch re-
actors usually affords a mixture of several products and raises
safety issues. Yu et al. employed precise residence-time control
and smart CF reactor design to improve the selectivi-
ty and safety in the nitration of p-difluorobenzene
(Scheme 5). The nitrating acid mixture (2.0 equiva-
lents of concentrated sulfuric acid and 1.1 equiva-
lents of fuming nitric acid) and p-difluorobenzene
were pumped through a thermostated tubular reac-
tor by separate pumps. The reaction was quenched
by ice in the collection vessel.

Different residence times were explored by adjust-
ing the length of the reaction tube while maintaining
a fixed flow rate. It can be seen from Figure 6 that
higher residence times led to higher product yields,
but also enhanced the formation of 1,4-difluoro-2,3-
dinitrobenzene as a byproduct. It is notable that only
negligibly small amounts of difluorophenol side
products were formed; this is possibly due to the su-
perior heat transfer of the CF reactor. To improve
the product selectivity further, two thermostated reactor
modules and a cooling module were connected to-
gether. The temperatures of the reactor modules were 30–
35 °C and 65–70 °C, and in each reactor zone the residence
time was set precisely to 1 min (0.3 min in the cooling zone).
1,4-Difluoro-2-nitrobenzene was obtained in a yield of 98%
with 99% gas-chromatography purity, which means that by-
products were hardly generated.

| Entry | Residence time [min] | Concentration [m] | Ratio [A:B:C] |
|-------|---------------------|------------------|--------------|
| 1     | 1                   | 0.05             | 1:9:3        |
| 2     | 2.5                 | 0.05             | nd:4:3[1]    |
| 3     | 5                   | 0.05             | nd:1:5[1]    |
| 4     | 10                  | 0.05             | nd:nd:1[1]   |
| 5     | 10                  | 0.1              | nd:1:6[1]    |
| 6     | 12.5                | 0.1              | nd:nd:1[1]   |

[a] nd: not detected
One of the best-selling five-membered heterocyclic pharmaceuticals is Rufinamide, an antiepileptic drug that contains a 1,2,3-triazole moiety. Hessel and co-workers established a novel and sustainable CF technique for the synthesis of Rufinamide, which relies greatly on precise residence-time control to govern the sensitive balance between the decomposition of the starting materials and the acceleration of the reaction at elevated temperatures.\(^\text{[18]}\) The key step in the synthesis of Rufinamide is the 1,3-dipolar cycloaddition of 2,6-difluorobenzyl azide with an appropriate dipolarophile. (E)-Methyl 3-methoxyacrylate was utilized as a nontoxic and inexpensive dipolarophile which results in the selective formation of the desired 1,4-disubstituted 1,2,3-triazole regioisomer without the need for an added catalyst (Figure 7). To attain a higher reaction rate, solvent-free conditions were applied.

It was found that the use of an elevated temperature is necessary for complete reaction homogeneity and for a sufficiently high reaction rate, but after a point this also leads to the decomposition of the azide, which worsens the yield. 210 °C was chosen as an ideal reaction temperature, and the residence time was then fine-tuned to obtain the optimum balance between the reaction rate and the rate of decomposition of the azide (Figure 7). The highest yield (83%) was achieved after 10 min. Longer residence times led to lower yields, due to the significant decomposition of the starting material. Without the strategic application of precise residence-time control, the decomposition would lower the yield of the desired compound. The CF procedure lacks most of the drawbacks of the batch synthesis, as it is rapid, safe, and straightforward.
2.6 Selective Heck reactions in CF

Jensen et al. developed an integrated CF system for self-optimization of the Heck reaction of 4-chlorobenzotrifluoride and 2,3-dihydrofuran (Scheme 6).\[^{19}\] The system maximized the yield of the monoarylated product by scanning the equivalents of the alkene and the residence time via the adjustment of the flow rate of the reactants, while the temperature was kept constant at 90°C. The combination of Pd(OAc)\(_2\) and tert-butyl-MePhos as ligand in n-butanol proved to be a sufficiently active and stable catalyst system which did not cause clogging in the reactor channels. A solution containing the aryl chloride, the palladium source, and an amine base was introduced together. The alkene was fed separately, and n-butanol was injected via a third syringe. The optimization was directed by the Nelder-Mead Simplex Method, and the yield was evaluated in every step by in-line HPLC analysis.

The results demonstrated that the yield of the monoarylated product improved significantly with the residence time until a plateau was reached at around 5.5 min. Longer residence times led to decreased yields, as a consequence of diarylated byproduct formation (Figure 8). Increase of the alkene excess resulted in higher yields. Optimum conditions were determined as a residence time of 6 min and an alkene excess of 5.0 equivalents, which corresponded to a yield of 83%.

To attain sustainable production, the Heck C–C coupling followed by hydrogenation for the synthesis of 1,2-diphenylethane was performed in a CF device with a solid-supported Pd as catalyst (Scheme 7).\[^{21}\]

A multichannel compact reactor was constructed for the synthesis of 1,2-diphenylethane. The reaction parameters were optimized, and a methodology orders of magnitudes faster than batch reactions was developed. Under batch conditions, the selectivity for 1,2-diphenylethane was lower than under CF conditions because a substantial amount of 1,1-diphenylethane was detected too. Nevertheless, under CF conditions the formation of cis-1,2-diphenylethane was also observed, and the residence time affected the selectivity and the conversion. On decrease of the residence time, the conversion was lower, as expected, but the selectivity towards 1,2-diphenylethane rather than 1,1-diphenylethane was increased (Figure 9). This observation suggests that the 1,2-disubstituted compound is the kinetic product. Here an inverse relationship was observed between the conversion and the selectivity.

2.7 Selective hydrogenations, reductions, and oxidations in CF

Among CF techniques, the most significant progress has been made in the field of CF gas-handling reactions in recent years, mainly driven by CF hydrogenation.\[^{22}\] With CF reactors, the handling of hazardous aggressive gases can be safely performed. Moreover, through the fine-tuning of the reaction parameters, selective transformations can be performed faster and more efficiently as compared with conventional methodologies. The selective reductions of alkynes to alkenes have been achieved in a wall-catalyzed segmented flow reactor by catalytic hydrogenation.\[^{23}\] The commercially available fused-silica capillaries contained a 6 μm thick layer of γ-Al\(_2\)O\(_3\) that was pretreated and impregnated with [Pd(OAc)\(_2\)] solution, which resulted in nanosized Pd particles evenly dispersed on the coating layer. With the application of this tubing, 3-methyl-1-pentyn-3-ol was selectively reduced to 3-methyl-1-penten-3-ol (Scheme 8).

Kinetic modelling showed that the maximum possible yield is 78–81%, which is obtained only at precisely the right residence time. The dependence of the selectivity of the reaction
on the residence time has been investigated. There is an optimum value where the formation of P1 displays a maximum value, and the overhydrogenation to P2 is still low. Any further variation of the residence time reduces the yield (Figure 10). At a shorter residence time, the conversion is lower in general, but at longer residence times, the formation of P2 increases, while the concentration of P1 decreases. In a one-day optimization, the theoretical optimum yield of P1 was achieved by using segmented flow.

The partial reduction of esters with diisobutylaluminium hydride (DIBALH) is not a popular route for aldehyde synthesis, as overreduction to the corresponding alcohol is a significant problem even at low temperatures. Jamison and co-workers exploited the benefits of CF processing together with careful residence-time control and revitalized the DIBALH reduction of esters to yield various aldehydes selectively. The residence-time dependence was investigated as a function of the reactor volume at constant flow rate and also as a function of the flow rate at constant reactor volume. The reduction of ethyl hydrocinnamate was initially studied at −78°C; methanol was introduced separately as a quenching agent to avoid overreduction (Figure 11). Interestingly, the conversion improved when the residence time was shortened at constant reactor volume by increasing the flow rate, and it was observed that at very high flow rates the outcome of the reaction was independent of the residence time (Table 3). These results indicate that the examined reaction proceeds very rapidly, and higher flow rates tend to improve mixing. At such elevated flow rates, the reaction outcome is influenced by the rapid mixing in the reactor channels. It is noteworthy that full conversion and complete selectivity were observed even at very short residence times. The methodology was extended to the selective reduction of a series of further esters.

An early example of CF reduction methodology was the application of diethylzinc and an immobilized chiral catalyst for...
the enantioselective synthesis of aromatic alcohols (Scheme 9). \[20\]

Ephedrine and camphor immobilized on polystyrene resins were used as catalysts in a bench-top flow apparatus operated with peristaltic pumps. The effects of the flow rate on the yield and enantioselectivity were investigated: lower flow rates resulted in higher yields and higher ee values. Moreover, the flow reactor displayed a better performance than with normal flask operations. The immobilized catalyst in flask operations was recycled six times.

Polymer monoliths containing a chiral 1,2-aminoalcohol derivative were used as catalysts in the reaction outlined in Scheme 9 in a mini-flow reactor. \[26\] The monolithic catalysts proved superior to standard polystyrene catalysts. Furthermore, the utilization of flow conditions resulted in enhanced catalytic activity, providing higher yield and selectivity.

Poljakoff and co-workers investigated the CF selective partial oxidation of methylpyridines, using molecular O\(_2\) as oxidant for the selective formation of pyridine carboxylic acids (isonicotinic, nicotinic, and picolinic acids) as precursors for a series of valuable products. \[27\] Manganese(II) bromide was employed as a homogeneous catalyst, and supercritical water (scH\(_2\)O) served as a cheap and green reaction medium. The oxidation of methylpyridines is known to produce aldehydes and pyridine itself (via decarboxylation) as byproducts. \[24\] The effects of the residence time, temperature, pressure, and catalyst concentration were therefore deeply analyzed to achieve selective carboxylic acid formation. It emerged that the residence time has a great impact on the product selectivity. In the case of 3-methylpyridine (at 360 °C), for example, the unwanted decarboxylation to pyridine could be successfully moderated through decrease of the residence time. As aldehyde formation remained negligible, the desired carboxylic acid could be obtained in a good yield of 50%.

### 2.8 CF cyclopropanation

Gold catalysis is of considerable current interest because of the massive number of unprecedented transformations, \[28\] for example, highly chemoselective and diastereoselective heterogeneous cyclopropanation reactions. The CF synthesis of cyclopropane derivatives has been achieved through the utilization of Au clusters as catalyst (2.0 ± 0.3 nm) encapsulated in a fourth-generation poly(amidoamine) (G4 PAMAM) dendrimer and loaded onto SBA-15, a mesoporous silica support, with a surface area of 760 m\(^2\) g\(^{-1}\). \[29\] The reaction is shown in Scheme 11.

![Scheme 9. Enantioselective synthesis of phenylpropanol derivatives.](image)

![Scheme 10. The oxidation of methylpyridines with molecular O\(_2\) as oxidant.](image)

Through this CF reaction, the results observed under batch conditions are maintained. Moreover, the catalyst remains active even after 8 h and can be regenerated by reoxidation very effectively, yielding a more active species relative to the starting catalyst. The chemoselectivity of the reaction was investigated as a function of the residence time in a CF reactor. For this purpose, a gold-catalyzed cascade cyclopropanation rearrangement was selected (Scheme 12).

![Scheme 11. CF synthesis of cyclopropane derivatives.](image)
action, the residence time played an important role in the
tuning of the reaction selectivity.

Stereoselective cyclopropanation has been carried out by
the use of immobilized bisoxazoline as catalyst and styrene
and ethyl diazoacetate as starting materials in batch and
mini-flow reactors (Scheme 13).[30, 31]

The conversion of the reaction exhibited a residence-time de-
pendence, that is, the longer the residence time, the higher the con-
version. Nonetheless, the chemoselectivity could not be influenced
by residence-time control. However, when a different monolithic cat-

The monolithic catalyst was synthesized by the polymeri-
ization of the starting 4-vinyl derivative. Through fine-tuning of the
residence time, the chemoselectivity of the reaction was
changed. At a residence time of 14 min, the yield for trans-cyclopropanes was ~15%, while for the cis isomers it was ~6%;
while at a residence time of 35 min, the corresponding yields were ~40% and ~10%, respectively. Consequently, upon in-
crease of the residence time by ~20 min, the yield of the trans-
leaching always occurs.[34] The silica-based mesoporous materi-
al MCM-41 was selected for the immobilization of the Grubbs/
Hoveyda 2 complex. This catalyst has been used for the ring-
opening/ring-closing metathesis (RO-RCM) reaction of cis-cy-
clooctene, yielding 1,9-cyclohexadecadiene (Scheme 15).[35]

This reaction is accompanied by side products such as other oligomers and polymers, compounds formed by double bond
isomerization and unsymmetrical metathetical cleavage. To
avoid the formation of byproducts, a complete reaction-param-
eter optimization was carried out, with fine-tuning of the pore
diameter of the mesoporous support, the substrate concentra-
tion, the temperature, and the residence time. Increase of the
residence time led to higher conversions (Figure 13a). Howev-
er, when the residence time was decreased, the selectivity to-
wards 1,9-cyclohexadecadiene was improved (Figure 13b).
Figure 13. Effects of the residence time on the conversion (a) and the selectivity (b) for the RO-RCM of cis-cyclooctene to 1,9-cyclohexadecadiene.

This observation implies that the small oligomers are kinetic products and are not formed through backbiting from a larger oligomer or polymer chain. Consequently, a high yield of the dimer product (1,9-cyclohexadecadiene) can be ensured only at low residence times in a CF device and the conversion is inversely proportional to the selectivity.

3 Summary and Outlook

The primary aim of this review has been to show that the strategic application of residence-time control is an efficient tool that the residence time can be fine-tuned and readily maintained in CF devices. It can be concluded that the residence time generally influences the conversion; for example, the longer the residence time, the higher the conversion. Such obvious examples have not been discussed in this review.

Flash chemical transformations, where appropriate residence-time control is crucial, have been discussed. The strategic application of residence-time control allows adequate and easy handling of very labile and reactive reagents. Consequently, merely by means of the fine-tuning of the residence time under general reaction conditions, higher conversions and yields can be achieved than with conventional batch technologies. Novel chemical windows have been opened in the field of organocatalytic and photochemical transformations too by strategic residence-time control. The neat, catalyst-free CF synthesis of Rufinamide, an anticonvulsant drug, has been described. Selected examples have been described where metal catalysts play a vital role, for example, the Heck cross-coupling reaction, selective hydrogenation on Pd surfaces, gold catalysis, and metathesis reactions. Examples have been shown for CF oxidation, reduction, and cyclopropanation reactions, where strategic residence-time control allows the formation of unprecedented reaction products not observed in batch reactions.

Through fine-tuning of the residence time for CF reaction optimization, harsh reaction conditions or aggressive reagents can be avoided. Importantly, the fine-tuning of the residence time can open up significant new fields. CF transformation may have the potential to revolutionize the fine-chemical and pharmaceutical industries. The search for such applications of CF systems started shortly after their discovery, and increasing numbers of studies are currently supporting their utility in drug development. Moreover, efforts in this area are expected to intensify.

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