Tetrahedron 69 (2013) 2885–2890

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The impact of Novel Process Windows on the Claisen rearrangement

Hiroki Kobayashi [a,b], Brian Driessen [a], Dannie J.G.P. van Osch [a], Ali Talla [a], Shinichi Ookawara [b], Timothy Noël [a,*], Volker Hessel [a,*]

[a] Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, Den Dolech 2, 5600 MB Eindhoven, The Netherlands
[b] Department of Chemical Engineering, Graduate School of Science and Engineering, Tokyo Institute of Technology, Meguroku, Tokyo 152-8552, Japan

ARTICLE INFO

Article history:
Received 5 December 2012
Received in revised form 19 January 2013
Accepted 11 February 2013
Available online 15 February 2013

Keywords:
Microreactors
Novel Process Windows
Flow chemistry
Claisen
High temperature

ABSTRACT

The impact of Novel Process Windows on the Claisen rearrangement in microflow was investigated. Elevated temperatures (up to 300 °C) were crucial to achieve full conversion of allyl phenyl ether in the Claisen rearrangement. We observed that 1-butanol was the optimal reaction solvent for this transformation in flow. Solvent-free reaction conditions were feasible for the Claisen rearrangement and provided quantitative yields of the target product at 280 °C and 100 bar. Also elevated reaction pressures (up to 300 bar) were investigated in the Claisen rearrangement. We found that thermal expansion and pressure-related compression phenomena cannot be ignored at such harsh reaction conditions. These phenomena lead to large deviations of the desired residence time (as calculated from the nominal flow rate) and have a clear impact on the observed reaction trends. Finally, we also investigated the temperature effect on the Johnson–Claisen rearrangement of cinnamyl alcohol. Quantitative yields were obtained at 200 °C and at 100 bar.

1. Introduction

In 2005, continuous manufacturing was selected by the ACS GCI Pharmaceutical Roundtable as the number one 'Key Green Engineering Research Area for Sustainable Manufacturing'.[1] While continuous manufacturing is a mainstay in chemical industries, such as the confectionary and petroleum industry, it has only recently received more interest from the pharmaceutical industry.[2,3] More specifically, microreactor technology has attracted attention as an enabling tool for novel reaction development and scale-up. The use of such microreactor devices has enabled synthetic chemists and process engineers to perform reactions with an unprecedented control over mixing, mass- and heat-transfer, safety, reaction/residence time, and other process parameters, which results in an enhanced reproducibility.[4] In addition, it allows the practitioner to utilize harsh reaction conditions (e.g., high temperature, pressure, and reactant concentration), which are far from the common laboratory practice, in a safe and reliable fashion. These new processing conditions, which can be attained by means of microreactor technology, have been called 'Novel Process Windows'.[5]

One reaction class that can benefit significantly from Novel Process Windows is the sigmatropic rearrangement. Such pericyclic reactions are typically initiated at high reaction temperatures and require in batch several hours reaction time to reach full conversion.[6] Therefore, catalytic versions of sigmatropic rearrangements were developed to reduce reaction times, to perform the reaction under milder conditions and to avoid side reactions.[7] To avoid the use of such toxic catalysts, green alternatives are strongly desired, which can accelerate sigmatropic rearrangements efficiently. One such strategy involves the use of microwave-assisted heating.[8] Whereas short reaction times and minimal by-product formation are obtained, limited scale-up potential of microwave chemistry remains a problem. Recently, flow chemistry has been employed to accelerate the sigmatropic rearrangement.[9]

Because of its unimolecular reaction mechanism, we have identified the Claisen rearrangement of allyl phenyl ether as an ideal reaction platform to investigate several parameters with respect to the Novel Process Windows concept. In this paper, we will discuss the influence of high temperature, high pressure, high concentration, and solvent effects on the Claisen rearrangement and the Johnson–Claisen rearrangement.

2. Results and discussion

In order to study the influence of the different aspects of Novel Process Windows on the outcome of the Claisen rearrangement of allyl phenyl ether, a microfluidic system was assembled as depicted in Figs. 1 and 2. Solutions of allyl phenyl ether were pumped into the microreactor system by means of HPLC pumps. The capillary

* Corresponding authors. Tel.: +31 40 247 2973; e-mail addresses: t.noel@tue.nl (T. Noël), v.hessel@tue.nl (V. Hessel).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.02.038

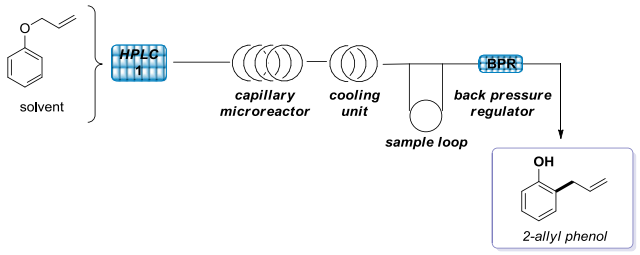
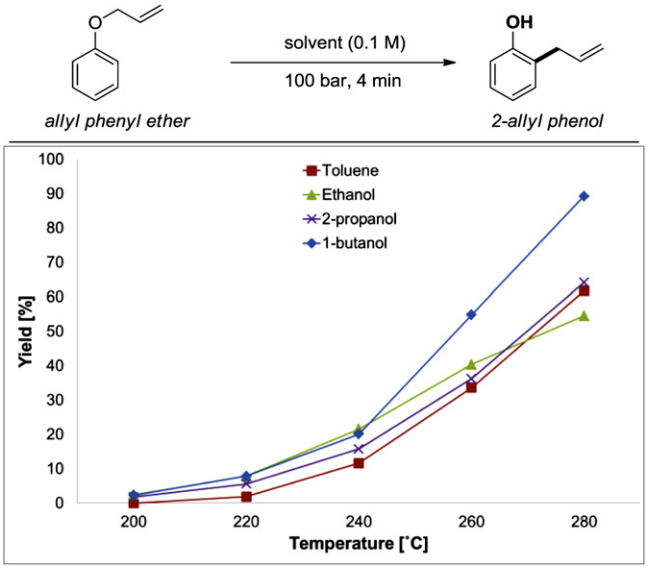


Fig. 1. Schematic representation of the microfluidic setup for the Claisen rearrangement of allyl phenyl ether to produce 2-allyl phenol.

Fig. 2. Microfluidic setup used for sigmatropic rearrangements in continuous-flow: (1) HPLC pumps, (2) heating bath with stainless steel capillary microreactor, (3) cooling bath, (4) sample loop, (5) back pressure regulator (BPR), (6) collection.

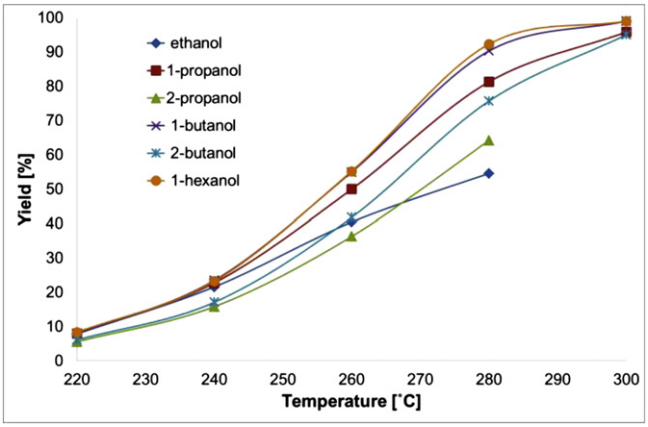
microreactor has a volume of 1 mL (stainless steel, 500 μm inner diameter, 5 m length) and was placed in a heating bath. After exiting the capillary reactor, the reaction medium is cooled to 15 °C in a 400 μL cooling unit (stainless steel, 500 μm inner diameter, 2 m length). The pressure in the microfluidic setup can be regulated by means of a back pressure regulator (BPR). The BPR utilized in this system can be varied in a range from 1 to 400 bar, thereby allowing to study the effect of pressure on the sigmatropic rearrangement. Although this BPR is very versatile for our purposes, it has a large internal volume of approximately 6 mL. Therefore, after the cooling unit, a sample loop is placed, which facilitates results gathering. In this fashion, results can be collected very rapidly and directly after the cooling unit. After the BPR, the product can be collected.

Our initial investigations focused on studying the temperature effect on the Claisen rearrangement. The use of high temperatures in sigmatropic rearrangement chemistry allows to reduce reaction times significantly.[10] However, such processing is rather difficult to attain under conventional batch conditions. In contrast, the combination of sealed microreactor technology and back pressure regulators provides opportunities to heat 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. We started with toluene as a solvent (concentration of allyl phenyl ether 0.1 M) and a residence time of 4 min.[9g] From Scheme 1, we can see that temperature has a very pronounced effect on the formation of the Claisen product, i.e., 2-allyl phenol. Below 240 °C, almost no product formation is observed. However, at high temperatures the Claisen rearrangement is much more efficient: 62% yield of 2-allyl phenol is obtained at 280 °C.



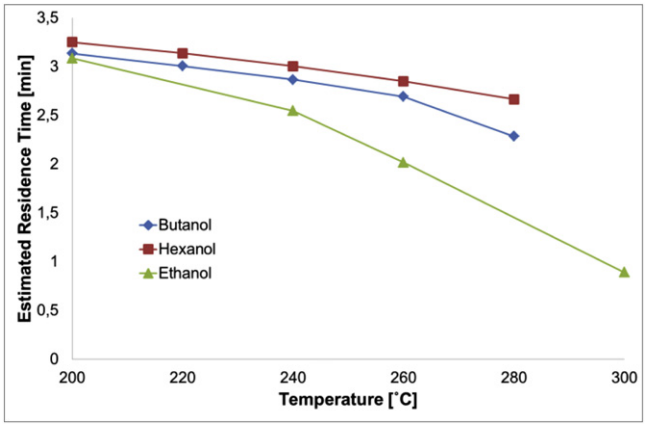
Scheme 1. Influence of solvent and temperature on the Claisen rearrangement of allyl phenyl ether. Reaction conditions: 0.1 M allyl phenyl ether in solvent, 100 bar, 4 min residence time, benzonitrile as internal standard. The yield was determined via HPLC analysis of the reaction mixture by comparison of the signal of the target product with the signal of the internal standard.

In order to reach higher yields, further reaction optimization was performed by varying the solvent system (Scheme 1). It is known that Claisen rearrangements are very dependent on solvent effects.[11,12] We found that by conducting the reaction in polar solvents, such as ethanol and 2-propanol, similar results were obtained as compared to toluene. However, a significant increase in yield was observed when 1-butanol was used as a solvent. Therefore, further investigation toward the nature of polar protic solvents was performed and is shown in Scheme 2. At 280 °C, the best results are obtained with primary alcohols with a longer carbon chain, i.e., 1-butanol and 1-hexanol. Secondary alcohols, such as 2-propanol and 2-butanol, are less efficient. The acceleration of the Claisen rearrangement in polar protic solvents can be attributed to their hydrogen-bonding capacity.[13] However, in contrast with observations under conventional batch conditions, the best results are in flow obtained with longer chain alcohols. Based on our experimental data, we have been able to calculate the activation energies for the Claisen rearrangement and this follows the same reaction order as observed in batch: ethanol>1-butanol≈1-hexanol.[14]



Scheme 2. Influence of polar protic solvents and temperature on the Claisen rearrangement of allyl phenyl ether. Reaction conditions: 0.1 M allyl phenyl ether in solvent, 100 bar, 4 min residence time, benzonitrile as internal standard. The yield was determined via HPLC analysis of the reaction mixture by comparison of the signal of the target product with the signal of the internal standard.

Therefore, we surmise that the observed trend in continuous-flow experiments is due to a different thermal expansion of the solvents.[15] Such thermal expansions are often neglected in many flow chemistry papers. However, as is evident from Scheme 3, large deviations of the desired residence time (i.e., 4 min as calculated from the nominal flow rate) are observed at high temperatures.[16,17] In addition, it is found that ethanol is much more expanded at high temperatures than 1-butanol and 1-hexanol, leading to significantly shorter residence time than the desired residence time. This finding can explain the observed trend in Schemes 1 and 2.



Scheme 3. Estimated residence time at elevated temperatures for 1-butanol, 1-hexanol, and ethanol.[16,17]

It is noteworthy that in all the experiments performed in this study no by-product formation could be detected via NMR, GC–FID, and HPLC–UV studies (Fig. 3). This was also evident by the good match between the calculated HPLC conversion and yield. We hypothesized that by-product formation is prevented by minimizing the exposure time in the heated zone to what is kinetically needed for the Claisen rearrangement itself. Extended reaction times at such elevated temperatures would result in the formation of isomers, e.g., by a double bond migration.

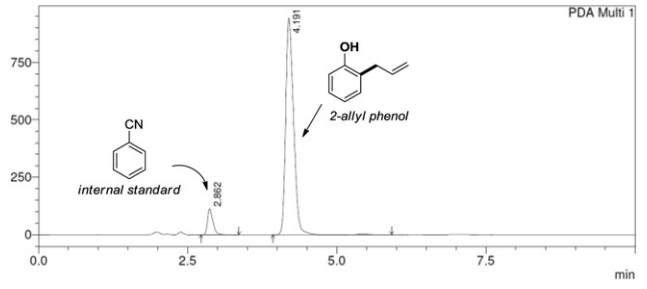
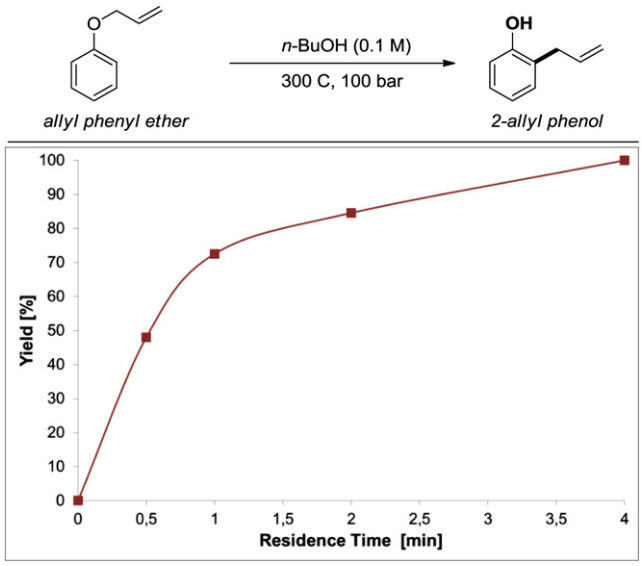


Fig. 3. A typical HPLC chromatogram of the crude reaction mixture after Claisen rearrangement of allyl phenyl ether. Reaction conditions: 0.1 M allyl phenyl ether in 1-butanol, 100 bar, 300 °C, 4 min residence time, benzonitrile as internal standard.

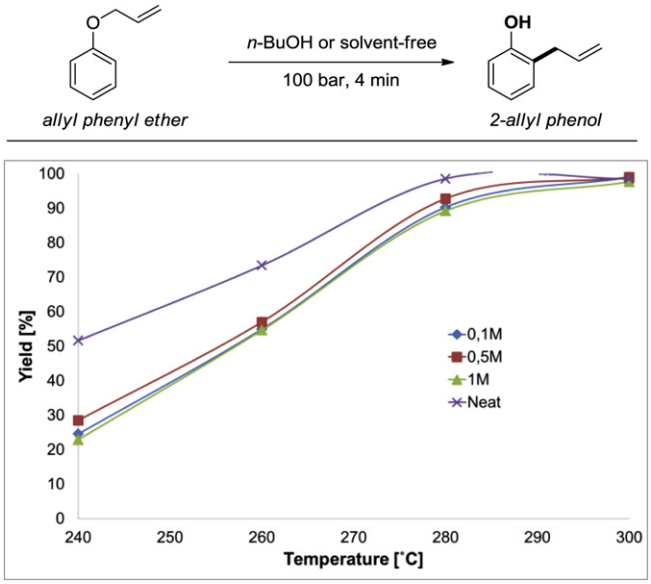
Since full conversion and quantitative yields were obtained within 4 min residence time, we examined whether even shorter residence times were feasible for the Claisen rearrangement of allyl phenyl ether (Scheme 4). However, lowering the residence time to 2 min is not sufficient to obtain full conversion; 82% yield of 2-allyl phenol was obtained.

Solvents play a key role in the development of many organic and inorganic synthetic transformations. In the pharmaceutical and fine chemical industry, solvent use constitute a share of 80–90% of the total mass utilization.[18] As we described above, solvent effects are also very pronounced in the Claisen rearrangement. Reducing the



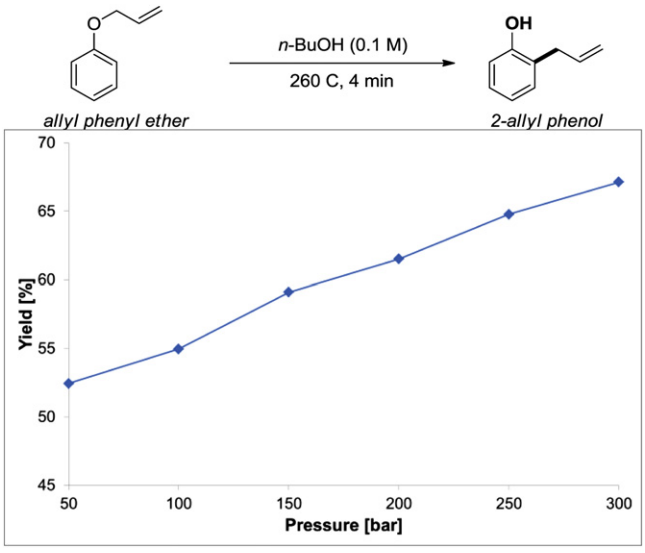
Scheme 4. Influence of the residence time on the Claisen rearrangement. Reaction conditions: 0.1 M allyl phenyl ether in 1-butanol, 100 bar, 300 °C, benzonitrile as internal standard. The yield was determined via HPLC analysis of the reaction mixture by comparison of the signal of the target product with the signal of the internal standard.

solvent consumption is however crucial to reduce waste generation. To address this need, we investigated if the Claisen rearrangement of allyl phenyl ether is affected by the concentration of the substrate. From Scheme 5, it is immediately clear that an increase of the concentration does not influence the reaction performance. However, the best solution to avoid any solvent issues is simply to perform the reaction under solvent-free reaction conditions. To realize this goal under continuous-flow microprocessing conditions, both reagents and products need to be in a liquid state to avoid clogging of the microchannels.[19,20] These requirements are met in the Claisen rearrangement of allyl phenyl ether; both the substrate and the target product are an oil at room temperature. To our delight, we observed that the Claisen rearrangement under neat reaction conditions proceeded well and afforded even increased yields when compared to diluted conditions (Scheme 5).

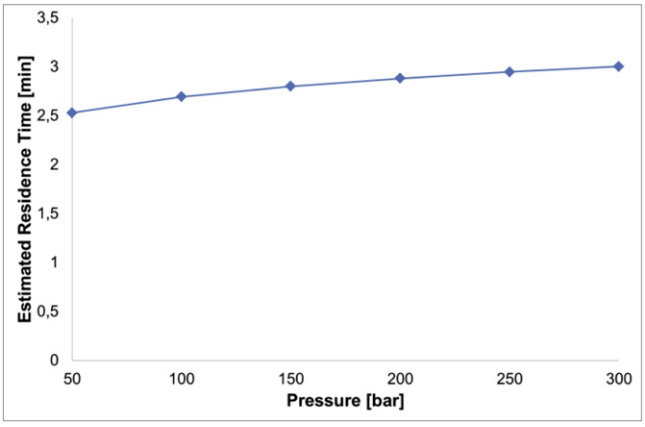


Scheme 5. Influence of reagent concentration on the Claisen rearrangement of allyl phenyl ether. Reaction conditions: 1-butanol or solvent-free, 100 bar, 4 min residence time, benzonitrile as internal standard. The yield was determined via HPLC analysis of the reaction mixture by comparison of the signal of the target product with the signal of the internal standard.

Another important physical parameter that can affect the reaction rate of the Claisen rearrangement is pressure.[21,22] Typically, transformations that are accompanied by a decrease in volume (activation volume) are accelerated by an increase in pressure. It has been shown in batch that the Claisen rearrangement can be accelerated by elevated pressures since high pressure favors the cyclic transition state.[23] The ability to change the back pressure in our microfluidic system prompted us to investigate the pressure dependence of the Claisen rearrangement of allyl phenyl ether in continuous-flow (Scheme 6). Hereto, we lowered the reaction temperature to 260 °C, which allows us to visualize potential variations in yield more clearly than at full conversion. We observed a significant increase in yield when we raised the pressure from 50 bar (53% yield) to 300 bar (68% yield). Although liquids are generally considered as incompressible fluids, at the elevated pressures and temperatures employed in this study this simplification is not valid anymore (Scheme 7).[24] We can conclude from Scheme 7 that there exists a significant difference in residence time of almost 30 s between the experiments performed at 50 bar and 300 bar. It is therefore difficult to attribute the increase in yield exclusively to pressure effects and we must take into account that part of the yield increase is due to prolonged reaction times.



Scheme 6. 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. The yield was determined via HPLC analysis of the reaction mixture by comparison of the signal of the target product with the signal of the internal standard.



Scheme 7. Estimated residence time at elevated pressures for 1-butanol.

Encouraged by the results obtained in the Claisen rearrangement of allyl phenyl ether, we next examined the Johnson–Claisen rearrangement in our microfluidic setup. This type of sigmatropic rearrangements involves the heating of an allylic alcohol and an excess of ethyl orthoacetate in the presence of an acid catalyst to yield an olefinic ester.[25] Our microfluidic setup was expanded with one additional HPLC pump for the addition of ethyl orthoacetate (Fig. 4).

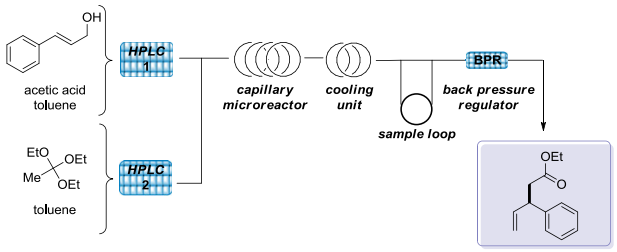
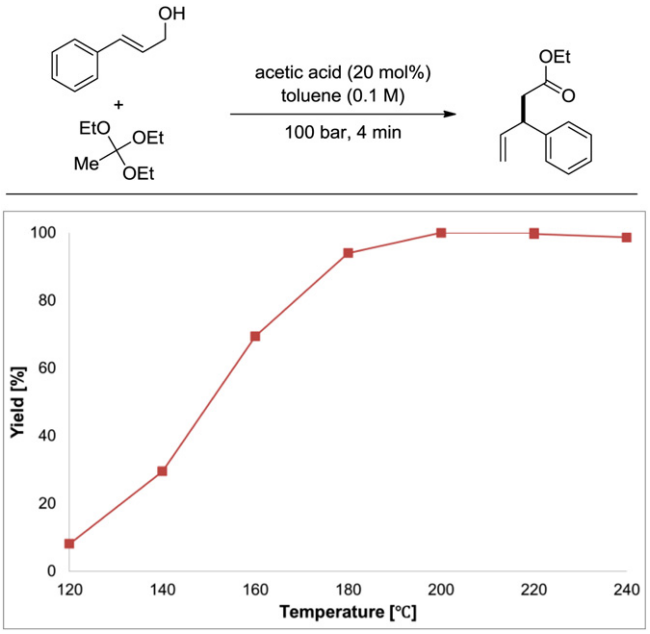


Fig. 4. Schematic representation of the microfluidic setup for the Johnson–Claisen rearrangement of cinnamyl alcohol to afford ethyl 3-phenylpent-4-enoate.

We found rapidly that the best reaction conditions involved the use of toluene as a solvent. In the absence of an acid catalyst, low conversions were usually obtained even at higher reaction temperatures. Optimal conversions were obtained within 4 min in the presence of 1.2 equiv of triethyl orthoacetate and 20 mol % acetic acid at high temperatures (Scheme 8). Full conversion was obtained at 200 °C.



Scheme 8. Influence of temperature on the Johnson–Claisen rearrangement of cinnamyl alcohol to afford ethyl 3-phenylpent-4-enoate. Reaction conditions: cinnamyl alcohol (0.1 M), triethyl orthoacetate (0.12 M), acetic acid (0.02 M), toluene, 100 bar, 4 min residence time, 1,3-dimethoxybenzene as internal standard. The yield was determined via HPLC analysis of the reaction mixture by comparison of the signal of the target product with the signal of the internal standard.

3. Conclusions

We have developed a high temperature, high pressure continuous-flow microreactor setup for the investigation of several aspects of the Novel Process Windows concept on the Claisen rearrangement of allyl phenyl ether (See Table 1 for an overview).

Table 1
Overview of the investigated aspects of the Novel Process Windows concept in the Claisen rearrangement of allyl phenyl ether[5]

Novel Process Windows	Results obtained in this study
High T processing	Full conversion was achieved at 300 °C
High p processing	15% Yield increase by increasing pressure
Routes at much increased concentration	- High concentrations are feasible without efficiency loss - Solvent-free conditions result in full conversion at 280 °C - Solvent effects: *n*-butanol optimal for flow processing
Safety and hazardous operations	High p and T processing can be done in microflow without comprimising safety of the environment
Process simplification	Full conversion can be obtained in 4 min under solvent free-conditions and in the absence of a catalyst

We have found that elevated temperatures (up to 300 °C) are mandatory to achieve full conversion and quantitative yields within 4 min residence time. In addition, interesting solvents effects were observed; with 1-butanol as the best solvent in microflow processing. This observation was in contrast with batch experiments. Explanation for this apparent mismatch is provided by solvent expansion phenomena, which lead to large deviations of the desired residence time (as calculated from the nominal flow rate). Solvent-free reaction conditions were feasible for the Claisen rearrangement of allyl phenyl ether; quantitative yields for 2-allyl phenol were obtained at 280 °C and 100 bar. The influence of reaction pressure (up to 300 bar) was also investigated. An increase of 15% yield was observed at 260 °C by increasing the pressure from 50 to 300 bar. Due to solvent compression at such elevated pressures, we believe that this yield increase cannot be entirely attributed to pressure effects. Finally, we also studied the temperature influence on the Johnson–Claisen rearrangement of cinnamyl alcohol to afford ethyl 3-phenylpent-4-enoate. Optimal reaction conditions involved the use of toluene as a solvent, acetic acid as a catalyst, 200 °C, 100 bar, and 4 min residence time.

4. Experimental section

4.1. General reagent information

Allyl phenyl ether, cinnamyl alcohol, benzonitrile 1,3-dimethoxybenzene, 1-butanol, 1-hexanol, ethanol, isopropanol, toluene, and diethyl ether were purchased from Sigma–Aldrich chemical company and used as received. Acetic acid and triethyl orthoacetate were purchased from Fluka and used as received. Sodium hydrogen carbonate was purchased from Merck and used as received. For the flow experiment, solutions were prepared in volumetric flasks.

4.2. General analysis information

The isolated reaction product was characterized by GC/MS, ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. Mass spectra were measured on a Shimadzu, GCMS-QP2010 Ultra. Nuclear Magnetic Resonance spectra were recorded on a Varian 400 MHz instrument. All ^{1}H NMR are reported in δ units, parts per million (ppm), and were measured relative to the signal for tetramethylsilane (0 ppm) in the deuterated chloroform. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. IR spectra were taken on a Perkin–Elmer Spectrum One equipped with a Universal ATR sampling accessory. GC analyzes were performed on Varian 430-GC with an FID detector using a Varian capillary column CP-Sil 5 CB (60 m, 0.25 mm, 1 μm). HPLC analyzes were performed on Shimadzu UFLC XR (205 nm) using a GraceSmart RP 18 5u column (150 mm, 4.2 mm). Benzonitrile was used as an internal standard for determination of HPLC yield and conversion in the Claisen rearrangement of allyl phenyl ether. 1,3-Dimethoxybenzene was used as an internal standard for both GC and HPLC measurement in the Johnson–Claisen rearrangement to determine the HPLC yield and conversion.

4.3. Experimental setup

The experimental setup used for the Claisen rearrangement is shown in Fig. 1, while the one for the Johnson–Claisen rearrangement in flow is described in Fig. 4. Reaction solutions were fed by two HPLC pumps (Knauer, Smartline 1050) and mixed by an SS T-mixer (IDEX Health & Science, bore size 0.5 mm). The mixer is connected to SS capillary tube reactor (ID 0.5 mm, OD 1/16″, 5 m), which was submerged in a temperature controlled oil bath (Lauda, Proline P8). The reactor is connected to the cooling section made by SS capillary tube (ID 0.5 mm, OD 1/16″, 2 m), which was submerged in a water bath (Lauda, ECO Silver RE620S) at 15 °C. The cooling section is connected to a 6 port valve (VICI) equipped with a sampling loop. The reactor pressure is controlled by the back pressure regulator (Bronkhorst, EL-PRESS).

4.4. Typical experimental procedure for Schemes 1, 2 and 4–6

A volumetric flask (100 mL) was charged with allyl phenyl ether (1.34 g, 10.0 mmol), benzonitrile (206 mg, 2.0 mmol), and *n*-BuOH was added to make the solution volume 100 mL. The solution was introduced in the microfluidic experimental setup at 0.250 mL/min (Space time: 4 min) by means of a single HPLC pump. The samples were collected via the sample loop at 30 and 40 min after each experiment to ensure steady state data collection. The samples were analyzed with HPLC–UV for quantification via the internal standard method. Each data point in the plot constitutes the average of two samples. Key experiments were performed at least twice by two different persons to enhance the reproducibility of our experiments.

4.5. Isolated yield of 2-allyl phenol

A volumetric flask (100 mL) was charged with allyl phenyl ether (1.34 g, 10.0 mmol) and *n*-BuOH was added to make the solution volume 100 mL. The solution was introduced in the microfluidic experimental setup at 0.250 mL/min (Space time: 4 min) by means of a single HPLC pump. The reaction temperature was set at 300 °C, the pressure at 100 bar. The whole experimental setup was flushed for 90 min at the reaction condition in order to achieve steady state. The difference with the above mentioned experiments is attributed due to the large internal volume of the back pressure regulator. After that, a sample was collected at the exit of the experimental setup for exactly 100 min (2.50 mmol of product). Solvent was evaporated in vacuo and pure product was obtained as a colorless oil (0.319 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.42 (d, J=6.2 Hz, 2H), 5.00 (s, 1H), 5.14–5.18 (m, 2H), 5.98–6.08 (m, 1H), 6.81 (d, J=7.6 Hz, 1H), 6.89 (t, J=7.6 Hz, 1H), 7.11–7.16 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.1, 115.8, 116.5, 121.0, 125.3, 127.9, 130.5, 136.4, 154.1 ppm. IR (ATR, cm^{-1}): 3455, 1638, 1591, 1489, 1455, 1214, 1169, 996, 914, 749. EI-MS: 134 [M^{+}].

4.6. Typical experimental procedure for Scheme 8

A volumetric flask (50 mL) was charged with cinnamyl alcohol (1.34 g, 10.0 mmol), acetic acid (0.12 g, 2.0 mmol), 1,3-

dimethoxybenzene (0.27 g, 2.0 mmol), and toluene was added to make the solution volume 50 mL. A second volumetric flask (50 mL) was charged with triethyl orthoacetate (1.95 g, 12.0 mmol) and toluene was added to make the solution volume 50 mL. Both solutions were flowed through the microfluidic experimental setup at 0.125 mL/min (Space time: 4 min) by means of two HPLC pumps. The samples were collected via the sample loop at 30 and 40 min after each experiment to ensure steady state data collection. The samples were analyzed with HPLC–UV for quantification of cinnamyl alcohol via the internal standard method. Another sample was collected and extracted with 1 M aqueous $NaHCO_3$; the organic phase was analyzed by GC–FID for the quantification of reaction product. Each data point in the plot constitutes the average of two samples. Key experiments were performed at least twice by two different persons to enhance the reproducibility of our experiments.

4.7. Isolated yield of ethyl 3-phenylpent-4-enoate

Isolated yield was obtained at optimum reaction condition (220 °C, 100 bar). A volumetric flask (50 mL) was charged with cinnamyl alcohol (1.35 g, 10.0 mmol), acetic acid (0.13 g, 2.2 mmol), and toluene was added to make the solution volume 50 mL. A second volumetric flask (50 mL) was charged with triethyl orthoacetate (1.95 g, 12.0 mmol) and toluene was added to make the solution volume 50 mL. Both solutions were fed at 0.125 mL/min and whole experimental setup was flushed for 90 min at the reaction condition in order to achieve steady state. The difference with the above mentioned experiments is attributed due to the large internal volume of the back pressure regulator. After that, a sample was collected at the exit of the experimental setup for exactly 100 min (2.50 mmol of product). The collected sample was washed 1 M aqueous sodium hydrogen (25 mL) carbonate and the aqueous layer was washed with same amount of diethyl ether (25 mL) twice. The combined organic layers were dried by $MgSO_4$. After filtration of $MgSO_4$, solvents were evaporated in vacuo and pure product was obtained as a colorless oil (0.475 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, J=7.1 Hz, 3H), 2.68 (dd, J=7.5, 15.0 Hz, 1H), 2.75 (dd, J=8.2, 15.0 Hz, 1H), 3.86 (q, J=7.1 Hz, 1H), 4.07 (q, J=7.1 Hz, 2H), 5.05 (s, 1H), 5.09 (s, 1H), 5.94–6.02 (m, 1H), 7.20–7.32 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 40.3, 45.6, 60.4, 114.8, 126.7, 127.5, 128.6, 140.3, 142.4, 171.9 ppm. IR (ATR, cm^{-1}): 2982, 1733, 1493, 1453, 1371, 1255, 1157, 1031, 918, 757. EI-MS: 204 [M^+].

Acknowledgements

Funding by the Advanced European Research Council Grant 'Novel Process Windows – Boosted Micro Process Technology' under grant agreement number 267443 is kindly acknowledged. H.K. and S.O. would like to thank the Graduate School of Engineering, Tokyo Institute of Technology for financial support. T.N. would like to acknowledge the support of the Netherlands Organization for Scientific Research (NWO) for a VENI grant. We would like to thank Svetlana Borukhova for her help in the assembly of the experimental setup and Bruno Cortese for advice in the kinetic analysis of the experimental results.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.038.

References and notes

1. The American Chemical Society (ACS) Green Chemistry Institute (GCI) and global pharmaceutical companies founded the ACS GCI Pharmaceutical Roundtable, see also Ref. 2.
2. Jimenez-Gonzalez, C.; Poechlauer, P.; Broxterman, Q. B.; Yang, B.-S.; am Ende, D.; Baird, J.; Bertsch, C.; Hannah, D. E.; Dell'Orco, P.; Noorman, H.; Yee, S.; Reintjens, R.; Wells, A.; Massonneau, V.; Manley, J. *Org. Process Res. Dev.* **2011**, *15*, 900–911.
3. Poechlauer, P.; Manley, J.; Broxterman, R.; Gregertsen, B.; Ridemark, M. *Org. Process Res. Dev.* **2012**, http://dx.doi.org/10.1021/op300159y
4. For selected reviews about micro flow chemistry: (a) Noël, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010–5029; (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, 4583–4592; (c) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38–54; (d) Ley, S. *Chem. Rec.* **2012**, *12*, 378–390; (e) Geyer, K.; Gustafsson, T.; Seeberger, P. H. *Synlett* **2009**, 2382–2391; (f) Noël, T.; Hessel, V. *ChemSusChem* **2013**, http://dx.doi.org/10.1002/cssc.201200913
5. For reviews pertaining Novel Process Windows: (a) Hessel, V.; Vural Gursel, I.; Wang, Q.; Noël, T.; Lang, J. *Chem. Eng. Technol.* **2012**, *35*, 1184–1204; (b) Hessel, V.; Cortese, B.; de Croon, M. H. J. M. *Chem. Eng. Sci.* **2011**, *66*, 1426–1448; (c) Razzaq, T.; Kappe, C. O. *Chem.—Asian J.* **2010**, *5*, 1274–1289; (d) Hessel, V. *Chem. Eng. Technol.* **2009**, *32*, 1655–1681; (e) Hessel, V.; Kralisch, D.; Krtschil, U. *Energy Environ. Sci.* **2008**, *1*, 467–478.
6. (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452; (b) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
7. (a) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50; (b) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597–643.
8. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
9. (a) Haraguchi, R.; Takada, Y.; Matsubara, S. *Chem. Lett.* **2012**, *41*, 628–629; (b) Rincon, J. A.; Barberis, M.; Gonzalez-Esguevillas, M.; Johnson, M. D.; Niemeier, J. K.; Sun, W.-M. *Org. Process Res. Dev.* **2011**, *15*, 1428–1432; (c) Kawanami, H.; Sato, M.; Chatterjee, M.; Otabe, N.; Tuji, T.; Ikushima, Y.; Ishizaka, T.; Yokoyama, T.; Suzuki, T. M. *Chem. Eng. J.* **2011**, *167*, 572–577; (d) Wahab, B.; Ellames, G.; Passey, S.; Watts, P. *Tetrahedron* **2010**, *66*, 3861–3865; (e) Sato, M.; Otabe, N.; Tuji, T.; Matsushima, K.; Kawanami, H.; Chatterjee, M.; Yokoyama, T.; Ikushima, Y.; Suzuki, T. M. *Green Chem.* **2009**, *11*, 763–766; (f) Kong, L.; Lin, Q.; Lu, X.; Yang, Y.; Jia, Y.; Zhou, Y. *Green Chem.* **2009**, *11*, 1108–1111; (g) Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Chem. Eng. Technol.* **2009**, *32*, 1702–1716.
10. (a) Varas, A. C.; Noël, T.; Wang, Q.; Hessel, V. *ChemSusChem* **2012**, *5*, 1703–1707; (b) Noël, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900–8903; (c) Hessel, V.; Hofmann, C.; Löb, P.; Löhndorf, J.; Löwe, H.; Ziogas, A. *Org. Process Res. Dev.* **2005**, *9*, 479–489.
11. For a review about solvent effects on Claisen rearrangement: (a) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225.
12. Acevedo, O.; Armacost, K. *J. Am. Chem. Soc.* **2010**, *132*, 1966–1975.
13. Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228–9229.
14. We refer to the Electronic Supplementary data for a kinetic analysis of our experimental results obtained in the Claisen rearrangement of allyl phenyl ether.
15. For examples, of high temperature applications where solvent expansion is taken into account: (a) Martin, R. E.; Morawitz, F.; Kuratli, C.; Alker, A. M.; Alanine, A. I. *Eur. J. Org. Chem.* **2012**, 47–52; (b) Cantillo, D.; Sheibani, H.; Kappe, C. O. *J. Org. Chem.* **2012**, *77*, 2463–2473.
16. The liquid densities of 1-butanol, 1-hexanol were estimated via a correlation given by Cibulka and Zikovh, see Ref. 17b. These equations are valid until 250 °C and 217 °C, respectively. For comparison reasons, we also used the equations for higher temperatures. The densities of ethanol were obtained from Ref. 17c.
17. (a) Cibulka, I. *Fluid Phase Equilib.* **1993**, *89*, 1–18; (b) Cibulka, I.; Zikovh, M. *J. Chem. Eng. Data* **1994**, *39*, 876–886; (c) Bazaev, A. R.; Abdulagatov, I. M.; Bazaev, E. A.; Abdurashidova, A. *Int. J. Thermophys.* **2007**, *28*, 194–219; (d) Ambrose, D.; Walton, J. *Pure Appl. Chem.* **1989**, *61*, 1395–1403.
18. Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133–137.
19. For a review about microreactor clogging: (a) Hartman, R. L. *Org. Process Res. Dev.* **2012**, *16*, 870–887; (b) Flowers, B. S.; Hartman, R. L. *Challenges* **2012**, *3*, 194–211.
20. (a) Noël, T.; Naber, J. R.; Hartman, R. L.; McMullen, J. P.; Jensen, K. F.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 287–290; (b) Kuhn, S.; Noël, T.; Gu, L.; Heider, P. L.; Jensen, K. F. *Lab Chip* **2011**, *11*, 2488–2492; (c) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J.-i. *Org. Process Res. Dev.* **2010**, *14*, 405–410.
21. (a) van Eldik, R.; Klaerner, F. G. *High Pressure Chemistry*; Wiley-VCH: Weinheim, 2002; (b) Drljaca, A.; Hubbard, C. D.; van Eldik, R.; Asano, T.; Basilevsky, M. V.; le Noble, W. J. *Chem. Rev.* **1998**, *98*, 2167–2290; (c) van Eldik, R.; Asano, T.; le Noble, W. J. *Chem. Rev.* **1998**, *89*, 549–688.
22. For a review about high-pressure reactions in glass microreactors: (a) Verboom, W. *Chem. Eng. Technol.* **2009**, *32*, 1695–1701.
23. (a) Brower, K. R. *J. Am. Chem. Soc.* **1961**, *83*, 4370–4372; (b) Walling, C.; Naiman, M. *J. Am. Chem. Soc.* **1962**, *84*, 2628–2632.
24. Dymond, J. H.; Malhorta, R. *Int. J. Thermophys.* **1988**, *9*, 941–951.
25. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.