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Scalable Microwave-Assisted Johnson−Claisen Rearrangement with a Continuous Flow Microwave System

Hiromichi Egami,[†] Souma Tamaoki,[†] Masato Abe,[‡] Noriyuki Ohneda,[§] Takeo Yoshimura,[§] Tadashi Okamoto,[§] Hiromichi Odajima,[§] Nobuyuki Mase,[‡] Kazuhiro Takeda,[‡] and Yoshitaka Hamashima*,[†]

[†]School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan

[‡]Applied Chemistry and Biochemical Engineering Course, Department of Engineering, Graduate School of Integrated Science and Technology, Shizuoka University, 3-5-1 Johoku, Hamamatsu, Shizuoka 432-8561, Japan

[§]SAIDA FDS Inc., 143-10 Isshiki, Yaizu, Shizuoka 425-0054, Japan

Supporting Information

ABSTRACT: We demonstrated the rapid Johnson−Claisen rearrangement of allyl alcohol and triethyl orthoacetate with a continuous flow apparatus combined with a microwave reactor. The reaction could be carried out without solvent, and only a catalytic amount of acetic acid was sufficient to promote the reaction under microwave irradiation conditions. To confirm the optimal reaction conditions found experimentally, we performed Design of Experiments (DoE) by the Nelder−Mead method and a least-squares method regarding the amount of acetic acid and the flow rate. Consequently, the highest yield of the desired γ,δ-unsaturated ester was obtained, and the productivity at the reaction step of the continuous process was 89.5 g/h under the optimal conditions, suggesting that 2.1 kg of the product would be theoretically obtained in 1 day. We also investigated the Johnson−Claisen rearrangement using other allylic alcohols, and the corresponding products were obtained in good to high yields per unit of time.

KEYWORDS: *Johnson−Claisen rearrangement, microwave, flow chemistry, γ,δ-unsaturated ester*

INTRODUCTION

[3,3]-Sigmatropic rearrangements are recognized to be an important tool for constructing unique organic frameworks. Among them, the Johnson−Claisen rearrangement is particularly useful for the construction of a γ,δ-unsaturated ester framework from an allylic alcohol,[1,2] and it has often been utilized in the synthesis of natural and unnatural bioactive compounds.[2] Generally, external heating by an oil bath or a heat block has traditionally been used for this transformation.[2] While such methods are reliable, simple reflux conditions normally require a longer reaction time until the completion of the reaction. As the key to address this issue, high pressure and high temperature are known to be effective to accelerate the reaction dramatically.[2c]

Microwave (MW) irradiation is now a common method in synthetic organic chemistry because rapid heating can be achieved easily by direct heating of materials, including solvents.[3] The Johnson−Claisen rearrangement has been performed under MW irradiation conditions, and a considerable shortening of the reaction time was observed. In 1992, Jones reported that the Johnson−Claisen rearrangement of cyclic allylic alcohols under MW irradiation proceeded in high yields within 9 min in the presence of montmorillonite KSF.[4] Subsequently, a MW-assisted Johnson−Claisen rearrangement in DMF[5] and a solvent-free reaction[6] were reported. However, a large excess amount of triethyl orthoacetate was necessary in these reactions.

Continuous flow chemistry has attracted much attention from the viewpoint of manufacturing technology because it is expected to improve safety, to reduce energy consumption, and to be scalable by protraction of the reaction time.[7] Hessel applied a high-pressure flow system to the Johnson−Claisen rearrangement (220 °C, 100 bar), but the production scale was less than 0.5 g after 100 min.[8] Although MW irradiation would be effective to accelerate the reaction at high temperature, MW-assisted synthesis is quite difficult to scale up because of the limited penetration depth of microwaves and the limited irradiation power. Therefore, some groups have devised multimode MW applicators and stopped-flow systems to partly overcome the problem.[9] In this context, we previously developed a highly efficient single-mode MW applicator with a resonance cavity in which the irradiation frequency is tuned immediately using a technology to adjust the frequency for electronic power transfer detected in the resonator, and we revealed the unique features of the apparatus by demonstrating fundamental organic reactions such as the Fischer indole synthesis, the Diels−Alder reaction, and the Williamson ether synthesis in a continuous manner.[10,11] Subsequently, we have been pursuing synthetic applications of our flow MW apparatus. Herein we disclose the rapid and scalable Johnson−Claisen rearrangement. To the best of our knowledge, there has been no report of the Johnson−Claisen rearrangement using a continuous flow MW system.

RESULTS AND DISCUSSION

In order to optimize the continuous flow MW-assisted Johnson−Claisen rearrangement, we chose simple allyl alcohol

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(**1**) as a model substrate. Triethyl orthoacetate (**2**) and a catalytic amount of acetic acid were mixed with **1**, and the resulting solution was pumped into the MW applicator. A schematic illustration of our flow MW system is shown in Figure 1.[10,12] The irradiation power and flow rate were controlled and monitored by the software. Since the Johnson–Claisen rearrangement is known to become faster at higher temperature, the MW irradiation power was set at 200 W in a single mode, which is the maximum for our apparatus.[10,12] The volume of the helical tube (borosilicate glassware) in the cavity was approximately 6.2 mL, and the reaction temperature was monitored at the end of the reactor (using a thermocouple located inside the helical tube reactor). The line pressure was adjusted to 2.5 MPa, which is the maximum pressure for safe usage, by a backpressure regulator to avoid boiling of the materials, including ethanol and acetic acid. The yields were determined by GC analysis using a calibration curve method[12] to prevent non-negligible reduction of the product during evaporation.

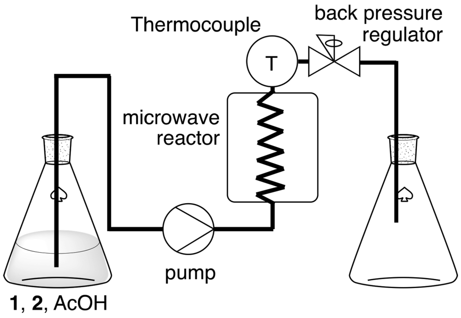
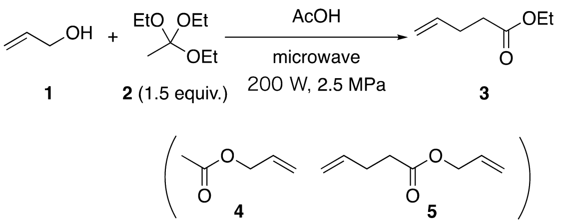


Figure 1. Flow microwave system.

The results of the screening of the reaction conditions are described in Table 1. First, the flow rate was examined (entries 1–6). Although only a 61% yield of the desired product was obtained at 9.0 mL/min (entry 6), a high yield of 91% was observed at 5.0 mL/min (entry 3). In this case, the reaction time was calculated to be only 74 s. The amount of acetic acid was screened next (entries 7–11). While the reaction efficiency was decreased with 0.03 equiv of acetic acid (entry 7), the best result was obtained when the reaction was operated with 0.2 equiv of acetic acid (entry 9). The desired product, **3**, was obtained in as high as 95% yield, accompanied by a small amount of allyl acetate (**4**) (entry 9).

To confirm the optimized reaction conditions, we performed a Design of Experiments (DoE)[13] analysis by the Nelder–Mead method[14] using the data listed for entries 1–11 (Figure 2a).[15] The Nelder–Mead method searches for the optimal conditions by reflection, expansion, and contraction of a simplex. This method is suitable for rough exploration compared with the least-squares method. In Figure 2, the impact of the flow rate and the amount of acetic acid on the yield of **3** was investigated.[15,16] According to the response surface obtained from the DoE study, a larger amount of acetic acid seemed necessary for the highest yield. Therefore, we conducted four additional reactions (entries 12–15). Interestingly, however, the yield decreased gradually as the amount of acetic acid was increased further (entries 9–15). This is probably due to the drop in the reaction temperature. Since acetic acid negatively affects the heating rate of alcoholic media under microwave heating conditions,[17] it seems difficult to estimate the exact impact of the acetic acid on the chemical yield separately. Because the obtained yields were inferior to that of entry 9, the DoE with a least-squares method[18] was next investigated using all of the data listed in Table 1 (entries 1–15) to search for the maximum point more exactly.[15] According to the response surface depicted in Figure 2b, the use of 0.25 equiv of acetic acid and a flow rate of 4.5 mL/min was suggested as the optimal conditions (entry 16). Indeed, the desired product **3** was formed in 96% yield (87% isolated yield) and the generation of the side product **4** was reduced, which was slightly better or almost equivalent to the best yield obtained experimentally. The present reaction could be scaled up easily. Thus, the reaction was run for 1 h under the optimal reaction conditions, and 89.5 g of **3** was successfully produced without difficulty after workup and purification (entry 17). In this case, the amount of the product was calculated to be 2.1 kg if the reaction were operated continuously for 1 day. In all cases examined in Table 1, only a trace amount of byproduct **5** was detected by GC analysis.

Table 1. Continuous Johnson–Claisen Rearrangement with 1 and 2



entry	flow rate [mL/min]	equiv of AcOH	temp. [°C]	yield of 3 [%][a]	yield of 4 [%][a]
1	2.0	0.1	239	87	trace
2	3.0	0.1	235	88	1
3	5.0	0.1	221	91	2
4	6.0	0.1	220	89	1
5	7.0	0.1	219	84	1
6	9.0	0.1	221	61	trace
7	5.0	0.03	230	78	trace
8	5.0	0.05	230	88	trace
9	5.0	0.2	227	95	4
10	5.0	0.3	226	91	4
11	5.0	0.35	217	89	2
12	5.0	0.45	214	87	2
13	4.5	0.5	212	86	1
14	5.0	0.6	209	79	1
15	5.0	0.7	207	75	1
16[b]	4.5	0.25	224	96 (87[c])	2
17[d]	4.5	0.25	224	96 (92[c])	trace

[a] The yields were determined by GC analysis. [b] Run under the conditions suggested by DoE with a least-squares method. [c] Isolated yield. [d] Run for 1 h.

Reactions of other allylic alcohols were carried out using the flow MW system (Chart 1).[12] Contrary to the reaction of simple allyl alcohol, allyl esters like **5** were formed in appreciable amounts in the crude mixtures.[12] Thus, the crude mixtures were treated with NaOEt or NaOMe to convert the allyl esters to the desired ethyl or methyl esters. A substituent at the *β*-position of the allylic alcohol did not have a significant impact on the reaction efficiency. Thus, when the reaction was carried out with *β*-methallyl alcohol as a substrate, the corresponding product **6** was obtained in high yield (91%). Trimethyl orthoacetate could also be used in this Johnson–

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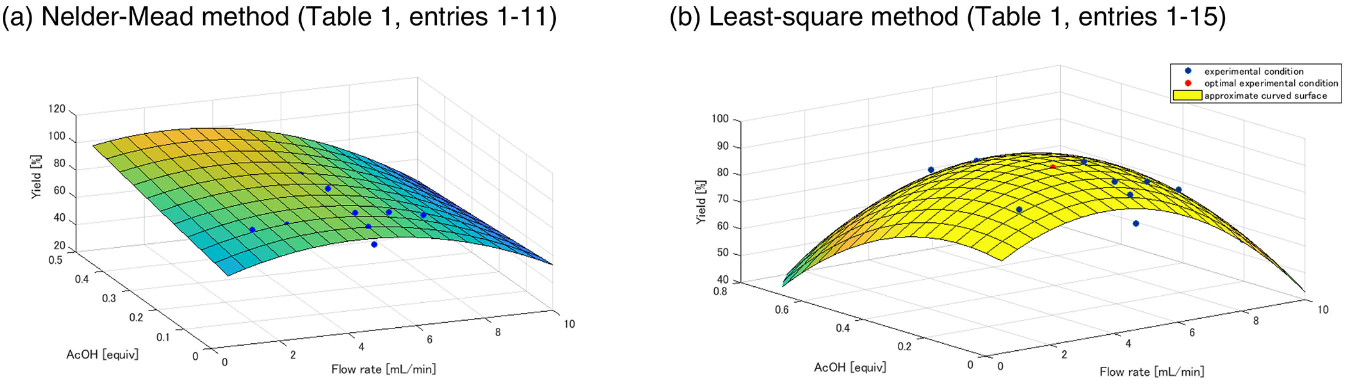
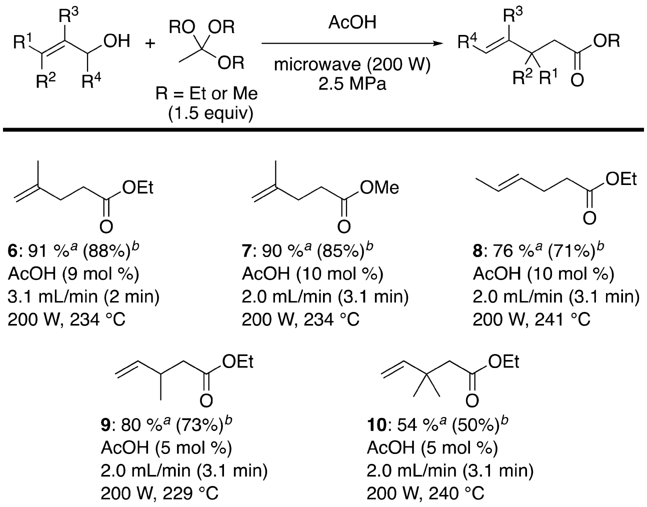


Figure 2. Response surfaces for the yield of **3** by the DoE technique.

Chart 1. Microwave-Assisted Continuous Johnson−Claisen Rearrangement



6: 91 %[a] (88%)[b]
AcOH (9 mol %)
3.1 mL/min (2 min)
200 W, 234 °C

7: 90 %[a] (85%)[b]
AcOH (10 mol %)
2.0 mL/min (3.1 min)
200 W, 234 °C

8: 76 %[a] (71%)[b]
AcOH (10 mol %)
2.0 mL/min (3.1 min)
200 W, 241 °C

9: 80 %[a] (73%)[b]
AcOH (5 mol %)
2.0 mL/min (3.1 min)
200 W, 229 °C

10: 54 %[a] (50%)[b]
AcOH (5 mol %)
2.0 mL/min (3.1 min)
200 W, 240 °C

[a]The yield was determined by NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [b]The value in parentheses is the isolated yield.

Claisen rearrangement without difficulty, and compound **7** was obtained in 90% yield. 3-Buten-2-ol, which is a secondary alcohol, was found to provide only the *E* isomer of **8** in 76% yield. Substitution at the γ-position of the allylic alcohol tended to decrease the reaction efficiency, probably because of steric hindrance in the transition state of the rearrangement. Nevertheless, the yield of **9** was still good. In the reaction of 3-methyl-2-buten-1-ol, the desired product **10** was obtained in modest yield (54%) under the described conditions. In this case, a lower flow rate to improve the yield was not applicable because of boiling in the reaction tube. Unfortunately, cinnamyl alcohol could not be used because unidentified byproducts were formed and the system became unstable, suggesting that the absorption wavelength and the dielectric loss of the reaction mixture might change during the reaction.

■ CONCLUSION

We have demonstrated the microwave-assisted continuous Johnson−Claisen rearrangement. The combination of a quick screening and the Design of Experiment technique provided the optimal conditions for the standard reaction with simple allyl alcohol. Various γ,δ-unsaturated esters were produced continuously in good to high yields, indicating the possibility of large-scale production. Further application of this system is ongoing in our group.

■ EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were measured on a JEOL ECX-500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million downfield from TMS (δ = 0 ppm) or $CDCl_3$ for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported on a scale relative to $CDCl_3$. Column chromatography was performed with silica gel N-60 (40−100 μm) purchased from Kanto Chemical Co., Inc. TLC analysis was performed on silica gel 60 F_{254}-coated glass plates (Merck). Visualization of TLC plates was carried out by means of UV irradiation at 254 nm and/or by spraying 12-molybdo(VI)phosphoric acid ethanol solution as the visualizing agent.

Experimental Procedure for Johnson−Claisen Rearrangement of Allyl Alcohol (1). Allyl alcohol (27.2 mL, 0.4 mol), triethyl orthoacetate (**2**)(109.4 mL, 0.6 mol), and acetic acid (5.7 mL, 0.1 mol) were charged into an Erlenmeyer flask. The mixture was pumped into the microwave reactor at a low rate of 4.5 mL/min under MW irradiation at 200 W. After 5 min, the exit temperature reached a steady state at 224 °C. At this point, the crude reaction mixture started to be collected for the next 1 min, while the exit temperature was maintained at 224 °C. A portion of the crude product was submitted to gas chromatography to determine the GC yield using *n*-decane as an internal standard. The organic material was diluted with Et_2O and washed with brine. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was evaporated with care, and the residue was purified by distillation to provide ethyl pent-4-enoate (**3**)[19a] (1.4 g, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.86−5.78 (m, 1H), 5.06 (qd, *J* = 1.7, 17.2 Hz, 1H), 5.00 (qd, *J* = 1.2, 10.3 Hz, 1H), 4.13 (q, *J* = 6.9 Hz, 2H), 2.42−2.35 (m, 4H), 1.25 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 136.6, 115.3, 60.1, 33.4, 28.8, 14.1.

Typical Procedure for Continuous Johnson−Claisen Rearrangement (Chart 1). β-Methallyl alcohol (33.9 mL, 0.4 mol), triethyl orthoacetate (109.4 mL, 0.6 mol), and acetic acid (2.1 mL, 36 mmol) were charged into an Erlenmeyer flask. The mixture was pumped into the microwave reactor at a flow rate of 3.1 mL/min under MW irradiation at 200 W. After 5 min, the exit temperature reached a steady state at 234 °C. At this point, the crude reaction mixture started to be collected for the next 1 min, while the exit temperature was maintained at 234 °C. The crude product was treated with NaOEt (2.9 g, 43 mmol) in EtOH. The mixture was neutralized with 1 N HCl aqueous solution. The organic material was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1 to 3:1) to provide ethyl 4-methylpent-4-enoate (**6**) (1.1 g, 88%) as a colorless oil.

*Ethyl 4-Methylpent-4-enoate (**6**).*[19b] Colorless oil (1.1 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.74 (s, 1H), 4.69 (s, 1H), 4.13 (q, *J* = 6.9 Hz, 2H), 2.47−2.44 (m, 2H), 2.35−2.32 (m, 2H), 1.74 (s, 3H), 1.26 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 144.0, 110.2, 60.2, 32.6, 32.6, 22.4, 14.1.

*Methyl 4-Methylpent-4-enoate (**7**).*[19c] Colorless oil (762 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.74 (s, 1H), 4.68 (s, 1H), 3.67 (s, 3H), 2.48−2.45 (m, 2H), 2.35−2.32 (m, 2H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 144.1, 110.3, 51.6, 32.6, 32.4, 22.5.

*Ethyl (E)-Hex-4-enoate (**8**).*[19d] Colorless oil (552 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.52−5.39 (m, 2H), 4.13 (q, *J* = 6.9 Hz, 2H), 2.36−2.33 (m, 2H), 2.32−2.28 (m, 2H), 1.64 (d, *J* = 5.7 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 129.1, 125.8, 59.9, 34.1, 27.7, 17.6, 14.0.

*Ethyl 3-Methylpent-4-enoate (**9**).*[19b] Colorless oil (573 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.77 (ddd, *J* = 6.9, 10.3, 17.2 Hz, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 2.72−2.64 (m, 1H), 2.34 (dd, *J* = 6.9, 14.9 Hz, 1H), 2.25 (dd, *J* = 7.5, 14.9 Hz, 1H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 142.3, 113.1, 60.0, 41.1, 34.3, 19.5, 14.1.

*Ethyl 3,3-Dimethylpent-4-enoate (**10**).*[19e] Colorless oil (416 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.90 (dd, *J* = 10.6, 17.5 Hz, 1H), 4.99−4.93 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 2.29 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 146.8, 110.7, 59.9, 46.7, 36.1, 26.8, 14.2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00185.

Flow microwave applicator and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hamashima@u-shizuoka-ken.ac.jp.

ORCID

Hiromichi Egami: 0000-0002-7784-4987
Yoshitaka Hamashima: 0000-0002-6509-8956

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. A Simple Stereoselective Version of the Claisen Rearrangement Leading to *trans*-Trisubstituted Olefinic Bonds. Synthesis of Squalene. *J. Am. Chem. Soc.* **1970**, *92*, 741−743.

(2) For selected reviews, see: (a) Martín Castro, A. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939−3002. (b) Majumdar, K. C.; Nandi, R. K. The Claisen rearrangement in the synthesis of bioactive natural products. *Tetrahedron* **2013**, *69*, 6921−6957. (c) Hessel, V.; Shahbazali, E.; Noël, T.; Zelentsov, S. The Claisen Rearrangement − Part 2: Impact Factor Analysis of the Claisen Rearrangement, in Batch and in Flow. *ChemBioEng Rev.* **2014**, *1*, 244−261. (d) Fernandes, R. A.; Chowdhury, A. K.; Kattanguru, P. The Orthoester Johnson−Claisen Rearrangement in the Synthesis of Bioactive Molecules, Natural Products, and Synthetic Intermediates − Recent Advances. *Eur. J. Org. Chem.* **2014**, *2014*, 2833−2871.

(3) (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (b) Horikoshi, S.; Serpone, N. *Microwaves in Catalysis*; Wiley-VCH: Weinheim, Germany, 2016.

(4) Huber, R. S.; Jones, G. B. Acceleration of the Ortho Ester Claisen Rearrangement by Clay-Catalyzed Microwave Thermolysis: Expeditious Route to Bicyclic Lactones. *J. Org. Chem.* **1992**, *57*, 5778−5780.

(5) (a) Srikrishna, A.; Nagaraju, S.; Kondaiah, P. Application of Microwave Heating Technique for Rapid Synthesis of γ,δ-Unsaturated Esters. *Tetrahedron* **1995**, *51*, 1809−1816. (b) Kueh, J. T. B.; O'Connor, P. D.; Hügel, H.; Brimble, M. A. Synthetic Studies towards the Anti-inflammatory Agent, Oleocanthal Using a Johnson−Claisen (Orthoester) Rearrangement Strategy. *ARKIVOC* **2009**, *2009* (vii), 58−71.

(6) Mehl, F.; Bombarda, I.; Franklin, C.; Gaydou, E. M. Optimization of the Microwave-Assisted Ortho Ester Claisen Rearrangement: Application to Monoterpenols. *Synth. Commun.* **2010**, *40*, 462−468.

(7) For selected recent reviews, see: (a) Pastre, J. C.; Browne, D. L.; Ley, S. V. Flow Chemistry Syntheses of Natural Products. *Chem. Soc. Rev.* **2013**, *42*, 8849−8869. (b) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. Flow Chemistry: Intelligent Processing of Gas−Liquid Transformations Using a Tube-in-Tube Reactor. *Acc. Chem. Res.* **2015**, *48*, 349−362. (c) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology−A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688−6728. (d) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process Res. Dev.* **2016**, *20*, 2−25. (e) Kobayashi, S. Flow "Fine" Synthesis: High Yielding and Selective Organic Synthesis by Flow Methods. *Chem. - Asian J.* **2016**, *11*, 425−436.

(8) Kobayashi, H.; Driessen, B.; van Osch, D. J. G. P.; Talla, A.; Ookawara, S.; Noël, T.; Hessel, V. The Impact of Novel Process Windows on the Claisen Rearrangement. *Tetrahedron* **2013**, *69*, 2885−2890.

(9) (a) Glasnov, T. N.; Kappe, C. O. Microwave-Assisted Synthesis under Continuous-Flow Conditions. *Macromol. Rapid Commun.* **2007**, *28*, 395−410. (b) Cablewski, T.; Faux, A. F.; Strauss, C. R. Development and Application of a Continuous Microwave Reactor for Organic Synthesis. *J. Org. Chem.* **1994**, *59*, 3408−3412. (c) Wilson, N. S.; Sarko, C. R.; Roth, G. P. Development and Applications of a Practical Continuous Flow Microwave Cell. *Org. Process Res. Dev.* **2004**, *8*, 535−538. (d) Comer, E.; Organ, M. G. A Microreactor for Microwave-Assisted Capillary (Continuous Flow) Organic Synthesis. *J. Am. Chem. Soc.* **2005**, *127*, 8160−8167. (e) Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. A Simple Continuous Flow Microwave Reactor. *J. Org. Chem.* **2005**, *70*, 7003−7006. (f) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. Microwave-Assisted Suzuki Coupling Reactions with an Encapsulated Palladium Catalyst for Batch and Continuous-Flow Transformations.

Chem. - Eur. J. **2006**, *12*, 4407−4416. (g) Moseley, J. D.; Woodman, E. K. Scaling-Out Pharmaceutical Reactions in an Automated Stop-Flow Microwave Reactor. *Org. Process Res. Dev.* **2008**, *12*, 967−981. (h) Damm, M.; Glasnov, T. N.; Kappe, C. O. Translating High-Temperature Microwave Chemistry to Scalable Continuous Flow Processes. *Org. Process Res. Dev.* **2010**, *14*, 215−224. (i) Dressen, M. H. C. L.; van de Kruijs, B. H. P.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. Flow Processing of Microwave-Assisted (Heterogeneous) Organic Reactions. *Org. Process Res. Dev.* **2010**, *14*, 351−361. (j) Bergamelli, F.; Iannelli, M.; Marafie, J. A.; Moseley, J. D. A Commercial Continuous Flow Microwave Reactor Evaluated for Scale-Up. *Org. Process Res. Dev.* **2010**, *14*, 926−930. (k) Shore, G.; Yoo, W.-J.; Li, C.-J.; Organ, M. G. Propargyl Amine Synthesis Catalysed by Gold and Copper Thin Films by Using Microwave-Assisted Continuous-Flow Organic Synthesis (MACOS). *Chem. - Eur. J.* **2010**, *16*, 126−133. (l) Wiles, C.; Watts, P. Translation of Microwave Methodology to Continuous Flow for the Efficient Synthesis of Diaryl Ethers via a Base-mediated S_NAr Reaction. *Beilstein J. Org. Chem.* **2011**, *7*, 1360−1371. (m) Benaskar, F.; Patil, N. G.; Engels, V.; Rebrov, E. V.; Meuldijk, J.; Hulshof, L. A.; Hessel, V.; Wheatley, A. E. H.; Schouten, J. C. Microwave-Assisted Cu-Catalyzed Ullmann Ether Synthesis in a Continuous-Flow Milli-Plant. *Chem. Eng. J.* **2012**, *207−208*, 426−439. (n) Ullah, F.; Zang, Q.; Javed, S.; Zhou, A.; Knudtson, C. A.; Bi, D.; Hanson, P. R.; Organ, M. G. Multicapillary Flow Reactor: Synthesis of 1,2,5-Thiadiazepane 1,1-Dioxide Library Utilizing One-Pot Elimination and Inter-/Intramolecular Double aza-Michael Addition via Microwave-Assisted Continuous-Flow Organic Synthesis (MACOS). *J. Flow Chem.* **2012**, *2*, 118−123. (o) Öhrngren, P.; Fardost, A.; Russo, F.; Schanche, J.-S.; Fagrell, M.; Larhed, M. Evaluation of a Nonresonant Microwave Applicator for Continuous-Flow Chemistry Applications. *Org. Process Res. Dev.* **2012**, *16*, 1053−1063. (p) Baxendale, I. R.; Hornung, C.; Ley, S. V.; Molina, J. M. M.; Wikström, A. Flow Microwave Technology and Microreactors in Synthesis. *Aust. J. Chem.* **2013**, *66*, 131−144. (q) Nishioka, M.; Miyakawa, M.; Daino, Y.; Kataoka, H.; Koda, H.; Sato, K.; Suzuki, T. M. Single-Mode Microwave Reactor Used for Continuous Flow Reactions under Elevated Pressure. *Ind. Eng. Chem. Res.* **2013**, *52*, 4683−4687. (r) Konda, V.; Rydfjord, J.; Sävmarker, J.; Larhed, M. Safe Palladium-Catalyzed Cross-Coupling with Microwave Heating Using Continuous-Flow Silicon Carbide Reactors. *Org. Process Res. Dev.* **2014**, *18*, 1413−1418.

(10) (a) Yokozawa, S.; Ohneda, N.; Muramatsu, K.; Okamoto, T.; Odajima, H.; Ikawa, T.; Sugiyama, J.; Fujita, M.; Sawairi, T.; Egami, H.; Hamashima, Y.; Egi, M.; Akai, S. Development of a Highly Efficient Single-Mode Microwave Applicator with a Resonant Cavity and Its Application to Continuous Flow Syntheses. *RSC Adv.* **2015**, *5*, 10204−10210. (b) Egami, H.; Sawairi, T.; Tamaoki, S.; Ohneda, N.; Okamoto, T.; Odajima, H.; Hamashima, Y. (*E*)-3-[4-(Pent-4-en-1-yloxy)phenyl]acrylic Acid. *Molbank* **2018**, *2018*, M996.

(11) Other groups have reported some fundamental reactions using the same flow microwave reactor. See: (a) Musio, B.; Mariani, F.; Sliwínski, E. P.; Kabeshov, M. A.; Odajima, H.; Ley, S. V. Combination of Enabling Technologies to Improve and Describe the Stereoselectivity of Wolff-Staudinger Cascade Reaction. *Synthesis* **2016**, *48*, 3515−3526. (b) Barham, J. P.; Tanaka, S.; Koyama, E.; Ohneda, N.; Okamoto, T.; Odajima, H.; Sugiyama, J.; Norikane, Y. Selective, Scalable Synthesis of C_{60}-Fullerene/Indene Monoadducts Using a Microwave Flow Applicator. *J. Org. Chem.* **2018**, *83*, 4348−4354. (c) Ichikawa, T.; Mizuno, M.; Ueda, S.; Ohneda, N.; Odajima, H.; Sawama, Y.; Monguchi, Y.; Sajiki, H. A Practical Method for Heterogeneously-Catalyzed Mizoroki−Heck Reaction: Flow System with Adjustment of Microwave Resonance as an Energy Source. *Tetrahedron* **2018**, *74*, 1810−1816.

(12) See the Supporting Information.

(13) Weissman, S. A.; Anderson, N. G. Design of Experiments (DoE) and Process Optimization. A Review of Recent Publications. *Org. Process Res. Dev.* **2015**, *19*, 1605−1633.

(14) (a) Nelder, J. A.; Mead, R. A Simplex Method for Function Minimization. *Comput. J.* **1965**, *7* (4), 308−313. (b) Landagaray, E.; Vaccher, C.; Yous, S.; Lipka, E. Design of experiments for enantiomeric separation in supercritical fluid chromatography. *J. Pharm. Biomed. Anal.* **2016**, *120*, 297−3−5. (c) Cortés-Borda, D.; Kutonova, K. V.; Jamet, C.; Trusova, M. E.; Zammattio, F.; Truchet, C.; Rodriguez-Zubiri, M.; Felpin, F.-X. Oprimizing the Heck−Matsuda Reaction in Flow with a Constraint-Adapted Direct Search Algorithm. *Org. Process Res. Dev.* **2016**, *20*, 1979−1987. (d) Hermann, P. D.; Cents, T.; Klemm, E.; Ziegenbalg, D. Determination of the Kinetics of the Ethoxylation of Octanol in Homogeneous Phase. *Ind. Eng. Chem. Res.* **2017**, *56*, 6176−6185.

(15) Explanatory variables in this study are the coefficients c_1-c_6 in the following equation:

$$z = c_1x^2 + c_2y^2 + c_3xy + c_4x + c_5y + c_6$$

where x is the amount of acetic acid, y is the flow rate, and z is the yield. The objective variable is the relative sum of squared errors (RSSE) between the experimental and estimated values. A second-order response surface was searched to minimize the RSSE in the six-dimensional space of c_1-c_6. Although the model could constrain the physical and chemical conditions, the search had no constraint. The RSSE values were 1.7% and 1.3% for Figure 2A and Figure 2B, respectively. To propose a successive search method for the optimal conditions, a rough initial RSSE study was acceptable. The surface shows the tolerances with respect to the amount of acetic acid and the flow rate.

(16) The yield should vary according to the amount of acetic acid, the flow rate, and the reaction temperature. However, the reaction temperature is correlated with the amount of acetic acid and the flow rate when the irradiation power is constant (see the Supporting Information). Thus, the optimization had to be carried out at variable temperature by varying the amount of acetic acid and the flow rate.

(17) (a) Heyding, R. D.; Winkler, C. A. Solvent Effect on Iodide Exchange. *Can. J. Chem.* **1951**, *29*, 790−803. (b) Routray, W.; Orsat, V. Dielectric Properties of Concentration-Dependent Ethanol + Acids Solutions at Different Temperatures. *J. Chem. Eng. Data* **2013**, *58*, 1650−1661.

(18) Fisher, R. A. The Goodness of Fit of Regression Formulae, and the Distribution of Regression Coefficients. *J. R. Stat. Soc.* **1922**, *85* (4), 597−612.

(19) (a) Durrwachter, J. R.; Wong, C.-H. Fructose 1,6-Diphosphate Aldolase Catalyzed Stereoselective Synthesis of *C*-Alkyl and *N*-Containing Sugars: Thermodynamically Controlled C−C Bond Formations. *J. Org. Chem.* **1988**, *53*, 4175−4181. (b) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. Palladium-Catalyzed Synthesis of Tetrahydrofurans from γ-Hydroxy Terminal Alkenes: Scope, Limitations, and Stereoselectivity. *J. Org. Chem.* **2005**, *70*, 3099−3107. (c) DeBenedetto, M. V.; Green, M. E.; Wan, S.; Park, J.-H.; Floreancig, P. E. Multicomponent Synthesis of α-Branched Amides. *Org. Lett.* **2009**, *11*, 835−838. (d) Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. Total Synthesis of (−)-Histrionicotoxin. *Org. Lett.* **2011**, *13*, 4446−4449. (e) Matsui, K.; Negishi, A.; Takahatake, Y.; Sugimoto, K.; Fujimoto, T.; Takashima, T.; Kondo, K. A Convenient Synthesis of Ethyl 3-(2,2-Dihaloethenyl)-2,2-dimethylcyclo-propanecarboxylates and Its Modifications for cis-Isomer Enrichment. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 221−227.

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