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# Highly selective non-catalytic Claisen rearrangement in a high-pressure and high-temperature water microreaction system

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ABSTRACT

High-pressure and high-temperature water (HPHT-$H_2O$) microreaction system was proven to be an efficient method to carry out the non-catalytic Claisen rearrangement. Allyl phenyl ether undergoes Claisen rearrangement to obtain *o*-allylphenol with a very high yield and selectivity of 98% within a short reaction time of 13.4 s at 265 °C and 5 MPa pressure. Compare to the solvent-free microreaction, HPHT-$H_2O$ plays an important role to accelerate the reaction as a catalyst by transferring a proton along locally formed hydrogen bond with the substrate. Finally, the obtained product can be separated completely from the aqueous suspension within the time range of 40 min to 24 h after the reaction. Even though the reaction has occurred in aqueous conditions, little side reactions, such as hydrolysis, hydration, or pyrolysis, was found.

## 1. Introduction

The Claisen rearrangement, is one of the fundamental reactions of sigmatropic rearrangement and offered a potentially useful tool to the C–C bond formation [1]. Since after the discovery of this reaction in 1912 by Claisen [2], the Claisen rearrangement has drawn significant attention for wide application to the synthesis of large variety of important intermediates, fine chemicals and natural products [3]. A variety of catalysts were reported to activate the reaction and induce the asymmetry with Lewis acids, such as $BCl_3$ [1a,4a], $R_2AlCl$ [4b], and $PdCl_2(MeCN)_2$ [4c], to build up the greener process by the reduction of energy consumption, reaction time and waste production [1b].

Here, we have attempted to focus on the development of greener Claisen rearrangement through the concept of the methodology based on the high-pressure and high-temperature water (HPHT-$H_2O$) and microreactor [5]. HPHT-$H_2O$ is commonly considered as a benign solvent for its non-toxicity and abundant natural occurrence, which received much attention from the viewpoint of green reaction medium. Physical properties like dielectric constant ($\varepsilon$) can be tuned easily by controlling the pressure and temperature [6]. This HPHT-$H_2O$ itself also acts as a catalyst [6a]. Previously, Mukaide et al. was studied Claisen rearrangement using flow-type high-pressure and high-temperature NMR measurement, and evaluated the reaction rate in the condition of subcritical water [7]. However, the reaction proceeds in sub- and supercritical water, exploring Claisen rearrangement in milder conditions to produce variety of products is important in terms of cost effectiveness and safety issues for the industrial fields. Thus, we introduce microreactor for high-pressure and high-temperature water reaction system to develop effective chemical micro processing reactor, which is generally defined as a continuous flow through regular domains with characteristic fluid channels of dimension much below those applied in the conventional apparatus, typically in the sub-millimeter range. These microreaction devices provide an enhancement of the mixing rate, and have efficient heat and mass transfer [8]. Therefore, HPHT-$H_2O$ in combination with microreaction system offers a continuous operation characterized by an instantaneous heating up to very high-temperature (over 200 °C) and a subsequent quenching of the substrates with vigorous mixing by high-pressure and high-temperature micromixer [5]. As a result, it would accelerate the reaction rate and prevent the consecutive hydrolysis and pyrolysis of the substrate. The obtained results confirm the feasibility of this approach to afford high selectivity, easy product separation and waste reduction compared to the conventional organic solvents or solvent-free conditions [9].

Scheme 1 represents the Claisen rearrangement of allyl phenyl ether (**1a**) to *o*-allylphenol (**2a**). According to the literature, in a non-catalytic reaction condition under the batchwise operation the reaction could proceed to the formation of **2a** [10]. Table 1 compares the result of reported non-catalytic batchwise reaction with the HPHT-$H_2O$ microreactor (runs 1–5). It is evident that

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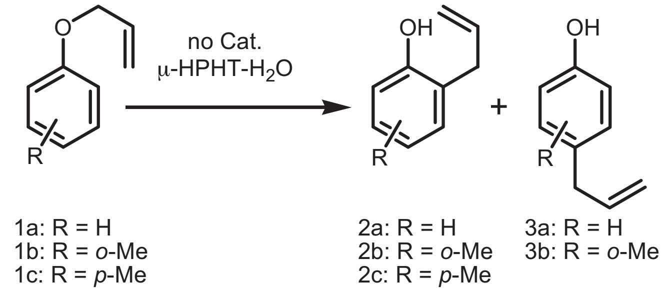


**Scheme 1.** Non-catalytic Claisen rearrangement in HPHT-$H_2O$ microreaction system.

in a solvent-free conventional heating method, **2a** was produced with 85% yield at 220 °C, 0.1 MPa pressure and the reaction time of 6 h (Table 1; run 1) [10a]. While in a similar batchwise process, the yield of **2a** was 84% in a shorter reaction time of 10 min, at 240 °C and 3.4 MPa using HPHT-$H_2O$ (Table 1; run 2) [10b]. Again, under the same batchwise process, as the temperature and the reaction time increased to 245 °C and 60 min, the yield of **2a** was decreased to 45% due to the formation of by-products like 2-hydroxypropylphenol and 2-methylcoumaran. Furthermore, exclusive formation of 2-methylcoumaran of 72% yield [10c] within 60 min was reported at 250 °C and 4.0 MPa pressure. Considering the solvent-free microwave heating process, **2a** was obtained with a poor yield of 21% at 325–361 °C, 0.1 MPa and 10 min (Table 1; run 3). However, the yield of **2a** was drastically improved to 92% using DMF as solvent at 300–315 °C, 0.1 MPa and in a shorter reaction time of 6 min (Table 1; run 4) [10c].

In this work an attempt has been made to describe a highly efficient non-catalytic Claisen rearrangement using a HPHT-$H_2O$ microreaction system.

## 2. Reaction system and methods

### 2.1. Chemicals

Reagent grade of allyl aryl ether (**1a**), 2-methyl allyl aryl ether (**1b**), 4-methyl allyl aryl ether (**1c**) were purchased from Tokyo Chemical Industry Co. Ltd. and Wako Pure Chemical Industries Ltd., and used as the reactants without further purifications.

### 2.2. Experimental procedure

The Claisen rearrangement with HPHT-$H_2O$ in microreaction system was carried out using a flow-type of reactor equipped with a high-pressure and high-temperature infrared spectroscopy (JASCO, FT-IR620) as shown in Fig. 1. The microreaction system was composed of an inlet micro-tube (i.d. 0.5 mm, length: 300 mm, SUS316), a micro-tee-mixer (i.d. 0.5 mm, SUS316) and a microreactor tube (length: 247 mm, i.d. 0.5 mm, SUS316) installed into a furnace (maximum electric power 0.5 kW) in place of the high-pressure and high-temperature IR flow cell except for the purpose of IR analysis. HPHT-$H_2O$ is generated by passing through the heating micro-tube (i.d. 0.5 mm, length: 500 cm) in the furnace with pump (JASCO PU-2086). Total Pressure was controlled by a back-pressure regulator (JASCO back-pressure regulator 880-81, varied from 0.1 to 30 MPa) at the end of the microreaction system.

The mixture of allyl aryl ether (**1a**, 90.0 g, 0.671 mol) and toluene (3.09 g, 33.5 mmol, 0.05 equiv.) as an internal standard was charged into a syringe pump (ISCO 260DX). The HPHT-$H_2O$ microreaction system can heat up the substrate to the desired temperature (varied from 200 to 300 °C) in the heating tube and then mixed rapidly with HPHT-$H_2O$ by micro-tee-mixer. The reaction was proceed by passing through the microreactor tube, followed by quenching to sufficiently low temperatures within 10 s while moving through a cooling flange and cooling coil (length: 460 cm, i.d. 0.5 mm, SUS316). The reaction time (=total residence time) was adjusted to be shorter than 10 min and finally pressure was reduced by a back-pressure regulator. The fluctuations in temperature and pressure were controlled within ±0.2 °C and 0.1 MPa, respectively.

Detailed analysis of the reaction mixture was performed by GC–MS/MS (Varian CP-3800-1200L) for qualitative analysis and GC-FID (Agilent Technologies Inc., GC6890N) for quantitative analysis using calibration curve of an authentic sample based on the internal standard of toluene.

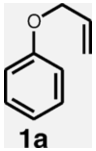
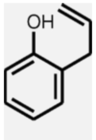
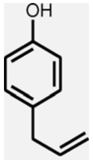
## 3. Results and discussion

Initially, the reaction condition (pressure and temperature) for Claisen rearrangement of allyl aryl ether (**1a**) in HPHT-$H_2O$ by microreaction system was optimized. The highest yield as well as the highest selectivity of **2a** was achieved at the optimized reaction condition of 5 MPa and 265 °C.

### 3.1. Claisen rearrangement

The results of the Claisen rearrangement of some allyl aryl ethers under various conditions were summarized in Table 1. When the reaction was conducted without HPHT-$H_2O$, **2a** was obtained with poor yield of 37% at 265 °C for 6 min (Table 1, run 6). It was reported that at 220 °C and the reaction time of >20 min Claisen rearrangement of allyl *p*-methoxy allyl aryl ether results 100% selectivity of the desired product using microreactor under the solvent-free condition [10d]. However, the reaction time of 20 min is still longer compared to the microwave irradiation method. The chemical microprocessing often best in terms of rate acceleration almost quantitative yield of **2a** was achieved within 149 s. Acevedo et al. theoretically studied the Claisen rearrangement in aqueous phase using QM/MM/MC simulation [11]. The rate acceleration for the rearrangement was shown to be correlated to increasing the site-specific hydrogen bonding between the oxygen atom of the reactant and the water molecules, where the accessibility of the interfacial waters to the solute plays large role on the rate accelerations was also proposed. Therefore, HPHT-$H_2O$ has potential to destabilize the reactant **1a** and accelerate the reaction into an excellent conversion (100%), yield (98%) and selectivity (98%) of **2a** (run 12). Interestingly, in spite of the almost same residence time in runs 9 and 10 (Table 1), yields are quite different (78% in run 9 and 95% in run 10) when flow rate of HPHT-$H_2O$ was changed. Furthermore, in the case of run 9, further reactions were observed to produce **3a**, **4a**, **5a**, and other unknown by-products as shown in Scheme 2. To clarify this result, the yield of **2a** was plotted against the reaction time (tee-mixer to the cooling coil, where the reaction would be accelerate by HPHT-$H_2O$) and shown in Fig. 2, which shows that as the reaction time increased the yield of **2a** was decreased. The proportional relationship between yield and the reaction time in HPHT-$H_2O$ implied that for micro reaction system the reaction time should be considered from the mixing point of substrate and HPHT-$H_2O$ to the back-pressure regulator as Claisen rearrangement after the mixing with HPHT-$H_2O$ could be much faster than without water [12]. Therefore, the reaction time should be evaluated by the residence time after the micromixer such as 15.3 and 12.8 s for runs 9 and 10, respectively. Surprisingly, a few seconds difference of reaction time in HPHT-$H_2O$ microreaction system is enough for by-product formation and over reaction such as Cope rearrangement to **3a**, hydration of allyl aryl ether to **4a**, and dehydration of **2a** to **5a**, etc. [14]. Thus, in case of run 8, the yield and selectivity of **2a** were lowered compared to case of run 12 by the production of those above-mentioned compounds and other unknown by-products.

**Table 1**
Claisen rearrangement from allyl aryl ether to allyl phenol by various methods.

| Run | Subst. | Product | Method | Reactor type | Cat. | Sol. | *T*/°C | *P*/MPa | Total residence time | Reaction time in HPHT-$H_2O$ | Conv./% | Yield **2** + **3**/% | Sel./% | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | **2** | **3** | |
| 1 |  **1a** |  **2a** | Conventional heating | B[a] | – | – | 220 | 0.1 | 6 h | ← | – | 85 | – | – | [1b,9a] |
| 2 | | | sub$H_2O$ | B | – | $H_2O$ | 240 | 3.4 | 10 min | ← | – | 84 | – | – | [9b] |
| 3 | | | Microwave irradiation | B | – | – | 325–361 | 0.1 | 10 min | ← | – | 21 | – | – | [9c] |
| 4 | | | | B | – | DMF | 300–315 | 0.1 | 6m in | ← | – | 92 | – | – | [9c] |
| 5 | |  **3a** | µ-Solvent free | F[b] | – | – | 220 | 0.1 | >20 min | ← | 100 | 100 | 100 | – | [9d] |
| 6 | | | | F[c] | – | – | 265 | 5 | 360 s | 0 s | 54 | 37 | 68 | | This work |
| 8 | | | µ-HPHT-$H_2O$[d] | F | – | $H_2O$ | 265 | 5 | 88.7 s[e] | 23.5 s | 33 | 14 | 44 | – | This work |
| 9 | | | | F | – | $H_2O$ | 265 | 5 | 81 s[f] | 15.3 s | 99.8 | 78 | 74 | 4 | This work |
| 10 | | | | F | – | $H_2O$ | 265 | 5 | 78 s[g] | 12.8 s | 99.8 | 95 | 95 | – | This work |
| 11 | | | | F | – | $H_2O$ | 265 | 5 | 151.6 s[h] | 15.3 s | 99.8 | 84 | 85 | – | This work |
| 12 | | | | F | – | $H_2O$ | 265 | 5 | 149 s[i] | 13.4 s | 99.8 | 98 | 98 | – | This work |

[a] Batch reaction.
[b] Substrate was 4-methoxy allyl aryl ether.
[c] Flow reaction.
[d] µ-HPHT-$H_2O$ = microreaction system with high pressure-high temperature water.
[e] Water flow rate of 2.49 g/min, substrate flow rate of 0.49 g/min.
[f] Water flow rate of 4.97 g/min, substrate flow rate of 0.49 g/min.
[g] Water flow rate of 6.96 g/min, substrate flow rate of 0.49 g/min.
[h] Water flow rate of 4.97 g/min, substrate flow rate of 0.25 g/min.
[i] Water flow rate of 6.96 g/min, substrate flow rate of 0.25 g/min.

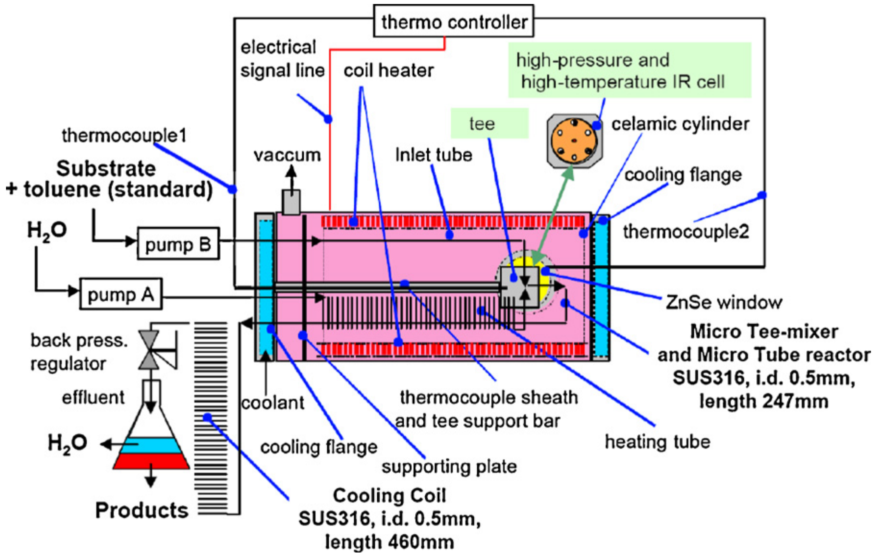
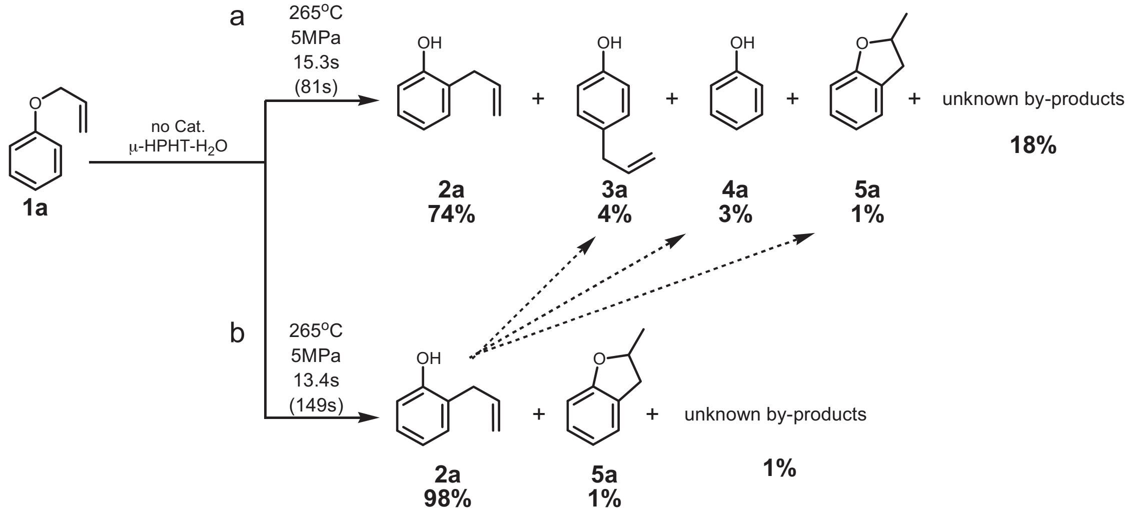


**Fig. 1.** Schematic diagram of HPHT-$H_2O$ microreactor apparatus for Claisen rearrangement.



**Scheme 2.** The reaction products from the Claisen rearrangement in HPHT-$H_2O$.

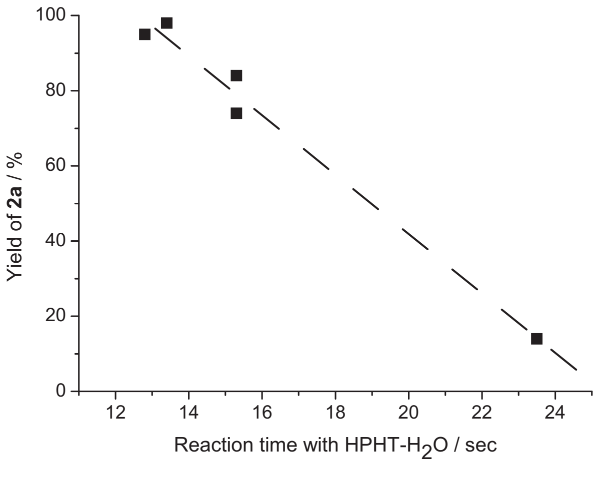
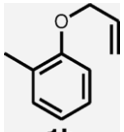
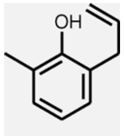
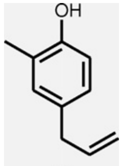
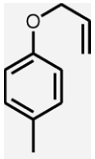
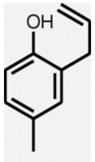


**Fig. 2.** Effect of reaction time on the yield of *o*-allylphenol (**2a**).

To extend the application of the HPHT-$H_2O$ microreaction system, Claisen rearrangement of *o*-methyl and *p*-methyl allyl aryl ether was studied and results are shown in Table 2. When *o*- and *p*-methyl allyl aryl ether were used, optimal reaction temperature (210 °C) was lowered compare to the unsubstituted allyl aryl ether (265 °C, run 12 in Table 1) under the same reaction condition (reaction time = 13.4 s). Compared to the conventional batchwise method (run 2), HPHT-$H_2O$ microrection method provides comparable yield and selectivity of the desired product within the reaction time of 13.4 s at lower temperature, which is even better than that by microwave irradiation method without any solvent [10c]. These results seem to be in good agreement with the theoretical study on the Claisen rearrangement, which suggested that the electron-donating group (*o*-methyl, and *p*-methyl) weaken the reacting carbon–oxygen bond and increase the rate for both thermal reaction [13].

For all the reactions studied, products were first obtained as a suspension in water after the reaction was over, but it accumulates at the bottom of the aqueous solution within 40 min to 24 h. The

**Table 2**
Claisen rearrangement from *o*-methyl and *p*-methyl allyl aryl ether to allyl phenol by various methods.

| Entry | Subst. | Product | Method | Reactor type | Cat. | Sol. | $T/^\circ C$ | $P$/MPa | Reaction time[a] | Conv./% | Yield **2** + **3**/% | Sel/% | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | **2** | **3** | |
| 1 |  **1b** |  **2b** | – | B | $BCl_3$ | PhCl | 0 | 0.1 | 0.2–2 h | 95 | 92 | 63 | 33 | [4a] |
| 2 | | | Conventional heating | B | – | – | 195–200 | 0.1 | – | – | 100 | 85 | 15 | [13a] |
| 3 | | | μ-HPHT-$H_2O$ | F | – | $H_2O$ | 180 | 5 | 13.4 s[a] | 58 | 57 | 79 | 19 | This work |
| 4 | |  **3b** | | F | – | $H_2O$ | 200 | 5 | 13.4 s[a] | 99 | 95 | 81 | 15 | This work |
| 5 | | | | F | – | $H_2O$ | 210 | 5 | 13.4 s[a] | 100 | 99 | 87 | 12 | This work |
| 6 | | | | F | – | $H_2O$ | 265 | 5 | 13.4 s[a] | 96 | 14 | 6 | 9 | This work |
| 7 |  **1c** |  **2c** | – | B | $BCl_3$ | PhCl | 10 | 0.1 | 10 min | – | 91 | – | – | [13b] |
| 8 | | | Conventional heating | B | – | $Ph_2O$ | 265 | 0.1 | 1 h | 100 | 55 | 55 | – | [9a] |
| 9 | | | μ-Solvent free | F | – | – | 200 | 0.1 | 36 min | – | 73 | – | – | [9d] |
| 10 | | | μ-HPHT-$H_2O$ | F | – | $H_2O$ | 210 | 5 | 13.4 s[a] | 99 | 93 | 94 | – | This work |

[a] Total residence time was 149 s. Water flow rate of 6.96 g/min, substrate flow rate of 0.25 g/min.

product can be easily separated and isolated almost quantitatively as nearly in the pure state.

## 4. Conclusion

We have demonstrated non-catalytic Claisen rearrangement of *o*-methyl and *p*-methyl allyl aryl ether by HPHT-$H_2O$ microreaction system, leading to the good yield over >95% within a short time. Even though the total residence time of the optimized reaction condition is 149 s, the Claisen rearrangement was found to be proceeded mainly after the mixing point of HPHT-$H_2O$ at micromixer for a 13.4 s of shorter reaction time. We also found that the methyl group (electron donating group) at *ortho*- and *para*-position, has a role to accelerate the reaction even at lower reaction temperature in HPHT-$H_2O$.

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## References

[1] (a) R.P. Lutz, Chem. Rev. 84 (1984) 205–247;
(b) A.M.M. Castro, Chem. Rev. 101 (2004) 2939–3002;
(c) M. Hiersemann, L. Abraham, Eur. J. Org. Chem. (2002) 1461–1471;
(d) F.E. Ziegler, Chem. Rev. 88 (1988) 1423;
(e) F.M. Sonnenberg, J. Org. Chem. 35 (1970) 3166–3167.

[2] L. Claisen, Chem. Ber. 45 (1912) 3157.

[3] (a) H. Ito, T. Taguchi, Chem. Soc. Rev. 28 (1999) 43–50;
(b) K. Hiratani, M. Albrecht, Chem. Soc. Rev. 37 (2008) 2413;
(c) E.A. Ilardi, C.E. Stivala, A. Zakarian, Chem. Soc. Rev. 38 (2009) 3133–3148.

[4] (a) J. Borgulya, R. Madeja, P. Fahrni, H.-J. Hansen, H. Schmid, R. Barner, Herv. Chim. Acta 56 (1973) 14–75;
(b) K. Takai, I. Mori, K. Oshima, H. Nozaki, Tetrahedron Lett. 22 (1981) 3985–3988;
(c) I.J.L. Baan, F. Bickelhaupt, Tetrahedron Lett. 27 (1986) 6267–6270;
(d) M. Hiersemann, Synlett (1999) 1823–1825.

[5] (a) H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, Angew. Chem. Int. 46 (2007) 5129–5132;
(b) Y. Ikushima, K. Hatakeda, O. Sato, M. Sato, A. Arai, Chem. Commun. (2002) 2208–2209;
(c) E. Garcia-Verdugo, Z. Liu, E. Ramirez, J. Fraga-Dubreuil, J.R. Hyde, P.A. Hamley, M. Polyakoff, Green Chem. 8 (2006) 359–364.

[6] (a) P.G. Jessop, W. Leitner, Chemical Synthesis Using Supercritical Fluids, Wiley-VCH, Weinheim, 1999;
(b) Y. Ikushima, K. Hatakeda, O. Sato, T. Yokoyama, M. Arai, J. Am. Chem. Soc. 122 (2000) 1908–1918;
(c) A.J. Belsky, P.G. Maiella, T.B. Brill, J. Phys. Chem. A 103 (1999) 4253–4260;
(d) M. Boero, T. Ikeshoji, C.C. Liew, K. Terakura, M. Parrinello, J. Am. Chem. Soc. 126 (2004) 6280–6286.

[7] M. Mukaide, Y. Urasaki, K. Takegoshi, O. Kajimoto, J. Supercrit. Fluids 42 (2007) 104–109.

[8] For recent reviews and books, see: (a) V. Hessel, S. Hardt, H. Löwe, Chemical Micro Process Engineering: Fundamentals, Modeling and Reactions, Wiley-VCH, Weinheim, 2004; (b) W. Ehrfeld, V. Hessel, H. Löwe, Microreactor: New Technology for Modern Chemistry, Wiley-VCH, Weinheim, 2000; (c) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, Angew. Chem. Int. Ed. 43 (2004) 406.

[9] (a) S. Narayan, J. Muldoon, M.G. Finn, V.V. Fokin, H.C. Kolb, K.B. Sharpless, Angew. Chem. Int. 44 (2005) 3275–3279;
(b) J.E. Klijn, J.B.F.N. Engberts, Nature 435 (2005) 746–747;
(c) D.G. Blackmond, A. Armstrong, V. Coombe, A. Wells, Angew. Chem. Int. 46 (2007) 3798.

[10] (a) W.N. White, D. Gwynn, R. Shlitt, C. Girard, W. Fife, J. Am. Chem. Soc. 80 (1958) 3271–3277;
(b) J. An, L. Bagnell, T. Cabelewski, C.R. Strauss, R.W. Tainor, J. Org. Chem. 62 (1997) 2505–2511;
(c) C. Raymond, J. Giguere, T.G. Bray, S.M. Duncan, Tetrahedron Lett. 41 (1986) 4945–4948;
(d) L. Kong, Q. Lin, X. Lv, Y. Yang, Y. Jia, Y. Zhou, Green Chem. 11 (2009) 1108–1111;
(e) K.D. Raner, C.R. Strauss, R.W. Trainor, J. Org. Chem. 60 (1995) 2456–2460.

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

[12] (a) W.N. White, E.F. Wolfarth, J. Org. Chem. 35 (1970) 2196–2199;
(b) W.N. White, C. Slater, W. Fife, J. Org. Chem. 26 (1961) 627–628;
(c) W.N. White, E.F. Wolfarth, J. Org. Chem. 35 (1970) 3585.

[13] (a) H.L. Goering, R.R. Jacobson, J. Am. Chem. Soc. 80 (1958) 3277–3285;
(b) A.L. Pincock, J.A. Pincock, R. Stefanova, J. Am. Chem. Soc. 124 (2002) 9768–9778.

[14] (a) E.N. Marvell, B. Richardson, R. Anderson, J.L. Stephenson, T. Crandall, J. Org. Chem. 30 (1965) 1032;
(b) P. Fahrni, A. Fabich, H. Schmid, Helv. Chim. Acta 43 (1960) 448.