

scCO₂ requires a trade-off between activity and selectivity in order to attain the best reaction performance, and the fine-tuning of the reaction conditions, including the phase behavior and the polarity of reaction media by changing the CO₂ pressure and temperature, is also necessary. We now describe the controlled condensation of **2** and **3** with the recently developed scCO₂-soluble, fluorinated Brønsted acids, C₆F₅CHTf₂ (**5a**: Tf = SO₂CF₃)^[15] and CF₃(CF₂)_{*n*}CH₂OC₆F₄CHTf₂ (**5b**: *n* = 8, **5c**: *n* = 12)^[16] in a batch system, giving the desired product **1** with good to excellent selectivity. An increase in the CO₂ pressure caused a significant improvement in the product selectivity. The reactions in a continuous-flow reactor were also examined, leading to an increase in the productivity of **1**.

We first measured the solubility of the fluorinated catalyst **5a** as well as the substrates **2** and **3** in scCO₂. The catalyst **5a** proved to be fairly soluble in scCO₂; the solubility was estimated to be 5.0 mmol/L by ¹⁹F NMR spectroscopy^[17] under supercritical conditions, 40 °C and 8.5 MPa. Extraction experiments at 100 °C and 20 MPa revealed that the solubilities of the substrates **2** and **3** are 3.5 and 51 mmol/L, respectively, under these conditions (see Supporting Information).

The condensation reaction of **2** with **3** catalyzed by the fluorinated molecular catalyst **5a** (**2** and **3**: 0.5 mmol, **5a**: 0.05 mmol) in scCO₂ was examined using the batch system. The reaction in the homogeneous scCO₂ phase at 35 MPa, 100 °C, proceeded to give the desired product **1** in 31% yield with 97% selectivity, in addition to the five-membered by-products **4** (1.1% yield) and the decomposition products, trimethylquinone or dehydration products,^[4] derived from **2** and **3** under the reaction conditions. The outcome of the reaction was delicately influenced by the CO₂ pressure as shown in Figure 1. A decrease in the CO₂ pressure to 10 through 20 MPa resulted in an increase in the product yield although with a slight decrease in the selectivity, reaching up to 62% yield and 94% selectivity at 20 MPa. The reactivity and selectivity markedly decreased below 10 MPa, and in the absence of CO₂ under neat conditions, resulted in product **1** in only 19% yield with 93% selectivity.

A visual inspection as well as the solubility test mentioned above revealed that above 20 MPa at 100 °C, the compound **3** and the catalyst **5a** are all miscible in CO₂, while the solid compound **2** (0.5 mmol) is not completely soluble in CO₂ based on the solubility test (3.5 mmol/L at 20 MPa; 17 mmol/L at 35 MPa). As shown in Figure 1 and Table 1, significant changes in yield and selectivity were observed around the saturation concentration of **2** in scCO₂. These results indicate that the single homogeneous phase of scCO₂ is crucial to attaining high product selectivity. In fact, under high dilution conditions, the reaction gave the desired product, although the yield was low (entry 1). In the reaction under higher concentration and lower CO₂ pressure conditions, the reactants **2** and **3** precipitate to form

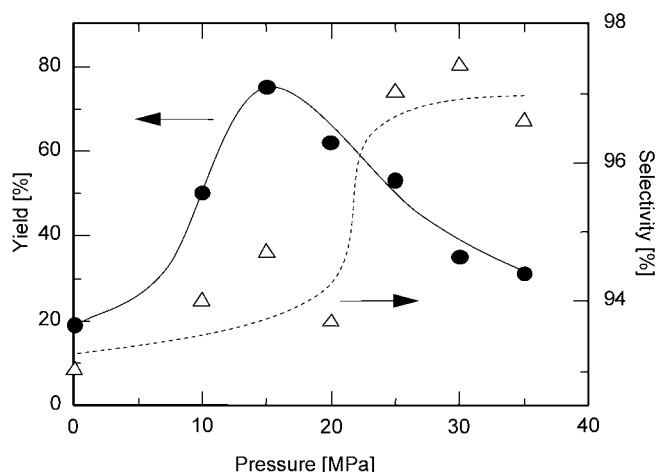


Figure 1. Pressure effect on the condensation of **2** with **3** in scCO₂ catalyzed by **5a**. Solid circles and open triangles represent the yield and selectivity, respectively. Reaction conditions: **2** and **3** 0.5 mmol, **5a** 0.05 mmol, 100 °C, reaction time 16 h.

the liquid phase, in which a neat reaction took place to give the undesired benzofuran derivatives **4** due to the higher polarity of the liquid phase formed during the reaction. The high selectivity attained in scCO₂ may be explained by the solvent effect^[11b,d] rather than the dilution effect because simple dilution to the corresponding concentration (0.01 mol/L) in heptane resulted in lowering of the selectivity of the product to 72% (entry 8). The present results markedly contrast with the reported ones obtained from the same reaction in scN₂O, in which no significant influence of the total pressure on the reactivity and selectivity was observed.^[5a] The reaction, however, seems to proceed totally in the liquid phase of the substrates due to the much higher concentration of the substrates (0.24–0.40 mol/L).

The low yield of **1** in scCO₂ is at least partly ascribed to the side reaction of **3** to give dehydration products such as phytadienes,^[4] which can be suppressed by slow addition of **3**.^[2,5] Indeed, addition of **3** at a rate of 2 mmol/h using a sample injector to the reaction mixture markedly improved the yield and selectivity as shown in entry 9, the yield of **1** reaching 69% while maintaining the purity (97%) at 20 MPa. Similarly, the strong acid catalysts including perfluorinated catalysts **5b** and **5c** as well as solid strong acid catalysts were found to effect the condensation reaction under the optimized conditions described in Table 2 to give the desired product with high selectivity. Again, the CO₂ single phase including reactants **2** and **3** over the solid catalyst is crucial to attaining high catalyst performance in terms of selectivity and reactivity.^[18]

The utilization of a continuous-flow fixed-bed reactor for the condensation of **2** with **3** over the solid catalyst, Amberlyst 15, caused a marked improvement in the efficiency of the reaction. The apparatus for the continu-

Table 1. Effect of the reaction conditions on the yield and selectivity of **1** in the batch reaction.^[a]

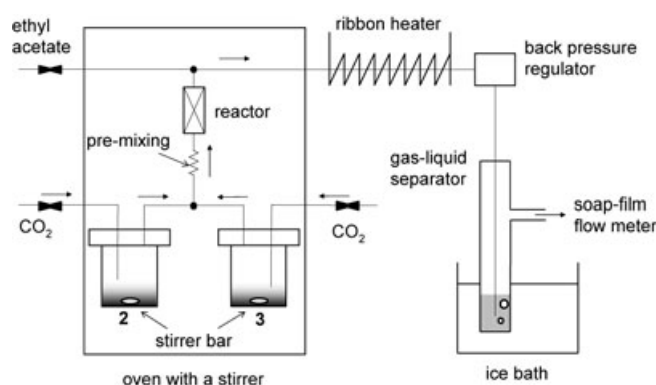
Entry	Solvent, MPa	2 and 3 [mmol]	5a [mmol]	Yield [%] ^[b]		Selectivity [%] ^[c]
				1	4	
1	CO ₂ , 20	0.1	0.01	9	<0.1	> 99
2	CO ₂ , 20	0.5	0.05	62	4.1	94
3	CO ₂ , 20	1.0	0.1	70	4.7	94
4	CO ₂ , 20	3.0	0.3	67	7.2	90
5	CO ₂ , 35	0.5	0.05	31	1.1	97
6	CO ₂ , 35	1.0	0.1	48	1.4	97
7	CO ₂ , 35	3.0	0.3	59	4.3	93
8 ^[d]	heptane	0.5	0.05	33	13	72
9 ^[e]	CO ₂ , 20	0.5	0.05	69	1.9	97

^[a] Conditions: 100 °C, 16 h in a 50-mL autoclave.^[b] Determined by GC.^[c] Defined as $1/(1+4)$.^[d] A solution of **3** in heptane was added dropwise over 15 min under azeotropic reflux with removal of water.^[2]^[e] Compound **3** was added to the reactor at a rate of 2 mmol/h with a sample injector.**Table 2.** Effect of the catalyst used for the condensation of **2** with **3** in scCO₂.^[a]

Entry	Catalyst	Yield [%] ^[b]		Selectivity [%] ^[c]
		1	4	
1	5a ^[d]	69	1.9	97
2	5b ^[d]	48	1.6	97
3	5c ^[d]	49	1.3	97
4	6 ^[e]	73	2.5	97
5	Amberlyst 15 ^[e]	73	7.6	90
6	Nafion NR50 ^[e]	74	4.6	94

^[a] Conditions: **2** and **3** were 0.5 mmol each, CO₂ 20 MPa, 100 °C, 16 h in a 50-mL autoclave. Compound **3** was added to the reactor at a rate of 2 mmol/h with a sample injector.^[b] Determined by GC.^[c] Defined as $1/(1+4)$.^[d] 0.05 mmol.^[e] 50 mg.

ous reaction is shown in Figure 2. To minimize the neat reaction and the dehydration of **3**, both **2** and **3** were introduced into the reactor as solutes of scCO₂. The flow rates were determined by separate extraction measurements so that both of the substrates were supplied to the reactor in the required molar ratio. Ethyl acetate was added to the product flow to prevent the choking of the highly viscous **1**. The reaction using the polystyrene-bound fluorosulfonic acid **6**^[16] as a solid catalyst was hampered by swelling of the catalyst in the reactor, while the solid acid catalyst, Amberlyst 15, was found to work well in scCO₂ in both the batch and continuous-flow reactors. The results are summarized in Table 3. Although the yield and selectivity in the Amberlyst-catalyzed batch reaction were unsatisfactory (entry 1), those in the continuous-flow reaction are significantly increased. The outcome of the reaction is delicately influenced by the

**Figure 2.** Experimental apparatus for the continuous-flow reaction.

reaction conditions. An excess of the reactant **3** was necessary to achieve the high yield of **1** (entry 2–6), probably because of the dehydrative self-condensation of **3** as a side reaction. Again, the CO₂ pressure also affected the yield and selectivity of **1**; the yield reached up to 80%, with 96% selectivity under the optimized conditions as shown in Table 3 (entry 5). This improvement may be explained by rapid removal of the coproduct water, which enhances the polarity of the reaction phase and often deactivates the acid catalyst, from the flow reactor.

In summary, this paper describes the controlled condensation of **2** with **3** to (all-*rac*)- α -tocopherol with fluorinated strong acids in scCO₂ in good selectivity and moderate yield. The outcome of the reaction was appreciably influenced by the phase behavior and the polarity of the reaction mixture, which can be tuned by changing the pressure of CO₂. The productivity in the Amberlyst-catalyzed continuous-flow reaction was improved compared to the batch reaction.

Table 3. Effect of CO₂ pressure and molar ratio of **2** to **3** on the yield and selectivity of **1** in the flow reaction.^[a]

Entry	MPa	Molar ratio (3 / 2)	Flow rate of CO ₂ to extract 3 [mL/min]	Yield [%] ^[b]		Selectivity [%] ^[c]
				1	4	
1 ^[d]	20	1.0	–	73	7.6	90
2	25	0.9	0.01	15	2.9	84
3	25	1.7	0.02	56	9.5	86
4	25	4.3	0.04	70	6.9	91
5	25	6.0	0.07	79	3.4	96
6	25	7.8	0.09	66	4.1	94

^[a] Conditions: 100 °C, 4 mm diameter and 50 mm height tubular reactor, 200 mg of Amberlyst 15, flow rate of the HPLC pump to extract **2** is 0.4 mL/min, W/F = 6.8×10^2 [cat.-g/(mol/h)].

^[b] Determined by GC.

^[c] Defined as $1/(1+4)$.

^[d] Batch reaction (0.5 mmol of **2** and **3**, 50 mg of Amberlyst 15, 16 h in a 50-mL autoclave).

Experimental Section

Safety warning: Operators of high-pressure equipment should take proper precautions to minimize the risk of personal injury.

The fluororous catalysts **5** and the polymer-supported catalyst **6** were prepared according to the literature,^[15,16] while **2**, **3**, Amberlyst 15, and Nafion NR50 were used as received. The ¹⁹F scNMR spectra were recorded on a JEOL LA-300 spectrometer using a zirconia cell;^[17a] dimethyl sulfoxide-*d*₆ in a sealed Pyrex tube was used as the deuterium lock. The chemical shifts are referenced to the signal of trifluorotoluene in (CD₃)₂SO at –64.0 ppm. The GC analyses were performed on a GL Science GC353B equipped with a DB-1 column.

Solubility Measurements of the Substrates and Catalyst

The solubilities of **2** and **3** in scCO₂ were measured by extraction experiments. The apparatus is shown in Figure S1 (see Supporting Information). An excess of **2** or **3** (ca. 50 mmol) in a 50-mL autoclave was warmed to 100 °C in an oven with a stirrer. Carbon dioxide was introduced into the autoclave with the total pressure kept constant by an automatic back pressure regulator attached to the outlet. To avoid the precipitation of the extract in the tube, ethyl acetate was mixed into the extract solution. The extracted substrate was collected with a gas–liquid separator. The flow rate of CO₂ was monitored by a soap-film flow meter. The solubilities of **2** and **3** at various pressures are listed in Table S1 (see Supporting Information).

The solubility of the fluororous catalyst **5a** in the scCO₂ phase was estimated by integration of the signals of **5a** and the internal standard (CF₃C₆H₅, 0.75 μ L, 6.2 μ mol) in the ¹⁹F scNMR spectra. The spectrum obtained at 84 atm and 40 °C indicated that the solubility of **5a** in scCO₂ under these conditions is 5.0 mmol/L.

Catalyst 5a: ¹⁹F NMR (282 MHz, scCO₂): δ = –157.9, –156.8, –142.6, –140.3, –127.7 (s, 1F each, C₆F₅), –75.2 (s, 6F, CF₃).

Standard Procedure for the Batch Reaction

Trimethylhydroquinone **2** was charged in a 50-mL autoclave equipped with a magnetic stirrer. The catalyst was placed inside a separate glass tube in the autoclave to avoid a neat reaction in neat **3** prior to CO₂ introduction. After the autoclave had been evacuated and flushed with argon repeatedly, **3** was added to the autoclave with a syringe. The autoclave was warmed to 100 °C, and then CO₂ was introduced. After stirring for 16 h, the reactor was cooled with a dry ice–methanol bath, and CO₂ was released from the reactor. The reactor was slowly warmed to room temperature, and the product was analyzed by GC. The yield was determined using squalane as an internal standard. The results are summarized in Table S2 (see Supporting Information).

Procedure for the Continuous-Flow Reaction

The apparatus for the reaction is shown in Figure 2. The tubular reactor (4 mm diameter and 50 mm height) loaded with a catalyst (200 mg), was set in an oven. An excess of **2** and **3** (ca. 50 mmol each) was charged under argon in two autoclaves placed in the same oven, from which these substrates were supplied to the reactor as solutes in scCO₂.

Prior to the continuous-flow reactions, the amounts of **2** extracted by scCO₂ from the autoclave had been measured at a fixed flow rate (0.4 mL/min) and various CO₂ pressures by separate extraction experiments with the apparatus shown in Figure S1 (see Supporting Information). Then, the flow rate for the extraction of **3** at each CO₂ pressure was determined by similar extraction measurements to realize the required molar ratio of **3** to **2** in the reactor.

After both the reactor and autoclaves were warmed to 100 °C for 30 min and the reactor was purged with CO₂, **2** and **3** in scCO₂ were introduced to the reactor. The product was collected by a gas–liquid separator, and the yield and selectivity of **1** were determined as described above.

Supporting Information Available

Experimental apparatus for the extraction of **2** and **3**, extraction experiments of **2** and **3** by scCO_2 , and effects of solvent and concentration of the yield and selectivity of **1** in the batch reaction.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 14078209) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and partially supported by the 21st century COE Program.

References and Notes

- [1] K.-U. Baldenius, L. von dem Bussche-Hünnefeld, E. Hilgemann, P. Hoppe, R. Stürmer, in: *Ullmann's Encyclopedia of Industrial Chemistry*, 6th edn., Vol. 38, Wiley-VCH, Weinheim, **2003**, pp. 109–294.
- [2] A. Hasegawa, K. Ishihara, H. Yamamoto, *Angew. Chem. Int. Ed.* **2003**, 42, 5731–5733.
- [3] M. Schneider, K. Zimmermann, F. Aquino, W. Bonrath, *Appl. Catal. A* **2001**, 220, 51–58.
- [4] F. Schager, W. Bonrath, *J. Catal.* **1999**, 182, 282–284.
- [5] a) S. Wang, W. Bonrath, H. Pauling, F. Kienzle, *J. Supercrit. Fluids* **2000**, 17, 135–143; b) W. Bonrath, R. Karge, in *High Pressure Chemistry*, (Eds.: R. V. Eldick, F.-G. Klamer), Wiley-VCH, Weinheim, **2002**.
- [6] M. Matsui, N. Karibe, K. Hayashi, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, 68, 3569–3571.
- [7] M. Matsui, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1996**, 69, 137–139.
- [8] K. Ishihara, M. Kubota, H. Yamamoto, *Synlett* **1996**, 1045–1046.
- [9] F. Schager, W. Bonrath, *Appl. Catal. A* **2000**, 202, 117–120.
- [10] a) W. Bonrath, A. Haas, E. Hoppmann, T. Netscher, H. Pauling, F. Schager, A. Wildermann, *Adv. Synth. Catal.* **2002**, 344, 37–39; b) T. Netscher, W. Bonrath, A. Haas, E. Hoppmann, H. Pauling, *Chimia* **2004**, 58, 153–155.
- [11] a) P. G. Jessop, T. Ikariya, R. Noyori, *Science* **1995**, 269, 1065–1069; b) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, 99, 475–493; c) A. Baiker, *Chem. Rev.* **1999**, 99, 453–473; d) P. G. Jessop, W. Leitner, (Eds.), *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH: Weinheim, **1999**; e) J. R. Hyde, P. Licence, D. Carter, M. Poliakoff, *Appl. Catal., A* **2001**, 222, 119–131; f) B. Subramaniam, C. J. Lyon, V. Arunajatesan, *Appl. Catal., B* **2002**, 37, 279–292; g) W. Leitner, *Acc. Chem. Res.* **2002**, 35, 746; h) M. F. Sellin, I. Bach, J. M. Webster, F. Montilla, V. Rosa, T. Aviles, M. Poliakoff, D. J. Cole-Hamilton, *J. Chem. Soc. Dalton Trans.* **2002**, 4569–4576; i) J.-D. Grunwaldt, R. Wandeler, A. Baiker, *Catal. Rev. – Sci. Eng.* **2003**, 45, 1–96.
- [12] R. M. Parkhurst, W. A. Skinner, in: *The Chemistry of Heterocyclic Compounds*, Vol. 36, (Eds.: G. P. Ellis, I. M. Lockhart), John Wiley and Sons, New York, **1981**, pp. 59–137.
- [13] F. M. D. Ismail, M. J. Hilton, M. Štefinović, *Tetrahedron Lett.* **1992**, 33, 3795–3796.
- [14] U. Svanholm, V. D. Parker, *J. Chem. Soc. Perkin Trans. 2* **1974**, 169–173.
- [15] K. Ishihara, A. Hasegawa, H. Yamamoto, *Angew. Chem. Int. Ed.* **2001**, 40, 4077–4079.
- [16] K. Ishihara, A. Hasegawa, H. Yamamoto, *Synlett* **2002**, 1299–1301.
- [17] a) Y. Kayaki, T. Suzuki, Y. Noguchi, S. Sakurai, M. Imanari, T. Ikariya, *Chem. Lett.* **2002**, 424–425; b) O. Ihata, Y. Kayaki, T. Ikariya, *Angew. Chem. Int. Ed.* **2004**, 43, 717–719; c) T. Tsukahara, Y. Kayaki, T. Ikariya, Y. Ikeda, *Angew. Chem. Int. Ed.* **2004**, 43, 3719–3722.
- [18] In the Amberyst-catalyzed reaction carried out in much higher concentrations of the substrates (0.29 mol/L), for example, the yield of **1** was reported to be only 60.7%, and the selectivity was not discussed.^[5] See also: R. Lowack, J. Meyer, M. Eggersdorfer, P. Grafen, *United States Patent* 5,523,420, **1996**.