

Solvent-Free Asymmetric Olefin Hydroformylation Catalyzed by Highly Cross-Linked Polystyrene-Supported (*R,S*)-BINAPHOS–Rh(I) Complex

Fumitoshi Shibahara,^{†,‡} Kyoko Nozaki,^{*,†,‡} and Tamejiro Hiyama[§]

Contribution from Conversion and Control by Advanced Chemistry, PRESTO, Japan Science and Technology, 1-8, Honcho 4-Chome, Kawaguchi 332-0012, Japan, Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan, and Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received February 1, 2003; Revised Manuscript Received April 27, 2003; E-mail: nozaki@chembio.t.u-tokyo.ac.jp

Abstract: Using an (*R,S*)-BINAPHOS–Rh(I) catalyst that is covalently anchored to a highly cross-linked polystyrene support, asymmetric hydroformylation of olefins was performed in the absence of organic solvents. The reaction of *cis*-2-butene, a gaseous substrate, provided (*S*)-2-methylbutanal with 100% regioselectivity and 82% ee upon treatment with H₂ (12 atm) and CO (12 atm) in a batchwise reactor equipped with a fixed bed. The polymer-supported catalyst was applicable to a continuous vapor-flow column reactor, and thus, 3,3,3-trifluoropropene was converted into (*S*)-2-trifluoromethylpropanal with an iso/normal ratio of 95/5 and 90% ee. Less volatile olefins, such as styrene, vinyl acetate, 1-alkenes, and fluorinated alkenes, were successfully converted into the corresponding isoaldehydes with high ee values, when they were injected through a supercritical CO₂-flow column reactor. Successive injection of a series of olefins realized the conversion of an olefin library into an optically active aldehyde library.

Introduction

Despite many advantages over heterogeneous catalysis in terms of catalyst selectivity and activity, homogeneous catalysis has two major drawbacks: separation of catalyst from products and use of organic solvents to suppress precipitation of catalyst metal. Separation of products and catalysts are performed most conveniently by phase separation. Thus, immobilization of organometallic catalysts on organic polymers or on silica gel has been considered to be one of the major challenges in homogeneous catalysis.¹

Although most supported catalysts are used in suspension with organic solvents, the same reactions may be carried out without organic solvents under flow-reaction systems. Poliakoff and van Leeuwen prepared and used silica-supported Rh–xantphos complexes for hydroformylation of 1-alkenes under continuous flow of supercritical carbon dioxide (scCO₂) without any metal leaching.² Another approach for the scCO₂ continuous flow process is the use of an ionic liquid as an immobilizing phase for catalyst, as reported for hydroformylation by Cole-Ham-

ilton^{3a} and for other reactions by Leitner.^{3b–c} Recently, van den Broeke reported hydrogenation of 1-alkenes in a continuous scCO₂ flow system using a bulky Rh catalyst bearing long perfluoroalkyl chains. The catalyst was separated by a microporous silica-membrane filter.⁴ These systems are directly applicable to a large-scale catalysis process. On the other hand, less attention has been paid on asymmetric catalysis in these systems. This is not surprising, since asymmetric catalysis usually needs finely tuned reaction conditions. Among all, solvent stabilization of the catalyst complex is usually an essential factor. For example, when scCO₂ is used as a solvent, enantioselectivity drops in many cases.^{5–8}

In 1993, an unsymmetrical phosphine–phosphite ligand, (*R,S*)-BINAPHOS, was invented and shown to attain excellent enantioselectivities in asymmetric hydroformylation of a wide range of prochiral olefins upon use in combination with rhodium(I).⁹ Although the Rh(I) complexes of bis-phosphorus ligands, all derived from D-(+)-glucose, were reported as another

[†] Japan Science and Technology.

[‡] The University of Tokyo.

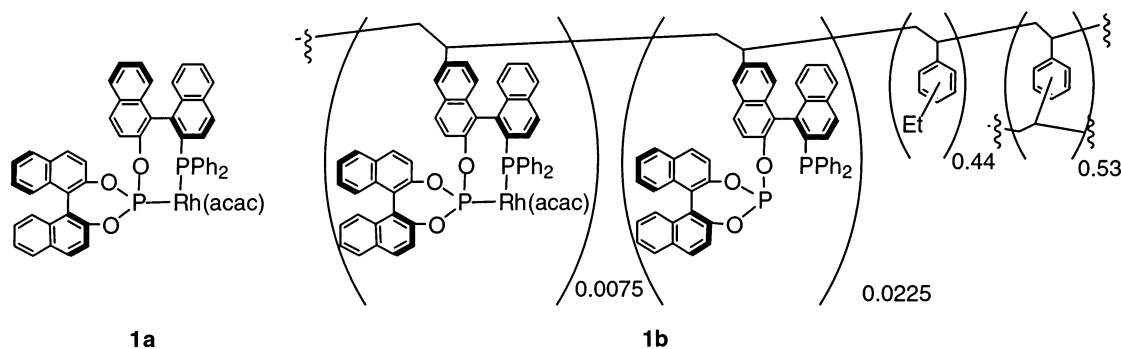
[§] Kyoto University.

[‡] Present address: Department of Chemistry, Gifu University, Yanagido, Gifu 501-1193 Japan.

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Chart 1



efficient catalyst for asymmetric hydroformylation, recently,¹⁰ even at this stage, (*R,S*)-BINAPHOS–Rh(I) (**1a**, Chart 1) still enjoys the widest applicability ever reported.¹¹

Previously, we immobilized **1a** on a highly cross-linked polystyrene support and demonstrated that the resulting catalyst **1b** exhibited excellent performance without any loss of selectivity.¹² Simple filtration enabled the separation and reuse of the polymer-supported catalyst **1b**. One of the unique features of immobilized catalyst **1b** is the extremely high content of divinylbenzenes (over 50 mol %) within the polymer support, whose pore size and surface area were precisely studied by Gagné, recently.¹³

As an approach to organic solvent-free catalyst for asymmetric hydroformylation, the use of supercritical CO₂ as a solvent was reported by Leitner^{6,7} and Ojima,⁸ independently. Although the catalytic activity and selectivities were lost to some extent when the insoluble unsupported (*R,S*)-BINAPHOS–Rh(I) complex was used in scCO₂,⁶ the catalyst-solubility problem has been overcome by using a perfluoroalkyl-substituted (*R,S*)-BINAPHOS–Rh(I) catalyst.

We designed three organic solvent-free reactors using polymer-supported **1b** on a fixed bed: a vapor-phase batchwise reactor,¹⁴ a continuous vapor-flow column reactor, and a continuous scCO₂-flow column reactor, as described below.

Results and Discussion

Vapor-Phase Asymmetric Hydroformylation of *cis*-2-Butene (2a**) using a Batchwise Reactor.** In our previous communication,^{14,15} we reported the vapor-phase asymmetric hydroformylation of volatile olefins using **1b** in Apparatus A (Figure 1). The initial catalytic activity and selectivities were

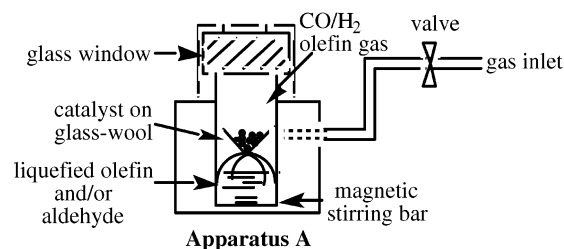


Figure 1. Apparatus A: A batchwise reactor. At the center of a glass-window-equipped autoclave, a stainless steel wire bed was placed, and polymer-supported chiral catalyst **1b** was mounted on the bed by the aid of glass wool. The surface of the liquefied substrate or product does not reach the bed. See ref 14.

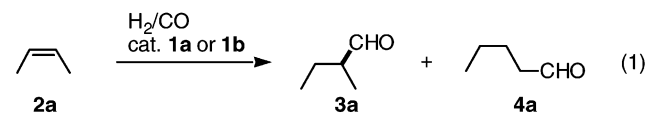
Table 1. Pressure Effects on the Vapor-Phase Asymmetric Hydroformylation of *cis*-2-Butene (**2a**) Catalyzed by **1b**^a

entry	<i>cis</i> -2-butene (atm)	syngas ^b (atm)	time (h)	TON	TOF (h ⁻¹)	% ee
1	3.0	24	2	20	10	82 (<i>S</i>)
2	3.5	21	6	52	9	18 (<i>S</i>)
3	2.6	32	6	28	5	75 (<i>S</i>)
4	liquefied	32	7	84	12	77 (<i>S</i>)
5	liquefied	33	12	156	13	79 (<i>S</i>)
6	liquefied	33	24	276	12	75 (<i>S</i>)
7 ^c	liquefied	33	48	3264	76	7 (<i>S</i>)
8 ^d	solution in benzene	32	8	184	23	82 (<i>S</i>)

^a Catalyst **1b** (ca. 2.5 μmol of Rh content) was employed at 60 °C. ^b Syngas: H₂/CO = 1/1. ^c Iso/normal = 92/8. ^d Homogeneous solution using **1a** in benzene. Data reported in ref 9b.

comparable to those of the homogeneous solution conditions. For example, trifluoropropene was converted into (*S*)-2-trifluoromethylpropanal with TOF of 114, *i/n* (iso/normal) ratio of 93/7, and 90% ee at 40 °C under H₂/CO pressure of 40 atm/40 atm.¹⁴ By ICP emission spectroscopy, no Rh was detectable in the products, with the experimental error range being less than 0.8% of the initially loaded Rh.¹⁴

During the further optimization of reaction conditions, we found that the initial pressures of hydrogen, carbon monoxide, and olefin significantly affected the turnover number of the reaction and enantiomeric excess of products. Results of vapor-phase asymmetric hydroformylation of *cis*-2-butene (**2a**) are summarized in Table 1. Using **1b**, (*S*)-2-methylbutanal (**3a**) of 82% ee was obtained after 2 h, starting with **2a** (3 atm) and syngas (total 24 atm, H₂/CO = 1/1), as shown in entry 1. The



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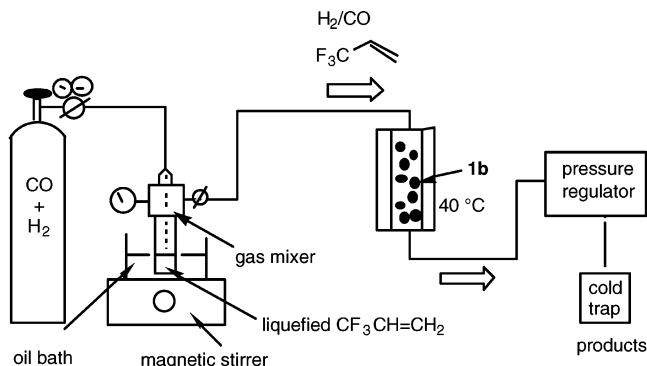
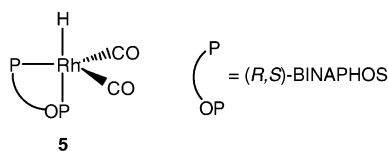


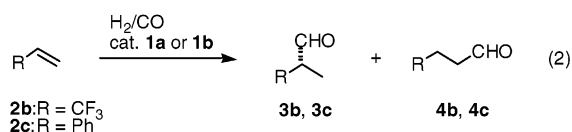
Figure 2. Asymmetric hydroformylation of 3,3,3-trifluoropropene (**2b**) using a continuous flow reactor.

TOF and % ee values are comparable to the ones obtained under homogeneous conditions (entry 8). In contrast, a longer reaction time of 6 h resulted in a lower enantioselectivity of 18% ee (entry 2). The drop of % ee could be avoided to some extent by raising the initial syngas pressure to total 32 atm (entry 3). For example, liquefied **2a** reacted with 32–33 atm of syngas to afford **3a** over 75% ee in 7–24 h (entries 4–6). Thus, the present reaction system favors higher substrate pressure. Even so, however, the % ee of **3a** was lost dramatically, after 48 h together with byproduct pentanal (**4a**, 8% yield), and all the aldehyde products were produced with much higher TOF of 76 h⁻¹ (entry 7). Longer reaction time should have produced a new species that seems to be more reactive but less selective than **1b**. Change of the catalyst character could be recognized by its color.¹⁶ The initial yellow color of **1b** became pale yellow when treated with H₂ and CO, suggesting the formation of RhH(CO)₂ species (**5**).⁹ During the reaction, the resin remained pale yellow,



but after a certain period, the color suddenly changed to red, due possibly to the formation of a new species.¹⁷ Thus, apparently, the rhodium hydride species derived from **1b** is less stable under this solvent-free vapor phase as compared with the reaction in benzene.

Vapor-Phase Asymmetric Hydroformylation of 3,3,3-Trifluoropropene in a Continuous Flow System. Polymer-supported complex **1b** was packed in a stainless column together with sea sand for filling the dead volume. This catalyst-packed column was first applied to asymmetric hydroformylation of 3,3,3-trifluoropropene (**2b**), a volatile olefin, under a high-



pressure continuous-flow system. The schematic drawing of the apparatus is illustrated in Figure 2 and the results are summarized in Table 2. Syngas (H₂/CO = 1/1) was allowed to move through a stainless autoclave in which a substrate olefin was liquefied. Thus, a mixture of syngas and an olefin was prepared, total pressure being regulated at 20 atm (entry 1) and 50 atm

Table 2. Continuous Vapor-Flow Asymmetric Hydroformylation of 3,3,3-Trifluoropropene (**2b**) Using a Column Filled with Catalyst **1b**^a

entry	total pressure of CF ₃ CH=CH ₂ , H ₂ , and CO (atm)	time (h)	TON	TOF (h ⁻¹)	i/n	% ee
1	20	4	22	5.5	88/12	82
2	50	0.5	4.5	9	95/5	90
3 ^b	solution in benzene	18	1152	64	95/5	93

^a Reaction conditions for entries 1 and 2: Total pressure was controlled by a BPR. The saturated CF₃CH=CH₂ pressure at room temperature was used. Initial pressure of syngas was controlled to be 1 atm higher than BPR. Syngas contained of H₂/CO = 1/1. ^b Homogeneous solution using **1a** in benzene. Data reported in ref 9b.

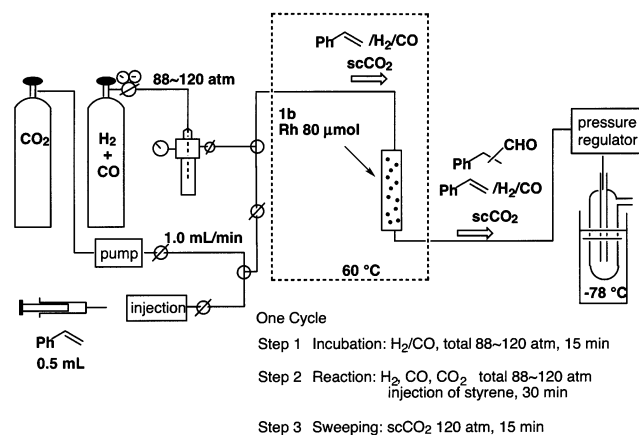


Figure 3. Asymmetric hydroformylation of styrene (**2c**) with stepwise injection to a scCO₂ flow reactor.

(entry 2) at 40 °C, and led to the catalyst column. The exit of the pressure regulator was cooled to -78 °C to trap products. As is readily seen, high selectivities achieved under homogeneous conditions were maintained, but the TOF remained at a low level (compare entries 2 and 3). This fact may be attributed either to strong affinity of the resulting aldehydes to the polymer catalyst, preventing product discharge, or alternatively to low olefin concentration in the mixed gas.

Stepwise Injection of Styrene under scCO₂ Flow. Since most of substrates used for asymmetric hydroformylation are much less volatile,¹¹ we next used scCO₂ as a mobile phase for the flow reaction, taking advantage that scCO₂ dissolves both gaseous and liquid substrates and reagents. Because hydroformylation is a reaction of mostly liquid or solid olefins with hydrogen gas and carbon monoxide gas, efficient delivery of all the substrates to the active center is essential for the reaction to proceed, and clearly, supercritical CO₂ is the best medium for this purpose. Shown in Figure 3 is a drawing of the present system. Styrene (**2c**) was injected portion wise into the column reactor under the flow of syngas and scCO₂, in the following manner: (1) incubation of catalyst syngas atmosphere (H₂/CO = 1/1, total 88 or 120 atm) for 15 min, (2) injection of styrene from the injector under the mixed gas flow (total 88 or 120 atm) for 30 min, and (3) sweeping products from the column with higher pressure of scCO₂ flow (120 atm) for 15 min.

(16) The catalyst color change is shown in the Supporting Information.

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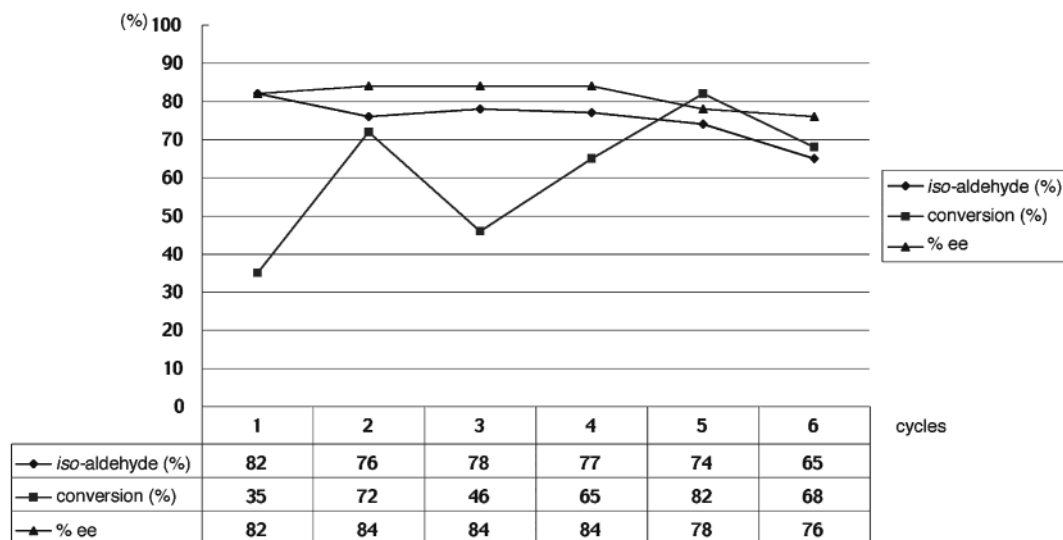


Figure 4. Asymmetric hydroformylation of styrene under continuous scCO_2 flow at total pressure of 88 atm: a plot of regioselectivity for iso, conversion of styrene to aldehydes, and enantioselectivity vs number of cycles.

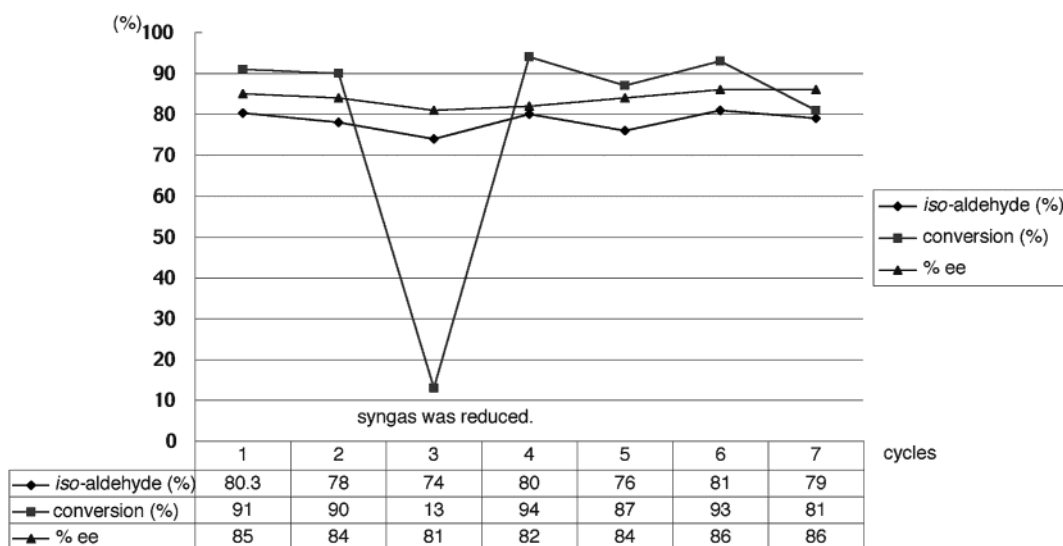


Figure 5. Asymmetric hydroformylation of styrene under continuous scCO_2 flow at a total pressure of 120 atm: a plot of regioselectivity for iso, conversion of styrene to aldehydes, and enantioselectivity vs number of cycles. At the third cycle, the total pressure of syngas was reduced.

The three-step operation was repeated for six or seven cycles at a total pressure of 88 atm (Figure 4) and 120 atm (Figure 5). The reaction proceeded smoothly, and the catalytic activity and selectivities were almost maintained. The reaction carried out with total 120 atm pressure gave better results: $\sim 90\%$ conversion, $\sim 85\%$ ee, and $\sim 80\%$ iso-selectivity. The selectivities are a little lower than the ones obtained using **1a** or **1b** in benzene ($>99\%$ conversion, 92% ee, and 89% iso-selectivity with **1a**;^{9b} and $>99\%$ conversion, 89% ee, and 84% iso-selectivity with **1b**)^{12a} and are comparable to the ones obtained with **1b** in hexane ($>99\%$ conversion, 81% ee, and 80% iso-selectivity).^{12a} The results accord with the description that the polarity of scCO_2 is comparable to hexane at lower density conditions: low CO_2 pressure and low temperature (120 atm, 60°C).^{5–8} When syngas pressure was reduced to a total of 88 atm or below, the conversion and selectivities decreased (Figure 4 and cycle 3 of Figure 5). The conversion and selectivities could be well-reproduced when the syngas pressure returned to 120 atm of

the mixed gas (Figure 5, steps 4–7). Thus, low catalytic activity under reduced syngas pressure is not due to catalyst inactivation but to an equilibrium between an inactive species and active rhodium hydride. As described, high syngas pressure is essential for satisfactory conversion and selectivities.

Sequential Injection of Different Olefins: Library Synthesis of Optically Active Aldehyde under scCO_2 Flow. Sequential injection is especially suitable for the hydroformylation of various kinds of olefins to give the corresponding chiral isoaldehydes in their optically active manner. Several olefins were subjected to hydroformylation sequentially using the flow reaction system described in Figure 3. The results are summarized in Table 3. Styrene (**2c**) was injected at the first, fourth, and eighth cycles with similar results to each other. Although the conversion of styrene to aldehydes varies to some extent,¹⁸ the constant selectivities suggest that the catalyst maintains its

(18) This may be due to the less homogeneous nature of the supported catalyst, for example, shape or pore size.

Table 3. Sequential Conversion of an Olefin Library (2c–h) to an Aldehyde Library^a

cycle	olefin	conv (%)	i/n	% ee
first	styrene (2c)	49	82/18	77
second	vinyl acetate (2d)	5	70/30	74
third	1-octene (2e)	47	21/79	73
fourth	1-hexene (2f)	40	21/79	60
fifth	styrene (2c)	36	81/19	82
sixth ^b	2,3,4,5,6-pentafluorostyrene (2g)	27	89/11	88
seventh ^b	CF ₃ (CF ₂) ₅ CH=CH ₂ (2h)	21	91/9	78
eighth	styrene (2c)	54	80/20	80

^a Continuous scCO₂ flow system (Figure 3) was used at 60 °C, with a total pressure of 120 atm. ^b At 40 °C.

performance during the repeated cycles. The results with other olefins, vinyl acetate (2d), 1-octene (2e), 1-hexene (2f), pentafluorostyrene (2g), and tridecafluoro-1-octene (2h), were comparable to the results obtained under homogeneous conditions.^{9b} After each cycle, the materials obtained in the cold trap were analyzed by ¹H NMR and GC to disclose that only the expected product aldehydes and the remaining substrates were present with neither products nor substrate of each previous cycle being contaminated. This system can be sequentially applicable to various substrates with a single catalyst, and thus, we consider that the system might preferably find applications in combinatorial synthesis and sequential conversion of an olefin library to an optically active aldehyde library. The enantiomeric enrichment of 60–80% ee may not be sufficient as a final product. However, for diversity-oriented synthesis, assays may be carried out with racemic mixture and with enantiomerically enriched mixture to compare. If the enantiomerically enriched sample shows any advantage over the racemic sample, then one would go forward to purify the enantiomers for further assays.

Conclusion

The asymmetric hydroformylation reactions discussed here have demonstrated successful use of the polymer-supported catalyst under organic solvent-free conditions, particularly in a flow system. Easy separation of the catalyst from the products has been realized using the flow systems. The absence of mechanical breakdown of the polymer catalyst prevented the loss of catalyst polymer by filtration, which was a problematic issue in a batchwise system without the fixed bed.^{12b} The flow reaction by the aid of scCO₂ as a mobile phase was applicable not only to the volatile olefins 2a and 2b but also to the less volatile olefins 2c–h. Using this new system, sequential injection of olefins enabled the conversion of an olefin library into an optically active aldehyde library, which shows the potential application of the scCO₂-flow reaction to combinatorial synthesis of chiral compounds.

Most importantly, the polymer matrixes presented are of potential use as a substitute for organic solvents, allowing the efficient collision of the substrates with the catalyst center. For example, it was essential for the BINAPHOS–Rh catalyst to be soluble in scCO₂ in order to achieve sufficient activity and selectivities when nonsupported catalysts were employed in this media.^{6–8} In contrast, despite the insoluble nature of polymer-supported 1b in scCO₂, the active center of the catalyst seems to have been provided with ideal circumstances for the asymmetric reaction in the present flow system.

Also, anchoring the catalyst onto the highly cross-linked polystyrene support realized the reaction environment wherein

the higher loading of the catalyst was possible. Recently, we found that the selectivities of asymmetric hydroformylation drop under high concentration of 1a (> 1.0 mM) in benzene.¹⁹ On a polymer support, the Rh centers are dispersedly attached to avoid the formation of undesirable dimeric species. In addition, recently we reported that the polystyrene-support might afford positive steric effect on the selectivities working as a favorable substituent of the ligand.¹⁵ We conclude that immobilization of homogeneous catalysts on a solid support should be regarded not only by its technical merits but also as a new type of catalyst design for asymmetric catalysis.

Experimental Section

General Remarks. All manipulations of oxygen- and moisture-sensitive materials were conducted under purified argon atmosphere (deoxygenated by passing through BASF-Catalyst R3-11 column at 80 °C) by the use of standard Schlenk techniques. TLC analyses were carried out by means of Merck Kieselgel 60 F₂₅₄, and silica gel chromatography was performed using Wakogel C-200. Nuclear magnetic resonance spectra were taken with a JEOL JNM-ECP500 or Varian Mercury 200 spectrometer. GLC analyses were performed on a Shimadzu GC-15A or Shimadzu GC-2010 gas chromatograph equipped with a flame ionization detector. Supercritical CO₂ was provided using a JASCO SCF–Get machine. The catalyst-filled column was heated by a JASCO CO-2060 plus apparatus. A JASCO SCF–Bpg regulator was used for controlling the back pressure. Most of the reagents were available from Wako Pure Chemical Industries Ltd. or Nacalai Tesque Ltd. without purification. All of the solvents used for the reactions were distilled under argon after drying over an appropriate drying agent.

Vapor-Phase Asymmetric Hydroformylation of *cis*-2-Butene (2a). Polymer-supported Rh(I)–(*R,S*)-BINAPHOS (1b, 118 mg, [Rh] ca. 5 μmol) was placed on the wire-bed as shown in Figure 1, Apparatus A.¹⁴ The wire-bed was fixed at the center of a window-equipped 33-mL autoclave. The whole was dried in vacuo. The autoclave was charged with *cis*-2-butene and syngas (H₂/CO = 1/1) and then heated at 60 °C. Other conditions are described in Table 1. All the volatile materials were leaked, and Ph₂CH₂ (8.40 μL, 50.0 μmol) was added to the crude products. Produced aldehydes were assayed by ¹H NMR to estimate yields and then treated with the Jones reagent to convert into the corresponding carboxylic acids. The enantiomeric excess of 2-methylbutanoic acid was measured by GC with a chiral column Chirasil-Dex CB, as was reported previously.^{9,12,19}

Asymmetric Hydroformylation of 3,3,3-Trifluoropropene (2b) through Continuous Flow System. Polymer-supported Rh(I)–(*R,S*)-BINAPHOS (1b,^{12b} 1.89 g, [Rh] ca. 80 μmol) was packed in a glass column (260 mm × φ8.0 mm) using sea sand to fill the dead space. In an autoclave (see Figure 3) was placed liquefied 3,3,3-trifluoropropene, and a syngas inlet was connected to the autoclave. The column was connected to the autoclave, and syngas was passed through the autoclave and then through the column. The exit pressure was adjusted to 20 or 50 atm with a back-pressure regulator (BPR). The mixed gas was passed for 30–240 min, and all the organic materials were collected at the exit (from the gas stream) by a cold trap at –78 °C. Reference compound Ph₂CH₂ (8.40 μL, 50.0 μmol) was added to the cold trap and the products were assayed by ¹H NMR. The results are summarized in Table 2.

Sequential Conversion of Olefins 2c–h into the Corresponding Aldehydes Using a Continuous Flow System under scCO₂ Flow. Polymer-supported Rh(I)–(*R,S*)-BINAPHOS (1b, 1.89 g, [Rh] ca. 80 μmol) was packed in a stainless column (260 mm × φ8.0 mm) using sea sand to fill the dead volume. Syngas (H₂/CO = 1/1) was flashed

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through the column at 60 °C and 88–95 or 120–125 atm for 15 min (incubation step). The exit pressure was adjusted to 88 or 120 atm with a BPR, and then compressed CO₂ was flashed through the column using a HPLC pump at a flow rate of 1 mL/min. Styrene (**2c**) was introduced into the gas stream by syringe via the injector, and the organic materials were collected at the exit by a cold trap at –78 °C (reaction step). After 30 min, syngas was replaced by compressed CO₂ (the flow rate was adjusted to 3 mL/min), and the CO₂ stream was maintained for 15 min (sweeping step). Reference compound Ph₂CH₂ (8.40 μL, 50.0 μmol)

was added to the materials in the cold trap for analysis by ¹H NMR. The results are summarized in Figures 4 and 5 and Table 3. Subsequent hydroformylation was carried out starting with the incubation step.

Supporting Information Available: Photographs of the catalyst color change. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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