JOC The Journal of Organic Chemistry
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Entrainer Effects on Enantiodifferentiating Photocyclization of 5-Hydroxy-1,1-diphenylpentene in Near-Critical and Supercritical Carbon Dioxide

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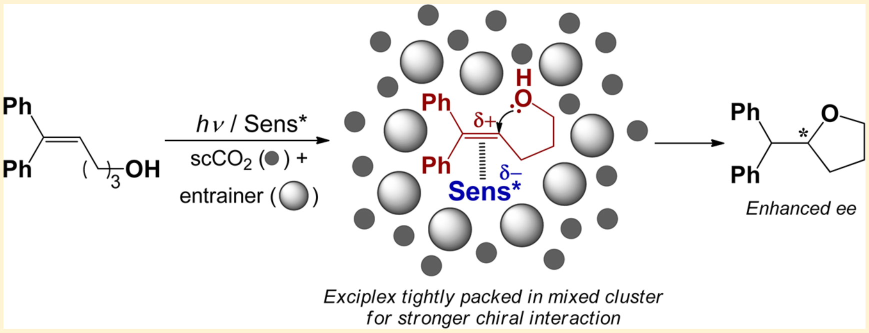
Ⓢ *Supporting Information*



ABSTRACT: Enantiodifferentiating photocyclization of 5-hydroxy-1,1-diphenyl-1-pentene (**1**) sensitized by bis(1,2;4,5-di-*O*-isopropylidene-*α*-fructopyranosyl) 1,4-naphthalenedicarboxylate (**2**) was performed in near-critical and supercritical carbon dioxide media containing organic entrainers to obtain a chiral tetrahydrofuran derivative (**3**) in enantiomeric excess (ee) higher than those obtained in conventional organic solvents. Interestingly, the entrainer-driven ee enhancement did not depend on the entrainer polarity, which is in contrast to the behavior of the ee observed upon selective solvation in nonpolar organic solvents. This indicates that entrainer clustering around the intervening exciplex is essential in order to keep the intimate sensitizer—substrate contact within the exciplex. Therefore, the clustering itself, rather than its property, is more crucial to prevent the dissociative diffusion to gaseous CO_2. The wider allowance in choosing the entrainer enables us to use more "green" solvents for achieving the ee enhancement, while reducing the environmental risk.

■ INTRODUCTION

Recent endeavors devoted to chiral photochemistry[1] have greatly improved the enantioselectivities of various uni- and bimolecular chiral photosensitized reactions and more crucially revealed the decisive roles of entropy in the critical enantiodifferentiation step, leading to unprecedented observations such as an inversion of product chirality at an "equipodal" temperature and an increase in enantiomeric excess (ee) at a higher reaction temperature.[2,3] It was further demonstrated that the other entropy-related factors, such as pressure[4] and solvation,[5] also play vital roles in several photochirogenic reactions. In particular, product chirality switching caused by the solvent is impressive. Thus, the antipodal (*E*)-isomer was produced by simply changing the solvent from pentane to diethyl ether upon photosensitization of (*Z*)-cyclooctene with tetrakis(1,2;4,5-di-*O*-isopropylidene-*α*-glucopyranosyl), i.e., di-acetone-glucosyl (DAG), pyromellitate,[5] for which the solvation of ether to the DAG moieties of the sensitizer and/or exciplex intermediate is likely to be responsible. Similarly, the ee of the anti-Markovnikov adduct obtained in the enantiodifferentiating polar photoaddition of methanol to 1,1-diphenylpropene was a critical function of the methanol content.[3] These findings prompted us to examine the photochirogeneses in supercritical carbon dioxide ($scCO_2$; critical point = 31 °C, 7.38 MPa), a medium that forms clusters fluctuating in time and space and is, therefore, intriguing from an entropic point of view.[6,7] In both uni- and bimolecular photochirogenic reactions conducted in $scCO_2$,[8,9] the product ee showed a keen dependence on pressure in near-critical carbon dioxide ($ncCO_2$) but underwent many modest changes at higher pressures. This contrasting behavior in nc- and $scCO_2$ is attributable to the dynamic density fluctuation augmented dramatically in the near-critical region.[10,11]

As reported previously,[3] the ee of the anti-Markovnikov adduct obtained in the above-mentioned reaction was critically affected by the microenvironmental polarity around the intervening radical-ionic exciplex. This is because the existence

Received: April 23, 2012
Published: June 8, 2012

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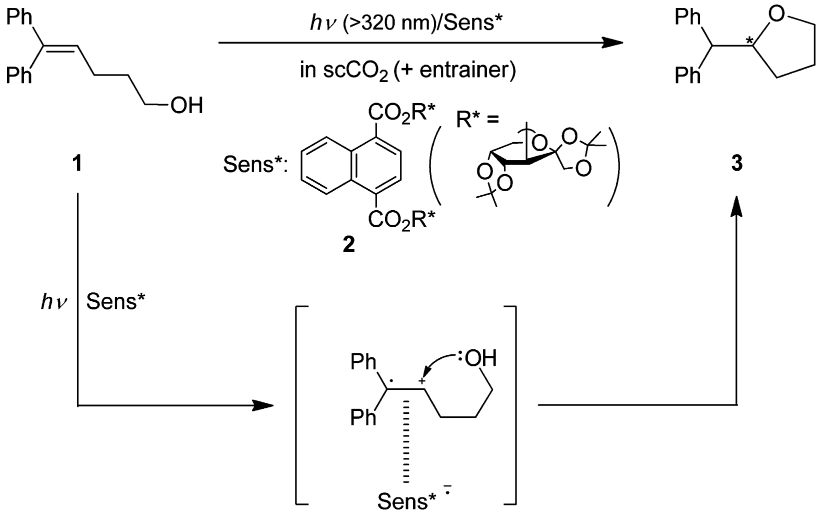
dx.doi.org/10.1021/jo300816w | *J. Org. Chem.* 2012, 77, 5681−5686

Scheme 1. Enantiodifferentiating Anti-Markovnikov Photocyclization of 5-Hydroxy-1,1-diphenylpentene (1) to Chiral 2-Diphenylmethyltetrahydrofuran (3) Sensitized by Bis(1,2;4,5-di-*O*-isopropylidene-*α*-fructopyranosyl) (or DAF) 1,4-Naphthalenedicarboxylate (2)



of methanol (up to 0.5 M), added as an essential reagent, inevitably deteriorates the diastereodifferentiating sensitizer–substrate interactions by facilitating the dissociation or solvent separation of the radical-ionic exciplex intermediate. To circumvent this dilemma, we prepared 5-hydroxy-1,1-diphenyl-1-pentenol (**1**) as a "self-containing" substrate with a built-in alcohol molecule and gained improved ee's for the anti-Markovnikov cyclization product (**3**) obtained upon sensitization with bis(1,2;4,5-di-*O*-isopropylidene-*α*-fructopyranosyl), i.e., diacetone-fructosyl (DAF), 1,4-naphthalenedicarboxylate (**2**) in organic solvents (Scheme 1).[12] In a recent communication,[13] we have demonstrated that diethyl ether, added as an entrainer, enhances the product ee in this enantiodifferentiating photocyclization performed in nc- and $scCO_2$. This observation is of particular interest, suggesting the positive role of entrainer clustering in manipulating the exciplex structure and, hence, the product ee upon photochirogenesis in nc- and $scCO_2$. In this study, we expanded the entrainer range and closely examined the effects of entrainer polarity and concentration to reveal the mechanism and general validity of the ee enhancement caused by the entrainer added to nc- and $scCO_2$.

RESULTS AND DISCUSSION

A close examination of the chiral HPLC trace from the irradiated sample, retrieved from the pressure vessel on a new chiral column, revealed a small peak half-overlapped with the minor enantiomer peak of **3** that had been overlooked and would have led to an underestimation of the product ee for the reaction conducted in CO_2 media in the previous study.[13] Hence, we reexamined the enantiodifferentiating photocyclization of **1** sensitized by **2** in nc- and $scCO_2$ at 45 °C. The irradiated reaction mixtures were subjected to medium-pressure column chromatography on silica gel to give chemically pure samples of product **3** (see Experimental Section for details) that were then analyzed by chiral HPLC to obtain ee's not significantly, but appreciably, higher than those reported in the previous paper.[13] The more reliable ee's thus obtained are listed in Table 1 (runs 7–15), along with the data obtained using conventional organic solvents at 0 and 25 °C (runs 1–6). [Table 1 lists only the essential data obtained at near-critical (ca. 8 MPa), unit reduced density (ca. 9 MPa), and supercritical pressure (ca. 12 and 18 MPa). See Table S1 in the Supporting Information for the full list.] The ee values obtained in the nc- and $scCO_2$ media are plotted as a function of pressure in Figure 1 (●) with the density fluctuation curve of CO_2 cited from the literature[11] in the background.

As can be seen from Figure 1 (●), the ee of **3** is not a straightforward function of the CO_2 pressure, particularly in the nc region, exhibiting a sharp depression at ca. 9 MPa followed by a rapid increase at 9–12 MPa to reach a quasi-plateau thereafter, indicating modest pressure effects in the sc region. Although we do not have a convincing rationale for the depression, the density fluctuation that is maximized at 9.6 MPa[11] appears to play an important role. The global decline of the ee throughout the nc region is more reasonably accounted for in terms of the increased population of the less-clustered exciplex intermediate, in which the self-clustering, or self-solvation, of the terminal hydroxyl in substrate **1** accelerates the exciplex dissociation to reduce the product's ee. The same rationalization would also apply to the occurrence of the ee depression near the density fluctuation maximum as an extreme case, since the population of smaller clusters in which the self-clustering of the intramolecular hydroxyl is enhanced is thought to be maximized at this pressure.

In contrast, the product's ee's (37–41%) obtained in $scCO_2$ (12–18 MPa) are appreciably larger than those obtained in conventional organic solvents (1–35% ee); compare runs 12–15 with runs 1–6 in Table 1. As anticipated, the use of acetonitrile as a solvent diminished the product's ee's to 1–5% as a consequence of the accelerated dissociation of the exciplex intermediate in the polar solvent and, therefore, should be avoided at least in the photochirogenesis in organic solvents.

The effects of the entrainer on the enantiodifferentiating photocyclization of **1** were examined by adding organic solvents of varying polarities, i.e., toluene, diethyl ether, and acetonitrile, to nc- and $scCO_2$ media. The ee's obtained in the presence of a 0.6 M entrainer are summarized in Table 1 (runs 16–23, 33–41, and 59–67) and plotted against CO_2 pressure in Figure 1. Somewhat surprisingly, all of the entrainers (toluene, ether, and acetonitrile) added to nc- and $scCO_2$ significantly enhanced the enantioselectivity to give the highest ee values among those

Table 1. Enantiodifferentiating Photocyclization of **1** Sensitized by **2** in Near-Critical and Supercritical Carbon Dioxide (nc- and $scCO_2$) and Conventional Organic Solvents[a,b]

run	medium	entrainer	concentration (M)	temperature (°C)	pressure (MPa)	ee (%)[c]
1	methylcyclohexane[d]	none	0	25	0.1	35
2				0	0.1	33
3	diethyl ether[d]	none	0	25	0.1	28
4				0	0.1	35
5	acetonitrile[d,e]	none	0	25	0.1	5
6				0	0.1	1
7	nc- and $scCO_2$	none	0	45	8.2	18
9					8.9	5
12					12.0	41
15					18.0	40
16		toluene	0.6	45	8.4	36
17					9.1	43
20					11.4	47
23					17.6	45
24		diethyl ether	0.3	45	8.2	17
26					8.8	21
29					12.2	44
32					18.4	46
33			0.6	45	7.8	28
35					8.8	35
38					12.1	43
41					18.3	47
42		acetonitrile	0.1	45	8.1	28
44					9.1	26
47					12.4	42
50					17.0	43
51			0.3	45	8.2	38
53					8.9	28
55					12.0	44
58					17.9	43
59			0.6	45	8.2	32
61					8.8	34
64					11.6	44
67					17.0	38
68			1.0	45	8.0	41
70					8.8	35
73					11.2	39
75					17.1	36

[a] This table contains only the essential data extracted from Table S1 in the Supporting Information, and hence the run number is not fully continuous. [b] [**1**] = 2 mM; [**2**] = 0.3 mM. [c] Enantiomeric excess of **3** determined by chiral HPLC analysis on a Chiralpak IB column eluted with *n*-hexane/isopropanol/1,2-dichloroethane (98:1:1), error in ee is less than ±2%. The sign of ee does not mean the sign of optical rotation or absolute configuration but is tentatively assigned according to the elution order. The first eluted enantiomer is given a positive sign. [d] Data from ref 12. [e] [**1**] = 20 mM; [**2**] = 3 mM.

obtained in pure solvent and CO_2 media. When compared with the low ee's (1–5%) obtained in pure acetonitrile (Table 1, runs 5 and 6),[12] the much higher ee's (32–44%) achieved by adding acetonitrile as an entrainer to nc- and $scCO_2$ are spectacular (Table 1, runs 59–67). This ee enhancement over the entire range of CO_2 pressure also contrasts with the unsuccessful attempts to improve the product ee of the same photocyclization, through preferential solvation of acetonitrile (or other polar solvents) added to nonpolar methylcyclohexane,[12] unveiling the unique nature and advantage of entrainer clustering in nc- and $scCO_2$ media. Another important feature is the very global and consistent ee enhancement by the entrainers of varying polarities, which is hardly anticipated from the conventional solvation phenomena, but beneficially allows us to use a wide variety of solvents, including environmentally more benign ones, for the ee enhancement through entrainer clustering. In this relation, it is interesting to briefly discuss the "cage" effect of the entrainer in $scCO_2$, which was proposed by Weedon et al.[14] to explain the enhanced product selectivity of photo-Fries rearrangement conducted in $scCO_2$ upon addition of methanol and 2-propanol. The entrainers employed in their and our studies are significantly different in polarity and hydrogen-bonding ability, and therefore, the clustering shell, or solvent cage, seems more "structured" in the methanol and 2-propanol cases. The major difference from ours is the behavior of less polar and non-hydrogen-bonding entrainers, which do not alter the product selectivity of the photo-Fries rearrangement.[14] Nevertheless, Weedon's "cage" and our "preferential clustering" may share a similar concept for explaining the confinement of reactive or excited species in a limited space,

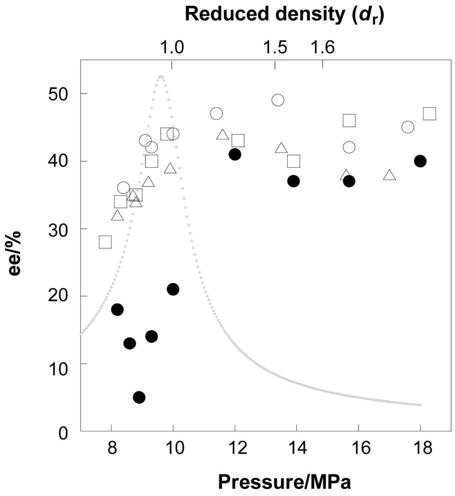


Figure 1. Pressure dependence of the density fluctuation in arbitrary units (gray dotted line) and the ee of **3** obtained in the enantiodifferentiating photocycloaddition of **1** sensitized by **2** in nc- and $scCO_2$ at 45 °C in the absence (●) and presence of 0.6 M toluene (○), ether (□), and acetonitrile (△) added as the entrainer.

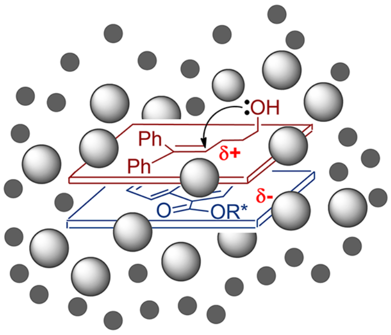


Figure 3. Schematic illustration of the preferential clustering of the entrainer to the exciplex of sensitizer **2** with substrate **1** in the nc- and $scCO_2$ media. Large shaded gray and small black dots represent the entrainer and CO_2 molecules, respectively.

although the term “clustering” seems more suitable for an event in supercritical fluid.

We further examined the effects of entrainer concentration on the ee by using 0−1.0 M polar acetonitrile to reveal a rapid growth of ee at 0.1 M, followed by a much slower increase at 0.6 M, and an apparent saturation thereafter in the nc region. In contrast, much smaller effects were observed in the sc region, as shown in Figure 2a and Table 1 (runs 42−75). Particularly, the same trends were observed upon addition of 0.3−0.6 M ether in both nc and sc regions (Figure 2b and Table 1, runs 24−41).

The above observations indicate that all of the entrainers added to nc- and $scCO_2$ media form a strong cluster around the exciplex intermediate that significantly affects the stereochemical outcomes, in particular in the nc region; for a schematic illustration of the preferential entrainer clustering to a polarized exciplex intermediate in $scCO_2$ media, see Figure 3. In sharp contrast to the negligible effect of selective solvation in organic solvents,[12] both polar and nonpolar entrainers are equally effective in enhancing the product ee in CO_2 media, suggesting that the clustering itself is more crucial than the properties of the cluster formed. This is likely because the diffusive dissociation of the exciplex intermediate to gaseous CO_2 media is strongly discouraged particularly in low-density $ncCO_2$.

The opaque nature of the nc- and $scCO_2$ media does not allow us to measure the UV−vis and CD spectra, but the static and time-correlated fluorescence measurements are feasible even in CO_2 media. Unfortunately, the exciplex intermediate is not fluorescent in the present case, but we can still estimate the microenvironmental polarity around an excited state of relevant species by using sensitizer **2**, which is a part of the intervening exciplex but less polarized. Hence, we measured the fluorescence spectra and fluorescence lifetimes of **2** in nc- and $scCO_2$ and also in representative nonpolar and polar organic solvents, both with and without an added cosolvent or entrainer. As can be seen from Table 2 (runs 1, 4, and 5), the fluorescence maximum (λ_{max}) in organic solvents shows steady bathochromic shifts from 396 to 419 nm and the lifetime (τ) continuous elongation from 5.8 to 10.5 ns with increasing solvent polarity from methylcyclohexane to acetonitrile, indicating stabilization of the excited singlet of **2** in polar solvents. The only exception is the use of toluene (run 3),

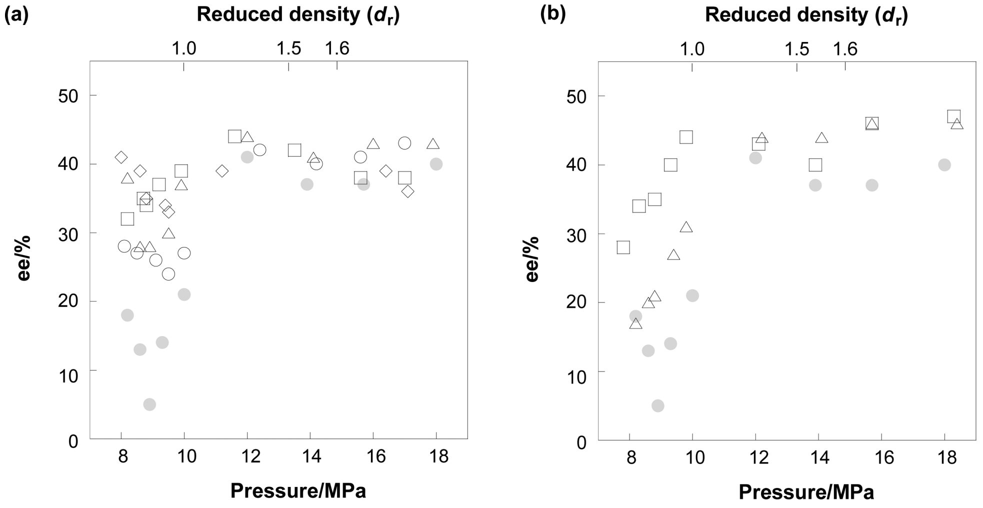


Figure 2. Pressure dependence of the ee of **3** obtained in the enantiodifferentiating photocycloaddition of **1** sensitized by **2** in the presence and absence of (a) acetonitrile or (b) diethyl ether at various concentrations in nc- and $scCO_2$ at 45 °C. [Entrainer] = 0 M (●), 0.1 M (○), 0.3 M (△), 0.6 M (□), and 1.0 M (◊).

Table 2. Fluorescence Maxima (λ_{max}) and Fluorescence Lifetimes (τ^0) of Sensitizer 2 in Various Organic Solvents at Room Temperature and in Near-Critical (9 and 10 MPa) and Supercritical Carbon Dioxide (18 MPa) at 45 °C in the Presence and Absence of an Entrainer or Cosolvent[a]

run	medium	additive[b]	pressure (MPa)	λ_{max} (nm)	τ (ns)
1	methylcyclohexane[c]	none	0.1	396	5.8
2		acetonitrile	0.1	402	7.1
3	toluene[c]	none	0.1	423	11.6
4	diethyl ether[c]	none	0.1	405	8.7
5	acetonitrile[c]	none	0.1	419	10.5
6	nc- and $scCO_2$	none[d]	9	398	7.0
7			10	398	6.9
8			18	399	6.6
9		toluene	9	407	9.3
10			10	407	8.9
11			18	406	8.1
12		diethyl ether[d]	9	399	7.1
13			10	399	7.0
14			18	399	6.7
15		acetonitrile[d]	9	403	8.1
16			10	402	7.8
17			18	402	7.4

[a] [**2**] = 0.01 mM; excitation at 340 nm. [b] [Additive] = 0.6 M. [c] Data from ref 12. [d] Data from ref 13.

which leads to a further stabilized (λ_{max} = 423 nm) and long-lived singlet (τ = 11.6 ns), presumably as a result of the $\pi-\pi$ stacking interaction with excited **2**. Using the λ_{max} and τ values as measures of the microenvironmental polarity, we can deduce that nc- and $scCO_2$ (runs 6–8: 398–398 nm, 6.6–7.0 ns) are certainly more "polar" than methylcyclohexane (run 1: 396 nm, 5.8 ns), but less "polar" than diethyl ether (run 4: 405 nm, 8.7 ns). This is in nice agreement with the reported data.[15]

Intriguingly, the addition of 0.6 M ether as an entrainer did not appreciably affect the λ_{max} and τ values, causing essentially no changes; compare runs 12–14 with runs 6–8 in Table 2. Similarly, the entrainer effects of toluene and acetonitrile (runs 9–11 and 15–17) were modest, inducing a 7–9 nm shift and 1.5–2.3 ns elongation for toluene and a 3–5 nm shift and 0.8–1.1 ns elongation for acetonitrile that are much smaller than those caused by changing the solvent from methylcyclohexane to toluene or to acetonitrile (23–27 nm shift and 4.7–5.8 ns elongation). Crucially, 0.6 M acetonitrile added to methylcyclohexane (run 2) caused the same shift to 402 nm and a slightly smaller elongation to 7.1 ns, compared with the shifts to 402–403 nm and elongation to 7.4–8.1 ns that were observed upon addition of 0.6 M acetonitrile to nc- and $scCO_2$ (runs 15–17). This implies insignificant differences between the selective solvation in the nonpolar organic solvent and entrainer clustering in nc- and $scCO_2$, at least from the microenvironmental point of view. Nevertheless, in the present case, the ee of product **3** was indeed enhanced by adding ether, toluene, and even acetonitrile as the entrainer (Table 1, runs 16–75; Figures 1 and 2). These apparently conflicting observations in the spectral versus product studies also led us to a conclusion that the discouraged dissociative diffusion of the exciplex intermediate to a gaseous environment is unique to the nc- and $scCO_2$ media and indispensable to keep the chiral sensitizer–substrate interactions in a cluster, while the microenvironmental properties of the cluster play significant roles in determining the product ee.

■ CONCLUSION

By using the enantiodifferentiating photocyclization of 5-hydroxy-1,1-diphenyl-1-pentene **1** sensitized by DAF 1,4-naphthalenedicarboxylate **2**, we have revealed several unique features of the entrainers added to nc- and $scCO_2$. Thus, the product ee was significantly enhanced by adding organic solvents as the entrainers in both the nc and sc regions to achieve 49%, the highest value ever reported for this photochirogenic reaction. Interestingly, the ee enhancement achieved by adding an entrainer is more pronounced than that induced by the selective solvation in a nonpolar solvent and globally observed for all of the examined entrainers, despite the very similar fluorescence spectral and lifetime behavior of the chiral sensitizer in the CO_2 and organic media in the presence and absence of acetonitrile added as an entrainer. These new findings enabled us to elucidate the origin and mechanism of the entrainer effect and also to practically apply the entrainer effect as a tool for enhancing the product ee. Mechanistically, the prevented dissociative diffusion of the exciplex intermediate to gaseous CO_2 is one of the important key concepts to understanding the unique spectral and photochirogenic behavior observed in the CO_2 media, while tolerance for the entrainer polarity allows us to use a much wider range of entrainers, thus contributing to the green sustainable chemistry. Both are also useful in further expanding the scope of chiral and achiral photochemistry in supercritical fluids.

■ EXPERIMENTAL SECTION

General. Fluorescence lifetimes were determined by the time-correlated single-photon counting technique.

All chemicals were used without further purification. Spectrograde solvents were used throughout the work. Carbon dioxide of 99.99% purity was used as received. 5-Hydroxy-1,1-diphenylpentene (**1**) was prepared as reported previously.[16]

Photolysis and Product Analysis. An ether solution containing a given amount of substrate **1** and sensitizer **2** was placed in a high-pressure vessel that was equipped with three sapphire windows for photoirradiation and spectral measurements. Next, the solvent was evaporated in vacuo to leave a residue, to which a desired amount of entrainer was added if necessary. Then, the top opening of the vessel was closed and carbon dioxide was introduced into the vessel until the desired pressure (7.8–18.3 MPa) was reached at the fixed temperature (45.0 ± 0.1 °C). Radiation from a 500 W ultra-high-pressure mercury lamp was collimated, passed through a water layer (to eliminate the infrared radiation) and a UV-D36B filter, and introduced into the pressure vessel.

After irradiation, the pressure was released very slowly at 0 °C, and the released gas was introduced with a stainless steel tube into ice-cooled diethyl ether to collect any volatile materials. An attempt was made to retrieve the residue in the vessel by washing several times with diethyl ether, but the repeated washing with ether was not sufficient to completely retrieve all of the remaining substrate and product formed because of the inherent nature of supercritical fluid. It intrudes and delivers the solute into narrow clearance gaps inside the vessel that organic solvents cannot reach. This situation made the conversion and chemical yield determination less reliable, as indicated by the rather large standard deviations of 6.5% (in conversion) and 16.3% (in yield) for three repeated runs under the same conditions (and hence not reported). On the other hand, the ee values reported are inherently reliable, as the intrusion into the gaps should not be enantiodifferentiating. Indeed, the standard deviation of the ee value was only 2.0%, which is comparable to or even better than those obtained for the same reaction conducted in organic solvents.

The combined ether solution retrieved from the vessel was first subjected to medium-pressure liquid chromatography on an Isolera One column eluted with a 95:5 hexane/diethyl ether mixture to a column volume (CV) = 1 and then with a 3.5% CV gradient to reach a 60:40 hexane/diethyl ether mixture at CV = 11. The fraction containing photoproduct **3** was collected at CV = 5.0−5.5. The ee of **3**, thus obtained, was determined by a chiral HPLC instrument equipped with a UV detector (detection at 220 nm). The chiral HPLC analyses were run at 5 °C on a Chiralpak IB column (5 μm particles, 4.6 mm $\phi \times 250$ mm) and eluted with a 98:1:1 *n*-hexane/isopropanol/1,2-dichloroethane mixture at a flow rate of 0.3 mL/min under an isocratic condition. The enantiomer peaks were well separated and appeared at retention times of 22 and 25 min, from the integrated areas of which the product's ee was calculated within an error of ±2%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full list of the photochemical reactions with and without an entrainer. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Research Activity Start-up (22850011) from the Japan Society for the Promotion of Science, a research grant from the Kansai Research Foundation for Technology Promotion (both for Y.N.), and a Grant-in-Aid for Scientific Research (A) (21245011) from JSPS (for Y.I.), all of which are gratefully acknowledged.

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