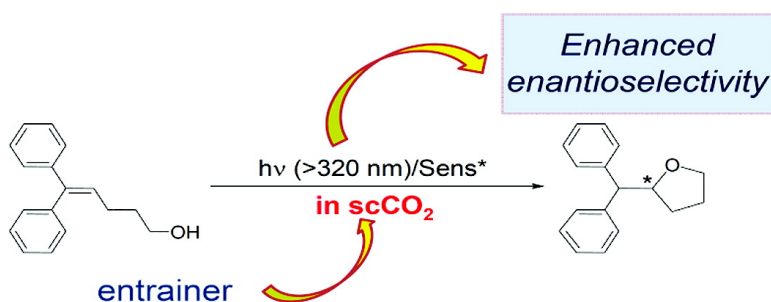


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J. Am. Chem. Soc., **2008**, 130 (24), 7526-7527 • DOI: 10.1021/ja801254z • Publication Date (Web): 24 May 2008

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Entrainer Effect on Photochirogenesis in Near- and Supercritical Carbon Dioxide: Dramatic Enhancement of Enantioselectivity

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Photochirogenesis, or chiral photochemistry,¹ has become popular in the past decade as a unique route to chiral compounds complementary to the conventional catalytic and enzymatic asymmetric syntheses. Thus, a variety of uni- and bimolecular enantiodifferentiating photoreactions have been investigated in detail to reveal the significant roles of various entropy-related factors, such as temperature,^{2,3} pressure,⁴ and solvation,⁵ in the critical enantiodifferentiation step occurring in an exciplex intermediate.

These findings prompted us to examine the effects of supercritical carbon dioxide (critical point: 31 °C, 7.38 MPa) as a dynamically fluctuating reaction medium on the photosensitized enantiodifferentiating geometrical isomerization of cyclooctene⁶ and polar addition of alcohols to 1,1-diphenyl-1-alkenes⁷ from the entropic point of view. Interestingly, the enantiodifferentiating photoaddition of alcohol to aromatic alkenes shows a sudden leap in product enantiomeric excess (ee) in a narrow pressure range transferring from near-critical to supercritical state, indicating a significant difference in clustering mechanism and/or cluster structure between near-critical and supercritical carbon dioxide (nc- and sc-CO₂) and also the vital role of clustering in determining the product's ee.

Naturally, we intended to manipulate the clustering behavior in nc- and sc-CO₂ through the entrainer effect, which is known to increase the solubility⁸ and reaction rate⁹ in sc-CO₂ but has never been applied to a photochirogenic reaction. However, in this enantiodifferentiating photoaddition to aromatic alkenes,⁷ a substantial amount of alcohol (0.5 M) has to be added to effectively capture the radical cationic intermediate formed upon electron-transfer interaction of substrate with chiral sensitizer. This does not allow us to closely examine the pure entrainer effect or to manipulate the product's ee by entrainer clustering in this photochirogenic system. Given this, we decided to use a "self-complete" photosubstrate that carries a hydroxyl group at the ω-position of 1,1-diphenyl-1-alkene for enabling the intramolecular nucleophilic attack to the olefinic moiety upon interaction with an excited sensitizer (Scheme 1).

In this study, we chose 5,5-diphenyl-4-penten-1-ol¹⁰ (**1**) as substrate and bis(1,2;4,5-di-*O*-isopropylidene- α -fructopyranosyl) 1,4-naphthalenedicarboxylate (**2**) as the chiral sensitizer to investigate the entrainer effect on the photochirogenic reaction in nc- and sc-CO₂.

The enantiodifferentiating photocyclization of **1** sensitized by **2** was first examined in conventional solvents of different polarities to give the results shown in Table 1. As reported by Mizuno et al.,¹⁰ the photocyclization was the major reaction pathway in all solvents examined and **3** was obtained as a sole product upon GC and HPLC analyses, although the yield was only modest.

Scheme 1. Enantiodifferentiating Photocyclization of 5,5-Diphenyl-4-penten-1-ol (**1**) to Chiral Cyclization Product (**3**) Sensitized by Bis(1,2;4,5-di-*O*-isopropylidene- α -fructopyranosyl) 1,4-naphthalenedicarboxylate (**2**) in Supercritical Carbon Dioxide and in Organic Solvent

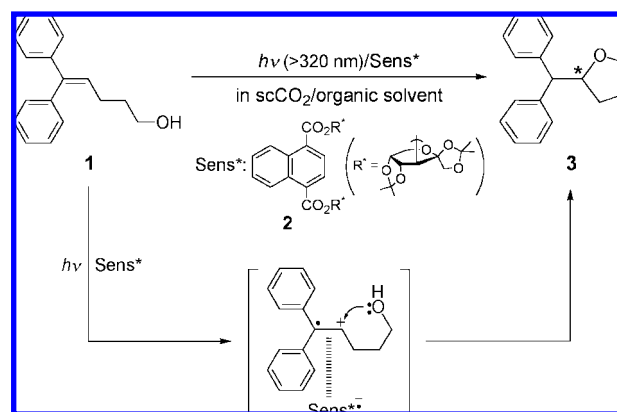


Table 1. Enantiodifferentiating Photocyclization of **1** to **3** Sensitized by **2** in Organic Solvents^a

solvent	additive ^b	temperature/°C	convl/% ^c	yield/% ^d	ee/% ^e
MCH ^f	none	20	g	g	20
	diethyl ether	20	g	g	27
toluene	none	40	46	27	27
	none	25	24	25	28
diethyl ether	none	25	68	12	22
acetonitrile	none	25	18	14	5

^a [1] = 20 mM, [2] = 3 mM; irradiated for 2 h. ^b [Diethyl ether] = 0.6 M. ^c Conversion determined by GC. ^d Yield based on consumed substrate. ^e Enantiomeric excess determined by chiral HPLC on a Daicel Chiralpak IB column; the absolute configuration of **3** is not known, and hence the first-eluted enantiomer is tentatively given a positive sign in the ee value; error <2%. ^f Methylcyclohexane. ^g Not determined.

The enantioselectivity of photocyclization was very sensitive to the solvent polarity to afford **3** in an ee as low as 5% in polar acetonitrile, where the initially diastereomeric radical ion pair shown in Scheme 1 is promptly solvent-separated or dissociated to deteriorate the chirogenic sensitizer–substrate interactions. In contrast, the product's ee was significantly increased up to 20–28% in less polar solvents, such as methylcyclohexane, toluene, and ether. On the other hand, the reaction temperature did not significantly affect the product's ee at least in toluene. In good agreement with the previous observation in the intermolecular photoaddition case,^{3b} the addition of 0.6 M ether to methylcyclohexane appreciably enhanced the ee from 20 to 27% (Table 1) as a result of the selective solvation to an exciplex intermediate. This indicates that tuning microenvironmental polarity around the exciplex is essential to improve the ee in this photochirogenic reaction.^{3b}

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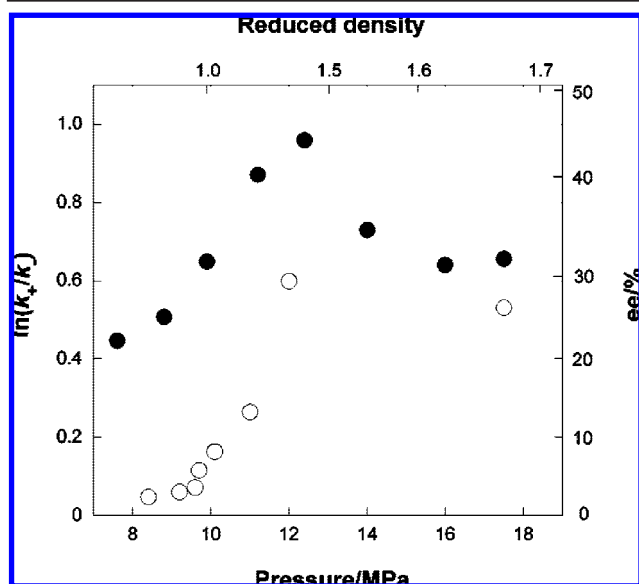


Figure 1. The logarithm of relative rate constant (k_+/k_-), calculated from the ee of **3**, as a function of pressure in the enantiodifferentiating photocyclization of **1** (2 mM) sensitized by **2** (0.3 mM) in sc-CO₂ at 45 °C in the presence (solid circle) and absence (open circle) of 0.6 M diethyl ether as an entrainer.

In CO₂ media at 45 °C, the ee of **3** was highly pressure-dependent, displaying a dramatic leap from nearly 0 in nc-CO₂ (8–10 MPa) to the maximum value of 29% in sc-CO₂ at 12 MPa, as shown in Figure 1 (open circles). In a previous work,⁷ we observed a similar but more abrupt leap of ee in an intermolecular version of this photocyclization, that is, the polar photoaddition of alcohols to 1,1-diphenyl-1-alkenes sensitized by the same chiral sensitizer **2**. Thus, the much lower ee in nc-CO₂ may be rationalized by the lower dielectric constant of nc-CO₂ than of sc-CO₂,^{11,12} which promotes strong non-enantioface-selective “self-clustering” of the terminal OH to the radical cationic alkene moiety, affording almost racemic product **3**. In more polarizable sc-CO₂, the self-clustering and the subsequent attack of terminal OH become more enantioface-selective to give a better ee. Similarly, diethyl ether added as an entrainer also tunes the cluster polarity around the exciplex and improves the product’s ee over the entire pressure range examined to give the ee of up to 45%, as shown in Figure 1 (solid circles). As anticipated from the difference in dielectric constant, the ee enhancement upon addition of ether is smaller in sc-CO₂ than in nc-CO₂. Interestingly, the ee profile obtained in the presence of ether exhibits an apparent peak at 12.4 MPa, which may be a chemical consequence of the occurrence of a ridge of density fluctuation separating the near- and supercritical regions.¹³

In this study, we have revealed for the first time the dramatic effect of entrainer (diethyl ether) on the enantiodifferentiating photocyclization performed in CO₂ media, which enables us to significantly increase the ee of photoproduct by simply adding the entrainer in particular to sc-CO₂. Similar enhancement of ee is achieved by adding the same amount of diethyl ether to methylcyclohexane, but the degree of enhancement is much larger in sc-CO₂. Although the detailed mechanism is not fully elucidated, it is

clear that the microenvironmental polarity tuning around the exciplex intermediate plays a decisive role in the critical enantiodifferentiating step, and the ether added as an entrainer to nc- and sc-CO₂ is obviously more effective at enhancing the product’s ee in comparison to a conventional organic solvent, revealing the unique features of CO₂ media. The present result will promote the use of environmentally benign CO₂ media in a variety of applications including asymmetric synthesis in ground and excited states.

Acknowledgment. Dedicated to Prof. Nicholas J. Turro on the occasion of his 70th birthday. We appreciate the financial support of this work by the ICORP Entropy Control Project (JST) to Y.I., the Global COE program (Osaka University) to Y.I., the JSPS Research Fellowship for Young Scientist to Y.N. (No. 08910), and the U.S. Department of Energy to F.V.B. (No. DEFG0290ER14143).

Supporting Information Available: Experimental details, the fluorescence spectra and lifetimes of sensitizer **2** in organic solvents and in nc- and sc-CO₂, and the fluorescence spectra of sensitizer **2** in the presence of substrate **1** in ether. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA801254Z