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Diastereoselectivity Control in Photosensitized Addition of Methanol to (*R*)-(+)-Limonene[†]

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Received April 1, 2002

Highly diastereodifferentiating bimolecular asymmetric photoreaction was achieved in the photosensitized polar addition of methanol to (*R*)-(+)-limonene. The diastereomeric excess (de) of the photoadduct could be controlled and fine-tuned by changing the internal/external factors such as solvent polarity, reaction temperature, and structure of the sensitizers. The de increased from 23% obtained upon xylene photosensitization in pure methanol at room temperature to >96% upon singlet sensitization with methyl benzoate at −75 °C in 0.5 M methanol/diethyl ether solution.

Introduction

Asymmetric synthesis is a field of vital importance in current chemistry, and a considerable amount of effort has been devoted in recent years. High enantio- and diastereoselectivities are the principal objectives or prerequisites when a new synthetic methodology is developed, or chiral compounds such as naturally occurring compounds and pharmaceuticals are synthesized. Since the first report on the asymmetric photosensitization of *trans*-1,2-diphenylcyclopropane by Hammond and Cole,[1] many studies have been carried out on the enantio- and diastereoselective photosensitized reactions.[2] The optical yields of photosensitized reactions, however, are still low to moderate in general.

It was recently shown that asymmetric photochemical reactions,[3–5] proceeding through the electronically excited state, are inherently free from the temperature restrictions and therefore advantageous for investigating the effect of the entropy factor upon stereoselectivity over a wide temperature range. In the diastereodifferentiating Paternò−Büchi photocycloaddition of optically active phenylglyoxylic esters with several alkenes, Scharf et al.[6] showed that the diastereoselectivity of the oxetane produced not only depends on the irradiation temperature but also gives a bent Eyring plot as a consequence of the alteration of the rate-determining step responsible for the diastereoselectivity, which unfortunately limits the maximum diastereomeric excess (de) below 70−75%. We have studied the enantiodifferentiating *Z*−*E* photoisomerization of cyclooctene sensitized by optically active sensitizers and observed the enhancement of the enantiomeric excess (ee) by changing the irradiation temperature and structure of the sensitizers. More recently, we have revealed that the product chirality can be controlled by changing the solvent polarity and pressure in this photoisomerization to give ee's of up to 74%.[7]

In the present study, the validity of our methodology to control the stereochemical outcome of photoreaction by changing external factors was examined in the photosensitized diastereodifferentiating addition of methanol to (*R*)-(+)-limonene (**1**).[8] Among the extensive works on the photochemical behavior of various cycloalkene derivatives,[9–12] Kropp et al.[9e] reported that *m*-xylene-sensitized photoreaction of **1** in methanol affords a 1:1.6 mixture of polar addition product, i.e., diastereomeric *cis*-

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[†] This paper is dedicated to the memory of the late Professor Sang Chul Shim of KAIST, deceased on Apr 10, 2002.

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(1) (a) Hammond G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256. (b) Murov, S. L.; Cole, R. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256.

(2) For reviews, see: (a) Rau, H. *Chem. Rev.* **1983**, *83*, 535. (b) Y. Inoue, *Chem. Rev.* **1992**, *92*, 741. (c) Everitt, S. R. L.; Inoue, Y. In *Organic Molecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Decker: New York, 1999; p 71. (d) Inoue, Y.; Wada, T.; Asaoka, S.; Sato, H.; Pete, J.-P. *Chem. Commun.* **2000**, 251.

(3) (a) Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3169. (b) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3173. (C) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *J. Org. Chem.* **2000**, 2227. (d) Bertrand, S.; Hoffmann, N.; Humbel, S.; Pete, J.-P. *J. Org. Chem.* **2000**, *65*, 8690.

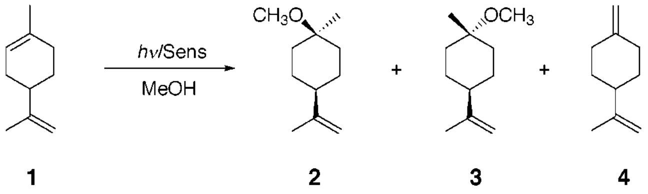
(4) (a) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433. (b) Leibovitch, M.; Plovsson, G.; Sundarababu, G.; Ramamurthy, V.; Scheffer, J. R.; Trotter, *J. Am. Chem. Soc.* **1996**, *118*, 1219. (c) Joy, A.; Scheffer, J. R.; Corbin, D. R.; Ramamurthy, V. *J. Chem. Soc., Chem. Commun.* **1998**, 1379. (d) Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728.

(5) (a) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Tortter, J. *Acc. Chem. Res.* **1996**, *29*, 203. (b) Leibovitch, M.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755. (c) Cheung, E.; Netherton, M. R.; Scheffer, J. R. *Tetrahedron Lett.* **1999**, *40*, 8737.

(6) (a) Koch, H.; Runsink, J.; Scharf H.-D.; Leismann, H. *Chem Ber.* **1985**, *118*, 1485. (b) Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Plath, M. W.; Runsink, J. *J. Am. Chem. Soc.* **1989**, *111*, 5376.

10.1021/jo025782o CCC: $22.00

SCHEME 1

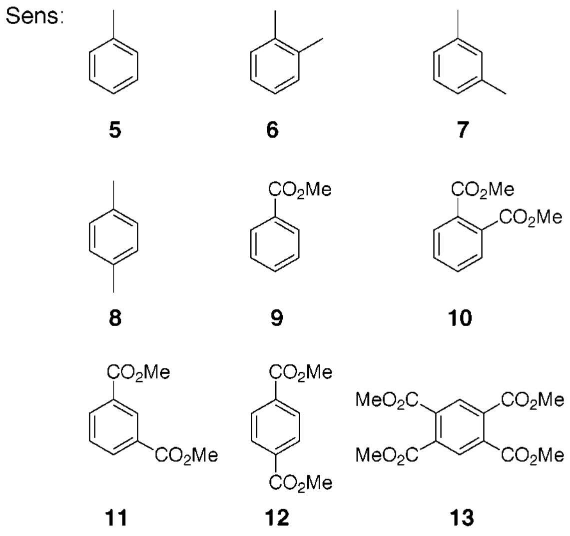


and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexane (**2** and **3**), and exocyclic isomer **4**, as shown in Scheme 1. The study was carried out in methanol solution at room temperature, and a low de of 23.1% in favor of **3** was obtained. We investigated this photosensitized diastereodifferentiating polar addition reaction under a variety of conditions by varying the solvent polarity, irradiation temperature, and structure and spin multiplicity of the photosensitizers to enhance the diastereoselectivity of the reaction.

Results and Discussion

Photosensitized Polar Addition of Methanol to (*R*)-(+)-Limonene. The photosensitized addition reactions of methanol to (*R*)-(+)-limonene (**1**) were carried out with varying temperature (25, 0, −40, −75 °C), solvent polarity (methanol, methylene chloride, diethyl ether, and pentane), methanol concentration (0.5 M to 100%), and structure of the photosensitizers (**5**−**13**; see Chart 1 and Table 1). Photosensitization with toluene and *o*-, *m*-, and *p*-xylene (**5**−**8**) under a variety of conditions gave three major products, i.e., *cis*- and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexane (**2** and **3**) and exocyclic isomer **4**; see runs 1−69 in Table 1.[13] The diastereomeric excess (de = ([**3**] − [**2**])/([**3**] + [**2**])) dramatically increased from practically 0% de in methylene chloride−30% methanol at 25 °C to ca. 96% de in diethyl ether−0.5 M methanol at −75 °C. Interestingly, these triplet sensitizers, toluene and *o*-, *m*-, and *p*-xylene, gave comparable de's in the same solvent at the same temperature.[14]

CHART 1



Singlet photosensitizations with benzenepolycarboxylates **9**−**13** gave the same products, but the de's obtained were consistently higher by 3−15% than those obtained in the triplet sensitization under comparable conditions, irrespective of the solvent composition and temperature employed; see runs 70−120 in Table 1. Furthermore, the chemical yield and product de were dependent on the structure of the sensitizer particularly in the singlet sensitized reaction. It is interesting that, while all of the triplet sensitizers **5**−**8** give practically the same de and yield under comparable conditions, the singlet sensitization leads to significant deviation in de and yield depending on the sensitizer structure. For example, methyl benzoate (**9**) gave 31.6% de in methanol at 25 °C, but the more bulky singlet sensitizer tetramethyl 1,2,4,5-benzenetetracarboxylate (**13**) gave 44.1% de under the same conditions. The singlet sensitized reactions often involve exciplex formation and subsequent energy transfer.[7] Hence, if the methanol addition proceeds within, or immediately after the dissociation of, the exciplex intermediate, such a singlet sensitized reaction should be strongly affected by the structural features such as the steric bulkiness of the sensitizer.

Solvent Polarity and Temperature Effects. The relationship between the solvent polarity and the product de was investigated by using solvents of different polarities, i.e. methanol, methylene chloride, and diethyl ether. The de's obtained upon triplet sensitization with *m*-xylene in diethyl ether and methylene chloride at 25,

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(7) (a) Inoue, Y.; Kunitomi, Y.; Takamuku, S.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 1024. (b) Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1672. (c) Takamuku, S.; Sakurai, H.; Inoue, Y.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1678. (d) Inoue, Y.; Yokoyama, T.; Yamasaki, N.; Tai, A. *J. Am. Chem. Soc.* **1989**, *111*, 6480. (e) Inoue, Y.; Shimoyama, H.; Yamasaki, N.; Tai, A. *Chem. Lett.* **1991**, 593. (f) Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1992**, *57*, 1332. (g) Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1011. (h) Inoue, Y.; Yamasaki, N.; Shimoyama, H.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1785. (i) Tsuneishi, H.; Hakushi, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1601. (j) Inoue, Y.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1997**, *119*, 472. (k) Inoue, Y.; Matsushima, E.; Wada, T. *J. Am. Chem. Soc.* **1998**, *120*, 10687. (l) Hoffmann, R.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10702. (m) Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitt, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, *122*, 406.

(8) Kim, D. S.; Shim, S. C.; Wada, T.; Inoue, Y. *Tetrahedron Lett.* **2001**, *42*, 4341.

(9) (a) Kropp, P. J. *J. Am. Chem. Soc.* **1966**, *88*, 4092. (b) Kropp, P. J.; Krauss, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 5199. (c) Kropp, P. J. *J. Am. Chem. Soc.* **1969**, *91*, 5783. (d) Kropp, P. J.; Krauss, H. J. *J. Am. Chem. Soc.* **1969**, *91*, 7466. (e) Kropp, P. J. *J. Org. Chem.* **1970**, *35*, 2435. (f) Kropp, P. J. *J. Am. Chem. Soc.* **1973**, *95*, 4611. (g) Kropp, P. J. *Org. Photochem.* **1979**, *4*, 1.

(10) (a) Marshall, J. A.; Wurth, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 3788. (b) Marshall, J. A. *Acc. Chem. Res.* **1969**, *2*, 33. (c) Marshall, J. A.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 648. (d) Marshall, J. A. *Science* **1970**, *170*, 137.

(11) (a) Bonneau, R.; Joussot-Dubien, J.; Yarwood, J.; Pereyre, J. *Tetrahedron Lett.* **1977**, 235. (b) Bonneau, R. F. d. V., Philippe *C. R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*, 631. (c) Bonneau, R. F. d. V., P.; Joussot-Dubien, J. *Nouv. J. Chim.* **1977**, *1*, 31. (d) Bonneau, R. J.-D., J.; Salem, L.; Yarwood, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 4329. (e) Schuster, D. I. B., R.; Dunn, D. A.; Rao, J. M.; Joussot-Dubien, J. *J. Am. Chem. Soc.* **1984**, *106*, 2706.

(12) Aguiar, A. M.; Aguiar, H. *J. Am. Chem. Soc.* **1966**, *88*, 4901. Shigemitsu, Y.; Arnold, D. R. *J. Chem. Soc., Chem. Commun.* **1975**, 407.

(13) For a review, see: (a) Verghese, J. *Perfum. Essent. Oil Rec.* **1968**, *59*, 439. (b) Kuczynski, L.; Kuczynski, H. *Rocz. Chem.* **1951**, *25*, 432.

(14) (a) Cundall, R. B. *Prog. React. Kinet.* **1964**, *2*, 165. (b) Hammond, G. S.; Turro, N. J.; Leermakers, P. A. *J. Phys. Chem.* **1962**, *66*, 1144. (c) Testa, A. C. *J. Org. Chem.* **1964**, *29*, 2461. (d) Morrison, H. *Tetrahedron Lett.* **1964**, 3653. (e) Nozaki, H.; Nisikawa, Y.; Kamatani, Y.; Noyori, R. *Tetrahedron Lett.* **1965**, 2161.

TABLE 1. Diastereodifferentiating Photoaddition of Methanol to (*R*)-(+)-Limonene[a] Sensitized by 5−13 in Various Solvents at 25, −40, and −75 °C

entry	sensitizer[b]	solvent	[methanol]	temp/°C	conversn[c]/%	yield[d]/%		de[e]/%
						4	**2 + 3**	
1	**5**	CH_2Cl_2	30%	25	89.5	9.3	37.6	−0.7
2				−40	93.1	10.5	50.2	2.7
3				−75	92.3	10.8	51.7	7.4
4		CH_3OH	100%	25	90.0	37.0	42.2	29.4
5				−40	93.0	37.0	49.2	36.4
6				−75	90.7	33.8	50.4	44.3
7		Et_2O	0.5 M	25	73.9	39.2	4.6	68.8
8				−40	90.2	30.4	7.5	80.5
9				−75	91.5	26.6	11.3	91.6
10	**6**	CH_2Cl_2	30%	25	82.9	7.4	30.4	2.4
11				−40	70.0	12.5	31.7	2.4
12				−75	93.5	23.5	45.4	6.8
13		CH_3OH		25	99.0	38.9	44.9	28.2
14				−40	99.0	39.8	51.4	37.1
15				−75	99.0	37.3	55.9	45.8
16		Et_2O	0.5 M	25	66.6	38.1	3.7	70.6
17				−40	86.2	32.7	5.7	79.6
18				−75	92.6	22.0	7.6	90.6
23	**7**	CH_2Cl_2	50%	25	99.0	6.8	33.2	8.4
19			30%	25	98.0	8.1	33.9	−2.8
20				0	95.7	13.8	46.2	−1.7
21				−40	88.6	19.2	48.8	2.3
22				−75	96.7	30.5	48.2	8.3
24			20%	25	98.7	7.2	36.8	−0.6
25			10%	25	98.0	9.5	33.4	−2.4
26			5%	25	95.5	10.4	30.5	−2.5
27			0.5 M	25	80.4	15.5	20.8	−2.5
28		CH_3OH	100%	25	97.0	32.8	40.4	28.1
29				0	74.9	24.9	29.3	30.3
30				−40	99.0	32.6	42.8	36.6
31				−75	99.0	27.4	40.9	46.7
32		Et_2O	50%	25	93.3	40.3	29.5	29.2
33				0	93.1	37.4	29.2	29.9
34				−40	93.3	41.4	36.8	33.8
35				−75	99.0	40.4	33.9	40.6
36			40%	25	96.6	48.9	30.0	30.2
37				0	83.7	46.6	28.3	30.5
28				−40	86.1	40.0	31.2	33.0
39				−75	98.4	39.8	28.4	41.3
40			30%	25	94.1	46.4	25.8	31.0
41				0	89.9	51.6	22.3	32.1
42				−40	91.8	40.5	22.8	41.5
43				−75	94.1	33.4	19.0	51.0
44			20%	25	94.1	47.0	22.3	31.7
45				0	92.3	57.8	18.4	33.2
46				−40	93.7	35.5	17.7	49.3
47				−75	92.7	30.8	16.3	65.7
48			10%	25	79.6	32.8	14.7	43.3
49				0	88.0	52.5	10.0	45.8
50				−40	95.3	33.2	16.9	60.0
51				−75	94.5	27.2	11.7	77.4
52			5%	25	81.3	47.0	7.0	52.4
53				0	41.9	27.0	8.5	63.8
54				−40	95.4	23.5	11.2	74.3
55				−75	96.7	25.1	10.6	86.3
56			0.5 M	25	84.1	55.6	5.4	65.6
57				0	89.6	52.8	5.6	69.2
58				−20	90.4	50.7	7.3	75.5
59				−40	94.0	47.3	9.6	79.5
60				−75	88.3	18.2	9.2	92.1
61	**8**	CH_2Cl_2	30%	25	89.1	8.9	37.8	0.5
62				−40	84.6	17.2	46.5	2.7
63				−75	96.1	26.3	50.9	7.7
64		CH_3OH	100%	25	80.0	32.9	37.5	29.5
65				−40	99.0	37.8	51.4	37.9
66				−75	99.0	35.0	53.0	46.9
67		Et_2O	0.5 M	25	95.3	51.4	5.4	59.1
68				−40	81.0	28.9	6.2	80.9
69				−75	97.8	24.8	7.8	87.1
70	**9**	CH_2Cl_2	30%	25	99.0	15.7	46.9	0.6
71				−40	91.2	18.8	37.9	4.6

Table 1 (Continued)

entry	sensitizer^b	solvent	[methanol]	temp/°C	conversn^c/%	yield^d/%		de^e/%
						4	**2** + **3**	
72				−75	87.1	22.4	31.2	11.1
73		CH_3OH	100%	25	98.0	24.8	30.0	31.6
74				−40	90.0	19.1	23.4	40.9
75				−75	95.0	25.0	34.1	48.7
76		Et_2O	30%	25	91.0	53.1	26.4	34.3
77				−40	93.8	40.1	20.5	42.5
78				−75	93.9	27.5	22.4	56.5
79			0.5 M	25	99.0	53.1	9.1	77.9
80				−40	97.0	30.7	16.1	93.9
81				−75	92.5	10.2	11.8	96.3
82	**10**	$CH_2\mathbf{Cl}_2$	30%	25	61.1	3.5	12.2	−2.6
83				−40	39.4	1.6	3.0	5.2
84				−75	46.2	1.5	2.8	18.9
85		CH_3OH	100%	25	34.2	2.0	2.5	39.1
86				−40	36.9	1.6	2.2	48.6
87				−75	35.5	2.1	2.5	57.9
88		Et_2O	0.5 M	25	16.6	3.8	*f*	*f*
89				−40	25.7	2.1	*f*	*f*
90				−75	34.6	1.0	*f*	*f*
91	**11**	$CH_2\mathbf{Cl}_2$	30%	25	90.9	12.7	39.5	2.6
92				−40	60.5	8.8	16.7	5.5
93				−75	53.5	9.2	13.0	21.1
94		CH_3OH	100%	25	97.0	18.4	22.2	33.4
95				−40	68.9	10.5	12.5	43.6
96				−75	63.4	11.5	15.8	51.1
97		Et_2O	30%	25	99.0	54.7	26.2	32.8
98				−40	75.4	15.8	10.6	45.3
99				−75	74.3	12.3	9.2	60.8
100			0.5 M	25	88.1	46.9	9.4	80.3
101				−40	67.5	20.8	8.1	92.1
102				−75	92.5	10.2	11.9	96.1
103	**12**	$CH_2\mathbf{Cl}_2$	30%	25	71.2	4.3	16.7	10.8
104				−40	46.8	2.4	5.3	4.5
105				−75	56.2	4.5	8.2	11.9
106		CH_3OH	100%	25	50.5	3.6	5.2	38.4
107				−40	43.2	3.7	5.0	50.5
108				−75	37.7	3.8	5.9	57.2
109		Et_2O	0.5 M	25	60.9	18.4	2.2	64.1
110				−40	40.0	4.0	1.3	*f*
111				−75	49.9	2.9	1.8	*f*
112	**13**	$CH_2\mathbf{Cl}_2$	30%	25	67.8	0.8	2.4	0
113				−40	52.0	0.8	1.6	5.2
114				−75	51.9	1.0	1.3	10.4
115		CH_3OH	100%	25	57.7	1.3	1.6	44.1
116				−40	47.4	1.0	1.4	48.4
117				−75	30.0	0.5	*f*	*f*
118		Et_2O	0.5 M	25	36.6	2.3	*f*	*f*
119				−20	50.1	1.4	*f*	*f*
120				−40	52.1	0.8	*f*	*f*

[a] [Substrate] = 5 mM. [b] [Sensitizer] = 2 mM; reaction scale 2 mL. [c] Loss of starting material determined by GC. [d] Chemical yield determined by GC on the basis of the initial concentration of substrate. [e] de = ([**3**] − [**2**])/([**3**] + [**2**]). [f] Value not determined.

−40, and −75 °C are plotted against the methanol concentration in Figure 1. The de profile at each temperature shows a critical dependence on the solvent polarity and methanol concentration particularly at low methanol concentrations below 20%. At 25 °C, the de increases only slightly from 28.1% in neat methanol to 31.7% in 20% methanol−ether, but rapidly to 43.3%, 52.4%, and then 65.6% with decreasing methanol content to 10%, 5%, and finally 0.5 M (ca. 1.7%), respectively. As can be seen from Figure 1 and Table 1, the irradiation at lower temperatures gave significantly enhanced de's at all methanol concentrations examined. Thus, the de curves (Figure 1) resemble each other, but are significantly lifted upward and become appreciably gentle by decreasing the temperature. Unexpectedly, the use of apparently less polar methylene chloride as solvent led to the complete losses of de (<3%) at low methanol concentrations (<30%), although the photoreaction in 50% methanol−methylene chloride gave 8.4% de.

As expected from the highly ionic nature of the intermediate involved in this polar photoaddition, the solvent polarity significantly affected the product de. The use of polar solvents is thought to be essential for high chemical yields, which however often leads to low product de, as exemplified in Table 1. To elucidate the nature of the solvent effect and also to optimize the solvent system, we carried out the *m*-xylene photosensitizations in polar and nonpolar solvents at 25 °C (Table 2). Relatively high de values of up to 53−54% were obtained in nonpolar pentane and methylcyclohexane solutions containing 0.5 M methanol, while low de was obtained in polar solvents, i.e., 9.6% de in 1,4-dioxane−30% methanol and 18.1% de

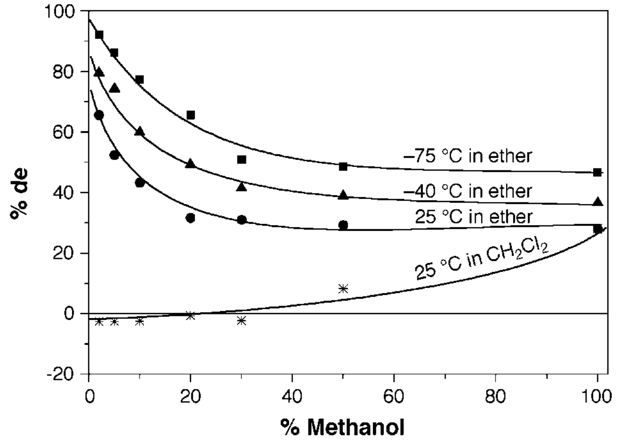

FIGURE 1. Effect of methanol concentration on the product de upon photoaddition of methanol to (*R*)-(+)-limonene (**1**) sensitized by *m*-xylene (**7**) in ether at 25, −40, and −75 °C and in methylene chloride at 25 °C.

TABLE 2. Solvent Effects on Product Diastereoselectivity upon Photosensitization of (*R*)-(+)-Limonene (1) with *m*-Xylene (7) at Different Temperatures

solvent	$\pi^{*\,a}$	[methanol]	de/% 25 °C	de/% −40 °C	de/% −75 °C
pentane	0.00	0.5 M	53.3	70.6	81.6
heptane	0.00	0.5 M	56.5	66.8	80.6
methylcyclohexane	0.00	0.5 M	53.6	70.0	80.4
hexane	0.00	30%	33.0	40.0	*b*
diethyl ether	0.27	30%	31.0	33.6	55.0
acetonitrile	0.75	30%	18.1	23.7	32.4
methylene chloride	0.82	30%	−2.8	2.3	8.3

[a] π^* = solvent polarizability parameter as a measure of the ability of solvent to stabilize a charge or dipole by virtue of its dielectric effect. [b] Not determined.

in acetonitrile−30% methanol. The global profile of the de values obtained in the diverse solvents does not correlate with those of the dielectric constant, dipole moment, or solvent polarity parameters (such as E_T or *Z*) of solvents, but nicely coincides with the trend of the charge stabilization capability parameter (π^*), with the exception of 1,4-dioxane ($\pi^* = 0.55$).[15] Thus, the product de at 25 °C in 30% methanol solution gradually increases in general with decreasing π^* values of pure solvents in the order −3% de in methylene chloride ($\pi^* = 0.82$) to 18% de in acetonitrile (0.75), 28% de in pure methanol (0.60), 31% de in diethyl ether (0.27), and 53−54% de in 0.5 M methanol solution in pentane and methylcyclohexane (0.00).

The acid-catalyzed addition of methanol to limonene **1** was carried out in the dark in 0.5 M methanol−diethyl ether at 25 °C in the presence of 0.1 M sulfuric acid to test the protonated intermediate. A complex mixture was obtained,[11d,16] but the product de was practically zero. This result is in sharp contrast to the high de of 65.6% obtained photochemically in neutral diethyl ether containing 0.5 M methanol (run 56), and clearly indicates that the thermal protonation gives quite different, poor diastereoselectivity.

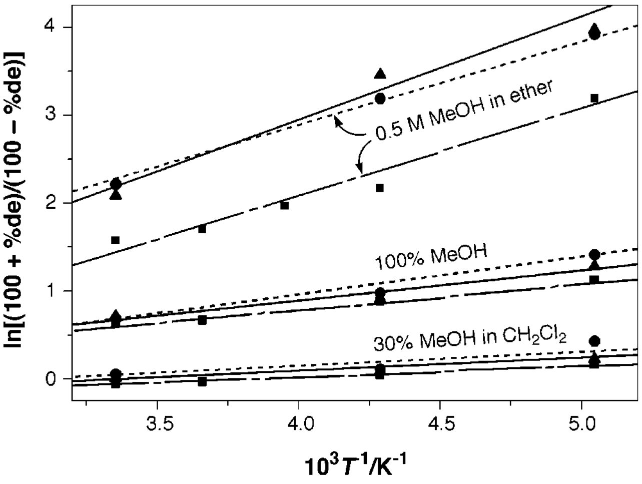

FIGURE 2. Temperature effects on the product de obtained upon sensitization with *m*-xylene (**7**) (■), methyl benzoate (**9**) (▲), and dimethyl phthalate (**10**) (●).

The photosensitized polar addition was investigated at various temperatures between +25 and −75 °C, employing alkylbenzenes **5**−**8** and benzenepolycarboxylates **9**−**11** as sensitizers, and the results are shown in Tables 1 and 2. To analyze the temperature effect on the differential activation parameters more quantitatively, the natural logarithm of the relative formation rate of **3** and **2**, $\ln(k_3/k_2) = \ln[(100 + \text{de})/(100 - \text{de})]$, is plotted against the reciprocal temperature, $1/T$, to give a good straight line (average $r^2 = 0.97$) for all sensitizers and solvents employed, as exemplified in Figure 2.

Obviously, the singlet and triplet sensitizers afford different lines particularly at low methanol contents, and both the slope ($-\Delta\Delta H^{\ddagger}/R$) and intercept ($\Delta\Delta S^{\ddagger}/R$) become greater as the solvent π^* value decreases from 30% methanol in methylene chloride to 30% methanol in diethyl ether and then to 0.5 M methanol in diethyl ether. Consequently, high product de can be achieved by using low π^* solvents at low reaction temperatures, for which the enthalpic and entropic terms are jointly responsible as discussed below.[6,7]

Activation Parameters. From the Eyring treatment of the temperature-dependent de, we can calculate the differential activation enthalpy and entropy ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) of diastereodifferentiation for each combination of sensitizer and solvent, by using eq 1,

$$\ln(k_3/k_2) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \qquad (1)$$

which is similar to that derived for the photosensitized enantiodifferentiation.[7] The $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values thus obtained are listed in Table 3. In all cases examined, both of the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values are negative and there exists the compensatory enthalpy−entropy relationship, giving a linear $\Delta\Delta H^{\ddagger}$−$\Delta\Delta S^{\ddagger}$ plot with a relatively good correlation coefficient ($r^2 = 0.91$). This indicates that a single diastereodifferentiation mechanism is operative and the process is governed simultaneously by the two

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[15] (a) Inoue, Y.; Takamuku, S.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1635. (b) Inoue, Y.; Ueoka, T.; Kuroda T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 983. (c) Inoue, Y.; Ueoka, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2053.

[16] (a) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 1076. (b) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic: New York, 1978, Chapter 3. (c) Kresge, A. J.; Chiang, Y.; Fitzgerald, P. H.; McDonald, R. S.; Schmid, G. H. *J. Am. Chem. Soc.* **1971**, *93*, 4907.

TABLE 3. Differential Activation Parameters for Diastereodifferentiating Photoaddition of Methanol to (*R*)−(+)-Limonene Sensitized by 5-12 in Methanol or Methanol-Diethyl Ether Mixture at 25 °C

	100% MeOH		30% MeOH		0.5 M MeOH	
sensitizer	$\Delta\Delta H^{\ddagger a}$	$\Delta\Delta S^{\ddagger b}$	$\Delta\Delta H^{\ddagger a}$	$\Delta\Delta S^{\ddagger b}$	$\Delta\Delta H^{\ddagger a}$	$\Delta\Delta S^{\ddagger b}$
5	−0.11	−0.16			−0.46	−2.38
6	−0.13	−0.48			−0.39	−1.51
7	−0.17	−1.05	−0.16	−0.77	−0.45	−3.13
8	−0.13	−0.41			−0.42	−2.42
9	−0.13	−0.32	−0.18	−0.85	−0.61	−3.16
10	−0.15	−0.32				
11	−0.14	−0.34	−0.23	−1.55	−0.54	−2.29
12	−0.16	−0.32	*c*	*c*	*c*	*c*

[a] In kcal/mol. [b] In cal/(mol K). [c] Not determined.

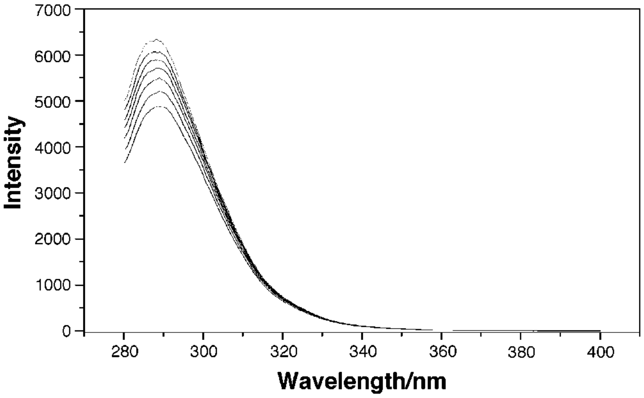


FIGURE 3. Fluorescence spectra of *m*-xylene (**7**) excited at 280 nm in methylene chloride−30% methanol solution in the presence of varying concentrations of limonene **1**: 0, 7.5, 15, 22.5, 30, 37.5, and 45 mM (from top to bottom).

factors ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) with equal significance.[7] In polar solvents, the $|\Delta\Delta H^{\ddagger}|$ and $|\Delta\Delta S^{\ddagger}|$ values are well less than 0.2 kcal/mol and 1 cal/(mol K), respectively. In contrast, much larger $|\Delta\Delta H^{\ddagger}|$ and $|\Delta\Delta S^{\ddagger}|$ values of 0.4−0.7 kcal/mol and 1.5−5.6 cal/(mol K) were obtained in less polar 0.5 M methanol−diethyl ether, which enable us to obtain de's in such a low polarity solvent at low temperatures as high as 96%.

Fluorescence Quenching. To elucidate the excited state and mechanism involved in this photosensitized polar addition, fluorescence quenching experiments were carried out with representative triplet and singlet sensitizers **7** and **13** in nondegassed pentane, methanol, and methylene chloride at 25 °C. The sensitizer fluorescence was quenched effectively in each case by adding substrate **1**. Typical quenching behaviors of **7** and **13** in three solvents are shown in Figures 3 and 4. A very weak, but appreciable, new emission was observed at longer wavelengths upon fluorescence quenching of **13** by **1** (Figure 4), which may be attributed to the exciplex fluorescence.

According to the Stern−Volmer equation for fluorescence quenching (eq 2), the relative fluorescence intensity ($I_F°/I_F$) in the presence and absence of substrate is plotted

$$I_F°/I_F = 1 + k_Q\tau_0[\mathrm{Q}] \qquad (2)$$

as a function of the concentration of added **1** to afford an excellent straight line for each combination of the sensitizer and solvent examined, as shown in Figure 5.

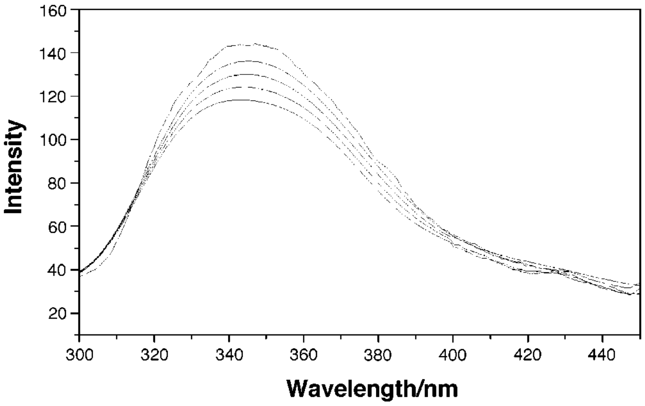


FIGURE 4. Fluorescence spectra of tetramethyl 1,2,4,5-benzenetetracarboxylate (**13**) excited at 270 nm in methanol solution in the presence of varying concentrations of limonene **1**: 0, 7.5, 15, 22.5, and 30 mM (from top to bottom).

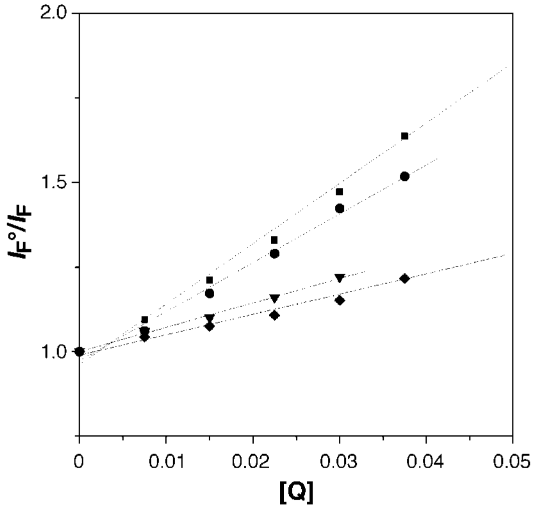


FIGURE 5. Stern−Volmer plots for the fluorescence quenching of **7** by **1** in pentane−0.5 M methanol (■), **7** by **1** in methanol solution (●), **7** by **1** in methylene chloride−30% methanol (▼), and **13** by **1** in methanol solution (◆).

TABLE 4. Fluorescence Quenching Parameters Obtained for Sensitizers 7 and 13 in the Presence of (*R*)-(+)-Limonene (1)

sensitizer	solvent	[methanol]	$k_Q\tau_0$/ M^{-1}	τ_0/ ns	k_Q/ 10^9 M^{-1} s^{-1}
7	n-C_5H_{12}	0.5 M	17.9	11.8	1.52
	CH_3OH	100%	14.4	9.7	1.48
	CH_2Cl_2	30%	6.0	8.6	0.70
13	CH_3OH	100%	7.2	0.5	14.4

From the Stern−Volmer constant ($k_Q\tau_0$) obtained as a slope of the plot and the fluorescence lifetime (τ_0) determined independently by the single-photon-counting technique, the apparent quenching rate constant (k_Q) for each sensitizer in each solvent can be calculated. The results are summarized in Table 4.

The quenching rate constant (k_Q) obtained for *m*-xylene sensitizer (**7**) is smaller by a factor of 10−20 than that for benzenetetracarboxylate sensitizer **13**, the latter of which is almost comparable to the diffusion-controlled rate constant in methanol ($k_{\mathrm{diff}} = 1.8 \times 10^{10}$ M^{-1} s^{-1}). These rate constants clearly indicate that the singlet

SCHEME 2

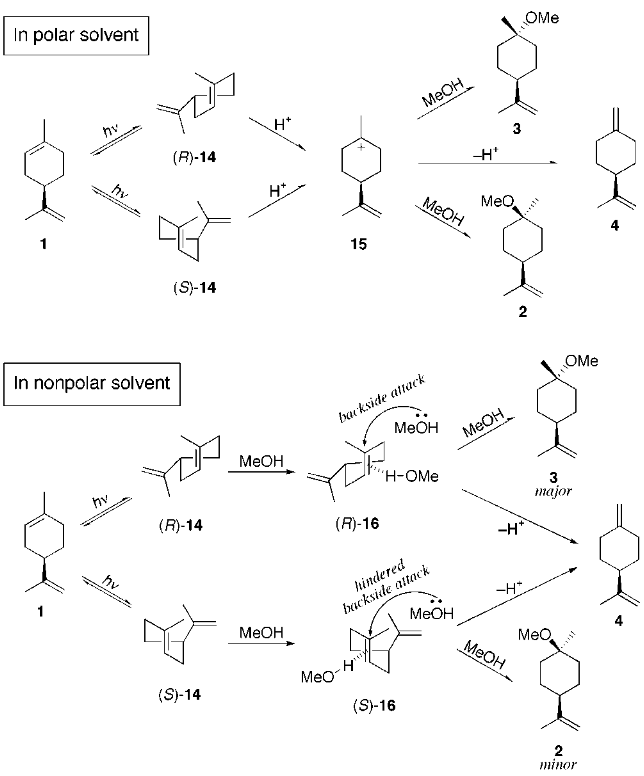
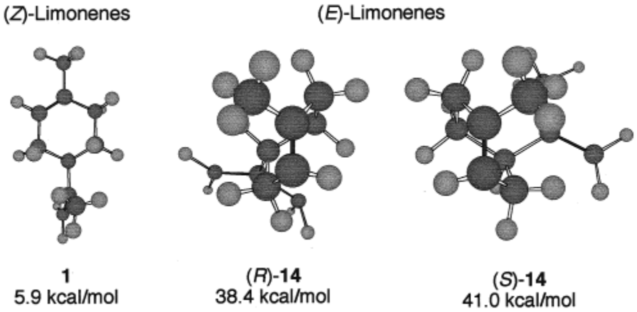


CHART 2. MM2-Optimized Structures of (*Z*)- and (*E*)-Limonenes



sensitization with **13** is extremely efficient while the corresponding process with xylene **7** is 10−20 times less efficient and therefore the triplet sensitization is more favored, although the singlet path cannot be completely ruled out particularly at high substrate concentrations.

Mechanism. From the fluorescence quenching experiments and the different de values obtained upon sensitization with alkylbenzene **7** and benzenepolycarboxylate **13**, intervention of two discrete mechanisms is proposed for the singlet- and triplet-photosensitized methanol addition to limonene.

In the triplet sensitization, the first step is the geometrical photoisomerization[16] of limonene to the highly strained *trans*-isomer, which is followed by protonation of the resulting reactive intermediate by methanol. This mechanism was supported by the studies on photoisomerization of cycloheptene and 1-phenylcyclohexene, which clearly demonstrate the intervention of a highly strained ground-state intermediate possessing a lifetime much longer than that expected for an electronically excited state.[16] In the present case, the photosensitized geometrical isomerization of *cis*-limonene **1** as the first step of the photoaddition produces two diastereomeric *trans*-limonenes, (*R*)- and (*S*)-**14**, as reactive intermediates, as illustrated in Scheme 2. MM2 calculations revealed that (*R*)- and (*S*)-**14** have different steric energies (SEs) of 38.4 and 41.0 kcal/mol, which are 32−35 kcal/mol higher than that of **1** (SE = 5.9 kcal/mol) (Chart 2). (*R*)- and (*S*)-**14** isomers possessing different steric energies and dipole moments are produced photochemically in different ratios depending on the solvent polarity and irradiation temperature.

The second step is the protonation of highly strained *trans*-isomers **14**, producing a common intermediate (**15**), which is in turn attacked by methanol to give adducts **2** and **3** or undergoes deprotonation to exocyclic isomer **4** (Scheme 2). In polar solvents, this mechanism is quite reasonable because the carbocation **15** can be stabilized in such solvents. However, the diastereoselectivity, attained upon the initial photoisomerization step, must be diminished or completely reset to zero in **15**, and the subsequent methanol attack will occur from both sides of the carbocation, probably at similar rates, ultimately giving the final products in a low de. On the contrary, the mechanism incorporating the carbocation **15** is not realistic in nonpolar solvents, since the free carbocation is no longer stabilized through the ion−dipole interaction or solvation, and hence such high de's (of up to 96%) are not expected to be obtained from the addition to **15**. It should be noted that the product de obtained in low-polarity solvents, such as diethyl ether, critically depends on the structure of the, particularly singlet, sensitizer employed. Thus, the substitution pattern of the sensitizer obviously affects the product de; i.e., *p*-xylene and terephthalate give appreciably lower de's than the corresponding *o*- and *m*-analogues.

To rationalize all of the above observations in less polar solvents, the pair of strongly hydrogen bonded species (*R*)- and (*S*)-**16** are proposed as plausible intermediates (Scheme 2). They are diastereomeric to each other and preserve the original de of **14** generated photochemically. The backside attack of methanol to (*R*)- and (*S*)-**16** affords adducts **3** and **2**, respectively, along with the deprotonation product **4**. It is crucial that there is no common intermediate or interconversion process involved in the mechanism, which is compatible with the distinctly different de's observed for each sensitizer. This mechanism can justify the effects of solvent polarity and reaction temperature on the de value (Table 2).[17] The high π^* value of methylene chloride or acetonitrile will stabilize the carbocation **15** and result in a low de value, whereas the low π^* value of diethyl ether or pentane will prefer the charge-dispersed intermediate **16** and lead to a high de value. At low temperatures, the hydrogen-bonding interaction is strengthened and the attack to the less hindered (*R*)-**16** is more favored, both of which accelerate the formation of the major product **3**, giving a higher de value.

In the singlet sensitization, relatively higher de values were obtained in general compared to the triplet-sensitized reactions, particularly in less polar solvents

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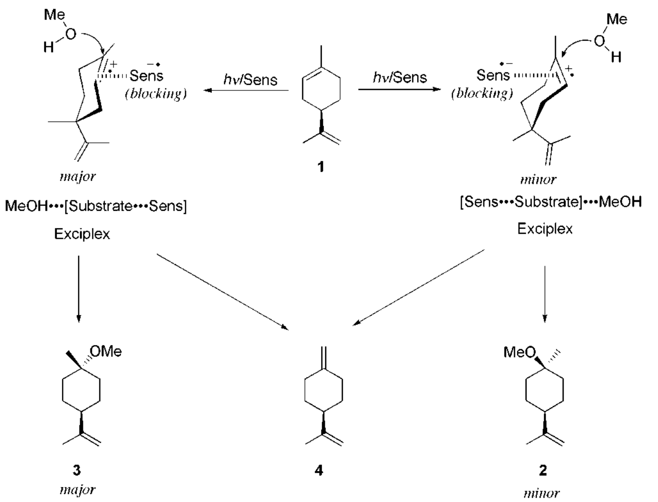
(17) We cannot rigorously exclude the involvement of a trace amount of photoproduced hydrogen chloride in the formation of photoproducts upon irradiation in methylene chloride, which may lead to the low de values.

SCHEME 3



such as diethyl ether. The fluorescence of singlet sensitizer **13** was quenched very efficiently by limonene despite its spectroscopic ("vertical") singlet energy being higher than that of **13**, indicating the intervention of a singlet exciplex. The singlet-sensitized enantiodifferentiating photoisomerization of *cis*-cyclooctene with optically active benzenepolycarboxylates is known to give the chiral *trans*-isomer in good to excellent ee's, which are much higher than those obtained in the triplet sensitization with optically active alkyl aryl ethers.[7] Such high ee's are reasonably accounted for in terms of the intimate chiral sensitizer−substrate interactions in the exciplex intermediate (Scheme 3). In the present case, we can also expect similar, or even more, intimate interactions between the singlet sensitizer and limonene in nonpolar solvents, since the latter is more electron rich than unsubstituted cyclohexene. However, as the reaction medium becomes polar, the radical ionic character of the exciplex increases and the chiral sensitizer−substrate interactions become weaker, leading to a lower de in **14**. In highly polar solvents, the reaction proceeds through a very loose exciplex, which is similar to intermediate **15**, and the stereochemical outcomes from the singlet and triplet sensitizations become similar, equally giving low de's, as described above. Another evidence of an exciplex intermediate in singlet sensitization is the change of the chemical yield and reaction conversion by changing the structure of the sensitizers. As shown in Table 1, photosensitization with methyl benzoate (**9**) gives 99% conversion in 30% methylene chloride at 25 °C, but that with bulky sensitizers, such as tetramethyl 1,2,4,5-benzenetetracarboxylate (**13**), gives 67.8% conversion upon irradiation for the same time and under the same reaction conditions. This result indicates that the singlet-sensitized reactions proceed through an exciplex intermediate and the exciplex formed plays a critical role in controlling the diastereomeric differentiation. Temperature and solvent polarity effects are also readily rationalized by the exciplex formation as described above.

Conclusion

In this study on the photosensitized diastereodifferentiating addition of methanol to limonene, we have demonstrated that the diastereoselectivity of the photoaddition reaction can be critically controlled and fine-tuned by several internal/external factors such as sensitizer structure, solvent polarity, and reaction temperature, and also that the product de can be enhanced from almost zero to >96% by optimizing these entropy-related factors. The idea of "entropy control" was originally proposed for the enantiodifferentiating photoisomerization, involving weakly interacting exciplex intermediates,[7] but is now shown to be applicable also to the photochemical diastereodifferentiation in a more explicit way, giving very high de's. Probably, the same methodology utilizing the entropy-related factors can be used rather widely not only for photochemical but also for thermal reactions and even for biochemical reactions, as far as the weak interactions are involved in the critical step or intermediate.

Experimental Section

General Procedures. High-resolution mass spectra were determined. Fluorescence lifetimes were measured with a 1×10^{-5} M solution of sensitizer in deaerated pentane, methanol, and methylene chloride by means of the time-correlated single-photon-counting method on an instrument equipped with a pulsed H_2 light source. The light source from the lamp was made monochromatic by a 10-cm monochromator, and the emission from the sample solution was detected through a filter.

The diastereomeric excess of the photoproduct was determined by gas chromatograpy over a 30-m capillary column (PEG) at 50−120 °C.

Materials. Pentane was stirred over concentrated sulfuric acid until the acid layer no longer turned yellow, washed with water, neutralized with aqueous sodium bicarbonate, dried over sodium sulfate, and distilled. Diethyl ether was refluxed over potassium hydroxide and distilled from sodium. Methanol was fractionally distilled from magnesium turnings. Methylene chloride was refluxed over calcium hydride and distilled from magnesium turnings. (*R*)-(+)-Limonene was purified by distillation, followed by column chromatography on activated alumina. Toluene and *o*-, *m*-, and *p*-xylene were shaken with concentrated sulfuric acid and then with water, dried over P_2O_5, distilled over sodium, and finally purified by column chromatography on activated alumina. Methyl benzoate was purified by fractional distillation. Dimethyl phthalate, dimethyl isophthalate, and dimethyl terephthalate were purified by recrystallization from methanol. Tetramethyl 1,2,4,5-benzenetetracarboxylate was prepared from the corresponding dianhydride and methanol and was purified by column chromatography over silica gel and the subsequent recrystallization from methanol.

Photolysis. All the irradiations were performed in a temperature-controlled water (25 °C), methanol−2-propanol (0 and −40 °C), or methanol−ethanol (−75 °C) bath. The light source employed was a conventional 300 W high-pressure mercury arc lamp fitted with a Vycor sleeve. A solution (2 mL), containing limonene **1** (5 mM), sensitizer **5**−**13** (2 mM), and dodecane (5 mM) added as an internal standard, was irradiated under an argon atmosphere in a quartz tube (1 cm i.d.) placed near the lamp surface, the whole system being immersed in the cooling bath.

For product isolation and identification, a preparative-scale irradiation was run. A methanol solution (300 mL) of **1** (0.5 M) was irradiated at 25 °C for 2 h. The photolyzed solution was evaporated to give a residue, from which products **2**−**4** were isolated by preparative gas chromatography.

Data for *cis*-4-Isopropenyl-1-methoxy-1-methylcyclohexane (2): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.66 (s, 2H), 3.21 (s, 3H), 1.86 (t, 1H, $J = 12$ Hz), 1.74 (s, 2H), 1.70 (s, 2H), 1.69

(s, 3H), 1.45 (t, 2H, $J = 15$ Hz), 1.31 (t, 2H, $J = 15$ Hz), 1.16 (s, 3H) ppm; ^{13}C NMR (CDCl$_3$, 100 MHz) δ 149.7, 108.4, 74.5, 48.4, 44.6, 36.2, 28.4, 21.1, 20.5 ppm; HRMS (M$^+$) *m*/*z* calcd for $C_{11}H_{20}O$ 168.1514, found 168.1554.

Data for *trans*-4-Isopropenyl-1-methoxy-1-methylcyclohexane (3): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.66 (s, 2H), 3.19 (s, 3H), 1.86(t, 1H, $J = 12$ Hz), 1.74(s, 2H), 1.70 (s, 2H), 1.69 (s, 3H), 1.45 (t, 2H, $J = 15$ Hz), 1.31(t, 2H, $J = 15$ Hz), 1.16(s, 3H) ppm; ^{13}C NMR (CDCl$_3$, 100 MHz) δ 149.7, 108.4, 74.5, 48.4, 44.6, 36.2, 28.4, 21.1, 20.5 ppm; HRMS (M$^+$) *m*/*z* calcd for $C_{11}H_{20}O$ 168.1514, found 168.1554.

Data for 1-Isopropenyl-4-methylenecyclohexane (4): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.66 (s, 2H), 4.59 (s, 2H), 2.31(t, 1H, $J = 6$ Hz), 2.03 (m, 4H), 1.69 (s, 3H), 1.29−1.23 (m, 4H) ppm; ^{13}C NMR (CDCl3, 100 MHz) δ 150.1, 149.3, 108.4, 106.9, 45.0, 34.8, 33.0, 20.8 ppm; HRMS (M$^+$) *m*/*z* calcd for $C_{10}H_{16}$ 136.1252, found 136.1255.

Acknowledgment. This work was supported by the Center for Molecular Design and Synthesis (KOSEF) and School of Molecular Science (BK-21).

JO025782O