Pergamon

Tetrahedron Letters 42 (2001) 4341–4344

TETRAHEDRON
LETTERS

Highly diastereoselective photoaddition of methanol to limonene

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Received 24 March 2001; revised 28 April 2001; accepted 2 May 2001

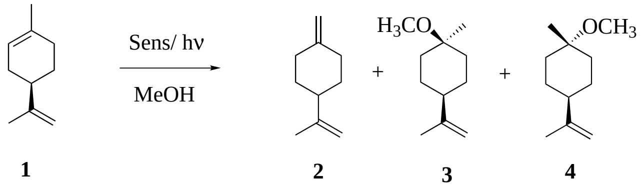
Abstract—Extremely high diastereomeric excess was achieved from the photosensitized polar addition of methanol to (*R*)-(+)-limonene **1**. Diastereomeric excess was varied from 28.1 to 96.3% depending on the solvent polarity, reaction temperature, and structure of sensitizer.

The development of highly stereoselective reactions is among the most challenging and intensively studied frontiers in organic synthesis. Hammond and Cole[1] pioneered the field of photochemical asymmetric induction by studying photosensitized isomerization of *trans*-1,2-diphenylcyclopropane utilizing a chiral naphthalene derivative as a sensitizer. Many photochemical studies[2] have been carried out since then but the optical yields obtained by photochemical asymmetric synthesis have been very low in general.

The solvent polarity, reaction temperature, and sensitizer structure are known to play a crucial role in asymmetric photochemical reactions as demonstrated by the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene and cycloheptene to the corresponding (*E*)-isomers sensitized by optically active polyalkyl benzenepolycarboxylates.[3b–d,4] The highest enantiomeric excess of 77% ee was obtained by optimizing the solvent polarity, reaction temperature, and sensitizer structure.[4k]

Kropp et al.[5] reported the *m*-xylene-photosensitized reaction of (*R*)-(+)-limonene (**1**) in methanol at room temperature, which affords exocyclic isomer (**2**) and diastereomeric *cis*- and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexanes (**3** and **4**) in a ratio of 1:6, as shown in Scheme 1.[9] Although the selective methanol addition to the endocyclic double bond via highly strained (*E*)-cyclohexene is unique to photochemistry, the reaction performed in neat methanol at room temperature gave a low diastereomeric excess (de) of 23.1%, where % de = (**4**−**3**)/(**4**+**3**)×100. In a series of efforts to synergistically control the stereoselectivity of asymmetric photoreactions by multiple entropy-related factors,[3d,4] we have succeeded to greatly improve the stereoselectivity of the photosensitized polar addition of methanol to (*R*)-(+)-limonene **1** by optimizing the internal and external variants.

As shown in Tables 1 and 2, the product de was a critical function of the solvent polarity, reaction temperature, and sensitizer structure and spin-state involved. Upon triplet sensitization with *m*-xylene at 25°C, the product de was significantly dependent on solvent polarity, increasing from 28.1 to 65.6% de by diluting methanol with diethyl ether from 100 to 1.7% (0.5 M) methanol. Lowering the reaction temperature from 25 to −75°C dramatically enhanced the de from 28.1 to 46.7% even in pure methanol and also from 65.6 to 92.1% in 1.7% methanol.



Scheme 1.

Keywords: asymmetric photochemical reaction; diastereomeric excess; limonene; solvent polarity; photosensitizer; temperature effect.

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PII: S0040-4039(01)00722-5

Table 1. Diastereoselective photoaddition of methanol to (*R*)-(+)-limonene **1** sensitized by *m*-xylene, methyl benzoate, and dimethyl phthalate at various temperatures[a]

Entry	Sensitizer	Solvent	Temperature (°C)	Conversion (%)	Yield (%)		de (%)
					2	**3**+**4**	
1	*m*-Xylene	Methanol	25	97.0	32.8	40.4	28.1
2			0	74.9	24.9	29.3	30.3
3			−40	99.0	32.6	42.8	36.6
4			−75	99.0	27.4	40.9	46.7
5		50% Methanol in ether	25	93.3	40.3	29.5	29.2
6			0	93.1	37.4	29.2	30.9
7			−40	93.3	41.4	36.8	38.8
8			−75	99.0	40.4	33.9	48.6
9		30% Methanol in ether	25	94.1	46.4	25.8	31.0
10			0	89.9	51.6	22.3	32.1
11			−40	91.8	40.5	22.8	41.5
12			−75	94.1	33.4	19.0	51.0
13		20% Methanol in ether	25	94.1	47.0	22.3	31.7
14			0	92.3	57.8	18.4	33.2
15			−40	93.7	35.5	17.7	49.3
16			−75	92.7	30.8	16.3	65.7
17		10% Methanol in ether	25	79.6	32.8	14.7	43.3
18			0	88.0	52.5	10.0	45.8
19			−40	95.3	33.2	16.9	60.0
20			−75	94.5	27.2	11.7	77.4
21		5% Methanol in ether	25	81.3	47.0	7.0	52.4
22			0	41.9	27.0	8.5	63.8
23			−40	95.4	23.5	11.2	74.3
24			−75	96.7	25.1	10.6	86.3
25		0.5 M Methanol in ether	25	84.1	55.6	5.4	65.6
26			0	89.6	52.8	5.6	69.2
27			−20	90.4	50.7	7.3	75.5
28			−40	94.0	47.3	9.6	79.5
29			−75	88.3	18.2	9.2	92.1
30	Methyl benzoate	Methanol	25	98.0	24.8	30.0	31.6
31			−40	90.0	19.1	23.4	40.9
32			−75	95.0	25.0	34.1	48.7
33		30% Methanol in ether	25	91.0	53.1	26.4	34.3
34			−40	93.8	40.1	20.5	42.5
35			−75	93.9	27.5	22.4	56.5
36		0.5 M Methanol in ether	25	99.0	53.1	9.1	77.9
37			−40	97.0	30.7	16.1	93.9
38			−75	92.5	10.2	11.8	96.3
39	Dimethyl phthalate	Methanol	25	97.0	18.4	22.2	33.4
40			−40	68.9	10.5	12.5	43.6
41			−75	63.4	11.5	15.8	51.1
42		30% Methanol in ether	25	99.0	54.7	26.2	32.8
43			−40	75.4	15.8	10.6	45.3
44			−75	74.3	12.3	9.2	60.8
45		0.5 M Methanol in ether	25	88.1	46.9	9.4	80.3
46			−40	67.5	20.8	8.1	92.1
47			−75	92.5	10.2	11.9	96.1

[a] All the solutions were irradiated for 1 h under an argon atmosphere; [limonene] = 5 mM, [sensitizer] = 2 mM.

In Fig. 1, the de's obtained upon triplet sensitization with *m*-xylene in methanol or methanol–ether mixture at 25, −40, and −75°C are plotted against the methanol contents. The de profile at each temperature shows a critical dependence on the solvent polarity particularly at low methanol contents below 20%. At 25°C, the de increases only slightly from 28.1% (100% methanol) to 31.7% (20% methanol), but rapidly to 43.3%, 52.4%, and then to 65.6% with decreasing the methanol contents to 10%, 5%, and finally to 0.5 M (ca. 1.7%),

Table 2. Diastereomeric excesses in various solvents.

Solvent[a]	π^{*b}	de (%)		
		25°C	−40°C	−75°C
Diethyl ether	0.27	31.0	33.6	55.0
Acetonitrile	0.75	18.1	23.7	32.4
Methylene chloride	0.82	−2.8	2.3	8.3

[a] In 30% methanol concentration.

[b] Index of solvent dipolarity/polarizability that measures the ability of the solvent to stabilize a charge or dipole by virtue of its dielectric effect.

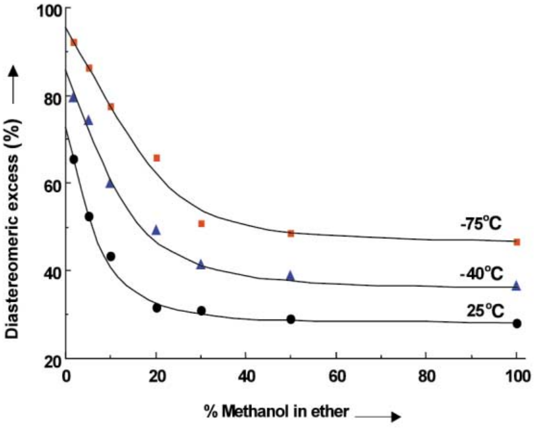

Figure 1. Solvent polarity effects on the diastereomeric excess (de) in the photoaddition of methanol to (*R*)-(+)-limonene (**1**) sensitized by *m*-xylene.

respectively (see entries 1, 5, 9, 13, 17, 21, and 25 in Table 1). As can be seen from Fig. 1 and Table 1, the irradiations at lower temperatures gave significantly enhanced de's at all methanol contents examined; the changing profile of de obtained at each temperature apparently resemble to each other but is significantly shifted upward and become appreciably gentle by lowering the temperature (Fig. 1). Simple extrapolations to 0% methanol, though no methanol adduct formation expected, would give the 'limiting' de's of ca. 75, 85, and 95% at 25, −40, and −78°C, respectively.

In order to get insights into the factors controlling the photochemical stereodifferentiation process, the enthalpic and entropic contributions ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) to the diastereodifferentiating photoaddition were evaluated by using the differential Eyring equation.[6] The natural logarithm of the relative rate of formation of **4** and **3** in different solvents, i.e. $\ln(k_4/k_3) = \ln[(100+\%\ \mathrm{de})/(100-\%\ \mathrm{de})]$, was plotted against the reciprocal temperature ($1/T$) to give a good straight line, i.e. $\ln(k_4/k_3) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R$, for each sensitizer in various solvents, as shown in Fig. 2.

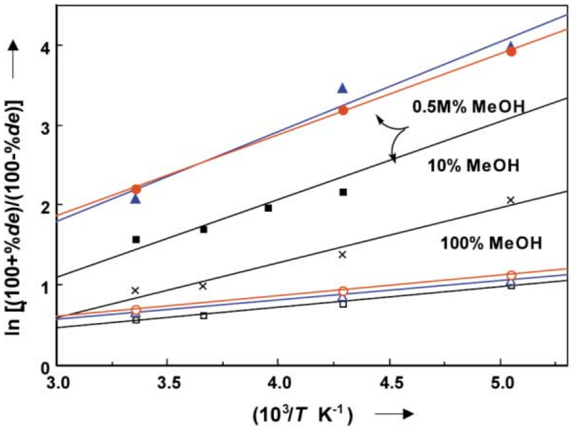

Figure 2. Temperature effects on the relative rate of formation of **4** and **3**, calculated by the equation $k_4/k_3 = (100+\%\ \mathrm{de})/(100-\%\ \mathrm{de})$, upon sensitization with *m*-xylene, methyl benzoate, and dimethyl phthalate. (▲) Dimethyl phthalate in 0.5 M methanol in diethyl ether. (●) Methyl benzoate in 0.5 M methanol in diethyl ether. (■) *m*-Xylene in 0.5 M methanol in diethyl ether. (×) *m*-Xylene in 10% methanol in diethyl ether. (○) Dimethyl phthalate in 100% methanol. (△) Methyl benzoate in 100% methanol. (□) *m*-Xylene in 100% methanol.

Obviously, the singlet and triplet sensitizers afford distinctly different lines particularly at low methanol contents, and both slope ($-\Delta\Delta H^{\ddagger}/R$) and intercept ($\Delta\Delta S^{\ddagger}/R$) become greater as the methanol contents decrease from 100 to 10% and then to 0.5 M (1.7%). In general, photochemistry does not require big thermal energy to promote reaction. The weak interactions that occur in the exciplex intermediate may be controlled mainly by entropy-related factors, such as temperature, pressure, and solvent. The enthalpy values of *m*-xylene, methyl benzoate, and dimethyl phthalate sensitized reactions are −0.45, −0.61, and −0.54 kcal/mol, respectively, at −78°C in 0.5 M methanol/diethyl ether. The entropy values are relatively high compared to enthalpy values: −3.13, −3.16, and −2.29 cal/mol. These results indicate that the high de can be achieved by using a solvent of low polarity at low reaction temperatures, for which the enthalpic and entropic terms are jointly responsible.[7]

Intriguingly, the photoreaction turned out to be very sensitive to the sensitizer employed. Singlet sensitizers, such as methyl benzoate (entries 30–38) and dimethyl phthalate (entries 39–47), gave the same products as the triplet sensitizer, but the de's obtained were consistently higher by 3–15% than those obtained in the triplet sensitization with *m*-xylene, irrespective of the solvent composition and temperature employed.[8] Similar tendencies have been reported for the enantiodifferentiating photosensitizations of several substrates.[4]

The highest de of >96% was attained by using methyl benzoate or dimethyl phthalate as a singlet sensitizer in the least-polar 0.5 M methanol at −75°C. Employing limonene as an enantiomeric substrate in the present study, we have found that not only the enantiodifferentiating[4] but also diastereodifferentiating photosensitized reactions can be critically controlled and fine-tuned by changing the internal/external factors, such as sensitizer, solvent, and temperature, to afford much enhanced de's of >96% by optimizing these factors.

Finally, we wish to emphasize that the enhancement of de was accomplished in this study not through the modification or functionalization of substrate but by optimizing the sensitizer structure and spin-state as well as the other external factors. This methodology, unique to photochemistry, should be quite useful and generally applicable, and inherently poor de's obtained upon direct irradiation of enantiomeric substrates can be improved by employing a proper sensitizer that governs the stereochemical outcome of asymmetric photoreaction through the excited-state interactions. Further investigation of the detailed mechanism and applications of this methodology to other systems are currently in progress.

Acknowledgements

This work was supported by the Center for Molecular Design and Synthesis-KOSEF and School of Molecular Science-BK21.

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6. From the Eyring equation, $\ln[(100+\%\ \mathrm{de})/(100-\%\ \mathrm{de})]=-\Delta\Delta H^{\ddagger}/RT+\Delta\Delta S^{\ddagger}/R$, the product de was governed not only by the enthalpy of activation ($\Delta\Delta H^{\ddagger}$) but also by the entropy of activation ($\Delta\Delta S^{\ddagger}$).
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9. Compound **2**: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ 4.66 (s, 2H), 4.59 (s, 2H), 2.31 (t, $J=6$ Hz, 1H), 2.03 (m, 4H), 1.69 (s, 3H), 1.29–1.23 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 150.1, 149.3, 108.4, 106.9, 45.0, 34.8, 33.0, 20.8; HRMS (M+) calcd for $C_{10}H_{16}$: 136.1252. Found: 136.1252. Compound **3**: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ 4.66 (s, 2H), 3.21 (s, 3H), 1.86 (t, $J=12$ Hz, 1H), 1.74 (s, 2H), 1.70 (s, 2H), 1.69 (s, 3H), 1.45 (t, $J=15$ Hz, 2H), 1.31 (t, $J=15$ Hz, 2H), 1.16 (s, 3H); ^{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; HRMS (M+) calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1554. Compound **4**: ^{1}H NMR (400 MHz, CDCl$_3$, 25°C, TMS): δ 4.66 (s, 2H), 3.19 (s, 3H), 1.86 (t, $J=12$ Hz, 1H), 1.74 (s, 2H), 1.70 (s, 2H), 1.69 (s, 3H), 1.45 (t, $J=15$ Hz, 2H), 1.31 (t, $J=15$ Hz, 2H), 1.16 (s, 3H); ^{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; HRMS (M+) calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1554.