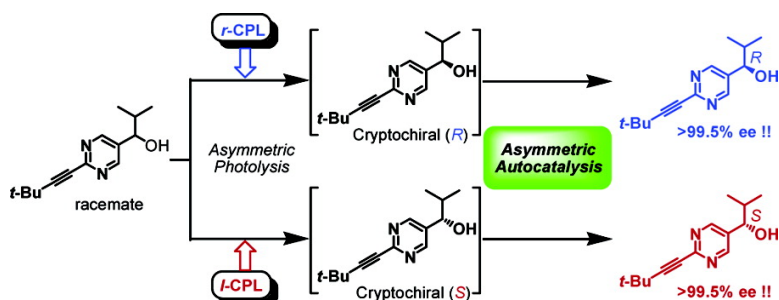


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Enantioselective Synthesis of Near Enantiopure Compound by Asymmetric Autocatalysis Triggered by Asymmetric Photolysis with Circularly Polarized Light

Tsuneomi Kawasaki,[†] Mirai Sato,[†] Saori Ishiguro,[†] Takahiro Saito,[†] Yosuke Morishita,[†] Itaru Sato,[†] Hideo Nishino,[‡] Yoshihisa Inoue,[‡] and Kenso Soai^{*,†}

Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601 Japan, and Entropy Control Project, ICORP (JST), Kamishinden, Toyonaka, Osaka, 560-0085 Japan

Received December 27, 2004; E-mail: soai@rs.kagu.tus.ac.jp

The origin of homochirality of biomolecules, such as L-amino acids, has attracted the interest of a wide range of scientists.¹ Right- and left-handed circularly polarized light (CPL) has long been proposed as one of the origins of chirality of organic compounds.^{1b,2} The occurrence of strong left (*l*-) or right (*r*-) handed CPL in nature has been observed in a star formation region of the Orion constellation.³ However, due to the very small anisotropy (*g*) factors of organic compounds, only very low (<2%) enantioenrichment of organic compounds has been induced particularly in the initial stages of asymmetric photolysis,^{2a,c,4a,b} photoequilibrium,^{4c,d} and photosynthesis^{4e,f} by irradiation using CPL.^{4g-i} Meanwhile, we have reported on asymmetric autocatalysis with an amplification of chirality,^{5,6} which enables the amplification of chirality from an extremely low to near enantiopure (>99.5% ee).^{6j} We have reported on the *indirect* correlation of the chirality of the CPL with the chiral compounds having a high enantiomeric excess in asymmetric autocatalysis. CPL-induced chiral compounds with a very low enantiomeric excess of which the structures are different from those of asymmetric autocatalyst act as chiral initiators of asymmetric autocatalysis.^{6b,e,k} However, the *direct* asymmetric synthesis of chiral compounds with a high enantiomeric excess using CPL remains a challenge.

Here, we report on a straightforward asymmetric synthesis of near enantiopure (>99.5% ee) compounds **1** by asymmetric photodecomposition of racemic pyrimidyl alkanol **1** by CPL followed by asymmetric autocatalysis (Scheme 1).

The photochemical reactions were carried out using the apparatus shown in Figure 1. The light source was a 500 W ultrahigh pressure Hg lamp. To produce the CPL, the parallel light was transmitted through a water filter to remove any infrared spectra, and then the resulting parallel light was passed through an interference filter and a polarizing filter to generate linearly polarized light. Finally, by passing the light through a quarter-wavelength plate, both *r*- and *l*-CPL was produced.

We found that asymmetric autocatalysis is triggered, indeed, by the enantioselective photolysis of racemic pyrimidyl alkanols by irradiation with CPL, as shown in Table 1. In a typical run, a sample of a racemic pyrimidyl alkanol **1** was divided into two parts, each of which was irradiated with *r*- or *l*-CPL ($\lambda = 290\text{--}390$ or 313 nm, respectively), and the photolyzate was concentrated in vacuo. The entire residue was used as the asymmetric autocatalyst without purification. The asymmetric autocatalysis of the irradiated **1** with *r*-CPL using 2-alkynylpyrimidine carbaldehyde **2** and diisopropylzinc (*i*-Pr₂Zn) afforded (*R*)-pyrimidyl alkanol **1** with 65% ee (series A, run A-1). In contrast, irradiation with *l*-CPL induced (*S*)-**1** with a 76% ee (run A-2). It should be noted that near enantiopure pyrimidyl alkanols **1** with >99.5% ee were obtained in conjunction

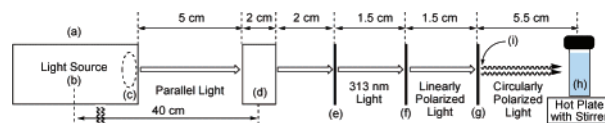
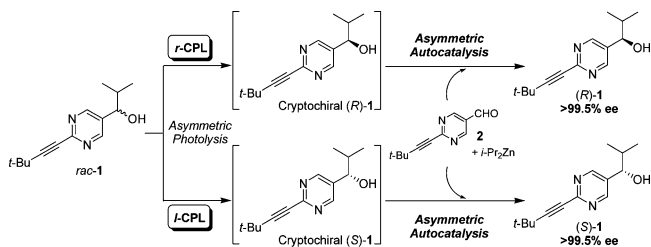


Figure 1. CPL irradiation apparatus: (a) lamp house (Model UI502Q, Ushio); (b) 500 W ultrahigh pressure Hg lamp (Model USH-500SC, Ushio); (c) collimator lens; (d) water layer (quartz cell, path (*l*) = 2 cm, transmittance at $\lambda = 313$ nm (Tr) = ca. 100%); (e) interference filter for 313 nm (Model BPF313 JASCO, FWHM = 11 nm, Tr = 60%) or 290–390 nm solution filter (*l* = 2 cm, Tr = 17%, see ref 7); (f) polarizing filter (Model SPFU-30C, Sigma Koki, Tr = 17%); (g) quarter-wavelength plate (JASCO, Tr = 90%, 99% CPL at $\lambda = 313$ nm); (h) reaction vessel (Model S15-SQ-10, GL Science, $1 \times 1 \times 4.5$ cm³, Tr = 85%); (i) photometric measurement of 313 nm CPL (>1.0 mW/cm²) was performed at this point using a photodiode (Model PD300-UV-SH, OPHIR as the head with a NOVA-II powermeter for $\lambda = 313$ nm).

Scheme 1. Short Pathway to Obtain a Near Enantiopure Compound by CPL Irradiation Followed by Asymmetric Autocatalysis



with three rounds of consecutive asymmetric autocatalysis as previously described (series B).^{6j} In addition, when a 313 nm interference filter was used instead of a 290–390 nm solution filter, the same correlation was observed, that is, *r*-CPL gave (*R*)-**1** and *l*-CPL induced (*S*)-**1** (series C and D). On CPL irradiation in air, **1** was photooxidized to afford isopropyl-5-pyrimidyl ketone in ca. 10% yield, and the irradiated pyrimidyl alkanol **1** was recovered in a yield of ca. 90% (series A–D). It was also found that under an argon atmosphere, photochemical reduction⁸ of the alkynyl moiety of **1** on irradiation with CPL gave 2-alkenylpyrimidyl alkanol^{9,10} (*E:Z* = ca. 1:1) in 20–40% yield with a recovery of **1** in ca. 50% (series E and F). The recovered 5-pyrimidyl alkanol **1** irradiated with *r*-CPL under an argon atmosphere gave (*R*)-pyrimidyl alkanol **1** with an 82% ee (run E-1). On the other hand, **1** irradiated with *l*-CPL under an argon atmosphere catalyzed to form the opposite enantiomer, (*S*)-pyrimidyl alkanol **1**, with an 80% ee (run E-2). These results were reproducible, that is, *r*-CPL provided (*R*)-**1**, and *l*-CPL induced (*S*)-**1** (series F). Thus, the asymmetric photodecomposition of racemic pyrimidyl alkanol **1** with CPL and the subsequent asymmetric autocatalysis afforded the near enantiopure (>99.5% ee) pyrimidyl alkanol with the same relationship existing between the handedness of the CPL and the absolute configuration of the resulting pyrimidyl alkanol.

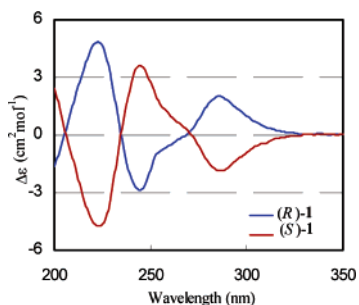
[†] Tokyo University of Science.

[‡] Entropy Control Project, ICORP (JST).

Table 1. Asymmetric Autocatalysis using Cryptochiral Pyrimidyl Alkanol **1** Generated by Photodecomposition of Racemic **1** by CPL

| run ^{a-d} | handedness of CPL | wavelength (nm) | 5-pyrimidyl alkanol 1 | | |
|-----------------------|-------------------|-----------------|------------------------------|---------------------|----------|
| | | | yield (%) ^e | ee (%) ^f | config |
| Series A | | | | | |
| A-1 | <i>r</i> | 290–390 | 96 | 65 | <i>R</i> |
| A-2 | <i>l</i> | 290–390 | 92 | 76 | <i>S</i> |
| Series B ^g | | | | | |
| B-1 | <i>r</i> | 290–390 | 98 | >99.5 | <i>R</i> |
| B-2 | <i>l</i> | 290–390 | 99 | >99.5 | <i>S</i> |
| Series C | | | | | |
| C-1 | <i>r</i> | 313 | 94 | 73 | <i>R</i> |
| C-2 | <i>l</i> | 313 | 89 | 90 | <i>S</i> |
| Series D | | | | | |
| D-1 | <i>r</i> | 313 | 95 | 69 | <i>R</i> |
| D-2 | <i>l</i> | 313 | 96 | 53 | <i>S</i> |
| Series E ^h | | | | | |
| E-1 | <i>r</i> | 313 | 94 | 82 | <i>R</i> |
| E-2 | <i>l</i> | 313 | 93 | 80 | <i>S</i> |
| Series F ^h | | | | | |
| F-1 | <i>r</i> | 313 | 92 | 71 | <i>R</i> |
| F-2 | <i>l</i> | 313 | 92 | 67 | <i>S</i> |

^a In the same series (series A–F), a sample of *rac*-**1** was divided into two parts, and these were irradiated with either *r*- or *l*-CPL. ^b Unless otherwise noted, a 0.1 M solution of *rac*-**1** in ethanol (1.0 mL) was irradiated with CPL for a period of 4 days at 40 °C in the presence of air (without degassing). ^c Unless otherwise noted, the irradiated sample was concentrated in vacuo and was subjected to asymmetric autocatalysis without further purification. ^d Molar ratio of cryptochiral **1**:aldehyde **2**:*i*-Pr₂Zn = 0.01:1.05:2.15. Aldehyde **2** and *i*-Pr₂Zn were added in three separate portions. ^e Isolated yields. ^f Enantiomeric excess was determined by HPLC using a chiral stationary phase. ^g After the irradiation with CPL, three rounds of consecutive asymmetric autocatalysis were performed as previously described (see ref 6j). ^h A 0.05 M solution of *rac*-**1** in 2-propanol (3.0 mL) was degassed by flushing it with argon and was then irradiated with CPL for a period of 4 days at 50 °C under an argon atmosphere. Then, the irradiated alkanol **1** was purified by TLC and subjected to asymmetric autocatalysis.

**Figure 2.** CD spectra of (*R*)- and (*S*)-pyrimidyl alkanol **1** with >99.5% ee in EtOH (1.0 mM) at room temperature.

These results clearly indicate the photochemical relationship between the handedness of the CPL and the absolute configuration of the resulting alkanol **1**. The correlation was rationalized by considering the chiroptical properties of alkanol **1**. As shown in Figure 2, the CD spectra ($\Delta\epsilon = \Delta\epsilon_l - \Delta\epsilon_r$) of (*R*)-**1** at 313 nm is positive, which means that (*R*)-**1** absorbs *l*-CPL ($\Delta\epsilon_l$) preferentially to *r*-CPL ($\Delta\epsilon_r$). Thus, the irradiation of *l*-CPL transforms (*R*)-**1** more rapidly than it transforms (*S*)-**1**, leaving cryptochiral¹¹ (*S*)-**1**. The enantiomeric excess of the residual **1** after ca. 10% oxidation by CPL was below the detection level of our HPLC analysis using a chiral stationary phase.¹² However, as a result of the extraordinary chiral amplification power of asymmetric autocatalysis,^{6j} this cryptochiral (*S*)-**1** was transformed into material of substantial enantiomeric purity. Correspondingly, *r*-CPL irradiation transforms (*S*)-**1** preferentially, and cryptochiral (*R*)-**1** remained.

In summary, we have demonstrated the enantioselective synthesis of near enantiopure compounds by asymmetric photodecomposition of racemic pyrimidyl alkanol by circularly polarized light followed

by asymmetric autocatalysis. This is the first example of asymmetric autocatalysis triggered *directly* by a chiral physical factor. We are currently investigating asymmetric autocatalysis triggered by other chiral physical powers.

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Supporting Information Available: Preparation of *rac*-**1**, production of CPL, photodecomposition of **1**, and asymmetric autocatalysis induced by cryptochiral **1** are described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- We also examined the asymmetric autocatalysis of alkanol **1** initiated by the photoreductive product, 2-alkenylpyrimidyl alkanol, separated from the irradiated mixture under an argon atmosphere. These irradiated olefins gave the opposite enantiomer of **1** to the cryptochiral **1** obtained from the same irradiation mixture, that is, the *r*-CPL-irradiated cryptochiral (*S*)-olefin gave (*S*)-**1** with an 88% ee, and the *l*-CPL-irradiated cryptochiral (*R*)-olefin induced (*R*)-**1** with a 76% ee. These correlations were reproducible.
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- The enantiomeric excess values estimated by calculation (refs 2c and 4b,i) of the residual **1** after 10 and 50% asymmetric photolysis of *rac*-**1** are ca. 0.005 and 0.03% ee, respectively (*g* factor of **1** is ca. 0.001 at 313 nm).

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