Enantioselective Synthesis

Asymmetric Synthesis Utilizing Circularly Polarized Light Mediated by the Photoequilibrium of Chiral Olefins in Conjunction with Asymmetric Autocatalysis**

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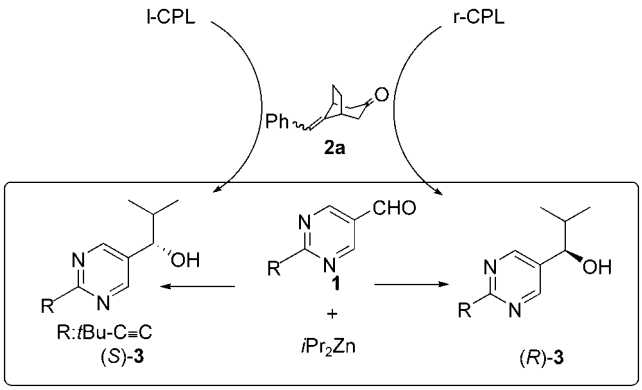
Right- or left-circularly polarized light (r- or l-CPL) has long been proposed as a physical factor in the origin of chirality in organic compounds.[1–4] Asymmetric photolysis,[5] asymmetric photosynthesis,[6] and asymmetric photoequilibrium[7] have been reported to induce only a slight imbalance (< 2% *ee*) in the chirality of organic compounds. The asymmetric photoequilibrium[7] of certain chiral olefins by CPL is of particular importance and has the advantage that the starting material is not consumed in the photoequilibrium. Although the tiny enantioenrichments (< 2% *ee*) of olefins induced by CPL have been correlated with the amplified helicity of polymers[8] and liquid crystals,[7d,9] to the best of our knowledge, chiral olefins[10] with such low *ee* values have never been correlated with a highly enantioenriched compound with a stereogenic center.

We recently reported asymmetric autocatalysis with amplification of enantioselectivity.[11,12] Several chiral molecules with a tiny imbalance of enantiomers work as chiral initiators in the asymmetric autocatalytic system.[11b,c,d,12]

We thought that high enantioselectivity induced by CPL could be realized if combined with asymmetric autocatalysis. Thus, we attempted an asymmetric synthesis by CPL mediated with a chiral olefin (Scheme 1). We employed olefin **2a**[7b] as a switchable chiral mediator for asymmetric autocatalysis. Racemic olefin **2a** was irradiated with r- or l-CPL for 48 hours,[7b] and then diisopropylzinc was treated with 2-alkynyl pyrimidine-5-carbaldehyde (**1**) in the presence of the irradiated olefin **2a** (Scheme 1). A solution of diisopropylzinc in hexane was slowly added to an ice-cooled solution of aldehyde **1** and chiral alkene **2a** in methylcyclohexane. The solution was then diluted with toluene and aldehyde **1** and diisopropylzinc were added portionwise to it. Aqueous workup gave enantiomerically enriched 2-alkynyl-5-pyrimidyl alkanol **3**. As shown in Table 1, the olefin **2a** irradiated with l-CPL gave (*S*)-5-pyrimidyl alkanol **3** in 90–97% *ee* (entries 1, 3, and 5). In contrast, irradiation with r-CPL induced the production of (*R*)-5-pyrimidyl alkanol **3** in 90–93% *ee* (entries 2, 4, and 6). Thus, the reproducibility of the correlation between the direction of CPL and the absolute configuration of pyrimidyl alkanol **3** has been confirmed. It should be noted that the *ee* value of alkanol **3** can be readily increased to > 99.5% *ee* by further asymmetric autocatalysis.[11e]



Scheme 1. Asymmetric synthesis by CPL mediated with a chiral olefin.

Table 1: Highly enantioselective synthesis of 5-pyrimidyl alkanol **3** mediated by chiral alkene **2a** irradiated with CPL.[a]

Entry	Chiral source	5-Pyrimidyl alkanol **3**	
		yield [%]	*ee* [%] (config.)
1	l-CPL	96	97 (*S*)
2	r-CPL	96	93 (*R*)
3	l-CPL	92	91 (*S*)
4	r-CPL	91	90 (*R*)
5[b]	l-CPL	93	90 (*S*)
6[b]	r-CPL	97	90 (*R*)

[a] Unless otherwise noted, aldehyde **1** (1.3 mmol) and diisopropylzinc (2.7 mmol) were added in four portions. Molar ratio of alkene **2a**/pyrimidine-5-carbaldehyde **1**/diisopropylzinc = 0.018/1.0/2.0. [b] Racemic **2a** was prepared independently and used as a mediator. Molar ratio of alkene **2a**/pyrimidine-5-carbaldehyde **1**/diisopropylzinc = 0.046/1.0/2.1.

The chiral olefins **2b–e** were also found to act as chiral initiators. Enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde **1** in the presence of chiral [(4-methylcyclohexylidene)methyl]benzene (**2b**) was examined (Scheme 2). The results are summarized in Table 1. When (*S*)-(+)-**2b** was used as a chiral initiator, (*R*)-5-pyrimidyl alkanol **3** was isolated in a yield of 97% and 96% *ee* (entry 1). However, when the opposite enantiomer of the chiral olefin (*R*)-(−)-**2b** was used as a chiral initiator, (*S*)-5-pyrimidyl alkanol **3** was isolated in a yield of 93% and 95% *ee* (entry 2). Thus, the absolute configurations of the produced 5-pyrimidyl alkanols **3** depend on that of the chiral olefin used. The use of chiral olefin **2b** with a moderate enantioenrichment as an inducer gave alkanol **3** with high *ee* values (entries 3 and 4). The 5-pyrimidyl alkanols **3** were obtained in the reaction in 93% and 95% *ee* using chiral olefin **2b** with 60% and 86% *ee*, respectively. Similarly, (+)-[(4-phenylcyclohexylidene)methyl]benzene (**2c**) functioned as a chiral initiator to give (*R*)-**3** in 95% *ee* (entry 5) and (−)-**2c** gave (*S*)-**3** in 96% *ee*

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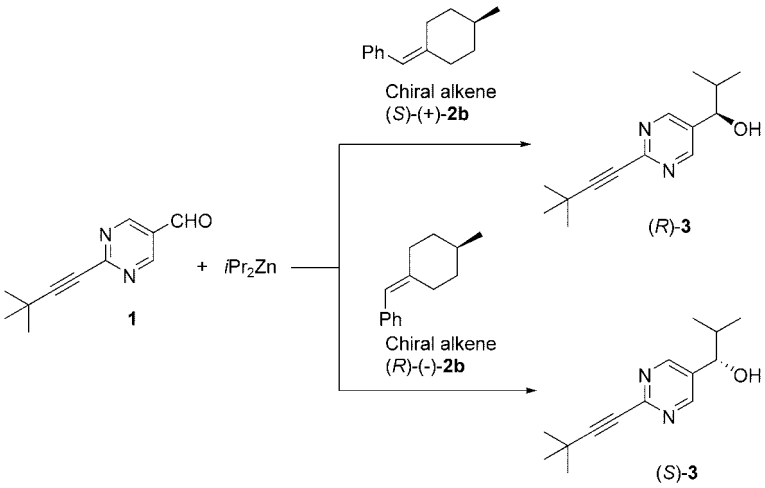

Scheme 2. Enantioselective addition of diisopropylzinc (iPr_2Zn) to pyrimidine-5-carbaldehyde compound **1** in the presence of chiral [(4-methylcyclohexylidene)methyl]-benzene (**2b**).

(entry 6). The conjugation of an olefin to the phenyl group is not essential. Thus, the presence of (*S*)-(−)-(4-phenycyclohexylidene)propane (**2d**) with an ethyl substituent at the double bond gave (*R*)-**3** with 96% *ee* and (*R*)-(+)-**2d** gave (*S*)-**3** with 96% *ee* (entries 7 and 8).

The treatment of chiral olefins with a ketone chromophore was also examined. In the presence of chiral olefin (+)-**2e**, (*R*)-pyrimidyl alkanol **3** was obtained with 91–95% *ee* (entries 9 and 11), while in the presence of (−)-**2e**, (*S*)-**3** (entries 10 and 12) was formed with 90–96% *ee*.

In summary, we have demonstrated that chiral olefins, even with low *ee* values, act as effective chiral inducers in asymmetric autocatalysis to yield products with high *ee* values. Moreover, we have realized a highly enantioselective asymmetric synthesis by CPL mediated with chiral olefins in conjunction with asymmetric autocatalysis. We believe that these results will significantly enhance the use of CPL and the asymmetric photoequilibrium of olefins in the study of the origin of homochirality.

Experimental Section

Representative procedure for the enantioselective synthesis of (*S*)-pyrimidyl alkanol **3** mediated with l-CPL induced olefin **2a**: Racemic **2a** (*ee* was below the detection level) was used after high-performance liquid chromatographic analysis on a chiral stationary phase (Chiralcel OD). A solution of **2a** (5.1 mg, 0.024 mmol) in cyclohexane (3 mL) was degassed by flushing argon through it for 10 min. CPL was produced from a 500-W ultra-high-pressure Hg lamp using a parallel light radiation unit (Ushio). The beam passed through a water cell (10 mm), a 313-nm interference filter, polarizing filter, and quarter-wavelength plate. After irradiation of the solution with l-CPL for 48 h, a CD spectrum was measured ($\Delta\varepsilon_{306} = -0.008\ cm^2 mol^{-1}$). The solution was concentrated and the residue was dissolved in methylcyclohexane (0.5 mL). Aldehyde **1** (4.7 mg, 0.025 mmol) was dissolved in this solution and the solution cooled to 0 °C. A 1.0 M solution of diisopropylzinc (0.08 mmol) in hexane was added at 0 °C over a period of 30 min. The mixture was stirred for 20 h at 0 °C. Toluene (1.9 mL), diisopropylzinc (0.2 mmol, 0.2 mL of a 1.0 M toluene solution), and a solution of aldehyde **1** (1.0 mL, 18.8 mg, 0.10 mmol) in toluene were added successively, and the reaction mixture was stirred for 2 h. Toluene (7.5 mL), diisopropylzinc (0.8 mmol, 0.8 mL of a 1.0 M toluene solution), and a solution of aldehyde **1** (2.0 mL, 75.3 mg, 0.40 mmol) in toluene were then added successively, and the mixture was stirred at 0 °C for additional 5 h. After the addition of toluene (15 mL), diisopropylzinc (1.6 mmol, 1.6 mL of a 1.0 M toluene solution), and a toluene solution of aldehyde **1** (4 mL, 151 mg, 0.80 mmol), the mixture was stirred for 2 h. Hydrochloric acid (6 mL, 1 M) and saturated aqueous sodium hydrogen carbonate (13 mL) were added successively to the mixture. The mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Purification of the residue by thin-layer chromatography on silica gel (eluant: hexane/ethyl acetate = 2/1, *v*/*v*) gave (*S*)-5-pyrimidyl alkanol **3** in 97% *ee* in a yield of 96% (294 mg).

Representative procedure for the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde induced by chiral olefins (Table 2, entry 1): A 1.0 M solution of diisopropylzinc

Table 2: Highly enantioselective synthesis of 5-pyrimidyl alkanol **3** using chiral olefins **2**.[a]

Entry	Alkene **2**			5-Pyrimidyl alkanol	
		ee [%][b]	$[\alpha]_D$ (config.)	Yield [%]	*ee* [%][b] (config.)
1	**2b**	99	+ (*S*)[c]	97	96 (*R*)
2	**2b**	98	− (*R*)[c]	93	95 (*S*)
3	**2b**	60	+ (*S*)[c]	93	93 (*R*)
4	**2b**	86	− (*R*)[c]	89	95 (*S*)
5	**2c**	94	+	94	95 (*R*)
6	**2c**	99	−	94	96 (*S*)
7	**2d**	58	− (*S*)[d]	93	96 (*R*)
8	**2d**	56	+ (*R*)[d]	97	96 (*S*)
9	**2e**	95	+	86	91 (*R*)
10	**2e**	87	−	85	90 (*S*)
11	**2e**	41	+	99	95 (*R*)
12	**2e**	30	−	98	96 (*S*)
13[e]	**2a**	98	+	96	98 (*S*)
14[e]	**2a**	96	−	99	98 (*R*)
15[f]	**2a**	5.0	+	95	97 (*S*)
16[f]	**2a**	5.3	−	97	97 (*R*)
17[f]	**2a**	1.3	+	96	95 (*S*)
18[f]	**2a**	1.8	−	85	97 (*R*)

[a] Unless otherwise noted, aldehyde **1** (0.53 mmol) and diisopropylzinc (1.08 mmol) were added in three portions. Molar ratio of alkene **2**/pyrimidine-5-carbaldehyde **1**/diisopropylzinc = 0.048/1.0/2.0. [b] The *ee* value was determined by high-performance liquid chromatographic analysis with a chiral stationary phase. [c] Absolute configuration was determined by comparison of the sign of the specific rotation to that reported in ref. [13]. [d] Absolute configuration was determined by the derivation from the chiral 3-substituted cyclohexanone. For details, see the Supporting Information. [e] Molar ratio of alkene **2a**/pyrimidine-5-carbaldehyde **1**/diisopropylzinc = 0.019/1.0/2.0. Aldehyde was added in four portions. [f] Molar ratio of alkene **2a**/pyrimidine-5-carbaldehyde **1**/diisopropylzinc = 0.095/1.0/2.0.

(0.08 mmol) in hexane at 0 °C was added over a period of 30 min to a solution of (*S*)-(+)-[(4-methylcyclohexylidene)methyl]benzene **2b** (4.7 mg, 0.025 mmol) and aldehyde **1** (4.7 mg, 0.025 mmol) in methylcyclohexane (0.5 mL). The mixture was stirred for 12 h at 0 °C. Toluene (1.9 mL), diisopropylzinc (0.2 mmol, 0.2 mL of a 1.0 M toluene solution), and a solution of aldehyde **1** (1.0 mL, 18.8 mg, 0.10 mmol) in toluene were added successively, and the reaction mixture was stirred for 0.5 h. Toluene (7.5 mL), diisopropylzinc (0.8 mmol, 0.8 mL of 1. 0 M toluene solution), and a toluene solution of aldehyde **1** (2.0 mL, 75.3 mg, 0.40 mmol) were then added successively, and the mixture was stirred at 0 °C for another 0.5 h. Saturated aqueous sodium hydrogen carbonate (15 mL) was added to the mixture. The mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Purification of the residue by thin-layer chromatography on silica gel (eluant: hexane/ethyl acetate = 3/2, *v*/*v*) gave (*R*)-pyrimidyl alkanol **3** in 96 % *ee* in a yield of 97 % (119 mg).

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