

Two-Component Liquid Crystals as Chiral Reaction Media: Highly Enantioselective Photodimerization of an Anthracene Derivative Driven by the Ordered Microenvironment**

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Inspired by natural systems like enzymes, chemists have long sought tailored microenvironments that can drive targeted chemical transformations in a highly selective manner.^[1–6] For this aim, a number of constrained reaction fields have been explored to date, including crystals,^[1] coordination polymers,^[2] zeolites,^[3] clays,^[4] and discrete hosts in homogeneous solutions.^[5] Among these classes of reaction fields, crystals are regarded as one of the most successful classes, in which reactive molecules are aligned in a highly defined manner with infinite periodicity. In particular, crystalline-state reaction fields can provide the ultimate environment for intra- and intermolecular photochemical reactions, leading to near-perfect regio- and stereocontrol, and providing access to realms unexplored in traditional chemistry using homogeneous media.^[2]

In spite of their prominent advantages, however, crystalline-phase reactions have not taken a leading role in current chemistry, owing mainly to the fatal problem of probability. In general, crystalline-phase reactions proceed only under limited conditions, in which crystal packings accidentally meet topochemically stipulated demands.^[2] To overcome such a limitation, liquid-crystalline phases should be considered as alternative constrained reaction media, as such phases are known to realize well-defined molecular alignment and partial molecular motion at the same time. In fact, liquid-crystalline reaction media have been extensively investigated in the last three decades,^[6] and recent works have expanded the scope of applicability of such reaction media to the

fabrication of mesoscaled supramolecular architectures.^[7] To date, however, the application of liquid-crystalline reaction media in stereocontrolled molecular transformations, especially enantioselective transformations, has been surprisingly limited.^[8] Herein, we report the first example of an asymmetric synthesis induced by a chiral liquid crystal (up to 81 % *ee*). Our novel approach employs two-component liquid crystals, which may be considered as “flexible crystals” or “ordered solvents”.

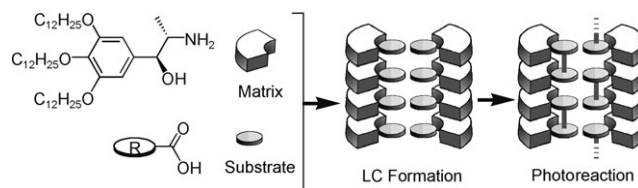
Recently, we reported intriguing two-component liquid crystals, which seemed attractive for the development of novel liquid-crystalline reaction media; several salts of amphiphilic carboxylic acids with amino alcohols were found to exist as thermotropic liquid crystals over wide thermal ranges.^[9] Likewise, the opposite combinations, that is, salts of amphiphilic amino alcohols with carboxylic acids, were also anticipated to exhibit liquid-crystalline phases. If photoreactive carboxylic acids were employed as a component of the latter combination, photoreactions in liquid-crystalline matrices might be easily conducted simply by photoirradiation of the liquid-crystalline salts (Scheme 1). In this case, the photoreactive substrates are expected to be confined in a unique reaction environment, where the relative orientation of the components is highly defined by multiple hydrogen-bonding interactions. The structural order of our system is undoubtedly higher than those of conventional liquid-crystalline reaction systems, in which substrates are randomly doped in partially ordered mesogens.^[6,8] In particular, enantiopure amphiphilic amino alcohols are expected to direct the reaction course in an enantioselective manner with high efficiency. Taking advantage of the noncovalent interactions between the matrix and substrate, the same amphiphilic amino alcohol might be able to be applied in the reactions of various photoreactive carboxylic acids. These aspects prompted us to develop a chiral, amphiphilic amino alcohol (**1**), of which the structure, being reminiscent of *Ephedra* alkaloids, is promising for chirality induction.

The amphiphilic amino alcohol **1** was synthesized from easily accessible building blocks and inexpensive reagents, as

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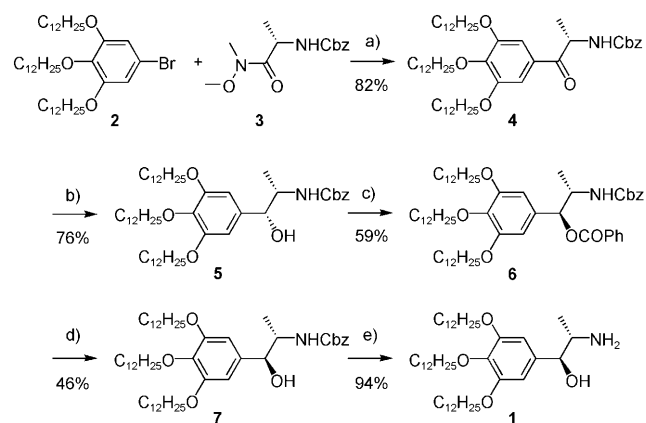
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Scheme 1. Photoreaction in a liquid-crystalline matrix.

outlined in Scheme 2. A bromobenzene derivative bearing three alkoxy chains (**2**)^[10] was lithiated with butyllithium and then coupled with an L-alanine derivative (**3**)^[11] to afford the ketone **4**.^[12] The subsequent hydride reduction of **4** by the classical Meerwein–Ponndorf–Verley method proceeded with excellent diastereoselectivity to give the alcohol **5** in an essentially diastereo- and enantiopure form.^[13] Then, the stereochemical configuration at the C1 position of **5** was inverted by the Mitsunobu reaction to give the corresponding benzoate **6**.^[14] Finally, the N- and O-protecting groups were cleaved to afford the target amino alcohol **1**.^[15]



Scheme 2. Synthesis of amphiphilic amino alcohol **1**. a) **2** (2.3 equiv), $nBuLi$ (2.3 equiv), diethyl ether/THF, $-78 \rightarrow -20^\circ C$, 4 h; b) $Al(OiPr)_3$ (0.3 equiv), $iPrOH$ /toluene, $50^\circ C$, 48 h; c) $PhCO_2H$ (2.0 equiv), PPh_3 (1.5 equiv), $iPrOCON=CO_2iPr$ (1.5 equiv), toluene, RT, 2 h; d) $LiAlH_4$ (4.0 equiv), THF, $0^\circ C$, 2 h; e) H_2 (1 atm), Pd/C (cat.), ethanol, RT, 12 h. Cbz = benzyloxycarbonyl.

Salts of the amino alcohol **1** with various carboxylic acids were prepared by mixing equimolar amounts of the two components, and the mesomorphic behavior of the resultant salts was studied by differential scanning calorimetry (DSC), polarized optical microscopy (POM), and X-ray diffraction (XRD). As summarized in Figure 1 a, **1** forms liquid-crystalline salts with a variety of carboxylic acids, including sorbic acid (**8a**), cinnamic acid (**8b**), and anthracenecarboxylic acids (**8c** and **8d**). During heating and cooling processes above room temperature, the salts of **8a–c** exhibited one or two kinds of smectic phases, whereas the salt of **8d** exhibited a rectangular columnar phase. A strong XRD reflection corresponding to a periodicity of 28–31 Å was detected for all of the liquid crystals, regardless of the packing mode (smectic or rectangular). Taking into account the unique periodicity, together with the amphiphilic nature of the **1–8** salts, these liquid-crystalline salts are believed to adopt a bilayer-like structure, as shown in Figure 1 b. As might be expected, the observed d spacings are shorter than those anticipated from the extended molecular length of **1**, most likely because of partial interdigitation of the aliphatic tails.

With these liquid-crystalline salts in hand, we attempted the in situ photoreaction of the carboxylic acid units. We first focused on the photodimerization of the anthracene derivatives **8c** and **8d**, a well-established [4+4] cycloaddition.^[16,17]

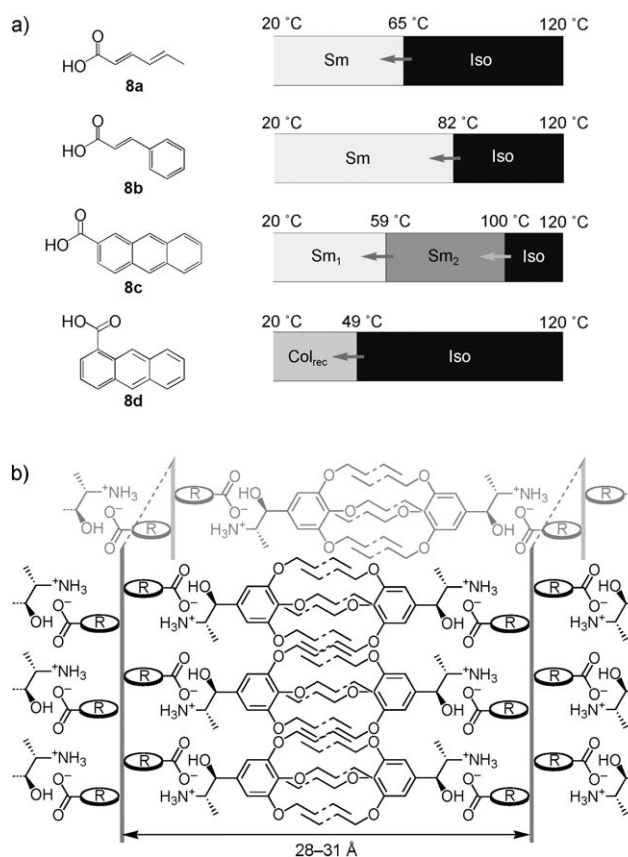
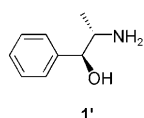


Figure 1. Liquid-crystalline salts **1–8**. a) Phase-transition behavior during a cooling process. Iso = isotropic, Sm = smectic, Col_{rec} = rectangular columnar. b) A proposed structure deduced from powder XRD studies.

However, despite the simplicity of the photochemical process, the regio- and stereochemical course of the photodimerization is complicated when laterally substituted anthracenes like **8c** and **8d** are used; owing to the dissymmetric shape of the reactive unit, the photodimerization gives rise to no less than four configurational isomers (head-to-head (HH) or head-to-tail (HT) isomers with *syn* or *anti* isomerism, denoted as *syn*^{HH}, *anti*^{HH}, *syn*^{HT}, and *anti*^{HT}), two of which each consist of a pair of C_2 -symmetric enantiomers ((*R*)/(*S*)-*anti*^{HH} and (*R*)/(*S*)-*syn*^{HT}).^[16,18] Within the framework of classical synthetic methodologies, regio-, stereo-, and enantiocontrol of this reaction seem to be difficult, and therefore, the environment-directed control of this reaction has attracted considerable recent attention.^[19]

The photodimerization of 2-anthracenecarboxylic acid (**8c**) was conducted by irradiation of the salt **1–8c** with UV/Vis light (a 500 W Hg lamp, $\lambda > 380$ nm). To investigate the characteristic features of this liquid-crystalline medium, the photoreaction was carried out in various phases, including smectic₁ (30 and $45^\circ C$ during the first cooling process), smectic₂ ($80^\circ C$ during the first cooling process), and isotropic ($110^\circ C$ during the first heating process) phases. Although the results of the photoreaction in the crystalline state would further clarify the characteristics of the liquid-crystalline medium, the salt **1–8c** did not exhibit a definite transition to a crystalline phase upon cooling to $-20^\circ C$. Therefore, by using



(1S,2S)-norpseudoephedrine (**1'**) in place of **1**, an analogous crystalline salt (**1'·8c**) was prepared and applied in the photoreaction.

After photoirradiation, the reaction mixture was treated with an excess amount of trimethylsilyldiazomethane to thoroughly esterify the carboxyl groups in the system (those in unreacted **8c**, the photodimers, and other products), and then subjected to preparative thin-layer chromatography (TLC) to remove the amphiphilic amino alcohol **1**. The composition of the recovered esters was determined by ¹H NMR spectroscopy and high-performance liquid chromatography (HPLC), which allowed us to unambiguously estimate the conversion of **8c** and the regio-, diastereo-, and enantioselectivities of the photodimerization.

As summarized in Table 1, the two smectic phases were found to realize acceptable reactivity to give a mixture of the target dimers (**9c**) in 23–55 % yield after photoirradiation for 3 hours (entries 1–3). In the isotropic phase, the photoreaction proceeded so fast that 87 % of the starting material were consumed under conditions differing only in phase and temperature (entry 4). In contrast, the crystalline phase of **1'·8c** did not provide any detectable amount of the photodimer **9c** (entry 5), as might be expected from the general properties of crystalline reaction fields. These observations indicated the superiority of the liquid-crystalline phases compared to the crystalline phase in the context of reaction probability.

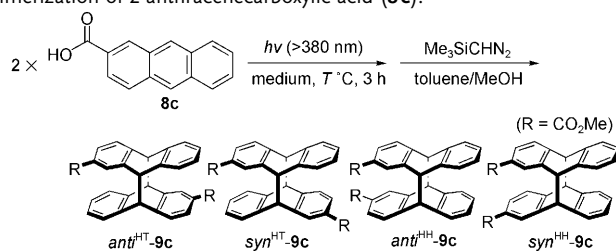
Quite interestingly, the regioselectivity (HH/HT ratio) of the photodimerization changed dramatically depending on the phase, which clearly demonstrates the peculiar property of liquid crystals as “constrained” reaction media. In fact, both of the smectic phases realized excellent regioselectivities to yield the HH dimers almost exclusively (HH/HT = 97.3–98.2; Table 1, entries 1–3). These regioselectivities are opposite to the usual tendency (HT > HH), which is governed by the relative stability of the products; the HH dimers have

been reported to be less stable than the HT dimers, owing to the electrostatic repulsion between the two carboxylate moieties.^[19] As far as we are aware, the HH/HT ratios achieved herein are among the highest reported for this kind of bimolecular photoreactions.^[6,16–19] These observations indicate that the high HH selectivities of the dimerizations are attributable not to an intrinsic preference of the starting material, but to the special environments provided by the liquid-crystalline matrices. Assuming a bilayer-like molecular alignment in the smectic phases, as depicted in Figure 1 b, an intralayer dimerization can reasonably elucidate the nearly exclusive formation of HH dimers.

Thus, highly HH-selective photodimerization of **8c** was established by using two kinds of liquid-crystalline reaction media. Nevertheless, the stereochemical outcome of the photodimerization, in terms of the *syn*^{HH}/*anti*^{HH} ratio, revealed striking differences between the two liquid-crystalline phases. Indeed, the smectic₁ phase afforded the *anti*^{HH} dimer as the main product (*syn*^{HH}/*anti*^{HH} = 26:72–28:70; Table 1, entries 1 and 2), whereas the smectic₂ phase yielded almost equal amounts of the two diastereomers (*syn*^{HH}/*anti*^{HH} = 44:53; entry 3). Although the origin of the *syn/anti* selectivity is unclear at present, we believe that the packing mode of the liquid-crystalline matrix has a large influence on the *syn/anti* selectivity, which is at least as large as the influence of the reaction temperature. Indeed, experiments conducted in the same phase (smectic₁) but at different temperatures (30 and 45 °C), resulted in virtually the same *syn/anti* selectivities (entries 1 and 2).

The liquid-crystalline media were found to offer reaction environments with excellent chirality-induction ability. Particularly, the photodimerization performed in the smectic₁ phase afforded the *anti*^{HH} dimer with high enantioselectivity (up to 81 % *ee*; Table 1, entries 1 and 2). In the case of the smectic₂ phase, the enantioselectivity was also at an appreciable level, although somewhat lower (48 % *ee*; entry 3). These results contrast strikingly with the insufficient enantioselectivity attained in the isotropic phase (9 % *ee*; entry 4). The outstanding enantioselectivities achieved in the smectic phases are not likely to be a simple chirality transfer within the discrete salt pair; the formation of a chiral supramolecular architecture would be essential for efficient chirality induction. To our knowledge, the reaction conducted in the smectic₁ phase is the first asymmetric synthesis induced by a chiral liquid crystal.^[8] Moreover, the present system provides a very rare example of an intermolecular photochemical reaction in which satisfactory yield and regio-, diastereo-, and enantioselectivities were simultaneously realized; the *anti*^{HH} dimer was produced in 34 % overall yield with 81 % *ee* (entry 2).^[19]

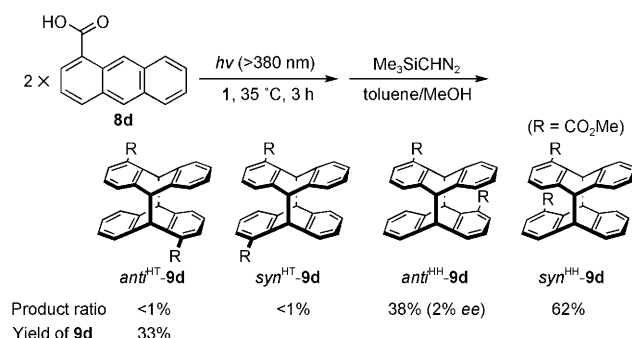
Table 1: Photodimerization of 2-anthracenecarboxylic acid (**8c**).



Entry	Medium	T [°C]	State ^[a]	Yield [%] ^[b]	Product ratio [%] ^[c]				<i>ee</i> [%] ^[d]
					<i>anti</i> ^{HT}	<i>syn</i> ^{HT}	<i>anti</i> ^{HH}	<i>syn</i> ^{HH}	
1	1	30	Sm ₁	23	1	1	72	26	+78
2	1	45	Sm ₁	48	1	1	70	28	+81
3	1	80	Sm ₂	55	1	2	53	44	+48
4	1	110	Iso	87	10	12	38	30	+9
5	1'	30	Cry	< 1	—	—	—	—	—
6 ^{[19k][e]}	H ₂ O	25	Sol	88	43	36	14	7	—
7 ^[19j]	CH ₂ Cl ₂	20	Sol	96	32	22	25	21	—

[a] Sm = smectic, Iso = isotropic, Cry = crystalline, Sol = solution. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC. [d] Enantiomeric excess of *anti*^{HH}-**9c** determined by chiral HPLC. [e] A phosphate buffer solution (pH 7.0) was used as the medium.

We next performed the *in situ* photodimerization of another anthracenecarboxylic acid (1-anthracenecarboxylic acid, **8d**)^[18, 19a–c] in a liquid-crystalline matrix to demonstrate the general utility of this strategy (Scheme 3). For example, the salt **1-8d** was irradiated with UV/Vis light at 35 °C, and the salt took on a rectangular columnar structure. The photodimerization of **8d** proceeded with excellent regioselectivity (HH/HT > 99:1) and notable diastereoselectivity (*syn*^{HH}/*anti*^{HH} = 62:38), as we expected. In this case, the chiral isomer (*anti*^{HH}) was not afforded as a major product, and its enantiomeric excess was unsatisfactory.



Scheme 3. Photodimerization of 1-anthracenecarboxylic acid (**8d**).

It is worth noting that both of the substrates **8c** and **8d** exhibited a strong propensity to form the thermodynamically unfavorable HH dimers, despite the lack of similarity in their molecular shapes. This peculiar regiochemical preference observed for the two substrates further supports our hypothesis that an intralayer dimerization predominantly proceeds in a bilayer-like liquid-crystalline matrix.

In summary, the present results unambiguously demonstrate that liquid-crystalline reaction media can induce remarkable regio-, diastereo-, and even enantioselectivities in a photochemical reaction, contrary to popular conceptions.^[8] In addition, liquid-crystalline reaction media were found to be tolerant toward variation in substrate shape, which is possibly one of the most novel features of such reaction fields compared with traditional solid-state reaction fields. Further exploration of this strategy would increase the expediency of chemistry in tailored reaction media, and would enhance our understanding of chemical events taking place in metastable states, such as organogels, micelles, monolayers, and bilayers, including cell-membranes.^[20]

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