



Diastereodifferentiating photodimerization of alkyl 2-naphthoates with chiral auxiliaries

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ABSTRACT

Photodimerization of alkyl 2-naphthoates with chiral auxiliaries resulted in cubane-like *anti* head-to-head photodimers in 93% yield and with up to 59% diastereomeric excess. After removal of the chiral auxiliaries enantiomers of cubane-like photodimer of 2-naphthalene carboxylic acid were obtained in 80% yield.

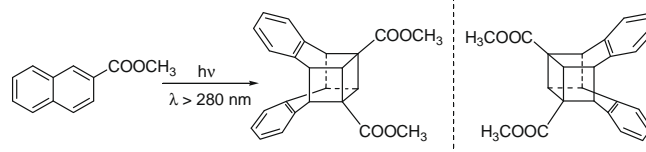
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Enantioselectivity in ground-state reactions is commonly achieved by developing appropriate catalytic systems, and great successes have been obtained during the past decades.^{1,2} In contrast, there are considerably fewer examples of asymmetric induction in photochemical transformations.^{3–9} A promising approach is to make use of a removable chiral auxiliary and to connect the auxiliary to the prochiral starting substrate by a covalent bond. The chiral auxiliary in this case can bring about asymmetric induction during the photochemical transformation and results in diastereomers. The yielding diastereomers can be easily separated, even if the asymmetric induction is low. After the removal of the chiral auxiliary, the enantiomerically pure products can be obtained.^{4,10–13}

Previously, we reported the photodimerization of methyl 2-naphthoate.^{14–17} Irradiation of this substrate results in a 'cubane-like' *anti* head-to-head photodimer as the unique product (Scheme 1). This photodimer is C₂-symmetric, thus possesses chirality. Our interests in the chirality of this photodimer originate from the fact that the cubane-like skeleton is strained and rigid, and the carboxylate can be derived into a variety of function groups. Thus, the derivatives of this photodimer might act as chiral ligands with C₂ axis, and show applications in asymmetric catalysis. Since a chiral alcohol as chiral auxiliary can be readily introduced on the naphthoate, and such chiral auxiliary is inert in the condition of irradiation and readily removed from the photodimer, one can expect that chiral auxiliary strategy might be a good choice for the synthesis of the enantiomerically pure

cubane-like photodimer. We found that this is indeed the case when the chiral auxiliary is properly selected.

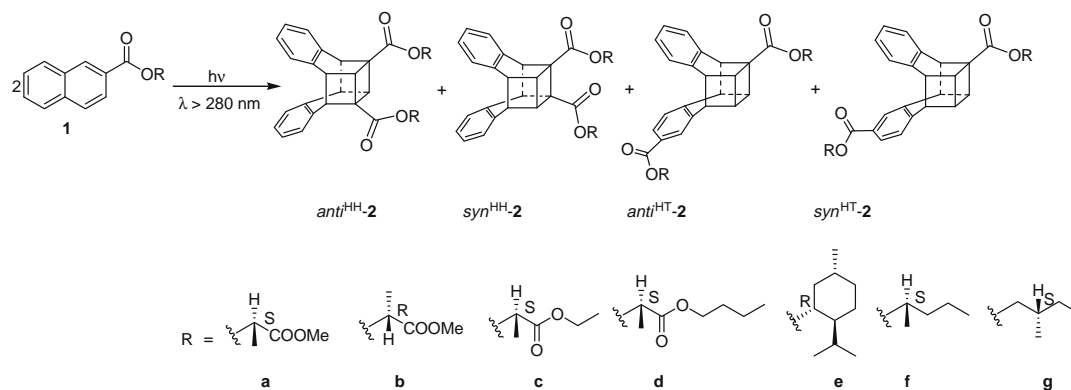
In the present Letter, we study the photodimerization of alkyl 2-naphthoates **1** with chiral auxiliaries as listed in Scheme 2 (**1a–1g**). We irradiated these substrates in degassed organic solutions (ca. 1.9 × 10⁻² M) with a light of wavelength longer than 280 nm.¹⁸ The photodimerization process was monitored by UV absorption spectroscopy. After irradiation the products were isolated by chromatographic column over silica and were analyzed by HPLC. In contrast with methyl 2-naphthoate (Scheme 1), all these substrates produce four isomers: head-to-head (HH, photodimerization between two substituted rings) or head-to-tail (HT, photodimerization between one substituted ring and one unsubstituted ring) isomers with *syn* or *anti* isomerism, denoted as *anti*^{HH}-**2**, *syn*^{HH}-**2**, *anti*^{HT}-**2**, and *syn*^{HT}-**2** (Scheme 2). For each substrate the sum of the four photodimer yields is close to 100% on the basis of the consumption of the starting material, suggesting that another two possible cubane-like photodimers produced via the photodimerization of the two unsubstituted rings (head-to-head



Scheme 1. Photodimerization of methyl 2-naphthoate.

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Scheme 2. The structure of the photodimers.

Table 1
Diastereoselectivity of photodimerization of alkyl 2-naphthoates

Substrate	Solvent	Temperature (°C)	Relative yield (%)			de ^a (%)		
			<i>anti</i> ^{HH} -2	<i>anti</i> ^{HT} -2	<i>syn</i> ^{HT} -2	<i>anti</i> ^{HH} -2	<i>anti</i> ^{HT} -2	<i>syn</i> ^{HT} -2
1a	Cyclohexane	20	88	8	4	−54	−30	32
1b	Cyclohexane	20	84	10	6	55	34	−35
1c	Cyclohexane	20	89	7	4	−58	−30	32
1d	Cyclohexane	20	93	4	3	−59	−27	−27
1e	Cyclohexane	20	76	16	8	−20	<5	−9
1f	Cyclohexane	20	93	5	2	22	<5	<5
1g	Cyclohexane	20	95	4	1	<5	<5	<5
1a	Cyclohexane	8	87	8	5	−56	−32	36
1a	Methanol	20	83	10	7	−44	−12	13
1a	Methanol	−5	84	9	7	−50	−11	11

^a de (%) = (A − B)/(A + B).

isomer with *syn* and *anti* isomerism) were not formed. The regioselectivity in the photodimerization in terms of the HH/HT ratio is clearly dependent on the substrate (Table 1). As expected, the substrate with a less bulky group (**1f** and **1g**) favors the formation of head-to-head photodimers. For any substrate the main product is *anti*^{HH}-2 and its yield accounts for 76–95% of the overall products. Although photodimer *syn*^{HH}-2 was isolated, the ratio of its yield to the total products is less than 2%. Thus in Table 1 only the relative yields of *anti*^{HH}-2, *anti*^{HT}-2, and *syn*^{HT}-2 are given. The regioselectivity in terms of the *anti*^{HT}/*syn*^{HT} ratio is less dependent on the chiral auxiliary.

Photodimers *anti*^{HH}-2, *anti*^{HT}-2, and *syn*^{HT}-2 each consist of a pair of diastereomers. We could resolve the diastereomeric mixtures of all the three photodimers by HPLC either with an achiral or a chiral column. Figure 1 shows the typical HPLC traces of photodimers of **1a** and **1b**. For each pair of diastereomers, the first peak on HPLC trace is arbitrarily assigned as **A** and the second peak as **B**. The ¹H NMR spectra of each optically pure diastereomer are given in Supplementary data. The circular dichroism (CD) spectra for each pair of diastereomers are mirror image, while their UV-vis absorption spectra are not distinguishable from each other. Figure 2 gives the examples of the CD spectra for pair of *anti*^{HH}-2a-A and *anti*^{HH}-2a-B and that of *anti*^{HH}-2b-A and *anti*^{HH}-2b-B. The de values for all the diastereomer pairs were calculated and are listed out in Table 1. Evidently, the degree of the asymmetric induction is controlled by the nature of the chiral auxiliary. First, the position of the chiral center in the auxiliary shows a remarkable influence on the chirality of the products. For the substrates with the chiral center immediately connected to the carboxyl group (**1a–1f**), appreciable level of diastereoselectivity (up to 59% de, Table 1, *anti*^{HH}-2d) was achieved. In contrast, the substrate with the chiral center separated from the carboxyl group by one carbon atom (**1g**) afforded very

low diastereoselectivity (<5% de for any diastereomeric pair). Second, for all the substrates the level of chiral induction in the formation of the head-to-head photodimer is significantly greater than that for the head-to-tail photodimers. For example, when the photodimerization is carried out in cyclohexane at 20 °C, the de

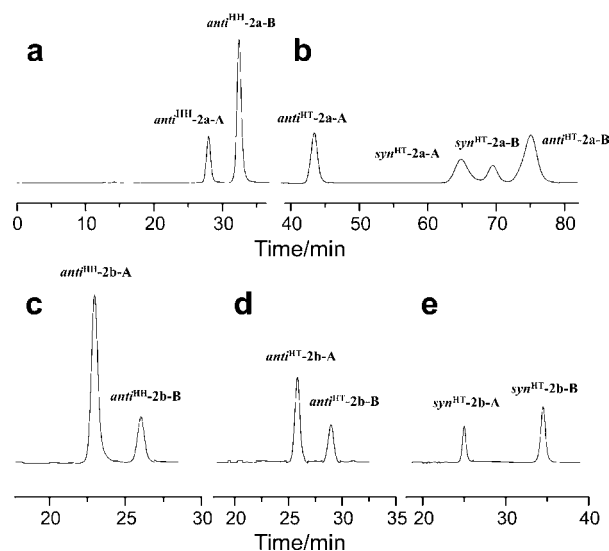


Figure 1. The typical HPLC traces of the *anti*^{HH}, *anti*^{HT}, and *syn*^{HT} photodimers of **1a** and **1b**; column: Daicel IA (chiral); eluting solvent: (a) hexane/ethanol = 7:3; (b) hexane/ethanol = 8:2; (c) hexane/isopropanol = 6:4; (d) hexane/ethanol = 5:5; and (e) hexane/isopropanol = 6:4. For each diastereomeric pair the first peak on the HPLC trace is termed as **A**, and the second peak as **B**.

values of the $anti^{HH}$ photodimers for **1a–1d** are in the range of 54–59%, while those for their $anti^{HT}$ and syn^{HT} photodimers are below 35%. This observation is consistent with the expectation that the steric interactions between the two chiral auxiliaries of the reactant molecules in the course of the formation of the head-to-head photodimers are greater, thereby the chiral induction is greater compared with those in the head-to-tail photodimer formation. Third, a comparison of the results for substrates **1a–1d** with **1e** shows that the bulky of chiral auxiliary is not the only factor of the chiral induction. Although the chiral auxiliary in **1e** is at least as bulky as those in **1a–1d**, the *de* values of all the photodimers for **1e** are evidently smaller than those for **1a–1d**. Fourth, **1a** and **1b** are configurational isomers. **1a** with (*S*)-chiral auxiliary enhanced formation of diastereomers **B** for $anti^{HH}$ and $anti^{HT}$ photodimers, and diastereomer **A** for syn^{HT} photodimer, while **1b** with (*R*)-chiral auxiliary enhanced formation of the opposite diastereomers for all the three photodimers, and their respective *de* values are almost identical. This result indicates that the system is well behaved in the sense that the optical antipode of the chiral auxiliary gave the opposite diastereomers of the products. We noted that **1d** and **1f** each also possesses an (*S*)-chiral auxiliary. However, in contrast with **1a** these substrates produce syn^{HT} -**2d-B** and $anti^{HH}$ -**2f-A** as their major diastereomer, respectively. Presently, the absolute configuration of the photodimers has not been established, and diastereomers **A** and **B** are defined in terms of their eluted sequence in the HPLC trace. The switch in the eluted sequence of the major and minor diastereomers of syn^{HT} -**2d** and $anti^{HH}$ -**2f** likely results from the difference in their chromatograph behavior. Indeed, by changing the eluting solvent, the eluted sequence can be switched. This conclusion is also supported by their respective CD spectra. For example, $anti^{HH}$ -**2f-A** shows negative effect in 190–205 nm and positive effect in 205–245 nm. This CD spectrum is the same as that of $anti^{HH}$ -**2a-B** and opposite to that of $anti^{HH}$ -**2a-A** (Fig. 2). This observation suggests that $anti^{HH}$ -**2f-A** and $anti^{HH}$ -**2a-B** have the same absolute configuration.

The influence of experimental condition on the regio- and diastereoselectivity in the photodimerization of these substrates was studied. Neither the irradiation time nor the concentration of the substrates has any significant influence on the product distribution. However, solvent can alter the degree of stereoselectivity. As shown in Table 1, in methanol at room temperature (20 °C) the HH/HT selectivity is slightly reduced, and the decrease in the diastereoselectivity of the photodimers is even more evident compared with the results in cyclohexane. The *de* value of $anti^{HH}$ -**2a** decreases from 54% in cyclohexane to 44% in methanol, and those of $anti^{HT}$ -**2a** and syn^{HT} -**2a** decrease from ca. 30% in cyclohexane to ca. 12% in methanol. The influence of temperature on the selectivity is somewhat complicated. While virtually no change in both the HH/HT selectivity and the diastereoselectivity of the products in

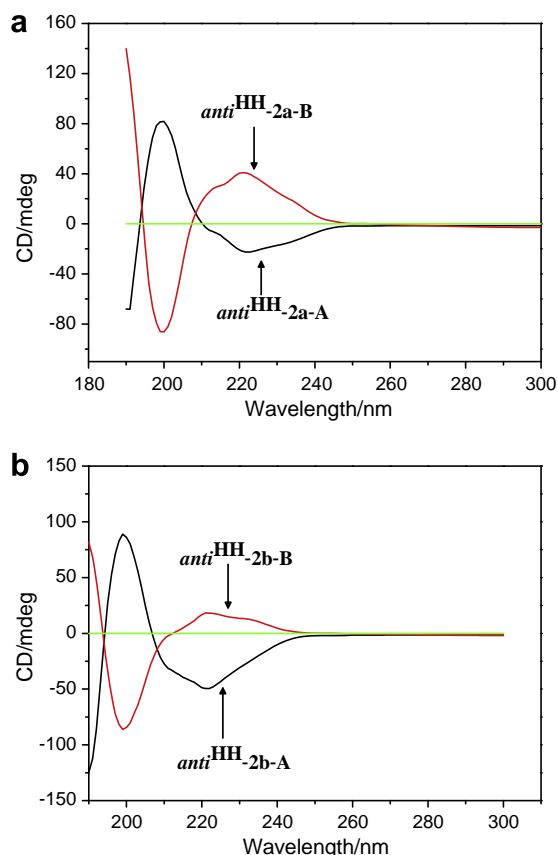
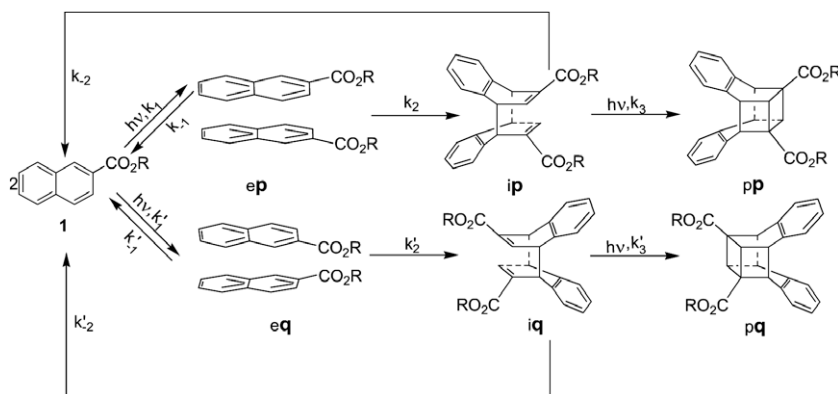


Figure 2. The CD spectra for the pair of $anti^{HH}$ -**2a-A** and $anti^{HH}$ -**2a-B** (a) and that of $anti^{HH}$ -**2b-A** and $anti^{HH}$ -**2b-B** (b).

cyclohexane is observed upon the decrease in temperature from 20 °C to 8 °C, in methanol at –5 °C the *de* for $anti^{HH}$ -**2a** (50%) is significantly increased compared with that at 20 °C (44%).

The mechanism of the stereoselectivity in the above-mentioned photodimerization has not been fully understood. We observed excimer emission under the substrate concentration used for synthesis. We have demonstrated that the yield of the photodimers is dependent on the square of the light intensity, suggesting that their formation is a two-photon process.¹⁹ Recently in the study of photodimerization of methyl 3-methoxy-2-naphthoate we could isolate the [4+4] cycloaddition intermediate, and provided the direct evidence for the two-photon mechanism in the formation of the cubane-like photodimer.²⁰ Thus, we proposed a tentative scheme to illustrate the diastereoselectivity in the formation of $anti^{HH}$ -**2** (Scheme 3). Absorption of the first photon by **1** leads to



Scheme 3. A tentative scheme for illustration of the asymmetric induction in the photodimerization of alkyl 2-naphthoates.

the formation of an excimer. The excimer either goes back to the starting substrate, or undergoes [4+4] cycloaddition yielding the intermediate. The intermediate now has two possible paths for further reaction: either absorption of the second photon to give the cubane-like photodimer, or cleavage to re-form the starting substrate that can then be fed back into the reaction cycle. The excimer and [4+4] intermediate all have two configuration isomers **p** and **q**. In the two isomers, the degree of the steric interactions between the two chiral auxiliaries is different. Thus, one of the isomers, for example, **ep** and **ip** preferentially undergoes forward reaction in the reaction sequence, and another isomer, **eq** and **iq** undergoes backward reaction. Thus, if the rate constants for the formation of excimers **ep** and **eq** (k_1 and k'_1) are reasonably assumed to be the same, the diastereoselectivity of the cubane-like photodimer (*anti*^{HH}-**2**) would be generated at two levels: in the first selectivity level the rate constant ratio of k_2/k_{-1} is greater than k'_2/k'_{-1} , and in the second level of selectivity k_3/k_{-2} is greater than k'_3/k'_{-2} .

The chiral auxiliaries in photodimers **2** can be easily removed by hydrolysis in Claisen base solution (6.25 M KOH in the mixed solvents of methanol and water with v/v 3:1). For example, refluxing the solution of *anti*^{HH}-**2a** at 90 °C for 3 h followed by quenching the hydrolysis with 1 N HCl at 0 °C afforded the cubane-like *anti*^{HH} photodimer of 2-naphthalene carboxylic acid (*anti*^{HH}-**3**) as a white precipitate in 80% yield. The hydrolysis of both the diastereomeric mixture of *anti*^{HH}-**2a** and its optically pure diastereomer (the major and the minor) was performed. Thus, both racemic and enantiomerically pure *anti*^{HH}-**3** were obtained. We were not able to prepare a single crystal from the enantiomerically pure *anti*^{HH}-**3**. However, the crystal of the racemic *anti*^{HH}-**3** enantiomer mixture was obtained by recrystallization from ethanol solution. X-ray analysis indicates that the cubane-like skeleton is well retained during the hydrolysis.²¹

To summarize, we have successfully made use of chiral auxiliary strategy to bring about the asymmetric induction in the photodimerization of alkyl 2-naphthoates for the first time. Moderate diastereomeric induction in the formation of the *anti*^{HH}-**2** photodimers was achieved. Spectroscopy and X-ray structural analysis revealed that the cubane-like skeleton of the *anti*^{HH} photodimer is well retained after the removal of the chiral auxiliary. We are currently applying this photodimer as a chiral ligand in asymmetric catalysis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.053.

References and notes

1. Cervinka, O. *Enantioselective Reactions in Organic Chemistry*; Ellis Horwood: London, 1995.
2. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley-Interscience: New York, 1994.
3. Everitt, S. R. L.; Inoue, Y.. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcell Dekker: New York, 1999; Vol. 3, p 71.
4. Hoffmann, N.; Peter, J.-P. In *Molecular and Supramolecular Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Chiral Photochemistry; Marcell Dekker: New York, 2004; Vol. 11, p 179.
5. Inoue, Y. In *Molecular and Supramolecular Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Chiral Photochemistry; Marcell Dekker: New York, 2004; Vol. 11, p P129.
6. Sivaguru, J.; Natarajan, A.; Kaanumalle, L. S.; Shailaja, J.; Uppili, S.; Joy, A.; Ramamurthy, V. *Acc. Chem. Res.* **2003**, *36*, 509.
7. Mori, T.; Weiss, R. G.; Inoue, Y. *J. Am. Chem. Soc.* **2004**, *126*, 8961.
8. Ishida, Y.; Kai, Y.; Kato, S. Y.; Misawa, A.; Amano, S.; Matsuoka, Y.; Saigo, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1.
9. Nishijima, M.; Wada, T.; Mori, T.; Pace, T. C. S.; Bohne, C.; Inoue, Y. *J. Am. Chem. Soc.* **2007**, *129*, 3478.
10. Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Plath, M. W.; Runsink, J. *J. Am. Chem. Soc.* **1989**, *111*, 5367.
11. Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed.* **1991**, *30*, 477.
12. Clayden, J.; Knowles, F. E.; Menet, C. *J. Am. Chem. Soc.* **2003**, *125*, 9278.
13. Tsutsumi, K.; Nakano, H.; Furutani, A.; Endou, K.; Merpuge, A.; Shintani, T.; Morimoto, T.; Kakiuchi, K. *J. Org. Chem.* **2004**, *69*, 785.
14. Tung, C.-H.; Wang, Y.-M. *J. Am. Chem. Soc.* **1990**, *112*, 6322.
15. Tung, C.-H.; Wu, L.-Z.; Yuan, Z.-Y.; Su, N. *J. Am. Chem. Soc.* **1998**, *120*, 11594.
16. Tung, C.-H.; Wu, L.-Z.; Zhang, L.-P.; Chen, B. *Acc. Chem. Res.* **2003**, *36*, 39.
17. Wu, X.-L.; Luo, L.; Lei, L.; Wu, L.-Z.; Liao, G.-H.; Tung, C.-H. *J. Org. Chem.* **2008**, *73*, 491.
18. The irradiation was carried out in organic solution with a 500 W high-pressure mercury lamp as a light source. For example, **1a** was dissolved in a degassed cyclohexane solution (250 mg, 1.9×10^{-2} M) in a Pyrex tube, which also served as a light filter to cut off the light below 280 nm. The irradiation was monitored by UV-vis absorption spectra. After irradiation the resulting mixture was concentrated under reduced pressure and the products were purified by column chromatography on silica with dichloromethane as the eluent to afford the mixture of dimers. The mixture of dimers was further separated by HPLC, using an achiral ODS-3 column and a chiral IA column.
19. Tung, C.-H.; Li, Y.; Yang, Z.-Q. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 947.
20. Luo, L.; Liao, G.-H.; Wu, X.-L.; Lei, L.; Tung, C.-H.; Wu, L.-Z. *J. Org. Chem.* **2009**, *74*, 3506.
21. Wu, X.-L.; Lei, L.; Wu, L.-Z.; Liao, G.-H.; Luo, L.; Shan, X.-F.; Zhang, L.-P.; Tung, C.-H. *Tetrahedron* **2007**, *63*, 3133.