This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Diastereoselective Photodimerization Reactions of Chromone-2-carboxamides to Construct a C₂-Chiral Scaffold

Fumitoshi Yagishita,* Nozomi Baba,* Yuki Ueda,* Satoshi Katabira,* Yoshio Kasashima, Takashi Mino and Masami Sakamoto* 

Irradiation of three chromone-2-carboxamides with a chiral auxiliary resulted in diastereoselective formation of a C₂-chiral anti-HH dimer scaffold. Selection of the solvent polarity and decreasing the temperature resulted in asymmetric induction with up to 84% diastereomeric excess (de).

Diastereoselectivity in photochemical reactions continues to be one of the main topics of current interest.¹ High-yield chiral induction has been achieved by the use of a chiral auxiliary and a prochiral starting material with a covalent bond.² The chiral auxiliary can contribute to asymmetric induction during the photochemical transformation to produce diastereomers. Recently, we reported a stereoselective photodimerization reaction of 2-chromonecarboxylic esters that exclusively formed anti-HH dimers among four possible dimers.³ In most cases, controlling the selectivity of the product is difficult, since several types of photodimer are produced. In rare cases, it was reported that alkyl 2-naphthoate selectively gave C₂ chiral cubane-like photodimers.⁴ In another case, coumarin and thiocoumarin in a host-guest inclusion complex also gave anti head-to-head (HH) dimers in a solid-state photoreaction.⁵ These very rare reactions selectively lead to C₂ chiral photodimers. Materials with C₂ symmetry are widely used as ligands in catalytic asymmetric synthesis and synthetic materials. Thus, the development of a new reaction leading to C₂ chiral materials would be extremely useful.⁶ In this work, we found that the intermolecular photoreaction of 2-chromonecarboxamides with chiral auxiliaries led to a highly controlled diastereoselective dimerization reaction to form a C₂-chiral scaffold.

Three chiral auxiliaries connected with amide substituents at the 2-position of the chromone structure were examined (Scheme 1). Chromonecarboxamides 1a–c were easily prepared from 2-chromonecarboxylic acid and the corresponding optically active amines (R)-1-phenethylamine, (R)-1-t-butylethylamine, and (S)-alanine methyl ester, respectively. Table 1 shows the results of the photochemical reaction under various conditions.

When an MeCN solution of 1a was irradiated with a Pyrex-filtered light from a 500 W high-pressure mercury lamp for 1 h at 20°C, the anti-HH dimer 2a was obtained as a sole product in 93% yield and with a diastereomeric excess (de) of 52% (Table 1, entry 1). The de value increased as the reaction temperature was reduced, giving 66% de and 84% de for 2a at –40 and –80°C, respectively (entries 2 and 3). EtCN was used instead of MeCN for low-temperature photolysis at –80°C because of the low melting point. Irradiation of 1a in benzene also gave stereoselective anti-HH dimers; however, the de was quite low (entry 4) in comparison to the photoreaction in polar solvent. We examined the photoreaction in other solvents such as MeOH, ether and THF; however, complex mixture was obtained.

![Scheme 1. Chromone-2-carboxamides having chiral auxiliaries with covalent bonds.](image_url)
solvent resulted in different behavior, and 2c was obtained as a main product (entry 14).

As the photodimerization reaction proceeds from the triplet excited state, we examined the photoreaction in the presence of the triplet sensitizer benzophenone. The photodimerization reaction proceeded more effectively and gave a higher conversion (entries 5, 10 and 15).

Table 1. Photodimerization reaction of chromone-2-carboxamides 1a–c under various conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>compds</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>conv (%)</th>
<th>yield of 2:2′ (%)</th>
<th>ratio of 2:2′</th>
<th>de of 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>MeCN</td>
<td>20</td>
<td>85</td>
<td>93</td>
<td>83.17</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>MeCN</td>
<td>–40</td>
<td>91</td>
<td>79</td>
<td>88.12</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>EtCN</td>
<td>–80</td>
<td>83</td>
<td>77</td>
<td>92.8</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>benzene</td>
<td>20</td>
<td>59</td>
<td>92</td>
<td>56.44</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>MeCN</td>
<td>20</td>
<td>97</td>
<td>90</td>
<td>83.17</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>MeCN</td>
<td>20</td>
<td>91</td>
<td>94</td>
<td>69.31</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>MeCN</td>
<td>–40</td>
<td>90</td>
<td>90</td>
<td>65.35</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>EtCN</td>
<td>–80</td>
<td>91</td>
<td>78</td>
<td>58.42</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>1b</td>
<td>benzene</td>
<td>20</td>
<td>60</td>
<td>99</td>
<td>72.28</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>MeCN</td>
<td>20</td>
<td>97</td>
<td>90</td>
<td>63.37</td>
<td>26</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>MeCN</td>
<td>20</td>
<td>92</td>
<td>85</td>
<td>43.57</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>MeCN</td>
<td>–40</td>
<td>93</td>
<td>91</td>
<td>39.61</td>
<td>22</td>
</tr>
<tr>
<td>13</td>
<td>1c</td>
<td>EtCN</td>
<td>–80</td>
<td>94</td>
<td>72</td>
<td>43.57</td>
<td>14</td>
</tr>
<tr>
<td>14</td>
<td>1c</td>
<td>benzene</td>
<td>20</td>
<td>76</td>
<td>93</td>
<td>72.28</td>
<td>44</td>
</tr>
<tr>
<td>15</td>
<td>1c</td>
<td>MeCN</td>
<td>20</td>
<td>99</td>
<td>91</td>
<td>45.55</td>
<td>10</td>
</tr>
</tbody>
</table>

Each 0.05 M MeCN solution of 1a–c was irradiated with a 500-W high-pressure mercury lamp for 1 h. Chemical yields were determined on the basis of consumed chromones 1a–c. Benzophenone (BP) (0.1 M) was used as a triplet sensitizer.

One of the earliest rationalizations of the regiochemistry of enone cycloaddition was put forward by Corey, who proposed that a ‘π complex’ was formed between the photoexcited enone and a counterpart such as an alkene. This is usefully predictive, and cases in which the rule breaks down can usually be accounted for by unfavourable steric interactions between the enone and the counterpart in more stable π complex orientation. Theoretical approaches to 2+2 photocycloaddition of enones to alkenes were also studied. In the photodimerization of chromones 1a–c leading to anti-HH dimers, the regio- and stereochemistry can be reasonably explained in terms of polarization and the steric interactions of reacting species, triplet excited and ground-state molecules.

Two plausible conformations, 1-A and 1-B, were suggested by theoretical DFT calculation using RB3LYP/6-31G in Gaussian 09W (Scheme 2 and Table 2). Planar conformations were sustained by conjugation between the chromone ring and the amide function. In all cases, conformer 1-A is more stable than that of 1-B, and the dipole moment of 1-A conformer was bigger than that of 1-B because of the orientation of two carbonyl groups. The diastereoselectivity of the photodimerization of 1-A was explainable in terms of the steric interactions caused by the chiral auxiliaries (Scheme 3). The triplet excited state of 1a-A can react with ground state of 1a-A while avoiding steric repulsion, leading to favourable formation of 2. As the reaction temperature was reduced, the selectivity of the reaction became higher, with a de of 84% obtained in the reaction at –80°C (Table 1, entry 3).
On the other hand, irradiation in benzene gave a low de (Table 1, entry 4). The different polarity of the conformers may play a role for the diastereoselectivity of the photodimerization (Scheme 3). In the case of 1a-B, the carbonyl function of the amide and the 4H-pyran-4-one part are oriented opposite to each other which reduces the polarity of the molecule (Table 2). Conformer 1a-B may therefore be somewhat stabilized by the non-polar solvent and thus reduce the diastereoselectivity. This effect is certainly increased by the fact that the polarity of one carbonyl group is strengthened by electron shift from the pyranone ring oxygen atom. In the case of 1b, the reason for the low de of the products is unclear; however, the bulky t-buty group may prevent control of the molecular conformation.

In the case of 1c, we used the (S)-isomer. As the ester group was more bulky than the methyl group, the reactive chromones 1c approached each other from the vacant site of methyl group, which meant that 2′c was obtained as the major product in MeCN solution. However, a high de was not obtained because the steric size of both substituents was not changed significantly (entries 11–13). On the other hand, irradiation of a non-polar benzene solution of 1c reversed the diastereoselectivity, and 2c was produced as a main product (entry 14). As in the case of 1a, dipole moment of 1c-A was decreased by the bond rotation to form conformer 1c-B which may be stabilized by the non-polar solvent and thus resulted in the inversion of the diastereoselectivity.

Unfortunately, NMR spectra in different polar solvents by changing the ratio of CDCl₃ and DMSO-d₆ did not reveal the conformational conversion between 1a and 1b. We cannot provide a full account for the diastereoselectivity; however, it seems that the conformational change depending on the solvent polarity is one of the important factors to control the stereoselectivity.

The absolute structure of diastereomeric photodimers 2a-2c, 2′a and 2′c were established by single-crystal X-ray analysis. As an example, a perspective view of both diastereomeric photodimers, 2a and 2′a, is shown in Figure 1. The dimer 2a shows R stereochemistry throughout the cyclobutane ring, while 2′a has S configurations.

![Figure 1](attachment:image.png)

**Figure 1.** Perspective view of absolute configurations of diastereomeric photodimers (a) 2a and (b) 2′a.

Furthermore, these photodimers were easily optically resolved by recrystallization, without a cumbersome procedure. Many C₂-symmetric materials are used as ligands for catalytic asymmetric synthesis and synthetic materials. We are now developing catalytic asymmetric synthesis methods using these C₂-chiral photodimers as ligands for organometallics.

**Conclusions**

We achieved high chiral induction in photochemical dimerization reactions leading to a C₂ chiral scaffold through the use of chiral auxiliaries and a prochiral starting material with a covalent bond. Selection of the polarity of the solvents and reduction of the temperature resulted in asymmetric induction with up to 84% de.

**Experimental**

General. NMR spectra were recorded in CDCl₃ solution on a Bruker 300 instrument operating at 300 MHz for ¹H- and ¹³C-NMR spectroscopy. Chemical shifts are reported in parts per million (ppm) relative to TMS as an internal standard. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Specific rotation was measured using a DIP 370 polarimeter (JASCO). X-ray single crystallographic analysis was conducted using a SMART APEX II or SMART APEX II ULTRA (Bruker AXS).

Preparation of 2-chromonecarboxamides 1a-c: A toluene solution containing commercially available 1.00 g (4.90 mmol) of 2-chromonecarboxylic acid, 1.19 g (10.0 mmol) of thionylchloride, and catalytic amount of DMF was reacted for 3 h at 90 °C. After removal of the solvent and excess amount of thionylchloride in vacuo, crude acid chloride was obtained and used for the subsequent reaction. To a toluene solution of crude acid chloride, (R)-1-phenylethylamine (1.19 g, 9.80 mmol) was added drop wise at 0 °C. After the reaction mixture was stirred for 2 h at room temperature, water and ethyl acetate were added, and the organic layer was extracted in the usual manner. After evaporation of the organic solvent in vacuo, the residual mixture was subjected to chromatography on silica gel, and the amide 1a was obtained in 85% yield.

The other 1b was prepared in the same manner. In the case of 1c, L-alanine methyl ester hydrochloride and triethylamine (5.0 eq) were used. The amide 1b was obtained in 97% yield and 1c was obtained 66% yield. The structure of 1a-c was determined on the basis of spectral data, and the crystal structure of 1a and 1b was also established by single crystal X-ray analysis.

(R)-N-(1-Phenylethyl)-2-chromonecarboxamide 1a: colorless crystal; mp 123-124 °C; [α]D²⁰ = −1.6 (c = 0.47, CHCl₃); IR (cm⁻¹, KBr) 3295, 1677, 1646; ¹H NMR (CDCl₃) δ 1.68 (d, J = 6.9 Hz, 3H), 5.30-5.40 (m, 1H), 7.08 (d, J = 22.10, 37.37, 49.00, 61.14, 82.51, 117.20, 122.75, 125.21, 125.95, 127.52, 127.58, 128.74, 128.95, 142.07, 151.12, 166.14; EI-MS: m/z 293 (M⁺, 49); HRMS (ESI-MS) m/z cale for C₁₆H₁₄O₂N⁺+H 294.1125, found 294.1114.

(R)-N-(1-t-Butylethyl)-2-chromonecarboxamide 1b: colorless crystal; mp 86-87 °C; [α]D²⁰ = −34.0 (c = 0.49, CHCl₃); IR (cm⁻¹, KBr) 2256, 3322, 1685, 1633; ¹H NMR (CDCl₃) δ 1.00 (s, 9H), 1.22
(S)-N-(1-Methoxypropylidene)-2-chromonecarboxamide 1c: colorless crystal; mp 105-106 °C; [α]D -24 = 42.3 (c = 0.50, CHCl₃); IR (cm⁻¹): 3427, 1702, 1676; ¹H NMR (CDCl₃) δ 1.59 (d, J = 7.2 Hz, 3H), 3.84 (s, 3H), 4.75-4.86 (m, 1H), 7.15 (s, 1H), 7.47 (t, J = 7.2 Hz, 1H), 5.77 (d, J = 8.4 Hz, 2H), 7.72-7.79 (m, 1H), 8.22 (dd, J = 1.6 Hz, 6.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 18.3, 48.5, 52.8, 112.3, 118.2, 124.3, 126.0, 134.6, 154.2, 155.2, 158.7, 159.8, 172.8, 178.0; HRMS (ESI-MS) m/z calc'd for C₁₉H₁₆O₃N⁺H⁺ 276.0863, found 276.0866.

X-Ray diffraction analysis data of 1a: Colorless prismatic crystals from chloroform-hexane, trigonal space group P3₁, a = 13.4187(3) Å, b = 13.4187(3) Å, c = 28.8186(6) Å, γ = 120.0 °, V = 4493.9(2) Å³, Z = 2, μ = 1.301 g/cm³, μ = 0.724 mm⁻¹. The structure was solved by the direct method of full matrix least-squares, where the final R and wR were 0.1240 and 0.3327 for 9005 reflections. CCDC 1010749.

X-Ray diffraction analysis data of 1b: Colorless prismatic crystals from chloroform-hexane, triclinic space group P1, a = 5.9167(9) Å, b = 10.9747(17) Å, c = 12.2265(18) Å, α = 64.4240(19) °, β = 82.5940(19) °, γ = 89.9950(19) °, V = 708.78(19) Å³, Z = 2, μ = 1.28 g/cm³, μ = 0.088 mm⁻¹. The structure was solved by the direct method of full matrix least-squares, where the final R and wR were 0.0398 and 0.1003 for 9005 reflections. CCDC 1010750.

Photochemical procedure of 1a-c: A 0.02M solution of 2-chromonecarboxamides 1 was deoxygenated by bubbling argon for 20 min and was irradiated for 2 h at various temperatures. After irradiation the solvent was removed in vacuo and photoproducts were separated by flash chromatography on silica gel. The diastereoselectivity was determined on the basis of NMR spectra.

anti-HH photodimer of (R)-N-(1-phenylethyl)-2-chromonecarboxamide 2a: colorless crystal; mp 245-246 °C; [α]D -71.0 (c = 0.51, CHCl₃); IR (cm⁻¹): 3354, 1705, 1675; ¹H NMR: (CDCl₃) δ 1.47 (d, J = 6.8 Hz, 6H), 4.28 (s, 2H), 5.05 (m, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 7.10 (t, J = 7.2 Hz, 2H), 7.26-7.33 (m, 10H), 7.45 (t, J = 9.0 Hz, 2H), 7.94 (dd, J = 1.7 Hz, 7.8 Hz, 2H); ¹³C NMR: (CDCl₃) δ 21.58, 46.70, 49.07, 85.98, 116.38, 120.24, 122.71, 126.10, 127.20, 127.77, 128.86, 135.65, 141.71, 158.36, 166.48, 188.87; HRMS (ESI-MS) m/z calc'd for C₁₇H₁₉O₃N⁺H⁺ 587.2165, found 587.2177.

anti-HH photodimer of (R)-N-(1-phenylethyl)-2-chromonecarboxamide 2a: colorless crystal; mp 245-246 °C; [α]D -71.0 (c = 0.51, CHCl₃); IR (cm⁻¹): 3354, 1705, 1675; ¹H NMR: (CDCl₃) δ 1.47 (d, J = 6.8 Hz, 6H), 4.28 (s, 2H), 5.05 (m, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 7.10 (t, J = 7.2 Hz, 2H), 7.26-7.33 (m, 10H), 7.45 (t, J = 9.0 Hz, 2H), 7.94 (dd, J = 1.7 Hz, 7.8 Hz, 2H); ¹³C NMR: (CDCl₃) δ 21.58, 46.70, 49.07, 85.98, 116.38, 120.24, 122.71, 126.10, 127.20, 127.77, 128.86, 135.65, 141.71, 158.36, 166.48, 188.87; HRMS (ESI-MS) m/z calc'd for C₁₇H₁₉O₃N⁺H⁺ 587.2165, found 587.2177.
X-Ray diffraction analysis data of photodimer 2a: Colorless prismatic crystals from chloroform-hexane, monoclinic space group \( P2_12_12_1 \), \( a = 9.7337(10) \text{ Å}, b = 13.9495(14) \text{ Å}, c = 22.1042(2) \text{ Å}, V = 3001.3(5) \text{ Å}^3, Z = 4, \rho = 1.298 \text{ g/cm}^3, \mu = 0.088 \text{ mm}^{-1} \). The structure was solved by the direct method of full matrix least-squares, where the final \( R \) and \( wR \) were 0.0469 and 0.1150 for 5358 reflections. CCDC 1010751.

X-Ray diffraction analysis data of photodimer 2b: Colorless prismatic crystals from chloroform-hexane, monoclinic space group \( P2_12_12_1 \), \( a = 7.704(18) \text{ Å}, b = 14.23(3) \text{ Å}, c = 26.50(6) \text{ Å}, V = 2906(11) \text{ Å}^3, Z = 4, \rho = 1.249 \text{ g/cm}^3, \mu = 0.086 \text{ mm}^{-1} \). The structure was solved by the direct method of full matrix least-squares, where the final \( R \) and \( wR \) were 0.0629 and 0.1531 for 5433 reflections. CCDC 1010753.

X-Ray diffraction analysis data of photodimer 2c: Colorless prismatic crystals, monoclinic space group \( P2_12_12_1 \), \( a = 8.021(3) \text{ Å}, b = 15.273(5) \text{ Å}, c = 21.484(7) \text{ Å}, V = 2631.9(15) \text{ Å}^3, Z = 4, \rho = 1.389 \text{ g/cm}^3, \mu = 0.107 \text{ mm}^{-1} \). The structure was solved by the direct method of full matrix least-squares, where the final \( R \) and \( wR \) were 0.0535 and 0.0896 for 5909 reflections. CCDC 1010754.

Acknowledgement

This work was supported by Grants-in-Aid for Scientific Research (Nos. 24655025 and 25288017) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Notes and references

Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A.
Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O.
Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox,