

## Metal Chelation in Asymmetric Diels-Alder Reaction (II)

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Diels-Alder reaction is one of the most effective methods to prepare complex organic molecules.<sup>1</sup> The reaction provides up to four stereogenic centers in one step. The asymmetric Diels-Alder reaction has been carried out using a chiral auxiliary and a chiral catalyst.<sup>2,3</sup> Chiral dienophiles were often employed as chiral auxiliaries, derived from many functional groups such as alcohols, amines, oxazolidinones, and sulfams.<sup>4-7</sup> Diels-Alder cycloadditions of chiral dienophiles with cyclopentadiene proceed with diastereofacial selectivity, giving either *endo-R* or *endo-S* compounds as a major component, depending on Lewis acids used.

In the reaction, the inverse asymmetric induction has been observed by the use of either monovalent Lewis acids or divalent Lewis acids. The reaction of the acrylate of (*S*)-ethyl lactate with cyclopentadiene proceeded with 86% *endo-S* selectivity in the presence of TiCl<sub>4</sub>, divalent Lewis acid, whereas did with 32% *endo-R* selectivity in the presence of BF<sub>3</sub>·Et<sub>2</sub>O, monovalent Lewis acid.<sup>5</sup> When a chiral dienophile which was prepared from benzyl ester of (*S*)-proline<sup>6</sup> or methyl ester of (*S*)-indoline-2-carboxylic acid<sup>7</sup> was employed in the reaction, a similar diastereofacial selectivity was also observed. Recently, we reported the similar selectivity in the reaction of methyl (2*S*,5*S*)-(5-*t*-butyldimethylsilyloxypiperidin-2-yl)ethanoate with cyclopentadiene.<sup>8</sup>

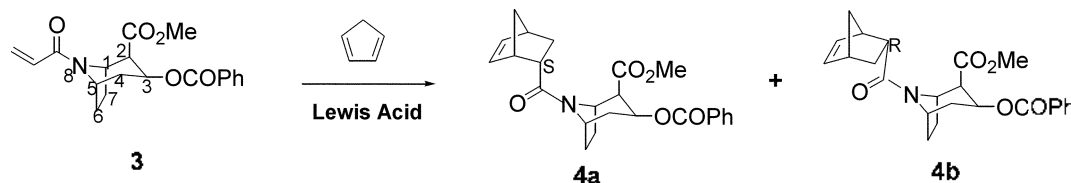
The different diastereoselectivity in the reaction was often rationalized by the chelation between dienophiles and Lewis acids.<sup>5-8</sup> The coordination between a metal and a substrate

was proven by X-Ray analysis; 5-membered ring complex was formed between TiCl<sub>4</sub> and ethyl lactate.<sup>9</sup> In the case of  $\alpha,\beta$ -unsaturated *N*-acyloxazolidinones, 6-membered chelation was proposed by a NMR spectral analysis.<sup>10</sup> According to Waldmann's<sup>6</sup> and Kim's reports,<sup>7</sup> 7-membered ring complex was formed between TiCl<sub>4</sub> and dienophiles. We also suggested that 8-membered chelation might affect the diastereoselectivity.

In this report, we tried to elucidate the effect of 8-membered ring complex in Diels-Alder reaction. Axial ester **3**, prepared from methyl 8-aza-3 $\beta$ -benzoyloxybicyclo[3.2.1]octane-2 $\beta$ -carboxylate, might be able to form 8-membered chelation between axial ester **3** and TiCl<sub>4</sub>, a divalent Lewis acid catalyst. Whereas equatorial ester **5** should not form any cyclic complex with *N*-acyl moiety.

As shown in Table 1, the amount of **4a** and **4b** was almost same when the reaction was taken place without a catalyst (entry 1). In the presence of monovalent Lewis acids, **4a** was given as a major compound in the reaction of **3** (entries 2, 3). However, divalent Lewis acids were employed in the reaction, **4b** was major (entries 4, 5). In the reaction of dienophile **3**, a best diastereoselectivity was obtained with AlCl<sub>3</sub> (entry 2). Again as shown in Table 2, without a catalyst, the amount of **6a** and **6b** was almost same in the reaction of **5**, the C2 epimer of **3** (entry 1). However, the reaction of dienophile **5** with cyclopentadiene proceeded with same diastereoselectivity to give **6a** as a major

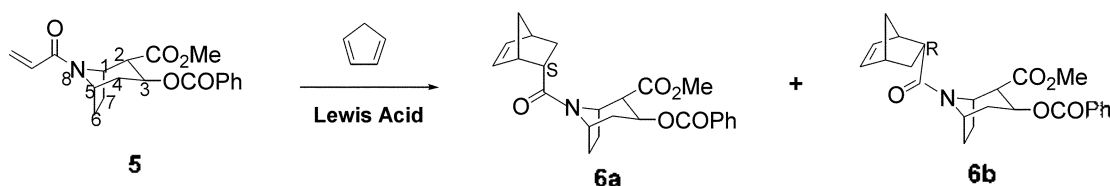
**Table 1.** Asymmetric Diels-Alder Reaction of **3** with cyclopentadiene



Entry	Lewis acid	Temp. (°C)	Time (h)	Yield (%)	<i>Endo</i> : <i>Exo</i> <sup>a</sup>	<i>Endo ds</i> <sup>b</sup>	Config. <sup>c</sup>
1	none	RT	72	30	70 : 30	1.5	S
2	AlCl <sub>3</sub>	0	15	88	78 : 22	99	S
3	ZnCl <sub>2</sub>	RT	18	83	68 : 32	98	S
4	TiCl <sub>4</sub>	0	16	80	63 : 37	73	R
5	Ti(OPr <sup>t</sup> ) <sub>4</sub>	RT	24	74	71 : 29	80	R

<sup>a</sup>The ratio of the amount of **4a** and **4b** to their corresponding *exo* isomers. <sup>b</sup>Calculated by the amounts of **4a** and **4b**. <sup>c</sup>The chirality of C2 position in the norbornene moiety of the major compound. The authentic **4b** was prepared from *endo*-(2*R*)-5-norbornene-2-carboxylic acid.<sup>6</sup>

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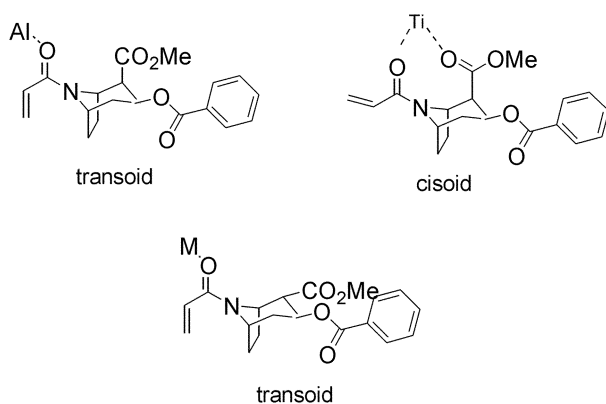
**Table 2.** Asymmetric Diels-Alder Reaction of **5** with cyclopentadiene

Entry	Lewis acid	Temp. (°C)	Time (h)	Yield (%)	Endo : Exo <sup>a</sup>	Endo ds <sup>b</sup>	Config. <sup>c</sup>
1	none	RT	72	25	68 : 32	1.1	S
2	AlCl <sub>3</sub>	0	15	85	75 : 25	11	S
3	ZnCl <sub>2</sub>	RT	20	82	62 : 38	14	S
4	TiCl <sub>4</sub>	0	17	77	66 : 34	16	S
5	Ti(OPr) <sub>4</sub>	RT	28	70	70 : 30	14	S

<sup>a</sup>The ratio of the amount of **6a** and **6b** to their corresponding *exo* isomers. <sup>b</sup>Calculated by the amounts of **6a** and **6b**. <sup>c</sup>The chirality of C2 position in the norbornene moiety of the major compound. The authentic **6b** was prepared from *endo*-(2*R*)-5-norbornene-2-carboxylic acid.<sup>6</sup>

compound, regardless of Lewis acids (entries 2-5).

TiCl<sub>4</sub>, a divalent metal compound, forms chelation with amide **3** and the ester carbonyl moiety, resulting that a *cisoid* conformation was preferred to the *transoid* one. On the other hand, AlCl<sub>3</sub>, a monovalent one, coordinated only by amide carbonyl group, resulting that the *transoid* one was favored.<sup>6-8</sup> As expected, a metal coordinated with the amide carbonyl group of compound **5**, and the same diastereomer was given as a major compound.



In Diels-Alder reaction, 8-membered chelation was once reported, but 8- or larger membered ring complex was often considered in other reactions, such as asymmetric hydrogenation,<sup>11</sup> allylic alkylation,<sup>12</sup> and so on.<sup>15</sup> In summary, Lewis acids apparently affected the diastereofacial selectivity. A divalent Lewis acid might be involved in the formation of 8-membered chelation which was effective enough to distinguish between the *transoid* and *cisoid* conformer of a *N*-acryloyl chiral dienophile in Diels-Alder reaction with cyclopentadiene.

### Experimental Section

All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Gemini

2000 (200 MHz) spectrometer in CDCl<sub>3</sub>. Column chromatographic purifications were performed using 70-230 mesh silica gel.

**Methyl *N*-acryl-8-aza-3β-benzoyloxybicyclo[3.2.1]octane-2β-carboxylate (3).** To a mixture of methyl 8-aza-3β-benzoyloxybicyclo[3.2.1]octane-2β-carboxylate (0.20 g, 0.69 mmol),<sup>14</sup> dichloromethane (5 mL), and triethylamine (0.084 g, 0.83 mmol) was added dropwise acryloyl chloride (0.087 g, 0.97 mmol) at 0 °C. After stirring for 2 h at rt, the mixture was quenched with 0.1 N HCl. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 1) to give a colorless oil (0.23 g, 97%). <sup>1</sup>H NMR δ 1.82-2.14 (m, 5H), 2.39-2.50 (m, 1H), 3.08-3.16 (m, 1H), 3.55, 3.60 (s, 3H), 4.43-4.51 (m, 1H), 4.90-5.07 (m, 1H), 5.40-5.51 (m, 1H), 5.58-5.66 (m, 1H), 6.22-6.25 (m, 2H), 7.30-7.35 (m, 3H), 7.86-7.90 (m, 2H); <sup>13</sup>C NMR δ 26.5, 28.7, 34.8, 49.1, 51.0, 53.7, 55.7, 66.5, 127.4, 127.8, 128.0, 129.8, 129.9, 133.4, 161.5, 165.9, 170.1; HRMS found *m/z* 344.0759 (MH<sup>+</sup>), C<sub>19</sub>H<sub>22</sub>NO<sub>5</sub> requires 344.3902.

**Methyl *N*-acryl-8-aza-3β-benzoyloxybicyclo[3.2.1]octane-2α-carboxylate (5).** Compound **5** was prepared from methyl 8-aza-3β-benzoyloxybicyclo[3.2.1]octane-2α-carboxylate<sup>14</sup> by the above mentioned method. <sup>1</sup>H NMR δ 1.80-2.50 (m, 6H), 2.85-3.18 (m, 1H), 3.59 (s, 3H), 4.28-4.60 (m, 1H), 4.70-4.96 (m, 1H), 5.60-5.80 (m, 2H), 6.26-6.40 (m, 2H), 7.22-7.54 (m, 3H), 7.86-7.98 (m, 2H); <sup>13</sup>C NMR δ 28.9, 29.8, 38.0, 50.6, 53.5, 54.1, 55.8, 67.7, 127.5, 128.5, 129.2, 129.8, 130.0, 133.3, 163.0, 165.7, 171.2.

**General procedure for Diels-Alder reaction.** To a stirred solution of **3** (0.050 g, 0.122 mmol) in dichloromethane (1.5 mL) was added a solution of 2 equiv. Lewis acid in dichloromethane (5 mL) at 0 °C. After stirring for 30 min, a solution of cyclopentadiene (0.04 g, 0.61 mmol) in dichloromethane (5 mL) was added during 10 h with a syringe pump at the respective temperature. The mixture was stirred for additional 5 h and then quenched with 0.1 N HCl. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The oily residue was

purified by column chromatography on silica gel (EtOAc/hexane, 1:3), and the yield and the diastereomeric ratio were determined by HPLC analysis.<sup>7</sup>

**4b**: <sup>1</sup>H NMR δ 1.24-1.49 (m, 4H), 1.73-2.11 (m, 5H), 2.65-3.17 (m, 5H), 3.65, 3.67 (s, 3H), 4.58-4.75 (m, 1H), 4.86-5.06 (m, 1H), 5.46-5.52 (m, 1H), 5.77-6.24 (m, 2H), 7.34-7.52 (m, 3H), 7.87-7.95 (m, 2H); <sup>13</sup>C NMR δ 27.0, 29.8, 30.2, 34.9, 41.9, 42.8, 46.5, 48.7, 49.9, 52.0, 53.0, 53.2, 66.8, 128.6, 129.8, 130.0, 133.0, 133.4, 136.5, 166.0, 169.9, 170.3; HRMS found *m/z* 410.1967 (MH<sup>+</sup>), C<sub>24</sub>H<sub>28</sub>NO<sub>3</sub> requires 410.1969.

**6b**: <sup>1</sup>H NMR δ 1.29-1.69 (m, 4H), 1.75-2.33 (m, 5H), 2.91-3.30 (m, 5H), 3.62 (s, 3H), 4.40-4.64 (m, 1H), 4.67-4.90 (m, 1H), 5.63-5.76 (m, 1H), 5.97-6.10 (m, 1H), 6.17-6.21 (m, 1H), 7.35-7.56 (m, 3H), 7.92-7.96 (m, 2H); <sup>13</sup>C NMR δ 27.0, 29.8, 30.2, 31.2, 42.9, 46.5, 49.9, 50.4, 51.2, 52.6, 53.2, 55.8, 67.8, 128.5, 129.8, 130.0, 132.5, 133.2, 138.3, 165.7, 170.9, 171.3.

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