The Influence of Ligand Side Chain on the Enantioselectivity of Lewis Acid Catalyzed Diels–Alder Reactions

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The design and synthesis of novel chiral catalysts for asymmetric reactions continues to be an important and active area of research. C₂-symmetric bis(oxazolines) (boxes) have proven to be excellent ligands in wide range of asymmetric carbon–carbon bond formation reactions including Diels–Alder reaction. Recently, a non-C₂-symmetric box bearing a meso backbone and a non-C₂-symmetric mono-oxazoline (mox) such as pyridyloxazoline or pyrosphinoarylloxazoline have also been shown to be effective ligands in the enantioselective catalytic Diels–Alder reaction. In previous paper we have reported that the magnesium-catalyzed Diels–Alder reaction of ethyl 2-benzoylacrylate and 1-phenyl-2-methylenebutane-1,3-dione gave the adduct enantioselectively with MgI₂ :I₂ (2:1:2) from (1:1:1) to (1:1:2) (entries 1, 3). The high asymmetric induction in the reaction can be rationalized by assuming that the reaction proceeds via the intermediary of a tetrahedral complex shown in Fig. 2, which is similar to that of the reaction of with MgI₂ –Cu(OTf)₂ complex, we next examined the contribution of the side chain at 2 position of oxazoline to the reaction. The remarkable depletion of ee was observed converting Cl to H (compare entries 3 and 6). This means that a group having hydrogen-bonding ability is necessary for high enantioselectivity. Furthermore the reaction did not proceed with Cu(OTf)₂ having non-chiral long chain substituent at 2 position under the same reaction condition (entry 7). This might be due to inhibition of flexible long chain for attack of cyclopentadiene to Mg₄–8 complex. Finally, the reactions with mox having different substituents such as isopropyl and tert-buty1 group at the chiral center of the oxazoline ring and the same side chain at 2-position as were examined. As can be seen from entries 9 and 10 the enantioselectivities were very poor, which might be attributed to the steric hindrance of bulky group adjacent the amide group resulting in prevention of hydrogen bond formation in the reactive species.

As Evans reported the very high enantioselectivity in the reaction of with 7c–Cu(OTf)₂ complex, we next examined the reaction with Cu(OTf)₂ (0.1 eq) as a Lewis acid (Table 2). However both endo- and exo-selectivities were lower than those with MgI₂ and the opposite enantiomer was formed with 6b (entry 3). The opposite enantiomer should be formed out with the complex prepared from 2 : MgI₂ : I₂ (1 : 1 : 1) (entries 1, 2). On the contrary, no significant temperature dependencies were found in the reaction with the complex prepared from 2 : MgI₂ : I₂ (2 : 1 : 2) (entries 3–5). At the same reaction temperature the enantiomeric excesses increased more than 20% by changing the complex composition from (2 : MgI₂ : I₂) to (1 : 1 : 1) to (2 : 1 : 2) (entries 1, 3). The opposite enantiomer should be formed from the complex. When oxazoline and amide carbonyl oxygen coordinate to magnesium and hydrogen bonding between the chloride and the amide hydrogen, the phenyl group of amide side-chain situate at nearly opposite side to the phenyl group at 4-position of oxazoline ring across magnesium. Thus cyclopentadiene should approaches from re face to the complex. Next, we examined the contribution of the side chain at 2 position of the oxazoline to the reaction. The remarkable depletion of ee was observed converting Cl to H (compare entries 3 and 6). This means that a group having hydrogen-bonding ability is necessary for high enantioselectivity. Furthermore the reaction did not proceed with 4 having non-chiral long chain substituent at 2 position under the same reaction condition (entry 7). This might be due to inhibition of flexible long chain for attack of cyclopentadiene to Mg₄–8 complex. Finally, the reactions with mox having different substituents such as isopropyl and tert-buty1 group at the chiral center of the oxazoline ring and the same side chain at 2-position as were examined. As can be seen from entries 9 and 10 the enantioselectivities were very poor, which might be attributed to the steric hindrance of bulky group adjacent the amide group resulting in prevention of hydrogen bond formation in the reactive species.

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The enantioselective Lewis acid-catalyzed Diels–Alder reaction of 3-(2-propenoyl)-1,3-oxazolidin-2-one 8 with cyclopentadiene was examined using a series of chiral mox ligands 2–6, deferring in the side chain at 2-position of the chiral oxazoline and in the nature of the substituent at the chiral center (4-position) of the oxazoline ring, and a combination of N-{[(1R)-2-chloro-1-phenylethyl]-2-[(4R)-4-phenyl-4,5-dihydrooxazol-2-yl]butyramide 2–MgI₂–I₂ was the most efficient catalyst.

Key words enantioselective Diels–Alder reaction; Lewis acid; chiral mono(oxazoline) (mox); N-{[(1R)-2-chloro-1-phenylethyl]-2-[(4R)-4-phenyl-4,5-dihydrooxazol-2-yl]butyramide; 3-(2-propenoyl)-1,3-oxazolidin-2-one

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via a square–planar complex analogous to box 6c–copper–7 complex proposed by Evans.6,24) or an octahedral complex22) like 1.

Table 1. Enantioselective Diels–Alder Reaction of 8 with Cyclopentadiene Using MgI₂ in CH₂Cl₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (eq)</th>
<th>I₂ (eq)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio 9n : 9x</th>
<th>endo-Isomer (9n)</th>
<th>% ee</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (0.1)</td>
<td>0.1</td>
<td>−50</td>
<td>23</td>
<td>83</td>
<td>95 : 5</td>
<td>61.4</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (0.1)</td>
<td>0.1</td>
<td>−70</td>
<td>24</td>
<td>82</td>
<td>95 : 5</td>
<td>77.5</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (0.2)</td>
<td>0.2</td>
<td>−50</td>
<td>6</td>
<td>84</td>
<td>94 : 6</td>
<td>85.5</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (0.2)</td>
<td>0.2</td>
<td>−70</td>
<td>29</td>
<td>71</td>
<td>94 : 6</td>
<td>90.7</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 (0.2)</td>
<td>0.2</td>
<td>−80</td>
<td>38</td>
<td>88</td>
<td>96 : 4</td>
<td>88.4</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 (0.2)</td>
<td>0.2</td>
<td>−50</td>
<td>94</td>
<td>73</td>
<td>88 : 12</td>
<td>36.9</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4 (0.2)</td>
<td>0.2</td>
<td>−50</td>
<td>48</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5 (0.2)</td>
<td>0.2</td>
<td>−70</td>
<td>17</td>
<td>80</td>
<td>95 : 5</td>
<td>3.2</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>6a (0.2)</td>
<td>0.2</td>
<td>−70</td>
<td>23</td>
<td>76</td>
<td>88 : 12</td>
<td>29.6</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>6b (0.2)</td>
<td>0.2</td>
<td>−70</td>
<td>24</td>
<td>78</td>
<td>93 : 7</td>
<td>18.5</td>
<td>R</td>
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</table>

Table 2. Enantioselective Diels–Alder Reaction of 8 with Cyclopentadiene Using Cu(OTf)₂ in CH₂Cl₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (eq)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio 9n : 9x</th>
<th>endo-Isomer (9n)</th>
<th>% ee</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (0.1)</td>
<td>−80</td>
<td>20</td>
<td>79</td>
<td>88 : 12</td>
<td>64.6</td>
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</tr>
<tr>
<td>2</td>
<td>6a (0.1)</td>
<td>−80</td>
<td>46</td>
<td>65</td>
<td>81 : 19</td>
<td>6.2</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6b (0.1)</td>
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<td>24</td>
<td>58</td>
<td>72 : 28</td>
<td>18.3</td>
<td>S</td>
<td></td>
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</tbody>
</table>

Fig. 1

Fig. 2

In conclusion N-[(1R)-2-chloro-1-phenylethyl]-2-ethyl-2-[(4R)-4-phenyl-4,5-dihydrooxazol-2-yl]butyramide 2 is also efficient ligand in the Diels–Alder reaction using 3-(2-propenoyl)-1,3-oxazolidin-2-one 8 as a dienophile.

Experimental
Melting points are uncorrected. MgSO₄ was used to dry organic layers
after extraction. Column chromatography was performed with Silica Gel 60 (Spherical, Kanto Chemical Co.). HPLC was carried out with a Daicel Chiralcel OD column (0.46×25 cm; eluate 0.1% propan-2-ol in hexane). NMR spectra were measured on a JEOL GX-270 spectrometer for samples in CDCl3 solution at 270 MHz for 1H and 67.89 MHz for 13C, and chemical shifts are expressed in δ-units using tetramethylsilane or chloroform as an internal standard. The spectra were recorded on a JASCO FT/IR-410 spectrometer. High-resolution mass spectra were obtained with a JEOL JMS-700 spectrometer.

Synthesis of Chiral Ligands. 2-Ethyl-2-[(4R)-4-phenyl-4,5-dihydrooxazol-2-yl]-N-(1R)-1-phenylethylbutramide 3

To a solution of 2,2-diethyl-N-[1R]-2-hydroxy-1-phenylethyl-N-[1R]-1-phenylethyl malonamide (1.61 g, 4.2 mmol), and Et3N (1.3 ml, 9.24 mmol) in CH2Cl2 (50 ml) was added methanesulfonyl chloride (0.36 ml, 4.62 mmol) in an ice-bath. The reaction mixture was allowed to warm to room temperature and stirring was continued for 20 min. The reaction mixture was then poured into saturated aqueous NH4Cl solution (50 ml). The organic layer was separated and the aqueous layer was extracted with CH2Cl2 (20 ml×2). The combined organic layers were washed with brine, dried and evaporated. The resulting crude mesylate was treated with 0.5M NaOH/MeOH–H2O (1:1) solution (16 ml) at reflux for 1.5 h. The reaction mixture was quenched with water (10 ml) and 5% aqueous Na2S2O3 (10 ml). The organic layer was washed with 5% aqueous Na2S2O3 (10 ml) and 5% aqueous Na2S2O3 (10 ml). The organic layer was dried and evaporated. The resulting residue was subjected to column chromatography to yield the adducts.

General Procedure for the Reaction of Enedione with Ph–oxo–Magnesium Complex  

A mixture of the ligands, MgI, and I in the solvent was used under the conditions shown in Table 2. The solvent was removed and the resulting complex was dissolved in CH2Cl2 (1.0 ml) and cooled to specified reaction temperature. To this solution 8 (141 mg, 1 mmol) in CH2Cl2 (1.5 ml) was added and stirred for 30 min, then cyclopentadiene (1.5 mmol) in CH2Cl2 (2.5 ml) was added slowly. After the reaction was completed the reaction mixture was quenched with water (10 ml) and washed with 5% aqueous Na2S2O3 (10 ml). The organic layer was dried and evaporated. The resulting residue was subjected to column chromatography to yield the adducts.

References