Asymmetric Introduction of Nucleophiles to the 2-Position of Pyrrolidine Ring through N-Acylpyrrolidinium Ion

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Asymmetric introduction of nucleophiles to the 2-position of pyrrolidine ring through \( N \)-acylpyrrolidinium ion

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Abstract- Asymmetric carbon-carbon bond-forming reaction at the 2-position of a pyrrolidine ring was achieved. The reaction involved a chiral Ti(IV) catalyzed coupling between 1-methoxycarbonyl-2-methoxypyrrolidine and silyl enol ethers to afford 2-substituted pyrrolidines with up to 53%ee.

Asymmetric introduction of carbon nucleophiles (\( \text{Nu}^- \)) onto cyclic \( N \)-acyliminium ions \( A \) \((n=0, 1)\) has been attracting much interest because it provides an efficient route for elaboration of optically active piperidine and pyrrolidine derivatives \( B \) through easily available prochiral \( A \) (Scheme 1).\(^1\)-\(^3\) However, in contrast with some reports on the preparation of optically active piperidines \( B \) \((n=1)\) by this method,\(^1\) there have been no studies on the successful preparation of optically active pyrrolidines \( B \) \((n=0)\).

We report herein the result of our effort to achieve asymmetric carbon-carbon forming reaction between \( A \) \((n=0)\) and \( \text{Nu}^- \) in the presence of chiral catalysts. The basic reaction we first surveyed is shown in Eq. 1 in which 1-methoxycarbonyl-2-methoxypyrrolidine (\( 1 \))\(^4\) as a precursor of \( A \) \((n=0)\), 1-tirmethylsiloxystyrene (\( 2a \)) as \( \text{Nu}^- \), and (\( R \))-BINOL-titanium dichloride complex (\( 3a \))\(^5\) as a chiral catalyst were used (Eq 1).\(^6\)

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In this reaction was formed the aimed product (4a) in good yields with low %ee's which were dependent on the used solvent (Eq 1). The other chiral catalysts (3b-g)\(^7\) in place of 3a were also examined in CH\(_2\)Cl\(_2\) but all of them gave disappointed %ee (Fig 1).

Then, we tried the reactions of 1 with 1-trimethylsiloxy-3,4-didehydronaphthalene (2b) in the presence of a chiral catalyst 3a to afford 4b as a mixture of diastereomers (Eq 2).
Interestingly, both the yield of 4b and the %ee of each stereoisomer were improved by carrying out the reaction in mesitylene as a solvent as shown in Eq. 2. On the basis of this result, a variety of silyl enol ethers 2b-2h was examined as Nu− under conditions using mesitylene as a solvent. The results are shown in Table 1.

Table 1. The reaction of 1 with nucleophiles 2b-h in mesitylene in the presence of 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product</th>
<th>Yield (%)</th>
<th>%de</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>4b</td>
<td>&gt;99</td>
<td>68</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>4c</td>
<td>98</td>
<td>76</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>4d</td>
<td>94</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>4e</td>
<td>84</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>4a</td>
<td>99</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>4f</td>
<td>91</td>
<td>-</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>4g</td>
<td>48</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>4h</td>
<td>78</td>
<td>-</td>
<td>33</td>
</tr>
</tbody>
</table>

2b-h (2 equiv.), 3a (0.1 equiv.) in mesitylene (3 mL) at rt for 12 h.

Although there was no data to speculate the absolute stereochemistry of stereoisomers of 4b-4d, chiral chromatographic analysis showed the %de's and the %ee's of each stereoisomer as indicated in Entries 1-3 of Table 1. The highest %ee so far obtained was 53% for major isomer of 4b (Entry 1).
In order to rationalize the reaction mechanism, the absolute stereochemistry of products 4 must be clarified. Among 4a-h, only (S)-4a and (S)-4f could be prepared from (S)-prolinol 5 according to the reported method (Eq 3).10

The enriched isomers of the products in the reaction of 1 with 2a and 2f in the presence of 3a were identical with (S)-4a and (S)-4f, respectively.11 On the basis of this result, we propose a mechanism shown in Scheme 2 for the enriched formation of (S)-4a,f in the reaction of 1 with 2a,f.

In conclusion, we presented herein the first method for asymmetric carbon-carbon forming reaction onto N-acylpyrrolidinium ion A (n=0, R=OMe). Although the observed enantioselectivities were low to moderate (up to 53%ee), further study to improve the stereoselectivity is under investigation on the basis of the proposed mechanism.
ACKNOWLEDGEMENT
Y. M. and O.O. thank the Ministry of Education, Culture, Sports, Science and Technology, Japan for Scientific Research on Priority Areas, (No. 420: Reaction Control of Dynamic Complexes) and the Japan Society for the Promotion of Science for Scientific Research (C) (15550094).

REFERENCES AND NOTES
6. A typical procedure: Under an aerobic atomosphere, to a solution of N,O-acetal 1 (0.159g, 1mmol) and silyl enol ether 2a (2 mmol, 385 mg) in mesitylene (3mL) was added a chiral catalyst 3a (0.1 mmol, 0.197mL) at room temperature. After stirring for 12 h, the reaction mixture was quenched with ice-water and the organic portion was extracted with ethyl acetate. After the organic layer was dried over MgSO4, the solvent was removed in vacuo. The residue was chromatographed on silica gel (ethyl acetate:n-hexane=1:3) to afford 4a in 99% yield.
9. The de’s and ee’s were determined by a chiral HPLC method, (4b) Daicel Chiralcel OD (4.6 mmφ, 50 cm), n-hexane: iso-propanol=15:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 30 min and 60 min for one diastereomer and 37 min and 53 min for the other diastereomer; (4c) Daicel Chiralcel OD (4.6 mmφ, 50 cm) + Chiralpak AD (4.6 mmφ, 50 cm), n-hexane: iso-propanol=12:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 59 min and 73 min for one diastereomer and 64 min and 69 min for the other diastereomer; (4d) Daicel Chiralcel OD (4.6 mmφ, 50 cm) + Chiralpak AD (4.6 mmφ, 50 cm), n-hexane: iso-propanol=12:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 33 min and 44 min for one diastereomer and 35 min and 59 min for the other diastereomer.
11. The ee’s were determined by a chiral HPLC method: Daicel Chiralcel OD (4.6 mmφ, 25 cm), n-hexane: iso-propanol=15:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 10 min for (S)-4a and 12 min for (R)- 4a; 19 min for (S)-4f and 28 min for (R)- 4f.