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 (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).

![Scheme 1](image)

Scheme 1. Enantioselective introduction of carbon nucleophile (Nu−)

We report herein the result of our effort to achieve asymmetric carbon-carbon forming reaction between A (n=0) and 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 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) in place of 3a were also examined in CH$_2$Cl$_2$ but all of them gave disappointed % ee (Figure 1).
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 $3a^a$

<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>

$^a$ $1$ (1 mmol), $2a$-$h$ (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\(^{10}\) and (S)-4f\(^{10}\) could be prepared from (S)-prolinol (5) according to the reported method (Eq. 3).\(^{11}\)

\[
\begin{align*}
\text{5} & \xrightarrow{1) \text{ClCO}_2\text{Me}} \text{6} \\
\text{5} & \xrightarrow{2) \text{TsCl}} \text{7} \\
\end{align*}
\]

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.\(^{12}\) 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.\(^{3,13}\)

Scheme 2. Proposed Mechanism

In conclusion, we presented herein the first method for asymmetric carbon-carbon forming reaction onto \(N\)-acylpyrrolidinium ion (A) (n=0, R=OMe), though 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

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REFERENCES AND NOTES


6. A typical procedure: Under an aerobic atomosphere, to a solution of N,O-acetal (1) (1 mmol, 0.159 g) and silyl enol ether (2a) (2 mmol, 0.385 g) in mesitylene (3 mL) was added a chiral catalyst (3a) (0.1 mmol, 0.197 mL) 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.

10. (S)-4a; [α]$_{D}^{23}$ -23.7 ° (c 1.1 CHCl$_3$). (S)-4f; [α]$_{D}^{29}$ -28.4 ° (c 1.0 CHCl$_3$).


12. 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.