Cysteine-Derived Organocatalyst in a Highly Enantioselective Intramolecular Michael Reaction

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The Michael reaction is an important carbon—carbon bond forming reaction for which the catalytic asymmetric version using metal carbanions has been developed with great success.1 In recent years, the organocatalyst-mediated Michael reaction has undergone rapid development, and excellent results have been reported for intermolecular reactions.2 To attain high enantioselectivity, the design of the organocatalyst is crucial, and we have developed diphenylprolinol silyl ether as an efficient catalyst for the Michael reaction of aldehydes and nitroalkenes.3 Only one excellent report has described the enantioselective, intramolecular, catalytic Michael reaction, an important method for the preparation of chiral, cyclic carbon skeletons from acyclic precursors, in which List and Fonseca reported the synthesis of chiral trans-disubstituted cyclopentanes from formyl enones.4

The bicyclo[4.3.0]nonene carbon skeleton is found in several natural products, such as the elinacines,5 axanes,6 and scabronines,7 and its asymmetric construction is a synthetic challenge. This skeleton could be synthesized from an achiral precursor, 4-substituted-4-(3-formylpropyl)cyclohexa-2,5-dien-1-one (1a), via asymmetric intramolecular Michael reaction with creation of three contiguous chiral centers in a single step, if selective reaction of one of the two enantiotopic \( \pi \)-bonds of 1 can be achieved (eq 1).

\[
\begin{align*}
\text{CH}_3\text{CN, } 0 \degree C & \rightarrow \text{CH}_3\text{CN, } 0 \degree C \\
1 & \rightarrow 2 \\
10 \text{ mol% organocatalyst} & \rightarrow 2 \\
& \rightarrow 3 \\
& \text{H column.} \\
& \text{Determined by HPLC using a chiral column.} \\
& \text{A } 20 \text{ mol % of the catalyst was employed.} \\
& \text{A } 5 \text{ mol % of the catalyst was employed.}
\end{align*}
\]

The achiral 1a possessing a benzyl group at the 4-position was selected as a model and was prepared from 3-ethoxycyclohex-2-en-1-one in six steps.8 When 1a was treated with a catalytic amount of \( L \)-proline, the reaction was slow, affording 2a in low yield and 11% ee (Table 1, entry 1). Low enantiomeric excess was obtained in the case of MacMillan’s catalyst 5,2a,2e while prolinol silyl ether, which is an effective catalyst in our aldehyde—nitroalkene Michael reaction,3 gave good yield and moderate enantiomeric excess. After screening various organocatalysts, the trifluoroacetic acid salt 9 of \( L \)-proline, the reaction was slow, affording 2a in low yield with high diastereo- and excellent enantioselectivity. This should be noted that the activity of catalyst 7 is much higher than that of MacMillan’s catalyst 5 under the present reaction conditions. The reaction using 7 was complete within 3 h, while the reaction using 5 had not finished even after 24 h.9

The generality of the present intramolecular Michael reaction was investigated, with the results summarized in Table 2. Not only benzyl but also alkyl groups, such as methyl and butyl, are tolerated in the 4-position. Other synthetically useful substituents, such as the allyl group, are also suitable, affording the bicyclo[4.3.0]nonene skeleton in good yield with high diastereo- and excellent enantioselectivity.

Next, the catalyst 7 was applied to the reaction of formyl enones 8 for the synthesis of chiral, disubstituted cyclopentane derivatives 9 via intramolecular Michael reaction (eq 2). When 8a was treated with 10 mol % of 7 at 0 \degree C, the reaction proceeded smoothly, affording the cis-isomer diastereo- and enantioselectively. Note-worthy is the selective formation of the cis-isomer, which is opposite

### Table 1. Effect of Catalyst on Asymmetric Intramolecular Michael Reaction of 1a (R = PhCH\(_2\))

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time/h</th>
<th>yield/(%^a)</th>
<th>ee of 2a/(%^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>24</td>
<td>34</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>24</td>
<td>48</td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>24</td>
<td>quant.</td>
<td>74:26</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>3</td>
<td>89</td>
<td>95:5</td>
</tr>
</tbody>
</table>

### Table 2. Asymmetric Intramolecular Michael Reaction of 1a

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>yield/(%^a)</th>
<th>ee of 2/(%^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>96:4</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>quant.</td>
<td>91:9</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>92:8</td>
<td>95</td>
</tr>
</tbody>
</table>

\(a\) Unless otherwise shown, reactions were conducted with 10 mol % of catalyst in CH\(_3\)CN at 0 \degree C. \(b\) Yield of isolated products of 2 and 3. \(c\) Determined by \(^1\)H NMR (400 MHz). \(d\) Determined by HPLC using a Chiralpak AS−H column. \(e\) A 20 mol % of the catalyst was employed. \(f\) A 5 mol % of the catalyst was employed.
to the result obtained with MacMillan’s catalyst 5, which was reported to give the trans-isomer stereoselectively with excellent enantioselectivity.4a Careful examination of the cis/trans ratio at different reaction times indicated that the cis-isomer is the kinetic product, while the trans-isomer is thermodynamically more stable. That is, the cis-isomer was obtained in good yield and excellent enantioselectivity after 4 h, but this yield decreased with time, with a concomitant increase in the trans-isomer. Both isomers are formed with excellent enantioselectivity (entry 2). As efficient isomerization can be realized by treatment of the isolated cis-isomer 9a with a catalytic amount of DBU in 10 min at 0 °C, the reaction was conducted in THF at room temperature.4b,4c The reaction was conducted at −20 °C.

In summary, the naphthylamide catalyst 7 derived from cysteine has been developed to act as an efficient organocatalyst of two different types of asymmetric intramolecular Michael reaction. In one, there is discrimination between two enantiotopic π-bonds, and a bicyclo[4.3.0]none is noneone is formed, and, in the other, between the enantiofaces of an α,β-ene giving cis-disubstituted cyclopentane skeletons. These compounds, containing three and two contiguous chiral centers, respectively, are formed in good yield with high diastereo- and excellent enantioselectivities. There is another noteworthy feature to this reaction: in the synthesis of the cyclopentane skeleton, the cis-isomer is synthesized diastereo- and enantioselectively, which is complementary to the intramolecular Michael reaction using Enders’ SAMP/RAMP-hydrazine methodology,4c and that using MacMillan’s catalyst,4b both of which afford the trans-isomer selectively.

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Supporting Information Available: Detailed experimental procedures, full characterization, copies of 1H, 13C NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References


(8) See Supporting Information for details.

(9) The free amine itself scarcely promoted the reaction.

(10) The reaction of 5 in THF under List’s conditions4d is also slow.


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