Copper ion-catalyzed regioselective introduction of active methylene groups into the γ-position of piperidine skeleton and its application to synthesis of (-)-cincholoiponic acid

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Abstracts: Copper ion-catalyzed regioselective introduction of active methylene groups into the γ-position of piperidine skeleton was exploited. In the case of using chiral ligand as an additive, this reaction proceeded with moderate enantioselectivities. This method was applied to synthesis of (-)-cincholoiponic acid from N-methoxycarbonylpiperidine.

Carbon-carbon bond forming reactions at the α-position of cyclic amines 1 through iminium ion intermediates A to afford α-alkylated cyclic amines 3 have attracted a lot of interest (Eq. (1)) since it provides one of the simplest routes for formation of 3 which are often found as important moiety of naturally occurring nitrogen heterocycles.1 We have already exploited electrochemical oxidation method through α-methoxylated piperidine 2 for the route.2

\[
\begin{align*}
\text{N} & \overset{Z}{\text{Z}} \overset{-2e}{\text{MeOH}} \quad \text{N} & \overset{Z}{\text{Z}} \overset{\text{OMe}}{\text{OMe}} \quad \left[ \overset{\text{N}}{\text{N}} \overset{Z}{\text{Z}} \right] \quad R' \quad \text{R} \\
1 & & 2 & \text{A} & 3
\end{align*}
\]

(1)

On the other hand, there have been only two methods for carbon-carbon bond forming reaction at the γ-position of 1, though γ-substituted piperidines are also worthwhile as synthetic intermediates for a variety of natural products and drug candidates.3 One is conjugate addition of some aryl groups to β,γ-didehydro-α-oxopiperidines,3e,g,i and the other is introduction of some nucleophiles to pyridinium salts.4,5,6 These methods however, are not applicable to piperidine derivatives possessing functionalized alkyl group at the γ-position, such as (-)-cincholoipionic acid (cis-1), (Fig. 1),7 which is a structural moiety in a variety of alkaloids, and any asymmetric alkylation has not been reported.8

This paper presents copper ion-catalyzed coupling reaction of α-methoxylated β,γ-didehydropiperidines 6 with active methylene compounds 7 to afford γ-substituted piperidines 9 without formation of undesired regioisomers 8 (Eq. (2))9,10 and its asymmetric application leading to formal synthesis of optically active cis-1 with

Figure 1

Key words: piperidine, nucleophilic substitution, copper, regioselective, asymmetric

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moderate enantioselectivity. The key starting compounds 6a,b (a11;R=H, b12;R=Et) are known to be prepared by electrochemical oxidation of N-methoxycarbonylpiperidine (4) through α-methoxylated piperidine 5.13

\[
\text{4} \xrightarrow{-2e} \text{MeOH} \quad \text{5} \quad \text{6a,b} \quad \text{8ap-br} \quad \text{9aq-bt}
\]

With 6a,b, we first tried the coupling reaction of 6a,b with dimethyl malonate (7p), methyl acetoacetate (7q), and 1,3-diketones 7r-t and found that the coupling reaction proceeded in the presence of Cu(OTf)2 (5mol%) in THF at room temperature for 12hrs to afford α-substituted piperidines 8ap-br and/or selectively γ-substituted piperidines 9aq-bt, the ratio being dependent on the structures of 6 and of nucleophiles 7. The results are shown in Table 1.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate 6a,b</th>
<th>active methylene compound</th>
<th>product yield (%)</th>
<th>ratio 8ap/9aq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a H</td>
<td>7p OMe OMe</td>
<td>8ap 68</td>
<td>9ap 0</td>
</tr>
<tr>
<td>2</td>
<td>6b Et</td>
<td>7p OMe OMe</td>
<td>8bp 70</td>
<td>9bp 11</td>
</tr>
<tr>
<td>3</td>
<td>6a</td>
<td>7q Me OMe</td>
<td>8aqb 41</td>
<td>9aqb 21</td>
</tr>
<tr>
<td>4</td>
<td>6b</td>
<td>7q Me OMe</td>
<td>8bq 0</td>
<td>9bq 85</td>
</tr>
<tr>
<td>5</td>
<td>6b</td>
<td>7r Me Me</td>
<td>8br 12</td>
<td>9br 37</td>
</tr>
<tr>
<td>6</td>
<td>6b</td>
<td>7s Me Ph</td>
<td>8bs 0</td>
<td>9bs 55</td>
</tr>
<tr>
<td>7</td>
<td>6b</td>
<td>7t Ph Ph</td>
<td>8bt 0</td>
<td>9bt 48</td>
</tr>
<tr>
<td>8</td>
<td>6b</td>
<td>7q Me Me</td>
<td>8bqb 22</td>
<td>9bqb 6</td>
</tr>
</tbody>
</table>

The observed regioselectivity (8a/9a) was noticeable. Dimethyl malonate (7p) as a nucleophile afforded α-substituted piperidines (8ap and 8bp) exclusively for 6a (entry 1) and mainly for 6b (entry 2), whereas the use of methyl acetoacetate (7q) decreased the ratio of 8a/9a for 6a (entry 3) and eventually resulted in formation of only 9bq for 6b (entry 4). Also a predominant formation of 9br-bt was observed in the reaction of 6b with 1,3-diketones 7r-t (entries 5-7), though the yields of the products were in general lower than those in cases using malonates and acetoacetates.14

In order to elucidate the mechanism for the high regioselectivity observed in the reaction of 6b and...
7q (entry 4), the reaction was carried out at 0°C to afford a mixture of 8bq and 9bq with a ratio of 77/23 in low yield (entry 8), whereas the treatment of a mixture of 8bq and 9bq (8bq/9bq=77/23) with Cu(OTf)₂ in THF at room temperature resulted in an exclusive formation of 9bq (Eq. (3)).

\[
\begin{align*}
8bq & + Cu(OTf)_2 \text{ (0.05equiv) in THF at rt (3)} \\
& \rightarrow 8bq : 9bq = 0 : 100
\end{align*}
\]

The selectivity can be explained in terms of the steric factor of both substrates and active methylene compounds as described later.

After finding the best conditions that γ-substituted piperidine 9bq was selectively formed, we then tried asymmetric reaction of 6b with 7q in the presence of Cu(OTf)₂ and chiral bisoxazoline ligand L. The result was interesting since a mixture of diastereomers 9bq* was generated in a ratio of 56/44, each of which had modest optical purity (43~44%ee) (Eq. (4)). However, asymmetric reaction was not observed in MeCN in place of THF as a solvent.

\[
\begin{align*}
6b & + 7q \text{ (1.5equiv in THF at rt (4))} \\
& \rightarrow 8bq : 9bq* = 88 : 44 (de=56 : 44, %ee=43 : 44) \\
& \quad \text{in THF} \\
& \rightarrow 8bq : 9bq* = 53 : 47 (de=55 : 45, %ee=0 : 0) \\
& \quad \text{in MeCN}
\end{align*}
\]

Further information to support the reaction mechanism was obtained when racemic α-substituted piperidine 8bq was treated with Cu(OTf)₂ in the presence of chiral ligand L in THF at room temperature. The product was 9bq* in a quantitative yield, and each of the diastereomers was optically active (Eq. (5)).

\[
\begin{align*}
8bq & \text{ (0.06equiv in THF at rt (5))} \\
& \rightarrow 9bq* = 100\% \text{ yield,} \\
& \quad \text{dr (%ee)=53 (0): 47 (0)}
\end{align*}
\]
These results strongly suggest that 8bq is a kinetically controlled product, while 9bq is a thermodynamically stable product, and the rearrangement of 8bq into 9bq• proceeds through an iminium ion Ab with an intermolecular mechanism (Scheme 1). The observed regioselectivity may be determined by the steric factor of both β-ethyl substituent of 6b and nucleophiles 7p-t, though the effect of the reactivity of nucleophiles on the regioselectivity is not ruled out.

![Scheme 1](image)

Finally, transformation of optically active 9bq• into cincholoiponic acid methyl ester HCl salt (cis-12)\textsuperscript{16} was achieved by the method described in Eq. (6), and the absolute configuration at the γ-position of cis-12, that is, the γ-position of 9bq•, was determined to be S by the comparison of the product cis-12 with the authentic sample.\textsuperscript{7a} It is known that the cis-12 is easily transformed into (-)-cincholoiponic acid (cis-1).

In summary, we present a facile method for selective introduction active methylene groups into the γ-position of piperidine skeleton and its application to the formal synthesis of (-)-cincholoiponic acid (cis-1).

Further studies on mechanistic aspects and the improvement of %ee are currently underway.

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**References and Notes**


9. Copper ion-catalyzed alkylation and phenylation, see: Shono, T.; Terauchi, J.; Ohki, Y.;


14. Table 1 shows only the yields of major products.

15. A typical experimental procedure: A solution of methyl acetoacetate (7q) (0.75 mmol), Cu(OTf)$_2$ (0.025 mmol) and chiral ligand L (0.03 mmol) in THF (1 mL) was stirred for 5 min at room temperature under a nitrogen atmosphere. Into the solution was added a solution of 6b (0.5 mmol) in THF (1 mL). After stirring for 12 hrs, the resulting mixture was poured into aqueous NaHCO$_3$ (5 mL). The organic portion was extracted with AcOEt (10 mL × 3) and dried over MgSO$_4$. The resulting solution was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/AcOEt = 5/1) to afford 9bq$^*$ (88% yield, diastereomer ratio = 56 (43%ee): 44 (44%ee)).

16. *cis-12* (recrystallization from MeOH-Acetone): [α]$^\text{D}_{29}$ -8.8 (c 2.5, MeOH) [lit.$^2$ [α]$^\text{D}_{29}$ -8.3 (c 1.0, MeOH)].