Kinetic resolution of vic-amino alcohols catalyzed by chiral Cu(II) complex

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Abstract—Kinetic resolution of N-benzyolated vic-amino alcohols was achieved by benzyolation in the presence of copper triflate and (R,R)-Ph-BOX as catalysts. The observed enantioselectivity was moderate to high. The method was applied to a kinetic resolution of racemic prolinol and piperidinemethanol derivatives as well as an asymmetric desymmetrization of 2-amino-1,3-diol derivatives.

Kinetic resolution has long continued to attract much interest in asymmetric synthesis because of its simple process for preparation of enantiomerically enriched compounds from an easily available racemic mixture.1,2 We recently explored an efficient method for kinetic resolution of 1,2-diols 1, which is based on a recognition of the 1,2-diol moiety with copper ion associated with some chiral ligand L* such as (R,R)-Ph-BOX to afford the activated 1,2-diol intermediates 2 followed by monobenzoylation (Eq 1).3-5 In continuing the study, we report herein kinetic resolution of vic-amino alcohols 4 affording optically active amino alcohols 5 (Eq 2).2d,j,6

Key words: kinetic resolution; vic-amino alcohol; monobenzoylation; chiral copper complex

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In advance of the kinetic resolution of 4, we first tried the benzoylation of N-protected amino alcohol 6a as a model compound to see whether it behaved in a similar way to 1,2-diols 1. The result showed that the reaction of 6a with BzCl afforded 7a in 96% yield, while 22% yield of 7a was observed in a reaction without copper triflate and the chiral ligand (Eq 3), suggesting that 6a might be recognized with copper ion/L* in a similar way to the kinetic resolution of 1.

Further data about the reactivity of 6a for the benzoylation were obtained in the competitive reactions between 6a with 6b-e (Eq 4, Table 1).

The results shown in Table 1 indicate that other protecting groups than the benzoyl group were entirely ineffective as N-protecting groups of vic-amino alcohols to be benzoylated.
Table 1. Competitive benzylation reaction between N-protected ethanol amines 6a-e<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>6b-e</th>
<th>Protecting Group</th>
<th>Products 7a-e</th>
<th>Ratio of 7a : 7b-e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6b</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;-t-Bu</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6c</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6d</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;Ph-Me</td>
<td>100 : 0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6e</td>
<td>COMe</td>
<td>100 : 0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The competitive reaction was carried out under the following conditions: 6a (0.5 mmol), 6b-e (0.5 mmol), BzCl (0.1 mmol), Cu(OTf)<sub>2</sub> and (R,R)-Ph-BOX (0.015 mmol), K<sub>2</sub>CO<sub>3</sub> (0.5 mmol), THF (2 mL), at rt for 3 h.

Furthermore, N-benzoylated aminoethanol 6a was subjected to competitive reactions with a variety of alcohols having a substituent at the β-position (Eq 5). The results are shown in Table 2, which shows that 6a was less reactive than 1,2-diol 8a but it was more reactive than benzoyloxyl-, ethoxyl-, or ethyl-substituted ethanols (8b-d).

On the basis of those results, we tried a kinetic resolution of dl-valinol derivatives 4ap-at by benzylation in which copper triflate and (R,R)-Ph-BOX were present. The results are shown in Table 3.
Table 3. Kinetic resolution of amino alcohols 4ap-at

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds 4ap-at</th>
<th>R</th>
<th>Products (S)-5ap-at</th>
<th>Recovered (R)-4ap-at</th>
<th>Selectivity (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4ap</td>
<td>H</td>
<td>5ap</td>
<td>4ap</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>4aq</td>
<td>p-Cl</td>
<td>5aq</td>
<td>4aq</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4ar</td>
<td>o-Cl</td>
<td>5ar</td>
<td>4ar</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>4as</td>
<td>p-OMe</td>
<td>5as</td>
<td>4as</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>4at</td>
<td>o-OMe</td>
<td>5at</td>
<td>4at</td>
<td>50</td>
</tr>
</tbody>
</table>

A moderate enantioselectivity (78% ee) was observed in a case of N-benzoylated valinol 4ap (Entry 1), but o-MeO-phenylcarbonylated valinol 4at gave the best result (Entry 5) among those examined (Entries 1-5). The s value was 50.

The other examples of kinetic resolution are shown in Eq 7.
Our attention was then focused on a kinetic resolution of \(N\)-alkylated \(N\)-benzoylethanolamine derivatives 10 because there have been known numerous naturally occurring compounds having an \(N\)-alkylethanolamine moiety.

So, we tried a competitive reaction between 6a and 6b to afford a mixture of 7a and 7b with a ratio of 50/50 (Eq 8), indicating that 6b had similar reactivity to 6a for the benzoylation, and suggesting an intermediary formation of intermediates 2' which corresponded to 2 derived from diols 1.

On the basis of this result, \(dl\)-prolinol (\(dl\)-11) and \(dl\)-piperidinemethanol (\(dl\)-13) were subjected (Eqs 9 and 10) to kinetic resolution under conditions similar to those for 4ap-4ft.\(^8\)
Also, 2-amino-1,3-diols 13 and 15 were asymmetrically desymmetrized by benzylation to afford optically active 14 and 16 in 97% yield with 95%ee and 88% yield with 94%ee, respectively (Eqs 11 and 12).9

The results shown in this paper are useful for preparation of optically active vic-amino alcohols, because our method is very simple and easy in operation in comparison with reported methods. The mechanistic details and an application of asymmetric desymmetrization are now under investigation.

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References and Notes


7. A kinetic resolution of dl-N-benzyl-α-piperidinemethanol under conditions similar to those for 4ap-4ft proceeded to afford the corresponding benzoate in 21% yield with 62% ee. This result supports an intermediary formation of intermediates 2'.

8. Typical procedure for kinetic resolution: Into a solution of Cu(OTf)2 (5.4 mg, 0.015 mmol) and (R,R)-Ph-Box ( 5.0 mg, 0.015 mmol ) in THF (2 mL) was added dl-12 (110 mg, 0.5 mmol), K2CO3 (69.1mg, 0.5 mmol), and benzoyl chloride (0.029 mL, 0.25 mmol). After being stirred for 3 h at rt, into the reaction mixture water (10 mL) was added. The organic portion was extracted with AcOEt (20mL x 3). The combined organic layer was dried over MgSO4 and the solvent was removed in vacuo. The residue was chromatographed on SiO2 (n-hexane: AcOEt=1:2) to afford (S)-13 (64.9 mg, 40% yield, 95% ee) and (R)-12 (53.0 mg, 48% yield, 79% ee).

Optical purities of product (S)-13 and recovered (R)-12 were determined by chiral HPLC: Daicel Chiralcel OD column (4.6 mmφ, 25 cm), n-hexane: isopropanol = 20:1, wavelength: 254 nm, flow rate: 1.0 mL/min. retention time for 13: 19.7 min (S)-(−)-13, 22.9 min (R)-(−)-13. retention time for 12: 18.1 min (S)-(−)-12, 20.2 min (R)-(−)-12.

9. The absolute stereoconfiguration of 14 and 16 has not yet been determined.

14: 1HNMR (300MHz, CDCl3) δ 1.54  (s, 3H), 3.79 (d, J=12.3Hz, 1H), 3.88 (d, J=12.3Hz, 1H), 4.42 (br s, 1H), 4.61 (d, J=11.7Hz, 1H), 4.69 (d, J=11.4Hz, 1H), 6.79 (br s, 1H), 7.40-7.64 (m, 6H), 7.77 (d, J=6.9Hz, 2H), 8.06 (d, J=7.2Hz, 2H).

HPLC: Daicel Chiralcel OD column (4.6 mmφ, 25 cm), n-hexane: isopropanol = 20:1, wavelength: 254 nm, flow rate: 1.0 mL/min. retention time: 31.7 min (−)-isomer, 36.7 min (+)-isomer). [α]26.5D -19.7 (c 2.0, CHCl3).

16: 1HNMR (300MHz, CDCl3) δ 1.75-2.02 (m, 3H), 2.18-2.28 (m, 2H), 3.40-3.60 (m, 2H), 3.95-4.02 (m, 2H), 4.81 (d, J=11.1Hz, 1H), 4.95 (d, J=11.4Hz, 1H), 5.63 (br t, J=5.7Hz, 1H), 7.28-7.52 (m, 7H), 7.56-7.63 (m, 1H), 8.07 (d, J=7.2Hz, 2H).

HPLC: Chiralpak AD column (4.6 mmφ, 25 cm), n-hexane: isopropanol = 5:1, wavelength: 254 nm, flow rate: 1.0 mL/min. retention time: 10.9 min (+)-isomer), 14.4 min (−)-isomer). [α]28.0D -50.4 (c 0.85, CHCl3).