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<td>Author(s)</td>
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Asymmetric desymmetrization of \textit{meso-vic}-diols by carbamoylation catalyzed with chiral Cu(II) complex

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Abstract—Asymmetric desymmetrization of \textit{meso-vic}-diols was achieved by carbamoylation in the presence of copper triflate and (S,S)-Ph-BOX as a catalyst without any use of bases. The method was successfully applied to asymmetric desymmetrization of five- to eight-membered cyclic \textit{meso-vic}-diols in high enantioselectivity with up to 93% ee.

We recently exploited an efficient method for kinetic resolution and asymmetric desymmetrization of vic-diols 1, which is based on recognition of the vic-diol moiety by a copper ion associated with chiral ligands such as (S,S)-Ph-BOX (A)\(^1\) to afford the activated vic-diol intermediates 2 followed by benzylation under basic conditions (Eq. 1).\(^2\) Basic conditions were essential in the benzylation to remove the generated hydrogen chloride. However, the products sometimes suffered from acyl transfer reaction\(^3\) under the basic conditions, decreasing the enantioselectivity of the products 3. So, it is worthwhile to find conditions in which kinetic resolution of \textit{dl}-1\(^4\) or asymmetric desymmetrization of \textit{meso}-1\(^5\) can be achieved under non-basic conditions. We report herein an asymmetric desymmetrization of \textit{meso}-1 by carbamoylation with isocyanates (R’NCO) under non-basic conditions to afford optically active \textit{meso-vic}-diol derivatives 4 (Eq. 2).

\[\text{Cu}^{2+} \quad \text{A} \quad \text{Cu}^{2+}\]

Key words: asymmetric desymmetrization; \textit{meso-vic}-diol; carbamoylation; chiral copper complex

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First of all, we tried the carbamoylation of *meso*-1,2-cyclohexanediol (1a) as a model compound in the reaction with phenylisocyanate without using any bases (Eq 3).  

The results are summarized in Table 1, which shows a dependence of the yield and % ee of the product 4a on the used metal ions, chiral ligands A-D, and solvents. That is, in THF as a solvent, the product 4a was obtained in 88-92% yield in the presence of copper triflate (Cu(OTf)₂) (entries 2 and 4) and with a moderately high % ee (76% ee) when both Cu(OTf)₂ and A were present (entry 4), while yield of 4a was low (2-11%) in the absence of Cu(OTf)₂ (entries 1 and 3). On the other hand, no enantioselectivity of 4a was observed in a case using Sn(OTf)₂ even in the presence of A, though yield of 4a was high (entry 11). The zinc ion was not also so effective (entry 10), and the other ligands B-D than A were ineffective even in the presence of Cu(OTf)₂ (entries 12-14). AcOEt and MeCN were usable instead of THF (entries 5 and 6), while CH₂Cl₂ and toluene were ineffective (entries 7 and 8).

Table 1. Asymmetric carbamoylation of *meso*-1,2-cyclohexanediol (1a)

<table>
<thead>
<tr>
<th>entry</th>
<th>metal ion catalyst</th>
<th>ligand</th>
<th>solvent</th>
<th>Product 4a yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>THF</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂</td>
<td>-</td>
<td>THF</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>A</td>
<td>THF</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂</td>
<td>A</td>
<td>THF</td>
<td>92</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)₂</td>
<td>A</td>
<td>AcOEt</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)₂</td>
<td>A</td>
<td>MeCN</td>
<td>87</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)₂</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>88</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂</td>
<td>A</td>
<td>toluene</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>CuCl₂</td>
<td>A</td>
<td>THF</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>Zn(OTf)₂</td>
<td>A</td>
<td>THF</td>
<td>47</td>
<td>24</td>
</tr>
<tr>
<td>11</td>
<td>Sn(OTf)₂</td>
<td>A</td>
<td>THF</td>
<td>91</td>
<td>racemic</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OTf)₂</td>
<td>B</td>
<td>THF</td>
<td>94</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OTf)₂</td>
<td>C</td>
<td>THF</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Cu(OTf)₂</td>
<td>D</td>
<td>THF</td>
<td>56</td>
<td>racemic</td>
</tr>
</tbody>
</table>

*1a 0.5 mmol, metal ion catalyst (0.05 mmol), ligand (0.05 mmol), PhNCO (0.5 mmol) in a solvent (2 mL) at rt for 0.5 h. b Determined by HPLC.*
A variety of isocyanates (R’NCO) besides phenylisocyanate were usable for carbamoylation of 1a under the reaction conditions similar to entry 4 in Table 1 (Eq. 4, Table 2).

\[
\begin{align*}
\text{OH} & \quad \text{R’NCO (1.0 equiv)} \\
\text{Cu(OTf)}_2 (0.1 \text{ equiv}) & \quad \text{A (0.1 equiv)} \\
\text{THF, rt, 0.5 h} & \quad \text{4a-9a}
\end{align*}
\]

### Table 2. Carbamoylation of 1a by various isocyanates\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>R’</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4a</td>
<td>92</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>p-ClPh</td>
<td>5a</td>
<td>93</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>p-MeOPh</td>
<td>6a</td>
<td>85</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>7a</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>1-Adamantyl</td>
<td>8a</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>1-Naphthyl</td>
<td>9a</td>
<td>77</td>
<td>77</td>
</tr>
</tbody>
</table>

\(^a\) 1a (0.5 mmol), Cu(OTf)_2 (0.05 mmol), A (0.05 mmol), R’NCO (0.5 mmol) in THF (2 mL) at rt for 0.5 h. \(^b\) Determined by HPLC.

With such almost satisfactory results for carbamoylation of 1a in hand, we tried carbamoylation of \(meso\)-1,2-cyclopentanediol (1b) under the reaction conditions and found that the reaction afforded 4b with 72% ee, while 1b was not asymmetrically desymmetrized by benzoylation with Cu(OTf)_2 and A in the presence of a base (Eq. 5).\(^8,9\)
Similarly, oxygen or nitrogen atom-containing five-membered diols 1c,d were asymmetrically desymmetrized by carbamoylation to afford 4c,d, whereas racemic products 3c,d were obtained by benzylation (Eq. 6).

Also, our method was applicable to an acyclic 1,2-diol 1e (Eq. 7), and 1,3-diol 10p (Eq. 8).
The reason why 1b-d could not be desymmetrized by benzoylation may be rationalized in terms of intramolecular acyl transfer of optically active 3b-d since optically active 3a\(^\text{12}\) lost some extent of its optical activity when 3a was subjected to the reaction conditions for a long time (12 h) (Eq. 9).\(^\text{13}\)

\[
\begin{align*}
3a & \quad \text{OH} \\
& \quad \text{in the presence of} \\
& \quad \text{K}_2\text{CO}_3 (1.5 \text{ equiv}), \text{Cu(OTf)}_2 (0.1 \text{ equiv}), \text{A} (0.1 \text{ equiv}), \text{K}_2\text{CO}_3 (1.5 \text{ equiv}) \\
& \quad \text{CH}_2\text{Cl}_2, \text{rt}, 12 \text{ h} \\
& \quad \text{quant. yield, 82\% ee} \quad \text{quant. yield, 95\% ee} \quad \text{quant. yield, 32\% ee}
\end{align*}
\]

In order to improve \% ee in carbamoylation of meso-1, we surveyed the effect of temperature on carbamoylation of five- to eight-membered meso-cycloalkanediols 1a,b,f,g with phenylisocyanate (Eq. 10). The results are shown in Table 3, which indicates that the \% ee’s were improved with up to 93\% ee at -40 °C in comparison with those obtained at room temperature.
Table 3. Asymmetric monocarbamoylation of \textit{meso}-1,2-diol 1a,b,f,g\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>n</th>
<th>product</th>
<th>-40 °C yield (%)</th>
<th>ee (%)</th>
<th>rt yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>1</td>
<td>4b</td>
<td>82</td>
<td>86</td>
<td>91</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2</td>
<td>4a</td>
<td>69</td>
<td>86</td>
<td>92</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>1f</td>
<td>3</td>
<td>4f</td>
<td>83</td>
<td>91</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>1g</td>
<td>4</td>
<td>4g</td>
<td>72</td>
<td>93</td>
<td>96</td>
<td>86</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1 (0.5 mmol), Cu(OTf)$_2$ (0.05 mmol), A (0.05 mmol), PhNCO (0.5 mmol) in THF (2 mL) for 0.5 h. \textsuperscript{b} Determined by HPLC.

The absolute stereoconfiguration of 4a was determined to be (1R,2S) by transformation of (+)-4a (74% ee) to (1R,2S)-(+)\textsuperscript{-}13\textsuperscript{14} (Eq. 11) which was the enantiomer of (1S,2R)-(--)\textsuperscript{-}3a\textsuperscript{15} (95% ee) (Eq. 12).

\begin{equation}
\begin{array}{c}
\text{(+)-4a} \\
74\% \text{ ee}
\end{array}
\xrightarrow{\text{BzCl (1.5 equiv)}}
\begin{array}{c}
\text{pyridine} \\
rt, 24 h
\end{array}
\begin{array}{c}
\text{(+)-13} \\
60\% \text{ yield, 71\% ee} \\
[\alpha]^{28}_D 38.6 \text{ (c 1.0, CHCl}_3\text{)}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{(-)-3a} \\
95\% \text{ ee}
\end{array}
\xrightarrow{\text{PhNCO (1.5 equiv)}}
\begin{array}{c}
\text{Me}_2\text{SnCl}_2 (0.1 \text{ equiv}) \\
THF, rt, 24 h
\end{array}
\begin{array}{c}
\text{(-)-13} \\
46\% \text{ yield, 93\% ee} \\
[\alpha]^{28}_D -48.5 \text{ (c 1.0, CHCl}_3\text{)}
\end{array}
\end{equation}

The absolute stereoconfiguration of (1R,2S)-4b was confirmed by its conversion to 14 (Eq. 13), which was found to possess a configuration of (1R,2S) on X-ray analysis.\textsuperscript{16,17}

\begin{equation}
\begin{array}{c}
\text{4b} \\
77\% \text{ ee}
\end{array}
\xrightarrow{\text{pyridine} \\
rt, 12 h}
\begin{array}{c}
\text{p-BrPhCOCl (3.0 equiv)}
\end{array}
\begin{array}{c}
\text{14} \\
66\% \text{ yield, 100\% ee} \text{ (after recrystallization)}
\end{array}
\end{equation}
The results shown in this paper are useful for a preparation of optically active meso-vic-diol derivatives 4, because our method is very simple, easily operable,18 and vic-diol selective.19 The mechanistic study and a kinetic resolution of dl-vic-diols in our carbamoylation are now under investigation.

Acknowledgements
Y. M. thanks the Japan Society for the Promotion of Science for Scientific Research (B) (17350051) for financial support. We are grateful to BRUKER AXS K. K. for X-ray structure determination of compound 14.

References and Notes
6. A typical procedure for asymmetric desymmetrization: Under an aerobic atmosphere, a solution of Cu(OTf)2 (18.1 mg, 0.05 mmol) and (S,S)-Ph-Box (A) (16.7 mg, 0.05 mmol) in THF (2 mL) was stirred for 10 min. Into the solution were added meso-1a (58.1 mg, 0.5 mmol) and phenylisocyanate (0.054 mL, 0.5 mmol, used as purchased). After being stirred for 0.5 h at rt, into the reaction mixture water
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=5:1) to afford (+)-4a (92% yield, 76% ee) as a white solid. mp 72-74°C; [α]²²D 4.9 (c 0.5, CHCl₃). ¹H NMR (300MHz, CDCl₃) δ 1.38-1.50 (m, 2H), 1.60-2.00 (m, 6H), 2.24 (br s, 1H), 3.96 (d, J=6.9Hz, 1H), 4.94 (d, J=8.1Hz, 1H), 6.84 (br s, 1H), 7.07 (t, J=7.2Hz, 1H), 7.28-7.45 (m, 4H). ¹³C NMR (75MHz, CDCl₃) δ 20.9, 21.7, 27.1, 30.1, 69.2, 74.7, 118.6, 123.3, 128.3, 137.7, 153.4. The optical purity of 4a was determined by chiral HPLC: Daicel Chiralcel OJ column (4.6 mmφ, 25 cm), n-hexane:isopropanol = 10:1, wavelength: 210 nm, flow rate: 1.0 mL/min. retention time: 7.7 min ((1S,2R)-(−)-4a), 12.0 min ((1R,2S)+(−)-4a).


8. Benzylation of 1b in the absence of a base hardly proceeded for 3 h.

9. Potassium carbonate (K₂CO₃) was usable as a base instead of N,N-diisopropylethylamine (DIPEA), which was used in our asymmetric monobenzylation of vic-diols. Monobenzylation of vic-diols using K₂CO₃ will be reported elsewhere by us.


11. The absolute stereoconfiguration of (-)-11p has not yet been determined. HPLC: Daicel Chiralpak AD column (4.6 mmφ, 25 cm), n-hexane: isopropanol = 10:1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 16.4 min ((−)-isomer), 18.2 min ((+)-isomer). [α]²³D -6.7 (c 0.5, CHCl₃).

12. Since optically active 3b was not easily obtainable, intramolecular acyl transfer of optically active 3a (95% ee), which was prepared by desymmetric monobenzylation of 1a described in ref. 2a and successive recrystallization, was examined.

13. Standing optically active carbamates 4a,e under the reaction conditions for 12 h did not cause any decrease of their optical purities.

14. Chiral HPLC condition: Daicel Chiralpak AD column (4.6 mmφ, 25 cm), n-hexane:
isopropanol = 5:1, wavelength; 254 nm, flow rate; 1.0 mL/min, retention time; 9.4 min \((1R,2S)-(+)-13\), 12.9 min \((1S,2R)-(-)-13\).


16. Compound \((1R,2S)-(+)-14\): mp 132-134 °C, \([\alpha]_{27}^D\) 59.4 \((c\ 1.0, \text{CHCl}_3)\), Chiral HPLC condition: Daicel Chiralcel OJ column \((4.6 \text{ mm}\phi, \ 25 \text{ cm})\), \(n\)-hexane:isopropanol = 10:1, wavelength; 254 nm, flow rate; 1.0 mL/min, retention time; 28.9 min \((1R,2S)-(+)-14\), 40.2 min \((1S,2R)-(-)-14\).

Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 619049. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

17. Absolute stereoconfiguration of \(4c-g\) shown in Eqs. 6, 7 and 10 was deduced on the basis of that of \(4a,b\).


19. Carbamoylation of \(1a\) proceeded even in the presence of cyclohexanol (1 equiv) to afford \(4a\) in a similar yield (94%) and optical purity (75% ee).