Copper complex catalyzed asymmetric monosulfonylation of meso-vic-diols

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Abstract- Asymmetric desymmetrization of meso-vic-diols was performed by tosylation in the presence of copper(II) triflate and (R,R)-Ph-BOX as a catalyst. The method was successfully applied to asymmetric desymmetrization of cyclic and acyclic meso-vic-diols in high enantioselectivity with up to >99% ee.

Nonenzymatic asymmetric desymmetrization of meso-vic-diols is a practically useful methodology for preparation of optically active compounds.1 We have 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(II) ion associated with a chiral ligand (R,R)-Ph-BOX2 to afford the activated vic-diol intermediates 2 followed by benzoylation under basic conditions 4 (Eq 1).3

\[
\begin{align*}
\text{R-OH} + \text{Cu}^{2+} + \text{L}^* & \rightarrow \text{R-O-Cu}^{2+} \cdot \text{L}^* \\
\text{R} & \text{H} \quad \text{R} & \text{H} \\
\text{H} & \text{R} & \text{H} \\
\text{O} & \text{Cu}^{2+} \cdot \text{L}^* & \text{Cu}^{2+} \cdot \text{L}^* \\
\text{R} & \text{H} & \text{R} & \text{H} \\
\text{O} & \text{Bz} & \text{Bz} \\
\text{R} & \text{H} & \text{R} & \text{H} \\
\text{O} & \text{Ph} & \text{Ph} \\
\text{L}^* & \text{(R,R)-Ph-BOX} & \\
\end{align*}
\]

Basic conditions were essential in the benzyolation to remove the generated hydrogen chloride. However, the product sometimes suffered from acyl transfer reaction4 under this conditions, decreasing the enantioselectivity of product 3. To solve this problem, we recently reported an asymmetric desymmetrization of meso-1 by carbamoylation with phenylisocyanate (PhNCO) under non-basic condition to afford optically active vic-diol derivatives (Eq 2).5

\[
\begin{align*}
\text{R-OH} + \text{PhNCO} & \rightarrow \text{R-O-CO-NPh} \\
\text{Cu(O Tf)}_2, (\text{R,R})\text{-Ph-BOX} & \text{without any bases} \\
\text{R} & \text{H} \\
\text{R} & \text{H} \\
\text{H} & \text{R} & \text{H} \\
\text{O} & \text{C} & \text{NPh} \\
\text{R} & \text{H} & \text{R} & \text{H} \\
\text{O} & \text{Ph} \\
\text{4} & 64 - 93\% \text{ ee} \\
\end{align*}
\]

However, in some cases, the enantioselectivity of monocarbamoylated products did not meet our expectations.5 We report herein an asymmetric desymmetrization of meso-vic-diols 1 by monosulfonylation6 to afford optically active vic-diol derivatives with high yields and excellent enantioselectivities.

Key words: asymmetric desymmetrization; meso-vic-diol; sulfonylation, copper complex

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We began by trying the asymmetric tosylation of meso-1,2-cyclohexanediol 1a as a model compound in the reaction with \(p\)-toluenesulfonyl chloride 5p, in the presence of copper (II) triflate and \((R,R)\)-Ph-BOX as a catalyst under different solvents and bases (Eq 3). The results are summarized in Table 1, which shows a dependence of the yield and % ee of the product 6ap on the used bases and solvents. The use of CH\(_2\)Cl\(_2\) in combination with K\(_2\)CO\(_3\) gave both high yield (94%) and high enantioselectivity (97% ee) (entry 1). Although AcOEt and \(i\)-PrOH gave high enantioselectivities, their yields were moderate compared to that of CH\(_2\)Cl\(_2\) (entries 2 and 3) THF and MeCN gave moderate ees with low yields (entries 4 and 5). On the other hand, screening of bases shows that NaHCO\(_3\) is as good a base for this reaction as K\(_2\)CO\(_3\) (entry 8). Other bases fall short either in terms of yield or enantioselectivity (entries 6, 7, 9-11).

![Equation 3](image)

Table 1. Asymmetric tosylation of meso-1,2-cyclohexanediol (1a)\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Product 6ap</th>
<th>Yield (%)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl(_2)</td>
<td>K(_2)CO(_3)</td>
<td>6ap</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>AcOEt</td>
<td>K(_2)CO(_3)</td>
<td>6ap</td>
<td>58</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>(i)-PrOH</td>
<td>K(_2)CO(_3)</td>
<td>6ap</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>K(_2)CO(_3)</td>
<td>6ap</td>
<td>25</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>K(_2)CO(_3)</td>
<td>6ap</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)Cl(_2)</td>
<td>Li(_2)CO(_3)</td>
<td>6ap</td>
<td>18</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)Cl(_2)</td>
<td>Na(_2)CO(_3)</td>
<td>6ap</td>
<td>68</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>CH(_2)Cl(_2)</td>
<td>NaHCO(_3)</td>
<td>6ap</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>CH(_2)Cl(_2)</td>
<td>Cs(_2)CO(_3)</td>
<td>6ap</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>CH(_2)Cl(_2)</td>
<td>DIPEA</td>
<td>6ap</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>11</td>
<td>CH(_2)Cl(_2)</td>
<td>Et(_3)N</td>
<td>6ap</td>
<td>39</td>
<td>63</td>
</tr>
</tbody>
</table>

\(^{a}\) 1a (0.5 mmol), Cu(OTf)\(_2\) (0.05 mmol), \((R,R)\)-Ph-BOX (0.05 mmol), \(p\)-TsCl 5p (0.6 mmol), base (0.75 mmol) in a solvent (2.0 mL) at rt for 12 h.

\(^{b}\) Determined by HPLC.

In addition to tosyl chloride, a variety of sulfonyl chlorides 5q-t (entries 1-4) except for mesyl chloride 5u (entry 5) were usable for asymmetric sulfonylation of 1a under the same reaction condition as entry 1 in Table 1 (Eq 4). The results are summarized in Table 2.

![Equation 4](image)
Table 2. Sulfonylation of 1a with various sulfonyl chlorides 5q-u<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;′&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5q : Ph</td>
<td>6aq</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>5r : p-NO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>6ar</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>5s : p-ClPh</td>
<td>6as</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>5t : p-OMEPh</td>
<td>6at</td>
<td>61</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>5u : Me</td>
<td>6au</td>
<td>93</td>
<td>77</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1a (0.5 mmol), Cu(OTf)<sub>2</sub> (0.05 mmol), (R,R)-Ph-BOX (0.05 mmol), sulfonyl chloride 5q-u (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at rt for 12 h.

<sup>b</sup> Determined by HPLC.

Then, in order to confirm generality and superiority of tosylation to benzoylation or phenylcarbamoylation, we investigated the asymmetric tosylation, benzoylation, and phenylcarbamoylation of various meso-vic-diols 1b-l (Eq 5).<sup>9</sup> The results are summarized in Table 3. Although meso-1,2-cyclopentanediols (1b) was transformed into the benzoylated product 3b in racemic form and the phenylcarbamoylated product 4b in moderate enantiomeric excess (72% ee), we succeeded in obtaining the tosylated product 6bp in 91% yield and 95% ee (entry 1). Various meso-cycloalkane- and meso-cycloalkene-diols 1c-g other than 1b were asymmetrically tosylated to afford monotosylated products 6cp-6gp in better yield and higher enantioselectivity than that of monobenzylated products 3c-g and monocarbamoylated products 4c-g (entries 2-6). Important to note is the asymmetric tosylation of nitrogen, oxygen, and sulfur atom-containing five membered diols 1h-j to obtain 6bp,hp-jp were much more effective than that of benzoylation and carbamoylation, respectively (entries 7-9). In the case of acyclic 1,2-diols 1k and 1l, asymmetric tosylation afforded excellent results similar to those of benzoylation but which were better than carbamoylation results (entries 10 and 11).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Tosylated product</th>
<th>Benzoylated product</th>
<th>Carbamoylated product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yield (%) ee (%)</td>
<td>Yield (%) ee (%)</td>
<td>Yield (%) ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>1b</td>
<td>6bp 91 95</td>
<td>3b 47 3</td>
<td>4b 91 72</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>6cp 81 99</td>
<td>3c 88 58</td>
<td>4c 83 83</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>6dp 96 98</td>
<td>3d 85 65</td>
<td>4d 96 86</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>6ep &gt;99 97</td>
<td>3e 68 93</td>
<td>4e 96 59</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>6fp &gt;99 99</td>
<td>3f 89 96</td>
<td>4f 88 67</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>6gp 86 98</td>
<td>3g 92 80</td>
<td>4g 86 50</td>
</tr>
<tr>
<td>7</td>
<td>1h</td>
<td>6hp 99 94</td>
<td>3h 82 racemic</td>
<td>4h 91 72</td>
</tr>
<tr>
<td>8</td>
<td>1i</td>
<td>6ip 80 95</td>
<td>3i 81 racemic</td>
<td>4i 99 64</td>
</tr>
<tr>
<td>9</td>
<td>1j</td>
<td>6jp 93 94</td>
<td>3j 63 8</td>
<td>4j 90 52</td>
</tr>
<tr>
<td>10</td>
<td>1k</td>
<td>6kp 88 &gt;99</td>
<td>3k 78 97</td>
<td>4k 94 70</td>
</tr>
<tr>
<td>11</td>
<td>1l</td>
<td>6lp 71 93</td>
<td>3l 36 96</td>
<td>4l 91 82</td>
</tr>
</tbody>
</table>

a 1b-1 (0.5 mmol), Cu(OTf)$_2$ (0.05 mmol), (R,R)-Ph-BOX (0.05 mmol), p-TsCl 5p (0.6 mmol), K$_2$CO$_3$ (0.75 mmol) in CH$_2$Cl$_2$ (2.0 mL) at rt for 12 h.
b 1b-1 (0.5 mmol), Cu(OTf)$_2$ (0.05 mmol), (R,R)-Ph-BOX (0.05 mmol), BzCl (0.5 mmol), K$_2$CO$_3$ (0.75 mmol) in CH$_2$Cl$_2$ (2.0 mL) at rt for 3 h.
c 1b-1 (0.5 mmol), Cu(OTf)$_2$ (0.05 mmol), (R,R)-Ph-BOX (0.05 mmol), PhNCO (0.5 mmol), in THF (2.0 mL) at rt for 0.5 h.
d Determined by HPLC.
In some cases, the reason why the tosylated products were obtained with higher enantioselectivity than the benzoylated products may be explained as follows. In the case of benzoylation, intramolecular acyl transfer of optically active 3a occurred for it to lose some extent of its optical activity when 3a was subjected to the basic conditions for a long time (Eq 6). On the other hand, acyl transfer of the monotosylated product 6ap did not occur under the basic conditions, so 6ap was obtained with high optical purity (Eq 7).

\[
\text{CH}_2\text{Cl}_2, \text{rt, 12 h}
\]

\[
\begin{array}{ccc}
\text{in the presence of} & \text{quant. yield, 82% ee} & \text{quant. yield, 95% ee} \\
K_2\text{CO}_3 (1.5 \text{ equiv}) & \text{quant. yield, 32% ee} & \\
\text{Cu(OTf)}_2 (0.1 \text{ equiv}), (R,R)-\text{Ph-BOX} (0.1 \text{ equiv}) & \text{Cu(OTf)}_2 (0.1 \text{ equiv}), (R,R)-\text{Ph-BOX} (0.1 \text{ equiv}), K_2\text{CO}_3 (1.5 \text{ equiv}) & \\
\end{array}
\]

The absolute stereoconfiguration of 6ap was determined to be (1S,2R) by transformation of 6ap to (1S,2R)-(--)\text{-}7\text{\textsuperscript{10}} (Eq 8) which was the same stereoconfiguration of (1S,2R)-(--)\text{-}7 derived from reported 8 (Eq 9).\text{\textsuperscript{11}}

\[
\text{OH}
\]

\[
\text{CH}_2\text{Cl}_2, \text{rt, 12 h}
\]

\[
\begin{array}{ccc}
\text{in the presence of} & \text{quant. yield, 97% ee} & \text{quant. yield, 97% ee} \\
K_2\text{CO}_3 (1.5 \text{ equiv}) & \text{quant. yield, 97% ee} & \\
\text{Cu(OTf)}_2 (0.1 \text{ equiv}), (R,R)-\text{Ph-BOX} (0.1 \text{ equiv}) & \text{Cu(OTf)}_2 (0.1 \text{ equiv}), (R,R)-\text{Ph-BOX} (0.1 \text{ equiv}), K_2\text{CO}_3 (1.5 \text{ equiv}) & \\
\end{array}
\]

It is convenient for chemical transformations of compound 7 into optically active compounds 9\text{--}11 that toslyoxy substituent of compound 7 is a good leaving group for S\textsubscript{N}2 reaction and E2 reaction. At first, 7 was treated with NaN\textsubscript{3} to obtain the azide compound 9 with complete stereo inversion, followed by reduction and benzoylation to afford the optically active vic-amino alcohol 10 (Eq 10).\text{\textsuperscript{12,14}} Also 7 was treated with DBU to obtain the optically active \alpha,\beta-unsaturated alcohol derivative 11 in good yield without any loss of the optical purity of 7 (Eq 11).\text{\textsuperscript{15}}
The results shown in this communication are practical method for a preparation of optically active monotosylated derivatives from meso-vic-diols. Asymmetric monotosylation method has generality for various meso-vic-diols and is superior to monobenzoylation or monocarbamoylation method. The mechanistic study of this monotosylation and its application to a kinetic resolution of dl-vic-diols are now under investigation.

Acknowledgements
This study was supported by a Grant-in-Aid for Scientific Research (B) (No. 17350051) from Japan Society for the Promotion of Science.

This paper is dedicated to the heartfelt memory of the late Professor Yoshihiro Matsumura of Nagasaki University.

References and notes


A typical procedure for asymmetric monotosylation: Under an aerobic atmosphere, a solution of 
\( \text{Cu(OTf)}_2 \) (18.1 mg, 0.05 mmol) and \((R,R)-\text{Ph-BOX}\) (16.7 mg, 0.05 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2 mL) was 
stirred for 10 min. Into the solution were added \( \text{meso-1a} \) (0.5 mmol), \( \text{K}_2\text{CO}_3 \) (103.7 mg, 0.75 mmol) and \( \text{p-TsCl} \) (114.4 mg, 0.6 mmol). After being stirred for 12 h at rt, the solution was poured in 
water and extracted with \( \text{AcOEt} \) (20 mL \( \times \) 3). The combined organic layer was dried over \( \text{MgSO}_4 \) 
and the solvent removed under reduced pressure. The residue was purified by silica gel column 
chromatography (\( n\)-hexane : \( \text{AcOEt} \) = 3 : 1) to afford \((1\text{S},2\text{R})-\text{6ap}\) (94% yield, 97% ee) as a colorless 
oil. \( \alpha \)\(^{19}\)D −8.1 (c 1.0, \( \text{CHCl}_3 \)). \( \text{IR (neat)} \) 3530, 2942, 1599, 1356, 1175 cm\(^{-1}\). \( \text{1H NMR (300 MHz, \text{CDCl}_3} \) \( \delta \) 7.82 (d, \( J \) = 8.7 Hz, 2H), 7.35 (d, \( J \) = 7.8 Hz, 2H), 4.68-4.58 (m, 1H), 3.88-3.78 (m, 1H), 
2.45 (s, 3H), 2.10-1.20 (m, 9H). \( \text{13C NMR (75 MHz, \text{CDCl}_3} \) \( \delta \) 144.6, 134.0, 129.7, 127.5, 83.0, 68.8, 30.1, 27.5, 21.5(2C), 20.6. \( \text{MS [LR-FAB(+)]} \): \( m/z \) 271 \( [\text{M+H}]^+ \). 

The optical purity of \( \text{6ap} \) was determined by chiral HPLC: Daicel Chiralcel OJ-H column (4.6 mm \( \phi \), 250 mm), 
\( n\)-hexane : isopropanol = 10 : 1, wavelength: 220 nm, flow rate : 1.0 ml/min, retention time: 15.2 min ((1\text{R},2\text{S})-(+)-\text{6ap}), 
16.9 min ((1\text{S},2\text{R})-(−)-\text{6ap}).

8. The use of \( \text{CuCl}_2 \) instead of \( \text{Cu(OTf)}_2 \) reduced the yield and % ee of the product \( \text{6ap} \) (69% yield, 
88% ee, respectively).

9. Monotosylation, monobenzoylation, and monophenylcarbamoylation of \( \text{meso-vic-diols} \) in the 
presence of \((R,R)-\text{Ph-BOX}\) occurred at the same position. The absolute stereoconfiguration of 
\( \text{6bp-6lp} \) shown in Eq 5 and Table 3 was deduced on the basis of that of \( \text{6ap} \).

10. Chiral HPLC condition: Daicel Chiralcel OJ-H column (4.6 mm \( \phi \), 250 mm), \( n\)-hexane : isopropanol 
= 5 : 1, wavelength: 220 nm, flow rate: 1.0 ml/min, retention time: 12.3 min ((1\text{S},2\text{R})-(−)-7), 19.5 min ((1\text{R},2\text{S})-(+)-7).


12. Compound \((1\text{R},2\text{R})-(−)-10\): mp 149–151 °C. \( [\alpha]_{D}^{21} \) −89.2 (c 1.0, \( \text{CHCl}_3 \)) [lit.\(^{13}\) \((1\text{S},2\text{S})-(+)-10\); \( [\alpha]_{D}^{12} \) +60.5 (c 1.0, \( \text{CHCl}_3 \)). HPLC chiralcel OD column (4.6 mmφ, 250 mm), \( n\)-hexane : isopropanol = 20 : 1, 
wavelength: 220 nm, flow rate: 1.0 ml/min, retention time: 11.1 min ((1\text{S},2\text{R})-(+)-10), 14.8 min 
((1\text{R},2\text{S})-(−)-10).


14. Compounds \( \text{9, 10} \) and/or their enantiomers might be good precursors for antiarrhythmic agents: 

15. The absolute stereoconfiguration was determined by comparing with specific rotation of authentic 
sample. See, ref. 16. Compound (\text{R})-\text{11}: \([\alpha]_{D}^{21} +224.9 \) (c 1.0, \( \text{CHCl}_3 \)). [lit.\(^{16}\) (S)-\text{11} (86% ee); \( [\alpha]_{D}^{25} \) −157.0 (c 0.45, \( \text{CHCl}_3 \)).

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Graduate School of Biomedical Sciences, Nagasaki University,1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

\[
\begin{align*}
\text{R-OH} & \xrightarrow{\text{TsCl (1.2 equiv)}} \text{R-OTs} \\
\text{Cu(OTf)}_2 (0.1 \text{ equiv}) & \quad \text{(R,R)-Ph-BOX (0.1 equiv)} \\
\text{K}_2\text{CO}_3 (1.5 \text{ equiv}) & \quad \text{CH}_2\text{Cl}_2, \text{ rt, 12 h}
\end{align*}
\]

up to >99% ee