Asymmetric tosylation of racemic 2-hydroxyalkanamides with chiral copper catalyst

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Dedicated to the memory of Professor Yoshihiro Matsumura

Abstract- Kinetic resolution of 2-hydroxyalkanamides was performed by tosylation in the presence of copper(II) triflate and (R,R)-Ph-BOX as a catalyst. This method was successfully applied to a variety of 2-hydroxyalkanamides in high enantioselectivity with up to 92% ee, and then tosylated product was easily transformed into optically active \( \alpha \)-amino acid derivatives.

Optically active 2-hydroxyalkanoic acid derivatives are important precursors for biologically active compounds.\(^1\) In particular, optically active 2-sulfonyloxyalkanoic acid derivatives are important precursors of \( \alpha \)-amino acids.\(^2\) A multitude of enzymatic kinetic resolution methods has been developed for preparation of optically pure 2-hydroxyalkanoic acid derivatives.\(^3\) To the best of our knowledge, for non-enzymatic methods has been reported only one by Reiser and co-workers in 2005.\(^4\) We recently reported an efficient method for kinetic resolution of 1,2-diols and \( \text{vic} \)-amino alcohols with copper(II) ion associated with chiral ligand (R,R)-Ph-BOX\(^5\) by benzoylation to obtain optically active alcohols with excellent enantioselectivity.\(^6\) In this communication, we apply our methodology to kinetic resolution of 2-hydroxyalkanamides 1 to afford optically active 2-tosyloxyalkanamides 3 with high yields and enantioselectivities, which is based on molecular recognition by Cu(II)–(R,R)-Ph-BOX complex to form the activated intermediates 2 followed by tosylation (Eq. 1).\(^7\)

Key words: Asymmetric sulfonylation; 2-Hydroxyalkanamide; 2-Tosyloxyalkanamide, Copper complex

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We began on investigation by trying the tosylation of methyl DL-mandelate (4) as a model compound to see whether it was recognized by chiral copper(II) complex. The result showed that in the absence of copper(II) triflate and (R,R)-Ph-BOX the reaction of 4 with TsCl afforded 5 in 37% yield (Eq. 2). However, in the presence of copper(II) triflate and (R,R)-Ph-BOX, any reaction did not proceed. In contrast, DL-mandelanilide (1a) was tosylated more efficiently in the presence of Cu(II)–(R,R)-Ph-BOX than in the absence of it (Eq. 3). These results suggests that 1a might be recognized with Cu(II)–(R,R)-Ph-BOX complex in the same way as kinetic resolution of 1,2-diols.

Next, we investigated the effect of solvents and bases so as to optimize reaction conditions for kinetic resolution of DL-1a by tosylation (Eq. 4). The results are
summarized in Table 1, which shows a dependence of the yield and % ee of the product 3a on the used base and solvent. Use of MeCN as a solvent and K$_2$CO$_3$ as a base gave tosylated product (S)-3a$^b$ in 42% yield and with a high enantioselectivity (80% ee) and selectivity $s^{11}$ value of 17 (Entry 1). Other solvents except for CH$_2$Cl$_2$ (Entry 6) were less effective (Entries 2-5). Although, Na$_2$CO$_3$, NaHCO$_3$ and Li$_2$CO$_3$ gave comparable $s$ value to K$_2$CO$_3$, the yield of (S)-3a was low (Entries 7-9). In the case of diisopropylethylamine (DIPEA), the yield of (S)-3a and ee was low compared to that of K$_2$CO$_3$ (Entry 10). The result of using 0.05 equiv of Cu(OTf)$_2$ and (R,R)-Ph-BOX was slightly inferior to that of using 0.1 equiv of chiral Cu(II) catalyst (Entry 11).

Utilizing the conditions optimized in Table 1, we screened the effect of amide substituents (Eq. 5). The results are shown in Table 2. The $s$ value of compound 1b substituted with chloro atom at the para position was slightly lower than that of 1c with
methyl group (Entries 1 and 2). Whereas aliphatic amide 1d was ineffective (entry 3), N,N-dialkylated mandelamide 1e was asymmetrically tosylated to afford (S)-3e with moderate enantioselectivity (68% ee) (Entry 4). This result indicates that N-H group is not essential. Unsubstituted mandelamide (1f) gave high s value of 29 with somewhat low conversion (Entry 5).

![Chemical structure]

**Table 2. Kinetic resolution of DL-mandelamide derivatives (DL-1b-f)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R2</th>
<th>R3</th>
<th>Product (S)-3b-f</th>
<th>Recovered (R)-1b-f</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yield (%)</td>
<td>ee (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1b</td>
<td>p-ClPh</td>
<td>3b 44</td>
<td>71</td>
<td>48 79 14</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>p-MePh</td>
<td>3c 29</td>
<td>80</td>
<td>65 69 18</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>Cyclohexyl</td>
<td>3d 30</td>
<td>30</td>
<td>52 18 2</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>-(CH2)5-</td>
<td>3e 50</td>
<td>68</td>
<td>50 73 11</td>
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<tr>
<td>5</td>
<td>1f</td>
<td>H</td>
<td>3f 28</td>
<td>90</td>
<td>61 43 29</td>
</tr>
</tbody>
</table>

\[ a \text{ 1b-f (0.5 mmol), Cu(OTf)}_2 (0.05 mmol), (R,R)-Ph-BOX (0.05 mmol), \text{p-TsCl (0.25 mmol), K}_2\text{CO}_3 (0.5 mmol) in MeCN (2.0 mL) at rt for 12 h.} \]

\[ b \text{ Determined by HPLC.} \]

Table 3 summarizes kinetic resolution of various 2-hydroxyalkanamides 1an-az by tosylation under the optimized reaction condition (Eq. 6).12 Straight chained 2-hydroxyalkanamides 1an-at were asymmetrically tosylated to afford corresponding optically active (S)-3an-at in moderate yield and high enantioselectivity (Entries 1-7). Compound 1au substituted with iPr group was kinetically resolved with high s value of 22 (Entry 8), while compound 1av substituted with tBu group fell short in terms of yield and enantioselectivity (Entry 9). Both cyclobutylated compound 1aw and cyclopentylated 1ax were asymmetrically tosylated to afford (S)-3aw and (S)-3ax with the highest s value of 61 (Entries 10 and 11), while cyclohexylated 1ay gave lower s value of 18 (Entry 12). Tosylation of lactam 1az did not almost proceed to afford 3az (Entry 13). This result might support an intermediary formation of N,O-chelated intermediate 2 in Eq. 1.
Tosyloxyl group is a good leaving group, thus (S)-3a undergoes S_N2 reaction with primary amine to form N-alkylated α-amino acid (R)-6 with a slight degree of racemization in high yield,^{15} while N,N-dialkylated derivative (R)-7 was obtained using secondary amine without any loss of optical purity (Eq. 7).

**Table 3. Kinetic resolution of DL-1an-az^a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>R^3</th>
<th>Product (S)-3an-az</th>
<th>Yield (%)</th>
<th>ee (%)^b</th>
<th>Recovered (R)-1an-az</th>
<th>Yield (%)</th>
<th>ee (%)^b</th>
<th>Selectivity</th>
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<tr>
<td>1</td>
<td>1an</td>
<td>Me</td>
<td>3an</td>
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<td>2</td>
<td>1ao</td>
<td>Et</td>
<td>3ao</td>
<td>44</td>
<td>83</td>
<td>44</td>
<td>61</td>
<td>20</td>
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<tr>
<td>3</td>
<td>1ap</td>
<td>nPr</td>
<td>3ap</td>
<td>42</td>
<td>85</td>
<td>48</td>
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<tr>
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<td>nBu</td>
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<td>3as</td>
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<td>60</td>
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<td>iPPr</td>
<td>3au</td>
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<td>57</td>
<td>69</td>
<td>22</td>
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<tr>
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<td>1av</td>
<td>tBu</td>
<td>3av</td>
<td>30</td>
<td>78</td>
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<td>36</td>
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<td></td>
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<tr>
<td>10</td>
<td>1aw</td>
<td>Cyclobutyl</td>
<td>3aw</td>
<td>30</td>
<td>92</td>
<td>50</td>
<td>82</td>
<td>61</td>
<td></td>
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<tr>
<td>11</td>
<td>1ax</td>
<td>Cyclopentyl</td>
<td>3ax</td>
<td>42</td>
<td>92</td>
<td>42</td>
<td>82</td>
<td>61</td>
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<tr>
<td>12</td>
<td>1ay</td>
<td>Cyclohexyl</td>
<td>3ay</td>
<td>30</td>
<td>80</td>
<td>64</td>
<td>67</td>
<td>18</td>
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<tr>
<td>13</td>
<td>1az</td>
<td>-CMe2-CH2-</td>
<td>3az</td>
<td>6</td>
<td>8</td>
<td>86</td>
<td>1</td>
<td>1</td>
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</table>

^a 1an-az (0.5 mmol), Cu(OTf)_2 (0.05 mmol), (R,R)-Ph-BOX (0.05 mmol), p-TsCl (0.25 mmol), K_2CO_3 (0.5 mmol) in MeCN (2.0 mL) at rt for 12 h.

^b Determined by HPLC.
In conclusion, we have demonstrated a new non-enzymatic method for kinetic resolution of 2-hydroxyalkanamides and converted the chiral tosylated products to optically active α-amino acid derivatives. The mechanistic study of this tosylation and its further synthetic application are underway.

**Acknowledgment**

O.O. and Y.D. are very grateful for a Grant-in-Aid for Scientific Research (C) (19550109) from Japan Society for the Promotion of Science and a Grant-in-Aid for Young Scientists (B) (19790017) from the Ministry of Education, Science, Sports and Culture, Japan, respectively.

**References and notes**


3. Recent literatures for kinetic resolution of 2-hydroxyalkanoic acid derivatives by


8. A typical procedure for kinetic resolution: Under an aerobic atmosphere, a solution of Cu(OTf)$_2$ (18.1 mg, 0.05 mmol) and (R,R)-Ph-BOX (16.7 mg, 0.05 mmol) in MeCN (2 mL) was stirred for 10 min. Into the solution were added $1a$ (113.5 mg, 0.5 mmol), potassium carbonate (69.1 mg, 0.5 mmol) and $p$-TsCl (47.7 mg, 0.25 mmol). After stirring for 12 h at rt, the solution was poured in water and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($n$-hexane : AcOEt = 3 : 1) to afford ($S$)-$3a$ (42% yield, 80% ee) as a white solid. m.p. 140-141 Ž. $[\alpha]_{26}^D$ +8.9 ($c$ 1.0, CHCl$_3$). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 (s, 1H), 7.71 (d, $J$ = 8.1 Hz, 2H), 7.48 (d, $J$ = 7.8 Hz, 2H),
7.35-7.22 (m, 9H), 7.17 (t, $J = 7.5$ Hz, 1H), 5.85 (s, 1H), 2.38 (s, 3H). HR-FAB[M+H]$^+$ calcd for C$_{21}$H$_{20}$NO$_4$S 381.1113 found 382.1111. The optical purity of 3a was determined by chiral HPLC: Daicel Chiralcel OD-H column (4.6 mm φ, 250 mm), n-hexane : isopropanol = 10 : 1, wavelength: 254 nm, flow rate: 1.0 ml/min, retention time: 17.3 min ((R)-3a), 18.7 min ((S)-3a).

9. The absolute stereoconfiguration of recovered (R)-1a was determined by comparing with specific rotation of authentic sample. Compound (R)-1a: [α]$^D_{25}$ −25.1 (c 2.36, acetone). [lit.$^{10}$ (R)-1a (71% ee); [α]$^D_{25}$ −22.3 (c 2.36, acetone)].


12. Absolute stereoconfigurations of recovered (R)-1an$^{13}$ and (R)-1au$^{14}$ were determined by comparing with specific rotation of authentic samples. Absolute stereoconfigurations of (S)-3ao-at,av-az shown in Eq. 6 and Table 3 were deduced on the basis of those of (S)-3a,an,au.


15. Absolute stereoconfiguration of (R)-6 was determined by comparison with specific rotation of (R)-6 derived from D-phenylglycine. Compound (R)-6: [α]$^D_{29}$ −15.9 (c 1.0 CHCl$_3$). [(R)-6 (92% ee) derived from D-phenylglycine; [α]$^D_{29}$ −18.3 (c 1.0, CHCl$_3$)].

16. Somewhat scaled up kinetic resolution of 1ao (2.0 mmol), which was carried out by using Cu(OTf)$_2$ (0.20 mmol), (R,R)-Ph-BOX (0.20 mmol), p-TsCl (1.0 mmol), and K$_2$CO$_3$ (2.0 mmol) in MeCN (5.0 mL) at rt for 8 h, afforded (S)-3ao (47% yield, 91% ee) and (R)-1ao (51% yield, 89% ee) with high s value of 65.
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