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 α-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 α-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 *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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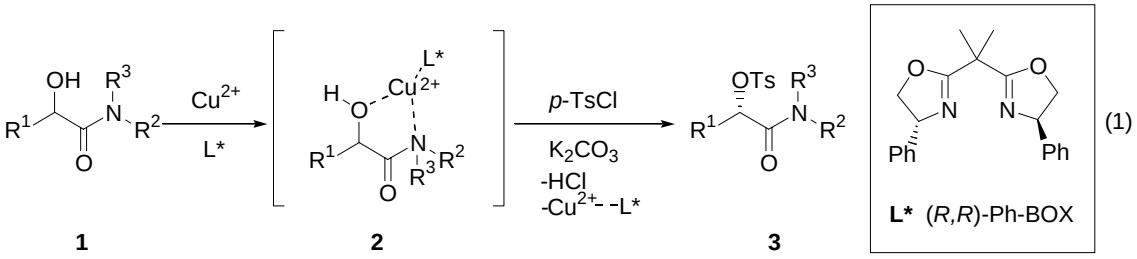
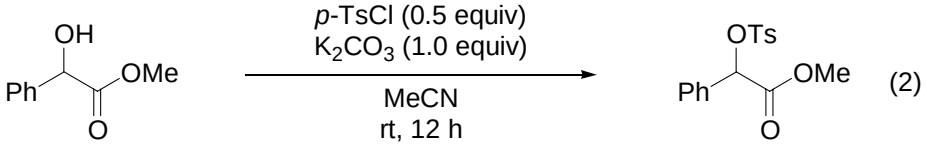


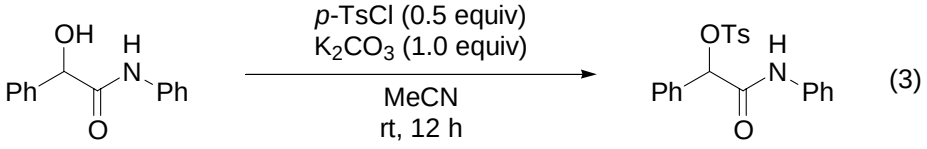
1 **2** **3**

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.



4 **5**

in the absence of $Cu(OTf)_2$ (0.1 equiv), and (*R*,*R*)-Ph-BOX (0.1 equiv)	37% yield
in the presence of $Cu(OTf)_2$ (0.1 equiv), and (*R*,*R*)-Ph-BOX (0.1 equiv)	0% yield



1a **3a**

in the absence of $Cu(OTf)_2$ (0.1 equiv), and (*R*,*R*)-Ph-BOX (0.1 equiv)	28% yield
in the presence of $Cu(OTf)_2$ (0.1 equiv), and (*R*,*R*)-Ph-BOX (0.1 equiv)	42% yield, 80% ee

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).[8] 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_2CO_3 as a base gave tosylated product (*S*)-**3a**[9] in 42% yield and with a high enantioselectivity (80% ee) and selectivity *s*[11] value of 17 (Entry 1). Other solvents except for CH_2Cl_2 (Entry 6) were less effective (Entries 2-5). Although, Na_2CO_3, $NaHCO_3$ and Li_2CO_3 gave comparable *s* value to K_2CO_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_2CO_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).

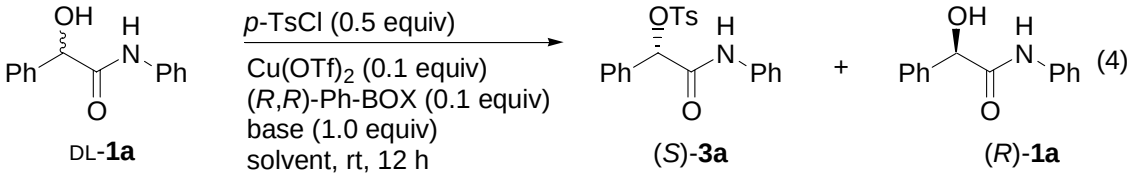


Table 1. Kinetic resolution of DL-mandelanilide (DL-**1a**)[a]

			Product (*S*)-**3a**		Recovered (*R*)-**1a**		Selectivity
Entry	Solvent	Base	Yield (%)	ee (%)[b]	Yield (%)	ee (%)[b]	*s*
1	MeCN	K_2CO_3	42	80	52	64	17
2	Et_2O	K_2CO_3	44	46	56	25	3
3	THF	K_2CO_3	28	59	62	17	5
4	Toluene	K_2CO_3	15	22	80	5	2
5	AcOEt	K_2CO_3	45	49	53	34	4
6	CH_2Cl_2	K_2CO_3	46	78	54	55	14
7	MeCN	Li_2CO_3	13	90	60	18	23
8	MeCN	Na_2CO_3	33	79	48	61	16
9	MeCN	$NaHCO_3$	15	86	80	8	14
10	MeCN	DIPEA	23	51	45	20	4
11[c]	MeCN	K_2CO_3	47	72	47	64	12

[a] DL-**1a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), *p*-TsCl (0.25 mmol), base (0.5 mmol) in a solvent (2.0 mL) at rt for 12 h.

[b] Determined by HPLC.

[c] DL-**1a** (0.5 mmol), $Cu(OTf)_2$ (0.025 mmol), (*R*,*R*)-Ph-BOX (0.025 mmol), *p*-TsCl (0.25 mmol), K_2CO_3 (0.5 mmol) in MeCN (2.0 mL) at rt for 12 h.

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).

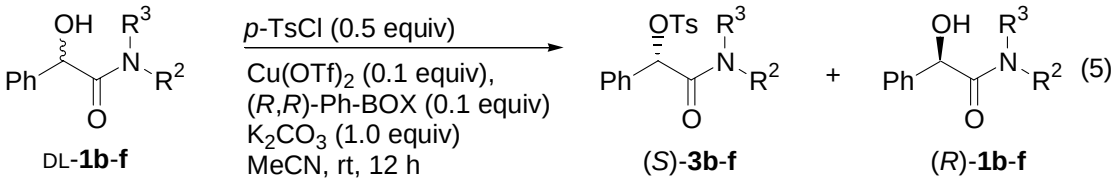


Table 2. Kinetic resolution of DL-mandelamide derivatives (DL-**1b-f**)[a]

Entry		R^2	R^3	Product (*S*)-**3b-f**			Recovered (*R*)-**1b-f**		Selectivity
					Yield (%)	ee (%)[b]	Yield (%)	ee (%)[b]	*s*
1	**1b**	*p*-ClPh	H	**3b**	44	71	48	79	14
2	**1c**	*p*-MePh	H	**3c**	29	80	65	69	18
3	**1d**	Cyclohexyl	H	**3d**	30	30	52	18	2
4	**1e**	$-(CH_2)_5-$		**3e**	50	68	50	73	11
5	**1f**	H	H	**3f**	28	90	61	43	29

[a] **1b-f** (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.

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 *i*Pr group was kinetically resolved with high *s* value of 22 (Entry 8), while compound **1av** substituted with *t*Bu 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.

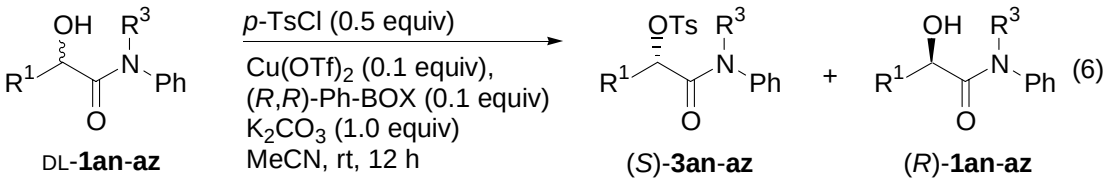
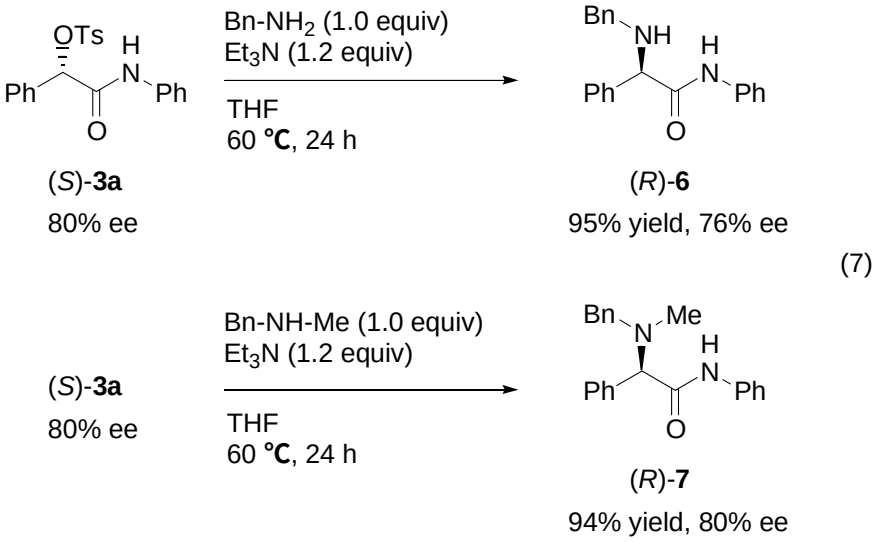


Table 3. Kinetic resolution of DL-**1an-az**[a]

Entry		R^1	R^3	Product (*S*)-**3an-az**			Recovered (*R*)-**1an-az**		Selectivity
					Yield (%)	ee (%)[b]	Yield (%)	ee (%)[b]	*s*
1	**1an**	Me	H	**3an**	26	90	70	24	24
2	**1ao**	Et	H	**3ao**	44	83	44	61	20
3	**1ap**	*n*Pr	H	**3ap**	42	85	48	56	22
4	**1aq**	*n*Bu	H	**3aq**	30	72	59	84	16
5	**1ar**	allyl	H	**3ar**	45	80	45	52	15
6	**1as**	$PhCH_2CH_2$	H	**3as**	38	87	56	57	26
7	**1at**	$C_6H_{11}CH_2$	H	**3at**	30	80	60	62	17
8	**1au**	*i*Pr	H	**3au**	40	83	57	69	22
9	**1av**	*t*Bu	H	**3av**	30	78	66	36	11
10	**1aw**	Cyclobutyl	H	**3aw**	30	92	50	82	61
11	**1ax**	Cyclopentyl	H	**3ax**	42	92	42	82	61
12	**1ay**	Cyclohexyl	H	**3ay**	30	80	64	67	18
13	**1az**	$-CMe_2-CH_2-$		**3az**	6	8	86	1	1

[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.

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).



In conclusion, we have demonstrated a new non-enzymatic method for kinetic resolution of 2-hydroxyalkanamides[16] 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.

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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 ℃. $[\alpha]^{26}_{D}$ +8.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 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 $C_{21}H_{20}NO_4S$ 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**: $[\alpha]^{27}_D$ –25.1 (*c* 2.36, acetone). [lit.[10] (*R*)-**1a** (71% ee); $[\alpha]^{25}_D$ –22.3 (*c* 2.36, acetone)].
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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**.
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15. Absolute stereoconfiguration of (*R*)-**6** was determined by comparison with specific rotation of (*R*)-**6** derived from D-phenylglycine. Compound (*R*)-**6**: $[\alpha]^{29}_D$ –15.9 (*c* 1.0 $CHCl_3$). [(*R*)-**6** (92% ee) derived from D-phenylglycine; $[\alpha]^{29}_D$ –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_2CO_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.

Graphical Abstract

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