Nonenzymatic Kinetic Resolution of 3-Hydroxyalkanamides with Chiral Copper Catalyst

Yosuke Demizu, Yuki Kubo, Yoshihiro Matsumura, Osamu Onomura*

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
Fax +81(95)8192476; E-mail: onomura@nagasaki-u.ac.jp

Received 29 October 2007

Abstract: Kinetic resolution of 3-hydroxyalkanamides with good to high selectivities was achieved by benzoylation using copper(II) triflate and (*R*,*R*)-PhBox [2,2′-isopropylidenebis(4-phenyl-2-oxazoline)] as catalyst, which also mediated enantioselective tosylation of 2,2-bis(hydroxymethyl)alkanamides with high efficiency.

Key words, kinetic resolution, 3-hydroxyalkanamides, acylations, chiral copper complex, molecular recognition

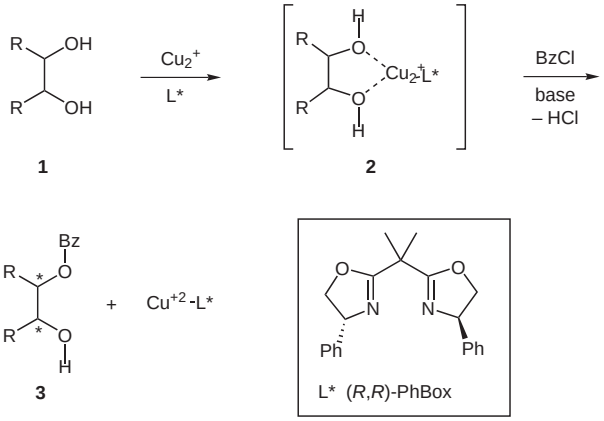
Optically active 3-hydroxyalkanoic acid derivatives are important precursors for the preparations of various biologically active compounds.[1] A variety of enzymatic kinetic resolution methods has been developed for the preparation of optically pure 3-hydroxyalkanoic acid derivatives.[2] To the best of our knowledge, nonenzymatic method has been little known to date.[3] Recently, we have reported an efficient method for kinetic resolution of 1,2-diols **1**. The method is based on the recognition of **1** by copper ion associated with chiral ligand (*R*,*R*)-PhBox[4] to afford the activated intermediates **2** followed by benzoylation (Scheme 1).[5–9]

We report herein nonenzymatic kinetic resolution of 3-hydroxyalkanamides by benzoylation with Cu(II)–(*R*,*R*)-PhBox catalyst affording optically active 3-hydroxyalkanamide derivatives in good to high yields and enantioselectivities.

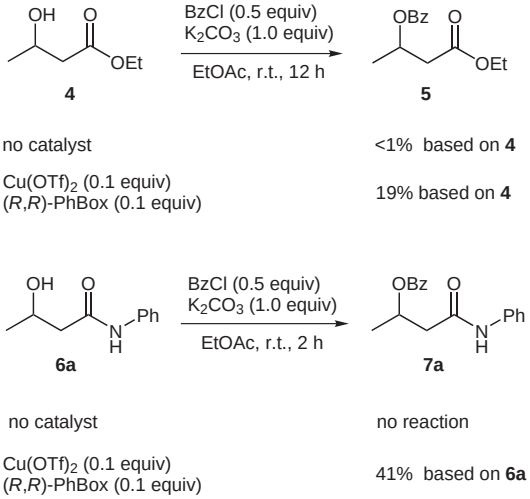
We began our investigation by trying the benzoylation of ethyl DL-3-hydroxybutanoate (**4**) as a model compound to see whether it could be recognized by chiral copper(II) complex or not. We found out the following: in the absence of copper(II) triflate and (*R*,*R*)-PhBox the reaction of **4** with BzCl barely took place, while in the presence of the catalysts, benzoylated product **5** was obtained in 19% yield based on **4**. In contrast, DL-3-hydroxy-*N*-phenylbutanamide (**6a**) was benzoylated more efficiently in the presence of Cu(II)–(*R*,*R*)-PhBox to afford the benzoylated product **7a** in 41% yield (Scheme 2). These results imply that **6a** was efficiently recognized by the Cu(II)–(*R*,*R*)-PhBox complex.

Next, we tried the competitive reaction between **6a** and 2,4-pentanediol (**8**) (*syn*/*anti* ≈ 50:50) with or without Cu(II)–(*R*,*R*)-PhBox (Scheme 3). In the presence of Cu(II)–(*R*,*R*)-PhBox or Cu(II)–*rac*-PhBox, **7a** was exclusively formed, whereas in the absence of Cu(II)–(*R*,*R*)-PhBox only the monobenzoylated diol **9** (*syn*/*anti* ≈ 63:37) was generated. From these results, we deduced that **6a** was preferentially recognized over **8** by the copper catalyst.[10,11] Acceleration of benzoylation of **6a** was also observed in the presence of $Cu(OTf)_2$ without (*R*,*R*)- or *rac*-PhBox.

In our quest to get excellent reaction conditions for kinetic resolution of DL-**6a**, we investigated the effect of bases and solvents on benzoylation.[12] These results are summarized in Table 1. They show a dependence of yield and

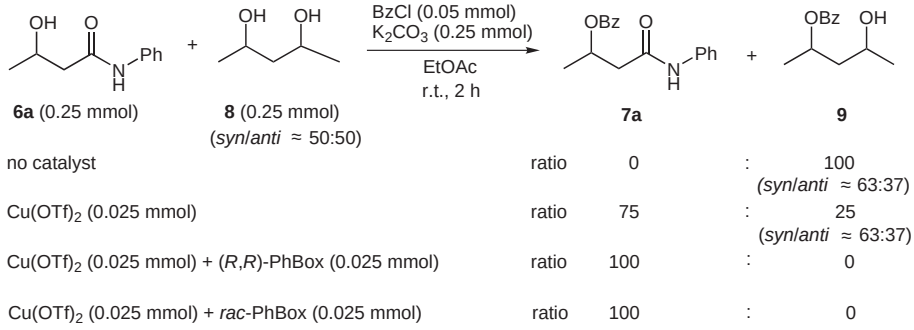


Scheme 1 Asymmetric benzoylation of 1,2-diols **1** based on the recognition by Cu(II)–(*R*,*R*)-PhBox



Scheme 2 Benzoylation of ester **4** and amide **6a** in the absence or presence of $Cu(OTf)_2$ and (*R*,*R*)-PhBox

SYNLETT 2008, No. 3, pp 0433–0437
Advanced online publication: 16.01.2008
DOI: 10.1055/s-2008-1032057; Art ID: U10507ST

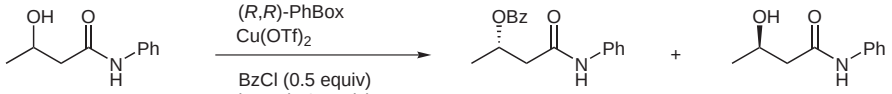


Scheme 3 Competitive reaction between **6a** and **8** by benzoylation in the absence or presence of $Cu(OTf)_2$ and (*R*,*R*)- or *rac*-PhBox

%ee of the product **7a** as well as the reaction time on the solvents and bases used. Use of EtOAc as a solvent and K_2CO_3 as a base gave (*S*)-**7a**[13,14] in 41% yield and a high enantioselectivity (85% ee) with a selectivity *s* value[15] of 27 for two hours (entry 1). THF and 1,4-dioxane gave comparable results to EtOAc (entries 2 and 3), while CH_2Cl_2 and Et_2O were less efficient (entries 4 and 5). Moreover, use of alcohols such as *i*-PrOH or EtOH gave (*S*)-**7a** in high enantioselectivity (entries 6 and 7). K_2CO_3 was the most effective base (entry 1) among the tested bases (entries 8–11). Use of 0.05 equivalent of $Cu(OTf)_2$ and (*R*,*R*)-PhBox led to a slightly inferior result compared to that using 0.1 equivalent of chiral Cu(II) catalyst (entry 12).

Utilizing the conditions optimized in Table 1, we screened the effect of amide N-substituents shown in Table 2. The *s* value of *N*-4-chlorophenyl amide **6b** was slightly lower than that of **6a** (entry 1), while *N*-4-methylphenyl amide **6c** gave high *s* value of 34 (entry 2). Benzoylation of *N*-3,5-dimethylphenyl amide **6d** and the corresponding hexafluorinated amide **6e** required longer reaction times, and the *s* values were moderate for **6d** and

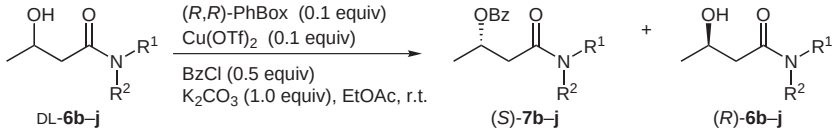
Table 1 Kinetic Resolution of DL-3-Hydroxy-*N*-phenylbutanamide (DL-**6a**)[a]



Entry	Solvent	Base	Time (h)	Product (*S*)-**7a**		Recovered (*R*)-**6a**		Selectivity *s*
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
1	EtOAc	K_2CO_3	2	41	85	52	74	27
2	THF	K_2CO_3	2	45	83	55	64	21
3	1,4-dioxane	K_2CO_3	12	44	85	56	52	21
4	CH_2Cl_2	K_2CO_3	12	38	74	62	45	10
5	Et_2O	K_2CO_3	2	40	75	60	48	11
6	*i*-PrOH	K_2CO_3	12	37	78	63	47	13
7	EtOH	K_2CO_3	24	18	88	82	27	20
8	EtOAc	Li_2CO_3	24	26	68	74	28	7
9	EtOAc	Na_2CO_3	24	45	82	46	80	25
10	EtOAc	$NaHCO_3$	24	48	70	52	64	11
11	EtOAc	DIPEA	24	30	73	70	36	9
12[c]	EtOAc	K_2CO_3	2	37	85	63	56	22

[a] Reaction conditions: DL-**6a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-PhBox (0.05 mmol), BzCl (0.25 mmol), base (0.5 mmol) in a solvent (2.0 mL) at r.t.
[b] Determined by HPLC.
[c] Reaction conditions: DL-**6a** (0.5 mmol), $Cu(OTf)_2$ (0.025 mmol), (*R*,*R*)-PhBox (0.025 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in EtOAc (2.0 mL) at r.t.

Table 2 Kinetic Resolution of DL-3-Hydroxybutanamide Derivatives DL-**6b–j**[a]

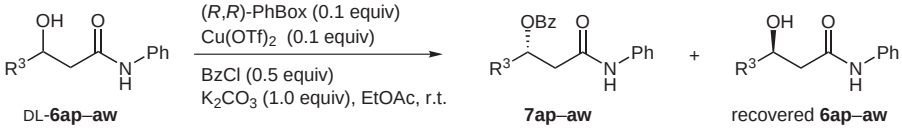


DL-**6b–j** (*S*)-**7b–j** (*R*)-**6b–j**

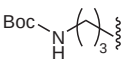
Entry	Substrate	R^1	R^2	Time (h)	Product (*S*)-**7b–j**[b]			Recovered (*R*)-**6b–j**		Selectivity *s*
						Yield (%)	ee[c] (%)	Yield (%)	ee[c] (%)	
1	**6b**	4-ClC_6H_4	H	2	**7b**	46	79	54	66	17
2	**6c**	4-MeC_6H_4	H	3	**7c**	44	88	56	73	34
3	**6d**	3,5-diMeC_6H_3	H	24	**7d**	47	78	53	65	16
4	**6e**	3,5-di$CF_3C_6H_3$	H	24	**7e**	30	57	70	27	5
5	**6f**	2-MeC_6H_4	H	1.5	**7f**	37	89	63	56	30
6	**6g**	Bn	H	3	**7g**	48	78	47	65	16
7	**6h**	Ph	Me	12	**7h**	37	84	53	60	21
8	**6i**	Me	Me	3	**7i**	46	76	7	31	10
9	**6j**	–$(CH_2)_2O(CH_2)_2$–		24	**7j**	39	82	23	57	18

[a] Reaction conditions: DL-**6b–j** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-PhBox (0.05 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in EtOAc (2.0 mL) at r.t.
[b] Absolute stereoconfigurations of **7b–j** were deduced on the basis of that of (*S*)-**7a**.
[c] Determined by HPLC.

Table 3 Kinetic Resolution of Various DL-3-Hydroxyalkanamides DL-**6ap–aw**[a]



DL-**6ap–aw** **7ap–aw** recovered **6ap–aw**

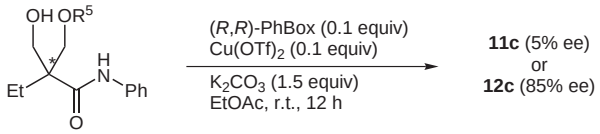
Entry	Substrate	R^3	Time (h)	Product **7ap–aw**			Recovered **6ap–aw**			Selectivity *s*
					Yield (%)	ee[b] (%)		Yield (%)	ee[b] (%)	
1	**6ap**	Et	12	(*S*)-**7ap**	38	67	(*R*)-**6ap**	62	41	8
2	**6aq**	*n*-Pr	24	(*S*)-**7aq**	34	68	(*R*)-**6aq**	64	45	8
3	**6ar**	*i*-Pr	24	(*R*)-**7ar**	20	64	(*S*)-**6ar**	80	24	6
4	**6as**	*i*-Bu	24	(*S*)-**7as**	23	58	(*R*)-**6as**	52	37	5
5	**6at**	cyclohexyl	24	**7at**	0	–	**6at**	100	0	–
6	**6au**	Ph	24	(*R*)-**7au**	18	74	(*S*)-**6au**	82	20	8
7	**6av**		2	(*S*)-**7av**	40	80	(*R*)-**6av**	60	58	16
8	**6aw**		12	(*S*)-**7aw**	40	82	(*R*)-**6aw**	50	55	18

[a] Reaction conditions: **6ap–aw** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-PhBox (0.05 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in EtOAc (2 mL) at r.t.
[b] Determined by HPLC.

poor for **6e** (entries 3 and 4). *N*-2-Methylphenyl amide **6f** was smoothly asymmetrically benzoylated to afford **7f** with 89% ee. *N*-Benzyl amide **6g** was inferior to *N*-phenyl amide **6a** (entry 6). *N*,*N*-Disubstituted amides **6h**, **6i** and **6j** also gave slightly lower *s* values compared to that of **6a** (entries 7–9).

Table 3 summarizes kinetic resolution of various 3-hydroxyalkanamides **6ap**–**aw** by benzoylation under the optimized reaction condition. Compounds **6ap** substituted with Et and **6aq** with *n*-Pr group were asymmetrically benzoylated to afford the corresponding optically active (*S*)-**7ap**[16] and (*S*)-**7aq**,[16] respectively, in good yield and moderate enantioselectivity, (entries 1 and 2). Although compounds **6ar** and **6as** substituted with *i*-Pr and *i*-Bu, respectively, were kinetically resolved with moderate enantioselectivity, the yield was low (entries 3 and 4). Benzoylation of cyclohexylated compound **6at** did not proceed (entry 5), while phenylated **6au** was benzoylated to afford (*R*)-**7au**[17] in moderate yield and good enantioselectivity (entry 6). Straight-chained carbon compounds **6av** terminally functionalized with Br atom and **6aw** with *N*-Boc-protected amino group gave good *s* value of 16 and 18, respectively (entries 7 and 8).

To increase the scope of our reaction, we tried enantioselective benzoylation and tosylation[18] of 2,2-bis(hydroxymethyl)alkanamides **10a**–**c**. The results are shown in Table 4. Asymmetric benzoylation and tosylation of **10a**–**c** smoothly proceeded to give the corresponding monobenzoylated compounds **11a**–**c**[19] and monotosylated compounds **12a**–**c**[19] with good to high yields and enantioselectivities (entries 1–6). It is noteworthy that **12a**–**c** were obtained in higher enantiomeric purity than **11a**–**c** (entries 4–6), partially due to an intramolecular acyl transfer[20] which caused racemization of optically pure benzoylated compound **11c**, but did not happen in the case of tosylation. This is illustrated in Scheme 4.

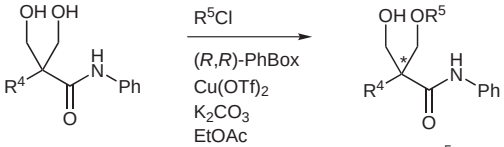


11c R^5 = Bz (71% ee)
12c R^5 = Ts (85% ee)

Scheme 4 Racemization of **11c** and **12c**

In summary, we have accomplished the nonenzymatic kinetic resolution of 3-hydroxyalkanamides by benzoylation and desymmetrization of 2,2-bis(hydroxymethyl)alkanamides by tosylation utilizing chiral copper catalyst. The mechanistic study of these reactions and their synthetic applications[21] are underway.

Table 4 Asymmetric Benzoylation and Tosylation of Prochiral **10a**–**c**[a]



10a–**c**

11a–**c** R^5 = Bz
12a–**c** R^5 = Ts

Entry	Substrate	R^4	R^5	Product	Yield (%)	ee[b] (%)
1	**10a**	H	Bz	**11a**	73	75
2	**10b**	Me	Bz	**11b**	95	77
3	**10c**	Et	Bz	**11c**	76	71
4	**10a**	H	Ts	**12a**	89	85
5	**10b**	Me	Ts	**12b**	99	90
6	**10c**	Et	Ts	**12c**	85	85

[a] Reaction conditions: **10a**–**c** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-PhBox (0.05 mmol), R^5Cl (0.5 mmol), K_2CO_3 (0.75 mmol) in EtOAc (2 mL) at r.t. for 4 h (benzoylation) or 12 h (tosylation).
[b] Determined by HPLC.

Acknowledgment

O.O. and Y.D. are grateful for a Grant-in-Aid for Scientific Research (C) (19550109) from the 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

(1) (a) Berks, A. H. *Tetrahedron* **1996**, *52*, 331. (b) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2002**, *344*, 947. (c) Genet, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908. (d) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779.
(2) For recent literature on kinetic resolution of 3-hydroxyalkanoic acid derivatives by enzymatic methods, see: (a) Xu, C.; Yuan, C. *Tetrahedron* **2005**, *61*, 2169. (b) Turcu, M. C.; Kiljunen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2007**, *18*, 1682.
(3) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212.
(4) For a recent review of chiral bis(oxazoline) ligands, see: Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.
(5) For monobenzoylation, see: Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052.
(6) For monocarbamoylation, see: Matsumoto, K.; Mitsuda, M.; Ushijima, N.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 8453.
(7) For monooxidation of 1,2-diols, see: Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* **2007**, *48*, 8668.

(8) For benzoylation of *vic*-aminoalcohols, see: Mitsuda, M.; Tanaka, T.; Tanaka, T.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 8073.
(9) For a review, see: Matsumura, Y.; Onomura, O.; Demizu, Y. *Yuki Gosei Kagaku Kyokaishi* **2007**, *65*, 216.
(10) For representative literature on nonenzymatic asymmetric desymmetrization of 1,3-diols, see: (a) Monocarbamoylation: Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201. For monobenzoylation, see: (b) Oriyama, T.; Taguchi, H.; Terakado, D.; Sano, T. *Chem. Lett.* **2002**, *31*, 26. (c) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410. (d) Mizuta, S.; Tsuzuki, T.; Fujimoto, T.; Yamamoto, Y. *Org. Lett.* **2005**, *7*, 3633.
(11) For monoacetylation of 2-amino-1,3-diols, see: Honjo, T.; Nakano, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. *Org. Lett.* **2007**, *9*, 509.
(12) **Typical Procedure** for **Kinetic Resolution**: To a solution of $Cu(OTf)_2$ (0.05 mmol, 18.1 mg) and (*R*,*R*)-PhBox (0.05 mmol, 16.7 mg) in EtOAc (2 mL) were added DL-**6a** (0.5 mmol, 89.6 mg), K_2CO_3 (0.5 mmol, 69.1 mg) and benzoyl chloride (0.25 mmol, 0.029 mL). After stirring for 2 h at r.t., to the reaction mixture H_2O (10 mL) was added. The organic portion was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on SiO_2 (*n*-hexane–EtOAc, 3:1) to afford (*S*)-**7a** (58.1 mg, 41% yield, 85% ee) as a white solid; mp 98–99 °C; $[\alpha]_D^{23}$ +55.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.2 Hz, 1 H), 7.78 (br s, 1 H), 7.56 (t, *J* = 9.0 Hz, 1 H), 7.38–7.51 (m, 4 H), 7.29 (t, *J* = 9.0 Hz, 3 H), 7.09 (t, *J* = 9.0 Hz, 1 H), 5.50–5.63 (m, 1 H), 2.85 (dd, *J* = 6.3, 14.4 Hz, 1 H), 2.68 (dd, *J* = 6.3, 14.4 Hz, 1 H), 1.51 (d, *J* = 6.3 Hz, 3 H). Optical purity of product (*S*)-**7a** was determined by chiral HPLC: Dicel Chiralcel OD-H column (ϕ: 4.6 mm, l: 250 mm), *n*-hexane–isopropanol (10:1), wavelength: λ = 220 nm, flow rate: 1.0 mL/min, t_R = 20.0 min [(*R*)-**7a**], t_R = 22.5 min [(*S*)-**7a**].
(13) The absolute stereoconfiguration of recovered (*R*)-**6a** was determined by comparing with the specific rotation of an authentic sample. Compound (*R*)-**6a** (74% ee): $[\alpha]_D^{22}$ –28.6 (*c* = 1.1, $CHCl_3$) [lit.[14] (*R*)-**6a** $[\alpha]_D^{20}$ –37 (*c* = 1.0, $CHCl_3$)].
(14) Gendre, P. L.; Offenvecher, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron: Asymmetry* **1998**, *9*, 2279.
(15) The selectivity factor *s* was determined using the equation $s = k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee_A)]/\ln[(1 - C)(1 + ee_A)]$, where $C = ee_A/(ee_A + ee_B)$, ee_A = ee of recovered starting material, ee_B = ee of product: Kagan H. B., Fiaud J. C.; *Topics in Stereochemistry*; Vol. 18. Eliel E. L.; Wiley & Sons: New York, **1988**; 249–330.
(16) Absolute stereoconfigurations of **7ap**–**at**,**av**,**aw** shown in Table 3 were deduced on the basis of those of (*S*)-**7a** and (*R*)-**7au**.
(17) The absolute stereoconfiguration of (*R*)-**7au** was determined by comparing with that of authentic (*S*)-**7au**, which was prepared from commercially available (*S*)-(–)-3-hydroxy-3-phenylpropionitrile: Dicel Chiralcel OD-H column (ϕ: 4.6 mm, l: 250 mm), *n*-hexane–isopropanol (10:1), wavelength: λ = 220 nm, flow rate: 1.0 mL/min, t_R = 36 min [(*R*)-**7au**], t_R = 42 min [(*S*)-**7au**]. (*R*)-**7au** (74% ee): $[\alpha]_D^{25}$ –13.8 (*c* = 1.0, $CHCl_3$).
(18) Kinetic resolution of DL-**6a** with *p*-TsCl gave *S*-configured tosylated product with somewhat lower yield (36%) and enantioselectivity (67% ee) than those of benzoylation.
(19) Specific rotations. **11a**: $[\alpha]_D^{28}$ –16.4 (*c* = 1.0, $CHCl_3$). **11b**: $[\alpha]_D^{28}$ +6.9 (*c* = 1.0, $CHCl_3$). **11c**: $[\alpha]_D^{28}$ +0.6 (*c* = 1.0, $CHCl_3$). **12a**: $[\alpha]_D^{24}$ +15.2 (*c* = 0.95, $CHCl_3$). **12b**: $[\alpha]_D^{24}$ –21.8 (*c* = 1.0, $CHCl_3$). **12c**: $[\alpha]_D^{26}$ –43.2 (*c* = 1.0, $CHCl_3$).
(20) Edin, M.; Martín-Matute, B.; Bäckvall, J.-E. *Tetrahedron: Asymmetry* **2006**, *17*, 708.
(21) Mesylation of (*R*)-**6a** followed by cyclization under basic conditions gave the corresponding optically active β-lactam with complete stereoinversion.[16]
(22) Sakaki, J.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 2952.