Non-enzymatic kinetic resolution of 3-hydroxyalkanamides with chiral copper catalyst

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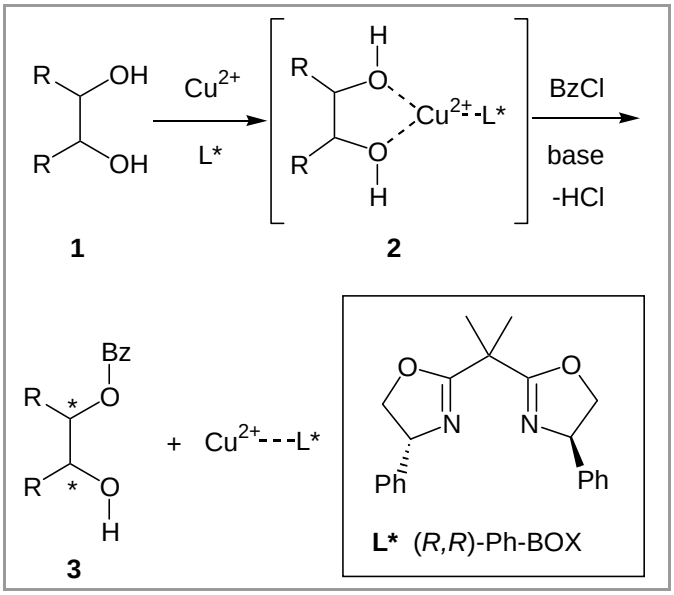
Abstract: Kinetic resolution of 3-hydroxyalkanamides with good to high selectivities was achieved by benzoylation using copper(II) triflate and (*R*,*R*)-Ph-BOX as a catalyst, which also mediated enantioselective tosylation of 2,2-bis(hydroxymethy)alkanamides with high efficiency.

Key words: Kinetic resolution, 3-Hydroxyalkanamides, Acylations, Chiral copper complex, Molecular recognition

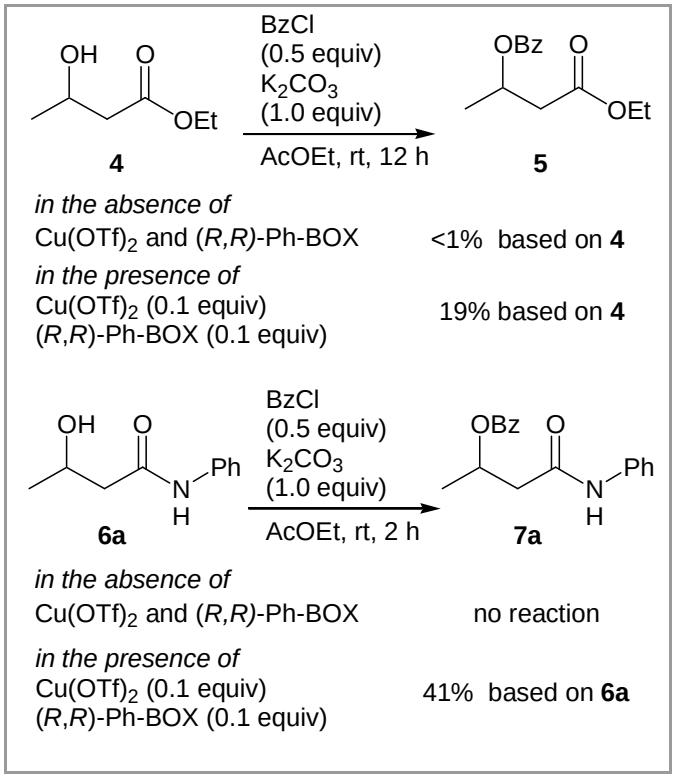
Optically active 3-hydroxyalkanoic acid derivatives are important precursors for preparations of various biologically active compounds.[1] A variety of enzymatic kinetic resolution methods has been developed for preparation of optically pure 3-hydroxyalkanoic acid derivatives.[2] To the best of our knowledge, non-enzymatic 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 recognition of **1** by copper ion associated with chiral ligand (*R*,*R*)-Ph-BOX[4] to afford the activated intermediates **2** followed by benzoylation (Scheme 1).[5]



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

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

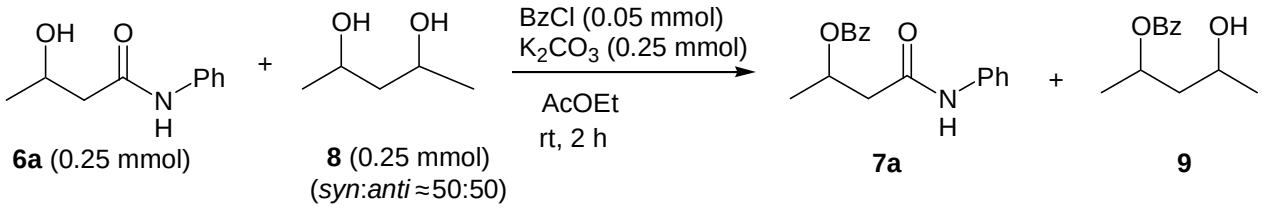
We began our investigation by trying benzoylation of ethyl DL-3-hydroxybutanoate (**4**) as a model compound to see whether it could be recognized by chiral copper(II) complex or not. We found out the following, in the absence of copper(II) triflate and (*R*,*R*)-Ph-BOX the reaction of **4** with BzCl did not almost proceed, 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*)-Ph-BOX to afford benzoylated product **7a** in 41% yield (Scheme 2). These results imply that **6a** was efficiently recognized by Cu(II)–(*R*,*R*)-Ph-BOX complex.



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

Next, we tried competitive reaction between **6a** and 2,4-pentanediol (**8**) (*syn*:*anti*≈50:50) with or without Cu(II)–(*R*,*R*)-Ph-BOX (Scheme 3). In the presence of Cu(II)–(*R*,*R*)-Ph-BOX or Cu(II)–*racemic*-Ph-BOX **7a** was exclusively formed, whereas in the absence of Cu(II)–(*R*,*R*)-Ph-BOX only monobenzoylated diol **9** (*syn*:*anti*≈63:37) was generated. From these results, we deduced that **6a** is preferentially recognized over **8** by

the copper catalyst.[6] Acceleration for benzoylaiton of **6a** was also observed in the presence of $Cu(OTf)_2$ without (*R*,*R*)- (or *racemic*-) Ph-BOX.



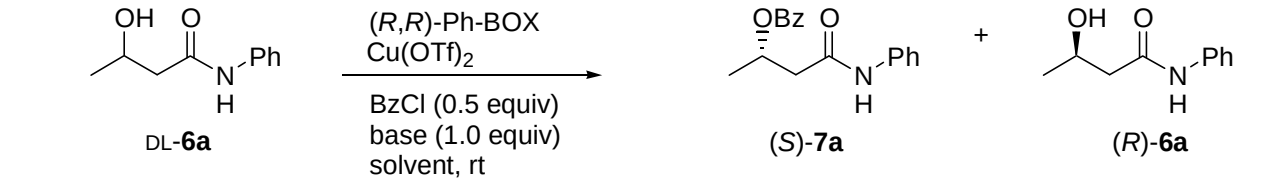
6a (0.25 mmol) **8** (0.25 mmol) (*syn*:*anti* ≈ 50:50) **7a** **9**

in the absence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX	*ratio*	0	:	100 (*syn*:*anti* ≈ 63:37)
in the presence of $Cu(OTf)_2$ (0.025 mmol)	*ratio*	75	:	25 (*syn*:*anti* ≈ 63:37)
in the presence of $Cu(OTf)_2$ (0.025 mmol) and (*R*,*R*)-Ph-BOX (0.025 mmol)	*ratio*	100	:	0
in the presence of $Cu(OTf)_2$ (0.025 mmol) and *racemic*-Ph-BOX (0.025 mmol)	*ratio*	100	:	0

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

In our quest to get excellent reaction conditions for kinetic resolution of DL-**6a**, we investigated the effect of bases and solvents on benzoylation.[7] These results are summarized in Table 1. They show a dependence of yield and % ee of the product **7a** as well as the reaction time on the solvents and bases used. Use of AcOEt as a solvent and K_2CO_3 as a base gave (*S*)-**7a**[8] in 41% yield and a high enantioselectivity (85% ee) with a selectivity *s* value[10] of 27 for 2h (Entry 1). THF and 1,4-dioxane gave comparable results to AcOEt (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 equiv of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX led to slightly inferior result compared to using 0.1 equiv of chiral Cu(II) catalyst (Entry 12).

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



DL-**6a** (*S*)-**7a** (*R*)-**6a**

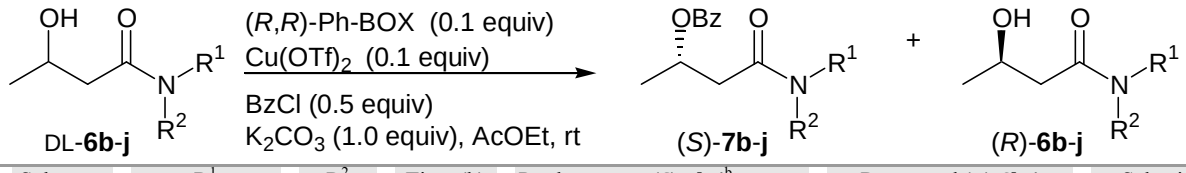
Entry	Solvent	Base	Time (h)	Product (*S*)-**7a**		Recovered (*R*)-**6a**		Selectivity
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	*s*
1	AcOEt	K_2CO_3	2	41	85	52	74	27
2	THF	K_2CO_3	2	45	83	55	64	21
3	1,4-dioxane	K_2CO_3	12	44	85	56	52	21
4	CH_2Cl_2	K_2CO_3	12	38	74	62	45	10
5	Et_2O	K_2CO_3	2	40	75	60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

[a] DL-**6a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), BzCl (0.25 mmol), base (0.5 mmol) in a solvent (2.0 mL) at rt.
[b] Determined by HPLC.
[c] DL-**6a** (0.5 mmol), $Cu(OTf)_2$ (0.025 mmol), (*R*,*R*)-Ph-BOX (0.025 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in AcOEt (2.0 mL) at rt.

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 time, and the *s* values were moderate for **6d** and 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 2 Kinetic resolution of DL-3-hydroxybutanamide derivatives (DL-**6b-j**)[a]

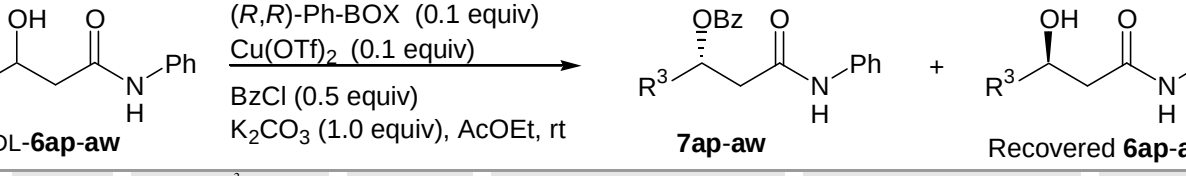


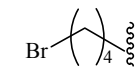
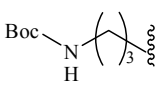
Entry	Substrate	R^1	R^2	Time (h)	Product	(*S*)-**7b-j**[b] Yield (%)	(*S*)-**7b-j**[b] ee[c] (%)	Recovered (*R*)-**6b-j** Yield (%)	Recovered (*R*)-**6b-j** ee[c] (%)	Selectivity *s*
1	**6b**	4-ClC_6H_4	H	2	**7b**	46	79	54	66	17
2	**6c**	4-MeC_6H_4	H	3	**7c**	44	88	56	73	34
3	**6d**	3,5-diMeC_6H_3	H	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**	$-(CH_2)_2-O-(CH_2)_2-$		24	**7j**	39	82	23	57	18

[a] DL-**6b-j** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in AcOEt (2.0 mL) at rt.
[b] Absolute stereoconfigurations of **7b-j** were deduced on the basis of that of (*S*)-**7a**.
[c] Determined by HPLC.

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 corresponding optically active (*S*)-**7ap**[11] and (*S*)-**7aq**[11] in good yield and moderate enantioselectivity, respectively (Entries 1 and 2). Although compounds **6ar** and **6as** substituted with *i*Pr and *i*Bu 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**[12] in moderate yield and good enantioselectivity (Entry 6). Straight carbon-chained compounds **6av** terminally fuctionalized with Br atom and **6aw** with *N*-Boc protected amino group gave good *s* value of 16 and 18, respectively (Entries 7 and 8).

Table 3 Kinetic resolution of various DL-3-hydroxyalkanamides (DL-**6ap-aw**)[a]



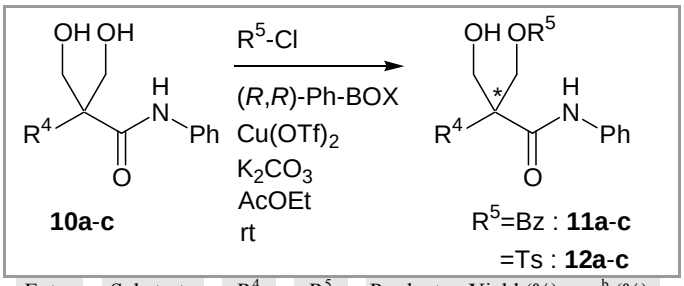
Entry	Substrate	R^3	Time (h)	Product	**7ap-aw** Yield (%)	**7ap-aw** ee[b] (%)	Recovered	**6ap-aw** Yield (%)	**6ap-aw** ee[b] (%)	Selectivity *s*
1	**6ap**	Et	12	(*S*)-**7ap**	38	67	(*R*)-**6ap**	62	41	8
2	**6aq**	*n*Pr	24	(*S*)-**7aq**	34	68	(*R*)-**6aq**	64	45	8
3	**6ar**	*i*Pr	24	(*R*)-**7ar**	20	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] **6ap-aw** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), BzCl (0.25 mmol), K_2CO_3 (0.5 mmol) in AcOEt (2 mL) at rt.
[b] Determined by HPLC.

To increase the scope of our reaction, we tried enantioselective benzoylation and tosylation[13] 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 mono-benzoylated compounds **11a-c**[14] and mono-tosylated compounds **12a-c**[14] with good to high yields and enantioselectivities (Entries 1-6). It is note-

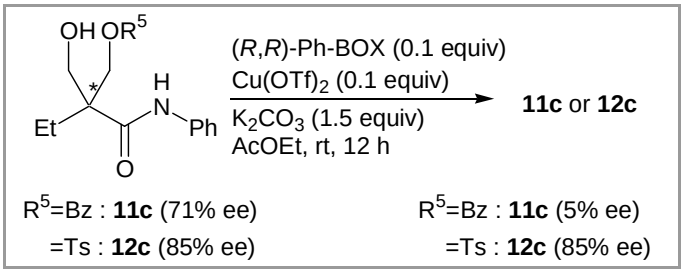
worthy to state that **12a-c** were obtained in higher enantiomeric purity than those of **11a-c** (Entries 4-6), partially due to an intramolecular acyl transfer[15] which caused racemization of optically pure benzoylated compound **11c**, but did not happen in the case of tosylation. This is illustrated in Scheme 4.

Table 4 Asymmetric benzoylation and tosylation of prochiral **10a-c**[a]



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] **10a-c** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R,R*)-Ph-BOX (0.05 mmol), R^5-Cl (0.5 mmol), K_2CO_3 (0.75 mmol) in AcOEt (2 mL) at rt for 4 h (benzoylation) or 12 h (tosylation).
[b] Determined by HPLC.



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

In summary, we have accomplished the non-enzymatic 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[16] are underway.

Acknowledgment

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(7) Typical procedure for kinetic resolution: Into a solution of $Cu(OTf)_2$ (0.05 mmol, 18.1 mg) and (*R,R*)-Ph-BOX (0.05 mmol, 16.7 mg) in AcOEt (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 rt, to the reaction mixture water (10 mL) was added. The organic portion was extracted with AcOEt (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and solvent removed in vacuo. The residue was chromatographed on SiO_2 (*n*-hexane : AcOEt = 3 : 1) to afford (*S*)-**7a** (58.1 mg, 41% yield, 85% ee) as a white solid. M.p. 98-99 °C. $[\alpha]^{23}_D$ +55.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.2 Hz, 1H), 7.78 (br s, 1H), 7.56 (t, *J* = 9.0 Hz, 1H), 7.51-7.38 (m, 4H), 7.29 (t, *J* = 9.0 Hz, 3H), 7.09 (t, *J* = 9.0 Hz, 1H), 5.63-5.50 (m, 1H), 2.85 (dd, *J* = 6.3, 14.4 Hz, 1H), 2.68 (dd, *J* = 6.3, 14.4 Hz, 1H), 1.51 (d, *J* = 6.3 Hz, 3H). Optical purity of product (*S*)-**7a** was determined by chiral HPLC: Dicel Chiralcel OD-H column (4.6 mmϕ, 250 mm), *n*-hexane : isopropanol = 10 : 1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 20.0 min ((*R*)-**7a**), 22.5 min ((*S*)-**7a**).

(8) The absolute stereoconfiguration of recovered (*R*)-**6a** was determined by comparing with specific rotation of authentic sample. Compound (*R*)-**6a** (74% ee): $[\alpha]^{22}_D$ −28.6 (*c* 1.1, $CHCl_3$). [lit.[9] (*R*)-**6a** $[\alpha]^{20}_D$ −37 (*c* 1.0, $CHCl_3$)].

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(11) Absolute stereoconfigurations of **7ap**-**at**,**av**,**aw** shown in Table 3 were deduced on the basis of those of (*S*)-**7a** and (*R*)-**7au**.
(12) 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 (4.6 mmϕ, 250 mm), *n*-hexane : isopropanol = 10 : 1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 36 min ((*R*)-**7au**), 42 min ((*S*)-**7au**). (*R*)-**7au** (74% ee): $[\alpha]^{25}_D$ −13.8 (*c* 1.0, $CHCl_3$).
(13) Kinetic resolution of DL-**6a** with *p*-TsCl gave (*S*)-tosylated product with somewhat lower yield (36%) and enantioselectivity (67% ee) than those of benzoylation.
(14) Specific rotations, **11a**: $[\alpha]^{28}_D$ −16.4 (*c* 1.0, $CHCl_3$). **11b**: $[\alpha]^{28}_D$ +6.9 (*c* 1.0, $CHCl_3$). **11c**: $[\alpha]^{28}_D$ +0.6 (*c* 1.0, $CHCl_3$). **12a**: $[\alpha]^{24}_D$ +15.2 (*c* 0.95, $CHCl_3$). **12b**: $[\alpha]^{24}_D$ −21.8 (*c* 1.0, $CHCl_3$). **12c**: $[\alpha]^{26}_D$ −43.2 (*c* 1.0, $CHCl_3$).
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