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Kinetic resolution of *vic*-amino alcohols catalyzed by a chiral Cu(II) complex

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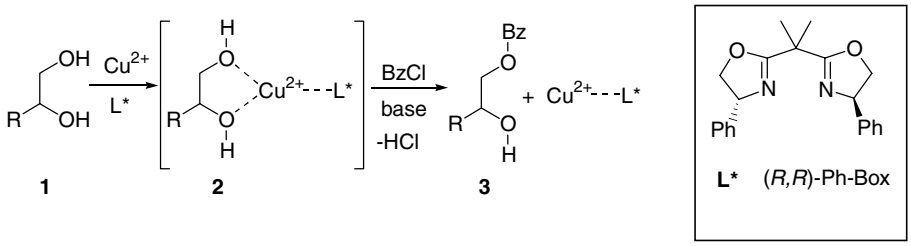
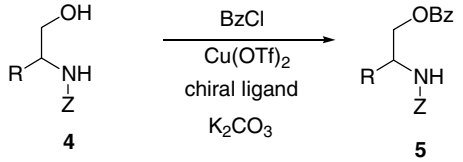
Abstract—Kinetic resolution of N-benzoylated *vic*-amino alcohols was achieved by benzoylation in the presence of copper triflate and (*R*,*R*)-Ph-BOX as catalysts. The observed enantioselectivity was moderate to high. The method was applied to a kinetic resolution of racemic prolinol and piperidinemethanol derivatives as well as an asymmetric desymmetrization of 2-amino-1,3-diol derivatives.

Kinetic resolution has long continued to attract much interest in asymmetric synthesis because of its simple process for preparation of enantiomerically enriched compounds from an easily available racemic mixture.[1,2] We recently explored an efficient method for kinetic resolution of 1,2-diols **1**, which is based on a recognition of the 1,2-diol moiety with copper ion associated with some chiral ligand L* such as (*R*,*R*)-Ph-BOX to afford the activated 1,2-diol intermediates **2** followed by monobenzoylation (Eq. 1).[3–5] In continuing the study, we report herein kinetic resolution of *vic*-amino alcohols **4** affording optically active amino alcohols **5** (Eq. 2).[2d,j,6]

In advance of the kinetic resolution of **4**, we first tried the benzoylation of N-protected amino alcohol **6a** as a model compound to see whether it behaved in a similar way as that of 1,2-diols **1**. The result showed that the reaction of **6a** with BzCl afforded **7a** in 96% yield, while 22% yield of **7a** was observed in a reaction without copper triflate and the chiral ligand (Eq. 3), suggesting that



(1)



(2)

Keywords: Kinetic resolution; *vic*-Amino alcohol; Monobenzoylation; Chiral copper complex.
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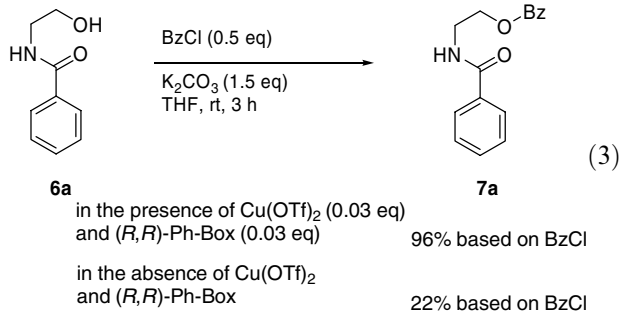
6a might be recognized with copper ion/L* in a similar manner to the kinetic resolution of **1**.



(3)

Further data about the reactivity of **6a** for the benzoylation were obtained in the competitive reactions between **6a** with **6b–e** (Eq. 4, Table 1).

The results shown in Table 1 indicate that other protecting groups than the benzoyl group were entirely ineffective as *N*-protecting groups of *vic*-amino alcohols to be benzoylated.

Furthermore, N-benzoylated aminoethanol **6a** was subjected to competitive reactions with a variety of alcohols having a substituent at the β-position (Eq. 5). The results are shown in Table 2, which shows that **6a** was less

Table 1. Competitive benzoylation reaction between N-protected ethanol amines **6a–e**[a]

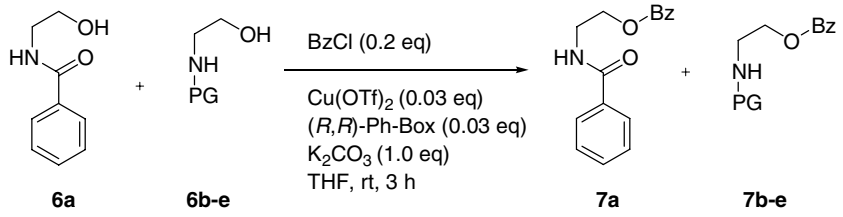
Entry	**6b–e**	Protecting group	Products **7a–e** Ratio of **7a**:**7b–e**
1	**6b**	CO_2t-Bu	100:0
2	**6c**	CO_2CH_2Ph	100:0
3	**6d**	SO_2Php-Me	100:0
4	**6e**	COMe	100:0

[a] The competitive reaction was carried out under the following conditions: **6a** (0.5 mmol), **6b–e** (0.5 mmol), BzCl (0.1 mmol), $Cu(OTf)_2$ and (*R*,*R*)-Ph-Box (0.015 mmol), K_2CO_3 (0.5 mmol), THF (2 mL), at rt for 3 h.

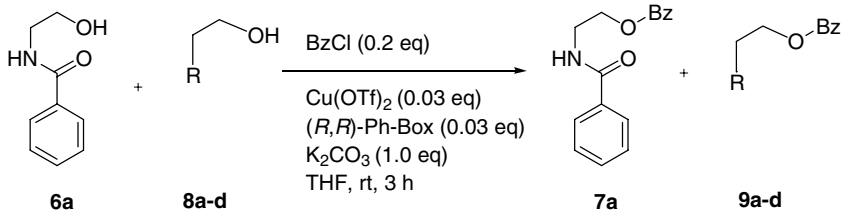
Table 2. Competitive benzoylation reaction of **6a** with alcohols **8a–d**[a]

Entry	**8a–d**	R	Products **7a**, **9a–d** Ratio of **7a**:**9a–d**
1	**8a**	OH	11:89
2	**8b**	OBz	100:0
3	**8c**	OEt	100:0
4	**8d**	Et	100:0

[a] The competitive reaction was carried out under the following conditions: **6a** (0.5 mmol), **8a–d** (0.5 mmol), BzCl (0.1 mmol), $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX (0.015 mmol), K_2CO_3 (0.5 mmol), THF (2 mL), at rt for 3 h.



(4)



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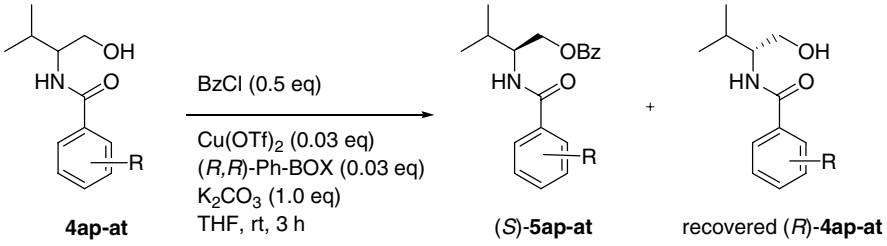

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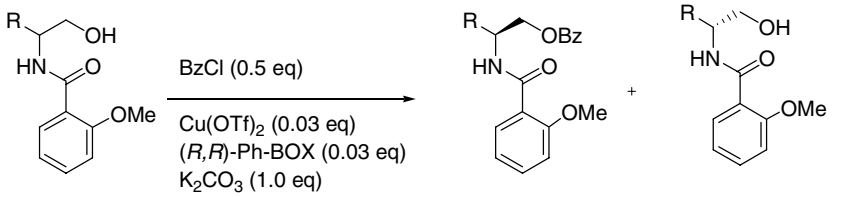


(7)

R=Me	**5bt**; 34% yield, 89% ee	**4bt**; 62% yield, 54% ee	*s*=29
R=Et	**5ct**; 41% yield, 86% ee	**4ct**; 42% yield, 68% ee	*s*=28
R=Ph	**5dt**; 26% yield, 85% ee	**4dt**; 62% yield, 36% ee	*s*=18
R=*p*-ClPhCH$_2$	**5et**; 33% yield, 87% ee	**4et**; 51% yield, 80% ee	*s*=35
R=*p*-MeOPhCH$_2$	**5ft**; 32% yield, 85% ee	**4ft**; 65% yield, 30% ee	*s*=16

Table 3. Kinetic resolution of amino alcohols **4ap–at**

Entry	Compounds	R	Products (*S*)-**5ap–at**		Recovered (*R*)-**4ap–at**			Selectivity (*s*)[a]
	4ap–at		Yield (%)	% ee		Yield (%)	% ee	
1	**4ap**	H	**5ap**	26	78	**4ap**	62	32	11
2	**4aq**	*p*-Cl	**5aq**	30	46	**4aq**	73	16	3
3	**4ar**	*o*-Cl	**5ar**	20	77	**4ar**	72	30	10
4	**4as**	*p*-OMe	**5as**	45	83	**4as**	53	62	20
5	**4at**	*o*-OMe	**5at**	36	93	**4at**	59	55	50

[a] Ref. 1a.

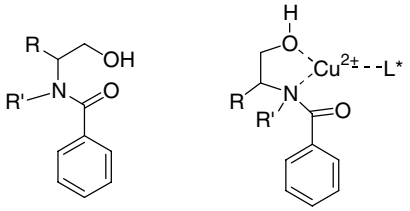
reactive than 1,2-diol **8a** but it was more reactive than benzoyloxy-, ethoxyl- or ethyl-substituted ethanols (**8b–d**).

On the basis of those results, we tried a kinetic resolution of *dl*-valinol derivatives **4ap–at** by benzoylation in which copper triflate and (*R*,*R*)-Ph-BOX were present. The results are shown in Table 3.

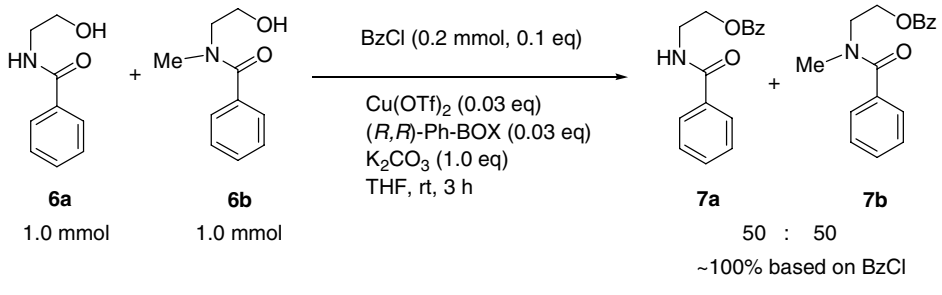
A moderate enantioselectivity (78% ee) was observed in the case of N-benzoylated valinol **4ap** (entry 1), but *o*-MeO-phenylcarbonylated valinol **4at** gave the best result (entry 5) among those examined (entries 1-5). The *s* value[1a] was 50.

The other examples of kinetic resolution are shown in Eq. 7.

Our attention was then focused on a kinetic resolution of N-alkylated *N*-benzoylethanolamine derivatives **10** because there have been known numerous naturally occurring compounds having an *N*-alkylethanolamine moiety.



So, we tried a competitive reaction between **6a** and **6b** to afford a mixture of **7a** and **7b** with a ratio of 50/50 (Eq.



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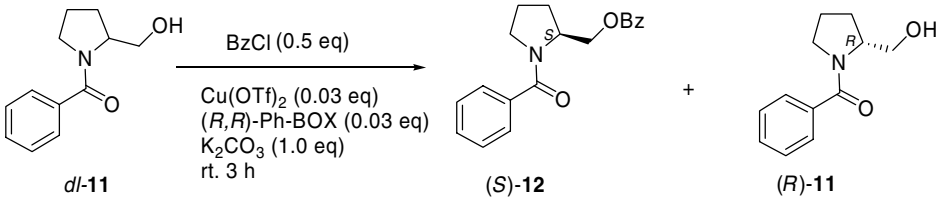
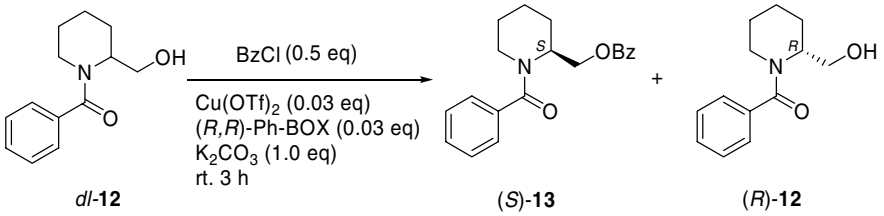


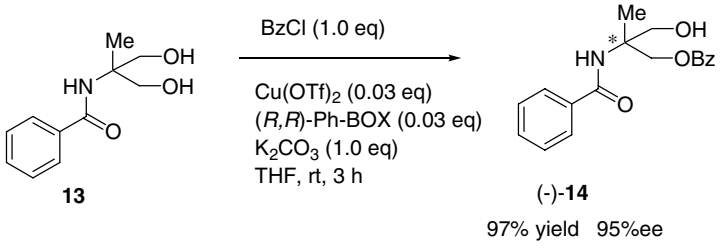
(9)

in THF	49% yield	94% ee	44% yield	95% ee	s=118
in Et_2O	43% yield	97% ee	57% yield	84% ee	s=174



(10)

in THF	40% yield	95% ee	48% yield	79% ee	s=95
in Et_2O	49%yield	95% ee	50% yield	98% ee	s=177



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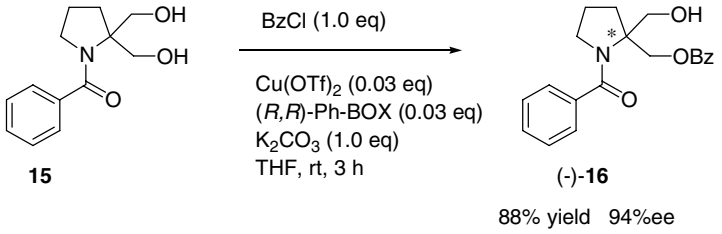

(12)

8), indicating that **6b** had similar reactivity to **6a** for the benzoylation, and suggesting an intermediary formation of intermediates **2**′,[7] which corresponded to **2** derived from diols **1**.

On the basis of this result, *dl*-prolinol (*dl*-**11**) and *dl*-piperidinemethanol (*dl*-**13**) were subjected (Eqs. 9 and 10) to kinetic resolution under conditions similar to those for **4ap**–**4ft**.[8]

Also, 2-amino-1,3-diols **13** and **15** were asymmetrically desymmetrized by benzoylation to afford optically active **14** and **16** in 97% yield with 95% ee and 88% yield with 94% ee, respectively (Eqs. 11 and 12).[9]

The results shown in this paper are useful for the preparation of optically active *vic*-amino alcohols, because our method is very simple and easy in operation in comparison with the reported methods. The mechanistic details and an application of asymmetric desymmetrization are now under investigation.

Acknowledgement

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7. A kinetic resolution of *dl*-*N*-benzyl-α-piperidinemethanol under conditions similar to those for **4ap**–**4ft** proceeded to afford the corresponding benzoate in 21% yield with 62% ee. This result supports an intermediary formation of intermediates **2′**.

8. Typical procedure for kinetic resolution: Into a solution of $Cu(OTf)_2$ (5.4 mg, 0.015 mmol) and (*R*,*R*)-Ph-Box (5.0 mg, 0.015 mmol) in THF (2 mL) were added *dl*-**12** (110 mg, 0.5 mmol), K_2CO_3 (69.1 mg, 0.5 mmol) and benzoyl chloride (0.029 mL, 0.25 mmol). After being stirred for 3 h at rt, into the reaction mixture water (10 mL) was added. The organic portion was extracted with AcOEt (20 mL × 3). 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–AcOEt = 1:2) to afford (*S*)-**13** (64.9 mg, 40% yield, 95% ee) and (*R*)-**12** (53.0 mg, 48% yield, 79% ee). Optical purities of product (*S*)-**13** and recovered (*R*)-**12** were determined by chiral HPLC: Daicel Chiralcel OD column (4.6 mm ∅, 25 cm), *n*-hexane–isopropanol = 20:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time for **13**: 19.7 min ((*S*)-(−)-**13**), 22.9 min ((*R*)-(+)-**13**). retention time for **12**: 18.1 min ((*S*)-(−)-**12**), 20.2 min ((*R*)-(+)-**12**).

9. The absolute stereoconfigurations of **14** and **16** have not yet been determined. Compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 3H), 3.79 (d, $J = 12.3$ Hz, 1H), 3.88 (d, $J = 12.3$ Hz, 1H), 4.42 (br s, 1H), 4.61 (d, $J = 11.7$ Hz, 1H), 4.69 (d, $J = 11.4$ Hz, 1H), 6.79 (br s, 1H), 7.40–7.64 (m, 6H), 7.77 (d, $J = 6.9$ Hz, 2H), 8.06 (d, $J = 7.2$ Hz, 2H). HPLC: Daicel Chiralcel OD column (4.6 mm ∅, 25 cm), *n*-hexane/isopropanol = 20:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 31.7 min ((−)-isomer), 36.7 min ((+)-isomer). $[\alpha]_D^{26.5}$ −19.7 (*c* 2.0, $CHCl_3$).
Compound **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75–2.02 (m, 3H), 2.18–2.28 (m, 1H), 3.40–3.60 (m, 2H), 3.95–4.02 (m, 2H), 4.81 (d, $J = 11.1$ Hz, 1H), 4.95 (d, $J = 11.4$ Hz, 1H), 5.63 (br t, $J = 5.7$ Hz, 1H), 7.28–7.52 (m, 7H), 7.56–7.63 (m, 1H), 8.07 (d, $J = 7.2$ Hz, 2H). HPLC: Chiralpak AD column (4.6 mm ∅, 25 cm), *n*-hexane/isopropanol = 5:1, wavelength: 254 nm, flow rate: 1.0 mL/min. retention time: 10.9 min ((+)-isomer), 14.4 min ((−)-isomer). $[\alpha]_D^{28.0}$ −50.4 (*c* 0.85, $CHCl_3$).