

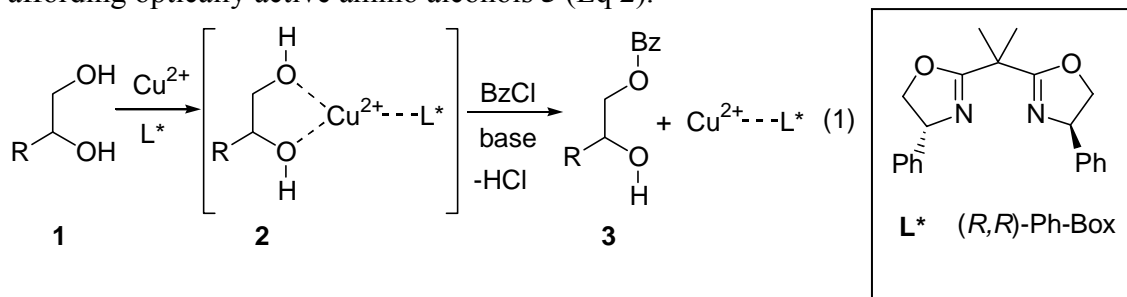
Kinetic resolution of *vic*-amino alcohols catalyzed by chiral Cu(II) complex

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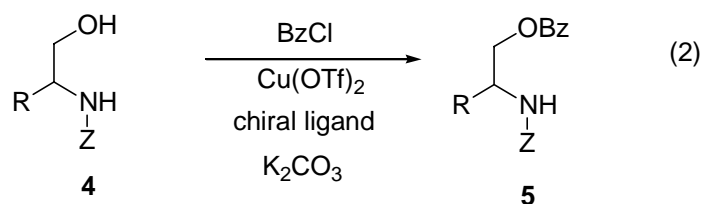
Abstract— Kinetic resolution of *N*-benzoylated *vic*-amino alcohols was achieved by benzoylation in the presence of copper triflate and (*R,R*)-Ph-BOX as catalysts. The observed enantioselectivity was moderate to high. The method was applied to a kinetic resolution of racemic prolinol and piperidinemethanol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

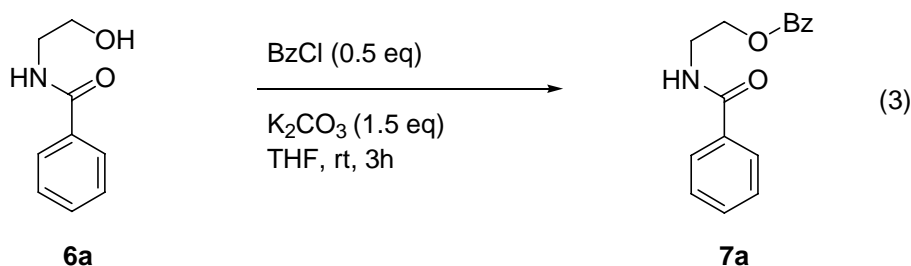


Key words: kinetic resolution; *vic*-amino alcohol; monobenzoylation; chiral copper complex

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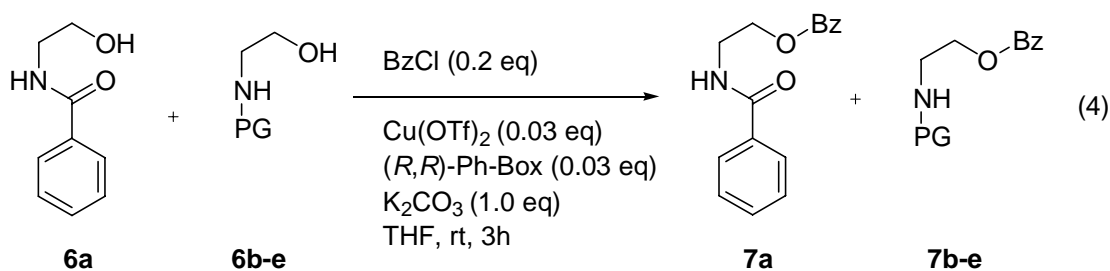


In advance of the kinetic resolution of **4**, we first tried the benzoylation of *N*-protected amino alcohol **6a** as a model compound to see whether it behaved in a similar way to 1,2-diols **1**. The result showed that the reaction of **6a** with BzCl afforded **7a** in 96% yield, while 22% yield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



in the presence of Cu(OTf)₂ (0.03eq)
 and (*R,R*)-Ph-Box (0.03eq) 96% based on BzCl
 in the absence of Cu(OTf)₂
 and (*R,R*)-Ph-Box 22% based on BzCl

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.

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 ₂ t-Bu	100 : 0
2	6c	CO ₂ CH ₂ Ph	100 : 0
3	6d	SO ₂ Ph <i>p</i> -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), K₂CO₃ (0.5 mmol), THF (2 mL), at rt for 3 h.

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

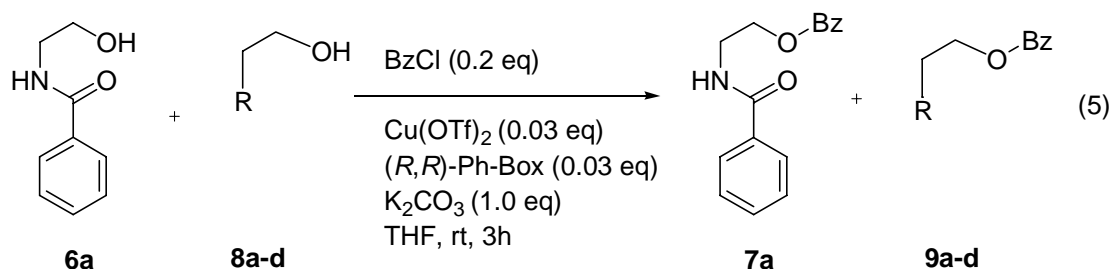


Table 2. Competitive benzoylation reaction of **6a** with alcohols **8a-d**^a

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), K₂CO₃ (0.5 mmol), THF (2 mL), at rt for 3 h.

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.

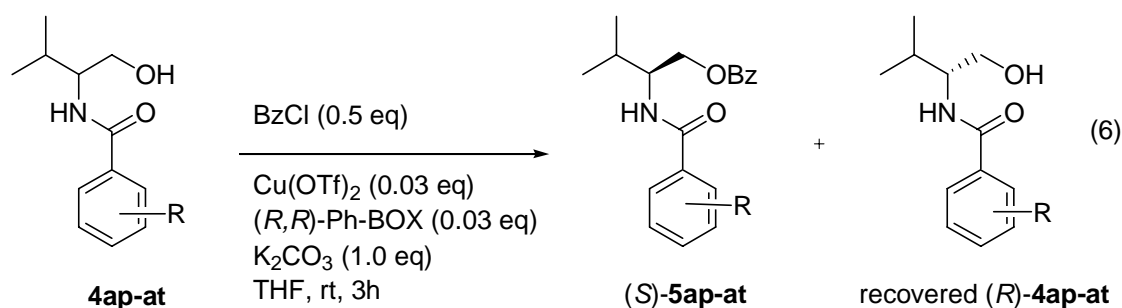


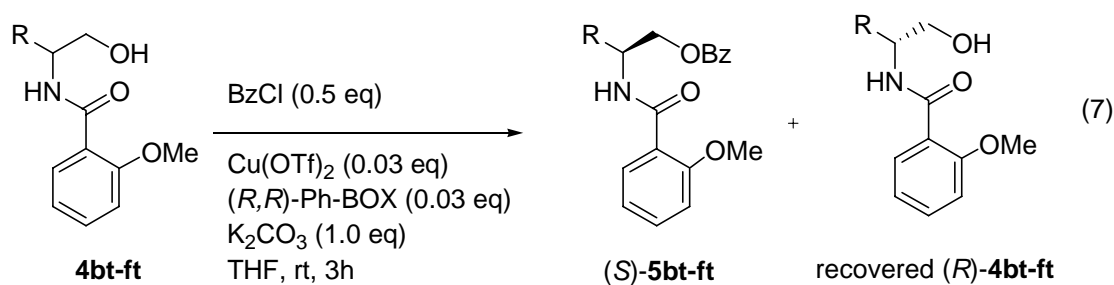
Table 3. Kinetic resolution of amino alcohols **4ap-at**

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

^a Reference 1a.

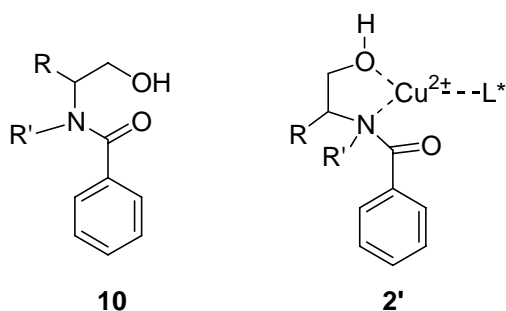
A moderate enantioselectivity (78% ee) was observed in a case of *N*-benzoylated valinol **4ap** (Entry 1), but *o*-MeO-phenylcarbonylated valinol **4at** gave the best result (Entry 5) among those examined (Entries 1-5). The *s* value^{1a} was 50.

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

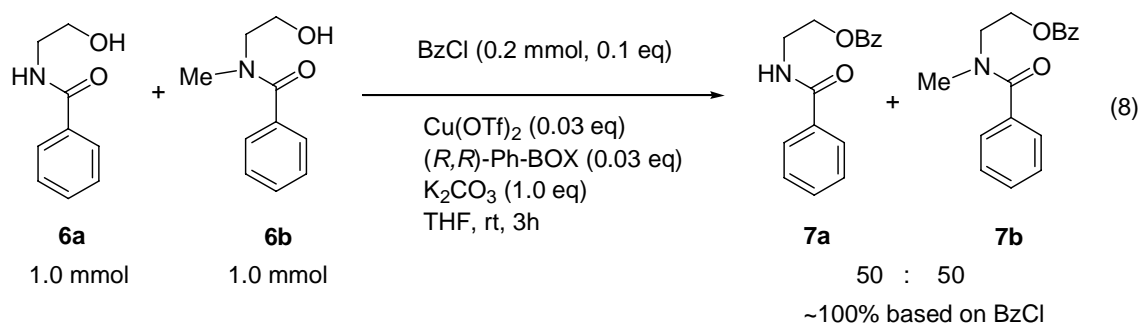


R=Me	5bt ; 34% yield, 89% ee	4bt ; 62% yield, 54% ee	<i>s</i> =29
R=Et	5ct ; 41% yield, 86% ee	4ct ; 42% yield, 68% ee	<i>s</i> =28
R=Ph	5dt ; 26% yield, 85% ee	4dt ; 62% yield, 36% ee	<i>s</i> =18
R= <i>p</i> -ClPhCH ₂	5et ; 33% yield, 87% ee	4et ; 51% yield, 80% ee	<i>s</i> =35
R= <i>p</i> -MeOPhCH ₂	5ft ; 32% yield, 85% ee	4ft ; 65% yield, 30% ee	<i>s</i> =16

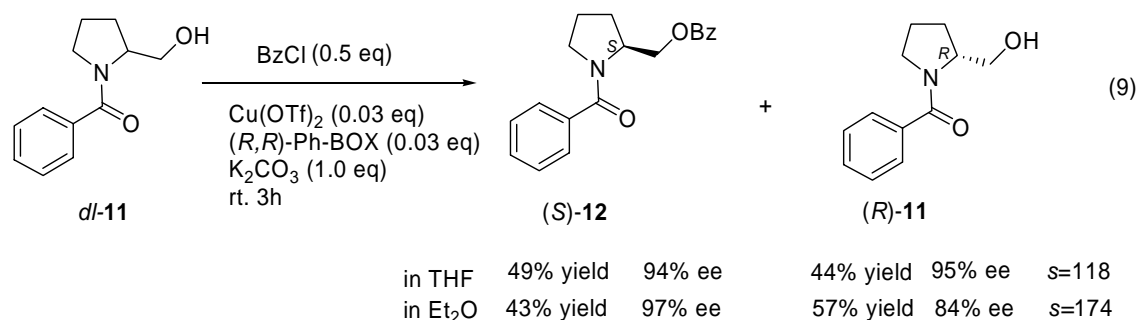
Our attention was then focused on a kinetic resolution of *N*-alkylated *N*-benzolyethanolamine derivatives **10** because there have been known numerous naturally occurring compounds having an *N*-alkylethanolamine moiety.

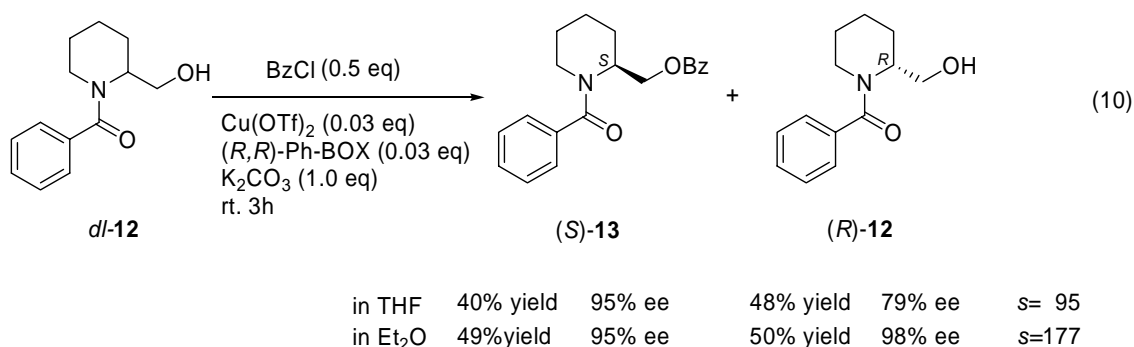


So, we tried a competitive reaction between **6a** and **6b** to afford a mixture of **7a** and **7b** with a ratio of 50/50 (Eq 8), indicating that **6b** had similar reactivity to **6a** for the benzoylation, and suggesting an intermediary formation of intermediates **2'**⁷ which corresponded to **2** derived from diols **1**.

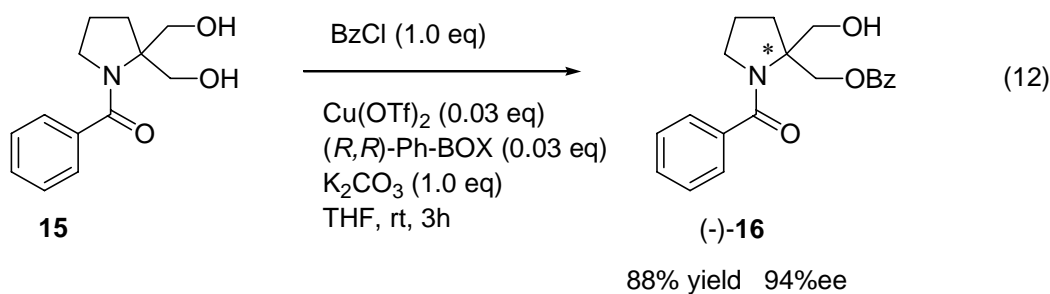
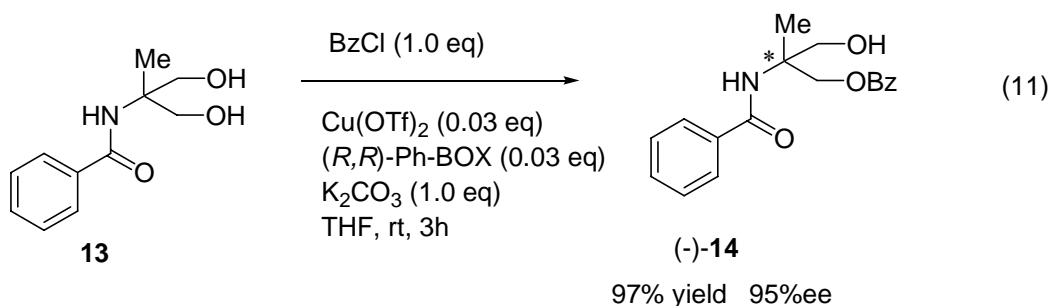


On the basis of this result, *dl*-prolinol (*dl*-**11**) and *dl*-piperidinemethanol (*dl*-**13**) were subjected (Eqs 9 and 10) to kinetic resolution under conditions similar to those for **4ap-4ft**.⁸





Also, 2-amino-1,3-diols **13** and **15** were asymmetrically desymmetrized by benzylation 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 preparation of optically active *vic*-amino alcohols, because our method is very simple and easy in operation in comparison with reported methods. The mechanistic details and an application of asymmetric desymmetrization are now under investigation.

Acknowledgement

Y. M. thanks the Japan Society for the Promotion of Science for Scientific Research (B) (17350051) for financial support.

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- 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'**.
 - 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) was added *dl*-**12** (110 mg, 0.5 mmol), K₂CO₃ (69.1mg, 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 (20mL x 3). The combined organic layer was dried over MgSO₄ and the solvent was removed *in vacuo*. The residue was chromatographed on SiO₂ (*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 ϕ , 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**), 22.9min ((*R*)-(+)-**13**). retention time for **12**: 18.1min ((*S*)-(-)-**12**), 20.2min ((*R*)-(+)-**12**).
 - The absolute stereoconfiguration of **14** and **16** has not yet been determined.
14: ¹HNMR (300MHz, CDCl₃) δ 1.54 (s, 3H), 3.79 (d, *J*=12.3Hz, 1H), 3.88 (d, *J*=12.3Hz, 1H), 4.42 (br s, 1H), 4.61 (d, *J*=11.7Hz, 1H), 4.69 (d, *J*=11.4Hz, 1H), 6.79 (br s, 1H), 7.40-7.64 (m, 6H), 7.77 (d, *J*=6.9Hz, 2H), 8.06 (d, *J*=7.2Hz, 2H). HPLC: Daicel Chiralcel OD column (4.6 mm ϕ , 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, CHCl₃).
16: ¹HNMR (300MHz, CDCl₃) 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*=11.1Hz, 1H), 4.95 (d, *J*=11.4Hz, 1H), 5.63 (br t, *J*=5.7Hz, 1H), 7.28-7.52 (m, 7H), 7.56-7.63 (m, 1H), 8.07 (d, *J*=7.2Hz, 2H). HPLC: Chiralpak AD column (4.6 mm ϕ , 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, CHCl₃).

