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Asymmetric desymmetrization of *meso-vic*-diols by carbamoylation catalyzed with a chiral Cu(II) complex

Kazuya Matsumoto, Masaru Mitsuda, Nobuto Ushijima, Yosuke Demizu, Osamu Onomura and Yoshihiro Matsumura*

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

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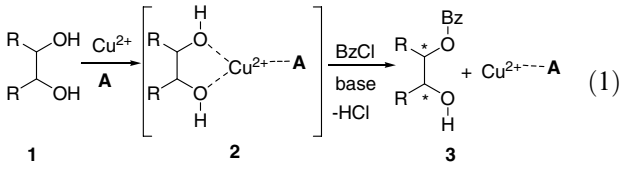
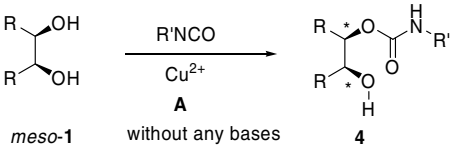
Abstract—Asymmetric desymmetrization of *meso-vic*-diols was achieved by carbamoylation in the presence of copper triflate and (*S*,*S*)-Ph-BOX as a catalyst without any use of bases. The method was successfully applied to asymmetric desymmetrization of five- to eight-membered cyclic *meso-vic*-diols in high enantioselectivity with up to 93% ee.

We recently exploited an efficient method for kinetic resolution and asymmetric desymmetrization of *vic*-diols **1**, which is based on recognition of the *vic*-diol moiety by a copper ion associated with chiral ligands such as (*S*,*S*)-Ph-BOX (**A**)[1] to afford the activated *vic*-diol intermediates **2** followed by benzoylation under basic conditions (Eq. 1).[2] Basic conditions were essential in the benzoylation to remove the generated hydrogen chloride. However, the products sometimes suffered from acyl transfer reaction[3] under the basic conditions, decreasing the enantioselectivity of the products **3**. So, it is worthwhile to find conditions in which kinetic resolution of *dl*-**1**[4] or asymmetric desymmetrization of *meso*-**1**[5] can be achieved under non-basic conditions. We report herein an asymmetric desymmetrization of *meso*-**1** by carbamoylation with isocyanates (R′NCO) under non-basic conditions to afford optically active *meso-vic*-diol derivatives **4** (Eq. 2).

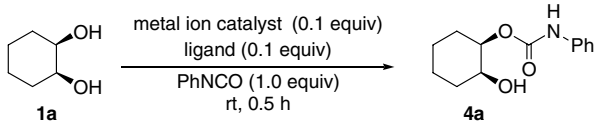


1 2 3 (1)



meso-**1** **4** (2)

First of all, we tried the carbamoylation of *meso*-1,2-cyclohexanediol (**1a**) as a model compound in the reaction with phenylisocyanate without using any bases (Eq. 3).[6]



1a **4a** (3)

The results are summarized in Table 1, which shows a dependence of the yield and % ee of the product **4a** on the used metal ions, chiral ligands **A**–**D**,[7] and solvents. That is, in THF as a solvent, the product **4a** was obtained in 88–92% yield in the presence of copper triflate ($Cu(OTf)_2$) (entries 2 and 4) and with a moderately high % ee (76% ee) when both $Cu(OTf)_2$ and **A** were present (entry 4), while yield of **4a** was low (2–11%) in the absence of $Cu(OTf)_2$ (entries 1 and 3). On the other hand, no enantioselectivity of **4a** was observed in a case using $Sn(OTf)_2$ even in the presence of **A**, though yield of **4a** was high (entry 11). The zinc ion was also not so effective (entry 10), and the other ligands **B**–**D** other

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* Corresponding author. Tel.: +81 95 819 2429; fax: +81 95 819 2476; e-mail: matumura@net.nagasaki-u.ac.jp

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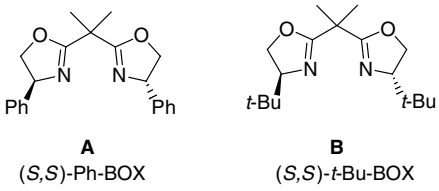
Table 1. Asymmetric carbamylation of *meso*-1,2-cyclohexanediol (**1a**)[a]

Entry	Metal ion catalyst	Ligand	Solvent	Product **4a**	
				Yield (%)	ee (%)[b]
1	—	—	THF	2	—
2	$Cu(OTf)_2$	—	THF	88	—
3	—	**A**	THF	11	17
4	$Cu(OTf)_2$	**A**	THF	92	76
5	$Cu(OTf)_2$	**A**	AcOEt	88	77
6	$Cu(OTf)_2$	**A**	MeCN	87	79
7	$Cu(OTf)_2$	**A**	CH_2Cl_2	88	66
8	$Cu(OTf)_2$	**A**	Toluene	86	12
9	$CuCl_2$	**A**	THF	11	18
10	$Zn(OTf)_2$	**A**	THF	47	24
11	$Sn(OTf)_2$	**A**	THF	91	*Racemic*
12	$Cu(OTf)_2$	**B**	THF	94	30
13	$Cu(OTf)_2$	**C**	THF	<1	—
14	$Cu(OTf)_2$	**D**	THF	56	*Racemic*

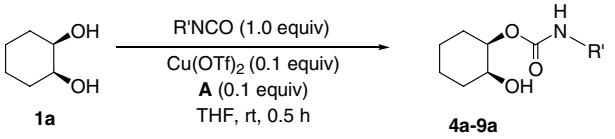
[a] **1a** (0.5 mmol), metal ion catalyst (0.05 mmol), ligand (0.05 mmol), PhNCO (0.5 mmol) in a solvent (2 mL) at rt for 0.5 h.
[b] Determined by HPLC.

than **A** were ineffective even in the presence of $Cu(OTf)_2$ (entries 12–14). AcOEt and MeCN were usable instead of THF (entries 5 and 6), while CH_2Cl_2 and toluene were ineffective (entries 7 and 8).



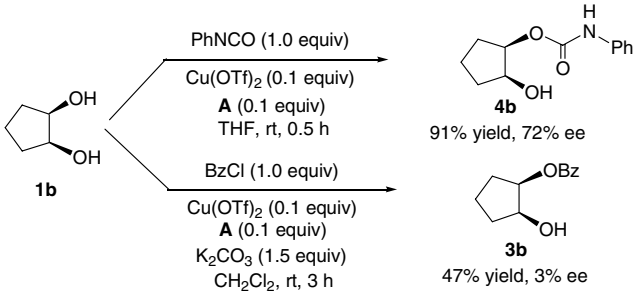
A (*S,S*)-Ph-BOX; **B** (*S,S*)-*t*-Bu-BOX; **C** (*S,S*)-Ph-PyBOX; **D**

A variety of isocyanates (R′NCO) besides phenylisocyanate were usable for carbamoylation of **1a** under the reaction conditions similar to entry 4 in Table 1 (Eq. 4, Table 2).



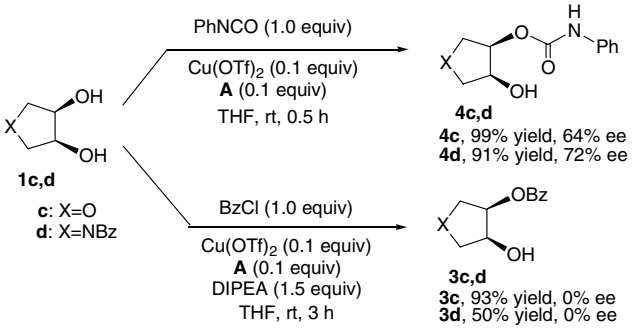
(4)

With almost such satisfactory results for carbamoylation of **1a** in hand, we tried carbamoylation of *meso*-1,2-cyclopentanediol (**1b**) under the reaction conditions and found that the reaction afforded **4b** with 72% ee, while **1b** was not asymmetrically desymmetrized by benzoylation with $Cu(OTf)_2$ and **A** in the presence of a base (Eq. 5).[8,9]



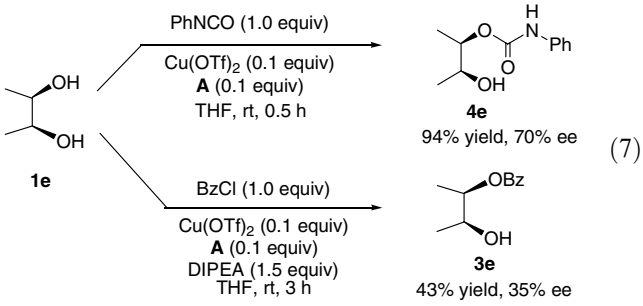
(5)

Similarly, oxygen or nitrogen atom-containing five-membered diols **1c**,**d** were asymmetrically desymmetrized by carbamoylation to afford **4c**,**d**, whereas *racemic* products **3c**,**d** were obtained by benzoylation (Eq. 6).



(6)

Also, our method was applicable to an acyclic 1,2-diol **1e** (Eq. 7), and 1,3-diol **10p** (Eq. 8).[8,10,11]

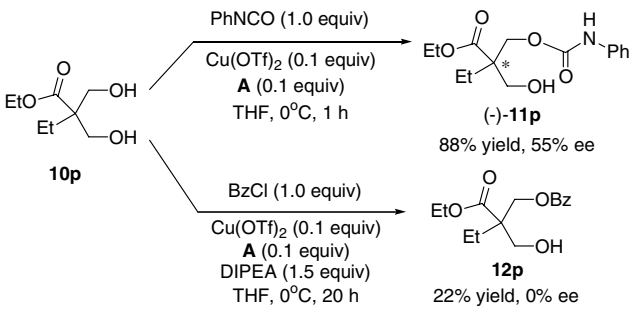


(7)

Table 2. Carbamoylation of **1a** by various isocyanates[a]

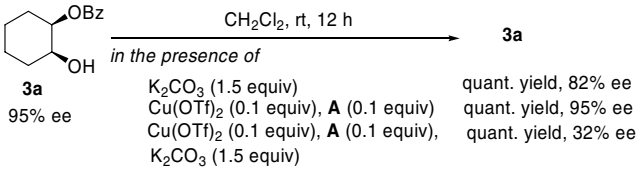
Entry	R′	Product	Yield (%)	ee[b] (%)
1	Ph	**4a**	92	76
2	*p*-ClPh	**5a**	93	76
3	*p*-MeOPh	**6a**	85	68
4	*t*-Bu	**7a**	50	75
5	1-Adamantyl	**8a**	68	62
6	1-Naphthyl	**9a**	77	77

[a] **1a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), **A** (0.05 mmol), R′NCO (0.5 mmol) in THF (2 mL) at rt for 0.5 h.
[b] Determined by HPLC.



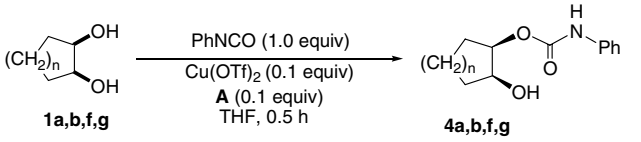
(8)

The reason why **1b–d** could not be desymmetrized by benzoylation may be rationalized in terms of intramolecular acyl transfer of optically active **3b–d** since optically active **3a**[12] lost some extent of its optical activity when **3a** was subjected to the reaction conditions for a long time (12 h) (Eq. 9).[13]



(9)

In order to improve % ee in carbamoylation of *meso*-**1**, we surveyed the effect of temperature on carbamoylation of five- to eight-membered *meso*-cycloalkanediols **1a**,**b**,**f**,**g** with phenylisocyanate (Eq. 10). The results are shown in Table 3, which indicates that the % ee's were improved with up to 93% ee at −40 °C in comparison with those obtained at room temperature.



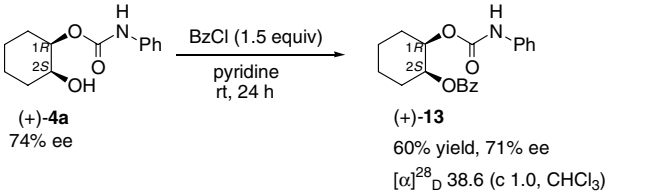
(10)

The absolute stereoconfiguration of **4a** was determined to be (1*R*,2*S*) by transformation of (+)-**4a** (74% ee) to (1*R*,2*S*)-(+)-**13**[14] (Eq. 11) which was the enantiomer of (1*S*,2*R*)-(−)-**13** derived from reported (1*R*,2*S*)-(−)-**3a**[15] (95% ee) (Eq. 12).

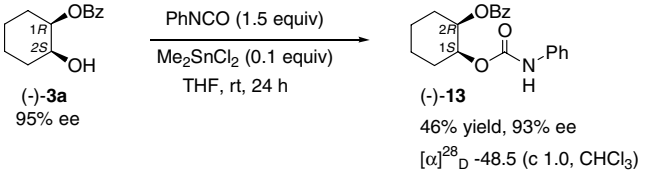
Table 3. Asymmetric monocarbamoylation of *meso*-1,2-diol **1a**,**b**,**f**,**g**[a]

Entry	Substrate	*n*	Product	−40 °C		rt	
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)
1	**1b**	1	**4b**	82	86	91	72
2	**1a**	2	**4a**	69	86	92	76
3	**1f**	3	**4f**	83	91	83	83
4	**1g**	4	**4g**	72	93	96	86

[a] **1** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), **A** (0.05 mmol), PhNCO (0.5 mmol) in THF (2 mL) for 0.5 h.
[b] Determined by HPLC.

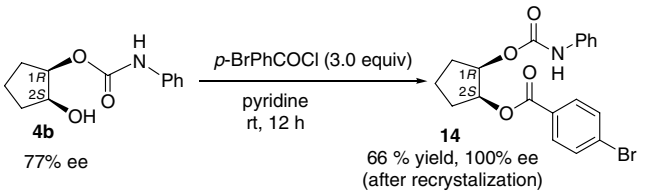


(11)



(12)

The absolute stereoconfiguration of (1*R*,2*S*)-**4b** was confirmed by its conversion to **14** (Eq. 13), which was found to possess a configuration of (1*R*,2*S*) on the X-ray analysis.[16,17]



(13)

The results shown in this letter are useful for a preparation of optically active *meso-vic*-diol derivatives **4**, because our method is very simple, easily operable,[18] and *vic*-diol selective.[19] The mechanistic study and a kinetic resolution of *dl-vic*-diols in our carbamoylation are now under investigation.

Acknowledgements

Y.M. thanks the Japan Society for the Promotion of Science for Scientific Research (B) (17350051) for financial support. We are grateful to BRUKER AXS K. K. for X-ray structure determination of compound **14**.

References and notes

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6. A typical procedure for asymmetric desymmetrization: Under an aerobic atmosphere, a solution of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and (*S*,*S*)-Ph-Box (**A**) (16.7 mg, 0.05 mmol) in THF (2 mL) was stirred for 10 min. Into the solution were added *meso*-**1a** (58.1 mg, 0.5 mmol) and phenylisocyanate (0.054 mL, 0.5 mmol, used as purchased). After being stirred for 0.5 h at rt, water (10 mL) was added into the reaction mixture. 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 = 5:1) to afford (+)-**4a** (92% yield, 76% ee) as a white solid.
Mp 72–74 °C; $[\alpha]_D^{22}$ 4.9 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.38–1.50 (m, 2H), 1.60–2.00 (m, 6H), 2.24 (br s, 1H), 3.96 (d, $J = 6.9$ Hz, 1H), 4.94 (d, $J = 8.1$ Hz, 1H), 6.84 (br s, 1H), 7.07 (t, $J = 7.2$ Hz, 1H), 7.28–7.45 (m, 4H). ^{13}CNMR (75 MHz, $CDCl_3$) δ 20.9, 21.7, 27.1, 30.1, 69.2, 74.7, 118.6, 123.3, 128.3, 137.7, 153.4.
The optical purity of **4a** was determined by chiral HPLC: Daicel Chiralcel OJ column (4.6 mm ∅, 25 cm), *n*-hexane:isopropanol = 10:1, wavelength: 210 nm, flow rate: 1.0 mL/min, retention time: 7.7 min ((1*S*,2*R*)-(−)-**4a**), 12.0 min ((1*R*,2*S*)-(+)-**4a**).
7. For (*S*,*S*)-*t*-Bu-BOX (**B**): (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728; For (*S*,*S*)-Ph-PyBOX (**C**): (b) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846–848; (c) Chelucci, G.; Deriu, S.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3803–3810; For **D**: (d) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751–3754.
8. Benzoylation of **1b** in the absence of a base hardly proceeded for 3 h.
9. Potassium carbonate (K_2CO_3) was usable as a base instead of *N*,*N*-diisopropylethyl-amine (DIPEA), which was used in our asymmetric monobenzoylation of *vic*-diols.[2] Monobenzoylation of *vic*-diols using K_2CO_3 will be reported elsewhere by us.
10. Asymmetric monocarbamoylation of *meso*-1,3-diols catalyzed by chiral organotins (up to 42% ee): Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201–3204.
11. The absolute stereoconfiguration of (−)-**11p** has not yet been determined.
HPLC: Daicel Chiralpak AD column (4.6 mm ∅, 25 cm), *n*-hexane:isopropanol = 10:1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 16.4 min ((−)-isomer), 18.2 min ((+)-isomer). $[\alpha]_D^{23.8}$ −6.7 (*c* 0.5, $CHCl_3$).
12. Since optically active **3b** was not easily obtainable, intramolecular acyl transfer of optically active **3a** (95% ee), which was prepared by desymmetric monobenzoylation of **1a** described in Ref. 2a and successive recrystallization, was examined.
13. Standing optically active carbamates **4a**,**e** under the reaction conditions for 12 h did not cause any decrease of their optical purities.
14. Chiral HPLC condition: Daicel Chiralpak AD column (4.6 mm ∅, 25 cm), *n*-hexane:isopropanol = 5:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 9.4 min ((1*R*,2*S*)-(+)-**13**), 12.9 min ((1*S*,2*R*)-(−)-**13**).
15. Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170.
16. Compound (1*R*,2*S*)-(+)-**14**: mp 132–134 °C, $[\alpha]_D^{27}$ 59.4 (*c* 1.0, $CHCl_3$), Chiral HPLC condition: Daicel Chiralcel OJ column (4.6 mm ∅, 25 cm), *n*-hexane:isopropanol = 10:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 28.9 min ((1*R*,2*S*)-(+)-**14**), 40.2 min ((1*S*,2*R*)-(−)-**14**).
Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 619049. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
17. Absolute stereoconfiguration of **4c**–**g** shown in Eqs. 6, 7 and 10 was deduced on the basis of that of **4a**,**b**.
18. Bhowmick, K. C.; Joshi, N. N. *Tetrahedron: Asymmetry* **2006**, *17*, 1901–1929.
19. Carbamoylation of **1a** proceeded even in the presence of cyclohexanol (1 equiv) to afford **4a** in a similar yield (94%) and optical purity (75% ee).