Asymmetric oxidation of 1,2-diols using *N*-bromosuccinimide in the presence of chiral copper catalyst

Osamu Onomura,* Hitomi Arimoto, Yoshihiro Matsumura, and Yosuke Demizu

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

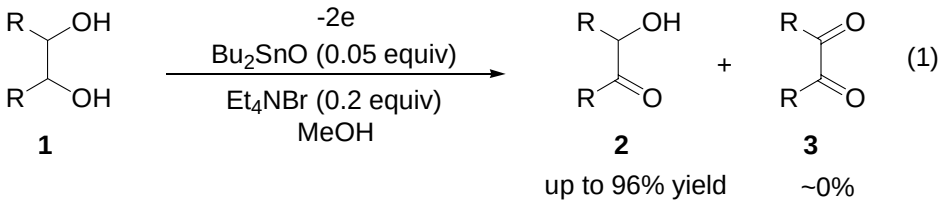
Dedicated to the memory of the late Professor Yoshihiko Ito

Abstract- Asymmetric oxidation of 1,2-diols using *N*-bromosuccinimide (NBS) in the presence of copper(II) triflate and (*R*,*R*)-Ph-BOX has been exploited. This oxidation was applicable to asymmetric desymmetrization of *meso*-hydrobenzoin and kinetic resolution of *dl*-hydrobenzoin and *racemic*-cycloalkane-*cis*-1,2-diols to afford optically active α-ketoalcohols with good to high enantiomeric excess.

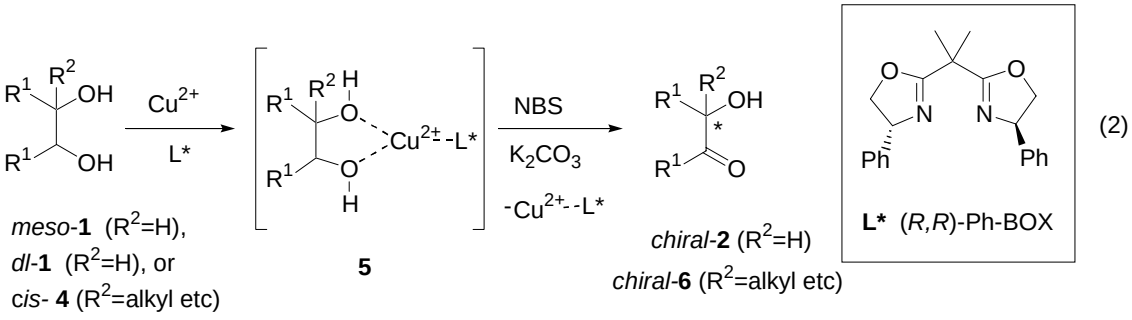
The oxidation of a hydroxyl group into a carbonyl group is a basic and important organic reaction.[1] Selective oxidation of 1,2-diols to the corresponding α-ketoalcohols was reported in 1974 by utilizing a stoichiometric amount of dibutyltinoxide (Bu_2SnO) which forms dibutylstannylenes followed by brominolysis,[2] and the method has been applied to fine chemistry as exemplified by the synthesis of (+)-spectinomycin[3] and the oxidation of unprotected sugars.[4,5] From the standpoint of green chemistry, we have recently reported efficient oxidation of 1,2-diols **1** by electrochemical method using a catalytic amount of Bu_2SnO and bromide ion to afford α-ketoalcohols **2** in high yield without 1,2-diketones **3** (Eq. 1).[6] Also, chemical oxidation of **1** using *N*-bromosuccinimide (NBS) (1 equiv) and Bu_2SnO (0.1 equiv) in the presence of K_2CO_3 (1 equiv) proceeded to afford **2**.[7] To the best of our knowledge, catalytic asymmetric oxidation[8] of **1** to **2** has not been known except for two examples using *semi*-catalytic amount of chiral dioxiranes[9] or chiral hypervalent iodine.[10]

Key words: Asymmetric oxidation; *vic*-Diol; α-Ketoalcohol, Copper complex

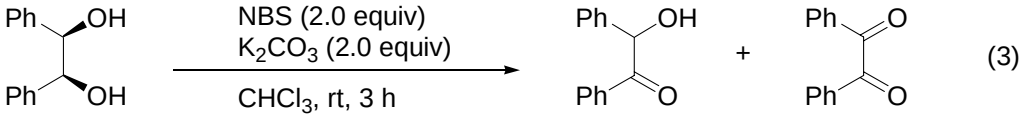
* Corresponding author, Tel +81-95-819-2429, Fax +81-95-819-2476, E-mail onomura@nagasaki-u.ac.jp (O. Onomura)



We wish to report herein a catalytic asymmetric oxidation of (*meso* or *dl*)-1,2-diols *meso*- or *dl*-**1**, or *cis*-1,2-diols **4** to afford the corresponding optically active α-ketoalcohols *chiral*-**2** or *chiral*-**6** in good to high yield and enantioselectivity, which is based on recognition of the diol-moiety by a copper(II) ion associated with (*R*,*R*)-Ph-BOX complex[11,12] to form the activated intermediates **5** followed by oxidation with NBS[13] as an oxidant (Eq. 2).



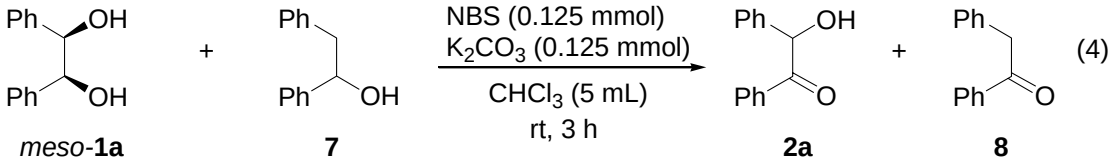
We began by trying an oxidation of *meso*-hydrobenzoin (*meso*-**1a**) using NBS as an oxidant to see whether *meso*-**1a** was recognized by the Cu(II)–(*R*,*R*)-Ph-BOX complex under the above stated oxidation condition or not. The oxidation of *meso*-**1a** in the presence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX predominantly afforded mono-oxidized product **2a** (83% yield) along with small amount of di-oxidized product **3a** (17% yield), while there was almost no oxidation in the absence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX (Eq. 3). These results suggested that *meso*-**1a** is recognized by the Cu(II)–(*R*,*R*)-Ph-BOX complex under these oxidation conditions. Acceleration of the oxidation was also observed in the presence of $Cu(OTf)_2$ without (*R*,*R*)-Ph-BOX to afford **2a** in high yield (91%).[14]



meso-**1a** **2a** **3a** (3)

in the presence of $Cu(OTf)_2$ (0.1 equiv) and (*R,R)*-Ph-BOX (0.1 equiv)	83%	17%
in the presence of $Cu(OTf)_2$ (0.1 equiv)	91%	9%
in the absence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX	4%	0%

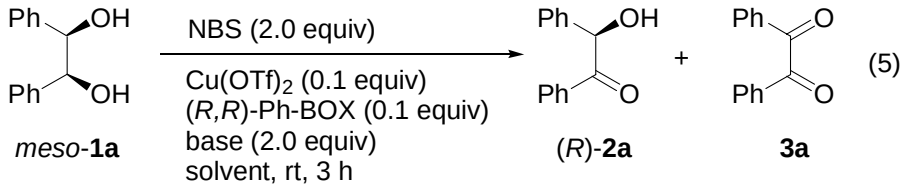
Then, we tried competitive reaction between diol *meso*-**1a** and monool **7** (Eq. 4). In the absence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX, *meso*-**1a** and **7** were oxidized to **2a** and **8** with almost same ratio. On the other hand, in the presence of Cu(II)–(*R*,*R*)-Ph-BOX, **2a** was predominantly obtained**.** This result indicates that *meso*-1,2-diol was more preferentially-recognized with the Cu(II)–(*R*,*R*)-Ph-BOX catalyst than monool.



meso-**1a** (0.25 mmol) **7** (0.25 mmol) (4)

	ratio	
	2a :	**8**
in the presence of $Cu(OTf)_2$ (0.025 mmol), (*R*,*R*)-Ph-BOX (0.025 mmol)	84 :	16
in the absence of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX	57 :	43

Next, we investigated effect of solvents and bases so as to optimize reaction conditions for the asymmetric oxidation of *meso*-**1a** (Eq. 5).[15] The results are summarized in Table 1. $CHCl_3$ is the best solvent for the reaction in terms of enantiomeric excess (entry 1). CH_2Cl_2, THF, CH_3CN and AcOEt give high yield of product (*R*)-**2a** although the enantioselectivity is very low or sometime racemic mixture (entries2-5). MeOH gives very low yield with moderate enantioselectivity (entry 6). In the case of bases, K_2CO_3 emerged as the best base especially when used in combination with $CHCl_3$ (entry 1). Na_2CO_3 and $NaHCO_3$ give comparable results to that of K_2CO_3 (entries 8 and 9). Other bases fall short in terms of yield or enantioselectivity (entries 7, 10, 11).



(5)

Table 1. Asymmetric oxidation of *meso*-hydrobenzoin (*meso*-**1a**)[a]

Entry	Solvent	Base	(*R*)-**2a**		**3a**
			Yield (%)	ee (%)[b]	Yield (%)
1	$CHCl_3$	K_2CO_3	83	72	17
2	CH_2Cl_2	K_2CO_3	92	26	8
3	THF	K_2CO_3	87	29	13
4	CH_3CN	K_2CO_3	88	0	12
5	AcOEt	K_2CO_3	87	23	13
6	MeOH	K_2CO_3	9	46	25
7	$CHCl_3$	Li_2CO_3	88	59	12
8	$CHCl_3$	Na_2CO_3	96	66	4
9	$CHCl_3$	$NaHCO_3$	91	67	9
10	$CHCl_3$	KOH	79	29	21
11	$CHCl_3$	2,6-lutidine	97	15	3

[a] *meso*-**1a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), NBS (1.0 mmol), base (1.0 mmol) in a solvent (5.0 mL) at rt for 3 h.
[b] Determined by HPLC.

Utilizing the conditions optimized in Table 1, we screened other halogen compounds as oxidants in this reaction (Eq. 6). The results are shown in Table 2. In addition to NBS, *N*-bromophthalimide (entry 4) was usable for asymmetric oxidation, while other oxidants (entries 1-3) were less effective. The use of 1.5 equiv of NBS or *N*-bromophthalimide gave (*R*)-**2a** in high yield and moderate enantioselectivity, respectively (entries 6 and 8). Using 1.5 equiv of NBS, 0.05 or 0.2 equiv of $Cu(OTf)_2$ and (*R*,*R*)-Ph-BOX afforded almost similar results to that using 0.1 equiv of chiral Cu(II) catalyst (entries 9 and 10). Whereas using 0.01 equiv of chiral Cu(II) catalyst slightly reduced the enantioselectivity (entry 11), use of the same amount of $Cu(OTf)_2$ and slightly excess amount of (*R*,*R*)-Ph-BOX was effective (entry 12). In case of using 0.1 equiv of $Cu(OTf)_2$, varying the amounts of (*R*,*R*)-Ph-BOX showed no effect on the yields and the enantioselectivities (entries 13 and 14).

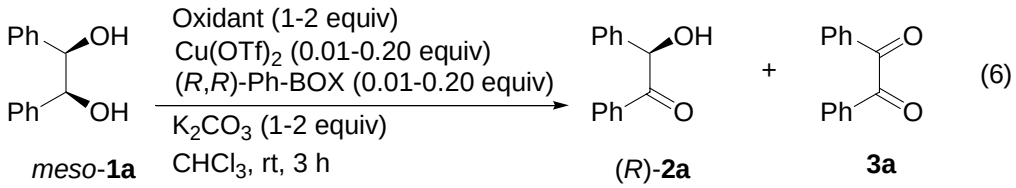
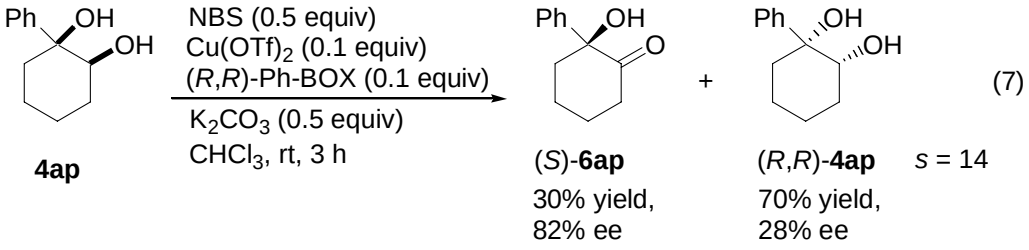


Table 2. Oxidation of *meso*-**1a** by some oxidants[a]

Entry	Oxidant	Equiv of oxidant	Equiv of $Cu(OTf)_2$	Equiv of (*R*,*R*)-Ph-BOX	(*R*)-**2a**		**3a**
					Yield (%)	ee (%)[b]	Yield (%)
1	NCS	2.0	0.1	0.1	26	6	2
2	NIS	2.0	0.1	0.1	88	9	10
3	Br_2	2.0	0.1	0.1	59	43	5
4	*N*-Bromophthalimide	2.0	0.1	0.1	72	71	28
5	NBS	1.0	0.1	0.1	63	67	2
6	NBS	1.5	0.1	0.1	94	70	6
7	*N*-Bromophthalimide	1.0	0.1	0.1	91	69	0
8	*N*-Bromophthalimide	1.5	0.1	0.1	97	76	3
9	NBS	1.5	0.2	0.2	96	69	4
10	NBS	1.5	0.05	0.05	94	68	6
11	NBS	1.5	0.01	0.01	96	63	4
12	NBS	1.5	0.01	0.012	94	69	6
13	NBS	1.5	0.1	0.12	93	70	7
14	NBS	1.5	0.1	0.2	95	69	2

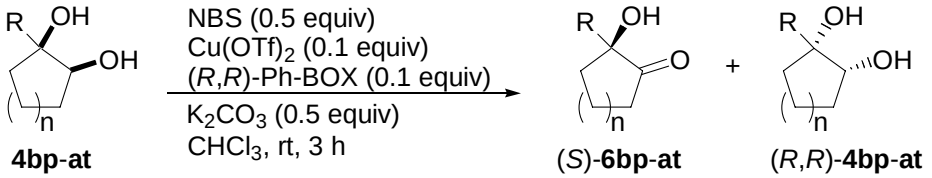
[a] *meso*-**1a** (0.5 mmol), oxidant (0.5-1.0 mmol), $Cu(OTf)_2$ (0.005-0.1 mmol), (*R*,*R*)-Ph-BOX (0.005-0.1 mmol), K_2CO_3 (1.0 equiv to oxidant) in $CHCl_3$ (5.0 mL) at rt for 3 h.
[b] Determined by HPLC.

Then, we applied this methodology to the kinetic resolution of *cis*-cyclohexane-1,2-diol derivative **4ap** (Eq. 7). Compound **4ap** was enantioselectively oxidized with NBS and the Cu(II)–(*R*,*R*)-Ph-BOX complex to afford α-ketoalcohol (*S*)-**6ap**[17] with moderate yield (30%) and selectivity (*s*) value of 14.[19]



Asymmetric oxidation of other cycloalkane-*cis*-1,2-diols **4bp**-**at** is summarized in Table 3 (Eq. 8).[20] The chemical yield of **6bp**-**dp** and *s* value varied significantly depending on

the ring size. That is, the larger the ring size, the better the yield and *s* value obtained (entries 1-3). R substituent also influenced the *s* value (entries 4-7). Compound **4at** with a cyclohexyl substituent was asymmetrically oxidized to afford **6at** in higher enantioselectivity (85% ee, entry 7) than **6aq** with a methyl substituent (5% ee, entry 4), **6ar** with an isopropyl substituent (74% ee, entry 5) and **6as** with a benzyl substituent (48% ee, entry 6).



4bp-**at** (*S*)-**6bp**-**at** (*R*,*R*)-**4bp**-**at** (8)

Table 3. Asymmetric oxidation of *cis*-1,2-diols (**4bp**-**at**)[a]

Entry		n	R	α-Ketoalcohol			Recovered diol		*s*
					Yield (%)	ee (%)[b]	Yield (%)	ee (%)[b]	
1	**4bp**	1	Ph	**6bp**	23	76	77	24	9
2	**4cp**	3	Ph	**6cp**	35	84	65	30	15
3	**4dp**	4	Ph	**6dp**	42	82	58	58	18
4	**4aq**	2	Me	**6aq**	32	5	68	ND[c]	–
5	**4ar**	2	*i*Pr	**6ar**	30	74	70	45[d]	10
6	**4as**	2	Bn	**6as**	33	48	67	32	4
7	**4at**	2	Cy[e]	**6at**	29	85	67	48[d]	19

[a] **4bp**-**at** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), NBS (0.25 mmol), K_2CO_3 (0.25 mmol) in $CHCl_3$ (5.0 mL) at rt for 3 h.

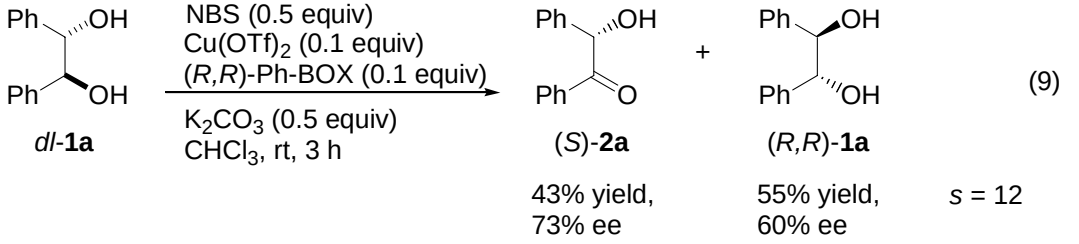
[b] Determined by HPLC using chiral columns: Daicel Chiralcel OJ-H for **4bp**, **4cp**, **4as**, **6bp**, **6cp**, **6dp**; Chiralpak AS for **4dp**, **4ar**,[d] **6ar**; Chiralpak AD for **4at**,[d] **6as**, **6at**; Chiralcel OC for **6ap**.

[c] Not determined.

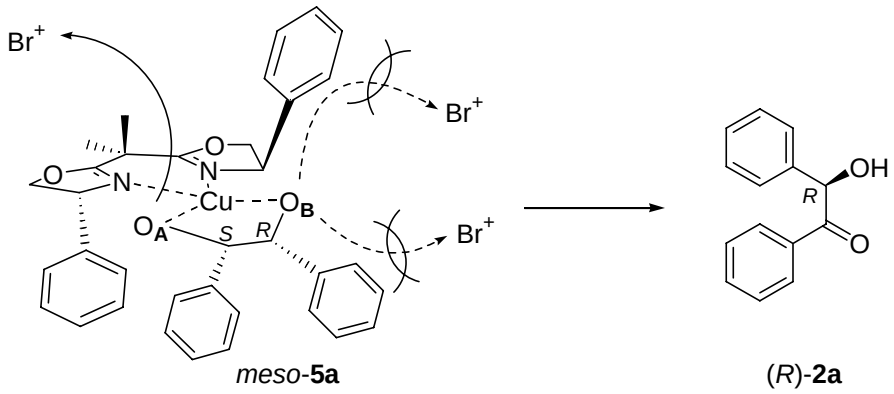
[d] Ee of the corresponding 2-phenylcarbamoylated compound.

[e] Cyclohexyl.

This method was then applied to the kinetic resolution of *dl*-hydrobenzoin (*dl*-**1a**), where (*S*)-benzoin ((*S*)-**2a**) was obtained with 43% yield and 73% ee (Eq. 9).

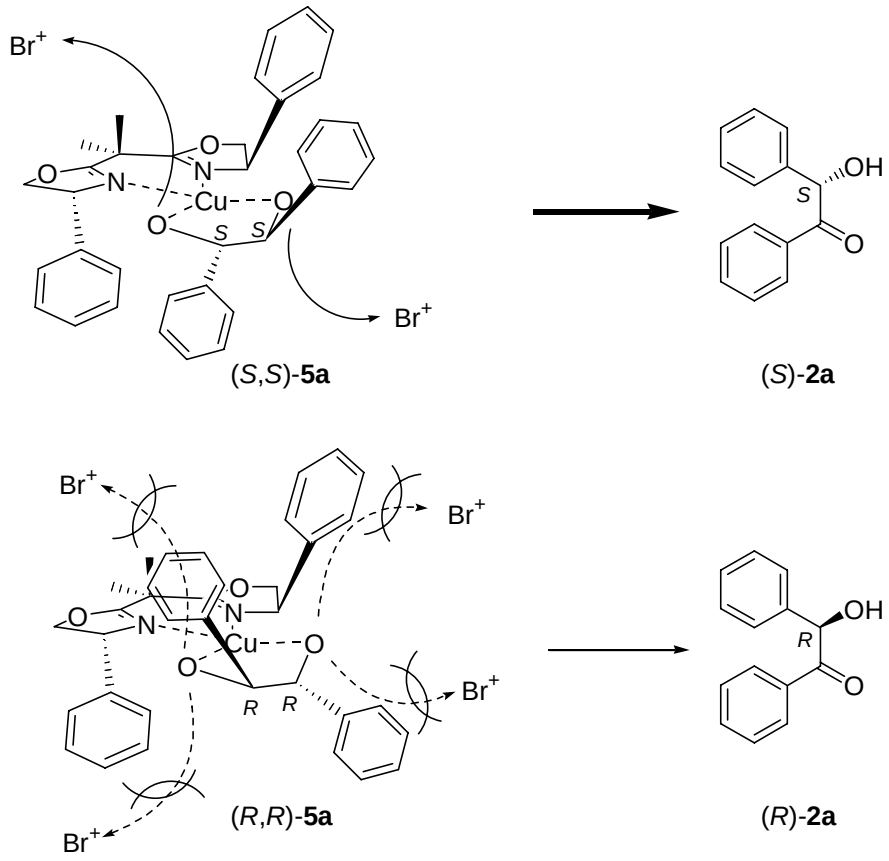


Scheme 1 shows our proposed mechanism for asymmetric oxidation of *meso*-**1a** catalyzed by Cu(II)–(*R*,*R*)-Ph-BOX. Possibly, Br^+ approaches the less crowded alkoxide O_A compared with O_B of the activated intermediate *meso*-**5a** which is generated from **1a** with Cu(II)–(*R*,*R*)-Ph-BOX, to afford (*R*)-**2a**.



Scheme 1. Plausible stereochemical course for desymmetrization of *meso*-**1a**.

Scheme 2 shows our proposed mechanism for kinetic resolution of *dl*-**1a** catalyzed by Cu(II)–(*R*,*R*)-Ph-BOX. Although the activated intermediate (*R*,*R*)-**5a** might be formed more easily than (*S*,*S*)-**5a**, Br^+ predominantly approaches the less crowded intermediate (*S*,*S*)-**5a** to afford (*S*)-**2a**.



Scheme 2. Plausible stereochemical course for kinetic resolution of *dl*-**1a**.

The results presented in this communication are novel for asymmetric oxidation of 1,2-diols to afford enantiomerically enriched α-ketoalcohols. Its synthetic application and mechanistic study are underway.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research (B) (No. 17350051) from Japan Society for the Promotion of Science.

References and notes

1. Recent reviews: (a) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003,** 1977-1986. (b) Irie, R.; Katsuki, T. *Chemical Record* **2004,** *4*, 96-109. (c) Mallat, T.; Baiker, A. *Chem. Rev.* **2004,** *104*, 3037-3058. (d) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227-8241.
2. (a) David, S. *C. R. Acad. Sci. Paris, Serie C* **1974,** *278*, 1051-1053. (b) David, S.; Theffry, A. *J. Chem. Soc. Perkin 1* **1979,** 1568-1573.

3. Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979,** *101*, 5839-5841.
4. (a) Tsuda, Y.; Hanajima, M.; Yoshimoto, K. *Chem. Pharm. Bull.* **1983,** *31*, 3778-3788. (b) Tsuda, Y.; Hanajima, M.; Matsuhira, N.; Okuno, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989,** *37*, 2344-2350. (c) Liu, H. M.; Sato, Y.; Tsuda, Y. *Chem. Pharm. Bull.* **1993,** *41*, 491-501.
5. Fernandez-Mayoralas, A.; Bernabe, M.; Martin-Lomas, M. *Tetrahedron* **1988,** *44*, 4877-4882.
6. Maki, T.; Fukae, K.; Harasawa, H.; Ohishi, T.; Matsumura, Y.; Onomura, O. *Tetrahedron Lett.* **1998**, *39*, 651-654.
7. Reaction conditions: in $CHCl_3$, at rt, for 3 h; from *meso*-hydrobenzoin (**1a**) to benzoin (**2a**) in 65% and benzil (**3a**) in 18% yield.
8. Representative literatures for catalytic asymmetric oxidation of 1,3- and/or 1,4-diols: (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001,** *123*, 7725-7726. (b) Tanaka, H.; Kawakami, Y.; Goto, K.; Kuroboshi, M. *Tetrahedron Lett.* **2001**, *42*, 445-448. (c) Kashiwagi, Y.; Kurushima, F.; Chiba, S.; Anzai, J.; Osa, T.; Bobbitt, J. M. *Chem. Commun.* **2003**, 114-115. (d) Mandal, S. K.; Sigman, M. S. *J. Org. Chem.* **2003,** *68*, 7535-7537. (e) Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. *Tetrahedron Lett.* **2003**, *44*, 2003-2006. (f) Shimizu, H.; Onitsuka, S.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2005,** *127*, 5396-5413. (g) Nakamura, Y.; Egami, H.; Matsumoto, K.; Uchida, T.; Katsuki, T. *Tetrahedron* **2007,** *63*, 6383-6387.
9. (a) Jakka, K.; Zhao, C-. G. *Org. Lett.* **2006,** *8*, 3013-3015. Stoichiometric method; (b) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993,** *58*, 3600-3601. (c) Adam, W.; Saha-Möller, C. R.; Zhao, C-. G. *J. Org. Chem.* **1999,** *64*, 7492-7497.
10. Ladziata, U.; Carlson, J.; Zhdankin, V. V. *Tetrahedron Lett.* **2006,** *47*, 6301-6304.
11. Some of asymmetric reactions catalyzed with Cu(II)–Ph-BOX reported by us: Monobenzoylation of 1,2-diols; (a) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura. O. *J. Am. Chem. Soc.* **2003,** *125*, 2052-2053. Monocarbamoylation of 1,2-diols; (b) Matsumoto, K.; Mitsuda, M.; Ushijima, N.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006,** *47*, 8453-8456. Monosulfonylation of 1,2-diols; (c) Demizu, Y.; Matsumoto, K.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2007,** *48*, 7605-7609. Benzoylation of 2-aminoalcohols; (d) Mitsuda, M.; Tanaka, T.; Tanaka, T.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006,** *47*, 8073-8077. Alkylation into iminium ions; (e) Matsumura, Y.; Minato, D.; Onomura, O. *J. Organomet. Chem.* **2007,** *692*, 654-663.
12. A recent review of chiral bis(oxazoline) ligands: Desimoni, G.; Faita, G.; Jørgensen,

K. A. *Chem. Rev.* **2006,** *106,* 3561-3651.

13. Recently, oxidation of 1,2-diols to 1,2-diketones using NBS as an oxidant has been reported: Khurana, J. M.; Kandpal, B. M. *Tetrahedron Lett.* **2003,** *44,* 4909-4912.
14. The activated intermediates **5** are transformed by K_2CO_3 to the copper(II) alkoxide,[11a] which might be more easily oxidized than the corresponding diols.
15. A typical procedure for asymmetric oxidation: Under an aerobic atmosphere, a solution of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and (*R*,*R*)-Ph-BOX (16.7 mg, 0.05 mmol) in $CHCl_3$ (5 mL) was stirred for 10 min. Into the solution were added **1a** (0.5 mmol), potassium carbonate (138 mg, 1.0 mmol) and NBS (178 mg, 1.0 mmol). After stirring for 3 h at rt, the solution was poured in 10% aqueous $Na_2S_2O_3$ and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 15 : 1) to afford (*R*)-**2a** (83% yield, 72% ee) as a white solid. m.p. 135-137 ℃. $[\alpha]^{26}_D$ −77.7 (*c* 1.5, acetone) [lit.[16] (*S*)-**2a** (>98% ee)**;** $[\alpha]^{22}_D$ +111.9 (*c* 1.5, acetone)]. The optical purity of (*R*)-**2a** was determined by chiral HPLC: Daicel Chiralcel OJ-H column (4.6 mm ϕ, 250 mm), *n*-hexane : isopropanol = 10 : 1, wavelength: 210 nm, flow rate: 1.0 ml/min, retention time: 20.5 min ((*R*)-(+)-**2a**), 24.5 min ((*S*)-(−)-**2a**).
16. The absolute configuration of (*R*)-**2a** was determined by comparing with specific rotation of authentic sample. Demir, A. S.; Şeşenoglu, Ö. *Org. Lett.* **2003,** *5,* 2047-2050.
17. The absolute stereoconfiguration of recovered (*R*,*R*)-**4ap** was determined by comparing with specific rotation of authentic sample. Compound (*R*,*R*)-**4ap**: $[\alpha]^{25}_D$ −3.5 (*c* 1.2, EtOH). [lit.[18] (*R*,*R*)-**4ap** (>99% ee); $[\alpha]^{25}_D$ −7.1 (*c* 1.2, 95% EtOH)]
18. Huang, J.; Corey, E. J. *Org. Lett.* **2003,** *5,* 3455-3458.
19. Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry; Eliel, E. L., Ed.; Wiley & Sons: New York,* **1988,** *Vol. 18,* 249-330.
20. Absolute stereoconfiguration of **6bp-at** shown in Eq. 8 and Table 3 was deduced on the basis of that of **6ap**.

Graphical Abstract

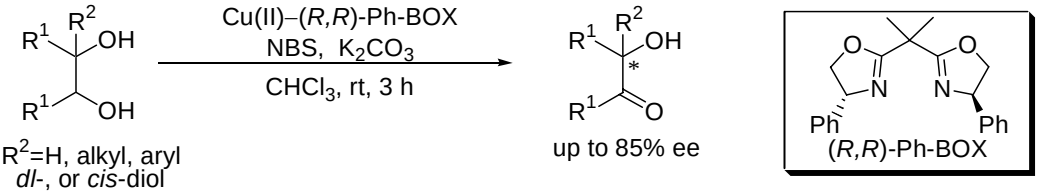
To create your abstract, type over the instructions in the template box below.

Fonts or abstract dimensions should not be changed or alt

Asymmetric oxidation of 1,2-diols using *N*-bromo-succinimide in the presence of chiral copper catalyst

Leave this area blank for abstract info.

Osamu Onomura,* Hitomi Arimoto, Yoshihiro Matsumura, Yosuke Demizu



R^2=H, alkyl, aryl
dl-, or *cis*-diol

up to 85% ee

(*R*,*R*)-Ph-BOX