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Copper complex catalyzed asymmetric monosulfonylation of *meso-vic*-diols

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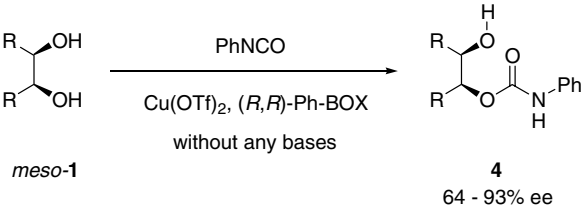
This Letter is dedicated to the heartfelt memory of the late Professor Yoshihiro Matsumura

Abstract—Asymmetric desymmetrization of *meso-vic*-diols was performed by tosylation in the presence of copper(II) triflate and (*R*,*R*)-Ph-BOX as a catalyst. The method was successfully applied to asymmetric desymmetrization of cyclic and acyclic *meso-vic*-diols in high enantioselectivity with up to >99% ee.

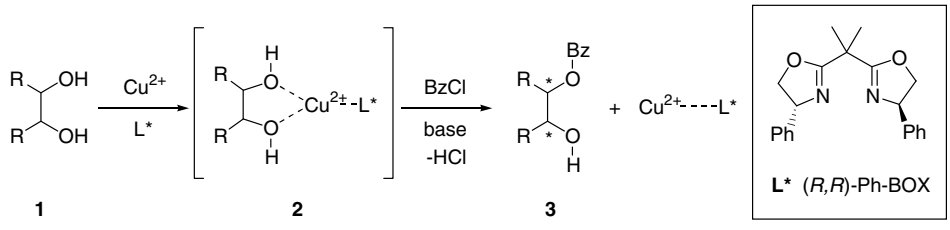
Nonenzymatic asymmetric desymmetrization of *meso-vic*-diols is a practically useful methodology for the preparation of optically active compounds.[1] We have exploited an efficient method for kinetic resolution and asymmetric desymmetrization of *vic*-diols **1**, which is based on the recognition of the *vic*-diol moiety by a copper(II) ion associated with a chiral ligand (*R*,*R*)-Ph-BOX[2] to afford the activated *vic*-diol intermediates **2** followed by benzoylation under basic conditions (Eq. 1).[3]

Basic conditions were essential in the benzoylation to remove the generated hydrogen chloride. However, the product sometimes suffered from acyl transfer reaction[4] under these conditions, decreasing the enantioselectivity of product **3**. To solve this problem, we recently reported an asymmetric desymmetrization of *meso*-**1** by carbamoylation with phenylisocyanate (PhNCO) under non-basic condition to afford optically active *vic*-diol derivatives **4** (Eq. 2).[5]



(2)

However, in some cases, the enantioselectivity of monocarbamoylated products did not meet our expecta-



(1)

Keywords: Asymmetric desymmetrization; *meso-vic*-Diol; Sulfonylation; Copper complex.
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✠ Deceased.

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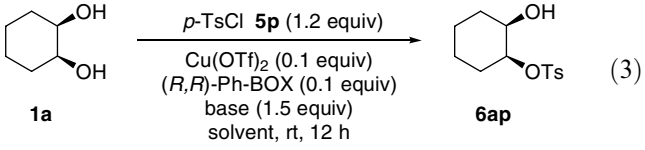
Table 1. Asymmetric tosylation of *meso*-1,2-cyclohexanediol (**1a**)[a]

Entry	Solvent	Base	Product **6ap**	
			Yield (%)	ee[b] (%)
1	CH_2Cl_2	K_2CO_3	94	97
2	AcOEt	K_2CO_3	58	88
3	*i*-PrOH	K_2CO_3	73	92
4	THF	K_2CO_3	25	72
5	MeCN	K_2CO_3	50	80
6	CH_2Cl_2	Li_2CO_3	18	92
7	CH_2Cl_2	Na_2CO_3	68	94
8	CH_2Cl_2	$NaHCO_3$	91	95
9	CH_2Cl_2	Cs_2CO_3	17	22
10	CH_2Cl_2	DIPEA	55	74
11	CH_2Cl_2	Et_3N	39	63

[a] **1a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), *p*-TsCl **5p** (0.6 mmol), base (0.75 mmol) in a solvent (2.0 mL) at rt for 12 h.
[b] Determined by HPLC.

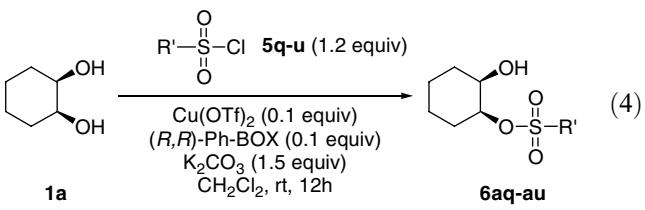
tions.[5] We report herein an asymmetric desymmetrization of *meso*-*vic*-diols **1** by monosulfonylation[6] to afford optically active *vic*-diol derivatives with high yields and excellent enantioselectivities.

We began by trying the asymmetric tosylation of *meso*-1,2-cyclohexanediol (**1a**) as a model compound in the reaction with *p*-toluenesulfonyl chloride **5p**, in the presence of copper(II) triflate and (*R*,*R*)-Ph-BOX as a catalyst under different solvents and bases (Eq. 3).[7] The results are summarized in Table 1, which show a dependence of the yield and % ee of the product **6ap** on the used bases and solvents. The use of CH_2Cl_2 in combination with K_2CO_3 gave both high yield (94%) and high enantioselectivity (97% ee) (entry 1).[8] Although AcOEt and *i*-PrOH gave high enantioselectivities, their yields were moderate compared to that of CH_2Cl_2 (entries 2 and 3). THF and MeCN gave moderate ees with low yields (entries 4 and 5). On the other hand, screening of bases shows that $NaHCO_3$ is as good a base for this reaction as K_2CO_3 (entry 8). Other bases fall short either in terms of yield or enantioselectivity (entries 6, 7, 9–11).



(3)

In addition to tosyl chloride, a variety of sulfonyl chlorides **5q**–**t** (entries 1–4) except for mesyl chloride **5u** (entry 5) were usable for asymmetric sulfonylation of **1a** under the same reaction condition as shown in entry 1 of Table 1 (Eq. 4). The results are summarized in Table 2.



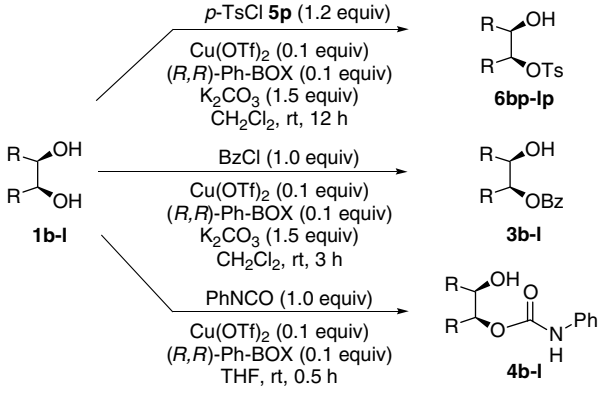
(4)

Table 2. Sulfonylation of **1a** with various sulfonyl chlorides **5q**–**u**[a]

Entry	R′	Product	Yield (%)	ee[b] (%)
1	**5q**: Ph	**6aq**	91	98
2	**5r**: *p*-No_2Ph	**6ar**	59	92
3	**5s**: *p*-ClPh	**6as**	93	93
4	**5t**: *p*-MeOPh	**6at**	61	94
5	**5u**: Me	**6au**	93	77

[a] **1a** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), sulfonyl chloride **5q**–**u** (0.6 mmol), K_2CO_3 (0.75 mmol) in CH_2Cl_2 (2.0 mL) at rt for 12 h.
[b] Determined by HPLC.

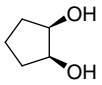
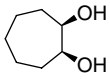
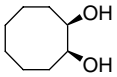
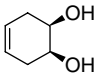
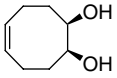
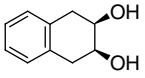
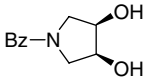
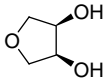
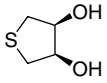
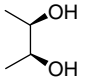
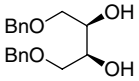
Then, in order to confirm the generality and superiority of tosylation to benzoylation or phenylcarbamoylation, we investigated the asymmetric tosylation, benzoylation, and phenylcarbamoylation of various *meso*-*vic*-diols **1b**–**l** (Eq. 5).[9] The results are summarized in Table 3. Although *meso*-1,2-cyclopentanediols (**1b**) were transformed into the benzoylated product **3b** in *racemic* form and the phenylcarbamoylated product **4b** in moderate enantiomeric excess (72% ee), we succeeded in obtaining the tosylated product **6bp** in 91% yield and 95% ee (entry 1). Various *meso*-cycloalkane- and *meso*-cycloalkene-diols **1c**–**g** other than **1b** were asymmetrically tosylated to afford monotosylated products **6cp**–**gp** in better yield and higher enantioselectivity than those of monobenzoylated products **3c**–**g** and monocarbamoylated products **4c**–**g** (entries 2–6). It is important to note that the asymmetric tosylation of nitrogen, oxygen, and sulfur atom-containing five membered diols **1h**–**j** to obtain **6hp**–**jp** were much more effective than those of benzoylation and carbamoylation, respectively (entries 7–9). In the case of acyclic 1,2-diols **1k** and **1l**, asymmetric tosylation afforded excellent results similar to those of benzoylation but which were better than carbamoylation results (entries 10 and 11).



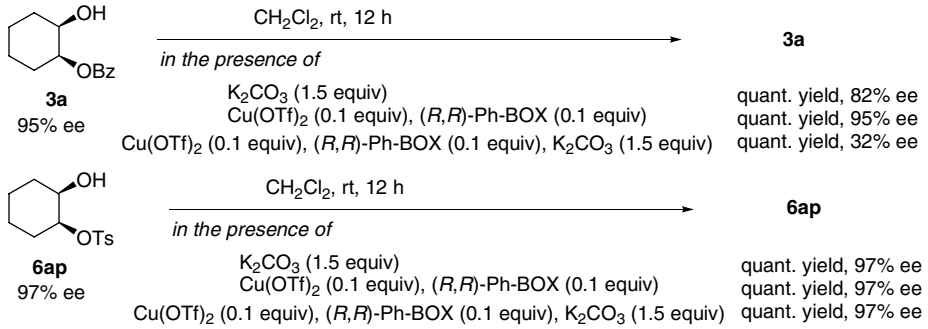
(5)

In some cases, the reason why the tosylated products were obtained with higher enantioselectivity than the benzoylated products may be explained as follows. In the case of benzoylation, intramolecular acyl transfer of optically active **3a** occurred for it to lose some extent of its optical activity when **3a** was subjected to the basic conditions for a long time (Eq. 6).[4] On the other hand, acyl transfer of the monotosylated product **6ap** did not occur under the basic conditions, so **6ap** was obtained with high optical purity (Eq. 7).

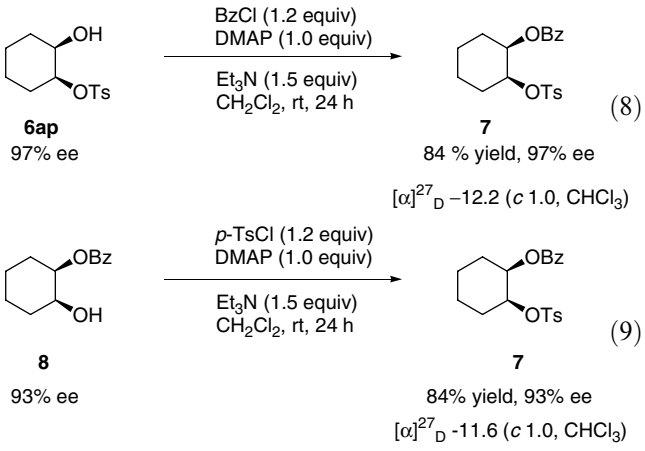
Table 3. Asymmetric tosylation[a] and benzoylation[b] and carbamoylation[c] of *meso*-1,2-diols **1b–l**

Entry	Substrate		Tosylated product			Benzoylated product			Carbamoylated product		
				Yield (%)	ee[d] (%)		Yield (%)	ee[d] (%)		Yield (%)	ee[d] (%)
1	**1b**		**6bp**	91	95	**3b**	47	3	**4b**	91	72
2	**1c**		**6cp**	81	99	**3c**	88	58	**4c**	83	83
3	**1d**		**6dp**	96	98	**3d**	85	65	**4d**	96	86
4	**1e**		**6ep**	>99	97	**3e**	68	93	**4e**	96	59
5	**1f**		**6fp**	>99	99	**3f**	89	96	**4f**	88	67
6	**1g**		**6gp**	86	98	**3g**	92	80	**4g**	86	50
7	**1h**		**6hp**	99	94	**3h**	82	*Racemic*	**4h**	91	72
8	**1i**		**6ip**	80	95	**3i**	81	*Racemic*	**4i**	99	64
9	**1j**		**6jp**	93	94	**3j**	63	8	**4j**	90	52
10	**1k**		**6kp**	88	>99	**3k**	78	97	**4k**	94	70
11	**1l**		**6lp**	71	93	**3l**	36	96	**4l**	91	82

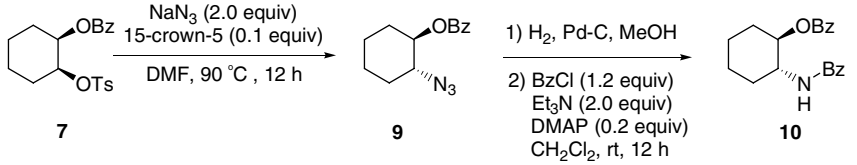
[a] **1b–l** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), *p*-TsCl **5p** (0.6 mmol), K_2CO_3 (0.75 mmol) in CH_2Cl_2 (2.0 mL) at rt for 12 h.
[b] **1b–l** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), BzCl (0.5 mmol), K_2CO_3 (0.75 mmol) in CH_2Cl_2 (2.0 mL) at rt for 3 h.
[c] **1b–l** (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), PhNCO (0.5 mmol), in THF (2.0 mL) at rt for 0.5 h.
[d] Determined by HPLC.

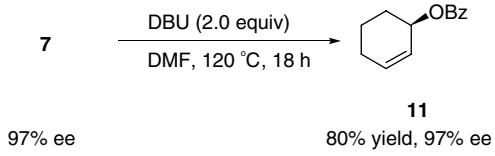


The absolute stereoconfiguration of **6ap** was determined to be (1*S*,2*R*) by transformation of **6ap** to (1*S*,2*R*)-(−)-**7**[10] (Eq. 8), which was the same stereoconfiguration of (1*S*,2*R*)-(−)-**7** derived from reported **8** (Eq. 9).[11]



It is convenient for chemical transformations of compound **7** into optically active compounds **9**–**11** that tosyloxy substituent of compound **7** is a good leaving group for S_N2 reaction and E2 reaction. At first, **7** was treated with NaN_3 to obtain the azide compound **9** with complete stereoinversion, followed by reduction and benzoylation to afford the optically active *vic*-amino alcohol **10** (Eq. 10).[12,14] Also **7** was treated with DBU to obtain the optically active α,β-unsaturated alcohol derivative **11** in good yield without any loss of the optical purity of **7** (Eq. 11).[15]





The results shown in this Letter are practical methods for preparation of optically active monotosylated derivatives from *meso*-*vic*-diols. Asymmetric monotosylation method has generality for various *meso*-*vic*-diols and is superior to monobenzoylation or monocarbamoylation method. The mechanistic study of this monotosylation and its application to a kinetic resolution of *dl*-*vic*-diols are now under investigation.

Acknowledgments

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7. A typical procedure for asymmetric monotosylation: 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 CH_2Cl_2 (2 mL) was stirred for 10 min. Into the solution were added *meso*-**1a** (0.5 mmol), K_2CO_3 (103.7 mg, 0.75 mmol), and *p*-TsCl **5p** (114.4 mg, 0.6 mmol). After being stirred for 12 h at rt, the solution was poured in water and extracted with AcOEt (20 mL × 3). The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane–AcOEt = 3:1) to afford (1*S*,2*R*)-**6ap** (94% yield, 97% ee) as a colorless oil. $[\alpha]_D^{19}$ −8.1 (*c* 1.0, $CHCl_3$). IR (neat) 3530, 2942, 1599, 1356, 1175 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 4.68–4.58 (m, 1H), 3.88–3.78 (m, 1H), 2.45 (s, 3H), 2.10–1.20 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 134.0, 129.7, 127.5, 83.0, 68.8, 30.1, 27.5, 21.5(2C), 20.6. MS [LR-FAB(+)]: *m*/*z* 271 $[M+H]^+$. The optical purity of **6ap** was determined by chiral HPLC: Daicel Chiralcel OJ-H column (4.6 mm ∅, 250 mm), *n*-

hexane–*i*-PrOH = 10:1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 15.2 min ((1*R*,2*S*)-(+)-**6ap**), 16.9 min ((1*S*,2*R*)-(−)-**6ap**).

8. The use of $CuCl_2$ instead of $Cu(OTf)_2$ reduced the yield and % ee of the product **6ap** (69% yield, 88% ee, respectively).
9. Monotosylation, monobenzoylation, and monophenylcarbamoylation of *meso*-*vic*-diols in the presence of (*R*,*R*)-Ph-BOX occurred at the same position. The absolute stereoconfiguration of **6bp**–**lp** shown in Eq. 5 and Table 3 was deduced on the basis of that of **6ap**.
10. Chiral HPLC condition: Daicel Chiralcel OJ-H column (4.6 mm ∅, 250 mm), *n*-hexane–isopropanol = 5:1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 12.3 min ((1*S*,2*R*)-(−)-**7**), 19.5 min ((1*R*,2*S*)-(+)-**7**).
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12. Compound (1*R*,2*R*)-(−)-**10**: mp 149–151 °C. $[\alpha]_D^{21}$ −89.2 (*c* 1.0, $CHCl_3$) [lit.[13] (1*S*,2*S*)-(+)-**10**; $[\alpha]_D^{12}$ +60.5 (*c* 1.0, $CHCl_3$)]. HPLC chiralcel OD column (4.6 mm ∅, 250 mm), *n*-hexane–*i*-PrOH = 20:1, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 11.1 min ((1*S*,2*S*)-(+)-**10**), 14.8 min ((1*R*,2*R*)-(−)-**10**).
13. Nishida, A.; Shirato, F.; Nakagawa, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3789–3806.
14. Compounds **9**, **10** and/or their enantiomers might be good precursors for antiarrhythmic agents: Plouvier, B.; Beatch, G. N.; Jung, G. L.; Zolotoy, A.; Sheng, T.; Clohs, L.; Barret, T. D.; Fedida, D.; Wang, W. Q.; Zhu, J. J.; Liu, Y.; Abraham, S.; Lynn, L.; Dong, Y.; Wall, R. A.; Walker, M. J. A. *J. Med. Chem.* **2007**, *50*, 2818–2841.
15. The absolute stereoconfiguration was determined by comparing with specific rotation of authentic sample. See Ref. 16. Compound (*R*)-**11**: $[\alpha]_D^{21}$ +224.9 (*c* 1.0, $CHCl_3$). [lit.[16] (*S*)-**11** (86% ee); $[\alpha]_D^{25}$ −157.0 (*c* 0.45, $CHCl_3$)].
16. Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961–2967.