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Kinetic resolution of D,L-*myo*-inositol derivatives catalyzed by chiral Cu(II) complex

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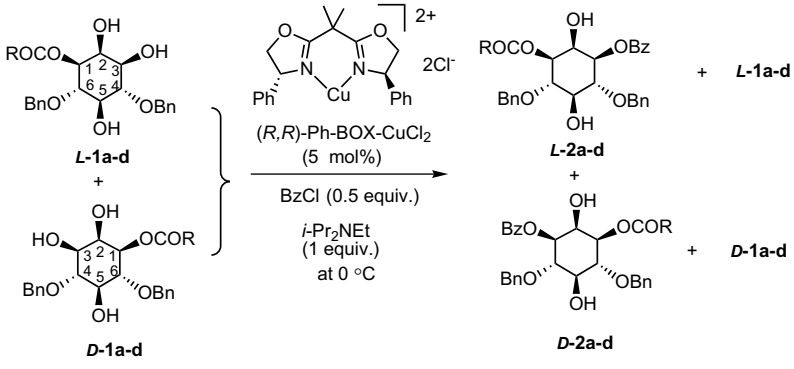
Abstract—Kinetic resolution of D,L-*myo*-inositol derivatives having a 1,2-diol functionality by monobenzoylation was achieved using (*R*,*R*)-Ph-BOX-Cu(II) as a catalyst. The monobenzoylation preferentially took place at the 1,2-diol functionality via a highly enantiodiscriminatory process, which was largely influenced by a substituent at the position adjacent to the 1,2-diol functionality. This method was applied to a synthesis of biologically important D-inositol-1-phosphate.

Kinetic resolution has long continued to attract much interest in asymmetric synthesis because of its simple process for preparation of enantiomerically enriched compounds from easily available *racemic* mixture.[1,2] We have recently exploited an efficient method for kinetic resolution of 1,2-diols using a selective monobenzoylation reaction catalyzed by (*R*,*R*)-Ph-BOX-$CuCl_2$.[3] As an application of the method, we report herein a kinetic resolution of D,L-*myo*-inositol derivatives D,L-**1a**–**d** (Eq. 1) and utilization of this kinetic resolution to a synthesis of D-inositol-1-phosphate (**3**), a biologically important compound related to the intracellular signaling process.[4] Although a variety of synthetic methods for **3** via utilization of chiral starting compounds,[5] a resolution of diastereoisomers,[6] and an enzymatic asymmetric induction[7] have been developed, there have been few reports for its synthesis using chiral catalysts.[8]



(1)

The racemic inositol derivatives D,L-**1a**–**d** were readily prepared from 4,6-dibenzylated *myo*-inositol according to the reported procedure.[9] Benzoylation of D,L-**1a**–**d** was carried out as follows. Benzoyl chloride (0.5 equiv)

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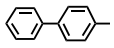
Table 1. Benzoylation of *myo*-inositol derivatives **1a–d**

Run	R	*myo*-Inositol derivatives **1a–d**	Products **2a–d**	**2a–d**	
				Yield[a] (%)	% Ee[b]
1	Me	**1a**	**2a**	25	60
2	*i*-Pr	**1b**	**2b**	36	67
3	*i*-Bu	**1c**	**2c**	37	74
4		**1d**	**2d**	35	91

[a] Isolated yield based on **1a–d**.

[b] Determined by chiral solid-phase HPLC. For **2a–c**: Daicel Chiralcel OD (4.6 mmϕ × 25 cm), wave length = 254 nm, flow rate = 1.0 mL/min, *n*-hexane–2-propanol = 5:1, retention time: L-**2a**; 11.5 min, D-**2a**; 23.9 min, L-**2b**; 9.3 min, D-**2b**; 15.1 min, L-**2c**; 7.1 min, D-**2c**; 9.5 min; for **2d**: Daicel Chiralpak AS (4.6 mmϕ × 25 cm), wave length = 254 nm, *n*-hexane–2-propanol = 5:1, retention time: 19.6 min (for L-**2d**), 25.2 min (for D-**2d**).

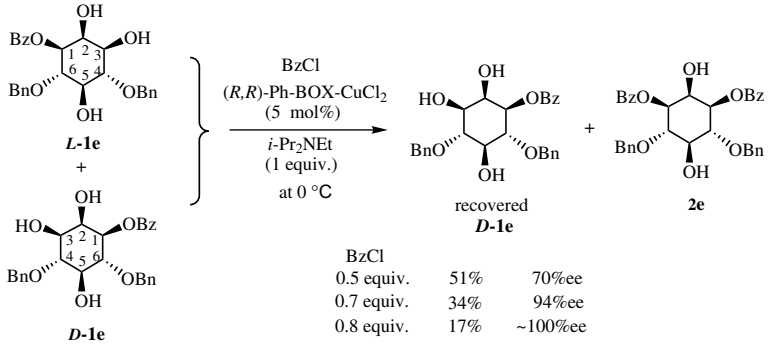
was added into a solution of D,L-**1a–d** in CH_2Cl_2 in the presence of (*R*,*R*)-Ph-BOX-$CuCl_2$ (5 mol%)[10] and *i*-Pr_2NEt (1.0 equiv) at 0 °C to afford 3-monobenzoylated compounds **2a–d** with a recovery of **1a–d**.[11] The results are shown in Table 1.

In this benzoylation reaction, the following points were remarkable. (1) The benzoylation did not occur at the 5-OH group but selectively took place at 2,3-$(OH)_2$. (2) The reaction mainly gave the 3-O-benzoylated product in yields of 25–44% with a small amount of a 2-benzoylated product.[12] (3) The enantiomerically enriched isomer was L with 60–91% ee. (4) The % ee's were dependent on the kind of the 3-acyl group, and the maximum ee (91% ee) was observed in the benzoylation of **1d** (entry 4).

On the basis of those results, we propose a working hypothesis for the reaction mechanism (Fig. 1), in which the L-intermediate from L-**1** is more preferentially formed than the D-intermediate from D-**1** because of the steric repulsion between Ph of oxazoline ring and R groups, and BzCl attacks more easily the oxygen atom at C-3 (between *cis* and *trans* adjacent substituents) of the L-intermediate than the oxygen atom at C-2 (between *cis* and *cis* adjacent substituents).

The kinetic resolution of D,L-**1e** (R = Ph) was ambiguous because the product **2e** was a *meso* isomer but the enantioselectivity was not low (*s* = ~9.5)[13] (Eq. 2).

This catalytic kinetic resolution was applied to a synthesis of biologically important inositol-1-phosphate (Eq. 3). That is, D,L-**1e** was subjected to the kinetic resolution using benzoyl chloride in the presence of (*R*,*R*)-Ph-BOX-$CuCl_2$ (5 mol%) and *i*-Pr_2NEt (1.0 equiv) at 0 °C in CH_2Cl_2. Although the benzoylated product **2e** was a *meso* isomer, the recovered **1e** showed optical activity depending on the amount of BzCl (Eq. 2):[14] 70% ee for 0.5 equiv BzCl; 94% ee for 0.5 equiv BzCl; ~100% ee[15]



(2)

for 0.8 equiv BzCl. The yields were 51%, 34%, and 17% based on the used D,L-**1e**, respectively. The optically pure D-**1e** was used for a synthesis of D-inositol-1-phosphate **3** according to procedures similar to reported ones (**3**: 100% ee) (Eq. 3).[7c]

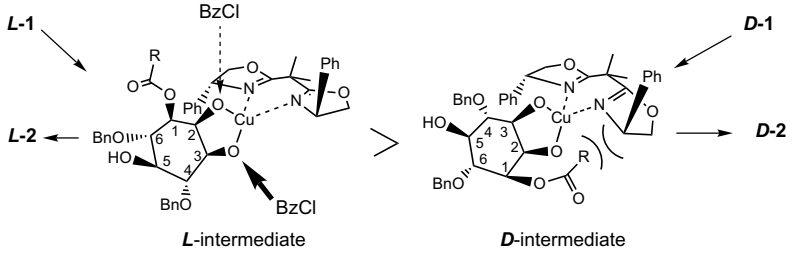
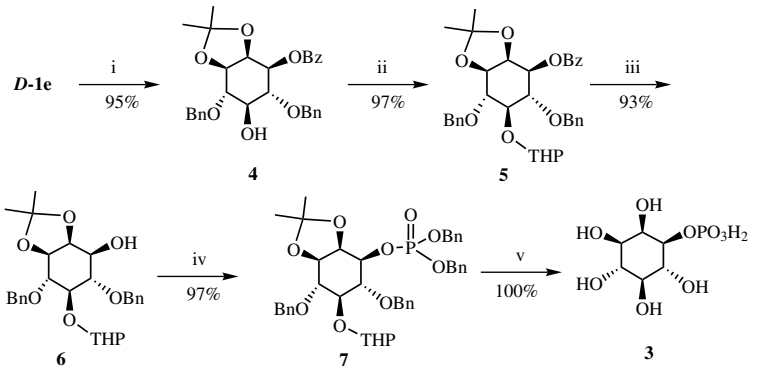


Figure 1. Working hypothesis for a reaction mechanism.



(3)

(i) 2,2-Dimethoxypropane (6.4 equiv), *p*-TsOH (2 mol%), acetone, rt. (ii) 3,4-Didehydro-2*H*-pyran (2.4 equiv), *p*-TsOH (1.4 mol%), CH_2Cl_2, rt. (iii) KOH (3 equiv), $HOCH_2CH_2OH$, rt. (iv) (a) 1*H*-Tetrazole (2 equiv), dibenzyl diisopropylphosphoramidite (1.5 equiv), CH_2Cl_2, rt; (b) *m*-CPBA (3 equiv), CH_2Cl_2, 0 °C. (v) 10% Pd/C, MeOH/H_2O (80/20), H_2, rt.

Acknowledgements

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11. A typical experimental procedure for benzoylation of D,L-**1a–d**: Benzoyl chloride (0.5 equiv) was added into a

solution of D,L-**1d** (1.0 mmol) in CH_2Cl_2 (5 mL) in the presence of (*R*,*R*)-Ph-BOX-$CuCl_2$ (5 mol%) and *i*-Pr_2NEt (1.0 equiv) at 0 °C. After stirring for 2 h, the reaction mixture was added onto water (10 mL) and the product was extracted with CH_2Cl_2 (10 mL×3). Combined organic layers were dried over $MgSO_4$. After removal of organic solvent, the residue was chromatographed on silica gel to afford 3-monobenzoylated compound **2d** in 35% yield with a recovery of **1d** (51%). The ee of **2d** was determined by chiral solid-phase HPLC, see: footnote of Table 1.

12. The amount of byproducts was less than 10% of **2a**–**d**, though identification of the byproducts was not achieved.
13. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–331.
14. Determined by chiral solid-phase HPLC. Daicel Chiralcel OD (4.6 mmϕ × 25 cm), *n*-hexane–2-propanol = 3:1, wavelength = 254 nm, flow rate = 1.0 mL/min, retention time: 9.3 min (for D-**1e**), 14.9 min (for L-**1e**).
15. $[\alpha]_D^{30}$ −71.0 (*c* 1.0, MeOH).