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Asymmetric Desymmetrization of 4,5-Epoxycyclohex-1-ene by Enantioselective Allylic Oxidation

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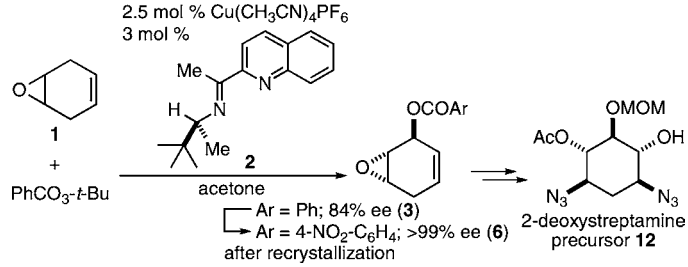
ABSTRACT



Asymmetric desymmetrization of allylic oxidation of 4,5-epoxycyclohex-1-ene (1) took place in the presence of 2.5 mol % of $Cu(CH_3CN)_4PF_6$ and 3 mol % of chiral *N,N*-bidentate ligand (*S*)-2 to afford (3*S*,4*S*,5*S*)-3-benzoyloxy-4,5-epoxycyclohex-1-ene (3) in 84% ee, which was increased up to >99% ee after recrystallization of 3-4′-nitrobenzoyloxy derivative 6. Optically pure 6 proved to be a key intermediate for enantioselective synthesis of *O*-protected 2-deoxystreptamine (2-DOS) precursor 12.

There have been many reports on asymmetric allylic oxidation of olefins with *tert*-butyl perbenzoate.[1,2] However, these reactions still have problems to be overcome such as substrate limitations and poor reactivity.[3] In practice, only some simple cycloalkenes were suitable substrates for this oxidative reaction. Olefins with other functional groups have only rarely been explored as substrates presumably due to their poor tolerance to the oxidative conditions.[4] Recently, we developed a chiral *N,N*-bidentate imine (Schiff base)-copper catalyst for asymmetric allylic oxidation of simple cyclic olefins which exhibited high reactivity as well as good enantioselectivity.[5] In this paper, we will disclose the first example of allylic oxidation of a *meso* cyclic epoxyolefin, which will lead to products with high potential toward further transformations, especially considering the existence of the double bond and epoxy group.

We first examined the effect of copper precursors combined with chiral imine (Schiff base) **2** on reactivity and enantioselectivity (Table 1).

With use of $Cu(OTf)_2$, *tert*-butyl perbenzoate disappeared in 5 h, but only trace amounts of products were detected (entry 1). The $Cu(OTf)_2-PhNHNH_2$ system, which is an effective copper source for simple cyclic olefins, gave complicated products, although the perester disappeared in 3 h. The use of $CuOTf{\cdot}0.5C_6H_6$ afforded a mixture of **3** and **4** in 40% yield after 15 h. The use of $Cu(CH_3CN)_4PF_6$ was found to be the best choice as the copper source and gave higher yields and ee values. When 4,5-epoxycyclohex-1-ene

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(1) For reviews, see: (a) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567–3571. (b) Andrus, M. B.; Lahley, J. C. *Tetrahedron* **2002**, *58*, 845–866.

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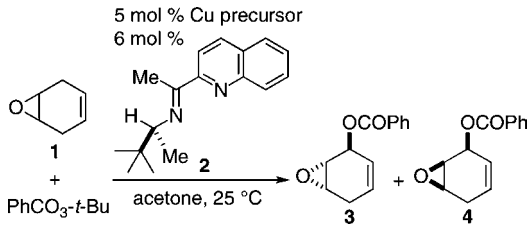
Table 1. Enantioselective Allylic Oxidation of 4,5-Epoxycyclohex-1-ene (**1**)

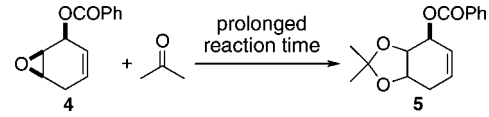


entry	Cu precursor	time/h	yield/%[a]	**3**/**4**	ee of **3**[b]	ee of **4**[c]
1	$Cu(OTf)_2$	5	trace			
2	$Cu(OTf)_2$−$PhNHNH_2$	3	trace			
3	$CuOTf{\cdot}0.5C_6H_6$	15	40	1/1	82	79
4	$Cu(CH_3CN)_4PF_6$	16	75	1/1	85	89
5[d]	$Cu(CH_3CN)_4PF_6$	72	46	1/1	90	92
6	$Cu(CH_3CN)_4PF_6$	40	32	>99/1	85	

[a] Isolated yield of **3** and **4**. [b] Determined by ^1H NMR and HPLC. [c] Determined by HPLC (Chiralpak AS). [d] The reaction was carried out at 0 °C.

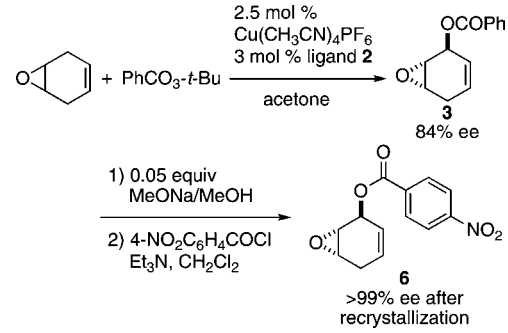
was treated with *tert*-butyl perbenzoate in the presence of 5 mol % of $Cu(CH_3CN)_4PF_6$ and 6 mol % of chiral imine (Schiff base) ligand **2** at 25 °C in acetone, *trans*-3-benzoyloxy-4,5-epoxycyclohex-1-ene (**3**) and its *cis* isomer **4** were obtained nonselectively (75% yield), though the ee values of both isomers were relatively high, i.e., 85% ee for **3** and 89% ee for **4**. When the reaction was carried out at 0 °C, *trans*-**3** and *cis*-**4** were obtained in up to 90% ee and 92% ee, respectively. It should be mentioned that the reports of asymmetric allylic oxidation of functionalized cyclic olefins are only a few.[6] It is interesting that a prolonged reaction time (40 h) increased the *trans*/*cis* isomer ratio up to >99/1, though the yield was lower. We confirmed that the prolonged reaction time caused the *cis* isomer to react

Scheme 1



with the solvent, affording **5** in 25% yield[7,8] (Scheme 1). When *tert*-butyl *p*-nitroperbenzoate[2g] was used instead of *tert*-butyl perbenzoate, the desired *trans* isomer **3** was obtained resulting in 82% ee and >99% ee after recrystallization in only 15% yield. Furthermore, *tert*-butyl *p*-nitroperbenzoate is not commercially abvailable, so we had to prepare it according to the reported method.[2g] Therefore, we selected the route as shown Scheme 2. It should be

Scheme 2



mentioned that 1,3-dioxolane **5** was not observed when the perester existed. It seemed that the valence state of copper in the presence of the perester, proposed as Cu(III), did not catalyze the transformation of **4** to **5**. As for the structure of **4**, we determined it as the *cis* isomer of **3**. Judging from the COSY spectrum of the 1,3-dioxolane **5** from the *cis* isomer **4**, lack of correlation of the double bond protons and the neighboring protons of the 1,3-dioxolane should exclude the possibility of the regioisomeric compound (see the Supporting Information, p 8).

Optically active **3** was then transformed into its derivative **6**, which had better crystallinity, in order to improve the optical purity by recrystallization. It was possible to use a lower load of catalyst (2.5 mol %) without a deleterious effect on the enantioselectivity (84% ee). As expected, the ee of **6** was improved to >99% ee in 23% yield after recrystallization

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(6) (a) Clak, J. S.; Clarke, M.-R.; Clough, J.; Blake, A. J.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 9447–9450. See, also their original: Clark, J. S.; Tolhurst, K. F.; Taylor, M.; Swallow, S. L. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1167–1169. (b) Reference 4. (c) Reference 2b and references cited therein.

(7) The stereochemistry of 1,3-dioxolane **5** is not determined at present. We represented the 2D-NMR (COSY) spectrum of 1,3-dioxolane **5** in the Supporting Information.

(8) Formation of 1,3-dioxolanes from epoxides: (a) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Monari, M.; Piccinelli, F. *Adv. Synth. Catal.* **2007**, *349*, 1256–2264. (b) Solladie-Cavallo, A.; Choucair, E.; Balaz, M.; Lupattelli, P.; Bonini, C.; Di Blasio, N. *Eur. J. Org. Chem.* **2006**, 3307–3011. (c) Procopio, A.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Nardi, M.; Russo, B. *Adv. Synth. Catal.* **2006**, *348*, 1447–1450. (d) Vyvyan, J. R.; Meyer, J. A.; Meyer, K. D. *J. Org. Chem.* **2003**, *68*, 9144–9147.

from compound **1** (three steps) (Scheme 2). This procedure was successfully carried out on a 15-g scale.[9]

The relative configuration of **6** was determined by X-ray analysis as shown in Figure 1. The absolute configuration

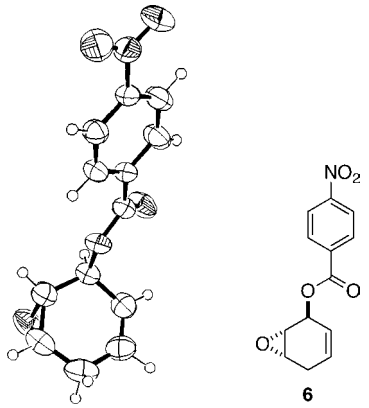


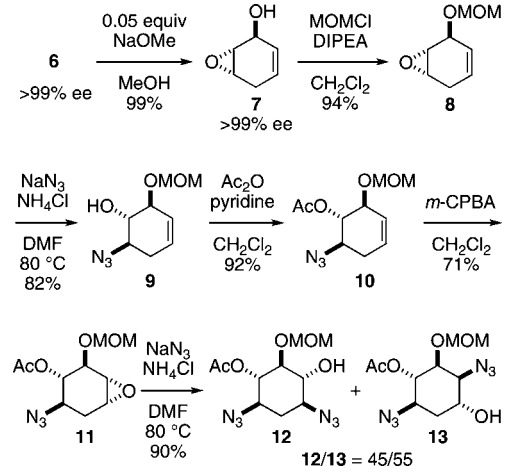
Figure 1. ORTEP diagram of **6** with ellipsoids set at 50% probability.

of **6** was assigned as (3*S*,4*S*,5*S*) by conversion to a known compound **14**.[10,11]

Then we applied the present method to the synthsis of *O*-protected 2-deoxystreptamine (2-DOS) precursor. Recently, 2-DOS and its analogues have attracted much interest as the central scaffold of clinically important aminoglycoside antibiotics, and the first generation of RNA-targeted ligands has already been designed.[12,13] From a synthetic perspective, enantiopure 2-DOS derivatives pose an interesting synthetic challenge due to the five contiguous stereogenic centers, thus numerous attempts including chemical or enzymatic desymmetrization of *meso*-2-deoxystreptamine,[13a,14] degradation of neomycin and kanamycin,[15] and total synthesis from a chiral pool[16] have been made. Therefore, we applied our asymmetric desymmetrization by allylic oxidation of 4,5-epoxycyclohex-1-ene (**1**) giving enantiopure alcohol **7** to a straightforward synthsis of *O*-protected 2-DOS precursor and its regioisomer as the key step.

The synthesis of optically pure 4,5-*O*-protected 2-deoxystreptamine is summarized in Scheme 3. Treatment of **6** with

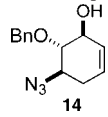
Scheme 3



0.05 equiv of NaOMe/methanol solution afforded enantiopure alcohol **7** quantitatively. It should be mentioned that this is the first report of an optically active form of **7**.[17] After MOM protection, ring-opening of compound **8** with NaN_3 afforded

(9) A typical experimental procedure is as follows: A solution of ligand **2** (0.61 g, 2.4 mmol) and $Cu(CH_3CN)_4PF_6$ (0.76 g, 2.0 mmol) in acetone (100 mL) was stirred at rt for 1 h. To this dark red solution was added the epoxide **1** (15.4 g, 160 mmol), followed by dropwise addition of a solution of $PhCO_3$-*t*-Bu (15.6 g, 80.0 mmol) in acetone (20 mL) over 1 h. The reaction was stirred at 25 °C until the *cis* isomer **4** completely disappeared, which was judged by HPLC analysis. Then acetone was removed and the residue was dissolved in EtOAc (200 mL). The solution was washed with sat. $NaHCO_3$ solution (2 × 30 mL) and dried with Na_2SO_4. After removal of the solvent, the residue was passed through a short pad of silica, using hexane/EtOAc (8:1) as eluent, to give crude **3** as an oil (12.5 g), which was contaminated with the by-product **5**. The crude oil was dissolved in methanol (100 mL) and a NaOMe solution (prepared from Na (65 mg, 2.82 mmol) and methanol (6 mL)) was added. After 2 h, the reaction was quenched with acetic acid (0.18 g, 3.0 mmol). After complete removal of methanol, the residue was dissolved in CH_2Cl_2 (150 mL) and Et_3N (10 mL, 71 mmol) and a solution of 4-nitrobenzoyl chloride (10.8 g, 58 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 30 min. The mixture was stirred at rt overnight and sat. $NaHCO_3$ solution was added to quench the reaction. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with $NaHCO_3$ solution and dried (Na_2SO_4). After removal of solvent, the residue was passed through a short pad of silica gel to give a white solid. The solid was recrystallized from hot hexane/EtOAc solution (120 mL/30 mL) to afford enantiopure **6** as a colorless slice (9.5 g, 23% for three steps). R_f = 0.30 (hexane/EtOAc = 2/1); mp 125−127 °C; $[\alpha]^{21}_D$ +209 (*c* 0.5, $CHCl_3$, 99.1% ee). The ee value was determined by HPLC on a Chirapak AS column (hexane/2-propanol = 90/10, 1.0 mL/min, t_R of major isomer (3*S*,4*S*,5*S*): 20.9 min; t_R of major isomer (3*R*,4*R*,5*R*): 23.7 min).

(10) To confirm the absolute configuration of **6**, we transformed **6** to (1*S*,5*R*,6*S*)-5-azido-6-benzyloxycyclohex-2-en-1-ol (**14**) in several steps. $[\alpha]^{22}_D$ of synthetic sample was +110.5 (*c* 1.0, $CHCl_3$); lit.[15] $[\alpha]_D$ (derived from D-glucose in 13 steps) was $[\alpha]_D$ +106.2 (*c* 1.16, $CHCl_3$). The details of the transformation of **3** to **14** will be published in a separate paper.



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(12) For a review of 2-DOS, see: Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775–791.

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9 regioselectively. Epoxidation of acetate-protected **10** with *m*-CPBA followed by ring-opening of **11** gave a mixture of **12**[13c] and its regioisomer **13** in 90% yield (**12**/**13** = 45/55), which were readily separated by chromatography.

In conclusion, we have revealed a straightforward enantioselective synthesis of 4,5-*O*-protected 2-deoxystreptamine based on asymmetric desymmetrization of 4,5-epoxycyclohex-1-ene. Asymmetric allylic oxidation took place in the presence of 2.5 mol % of $Cu(CH_3CN)_4PF_6$ and 3 mol % of chiral *N*,*N*-bidentate ligand **2** to afford 3-benzoyloxy-4,5-epoxycyclohex-1-ene (**3**) in 84% ee, which was increased to >99% ee after recrystallization of 4-nitrobenzoyloxy derivative **6**. *This method generates three carbon stereogenic centers in one reaction utilizing an asymmetric desymmetric reaction.* We believe this method provides a useful protocol for the asymmetric version of the Kharasch−Sosnovosky allylic oxidation reaction of functionalized cycloalkenes.

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Supporting Information Available: Details of experimental procedures and characterization data (^1H, ^{13}C, and COSY NMR, IR, mass spectrometry, elementary analyses for all new compounds, HPLC and GC profiles, and a CIF file of **6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For racemic synthesis of **7**, Delft and his co-workers reported the synthesis of racemic **7** starting from the Diels−Alder adduct of cyclopentadiene and *p*-benzoquinone in six steps. See: Busscher, G. F.; Groothuys, S.; Gelder, R.; Rutjes, F. P. J. T.; Delft, F. L. *J. Org. Chem.* **2004**, *69*, 4477–4481.