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A New Synthesis of Optically Active trans β-Amino Alcohols by Asymmetric Ring-opening of Symmetrical Oxiranes

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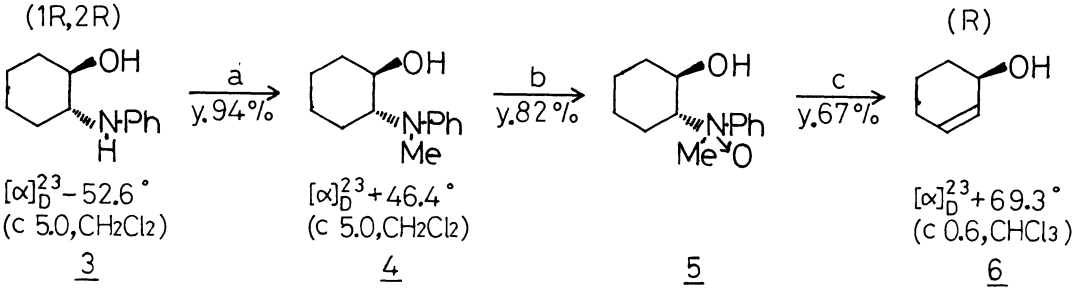
The asymmetric ring-opening of symmetrical oxiranes with aniline or trimethylsilyl azide is effectively catalyzed by zinc (2R,3R)-tartrate or cupric (2R,3R)-tartrate to give trans N-phenyl β-amino alcohol or trans O-trimethylsilyl 2-azido alcohols in 17-52% ee. The latter azido products can be easily converted into optically active trans β-amino alcohols by two-step procedure.

Recent extensive studies on regioselective ring-opening of oxiranes with various nucleophiles led to general understanding of this type of reactions.[1] On the other hand, only a few results are known about asymmetric ring-opening of oxiranes.[2]

In the previous paper,[3] we reported the asymmetric ring-opening of cyclohexene oxide with various thiols in 52-85% ee by the use of zinc (2R,3R)-tartrate as a heterogeneous chiral Lewis acid catalyst. In this communication, we wish to describe an asymmetric synthesis of trans β-amino alcohols by the newly developed methodology, that is asymmetric ring-opening of symmetrical oxiranes in the presence of a chiral catalyst.

In the first place, we examined the reactions of cyclohexene oxide (1a) with ammonia, benzylamine, and aniline in the presence of zinc (2R,3R)-tartrate (2). By the use of basic nucleophiles such as ammonia and benzylamine, no reaction took place at room temperature, because the activity of catalyst (2) as a Lewis acid was decreased by the tight coordination with those nucleophiles. On the other hand, weakly basic nucleophile such as aniline gave (1R,2R)-(-)-N-phenyl-2-aminocyclohexanol (3) under the following reaction conditions, though the reaction proceeded incompletely. In a CH_2Cl_2 (25 ml) solution of 1a (0.98 g, 10 mmol) and aniline (0.93 g, 10 mmol) was suspended 2 (0.21 g, 1 mmol). This heterogeneous mixture was stirred at room temperature for 7 d. After filtration of 2, the filtrate was concentrated and purified by silica-gel column chromatography (hexane / ethyl acetate = 6 / 1) to afford 3 (0.54 g, 28% yield, $[\alpha]_D^{23}$ - 52.6° (c 5.0, CH_2Cl_2)). The absolute configuration of 3 was confirmed to be (1R,2R) by the conversion into (R)-(+)-2-cyclohexen-1-ol (6)[4] as shown in Scheme 1. The enantiomeric excess of 3 was determined to be 52% by ^{1}H-NMR measurement of the MTPA ester of (1R,2R)-N-methyl-N-phenyl-2-aminocyclohexanol (4) derived from 3 by N-methylation.



a) Me_2SO_4-K_2CO_3/MeOH. b) m-CPBA/CH_2Cl_2. c) 140°C/20 mmHg.

Scheme 1.

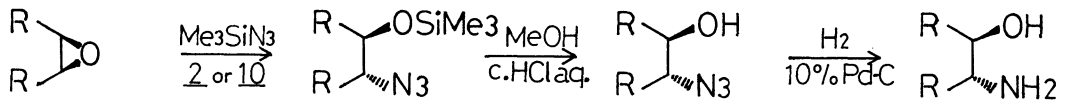
In order to avoid the deactivation of 2, the reaction between 1a and non-basic nucleophile such as trimethylsilyl azide was tried in the presence of 2 according to the procedure reported by L. Birkofer et al.[5] who reported the ring-opening of 1a with trimethylsilyl azide catalyzed by zinc chloride to give racemic trans O-trimethylsilyl-2-azidocyclohexanol. Then, it was found that (1R,2R)-(+)-O-trimethylsilyl-2-azidocyclohexanol (7a) was obtained in moderate optical yield. After examination of various reaction conditions such as solvent, concentration, molar ratio of 1a and trimethylsilyl azide, and amount of catalyst (2), the best result was achieved under the following conditions. To a benzene (5 ml) solution of 1a (0.98 g, 10 mmol) and trimethylsilyl azide (1.38 g, 12 mmol) was suspended 2 (0.21 g, 1 mmol). The heterogeneous mixture was stirred at room temperature for 14 d. After filtration of 2, the filtrate was concentrated and purified by Kugelrohr distillation (110 °C / 5 mmHg) to afford 7a (2.04 g, 96% yield, $[\alpha]_D^{23}$ +10.9°(c 2.0, CH_2Cl_2), 42% ee).

When t-butyldimethylsilyl azide and triethylsilyl azide were employed in place of trimethylsilyl azide in the above experiment, almost no products were given due to their severe steric hindrances, while dimethylethylsilyl azide and dimethylisopropylsilyl azide gave the corresponding ring-opening products in 15% ee, respectively. Furthermore, besides 2, we screened several metal (II) (2R,3R)-tartrates, and found that cupric (2R,3R)-tartrate (10)[6] was also an effective chiral catalyst.

The results of asymmetric ring-opening of 1a, cyclopentene oxide (1b), and cis-2,3-butene oxide (1c) with trimethylsilyl azide catalyzed by 2 or 10 are summarized in Table 1. The ring-opening products (7a-c) were refluxed with methanol in the presence of a small amount of concd HCl aq to give desilylated products (8a-c), and the catalytic hydrogenolysis of 8a-c with 10% Pd-C in methanol afforded optically active trans β-amino alcohols (9a-c) whose absolute configurations have already been known to be (1R,2R).[7-9] These results are also listed in Table 1.

In the reaction of oxirane with trimethylsilyl azide catalyzed by 2 or 10, it may be possible to consider that hydrogen azide is generated by the reaction of trimethylsilyl azide with hydroxy group of tartrate ligand, and hydrogen azide thus formed reacts with oxirane to give trans 2-azido alcohol which is, in turn, silylated by trimethylsilyl azide to give trans O-trimethylsilyl 2-azido alcohol along with the regeneration of hydrogen azide. To examine this possibility,

Table 1. Synthesis of optically active (1R,2R)-β-amino alcohols [a]



1a-c 7a-c 8a-c 9a-c

a;R-R = -$(CH_2)_4$- , b;R-R = -$(CH_2)_3$- , c;R=-CH_3

Oxiranes	Catalyst	Yield / % [b]			$[\alpha]_D^{23}$(c 2.0, CH_2Cl_2)/°		$[\alpha]_D^{23}$/ °	ee / % [f]
		7	8	9	7	8	9	
1a	2	96	92	86	+10.9	-30.8	-15.9 [c]	42
	10	96			+ 5.45			21
1b	2	88			- 8.86			27
	10	85	91	94	-10.1	-21.0	-10.2 [d]	31
1c	2	85			- 1.47			17
	10	80	86	95	- 3.35	-37.8	- 6.84 [e]	40

a) Oxirane (10 mmol), Trimethylsilyl azide (12 mmol), Catalyst (1 mmol), Benzene (5 ml), Room temperature, 14 d.

b) Isolated yield by Kugelrohr distillation. All products gave satisfactory NMR and IR spectra.

c) (c 1.3, H_2O); lit.[7] $[\alpha]_D^{22}$ -37.6° (c 1.3, H_2O).

d) (c 1.7, EtOH); lit.[8] $[\alpha]_D^{20}$ -33.3° (c 1.7, EtOH).

e) (neat); lit.[9] $[\alpha]_D^{25}$ -17.05° (neat).

f) Calculated based on the reported optical rotations.

the reaction of 1a and hydrogen azide generated from trimethylsilyl azide by adding equimolar amount of acetic acid in the presence of 2 was tried. It was found that the reaction was completed within 1 h, and optically inactive 8a was obtained in 88% yield. This result indicates that the true nucleophile should be trimethylsilyl azide and not hydrogen azide. The hydroxy group of tartrate ligand does not react with trimethylsilyl azide because of the insolubility of 2 or 10 in organic solvent.

In the case of using aniline as a nucleophile, moderately polar solvent such as CH_2Cl_2 and low concentration (0.4 mol/l) are necessary for the best optical yield to avoid the tight coordination of the ring-opening product (3) to the catalyst (2) and the interference of 3 with the asymmetric interaction between substrates and catalyst. These tendencies are almost the same as those of the asymmetric ring-opening of 1a with thiols described in the previous paper.[3] On the other hand, in the case of trimethylsilyl azide, less polar solvent such as benzene and high concentration (2 mol/l) are sufficient because the silylated products (7a-c) have less ability to coordinate to catalyst and would not interfere with the asymmetric interaction between substrates and catalyst.

In spite of the unsatisfactory optical yields, it should be noteworthy that optically active trans β-amino alcohols are obtained by a newly developed strategy, that is the asymmetric ring-opening of symmetrical oxiranes with aniline and

trimethylsilyl azide by the use of zinc (2R,3R)-tartrate or cupric (2R,3R)-tartrate as a heterogeneous chiral catalyst. Further studies for improvement of optical yield and acceleration of reaction rate are now in progress.

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