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Catalytic Asymmetric Synthesis of Chiral Diol, Bis[2-(1-hydroxyalkyl)-phenyl]ether, an Asymmetric Autocatalytic Reaction[1]

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Abstract: Chiral diols, bis[2-(1-hydroxyalkyl)phenyl]ethers, with very high e.e.'s are synthesized by catalytic enantioselective alkylation of bis(2-formylphenyl)ether. Zinc alkoxides of chiral diols were found to work as asymmetric autocatalysts in the reaction between bis(2-formylphenyl)ether and dialkylzincs.

Chiral diols are useful chiral auxiliaries, ligands and catalysts in enantioselective synthesis.[2] We recently reported a catalytic diastereodivergent synthesis of vicinal diols by the catalyzed alkylation of α-chiral α-siloxyaldehydes.[3]

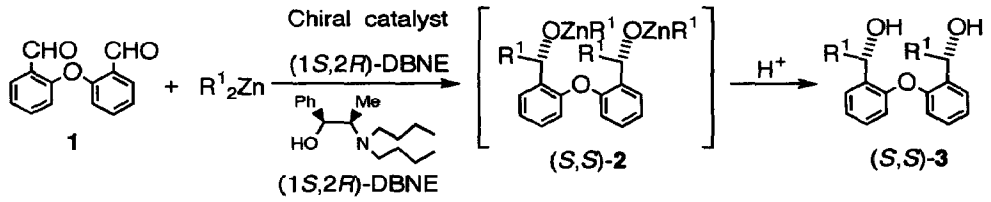
On the other hand, an asymmetric autocatalytic reaction is a reaction in which the structures of the chiral catalyst and the product are the same, and in which the chiral product itself plays the role of the chiral catalyst.[4] The process is the auto-multiplication of a chiral molecule. Unlike conventional catalytic asymmetric reactions, an asymmetric autocatalytic reaction doesn't require the removal of the chiral catalyst from the product. We have reported the first asymmetric auto*catalytic* reaction between 3-pyridinecarboxaldehyde and dialkylzincs using zinc alkoxides of chiral 3-pyridylalkylalcohols as asymmetric auto*catalysts*.[5,6]

Enantioselective additions of dialkylzincs to aldehydes are of current interest. Various types of chiral catalysts, including chiral 1,2-diphenyl-1,2-ethanediol,[7] have been utilized.[8]

We wish to report catalytic enantioselective syntheses of the new chiral diols {bis[2-(1-hydroxyalkyl)phenyl]ether (**3**)}, with a C_2-symmetry axis, by the alkylation of bis(2-formylphenyl)ether (**1**) (Scheme 1), and an asymmetric autocatalytic reaction of their zinc alkoxide derivatives (Scheme 2).

When dialdehyde **1** (1.0 mmol) was treated with diethylzinc in the presence of (1*S*, 2*R*)-*N*,*N*-dibutylnorephedrine (DBNE, 0.1 mmol, 10 mol%),[9] (*S*,*S*)-bis[2-(1-hydroxypropyl)phenyl]ether(**3a**)[10] with 98% e.e. was obtained in 79% yield (*dl*/*meso* = 82/18) (Table 1, Entry 1). When diisopropylzinc was employed in the presence of 10 mol% of DBNE, optically active (*S*,*S*)-bis[2-(1-hydroxy-2-methylpropyl)phenyl]ether (**3b**) with 99.2% e.e. was obtained. The e.e. of **3b** increased to 100% e.e. (*dl* / *meso* = 95 / 5) when 40 mol% of (1*S*, 2*R*)-DBNE was employed (Table 1, Entry 2). Optically active (**3a,b**) were separated from the *meso*-isomers by silica gel TLC.

We then examined the asymmetric autocatalytic reaction using chiral diol (**3**). When dialdehyde **1** (1.0 mmol) was treated with Et_2Zn (5 mmol) in the presence of 0.20 mmol (20 mol%) of the chiral diol (*S*,*S*)-**3a** (98% e.e., *dl*/*meso* = 99.5/0.5) as a chiral catalyst in a mixed solvent of toluene and hexane at room temperature, 0.65 mmol of the diol which contains the newly synthesized diol and the diol used as catalyst



Scheme 1. Enantioselective Synthesis of Chiral Diol **3**.

Table 1. Asymmetric synthesis of chiral diol (**3**) from dialdehyde (**1**) using (1*S*, 2*R*)-DBNE as a chiral catalyst

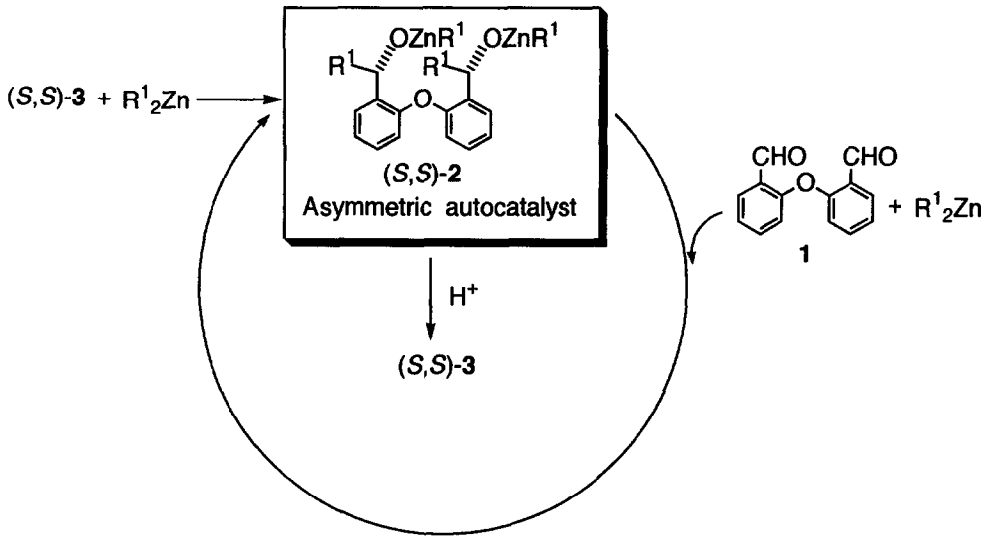
Entry[a]	R^1_2Zn	Time (h)	Diol (**3**)				
				Yield (%)	(*dl* : *meso*)	$[\alpha]_D$ (*c*, EtOH) of *dl* isomer	E.e.(%)[b]
1	Et_2Zn	4.0	**3a**	79	(82 : 18)	$[\alpha]_D^{23}$ -38.76 (1.2)	98
2	*i*-Pr_2Zn	4.5	**3b**	29	(95 : 5)	$[\alpha]_D^{26}$ -54.87 (1.1)	100

[a] Reactions were run in a mixed solvent of toluene and hexane at room temperature. Molar ratio, dialdehyde (**1**) : R^1_2Zn : (1*S*, 2*R*)-DBNE = 1: 5 : 0.1 (entry 1) and 1 : 4 : 0.4 (entry 2).

[b] Determined by HPLC analyses using a chiral column (Daicel Chiralcel OD, entry 1; OF, entry 2).

(0.20 mmol) was obtained. This result showed that the synthetic yield of the newly formed **3a** was 45% (0.6509 - 0.2000 = 0.4509 mmol). The HPLC analysis of the diol using a chiral column and the calculation [deduction of the amount of the **3a** (0.2 mmol) used] showed that the newly formed diol possesses the enantiomeric purity of 9.2% e.e. (*dl* /*meso* = 62/38) (Table 2, Entry 1). When chiral diol (*S*, *S*)-**3a** (0.50 mmol, 50 mol%) was used, (*S*, *S*)-**3a** with 12% e.e. was newly formed in 46% yield (Table 2, Entry 3). In the isopropylation, the reaction between dialdehyde **1** and *i*-Pr_2Zn using chiral diol (*S*, *S*)-**3b** (100% e.e.) afforded newly formed (*S*, *S*)-**3b** with 20 % e.e. in 5.6% (*dl*/*meso* = 77/23) yield (Table 2, Entry 4).

A typical experimental procedure is as follows: To a mixture of dialdehyde **1** (0.226g, 1.0 mmol) and bis[2-(1-hydroypropyl)phenyl]ether (*S*, *S*)-(**3a**) [0.0573g, 0.2 mmol, 20 mol%, 98% e.e., containing (*S*, *S*)-**3a**(0.0564g), (*R*, *R*)-**3a**(0.0005g), (*R*, *S*)-**3a** (meso) (0.0004g)] in toluene (4 ml), Et_2Zn (5.0 mmol, 5.0 ml of 1 M toluene solution) was added at 0 °C. The mixture was stirred for 3 d at room temperature, and the reaction was quenched by the addition of satd. aq. NH_4Cl (10 ml). The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated. Purification on silica gel TLC (developing solvent, dichloromethane/ethyl acetate = 10/1, developed twice) afforded a mixture of the newly formed diol and the catalyst diol (0.0573g) in a total amount of 0.1864g (0.6509 mmol). HPLC analysis using a chiral column (Daicel Chiralcel OD) showed that the mixture contains (*S*, *S*)-**3a**(0.0996g), (*R*, *R*)-**3a**(0.0364g), *meso*-**3a**(0.0504g). Thus, after the deduction of the amount of the catalyst, the amounts of the stereoisomers of newly formed diol were (*S*, *S*)-**3a**(0.0432g), (*R*, *R*)-**3a**(0.0359g), and *meso*-**3a**(0.0500g). The newly formed diol (*dl*/*meso* = 62 / 38) has an enantiomeric purity of 9.2% e.e. of the same (*S*, *S*)-configuration with that of the asymmetric autocatalyst (*S*, *S*). The amount of the newly formed diol was 0.1291g (0.1864-0.0573=0.1291) and the yield was 45% .



Scheme 2. Asymmetric Autocatalytic Reaction.

Table 2. Asymmetric autocatalytic reaction between dialdehyde (**1**) and dialkylzinc using chiral bis(zinc alkoxide) (**2**) derived from chiral diol (*S*,*S*)-(**3**)

Entry[a]	R^1_2Zn	Catalyst **3** (mol%)	Solvent	Temp.(°C)	Recovered cat. and Product (%)	Newly formed product (*S*,*S*)-**3**		
						Yield(%)(*dl*:*meso*)		E.e.(%)[b]
1	Et_2Zn	**3a** (20)	tol.	room temp.	65	**3a** 45	(62 : 38)	9.2
2	Et_2Zn	**3a** (20)	tol.-hex.	room temp.	57	**3a** 37	(60 : 40)	8.6
3	Et_2Zn	**3a** (50)	tol.-hex.	room temp.	96	**3a** 46	(64 : 36)	12
4	*i*-Pr_2Zn	**3b** (20)	tol.-hex.	0	25.6	**3b** 5.6	(77 : 23)	20

[a] Molar ratio, dialdehyde (**1**) : R^1_2Zn = 1 : 4.2-5.6. Reaction time was 3 d.

[b] See footnote b in Table 1.

It should be noted that, in all cases, *the predominant configurations of the chiral diols formed in the reaction were the same with those of the chiral diols used as the catalyst.* Because dialkylzinc is known to react with *sec*-alcohol to form alkylzinc alkoxide,[11] chiral bis(alkylzinc alkoxide) (**2**) formed *in situ* seems to work as asymmetric autocatalyst and produced itself in the reaction.

As described, chiral diols with very high enantiomeric purities were synthesized from the enantioselective alkylation of bis(2-formylphenyl)ether. Asymmetric autocatalytic reaction was observed using the bis(zinc alkoxides) derived from chiral diols. Although the induced degrees of the present asymmetric autocatalyst (**2**) in the dialkylation of dialdehyde (**1**) were not large, chiral diols [consequently as bis(zinc alkoxide)] were found to become asymmetric autocatalysts in the reaction between dialdehyde and dialkylzincs. A chiral diol possessing a more appropriate structure may become a more efficient asymmetric autocatalyst. Further studies are in progress in our laboratories.

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