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Asymmetric Synthesis of Chiral Diols by the Catalytic Enantioselective Dialkylation of Tere-, Iso-, and Phthalaldehydes and by a Catalytic Enantioselective Autoinductive Reaction

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Abstract: Optically pure aromatic diols were synthesized by the highly enantioselective dialkylation of aromatic dialdehydes with dialkylzincs in the presence of a catalytic amount of chiral aminoalcohol **1** or chiral thiophosphoramide alcohol **2** with Ti(O-*i*-Pr)$_4$. The chiral titanium(IV) alkoxide of **4b**, a diisopropylated product of isophthalaldehyde, catalyzed the addition of diisopropylzinc to isophthalaldehyde to gave a chiral zinc alkoxide of **4b** with the same configuration by an enantioselective autoinductive reaction (up to 44% e.e.). Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Optically active C_2-symmetrical bifunctional compounds are promising chiral source for the use as chiral auxiliaries in asymmetric synthesis.[1] The value of chiral diols has been particularly recognized: Many chiral diols are known to be useful chiral ligands and diols are easily transformed into other functional groups. In a preliminary communication,[2] we previously reported that the enantioselective diethylation of terephtalaldehyde is useful for preparing an optically pure diol.

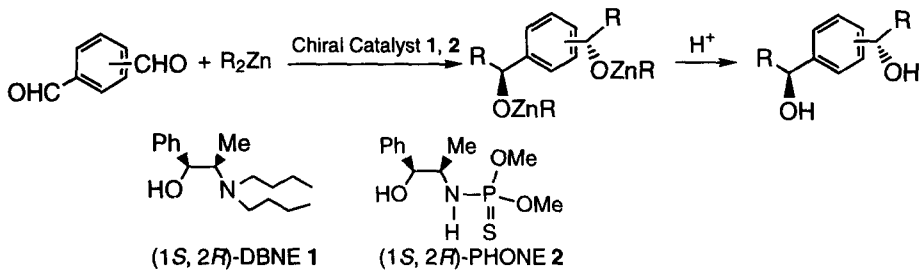
On the other hand, development of the catalytic enantioselective autoinductive reactions, in which the structures of the chiral source and the product are consistent, is also a very attractive target because the process does not require any chiral source other than the chiral product itself. Alberts and Wynberg[3] first reported a catalytic enantioselective autoinductive reaction (32% e.e.) in which the enantioselective ethylation of benzaldehyde with diethylzinc was catalyzed by the orthotitanate of (*R*)-1-phenylpropan-1-ol-d_1. Thus, the development of a catalytic asymmetric autoinductive reaction with a higher e.e. is a challenging problem.

We report here that 1) catalytic amounts of a chiral aminoalcohol and a chiral thiophosphoramide alcohol catalyze the highly enantioselective alkylation of phthalaldehydes by dialkylzincs to provide optically pure diols; and 2) the titanium(IV) alkoxide of a chiral diisopropylated product of isophthalaldehyde possesses catalytic activity for an enantioselective autoinductive reaction in the addition of dialkylzinc to isophthalaldehyde to provide a chiral zinc alkoxide.

RESULTS AND DISCUSSION

Enantioselective dialkylation of tere-, iso-, and phthalaldehydes using chiral aminoalcohol and thiophosphoramide as chiral catalysts

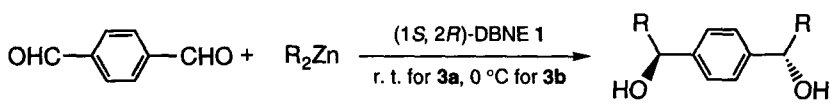
We investigated the enantioselective alkylation of phthalaldehydes by diakylzincs using aminoalcohols[4] and their derivatives as chiral catalysts. In the enantioselective dialkylation of aromatic dialdehydes, (1*S*, 2*R*)-*N*, *N*-dibutylnorephedrine (DBNE) **1**[5] and (1*S*, 2*R*)-*N*-(*O*, *O*-dimethylthiophosphoryl)norephedrine (PHONE) **2**[6] with $Ti(O\text{-}i\text{-}Pr)_4$[7] as chiral catalysts gave sufficient enantioselectivity for ethylation and isopropylation (Scheme 1).



(1*S*, 2*R*)-DBNE **1** (1*S*, 2*R*)-PHONE **2**

Scheme 1

The results of the enantioselective dialkylation of terephthalaldehyde are shown in Table 1. Enantioselective diethylation of terephthalaldehyde[7d] using (1*S*, 2*R*)-DBNE **1** gave optically pure (*S*, *S*)-**3a** in 74% yield (Entry 1).[2] Enantioselective isopropylation also proceeded to give enantiomerically pure diol (*S*, *S*)-**3b** (>99% e.e.) in a yield of 66% using 0.5 equivalents of chiral catalyst **1** (Entry 2).



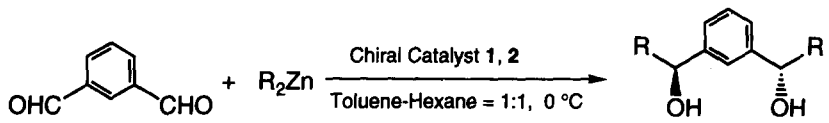
3a (R = Et), **3b** (R = *i*-Pr) (1)

Table 1. A Catalytic Enantioselective Dialkylation of Terephthalaldehyde.

Entry	R (X eq.)	Solvent[a]	Equivalent of **1**	Yield / %	E. e. / %[b]	*dl* / *meso*[b]
1	Et (4.0)	THF-Hex.	0.2	74	> 99	80 /20
2	*i*-Pr (4.4)	Tol.-Hex.	0.5	66	> 99	91 / 9

[a] Hex.=Hexane, Tol.=Toluene. [b] Determined by HPLC analysis using a chiral column.

Enantioselective diethylation of isophthalaldehyde[7d] was performed in the presence of a catalytic amount of (1*S*, 2*R*)-DBNE **1** or (1*S*, 2*R*)-PHONE **2**[6] in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ (Table 2). Under each condition of ethylation, enantiomerically pure diol **4a** was obtained. The chemical yield and diastereoselectivity were both higher under the latter condition. Isopropylation proceeded with almost perfect enantio- and diastereoselectivity in the presence of a catalytic amount of (1*S*, 2*R*)-DBNE **1**.



(2)

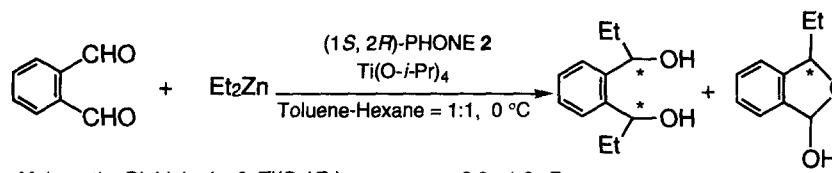
4a (R = Et), **4b** (R = *i*-Pr)

Table 2. A Catalytic Enantioselective Dialkylation of Isophthalaldehyde.

Entry	R (Xeq.)	Chiral Catalyst(eq.)	Yield / %	E. e. / %[a]	*dl* / *meso*[a]
1	Et (4.4)	(1*S*,2*R*)-DBNE **1** (0.2)	70	> 99	89 /11
2[b]	Et (6.0)	(1*S*,2*R*)-PHONE **2** (0.3)	94	> 99	92 /8
3	*i*-Pr (4.4)	(1*S*,2*R*)-DBNE **1** (0.2)	60	> 99	>99 / 1

[a] Determined by HPLC analysis using a chiral column. [b] Ti(O-*i*-Pr)$_4$ (1.6 eq.) was added.

The enantioselectve diethylation of phthalaldehyde was examined (Eq.3). The reaction using diethylzinc in the presence of the chiral aminoalcohols gave lactol **6** as a major product by the *in situ* cyclization of monoalkylated alcohol.[8] It was found that the use of thiophosphoramide **2**[6] in the presence of Ti(O-*i*-Pr)$_4$ gave chiral diol **5** as a major product in 92% e.e. The second alkylation of monoalkylated alcohol proceeds rather than the cyclization because of the higher activity[6] of the chiral catalyst generated from thiophosphoramide **2**, Ti(O-*i*-Pr)$_4$ and Et$_2$Zn.



(3)

Molar ratio. Dialdehyde: **2**: Ti(O-*i*-Pr)$_4$: Et$_2$Zn =1 : 0.3 : 1.6 : 7

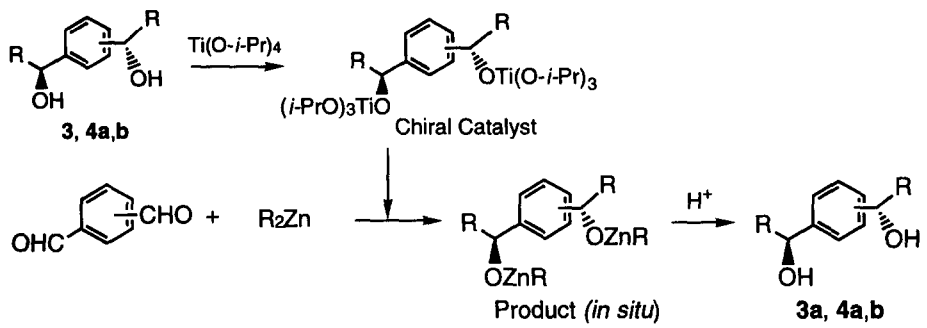
5 64% 92% e.e. *dl* / *meso* = 9 / 91

6 21%

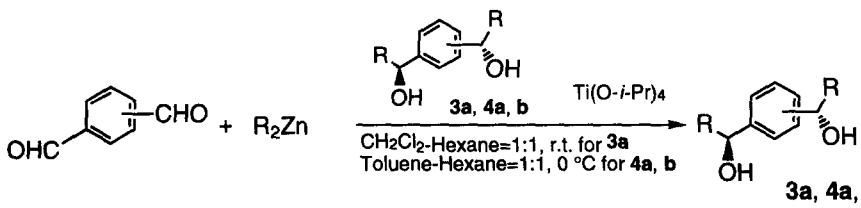
Enantioselective dialkylation of tere- and isophthalaldehydes by an asymmetric autoinductive reaction

We examined a catalytic enantioselective autoinductive reaction in the dialkylation of tere- and isophthalaldehyde by dialkylzinc reagents in the presence of chiral titanium alkoxide prepared *in situ* from chiral diols and Ti(O-*i*-Pr)$_4$ (Scheme 2).

The enantioselective autoinductive reactions using the diols **3a**, **4a**, and **4b** as a chiral source were examined (Table 3). Chiral titanium alkoxides were prepared *in situ* by treating the diols **3a**, **4a**, and **4b** (30 mol % against dialdehyde) and Ti(O-*i*-Pr)$_4$ (80 mol%) in mixed solvents. A toluene solution of dialkylzinc was added to the mixture at -30 °C, and the dialdehydes were added at 0 °C. After quenching the reaction and purification of the products, the chemical and optical yields of newly formed diols **3a**, **4a**, and **4b** were calculated by subtracting the amount of the original diols used as a chiral catalyst from the amount of the obtained diols.



Scheme 2



(4)

Table 3. Enantioselective Autoinductive Dialkylation of Tere- and Isophthalaldehyde.

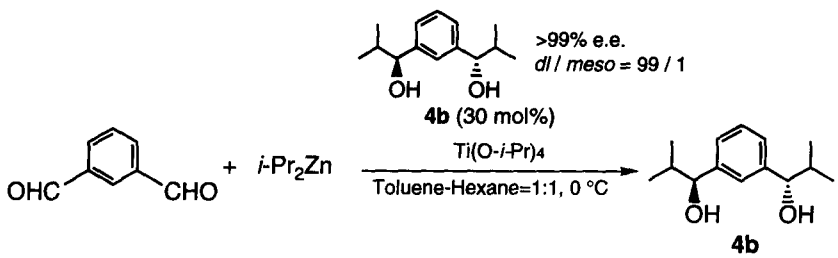
Entry[a]	R(Xeq.)		Chiral Catalyst		Newly Formed Chiral Diol[b]		
			E.e.(%)	*dl/meso*	Yield(%)	E.e.(%)[c]	*dl/meso*[c]
1	Et(4.0)	**3a**	>99	80/20	91	6	50/50
2	*i*-Pr(6.0)	**4a**	>99	92/8	83	11	61/39
3	*i*-Pr(6.0)	**4b**	>99	99/1	65	30	67/33

[a] Molar ratio. Dialdehyde : Diol (**3a**, **4a**, **b**) : Ti(O-*i*-Pr)$_4$ = 1 : 0.3 : 0.8. [b] The original diol used as a catalyst was excluded from the obtained diol by calculation. [c] Determined by HPLC analysis using a chiral column.

Optically active diols **3a**, **4a**, and **4b** with the same configurations as the chiral catalysts were formed (Entries 1-3). It should be noted that **4b**, a diisopropylated diol of isophthalaldehyde, possesses higher enantioselectivity as a chiral source in the autoinductive reaction than **3a** or **4a**.

To further improve the enantioselectivity, the molar ratio of Ti(O-*i*-Pr)$_4$ was varied (60 -120 mol%) relative to that of isophthalaldehyde, while that of chiral diol **4b** was fixed at 30 mol% (Table 4). The use of 80 mol% of Ti(O-*i*-Pr)$_4$ gave the best result (30% e.e.) (Entry 3).

We next examined the effect of the molar ratio of chiral diol **4b** (Table 5). When 40 mol% of **4b** was used, newly formed **4b** was obtained in the best enantiomeric excess (44% e.e.) (Entry 5). Thus, the optimum ratio of chiral diol **4b** *vs.* Ti(O-*i*-Pr)$_4$ was 1 : 2. This observation suggests that the di-titanium alkoxide of chiral diol **4b** is effective for the asymmetric dialkylation of isophthalaldehyde, as shown in Scheme 2.

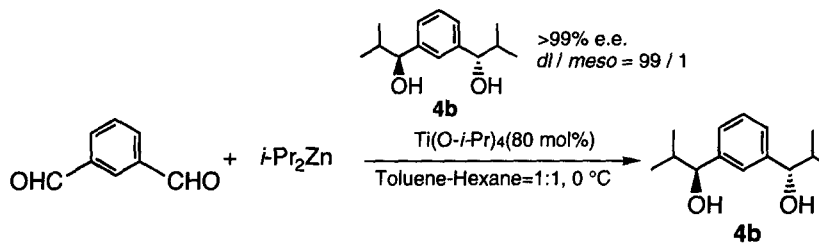


(5)

Table 4. Screening of the molar ratio of $Ti(O\text{-}i\text{-}Pr)_4$ in the enantioselective autoinductive diisopropylation of isophthalaldehyde.

Entry	$Ti(O\text{-}i\text{-}Pr)_4$ (mol%)	Time (h)	Newly Formed Chiral Diol **4b**[b]		
			Yield(%)	E.e.(%)[c]	*dl /meso*[c]
1	60	101	35	14	61/39
2	70	114	30	20	57/43
3	80	91	65	30	67/33
4	90	70	66	29	68/32
5	100	73	65	26	66/34
6	120	69	69	25	68/32

[a] Molar ratio. Isophalaldehyde : **4b** : $i\text{-}Pr_2Zn$ = 1 : 0.3 : 6. [b] The original diol used as a catalyst was excluded from the obtained diol by calculation. [c] Determined by HPLC analysis using a chiral column.



(6)

Table 5. Effect of the amount of chiral diol **4b** in the enantioselective autoinductive diisopropylation.

Entry[a]	Chiral Diol **4b** (mol%)	Time (h)	Newly Formed Chiral Diol **4b**[b]		
			Yield(%)	E.e.(%)[c]	*dl /meso*[c]
1	15	123	51	15	67/33
2	20	92	42	25	61/39
3	30	91	65	30	67/33
4	35	89	60	31	66/34
5	40	95	61	44	67/33
6	45	70	62	44	68/32

[a] Molar ratio. Isophalaldehyde : $Ti(O\text{-}i\text{-}Pr)_4$: $i\text{-}Pr_2Zn$ = 1 : 0.8 : 6. [b] The original diol used as a catalyst was excluded from the obtained diol by calculation. [c] Determined by HPLC analysis using a chiral column.

In summary, optically pure diols were prepared by the enantioselective addition of dialkylzincs to phthalaldehydes in the presence of a catalytic amount of (1*S*, 2*R*)-DBNE **1** or (1*S*, 2*R*)-PHONE **2** with $Ti(O\text{-}i\text{-}Pr)_4$. In addition, we also realized an enantioselective autoinductive reaction in the diisopropylation of isophthalaldehyde using titanium alkoxide of chiral diol **4b** as a chiral source.

EXPERIMENTAL

General: ^{1}H-NMR spectra were recorded on a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 260-30 spectrometer. Optical rotations were measured using a Jasco DIP-181 polarimeter. Hexane, toluene, and CH_2Cl_2 were distilled from CaH_2, and THF was distilled from $LiAlH_4$ before use. $Ti(O\text{-}i\text{-}Pr)_4$ was freshly distilled. All reactions were carried out under an argon atmosphere.

(*S, S*)-1,4-Bis(1-hydroxypropyl)benzene 3a.[2] (Table 1, Entry 1) A mixture of a THF solution (4 ml) of (1*S*, 2*R*)-DBNE[5] **1** (105.4 mg, 0.40 mmol) and 1 M hexane solution of diethylzinc (8.8 ml, 8.8 mmol) was stirred for 30 min at 0 °C, then terephthalaldehyde (268.3 mg, 2.00 mmol) was added in a THF solution (4 ml). The reaction mixture was refluxed for 40 min, and then quenched by the addition of sat. aq. NH_4Cl (5 ml) at 0 °C. The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude on silica gel TLC (thin-layer chromatography) gave diol **3a** (287.5 mg, 1.48 mmol, 74%). Optical purity was determined to be >99% e.e. (*dl/meso* = 80/20) by HPLC analysis using a chiral column (Daicel Chiralcel AD: 4 x 250 mm, 254 nm UV detector, 35 °C, eluent: 3% 2-propanol in hexane, flow rate: 1.5 ml/min, retention time (min) 20.9 for the minor-**3a**, 23.1 for the major-**3a**, 25.9 for the *meso*-**3a**). The absolute configuration was determined by analogy to the ethylated product of benzaldehyde.[5] Spectral data agreed with those in literature.[7d]

General procedure for the asymmetric dialkylation of tere- and isophthalaldehydes using (1*S*, 2*R*)-DBNE 1 as a chiral catalyst. (Table 1, Entry 2; Table 2, Entries 1 and 3) A mixture of a toluene solution (4 ml) of (1*S*, 2*R*)-DBNE[5] **1** (105.4 mg, 0.40 mmol) and 1 M hexane solution of diethylzinc (8.8 ml, 8.8 mmol) was stirred for 30 min at 0 °C, then tere- or isophthalaldehyde (268.3 mg, 2.00 mmol) was added in a toluene solution (4 ml) at 0 °C. The reaction mixture was stirred for 24 h at 0 °C, and then quenched by the addition of sat. aq. NH_4Cl (5 ml) at 0 °C. The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude on silica gel TLC (thin-layer chromatography) gave diol **3a**, **4a**, **b**.

General procedure for the asymmetric dialkylation of iso- and phthalaldehydes using (1*S*, 2*R*)-PHONE 2 as a chiral catalyst in the presence of $Ti(O\text{-}i\text{-}Pr)_4$. (Table 2, Entry 2; Eq. 3) A mixture of (1*S*, 2*R*)-PHONE[6] **2** (165.1 mg, 0.60 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.94 ml, 3.20 mmol) was stirred for 20 min at 80 °C in toluene (2 ml), then at -30 °C 1 M hexane solution of diethylzinc (6.0 or 7.0 ml, 6.0 or 7.0 mmol) was added. After the reaction mixture was stirred for 20 min at -30 °C, iso- or phthalaldehyde (268.3 mg, 2.00 mmol) was added in a toluene solution (5 ml) at 0 °C. The reaction mixture was stirred for 24 h at 0 °C. The procedures for the quenching and purification are the same as above.

(*S*, *S*)-1,4-Bis(1-hydroxy-2-methylpropyl)benzene 3b. Optical purity was determined to be >99% e.e. (*dl/meso* = 91/9) by HPLC analysis using a chiral column (Daicel Chiralcel AD: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 1.0 ml/min, retention time (min) 30.0

for the minor-**3b**, 39.3 for the major-**3b**, 44.0 for the *meso*-**3b**). The absolute configuration was determined by analogy to the isopropylated product of benzaldehyde.[5] The physical and spectral data were measured as a mixture of *dl* and *meso* isomers. Mp. 68.0-69.0 °C (hexane); $[\alpha]_D^{26.0}$ -46.26° (*c* 1.95, $CHCl_3$); IR (KBr disk) 3320 cm^{-1}; ^{1}H-NMR δ= 0.79 (d, 3Hx2, *J* = 6.9 Hz), 1.00 (d, 3Hx2, *J* = 6.6 Hz), 1.80 (bs, 1Hx2), 1.89-2.02 (dtt, 1Hx2, *J* = 6.6, 6.6, 6.9 Hz), 4.37 (d, 1Hx2, *J* = 6.6 Hz), 7.29 (s, 4H); HRMS found m/z 222.1622, calcd for $C_{14}H_{22}O_2$: M, 222.1621.

(*S, S*)-1,3-Bis(1-hydroxypropyl)benzene 4a. Optical purity was determined to be >99% e.e. (*dl/meso* = 92/8) by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, 40 °C, eluent: 3% 2-propanol in hexane, flow rate: 0.5 ml/min, retention time (min) 118.8 for the *meso*-**3a**, 126.6 for the major-**3a**, 135.0 for the minor-**3a**). The absolute configuration was determined by analogy to the ethylated product of benzaldehyde.[5] Spectral data agreed with those in literature.[7d]

(*S, S*)-1,3-Bis(1-hydroxy-2-methylpropyl)benzene 4b. Optical purity was determined to be >99% e.e. (*dl/meso* = >99/1) by HPLC analysis using a chiral column (Daicel Chiralcel AD: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 1.0 ml/min, retention time (min) 46.0 for the *meso*-**4b**, 54.5 for the major-**4b**, 69.2 for the minor-**4b**). Absolute configuration was determined by analogy with that of isopropylated product of benzaldehyde.[5] Mp. 46.0-47.0 °C (hexane); $[\alpha]_D^{27.0}$ -50.73° (*c* 2.04, $CHCl_3$); IR (KBr disk) 3298 cm^{-1}; ^{1}H-NMR δ= 0.79 (d, 3Hx2, *J* = 7.0 Hz), 0.99 (d, 3Hx2, *J* = 6.7 Hz), 1.90-1.98 (m, 1Hx2+1Hx2), 4.36 (d, 1Hx2, *J* = 6.7 Hz), 7.20-7.30 (m, 4H); Anal. calcd for $C_{14}H_{22}O_2$: C75.63, H9.97%; Found: C75.64, H9.65%.

1,2-Bis(1-hydroxypropyl)benzene 5. Optical purity was determined to be 92% e.e. (*dl/meso*= 9/91) by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 0.5 ml/min, retention time (min) 30.9 for the minor-**5**, 34.7 for the major-**5**, 39.3 for the *meso*-**5**). *dl* isomer: Mp. 52.5-53.5 °C (hexane); $[\alpha]_D^{25.5}$ +100.22° (*c* 1.03, $CHCl_3$); IR (KBr disk) 3273 cm^{-1}; ^{1}H-NMR δ= 0.98 (t, 3Hx2, *J* = 7.4 Hz), 1.78-1.92 (m, 2Hx2), 2.19 (bs, 1Hx2), 4.92 (dd, 1Hx2, *J* = 6.0, 7.5 Hz), 7.26-7.32 (m, 2H), 7.41-7.45 (m, 2H); HRMS found m/z 176.1194., calcd for $C_{12}H_{18}O_2$-H_2O: M, 176.1202. *meso* isomer: Mp. 94-95 °C; IR (KBr disk) 3283 cm^{-1}; ^{1}H-NMR δ= 0.94 (t, 3Hx2, *J* = 7.4 Hz), 1.68-1.91 (m, 2Hx2), 2.90 (bs, 1Hx2), 4.79 (dd, 1Hx2, *J* = 6.0, 7.5 Hz), 7.26-7.32 (m, 2H), 7.38-7.46 (m, 2H); Anal. calcd for $C_{12}H_{18}O_2$: C74.19, H9.34%; Found: C74.04, H9.07%.

3-Ethyl-2-oxaindan-1-ol 6. Spectral data agreed with those in literature.[8]

Typical experimental procedure and calculation of the optical and chemical yields of the newly formed diol in the asymmetric autoinductive reaction. (Table 5, Entry 5) To a toluene solution (1.5 ml) of chiral diol **4b** (44.5 mg, 0.20 mmol), which included the (*S,S*)-isomer (43.8 mg) and *meso* isomer (0.7 mg), was added $Ti(O\text{-}i\text{-}Pr)_4$ (0.12 ml, 0.39 mmol) at room temperature. The mixture was then heated to 80 °C and stirred at that temperature for 20 min. After 1.0 M hexane solution of diisopropylzinc (6 ml, 6 mmol, 3.0 equiv.) was added at -30 °C, the reaction mixture was stirred at -30 °C for an additional 20 min. A toluene solution (4.5 ml) of isophthalaldehyde (67.1 mg, 0.50 mmol) was added and the mixture was stirred for 95 h at 0 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl. The resultant mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The combined extract was dried over Na_2SO_4 and evaporated under the reduced pressure. The residue was purified by silica gel TLC (eluent, CH_2Cl_2 / MeOH=50/1, then hexane/ethyl acetate = 2/1, *v/v*) to give the chiral diol **4b** (112.6 mg) with 71.3% e.e., *dl/meso* = 79/21, *i.e.*, (*S, S*)-isomer (76.5 mg), (*R, R*)-isomer (12.8 mg), *meso* isomer (23.2 mg). The amount

of newly formed **4b** was 112.6 - 44.5 = 68.1 mg (61%) with 44% e.e. *dl/meso* = 67/33 [(*S*, *S*)-isomer (76.5 - 43.8 = 32.7 mg), (*R*, *R*)-isomer (12.8 mg), *meso* isomer (23.2 - 0.7 = 22.5 mg)].

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