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Truly Catalytic and Enantioselective Pinacol Coupling of Aryl Aldehydes Mediated by Chiral Ti(III) Complexes†

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A variety of chiral Ti(IV) complexes were reduced in situ with zinc in acetonitrile. The resulting chiral Ti(III) complexes were found to catalyze the pinacol coupling reaction stereoselectively. The best results were obtained from the Ti−SALEN complex, which was found to be an efficient catalyst at 10 mol % concentration. Various aromatic aldehydes were coupled to obtain chiral hydrobenzoin derivatives with high diastereoselectivity and enantioselectivity. A plausible mechanism is proposed that rationalizes the stereochemical outcome of the reaction.

Introduction

Enantiomerically pure hydrobenzoins have proved to be very useful chiral auxiliaries[1] and ligands[2] for stereoselective organic synthesis. These diols, which were previously accessible only through resolution,[3] can be now obtained by dihydroxylation of olefins[4] and reduction of benzils.[5] However, enantioselective synthesis through carbon−carbon bond formation has not been very successful.[6]

Traditionally pinacol coupling reactions have been performed using stoichiometric amounts of low-valent metals, which provided poor stereoselectivity. The introduction of a catalytic cycle by Fürstner and Hupperts in 1995[7] rendered the reaction an attractive methodology for carbon−carbon bond formation. In recent years, the catalytic pinacol coupling reaction has been accomplished in moderate to high diastereoselectivity using complexes derived from Ce,[8] Cr,[9] V,[10] Sm,[11] Ru,[12] In,[13] and Ti.[14] However, high enantioselectivity in pinacol coupling reactions has remained elusive through stoichiometric[15] as well as catalytic protocols.[16] Very recently, Riant and co-workers reported pinacol coupling using a titanium−Schiff base complex.[17] While the enantioselectivity was good when a stoichiometric amount of the complex was used, it was only moderate with a catalytic cycle.

Results and Discussion

Low-valent titanium offers tremendous potential for stereoselective organic synthesis.[18] We have been pursuing chiral low-valent titanium complexes for several reactions, including the pinacol coupling reaction. For this reaction, we systematically explored the role of bidentate (**1**), tridentate (**2**), and tetradentate ligands (**3**

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† Dedicated to Prof. Goverdhan Mehta on his 60th birthday.

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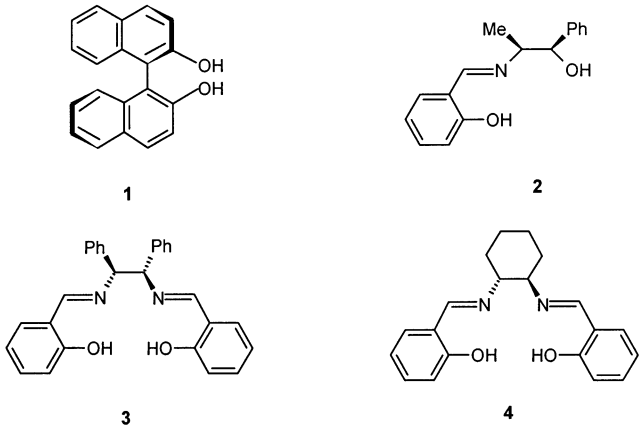
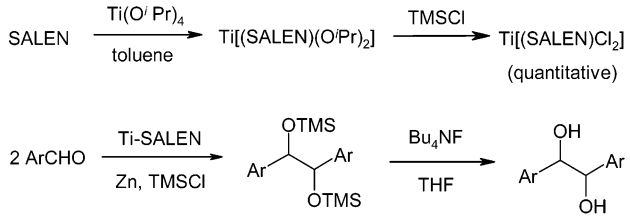


FIGURE 1. Select ligands examined for pinacol coupling reaction.

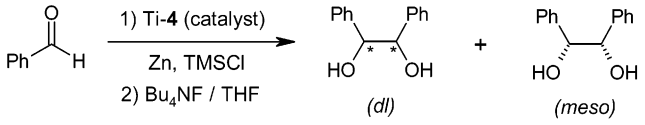
SCHEME 1. Preparation of Ti(IV)−SALEN Complexes and Catalysis of Pinacol Coupling



and **4**) (Figure 1). Among these, the titanium(IV) complex of **1** has been utilized very well for glyoxylate−ene reactions.[19] Ligand **3** has been used for epoxidation of unfunctionalized olefins[20]and trimethylsilylcyanation of aldehydes.[21] The titanium complex of **4** has been known for quite some time but never characterized or used for any reaction.[22] We found that titanium(IV) complexes derived from **3** and **4** are very stable,and not sensitive toward air/moisture. These can be easily prepared by mixing Ti(O^{i}Pr)$_4$ and SALEN in toluene followed by ligand exchange with excess TMSCl (Scheme 1).

In our preliminary investigation, we carried out the coupling of benzaldehyde in acetonitrile with 10 mol % catalyst concentration, a stoichiometric amount of TMSCl, and various metals as reductants. Al, Mg, and Fe did not work at all. Mn did bring about a slow reaction, but the product (after desilylation) had poor diastereoselectivity. The best results in terms of reaction rate, yield, and diastereoselectivity were provided by Zn as the reductant. Ligands **1**−**3** provided poor to moderate diastereoselectivity and, hence, were not examined further. Gratifying results were obtained with Ti−**4** as the catalyst (Table 1). To study the effect of solvent, we also performed the reaction in THF and DME. Although the yields were comparable, substantial lowering of diastereoselectivity was observed. While THF gave a poor

TABLE 1. Pinacol Coupling Reaction of Benzaldehyde under Various Conditions



entry	solvent	*T* (°C)	cat. concd (mol %)	additive	yield[a] (%)	*dl*/*meso*[b]	ee[c] (%)
1	DME	25	10		89	84:16	
2	THF	25	10		70	58:42	
3	CH_3CN	25	10		88	95:5	64
4	CH_3CN	0	10		90	96:4	84
5	**CH_3CN**	**−10**	**10**		**94**	**98:2**	**95**
6	CH_3CN	−40	10		92	93:7	64
7	CH_3CN	25	20		82	96:4	72
8	CH_3CN	25	5		70	82:18	
9	CH_3CN	25	10	$MgBr_2$	70	50:50	
10	CH_3CN	25	10	$ZnBr_2$	88	98:2	75
11	CH_3CN	25	10	dioxane	84	93:7	60

[a] Isolated and purified product. [b] Determined by ^{1}H NMR. [c] Determined by rotation.

dl/*meso* ratio (58:42), in DME it was 84:16. The next parameter, temperature, had a significant effect. The enantioselectivity increased from 64% at room temperature to 95% at −10 °C. Further lowering of the temperature seemed to have an unfavorable effect on enantioselectivity. The increase in catalyst concentration from 10 to 20 mol % shortens the reaction time to about half, but with almost no effect on enantioselectivity. A decrease in the catalyst concentration to 5 mol % slowed the reaction rate, and the % ee dropped to 82%. We also examined the effect of additives on the reaction outcome. Unlike the report by Gansäur,[23] the diastereoselectivity significantly decreased on adding $MgBr_2$, whereas $ZnBr_2$ was rather inert. Weakly coordinating additives such as dioxane brought about reduction in enantioselectivity. Strongly coordinating additives like TMEDA completely arrested the reaction. The reaction can be monitored visually since the color is dark blue initially, turns green if the catalyst is not regenerated efficiently, and becomes reddish brown if the catalyst is quenched.

After optimization of all the reaction parameters, we examined general applicability of our protocol. As is evident from Table 2, decent results were obtained with a variety of aryl aldehydes. Electron-donating groups in general lead to better stereoselectivity. A heteroatom on the aryl ring (entry 9) brings down the enantioselectivity considerably. Steric hindrance also affected the yield as well as the diastereoselectivity (entry 3 and 7). This difficulty, however, can be overcome by increasing the catalyst loading to 20 mol %. In most cases, a single crystallization provides homochiral product. It is noteworthy that consistently (*R*,*R*)-hydrobenzoins were produced using (*R*,*R*)-SALEN as the ligand. We also examined the stereoelectronic effects by using SALEN ligands with NO_2 and ^{t}Bu groups on the phenyl ring. However, such effects were detrimental and the parent ligand proved to be the best.

As for the mechanism of the reaction, the most plausible pathway is the dimerization of the aldehyde radicals generated by the SET process.[6b] Reduction of

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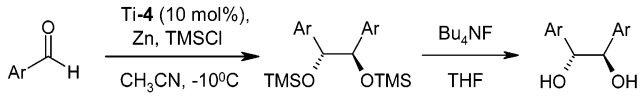
TABLE 2. Pinacol Coupling Reaction of Representative Aryl Aldehydes



entry	aldehydes (Ar)	time (h)	yield[a] (%)	*dl*/*meso*[b]	ee[c] (%)
1	phenyl	4	94	98:2	95
2	*p*-tolyl	4	84	91:9	96
3	*o*-tolyl	4	75[e]	96:4	82
4	*p*-anisyl	3	72	100:0	78
5	*p*-chlorophenyl	4	79	89:11	68
6	*p*-fluorophenyl	5	65	90:10	68[d]
7	1-naphthyl	5	88[e]	91:9	86
8	2-naphthyl	4	82	94:6	91
9	2-furyl	3	86	93:7	50

[a] Isolated and purified product. [b] Determined by ^{1}H NMR. [c] Determined by rotation. [d] Determined by NMR shift experiment using Eu(hfc)$_3$. [e] 20 mol % of catalyst was used.

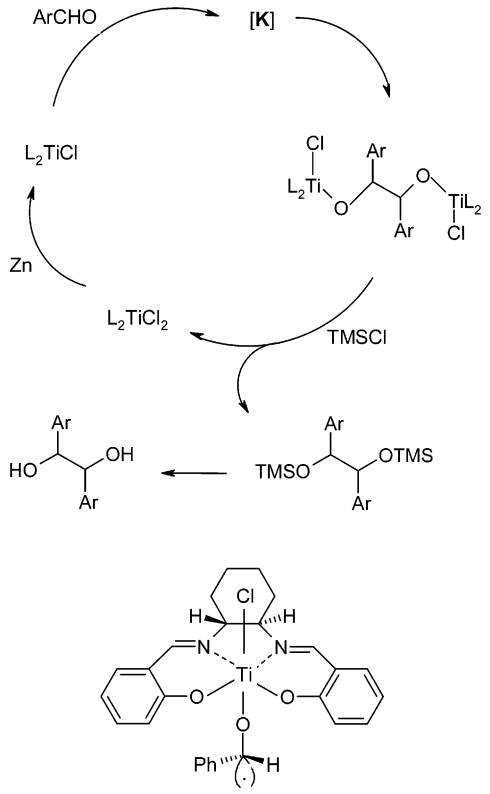


FIGURE 2. Plausible reaction mechanism.

Ti(IV) complex with Zn generates a Ti(III) species with two oxygen, two nitrogen, and a chlorine atom at the five corners of a twisted square pyramid (based on modeling studies). The aldehyde immediately forms a bond with the metal atom where a significant unpaired electron density resides at the carbon center generating a carbon radical.[24] While coupling with another radical, the two aryl groups orient trans to each other favoring a *dl* stereochemistry in the product.[14c,23,24] The α-H atom of the C−N bond of the cyclohexane plays a key role in enantioselection, as shown in Figure 2. We believe that the steric interaction between the aryl group of aldehyde and the α-hydrogen atom of ligand favor the transition state shown as **K** (simplified assembly), which then explains the stereochemical outcome of the reaction.[25] This mechanism also explains our observation that increasing the steric bulk on the phenyl ring of SALEN provides poor selectivity. Since we did not detect any McMurry coupling product, the formation of any Ti(II) intermediate is ruled out.

Conclusion

In conclusion, we have presented a catalytic and enantioselecive protocol for the pinacol coupling of aryl aldehydes using easily accessible reagents. Our efforts are in progress to understand the structure−reactivity relationship of the catalyst and extend the scope of the reaction to aliphatic aldehydes, ketones, and imines.

Experimental Section

General Methods. Chemical shifts in ^{1}H NMR are reported with tetramethylsilane (TMS) and DMSO-d_6 as the internal standard. Abbreviations for ^{1}H NMR: s = singlet, d = doublet, m = multiplet, b = broad, Ar = aromatic. The reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plates. The products were purified by "flash chromatography" using silica gel (200−400 mesh) as the sorbent and hexanes−ethyl acetate mixture as the eluent. All the reactions were conducted in dried glassware under an atmosphere of argon. All chemicals and solvents were freshly dried and degassed before use. Ligand **4** was prepared according to the literature procedure.[26]

Analytical data of all known compounds were compared with the literature (reference quoted), and new compounds were fully characterized.

General Procedure for the Preparation of Ti Complexes from 2−4. To a solution of Ti(O^{i}Pr)$_4$ (1.0 M in toluene; 5 mL, 5 mmol, 1 equiv) was added SALEN (2.5 M in toluene; 2 mL, 5 mmol, 1 equiv) under argon atmosphere. The resulting homogeneous solution was stirred at room temperature until the starting material disappeared (checked by TLC). The reaction mixture was diluted with 40 mL of toluene and treated dropwise with TMSCl (1.26 mL, 10 mmol, 2 equiv). Immediately, the complex started precipitating out as a red solid. After the mixture was stirred for 4 h, the solid was filtered through a sintered funnel and dried under reduced pressure.

Representative Procedure for Pinacol Coupling. A round-bottom flask equipped with a magetic stir bar was charged with catalyst Ti−**4** (0.18 g, 0.4 mmol, 0.1 equiv) and Zn dust (0.52 g, 8 mmol, 2 equiv). The system was thoroughly flushed with argon. Anhydrous and degassed acetonitrile (4 mL) was added, and the resulting blue mixture was stirred for 0.5 h at room temperature. It was then cooled to the desired temperature, and aldehyde (4 mmol, 1 equiv) was added in one lot followed by a dropwise addition of TMSCl (0.76 mL, 6 mmol, 1.5 equiv) diluted with acetonitrile (1 mL). Stirring was continued until the time indicated in Table 2, and the progression of the reaction was monitored through GC. The reaction was quenched with MeOH (0.1 mL) and filtered, and most of the solvent was evaporated under reduced pressure. The resulting residue was stirred for 10 min with TBAF (1 M in THF; 5 mL, 5 mmol, 1.25 equiv). The reaction mixture was diluted with EtOAc (20 mL), washed with brine, and dried over anhydrous Na_2SO_4. The product was isolated as usual and

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purified by flash chromatography on silica gel using hexanes−EtOAc as the eluent.

Ligand−2. A mixture of (1*R*,2*S*)-norephedrine (1.51 g, 10 mmol) and salicaldehyde (1.2 mL, 10 mmol) in CH_2Cl_2 (15 mL) in the presence of anhydrous Na_2SO_4 (3 g) afforded ligand **2** almost quantitatively as a viscous liquid within 2 h of stirring at room temperature. $[\alpha]_D = +152.21$ ($c = 7.17$; MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (d, $J = 6.84$ Hz, 3 H, C*H*$_3$), 2.06 (bs, 1 H, O*H*), 3.64 (m, 1 H, C*H*), 4.80 (d, $J = 5.38$ Hz, 1 H, C*H*), 6.8−6.94 (m, 2 H, H_{Ar}), 7.14−7.36 (m, 6 H, H_{Ar}), 8.21 (s, 1 H, C*H*), 13.24 (bs, 1 H, O*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.93, 70.09, 77.74, 96.19, 117.03, 118.50, 118.76, 126.88, 127.91, 128.28, 131.44, 132.32, 141.03, 161.18, 164.67 ppm. IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3417, 3060, 3029, 2974, 2873, 1631. Anal. Calcd for $C_{16}H_{17}N0_2$: C, 75.26; H, 6.72; N, 5.49. Found: C, 75.48; H, 6.76; N, 5.52.

Ti−4 Complex. According to the general protocol, SALEN (ligand **4**) (1.61 g, 5 mmol), Ti(O^{i}Pr)$_4$ (5 mL, 1 M in toluene, 5 mmol), and TMSCl (1.3 mL, 10 mmol) afforded Ti−**4** within 8 h at room temperature. $[\alpha]_D = +514.3$ ($c = 0.014$, $CHCl_3$). Mp: 330−350 °C dec. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43−1.47 (m, 2 H, C*H*$_2$), 1.61−1.67 (m, 2 H, C*H*$_2$), 2.10−2.16 (m, 2 H, C*H*$_2$), 2.59−2.61 (m, 2 H, C*H*$_2$), 4.06−4.08(m, 2 H, C*H*$_2$), 6.9 (d, $J = 8.26$ Hz, 2 H. H_{Ar}), 7.12−7.15 (m, 2 H, H_{Ar}), 7.56−7.62 (m, 4 H, H_{Ar}), 8.39 (s, 2 H, C*H*) ppm. ^{13}C NMR (500 MHz, $CDCL_3$): δ 24.11, 28.69, 67.75, 116.42, 122.71, 125.45, 135.00, 136.40, 159.59, 162.52. Anal. Calcd. for $C_{20}H_{20}N_2O_2Cl_2Ti$: C, 54.72; H 4.60; N, 6.38. Found: C, 54.84; H, 4.61; N, 6.40.

(*R*,*R*)-(+)-1,2-Diphenylethane-1,2-diol. According to the general protocol, benzaldehyde (0.42 mL, 4 mmol), Ti−**4** (0.18 g, 0.4 mmol, 10 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-diphenylethane-1,2-diol within 4 h at −10 °C. $[\alpha]_D = +89.4$ ($c = 1$, EtOH). Mp: 148−150°C [lit.[5a] $[\alpha]_D = -94.5$ ($c = 1$, EtOH) for 100% ee *S*,*S*-enantiomer. Mp: 148−150 °C]. NMR shows a *dl*/*meso* ratio of 98:2.

(*R*,*R*)-(+)-1,2-Di(*p*-methylphenyl)ethane-1,2-diol. According to the general protocol, *p*-methylbenzaldehyde (0.48 mL, 4 mmol), Ti−**4** (0.18 g, 0.4 mmol, 10 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*p*-methylphenyl)ethane-1,2-diol within 4 h at −10 °C. $[\alpha]_D = +98.4$ ($c = 1$, EtOH). Mp: 105−107°C [lit.[5a] $[\alpha]_D = -102.5$ ($c = 1$, EtOH) for 100% ee *S*,*S*-enantiomer. Mp: 105−107 °C)]. NMR shows a *dl*/*meso* ratio of 91:9.

(*R*,*R*)-(+)-1,2-Di(*o*-methylphenyl)ethane-1,2-diol. According to the general protocol, *o*-methylbenzaldehyde (0.46 mL, 4 mmol), Ti−**4** (0.36 g, 0.8 mmol, 20 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*o*-methylphenyl)ethane-1,2-diol within 4 h at −10 °C. $[\alpha]_D = +53.3$ ($c = 1$, EtOH). Mp: 108−110 °C. [lit.[1g] $[\alpha]_D = -64.8$ ($c = 0.83$, EtOH) for 100% ee *S*,*S*-enantiomer. Mp: 109−110 °C]. NMR shows a *dl*/*meso* ratio of 96:4.

(*R*,*R*)-(+)-1,2-Di(*p*-methoxylphenyl)ethane-1,2-diol. According to the general protocol, *p*-methoxybenzaldehyde (0.48 mL, 4 mmol), Ti−**4** (0.18 g, 0.4 mmol, 10 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-bis(paramethoxyphenyl)ethane-1,2-diol within 3 h at −10 °C. $[\alpha]_D = +92.3$ ($c = 1$, EtOH). Mp: 132−134 °C [lit.[5a] $[\alpha]_D = -118.3$ ($c = 1$, EtOH) for 100% ee *S*,*S*-enantiomer. Mp: 132−134 °C)]. NMR shows only *dl* isomer.

(*R*,*R*)-(+)-1,2-Di(*p*-chlorophenyl)ethane-1,2-diol. According to the general protocol, *p*-chlorobenzaldehyde (0.56 g, 4 mmol), Ti−**4** (0.18 g, 0.4 mmol, 10 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*p*-chlorophenyl)ethane-1,2-diol within 4 h at −10 °C. $[\alpha]_D = +63.3$ ($c = 1$, EtOH). Mp: 130 °C [lit.[27] $[\alpha]_D = +93$ ($c = 1$, EtOH) for 100% ee *R*,*R*-enantiomer. Mp: 127 °C)]. NMR shows a *dl*/*meso* ratio of 89:11.

(*R*,*R*)-(+)-1,2-Di(*p*-fluorophenyl)ethane-1,2-diol. According to the general protocol, *p*-fluorobenzaldehyde (0.43 mL, 4 mmol), Ti−**4** (0.18 g, 0.4 mmol, 10 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*p*-fluorophenyl)ethane-1,2-diol within 5 h at −10 °C. $[\alpha]_D = +36.0$ ($c = 1$, EtOH) [lit.[5b] $[\alpha]_D = +53$ ($c = 1.10$, EtOH) for 100% ee *R*,*R*-enantiomer]. Mp: 134−135 °C (lit.[28] mp: 108−110 °C). NMR shows a *dl*/*meso* ratio of 90:10.

(*R*,*R*)-(+)-1,2-Di(1′-naphthyl)ethane-1,2-diol. According to the general protocol, 1-naphthaldehyde (0.54 mL, 4 mmol), Ti−**4** (0.36 g, 0.8 mmol, 20 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(1′-naphthyl)ethane-1,2-diol within 5 h at −10 °C. $[\alpha]_D = +58.5$ ($c = 1$, THF) [lit.[29] $[\alpha]_D = +68$ ($c = 0.86$, THF) for 100% ee *R*,*R*-enantiomer]. Mp: 174−175 °C. NMR shows a *dl*/*meso* ratio of 91:9. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (bs, 2 H, O*H*), 5.73 (s, 2 H, C*H*), 7.21−7.83 (m, 14 H, H_{Ar}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 74.50, 123.02, 124.86, 125.12, 125.34, 125.74, 128.57, 128.68, 133.72, 136.14 ppm. IR (Nujol): $\tilde{\nu}$ (cm^{-1}) = 3339. Anal. Calcd for $C_{22}H_{18}0_2$: C, 84.04; H, 5.78. Found: C, 84.10; H, 5.76.

(*R*,*R*)-(+)-1,2-Di(2′-naphthyl)ethane-1,2-diol. According to the general protocol, 2-naphthyldehyde (0.63 g, 4 mmol), Ti−**4** (0.36 g, 0.8 mmol, 20 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(2′-naphthyl)ethane-1,2-diol within 4 h at −10 °C. $[\alpha]_D = +203.8$ ($c = 1$, THF). Mp: 243 °C [lit.[29] $[\alpha]_D = +224$ ($c = 1$, THF) for 100% ee *R*,*R*-enantiomer. Mp: 242−244 °C)]. NMR shows a *dl*/*meso* ratio of 94:6.

(*R*,*R*)-(+)-1,2-Di(2′-furyl)ethane-1,2-diol. According to the general protocol, *2*-furaldehyde (0.33 mL, 4 mmol), Ti−**4** (0.18 g, 0.4 mmol, 10 mol %), Zn (0.52 g, 8 mmol), and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(2′-furyl)-ethane-1,2-diol within 3 h at −10 °C. $[\alpha]_D = +15.5$ ($c = 1$, EtOH) [lit.[5a] $[\alpha]_D = -31.0$ ($c = 1$, EtOH) for 100% ee *S*,*S*-enantiomer]. NMR shows a *dl*/*meso* ratio of 93:7. The compound is a viscous liquid and deteriorates rapidly at ambient temperature. Therefore, it was difficult to crystallize.

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Note Added after ASAP Posting. Structure **2** in Figure 1 had errors in the version posted ASAP on June 12, 2003; the corrected version was posted June 16, 2003.

Supporting Information Available: ^{1}H NMR spectra of all the reported products. This material is available free of charge via the Internet at http://pubs.acs.org.

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