Studies on Enantioselective Addition of Chiral Titanium Reagents to Aromatic Aldehydes

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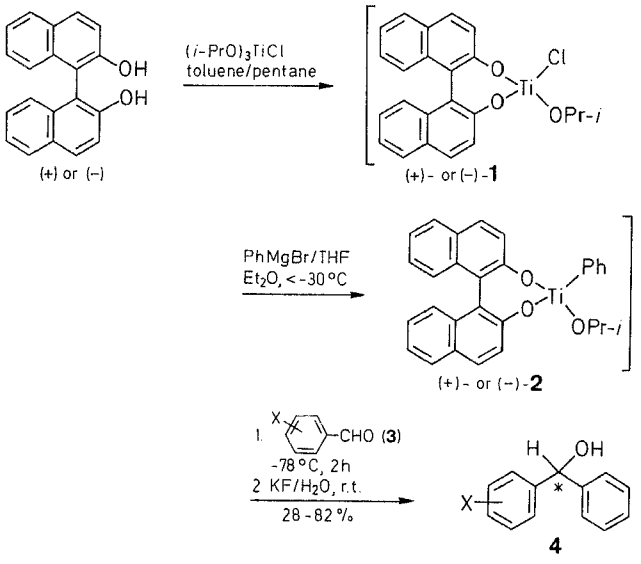
A series of substituted chiral benzhydrols were synthesized by reaction of aromatic aldehydes with the chiral intermediates formed from chiral titanates and arylmagnesium halides. The effect of substituents on the enantioselectivity of the reaction is studied. The reactions are carried out with two different chiral intermediates using two different procedures.

It has been reported[1] that alcohols with high ee values are obtained in the reaction of the intermediates formed from chiral titanates and arylmagnesium halides with aromatic aldehydes. However, the effect of substituents on the aromatic aldehyde in this enantioselective reaction has hitherto not been investigated. We have synthesized eleven optically active substituted benzhydrols and studied the temperature and substituent effects on the enantioselectivity of the reaction using HPLC analysis. We found that below $-78\,^{\circ}C$ almost no benzhydrol was formed within 1.5 h, the aldehyde being quantitatively recovered. When temperature was gradually raised the reaction took place rapidly and was completed within 2.4 h. Longer reaction times at room temperature did not improve the yield of benzhydrol.

We first prepared benzhydrols **4** by the method of Lit.[1] in which the chiral chloridotitanate **1** is converted into the intermediate chiral titanate **2** by reaction with phenylmagnesium bromide which is then submitted to the reaction with the substituted benzaldehyde **3** (Method A):



We then prepared benzhydrols **4** by the simpler Method B, in which chiral 1,1′-binaphthalene-2,2′-diyldioxy(diisopropoxy)titanium (**5**) is allowed to react with phenylmagnesium bromide and the substituted aromatic aldehyde **3** is added after 30 min, good yields and high ee values being obtained.

The ee values of all chiral products were determined by ^{1}H-NMR spectrometry in the presence of a chiral shift reagent and by comparison with the specific rotations of the pure enantiomers.

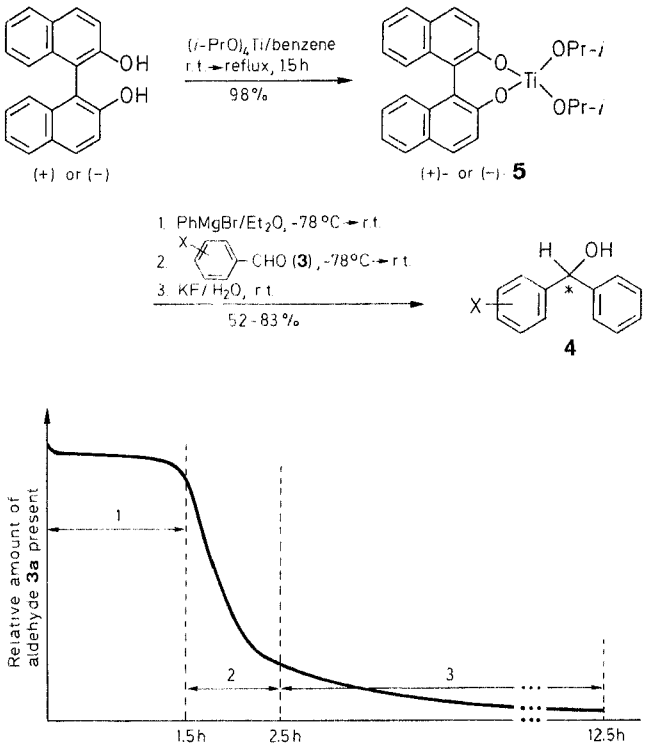


Figure. Reaction of titanate **5** with 2-methoxybenzaldehyde (**3a**) as monitored by determining the relative amount of aldehyde **3a** present in the reaction mixture by HPLC:
1. Reaction at $-78\,^{\circ}C$ for 1.5 h.
2. The temperature is allowed to rise to $+10\,^{\circ}C$ over 1 h.
3. The mixture is kept at $+15\,^{\circ}C$ for 10 h.

In the case of 2-alkoxybenzaldehydes **3** (X = 2-OR), the ee's of benzhydrols **4** decrease with the bulkiness of the *O*-alkyl groups, i.e., in the order 2-OMe (**4a**, 95% ee), 2-OEt (**4b**, 28% ee), 2-OPr-*n* (**4c**, 6.8% ee). In these cases, the reactions might proceed via complexes between the titanate and the alkoxybenzaldehyde. On the other hand, it is known that Grignard reagents react with titanates to form "ate" complexes.[2]

Despite of the different chiral titanates used, Methods A and B both yield comparable asymmetric products, with Method B giving better results. For electron-donating *o*- and *p*-substituents, levorotatory products are obtained when (−)-2,2′-dihydroxy-1,1′-binaphthalene is used as the chiral chelating agent while electron-withdrawing substituents lead to reverse products when the same (−)-2,2′-dihydroxy-1,1′-binaphthalene is used as the chelating agent (Tables 1 and 2). According to our results, Method B is the more efficient method; in addition, the chiral 1,1′-binaphthalene-2,2′-dioxy(diisopropoxy)titanium **5** is a stable reagent and thus convenient to work with.

All reactions are carried out under pure argon. Melting points were determined using a PHMK 81/3001 apparatus and are not corrected. HPLC was run on a HP-1090 apparatus. IR spectra were recorded on a IR-408 spectrophotometer. ^{1}H-NMR were recorded on a JEOL FX-90Q NMR at 89.55 MHz and on a JNMPMX at 60 MHz. Specific rotations were measured with a WZZ-1 automatic polarimeter.

(+)- or (−)-1,1′-Binaphthalene-2,2′-diyldioxy(diisopropoxy)titanium [(+)- or (−)-5]:

(+)- or (−)-2,2′-Dihydroxy-1,1′-binaphthalene (7.05 g, 2.1 mmol) is placed in a 250 mL three-necked flask containing benzene (120 mL). To this is added dropwise and with stirring (*i*-PrO)$_4$Ti (7 g, 2.4 mmol). After the addition is complete, the mixture is refluxed for 1.5 h. Then the solvent is evaporated and the residue is dried under reduced pressure to give product **5** as a brick-yellow solid; yield: 0.88 mg (98%). The product is a prismatic crystalline substance, unstable above 300 °C.

Table 1. Preparation of Benzhydrols **4** by Method A

X in **3** and **4**	Titanates **1** and **2**	Product	Yield (%)	mp[a] (°C)	$[\alpha]_D^{20}$ found	$[\alpha]_D^{20}$ calculated[b]	ee[c] (%)	Molecular Formula[d] or Ref.
2-OMe	(−)	(−)-**4a**	38	oil	−68.1° (*c* = 0.67, THF)	−68.1°	>95	$C_{14}H_{14}O_2$ (214.3)
2-OEt	(−)	(−)-**4b**	45	76–77	−12.0° (*c* = 0.70, $CHCl_3$)	−43.0°	28	$C_{15}H_{16}O_2$ (228.3)
2-OPr-*n*	(−)	(−)-**4c**	40	67–69	−4.5° (*c* = 0.56, THF)	−66.2°	6.8	$C_{16}H_{18}O_2$ (242.3)
4-NO_2	(+)	(−)-**4d**	68	73–74[e]	+56.1° (*c* = 0.43, $CHCl_3$)	+74.9°[e]	88	–[f]
3-Br	(−)	(+)-**4e**	60	51–52	+33.8° (*c* = 2.5, THF)	+33.8°	>95	$C_{13}H_{11}BrO$ (263.1)
3-Cl	(−)	(+)-**4f**	28	40–41	+30.3° (*c* = 1.12, acetone)	+30.3°	>95	$C_{13}H_{11}ClO$ (218.7)
2,4-di-OMe	(−)	(−)-**4g**	65	45–46	−16.6° (*c* = 0.82, acetone)	−70.0°	24	$C_{15}H_{16}O_3$ (244.3)
2-Cl	(−)	(−)-**4h**	35	65–66[e]	−19.9° (*c* = 0.52, acetone)	−19.9°	>95	$C_{13}H_{11}ClO$ (218.7)
4-OMe	(−)	(−)-**4i**	56	62–63	−11.5° (*c* = 0.52, acetone)	−11.5°	>95	–[3]
4-Cl	(−)	(+)-**4j**	32	59–60[e]	+13.7° (*c* = 0.98, $CHCl_3$)	+13.7°[e]	100	$C_{13}H_{11}ClO$ (218.7)
3,4-(OCH_2O)	(−)	(−)-**4k**	82	33–34	−0.87 (*c* = 0.80, acetone)	−1.1°	80	$C_{14}H_{12}O_3$ (228.2)

[a] Uncorrected.
[b] Specific rotation of pure enantiomer calculated from ee and observed $[\alpha]_D^{20}$.
[c] Determined from the α-CH signal in the ^{1}H-NMR spectrum of products **4** in the presence of $Eu(TFC)_3$, with an accuracy of 95%.
[d] Satisfactory microanalyses obtained: C ±0.15, H ±0.05.
[e] From Ref. 3.

Table 2. Preparation of Benzhydrols **4** by Method B

X in **3** and **4**	Titanate **5**	Product	Yield (%)	$[\alpha]_D^{20}$ found	ee[c] (%)
4-NO_2	(+)	(−)-**4d**	73	−58.2° (*c* = 1.00, $CHCl_3$)	90
	(−)	(+)-**4d**	71	+57.1° (*c* = 1.00, $CHCl_3$)	89
3-Br	(+)	(−)-**4e**	81	−34.2° (*c* = 2.5, THF)	>95
	(−)	(+)-**4e**	75	+34.0° (*c* = 2.5, THF)	>95
2,4-di-OMe	(+)	(+)-**4g**	83	+16.8° (*c* = 0.82, acetone)	24.5
	(−)	(−)-**4g**	80	−17.0° (*c* = 0.80, acetone)	25
4-Cl	(+)	(−)-**4j**	57	−14.1° (*c* = 1.00, $CHCl_3$)	100
	(−)	(+)-**4j**	52	+13.8° (*c* = 0.98, $CHCl_3$)	100

[c] See Table 1.

Table 3. Spectral Data of Compounds **4**

Compound	IR (KBr)[a] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ
4a	3517 (s), 3418 (s), 1491 (s), 1296 (s)	7.20 (7H, m); 6.80 (2H, m); 5.90 (1H, s); 3.72 (3H, s); 2.78 (1H, s)
4b	3320 (s), 1491 (s), 1244 (s), 1039 (s)	7.38 (9H, m); 6.10 (1H, s); 4.00 (2H, q); 3.12 (1H, s); 1.30 (3H, t)
4c	3320 (s), 1450 (s), 1286 (s), 1245 (s)	7.39 (9H, m); 6.10 (1H, s); 4.00 (2H, t); 3.02 (1H, s); 1.70 (2H, m); 1.00 (3H, t)
4d	Lit.[1]	
4e	3207 (s), 1450 (s), 1029 (s), 785 (s)	7.50 (9H, m); 5.80 (1H, s); 2.30 (1H, s)
4f	3345 (s), 1597 (s), 1425 (s), 1187 (s)	7.36 (6H, s); 7.21 (3H, s); 5.78 (1H, s); 2.22 (1H, s)
4g	3396 (s), 1614 (s), 1499 (s), 1458 (s)	6.50 (6H, m); 7.05 (2H, m); 6.08 (1H, s); 3.77 (6H, s); 2.92 (1H, s)
4h	3353 (s), 1029 (s), 752 (s), 695 (s)	7.30 (9H, m); 6.15 (1H, s); 2.80 (1H, s)
4i	3510 (s), 1259 (s), 1091 (s), 810 (s)	7.30 (7H, m); 6.75 (2H, m); 5.66 (1H, s); 3.75 (3H, s); 2.45 (1H, s)
4j	Lit.[3]	
4k	3394 (s), 1482 (s), 1441 (s), 925 (s)	7.34 (5H, m); 6.75 (3H, d); 5.90 (2H, s); 5.70 (1H, s); 2.34 (1H, s)

[a] Recorded on an IR-408 infrared spectrophotometer.
[b] Obtained on a JNMPMX 60 MHz NMR spectrometer.

(+)- or (−)-Benzhydrols 4:

Method A; Typical Procedure:

(−)-2-Methoxybenzhydrol [(−)-**4a**]: A 100 mL three-necked flask is charged with toluene (80 mL) and (−)-2,2′-dihydroxy-1,1′-binaphthalene [1.91 g, 6.68 mmol; $[\alpha]_D^{20}$ −34.1° (*c* = 0.2)] and this suspension is heated to boiling until a clear solution is obtained. The solution is cooled to room temperature and a solution of (*i*-PrO)$_3$TiCl (1.74 g, 6.68 mmol) in pentane (8.2 mL) is added. The solvent is then distilled off and the residue is dissolved in THF (70 mL). This solution is cooled to −30 °C and a solution of PhMgBr (6.68 mmol) in Et_2O (60 mL) is added dropwise, with stirring, over 30 min. The mixture is then cooled to −78 °C, 2-methoxybenzaldehyde (**3a**; 6.5 g, 1.37 mmol) is added, stirring is continued for 2 h at −78 °C and at room temperature overnight. The mixture is hydrolyzed by the addition of saturated aqueous KF (50 mL) and the organic layer is separated and dried with drierite. The solvent is evaporated and the oily residue is column-chromatographed on silica gel using petroleum ether/Et_2O/anhydrous MeOH (67:23:10) as eluent. The eluate is evaporated to give product (−)-**4a** as an oil; yield: 0.49 g (38%); $[\alpha]_D^{20}$ −68.1° (*c* = 0.67, THF).

Method B; General Procedure:

Substituted (+)- or (−)-Benzhydrols **4**: A 100 mL three-necked flask is charged with toluene (80 mL) and the titanate (+)- or (−)-**5** (3.07 g, 6.8 mmol) and a solution of PhMgBr (6.8 mmol) in Et_2O (60 mL) is added at −78 °C with stirring. The mixture is then allowed to warm to room temperature and stirring is continued for 30 min. The mixture is again cooled to −78 °C, a solution of an aromatic aldehyde **3** (6.2 mmol) in ether (15 mL) is added, and stirring is continued overnight while the mixture is allowed to warm to room temperature. It is then hydrolyzed by the addition of saturated aqueous KF (50 mL) and worked up as in Method A.

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(1) Seebach, D. *Chem. Ber.* **1985**, *118*, 3673.
(2) Reetz, M.T. *Topics in Current Chemistry*, Vol. 106, Boschke, F.L. (ed.), Springer Verlag, Berlin, 1982.
For reviews on the use of titanium derivatives in organic synthesis, see:
Seebach, D., Weidmann, B., Widler, L., in: *Modern Synthetic Methods*, Scheffold, R. (ed.), Sauerländer, Aarau and J. Wiley & Sons, New York, 1983, p. 217.
Seebach, D., Weidmann, B. *Angew. Chem.* **1983**, *95*, 12; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31.
(3) Green, G.H. *J. Chem. Soc.* **1950**, 751.