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ASYMMETRIC INDUCTION CATALYZED BY CONJUGATE BASES OF CHIRAL PROTON ACIDS AS LIGANDS: ENANTIOSELECTIVE ADDITION OF DIALKYLZINC-ORTHOTITANATE COMPLEX TO BENZALDEHYDE WITH CATALYTIC ABILITY OF A REMARKABLE HIGH ORDER

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Summary: The addition of diethylzinc-orthotitanate complex to benzaldehyde catalyzed by 0.0001~ 0.04 equiv of chiral sulfonamide-titanate complex in toluene at 0~ -30° gives optically active 1-phenylpropanol in both high ee and chemical yields. NMR study suggests alkyltitanium is generated from diethylzinc and the titanate in situ.

There have been a number of papers describing enantioselective reactions mediated by a wide variety of metal complexes obtained by mixing alkylated derivatives, alkoxides, halides, and hydrides of aluminum, boron, tin, titanium, and zinc with various chiral alcohols or amines, and a number of systems have been devised to give high enantioselectivity in stoichiometric or catalytic use of chiral sourses1). In the catalytic process, the accelerating effect of the catalyst seems to be essential in addition to the stereocontrol and the facile exchange of the product with the substrate on the catalyst. We also assumed that the increase of acceptor character by introducing more electon-withdrawing groups than the alcohols or the amines would be important to realize high acceleration. We selected chiral sulfonamides as ligands for the catalysts from the following reasons. The acidity of trifluoromethanesufonamide and anilide is comparable to that of ordinary carboxylic acids2). When a (chiral-N-monoalkyl)-sulfonamide coordinates to a metal atom, the N atom connects with the metal atom directly, and hence the metal atom is under the strong influence of the chirality.

It is known that no reaction occurs between dialkylzinc and arylaldehydes in nonpolar solvents. However, we designed to mix dialkylzincs with orthotitanate ester to form alkyltitanium *in situ* and to treat the resulting complex with aldehydes. Indeed, a mixture of $ZnEt_2$ (1.2eq) and $Ti(O^iPr)_4$ (0.02eq) reacted with benzaldehyde (1.0eq) (r.t., 12hr, toluene) to give 1-phenylpropanol in good yield accompanied with a little of benzylalcohol. The ^1H NMR spectrum of the 1:1 mixture of $ZnEt_2$ and $Ti(O^iPr)_4$ in toluene-d_8 was found complicated by the equilibrium which proved dependent on the concentration as indicated in ref. 3). The ^1H NMR spectrum4) in 20μmole/ml at 20°C cleanly revealed at least two kinds of ethyl groups : +0.59ppm(q), +1.57ppm(t) (due to $EtZnO^iPr$) ; +0.67ppm(q), +1.65ppm(t), and at least five kinds of isopropyl groups : +4.05ppm(dq) (due to $EtZnO^iPr$) ; +4.43ppm(q); +4.59ppm(bq); +4.91ppm(q); +4.99ppm(dq). The ethyl group of $ZnEt_2$ with proton peaks at +0.19ppm(q) and +1.19ppm(t) disappeared. ^1H NMR analysis showed the proportion of $EtZnO^iPr$ increased with decreasing concentration. Accordingly, the NMR analysis suggested that the

1:1 mixture of $ZnEt_2$ and $Ti(O^iPr)_4$ generated various kinds of species including ethyltitanium compound in the equilibrium mixture.

Ligand exchange of $Ti(O^iPr)_4$ with chiral sulfonamide was designed, and *trans*-cyclohexane-1,2-diamine was selected as chiral source because the racemate is commercially available. According to the method by Whitney[5], the *trans*-diamine was resolved with optically pure tartaric acids and both enantiomers were obtained. They were converted into several kinds of disufonamides. The racemate of the di-α-naphthalenesulfonamide was found cleanly separated on optically active HPLC column (DAICEL CHEMICAL Ind. Ltd., OT-(+))[6], and hence the optical purity of the diamine was determined to be 99%ee after resolution and 99.99%ee< after the following recrystalization of the tartrate salt from water. Several disulfonylderivatives **2a**-**2e**[7] of (-)-*trans*-cyclohexane-1(*R*),2(*R*)-diamine were used for the addition of dialkylzinc-tetraisopropylorthotitanate complex to benzaldehyde as shown in *Scheme* I. The results are summerized in *Table* I. Chemical and optical yields increased with the use of fluorinated sulfonamides **2d** at even lower temperature as compared with those of **2a**-**2c** (entry 1-6). In spite of excess use of orthotitanate to ligand **2**, the optical purity was found still high (entry 7, 8). Obviously, the excess titanate accelerated the reaction (entry 6, 8). We were encouraged by this finding and carried out the reaction with equimolar amounts of the titanate and dialkylzinc **3** giving the product in quantitative yields with still high ee (entry12-16). Even the use of a trace amount of **2d** was found efficient (entry 15-16). Although dibutylzinc **3b** was less reactive than diethylzinc **3a**, the product **5b** was obtained in quantitative yields with high ee (entry 17-19). The complex of the butylmagnesium reagent with the titanate gave the product **5b** in good yield but in moderate ee (entry 20).

Scheme I. Enantioselective Addition of Dialkylzinc-Orthotitanate Complex to Benzaldehyde

A typical procedure (entry 13, 0.02 equiv of **2d**, -20°C, 1.2equiv of $Ti(O^iPr)_4$, 1.2equiv of $ZnEt_2$) is shown as follows: In a frame-dried round-bottom flask was placed **2d** (189mg, 0.5mmol), under argon. To this were added degassed toluene (10ml) and $Ti(O^iPr)_4$ (8.53g, 30mmol), and the mixture was stirred at 40°C for 20min. After cooling to -78°C, a 1.0M hexane solution of $ZnEt_2$ (30ml, 30mmol) was added to the solution. In a moment, the solution turned orange. To the resulting solution was added benzaldehyde (2.12g, 25mmol in toluene 2ml) and the mixture was warmed up to -20°C, stirred for 2h, and quenched by adding aqueous 2N-HCl solution. After usual extractive workup and distillation, 1(*S*)-phenylpropanol **5a** was obtained in 96% (3.3g) as an oil (98%ee, $[\alpha]_D^{22}$ -48.6° (*c* 5.13, $CHCl_3$) [lit. $[\alpha]_D^{22}$ -47.6° (*c* 6.11, $CHCl_3$) as 98%ee[1c)]]). In the same way, **5b** was obtained in 99% as crystals[8] (entry 17, m.p. 32~33.5°, 98%ee, $[\alpha]_D^{25}$ -37.9° (*c* 3.13, C_6H_6) without recrystalization [lit. for *R*-isomer, $[\alpha]_D^{25}$ +35.7° (*c* 3.00, C_6H_6)]). The optical purity of **5a** and **5b** was determined by HPLC analysis (column, DAICEL CHEMICAL Ind. Ltd., OB)[9].

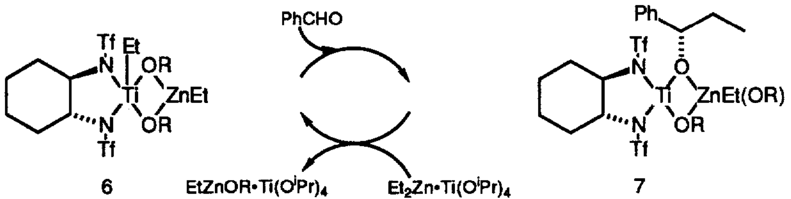
We assume that the asymmetric reaction probably proceeds through the catalytic cycle as shown in *Scheme* II. The high acceleration and the high stereocontrol realized by the present approach may be

Table I.

Entry[a]	ligand	(equiv)[b]	$Ti(O^iPr)_4$ (equiv)[b]	Nu	(equiv)[b]	temp.	time (hr)	c.y.[c] (%)	%ee[d] (confign)[e]
1	**2a**	0.04	0.048	**3a**	1.2	r.t.	22	87	94(*S*)
2	**2b**	0.04	0.048	**3a**	1.2	r.t.	22	90	89(*S*)
3	**2c**	0.04	0.048	**3a**	1.2	r.t.	22	85	64(*S*)
4	**2d**	0.04	0.048	**3a**	1.2	0	2	99	98(*S*)
5	**2d**	0.02	0.02	**3a**	1.2	0	2	99	97(*S*)[f]
6	**2d**	0.01	0.01	**3a**	1.2	0	234	89	96(*S*)
7	**2d**	0.02	0.2	**3a**	1.2	0	2	99	99(*S*)
8	**2d**	0.005	0.02	**3a**	1.2	0	16	93	99(*S*)
9	**2d**	0.002	0.008	**3a**	1.2	0	222	93	45(*S*)
10	**2a**	0.04	1.2	**3a**	1.2	0	20	97	72(*S*)
11	**2b**	0.04	1.2	**3a**	1.2	0	9	97	66(*S*)
12	**2c**	0.04	1.2	**3a**	1.2	0	20	98	99(*S*)
13	**2d**	0.02	1.2	**3a**	1.2	-20	1.5	98	98(*S*)[g]
14	**2d**	0.005	1.2	**3a**	1.2	-30	2.5	98	99(*S*)
15	**2d**	0.0005	1.2	**3a**	1.2	-20	2	97	98(*S*)
16	**2d**	0.0001	1.2	**3a**	1.2	-20	11	98	68(*S*)
17	**2d**	0.02	1.5	**3b**	1.5	-30	2	99	98(*S*)[h]
18	**2d**	0.005	1.3	**3b**	1.3	-20	3	97	94(*S*)
19	**2e**	0.02	1.5	**3b**	1.5	-30	2.5	99	97(*S*)
20	**2d**	0.04	1.2	$^nBuMgO^iPr$	1.2	0	4	85	61(*S*)

[a] Solvent was: entry 1-16, hexane-toluene; entry 17-20, toluene. [b] Based on benzaldehyde. [c] Isolated yields. [d] Determined by HPLC using DAICEL optically active colunm OB. See ref.9). [e] Absolute configuration. [f] $[\alpha]_D^{22}$ -47.3°(*c* 5.68, $CHCl_3$) [lit. $[\alpha]_D^{22}$ -47.6°(*c* 6.11, $CHCl_3$) as 98%ee1c)]. [g] $[\alpha]_D^{22}$-48.6°(*c* 5.13, $CHCl_3$). [h] $[\alpha]_D^{25}$ -37.9°(*c* 3.13, C_6H_6) m.p.32~33.5°C [lit. for *R*-isomer, $[\alpha]_D^{25}$ +35.7° (*c* 3.00, C_6H_6)8)].

Scheme II.



R=^{i}Pr, 1(*S*)-phenyl-1-propyl turn-over ~2000, 98%ee(entry 15)

due to the enhanced Lewis acidity and the strong influence of the chirality of the ligand near from the metal atom, respectively. This new approach is now under extensive investigation for the design of other asymmetric induction.

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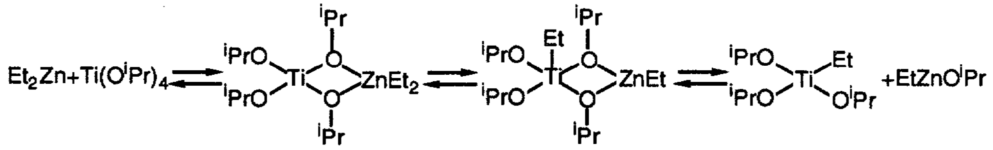

4) The NMR sample was prepared with a 1.78M benzene solution of $ZnEt_2$, and proton chemical shift was based on benzene as +7.20ppm.
5) a) Dolores Gracian, and Harry P. Schultz, *J. Org. Chem.*, **1971**, *36*, 3989. b) Thomas A. Whitney, *J. Org. Chem.*, **1980**, *45*, 4214.
6) eluent, MeOH; flow rate, 1.0ml/min; column temp., 5°C; detection, 254nm; (-)-*R* isomer, t_R 6.6min, (+)-*S* isomer, t_R 11.2min with equal intensities.
7) **2a**, $[\alpha]^{24}_{D}$ +72.6° (*c* 3.03, pyridine); **2b**, $[\alpha]^{24}_{D}$ -20.1° (*c* 3.07, pyridine); **2c**, $[\alpha]^{24}_{D}$ -10.5° (*c* 3.19, pyridine); **2d**, $[\alpha]^{24}_{D}$ -43.5° (*c* 3.25, pyridine); **2e**, $[\alpha]^{24}_{D}$ -17.1° (*c* 3.01, pyridine).
8) We obtained **5b** as a crystalline material for the first time. No clear m.p. has been reported, see: Jean-Paul Mazaleyrat and Donald Cram, *J. Am. Chem. Soc.*, **1981**, *103*, 4485.
9) a) **5a**: eluent, 2% 2-propanol in hexane; flow rate, 0.5ml/min; detection, 254nm; the *S* isomer, t_R 19.5min, *R* isomer, t_R 23.0min with equal intensities. b) **5b**: eluent, 1% 2-propanol in hexane; flow rate, 1.0ml/min; detection, 254nm; *S* -isomer, t_R 25.5min, *R* -isomer, t_R 37.4min with equal intensities.

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