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Enantioselective Reaction of Aldehydes with Chiral Alkyltitanium Ate-Complexes

HIROSHI TAKAHASHI,* AKIHIRO KAWABATA, HIROYUKI NIWA,
and KIMIO HIGASHIYAMA

Institute of Medicinal Chemistry, Hoshi University,
2-4-41, Ebara, Shinagawa, Tokyo 142, Japan

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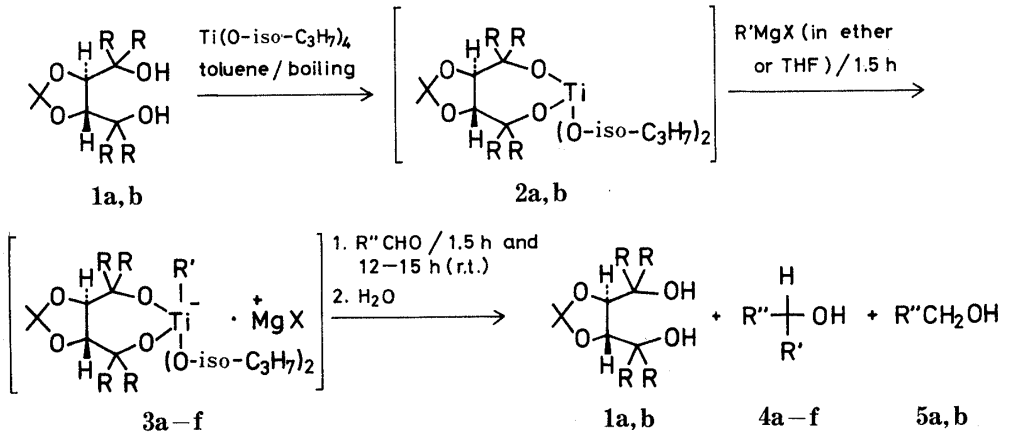
Enantioselective reaction of aldehydes using alkyltitanium (2*R*,3*R*)-2,3-(isopropylidenedioxy)-butane-1,4-dioxide diisopropoxide ate-complexes was achieved in 65—80% yields and 9.9—54.0% enantiomeric excesses. The reduction products were obtained as by-products in 10—25% yields.

Keywords——aldehyde; alkyltitanium; 1-aryl-1-alkanol; arylmethanol; ate-complex; enantiomeric excess; enantioselective reaction; (2*R*,3*R*)-2,3-(isopropylidenedioxy)butane-1,4-dioxide

The enantioselective reaction of aldehyde with methyltitanium (*S*)-*N*-acylpyrrolidinylmethoxide diisopropoxides has been reported.[1] In this paper, we with to report an enantioselective reaction of aldehydes using alkyltitanium (2*R*,3*R*)-2,3-(isopropylidenedioxy)butane-1,4-dioxide diisopropoxide ate-complexes. Reactions using allyltitanium tetraisopropoxide and tetra (dimethylamide) ate-complexes have been reported by Reetz *et al.*,[2,3] but no reaction using chiral titanium ate-complex has yet been described.

The preparation of the titanium (2*R*,3*R*)-2,3-(isopropylidenedioxy)butane-1,4-dioxide



1, 2	R	3	R	R′	4	R′	R″	5	R″
a	H	**a**	H	Me	**a**	Me	Ph	**a**	Ph
b	Ph	**b**	Ph	Me	**b**	Me	$C_{10}H_7$	**b**	$C_{10}H_7$
		c	Ph	Et	**c**	Et	Ph		
		d	Ph	n-C_3H_7	**d**	n-C_3H_7	Ph		
		e	Ph	$CH_2=CHCH_2$	**e**	$CH_2=CHCH_2$	Ph		
		f	Ph	$C_6H_5CH_2$	**f**	$C_6H_5CH_2$	Ph		

Chart 1

TABLE I. Enantioselective Reaction of Aldehydes with Chiral Alkyltitanium Ate-Complexes

Entry No.	R	R′	R″	Reaction conditions[a]			1-Aryl-1-alkanol							Arylmethanol	
				Temp. (°C)	Solvent[b]	(ml)	No.	Yield (%)	$[\alpha]_D$	(*c*)	Solvent[c]	ee[d] (%)	Configuration[e]	No.	Yield (%)
1	H	Me	Ph	−50—−55	DME	(50)	**4a**	70	+4.3	(1.51)	cy	10.0	*R*	**5a**	20
2	H	Me	$C_{10}H_7$	−50—−55	DME	(50)	**4b**	68	+7.6	(2.31)	et	9.9	*R*	**5b**	18
3	Ph	Me	Ph	−78	DME	(50)	**4a**	73	+6.9	(1.38)	cy	15.9	*R*	**5a**	23
4	Ph	Me	$C_{10}H_7$	−50—−55	DME	(50)	**4b**	72	+14.6	(1.50)	et	19.1	*R*	**5b**	20
5	Ph	Me	Ph	−50—−55	tolu	(35)	**4a**	80	+13.1	(1.33)	cy	30.3	*R*	**5a**	10
6	Ph	Me	$C_{10}H_7$	−50—−55	tolu	(35)	**4b**	75	+23.8	(1.13)	et	31.1	*R*	**5b**	11
7	Ph	Me	Ph	−78	tolu	(20)	**4a**	74	+23.0	(1.00)	cy	53.5	*R*	**5a**	13
8	Ph	Me	$C_{10}H_7$	−78	tolu	(20)	**4b**	72	+32.2	(1.27)	et	42.1	*R*	**5b**	15
9	Ph	Et	Ph	−78	tolu	(20)	**4c**	70	+20.4	(0.47)	ac	43.4	*R*	**5a**	20
10	Ph	*n*-C_3H_7	Ph	−78	tolu	(20)	**4d**	65	+8.3	(1.20)	be	18.1	*R*	**5a**	25
11	Ph	$CH_2=CHCH_2$	Ph	−78	tolu	(20)	**4e**	68	−26.1	(2.14)	be	54.0	*R*/*S*[f]	**5a**	21
12	Ph	$C_6H_5CH_2$	Ph	−78	tolu	(20)	**4f**	65	+14.5	(1.05)	et	25.9	*S*	**5a**	25

a) (2*R*,3*R*)-2,3-(Isopropylidenedioxy)butane-1,4-diol (6 mmol), titanium tetraisopropoxide (6 mmol), alkylmagnesium halide (6 mmol), and aldehyde (3 mmol) were used. *b*) DME, 1,2-dimethoxyethane; tolu, toluene. *c*) The optical rotations are measured at 20—23 °C, and the solvents are cy, cyclopentane; et, ethanol; ac, acetone; be, benzene. *d*) Enantiomeric excess. *e*) Configuration of the major component. *f*) The absolute configuration is unknown.

diisopropoxides (**2a** and **2b**) was readily achieved by boiling of a mixture of titanium tetraisopropoxide and the chiral auxiliaries (**1a** and **1b**) in anhydrous toluene, and by removal of the azeotropic mixture. This method was modified for the preparation of chlorotitanium (2*R*,3*R*)-2,3-(isopropylidenedioxy)butane-1,4-dioxide isopropoxides.[4] The titanium complexes (**2a** and **2b**) thus prepared were converted into the alkyltitanium ate-complexes (**3a**—**f**) by reaction with an equimolar amount of alkylmagnesium halide. The structures of **3a**—**f** were based on the analogy with the allyltitanium ate-complexes.[3] The reaction of aldehydes using **3a**—**f** proceeded to give 1-aryl-1-alkanols (**4a**—**f**) in 65—80% yields, whereas arylmethanols (**5a** and **5b**) were obtained as by-products in 10—25% yields. The chiral auxiliaries were recovered in almost quantitative yields and the optical purities were unaltered.

The structures of the 1-aryl-1-alkanols (**4a**—**f**) and the arylmethanols (**5a** and **5b**) were confirmed by proton nuclear magnetic resonance (^{1}H-NMR) spectral analysis. The values of enantiomeric excess (ee) of **4a**—**f** were estimated by comparison of the specific rotations with those of optically pure compounds,[5-10] and it was found that these reactions occurred with 9.9—54.0% enantioselectivities. On the other hand, the formation of **5a** and **5b** can be interpreted in terms of Meerwein–Ponndrof–Varley type reduction of aldehydes with the metal alkoxide reagents.[4,11]

In conclusion, the enantioselective reaction using the chiral alkyltitanium ate-complexes showed the following characteristics. (1) The bulkiness of the substituent of the chiral auxiliaries seemed to play an important role in the asymmetric induction (entries 1—4). (2) The use of toluene in the reaction gave higher enantiomeric excess than that of 1,2-dimethoxyethane (DME) as a solvent (entries 3—6), and the enantiomeric excess was dependent on the concentration of the reaction mixture (entries 5—8). (3) Finally, the reaction using the chiral alkyltitanium ate-complexes showed about 18—54% enantioselectivities (entries 7—12).

Experimental

The ^{1}H-NMR spectra were obtained with a JEOL JNM-FX100 spectrometer, and the optical rotations were measured at 20—23 °C with a Jasco DIP-360 digital polarimeter.

General Procedure for the Reaction of Aldehyde with Chiral Alkyltitanium Ate-Complex——A solution of (2*R*,3*R*)-2,3-(isopropylidenedioxy)butane-1,4-diol (**1a** and **1b**; 6 mmol) and titanium tetraisopropoxide (1.7 g, 6 mmol) in toluene (160 ml) was boiled, and isopropanol was completely removed from the mixture. The solvent was evaporated off and the residue was dried under reduced pressure. The resulting white powder was dissolved in DME or toluene. Grignard reagent (MeMgBr, 6 mmol in 2 ml of Et_2O; EtMgBr, n-C_3H_7MgBr, $CH_2=CHCH_2MgBr$, and $C_6H_5CH_2MgCl$, 6 mmol in 4 ml of tetrahydrofuran) was added dropwise to the above solution at −50— −55 or −78 °C over a period of 15 min under a nitrogen atmosphere, and the resulting mixture was stirred at the same temperature for 1.5 h. A solution of aldehyde (benzaldehyde or naphthalenecarbaldehyde, 3 mmol) in DME or toluene (5 ml) was then added at −50— −55 or −78 °C. The resulting mixture was stirred at the same temperature for 1.5 h, and at room temperature for 12—15 h. After treatment with a small amount of water, the resulting white precipitate was filtered off, and the filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel with CH_2Cl_2–benzene to give a mixture of 1-aryl-1-alkanol and arylmethanol as a colorless oil. The ratio of the two products was estimated by ^{1}H-NMR spectrometric analysis (in the case of entries 1—8) or gas chromatographic analysis (in the case of entries 9—12). The yields are summarized in Table I. The mixture was rechromatographed on silica gel and the structures of **4a**—**f**, **5a**, and **5b** were confirmed by ^{1}H-NMR spectral analysis. The specific rotations of **4a**—**f** were measured, and the enantiomeric excess and the configuration were estimated by comparison with the following values: (*R*)-**4a**, +43.1° (c=7.19, cyclopentane)[5]; (*R*)-**4b**, +76.4° (c=4.81, ethanol)[6]; (*R*)-**4c**, +47.0° (acetone)[7]; (*S*)-**4d**, −45.9° (c=6.1, benzene)[8]; **4e**, +48.3° (c=6.74, benzene)[9]; (*S*)−**4f**, +55.9° (c=1.40, ethanol).[10] The experimental results are summarized in Table I.

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