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Stereoselective Aldol Reaction Using Titanium Ate Complexes - An Efficient Method For Achieving Anti Aldol Selectivity

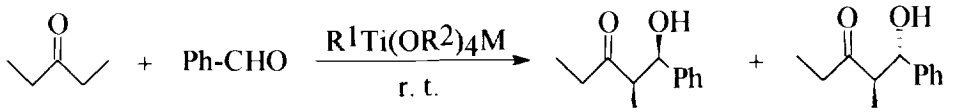
Rainer Mahrwald

Fachbereich Chemie der Humboldt Universität Berlin, Hessische Straße 1-2, D-10115 Berlin, Germany

Abstract: Carbonyl compounds react in the presence of titanium ate complexes in the sense of an aldol reaction. The influence of ligands on controlling stereoselection of syn and anti aldol products of the titanium ate complexes used are described. High yield of anti aldol products was observed by using sterically hindered aliphatic aldehydes.

Titanium(IV) alkoxides are used in many areas of organic synthesis.[1] They are widely employed in the aldol reaction for generating the corresponding titanium enolates.[2] Titanium enolates were obtained by reaction of lithium enolates with chlorotitanium(IV) alkoxides.[3] Titanium ate complexes were also used in aldol reaction, however without achieving the envisoned control of stereoselectivity.[4]
In many cases the aldol reaction of benzaldehyde (**2**) and diethyl ketone (**1**) was adopted as a model reaction for investigating the stereoselection. Most of the procedures of the aldol reaction of benzaldehyde / diethyl ketone described in the literature gave *syn* aldol product **3** with a high degree of diastereoselection.[5] But there are only a few examples of procedures favouring the *anti* product **4**.[6-8]
Herein we describe an efficient method for synthesizing *anti* aldol products with a high degree of stereoselection. Reaction of carbonyl compounds in the presence of titanium ate complexes yielded the *syn* and *anti* aldol products (Scheme 1).
The titanium ate complexes were prepared in situ simply by mixing equimolar amounts of titanium(IV) alkoxides and metal alkyls. As expected, exclusion of either titanium(IV) alkoxide or phenylmagnesium bromide did not result in aldol formation. Treatment of carbonyl compounds with titanium(IV) alkoxide alone resulted in an aldol condensation.[9]

Scheme 1



1 2 **3** syn **4** anti

R^1 = Me, Bu, Ph, 2-Mesityl
R^2 = Et, iso-Pr, tert-Bu, Trityl
M = Li, Mg

The reaction was carried out under thermodynamic control at room temperature over a period of ca. 5-10 hours. No alkylation of the carbonyl compounds by the metal alkyls, used for generating the ate complexes, was detected. The formation of α,ß-unsaturated carbonyl compounds, obtained by the reaction of carbonyl compounds and titanium(IV) alkoxides, was not observed.[9] Best results in stereoselection were achieved by working in inert solvents (toluene, hexane, acetonitrile). In contrast, when diethyl ether or tetrahydrofuran was used as solvent a decrease in stereoselection was observed. Table 1 presents the influence of the size of the alkoxy group of the used titanium(IV) alkoxides on this type of aldol reaction.

Table 1. Aldol Reactions of Diethyl ketone with Benzaldehyde in the Presence of $BuTi(OR)_4Li$

Entry	yield, %	R	syn **3**	anti **4**
1	68	Et	63	37
2	74	iso - Pr	45	55
3	82	tert - Bu	38	62
4	63	Trityl	23	77

The data clearly show that the amount of *anti* product **4** increases when ate complexes with bulky titanium(IV) alkoxides are used. Also the size of the alkyl groups in the metal alkyls used for generating the ate complexes influences the *syn* / *anti* ratio of the aldol products. Reactions performed according to Table 2 show a similiar tendency.

The more bulkier the alkyl group, the higher the yield of the *anti* product **4**. Obviously, there is a limit to influence the stereoselection of this reaction by ligand exchange. When Grignard reagents with bulky ligands are used, the *syn / anti* ratio reaches a final value of approximately 20/80 (Table 2, entries 6, 7). The ligand exchange of the titanium(IV) alkoxides used shows a similiar limitation (Table 1). Bulky titanium(IV) alkoxides resulted in longer reaction times.

Table 2. Aldol Reaction of Diethyl ketone with Benzaldehyde in the Presence of Different Ate Complexes $R^1Ti(OPr)_4M$

Entry	yield, %	R^1-M	syn **3**	anti **4**
1	73	MeLi	42	58
2	82	BuLi	45	55
3	74	PhLi	54	46
4	52	MeMgCl	46	54
5	63	BuMgCl	26	74
6	77	PhMgBr	21	79
7	73	2-Mesityl-MgBr	25	75

When a 1:1 mixture of benzaldehyde / diethyl ketone were treated with ate complexes of titanium(IV) isopropoxytris(triphenylmethoxide) /phenylmagnesium bromide no aldol reaction at all occurred. Aldol reactions with titanate complexes synthesized from the corresponding lithium alkyls resulted in much lower stereoselections (Table 2, comparing entries 2 and 5 or 3 and 6).

In order to test its applicability the procedure developed herein was applied to the aldol reaction of aliphatic aldehydes with diethyl ketone. The following aldol reactions with aliphatic aldehydes were performed in the presence of titanium(IV) alkoxide / phenylmagnesium bromide complexes (Scheme 2). High *anti* selectivities were observed. Even by the aldol reaction of n-butanal (**5**) / diethyl ketone a ratio of approximately 80/20 (*anti/syn*) of the aldols formed was obtained (Table 3, entries 1, 2, 3). In order to gain a better understanding of the reaction mechanism, the aldol reaction of a 1:1 mixture of benzaldehyde / diethyl ketone was monitored by NMR spectroscopy and chromatography. The reaction was performed at room temperature in toluene with equimolar amounts of ate complexes and carbonyl compounds. After 1h 15-20% exclusively the *syn* aldol **3** was dedected, whereas upon further progress of the reaction the formation of the *anti* product **4** was also observed. The ratio of *anti / syn* aldol products **4 / 3** decreased continously. After 10 h at room temperature, a ratio of 83/17 *(anti/syn)* was reached. These results of stereoselection clearly indicate that an equilibration of the aldol products formed under thermodynamic control is attained

Scheme 2

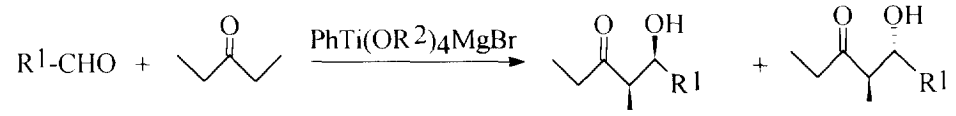
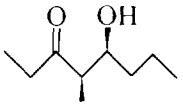
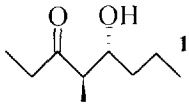
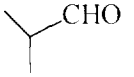
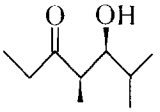
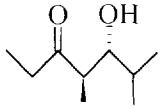
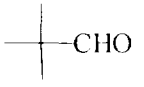
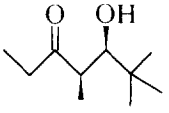
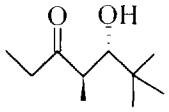
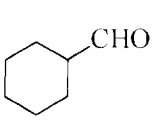
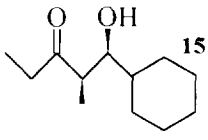
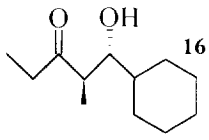


Table 3. Aldol Reactions of Diethyl Ketone with Aliphatic Aldehydes in the Presence of $PhTi(OR^2)_4MgBr$

Entry	R^1-CHO	R^2	yield, %	syn	anti
	 **5**			 **9**	 **10**
1		Et	64	23	77
2		iso-Pr	81	16	84
3		tert-Bu	58	21	79
	 **6**			 **11**	 **12**
4		Et	67	3	97
5		iso-Pr	72	< 2	> 98
6		tert-Bu	75	5	95
	 **7**			 **13**	 **14**
7		Et	84	< 2	> 98
8		iso-Pr	78	< 1	> 99
9		tert-Bu	67	2	> 98
	 **8**			 **15**	 **16**
10		Et	62	3	97
11		iso-Pr	77	2	98
12		tert-Bu	71	4	96

Liotta et al.[8] obtained similiar results by equilibrations of aldol products in the presence of $MgBr_2 \cdot Et_2O$ or chloromagnesium diisopropylamide. When isobutyraldehyde (**6**) was treated with diethyl ketone in the presence of titanium ate complexes (Table 3, entries 4, 5, 6, >98 *anti* : < 2 *syn*) higher *anti* selectivities were observed (91 *anti* : 9 *syn*[8]).
The same results were obtained by equilibration with ate complexes of the pure aldol products. *Syn* aldol **3** was treated at room temperature with equimolar amounts of a titanium(IV) isopropoxide / phenylmagnesium bromide complex in toluene. After 10 hours the ratio (81/19 - *anti/syn*) was obtained. No side reactions were detected.
Mulzer et al.[10] observed similiar stereoselections by investigating the aldol reaction of carboxylic acid dianions with aldehydes under conditions of kinetic and thermodynamic control. In the cases of steric repulsion (by using pivaldehyde (**6**) or isobutyraldehyde (**7**) in the aldol reaction), high *anti* selectivities were observed under conditions of thermodynamic control. However when aliphatic aldehydes (propionaldehyde, acetaldehyde) were used no differences between working under kinetic or thermodynamic control were observed; no stereoselection at all was obtained. The procedure described herein allows to synthesize *anti* aldols of aliphatic aldehydes with a high degree of stereoselection (Table 3, entries 1-3).
The *syn/anti* selectivity was determined by ^1H and ^{13}C NMR spectroscopy. The structure of the ate complexes used could not be determined. The ate complexes of titanium(IV) alkoxides are useful reagents for the synthesis of *anti* aldol products. Further investigations to clarify the mechanism are under way.

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker WP 200 SY at 200 MHz and the ^{13}C NMR spectra were obtained at 75 MHz on a Varian Gemini 300 instrument. Chemical shifts are related to tetramethylsilane.

1-Hydroxy-2-methyl-1-phenyl-3-pentanone[11] **(3,4). General procedure.** - To 1.5 ml (5 mmol) of titanium(IV) isopropoxide in 5 ml of abs. toluene 1.7 ml phenylmagnesium bromide (5 mmol, 3 mol solution) were added at 0° C under inert conditions. The solution was warmed to room temperature and stirred for one hour. 750 µl (7.5 mmol) of diethyl ketone were slowly added followed by carfully adding 500 µl (5 mmol) of benzaldehyde. After 10 h at room temperature, 50 ml of diethyl ether were added and the organic phase was extracted with water until neutral reaction. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated i. vac. The *syn/anti* ratio of the crude aldol product was determined by ^1H and ^{13}C NMR spectroscopy. The pure aldol products were obtained by flash chromatography using hexane / ethyl acetate (94/6) as eluent; 760 mg (79% yield).

The following spectroscopic data were used for the determination of the *syn* / *anti* ratio: ^{1}H NMR δ ($CDCl_3$) 4.92 (1H, d, J = 4.4 Hz, H-C(1)) for the *syn* aldol **3** and 4.64 (1H, d, J = 8.3 Hz, H-C(1)) for the *anti* diastereoisomer **4**. ^{13}C NMR δ ($CDCl_3$) 215.4, 142.5, 128.1, 127.3, 126.1, 73.9, 53.0, 35.5, 11.4, 7.3 for the *syn* aldol **3** and 215.8, 142.5, 128.1, 127.3, 126.1, 76.6, 52.7, 36.4, 14.1, 7.3 for the corresponding *anti* diastereoisomer **4**.

anti-1-Hydroxy-2-methyl-1-phenyl-3-pentanone[11] **(4). General procedure for equilibration**. - 1.6 ml (5.2 mmol) of titanium(IV) isopropoxide were dissolved in 10 ml of toluene. 1.8 ml (5.2 mmol) of phenylmagnesium bromide were carefully added at 0° C. Stirring was continued for 1 h at room temperature. Then 1.0 g (5.2 mmol) of a mixture of *syn* (**3**) and *anti* aldol (**4**) (ratio: 90 / 20 (syn / anti)) in 1 ml of toluene was added. After 10 h the reaction mixture was worked up as described above. 890 mg (89% yield) were obtained by flash chromatography. A *anti* / *syn* ratio of 81 / 19 (**4** / **3**) was detected by ^{1}H and ^{13}C NMR spectroscopy.

5-Hydroxy-4-methyl-3-octanone[12] **(9, 10)**. By using procedure A a mixture of the aldols **9** and **10** were obtained in 81% yields after 6 h at room temperature. The pure diastereoisomer were separated by flash chromatography. The following data were used for the estimation of the *syn* / *anti* ratio: ^{1}H NMR δ ($CDCl_3$) 3.71 (1H, ddd, J = 10.0, 6.6, 3.3 Hz, H-C(5)) for the *anti* aldol **10** and 3.96 (1H, ddd, J = 8.5, 4.4, 3.3 Hz, H-C(5)) for the corresponding *syn* diastereoisomer **9**.^{13}C NMR δ ($CDCl_3$) 216.4, 73.4, 51.4, 36.9, 36.1, 19.3, 13.9, 13.8, 7.6 for the *anti* aldol **10** and 216.2, 71.2, 50.5, 36.6, 35.2, 18.8, 14.1, 10.4, 7.6 for the *syn* diastereoisomer **9**.

anti-5-Hydroxy-4,6-dimethyl-3-heptanone[12] **(12)**. To 1.5 ml (5 mmol) of titanium(IV) isopropoxide in 5 ml of abs. toluene 1.7 ml phenylmagnesium bromide (5 mmol, 3 mol solution) were added at 0° C under inert conditions. The solution was warmed to room temperature and stirred for one hour. 750 µl (7.5 mmol) of diethyl ketone were slowly added followed by carfully adding 450 µl (5 mmol) of isobutyraldehyde (**6**). After 6 h at room temperature, 50 ml of diethyl ether were added and the organic phase was extracted with water until neutral reaction. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated i. vac. The pure aldol product were obtained by flash chromatography using hexane / ethyl acetate (96/4) as eluent; 570 mg (72% yield). ^{1}H NMR δ ($CDCl_3$) 3.41 (1H, t, J = 7 Hz, H-C(5)), 2.64 (1H, t, 6 Hz), 2.50 (2H, m), 1.61(1H, m), 1.30 - 0.80 (12H, m). ^{13}C NMR δ ($CDCl_3$) 217.1, 78.3, 48.3, 36.2, 30.5, 19.9, 19.1, 14.4, 7.8.

anti-5-Hydroxy-4,6,6-trimethyl-3-heptanone[4,13] **(14)**. To 1.5 ml (5 mmol) of titanium(IV) isopropoxide in 5 ml of abs. toluene 1.7 ml phenylmagnesium bromide (5 mmol, 3 mol solution) were added at 0° C under inert conditions. The solution was warmed to room temperature and stirred for one hour. 750 µl (7.5 mmol) of diethyl

ketone were slowly added followed by carfully adding 540 µl (5 mmol) of pivalaldehyde (**7**). After 8 h at room temperature, 50 ml of diethyl ether were added and the organic phase was extracted with water until neutral reaction. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated i. vac. The pure aldol product were obtained by flash chromatography using dichloromethane / acetone (99.5/0.5) as eluent; 670 mg yield (78% yield). ^1H NMR δ ($CDCl_3$) 3.16 (1H, d, J = 2.9 Hz, H-C(5)), 2.82 (1H, d, J = 2.9 Hz), 2.53 (2H, q, J = 7 Hz), 1.13 (3H, d, J = 7 Hz), 1.01 (3H, t, J = 7 Hz), 0.92 (9H, s). ^{13}C NMR δ ($CDCl_3$) 219.4, 84.3, 43.2, 36.3, 35.5, 26.2, 17.5, 6.9.

anti-1-Hydroxy-2-methyl-1-cyclohexyl-3-pentanone[4] (**16**). To 1.5 ml (5 mmol) of titanium(IV) isopropoxide in 5 ml of abs. toluene 1.7 ml phenylmagnesium bromide (5 mmol, 3 mol solution) were added at 0° C under inert conditions. The solution was warmed to room temperature and stirred for one hour. 750 µl (7.5 mmol) of diethyl ketone were slowly added followed by carfully adding 610 µl (5 mmol) of cyclohexanecarboxaldehyde (**8**). After 8 h at room temperature, 50 ml of diethyl ether were added and the organic phase was extracted with water until neutral reaction. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated i. vac. The pure aldol product were obtained by flash chromatography using hexane / ethyl acetate (96 / 4) as eluent; 760 mg yield (77% yield). ^1H NMR δ ($CDCl_3$) 3.43 (1H, dd, J = 6.8, 5.2 Hz, H-C(1)), 2.80 - 2.40 (4H, m), 1.60 - 1.80 (10H, m), 1.11 (3H, d, J = 7.2 Hz), 1.01 (3H, t, J = 7.1 Hz). ^{13}C NMR δ ($CDCl_3$) 216.9, 78.0, 47.7, 40.7, 36.2, 30.4, 26.6, 26.2, 26.0, 25.7, 14.5, 7.5.

REFERENCES

1. Seebach, D.; Weidmann, B.; Widler, L. In *Modern synthetic methods*; Sheffold, R. Ed.; Salle - Sauerländer: Frankfurt, **1983**. *Vol.3*; pp. 217-253; Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31-45; Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem.* **1983**, *55*, 1787-1822; Reetz, M.T. *Organotitanium reagents in organic synthesis*; Springer Verlag: Berlin, **1986**.

2. Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99-111; Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Rothe-Streit, P.; Rils, G. *Pure Appl. Chem.* **1992**, *64*, 1897-1910; Duthaler, R. O.; Hafner, A.; Riedicker, M. In *Organic Synthesis via Organometallics*; Dötz, K. H., Hoffmann, R. W. Eds.; Vieweg: **1991**; pp. 285-310; Duthaler, R. O.; Herold, R.; Lottenbach, W.; Oertle, K.; Riedicker, M. *Angew. Chem.* **1989**, *101*, 490-491; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495-496;

Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489-2499.

3. Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, **1991**, *Volume 2*; Chapter 1.9., pp. 301 - 319;
Reetz, M.T. In *Topics in Current Chemistry*; Boschke, F. L. Ed.; Springer Verlag: Berlin **1982**, *106*, pp. 3-54;
Botrill, M.; Gavens, P. D.; Kelland, J. W.; McMeeking, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F G. A.; Abel, E. W. Eds.; Pergamon Press: Oxford, **1982**, Chapter 22.

4. Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691-4694.

5. Lithiumenolate: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081;
boronenolate: Gennari, C.; Cardani, S.; Colombo, L.; Scolastico, C. *Tetrahedron Lett.* **1984**, *25*, 2283-2286;
Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099- 3111;
silylenolate: Sohn, J. E. (1980) Ph.D.Thesis, Univ.of California, Berkeley;
zincenolate:Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 467-470;
zirkoniumenolate: Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, *21*, 4607-4610;
titaniumenolate: see [4].

6. Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, K. *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442.

7. Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew. Chem.* **1993**, *105*, 1717-1719; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1618-1620.

8. Swiss, K. A.; Woo-Baeg Choi; Liotta, D. C.; Abdel-Magid, A. F.; Maryanoff, C. A. *J. Org. Chem.* **1991**, *56*, 5978-5980.

9. Mahrwald, R.; Schick, H. *Synthesis* **1990**, 592-595.

10. Mulzer, J.; Zippel, M.; Brüntrup, G.; Segner, J.; Finke, J. *Liebigs Ann.Chem.* **1980**, 1108-1134.

11. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099- 3111.

12. Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663-4684.

13. Dubois, J. E.; Fellmann, P. *Tetrahedron Lett.* **1975**, *17*, 1225-1228.

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