Catalytic, Diastereoselective Aldol Reactions Using Titanium(IV) Halides

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The aldol reaction in the presence of titanium halides is described. Good yields of aldols **10–17** were obtained even with only catalytic amounts of titanium tetrafluoride. The reactions were carried out in the absence of a base.

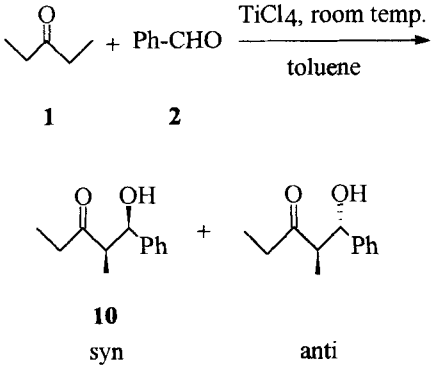
The aldol reaction is one of the most powerful tools for the construction of carbon-carbon bonds. Conventional aldol reactions are performed usually by using geometrically-defined enolates and carbonyl compounds as starting materials[1].

Aldol reactions of titanium enolates were described: Lithium enolates or trimethylsilyl enol ether react with chlorotitanium compounds (e.g. chlorotitanium triisopropoxide) and subsequently with a carbonyl compound[2]. The aldol reaction of trimethylsilyl enol ether with aldehydes or ketones in the presence of titanium(IV) chloride proceeds without formation of the titanium enolate[3]. The powerful activation of the carbonyl group by titanium(IV) chloride provides the driving force for this reaction. Trichlorotitanium enolates of aromatic aldehydes and ketones prepared in situ by treatment with titanium(IV) chloride and triethylamine afford the *syn* aldols[4].

In this paper we show that complexes of titanium(IV) chloride and carbonyl compounds undergo aldol reactions even in the absence of a base[4].

A complex of titanium(IV) chloride and benzaldehyde (1:1) reacts with one equivalent of diethyl ketone within 90 min to give the *syn* and *anti* aldol (Scheme 1).

Scheme 1



In general, there are two possibilities for carrying out the reaction. One way is to simply mix the carbonyl compounds with equimolar amounts of titanium(IV) chloride in an inert solvent (toluene, hexane, acetonitrile) at room temperature. However, reactions of the isolated complexes of carbonyl compounds with aldehydes or ketones gave the same results. The reaction must be monitored by chromatography, because side reactions may occur after the completion of the aldol reaction. Dehydration, as observed in aldol reactions in the presence of titanium(IV) alkoxides, did not occur[6]. When substituted titanium(IV) compounds (i.e. trichlorotitanium isopropoxide) were used, acetalization of carbonyl compounds was observed[7].

Working with catalytic amounts of titanium(IV) halides is also possible. Using 5 mol-% of titanium(IV) fluoride in toluene, we obtained aldols in 82% yield (Table 1, entry 5). The reaction was performed in propionitrile. Catalytic amounts of titanium(IV) fluoride were added successively[5].

Table 1. Aldol reaction of ketones with benzaldehyde in the presence of $TiCl_4$

entry	ketone	time[h]	major product	yield[%]	syn/anti[a]
1		2		92	93:7
2		3.5		84	85:15[b]
3		3		78	77:23[c]
4		2.5		89	66:34[d]
5	**1**	24	**10**	82	77:23[e]
6	**3**	2	**11**	86	>97:<3
7	**4**	4	**12**	71	96:4
8	**5**	16	**13**	82	>98:<2

[a] The ratio was determined by ^1H- and ^{13}C-NMR spectroscopy. The reactions were carried out in toluene, if not stated otherwise. – [b] Tetrahydrofuran. – [c] 1-Butoxy-2-methoxyethane. – [d] Chloroform. – [e] 5 mol-% TiF_4, propionitrile, room temperature, 24 h.

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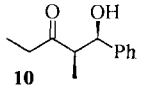
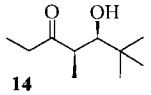
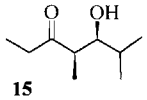
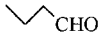
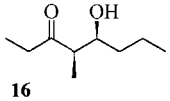
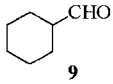
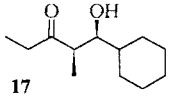
High *syn* selectivity was observed when benzaldehyde and ketones reacted in the presence of titanium(IV) chloride (Table 1). The selectivity depends on the solvents used. The best results were obtained with toluene (Table 1, entry 1), whereas lower selectivities were found by using tetrahydrofuran or chloroform (entries 2 and 4).

Different results were obtained in reactions of diethyl ketone with several aldehydes in the presence of titanium(IV) chloride (Table 2). Pivalaldehyde (**6**), an aldehyde with bulky groups and reduced carbonyl activity, reacted slowly giving lower yields (Table 2, entry 2). Lower selectivities were observed, when *n*-butyraldehyde **8** (entry 4) or cyclohexanecarboxaldehyde (**9**) (entry 5) was treated with diethyl ketone in the presence of titanium(IV) chloride. A comparison of the results of the reaction of benzaldehyde (Table 2, entry 1) and **9** (entry 5) reveals that electronic effects seem to play an important role in controlling diastereoselectivity.

Similar reactions were reported by Seebach[8] and Evans[9]. Ketones were treated with boron trichloride and ethyldiisopropylamine[8] or with titanium(IV) chloride and ethyldiisopropylamine[9] and then treated with several aldehydes. The method presented here works in the absence of a base.

Table 2. Aldol reaction of aldehydes with diethyl ketone in the presence of $TiCl_4$

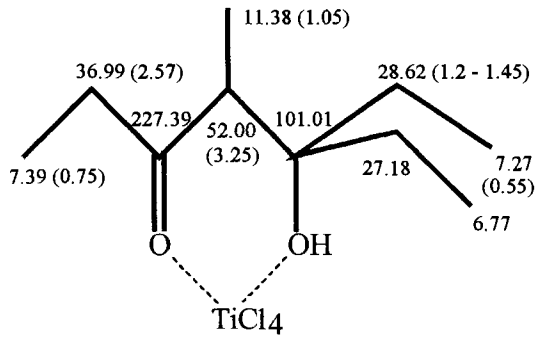
entry	aldehyde	time[h]	major product	yield[%]	syn/anti[a]
1	Ph-CHO **2**	2	 **10**	92	93: 7
2	 **6**	16	 **14**	51	75:25
3	 **7**	3	 **15**	63	68:32
4	 **8**	3.5	 **16**	78	78:22
5	 **9**	4	 **17**	76	62:38

[a] The ratio was determined by ^{1}H- and ^{13}C-NMR spectroscopy. The reactions were carried out in toluene at room temperature.

The mechanism of the aldol reaction of diethyl ketone in the presence of titanium(IV) chloride was studied by ^{13}C- and ^{1}H-NMR spectroscopy. The typical signals of the chlorotitanium enolate of diethyl ketone (^{13}C NMR: δ = 175.4 and 108.7, ^{1}H NMR: δ = 4.67[10]) were not observed (Scheme 2). The δ values in Schemes 2 and 3 were obtained by ^{13}C-NMR spectroscopy (in brackets ^{1}H-NMR data, CD_3CN).

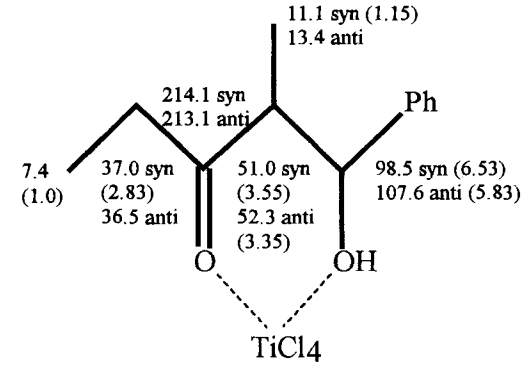
Similar results were obtained by investigating the aldol reaction of benzaldehyde with diethyl ketone in the presence

Scheme 2



of titanium(IV) chloride by means of NMR spectroscopy (Scheme 3).

Scheme 3



The data observed during the reaction allow us to assume a cyclic reaction structure that does not involve the titanium enolate. Further investigations are under way to clarify the mechanism.

Experimental

^{1}H and ^{13}C NMR: Bruker WP 200 SY (200 MHz) and Varian Gemini 300 (75 MHz), resp.; chemical shifts are related to tetramethylsilane. – Low-resolution electron impact mass spectra: GC/MS Datensystem HP 5985 B. – Microanalyses: Carlo Erba autoanalyzer 1106.

General Procedure A: Representative aldol reaction with isolated carbonyl titanium(IV) chloride complexes:

Benzaldehyde/Titanium(IV) Chloride Complex: Titanium(IV) chloride (550 µl, 5.0 mmol) was dissolved under inert conditions in 10 ml of anhydrous toluene. Benzaldehyde (510 µl, 5.0 mmol) was added to the solution at room temp. The resulting suspension was stirred for 30 min, the yellow precipitate was filtered off and recrystallized from toluene. – ^{1}H NMR ($CDCl_3$): δ = 7.64 (m, 2H), 7.87 (m, 1H), 8.13 (m, 2H) (aromatic H), 9.95 (s, 1H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 130.03, 133.81, 139.45 (aromatic C), 200.17 (CHO). – MS (70 eV), *m/z* (%): 270 (6) [$M^+ - C_2H_2$], 235 (3) [$M^+ - C_2H_2 - Cl$], 219 (1) [$M^+ - C_6H_5$], 190 (20) [$M^+ - C_6H_5CHO$], 155 (40) [$M^+ - C_6H_5CHO - Cl$], 106 (100) [$M^+ - TiCl_4$]. – $C_7H_6Cl_4OTi$ (295.8): calcd. C 28.42, H 2.05; found: C 28.97, H 2.48.

Aldol Reaction of Diethyl Ketone with Isolated Benzaldehyde/Titanium(IV) Chloride Complex: The benzaldehyde titanium(IV) chloride complex (1.5 g, 5.1 mmol) was suspended under inert con-

ditions in 10 ml of anhydrous toluene. Diethyl ketone (800 µl, 7.5 mmol) was added slowly at room temp. to the suspension which turned into a clear, gold-colored solution. After 1.5 h, 50 ml of diethyl ether was added, and the organic phase was extracted with water until the water phase was neutral. The organic layer was separated, dried (Na_2SO_4), and the filtrate concentrated in vacuo. The *syn*/*anti* ratio of the crude aldol product was determined by ^1H- and ^{13}C-NMR spectroscopy.

General Procedure B

Representative Aldol Reaction Without Isolated Titanium(IV) Chloride Complexes: Benzaldehyde (1.0 ml, 10 mmol) and 1.1 ml (10 mmol) of diethyl ketone were added to 20 ml of anhydrous toluene. Under inert conditions 1.1 ml (10 mmol) of titanium(IV) chloride was added to this solution at room temp. The solution was stirred for 1 h and worked up as described above. For the estimation of the yields, the aldol products were purified by flash chromatography using hexane/ethylacetate (94:6) as eluent.

General Procedure C

Representative Aldol Reaction Using Catalytic Amounts of Titanium(IV) Fluoride: Benzaldehyde (1.0 ml, 10 mmol) and 1.1 ml (10 mmol) of diethyl ketone were dissolved in 20 ml of anhydrous propionitrile under inert conditions. Titanium(IV) fluoride (62 mg, 0.5 mmol) was added successively at room temp. over a period of 24 h. The reaction mixture was worked up as described above. The following data were used for the estimation of the *syn*/*anti* ratio.

syn-1-Hydroxy-2-methyl-1-phenyl-3-pentanone[11] (**10**): ^1H NMR ($CDCl_3$): δ = 4.92 (d, *J* = 4.4 Hz, 1H, C*H*OH); the corresponding *anti* diastereoisomer gives a signal at δ = 4.64 (d, *J* = 8.3 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 215.4 (C=O), 142.5, 128.1, 127.3, 126.1 (aromatic C), 73.9 (CHOH), 53.0 (*C*HCH$_3$), 35.5 (CH_2), 11.4, 7.3 (CH_3); *anti* diastereoisomer: δ = 215.8, 142.5, 128.1, 127.3, 126.1, 76.6, 52.7, 36.4, 14.1, 7.3.

syn-2-(α-Hydroxybenzyl)cyclopentanone[12,13] (**11**): ^1H NMR ($CDCl_3$): δ = 5.16 (d, *J* = 2.0 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 4.68 (d, *J* = 9.0 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 222.3 (C=O), 141.7, 128.2, 127.7, 126.5 (aromatic C), 74.6 (CHOH), 55.3 (CH), 38.6, 26.4, 20.3 (CH_2); *anti* diastereoisomer: δ = 222.6, 141.5, 128.2, 127.7, 126.5, 71.3, 56.0, 39.6, 26.8, 20.3.

syn-2-(α-Hydroxybenzyl)cyclohexanone[12,13] (**12**): ^1H NMR ($CDCl_3$): δ = 5.40 (d, *J* = 2.5 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 4.83 (d, *J* = 9.0 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 210.6 (C=O), 139.5, 128.3, 128.1, 125.3 (aromatic C), 77.3 (CHOH), 58.6 (CH), 43.9, 34.3, 26.9, 25.6 (CH_2); *anti* diastereoisomer: δ = 210.9, 139.4, 128.5, 128.1, 125.3, 71.8, 57.9, 43.6, 33.3, 26.5, 25.5.

syn-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone[8] (**13**): ^1H NMR ($CDCl_3$): δ = 5.18 (d, *J* = 3.5 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 5.00 (d, *J* = 8.5 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 205.2 (C=O), 143.1, 137.1, 128.9, 128.5, 128.4, 128.1, 127.9, 126.1 (aromatic C), 73.3 (CHOH), 47.3 (CH), 11.5 (CH_3); *anti* diastereoisomer: δ = 205.3, 143.4, 137.5, 128.7, 128.5, 128.4, 128.1, 127.9, 126.5, 74.4, 47.9, 14.3.

syn-5-Hydroxy-4,6,6-trimethyl-3-heptanone[14] (**14**): ^1H NMR ($CDCl_3$): δ = 3.58 (d, *J* = 3.5 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 3.16 (d, *J* = 2.9 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 219.5 (C=O), 77.1 (CHOH), 46.7 (CH), 37.4 (q, C), 35.5 (CH_2), 26.7, 11.6, 7.4 (CH_3); *anti* diastereoisomer: δ = 219.4, 84.3, 43.2, 36.3, 35.5, 26.2, 17.5, 6.9.

syn-5-Hydroxy-4,6-dimethyl-3-heptanone[9] (**15**): ^1H NMR ($CDCl_3$): δ = 3.48 (dd, *J* = 7.9, 3.8 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 3.41 (t, *J* = 7 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 216.6 (C=O), 76.4 (CHOH), 47.5 (CH), 34.8 (CH_2), 30.7 [$CH(CH_3)_2$], 19.1, 18.9, 9.7, 7.6 (CH_3); *anti* diastereoisomer: δ = 217.1, 78.3, 48.3, 36.2, 30.5, 19.9, 19.1, 14.4, 7.8.

syn-5-Hydroxy-4-methyl-3-octanone[9] (**16**): ^1H NMR ($CDCl_3$): δ = 3.96 (ddd, *J* = 8.5, 4.4, 3.3 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 3.71 (ddd, *J* = 10.0, 6.6, 3.3 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 216.2 (C=O), 71.2 (CHOH), 50.5 (CH), 36.6 (CH_2OH), 35.2 (*C*H$_2$C=O), 18.8 (*C*H$_2$CH$_3$), 14.1, 10.4, 7.6 (CH_3); *anti* diastereoisomer: δ = 216.4, 73.4, 51.4, 36.9, 36.1, 19.3, 13.9, 13.8, 7.6.

syn-1-Cyclohexyl-1-hydroxy-2-methyl-3-pentanone[2c,12] (**17**): ^1H NMR ($CDCl_3$): δ = 3.59 (dd, *J* = 8.5, 2.9 Hz, 1H, C*H*OH); *anti* diastereoisomer: δ = 3.43 (dd, *J* = 6.8, 5.2 Hz, 1H, C*H*OH). – ^{13}C NMR ($CDCl_3$): δ = 216.3 (C=O), 75.4 (C*H*OH), 47.2 (*C*HCH$_3$), 40.4 (CH), 34.7, 29.3, 26.6, 26.5, 26.0, 25.7 (CH_2), 9.6, 7.7 (CH_3); *anti* diastereoisomer: δ = 216.9, 78.0, 47.7, 40.7, 36.2, 30.4, 26.6, 26.2, 26.0, 25.7, 14.5, 7.5.

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