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DIASTEREOSELECTIVE ALDOL CONDENSATION OF DIRECTLY GENERATED TITANIUM ENOLATES OF ACTIVATED ESTERS.

Rita Annunziata, Mauro Cinquini,* Franco Cozzi,* Pier Giorgio Cozzi,
and Emanuela Consolandi.
Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università
Via C. Golgi 19, 20133 Milano, Italy.

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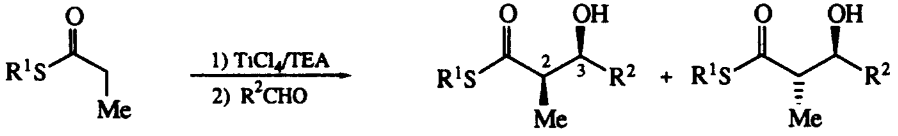
Abstract Simply generated ($TiCl_4$, Et_3N, -78°C) titanium enolates of some thioesters and α-thio substituted esters undergo aldol condensations with achiral and chiral aldehydes with low to high stereoselectivity. An ^1H-NMR study of the $TiCl_4$/ester complexation and of the enolization process is presented The relation between the enolate structure and the aldol product stereochemistry is discussed

The design of new methods to perform important reactions is a challenging goal in modern organic synthesis. The fundamental role played by the chemistry of enolates spurred the search for mild and simple process for their generation Recently it was found[1-3] that addition of $TiCl_4$ to a cooled (-78°C) methylene chloride solution of a ketone followed by treatment with a tertiary amine led to the direct formation of titanium enolates,[4] that otherwise have been obtained only by transmetalation from lithium enolates or silyl enol ethers,[4] or by acylation of a titanocene methylene complex.[5] The same authors[1-3] described the aldol[1] or Knoevenagel[2,3] condensation of these directly generated titanium enolates with aldehydes. More recently, Evans[6-8] extended this convenient methodology to other enolate precursors (N-acyloxazolidones and N-acylsultams) that were reacted with various electrophiles (including acetals, alkylating agents, and Michael acceptors), and anticipated[6] that other carbonyl compounds could undergo this simple enolization process We here report that readily enolizable esters such as thioester and α-thiosubstituted esters can be easily transformed by the $TiCl_4$/triethylamine (TEA) protocol into the corresponding titanium enolates, and that these compounds react with aldehydes to afford aldol products.

The reaction of thioesters **1-5** with aldehydes **6-8** was investigated first (Table 1) As can be seen from the reported data the aldol condensation occurs in good yields in dichloromethane. The use of different solvents (tested only for the reaction of S-phenyl-

Table 1. Diastereoselective aldol condensation of thioesters **1-5** with aldehydes **6-8**



1 - 5 **6 - 8** **9a - 19a** **9b - 19b**

Ester	Aldehyde	R^1	R^2	Product	Yield %	Diastereomeric[b] ratio a	b
1	**6**	Ph	Ph	**9**	70	85	15
1	**6**	Ph	Ph	**9**	50[c]	84	16
1	**6**	Ph	Ph	**9**	-[d]		
1	**7**	Ph	Pr-n	**10**	68	78	22
1	**8**	Ph	Pr-i	**11**	65	89	11
2	**6**	Bu-t	Ph	**12**	77	86	14
2	**7**	Bu-t	Pr-n	**13**	72	69	31
2	**8**	Bu-t	Pr-i	**14**	75	71	29
3	**6**	2-Py[e]	Ph	**15**	69	48	52
3	**7**	2-Py[e]	Pr-n	**16**	56	49	51
3	**8**	2-Py[e]	Pr-i	**17**	69	29	71
4	**6**	2-MeOPh	Ph	**18**	71	87	13
5	**6**	C_6F_5	Ph	**19**	40	95	5

[a] Isolated yield [b] As determined on the crude products by 300 MHz ^{1}H-NMR [c] In toluene. [d] In Et_2O, see text [e] 2-Py= 2-pyridyl.

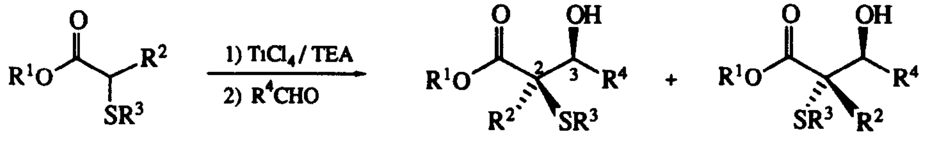
thiopropionate **1** with benzaldehyde **6** led to a lower yield of aldol adduct in toluene, and to the formation of 5-phenylthio-2-methyl-3-oxopentanoate[9] (i.e the self-condensation product of **1**) in diethylether (65%) In the case of thioesters **1** and **2** the reaction occurs with moderate to good diastereoselectivity in favour of the syn configurated compound, as shown by 300 MHz ^{1}H-NMR analysis of the crude product. The stereochemical assignment resided on comparison with the reported values of the chemical shift and of the coupling constant for the Me-CH-CH-OH protons of syn and anti isomers of compounds **9-14**.[9-11] On the other hand, the condensation of the titanium enolate of 2-pyridylthiopropionate **3**[12] with **6-8** were stereorandom or showed moderate anti-stereoselectivity.[13]

In order to determine if there was a correlation between the stereochemical outcome of these aldol condensations with the titanium enolate geometry, we performed the reaction of esters **1** and **3** with **6** in CD_2Cl_2 at -78°C, and we monitored it by ^{1}H-NMR spectroscopy at low temperature Upon addition of $TiCl_4$ to the 0.1 M solution of the thiophenyl derivative **1**, two sets of signals in approximately 90 10 ratio appeared for the methylene and methyl protons of **1**, at 3 18 and 1 40 ppm (major) and at 2.63 and 1.00 ppm (minor), respectively When TEA was added, these signals disappeared, the enolate formation being complete in less than 15 min, to give rise to two quartets at 6 53 and 5 85 ppm and to two doublets at 2.03 and 2.15 ppm in 55 45 ratio This ratio did not change within 2 hours from the addition of TEA (while minor traces of the self-condensation product of **1** could be observed in the spectrum) Finally, addition of benzaldehyde led to the simoultaneous and complete disappearance of the enolate signals.

In the case of the 2-pyridylthioester **3**, the addition of $TiCl_4$[14] resulted in the formation of two sets of signals in 66 34 ratio at 2 70 and 1 01 (major), and at 3.05 and 1.37 ppm (minor), respectively. When TEA was added, two quartets at 5 32 and 4 93 ppm (20 80 ratio) and two doublets at 1.81 and 1.76 ppm (80 20 ratio) appeared in the spectrum As before, this ratio did not change over a period of 2 hours and the enolate signals disappeared simoultaneously and completely upon benzaldehyde addition

A tentative interpretation of these results is as follows a) there are different binding modes for $TiCl_4$[15] with thioesters, as clearly indicated by the behaviour of **1** and **3**, although we have the only evidence of a change in the colour of the solution,[14] it seems reasonable that in the case of **3** the complex features an intramolecular chelation between the pyridine nitrogen and the titanium atom b) Enolate formation is not a stereoselective process for thioester **1**, while it is fairly stereoselective in the case of **3**. Since attempts to generate stereoselectively these enolates from the E or Z trimethylsilyl ketene acetals[11] of **1** and **3** by reaction with $TiCl_4$ resulted in extensive decomposition of the starting material,[16] we cannot firmly assign[17] any configuration to the observed enolates However it is evident that the stereochemical outcome of the condensation of **1** and **3** with aldehydes does not correlate with the enolate geometry, in

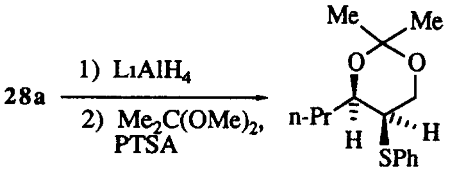
Table 2. Diastereoselective aldol condensation of α-thiosubstituted esters **20-23** with aldehydes **6-8**.



20 - 23 **6 - 8** **24a - 34a** **24b - 34b**

Ester	R^1	R^2	R^3	R^4	Product	Yield%[a]	Diastereisomeric ratio **a**	**b**[b]
20	Et	H	Bu-n	Ph	**24**	80	94	6
20	Et	H	Bu-n	Pr-n	**25**	74	76	24
20	Et	H	Bu-n	Pr-i	**26**	73	84	16
21	Et	H	Ph	Ph	**27**	76	90	10
21	Et	H	Ph	Pr-n	**28**	66	79	21
21	Et	H	Ph	Pr-i	**29**	64	84	16
22	Bu-t	H	Bu-n	Ph	**30**	54	75	25
22	Bu-t	H	Bu-n	Pr-n	**31**	42	57	43
23	Et	Me	Bu-n	Ph	**32**	90	95	5
23	Et	Me	Bu-n	Pr-n	**33**	71	88	12
23	Et	Me	Bu-n	Pr-i	**34**	76	88	12

[a] Isolated yields. [b] As determined on the crude products by 300 MHz ^{1}H-NMR



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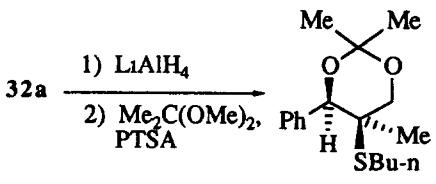

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contrast to the aldol reaction of the dialkylboron enolates of thioesters **1** and **2**,[10,18] a process that is more stereoselective than the one here described.[7,19] It must also be noted that we do not observe any stereoconvergency in the reaction of these titanium enolates, and therefore our method is less stereoselective than the aldol condensation of the dialkoxyboron enolates of thioesters.[9]

On these bases any rationalization of the stereochemical result of the reaction can be purely speculative, and more work is required to propose a reasonable explanation. The possibilities that these titanium enolate can exist as aggregates in solution[7] is likely to make this task more difficult However, we can anticipate that the different behaviour observed in the case of the 2-pyridylthio derivative **3** is not due solely to the possibility of intramolecular chelation or to the electron poor nature of the pyridine ring Indeed (Table 1) the reactions of 2-methoxyphenylthio ester **4** or of pentafluorophenylthio ester **5** with **6** gave the syn aldols, **18a** and **19a** as largely predominant products

We next examined the possibility of generating the titanium enolate of other esters that are activated enough to be enolized in these conditions Therefore we selected the α-thio substituted esters **20-23** that were tested in the reactions collected in Table 2.[20,21] As can be seen from the reported data the reaction occurs in good yields with α-thioacetate and α-thiopropionate derivatives The diastereoselectivity ranges from moderate to good and increases on passing from butyraldehyde to iso-butyraldehyde to benzaldehyde. Syn products are always obtained as predominant isomers over their anti counterparts, as determined by 300 MHz ^{1}H-NMR spectroscopy. The stereochemical assignment was based on the conversion[21,22] of compounds **28a** to the corresponding 2,2-dimethyl-1,3-dioxane derivative **35**, and on the observation that the HC-4/HC-5 coupling constant value for this compound was 2.2 Hz This is in line with the values of coupling constants reported[21] for syn isomers of compounds very similar to **35**.[23] The configuration of compound **32a** was established by conversion to the 1,3-dioxane derivative **36** and NOE experiments.

A comparison between these reactions and those of dialkylboron enolates of related α-thio substituted esters[21] indicates that also in this case titanium enolates give rise to lower degree of stereocontrol in the formation of the aldol adducts. However, in contrast with the results of thioester **2** (mainly syn aldols with titanium enolates, mainly anti aldols with dialkylboron enolates[10]). and in agreement with those of thioester **1**[18], titanium and boron enolates reactions of α-thio substituted esters afford syn configurated products. Since the reasons of this puzzling behaviour were unclear, an ^{1}H-NMR study analogous to that described above for the enolates of **1** and **3** was undertaken with **20** and **23**

In the case of acetate **20** a single complex was formed upon addition of TiCl$_4$ at -78°C, a peculiar feature of this adduct was the diastereotopicity of the protons of the two CH$_2$ groups flanking the sulphur atom.[24] The formation of a rigid five-membered titanium chelate involving the sulphur atom and the carbonyl oxygen can account for this observation.[25] TEA addition resulted in the fast and complete formation of a single enolate, as indicated by the appearance of a sharp singlet at 4.38 ppm [26] The spectrum remained unchanged when the sample was warmed-up to -40°C, while at 0°C the enolate began to decompose.

By addition of TiCl$_4$ at -78°C to propionate **23** two complexes were formed in a 73 27 ratio. The major adduct displayed a quartet at 4 15 ppm for the methine proton and a doublet at 1.84 ppm for the methyl group. The minor adduct showed these signals at 4.76 and 1 68 ppm, respectively TEA addition generated a single enolate, featuring the methyl signal as a sharp singlet at 1.98 ppm.[26] No change in the spectrum was observed upon warming the sample up to 0°C

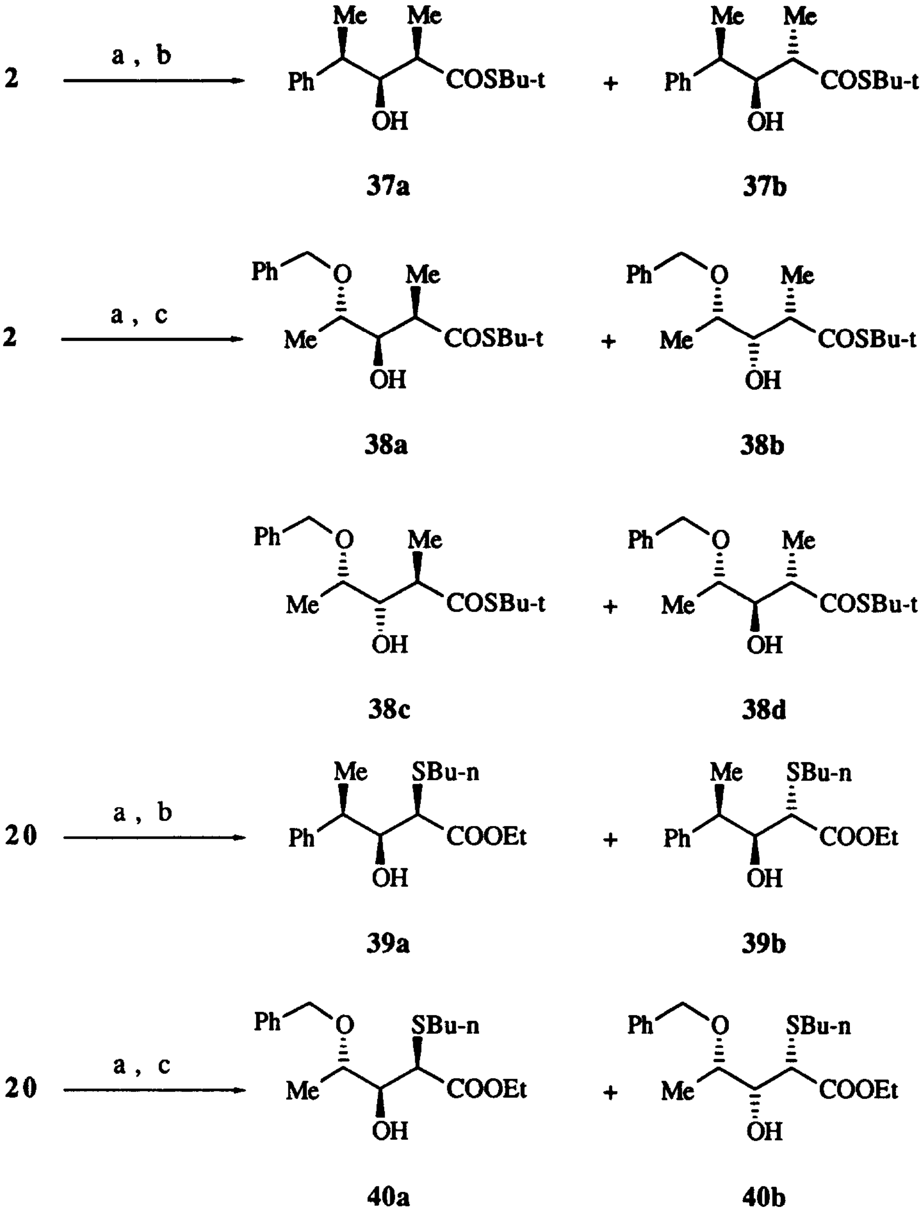
It must be noted that despite the presence of a single titanium enolate for both **20** and **23**, their reactions with aldehydes **6-8** occurred with different degrees of stereoselection. Therefore, as in the case of thioesters **1-5**, it seems unlikely that a straightforward correlation between the stereochemical outcome of the aldol condensation and the geometry of the enolates of α-thio esters **20-23** can be established

Finally, the reaction of the titanium enolates of t-butylthiopropionate **2** and of ethyl (butylthio)acetate **20** with two representative chiral aldehydes was investigated (Scheme)

Condensation of **2** with 2-phenylpropanal gave a 70 30 mixture of two products **37a,b** in 71% yield. On the basis of their ^{13}C-NMR spectra[11] the 2,3-*syn*-3,4-*syn* configuration was assigned to the major isomer **37a**, and the 2,3-*anti*-3,4-*syn* configuration to the minor one, **37b**. Thus, in line with the result of the reaction of **2** with 2-methylpropanal, that gave **14a**, **14b** in a ratio 71 29, the "simple" diastereoselection is moderate, while the diastereofacial preference in favour of the Cram[27] product is complete.

The reaction of **2** with (S)-O-benzyllactaldehyde gave the four possible products **38a,b,c,d** (44 26 24 6 **a b c d** ratio by ^{1}H-NMR) in 80% yield. The configurational assignment was based on the comparison of the ^{13}C spectra of the products with those reported in the literature [11]

In this case, while the moderate "simple" diastereoselectivity of the reaction of ester **2** is maintained (2,3-*syn* 2,3-*anti* ratio 70 30), the diastereofacial control is completely lost (3,4-*syn* 3,4-*anti* ratio 50 50).



Scheme. Reagents a, $TiCl_4$, TEA, b, 2-phenylpropanal, c, (S)-O-benzyllactaldehyde

The reaction of ester **20** with 2-phenylpropanal afforded a 88 12 mixture of aldols **39a** and **39b** in 76% yield. On the basis of their ^{1}H and ^{13}C-NMR spectra, and of the reasonable assumption that this reaction proceeds with a "simple" diastereoselection similar to that observed for the condensation of **20** with **8** (syn anti ratio 84.16), the 2,3-syn-3,4-syn configuration was tentatively assigned to **39a** and the 2,3-anti-3,4-syn one to **39b** This indicates that the diastereofacial control exerted by these titanium enolates with non--heterosubstituted chiral aldehydes can be very high. On the other hand, the condensation of **20** with (S)-O-benzyllactaldehyde showed a poor diastereofacial control, but a high level of "simple" diastereoselectivity, affording (84% yield) 2,3-syn-3,4-anti compound **40a** and 2,3-syn-3,4-syn compound **40b** in a 58 42 ratio, this stereochemical assignment being based on ^{1}H and ^{13}C-NMR chemical shift trends.

In conclusion we have shown that the simply generated titanium enolates of some ready enolizable thioesters and α-thio substituted esters undergo aldol condensation with aldehydes with various degrees of of stereocontrol that mainly depends on the ester structure.The application of this methodology to β-lactone[28] and β-lactam[29] synthesis, as well as the extension to activated esters bearing chiral auxiliaries is under active investigation in our laboratories.

Acknowledgements. Partial financial support by MURST-Roma is gratefully acknowledged.

Experimental.

NMR spectra were recorded on a Bruker WP-80 or a Varian Xl-300 instrument using $CDCl_3$ or CD_2Cl_2 as solvent, chemical shifts are in ppm downfield from TMS. IR spectra were recorded on a Perkin Elmer 377 instrument. Elemental analyses were obtained on a Perkin Elmer 240 instrument THF and Et_2O were distilled from $LiAlH_4$, benzene and toluene from sodium, CH_2Cl_2 from CaH_2; Et_3N from KOH Dry solvents were stored under Argon over molecular sieves. Esters **1**,[9] **2**,[10] **20**,[30] **21**,[31] **22**,[30] aldols **9**,[9] **11**,[18] **12**,[10] **13**,[10] **14**,[10] 37,[11] 38,[11] and (S)-O-benzyllactaldehyde[32] were known compounds.

Synthesis of thioesters. General procedure.[33]

To a cooled (0°C) 0 5 M solution of thiol (10-50 mmol) and triethylamine (1.1 mol equiv.) in dry dichloromethane, freshly distilled propionyl chloride (1 mol. equiv) in dichloro-

Table 3. Relevant ^{1}H and ^{13}C-NMR data of compounds **10, 15-19.**

Compound	H-C_2	H-C_3	Me-C_2	$J_{2,3}$	C-2	C-3	Me-C_2
10a	2.82	3.99	1.31	3.8	52.9	71.6	11.6
10b	2.87	3.76	1.33	8.0	53.5	73.6	15.2
15a	3.07	5.21	1.25	4.0	55.5	73.6	11.2
15b	3.13	4.86	1.07	8.7	56.0	76.6	15.2
16a	2.83	4.03	1.31	3.5	54.4	71.0	11.2
16b	2.87	3.79	1.33	5.8	53.7	73.5	14.9
17a	2.96	3.68	1.29	3.9	51.8	77.0	11.1
17b	2.98	3.49	1.30	6.8	51.3	78.5	15.4
18a	3.10	5.20	1.33	3.7	56.0	73.7	11.2
18b	3.13	4.83	1.11	8.5	55.4	76.9	15.3
19a	3.12	5.10	1.32	5.0	55.6	74.0	11.8
19b	3.29	5.10	1.35	8.0	54.0	76.3	13.0

methane (2 ml/mmol) was added dropwise. After 30 min stirring at 0°C the reaction mixture was poured into cold water. The organic phase was separated and washed with a 5% aqueous solution of sodium hydroxide and with water, dried, and concentrated under reduced pressure. The products were obtained as oils and were generally pure enough to be used as such. Samples for elemental analysis were prepared by flash chromatography with hexanes diethylether mixtures as eluant.

S-(2-Pyridyl)propanethioate 3 was obtained in 92% yield with a 70 30 hexanes diethylether mixture as eluant. Found C, 57.39, H, 5.36, N, 8.41. C_8H_9NOS requires C, 57.46, H, 5.42, N, 8.38. ^{1}H-NMR δ 7.15-8.60 (m, 4H), 2.70 (q, 2H, J= 7.0 Hz), 1.15 (t, 3H, J= 7.0 Hz). IR ν 2980, 1695, 1560, 1415, 1080, 1010, 915, 765, 700 cm^{-1}.

S-(2-Methoxyphenyl)propanethioate 4 was obtained in 57% yield with a 90 10 hexanes diethylether mixture as eluant. Found C, 61.27, H, 6.22. $C_{10}H_{12}O_2S$ requires C, 61.20, H, 6.16. ^{1}H-NMR δ 6.85 - 7.45 (m, 4H), 3.85 (s, 3H), 2.60 (q, 2H, J= 7.3 Hz), 1.15 (t, 3H, J= 7.3 Hz). IR ν 2960, 1680, 1580, 1450, 1230, 940, 750 cm^{-1}.

S-(Pentafluorophenyl)propanethioate 5 was obtained in 79% yield with a 95 5 hexanes diethylether mixture as eluant. Found C, 42.21, H, 2.00. $C_9H_5F_5OS$ requires C,

Table 4. Relevant ^{1}H and ^{13}C-NMR data of compounds **24-34, 39, 40**.

Compound	H-C_2	H-C_3	$J_{2,3}$	C-2	C-3	$\underline{Me}$-C_2
24a	3.40	4.89	8.1	55.8	72.1	-
24b	3.48	4.91	8.6	53.4	74.7	-
25a	3.14	3.87	7.0	53.6	69.5	-
25b	3.22	3 88	7.0	52 1	71 5	-
26a	3.29	3 65	7 0	51 5	74.1	-
26b	3 36	3 67	7 5	49.6	76.3	-
27a	3 83	5 01	7.5	60.1	72 8	-
28a	3 60	3 98	6 0	58 0	70 5	-
28b	3.64	3.92	7 0	56.3	71 6	-
29a	3.73	3 70	6 0	56 0	75 2	-
29b	3.77	3 68	6 8	53 9	76 6	-
30a	3 32	4.85	8 3	56 7	72 3	-
30b	3.43	4.91	7 9	54 0	74 7	-
31a	3.03	3 83	7 0	54 7	69 6	-
31b	3 13	3.82	7 5	53 0	71 7	-
32a	-	5.18	-	57 4	73 0	16 5
32b	-	5 12	-	55 8	76 7	17 6
33a	-	3.91	-	56 5	71.1	16 1
33b	-	3 96	-	55 2	73 8	17.0
34a	-	3 87	-	56.5	74 6	15.8
34b	-	3.98	-	55.1	79.4	19.1
39a	2 97	4.10	4.0	50.6	74 8	-
39b	3.15	3.95	6.0	48.9	77 0	-
40a	3.53	3.81	8 8	50.5	74 3	-
40b	3 47	3.73	9 4	49.4	75 0	-

42.19, H, 1.97 ^{1}H-NMR δ 2 80 (q, 2H, J= 7.0 Hz), 1 20 (t, 3H, J= 7 0 Hz) IR ν 2960, 1725, 1640, 1485, 1090, 970, 920 cm^{-1}

Ethyl-(2-butylthio)propanoate 23 was prepared from ethyl-2-bromopropanoate by halogen displacement with sodium butylthiolate in EtOH at RT. The product was obtained in 84% yield as an oil by flash chromatography with a 90·10 hexanes·diethylether mixture as eluant Found C, 56.91, H, 9.56 $C_9H_{18}O_2S$ requires C, 56.80, H, 9.53. ^{1}H-NMR δ 4.30 (q, 2H, J= 7 0 Hz), 3 55 (q, 1H, J= 7 0 Hz), 2 65-2 90 (m, 2H); 1.40-1 90 (m, 4H), 1.60 (d, 3H), 1 45 (t, 3H), 0 95-1.10 (m, 3H). IR ν 2940, 1720, 1440, 1320, 1250, 1155, 1060 cm^{-1}

Aldol condensation of titanium enolates with aldehydes. General procedure.

To a cooled (-78°C) 0 1 M solution of ester (0.5-5 mmol) in dry dichloromethane, a ^{1}M solution of $TiCl_4$ in dichloromethane (1 mol equiv) was added dropwise After 2 min. stirring at -78°C, triethylamine (1 mol equiv) was added dropwise and the mixture kept a -78°C for 30 min The aldehyde (1 mol equiv) was then added and stirring was continued at -78°C for a period ranging from 2 to 12 h without relevant changes in yield and stereoselectivity. The reaction was quenched by addition of 5% aqueous $NaHCO_3$, the mixture was filtered through celite, the organic phase was separated, washed with water, dried, and concentrated to give the crude product that was analyzed by ^{1}H NMR. The product was then purified by flash chromatography with hexanes diethylether mixtures as eluant. Yields are indicated in Table 1 and 2 and in the text, relevant NMR data are collected in Tables 3 and 4

Compound 10 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 65 39, H, 7 56 $C_{13}H_{18}O_2S$ requires C, 65 61, H, 7 61 IR ν 3500, 2960, 1710, 1455, 1380, 960 cm^{-1}

Compound 15 was obtained with a 50 50 hexanes diethylether mixture as eluant Found C, 65 79, H, 5 60, N, 5 19 $C_{15}H_{15}NO_2S$ requires C, 65 91, H, 5 53, N, 5 12 IR ν 3400, 2960, 1700, 1550, 1430, 1130, 750 cm^{-1}.

Compound 16 was obtained with a 50 50 hexanes diethylether mixture as eluant Found C, 60.31, H, 7.24, N, 5.80. $C_{12}H_{17}NO_2S$ requires C, 60.22, H, 7.16, N, 5 85 IR ν 3400, 2940, 1690, 1560, 1420, 1120, 760 cm^{-1}

Compound 17 was obtained with a 50 50 hexanes diethylether mixture as eluant. Found C, 60 33, H, 7 24, H, 5 91 $C_{12}H_{17}NO_2S$ requires C, 60.22, H, 7.16, N, 5.85 IR ν 3400, 2940, 1695, 1560, 1440, 1420, 1120, 940, 760 cm^{-1}

Compound 18 was obtained with a 70 30 hexanes diethylether mixture as eluant Found C, 67 41, H, 5 97 $C_{17}H_{18}O_3S$ requires C, 67.52, H, 6 00 IR ν 3450, 2940, 1670, 1580, 1450, 1230, 950, 750 cm^{-1}.

Compound 19 was obtained with a 80 20 hexanes diethylether mixture as eluant Found C, 52 91, H, 2.96 $C_{16}H_{11}F_5O_2S$ requires C, 53.04, H, 3 06 IR ν 3400, 2940, 1680, 1560, 1450, 1310, 1240, 950, 760 cm^{-1}.

Compound 24 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 63.70, H, 7.79 $C_{15}H_{22}O_3S$ requires C, 63.80, H, 7.85. IR ν 3450, 2940, 1720, 1445, 1260, 1140, 1030, 760 cm^{-1}.

Compound 25 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 57.91, H, 9 68 $C_{12}H_{24}O_3S$ requires C, 58.03, H, 9.74. IR ν 3400, 2950, 1720, 1440, 1255, 1140, 1030, 760 cm^{-1}.

Compound 26 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 58.11; H, 9.77 $C_{12}H_{24}O_3S$ requires C, 58.03, H, 9.74. IR ν 3450, 2960, 1720, 1445, 1260, 1140, 1030, 750 cm^{-1}.

Compound 27 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found· C, 67.63, H, 5.91. $C_{17}H_{18}O_3S$ requires C, 67.52, H, 6.00. IR ν 3400, 3000, 2960, 1720, 1445, 1260, 1140, 1040, 750 cm^{-1}.

Compound 28 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 62.54, H, 7 48 $C_{14}H_{20}O_3S$ requires: C, 62 66, H, 7.51. IR ν 3400, 2940, 1720, 1450, 1260, 1130, 1030, 750 cm^{-1}.

Compound 29 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 62.71, N, 7 60 $C_{14}H_{20}O_3S$ requires C, 62.66, H, 7 51. IR ν 3400, 2960, 1720, 1450, 1255, 1140, 1030, 750 cm^{-1}.

Compound 30 was obtained with a 75 25 hexanes diethylether mixture as eluant Found C, 65.75, H, 8 54 $C_{17}H_{26}O_3S$ requires C, 65.77, H, 8.44 IR ν 3400, 3000, 2940, 1720, 1450, 1255, 1140, 1035, 760 cm^{-1}.

Compound 31 was obtained with a 75 25 hexanes diethylether mixture as eluant. Found C, 60.90, H, 10.17. $C_{14}H_{28}O_3S$ requires C, 60.83, H, 10 21. IR ν 3400, 2960, 1720, 1455, 1255, 1140, 1040, 760 cm^{-1}.

Compound 32 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 64 66, H, 8.01. $C_{16}H_{24}O_3S$ requires C, 64.83, H, 8.16 IR ν 3400, 2960, 1720, 1455, 1260, 1130, 1035, 760 cm^{-1}

Compound 33 was obtained with a 70·30 hexanes diethylether mixture as eluant Found C, 59 69, H, 10.06. $C_{13}H_{26}O_3S$ requires C, 59.50, H, 9 99 IR ν 3450, 2940, 1715, 1450, 1255, 1140, 1040, 760 cm^{-1}.

Compound 34 was obtained with a 70 30 hexanes diethylether mixture as eluant. Found C, 59.61, H,9.93 $C_{13}H_{26}O_3S$ requires C, 59 50, H, 9 99 IR ν 3400, 2940, 1720, 1450, 1240, 1100, 1035, 720 cm^{-1}.

Compound 39 was obtained with a 70 30 hexanes diethylether mixture as eluant Found C, 65.58, H, 8.55. $C_{17}H_{26}O_3S$ requires C, 65.77, H, 8.44. IR ν 3450, 2940, 1720, 1445, 1260, 1140, 1030, 760 cm^{-1}.

Compound 40 was obtained with a 65 35 hexanes diethylether mixture as eluant Found C, 63 63, H, 8.31. $C_{18}H_{28}O_4S$ requires C, 63.50, H, 8 29 IR ν 3450, 2950, 1720, 1450, 1260, 1140, 1040, 750 cm^{-1}.

Synthesis of ketals 35 and 36. General Procedure.[21]

To a stirred suspension of $LiAlH_4$ (2 mmol, 0.076 mg) in diethylether (10 ml) cooled at 0°C, a solution of aldol **27a** or **32a** (0.5 mmol) in diethylether (5 ml) was added dropwise over a 5 min period The cooling bath was removed and the mixture stirred on RT for 4 h. Usual work-up gave the crude diols in virtually quantitative yields. These were dissolved in a 50.50 mixture of acetone 2,2-dimethoxypropane (3 ml), a catalytic amount of p-toluenesulphonic acid was added and the mixture stirred overnight at RT. The products were isolated as oils by flash chromatography with a 80 20 hexanes diethylether mixture as eluant

Compound 35. Found C, 67.87, H, 8 21. $C_{15}H_{22}O_2S$ requires C, 67 63, H, 8.32 ^{1}H NMR δ 7.21-7.46 (m, 5H), 4.21 (dd, 1H, J= 2 5, 11 0 Hz), 4 13 (dt, 1H, J= 2 2, 6 0 Hz), 3.96 (dd, 1H, J= 2.3, 11.0 Hz), 3.04 (ddd, 1H, J= 2.2, 2.3, 2 5 Hz), 1 67-1.79 (m, 2H), 1.58-1.65 (m, 2H), 1.46 (s, 6H), 1 30-1.42 (m, 2H), 0.91 (t, 3H, J= 7 3 Hz).

Compound 36. Found C, 72 91, H, 9 86 $C_{17}H_{27}O_2S$ requires C, 73 06, H, 9.74 ^{1}H NMR δ 7 28-7.45 (m, 5H), 4.79 (s, 1H), 3 98 (d, 1H, J= 11 5 Hz), 3.72 (d, 1H, J= 11.5 Hz), 1 70-2 25 (m, 2H), 1.57 (s, 3H), 1 52 (s, 3H), 1.17-1 31 (m, 4H), 1 15 (s, 3H), 0 79 (t, 3H, J= 7 0 Hz).

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d not detect any self-condensation product of **3** even in reactions carried out
ylether or at higher temperatures.
reochemical assignment was based on the reasonable assumption that also in the
compounds **15-17** the CH-O proton of the syn isomers resonates at lower field
at of the anti one, and that the MeCH-CHOH coupling contant values of syn
were smaller that t of the anti products. ^{13}C-NMR chemical shift trends
ed the attribution.
case the solution becomes red-purple before addition of TEA, a colour change
ly ascribed to titanium enolate formation. However, the ^{1}H-NMR experiments
s the presence of detectable amounts of the enolate, furthermore, the TiCl$_4$/**3**
does not react with aldehydes, and TEA is required for the reaction to occur.
, we found that pyridine is not effective in generating the titanium enolate

studies on adducts of TiCl$_4$ with neutral Lewis bases see Turin, E., Nielson,
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mixture of TiCl$_4$ and TMS ketene acetal of **1** did not result in the formation of
duct of the Mukaiyama aldol condensation.
figurations could be tentatively extrapolated from those of the corresponding
tene acetals by comparison of the chemical shift values of the CH$_3$-HC=
On this basis for instance the major enolate derived from **3** should feature
CIP rules) stereochemistry
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n exist only in the Z configuration, gave exclusively the corresponding
dol in 24% yield
enosubstituted propionate esters can be enolized as well in these conditions.
tance ethyl 2-bromopropionate and methyl 2-chloropropionate were converted
eir titanium enolates and reacted with benzaldehyde to give the aldol adducts
nd 80% yield, respectively Syn isomers predominate in both cases (70 30 and
yn anti ratios, respectively) as determined by NOE experiments. Halogeno
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H$_2$ protons gave rise to two multiplets at 2.90 and 3.17 ppm
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