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ALDOL REACTION OF TRICHLOROTITANIUM ENOLATES. REVALUATION OF THE BOAT TRANSITION STATE

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Summary: The trichlorotitanium enolates generally undergo an erythro selective aldol reaction except one case which gives a threo aldol. A new form of the boat transition state has been proposed.

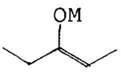
The chair transition state (TS) hypothesis has been the central dogma in aldol chemistry.[1] Here we present an example of the aldol reaction preferring a boat TS and some evidence of the general importance of this TS in the aldol reactions of common metal enolates.

The case that we now report concerns with the trichlorotitanium enolates, which are available by the reaction of enol silyl ethers with $TiCl_4$.[2,3] The enolates examined in this study represent a set of structures suitable for the examination of the TS of the aldol reaction.

The aldol reaction of the titanium enolate was generally very rapid and kinetically controlled.[4] The results are summarized in Table 1. The remarkable features of the observed stereoselectivity are: (1) The erythro selection in the cyclohexanone series, 4b—7b, (entries 5—10) and (2) the striking reversal observed for the enolate 8b (entries 11 and 12).

The conventional protocols [1] fail to offer adequate explanations to these results. The strongly electrophilic character of the $TiCl_3$ group renders the possibility of an "open" TS highly unlikely. Among cyclic TS hypotheses, the chair TS 10 (R^2 = H), in which R^1 is placed in the axial position, must be rejected as the path leading to the erythro aldol from 4b. Otherwise, the threo selection with 8b as well as the normal erythro preference with 1b becomes unreasonable. The previously proposed (parallel) boat TS 11 assumes repulsion between R^1 and R^2, and R and R^3,[1a] and therefore predicts a bad mixture of isomers from 8b and threo aldol from 4b. The present results, however, can be rationalized by considering a newly defined boat TS as the lowest energy TS and the usual chair form 9[1] as the second alternative. Given the relatively long Ti-O bond length,[1a] the tilt boat TS 12 that we consider seems reasonably free of strain. The virtue of this boat TS is its concordance to the well-established Burgi-Dinitz trajectory in the nucleophilic attack to a carbonyl group.[5]

a: M = $SiMe_3$
b: M = $TiCl_3$
c: M = BBu_2
d: M = Li



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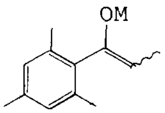
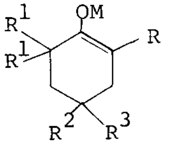
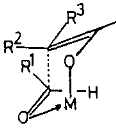


2: (Z)
3: (E)



	R	R^1	R^2	R^3
4:	H	H	H	H
5:	H	Me	H	H
6:	H	H	Me	Me
7:	H	H	t-Bu	H
8:	Me	H	H	H



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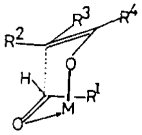

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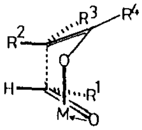

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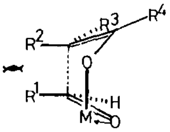

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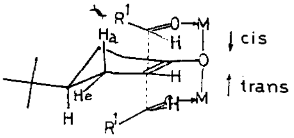

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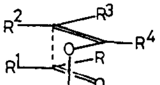

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Examine the validity of the new hypothesis first for the erythro selection of 4b (entries 5—7); the tilting disposition of the reactants in this boat TS makes the erythro-forming 12 (R^2 = H) more favorable than the alternative 13, in which steric compression between R^1 and R^2 becomes severe. Introduction of a methyl group (R^2 = Me) to the enolate raises the energy of both 12 and 13. Therefore 8b gives the threo aldol via the usual low energy chair TS 9 (entries 11 and 12). A similar situation arises with the (Z)-enolate 1b. The boat TS 12 (R^2 = Me, R^3 = H) being unavailable, 1b gives the erythro aldol via 9.

The 6,6-dimethyl group on the ring (5b) placed close to the reacting centers, slightly disfavors the erythro production, but the 4,4-dimethyl group (6b) has little effect (entries 8 and 9). The reaction of the conformationally rigid 7b (entry 10) occurs preferentially via the trans-boat TS (14-trans).[6] The cis-boat (14-cis) experiences the interaction with the C-3 pseudoaxial hydrogen (H_a), while such a strain is less obvious with 14-trans, since H_e is away from the approaching aldehyde. It is of note that the non-equivalency of H_a and H_e disappears in an acyclic system. The reaction of 2b and 3b was anomalously slow, not completing below 0 °C, and the results (entries 3 and 4) may not necessarily reflect the kinetic pathways. The present hypothesis suggests that the mesityl group with its flanking methyl groups may raise the energy of the boat TS, as appears to be the case with 5.

An important corollary to the present proposal is the fact that it accounts for the otherwise confusing behavior of the boron and the lithium enolates that we found. Our observation consists of the dramatic enhancement of the threo selectivity on passing from 4c to 8c[7] and from 4d to 8d (Table 2). These results are puzzling on the basis of the conventional chair TS, but readily understood by the tilt boat 9 as a route to the erythro (minor) aldol. The generally lower levels of the threo selection with (E)-enolates, particularly in the cyclohexanone series,[1] are therefore better accounted for by assuming the erythro-forming 12 (R^2 = H) in addition to the diastereomeric chair TS's.

The origin of the boat TS preference is presently unclear,[8], but the metal-oxygen bond length may be critical.[3] Secondary orbital interaction favoring the "endo" arrangement of the reactants may be suspected as the ultimate cause of the selectivity.

Table 1. Aldol Reaction of Trichlorotitanium Enolates

Entry	Enolate	Aldehyde	Temp °C	Time	Erythro:[a] threo	% yield[b]
1	1b	PhCHO	-70	1 min	81:19	75
2	1b	iso-PrCHO	-70	1 min	75:25[c]	63[d]
3	2b + 3b (86:14)	PhCHO	0	15 min	63:37	52
4	2b + 3b (50:50)	PhCHO	0--20	1 h	53:47	90
5	4b	PhCHO	-70	4 min	89:11	88[d]
6	4b	PhCHO	-70 20	15 min 10 min	86:14	83
7	4b	n-PrCHO	-70	5 sec	65:35	61[d]
8	5b	PhCHO	-70	5 sec	58:42	45
9	6b	PhCHO	-70	5 sec	81:19	62
10	7b	PhCHO	-70	1 min	55:45 cis 77:23 trans	15 32
11	8b	PhCHO	-70	5 sec	12:88[e]	29[f]
12	8b	n-PrCHO	-70	5 sec	10:90[e,g]	34

a:The ratio was determined by the proton NMR signals of the CHOH protons (ref 1). b:The yield (unoptimized) was determined by NMR analysis of the crude product with an internal standard, unless otherwise noted. c:Determined by capillary GLC, PEG-20M, 20 m. d:Isolated yield. e:Determined by reversed phase HPLC (water/acetonitrile) and by proton NMR. See ref 4 for the assignment. f:The reaction was slow at low temperatures; 61% yield at 26 °C, e:t = 15:85. g: The Pr(fod) induced proton NMR sift of the singlet of the 2-methyl group is a useful indicator of the diastereoselectivity. The assignment was made in analogy with the results in entry 11 above.

Table 2. Diastereoselectivity of Boron and Lithium Enolates[a]

Entry	Enolate	Aldehyde	M = BBu_2[b]		M = Li[c]	
			Erythro: threo	% yield	Erythro: threo	% yield
1	4	PhCHO	33:67	(ref 9)	48:52	(ref 10)
2	5	PhCHO			13:87	(ref 10)
3	8	PhCHO	0.5:99.5[d]	60		
4	8	n-PrCHO	3:>97[d]	31	27:73	58[d]

a: The kinetic selectivity at -70 to -78 °C. b: Performed in Et_2O. c: Performed in THF. d: See Table 1, note e.

References and Notes

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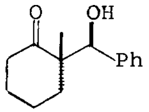
3. Other titanium enolates, apparently more nucleophilic ones, are also erythro selective. The crucial experiment with 8 has not been reported. Reetz, M. R.; Peter, R. Tetrahedron Lett. 1981, 22, 4691.
4. The reaction of 4b is representative. To a solution of $TiCl_4$ (33 µl, 0.3 mmol) in 0.5 ml of methylene chloride was added 4a at 20 °C and the deep red solution was kept at that temperature of 2 min. Chlorotrimethylsilane, a side product, was not removed since independent runs monitored by ^1H NMR had shown the inertness of this substance. The mixture diluted with 6 ml of methylene chloride was cooled to -70 °C and benzaldehyde (26 mg, 0.25 mmol) was added at once. After 4 min, 2 ml of water was added at once. Usual workup afforded 45 mg of the aldol product as a solid (89% yield, 89% erythro). The stereochemical assignment of the threo aldol (i) obtained from 8 relies on the X-ray analysis by Prof. P. L. Stotter of Texas, USA; see Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. J. Org. Chem. 1983, 48, 0000.



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6. The diastereomeric aldol adducts were separated by MPLC and individually hydrogenolized (H_2/Pd-C/EtOH/AcOH) to cis- and trans-2-benzyl-4-tert-butylcyclohexanones. Equilibration under basic conditions confirmed the cis-trans assignment of these products.
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8. The origin of the chair TS preference is not clear either (ref 1). The boat TS has already been invoked some times without detailed stereochemical description. The boat TS could be a quite common phenomenon, and the following examples represent the cases seemingly similar to the present one. (a) Ref 3. (b) Evans, D. A.; McGee, L. Tet. Lett. 1980, 3975. (c) Yanamoto, Y.; Maruyama, K. ibid. 1980, 4607. (d) Harada, T.; Mukaiyama, T. Chem. Lett. 1982, 467. (e) Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. Chem. Lett. 1982, 353. (f) Yamamoto, Y.; Yatagai, H.; Maruyama, K. J. Chem. Soc., Chem. Commun. 1881, 162.
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