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STEREOSELECTIVE ALDOL REACTIONS OF γ-THIOBUTYROLACTONE: THE BENZALDEHYDE ANOMALY.

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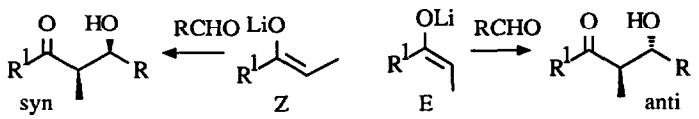
Abstract- *Different protocols (lithium enolate reactions, fluoride catalyzed and Lewis acid mediated silyl ketene acetal reactions) were studied to achieve stereoselectivity in the aldol reactions of γ-thiobutyrolactone: in all cases benzaldehyde showed a striking peculiarity compared to aliphatic aldehydes.*

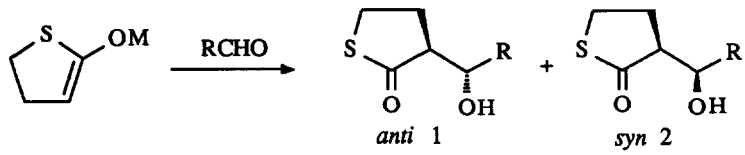
It is generally known and frequently cited that lithium Z enolates are more stereoselective (depending on the size of R^1) than E enolates.[1]



Recent reports on the stereoselectivity of the aldol reactions of lithium enolates derived from cyclic ketones with aldehydes[2,3] have questioned previous data commonly accepted: it has been shown that the low *anti-syn* ratio obtained in the condensation of cyclohexanone lithium enolate with benzaldehyde (52:48 at -72°C)[4b] is due to equilibration, and that the kinetic ratio is at least 5:1.[2a,3b] Other aldehydes are highly *anti* selective (7-100:1).[2a] Here we report that the lithium enolate derived from γ-thiobutyrolactone reacts with various aldehydes with high *anti* selectivity, except for benzaldehyde which gives a ca. 1:1 ratio (Table I). The observed ratio (56:44, entry 1) is close to the real kinetic ratio, which is estimated to be ca. 50:50. This was proved by the following experiments: (a) pure *anti* adduct 1 (R=Ph) gave only traces (1-2%) of *syn* adduct 2 (R=Ph) when treated with LDA under the same reaction conditions (-78°C, 3 min) (b) pure *syn* adduct 2 gave small amounts of *anti* 1 (10%) when treated with LDA under the same reaction conditions (c) equilibration (-20°C, 3h) favors the *anti* vs. the *syn* aldolate (entry 2, 66:34). If we believe that the results shown in Table I are nicely accomodated by the Zimmermann-Traxler chair transition state[1] **I**, it is difficult to understand why the kinetic ratio, which seems to follow roughly the steric demand of R, falls with benzaldehyde. The only reasonable explanation is that the competing boat transition state[1] **II** is stabilized when R=Ph. This behavior is not unprecedented: cyclohexanone derived enolborates are *syn* selective with aromatic aldehydes and *anti* selective with isobutyraldehyde.[5]

The results given above demonstrate once more that while Z enolates lead reliably to *syn* aldols, the stereochemical course of lithium E enolates remains unpredictable. Even minor changes in the enolate or in the

aldehyde structure (particularly the aldehyde aromatic character) change the diastereoselectivity.

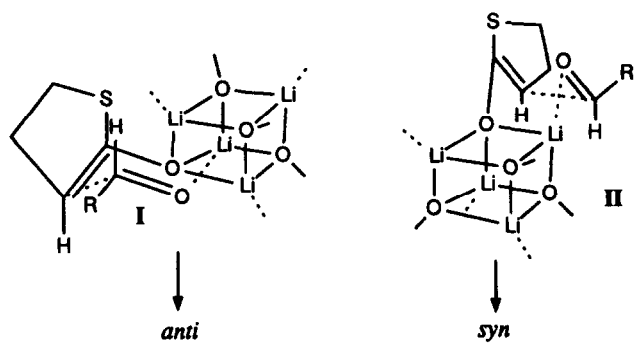


anti 1 *syn* 2

Table I

Entry	M	R	anti:syn		% yield
1	Li	Ph[a]	56	44	89
2	Li	Ph[b]	66	34	71
3	Li	iPr[a]	90	10	81
4	Li	C_6H_{11}[a]	92	8	80
5	Li	nC_6H_{13}[a]	80	20	79
6	Li	tBu[a]	95	5	70

[a]The reaction was run in THF at -78°C, adding a pre-cooled solution of the aldehyde (1 mol.equiv.) to the lithium enolate (1 mol.equiv.), prepared with 1 mol.equiv. of LDA at -78°C. The mixture was quenched after a few minutes with NH_4Cl sat. aqueous solution. [b]The reaction was warmed up to -20°C and stirred at -20°C for 3 h before quenching.



Also in the reactions of the silyl ketene acetal derived from γ-thiobutyrolactone there is a striking difference between benzaldehyde and all other aldehydes (Table II). In the reactions mediated by a catalytic amount of fluoride ion,[6] the *syn:anti* ratios follow again roughly the steric demand of R, except for benzaldehyde. The *syn* selectivity of these reactions was rationalized by Nakamura, Kuwajima and coworkers[6a] using the competing non-chelate transition structure models "extended" **III** and "skew" **IV**.

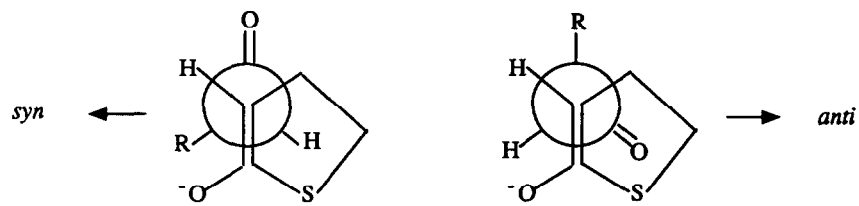
The low *syn:anti* ratio in the case of benzaldehyde (entry 1) is not a real kinetic ratio, and is due to partial equilibration. Equilibration *via* retroaldol reaction is documented (fluoride catalyzed reaction of cyclohexanone enol silyl ether with benzaldehyde),[7] and occurs with benzaldehyde even though 2.0 mol.equiv. of Me_3SiF were

used to trap the final aldolate and stop the retroaldol process. When the reaction was quenched after a few minutes, a higher *syn:anti* ratio was obtained (up to 90:10) together with a lower yield (20-30%).

Table II

Entry	M	Promoter	R	anti:syn		%yield
1	$SiMe_3$	10% Bu_4NF[a]	Ph	22	78	78
2	$SiMe_3$	10% Bu_4NF[a]	iPr	<5	>95	75
3	$SiMe_3$	10% Bu_4NF[a]	C_6H_{11}	<5	>95	79
4	$SiMe_3$	10% Bu_4NF[a]	nC_6H_{13}	13	87	72
5	$SiMe_3$	10% Bu_4NF[a]	tBu	<5	>95	70
6	$SiMe_3$	$TiCl_4PPh_3$[b]	Ph	>95	<5	77
7	$SiMe_2Bu^t$	$TiCl_4PPh_3$[b]	iPr	15	85	75

[a]The reaction was run in THF at -78°C in the presence of 0.1 mol.equiv. of Bu_4NF and 2.0 mol.equiv. of Me_3SiF. After 2 h at -78°C the mixture was quenched with Et_2O and pH 7 phosphate buffer. Then the mixture was desilylated by treatment with 0.2 M HCl in 4:1 MeOH-H_2O. [b]The reaction was run in methylene chloride at -78°C by adding 1 mol.equiv. of aldehyde to 1 mol.equiv. of $TiCl_4$-PPh_3 complex (preformed at room temperature). Then 1.5 mol.equiv. of silyl ketene acetal was added at -78°C and the mixture was quenched after 1.5 h.



On the contrary, the $TiCl_4$-PPh_3 variant of the Mukaiyama aldol reaction[6b,8] is known to give good *anti:syn* ratios only with unsaturated and aromatic aldehydes. In fact the *anti:syn* ratio with benzaldehyde is excellent (entry 6), compared to the reaction mediated by $TiCl_4$(74:26) or other Lewis acids (BF_3OEt_2 75:25; $SnCl_4$ 60:40; $MgBr_2$ 50:50; ZnI_2 57:43).

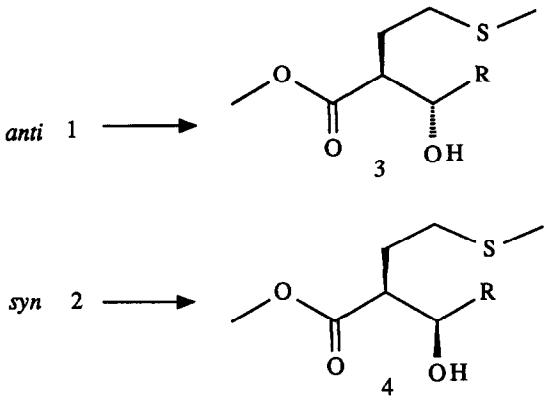
With aliphatic aldehydes (e.g. isobutyraldehyde) the same reaction gave a very low yield (20-30%) of a 80:20 *syn:anti* mixture. The yield was improved by the use of the t-butyldimethylsilyl ketene acetal, while the ratio remained similar (85:15, entry 7). Other Lewis acids were also *syn* selective (e.g. BF_3OEt_2 72:28).

The importance of the aromatic groups in the Lewis acid ($TiCl_4$) mediated aldol reactions of silyl ketene acetals was recently addressed,[9] but a good rationale is still missing.

All the isolated *anti* and *syn* diastereoisomers were separately converted in ≥ 90% yield and without detectable epimerization to methylesters 3 and 4, by treatment with MeONa (2 mol.equiv.) and MeI (3 mol.equiv.) in methanol at -20°C.[10]

In this way a stereoselective entry towards these acyclic compounds was developed based on cyclic enolate stereoselection. Methylesters 3 and 4 are interesting compounds because of the presence of the methylthio group,

which can be easily transformed into other functional groups or direct other stereoselective reactions.[11]



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(10) All new compounds were fully characterized by elemental analysis (C,H), IR, capillary VPC, ^{1}H NMR. Ratios were determined on the crude reaction mixtures by capillary VPC and ^{1}H NMR, integrating the typical C<u>H</u>OH signals.[12] *Anti* 1, δ C<u>H</u>OD(ppm), mult., J(Hz) : R=Ph 4.81,d,J=8.97; R=iPr 3.63,dd,J=9.0,3.0; R=C_6H_{11} 3.57,dd,J=6.7,1.9; R=nC_6H_{13} 3.78,m,J=7.80 (from decoupling experiments); R=tBu 3.40,d,J=5.5. *Syn* 2, δ C<u>H</u>OD(ppm), mult., J(Hz) : R=Ph 5.38,d,J=2.7; R=iPr 3.77,dd,J=9.0,3.5; R=C_6H_{11} 3.81,dd,J=9.0,2.2; R=nC_6H_{13} 4.15,m,J=2.5 (from decoupling experiments); R=tBu 3.97,d,J=1.0.

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