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HIGH DIASTEREOSELECTIVITY IN LEWIS ACID MEDIATED ALDOL CONDENSATIONS USING THIOESTER SILYL KETENE ACETALS.

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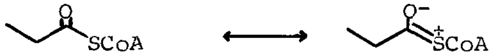
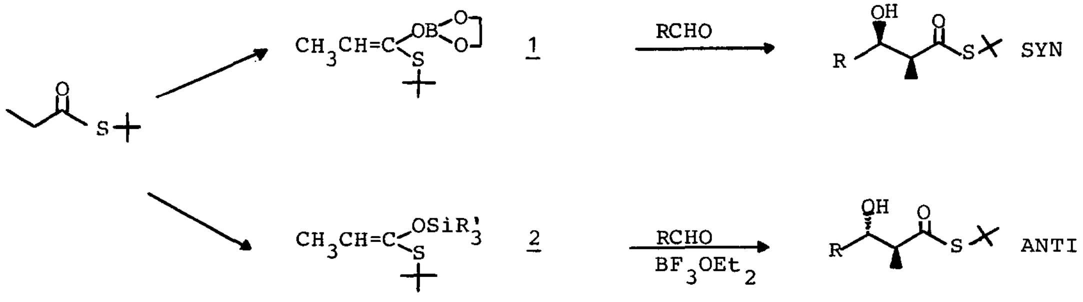
SUMMARY: BF_3OEt_2 mediated aldol condensations of thioester silyl ketene acetals are stereoconvergent, and exhibit high internal (anti) and relative (Cram) diastereoselectivity.

Thioesters have attracted the interest of organic chemists since the discovery that they are used by Nature in enzymatic acylation processes. The relative weakness of the overlapping of the C(2p) and S(3p) orbitals in carbon-sulfur double bond $C=\overset{+}{S}-R$, when compared with $C=\overset{+}{O}-R$, makes the contribution to the stability of thioesters of the resonance form depicted below much less important than in the corresponding esters. 

As a result, the α-hydrogen acidity is enhanced, and processes like enolate formation and Claisen condensation are favored.[1] Synthetic chemists have used thioester enolates in the aldol condensation to biomimetically synthesize complex natural products.[2] We have recently shown that alkenyloxy dialkoxy boranes 1 derived from thioesters are stereoconvergent: both Z and E enolates react with aldehydes to give syn aldol condensation products with excellent selectivity.[3] (Table, entries 1,5,9,11,13,15,17).

Here we report that thioester silyl ketene acetals 2 react with aldehydes in the presence of BF_3OEt_2 to give anti aldol condensation products with good yield and selectivity.

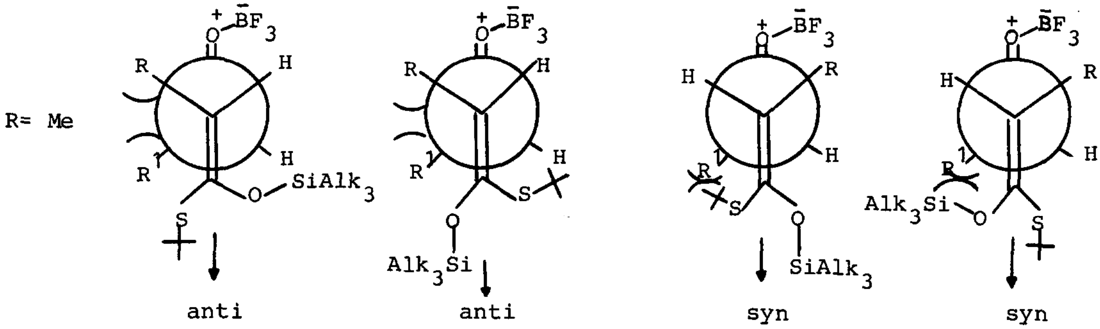


Unlike the corresponding ester silyl ketene acetals, which show complete lack or low levels of stereoselectivity, depending on the starting double bond geometry,[4] the thioester analogs are stereoconvergent: they give anti aldols independent of the starting geometry of the double bond.

Tert-butyl thiopropionate[5] was enolized to give either the kinetic (LDA, -78°C,THF)[6] or the thermodynamic enolate (LDA,-78°C, THF-HMPA).[7] The kinetic enolate was then trapped using $Me_2tBuSiOTf$ to give the pure Z compound 3 (Z-E > 95:5), while the thermodynamic enolate was trapped with $Me_2tBuSiCl$ to give the pure E compound 4 (E-Z > 95:5).

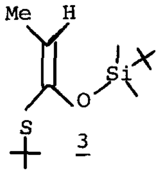
As both the E and Z compounds gave almost identical results (Table; entries 2,3; 6,7), the more practical silyl ether 5, obtained as a 9:1 Z-E mixture trapping the kinetic enolate with Me_3SiCl, could also be used.

The observed anti preference independent of the silyl ether geometry of this BF_3OEt_2[8] catalyzed condensation is in accord with an acyclic extended transition state.



The gauche steric repulsion between R and R^1, which disfavours the transition states leading to the anti isomer in related models,[9] is here overwhelmed by the significant steric repulsion between $-R^1$ and -tBu or $-R^1$ and $-SiAlk_3$, suffered by the transition states leading to the syn isomer.[10,12]

As the BF_3-mediated enolsilane additions to chiral aldehydes are highly diastereoface-selective[11], this method offers good opportunities of selectively generating three stereocenters with a single reaction, as shown in the Table, entry 18 (anti-syn = 13:1 ; Cram-antiCram= 50:1). Further work in this area is in progress.



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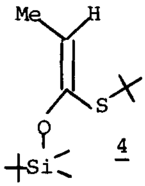

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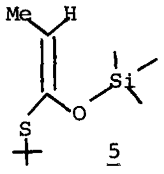

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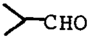
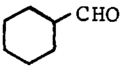
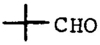
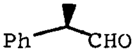
TABLE

Entry	Reagent	Aldehyde	% Yield[a]	Anti-syn ratio
1	$\underline{1}$[b]	PhCHO	72	1:25[e]
2	$\underline{3}/BF_3OEt_2$[c]		95	21:1[e]
3	$\underline{4}/BF_3OEt_2$[c]		93	26:1[e]
4	$\underline{5}/BF_3OEt_2$[c]		96	19:1[e]
5	$\underline{1}$[b]	n-C_5H_{11}CHO	70	1:30[f]
6	$\underline{3}/BF_3OEt_2$[d]		90	8:1 [f]
7	$\underline{4}/BF_3OEt_2$[d]		92	7:1 [f]
8	$\underline{5}/BF_3OEt_2$[d]		95	11:1[f]
9	$\underline{1}$[b]		66	1:46[f]
10	$\underline{4}/BF_3OEt_2$[d]		93	10:1[f]
11	$\underline{1}$[b]		68	1:35[f]
12	$\underline{5}/BF_3OEt_2$[d]		95	10:1[f]
13	$\underline{1}$[b]		58	1:20[f]
14	$\underline{4}/BF_3OEt_2$[d]		15[h]	8:1 [f]
15	$\underline{1}$[b]		70	1:30[e]
16	$\underline{4}/BF_3OEt_2$[d]		85	13:1[e]
17	$\underline{1}$[b]		68	1:52 (C/AC 12:1)[g]
18	$\underline{4}/BF_3OEt_2$[d]		75	13:1 (C/AC 50:1)[g]

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[a] Isolated yield. Compounds were purified by flash-chromatography.

[b] Reagent $\underline{1}$ was obtained using ethylenechloroboronate (ECB) and diisopropyl ethylamine (DPEA) as described in ref.3. To 2.0 mol.equiv. of reagent $\underline{1}$ in CH_2Cl_2 at -78°C, the aldehyde (1.0 mol.equiv.) was added dropwise. The reaction was slowly warmed up to 0°C, then quenched and worked-up as usual.

[c] To a mixture of 1.0 mol.equiv. of aldehyde and 1.0 mol.equiv. of BF_3OEt_2 in CH_2Cl_2 at -78°C, the silyl ether (1.5 mol.equiv.) was added dropwise. After 30 min at -78°C, the reaction was quenched with pH 7 phosphate buffer and worked-up as usual.

[d] To a mixture of 1.0 mol.equiv. of aldehyde and 1.5 mol.equiv. of silylether, in CH_2Cl_2 at -78°C, BF_3OEt_2 (1.0 mol.equiv.) was added dropwise. After 30 min at -78°C, the reaction was quenched with pH 7 phosphate buffer and worked-up as usual. This procedure must be followed with enolizable aldehydes.

[e] Ratio determined on the crude reaction mixtures by ^1H NMR and by HPLC.

[f] Ratio determined on the crude reaction mixtures by ^1H NMR and by capillary VPC.

[g] Ratio determined as reported in ref.3(b).

[h] The reaction was warmed up to -10, and stirred 2 HR at -10°C before quenching.

NOTES AND REFERENCES

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2 D.A. Evans, J.V. Nelson, E.Vogel, T.R. Taber, J.Am.Chem.Soc.,103,3099(1981), and references therein; M.Hirama, S. Masamune, Tetrahedron Letters, 2225 (1979); M. Hirama, D.S. Garvey, L.D.-L.Lu, S.Masamune, Tetrahedron Letters, 3937(1979); D.A.Evans, J.V.Nelson, T.R.Taber,Top.Stereochem., 13,1(1982), and references therein; S.Masamune, Pure and applied Chemistry, 197 (1981), and references therein.

3 (a) C. Gennari, L.Colombo, S. Cardani, C. Scolastico, Tetrahedron Letters, 2283 (1984); (b) C. Gennari, A. Bernardi, S. Cardani, C. Scolastico, Tetrahedron , in press.

4 C.H. Heathcock, in Asymmetric Synthesis, Vol.3, Part B, ed. by J.D. Morrison, Academic Press, 1984, p.136-144, and references therein.

5 Tert-butyl thiopropionate was synthesized from propionyl chloride and tert-butylthiol in CH$_2$Cl$_2$-pyridine (b.p. 46°C/ 16 mmHg).
T-Butyl proved to be better than other alkyl groups or phenyl in promoting high ratios in both the syn- and the anti-selective reactions described here.

6 D.A. Evans, L.R. McGee, Tetrahedron Letters, 3975(1980).

7 R.E. Ireland, R.H. Mueller, A.K.Willard, J.Am.Chem.Soc.,98, 2868(1976).

8 BF$_3$OEt$_2$ proved to be better than other Lewis acids, including TiCl$_4$, BCl$_3$, SnCl$_4$, ethylenechloroboronate (ECB) in promoting high anti-syn ratios.

9 R. Noyori, I. Nishida, J. Sakata, J.Am.Chem.Soc.,105,1598(1983); ibid., 103, 2106(1981).

10 For a discussion on the possible transition states of Lewis acid mediated aldol condensations, see J.E. Dubois, G.Axiotis, E. Bertounesque, Tetrahedron Letters, 4655(1984), and references therein. An inversion from the anti to the syn preference was reported when bulky substituents (R=tBu) were used in the silyl ether moiety. This is nicely explained by our model : the gauche steric repulsion between R and R^1 becomes determining. In our reaction, it is interesting to observe that using pivalaldehyde (R= Me; R^1=tBu) the reaction product was obtained in very low yield (Table, entry 14). According to our model, both the transition states leading to the syn and to the anti isomers are disfavoured by the bulkiness of R^1, and the reaction is likely to become sluggish.
For the conformational analysis of silyl ketene acetals, see C.S.Wilkox, R.E. Babston, J.Org.Chem., 49, 1451(1984).

11 C.H. Heathcock, L.A. Flippin, J.Am.Chem.Soc., 105, 1667(1983); M.T. Reetz, K.Kesseler, J.C.S.Chem.Commun.,1079 (1984); M.T. Reetz, Angew. Chem. Int.Ed. Engl., 23, 556(1984), and references therein.

12 For a similar acyclic extended transition state see also J.T. Welch, K.W. Seper, Tetrahedron Letters, 5247 (1984).

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