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STEREOSELECTIVE ALDOL ADDITIONS TO α-ALKOXY ALDEHYDES USING THIOESTER SILYL KETENE ACETALS.

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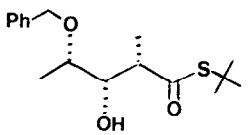
Abstract: Relative stereochemistry (chelation) effectively controls internal stereochemistry (syn-anti) in the addition of thiopropionate equivalents to O-benzyl lactic aldehyde.

Thioesters offer relevant synthetic opportunities to organic chemists. They can be easily transformed to acids, aldehydes, alcohols, esters, ketones under mild conditions and in high yield. Besides, they are more similar electronically to ketones than esters.[1] This aspect is particularly important as it permits the extension to thioesters of the selectivity shown by ketone enolsilylethers and enolates.[2,3] Moreover, thioester silyl ketene acetals, due to their "pinwheel" conformational bias,[4] can be modulated by changing the steric bulkyness of the -SR or of the O-SiR^1_3 groups, which are irrelevant to the synthetic target. We recently took advantage of these principles to develop a new stereoconvergent, BF_3OEt_2 mediated aldol condensation process, which exhibits high internal (anti) and relative (Cram) diastereoselectivity.[2a]

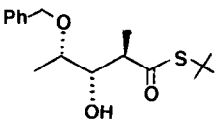
Here we report that thioester silyl ketene acetals are useful intermediates in the stereoselective aldol additions to α-alkoxy aldehydes.

$SnCl_4$ Mediated aldol additions of thioester silyl ketene acetals to achiral aliphatic aldehydes are only slightly anti-selective (see, for example, Table 2, entries 1,2). On the contrary the additions to O-benzyl lactic aldehyde are highly selective: no Felkin product was obtained, and the syn-anti ratio was up to 30:1 (Table 1). A reversal of the internal selectivity (from anti to syn) determined by the relative selectivity (chelation control) had already been observed for ketone enolsilylethers.[5]



1

SYN-CHELATED



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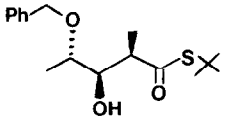
ANTI-CHELATED



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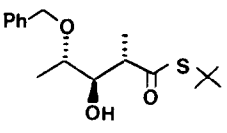
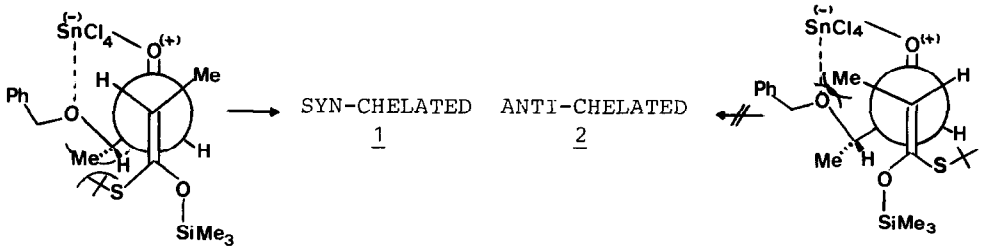
SYN-FELKIN



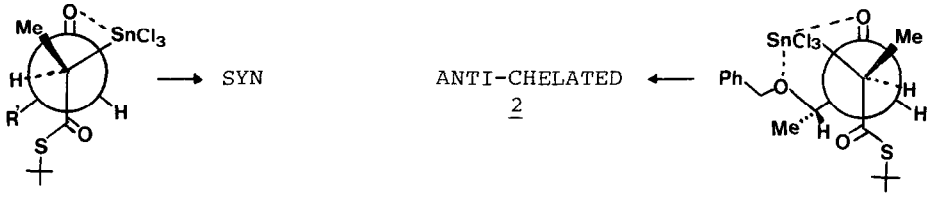
4

ANTI-FELKIN

In terms of the proposed acyclic extended transition state, the gauche steric repulsion between Me and the aldehyde residue, which is usually overwhelmed by the steric repulsion between S-tBu and the aldehyde residue, here becomes determining because of the conformational changes forced by the Lewis acid (chelation control).

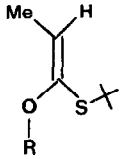


By treating trimethylsilyl ketene acetals (5,6) with $SnCl_4$ in CH_2Cl_2 at -78°C for 1 hr, the α-trichlorostannylthioester 7 was obtained in high yield.[6] This stannylthioester reacted with regular aliphatic aldehydes to give the syn adduct with excellent selectivity (72:1, see Table 2-entry 3). On the contrary the addition to O-benzyl lactic aldehyde gave the anti-chelated product 2 as the major isomer (9:1, see Table 1-entry 5).[7]

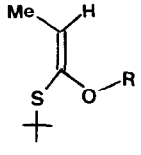


Again relative stereochemistry (chelation) effectively controls internal stereochemistry. Selectively synthesizing the Felkin-type compounds 3 and 4 is more problematic: some success was obtained using a fluoride induced reaction to obtain the syn-Felkin adduct 3 (Table 1-entries 6,7).[8]

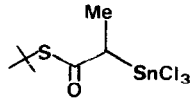
More work in this area (additions to α-methyl-β-alkoxy-, β-methyl-β-alkoxy-, α,β-dialkoxy-aldehydes) and mechanistic details will be reported in a full paper.[9]



5 R= $SiMe_3$
8 R= $SiMe_2tBu$



6 R= $SiMe_3$
9 R= $SiMe_2tBu$



7

TABLE 1. Additions to (S)-(+)-O-benzyl lactic aldehyde.[a]

Entry	Reagent	% Yield[b]	Ratios[c] (%)			
1	5/$SnCl_4$[d,g]	90	1 (95)	2 (5)		
2	6/$SnCl_4$[d,g]	87	1 (85)	2 (15)		
3	8/$SnCl_4$[d]	89	1 (97)	2 (3)		
4	9/$SnCl_4$[d]	90	1 (76)	2 (24)		
5	7[e]	75	1 (10)	2 (90)		
6	5/Bu_4NF[f]	72	1 (16)	2 (3)	3 (73)	4 (8)
7	6/Bu_4NF[f]	68	1 (13)	2 (3)	3 (72)	4 (12)

a Prepared from (S)-(+)-Ethyl lactate according to the following references: K.Mislow, e.a., J.Am.Chem.Soc., 84,1940(1962); C.H.Heathcock, e.a., J.Org. Chem.,46, 2298(1981).
b Isolated yields. Compounds were purified by flash chromatography.
c Ratios determined on the crude reaction mixtures by capillary VPC. The isomers were identified as described in ref. 2(b).
d $SnCl_4$ (1.0 mol.eq.) was added to the aldehyde (1.0 mol.eq.) in CH_2Cl_2 at -78°. After 2 min, the silyl ether (1.5 mol.eq.) was added. After 30 min at -78°C, the mixture was quenched and worked-up as usual.
e $SnCl_4$ (1.5 mol.eq.) was added to the silyl ether 5 or 6 (1.5 mol.eq.) in CH_2Cl_2 at -78°C. After 1 hr the aldehyde (1.0 mol.eq.) was added. The mixture was slowly warmed up to -20°C, quenched and worked-up as usual.
f To a solution of the aldehyde (1.0 mol.eq.) and silyl ether (1.5 mol.eq.) in THF at -78°C, nBu_4NF (0.06 mol.eq.) was added. After 20 min at -78°C, the mixture was quenched and worked-up as usual.
g Almost the same result (slightly worse ratio) was obtained in this case using $TiCl_4$ instead of $SnCl_4$.

TABLE 2. Comparison data. Additions to achiral aldehydes.

Entry	Reagent	Aldehyde	% Yield	Syn-anti ratio
1	5/$SnCl_4$[a]	Me_2CHCHO	86	1 : 1.4
2	6/$SnCl_4$[a]	Me_2CHCHO	80	1 : 1.4
3	7[b]	Me_2CHCHO	45	72 : 1
4	5/Bu_4NF[c]	PhCHO	91	18 : 1
5	6/Bu_4NF[c]	PhCHO	42	1.3: 1

a To a mixture of aldehyde (1.0 mol.eq.) and silyl ether (1.5 mol.eq.) in CH_2Cl_2 at -78°C, $SnCl_4$ (1.0 mol.eq.) was added. After 20 min at -78° the mixture was quenched and worked-up as usual.
b $SnCl_4$ (1.0 mol.eq.) was added to the silyl ether 5 or 6 (1.0 mol.eq.) in CH_2Cl_2 at -78°C. After 1 hr the aldehyde (1.0 mol.eq.) was added. The mixture was slowly warmed up to 0°C, quenched and worked-up as usual.
c see footnote f, Table 1.

NOTES AND REFERENCES

1. M.W. Cronyn, M.Pin Chang, R.A. Wall, J.Amer.Chem.Soc.,77, 3031 (1955), and references therein.

2.(a) C. Gennari, A. Bernardi, S. Cardani, C. Scolastico, Tetrahedron Letters, in press; (b) Tetrahedron, 40, 4059 (1984) ;(c) C. Gennari, L. Colombo, S. Cardani, C. Scolastico, Tetrahedron Letters, 2283 (1984).

3. C.H. Heathcock, in Asymmetric Synthesis, Vol.3, part B, ed. by J.D. Morrison Academic Press, 1984, p.111-212, and references therein.

4. C.S. Wilkox, R.E. Babston, J.Org.Chem.,49, 1451(1984).

5. M.T. Reetz, Angew.Chem.Int.Ed.Engl., 23, 556(1984), and references therein; M.T. Reetz, K. Kesseler, A. Jung, Tetrahedron, 40, 4327(1984).

6. Following the transformation by ^{1}H-NMR (CD_2Cl_2, -50°C), the vinyl proton of both 5 (5.12, q) and 6 (5.16, q) disappeared with the clean formation of 7 (4.48,q, J=7.81 Hz). For references to α -trichlorostannyl ketones see: E. Nakamura, I. Kuwajima, Chem.Letters, 59(1983); Tetrahedron Letters, 3347 (1983). The chemical shift of the methyne proton is incompatible with a trichlorostannyl enolate structure.

7. Comment on the transition state models for the α-trichlorostannyl thioester: the carbon-tin bond cleavage has been hypothesized to occur with retention of stereochemistry.

8. E. Nakamura, M. Shimizu, J. Kuwajima, J. Sakata, K. Yokoyama, R. Noyori, J.Org.Chem.,48, 932 (1983); M.T. Reetz, K. Kesseler, J.C.S. Chem. Commun., 1079 (1984).

9. For recent progress in this area, see: C.H. Heathcock, S. Kiyooka, T.A. Blumenkopf, J.Org.Chem., 49, 4214 (1984); K. Head, T.L. Macdonald, J.Org.Chem., 50, 422 (1985); C.H. Heathcock, K.T. Hug, L.A. Flippin, Tetrahedron Letters, 5973 (1984).

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