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# Diastereoselective Addition of a Silylketene Acetal to Chiral α-Thioaldehydes.

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Abstract. Chiral α-thioaldehydes **2-6** undergo chelation or non-chelation controlled addition of silylketene acetal **1**, depending on the nature of the Lewis acid catalyst and of the ligands at the stereocenter.

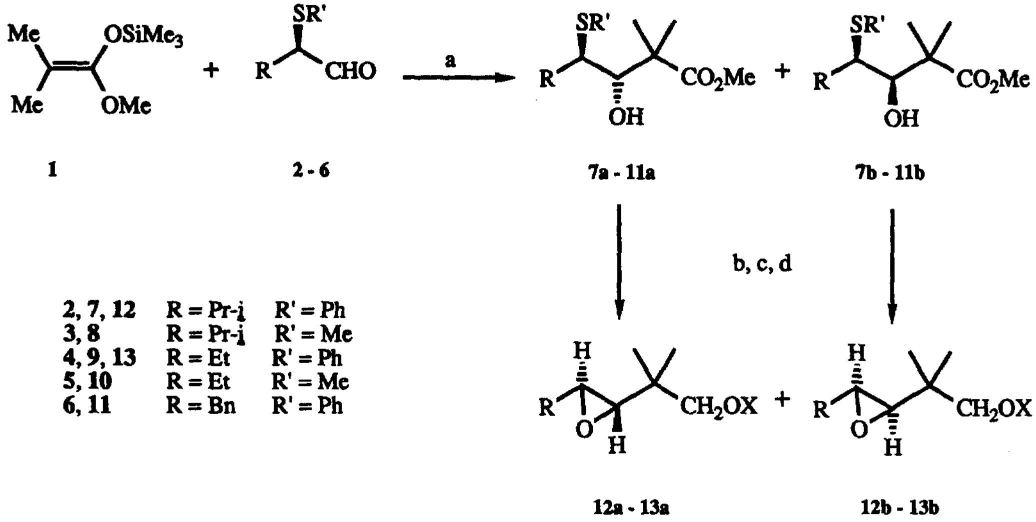
Lewis acid (L.a.) promoted addition of silyl enolethers and silylketene acetals to aldehydes represents an efficient alternative to the classic aldol condensation.[1] This methodology can give high diastereofacial selectivity in the addition to chiral aldehydes.[2] When the aldehyde features a heterosubstituted ligand at the stereocenter two scenarios are possible: a highly stereoselective process arising from the combination of a chelating L.a. with a ligand prone to chelation, or a discretely stereocontrolled addition resulting from the use of non-chelating ligand and/or L.a.[3] Most of the data reported so far were obtained with aldehydes bearing oxygen or nitrogen containing ligands;[2] we here report the first study on the diastereoselective addition of a non stereogenic silylketene acetal, **1**, to chiral, racemic α-thioaldehydes[4,5] **2-6** (Scheme).[6]

A survey of various catalysts was carried out reacting **1** and **2** to give **7a,b** (Table 1). Diastereoisomeric excesses (d.e.) were evaluated by 300 MHz $^1$H-NMR spectroscopy on the crude products and confirmed by separating the isomers by flash chromatography.[7] Structural assignment resided on chemical correlation of pure **7a** and **7b** to the corresponding epoxides as described in the Scheme: from **7a** trans-epoxide **12a** (J = 2.5 Hz), and from **7b** cis-epoxide **12b** (J = 4.5 Hz) were obtained, respectively.

As can be seen from the reported data the use of $SnCl_4$, $EtAlCl_2$, and $BF_3.Et_2O$ led exclusively to anti product **7a**, while with $MgBr_2$ and $TiCl_4$ syn isomer **7b** was obtained in good excess. To get a better understanding of the stereochemical outcome of this reaction we investigated the addition of **1** to α-thioaldehydes **3-6** (featuring different R and R' groups) in the presence of selected L.a. to give **8a,b-11a,b** (Scheme). The results were collected in Table 2. As for the case of **7a,b**, 300 MHz $^1$H-NMR spectroscopy, isomer separation,[6] and conversion to epoxides **12a,b-13a,b** allowed d.e. determination and structural assignment.

By examining the data of the Tables the following conclusions can be drawn:

## Scheme

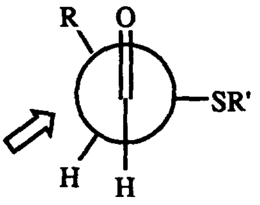


| | | |
|---|---|---|
| **2, 7, 12** | R = Pr-i | R' = Ph |
| **3, 8** | R = Pr-i | R' = Me |
| **4, 9, 13** | R = Et | R' = Ph |
| **5, 10** | R = Et | R' = Me |
| **6, 11** | R = Bn | R' = Ph |

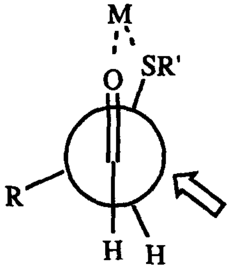
X = $SiPh_2Bu$-t

Reagents: a: see Tables 1 and 2. b: $LiAlH_4$, $Et_2O$, RT. c: t-$BuPh_2SiCl$, Imidazole, DMF, RT.
d: $Me_3OBF_4$, $CH_2Cl_2$, RT; then 1N NaOH, RT.

For all compounds only one enantiomer is shown for simplicity.



**14**



**15**

**Table 1.** Diastereoselective synthesis of **7a,b** by addition of **1** to **2.**[a]

| Entry | L.a. | Temperature,°C | Yield %[b] | **7a:7b**[c] |
|---|---|---|---|---|
| 1 | $MgBr_2$[d] | -40 | 81 | 13:87 |
| 2 | $TiCl_4$ | -78 | 86 | 20:80 |
| 3 | $ZnI_2$[e] | 25 | 60 | 45:55 |
| 4 | $SnCl_4$ | -78 | 78 | $\geqslant$98: 2 |
| 5 | $EtAlCl_2$ | -78 | 50 | $\geqslant$98: 2 |
| 6 | $BF_3.Et_2O$ | -78 | 87 | $\geqslant$98: 2 |
| 7 | TBAF[f] | -78 | 30 | 75:25 |

[a] Unless otherwise stated all reactions were carried out on 0.5-1.0 mmol scale in 5-10 ml of $CH_2Cl_2$ with a 1:1:1.5 **2**:L.a.:**1** ratio for 2-4 h. Entries 1, 3, 7 required HCl/MeOH work-up. [b] Isolated yields after chromatography. [c] Determined as described in the text. [d] Used as 1M solution in $Et_2O$/benzene. [e] 0.05 mol equiv in $CH_3CN$. [f] 1.1 mol equiv in THF.

**Table 2.** Diastereoselective synthesis of **8a,b-11a,b** by addition of **1** to **3-6.**[a]

| Entry | Aldehyde | L.a. | Product | Yield % | **a:b** |
|---|---|---|---|---|---|
| 1 | **3** | $MgBr_2$ | **8a,b** | 61 | 10:90 |
| 2 | **3** | $TiCl_4$ | **8a,b** | 76 | 7:93 |
| 3 | **3** | $SnCl_4$ | **8a,b** | 84 | 48:52 |
| 4 | **3** | $BF_3.Et_2O$ | **8a,b** | 90 | $\geqslant$98: 2 |
| 5 | **4** | $MgBr_2$ | **9a,b** | 70 | 73:27 |
| 6 | **4** | $TiCl_4$ | **9a,b** | 65 | 70:30 |
| 7 | **4** | $SnCl_4$ | **9a,b** | 83 | $\geqslant$98: 2 |
| 8 | **4** | $BF_3.Et_2O$ | **9a,b** | 71 | $\geqslant$98: 2 |
| 9 | **5** | $MgBr_2$ | **10a,b** | 70 | 69:31 |
| 10 | **5** | $TiCl_4$ | **10a,b** | 83 | 11:89 |
| 11 | **5** | $SnCl_4$ | **10a,b** | 91 | 50:50 |
| 12 | **5** | $BF_3.Et_2O$ | **10a,b** | 72 | $\geqslant$98: 2 |
| 13 | **6** | $MgBr_2$ | **11a,b** | 80 | 50:50 |
| 14 | **6** | $TiCl_4$ | **11a,b** | 80 | 76:24 |
| 15 | **6** | $SnCl_4$ | **11a,b** | 82 | $\geqslant$98: 2 |
| 16 | **6** | $BF_3.Et_2O$ | **11a,b** | 72 | $\geqslant$98: 2 |

[a] For experimental conditions, yields and d.e. determinations see Table 1 and text.

1) Non-chelating $BF_3.Et_2O$ secures complete anti selectivity independently from the bulkiness of both R and R' groups.
2) $SnCl_4$ acts as a non-chelating catalyst when R' = Ph, but leads to stereorandom reaction when R' = Me: in this case the less sterically requiring Me group allows some chelation at sulfur, and attack on both diastereofaces is possible.
3) Good chelation control (and appreciable excess of syn products) is obtained only with chelating L.a., small R' group, and large R group.

On this basis we propose the two transition structures depicted in the Scheme. 1 as tentative rationals for this reaction. Felkin-Anh[8] t.s. **14** accounts for the formation of anti products, while Cram's cyclic[9] t.s. **15** should be at work when chelation is possible. Work is in progress to confirm this proposal, to extend this reaction to stereogenic silylketene acetals, and to evaluate the potentialities of α-thioaldehydes in other L.a. catalyzed reactions.[10]

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## References and Notes.

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5) For other stereoselective reactions of α-thioaldehydes see: M. Shimagaki, H. Takuso, T. Oishi, Tetrahedron Lett., 6235, 1985;M. Shimagaki, T. Maeda, Y. Matsuzaki, I. Hori, T. Nakata, T. Oishi, Tetrahedron Lett., 4775, 1984; V.A. Aggarwal, I. Coldham, S. McIntyre, F.H. Sasbury, M.J. Villa, S. Warren, Tetrahedron Lett., 4885, 1988; I. Coldham, E.W. Collington, P. Hallett, S. Warren, Tetrahedron Lett., 5321, 1988.
6) All new compounds gave analytical and spectral data in agreement with the proposed structure.
7) Syn products were always eluted first than anti ones (9:1 hexanes:diethylether mixture as eluant ; $\Delta r_f \geqslant 0.3$, silica gel).
8) N.T. Anh, Top. Curr. Chem., **88**, 145, 1980; for the "large" role of an alkylthio group see: S.V. Frye, E.L. Eliel, J. Am. Chem. Soc., **110**, 484, 1988; F. Bernardi, A. Bottoni, A. Venturini, A. Mangini, J. Am. Chem. Soc., **108**, 8171, 1986; H.J. Reich, R.C. Holtan, C. Bolm, J. Am. Chem. Soc., **112**, 5609, 1990.
9) E.L. Eliel, Asymmetric Synthesis, J.D. Morrison, Ed.; Wiley, vol. 2, p. 125, 1985.
10) $BF_3.Et_2O$ catalyzed Hetero Diels-Alder cycloaddition of Danishefsky's diene to **5** followed by TFA work-up gave a highly (d.e. = 96:4) stereoselective reaction.

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