Stereocontrol in the Mukaiyama Aldol Addition to Chiral α- and β-Thio-Substituted Aldehydes

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A series of racemic α-thio-, β-thio-, and α-methyl-β-thio-substituted aldehydes has been prepared, and their Lewis acid promoted aldol condensation with nonstereogenic and stereogenic silylketene acetals and silyl enolethers has been studied. With α-thio-substituted aldehydes, a high level of non-chelation-controlled diastereofacial selectivity can be easily achieved, while chelation control requires a strongly chelating catalyst *and* a small, aliphatic S-protecting group. Some examples of addition of stereogenic nucleophiles occurring with efficient diastereofacial syn simple stereoselection are also reported. The reactions of β-thio-substituted aldehydes are less stereoselective, in particular when the stereocenter is in the β-position. Models of stereoselection are presented to rationalize the results that were compared with those obtained in similar reactions with chiral alkoxy aldehydes.

The Lewis acid (LA) promoted addition of silyl enol ethers and silylketene acetals[1] to chiral aldehydes generally occurs with good diastereofacial selection.[2] In the case of nonheterosubstituted aldehydes,[2,3] syn products are obtained with a diastereoselectivity generally higher than that observed for the corresponding metal enolate addition.[4] When a heteroatom-containing substituent is present at the stereocenter of the aldehyde, the nature of the LA and of the heteroatom protecting group dictates the stereochemical course of the reaction:[2,5,6] nonchelating LA and/or chelation-preventing protecting groups lead to anti products, as predicted by the Felkin–Anh model.[7] When chelation is possible, syn products are obtained via Cram's cyclic transition states.[4]

A great deal of data[2,5] have been collected for the Mukaiyama aldol condensation with chiral alkoxy and amino aldehydes, and protecting groups that allow or prevent chelation have been identified for both heteroatoms.[8,9] Surprisingly, the LA-catalyzed aldol addition to thio-substituted chiral aldehydes[10,11] and ketones[12] has not been investigated, notwithstanding the great number of biologically relevant compounds that feature sulfur-containing groups and the wide range of synthetic opportunites offered by manipulation of thio-substituted functional groups.[13]

Scheme I

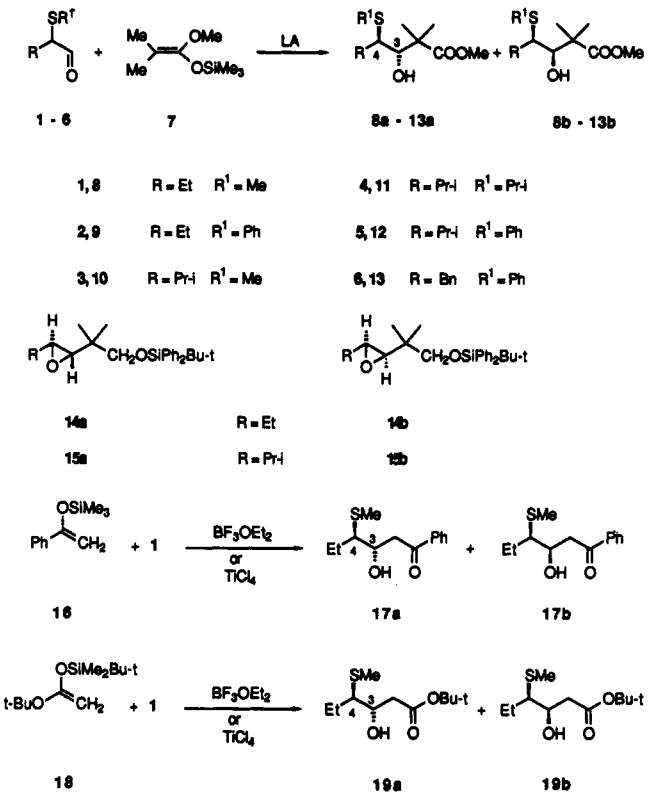

Table I. Diastereoselective Synthesis of Aldol 12a,b by Addition of Silylketene Acetal 7 to Aldehyde 5

Lewis acid	T, °C	yield,[a] %	12a:12b[b]
$BF_3{\cdot}OEt_2$	−78	87	>98:2
$EtAlCl_2$	−78	50	>98:2
$SnCl_4$	−78	78	>98:2
ZnI_2[c]	25	60	45:55
$TiCl_4$	−78	86	20:80
$MgBr_2$	−40	81	13:87

[a] Isolated yields. [b] As determined on the crude products. [c] 0.05 mol equiv of catalyst in acetonitrile as solvent.

(1) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

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(3) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

(4) (a) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Wiley: New York, 1985; Vol. 2, p 125. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.

(5) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(6) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327.

(7) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(8) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 613 and references therein.

(9) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103 and references therein.

(10) For other stereoselective additions to chiral thiosubstituted aldehydes see: (a) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, 4775. (b) Shimagaki, M.; Takubo, H.; Oishi, T. *Tetrahedron Lett.* **1985**, 6235. (c) Aggarwal, V. K.; Warren, S. *Tetrahedron Lett.* **1987**, 1925. (d) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, 1461. (e) Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Sansbury, F. H.; Villa, M.-J.; Warren, S. *Tetrahedron Lett.* **1988**, 4885. (f) Coldham, I.; Collington, E. W.; Hallett, P.; Warren, S. *Tetrahedron Lett.* **1988**, 5321. (g) McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, 3457. (h) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116.

(11) The LA-promoted addition of silylated carbon nucleophiles to α-sulfeny acetals has been recently reported: Saigo, K.; Kudo, K.; Hashimoto, Y.; Kimoto, H.; Hasegawa, M. *Chem. Lett.* **1990**, 941.

(12) For stereoselective additions to chiral thiosubstituted ketones see: (a) Shimagaki, M.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, 4779. (b) Carreno, C. M.; Dominguez, E.; Garcia-Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619. (c) Brown, M. D.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 817. (d) Konosu, T.; Takeda, N.; Tajima, Y.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 1258. (e) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609.

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Table II. Diastereoselective Synthesis of Aldols 8a,b–11a,b and 13a,b from Aldehydes 1–4, and 6 and Silylketene Acetal 7

aldehyde	Lewis acid	product	yield, %	diastereoisomeric ratio a:b
1	BF_3·OEt_2	8a,b	72	>98:2
1	$SnCl_4$	8a,b	91	50:50
1	$TiCl_4$	8a,b	83	11:89
1	$MgBr_2$	8a,b	79	69:31
2	BF_3·OEt_2	9a,b	71	>98:2
2	$SnCl_4$	9a,b	83	>98:2
2	$TiCl_4$	9a,b	65	70:30
2	$MgBr_2$	9a,b	70	73:27
3	BF_3·OEt_2	10a,b	90	>98:2
3	$SnCl_4$	10a,b	84	48:52
3	$TiCl_4$	10a,b	76	7:93
3	$MgBr_2$	10a,b	61	10:90
4	BF_3·OEt_2	11a,b	90	>98:2
4	$SnCl_4$	11a,b	77	50:50
4	$TiCl_4$	11a,b	78	22:78
6	BF_3·OEt_2	13a,b	72	>98:2
6	$SnCl_4$	13a,b	82	>98:2
6	$TiCl_4$	13a,b	80	76:24
6	$MgBr_2$	13a,b	80	50:50

We report here a study on the diastereoselectivity of the addition of silylated carbon nucleophiles to chiral α- and β-thiosubstituted aldehydes that shows the potentialities of the sulfur-containing group as element of stereocontrol.

Addition to α-Thio-Substituted Aldehydes.[14] α-Thio-substituted aldehydes 1–6 (Scheme I) were prepared according to Ugi's method[15] that was found to be of wider applicability than other syntheses.[16] They were reacted at low temperature with nonstereogenic silylketene acetal 7 in CH_2Cl_2 to give aldols **8a,b–13a,b**. Proper reaction conditions were established by condensing **5** with **7** to give **12a,b** in the presence of various LA catalysts. The results are collected in Table I. Diastereoisomeric ratios were determined by 300-MHz ^1H NMR spectroscopy on the crude products. These were purified by flash chromatography, and diastereoisomer separation confirmed the NMR evaluation. Assignment of stereochemistry was based on the conversion of **12a** and **12b** to the corresponding epoxides **14a** and **14b**, respectively,[17] easily distinguishable from the value of the epoxide coupling constant (*trans*-epoxide: J = 2.5 Hz; *cis*-epoxide: J = 4.5 Hz).[19]

As can be seen from the reported data, the sense of diastereoselectivity can be changed by simply changing the nature of the LA promoter. Anti diastereoisomer **12a** could be obtained as the only product by the use of BF_3·OEt_2, $EtAlCl_2$, or $SnCl_4$, while $TiCl_4$ and $MgBr_2$ gave a good (but lower) excess of the syn product **12b**. On the basis of chemical yields and diastereoselections, BF_3·OEt_2, $SnCl_4$, $MgBr_2$, and $TiCl_4$ were selected as representative catalysts and employed in the reaction of **7** with aldehydes 1–4 and

Scheme II

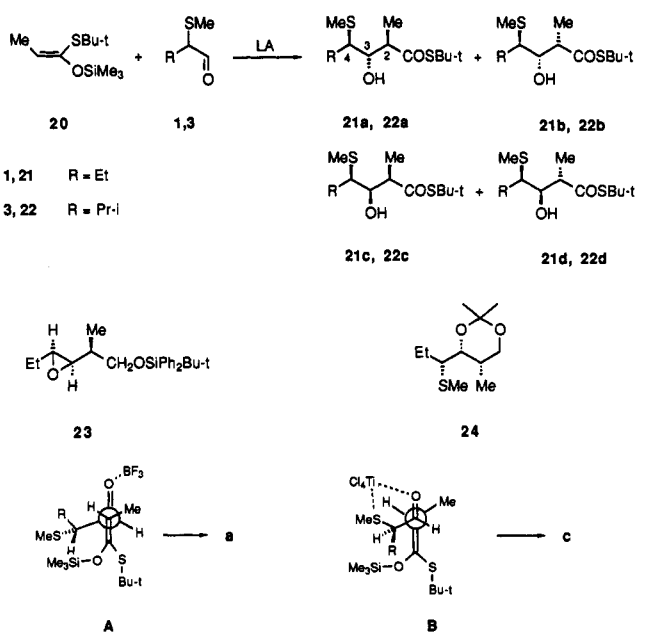


Table III. Diastereoselective Synthesis of Aldols 21 and 22 from Silylketene Acetal 20 and Aldehydes 1 and 3

aldehyde	Lewis acid	product	yield, %	diastereoisomeric ratio a:b:c:d
1	BF_3·OEt_2	21	83	91:9:0:0
1	$TiCl_4$	21	81	0:0:100:0
3	BF_3·OEt_2	22	78	88:5:0:7
3	$TiCl_4$	22	72	0:0:95:5

6 featuring R and R^1 groups of different steric and electronic nature. The results are collected in Table II. Also in this case conversion to epoxides **14a,b** and **15a,b** was used to confirm the structural assignment.[20] A few trends can be pointed out by examining the reported results. Whatever the nature of the R and R^1 groups, non-chelation-controlled anti products can be prepared in excellent yield and diastereoselection by the use of nonchelating BF_3·OEt_2. Chelation-controlled syn-configurated isomers are more difficult to obtain: they require the combination of a chelating LA such as $TiCl_4$ with a relatively large R group (Pr-i better than Et or $PhCH_2$) *and* a R^1 sulfur protecting group that must be small and/or not able to delocalize the sulfur lone pairs (Me better than Pr-i or Ph). $SnCl_4$ catalyst affords a good excess of anti-configurated products only with SPh-substituted aldehydes. This catalyst seems less prone to chelation than $TiCl_4$ in these reactions, and the presence of a Ph group at sulfur prevents chelation both sterically and stereoelectronically. Indeed, in the case of aldehyde 4 (R = R^1 = Pr-i), that features a sulfur substituent as bulky as a Ph, a stereorandom reaction was observed with $SnCl_4$. The possibility that the SPh group is a more "electronegative" ligand[7] than SPr-i, and therefore leads to more anti- selective reactions, can also contribute to the stereochemical result. Other nonstereogenic silylated carbon nucleophiles were tested with aldehyde **1** (Scheme I). Acetophenone trimethylsilyl enol ether **16** gave exclusively anti aldol **17a** in the presence of BF_3·OEt_2, while the syn isomer **17b** was largely predominant (**17a:17b** = 17:83) with $TiCl_4$ as LA catalyst.

(14) A preliminar account of part of this work has been published: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *Tetrahedron Lett.* **1990**, 6733.

(15) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159. This method opens access to optically active compounds as well.

(16) (a) Seebach, D.; Teschner, M. *Chem. Ber.* **1976**, *109*, 1601. (b) Matteson, D. S.; Ray, R. *J. Org. Chem.* **1982**, *47*, 2479. (c) de Groot, A.; Jansen, B. J. M. *Synthesis* **1985**, 434. (d) Kojima, K.; Koyama, K.; Ameniya, S. *Tetrahedron* **1985**, *41*, 4449. (e) Aggarwal, V. K.; Warren, S. *Tetrahedron Lett.* **1986**, 101. (f) Otera, J. *Synthesis* **1988**, 95.

(17) Reduction of the methyl ester to the alcohol and protection with a bulky silylating agent before epoxide ring closure secured best yields in this transformation.[18]

(18) Guanti, G.; Banfi, L.; Narisano, E.; Thea, S. *Chem. Lett.* **1988**, 1683.

(19) A number of configurational assignments of diastereoisomeric α-thio-substituted alcohols based on epoxide ring formation have been reported. For recent examples see refs 10h and 18.

(20) Chromatography elution orders and chemical shift and coupling constant trend consideration strongly suggest the configuration of the products that were not correlated to compounds of known stereochemistry.

Table IV. Diastereoselective Synthesis of Aldols 30a,b–33a,b by Addition of Silylketene Acetal 7 to Aldehydes 25–28

aldehyde	Lewis acid	product	yield, %	diastereoisomeric ratio a:b
25	$BF_3{\cdot}OEt_2$	**29a,b**	80	62:38
25	$SnCl_4$	**29a,b**	53	55:45
25	$TiCl_4$	**29a,b**	65	78:22
26	$BF_3{\cdot}OEt_2$	**30a,b**	89	53:47
26	$TiCl_4$	**30a,b**	92	55:45
27	$BF_3{\cdot}OEt_2$	**31a,b**	76	54:46
27	$TiCl_4$	**31a,b**	63	77:23
28	$TiCl_4$	**32a,b**	58	80:20

tert-Butyldimethylsilylketene acetals **18** reacted with **1** to give only *anti*-**19a** with $BF_3{\cdot}OEt_2$ and a poor excess of **19a** over **19b** (57:43) in the $TiCl_4$-catalyzed reaction. Thus, it is clear that while the above-mentioned general trends still hold true, there is some dependence of the stereoselection on the nucleophile structure that seems more difficult to explain. Standard Felkin–Anh[7] and Cram cyclic[4] models can rationalize the formation of anti and syn products, respectively. The well-recognized tendency[12e,21] of an alkyl- or arylthio group to play the role of the "large" ligand in the Felkin–Anh transition structure accounts for the high anti selectivity observed.

The condensation between stereogenic silylketene acetal **20**[20a] and aldehydes **1** and **3** to give aldols **21** and **22** under $BF_3{\cdot}OEt_2$ and $TiCl_4$ catalysis was then examined (Scheme II and Table III). In both cases the four possible diastereoisomeric products have been prepared via the lithium enolate of (*tert*-butylthio)propionate (the precursor of **20**) to be sure that all the products could be recognized, if present, by the NMR analysis. The configuration of product **21c** was unambigously established by converting it into epoxide **23** (see above), that showed an epoxide *J* value of 4.5 Hz and a cis configuration at C-3/C-4, and into acetonide **24**, for which the Me*CHCHO* coupling constant of 2.3 Hz indicated a syn arrangement at C-2/C-3.[23] The reported data point out that the high diastereofacial preference observed for the condensation of nonstereogenic nucleophiles with **1** and **3** is maintained with both catalysts. Simple diastereoselection is also very good and favors C-2/C-3 anti products with $BF_3{\cdot}OEt_2$ and C-2/C-3 syn products with $TiCl_4$.[24] These results could be rationalized on the basis of the staggered transition structures A and B proposed by Heathcock and Gennari[2,22] for the Mukaiyama aldol process in general, and for the addition of **20** to chiral chelatable aldehydes in particular. A useful comparison can be made between the $BF_3{\cdot}OEt_2$-mediated additions of **20** to **1** and to 2-(benzyloxy)propanal.[22a] The latter reaction gave all the four possible isomers, the C-2/C-3-anti-C-3/C-4-anti product accounting for 60% of the total yield. This is again a clear indication that the SR^1 group of α-thiosubstituted aldehyde is indeed an excellent "large" group in the Felkin–Anh model.[7]

Table V. Diastereoselective Synthesis of Aldols 35a,b, 36a,b, and 37 from Aldehyde 34 and Silyl Derivatives 7, 16, and 20

Lewis acid	product	yield, %	diastereoisomeric ratio a:b
$BF_3{\cdot}OEt_2$	**35a,b**	72	71:29
$TiCl_4$	**35a,b**	69	2:>98
$BF_3{\cdot}OEt_2$	**36a,b**	77	70:30
$TiCl_4$	**36a,b**	78	17:83
$TiCl_4$	**37**	75	*a*

[a] A single isomeric product was obtained (see text).

Table VI. Relevant ^1H and ^{13}C NMR Data of Aldols 8a,b–13a,b, 17a,b, and 19a,b (See Scheme I for Numbering)

compd	H-C3	H-C4	$J_{3,4}$	C-3	C-4
8a	3.87	2.37	5.0	78.1	51.2
8b	3.55	2.42	2.5	79.0	51.6
9a	3.91	3.10	3.0	78.4	54.9
9b	3.73	3.08	3.0	78.0	54.9
10a	3.89	2.38	7.6	77.1	58.8
10b	3.62	2.42	2.5	77.8	58.4
11a	3.91	2.63	5.3	79.2	54.8
11b	3.62	2.69	4.1	75.8	55.7
12a	3.98	3.15	6.2	78.4	59.6
12b	3.79	3.21	3.0	76.4	59.5
13a	3.99	3.42	3.1	78.8	55.3
13b	3.56	3.39	1.0	77.5	54.5
17a	4.32	2.62	5.8	69.8	54.7
17b	4.38	2.53	4.6	69.5	54.9
19a	4.07	2.40	4.8	69.8	55.0
19b	4.06	2.48	4.5	70.0	51.1

Table VII. Relevant ^1H and ^{13}C NMR Data of Aldols 21a–c and 22a–d (See Scheme II for Numbering)

compd	H-C2	H-C3	H-C4	$J_{2,3}$	$J_{3,4}$	C-2	C-3	C-4
21a	3.04	3.70	2.48	5.8	5.8	49.9	74.5	53.2
21b	3.04	3.85	2.45	5.8	5.8	50.6	72.7	52.1
21c	2.83	3.83	2.48	6.0	6.0	52.0	73.7	54.2
22a	3.50	3.30	2.40	4.6	4.6	49.3	75.7	60.5
22b	3.23	3.86	2.31	4.0	4.2	50.0	72.3	58.4
22c	2.81	3.90	2.42	7.0	4.6	52.7	73.9	61.4
22d	2.96	3.93	2.33	6.6	4.5	53.0	74.6	59.3

Addition to β-Thio-Substituted Aldehydes. β-Thio-substituted aldehydes **25–28** (Scheme III) were prepared by addition of R^1SH to the corresponding unsaturated aldehydes. Their reaction with nonstereogenic **7** was investigated and found to occur with poor diastereoselectivity (Table IV) to give aldols **29a,b–32a,b.** As usual, diastereisomeric ratios were evaluated by 300-MHz ^1H NMR spectroscopy on the crude products and confirmed, when possible, by isomer separation. The stereochemical assignment was established in the case of compound **32a** that gave, upon hydrolysis of the thioester function and reaction with benzaldehyde, emithioketal **33**, the structure of which was determined by NOE experiments. Moreover, **32a** was correlated to **29a** by hydrolysis/S-alkylation, thus showing that these products share the same anti stereochemistry at the stereocenters.[20] On making some comments about the results of Table IV, it must be stressed that both $BF_3{\cdot}OEt_2$ and $TiCl_4$ reactions afforded anti products as major isomers. $TiCl_4$ secured slightly better diastereoselectivity than $BF_3{\cdot}OEt_2$. Although the proposal of a model to explain these low stereoselections can be an exercise in speculation, the hypothesis can be made that anti products are formed through the chelated transition structure C with $TiCl_4$ as catalyst[25] and through the acyclic

(21) (a) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484. (b) Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* **1986**, *108*, 8171. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Fuchicello, A. *Tetrahedron* **1991**, *47*, 3853.

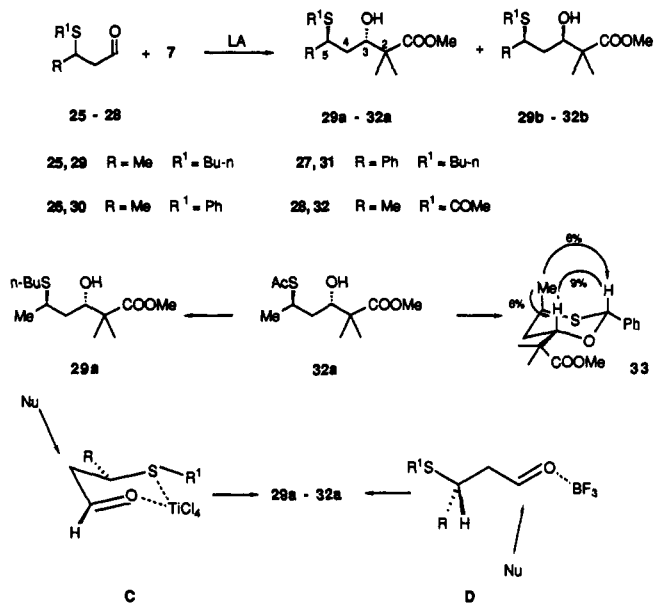
(22) (a) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893. (b) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.

(23) (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753. (b) Sugano, Y.; Naruto, S. *Chem. Pharm. Bull.* **1988**, *36*, 4619; (c) *Ibid.* **1989**, *37*, 840.

(24) Good diastereoselection can be obtained also with other silyl derivatives. For instance, the reaction of **1** with *tert*-butyldimethylsilylketene acetal of ethyl propionate under $TiCl_4$ catalysis gave the products corresponding to **21c** and **21d** in 95:5 ratio and 56% yield; condensation of the trimethylsilyl enol ether of propiophenone with **1** promoted by $TiCl_4$ gave (70% yield) the four possible isomers among which the C-2/C-3-syn-C-3/C-4-syn- product was largely predominant (94%).

(25) A chelate complex between a β-alkoxy aldehyde and $TiCl_4$ has been observed: Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

Scheme III



Scheme IV

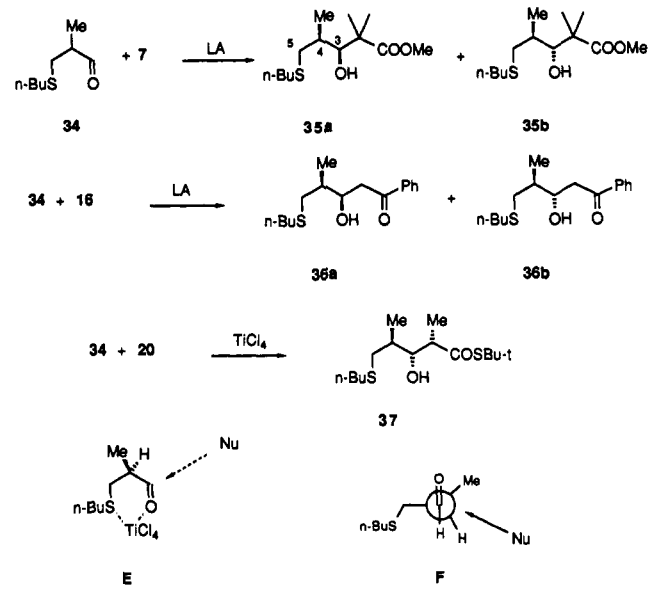


Table VIII. Relevant ^1H and ^{13}C NMR Data of Aldols 29a,b–32a,b, 35a,b, 36a,b, and 37 (See Schemes III and IV for Numbering)

compd	H-C3	H-C5	C-3	C-4	C-5
29a	3.96	2.98	73.9	38.5	37.4
29b	3.73	2.94	74.6	38.9	37.4
30a	4.07	3.49	73.9	38.4	40.9
30b	3.76	3.48	74.0	38.4	39.6
31a	3.75	4.09	74.3	39.2	46.9
31b	3.30	4.08	74.1	38.4	46.4
32a	3.71	3.78	77.3	38.8	37.0
32b	3.70	3.76	77.5	38.8	36.4

	H-C3	H-C4	Me-C4	$J_{3,4}$	C-3	C-4	Me-4
35a	3.66	1.87	0.83	2.0	78.5	34.7	13.0
35b	3.60	1.90	1.04	6.0	80.2	36.0	18.0
36a	4.36	1.79	1.05	3.5	69.4	38.4	14.0
36b	4.12	1.89	1.05	6.7	70.9	38.6	15.8
37	3.73	1.77	0.95	8.4	74.9	36.3	15.7

conformation D (adopted to minimize steric repulsion) with BF_3·OEt_2. The chelation hypothesis seems to be supported by the lower degree of stereoselection observed when R^1 = Ph (see above) as in compound **30a,b**. Obviously, if one disregards chelation in this case, transition state D (with $TiCl_4$ replacing BF_3·OEt_2) can also be at work with this catalyst. Only a few examples of Mukaiyama aldol reactions on a β-alkoxy aldehyde featuring a β-stereocenter have been reported.[2,6,26] They were shown to proceed in a highly diastereoselective fashion through a six-membered chelate[25] with $TiCl_4$ and via a "chelation-simulating" acyclic transition state[26] similar to the one here proposed with gaseous BF_3. Whatever the origins of the diastereoselectivity of these reactions could be, the stereocenter seems too far away from the carbonyl to promote a highly diastereofacial differentiating process.

α-Methyl-β-thio aldehyde **34** was therefore prepared and reacted with silyl derivatives **7**, **16**, and **20** in the usual conditions (Scheme IV and Table V) to give **35a,b**, **36a,b**, and **37**. The reported data clearly showed poor syn selectivity for the BF_3·OEt_2-mediated reactions, while $TiCl_4$ led to more stereoselective processes affording anti-configurated products. Remarkably, addition of **20** under $TiCl_4$ catalysis gave the C-2/C-3-syn-C-3/C-4-anti isomer **37** as the only product.[27] Models E and F can be tentatively used to account for the observed stereochemical outcome. A number of similar highly diastereoselective reactions on α-methyl-β-alkoxy aldehydes[2,6,22,26] have been rationalized[25] by an identical explanation. With nonchelating catalyst as BF_3·OEt_2 the diastereofacial selection merely depends on the difference in steric bulk between the ligands at the stereocenter: since the CH_2SBu-n group is comparable in size to a methyl, the BF_3·OEt_2-catalyzed reaction necessarily occurs with low syn diastereoselectivity. Similar reasoning was used to rationalize BF_3·OEt_2-promoted addition of **7** and other nonstereogenic silylated nucleophiles to 3-(benzyloxy)-2-methylpropanal that showed a moderate preference for syn-configurated products.[2,22,28]

Conclusion

In conclusion, we have shown that a thio-substituted stereocenter in α- or β-position on a chiral aldehyde can be exploited to promote good levels of diastereofacial control in the Mukaiyama aldol addition of silylated carbon nucleophiles. A comparison between our results and those obtained in related reactions with chiral alkoxyaldehydes indicates that a thiosubstituted group at the stereocenter gives rise to more selective nonchelation and less selective chelation-controlled processes with respect to an alkoxy substituent. The extension of these findings to other addition reactions to thio-substituted aldehydes is currently underway in our laboratories.

Experimental Section

^1H and ^{13}C NMR spectra were obtained on a 80- or a 300-MHz instrument in $CDCl_3$ as solvent. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent. All reactions employing dry solvents were run under argon. THF and Et_2O were distilled from $LiAlH_4$, CH_2Cl_2 and Et_3N from CaH_2, benzene from Na, CH_3CN from P_2O_5; dry solvents were stored over molecular sieves under argon.

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$TiCl_4$, $SnCl_4$, $EtAlCl_2$ were used as commercially available 1 M solution in CH_2Cl_2; BF_3·OEt_2 was distilled before use an used neat; $MgBr_2$ was employed as a 1 M solution in Et_2O–benzene.

Aldehydes **1**,[29] **2**,[30] **3**,[15] **5**,[15] **6**,[16b] **25**,[31] **26**,[32] and **34**[33] were known compounds. Silyl derivatives **16**,[6] **18**,[6] and **20**[22a] were prepared according to literature procedures.

3-Methyl-2-[(1-methylethyl)thio]butanal (4), prepared according to Ugi et al.,[15] was a pale yellow oil, bp 90 °C (2 mmHg): ^1H NMR δ 9.20 (d, 1 H, J = 5.7 Hz), 2.86 (dd, 1 H, J = 5.7, 9.0 Hz), 2.51–3.15 (m, 1 H), 0.90–1.31 (m, 13 H); IR 1718 cm^{-1}. Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06. Found: C, 60.07; H, 9.96.

3-(Butylthio)benzenepropanal (27) was a yellow oil prepared in 72% yield by thiol addition to cinnamaldehyde[32] and purified by flash chromatography with a 80:20 hexanes/Et_2O mixture as eluant: ^1H NMR δ 9.63 (t, 1 H, J = 2.0 Hz), 7.08–7.47 (m, 5 H), 4.31 (t, 1 H, J = 7.2 Hz), 2.95 (dd, 2 H, J = 2.0, 7.3 Hz), 2.15–2.50 (m, 2 H), 1.05–1.65 (m, 4 H), 0.90 (m, 3 H); IR 1729 cm^{-1}. Anal. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.06; H, 8.27.

3-(*S*-Acetylmercapto)butanal (28) was an orange oil prepared in 54% yield by thiolacetic acid addition to crotonaldehyde and purified by flash chromatography with 80:20 hexanes/Et_2O mixture as eluant: ^1H NMR δ 9.70 (t, 1 H, J = 1.5 Hz), 3.95–4.05 (m, 1 H), 2.60–2.85 (m, 2 H), 2.31 (s, 3 H), 1.36 (d, 3 H, J = 7.0 Hz); IR 1729, 1690 cm^{-1}. Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89. Found: C, 49.50; H, 7.00.

General Procedure for the Aldol Addition. To a stirred 0.1 M solution of aldehyde (0.5–2.0 mmol) in CH_2Cl_2 cooled at −78 °C was added the LA (1.0 molar equiv) dropwise over a 2-min period. After 10 min of stirring at −78 °C, the nucleophile was added very slowly (5 to 10 min) and the mixture stirred for 1 h at −78 °C (−40 °C for $MgBr_2$-catalyzed reactions). The reaction was quenched by phosphate buffer addition at −78 °C, and the mixture was warmed to rt and filtered (if necessary) through a Celite cake. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2, and the combined organic extracts were dried, concentrated, and analyzed by NMR. The products were purified by flash chromatography with hexanes/Et_2O mixtures as eluants. For each compound, physical status and eluting mixture are reported in brackets after the structure number. Yields, diastereoisomeric ratios, and relvant NMR data are collected in the tables.

2,2-Dimethyl-3-hydroxy-4-(methylthio)hexanoic acid methyl ester (8a,b) [oil, 60:40]: IR 3550, 2940, 1735, 1140 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15. Found: C, 54.35; H, 9.27.

2,2-Dimethyl-3-hydroxy-4-(phenylthio)hexanoic acid methyl ester (9a,b) [oil, 60:40]: IR 3550, 2940, 1735, 1140 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_3S$: C, 63.34; H, 8.50. Found: C, 63.58; H, 8.63.

2,2,5-Trimethyl-3-hydroxy-4-(methylthio)hexanoic acid methyl ester (10a,b) [oil, 60:40]: IR 3500, 2950, 1737, 1140 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_3S$: C, 56.37; H, 9.46. Found: C, 56.49; H, 9.58.

2,2,5-Trimethyl-3-hydroxy-4-[(1-methylethyl)thio]hexanoic acid methyl ester (11a,b) [oil, 60:40]: IR 3500, 2950, 1740, 1140 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_3S$: C, 59.50; H, 9.99. Found: C, 59.71; H, 10.10.

2,2,5-Trimethyl-3-hydroxy-4-(phenylthio)hexanoic acid methyl ester (12a,b) [oil, 60:40]: IR 3500, 2940, 1740, 1140 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 64.63; H, 8.30.

2,2-Dimethyl-3-hydroxy-4-(phenylthio)-5-phenylpentanoic acid methyl ester (13a,b) [low melting material, 70:30]: IR 3400, 2940, 1740, 1140 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 7.02. Found: C, 69.87; H, 6.91.

3-Hydroxy-4-(methylthio)-1-phenylhexan-1-one (17a,b) [oil, 55:45]: IR 3450, 2950, 1690, 1220 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.79; H, 7.77.

3-Hydroxy-4-(methylthio)hexanoic acid 1,1-dimethylethyl ester (19a,b) [oil, 60:40]: IR 3500, 2940, 1730, 1140 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_3S$: C, 56.38; H, 9.46. Found: C, 56.52; H, 9.40.

2-Methyl-3-hydroxy-4-(methylthio)hexanoic acid *S*-(1,1-dimethylethyl)thio ester (21a–c) [oil, 75:25]: IR 3480, 2940, 1700, 960 cm^{-1}. Anal. Calcd for $C_{12}H_{24}O_2S_2$: C, 54.50; H, 9.15. Found: C, 54.25; H, 9.25.

2,5-Dimethyl-3-hydroxy-4-(methylthio)hexanoic acid *S*-(1,1-dimethylethyl)thio ester (22a–d) [oil, 75:25]: IR 3400, 2940, 1695, 970 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_2S_2$: C, 56.07; H, 9.41. Found: C, 55.91; H, 9.50.

2,2-Dimethyl-3-hydroxy-5-(butylthio)hexanoic acid methyl ester (29a,b) [oil, 60:40]: IR 3450, 2940, 1740, 1140 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_3S$: C, 59.50; H, 9.99. Found: C, 59.37; H, 10.11.

2,2-Dimethyl-3-hydroxy-5-(phenylthio)hexanoic acid methyl ester (30a,b) [waxeous material, 60:40]: IR 3520, 2960, 1732, 1135 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.86. Found: C, 63.60; H, 7.71.

2,2-Dimethyl-3-hydroxy-5-(butylthio)-5-phenylpentanoic acid methyl ester (31a,b) [low melting material, 60:40]: IR 3500, 2940, 1740, 1140 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_3S$: C, 66.63; H, 8.70. Found: C, 66.88; H, 8.81.

2,2-Dimethyl-3-hydroxy-5-(*S*-mercaptoacetyl)hexanoic acid methyl ester (32a,b) [oil, 50:50]: IR 3500, 2940, 1740, 1695, 1140, 970 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.06; H, 8.31.

2,2,4-Trimethyl-3-hydroxy-5-(butylthio)pentanoic acid methyl ester (35a,b) [oil, 60:40]: IR 3500, 2940, 1735, 1140 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_3S$: C, 59.50; H, 9.99. Found: C, 59.68; H, 10.12.

3-Hydroxy-4-methyl-5-(butylthio)-1-phenylpentan-1-one (36a,b) [oil, 60:40]: IR 3400, 2950, 1680, 1050 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63. Found: C, 68.68; H, 8.75.

2,4-Dimethyl-3-hydroxy-5-(butylthio)pentanoic acid *S*-(1,1-dimethylethyl)thio ester (37) [low melting material, 70:30]: IR 3400, 2940, 1695, 970 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_2S_2$: C, 58.78; H, 9.86. Found: C, 58.70; H, 9.71.

General Procedure for the Synthesis of Epoxides 14a,b, 15a,b, and 23. These compounds have been prepared in three steps from the corresponding esters.[18] $LiAlH_4$ reduction in Et_2O gave the alcohols in virtually quantitative yield. These were not purified, but directly subjected to protection of the primary hydroxyl group with *tert*-butyldimethyl chlorosilane (DMF, imidazole, rt, overnight).

The silyl derivatives were purified by flash chromatography with 90:10 hexanes/Et_2O mixture as eluant to give the products in 73–87% yield. A 1 M solution of these compounds in CH_2Cl_2 was treated with a 3-fold excess of trimethyloxonium tetrafluoroborate (rt, 20 h) and then with an equal volume of 1 N aqueous solution of NaOH. After stirring the two-phase mixture at rt for 6–10 h, water and CH_2Cl_2 were added, and the organic phase was separated, washed with water, dried, and evaporated to give the crude products that were purified by flash chromatography with a 60:40 hexanes/Et_2O mixture as eluant. Epoxides **14a** and **14b** were oils. Anal. Calcd for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.08; H, 9.11. Relevant ^1H NMR data of **14a**: δ 2.88 (dt, 1 H, J = 2.4, 6.0 Hz), 2.75 (d, 1 H, J = 2.4 Hz), 1.01 (s, 6 H). Of 14b: δ 2.95 (d, 1 H, J = 4.7 Hz), 2.82 (dt, 1 H, J = 4.7, 6.1 Hz), 1.06 (s, 6 H). Epoxides **15a** and **15b** were oils. Anal. Calcd for $C_{25}H_{36}O_2Si$: C, 75.70; H, 9.15. Found: C, 75.49; H, 9.08. Relevant ^1H NMR data of **15a**: δ 2.80 (d, 1 H, J = 2.5 Hz), 2.66 (dd, 1 H, J = 2.5, 7.4 Hz), 1.03 and 0.96 (2s, 6 H). Of 15b: δ 3.02 (d, 1, J = 4.5 Hz), 2.53 (dd, 1 H, J 4.5, 9.8 Hz), 1.08 and 0.94 (2s, 6 H). Epoxide **23** was an oil. Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 75.16; H, 8.61. Relevant ^1H NMR data: δ 2.87 (dd, 1 H, J = 4.3, 9.3 Hz), 2.77 (dt, 1 H, J = 4.5, 7.4 Hz), 1.63 (dq, 1 H, J = 6.0, 9.3 Hz), 1.13 (d, 3 H, J = 6.0 Hz).

Synthesis of Acetonide 24. To a stirred solution of the crude diol obtained by reduction of **21c** (0.6 mmol) in a 50:50 mixture of acetone and 2,2-dimethoxypropane (5 mL) was added a catalytic amount of PTSA and the mixture stirred overnight at rt. Solid $NaHCO_3$ was then added, and the suspension was filtered and evaporated to give the crude product that was purified by flash chromatography with a 70:30 hexanes/Et_2O mixture as eluant. The product was an oil. Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.51;

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H, 10.16. Found: C, 60.47; H, 10.31. Relevant ^{1}H NMR data: δ 4.08 (dd, 1 H, J = 2.0, 3.0 Hz), 3.88 (dd, 1 H, J = 2.3, 10.0 Hz), 3.59 (dd, 1 H, J = 2.0, 3.0 Hz), 2.49 (dt, 1 H, J = 7.0, 10.0 Hz).

Synthesis of Emithioketal 33. This product was obtained from **32a** in two steps involving selective hydrolysis of the thioester function (MeONa in MeOH, 0 °C, 2 h) and PTSA-catalyzed reaction with freshly distilled benzaldehyde in THF as solvent (15 h, rt). Compound **33** was an oil that was purified by flash chromatography with a 80:20 hexanes/Et_2O mixture as eluant. Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.58; H, 7.71. Relevant ^{1}H NMR data: δ 6.08 (s, 1 H), 4.14 (dd, 1 H, J = 2.0, 12.0 Hz), 3.30 (dd, 1 H, J = 3.1, 5.4 Hz).

Lewis Acid-Promoted 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-allylenamines

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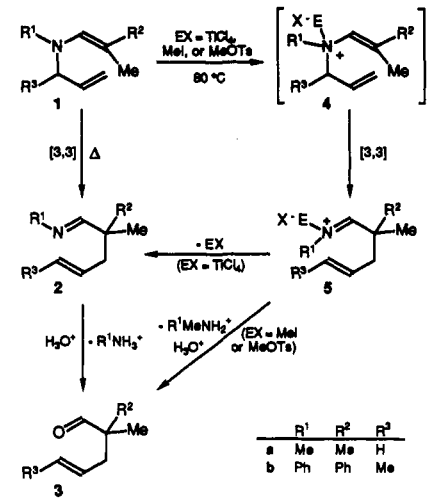
The 3-aza-Cope rearrangement of the *N*-alkyl-*N*-allylenamines derived from isobutyraldehyde, which proceeds thermally at 250 °C, has been accelerated by a variety of electrophilic reagents to give γ,δ-unsaturated imines. Protic acids, such as HCl (0.5 equiv), and the Lewis acidic reagents $TiCl_4$ (0.1–0.2 equiv), $Et_2O{\cdot}BF_3$ (0.5 equiv), and $AlMe_3$ (1.0 equiv) produced complete [3,3] rearrangement of substrates at 111 °C. By increasing the Lewis acidity of the aluminum reagents, this transformation was achieved at 50 °C with $ClAlMe_2$, Cl_2AlMe, and methylaluminum bis(2,6-diphenylphenoxide). Reaction conditions were studied initially by GLC analysis of the *N*-isobutyl derivative. These optimum conditions were then used to obtain isolated yields of 59–99% for rearrangement and in situ $LiAlH_4$ reduction of the analogous *N*-methylcyclohexyl substrate to the corresponding δ,ε-unsaturated amine. Substrates derived from 2-phenylpropanal, *n*-butanal, cyclohexanone, and cyclopentanone were used to examine the general effectiveness of HCl, $TiCl_4$, and $AlMe_3$ as reagents for acceleration of the [3,3] rearrangement. The most versatile and efficient reagent for promoting this reaction, $AlMe_3$, produced overall yields of 83–96% for the two-step rearrangement and reduction of these substrates.

Introduction

The [3,3] sigmatropic shift of allyl vinyl ethers, the Claisen rearrangement, has had significant impact on the regio- and stereochemically controlled formation of carbon–carbon bonds, and mechanistic studies of this rearrangement have provided important insight into these and related pericyclic processes.[1] While the analogous 3-aza-Cope rearrangement of allylenamine substrates has many of the same advantages, there are intrinsic properties of this nitrogen system that provide for some unique synthetic opportunities (**1** to **2**, Scheme I). Included in these features are the higher *E*–*Z* control of enamine geometry, which presents a valuable alternative to the less selective enol ether formation,[1g] and the availability of optically active allylamines from amino acid sources.[2] A rather intriguing feature of this substrate is the presence of an asymmetric heteroatom at the 3-position, a property which the allyl vinyl ether substrates lack.[3]

Scheme I



Despite the attractive possibilities of this reaction, the 3-aza-Cope rearrangement has been of limited synthetic utility due, in part, to the elevated temperatures required for thermally induced rearrangement, 250 °C for **1a** to **2a** and 205 °C for **1b** to **2b**.[4] In order to overcome these limitations, a number of methods for accelerating this rearrangement have appeared involving manipulation of the electron density of the atoms in the six-membered transition state. An increase in electron density at the enamine functionality through the use of *N*-allylketene *N*,*O*-acetals produced rearrangement at 180–190 °C, a significant decrease from the 250 °C required for the corresponding enamines.[3,5] A similar [3,3] rearrangement occurred for a substrate with a dialkylamine substituent,

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