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CONCERNING THE ROLE OF LEWIS ACIDS IN CHELATION CONTROLLED ADDITION TO CHIRAL ALKOXY ALDEHYDES

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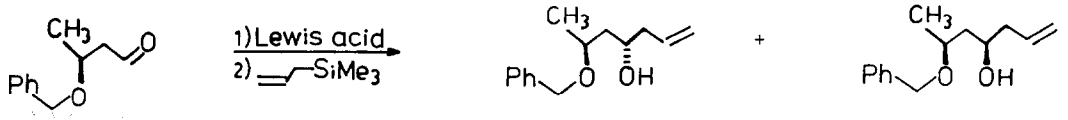
Summary: Chiral α- and β-alkoxy aldehydes react stereoselectively with various C-nucleophiles in the presence of Lewis acids to provide chelation controlled adducts.

We have previously demonstrated that chiral α- and β-alkoxy aldehydes undergo chelation controlled addition reactions with Lewis acidic titanium reagents of the type CH_3TiCl_3 or $TiCl_4$/allylsilanes and $TiCl_4$/enolsilanes, 1,3 [1] and 1,2 [2] asymmetric induction being >90% and yields >80%.

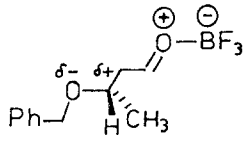
We were therefore surprised at the recent report of Kiyooka and Heathcock[3], who subsequently carried out a few of the same reactions using identical substrates and reagents, and who came to the conclusion that in allylsilane additions $TiCl_4$ gives only chlorine-containing products in contrast to $SnCl_4$. In this Letter we 1) clear up the discrepancy, and 2) report novel effects using other Lewis acids.

All of the reactions which we described were carried out at -78 °C, as stated[1,2]. For example, "complexation of 1 using $TiCl_4$ followed by addition of allylsilanes or dibutylzinc at -78 °C also resulted in stereoselectivities of ≥90%"[1]. Kiyooka and Heathcock provide essentially no experimental details, e.g., no information regarding temperature[3]. We therefore speculated that they mixed 1 and $TiCl_4$ at room temperature, cooled to -78 °C and then added allylsilanes. Indeed, if this is done, no addition products 2/3 are formed, because $TiCl_4$ decomposes the aldehyde 1 at temperatures above ∿-40 °C. Complete experimental details for optimum reactions are given in footnote[4] of this Letter.



1 2 3

In order to define synthetic and mechanistic aspects of chelation control more closely, we have been testing other Lewis acids. Preliminary results show some expected, but also some unusual effects (Table 1). Thus, $SnCl_4$ behaves just like $TiCl_4$, both being capable of forming six-coordinate octahedral complexes[5]. $ZnCl_2$ is too mild to induce allyl addition, $SbCl_5$ is so harsh that substrate decomposition occurs even at -100 °C. The reactions mediated by BF_3-etherate and BF_3 (g) represent the real surprise. Although BF_3 has only one coordination site and should thus be incapable of chelation[5,6], the "chelation controlled" product 2 dominates! We propose that normal complexation of 1 by BF_3 may result in conformations 4 or 5, which are attacked from the less hindered π-face[7]. Dipolar repulsion could be decisive here, which is less important in the non-complexed form. Thus, 4/5 seem more probable than 6. Kiyooka and Heathcock did not report this effect, because their chemical yield was 0% (no temperature given)[3].



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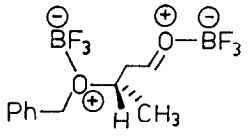

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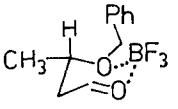

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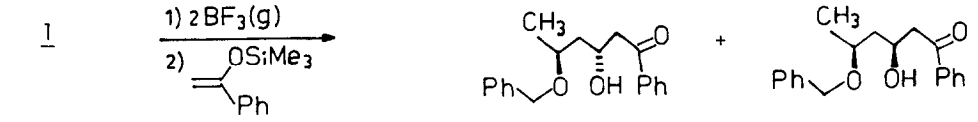
Table 1: Reaction of 1 with allyltrimethylsilane and various Lewis acids[a]

Lewis acid	Temp. of Lewis acid addn.(°C)	Temp. of reaction (°C)	Solvent	Time (h)	2 : 3
$TiCl_4$	-78	-78	CH_2Cl_2	2	95 : 5
$SnCl_4$	-78	-78	CH_2Cl_2	2	95 : 5
$BF_3 \cdot OEt_2$	-78	-78	CH_2Cl_2	2	85 : 15
$BF_3 \cdot OEt_2$	-78	-78	THF	2	--[b]
2 BF_3 (g)[c]	-78	-78	CH_2Cl_2	2	91 : 9
$AlCl_3$[d]	-78	-78	CH_2Cl_2	2	--[b]
$AlCl_3$[d]	+22	-78	CH_2Cl_2	2	--[e]
$AlCl_3$[f]	-78	-78	CH_2Cl_2	2	89 : 11
$ZnCl_2$[d]	-78	-78	CH_2Cl_2	2	--[b]
$ZnCl_2$[d]	+22	+22	CH_2Cl_2	2	--[b]
$SbCl_5$[g]	-78	-78	CH_2Cl_2	2	--[e]
$SbCl_5$[g]	-100	-100	CH_2Cl_2	0.25	--[e]
$SnCl_2$[h]	+22	+22	CH_2Cl_2	2	--[b]

a) Ratio of Lewis acid to 1 was 1:1, except as stated; time for complexation: ∿10 min; conversion to 2/3 >85%, except as stated.
b) No reaction.
c) BF_3 gas was bubbled through solution of 1 at -78 °C for 10 min., i.e., probably two BF_3 molecules attached to 1.
d) Much of Lewis acid did not dissolve.
e) Extensive decomposition of substrate.
f) Time for complexation : 2 h ; much of $AlCl_3$ dissolved, but solution was somewhat cloudy.
g) Time for complexation: 1 minute.
h) Time for complexation: 2 h; solution was still very milky.

The above phenomenon appears to be general, since enolsilanes also add stereoselectively (7 : 8 = 85 : 15; yield 82%). The BF_3(g)-induced addition of the Z-trimethylsilyl enol ether derived from propiophenone also delivers the "chelation controlled" product preferentially (total chelation : total non-chelation = 82 : 18), but the additional stereoselectivity (simple diastereoselectivity) is low (in each case syn/anti mixture ~2 : 1). In contrast, $TiCl_4$ affords essentially only one of the four diastereomers (chelation and syn) [1]. The Mukaiyama aldol addition to normal aldehydes devoid of chelating alkoxy groups affords syn/anti mixtures. We have previously proposed a model to explain the unexpected high syn-selectivity in chelation controlled Mukaiyama additions[1,2]. Thus, the degree of simple diastereoselectivity provides a mechanistic means to distinguish between chelation and non-chelation in Lewis acid mediated reactions ($TiCl_4$ or $SnCl_4$ vs. BF_3), at least in these simple cases.



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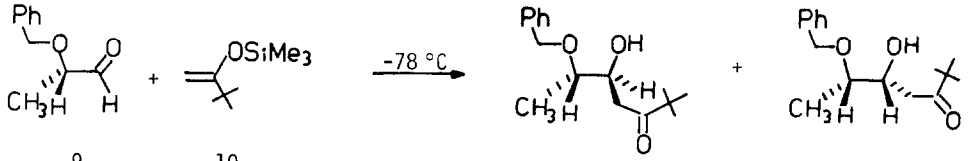
Concerning 1,2 asymmetric induction via chelation, we reported, inter alia, the $TiCl_4$ induced reaction of 9 with allylsilanes (mixing $TiCl_4$ and reacting, both at -78 °C) to provide 95 : 5 diastereomeric ratios of addition products (yields >80%). Kiyooka and Heathcock again report 0% yield (no temp. given)[3]. As before, we know that the complex, in this case 9/$TiCl_4$, decomposes at temperatures above -50 °C [8]. In contrast, 9/$SnCl_4$ is stable at +22 °C for at least 5 minutes. This suggests that in case of very sensitive substrates (which have not yet been studied), $SnCl_4$ may be the Lewis acid of choice.

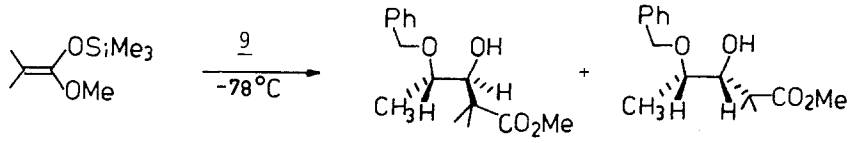
We have also described several Mukaiyama additions to 9/$TiCl_4$ [2], and now report that $TiCl_4$ and $SnCl_4$ generally afford the same results, e.g. 9 + 10 ; (11 : 12 => 95 : 5; yield ~81%). Kiyooka and Heathcock[3] cite an earlier paper[9] by the same group in which 10 was supposed to have been reacted with 9/BF_3 to afford a 1:1 mixture of 11 and 12. However, the earlier paper [9] makes no mention of 9 or any other α- or β-alkoxy aldehyde, so that no information regarding yield is available.



9 10 11 12

The Z-trimethylsilyl enol ether from propiophenone reacts with 9/$TiCl_4$ to afford essentially only one of four diastereomers as shown by an X-ray analysis [2]; we observed that $SnCl_4$ affords the same result under identical conditions. The first case of chelation controlled ester enolate addition to α-alkoxy aldehydes using $TiCl_4$ or $SnCl_4$ is shown below. It makes no difference whether $SnCl_4$ is added at -78 °C and then the complex reacted with 13 at this temperature, or whether $SnCl_4$ is added at +22 °C, the complex cooled to -78 °C and then reacted with 13.

BF_3 reverses diastereoselectivity, but this is best accomplished by using the Li-enolate (14:15=18:82) or better the $Ti(NEt_2)_3$-enolate[10] at -78 °C (14:15=12:88). Yields in all cases are >85%. A general discussion concerning control of chelation or non-chelation by changing the ligands at titanium is given in ref.[2]. Remarkable control of stereoselection can also be achieved in certain aldol additions via Li^+ cooordination with alkoxy substituents as shown by Masamune[11].



13		14		15
	$TiCl_4$	>97	:	<3
	$SnCl_4$	>97	:	<3
	$BF_3 \cdot OEt_2$	35	:	65

Acknowledgement: This work was supported by Fonds der Chemischen Industrie and DFG.

Footnotes:

1) M.T.Reetz and A.Jung, J.Am.Chem.Soc. 105, 4833 (1983).

2) M.T.Reetz, K.Kesseler, S.Schmidtberger, B.Wenderoth and R.Steinbach, Angew.Chem., December issue, 1983.

3) S.Kiyooka and C.H.Heathcock, Tetrahedron Lett. 1983, 4765.

4) Synthesis of 2/3: To a solution of 0.530 g (3 mmol) of 1 in 40 ml dry CH_2Cl_2 is added 0.57 g (3 mmol) $TiCl_4$ at -78 °C. After 10 minutes 0.41 g (3,6 mmol) allyltrimethylsilane (cooled to -78 °C) is added and the mixture stirred under nitrogen at -78 °C for 2 h. The mixture is poured onto 100 ml of H_2O, the aqueous phase extracted twice with 50 ml ether and the combined organic phases washed with 10% $NaHCO_3$ and NaCl solutions. After drying over $MgSO_4$ and stripping off the solvent, a ^{13}C-NMR spectrum of the crude product is recorded. It shows >95% conversion and a 2:3 ratio of 95: 5, identified by authentic samples (R.W.Hoffmann, private communication and K.J.Geuecke, Dissertation, Univ. Marburg, 1981; see also footnote no. 11 of ref.[1]). Kugelrohr distillation at 100 °C/0.1 torr affords 0.56 g (85%) of product. In all cases racemic aldehydes were used (one form shown arbitrarly).

5) E.N.Guryanova, I.P.Goldshtein and I.P.Romm, Donor-Acceptor Bond, Wiley, N.Y. 1975.

6) In their elegant synthesis of the Prelog-Djerassi lactonic acid, K.Maruyama, Y.Ishihara and Y.Yamamoto (Tetrahedron Lett. 1981, 4235) postulate BF_3 chelation between an aldehyde and ester function to explain the remarkable stereoselectivity of crotyltin addition. Alternative mechanisms were not discussed, e.g., displacement of fluorine from boron or BF_3 induced addition of the aldehyde O-atom to the ester function followed by addition of crotyltin.

7) Alternatively, a U-shaped conformation in which electrostatic attraction between BF_3 at the ether group and the partial positive aldehyde moiety would also simulate chelation.

8) S.Schmidtberger, Diplomarbeit (Master's Thesis), Univ. Marburg, April 1983.

9) C.H.Heathcock and L.A.Flippin, J.Am.Chem.Soc. 105, 1667 (1983).

10) M.T.Reetz and R.Peter, Tetrahedron Lett. 1981, 4691.

11) S.Masamune, J.W.Ellingboe and W.Choy, J.Am.Chem.Soc. 104, 5526 (1982).