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# APPARENT CHELATION CONTROL IN ALDOL REACTIONS OF CHIRAL (Me$_2$CHO)$_3$Ti-ENOLATES

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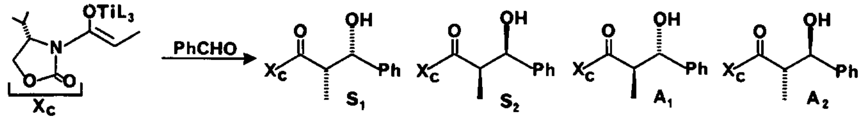
Abstract: Directed aldol reactions of chiral (Me$_2$CHO)$_3$Ti-enolates give the opposite diastereofacial selectivity compared with the corresponding boron enolates. This stereochemical reversal is best explained if the Ti reactions involve chelation (not possible with boron, and previously thought to be unfavorable with (Me$_2$CHO)$_3$Ti-enolates). Changing the solvent from THF to diethyl ether significantly enhances the hypothesized chelation effect. Use of Ti or boron thus permits convenient synthesis of either product enantiomer, starting from that one chiral auxiliary whose configuration is readily and inexpensively derived from natural sources.

We have found (1) that directed aldol reactions of chiral (Me$_2$CHO)$_3$Ti-enolates give diastereofacial selectivity favoring the product expected from chelation control,[1,2] opposite and complementary to the diastereofacial selectivity of the corresponding boron enolates. This is the first observation consistent with chelation control for titanium enolates bearing alkoxy ligands, previously suggested to be incapable of such chelation control (in contrast to the more Lewis-acidic Cl$_3$Ti-enolates).[2,3] We have also found (2) a significant solvent effect favoring the product expected from chelation control in diethyl ether relative to THF; (3) a strong effect of excess Ti, analogous to that recently observed in this laboratory,[4] where Li, present in the usual in-situ preparation of (Me$_2$CHO)$_3$Ti-enolates, was shown to interfere with selectivity unless excess Ti was used; and (4) a useful (92%) level of selectivity favoring the aldol product diastereomer expected from chelation control.

Research on the aldol reaction has increasingly focused on stereoselectivity.[2,5-7] As part of our program on stereocontrol in aldol reactions of titanium enolates, we were particularly interested in the chiral imide[8] enolate shown in eq. 1. This system had shown very high dia-

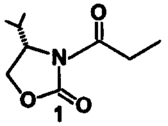


(1)

stereofacial (df) selectivity in aldol reactions of the corresponding di-n-butylboron enolate, giving S$_1$, the product expected in the absence of chelation (see 3 and 4 below).[8] The corresponding lithium enolate had given very high df selectivity in alkylations, favoring the product expected from chelation control,[9] yet low df selectivity in aldol reactions.[8] Nevertheless, df selectivity attributed to chelation control had been observed in aldol reactions of other Li-enolates.[10-14] We reasoned that use of a titanium enolate would give chelation control,[2] while at the same time the presence of ligands L (eq. 1) at Ti would enhance df selectivity in analogy with explanations given for high selectivities of boron enolates.[15-17] There was a report of low levels of diastereoselectivity in Ti-mediated aldol reactions of achiral amides,[18] but it seemed possible that these reactions actually involved Ti-ate complexes and/or interference by Li-enolates, as we had recently observed with another Ti-enolate.[4] Our experiments do indeed show that high df selectivity favoring $\underline{S_2}$ (eq. 1), the product expected from chelation control, can be be achieved.

Advantages of this Ti-enolate (eq. 1) include low cost, recyclability,[8] low toxicity and ease of work-up.[19,20] Moreover, simple diastereoselectivity in Ti-mediated aldol reactions has been reported,[21,22] high levels of df selectivity have been shown in one case using a chiral α-alkoxyaldehyde and achiral Ti-enolates,[3,23] and very high levels of nonchelation-controlled df selectivity have been achieved in Ti-mediated aldol reactions studied in this laboratory.[4]

N-acyloxazolidones 1 and 2 were synthesized as described[8] from L-valinol,[24] and their Ti-mediated aldol reactions were carried out as follows, similarly to a prior report.[25] Either 1 or 3 equiv. of $ClTi(OCHMe_2)_3$ in hexane (1 M) or neat and freshly distilled was added to 1 equiv. of Li-enolate prepared[26] and maintained at -78°C. The reaction mixture was then allowed to warm to -40°C over 1 h, followed by reaction with 1 equiv. of aldehyde for 2-3 h at -78°C.



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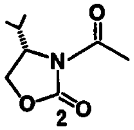

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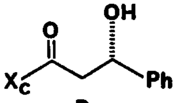

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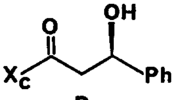

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Table I shows results from aldol reactions of 1 and 2 with benzaldehyde under a variety of

Table I. Diastereomeric Products from Aldol Reactions of 1 and 2 with Benzaldehyde

| Entry | Imide | Solvent | Metal (Equivalents) | Ratio[a,b,c] $S_1(D_1)$ | $S_2(D_2)$ | $A_1$ | $A_2$ |
|---|---|---|---|---|---|---|---|
| 1 | 1 | $Et_2O$ | Li | 17 | 24 | 59 | d |
| 2 | 1 | THF | Li | 12 | 26 | 62 | d |
| 3 | 1 | $Et_2O$ | $ClTi(OiPr)_3$ (1.0) | 16 | 58 | 26 | d |
| 4 | 1 | $Et_2O$ | $ClTi(OiPr)_3$ (3.0) | 5 | 92 | 3 | d |
| 5 | 1 | $iPr_2O$ | $ClTi(OiPr)_3$ (1.0) | 12 | 58 | 30 | d |
| 6 | 1 | $iPr_2O$ | $ClTi(OiPr)_3$ (3.0) | 5 | 88 | 7 | d |
| 7 | 1 | THF | $ClTi(OiPr)_3$ (1.0) | 77 | 16 | 7 | d |
| 8 | 1 | THF | $ClTi(OiPr)_3$ (3.0) | 13 | 84 | 3 | d |
| 9 | 2 | THF | Li | 87 | 13 | e | e |
| 10 | 2 | THF | $ClTi(OiPr)_3$ (3.0) | 46 | 54 | e | e |
| 11 | 2 | $Et_2O$ | $ClTi(OiPr)_3$ (3.0) | 25 | 75 | e | e |

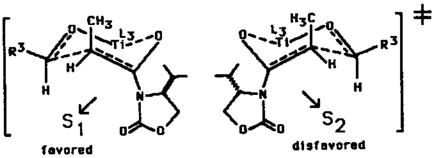
[a] Products conclusively identified by comparison with previous data.[8] [b] Ratios quantitated by $^1H$ NMR of crude mixture or $^{19}F$ NMR of trifluoroacetates.[27] [c] Good yields were obtained for the synthetically useful reaction (entry 4). [d] Product not observed by $^1H$ NMR. [e] Product not applicable.

conditions. Particularly striking are the large improvements in selectivity on changing from 1 to 3 mol equiv. of $ClTi(OCHMe_2)_3$, giving a 5-fold increase in selectivity within the syn manifold favoring $S_2$, the product expected from chelation control,[1] in $Et_2O$ (over 30-fold in THF) and also increases in syn/anti selectivity. These effects are analogous to the improvements in selectivity we have previously shown, in a non-chelation controlled reaction, to result from involvement of Li in reactions involving 1 mol equiv. of Ti reagent.[4] Entry 7 cannot be explained simply by competing Li enolate,[4,28] however (cf. entry 2), as the Li reaction produces much $A_1$. Competition of a titanium "ate" complex[29] having a chloro ligand is a possible explanation; the extra negative charge at Ti should relatively disfavor a chelated transition state. Excess $ClTi(OCHMe_2)_3$ would compete for the extra Cl, forming new "ate" complexes and increasing the equilibrium concentration of normal Ti enolates.

A substantial solvent effect is also observed for $Et_2O$ vs. THF; $iPr_2O$ is similar to $Et_2O$, consistent with the greater solvating power of THF, which would tend to reduce the ability of Ti to chelate and thus tend to reduce the amount of chelation-controlled product. Precedent exists for this type of interpretation.[30]

Parallel results are observed with 2 (entries 10, 11). The selectivities are much lower than with 1, a well-known occurrence with unsubstituted enolates.[6,16] Nevertheless, the Ti enolate gives a reversal of selectivity (favoring $D_2$) compared with the boron enolate of 2 (favoring $D_1$).[8]

Space-filling models of probable[2,31] unchelated[5,16] (3) and chelated[16,32] (4) transition states (TS), taking account of bond angles at Ti,[33] indicate that products $S_1$ and $S_2$ are favored, respectively.[34] Models also show that repulsion between enolate $CH_3$ group and metal ligands is a major factor destabilizing a boat TS relative to 3 and 4. A chelated boat[2] TS would favor $D_1$ and $A_1$, giving a needed explanation[34] for substantial $D_1$ with 2 ($CH_3$ absent)[36] and possibly for increased $D_1$ and $A_1$ with Li (Table I) [Li (smaller) could decrease the boat repulsion, but this depends on the state of aggregation of the TS] and increased $A_1$ with smaller Ti ligands (unpublished).[36]



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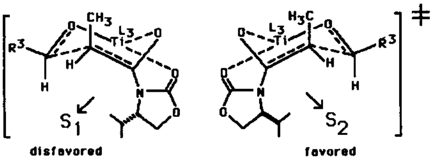

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We have demonstrated the possibility of obtaining high stereoselectivity in this titanium-mediated aldol reaction and in particular the ability to obtain either $S_1$ or $S_2$ at will from the same chiral substrate, readily available from natural L-valine, simply by employing its boron[8] or titanium enolate, respectively. Experimental discoveries also include a strong solvent effect on df selectivity and probable Li interference[4] if only 1 equiv. of Ti is used. Since we have now seen the need for excess Ti to insure a true Ti-enolate reaction in two distinct cases, it seems possible that some literature results on Ti-mediated aldol reactions may be altered by reinvestigation with excess titanium. Mechanistically, the most consistent hypothesis is that this reaction (eq. 1) exhibits chelation control.[1,9] We plan to investigate the scope, improvement, and further applications of these results.

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