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VERY HIGH DIASTEREOFACIAL SELECTIVITIES IN CONVENIENT TITANIUM-MEDIATED ALDOL REACTIONS

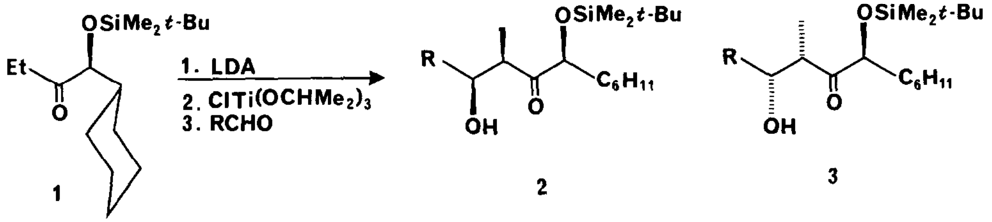
Craig Siegel and Edward R. Thornton*
Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104

Abstract: Very high ($\geq$ 99%) diastereofacial selectivities in aldol reactions of a chiral titanium enolate with a variety of aldehydes can be conveniently achieved. The ease of preparation of $-Ti(OCHMe_2)_3$ enolates, low cost, low toxicity, and ease of work-up make this a very useful method for synthesis of chirally pure substances.

We wish to report the first example of diastereofacial selectivity using a chiral titanium enolate. We have found that (1) very high ($\geq$ 99%) diastereofacial selectivities, not previously available with titanium enolates,[1-3] can be achieved, (2) the simplicity of preparation of titanium enolates and ease of product work-up[4] make the present methodology quite attractive for preparation of chirally pure substances, and (3) lithium, present in the preparation of titanium enolates, is a heretofore unrecognized agent which can preclude very high selectivities, but this influence can readily be prevented.

A few examples of aldol reactions with titanium enolates have previously been reported.[1-6] Syn/anti selectivities have been observed but are not extraordinary.[5,6] One case of diastereofacial selectivity (up to only 89%) has been shown using a chiral α-alkoxyaldehyde and achiral titanium enolates.[2,3] Because diastereofacial selectivity at the 99% level had not been achieved, we deemed it necessary, as the first stage of our program on stereocontrol in aldol reactions of titanium enolates, to demonstrate experimentally that titanium enolates are in fact capable of producing such high levels of stereocontrol.

The chiral ketone 1 (eq. 1) was a particularly attractive substrate, since the corresponding boron enolate had given very high diastereofacial selectivities, the enantiomer is also readily available, and the aldol products are readily desilylated and oxidized to give chiral carboxylic acids.[7] A similar substrate had been previously developed and shown to give diastereofacial selectivity in aldol reactions of its lithium enolate.[8]



(1)

A general procedure for the aldol reaction is as follows. The Li enolate of chiral ketone 1, generated with LDA in THF, is quenched with 3-4 equiv. of $ClTi(OCHMe_2)_3$ at -78°C. After warming to -30°C over 2 h, the aldehyde is added at -78°C. The solution is warmed to -40°C over 3-4 h, and the reaction is quenched with a solution of NH_4F.

Our results with a variety of aldehydes are summarized in Table I. In no case was any of the corresponding anti isomer observed. The diastereofacial selectivities of those reactions with 3.0 equiv. or more of $ClTi(OCHMe_2)_3$ are $\geq$ 99:1, and the major syn isomer 2 (eq. 1) is the same one observed by Masamune et al.[7,9] We have preliminary results which also show a *very* high diastereofacial selectivity for pivalaldehyde. From an experimental point of view, an excess of the titanium reagent is the best method to achieve high selectivity.[10]

Table I. Diastereofacial Selectivities for Aldol Reaction (Eq. 1)

Aldehyde	Metal (Equivalents)		Ratio 2:3^{a,b}
CH_3CH_2CHO	Li		83:17
	$ClTi(OCHMe_2)_3$	(1.0)	97:3
	"	(4.0)	99:1
	"	(1.0)^c	97:3
PhCHO	Li		55:45
	$ClTi(OCHMe_2)_3$	(1.0)	87:13
	"	(3.0)	99:1
	"	(1.0)^c	98:2
$(CH_3)_2CHCHO$	Li		76:24
	$ClTi(OCHMe_2)_3$	(1.0)	75:25
	"	(3.0)	$\geq$99:1
	"	(1.0)^c	$\geq$99:1

[a] Products identified by comparison with results of Masamune et al.[7,9] Yields ranged from 74-85% when excess Ti was present. [b] Ratios determined by ^1H NMR of crude mixture or ^{19}F NMR of trifluoroacetates.[11] [c] 1.0 Equivalent of 12-crown-4 added.

The observed syn selectivity and diastereofacial selectivity favoring 2 can both be readily explained by the nonchelated chair transition state model, as suggested for the reactions of the boron enolate corresponding to 1.[7] This is not to say that the chair transition state model is required, only that this attractive model does nicely explain the data.[12] Chelation to the siloxy oxygen has been postulated to explain the opposite diastereofacial selectivity in one analogous reaction,[8] but this difference is consistent with space-filling models, which indicate that (a) with *lithium* enolates, the chelated transition state is disfavored in the present system by a significant repulsive interaction between the aldehyde H and a CH_3-Si group, which is avoided in the analogous case[8] which gives opposite stereochemistry, and (b) with the present *titanium* enolate, taking account of the ligands and bond angles,[14] the chelated transition state is strongly disfavored by the presence of the bulky isopropoxy ligands on the titanium center.

The dramatic increase in selectivity for the branched aldehydes upon addition of 12-crown-4 indicates the involvement of the lithium cation in the less selective reactions. 12-Crown-4 has been shown to complex lithium selectively.[15,16] We have also observed that a $\geq$ 2 equiv. excess of Ti with respect to the LDA is the controlling factor, not an excess as compared to the ketone. These observations suggest that an equilibrium exists between a Li species[17] and a titanium enolate.

The most reasonable (though not unique[17]) explanation for at least a significant part of this effect is involvement of the lithium enolate. Because the lithium enolate is much more reactive and less stereoselective (Table I) than the titanium enolate, bulkier aldehydes would be expected to slow the Li reaction less than the Ti and thus increase the Li/Ti rate ratio. As can be seen from Table I, the branched aldehydes have the lower diastereofacial selectivity (more like Li) with 1.0 equiv. of $ClTi(OCHMe_2)_3$. The use of excess titanium reagent apparently drives the equilibrium to the titanium enolate side. To our knowledge, this type of effect has not been reported for titanium-mediated aldol reactions.

Our results indicate that Ti enolates will prove to be useful in generating very high diastereoselectivities. It now seems possible to take full advantage of special properties such as the potential for chelation control,[1] as well as the low cost, low toxicity, and ease of work-up of titanium enolates bearing alkoxide ligands.

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References and Notes

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9. The major syn isomers 2 had ^1H NMR data identical within experimental uncertainty to the pre-previous NMR data on each of these structures, whose stereochemistries were conclusively proven.[7] In our products from lithium enolates, both diastereomers were detected, and the second one (3) was shown in each case to differ conclusively in ^1H NMR from our (and previous workers') data on 2, thus establishing the identity of the major product in both the lithium and titanium reactions as 2.

10. 12-Crown-4 ether is more expensive than $ClTi(OCHMe_2)_3$ and hampers separation of products.

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12. For example, open transition states[13] could conceivably explain the results, although space-filling molecular models indicate that, in this system, the bulk of the cyclohexyl and t-butyldimethylsilyl moieties would probably cause open transition states to favor anti, or at least not exclusively syn, products.

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14. Cf. Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Intl. Edit. Engl.* *1985*, *24*, 112-114, which gives a crystal structure showing the geometry of a $TiCl_4$ complex with two carbonyl groups of a diester dienophile.

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17. The lithium species could be, for example, the lithium enolate or a lithium titanium ate complex, or both. Cf. Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem.* *1983*, *55*, 1807-1822. The Li enolate could be present in very small amounts and still have this effect, as it is much more reactive than the corresponding Ti enolate; as long as Li and Ti enolates were in rapid equilibrium, the Li enolate would be replenished as it reacted.

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