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New Chiral Acetate Imide Enolate for Stereoselective Aldol Reactions

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Abstract: The chiral imide acetate 4 reacts upon lithium and titanium enolate formation conditions with aldehydes in a stereoselective manner. Remarkably, aldols obtained from aromatic and α , β -unsaturated aldehydes exhibited opposite stereochemistry than those obtained from aliphatic aldehydes. Copyright © 1996 Published by Elsevier Science Ltd

The aldol reaction is an important tool for the asymmetric C-C bond construction that plays a fundamental role in modern organic synthesis.¹ Although there have recently arosed alternative techniques for the control of the stereochemistry of aldol products, probably the most general methodology developed to this end is based on the use of chiral auxiliaries.^{1,2} The acylated compounds of both Evans α -amino acid-derived oxazolidinones³ and Oppolzer's camphorsultam derivatives⁴ have defined the standard parameters for successful aldol reactions with α -substituted enolates and have provided the basis for the development of new auxiliaries to accomplish this goal with high chemical yields and stereoselectivities.⁵ In contrast, little or not selectivity has often been observed for chiral enolate equivalents of acetate, where no α -substituent is present.⁶ Although recent progress in this area has been made using chiral acetate enolates of boron,⁷ titanium,⁸ tin,⁹ aluminium,^{9,10} zirconium^{9a}, copper^{9a} and magnesium^{9b} metals, the asymmetric aldol reactions by using the corresponding lithium enolates has remained an unrealized goal¹¹ and, in general, no satisfactory auxiliaries have been described for this case. The recent papers by Kunieda,¹² on one hand, and by Yan,¹³ on the other hand, revealing the use of both 1 and 2 for acetate aldol reactions, respectively, have prompted us to report our own results on this subject.





Recently we have reported on the use of the camphor-derived auxiliaries 3a and 3b for asymmetric alkylations, conjugate additions and Diels-Alder reactions.¹⁴ As an extension of such auxiliaries in reactions

of particularly inherent poor diastereoselectivity we devised the lithium enolate of 4, readily obtained via acylation of 3a and subsequent treatment of the resulting 4 with LDA, as a candidate to be evaluated for acetate aldol reactions. Results are listed in Table 1 and, as it can be observed, in reactions with aromatic, α , β -unsaturated and aliphatic aldehydes both chemical yields and diastereoselectivities are reasonably good, specially in the former case. The superiority of the auxiliary 3a is particularly evidenced in some instances. For example, the condensation of the lithium enolate of 4 with isobutyraldehyde afforded the aldol adducts 5g and 6g in a 75:25 diastereomeric ratio (entry 9), while lithium enolate of 1 gives a 54:46 mixture.¹² Similarly, whilst the different boron enolates derived from 2 react with benzaldehyde to afford the corresponding diastereomeric aldols in a 25:75 to 56:44 range,¹³ the lithium enolate of 4 produces the same aldols in a 8:92 ratio (entry 1).



The stereochemical assignments of the aldol products 5 and 6 (R: Ph, (E)-PhCH=CH, 1 Pr, t Bu) were carried out by removal of the chiral auxiliary under standard conditions, 15 affording the expected carboxylic acids 7 and 8 along with the recovery of the auxiliary (85-90%), and comparison of the observed optical rotations of the β -hydroxy acids with the published values. 16

Entry	r R	Metal	Yield,%a	5: 6 b,c	Entry	R	Metal	Yield,%a	5: 6 b,c
1	Ph	Li	84	8:92	8	(CH ₃) ₂ C=CH	Li	71	36:64
2		Ti	65	88:12	9	(CH ₃) ₂ CH	Li	77	75:25
3	pCH ₃ C ₆ H ₄	Li	75	6:94	10		Ti	85	17:83
4	pClC ₆ H ₄	Li	88	9:91	11	(CH ₃) ₃ C	Li	83	77:23
5	CH ₃ CH=CH	Li	73	15:85	12		Ti	74	47:53
6	PhCH=CH	Li	69	17:83	13	PhCH ₂ CH ₂	Li	75	70:30
7		Ti	70	86:14	14		Ti	37	42:58

Table 1. Aldol reactions of Li and Ti enolates of 4 with representative aldehydes.

^a Yield of 5+6 combined product after purification by column chromatography. ^b Determined by both ¹³C NMR and HPLC analysis of the reaction crude. ^c Diastereomer 5 showed minor R.T. on the HPLC elution sequence in all cases.

On the other hand, one remarkable feature of the experiments carried out with the lithium enolate of 4 relies on the effect exerted by the nature of the aldehyde on the stereochemical outcome of the reactions. Thus aromatic (entries 1,3 and 4) and α , β -unsaturated aldehydes (entries 5, 6 and 8) exhibit opposite facial selectivity as compared with aliphatic aldehydes (entries 9, 11 and 13). To our knowledge this is the first example of a chiral auxiliary producing this general observation for acetate enolates.¹⁷ More striking, in the

relevant cases where high stereoselectivity has been achieved no facial reversal has been reported at all, and aldehydes showed uniform behaviour.¹⁸ These observations prompted us to check whether or not this facial reversal exerted by the aldehyde partner has some generality. Thus we carried out the same reactions using the chlorotitanium enolate of 4, generated by treatment of 4 with DIPEA and TiCl₄ in CH₂Cl₂.¹⁹ Actually, although lower diastereoselectivities are attained with aliphatic aldehydes, the same opposite facial selectivity was again shown by aromatic and α , β -unsaturated aldehydes (entries 2 and 7) related to that of aliphatic aldehydes (entries 10, 12 and 14).





To ensure the potential of the new auxiliary for acetate aldol reactions, we carried out the condensation between 4 and the chiral aldehyde 9 under both titanium and lithium enolate formation conditions, affording the corresponding adducts 10 and 11 as the major products, respectively (Scheme 2). By this means the chiral auxiliary that has been developed has the ability to amplify the very low diastereofacial preference exhibited by the aldehyde 7 in its reaction with achiral enolates²⁰ and, therefore, it is reasonable to anticipate that the same trend in facial selectivity may also take place with other chiral aldehydes.²¹

In conclusion, from the above results it is clear that this approach to acetate aldols nicely complements the existing chiral auxiliary-based methodologies and should be readily extended to further applications in aldol condensation processes.

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