Endo-2-Methyl-Bicyclo[2.2.1]-Hept-5-enyl Ethyl Ketone : An Useful and Highly Stereoselective Synthon for Aldol Reactions.

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Abstract : An excellent aldehyde diastereofacial selectivity has been observed during the aldol condensation between the lithium enolate of endo-2-methyl-bicyclo[2.2.1]-hept-5-enyl ethyl ketone 1 and a variety of α -methyl chiral aldehydes. 2-Aryl- and 2-vinyl-propionaldehyde gave rise to the predicted syn, syn "Felkin-Anh" diastereoisomers. In contrast β -alkoxy or β -silyloxy α -methyl aldehydes lead to the syn, anti aldols arising from an apparent chelation control.

It has been now well established that, in aldol reactions, a good relationship exists between main group enolate geometry and aldol relative configuration (simple diastereoselection) if the non reacting carbonyl ligand is sterically bulky ¹. Following these considerations, several classes of ketone enolates have then been recently developed ², providing an highly stereoselective access to syn aldols. In the reactions of these enolates with chiral aldehydes, the aldehyde diastereofacial selectivity is not always high and the factors governing this selectivity are still not totally unsderstood. Actually either Felkin-Anh ³ or Cram chelate ⁴ models are not sufficient to explain the selectivity of all the aldol reactions involving Z enolates ¹. Very recently ⁵ Roush proposed transition state models for aldol reactions between ethyl ketone lithium or boron enolates and α -methyl chiral aldehydes RCH(Me)CHO in which gauche pentane interactions were minimized. Following this model, the aldehyde diastereofacial selectivity was closely related to the steric bulk of R, the syn syn ("normal Felkin Anh") diastereoisomer being preponderant if R is smaller than CH₃.

We wish to report in this note that the lithium Z(O)-enolate of endo-2-methyl-bicyclo[2.2.1]-hept-5enyl ethyl ketone 1 ^{2d} exhibits an excellent to exceptional level of diastereofacial selectivity in reactions with various α -methyl chiral aldehydes and that the selectivities observed are not in total agreement with the model proposed by Roush ⁵.

The Z(O)-lithium enolate of ethyl ketone 1, generated by deprotonation with lithium hexamethyldisylazide (LHMDS) in THF, has been reacted with several α -methyl chiral aldehydes and the resulting aldols, after protection as silvl ethers have been thermolyzed (500°C, contact time < 1 s) to afford the diastereoisomeric α,β -ethylenic ketones 3 and 4 6.7. The results of such transformations are summarized in the Table.



Table : Diastereoselectivity of aldol reactions between 1 and α -methyl chiral aldehydes

Entry	Aldehyde	R	Ratio 3/4 ^{a)}	Aldolisation b) Yield %	<u>Thermolysis</u> b) Yield %
1	2 a	Ph	> 98/2	75	95
2	2 b	p.MeO Ph	97/3	89	90
3	.2 C	Me₂C≖CH-	95/5	76	84
4	2 d	H₂C=CH-	80/20	63 ^{C)}	82
5	2 e	A?	90/10	57 ^{C)}	80
6	2 f	PhCH ₂ OCH ₂ -	12/88	85	92
7	2 g	tBuMe ₂ SiOCH ₂	11/89	73	85
8	2 h	(iPr)₃SiOCH₂-	15/85	87	80

a) The ratios have been determined by careful examination of the ¹H NMR spectra of the crude mixtures and confirmed in some cases by weighting the pure separated aldol diastereomers.

b) Yields are given for isolated products purified by silicagel chromatography.

c) Based on recovered ketone 1.

The relative stereochemistry of the products 3 and 4 has been determined after deprotection and selective reduction or ketalisation either by X-ray cristallography (2a,b) or ¹H NMR (2f-h) or chemical correlation (2c-e). Representative examples are given in Fig. 1 and 2 for the determination of the stereochemistry of 3a, 3h and 4h after transformation respectively in 5a, 5h and 6h.





Fig. 1 - X ray crystal structure of compound 5a



Fig. 2 - Selected ¹H NMR data ⁸ for 5h and 6h (C_6D_6 , 250 MHz)

As shown in the Table, 2-aryl- and 2-vinyl-propionaldehydes 2a-d gave rise with an excellent selectivity (to our knowledge the best selectivity observed for such aldolisations) to the predicted Felkin diastereoisomer and these results are in good agreement with the model described by Roush. If the syn, anti configuration of the major diastereoisomer arising from the reaction of the alkyl ketone 1 with the β -benzyloxy aldehyde 2f (entry 6) could be easily explained by a Cram chelate model 4, we were surprised to observe the same selectivity during the reactions of 1 with the β -tertiobutyldimethylsilyloxy- and a fortiori the β -triisopropylsilyloxy-aldehydes 2g and 2h (entries 7 and 8) 9. Such bulky protective group and particularly the triisopropyl group have been shown to preclude the formation of chelates 10 and, here again, these results can be rationalized by considering the Roush model. In contrast, the aldehyde 2e in which the norbornenyl substituent is, by far, sterically bulkier than a methyl group, provided after aldol condensation and double retro-Diels-Alder reaction the syn, syn "Felkin" diastereoisomer identical to the one already obtained by the reaction of 1 with the vinylaldehyde 2d. This observation is in total contradiction with the transition state model considered above and thus it seems that steric factors alone are not sufficient to explain the stereoselectivity of aldol reactions between ethyl ketones and α -methyl chiral aldehydes.

The enantioselective synthesis of polyhydroxylated compounds based on the selective aldol condensation between the ethyl ketone 1 and chiral non racemic α -methyl aldehydes is currently in progress.

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References and Notes

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- 6) All the products are racemic. For clarity only one enantiomer is represented.
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