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INFLUENCE OF ENOLATE GEOMETRY ON THE STEREOCHEMISTRY OF MICHAEL ADDITIONS OF KETONE ENOLATES TO α,β-UNSATURATED KETONES[1]

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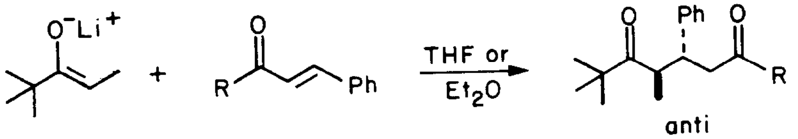
Abstract: Preformed lithium enolates of ketones react with acyclic α,β-unsaturated ketones to give 1,5-diketones in good chemical yields. A strong correlation exists between enolate geometry and product stereochemistry; enolates having the Z configuration provide anti addition products while E enolates usually provide the syn diastereomers.

The addition of active methylene compounds to α,β-unsaturated ketones and esters (Michael addition reaction) is an important reaction in synthetic chemistry.[2] When the reaction involves a prochiral enolate and a prochiral acceptor, the possibility of simple or internal diastereoselectivity arises. Effective control of the stereochemical outcome of such reactions has obvious synthetic potential and has been investigated by a number of groups.[3-5]

The "kinetic" version of this reaction, wherein a stoichiometric amount of a preformed ketone enolate is added to an α,β-unsaturated ketone, is generally believed to be of limited scope.[6] Gorrichon and co-workers, however, have found that the addition of enolate **1z** to enones **5** and **6** provides the anti diastereomers **11** and **12** in high regio- and stereoselectivity.[5] Because of our interest in discovering the factors controlling the stereochemical outcome of kinetic Michael additions,[4] we have carried out an investigation of the scope and generality of this reaction. In this Letter we report the initial results from this study, which have revealed that there is a strong general correlation between ketone enolate geometry and Michael addition stereochemistry.

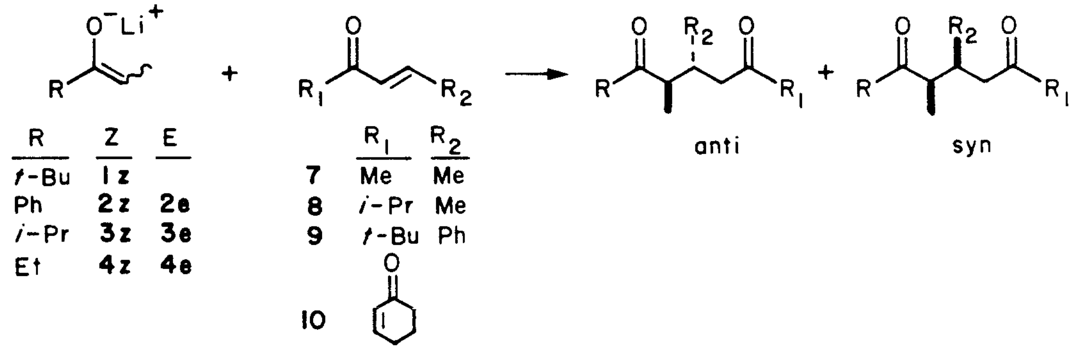


1z

5: R = Me
6: R = Ph

11: R = Me
12: R = Ph

Enolates 1-4 and enones 7-10 were chosen for study. In general, enolates were prepared from the corresponding enol silanes and methyllithium;[7] enolate **1z** may be obtained by treatment of the corresponding ketone with LDA. Exact enolate ratios used in each reaction were determined by removing an aliquot and trapping with chlorotrimethylsilane; the resulting enol silanes were analyzed by capillary GLC and ^1H NMR to obtain E/Z ratios. Stereostructures of the products were assigned by comparison to previously prepared compounds (entries 2, 3, 5, 7, 9, 10, Table I),[8] systematic shifts in the ^1H NMR spectra (entries 1, 8, 11, 12),[9] or by inference (entry 4).[10]



Results are summarized in Table I.[11] With the exception of entry 6, all of the reactions occur in good chemical yields. Products of 1,2 addition were not observed in any case. Additionally, Table I reveals excellent anti diastereoselectivity for all the Z enolates used (enolates **1z**-**4z**; entries 1-5, 7-8). In all cases, the percentage of the anti isomer formed is equal within experimental error to the percentage of the Z enolate used.

As a group, E enolates (2e, 3e, and 4e) tend towards syn selectivity. However, with these enolates there appears to be a correlation between the size of the substituent on the enolate and the magnitude of syn selectivity, with larger groups being more syn selective. At this point we have been unable to resolve whether the lower selectivity seen with enolate 4e is a result of lower kinetic selectivity or a greater intrinsic ability for this enolate to isomerize partially to the more stable Z enolate under the conditions of the reaction.[12] Additionally, since mixtures of enolates were necessarily used, differences in the relative rates of reaction of the E and Z enolates, as is likely,[14] would result in

TABLE 1: Stereochemistry of Michael Reactions

1	**1z**	<1:99	**9**	THF	-78	70	>99:1
2	**2z**	2:98	**9**	THF	-78	87	98:2
3	**2z**	2:98	**9**	THF/HMPA	-78	80	96:4
4	**2z**	2:98	**7**	THF	-78	65	>97:3
5	**2z**	2:98	**8**	THF	-78	63	>97:3
6	**2z**	2:98	**10**	THF	-78	0[a]	---
7	**3z**	4:96	**9**	THF	-78	88	95:5
8	**4z**	15:85	**9**	THF	-78	78	88:12
9	**2e**	87:13	**9**	THF	-20	67	17:83
10	**3e**	90:10	**9**	THF	-78	87	10:90
11	**4e**	81:19	**9**	THF	-78	88	61:39
12	**4e**	81:19	**9**	THF/HMPA	-78	98	32:68

a. No addition products were isolated.

substantial deviations in syn/anti product ratios from the E/Z enolate ratios. Addition of HMPA[15] to E enolate **4e** prior to the Michael reaction results in enhanced syn selectivity (entry 12). Little or no change in stereoselectivity was observed when HMPA was added to Z enolate **2z** (entry 3).

In conclusion, preformed lithium enolates from a variety of ketones can be added with high regio- and stereoselectivity to a variety of enones in good chemical yields. A correlation between enolate geometry and product stereostructure can be observed. The Z enolates provide anti stereoisomers in diastereomeric ratios essentially identical to the starting enolate ratio. The more hindered E enolates provide syn diastereomers in ratios that approach the starting enolate ratio.

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10. Since the reaction of enolate **2z** with enones **8** and **9** gives predominantly the anti diastereomer it is likely that this isomer is also the anti diastereomer.

11. The additions were typically carried out by adding one equivalent of the enone to a 0.6-0.7 M solution of two equivalents of the enolate cooled to -78 °C. After a 24-h period, the reactions were quenched with satd aqueous NH_4Cl and worked up to provide the crude product. Diastereomer ratios were determined by capillary GLC and/or ^{13}C NMR spectroscopy. Control experiments revealed that no equilibration of Michael adducts occurred under the conditions of the reaction.

12. A potential manifold for this equilibration is reversible 1,2 addition to either the enone or to the already formed Michael adducts.[13] Since enolate **4e** is less sterically encumbered than enolate **3e** and **2e**, it might have a higher propensity for 1,2-addition and thus equilibrate more rapidly resulting in the lower observed selectivity. See also ref 4b.

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15. Hexamethylphosphoric triamide (HMPA, 4 equivalents) was added at -78 °C to a THF solution of the enolate.

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