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DIASTEREOSELECTIVE ALDOL CONDENSATIONS OF TIN ENOLATES WITH ALDEHYDES

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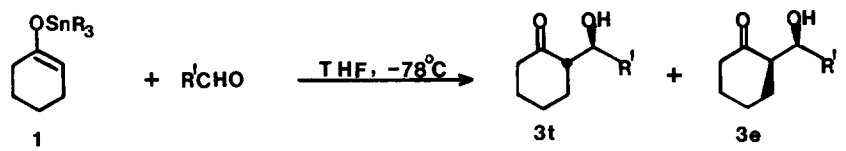
Abstract: The reaction of tin enolates of cyclohexanone or propiophenone with benzaldehyde at -78°C gives predominately the threo aldol diastereomer.

The aldol condensation reaction is one of the most straightforward methods of forming a carbon-carbon bond and constructing a framework with the oxygen functionality in a 1,3-relationship. The importance of this reaction in the synthesis of macrolide and ionophore antibiotics has kindled the discovery of a number of these reactions that are highly stereoselective.[1]

Because of our success in effecting coupling reactions between electrophiles and a variety of tin reagents,[2] and the knowledge that enolstannanes serve as nucleophiles in coupling reactions with electrophiles,[3] the reactions of enolstannanes with aldehydes were undertaken to determine the stereoselectivity that could be achieved. While this investigation was in progress, the reaction of aldehydes with tin enolates generated *in situ* under kinetic control to give moderate erythro selectivity was reported.[4] These results are somewhat conflicting with our findings, since we observed predominate threo selectivity.

The reaction of the enolstannanes of cyclohexanone (**1**) or propiophenone (**2**) with aldehydes under kinetic control gave predominately threo isomers (**3t** and **4t**).[5] In these reactions, the tin enolates were first isolated and then purified before use.



1 3t 3e

2 4t 4e

To a solution of 1 mmol of aldehyde in THF at -78° C was added slowly 1 mmol of enolstannane[6] in THF with stirring. The reaction was allowed to proceed for 5-6 hours at -78°C and was then quenched with aqueous methanol. The mixture was allowed to warm to ambient temperature, the aqueous mixture was extracted with ether, and the ether extract was dried. The residue after ether evaporation was analyzed by ^{1}H NMR, and/or HPLC (reverse phase). Column chromatography (silica gel, 1:4 ether:hexane) was used to isolate pure product (Table 1).

Table 1

Reactions of Enolstannanes with Aldehydes

Enolstannane, R		Aldehyde, R'	T°C/t,h	Yield %	threo[a]	erythro[a]
1	n-Bu	Ph	-78/5	78	80	20
			+45/2	86	23	77
	Et	Ph	-78/5	89	92	8
			+45/5	90	30	70
	Me	Ph	-78/5.5	88	92	8
2	n-Bu	Ph	-78/6	50	88	12
		i-Pr	-78/7	50	75[c]	25
		$PhCH_2$	-78/7	95	95[b]	5
			+43/6	>95	10	90[b]
		n-Pr	-78/5	75	90[c]	10
	Et	Ph	-78/7	50	90	10
		i-Pr	-78/7	48	93[c]	7

a. ^{1}H NMR coupling constants observed for **3t** and **3e** were 9 and 3 Hz, respectively; for **4t** and **4e**, 8 and 3 Hz, respectively (R'=Ph). The small methyl group on the 2-position of the 1,3-oxygenated framework allows the assignments based on the hydrogen bonded conformation that places the hydrogens on the carbons bearing the hydroxyl and methyl groups anti for the threo isomer.[8]

b. Assignments for **4t** and **4e** ($R'=C_6H_5CD_2$) were made on the basis of J=5.6 and 3.2 Hz, respectively.

c. The threo, erythro assignment made by analogy to **4t**, R'=Ph and $PhCD_2$.

The diastereo assignments were made based on the ^{1}H NMR coupling constants of the proton on the carbon bearing the hydroxyl group as reported for **3t** (8.4 Hz) and **3e** (2.4 Hz)[7] as well as for **4t** (9.0 Hz) and **4e** (3.0 Hz);[5] R' = Ph.

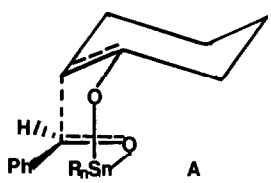
The threo selectivity is dependent on the ancillary organo groups on the tin enolate, trimethyl- and triethyltin enolates producing higher selectivity than tributyltin enolates. At higher temperatures, predominate erythro selectivity is observed. This is in contrast to the report that triphenyltin enoltes, formed *in situ* from the reaction of lithium enolates of cyclohexanone or 2-butanone with triphenyltin chloride, react with benzaldehyde at -78 °C to give erythro products, and that tributyl- and trimethyltin enolates of cyclohexanone are non-

selective. Although we have observed the larger organo groups on tin reduce the threo selectivity, it would not be expected that the phenyl group would be responsible for a complete reversal[4] of the diastereoselectivity.

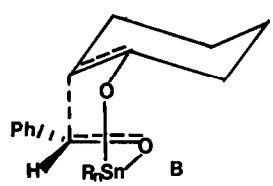
Enolate geometry is important in controlling diastereoselectivity in some, but not all metal enolates.[1] In this work, the E-geometry of enolstannane **1** , affords threo selection. Tributyl enolstannanes of 2-butanone and 3-pentanone were reported[9] to consist of mixture of 77 and 30 percent C-derivatives, respectively (vs. O-derivatives), the enolstannane from 2-butanone being 100% E and that from 3-pentanone being 75% E.

At 25°C and at -78°C, the ^{1}H NMR spectrum of **2** in THF showed a 9:1 ratio of C-derivative to O-derivative. The ^{13}C spectrum of **2** showed, a major signal at 100.7 ppm, corresponding to the vinyl carbon, but in absence of further information, the assignment, E or Z cannot be made.[5] When aldehyde was added to this mixture of C- and O-stannanes in THF at -78 °C, the enolate disappeared immediately, leaving only the ^{1}H NMR spectrum of the C-derivative. Thus, the reactive species is the tin enolate, and by analogy to 2-butanone, the E-isomer (**2**) is shown. Further reaction apparently requires isomerization of C-stannane to enolate.

Threo selectivity in the case of the cyclohexanone enolstannane can be explained using the classical chair transition state, but also is consistent with a favored boat transition state A, which yields more of the erythro product through transition state B as the groups (R) on tin becomes larger. The boat transition state also is consistent with the threo selectivity of **2** , if indeed the E-enolate is the isomer involved. The reasons for the predominate formation of the erythro aldols at higher temperatures are not clear. When the threo aldol stannate of **4t** generated at -78°C was not quenched, but instead allowed to warm to 45°C for 3 h before quenching, the threo to erythro ratio, **4t:4e** , remained the same, 92:8. Thus, **4e** does not appear to be a thermodynamic product.



A



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