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Aldol Reactions of Methyl (2-tributylstannyl)tetrahydrofuran-3-ylcarboxylate Lithium Enolate

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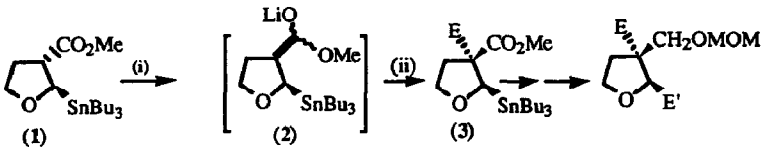
Abstract: *The aldol reactions and subsequent transmetallation of β-stannylpropionates is described.*

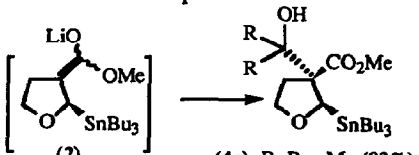
We recently reported[1] that the lithium enolate (2) undergoes clean alkylation reactions generating the stannanes (3) with high levels of asymmetric induction (d.s. > 99:5). The stannanes (3) serve as useful intermediates for the stereoselective synthesis of 2,3,3-trisubstituted tetrahydrofurans[1] as outlined in **Scheme 1**. As a continuation of our studies in this area we wish to report our intial results concerning the aldol reactions of the enolate (2).



Reagents and conditions:- (i) LDA, 1.1 eq.; THF; -78°C; (ii) E⁺; THF; -78°C.

Scheme 1

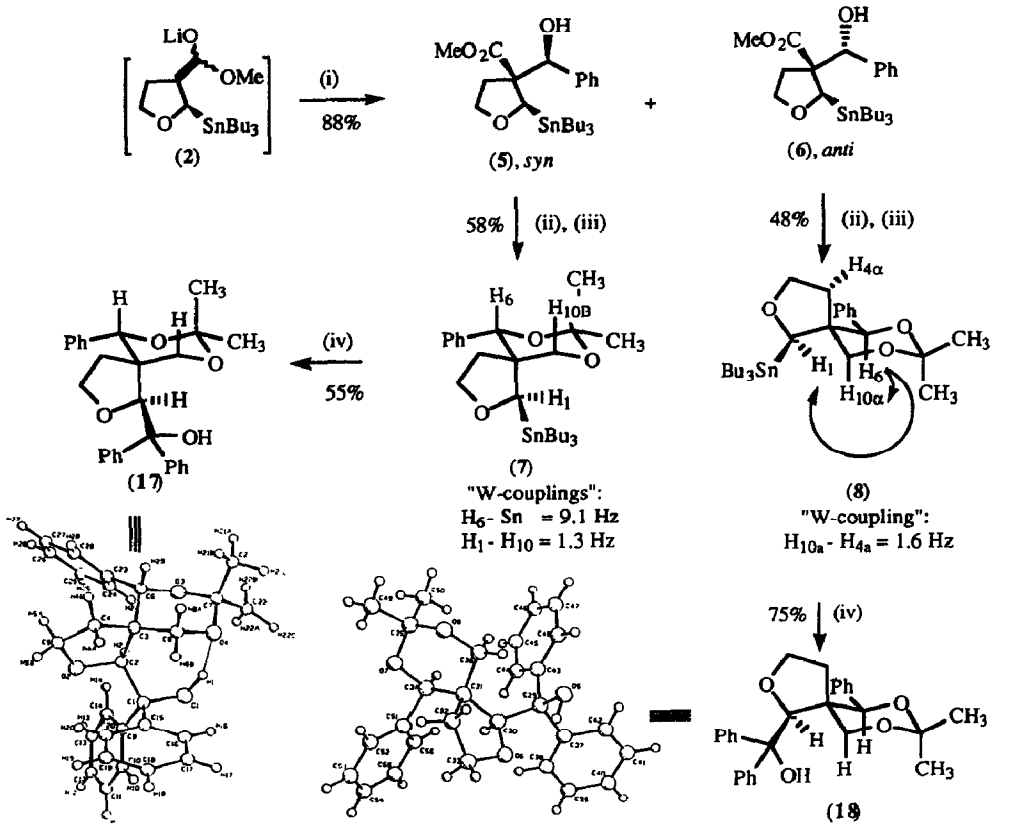
Generation of the enolate (2) as previously described ((1); LDA, 1.1 eq.; THF; -78 °C; 15 mins.) and reaction with symmetrical ketones such as acetone or cyclohexanone (1.1 eq.; -78 °C) followed by an ammonium chloride quench at -78 °C after 15 minutes afforded the diastereoisomerically pure aldol adducts (4) and (4a) in good isolated yield (83% and 52% after chromatography), **Scheme 2**. From our previous studies[1] we assume that the electrophiles approach the face of the enolate *anti* to the bulky tributylstannyl residue, an assertion which has been substantiated by subsequent chemical manipulations.



(4a) R, R = Me (83%)
(4b) R, R = $(CH_2)_5$ (52%)

Scheme 2

We next turned our attention to the use of prochiral aldehydes in these aldol reactions. Reaction of the enolate (**2**) with benzaldehyde, as above, afforded a 2:3 (*syn : anti*) mixture of the two diastereoisomeric aldol products (**5**) and (**6**) in good overall yield (88%). Stereochemical assignments were made upon the basis of extensive nmr studies on the dioxolane derivatives (**7**) and (**8**), which were readily prepared in a two step sequence from the esters (**5**) and (**6**) respectively, **Scheme 3**. NOED spectra of the diastereoisomeric dioxolanes (**7**) and (**8**) indicated that in both cases the phenyl substituent was equatorially disposed and that the dioxolane rings adopted chair conformations. In the case of the dioxolane (**8**), derived from the major (*anti*) aldol product (**6**), both H_1 (δ 3.62 ppm) and $H_{10\alpha}$ (δ 3.90 ppm) experienced 1% enhancements upon irradiation of H_6 (δ 4.96 ppm); the existence of a long range "W-coupling" of 1.6 Hz between $H_{4\alpha}$ and $H_{10\alpha}$ provided further support for the stereochemical assignment in (**8**) as being 1R*, 5S*, 6R* and hence that of the aldol adduct (**6**) as 2R*, 3R*, 6R*. In the case of the dioxolane (**7**) derived from the minor (*syn*) aldol adduct (**5**), irradiation of H_6 caused a 1% enhancement of $H_{10\beta}$; H_6 and $H_{10\beta}$ exhibited long range "W-couplings" to the tin moiety at C_2 (9.1 Hz) and to H_2 (1.3 Hz) respectively: this suggests 1R*, 5S*, 6S* relative stereochemistry for (**7**) which translates to 2R*, 3R*, 6S* (*i.e. syn*) relative stereochemistry for the aldol adduct (**5**).



Reagents and conditions:- (i) PhCHO, 1.1 eq.; THF; - 78 °C; (ii) DIBAL-H, 3.3 eq.; 0 °C; THF; (iii) $(CH_3)_2C(OMe)_2$; $SnCl_2$, cat.; DME; (iv) (a) n-BuLi, 1.1 eq.; THF; - 78 °C; (b) Ph_2CO, 1.1 eq.; THF; - 20 °C.

Scheme 3

Reaction of the enolate (**2**) with aliphatic aldehydes resulted in enhanced levels of asymmetric induction at C_6; the level of induction is proportional to the increase in steric bulk of the alkyl groups attached to the aldehyde

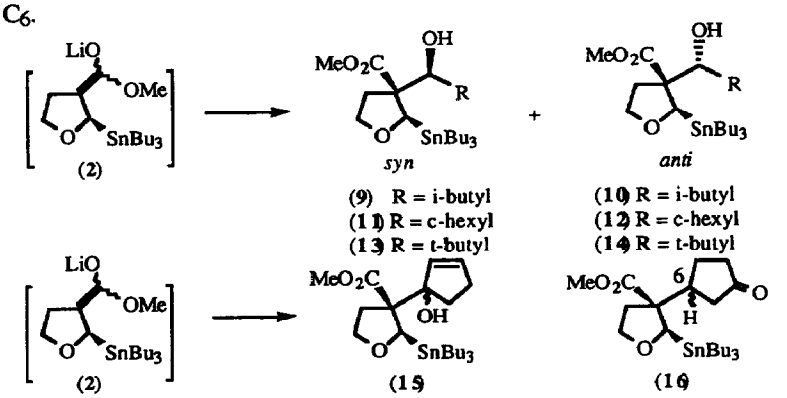
(Table, entries 4, 5, 6). On going from isovaleraldehyde to pivaldehyde the *syn* : *anti* ratio increased from 65:35 to >99:1. Of note is the observation that the *sense* of induction changes on going from benzaldehyde to aliphatic aldehydes.

Table

Entry	Carbonyl Compound	*syn* : *anti*	(Product)/Yield [§]
1	CH_3COCH_3	-	(4a); 83%
2	cyclohexanone	-	(4b); 52%
3	PhCHO	40 : 60	(5) + (6); 88%
4	$(CH_3)_2CHCH_2CHO$	65 : 35	(9) + (10); 76%
5	c-hexylCHO	80 : 20	(11) + (12); 83%
6	$(CH_3)_3CHO$	>99 : 1	(13) + (14); 60%
7	cyclopent-2-ene-1-one	-	(15)[¢]; 30%+ (16)[∞]; 30%

[§] Characterised by ^1H and ^{13}C nmr; ir; high resolution mass spectrometry.
[¢] Isolated as 1:1 mixture of diatereoisomers. [∞] Isolated as a single diastereoisomer.

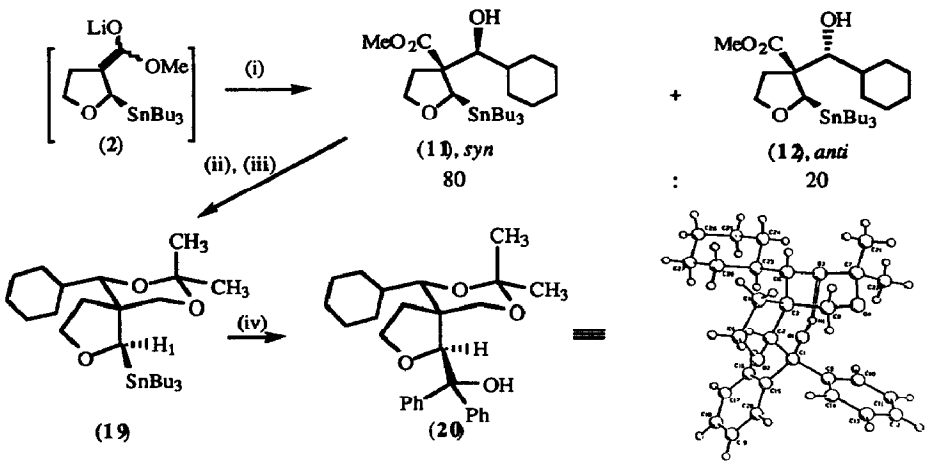
Finally, reaction of the enolate with cyclopent-2-ene-1-one afforded the 1,2-adduct (**15**) (30%; isolated as a 1:1 mixture of diastereoisomers) and the 1,4-adduct (**16**) (30%) as a single diastereoisomer of undefined relative stereochemistry at C_6.



Scheme 4

Stereochemical assignments in the case of the adducts (**9**) to (**14**) are based on subsequent chemical manipulation of the carbon-tin bond providing access to crystalline samples suitable for nmr or crystallographic analysis. In order to verify that transmetallation of the carbon-tin bond in these substrates could be manipulated in a stereospecific manner, the diastereoisomerically pure stannanes (**7**) and (**8**) were subjected to transmetallation (n-BuLi, 1.1 eq.; THF; -78 °C; 30 min.) which upon trapping with benzophenone (1.1 eq.; THF; -20 °C) afforded the crystalline derivatives[2] (**17**) and (**18**) in good overall yields (55% and 75% respectively), **Scheme 3**. Single crystal X-ray analyses of these derivatives established that the transmetallation-alkylation sequence had proceeded with overall retention of configuration, as anticipated from our earlier observations in this series of compounds[1].

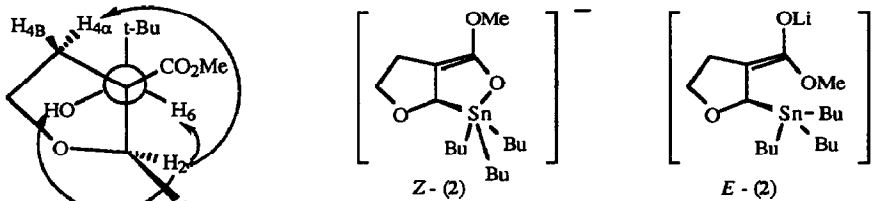
Thus, the major isomer (**11**) from the reaction of the enolate (**2**) with cyclohexylcarboxaldehyde was converted to the the dioxolane (**19**) in 44% overall yield, **Scheme 5**. In an unoptimised sequence, reaction of the stannane (**19**) with n-BuLi (1.1 eq.; THF; -78 °C) followed by alkylation with benzophenone (1.1 eq.; THF; -78 °C) afforded the crystalline adduct (**20**) in 38% overall yield. A single crystal X-ray crystallographic analysis[2] indicated that the alcohol (**20**) had 1R*, 5S*, 6S* relative stereochemistry, which extrapolates to 2R*,



Reagents and conditions:- (i) c-$C_6H_{11}CHO$, 1.1 eq.; THF; - 78 °C; (ii) (a) DIBAL-H, 4.0 eq.; 0 °C; THF; (b) $NaBH_4$, 1 eq, MeOH; 55% (iii) $(CH_3)_2C(OMe)_2$; $SnCl_2$, cat.; DME; 81%; (iv) (a) n-BuLi, 1.1 eq.; THF; - 78 °C; (b) Ph_2CO, 1.1 eq.; THF; - 78 °C; 38%.

Scheme 5

3R*, 6S* (*i.e. syn*) relative stereochemistry for the original aldol adduct (**11**). We tentatively based our assignment of relative stereochemistry in the adducts (**9**) and (**13**) on this stereochemical correlation, regarding the stereochemical course of the aldol reaction with benzaldehyde to be anomalous[3]. Subsequent NOED studies and chemical modification on these aldol products is in agreement with this assertion. For example, in the case of the adduct (**13**), NOED experiments show that irradiation of H_2 (δ 4.20 ppm) causes enhancements at $H_{4\alpha}$ (2.4 %) and H_6 (3.2%) and the hydroxyl proton (4.6%); critically, irradiation of H_6 does not effect an enhancement of $H_{4\alpha}$. We conclude therefore that the adduct has 2R*, 3R*, 6S* (*syn*) relative stereochemistry, and that the t-butyl side-chain adopts an anti-periplanar orientation with respect to C_2-C_3 thereby minimising non-bonded interactions between the hydroxyalkyl side chain and the heterocyclic template, **Figure**.



Figure

Currently we are trying to determine the effect of the β – stannyl moiety upon the stereochemistry of enolate generation (*i.e.* does the hypervalent "ate"- complex[4] *Z* - (**2**) play a role in terms of enolate stabilisation in or product stereochemistry ?) and to utilise intermediates such as (**3**) in target-orientated synthesis.

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References

1. Zhao, Y.; Beddoes, R. L.; Quayle, P. *Tetrahedron Letters*, **1994**, *35*, Submitted.
2. Details of these structure determinations will appear elsewhere.
3. see Amoroso, R.; Cardillo, G.; Mobili, G.; Tomasini, C. *Tetrahedron : Asymmetry*, **1993**, *4*, 2241
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