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A Stereospecific Synthesis of 2,3-Disubstituted Tetrahydrofuran Derivatives

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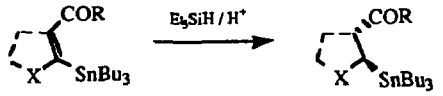
Abstract: *A stereospecific synthesis of 2,3-difunctionalised tetrahydrofurans via a transmetallation-alkylation sequence of the corresponding 2-(tri-butylstannyl)tetrahydrofurans is described.*

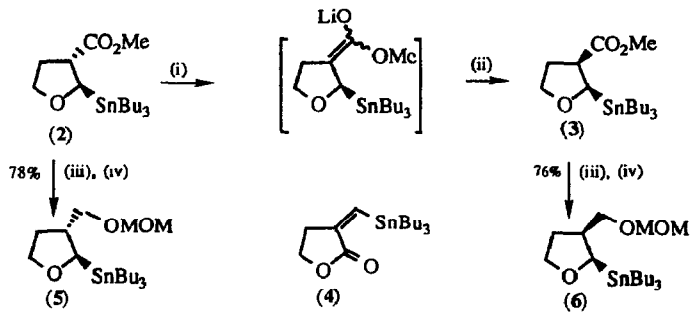
We recently described[1] a facile method for the reduction of β-tributylstannylacrylate derivatives leading to the α-heterofunctionalised stannanes (**1**), **Scheme 1**, and now wish to report that these stannanes serve as useful intermediates for the preparation of 2,3-disubstituted tetrahydrofurans[2].



(1)

Scheme 1

Deprotonation of the *trans*-ester (**2**) under conditions of kinetic control (LDA, 1.1 eq.; THF; -78 °C; 30 mins.) generated the relatively stable enolate, which upon re-protonation (NH_4Cl; -78 °C) afforded the *cis*-ester (**3**) in 66% isolated yield, together with a minor amount (3%) of the rearranged lactone (**4**). Reduction of the ester (**3**) (Dibal-H, 2 eq.; 0 °C; 3 hrs.; 82%) and protection (MOM-Cl, 1.1 eq.; Hunig's base; CH_2Cl_2; 20 °C; 93%) afforded the diastereoisomerically pure stannane (**6**). A similar reduction-protection sequence afforded the



Reagents and condition s:- (i) LDA, 1.1 eq.; THF; -78°C, (ii) NH_4Cl; -78°C; 66%
(iii) Dibal-H, 2 eq.; THF; 0°C; (iv) MOM-Cl; Hunig's base; CH_2Cl_2, 20°C.

Scheme 2

trans-isomer (**5**) in equally high overall yield (78%). Stereochemical assignments in this sequence were based upon the comparison of nOe difference (NOED) spectra of the *cis*- and *trans*-MOM ethers (**5**) and (**6**), in particular, the mutual enhancement between H_2 and H_3 was found to be substantially greater in the case of the

cis-isomer (**6**) (13 - 18 %) when compared to that of the *trans*-isomer (**5**) (1 - 5 %), **Figure 1**. Subsequent chemical transformations and X-ray crystal structure determinations of suitable crystalline derivatives (*vide infra*) substantiated this assertion.

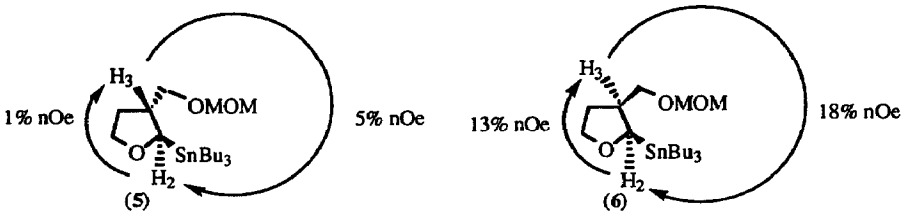
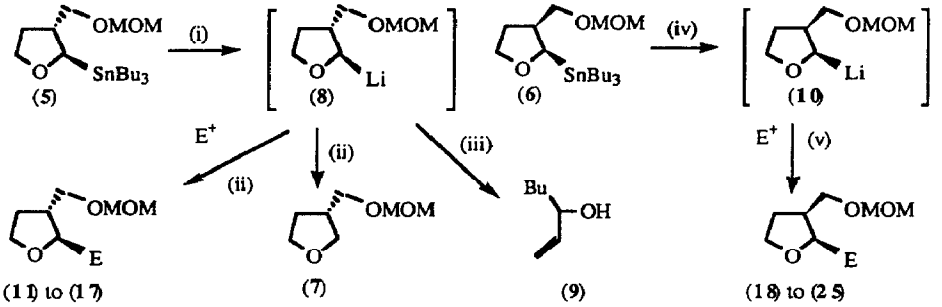


Figure 1

The fragmentation of 2-lithiotetrahydrofuran provides a useful method for the preparation of acetaldehyde lithium enolate[3]. We decided to investigate the effect of an (alkoxy)methyl- group at C_3 upon the rate of this fragmentation reaction. Transmetallation of the *trans*-isomer (**5**) (^{n}BuLi, 1.1 eq.; THF; -78 °C; 0.5 hrs.) followed by a proton quench (NH_4Cl; -78 °C) afforded the ether (**7**) in 69% isolated yield. The anion (**8**) appears to be stable at -50 °C but fragments between -20 °C and 0 °C. Indeed, transmetallation in the presence of an excess of ^{n}BuLi at -78 °C to 0 °C affords the adduct (**9**), albeit in low yield (12%). By comparison the anion (**10**), derived from the *cis*-isomer (**6**), appears to be appreciably more stable indicating little tendency for fragmentation at -20 °C.



Reagents and conditions:- (i) ^{n}BuLi, 1.1 eq.; THF, -78 °C; (ii) NH_4Cl or E^+; -78 °C; (iii) ^{n}BuLi, -78 °C to 0 °C; (iv) ^{n}BuLi, 1.1 eq.; THF, -78 °C; (v) E^+, -78 °C.

Scheme 3

We also surmised that the intermediate organolithiums (**8**) and (**10**) would be configurationally stable [4] and should undergo capture with suitable electrophiles with retention of configuration thereby generating 2,3-disubstituted tetrahydrofurans in a stereospecific manner. Gratifyingly, reaction of the anion (**8**) with benzophenone[5] (1.1 eq.; THF; -20 °C; 30 mins.) afforded the crystalline adduct (**11**) in 84% yield with less than 1% epimerisation at C_2. Similarly, transmetallation of the *cis*-stannane (**6**) (^{n}BuLi, 1.1 eq.; THF; -78 °C to -20 °C) generating the anion (**10**) and reaction with benzophenone (1.1 eq.; -20 °C) afforded the isomeric adduct (**18**), also in good yield (91%). The anion (**10**) appears to be configurationally stable for periods in excess of 60 minutes at -20 °C, showing little sign of fragmentation or epimerisation (< 1%) at C_2 during this time. In these two examples, unambiguous stereochemical assignments were made upon the basis of single crystal X-ray structure determinations[6], **Figure 2**.

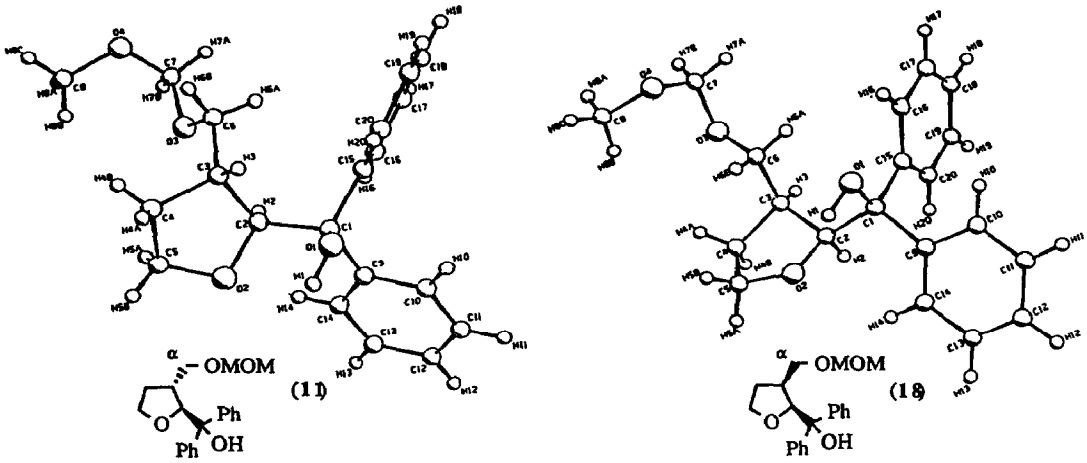


Figure 2

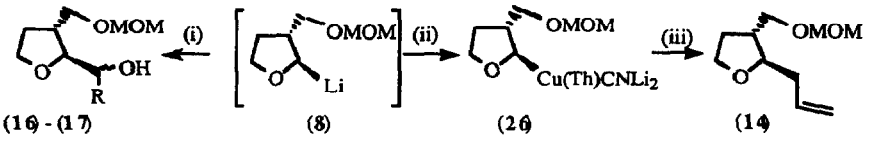
Subsequent investigations have demonstrated that the stannanes (**5**) and (**6**) undergo sequential transmetallation-alkylation reactions with a variety of electrophiles in good to excellent overall yields **Table**. Stereochemical assignments in the case of entries **3** to **8** and **10** to **16** are based upon extensive NOED correlations and high field (75 MHz) ^{13}C assignments. Of diagnostic use in these assignments was the observation that the $^{\alpha}C$ of the *cis*-series experiences a uniform upfield shift (Δ δ 1.5-3.3 ppm) in the ^{13}C spectrum relative to that in the *trans* -series, due to a "γ-gauche" compression effect[7]. Reaction of the anions (**8**) and (**10**) with aldehydes generated the desired carbinols as a 1:1 mixture of diastereoisomers at the newly created stereogenic centre, **Scheme 4** (**Table**; entries **7** to **8** and **14** to **16**).

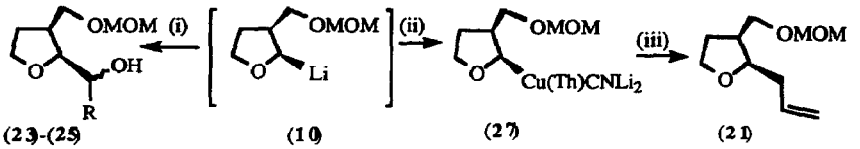
Table

Entry	Anion	Electrophile#	Product	Yield (%)§
1	(8)	NH_4Cl	(7)	69
2	(8)	PhCOPh°°	(11)	78
3	(8)	TMSCl	(12)	87
4	(8)	PhSSPh	(13)	83
5	(26)¶	C_3H_5Br	(14)	62
6	(8)	CH_3COCH_3	(15)	72
7	(8)	PhCHO	(16)	94$
8	(8)	2-Furaldehyde	(17)	88$
9	(10)	PhCOPh°°	(18)	91
10	(10)	TMSCl	(19)	84
11	(10)	PhSSPh	(20)	87
12	(27)¶	C_3H_5Br	(21)	69
13	(10)	CH_3COCH_3	(22)	79
14	(10)	PhCHO	(23)	95$
15	(10)	2-Furaldehyde	(24)	88$
16	(10)	C_4H_9CHO	(25)	41¥

Transmetallation - alkylation carried out at -78 °C;
°° Transmetallation at -78 °C followed by alkylation at -20 °C.
§ Refers to chromatographed material.
¶ (26) and (27) generated *in situ* from (8) and (10) by addition of (2-thienyl)Cu(CN)Li at -78 °C.
$ Isolated as a 1:1 mixture of diastereoisomers.
¥ Isolated as a 1:1 mixture of the diastereoisomeric 4-nitrobenzoate derivatives.

Reaction of the organolithium reagents (**8**) and (**10**) with alkyl halides (e.g. allyl bromide) was hampered by competing electron transfer processes. However, conversion of the anions (**8**) and (**10**) to the higher-order cuprates[8] (**26**) and (**27**) ((2-thienyl)Cu(CN)Li, 1 eq.; THF; -78 °C; 30 mins.) prior to alkylation afforded the alkylated tetrahydrofurans (**14**) and (**21**) in good yields (62% and 69% respectively) with retention of configuration[9] at C_2, **Scheme 4**.





Reagents and conditions:- (i) RCHO; THF; -78 °C; (ii) Cu(CN)(2-Th)Li, 1.1 eq.; THF; -78 °C; (iii) C_3H_5Br, 1.1 eq., -78 °C; 30 mins.

Scheme 4

In conclusion, we have demonstrated that 2,3-disubstituted tetrahydrofurans are accessible in a stereospecific manner from the readily available functionalised tetrahydrofuran-2-yl stannanes. Synthetic applications of this methodology are currently under investigation.

ACKNOWLEDGEMENTS.

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REFERENCES AND NOTES.

1. Zhao, Y.; Quayle, P.; Kuo, E. A. *Tetrahedron Letters*, preceding paper.
2. Racemic mixtures of compounds were prepared throughout; only one enantiomer shown for clarity. All new compounds were fully characterised by ^1H nmr (300 MHz), ^{13}C nmr (75 MHz), ir and / or high resolution mass spectrometry / combustion microanalysis.
3. see Still, W. C.; Sreekumur, C. *J. Am. Chem. Soc.*, **1980**, *102*, 1201; Cohen T.; Stokes, S. *Tetrahedron Letters*, **1993**, *34*, 8023; Sato, T. *Synthesis*, **1990**, 259 and refs. therein.
4. e.g. Tomooka, K.; Igarshi, T.; Nakai, T. *Tetrahedron Letters*, **1993**, *34*, 8139; for a mini review see Aggarwal, V. K. *Angew. Chem., Intd. Edn. Engl.*, **1994**, *33*, 175.
5. Benzophenone reacts sluggishly with the anions (**8**) and (**10**), requiring reaction temperatures of *ca* -20 °C to effect alkylation. All other alkylation reactions were conducted at -78 °C.
6. Zhao, Y; Beddoes, R. L.; Quayle, P. Unpublished results.
7. Tamaru, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Letters*, **1985**, *26*, 2885.
8. For a comprehensive review see Lipshutz, B. H.; Sengupta, S. *Organic Reactions*, **1992**, *41*, 135.
9. For related examples see Linderman, R. J.; Griedel, B. D. *J. Org. Chem.*, **1990**, *55*, 5428.

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