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[2,3]Wittig Rearrangement of Enantiomerically-Defined α-(Allyloxy)stannanes: Solid Evidence for Inversion of Configuration at the Lithium-Bearing Migrating Terminus

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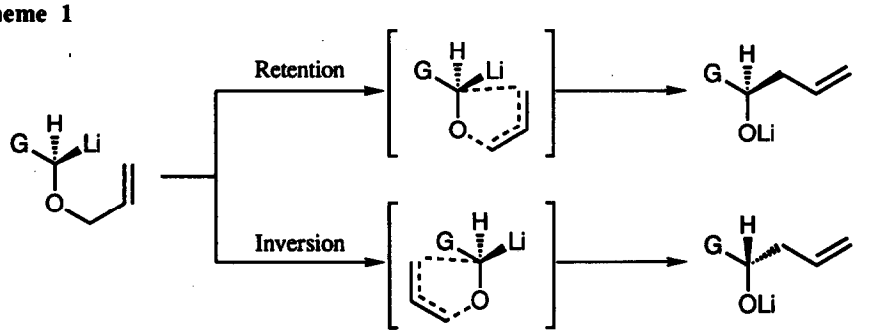
Abstract: *The [2,3]Wittig rearrangement of enantiomerically-defined α-(allyloxy)stannanes, prepared from (S)-1-tributylstannyl-1-propanol, with butyllithium is shown to proceed with essentially complete inversion of configuration at the lithium-bearing migrating terminus. This inversion stereochemistry is further confirmed by the rearrangement of diastereomerically-defined α-(allyloxy)stannanes.*

The [2,3]Wittig rearrangement has currently enjoyed widespread use in stereocontrolled synthesis.[1] However, the most fundamental question of [2,3]Wittig stereochemistry is the subject of much controversy that concerns the stereochemical course (inversion vs. retention) at the lithium-bearing terminus (Scheme 1). Conflicting conclusions might be drawn from the recent theoretical calculations on the transition state structures for the rearrangement of allyl lithiomethyl ether.[2, 3]

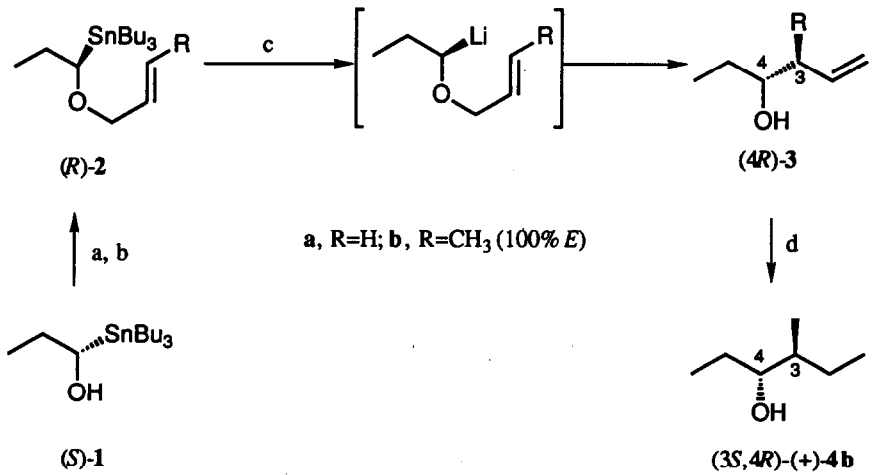
Scheme 1



More recently Verner and Cohen have reported the first experimental evidence for the inversion course in the reductive lithiation-based [2,3]Wittig process of a rather complicated, *diastereomerically-defined* tetrahydropyran system which considerably competes with the [1,2]Wittig process.[4] We now disclose more

clear-cut evidence for complete inversion of configuration in the transmetalative [2,3]Wittig process using the *enantiomerically-defined* α-(allyloxy)stannanes **2** as the substrates (Scheme 2).[5]

Scheme 2

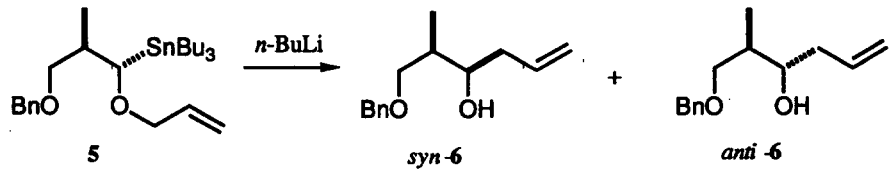


Reagents: (a) MsCl, Et_3N, CH_2Cl_2, -23 °C; (b) RCH=CHCH$_2$OK, Et_2O, 20 °C; (c) *n*-BuLi (1.5 equiv), THF, -78 °C; (d) H_2, Pd-C,MeOH, 20 °C.

The optically active substrates (*R*)-**2a** and (*R*)-**2b** required for this study were successfully prepared in *ca.* 65% overall yield from (*S*)-α-stannyl alcohol **1**[6] via mesylation followed by S_N2 reaction with the potassium allylic alcoholate which proceeds with complete inversion of configuration.[7, 8] Treatment of (*R*)-**2a** (62% ee)[9] with *n*-BuLi at -78 °C was found to afford the rearrangement product (*R*)-**3a** in 62% ee (90% yield).[10] A similar rearrangement of (*R*,*E*)-**2b** (88% ee, 100% *E*)[9] gave rise to the (3*S*,4*R*)-*anti* isomer **3b** in 87% ee and >99% de (95% yield).[11] Hydrogenation of **3b** furnished an ant pheromone[12] (3*S*,4*R*)-**4b**: $[\alpha]_D^{22}$ +2.2° ($CHCl_3$); lit.[12] $[\alpha]_D^{22}$ +2.5° ($CHCl_3$). Since complete retention of configuration has been well established for the Sn/Li exchange process involved,[13] these findings indicate clearly that the [2,3]Wittig rearrangement proceeds with essentially complete inversion of configuration at the Li-bearing terminus. This means that the lithium cation locates outside the pericyclic array in the transition state as predicted theoretically by Houk *et al.*[2] It should be noted that the extremely high *E* → *anti* diastereoselection observed here is also consistent with Houk's calculations.[2, 14]

This inversion stereochemistry was further confirmed by experiments using the *diastereomerically-defined* stannane **5**.[15] The rearrangement of the *anti*-rich substrates, prepared from the corresponding *syn*-rich α-stannyl alcohols[16] via the above-mentioned procedure, was found to afford the *syn*-rich products **6** (Scheme 3).[17]

Scheme 3



5 *syn*-**6** *anti*-**6**

63% *anti*	⟶	66 :	34	(91%)
82% *anti*	⟶	91 :	9	(94 %)

In summary, this work presents the strongest pieces of evidence in support of complete inversion of configuration at the Li-bearing migrating terminus in the [2,3]Wittig process via Sn/Li exchange. A key unanswered question is whether this inversion course is also the case for the synthetically more useful [2,3]Wittig variants induced by *direct lithiation*. In addition, this study opens a way to otherwise difficult preparations of enantiomerically-defined (α-alkoxy)alkylstannanes which would provide great opportunity to investigate the stereochemistry of various carbanion reactions. Further works along these lines are in progress.

References and Notes

1. For recent reviews; see: (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (b) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594. (c) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: London, **1991**; Vol. 3, 975-1014.
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4. Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375.
5. Presented at the 61st Annual Meeting of Chemical Society of Japan, Yokohama, April 1991.
6. Chang, P. C. -M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584. The MOM ether of (*S*)-**1** showed a positive optical rotation.
7. All attempts to prepare **2** via *O*-allylation of **1** with allyl halides or allyl tosylate failed.
8. The completete inversion of configuration in this S_N2 reaction was proved by the transformation of (*R*)-**2a** (62% ee) to (*R*)-**1** (62% ee) via the double bond migration (*t*-BuOK, DMSO, 50 °C) followed by hydrolysis of resulting enol ether (aq. HCl, acetone).
9. The %ee refers to that of the starting stannyl alcohol employed, which was determined by ^{1}H NMR of the MTPA ester.

10. The %ee was determined by ^{1}H NMR of the MTPA ester and the (*R*)-configuration was assigned by ^{1}H NMR comparison of the MTPA ester of 1-*t*-butyldiphenylsiloxy-4-hexanol derived from **3a** (BH_3•THF → *t*-$BuPh_2SiCl$) with an authentic sample prepared from (*R*)-(+)-γ-caprolactone.
11. The %ee was determined by HPLC analysis of its MTPA ester and the %de was determined by capillary GLC analysis. The *anti*-configuration was assigned by its GLC comparison with an authentic *syn*-rich sample prepared by the literature method: Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.
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13. (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.;McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.
14. Interestingly, the rearrangement of (*Z*)-**2b** (*racemic*) was found to provide *syn*-**3b** selectively (*syn*/*anti* = 90 : 10).
15. Quite recently R. Brückner (Würzburg) has also obtained evidence for inversion of configuration in the rearrangement using a related, diastereomerically-defined α-(allyloxy)stannane (personal communication). We thank him for sending the manuscript prior to publication.
16. Prepared via reaction of 3-benzyloxy-2-methylpropanal with (n-Bu)$_3$SnLi in THF (*syn*/*anti* = 66 : 34) and partially separated by column chromatography to afford the mixture of 82% *syn*. The *syn*-configuration of the major isomer was assigned by its transformation (with complete retention of configuration)[13] to 1-benzyloxy-2-methyl-3-butanol (MOMCl / (i-Pr)$_2$NEt → n-BuLi / Me_2SO_4 → HCl, MeOH) of which ^{1}H NMR data were correlated with those reported for an *anti*-rich mixture: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.
17. The stereochemical assignment was made by ^{1}H NMR comparison with the litrature values: Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. The diastereomeric ratio was determined by ^{13}C NMR assay. The reason for the discrepancy of %de between **5** and **6** is not clear at present, but might be due to the asymmetric induction involved.

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