Tetrahedron Letters,Vol.30,No.50,pp 7037-7040,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOMERICALLY ENRICHED ALLYLSTANNANES FROM CHIRAL ALLYLLITHIUM DERIVATIVES AND THEIR HIGHLY REGIO-, DIASTEREO- AND ENANTIOSELECTIVE HYDROXYALKYLATION#

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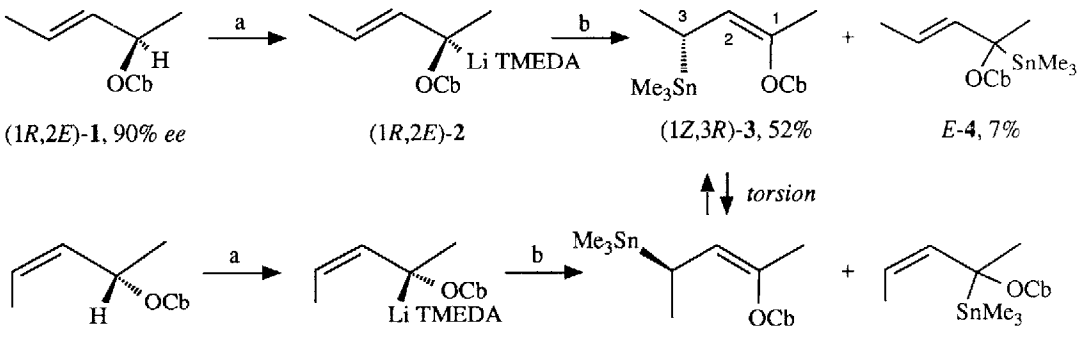
Summary: Chiral, non-racemic 1-lithio-2-alkenyl carbamates, generated by stereospecific deprotonation, are stannylated in a *syn*-S_E' reaction. The optically active allylstannanes thus obtained, undergo enantioselective homoaldol addition under the influence of $TiCl_4$.

Oxy-substituted allylic stannanes have some importance in stereocontrolled organic synthesis.[1,2] However, only few optically active alkenyl stannanes, prepared by resolution of the racemates, have been reported.[3] Furthermore, no information is available on the stereochemistry of the delithiostannylation in allylic systems, owing to the fact that configurationally stable chiral allyllithium derivatives were unknown.

Recently, we succeeded in generating the non-racemic α-lithiocarbamate (1*R*,2*E*)-**2** by stereospecific deprotonation[4] of the 2-alkenyl carbamate (1*R*,2*E*)-**1**, followed by its titanation and α-hydroxyalkylation. We now investigated the stannylation. The suspension of (1*R*,2*E*)-**2**, obtained from the carbamate (1*R*,2*E*)-**1**, 90% *ee*, was trapped at -70 °C with chlorotrimethylstannane.[5] After chromatographic separation of some unstable α-adduct **4**, the γ-stannane[6] (+)-(1*Z*,3*R*)-**3** was isolated with 52% yield, $[\alpha]_D^{20}$ = +133, c = 1.68, $CHCl_3$, (run 1). Starting from the stereoisomer (1*S*,2*Z*)-**1**, readily prepared from ethyl (*S*)-lactate[7], (+)-(1*Z*,3*R*)-**3**[6] (55%), $[\alpha]_D^{20}$ = +138, c = 1.88, $CHCl_3$, was also obtained besides 5% of (-)-(1*E*,3*S*)-**3**[5,6,8] (run 2), Scheme 1.

Scheme 1



(1*R*,2*E*)-**1**, 90% *ee* (1*R*,2*E*)-**2** (1*Z*,3*R*)-**3**, 52% *E*-**4**, 7%

(1*S*,2*Z*)-**1**, 100% *ee* (1*S*,2*Z*)-**2** (1*Z*,3*R*)-**3**, 55% *Z*-**4**, 6%

a: *s*-BuLi/TMEDA, *n*-hexane, -78° C
b: $ClSnMe_3$
Cb = $(C{=}O)NiPr_2$

+ (1*E*,3*S*)-**3**, 5%

The absolute configuration of the stannanes **3** was determined by the application of the Brewster rule[9] which gives reliable results in cases where the substituents at the stereogenic centre differ significantly in their polarizability (Me_3Sn > CH=CHOCb > CH_3 > H). Thus, the (*R*)-configuration was assigned to (+)-**3**. By chemical correlation, as outlined below (Scheme 2 and 3), the correct assignment is confirmed; the enantiomeric excess of the stannane (1*Z*,3*R*)-**3** was found to be >76% (run 1) and >83% (run 2), respectively. Hence, the delithiostannylation proceeds in a *syn*-S_E· fashion; the chirality transmission, including three further electrophilic substitution steps, is at least 80% *ee*.[10]

Unlike to α-(oxyallyl)stannanes,[3] **3** does not undergo an uncatalyzed addition reaction with benzaldehyde at 150 °C. In contrast, the presence of equimolar amounts of $TiCl_4$ in a solution of (1*Z*,3*R*)-**3** and of an aldehyde at -78 °C causes, surprisingly, the formation of the diastereomerically pure γ-addition products **6** with 82 to 83% *ee*[11,12,13] (Scheme 2, Table 1). The formal allylic retention contrasts to the regiochemical course of the usual Lewis acid catalyzed allylstannane reactions.[2] The result is best explained by assumption of a stereospecific formation (*syn*-S_E·) of the α-trichlorotitanium substituted intermediate **5** via TS **A** followed by the stereospecific aldehyde addition via TS **B** in the usual way.[4]

Since (1*Z*,3*R*)- and (1*E*,3*S*)-**3** differ in both stereogenic elements, a *syn*-stereospecific metal exchange must lead to the intermediate **5** with equal absolute configuration; hence, the separation of the minor stereoisomer is not necessary for this purpose.

Scheme 2

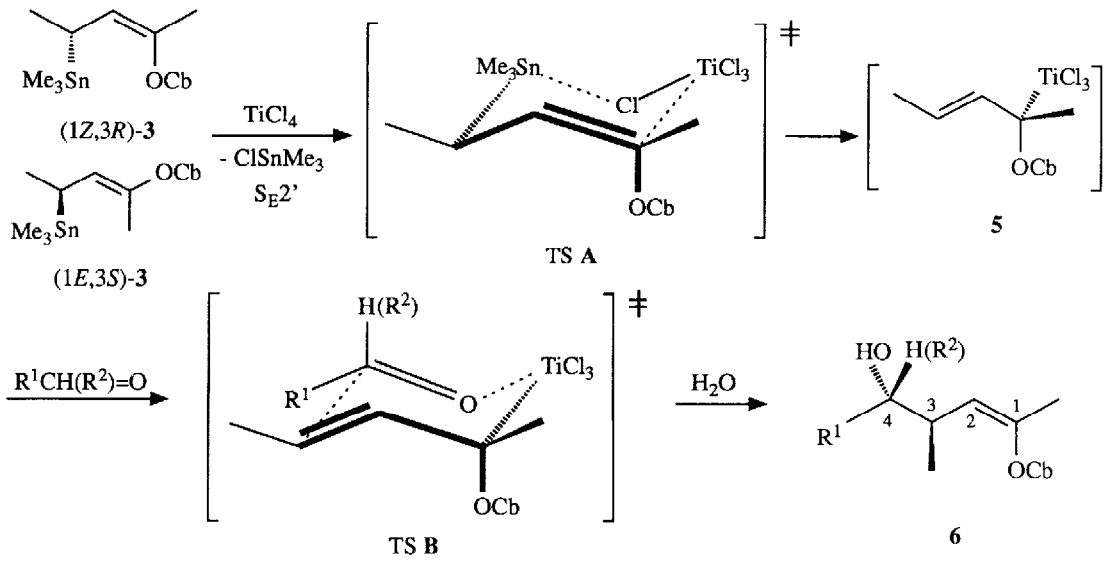
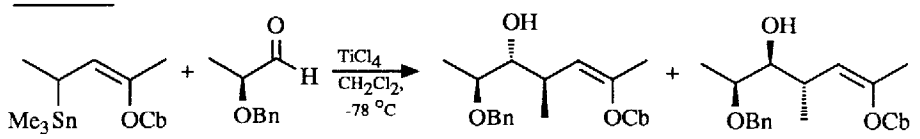


Table 1:	Educt	Product	R^1	R^2	Yield	ee[12]
	(1*Z*,3*R*)-**3** (run 2)	**6a**	$(CH_3)_2CH$	H	85%	82%
	(1*Z*,3*R*)-**3** (run 2)	**6b**	C_6H_5	CH_3	83%	83%

The reagent **5** exhibits a high degree of reagent-controlled chirality transfer: In the reaction of (1*Z*,3*R*)-**3**, prepared from (1*R*,2*E*)-**1**, with (*S*)-2-(benzyloxy)propanal (*S*)-**7**, the enantiomerically pure homoaldol adducts[4a] (-)-**8** and (+)-**9** were formed in a ratio of 88:12, whereas the reaction of *rac*-(1*Z*)-**3** gave both in equal amounts[14] (Scheme 3).

Scheme 3



3 (*S*)-**7** (-)-**8** (+)-**9**

rac-(1*Z*)-**3**	51	:	49
(1*Z*,3*R*)-**3**	88	:	12

Apart from constituting masked optically active γ-hydroxyketones, the carbamates **6a**, **8** or **9** have been utilized as enolate equivalents in a highly stereoselective Lewis acid catalyzed synthesis of substituted tetrahydrofurans.[15]

Acknowledgements: Generous support by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged.

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Dedicated to Professor Wolfgang Lüttke on the occasion of his 70th birthday.

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2. a) J.-P. Verlhac, J.-P. Quintard, M. Pereyre *J. Chem. Soc., Chem. Commun.* **1988**, 503; and references; b) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama *Tetrahedron* **1984**, *40*, 2239; c) C. Hull, S.V. Mortlock, E.J. Thomas *Tetrahedron Lett.* **1987**, *28*, 5343; d) M. Koreeda, Y. Tanaka *Tetrahedron Lett.* **1987**, *28*, 143; e) J.A. Marshall, B.S. Dehoff, S.L. Crooks *Tetrahedron Lett.* **1987**, *28*, 527; f) G. Keck, D.E. Abbott, M.R. Wiley *Tetrahedron Lett.* **1987**, *28*, 139; g) B.L. Chenard *Tetrahedron Lett.* **1986**, *27*, 2805; h) D. Seyferth, R.E. Mammarella, H.A. Klein *J. Organometal. Chem.* **1980**, *144*, 1.

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5. Typical procedure: To a solution of (1*S*,2*Z*)-**1** (1.0 mmol) and TMEDA (1.1 mmol) in *n*-pentane (2 mL), a solution of *sec.*-butyllithium (1.1 mmol) in cyclohexane/isopentane is introduced through a syringe below -70°C. After 1 h, chlorotrimethylstannane (1.3 mmol) in *n*-pentane (2 mL) is injected. Acidic aqueous workup and LC on silica gel (ether/pentane, 1:10) yielded 206 mg (55%) (1*Z*,3*R*)-**3**, 23 mg (6%) (2*Z*)-**4**, and 19 mg (5%) (1*E*,3*S*)-**3**.

6. (1*Z*,3*R*)-**3**: $[\alpha]_D^{20}$ = +133 (c = 1.68, $CHCl_3$); 300 MHz ^1H NMR ($CDCl_3$): δ = 0.045 (s, $SnMe_3$), 1.226 (d, 4-H_3), 1.231 [d, NCH(CH_3)$_2$], 1.889 (d, 1-CH_3), 2.199 (dq, 3-H), 3.78 and 4.05 (m, NC*H*), 4.893 (dq, 2-H); J_{iPr} = 7.18 Hz, $J_{1',2}$ = 0.98 Hz, $J_{2,3}$ = 11.36 Hz, $J_{3,4}$ = 7.32 Hz;
75 MHz ^{13}C NMR ($CDCl_3$): δ = -10.72 ($SnMe_3$), 17.77 (C-4), 18.22 (C-3), 19.65 (C-1'), 21.14 [NCH(CH_3)$_2$], 46.04 (NCH), 121.97 (C-2), 139.95 (C-1), 153.11 (C=O).
(1*E*,3*S*)-**3**: (contaminated by (1*Z*,3*R*)-**3**); 300 MHz ^1H NMR ($CDCl_3$): δ = 0.091 (s, $SnMe_3$), 1.229 [d, NCH(CH_3)$_2$], 1.278 (d, 4-H_3), 1.829 (d, 1-CH_3), 2.073 (dq, 3-H), 3.78 and 4.05 (m, NC*H*), 5.112 (dq, 2-H); J_{iPr} = 7.18 Hz, $J_{1',2}$ = 1.10 Hz, $J_{2,3}$ = 11.84 Hz, $J_{3,4}$ = 7.33 Hz;

75 MHz ^{13}C NMR ($CDCl_3$): δ = -10.87 ($SnMe_3$), 15.91 (C-1') 17.95 (C-4) 18.92 (C-3), 21.07 [NCH(CH_3)$_2$], 46.05 (NCH), 122.44 (C-2), 140.19 (C-1), 154.38 (C=O).

7. J.-R. Schwark, D. Hoppe *Synthesis*, in press.

8. As it follows from the analysis of α-substitution products of (*Z*)-**2**, in which the (2*Z*)-double bond is retained, no formation of (*E*)-**2** occurs under the reaction conditions.

9. a) B. Testa *Grundlagen der Organischen Stereochemie*, Verlag Chemie, Weinheim, 1983; b) J.H. Brewster *Top. Stereochem.* **1967**, *2*, 1; c) E.L. Eliel *Stereochemie der Kohlenstoffverbindungen*, Verlag Chemie, Weinheim, 1966.

10. We were unable to determine the enantiomeric composition of compounds **3** by direct methods. Its enantiomeric purities, most likely, are higher than concluded from the addition adducts **6**,**8**, and **9** since a "stereochemical leak" may exist in the tin titanium exchange: If, to a small extend, the 3-methyl group (TS **A**) occupies a pseudo-axial position, the stereocenter in **5** will be formed in some degree with opposite configuration.

11. Typical procedure: To a solution of (1Z,3R)-**3** (1.0 mmol) and the aldehyde or ketone (1.0 mmol) in CH_2Cl_2 (2 mL) at -78 °C, $TiCl_4$ (1.0 mmol) is added dropwise. After 0.5 h acidic aqueous workup followed by LC on silica gel, affords exclusively **6** or **8** and **9**.

12. The enantiomeric excess was determined by ^1H NMR using Eu(hfc)$_3$ (**6a**: 15mol%, **6b**: 5mol%).

13. (1*Z*,3*R*,4*S*)-**6a**: 300 MHz ^1H NMR ($CDCl_3$): δ = 0.741 (d, 3-CH_3), 0.852 (d, 6-H_3), 0.901 (d, 5-CH_3), 1.175 [d, NCH(CH_3)$_2$], 1.663 (qqd, 5-H), 1.807 (1-CH_3), 2.373 (ddq, 3-H), 2.836 (4-OH), 3.003 (dd, 4-H), 3.73 and 4.02 (m, NC*H*), 4.858 (dq, 2-H); J_{iPr} = 6.8 Hz, $J_{1',2}$ = 1.2 Hz, $J_{2,3}$ = 10.3 Hz, $J_{3,3'}$ = 6.8 Hz, $J_{3,4}$ = 8.3 Hz, $J_{4,5}$ = 3.4 Hz, $J_{5,5'}$ = 6.8 Hz, $J_{5,6}$ = 6.8 Hz;
75 MHz ^{13}C NMR ($CDCl_3$): δ = 14.52 (C-3'), 17.14 (C-6), 19.88 (C-1'), 20.05 (C-5'), 21.21 [NCH(CH_3)$_2$], 29.71 (C-5), 34.29 (C-3), 45.55 and 46.53 (NC*H*), 79.07 (C-4), 119.79 (C-2), 145.33 (C-1), 153.56 (C=O).
(1*Z*,3*R*,4*S*)-**6b**: 300 MHz ^1H NMR ($CDCl_3$): 0.774 (d, 3-CH_3), 1.285 [d, NCH(CH_3)$_2$], 1,519 (s, 4-CH_3), 1.920 (d, 1-CH_3), 2.696 (dq, 3-H), 3.64 (4-OH), 3.87 and 4.13 (m, NC*H*), 4.974 (dq, 2-H), 7.1 - 7.5 (C_6H_5); J_{iPr} = 7.0 Hz, $J_{1',2}$ = 1.1 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,3'}$ = 7.0 Hz;
75 MHz ^{13}C NMR ($CDCl_3$): δ = 16.281 (C-3'), 20.316 (C-1'), 20.61 and 21.45 [NCH(CH_3)$_2$], 22.993 (C-4'), 42.923 (C-3), 46.03 and 46.79 (NC*H*), 75.884 (C-4), 118.368 (C-2), 125.922 (Ph-3, Ph-5), 126.318 (Ph-4), 127.545 (Ph-2, Ph-6) 146.211 (C-1), 147.666 (Ph-1), 159.712 (C=O).

14. For the method of analysis see ref. 4a and R.W. Hoffmann, J. Lanz, R. Metternich, G. Tarara, D. Hoppe *Angew. Chem.* **1987**, *99*, 1196; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1145.

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(Received in Germany 30 September 1989)