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An Efficient Method in Stannylcupration of a Methyl Substituted Enyne or Alkyne by Kinetic Control Using Methanol

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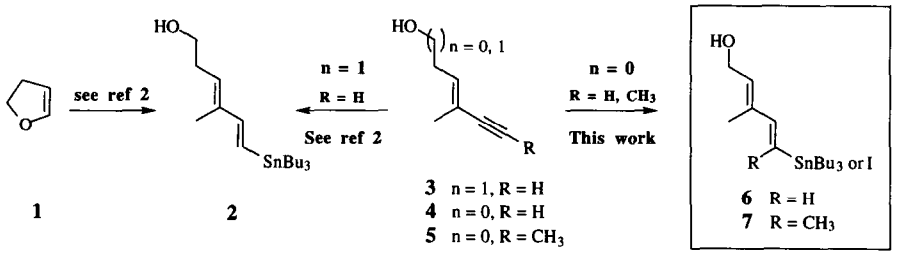
Abstract: Stannylcupration of enyne **5** was performed with the homostannylcuprate $(Bu_3Sn)_2CuCNLi_2$ to deliver in a stereoselective way the distal dienylstannane **7** in 77% yield. This reaction was reproducible only when methanol was added to the cuprate solution. In comparison, hydroboration or hydrozirconation reactions failed in this case to produce the corresponding boron or zirconium derivative. © 1997 Elsevier Science Ltd.

Dienylstannanes have become important intermediates in organic synthesis in the last ten years. Due to their stability and ability to perform transition metal catalyzed cross-coupling reactions and tin-lithium exchange reactions,[1] dienylstannanes are interesting building blocks for the total synthesis of dienic or polyenic natural compounds.

In a preceding study [2] an efficient preparation of substituted dienylstannanes such as **2** (82% yield) using a metallate rearrangement starting from the lithium derivative of **1** was developed (Scheme 1). After we described this new synthetic approach of dienylstannnes, a regio- and stereocontrolled stannylcupration of the enyne **3** was also performed to obtain compound **2** in a stereospecific manner in 85-90% yield.[2]

Scheme 1



The question we examine in this paper is the conversion of the methylated enyne **5** to the particular dimethyl diene derivative **7**, which we need for the total synthesis of a natural antibiotic. The enyne **4** is also used as a reference in the different reactions we examined to prepare **6** and **7**.

Hydroboration of acetylenic compounds [3] as well as enyne derivatives [4] has been reported but in this latter case only few examples of substituted enynes (on the triple bond function) were described and no example with a methyl-substituted enyne. Using the Brown methodology,[3a] hydroborations of the enyne **4** or **5** did not deliver the expected boranes derivatives **6a** or **7a** or the corresponding iodo compounds **6b** or **7b** after a boron-halogen exchange.[3c] Under hydrozirconation conditions using Schwartz' reagent [5] the enyne **4** reacted smoothly to furnish after a Zr-I_2 exchange the iodo compound **6b** in quantitative yield.[6] Using the same conditions methylated enyne **5** did not lead to the desired iodo derivative **7b** (Scheme 2).

These results led us to turn our efforts to the stannylcupration [7] of enyne **4**. Using the higher order $(Bu_3Sn)BuCuCNLi_2$ cyanocuprate,[8] [$(Bu_3Sn)BuCuCNLi_2$, 2 equiv, THF/Et_2O 3:1, -30°C to -20°C, 2 h, then NH_4Cl/NH_4OH 5:1, -20°C], the pure (*E,E*)-dienylstannane **6** was obtained in excellent yield.

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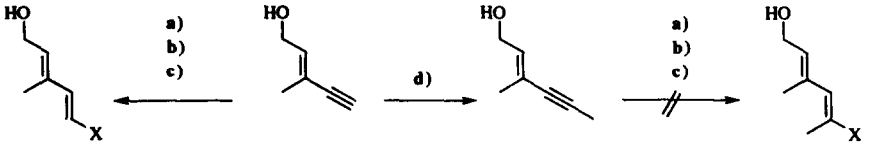
Scheme 2



6 X = $SnBu_3$ **92%**
6a X = $B(Sia)_2$ **0%**
6b X = I **>95%**

4

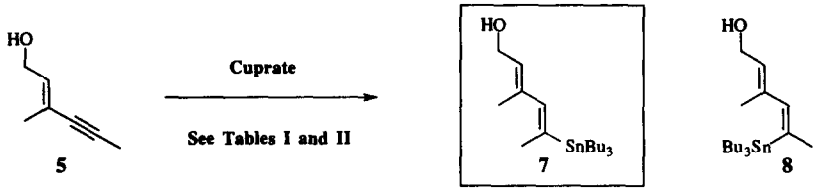
5

7 X = $SnBu_3$
7a X = $B(Sia)_2$
7b X = I

a) $(Bu_3Sn)BuCuCNLi_2$, THF/Et_2O 3:1, -40° -30°C, 1 h, → **6** 92%, **7** 0%. **b)** $BH(Sia)_2$, THF, -15°C to 0°C, → **6a** or **7a** 0%. **c)** $(H)ClZrCp_2$, THF, 40°C, then I_2, Et_2O, 0°C, → **6b** 93%, → **7b** 0%. **d)** *n*-BuLi,THF then MeI, → **5** > 95%.

Under the same thermic conditions the enyne derivative **5** did not react; when the reaction was performed using 4 equivalents of the cuprate for 12 h at -20°C, dienylstannane **7** was isolated in less than 5% yield (Table I, Entry 1).

Scheme 3



5 **7** **8**

Table I: Stannylcupration of enyne **5** in THF/Et_2O 3:1

Entry	Cuprate	T (°C)	t (h)	Yield (%)	7/8
1	4 equiv. $(Bu_3Sn)BuCuCNLi_2$	-20	12	**<5**	95:5
2	"	-10	"	44	95:5
3	"	-5	"	40	95:5
4	4 equiv. $(Bu_3Sn)MeCuCNLi_2$	-10	"	**62**	**95:5**
5	"	0	"	39	95:5
6	4 equiv. $(Bu_3Sn)_2CuCNLi_2$ *	-10	"	**16**	**95:5**

* This reaction was performed in pure THF

The best results were obtained when the reaction was performed at -10°C, the yield of **7** increasing to 44 % whereas the corresponding isomer **8** was also detected (**7/8** >95:5, Table I, see Entries 2-3). The homostannylcyanocuprate $(Bu_3Sn)_2CuCNLi_2$ [9] was also tested but reaction led to **7** in only 16% yield (Table I, Entry 6). On another hand when the methylcuprate $(Bu_3Sn)MeCuCNLi_2$ was used in place of the corresponding butylcuprate $(Bu_3Sn)BuCuCNLi_2$ the dienylstannane **7** was prepared in 62% yield (Table I, Entry 4).

At this time we thought that this problem was solved, but we were unable to reproduce these results some months later even when all the reactants were controlled and the stannylcupration reaction tested again!

One of the possible explanations for these non-reproducible results was the instability of the intermediate dienylcuprate in the reaction conditions we used (-5°C to -10°C for 12 h). We thus performed the stannylcupration reaction in presence of a proton source, as described by Piers,[10] Cummins,[11] and Oehlschlager,[12] with addition of methanol to the cuprate solution, in order to trap the intermediate dienylcuprate and insure the formation of the kinetic dienylstannane in a non-reversible way.

Using the homocuprate $(Bu_3Sn)_2CuCNLi_2$, stannylcupration was performed by gradual addition of MeOH. As depicted in Table II, the yield of dienylstannane **7** was improved from 27 to 71% when 4 to 110 equivalents of MeOH were added to the cuprate solution (Table II, see entries 7-11).[13] Under the same conditions (110 equiv. of MeOH), reactions of the mixed cyanocuprates $(Bu_3Sn)MeCuCNLi_2$ and $(Bu_3Sn)BuCuCNLi_2$ also delivered the expected dienylstannane **7** in 63% yield but compounds **7** and **8** where obtained in a 90:10 ratio (Table II, see entries 13, 14). The best result was at last obtained when 2

equivalents of the homocuprate $(Bu_3Sn)_2CuCNLi_2$ and 110 equivalents of MeOH were used, the dienylstannane **7** was produced in 77% yield on a 22 mmol scale (2.5g of enyne **5**, Table II, see entry 12).

Table II: Stannylcupration of enyne **5** in THF/MeOH

Entry	Cuprate	T (°C)	t (h)	MeOH (equiv)	Yield (%)	7/8
7	4 equiv. $(Bu_3Sn)_2CuCNLi_2$	-10	12	4	27	100:0
8	"	"	"	15	36	100:0
9	"	"	"	55	64	100:0
10	"	"	"	**110**	**71**	**100:0**
11	"	"	"	150	49	100:0
12	**2 equiv. $(Bu_3Sn)_2CuCNLi_2$**	**-10**	**12**	**110**	**77**	**100:0**
13	4 equiv. $(Bu_3Sn)BuCuCNLi_2$	"	"	110	**63**	**90:10**
14	4 equiv. $(Bu_3Sn)MeCuCNLi_2$	"	"	110	**63**	**90:10**

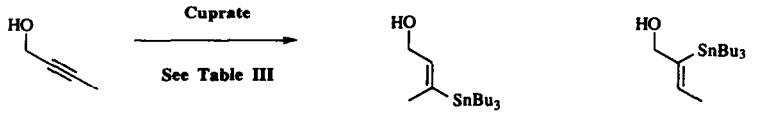
As shown in Table II the slow rate of the quench reaction required in this case 110 equivalents of MeOH for an efficient process,[14] especially when the homocuprate $(Bu_3Sn)_2CuCNLi_2$ was used.

The most interesting point in these conditions was to get a stereospecific, efficient and reproducible reaction. Compound 7 was obtained from enyne 5 as the pure (E,E) regio- and stereoisomeric derivative and could be considered as the kinetic product in this reaction.

In order to corroborate the beneficial effect of MeOH in stannylcupration reactions, we examined at the reactivity of the propargylic derivative **9**.

When the mixed cyanocuprate $(Bu_3Sn)BuCuCNLi_2$ was used, without MeOH addition, the reaction seemed to be reproducible but gave the pure proximal vinylstannane **11** in moderate yield (42%, Table III, entry 14); this isomer corresponding to a *trans* addition of the stannylcuprate is the thermodynamic product. The same reaction performed with the $(Bu_3Sn)MeCuCNLi_2$ cuprate led to the two vinylstannanes isomers **10** and **11** in a 65:35 ratio (54%, Table III, entry 16). Using the homocuprate $(Bu_3Sn)_2CuCNLi_2$ the stannylcupration reaction run in better yield (82%) to afford **10** and **11** in a 30:70 ratio (Table III, entry 18).

Scheme 4



9 **10** **11**

Table III: Stannylcupration of alkyne **9** in THF/MeOH at -10°C for 12 h

Entry	Cuprate	MeOH (equiv)	Yield (%)	10/11
14	4 equiv. $(Bu_3Sn)BuCuCNLi_2$	/	42	0:100
15	"	110	**71**	**100:0**
16	4 equiv. $(Bu_3Sn)MeCuCNLi_2$	/	54	65:35
17	"	110	**65**	**100:0**
18	4 equiv. $(Bu_3Sn)_2CuCNLi_2$	/	82	30:70
19	"	110	**70**	**100:0**

In these thermodynamic conditions, and depending of the cuprate, the regioisomers **10** and **11** are obtained in different ratio. When MeOH was added (110 equiv.) in the cuprate solution, stannylcupration reactions performed with the different stannylcuprates $(Bu_3Sn)BuCuCNLi_2$, $(Bu_3Sn)MeCuCNLi_2$ or $(Bu_3Sn)_2CuCNLi_2$ furnished, in all cases, the pure distal regioisomer **10** (Table III, entries 15, 17, 19) in 71%, 65% or 70% yield respectively, reaction leading to the kinetic isomer.

Standard stannylcupration reactions performed without MeOH are dependent on the nature of the cuprate and could deliver a mixture of dienylstannanes under thermodynamic control. Addition of MeOH to the cuprate solution led to the formation of the pure kinetic dienylstannane product and contributed to insure and increase of the yield in the stannylcuprations of methyl substituted enynes 5 or alkyne 9 in a spectacular manner.

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13) **Typical procedure (Table II, entry 12):** (2*E*,4*E*)-3-Methyl-5-(tributylstannyl)-hexa-2,4-dien-1-ol (**7**).
To a solution of hexabutylditin (52.8 g, 91.0 mmol, 4.0 equiv) in dry THF (200 mL) were added *n*-BuLi (57.0 mL, 1.6 M solution in hexane, 91.2 mmol, 4.0 equiv) at -78°C. The solution was stirred 30 min at -40°C. Then this mixture was added by a cannule to a suspension of CuCN (4.0 g, 43.1 mmol, 2.0 equiv) in dry THF (10 mL) at -78°C. The solution was stirred at -40°C until obtention of a clear yellow solution and dry MeOH (100 mL, 110 equiv) was added at -78°C, the yellow solution turn to a red gel. The temperature was allowed to warm to -40°C for 15 min, until obtention of a red solution. The enyne **5** (2.5 g, 22.6 mmol) in dry THF (20 mL) was added at -40°C to the cuprate solution and the temperature was allowed to warm to -10°C for one night. Then 50 mL of dry MeOH was added at -20°C; 15 min later 50 mL of water was added at -20°C. After 15 min the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (diethyl ether/petroleum ether 0:100 to 50:50) gave **7** as a colorless oil (7.1 g, 77 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H, $J\ ^1H\text{-}^{117}Sn = J\ ^1H\text{-}^{119}Sn$ = 73.0 Hz, H-4), 5.51 (t, 1H, J = 6.7 Hz, H-2), 4.26 (t, 2H, J = 6.7 Hz, H_2-1), 2.03 (s, 3H, $J\ ^1H\text{-}^{117}Sn = J\ ^1H\text{-}^{119}Sn$ = 47.0 Hz, H_3-6), 1.80 (s, 3H, CH_3-3), 1.57-1.47 [m, 7H, $Sn(CH_2\text{-}C\underline{H}_2\text{-}CH_2\text{-}CH_3)_3$, OH], 1.36-1.28 [m, 6H, $Sn(CH_2\text{-}CH_2\text{-}C\underline{H}_2\text{-}CH_3)_3$], 0.95-0.82 [m, 15H, $Sn(C\underline{H}_2\text{-}CH_2\text{-}CH_2\text{-}C\underline{H}_3)_3$].
^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6 (C-4, $J\ ^{13}C\text{-}^{117}Sn = J\ ^{13}C\text{-}^{119}Sn$ = 29.0 Hz), 141.8 (C-5), 136.3 (C-3), 128.0 (C-2), 59.6 (C-1), 29.3 [3 CH_2, $Sn(CH_2\text{-}\underline{C}H_2\text{-}CH_2\text{-}CH_3)_3$, $J\ ^{13}C\text{-}^{117}Sn = J\ ^{13}C\text{-}^{119}Sn$ = 20.0 Hz)], 27.4 [3 CH_2, $Sn(CH_2\text{-}CH_2\text{-}\underline{C}H_2\text{-}CH_3)_3$, $J\ ^{13}C\text{-}^{117}Sn = J\ ^{13}C\text{-}^{119}Sn$ = 52.0 Hz)], 21.2 [C-6, $J\ ^{13}C\text{-}^{117}Sn = J\ ^{13}C\text{-}^{119}Sn$ = 43.0 Hz)], 17.2 (CH_3-3), 13.6 (3 CH_3, $Sn(CH_2\text{-}CH_2\text{-}CH_2\text{-}\underline{C}H_3)_3$], 9.6 [3 CH_2, $Sn(\underline{C}H_2\text{-}CH_2\text{-}CH_2\text{-}CH_3)_3$, $J\ ^{13}C\text{-}^{117}Sn$ = 311.0 Hz, $J\ ^{13}C\text{-}^{119}Sn$ = 326.0 Hz)].

14) In the other cases (ref 10, 11, 12) only 1.5 to 60 equivalents of MeOH were used.

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