Regio- and Stereoselectivity in Stannyl- and Silylcupration of Alkynes and Enynes Using Proton Sources

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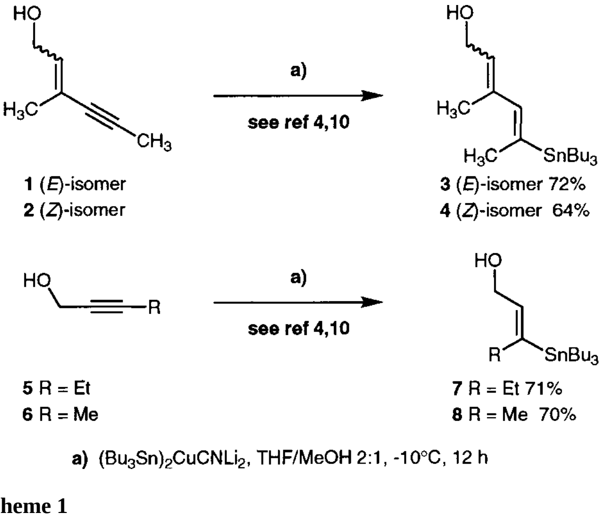
Abstract: Stannylcupration of alkyne **6** was performed using different proton sources such as phenols, alcohols and water; results showed that the cuprate reagent was not affected during the reaction. In all cases tested in presence of a proton source, the vinylstannane **10** corresponding to a *trans* addition was not produced, while the *distal* and *proximal* isomers **8** and **9** resulting from a *cis* addition were obtained in good yield. The **8/9** ratio was dependent on the reaction temperature, the acidity and the number of equivalents of the proton source. This study was also extended to the stannylcupration of enynes and silylcupration of alkynes and enynes.

In total synthesis of natural products, the problem of stereoselective construction of some unsaturated fragments has been resolved in many cases by the use of vinyl- or dienylstannanes which can be considered as important building blocks in this area. Stereoselective preparation of dienic or trienic systems from vinyl-and/or dienylstannanes was effected *via* transition-metal catalyzed cross-coupling reactions and/or tin-lithium exchange reactions as key reactions which proceeded with total retention of the geometry of vinyl or dienyl precursors.[1] For the stereoselective synthesis of (*Z*)- and/or (*E*)-vinylic stannanes, stannylcuprations[2] and Pd-catalyzed hydrostannylations[3] of alkynes and enynes have become for the last ten years the most utilized methods in total synthesis.

In a preceding work,[4] an efficient preparation of pure substituted dienylstannanes such as **3** and **4** (72% and 64% yield respectively) was described by stannylcupration of enynols **1** and **2** using methanol as a proton source while standard conditions did not work (Scheme 1). The same reaction applied to alkynes **5** and **6** [$(Bu_3Sn)_2CuCNLi_2$, THF/MeOH (110 equiv.), -10°C, 12h] also only gave the *distal* stannyl derivatives **7** and **8** in good yields (71% and 70% respectively).

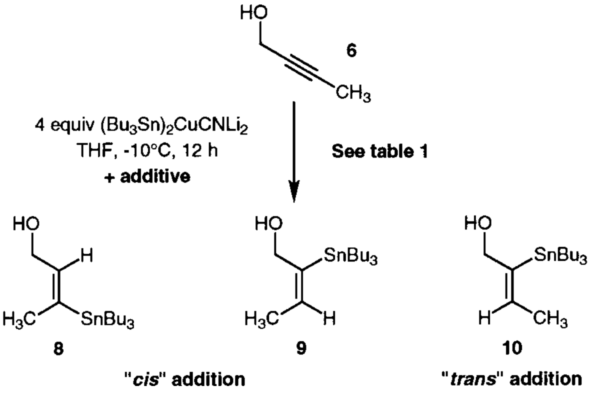


Scheme 1

Addition of a proton source such as MeOH or EtOH (1 to 2 equiv.) was first described by Piers and coworkers in 1980[5] for stannylcupration of α,β-acetylenic esters; addition of MeOH led in this case, by trapping of the *kinetic* adduct, to the (*E*)-derivative.[6] Stannylation of alkynes using the $Me_3SnCu{\bullet}Me_2S$ reagent and MeOH addition (60 equiv.) was also reported by this author as well as the use of acetic acid as proton source![7]An interesting NMR study was realized by Oehlschlager, proving that the intermediate vinylcuprate was quenched by methanol and also that the *proximal* stannyl derivative was the *kinetic* product in stannylcupration of alkynes.[5,8]

In this study we report stannyl- and silylcuprations of alkynes and enynes under different conditions involving addition of different proton sources to the cuprate solution.

Using the higher order $(Bu_3Sn)_2CuCNLi_2$ cyanocuprate,[9] (4 equiv., THF, -10°C, 12 h) and no additive, stannylcupration of alkyne **6** gave a 30:70 mixture of vinylstannanes **8** and **10** in 82% yield (Scheme 2, table 1, entry 1).[3,10] The pure *distal* derivative **8** was obtained in good yield (70%) when MeOH (110 equiv.) was added to the cuprate solution and when reaction was carried out at -10°C for 12 h; compound **9** was not obtained under these conditions nor the vinylstannane isomer **10** (Table 1, entry 2).



Scheme 2

Table 1 . Stannylcupration of alkyne **6**

Entry	Additive (equiv.)	pKa	T (°C)	Yield (%)	**8 / 9 / 10**
1	none	/	-10	82	30 : 0 : 70
2	MeOH (110)	15.5	"	70	100 : 0 : 0
3	PhOH (30)	10.0	"	88	86 : 14 : 0
4	AcOH (10)	4.6	"	78	87 : 13 : 0
5	2,4-diNO_2-PhOH (10)	4.1	"	80	85 : 15 : 0
6	2,4,6-triNO_2-PhOH (10)	0.3	"	0	/
7	H_2O (10)	14.0	-10	97	85 : 15 : 0
8	MeOH (110)	15.5	- 40	95	85 : 15 : 0
9	2,4-diNO_2-PhOH (10)	4.1	"	95	78 : 22 : 0

When phenol (30 equiv.) was added to the cuprate solution,[11,12] reaction performed at -10°C led to the formation of *distal* and *proximal* regioisomers **8** and **9** in 88% yield and a 86:14 ratio (Table 1, entry 3); in this case the more acidic phenol (pKa = 10.0) was able to trap the *kinetic proximal* stannane **9** more efficiently than methanol (pKa = 15.5). Similar results were obtained with acetic acid (pKa = 4.6) and 2,4-dinitrophenol (pKa = 4.1) and stannylcupration of **6** proceeded respectively in 78 and 85% yield, compounds **8** an **9** were produced in a 85:15 ratio (Entries 4 and 5). When a more acidic additive such as 2,4,6-trinitrophenol (pKa = 0.3) was added to the cuprate solution no reaction occurred (Entry 6) and the cuprate reagent seemed to be destroyed.

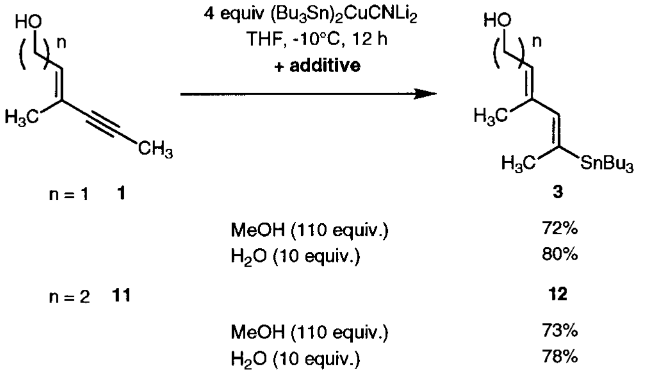
When stannylcupration was performed at lower temperature, - 40°C, in the cases where MeOH and 2,4-dinitrophenol were added to the cuprate solution, yields increased to 95% and stannane **9** was obtained in slightly better yields (Table 1, entries 8 and 9, respectively 85:15 and 78:22 ratios).

These results clearly establish that regioisomeric control is closely related to the reaction temperature. Addition of a proton source to the cuprate solution as an internal quench, can then increase the yield of the proximal stannyl derivative. The second, but important, positive effect of the addition of the proton source is to ensure the effective quench of the stannylcuprate adducts to give the stannyl derivatives. When the proton source has a pKa > 5[13] the higher cyanocuprate $(Bu_3Sn)_2CuCNLi_2$ is not destroyed even under drastic conditions (-10°C, 12 h). In all the cases we examined, the vinylstannane **10** resulting from a trans addition was never obtained when a proton source was used.

We also decided to use water as a proton source[14] and surprisingly the yield increased to 97% and vinylstannanes **8** and **9** were obtained in a 85:15 ratio (Entry 7).[15] In this reaction 10 equivalents of water were added to the cuprate which was not destroyed even after 10-12h reaction time.

In this particular case, water presents an intermediate acidity between methanol and phenol (pKa = 14), and only 10 equivalents of water were enough to give an excellent yield. This water effect cannot be at this time related to the pKa value and no explanation could be given without other experiments.

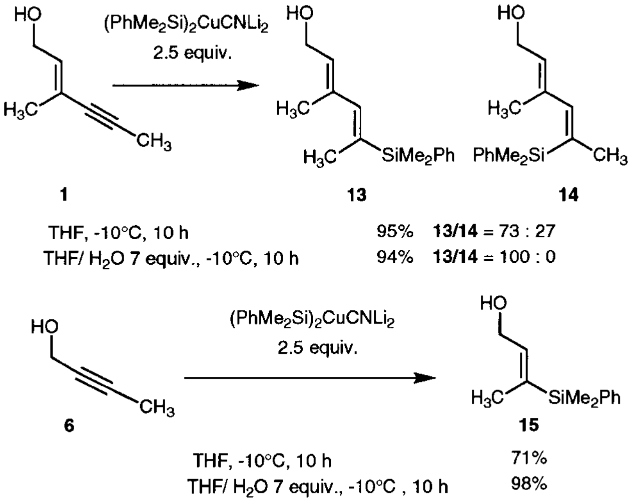
The scope of the reaction was extended to enynes. Treatment of enyne **1** with $(Bu_3Sn)_2CuCNLi_2$ gave only the *distal* diennylstannane **3** in 72% yield when methanol (110 equiv.) was added (Scheme 3); interestingly addition of 10 equiv. of water to the cuprate solution led to stannane **3** in 80% yield and starting material **1** was recovered in 20% yield.



Scheme 3

When the homologous enyne **11** was treated under the same conditions, stannyl derivative **12** was obtained as the only isomer in 73% yield (methanol addition) and 78% yield (water addition). In the case of water addition starting material **11** was recovered in 15% yield.

In another application of these results, silylcupration of enyne **1**[16] was realized by reaction with $(Me_2PhSi)_2CuCNLi_2$ [17] without additive. A 73:27 mixture of isomers **13** and **14** was obtained in 95% yield (Scheme 4). The same reaction using 7 equivalents of water gave only the pure *distal* silyl compound **13** in 94% yield.[18]



Scheme 4

When alkyne **6** was treated under the same drastic conditions (-10°C, 10 h), vinylsilane **15** was first obtained in a modest 71% yield when no additive was used, and in 98% yield when 7 equivalents of water were added.

Silylcuprates also could be used in presence of water even when the reaction was carried out at -10°C for 12 h. Yields increased and the pure *distal* derivative was obtained.

In this study it was shown that alcohols, phenol, acetic acid and water could be added to a solution of stannyl or silyl cuprate without damage to the reaction. Moreover beneficial effects were observed such as an increase in the overall yield and no formation of *trans* adduct or by-products.[19]

In adjusting the reaction temperature, the pKa (> 4 or 5) and the number of equivalents of the proton source, stannylcupration reactions can be modulated either towards the formation of pure *distal* adduct (high temperature) or to yield more of the *proximal* product (low temperature)

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References and Notes

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(14) The use of water as proton source was first evoked by Oshima K.; see ref 11 and 12.

(15) **Typical procedure, Table 1 entry 7:** To a solution of hexabutylditin (7.2 g, 12.5 mmol, 8.0 equiv.) in dry THF (20 mL) was added *n*-BuLi (1.6*M* solution in hexane, 7.8 mL, 12.5 mmol, 8.0 equiv.) at -78°C. The solution was stirred for 30 min at -40°C. Then the mixture was added *via* cannula to a suspension of CuCN (560 mg, 6.2 mmol, 4.0 equiv.) in dry THF (2 mL) at -78°C. The solution was stirred at -40°C until was obtained of a yellow solution and cooled to -78°C. Then water (280 µL, 15.6 mmol, 10 equiv.) was added and the 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 red solution was cooled to -78°C before the addition *via* cannula of alkyne **6** (110 mg, 1.56 mmol) in solution in THF (3 mL). The mixture was allowed to warm to the appropriate temperature and when the starting material had been consumed, the mixture was quenched by addition of brine. The aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on basic silica gel (diethyl ether/petroleum ether 0:100 to 50:50) to give compounds **8** (460 mg, 82% yield) and **9** (91 mg, 16% yield). Compounds **1-10** are described in ref 10.

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(18) **13:** To a suspension of CuCN (215 mg, 2.4 mmol, 2.5 equiv.) in dry THF (1 mL) was added *via* syringe the red solution of dimethyl(phenyl)silyl lithium[16] (0.6*M* solution in dry THF, 8.8 mL, 5.3 mmol, 5.5 equiv.) at -50°C. The suspension was stirred for 45 min at 0°C until a purple solution was obtained and cooled to -50°C. Then water (120 µL, 6.7 mmol, 7 equiv.) was added. The temperature was allowed to warm to between -20°C and -10°C for 10 min until the solution became deep-red. The deep-red solution was cooled to -50°C before addition *via* cannula of enyne **1** (105 mg, 0.94 mmol) in dry THF (3 mL). The mixture was allowed to warm to -10°C and after the starting material had been consumed, the mixture was quenched by addition of brine. The aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (diethyl ether/petroleum ether 0:100 to 50:50) to give compound **13** (222 mg, 94% yield).

13: ^{1}**H NMR** (200 MHz, $CDCl_3$) δ 7.61-7.52 (m, 2H, H-arom), 7.44-7.33 (m, 3H, H-arom), 6.24 (s, 1H, H-4), 5.60 (tq, 1H, J = 6.7, 1.6 Hz, H-2), 4.29 (d, 2H, J = 6.7 Hz, H_2-1), 2.09 (s, 1H, OH), 1.89 (d, 3H, J = 1.6 Hz, CH_3, CH_3-3), 1.84 (s, 3H, CH_3, H_3-6), 0.41 (s, 6H, $2CH_3$, Me_2Si). ^{13}**C NMR** (50 MHz, $CDCl_3$) δ 142.1 (C-2 or C-4), 138.1 (C-arom), 136.0 (C-3 or C-5), 135.7 (C-3 or C-5), 133.9 (C-arom), 129.0 (C-arom), 128.9 (C-2 or C-4), 127.7 (C-arom), 59.1 (C-1), 17.0 (CH_3, CH_3-3 or CH_3, C-6), 16.6 (CH_3, CH_3-3 or CH_3, C-6), -3.5 ($2CH_3$, Me_2Si).

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