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Trimethylstannylvinyl cuprates - - Generation and 1, 4 - Conjugate Addition to α,β - Unsaturated Ketones

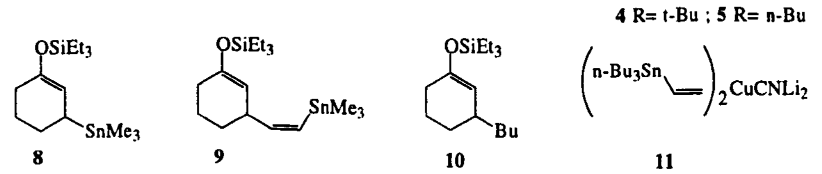
Oswy Z. Pereira and T. H. Chan*
Department of Chemistry,
McGill University, Montreal,
Quebec, Canada H3A 2K6

Abstract: *A new convenient route to the bis (trimethylstannylvinyl) cuprate reagent 6 is described. Its addition to α,β-unsaturated ketones has been compared with other mixed cuprates.*

The use of organostannanes in organic synthesis has seen an explosive growth in the last few years, especially as new, mild and efficient methods for their preparation have been developed.[1] In particular the deployment of vinylstannanes, as geometrically defined, latent vinyl anions has been reported in several recent synthesis of natural products including rapamycin[2a], taxol[2b], avermectins[2c], and various enediynes[2d]. In this connection, stannylvinyl cuprate reagents have been found to be useful as precursors to vinylstannanes because of their ease of reaction with electrophiles including conjugate addition to α, β- unsaturated ketones. Recently Marino[3] and Pulido/Fleming[4] have independently described the addition of tri-n-butyl-stannyl cuprates to acetylene as a way to afford the *cis* tri-n-butyl-stannylvinyl cuprate reagents.

We became interested in the use of various cis trimethylstannylvinyl cuprate reagents (**2**- **6**) because of the greater ease of manipulation and spectral simplicity of the trimethyltin moiety relative to the tri-n-butyltin reagents. We report here a convenient, novel route to the cuprate **6** and a new stannyl cuprate **7**.

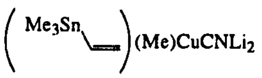
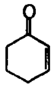
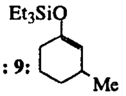
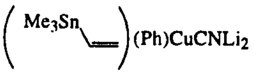
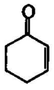
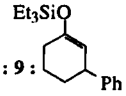
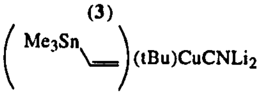
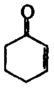
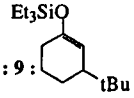
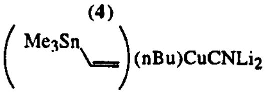
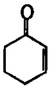
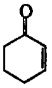
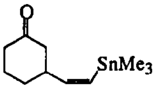
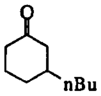
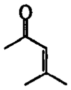
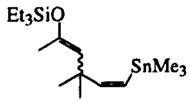
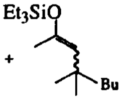
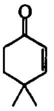
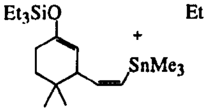
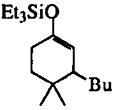
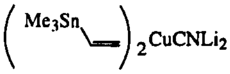
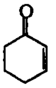
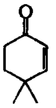
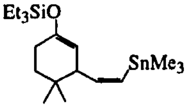
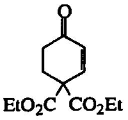
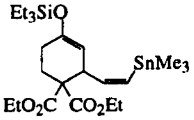
The conventional methods[5] of generating mixed stannyl cuprate via the addition to acetylene of the corresponding trimethylstannyl lithio species, invariably gave low yields (ca < 10%) of the desired vinyl reagents. We thus adopted the Lipshutz protocol[6] to generate the mixed stannyl cuprates **2-5** by using different organolithium reagents (Scheme1).



Scheme 1

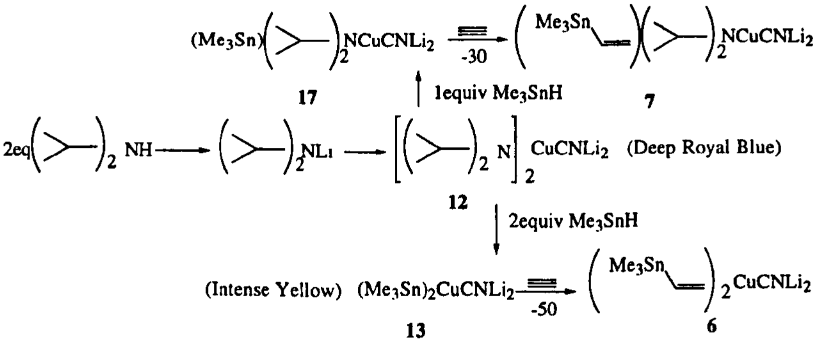
The mixed stannyl cuprates were then reacted with cyclohexenone in the presence of Et_3SiCl. It is clear from results summarized in Table 1 that in the case of **2** (entry 1), **3** (entry 2) and **4** (entry 3), incomplete addition to acetylene occurred, leading

Table 1

Entry	**Cuprate**	**Enone/Cond**	**Product**	**Ratio/Yield**
1	 (2)	 -78	8 : 9: 	1 : 1 : 1
2	 (3)	 -78	8 : 9 : 	4 : 1 : 5
3	 (4)	 -78	8 : 9 : 	2 : 1 : 0.5
4	 (5)	 -100	9 : 10	79 % : 9 %
5	(5)	 $BF_3.OEt_2$/-78	 + 	12% : 61%
6	(5)		 +  ca 1:1 inseparable mixture	1 : 1
7	(5)	 -78	 + 	52 % : 15 %
8	 (6)	 -78	8 : 9	0 % : 89 %
9	(6)	 -78		65 %
10	(6)			78 %

to addition products **8** (derived from **1**, R=Me or Ph or t-Bu) and **9** (derived from **2**, or **3** or **4**). In the case of **5**, little addition product **8** was obtained, indicating that the addition of **1** (R=n-Bu) to acetylene was complete. However, for most of the enones examined, transfer of the n-butyl group competed with the transfer of the trimethylstannylvinyl moiety to the enone. With cyclohexenone, under careful control of reaction conditions (-100°C, entry 4), adduct **9** was obtained in 79% yield, versus the butyl transfer adduct **10** obtained in 9% yield. Changing Et_3SiCl to $BF_3.OEt_2$ as the promoting reagent[7] served only to promote transfer of the butyl group (entry 5). Similar transfer of the butyl group from **5** to the enone was observed for the α,β-unsaturated ketones such as 4-methylpent-3-en-2-one (entry 6), and 4,4-dimethylcyclohex-2-enone (entry 7).

In his work on hindered enones, Marino reported[3] best results with homo bis(tri-n-butylstannyl) cuprate **11** and attributed this outcome to its superior reactivity. Given the results from the mixed trimethylstannyl cuprates **2-5**, we decided to explore the reactivity of the trimethylstannyl analog **6**. After considerable experimentation, we found[8] the protocol delineated in Scheme 2 to give synthetically useful yields of the reagent **6**. LDA was added to CuCN and LiCl in THF at -78° to generate a deep royal blue solution of **12**.

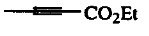


Scheme 2

Trimethyltin hydride was then added to give an intense yellow solution of **13**. The formation of **13** was confirmed by its reaction with an activated alkyne, methyl butynoate (**14**), at -78° to give the addition product **15** in 94% yield. Addition of **13** to acetylene did not occur at -78° but, at -50°, formation of the reagent **6** as a bright yellow solution took place. Addition of **6** to cyclohexenone (entries 8 and 9), 4,4-dimethylcyclohex-2-enone (entry 10) and 4,4-diethoxycarbonylcyclohex-2-enone (entry 11) all gave transfer of the trimethylstannylvinyl moiety in good yields.

Formation of the amidocuprate **12** has not been reported in the literature. Its existence in the present case is strongly implicated by the observation that when cyclohexenone and Et_3SiCl were added to the deep royal blue solution of **12**, the 1,3-diene **16** could be obtained, in 60% unoptimised yield. Jung[9] has demonstrated that 1,3-dienes of type **16** are not available through simple base mediated deprotonation at the γ position of 2-cyclohexenones under either kinetic or thermodynamic conditions. In all probability, **16** arises through silica catalysed Hoffman elimination of the initially formed amido adduct **18**, although direct γ-deprotonation by cuprate **12** cannot be excluded. This also led us to prepare the mixed trimethylstannylvinylamido cuprate **7** via the mixed reagent **17** formed by the addition of only one equivalent of trimethyltin hydride to **12**. Indeed, the mixed cuprate **7** reacted with cyclohexenone with complete selective transfer of the trimethystannylvinyl residue but, as expected, with somewhat poorer reactivity than the homo reagent **6**.

Although the structures of these cuprate reagents are not known with certainty at this time, their availability through the convenient route outlined in Scheme 2 will render them synthetically useful reagents.



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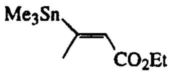

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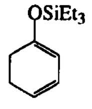

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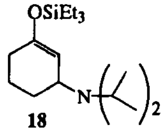

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8. **Typical Experimental Procedure** ; To diisopropyl amine (freshly distilled, 1.48 mL, 11.3 mmol, 1.2 eq) in dry THF (5 mL), at -78° under argon , was added n-BuLi (600 mg, 9.36 mmol) . After 30 mins the near colourless solution was transferred via cannula to cold (-78°) solution of CuCN (402 mg, 4.68 mmol) and lithium chloride (396 mg,9.36 mmol) in dry THF (20mL), at -78°, added over 2 mins. The initial colourless solution immediately turned mauve then royal blue. After 40 mins treated slowly, over 35 mins ,with Me_3SnH (1.51 g, 9.36 mmol). The colour rapidly changed to black then black/green and thence to an intense yellow. Solution kept at this temperature for 1h then treated at -78°, in a closed system, with gaseous acetylene (via inverted burrette, acetone free) (262 mL, 12.0 mmol, 2.5 eq w.r.t. CuCN) which was taken up in 17 mins. After 10 mins at -78°, resulting bright yellow solution was placed in a bath at -50° Left 1h under positive acetylene atmosphere, then 40 mins without. Solution was recooled to -78°, and treated rapidly with cyclohexanone (300 mg, 3.12 mmol) followed immediately by Et_3SiCl (940 mg, 6.24 mmol). After 15 min reaction was complete. After a further 15 min solution was poured into a mixture of ice-cold Et_2O: 1:4 NH_4OH /NH_4Cl. Stirred at RT for 15 min. Resulting deep blue mixture extracted with ether and purified either by Kugelrhor distillation (ca 110°C at 1 mm) or by flash column chromatography using (Pentane + 1% Et_3N) to afford **9** (1.1 g, 89%) as a clear colourless oil.
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