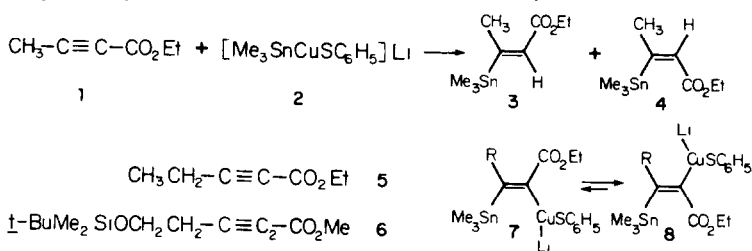


REACTION OF (TRIMETHYLSTANNYL)COPPER REAGENTS
 WITH α,β -ACETYLENIC ESTERS

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ABSTRACT. The stereochemical course of the conjugate addition of various (trimethylstannyl)cuprate (or copper) reagents to α,β -acetylenic esters is dependent on the constitution of the reagent and on the structure of the substrate.

Recently, it was reported¹ that the conjugate addition of lithium (phenylthio)(trimethylstannyl)cuprate (**2**)² to α,β -acetylenic esters (e.g. ethyl 2-butynoate, **1**)³ can be controlled experimentally so as to produce, stereoselectively, either of the geometrically isomeric products **3** (the product of kinetic control) or **4** (the product of thermodynamic control). Thus, reaction of **1** with **2** (THF, -78°C) in the presence of a small amount of methanol or ethanol produced the **E** isomer **3** (>99% isomerically pure). Apparently, under these reaction conditions, the "kinetic" intermediate (cf. **7**)⁴ protonates more rapidly than it isomerizes. In contrast, when **1** was allowed to react with **2** at -48°C (THF) for 4 hours and the reaction mixture was then treated with methanol, a mixture of **3** and the geometrically isomeric substance **4** (ratio 2 : 98, respectively) was produced. Thus, at higher temperatures in the absence of a proton source, it appears that equilibration of the intermediates (cf. **7** ⇌ **8**)⁴ takes place, with the equilibrium largely favoring **8**. Protonation of the latter species would then provide **4**.



We report herein results of recent experiments which disclose a number of interesting characteristics of the reaction of various (trimethylstannyl)cuprate (or copper) reagents with α,β -acetylenic esters. More explicitly, we report that the stereochemical outcome of these reactions is dependent on the nature of the reagent. For example, use of the (trimethylstannyl)-cuprate reagents **9**⁵ and **10**⁵ or the (trimethylstannyl)copper reagent **11**⁵ gave results which were significantly different from those obtained by use of lithium (phenylthio)(trimethylstannyl)cuprate (**2**). Furthermore, it has been found that the reaction of certain α,β -acetylenic esters [e.g. ethyl 4,4-dimethyl-2-pentynoate (**12**)^{9,10}, ethyl 4-(*tert*-butyldimethylsiloxy)-2-butynoate (**13**)⁹, ethyl propynoate (**14**)] with the cuprate reagent **2** does not provide results analogous to those obtained with the acetylenic esters **1**, **5** and **6**. Thus, the structure of the substrate ester also has an effect on the overall outcome of the reaction.

Table I summarizes some of the results obtained from allowing ethyl 2-butynoate (**1**) to react with the reagents **2**, **9**, **10**, and **11**. It can be seen that although all of the reagents

reacted quite efficiently with the acetylenic ester 1, only the (phenylthio) cuprate reagent 2

TABLE I

$$\text{CH}_3\text{-C}\equiv\text{C-CO}_2\text{Et} \longrightarrow \begin{array}{c} \text{CH}_3 \quad \text{CO}_2\text{Et} \\ \diagdown \quad / \\ \text{C} \\ / \quad \diagdown \\ \text{Me}_3\text{Sn} \quad \text{H} \end{array} \quad \text{3} \quad + \quad \begin{array}{c} \text{CH}_3 \quad \text{H} \\ \diagdown \quad / \\ \text{C} \\ / \quad \diagdown \\ \text{Me}_3\text{Sn} \quad \text{CO}_2\text{Et} \end{array} \quad \text{4}$$

Entry	Reagent, Conditions ^a	Yield(%) ^b	Ratio, <u>3</u> : <u>4</u> ^c
1	<u>2</u> , -48°C, 4h	85	2 : 98
2	<u>2</u> , -48°C, 4h	74	32 : 68
3	<u>10</u> , -48°C, 4h	82	>99 : < 1
4	<u>11</u> , -48°C, 3h	68	>99 : < 1
5	<u>11</u> , -78°C, 3h	76	>99 : < 1

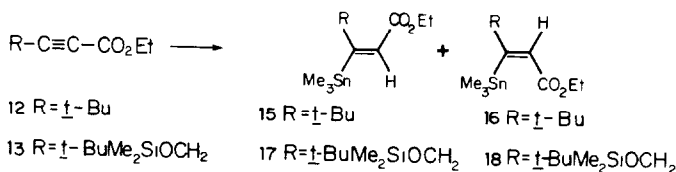
^a All reactions were carried out in THF with 1.3 equiv. reagent. ^b Yield of isolated, distilled product(s). ^c As determined by gas-liquid chromatography.

produced synthetically satisfactory yields of the "thermodynamic" product 4 (entry 1). The bis-(trimethylstannyl)cuprate 9, under identical conditions, provided a mixture of isomers (entry 2), while the reagents 10 and 11 yielded exclusively the "kinetic" product 3, even under conditions whereby reagent 2 gave very largely the geometric isomer 4 (entries 3,4 vs. entry 1). From a strictly synthetic point of view, it is pertinent to point out that the product with Z-stereochemistry (4) must be prepared by use of the cuprate reagent 2, while the E isomer 3 is probably most conveniently obtained by employing the (trimethylstannyl)copper reagent 11. The latter is very easily prepared and requires only one

equivalent of (trimethylstannyl)lithium.

A summary of results obtained from the reaction of reagents 2, 9, 10, and 11 with the acetylenic esters 12 and 13 can be found in Table II. In connection with these results, the following points should be noted. (a) In contrast to the transformations involving the esters 1, 5 and 6, the reaction of ethyl 4,4-dimethyl-2-pentynoate (12) with the cuprate reagent 2 was quite sluggish. In order to achieve complete reaction, longer reaction times and a considerable excess of reagent were required (entries 1,2). More importantly, when the reaction of 12 with 2 was carried out at -78°C in the presence of ethanol (entry 1), the product consisted very largely of the Z ester 16 (entry 1). A very similar result was obtained when the reaction was carried out at -48°C (entry 2). Apparently, the sterically bulky tert-butyl group not only impeded conjugate addition of the cuprate reagent to this acetylenic ester, but also destabilized the "kinetic" intermediate (cf. 7) sufficiently to allow isomerization to become faster than protonation, even in the presence of a proton source. (b) Comparison of the reactions summarized in entries 2-4, Table I, with those of entries 3-5, Table II, also provides some interesting contrasts. The reactions of reagents 9, 10 and 11 with 12 were considerably slower than the corresponding reactions with 1. Furthermore, although reagents 10 and 11 transformed 1 exclusively into the E butenoate 3, reaction of these two reagents with 12 afforded predominantly the Z isomer 16. Thus, regardless of the reagent employed, the presence of the bulky tert-butyl group precludes the possibility of preparing efficiently the E isomer 15. (c) Although reaction of the acetylenic ester 6 with the (phenylthio)cuprate reagent 2 provided results totally analogous to those obtained from similar reactions involving the structurally simpler acetylenic esters 1 and 5¹, the lower homolog of 6 (ester 13) reacted somewhat anomalously (entries 6, 7, Table II). Although the stereochemical outcomes of the reactions were similar to those recorded for 6, reaction of 13 with 2 gave significant amounts of product(s), (1, 11, Table II) resulting from transfer of the phenylthio group. Although the specific cause for this contrast remains obscure, it seems likely that electronic (as opposed to steric) factors must be involved, since the only real difference between 13 and 6 is that the

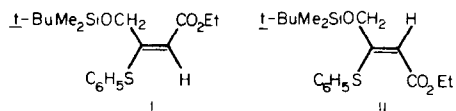
TABLE II



Entry	α, β -Acetylenic Ester	Reagent (equiv.), Conditions ^a	Yield (%) ^b	Ratio ^c		
				15	16	or 17 : 18
1	<u>12</u>	<u>2</u> (3.0), -78°C, 6h ^d	84	8	92	
2	<u>12</u>	<u>2</u> (3.0), -48°C, 4h	86	2	98	
3	<u>12</u>	<u>9</u> (3.0), -48°C, 6h	79	8	78 ^e	
4	<u>12</u>	<u>10</u> (3.0), 0°C, 60h	76	8	62 ^e	
5	<u>12</u>	<u>11</u> (3.0), -20°C, 6h ^f	79	12	80 ^e	
6	<u>13</u>	<u>2</u> (2.0), -78°C, 3h ^g	35 ^h	91	9	
7	<u>13</u>	<u>2</u> (1.3), -48°C, 4h	32 ⁱ	9	91	
8	<u>13</u>	<u>9</u> (1.3), -78°C, 3h	76	94	6	
9	<u>13</u>	<u>9</u> (1.3), -48°C, 4h	74	95	5	
10	<u>13</u>	<u>10</u> (2.0), -78°C, 3h ^d	80	97	3	
11	<u>13</u>	<u>10</u> (1.3), -78°C, 3h	80	95	5	
12	<u>13</u>	<u>10</u> (1.3), -48°C, 4h	82	94	6	
13	<u>13</u>	<u>11</u> (1.3), -48°C, 3h ^f	72	95	5	

^a All reactions were carried out in THF. ^b Yield of isolated, distilled product(s). ^c As determined by gas-liquid chromatography. ^d In the presence of 1.7 equiv. of ethanol. ^e A third component, thought to be ethyl (*E*)-4,4-dimethyl-2-trimethylstannyl-2-pentenoate, was also present. ^f HMPA (10% by volume) was added prior to addition of the acetylenic ester. ^g In the presence of 1.7 equiv. of methanol. ^h Also isolated, in 30% yield, was a 2:1 mixture of the unsaturated esters i and ii, respectively. ⁱ Also isolated, in 30% yield, was compound ii.

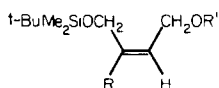
former substrate has the electron-withdrawing t-BuMe₂SiO group closer to the triple bond than does 6. Finally, in contrast to the reaction of 13 with 2, reactions of 13 with reagents 9, 10 and 11 provided efficiently and



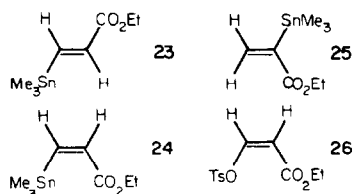
stereoselectively ethyl (*E*)-3-trimethylstannyl-4-(*tert*-butyldimethylsiloxy)-2-butenolate (17)

(entries 8-13, Table II). Interestingly, reduction (i-Bu₂AlH, ether, -78°→0°C) of the latter substance produced (90%) the alcohol 19, which could be transformed smoothly (CH₃OCH₂CH₂OCH₂Cl, i-Pr₂NEt, CH₂Cl₂, r.t.) into the MEM ether 20. Transmetalation of 20 (CH₃Li, THF, -78°C), followed by quenching of the resultant lithio species 21¹² with D₂O gave, in high yield, the monodeuterated alkene 22.

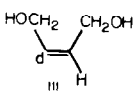
Reaction of the cuprate reagent 2 (1.1 equiv.) with ethyl propynoate (14) (THF, -100°C) in the presence of 3.0 equiv. of ethanol gave, in good yield, a mixture of the β -trimethylstannyl esters 23 and 24 (ratio 30:1)



19 R = SnMe₃, R' = H
20 R = SnMe₃, R' = MEM
21 R = Li, R' = MEM
22 R = D, R' = MEM



along with a small amount ($\sim 7\%$) of a third product, believed to 25. Purification of this mixture by preparative t.l.c. gave pure 23 in 60% yield. In contrast, reaction of 14 with 2 in the absence of ethanol failed to produce synthetically useful yields of 23 or 24. Presumably, the relatively acidic proton of the terminal acetylene moiety interfered with this conversion. However, the Z ester 24 was smoothly and efficiently prepared by reaction of ethyl (Z)-3-tosyloxy-2-propenoate (26)¹⁵ with the (trimethylstannyl)copper reagent 11 (THF, -48°C , 2h; -20°C , 1h; r.t. 1h)¹⁶. Subjecting the crude product to preparative t.l.c. afforded pure 24 in 61% yield¹⁷.

1. E. Piers and H.E. Morton, *J. Org. Chem.*, **45**, 4263 (1980). 2. E. Piers and H.E. Morton, *J. Chem. Soc., Chem. Commun.*, 1033 (1978). 3. Similar results were obtained when esters 5 and 6 were employed as starting materials¹. 4. It is not intended to imply actual structures by formulas 7 and 8; these are used only for the sake of clarity and convenience. See also E.J. Corey and J.A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 1851 (1969); J.B. Siddall, M. Biskup, and J.H. Fried, *J. Am. Chem. Soc.*, **91**, 1853 (1969). 5. Solutions (THF) of the reagents 9, 10 and 11 were prepared as follows. 9: Copper bromide-dimethyl sulfide complex⁶ (0.5 equiv.) was added to a solution (-78°C) of (trimethylstannyl)lithium⁷ (1.0 equiv.). 10: Solid (3-methoxy-3-methyl-1-butynyl)copper⁸ (1.0 equiv.) was added to a solution (-48°C) of (trimethylstannyl)lithium⁷ (1.0 equiv.). 11: Copper bromide-dimethylsulfide complex⁶ (1.0 equiv.) was added to a solution (-48°C) of (trimethylstannyl)lithium⁷ (1.0 equiv.). In each case, the deep red solution was allowed to stir for ~ 20 minutes before use. 6. H.O. House, C.Y. Chu, J.M. Wilkens and M.J. Umen, *J. Org. Chem.*, **40**, 1460 (1975). See also P.G.M. Wuts, *Synth. Commun.* **11**, 139 (1981). 7. W.C. Still, *J. Am. Chem. Soc.*, **99**, 4836 (1977). 8. E.J. Corey, D. Floyd, and B.H. Lipshutz, *J. Org. Chem.*, **43**, 3418 (1978). See also R.E. Atkinson, R.F. Curtis, and J.A. Taylor, *J. Chem. Soc. (C)*, 578 (1967). 9. The esters 12 and 13 were prepared by reaction of the appropriate acetylene [3,3-dimethyl-1-butyne, 3-(tert-butyl-dimethylsiloxy)propyne, respectively] with n-BuLi in THF (-78°C to -20°C), followed by treatment of the resulting lithium acetylides with ethyl chloroformate (-20°C to room temperature). The yields were 86% and 81%, respectively. 10. All structural assignments given herein are fully supported by appropriate spectroscopic data. With regards to compounds 3, 4, and 15-18, stereochemical assignments are based on the difference in chemical shift of the γ protons of the stereoisomeric products¹ and/or on the difference in coupling constants between the α proton and the ¹¹⁷Sn and ¹¹⁹Sn isotopes. Typically $|J(\text{Sn-H})| \approx 70$ Hz when the Me₃Sn group and the α proton are cis, but is much larger (≈ 120 Hz) when they are trans¹¹. New compounds gave satisfactory elemental analyses and/or high-resolution mass spectrometric measurements. 11. A.J. Leusink, H.A. Budding and J.W. Marsman, *J. Organometal. Chem.*, **9**, 285 (1967). 12. The vinyl-lithium reagent 20 corresponds to the stereochemically homogeneous d²-d³ synthon¹³ iii. This structural unit (or a modified version thereof) is found in a number of diterpenoids (e.g. portulal¹⁴).


13. Cf. D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **18**, 239 (1979). 14. Cf. T. Tokoroyama, K. Matsuo, H. Kotsuki, and R. Kanazawa, *Tetrahedron*, **36**, 3377, (1980). 15. We are grateful to Dr. G.S. Bates and Mr. S. Ramaswamy for a generous sample of compound 26. 16. For a more extensive investigation regarding the preparation of 3-(tri-n-butylstannyl)propenoates via similar chemistry, see the accompanying communication by D.E. Seitz and S. Lee. We are very grateful to Dr. Seitz for an exchange of information prior to publication. 17. Financial support from the Natural Sciences and Engineering Research Council of Canada (NSERCC) and NSERCC postgraduate scholarships (to J.M.C. and H.E.M.) are gratefully acknowledged.

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