Mechanistic, Spectroscopic and Synthetic Investigations of the Stannylcupration of Alkynyl Ethers

by

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B.Sc., Universidad de Costa Rica, 1985

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Degree: Doctor of Philosophy

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Mechanistic, Spectroscopic and Synthetic Investigations of the Stannylcupration of Alkynyl Ethers

Abstract

Stannylcupration of 1-alkynyl ethers with cuprates $(Bu_3Sn)_2Cu(CN)Li_2$ and $Bu_3SnCu(CN)Li$ was studied to develop conditions that yield *trans* 2- and 1-tri-*n*-butylstannylvinyl ethers stereo- and regioselectively in very good yields. Regioselectivity is a function of the reaction conditions. Thus, 1-tri-*n*-butylstannylvinyl ethers are obtained under kinetic conditions (-78 °C, THF/MeOH), while *trans*-2-tri-*n*-butylstannylvinyl ethers are obtained under thermodynamic control conditions (0 °C, THF/HMPA). Low temperature ^1H- and ^{13}C-NMR studies revealed that the ratios of the stannylvinyl ethers obtained upon work-up are a function of the proportions of the corresponding vinylcopper intermediates, which were spectroscopically identified.

Low temperature NMR studies revealed that, when prepared in the presence of HMPA, "higher order" cuprates such as $(Bu_3Sn)_2Cu(CN)Li_2$ and $Me_2Cu(CN)Li_2$ exist as mixtures with the Gilman-like cuprates [$(Bu_3Sn)_2CuLi$; Me_2CuLi] and lithium cyanide. The proportion of Gilman cuprate and lithium cyanide in these mixtures depends on the temperature of cuprate formation and the organic groups in the cuprate. When prepared in THF without HMPA the cyanide of the higher order cyanocuprates is bound in a manner that does not allow its displacement upon addition of HMPA.

A new synthesis of 1-alkynyl ethers was developed that involves transformation of an ester into the corresponding enolphosphate by the use of LDA and diethylchlorophosphate followed by elimination using *tert*-BuLi at -100 °C. This procedure is compatible with labile functional groups such as primary chlorides.

Stannylvinyl ethers obtained by stannylcupration of 1-alkynyl ethers proved to be useful synthetic equivalents of acetaldehyde in homologation procedures. Thus, when reacted with aldehydes in the presence of $BF_3(Et_2O)$, a 2-carbon chain extension ensued, stereospecifically producing the corresponding homologated *trans*- α, β-unsaturated aldehydes.

Overview

Enol ethers are useful synthetic intermediates in organic synthesis. While regio- and stereospecific syntheses of this functional group are cumbersome it can be envisioned that easy access could be achieved through (*cis*) stannylmetallation of acetylenic ethers. While methods for the alkylative replacement of each of the carbon metal bonds formed in this reaction are known, methods for the control of regiochemistry of stannylmetallation of acetylenic ethers are unexplored.

Chapter I describes stannylcupration and stannylalumination of acetylenic ethers and the development of conditions to control the regiochemistry of the addition. Insight into the reaction mechanism and the composition of the reagents used for this reaction and the intermediates formed in this process is described in Chapters I and II. The study of these intermediates was facilitated by the development of a new procedure for the synthesis of ^{13}C-labelled acetylenic ethers, which is described in Chapter III.

Finally, a new use of the tributylstannyl vinyl ethers, obtained by stannylcupration of acetylenic ethers in a 2-carbon chain extension of aldehydes is given in Chapter IV. This process stereospecifically gives the corresponding (E)-2-carbon homologated α, β-unsaturated aldehydes.

Dedication

To my parents and all the members of my family,
they have taught me a special meaning for the
word "home" during all these years.

To Ginna, for her constant support and comprehension,
the past four years have been the best of my life...

Acknowledgements

I specially wish to thank my Senior Supervisor, Dr. Cam Oehlschlager, for giving me all the freedom and support needed to perform the projects of my thesis with my own ideas. The experience obtained from this "educational process" became priceless and also made my stay at Simon Fraser University a gratifying and unique experience.

I also want to thank Marcy Tracey for her valuable job recording the NMR spectra.

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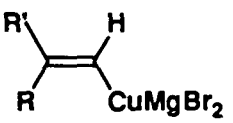
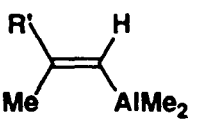
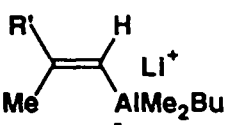
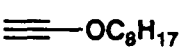
	2
	3
	4
	5
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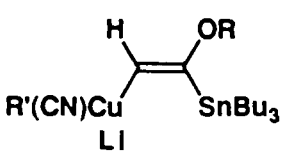
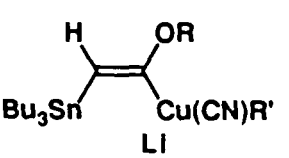
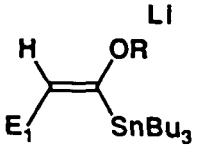
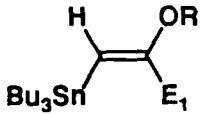
$(Bu_3Sn)MeCu(CN)Li_2$	6b
$(Bu_3Sn)Cu(CN)Li$	6c
	7
	8
	9



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$(Bu_3Sn)_2$

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Bu_3SnLi

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$Bu_3SnAlEt_2$

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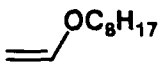

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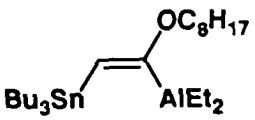

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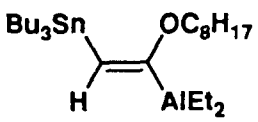

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$C_8H_{17}OH$

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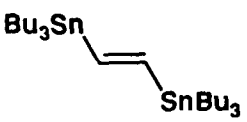

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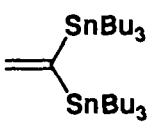

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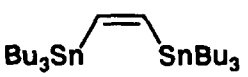

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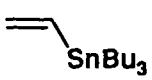

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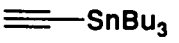

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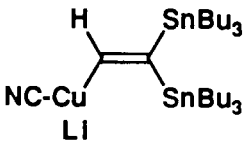

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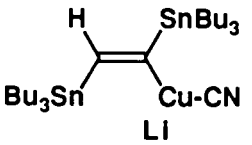

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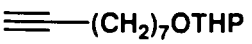

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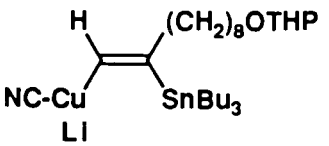

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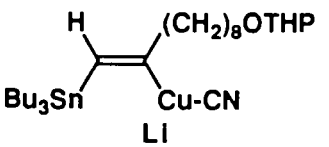

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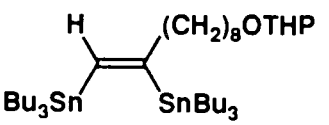

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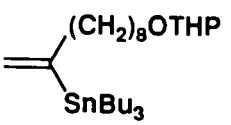

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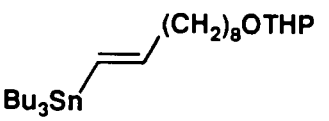

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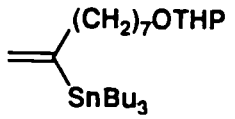

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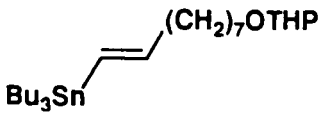

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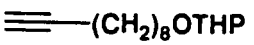

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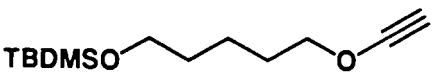

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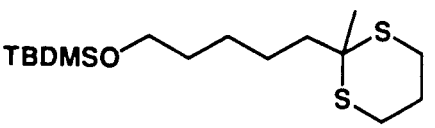

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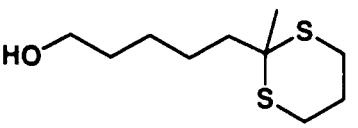

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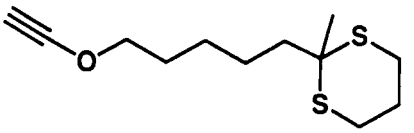

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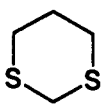

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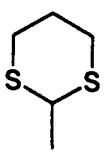

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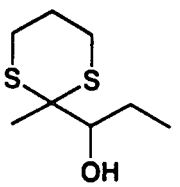

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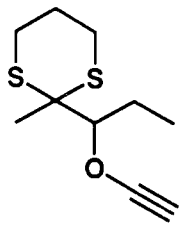

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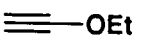

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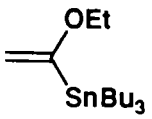

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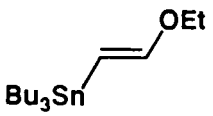

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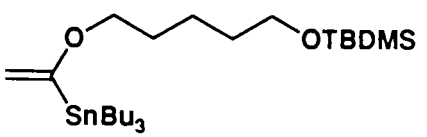

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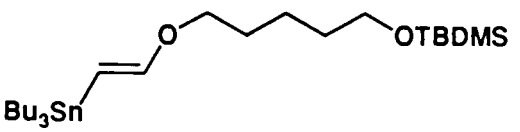

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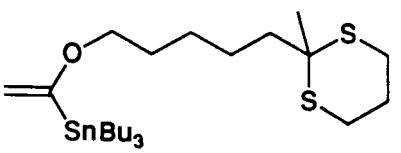

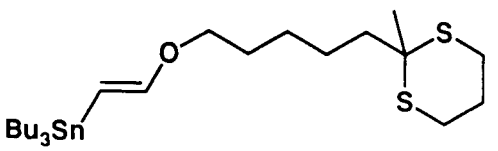

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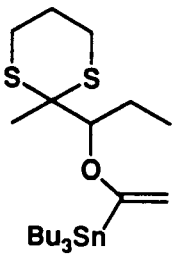

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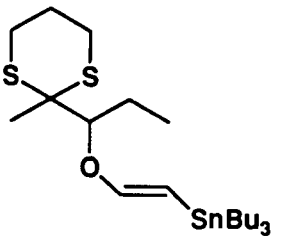

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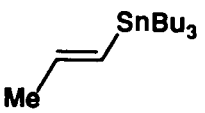
MeCu(CN)Li 56

MeSnBu3 57



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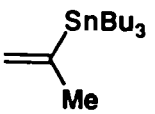

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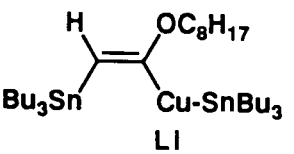
(Bu3Sn)2CuLi 60



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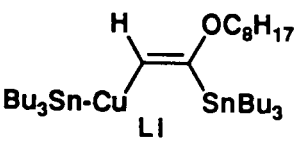

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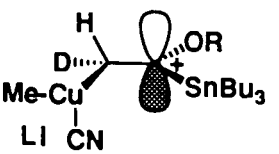

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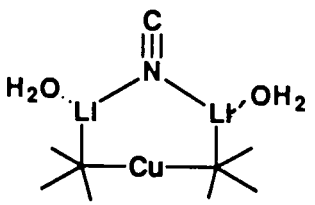
Me_2CuLi 64

$Me_2Cu(CN)Li_2$ 65



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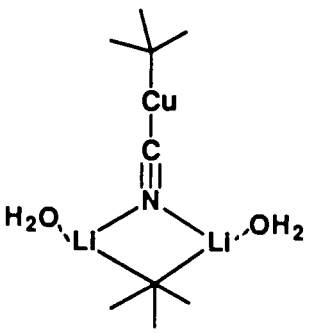

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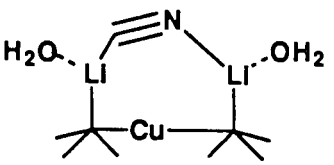

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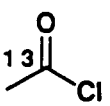

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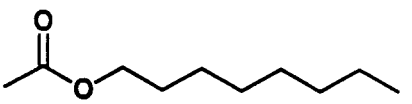

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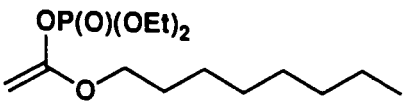

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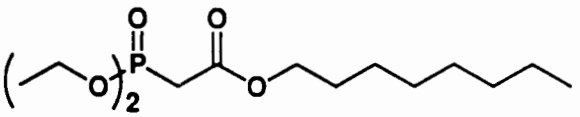

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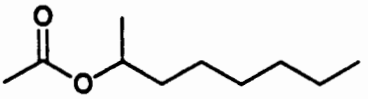

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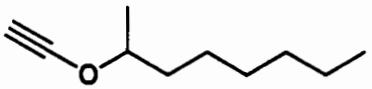

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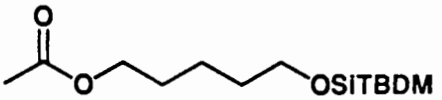

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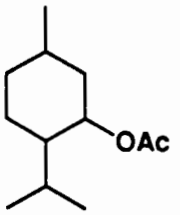

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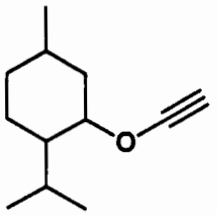

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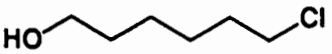

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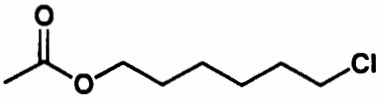

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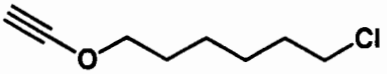

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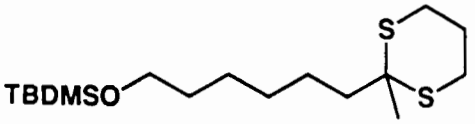

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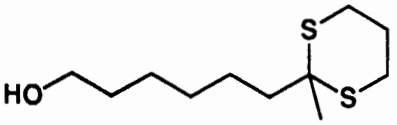

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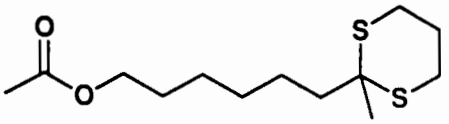

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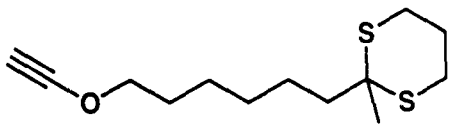

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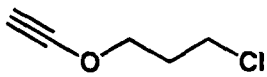

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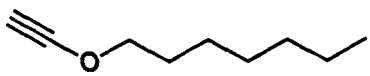

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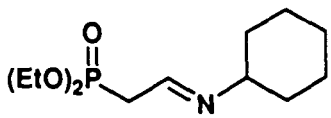

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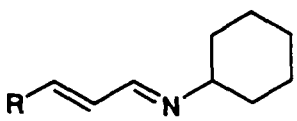

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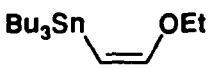

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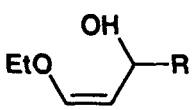

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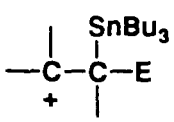

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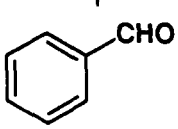

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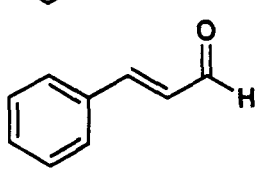

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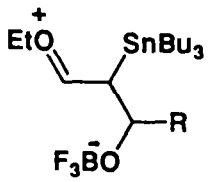

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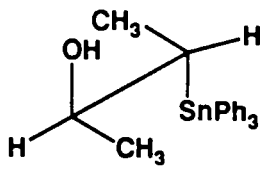

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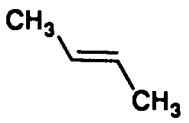

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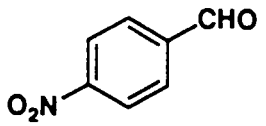

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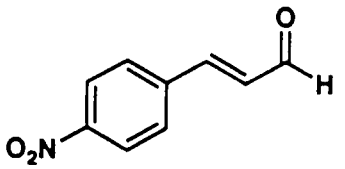

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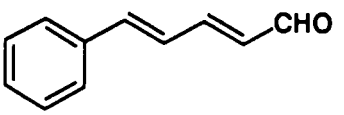

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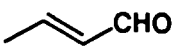

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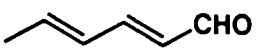

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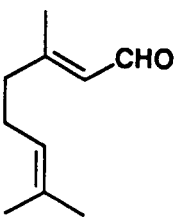

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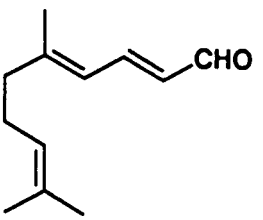

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Abbreviations

NMR	Nuclear Magnetic Resonance
THF	Tetrahydrofuran
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropyl amide
IR	Infrared
L.O.	Lower Order
H.O.	Higher Order
ppm	parts per million
cm^{-1}	reciprocal centimeters
Ph	Phenyl
GC	Gas chromatography
MS	Mass spectroscopy
equiv.	equivalent
MHz	Megahertz
Hz	Hertz
mL	milliliter
g	gram
h	hour
mmol	millimole
M	molar
N.R.	No reaction

CHAPTER I

Stannylmetallation of Acetylenic Ethers

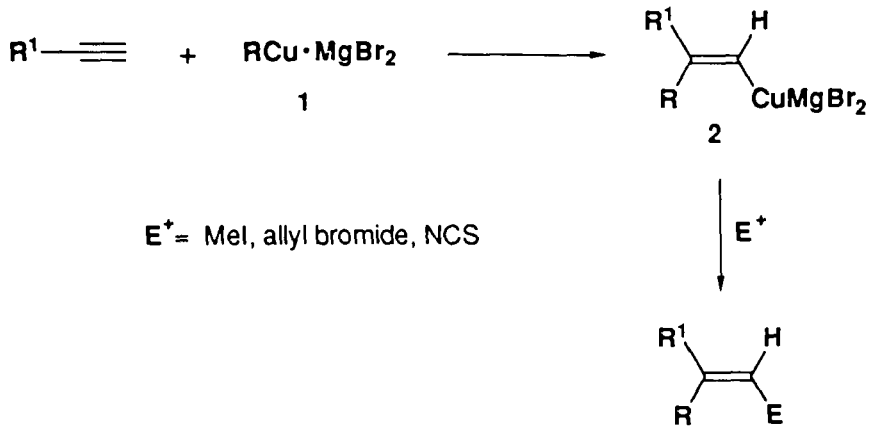
I.1 Introduction

One of the challenging problems in organic chemistry is the stereospecific synthesis of substituted olefins. This necessity has been increased by constant reports of isolation of olefinic natural products with biological activity. The control of stereochemistry is particularly important in the synthesis of compounds such as insect sex pheromones,[1] where the biological activity critically depends upon the stereochemical purity.

Many methods for the synthesis of olefins have been developed[2] over the last two decades. One of the synthetic strategies that has received special attention is the addition of reagents to acetylenes. Important procedures for these processes include the carbometallation and the metalometallation of triple bonds. Copper reagents have played a decisive role in those processes in which new carbon-carbon bonds are formed.[3]

Carbometallation, specially carbocupration, has been a very useful procedure for the synthesis of natural products. In 1971 Normant reported[4] that the magnesium-derived copper complexes **1**, could be added to acetylenes, and the vinyl copper intermediates thus formed (**2**) could be coupled with

selected electrophiles to obtain trisubstituted olefins (**Scheme I-1**). The addition of carbon and copper to the triple bond proceeds in a *syn* fashion.

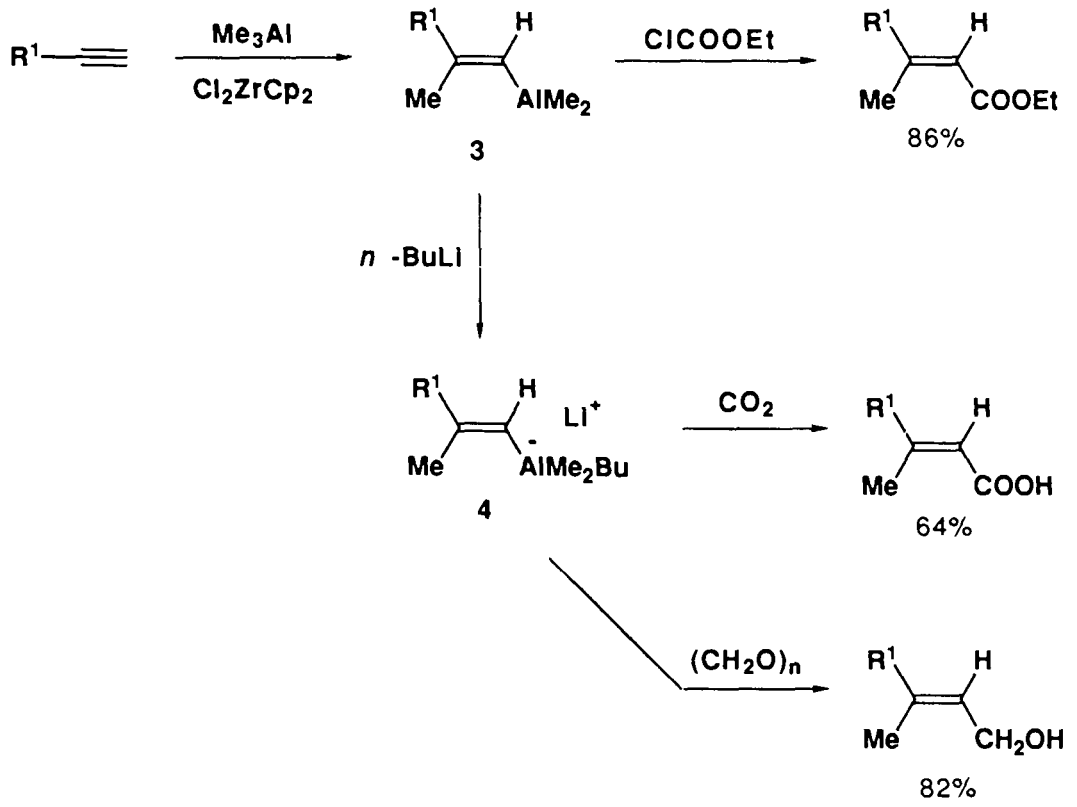


Scheme I-1. Addition of copper complex 1 to acetylenes[4]

The vinyl copper intermediates **2**, formed in this process, are not very reactive towards inactivated alkylating agents, thus some improvements to the reaction have been developed.[5] The use of a magnesium-derived dimethyl sulfide-cuprous bromide complex [$RCu(Me_2S)MgBr_2$], was found to have significant advantages[6] over copper complex **1**. With the use of the later, the dimeric by-products obtained with Normant's procedure were considerably reduced. Some of the drawbacks of these procedures are the large excess of the copper reagent used[5c] and the extremely long reaction times needed.[2e,6]

A very useful procedure for the synthesis of natural products specially those of terpenoid origin is Negishi's carboalumination.[7] The Zr-catalyzed carboalumination of acetylenes proceeds in a *syn* fashion with a very high regioselectivity (92-100%). The alanes thus obtained (**3**), or the corresponding

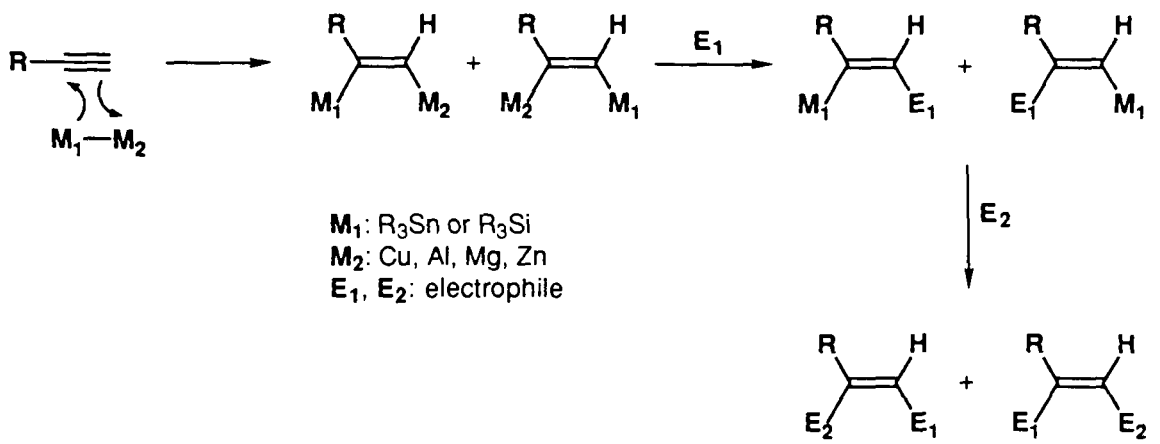
alanates **4**, can be reacted with electrophiles to obtain functionalized olefins stereospecifically (**Scheme I-2**). In spite of the fact that the carboalumination proceeds regioselectively in very good yields, the vinyl aluminum intermediates (**3**,**4**) are not very reactive towards alkyl halides.



Scheme I-2. Synthesis of functionalized (E)-3-methyl alkenes *via* Zr-catalyzed carboalumination.[7d-f]

A complementary methodology that in some cases can overcome some of the difficulties experienced in the carbometallation is the metalometallation.

Metalometallation of alkynes involves *cis* 1,2-addition of two metals to alkynes to produce adducts with two vinyl carbon-metal bonds of differential reactivity. These processes are of interest to organic chemists because they offer potential for stereo and regiospecific 1,2- addition of two electrophiles to alkynes. Such processes potentially allow synthesis of 1,2-disubstituted and trisubstituted olefins in single pot processes (**Scheme I-3**).



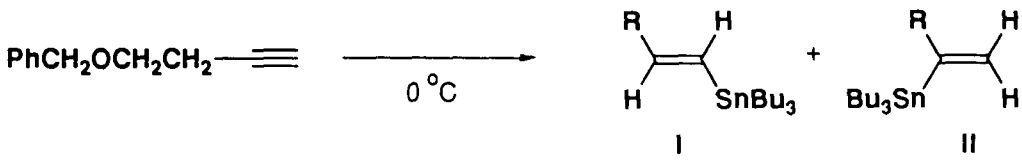
Scheme I-3. Synthesis of trisubstituted olefins by metallo-metallation of 1-alkynes.

Research into these reactions has occurred on several fronts. A few groups, including our own, are concerned with the scope and mechanism of metalometallations.[9,10,12,13] Others have made significant contributions to development of methods to elaborate the metallic adducts obtained from these reactions.[11b-e,14-17,28.]

Reagents participating in these reactions invariably include trialkylsilyl or trialkylstannyl derivatives associated with metals such as Li[8], Mg[9], Al[10], Cu[11], B[12] or Zn[13]. The high reactivity of vinyl organometallics containing Si and Sn generally requires electrophilic consumption of the more reactive organometallic centre prior to isolation of the adducts formed in metalometallations. Thus, these processes generally yield vinyl silyl or vinyl stannyl derivatives as the first isolable product (**Scheme I-3**).

The chemistry required to transform vinyl silanes[14] and vinylstannanes[15],[16],[17] to other functional groups is very highly developed. The chemistry of vinylstannanes has evolved due to the easy access to these stable organometallics. The most common methods for their preparation involve hydrostannylation,[18] copper catalyzed stannylmetallation[19] and stannylcupration[20] of alkynes.

The regioselectivity of stannylmetallation of 1-alkynes varies with the nature of the reagent (**Scheme I-4**), the solvent and the reaction conditions[10,19b]. One particularly important variable controlling the regiochemistry is temperature[21] (**Scheme I-5**).

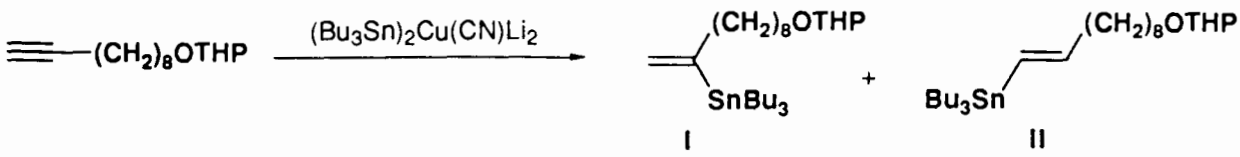


I II

Reagent [a]	Catalyst [b]	Ratio of I / II		Isolated Yield
		I	II	
$Bu_3SnMgMe$	CuCN	100	0	88
$Bu_3SnAlEt_2$	CuCN	81	19	86
$(Bu_3Sn)_2CuCNLi_2$	---	36	64	75
$Bu_3SnMgMe$	$CuBr\,SMe_2$	34	66	23
$(Bu_3Sn)_2Zn$	CuCN	26	74	63

[a] Three mol of Bu_3Sn-Metal reagent and one mol of acetylene compound.
[b] 5% mol of catalyst used.

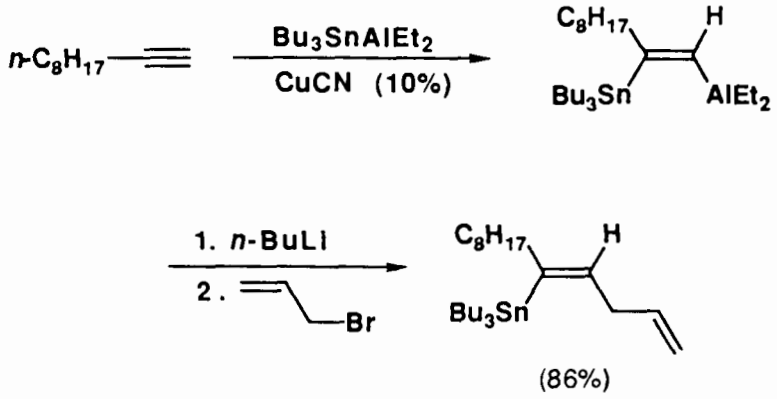
Scheme I-4. Variable regiochemistries obtained in the stannylmetallation of 1-alkynes[19]



Temperature	Ratio I : II	% yield
-78 °C	91 : 9	85
0 °C	15 : 85	95

Scheme I-5. Variation of the regiochemistry of the stannylcupration with temperature.[21]

In the case of stannylalumination of acetylenes, the vinylalanes, obtained by this process, can react with allyl bromides in good yields, providing a method for the synthesis of trisubstituted olefins[10c] (**Scheme 1-6**).



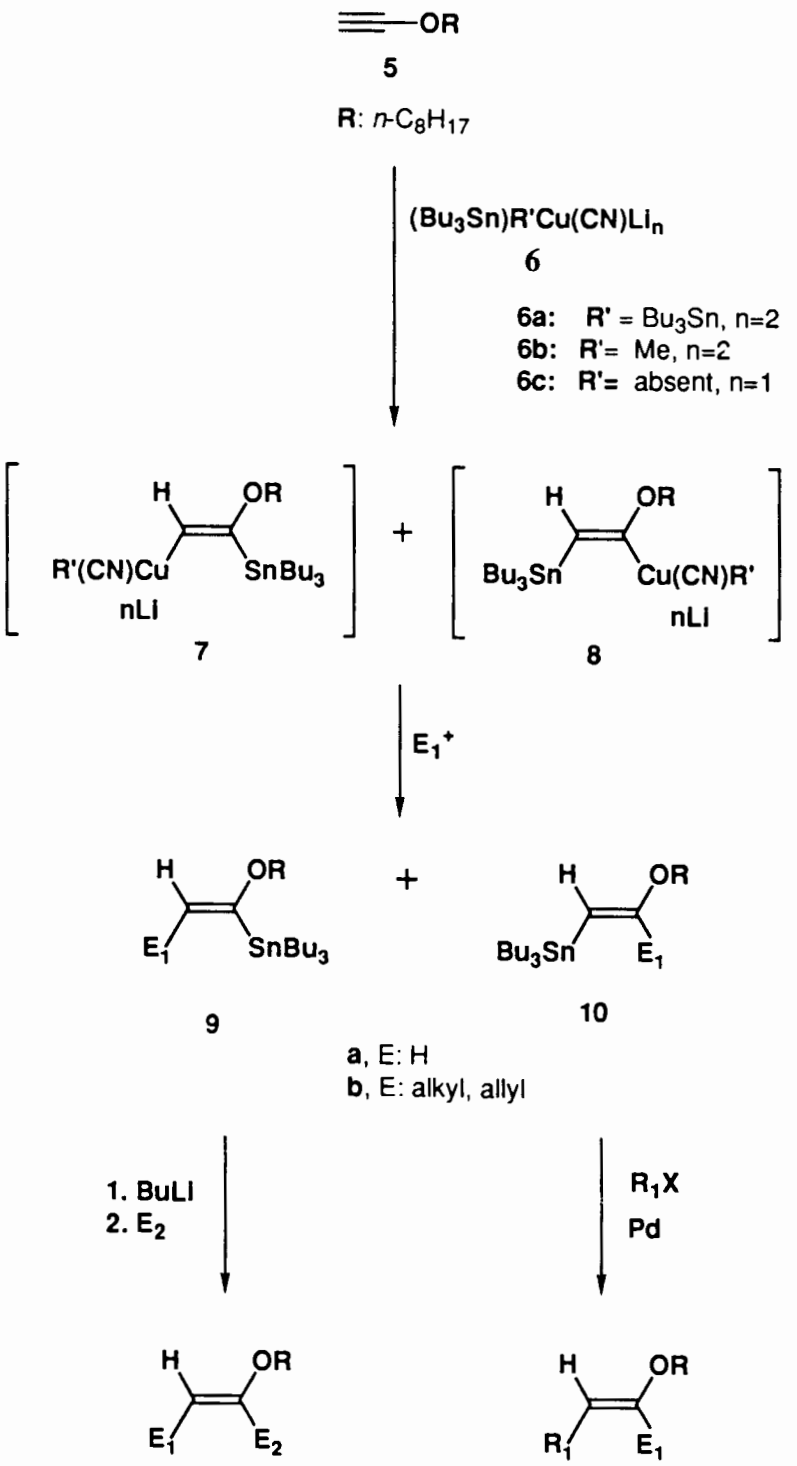
Scheme I-6. Synthesis of trisubstituted olefins *via* stannylalumination of alkynes.[10c]

When stannylcupration is applied to α,β-acetylenic esters,[22] propargylamines,[23] allenes,[24] propargylic acetals,[25] α,β-acetylenic amides[26] and conjugated enynes[27], this methodology exhibits high regio- and stereo selectivity.

The present investigation extends stannylcupration to acetylenic ethers (**5**) (**Scheme I-7**). Hydrolysis or further elaboration[28] of the bimetallic vinyl ethers **7** and **8**, obtained by the envisioned process, would allow stereospecific generation of α- or β-stannylated vinyl ethers **9** and **10**, respectively (**Scheme I-7**).

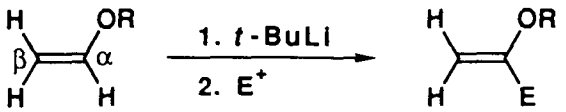
Transmetallation of the tributylstannyl moiety in **9** followed by further reaction with electrophiles, or Pd-cross coupling[16] of **10**, would provide a stereospecific route to α, β-disubstituted vinyl ethers (**Scheme I-7**). Such vinyl ethers are useful synthetic intermediates[29] in the preparation of furanones[30] and 1,3-diols.[31] Most syntheses of these moieties involve several steps[32] or vigorous reaction conditions.[31,33]

A useful procedure for the preparation of α-substituted methyl or ethyl vinyl ethers is lithiation and alkylation of the commercially available methoxy or ethoxyethenes respectively (**Scheme I-8**), using *t* -BuLi and *N* ,*N* ,*N'*,*N* '-tetramethylethylendiamine (TMEDA),[34] BuLi/*t*-BuOK[35] or *t*-BuLi in pentane.[36] Nevertheless, alkylation of vinyl ethers possessing β-alkyl substituents using these procedures has consistently failed.[37] An alternative synthetic strategy for



Scheme I-7. Stannyl cupration of acetylenic ether 5

preparation of these products is the palladium(0)-catalysed hydrostannylation of 1-alkoxy-1-alkynes.[37]



R= Et or Me

Scheme I-8. Lithiation-Alkylation of enol ethers.

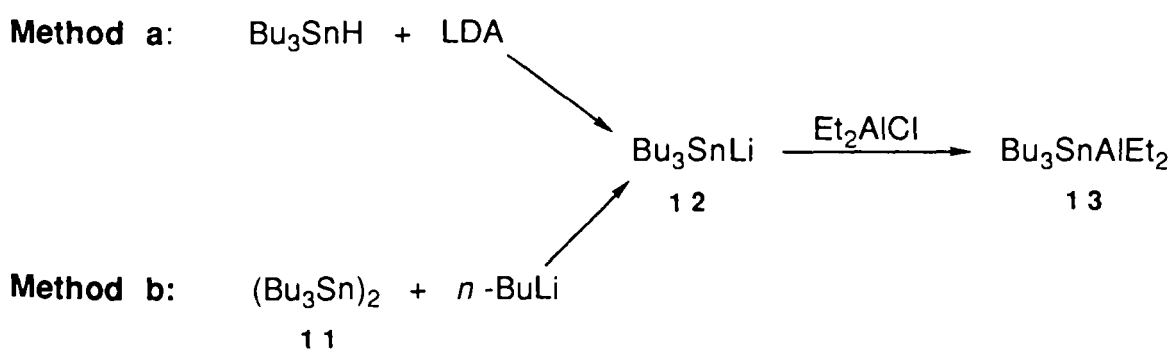
The current study developed experimental conditions for stannylmetallation of acetylenic ethers that allow control of the regiochemistry of addition producing α- or β-stannylated vinyl ethers **9** and **10** .

This chapter describes the effects of temperature, additives and stannylating reagent on the stannylalumination and stannylcupration of acetylenic ethers. A study of the mechanism of stannylcupration of acetylenic ethers by low temperature ^{1}H- and ^{13}C-NMR spectroscopy is also described.

I.2. Results and Discussion

I.2.1. Stannylalumination

Alkynyl ether **5**, was chosen as the substrate to probe the scope of stannylmetallation of acetylenic ethers since its relatively high boiling point would allow detection of unreacted starting material in crude reaction mixtures. The stannyl aluminum reagent, $Bu_3SnAlEt_2$, **13**, was selected as the initial bimetallic reagent of study to facilitate comparison with earlier studies in which this reagent was added to 1-alkynes.[10b,c] This reagent is easy to prepare from readily available reagents. Thus, addition of 1 equivalent of lithium tri-*n* -butyltin (Bu_3SnLi), **12**, to 1 equivalent of diethyl aluminum chloride (Et_2AlCl), gave **13**. Lithium tri-*n* -butyltin, **12**, was prepared either by reaction of LDA with tri-*n* -butyltin hydride (**Scheme I-9**, method **a**) or reaction of bis(tri-*n* -butyltin), **11**, with *n* -BuLi (**Scheme I-9**, method **b**). The method of preparation of **12** did not affect the yield or regiochemistry of reactions between **5** and **13**.

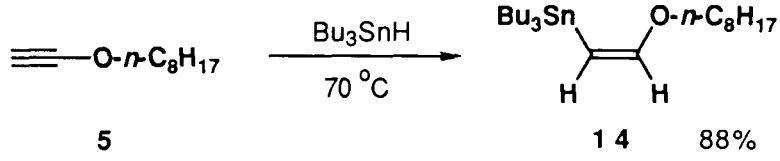


Scheme I-9. Formation of $Bu_3SnAlEt_2$, 13.

Initial reactions between equimolar amounts of **5** and **13**, in THF solutions at -30 °C and catalyzed by addition of CuCN (10 %)[10c] followed by quenching at this temperature with aqueous NH_4Cl gave **9a** in 38-50% yield. Remarkably, the *cis* isomer (**14**) was also obtained (**Table I-1**, entry 1). Significant amounts of **5** (>40 %), were found in these crude reaction mixtures. Several reactions, using a three fold excess of **13** were conducted in the expectation that all of **5** were consumed, however these conditions resulted in the formation of octyl vinyl ether,**15**, and bis(tributyltin),**11**, as the major products.

It has been reported that HMPA can reverse the regiochemistry of stannylalumination.[10c] In an attempt to obtain regioisomer **10a**, reaction of **5** with **13** was performed in the presence of HMPA at -30 or 0 °C (**Table I-1**, entries 2 and 3). Surprisingly, in the later case the *cis* isomer **14**, was obtained as the major product .

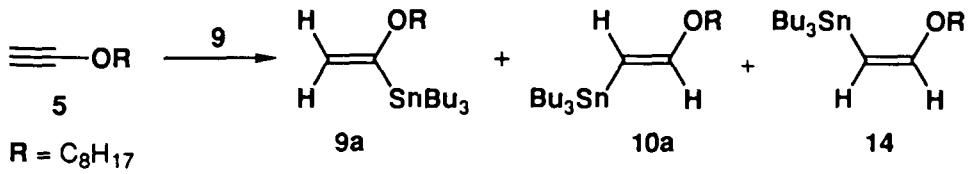
The identity of both **9a** and **14** was confirmed by ^1H and ^{13}C NMR spectroscopy. The identity of the latter was further confirmed by comparison with an authentic sample, prepared by hydrostannylation of **5** with tri-*n* -butyltin hydride (**Scheme I-10**).



5 **14** 88%

Scheme I-10. Synthesis of *cis* -2-tributylstannylvinyl octyl ether 14.

Table I-1. Reaction of Acetylenic Ether 5, with $Bu_3SnAlEt_2$, 13.



5 $R = C_8H_{17}$ 9a 10a 14

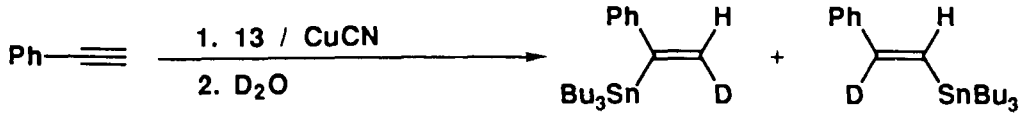
Entry	Conditions	Ratio 9a : 10a : 14			Yield [a] (%)
1	THF, -30 °C	84	–	16	38
2	THF / HMPA,[b] -30 °C[c]	64	4	32	44
3	THF / HMPA,[b] 0 °C[c]	25	–	75	35

[a] Calculated by GC and ^1H NMR analysis, based on acetylenic ether, using dodecane and triphenylmethane as internal standards respectively.

[b] 17 Equivalents of HMPA were used.

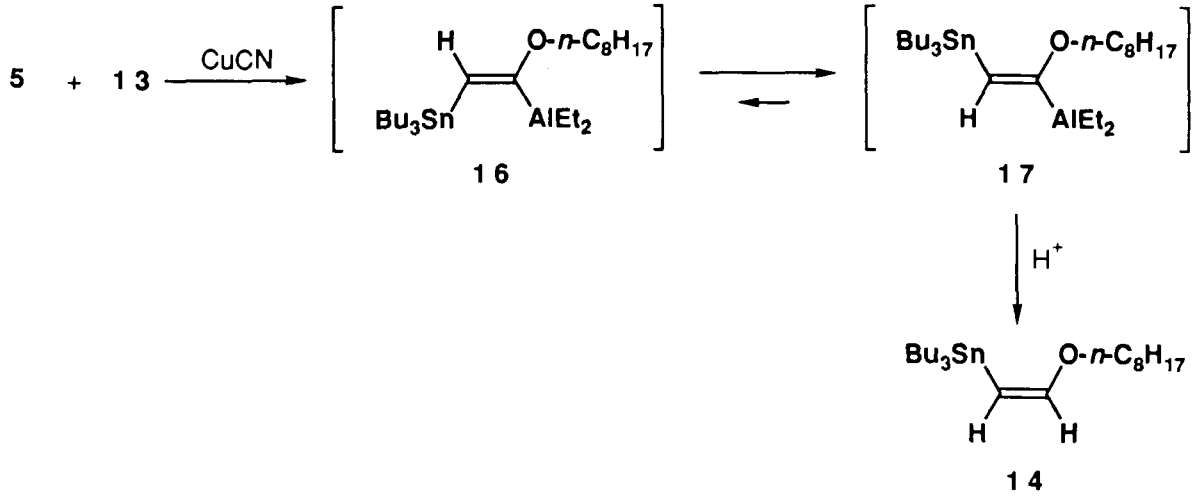
[c] External temperature.

It has been reported[10,19b] that addition of **13** to 1-alkynes is *cis* . Evidence for this was obtained[19b] by the reaction of phenylacetylene with **13**, followed by hydrolysis with deuterium oxide (**Scheme I-11**).



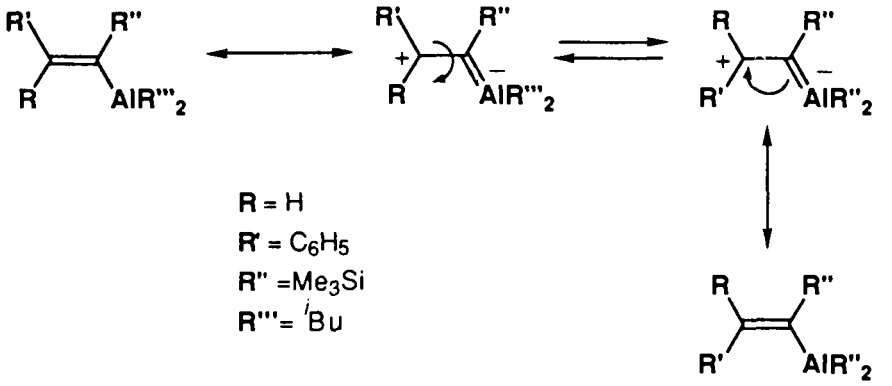
Scheme I-11. *cis* -Stannylalumination of phenylacetylene with 13.

A plausible rationalization for the formation of **14**, which is formally derived from a *trans* -addition is that the initial *cis* -adduct (**16**) isomerizes to **17** before hydrolysis to **14** (**Scheme I-12**).



Scheme I-12. Formation of regioisomer 14 in the reaction of 5 with 13.

It is known that 1-alkenylalanes undergo geometrical isomerization, the facility with which this occurs is governed by the alkene substituents (**Scheme I-13**). When R'=R''=Ph, isomerization requires prolonged heating at 100 °C,[38] but when R'=C_6H_5 and R''=$SiMe_3$ equilibration occurs at -10 °C.[39]



Scheme I-13. Isomerization of Vinylalanes[40]

It is believed that this process involves formation of a carbocation aluminate zwitterion in which the π–bond character between the carbons has been significantly reduced[40] (**Scheme I-13**).

A similar mechanism might operate in the isomerization of **16** to **17**, where R=$SnBu_3$, R'=H, R''=O*n*-C_8H_{17}, R'''=Et. The driving force for the latter process could be relief of the steric repulsion between the aluminum and stannyl groups in **16** which would be eliminated in **17**.

In the stannylalumination reactions conducted, vinylstannanes were obtained in low to moderate yields and regioselectivity was low (**Table I-1**).

The crude reaction mixtures obtained after hydroiysis contained significant amounts (50-60%) of tetrabutyltin and bis(tributyltin), which made isolation of vinylstannanes difficult. After several exploratory experiments the reaction of **13** with **5** was abandoned in favour of direct stannylcupration.

I.2.2. Stannylcupration

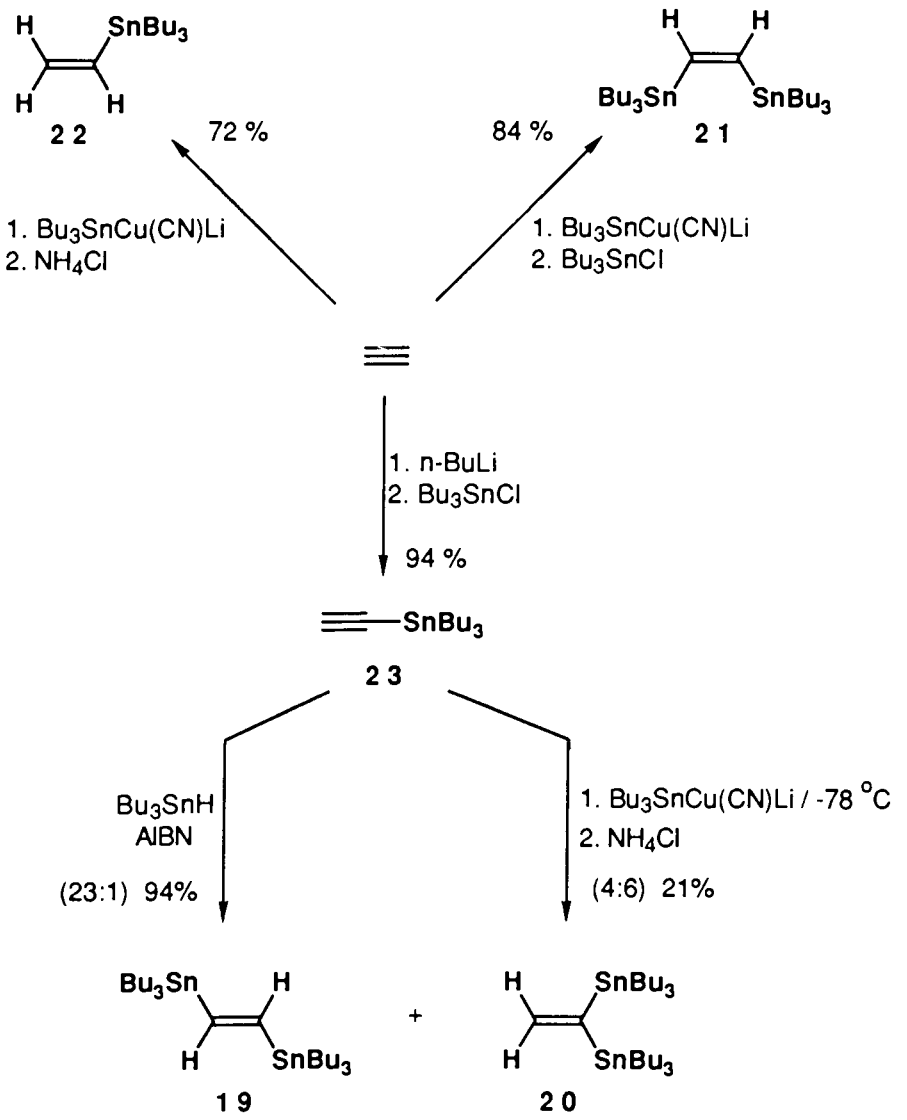
I.2.2.1. Synthetic Studies

The stannylating reagent chosen was the higher order stannylcyanocuprate **6a**. It is known that higher order stannylcyanocuprates $[(R_3Sn)_2Cu(CN)Li_2]$ are more reactive than Gilman type stannylcuprates $[(R_3Sn)_2CuLi]$.[41]

Reaction of **5** with **6a** in THF at -40 °C followed by warming to 0 °C and methanolysis gave mixtures of **9a** and **10a** (**Scheme I-7**) in a 4:6 ratio, in 42% yield based on the amount of **5** (**Table I-2**, entry 1). The principal (51%) non-stannylated product was 1-octanol **18**.

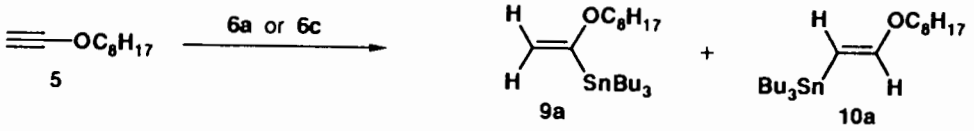
Three isomeric stannylated by-products (**19**, **20**, **21**) were formed in this reaction. ^{1}H-NMR analysis showed each contained olefinic hydrogens. Taken with the observed molecular weights (M^+-Bu= 549) these by-products were deduced to be isomers of bis(tributylstannyl)ethene. The identity of these by-

products was confirmed by comparison with authentic samples prepared as described in **Scheme I-14**.



Scheme I-14. Synthesis of compounds 19-23.

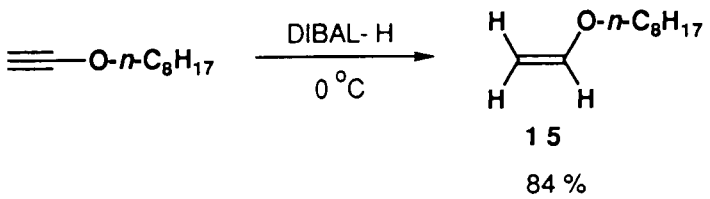
Table I-2. Stannylcupration of 5 under different reaction conditions.



Entry	Cuprate	Conditions (°C[d], solvent)	9a : 10a	Yield (%)	15[a] (%)	18[a] (%)	11[b] (%)	22[b] (%)	19[b] (%)	20[b] (%)	21[b] (%)
1	**6a**	-40 to 0, THF	40:60	42[a](21)[b]	5	51	55	7	1	3	3
2	**6a**	0, THF	16:84	45[a](22)[b]	8	42	67	10	(-)	(-)	1
3	**6a**	0, THF:HMPA[e]	5:95	94[a](47)[b]	6	(-)	48	(-)	(-)	(-)	(-)
4	**6a**	-78, THF	78:22	91[a](45)[b]	7	2	55	(-)	(-)	(-)	(-)
5c	**6a**	-78, THF	100:0	95[a](47)[b]	5	(-)	53	(-)	(-)	(-)	(-)
6	**6c**	0, THF:HMPA[e]	9:91	90[a](90)[b]	7	2	16	(-)	(-)	(-)	(-)
7c	**6c**	-78, THF	97:3	93[a](93)[b]	4	2	8	(-)	(-)	(-)	(-)

[a] Yields based on equivalents of **5** used. [b] Yields based on equivalents of tributyl stannyl anion used. [c] **5** was dissolved in dry MeOH. (-) Not detected. Yields were calculated by ^{1}H-NMR and capillary GC (~5% error), using triphenylmethane and dodecane as internal standards respectively. [d] External temperature. [e] 17 equivalents of HMPA were used.

Vinyl(tributyl)tin, **22**, octyl vinyl ether, **15** and bis(tributyltin), **11**, were also detected in the crude reaction mixture. These were identified by comparison with independently prepared authentic samples (**Scheme I-14**). Octyl vinyl ether, **15**, was prepared by reduction of octyl ethynyl ether **5**, according to **Scheme I-15**.



15

84 %

Scheme I-15. Synthesis of octyl vinyl ether 15.

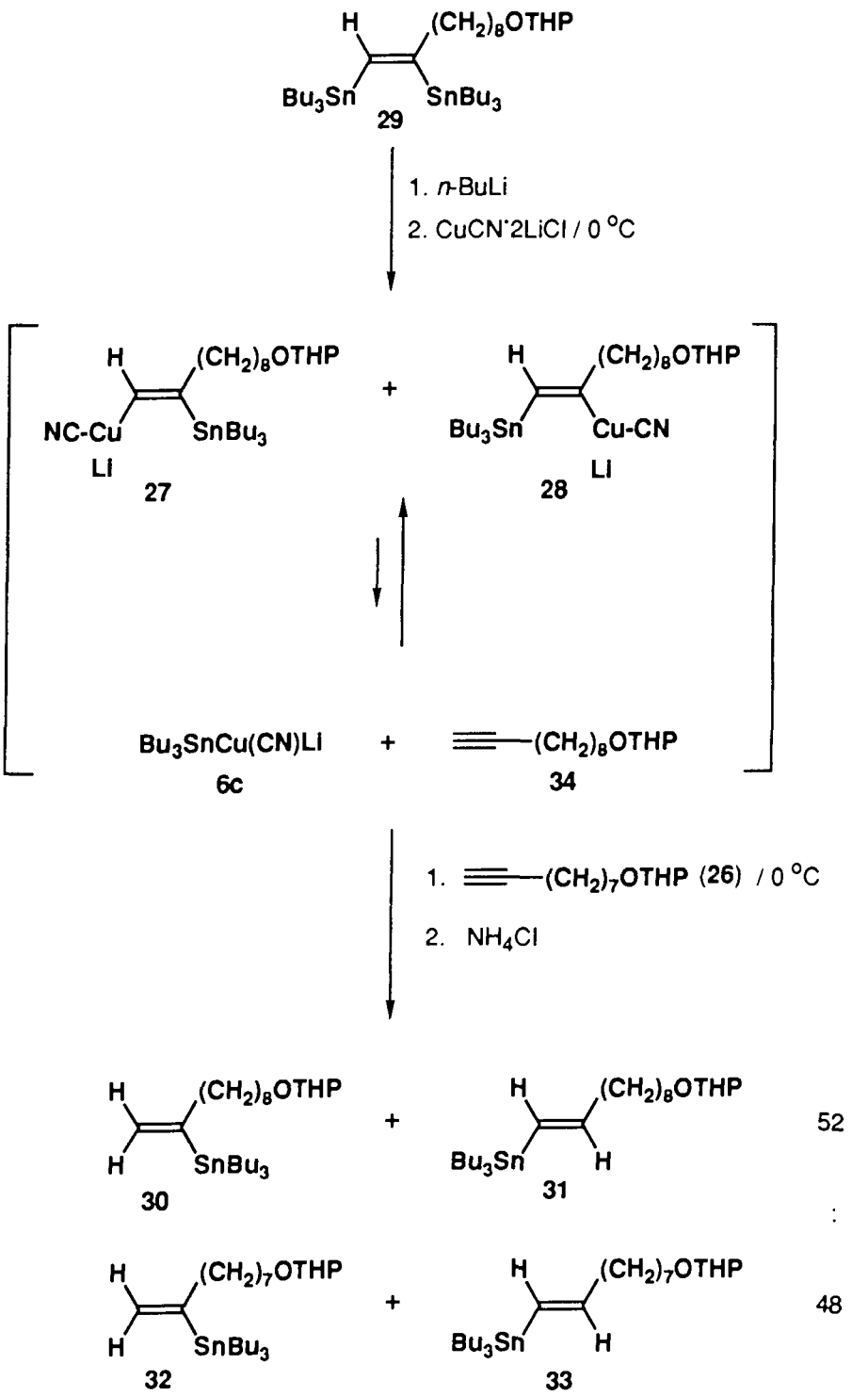
The reaction of **5** with **6a** at 0 °C yielded ~45% of **9a** and **10a** in a ratio of 16:84 (**Table I-2**, entry 2). 1-Octanol (**18**) and **15** were obtained in 42% and 8% yields, respectively. Lower amounts of **21** and **22** were also present in the crude reaction.

When higher order cuprate, **6a**, was prepared in the presence of HMPA (17 equiv.) and reacted with **5** at 0 °C, **9a** and **10a** were obtained in very good yield (94 %) and with improved regioselectivity favouring **10a** (1:19) (**Table I-2**, entry 3). Surprisingly, 1-octanol, **18**, and stannyl by-products (**19-22**) were not detected in reaction mixtures arising from this reaction. Presumably, HMPA stabilizes the presumed vinylcuprate intermediates resulting in improved yields and regioselectivity.

Improvement of regioselectivity in favor of **10a** by increasing the reaction temperature from -40 to 0 °C (**Table I-2**, entries 1 and 2), suggested that the addition could be reversible with the stannylcuprate adduct precursor of **10a** as the thermodynamic product. To obtain **9a**, the isomer presumed at this point to be derived from kinetically controlled stannylcupration, the reaction was conducted at -78 °C. Acetylenic ether **5**, dissolved in THF, was added to a cold (-78 °C) THF solution of cuprate **6a**. GC analysis of hydrolyzed aliquots of this reaction mixture revealed consumption of **5** after 10 min at -78 °C, even under the dilute conditions employed (ca. 0.07 M). Hydrolysis of the reaction mixture by addition of methanol at -78 °C gave **9a** and **10a** in a ratio of 78:22 (91 % yield, **Table I-2**, entry 4). Although regioisomer **9a** was the major product a significant proportion of **10a** was still produced.

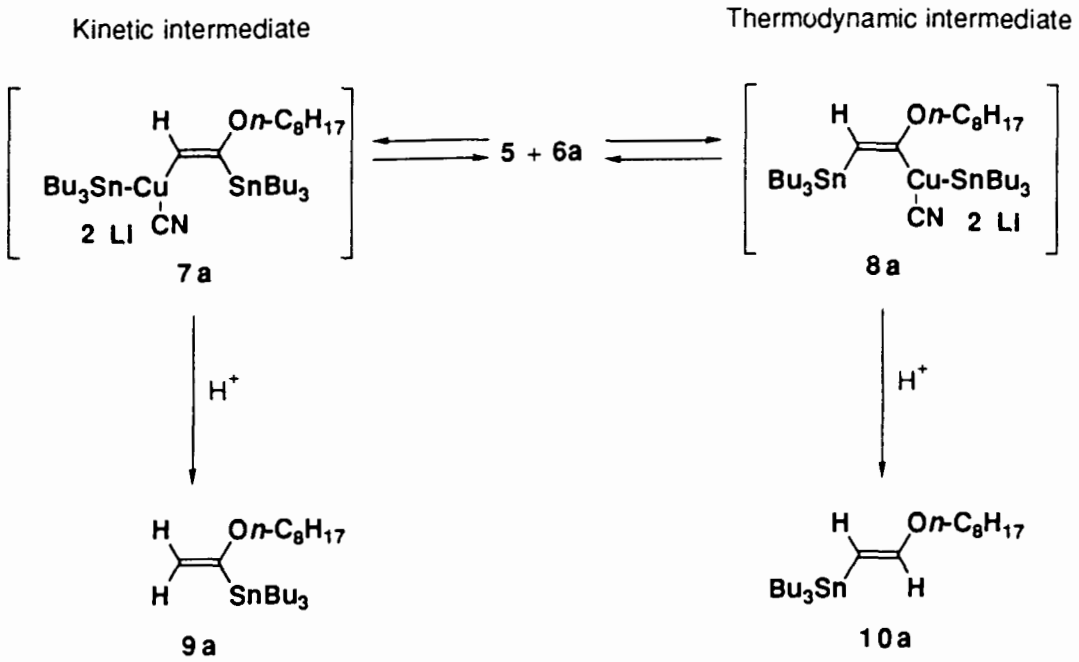
It has been established, by crossover experiments, that stannylcupration of alkynes is a reversible process.[21,42] Thus, addition of 1 equivalent of alkyne **26** to a solution of vinylcuprates **27** and **28**, obtained from reaction of vinyldistannane **29** with *n*-BuLi and CuCN·2LiCN (**Scheme I-16**), resulted in nearly equal quantities of the vinylstannanes **30**-**33**, obtained from stannylcupration of the corresponding alkynes (**26** and **34**) by **6c** (**Scheme I-16**).

The changes of regiochemistry observed when the temperature of reaction of **5** with **6a** was changed from 0 °C to -78 °C, suggest the reaction is under thermodynamic control at 0 °C and under kinetic control at -78 °C (**Table I-2**, entries 1-4). Using this mechanistic model the significant amount of **10a**



Scheme I-16. Crossover experiment showing the reversibility of stannylcupration[21,42]

(ca. 20 %) obtained at -78 °C (**Table I-2**, entry 4) would have arisen simultaneously with **9a** or *via* equilibration of the "kinetic adduct" **7a** to **8a** (**Scheme I-17**).

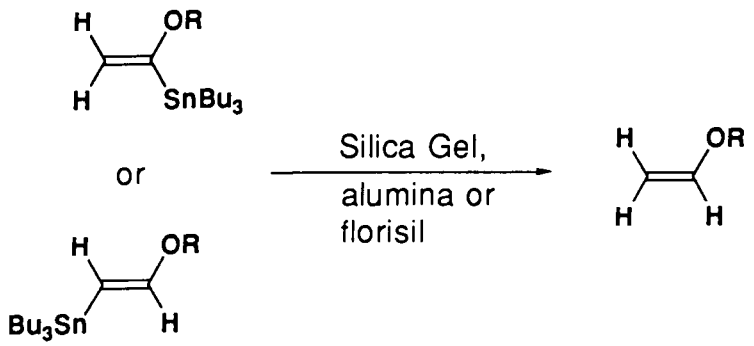


Scheme I-17. Kinetic and thermodynamic intermediates in the reaction of 5 with 6a.

If **7a** is the kinetic adduct it should be possible to capture it prior to equilibration by reaction of **5** and **6a** in the presence of methanol. The latter is known to hydrolyze vinyl cuprates but not stannyl cuprate reagents.[43] Thus, **5** was dissolved in dry methanol and added to a cold (-78 °C) THF solution of **6a**. Standard work-up yielded exclusively α-stannylated vinyl ether (internal isomer) **9a** in a very good yield (95%) (**Table I-2**, entry 5).

Formation of the higher order cuprate **6a**, requires addition of two equivalents of lithium tri-*n* -tributyltin, **12**, to one equivalent of copper cyanide. One of the tributylstannyl moieties is transferred to the triple bond of **5**, while the other one does not react, generating considerable amounts of tin by-products. In the crude reaction mixtures, products **9a** and **10a** were present in purities of 45-50 %.

Bis(tributyltin) **11** is always a product in reactions between **5** and **6a** which complicates isolation of the vinyl stannanes. Chromatographic purification of these vinyl stannanes is inconvenient because alkoxyalkenylstannanes **9** and **10** hydrolyze during chromatography (**Scheme I-18**).



Scheme I-18. Destannylation of alkoxy vinylstannanes in chromatographic supports.

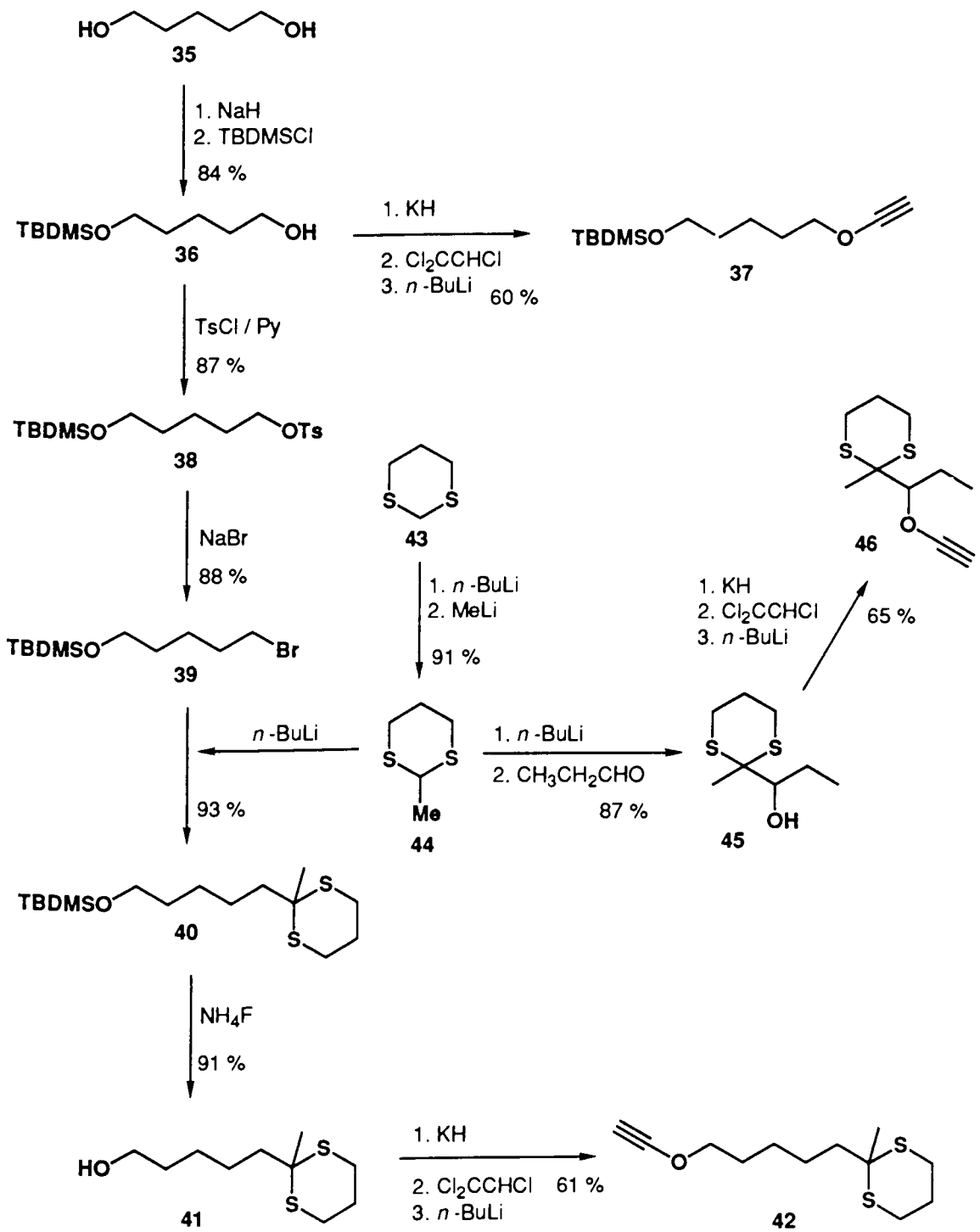
The utility of this stannylcupration process in synthesis would be more attractive if reagents could be found that would enable adducts **9** or **10** to be used as they are obtained from the initial work-up procedure.[37]

To reduce the amount of **11** and obtain mixtures of vinyl stannanes of higher initial purity, use of lower order cuprate, **6c**, was explored. It was reasoned that although lower order cuprates are less reactive than higher order cuprates, the presence of only one equivalent of tributyltin anion in **6c** should favour production of alkoxyvinylstannanes and lower amounts of **11**.

Reaction of **5** and **6c** was conducted using the same conditions developed for cuprate **6a** (**Table I-2**, entries 3 and 5 respectively). The lower order cuprate gave yields and proportions of **9a** and **10a** similar to those obtained with **6a** but with lower amounts of **11** (**Table I-2**, entries 6 and 7). Use of cuprate **6c**, as well as **6a**, at 0 °C required the presence of HMPA as a stabilization agent. Significant decomposition occurred when THF solutions of **6c** were warmed to 0 °C without this additive.

To demonstrate that reactions of **6a** or **6c** with **5** were applicable to functionalized alkynyl ethers the reactions of several acetylenic ethers with these cuprates at 0 and -78 °C were performed. The alkynyl ethers used in this comparison were **37**, **42** and **46** which were prepared according to **Scheme I-19**.

With functionalized alkoxy-alkynes cuprates **6a** and **6c** exhibited high regioselectivities favoring **9a** or **10a** depending on the reaction conditions (**Tables I-3** and **I-4**). With cuprate **6c**, vinyl stannanes were obtained in good yields with less than 10% contamination of **11**. GC analysis of the crude reaction mixtures obtained in reactions with this cuprate showed initial

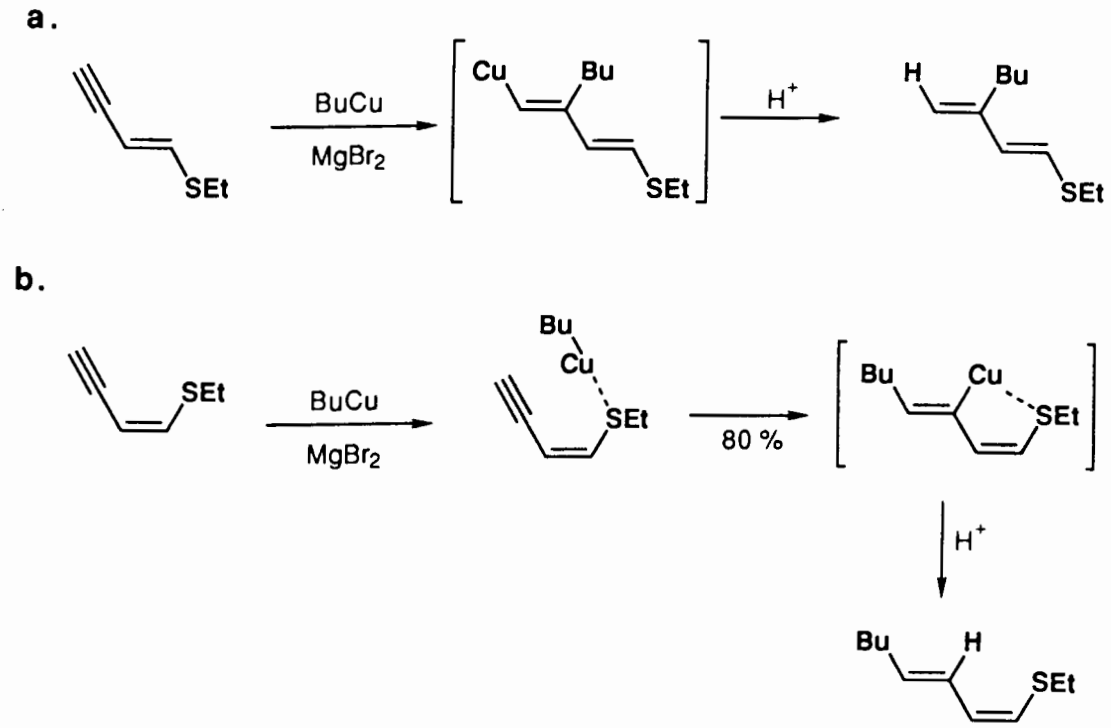


Scheme I-19. Synthesis of acetylenic ethers 37, 42 and 46.

vinylstannane purities of 80-90 %. These purities are sufficient for use of crude reaction mixtures in synthesis (see Chapter IV).

Interestingly, when a methanolic solution of **46** was reacted with **6a** at -78 °C, conditions designed to favor production of regioisomer **9**, a considerable amount (53% yield) of regioisomer **10** was obtained (**Table I-4**, entry 8). This is attributed to preferential formation of the intermediate with the regiochemistry of **8** due to coordination between copper and sulfur forming a six membered ring chelate as depicted in **Figure I-1**.

It is known that the location of coordinating nitrogen or sulfur near the triple bond, influences the regioselectivity of carbocupration, by coordination with the metal.[44] For example, different regioselectivities are obtained in carbocupration reactions of *cis* and *trans* ethyl-1-buten-3-ynyl sulfides. Thus, while only the internal alkynyl carbon is alkylated in the *trans* isomer (**Scheme I-20 a**), carbocupration of the *cis* isomer results only in alkylation of the terminal alkynyl carbon of the sulfide. In the latter case, formation of a sulfide-organocopper complex has been proposed to be an intermediate (**Scheme I-20 b**).



Scheme I-20. Directed effect of sulfur on carbocupration

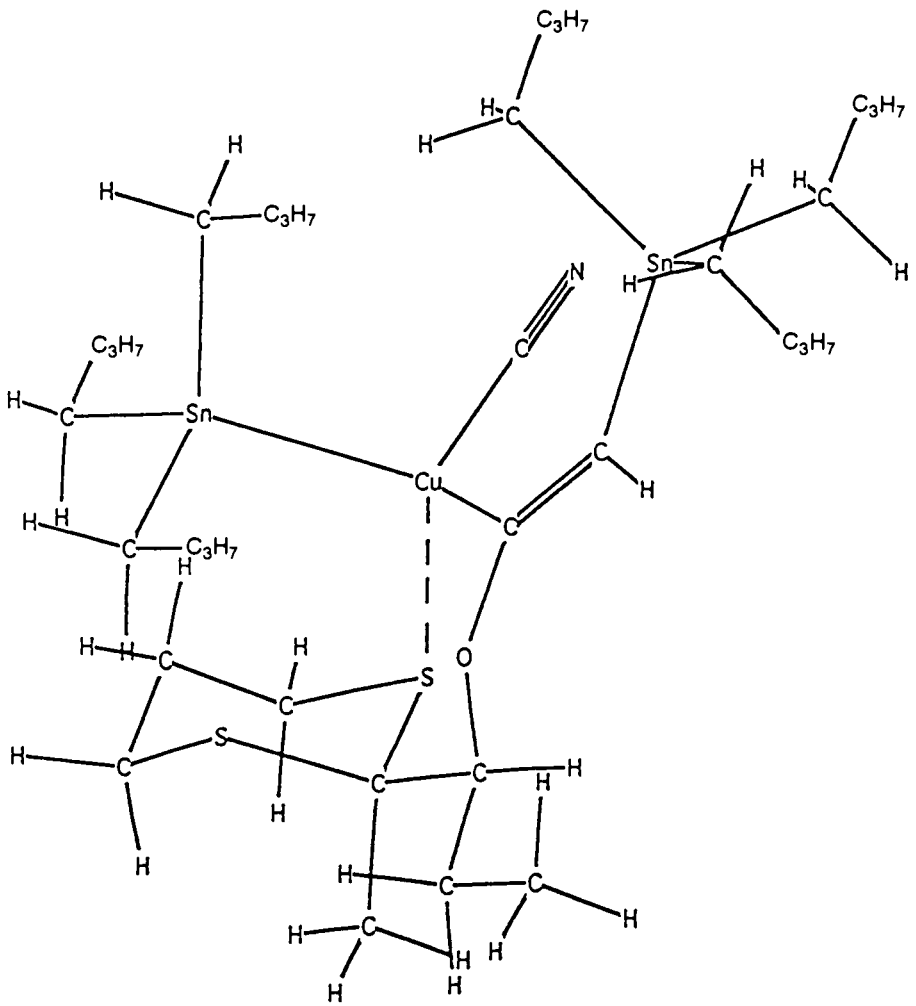
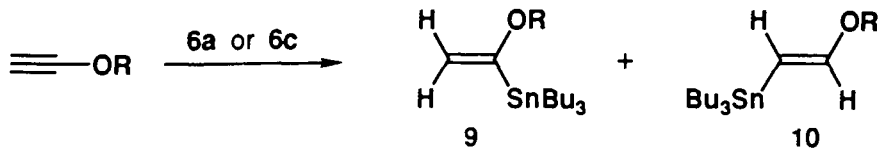
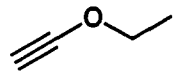
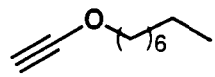
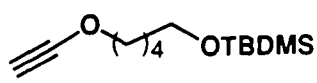
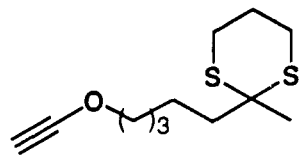
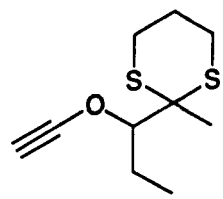


Figure I-1. Model of the vinylcopper intermediate **8**, formed in the reaction of **46** with $(Bu_3Sn)_2Cu(CN)Li_2$.

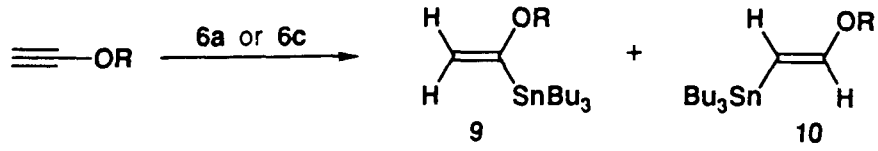
Table I-3. Reaction of Stannylcyanocuprates 6a and 6c with Functionalized Acetylenic Ethers at 0 °C in THF-HMPA

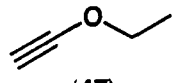
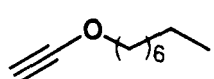
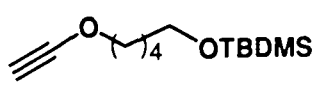
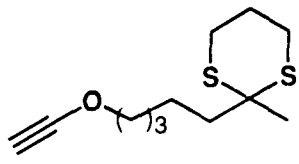
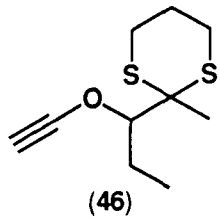


Entry	Acetylenic Ether (Compound no.)	Cuprate	9 : 10 (Compound #)	Yield [a] (%)
1	 (47)	6c	4 : 96 (48) (49)	92
2	 (5)	6a	5 : 95	94
3		6c	9 : 91 (9a) (10a)	90
4	 (37)	6a	10 : 90	91
5		6c	9 : 91 (50) (51)	95
6	 (42)	6a	7 : 93	90
7		6c	10 : 90 (52) (53)	85
8	 (46)	6a	0 : 100	90
9		6c	0 : 100 (54) (55)	92

[a] Calculated by GC and ^{1}H NMR analysis, based on acetylenic ether, using dodecane and triphenylmethane as internal standards respectively.

Table I-4. Reaction of Stannylcyanocuprates 6a and 6c with Functionalized Acetylenic Ethers at -78 °C in THF

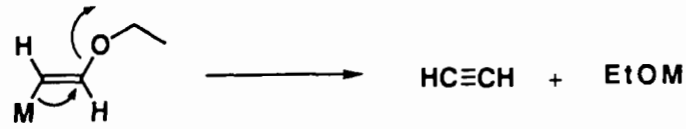


Entry	Acetylenic Ether (Compound no.)	Cuprate	9 : 10 (Compound #)	Yield [a] (%)
1	 (47)	6c	95 5 (48) (49)	90
2	 (5)	6a	100 : 0	95
3		6c	97 : 3 (9a) (10a)	93
4	 (37)	6a	100 : 0	92
5		6c	95 : 5 (50) (51)	95
6	 (42)	6a	90 : 10	85
7		6c	97 : 3 (52) (53)	80
8	 (46)	6a	41 : 59 (54) (55)	89

[a] Calculated by GC and ^{1}H NMR analysis, based on acetylenic ether, using dodecane and triphenylmethane as internal standards repectively.

I.2.2.2. Mechanistic Studies

In reactions between **5** and **6a** (**Table I-2**, entries 1-2), 1-octanol is presumed to be formed via 1,2-elimination of vinyl copper intermediate **7a**. It has been reported that the (*E*)-2-alkoxyvinyllithium[45] undergoes *trans*-elimination at -80 °C while the corresponding copper[46] species suffers this process at temperatures higher than -20 °C (**Scheme I-21**).

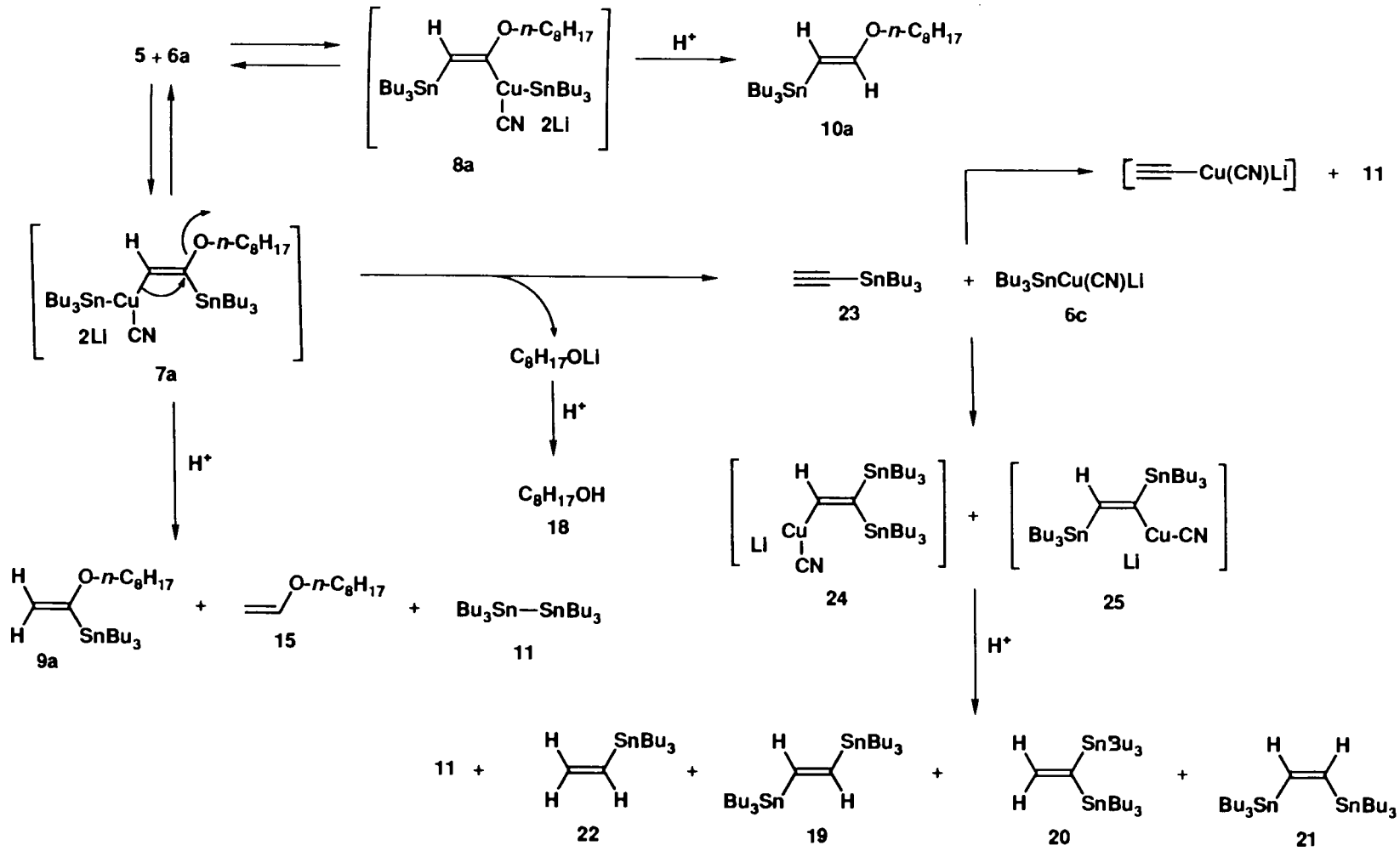


M: Li, Cu

Scheme I-21. 1,2-Elimination in *trans*-alkoxy vinyl metals.

Elimination of **7a** should produce ethynyl(tributyl)tin, **23**, and the lower order cuprate **6c** (**Scheme I-22**). While the former was not detected when the reaction was conducted in THF at 0 or -40 °C, the formation of **6c** was evidenced by a distinct color change in the reactions between **5** and **6a** when conducted in THF. The latter reactions turned orange, characteristic of THF solutions of lower order stannylcyanocuprates. When examined over several hours at 0 °C, HMPA containing reactions remained yellow, characteristic of higher order stannylcyanocuprates (compare entries 2 and 3, **Table I-2**).

Products **19-22** are envisioned as arising from reaction of **23** and cuprate **6c**. Hydrolysis of vinylcopper intermediates **24** and **25** thus formed, is viewed as giving rise to **20** and **19** respectively.



Scheme I-22. Reaction of 5 with higher order stannylcyano cuprate 6a in THF.

Isomerization of **25** and hydrolytic cleavage of the sterically hindered intermediate **24** are considered to give rise to **21** and **22**, respectively. To confirm the generation of **19-22** from this pathway, a control reaction between **23** and **6c** was performed using same experimental conditions as for reaction of **5** and **6a**. After methanolysis, products **19-22** and **11** were obtained (**Scheme I-23**).

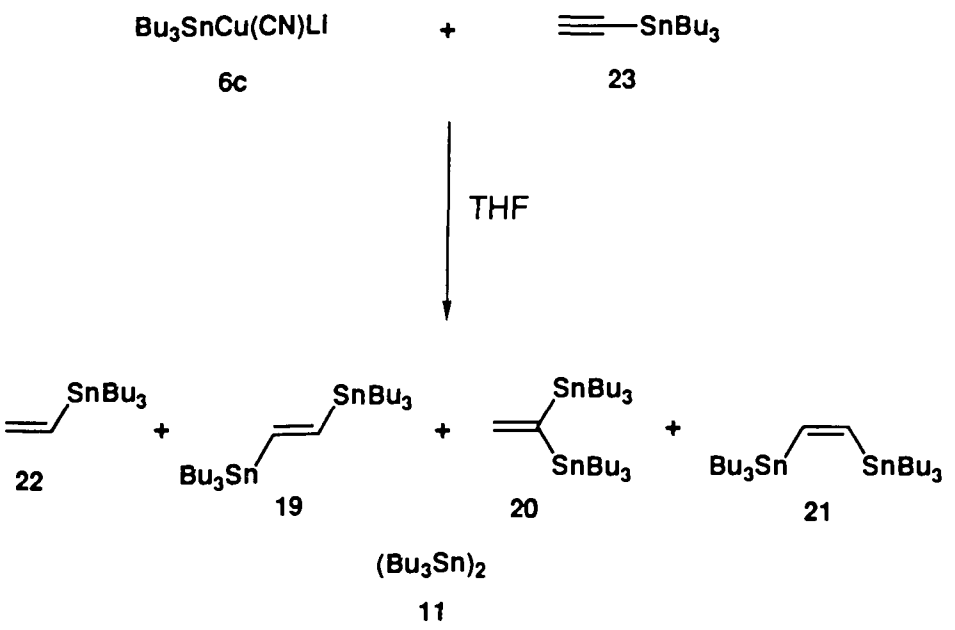
To confirm that the formation of **23** occurs from an elimination reaction of **7a**, a reaction between **5** and the mixed higher order cuprate $Bu_3SnMeCu(CN)Li_2$, **6b**, was conducted. It was expected that the initial addition would yield **7b** which would eliminate to give **23** and lower order cuprate **56** (**Scheme I-24**). Because the rate of methyl cupration is much slower than stannylcupration, these products (**23** and **56**) should not react as rapidly as **23** and **6c** would. Reaction of **5** and **6b** in THF (at -78 °C followed by warming to 0 °C) gave as the major products **9a** and **10a** (ca. 1:1, 20 %), **18** (25 %) and **15** (3 %). Indeed, the major stannylated by-products were methyl(tributyl)tin **57**, and ethynyltributyltin **23** (5%). Neither (*E*)-1-tributylstannylpropene **58** nor **59** were formed. A control reaction between **23** and **56** in THF at 0 °C yielded, after methanolysis, **57** as the only detectable product (96%).

Further evidence for the *trans*-elimination process, was obtained by variable temperature ^{1}H-NMR analysis of the reaction of **5** and **6b**. When the reaction was conducted at -78 °C in THF and the temperature gradually increased to 0 °C, a signal at -1.38 ppm assigned to **56**[47] emerged at the

expense of the signals in the olefinic region assigned to **7b** and **8b**. At 0 °C, two distinct peaks at δ= 5.33 ppm, ($^3J_{Sn-H}$= 179 Hz) and δ =4.94 ppm ($^2J_{Sn-H}$= 96 Hz), were observed for species **7b** and **8b**, respectively. Typical $^3J_{Sn-H}$ and $^2J_{Sn-H}$ values for (*E*)-2- and 1-(tributylstannylvinyl) ethers are in a range of 98-100 and 50-55 Hz, respectively.[48] The higher values observed in the present case might be due to the presence of covalent vinyl copper. It is known that the presence of electropositive elements attached to alkenes increases coupling constants in related systems.[49a,b]

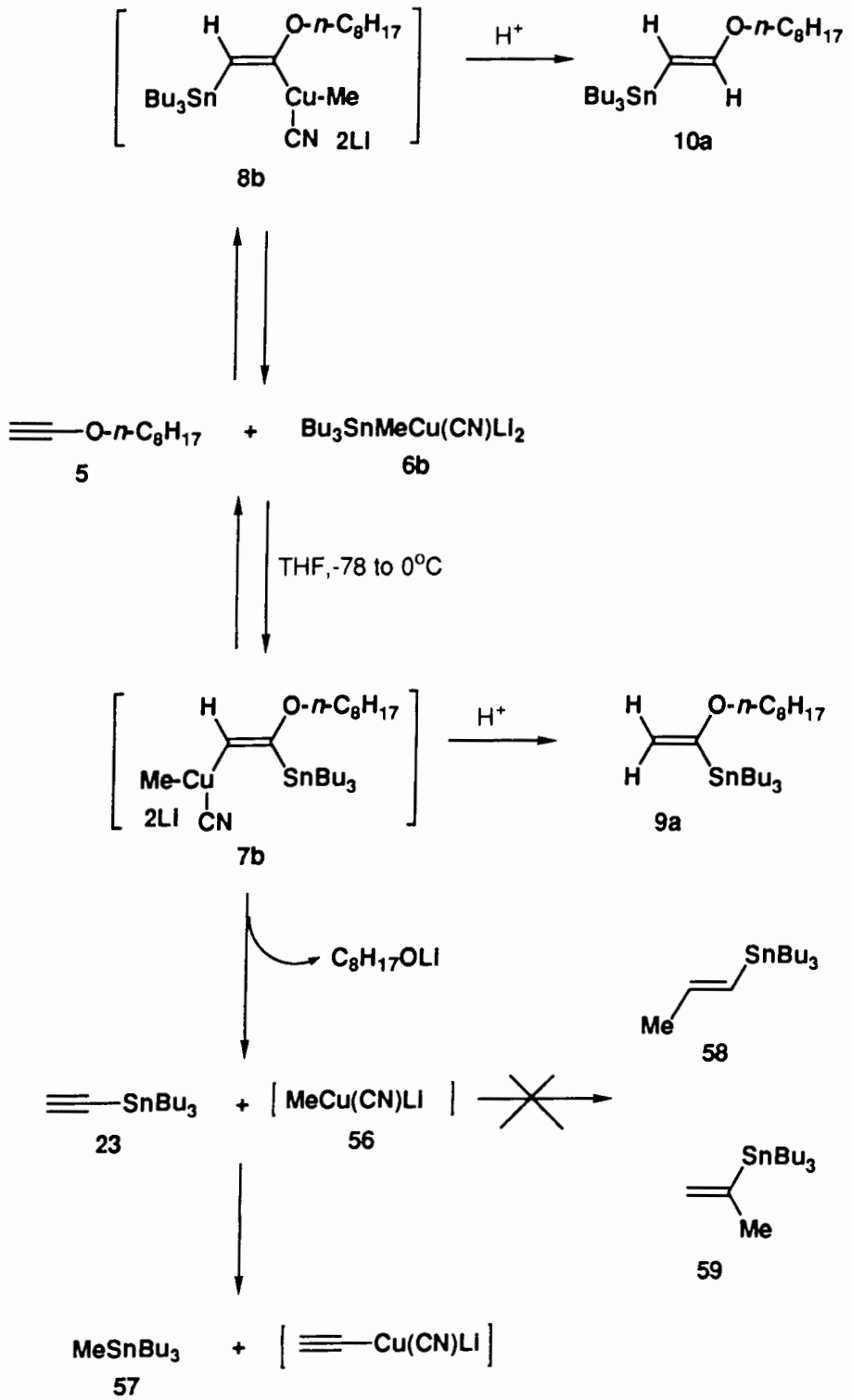
When the reaction of **5** and **6b** was conducted using **6b** prepared in the presence of HMPA (4 equivalents) and the solution slowly warmed from -78 to 0 °C, no significant change in intensity was observed in the ^{1}H NMR signals attributed to the olefinic hydrogens of **7b** and **8b**. Furthermore, a signal attributable to **56** was not observed. These observations indicate that HMPA retards the elimination of the *trans*-alkoxyvinyl intermediate, **7b**, which reduces the rate of formation of octanol. This observation is consistent with the results obtained for the reaction of cuprates, **6a** and **6c**, prepared in the presence of HMPA, with **5** at 0 °C (**Table I-2**, entries 3 and 6). In the present reaction, after equilibration (0.5 h at -78 °C), the ratio of **7b** to **8b** was ~ 1:4 (**Figure I-2**) and did not change as the solution was warmed from -78 °C to 0 °C in THF/HMPA solutions. The presence of several signals at this temperature might be due to the presence of different agregation states. Under the conditions used in this study we were unable to obtain NMR spectra of solutions of **5** and **6b** in which **7b** was a major regioisomer. Because reaction of **5** and **6a** at -78 °C in the

presence of methanol produces mixtures rich in **9a** (**Table I-2**, entry 5), the conversion of **7** to **8** must be rapid at -78 °C in the absence of methanol.



Conditions	Yield (%)				
	22	**19**	**20**	**21**	**11**
- 40 °C to 0 °C:	7	8	2	11	72
0 °C:	8	3	1	7	81

Scheme I-23 . Reaction of 23 with lower order cuprate 6c



Scheme I-24. Reaction of 5 and higher order cuprate 6b

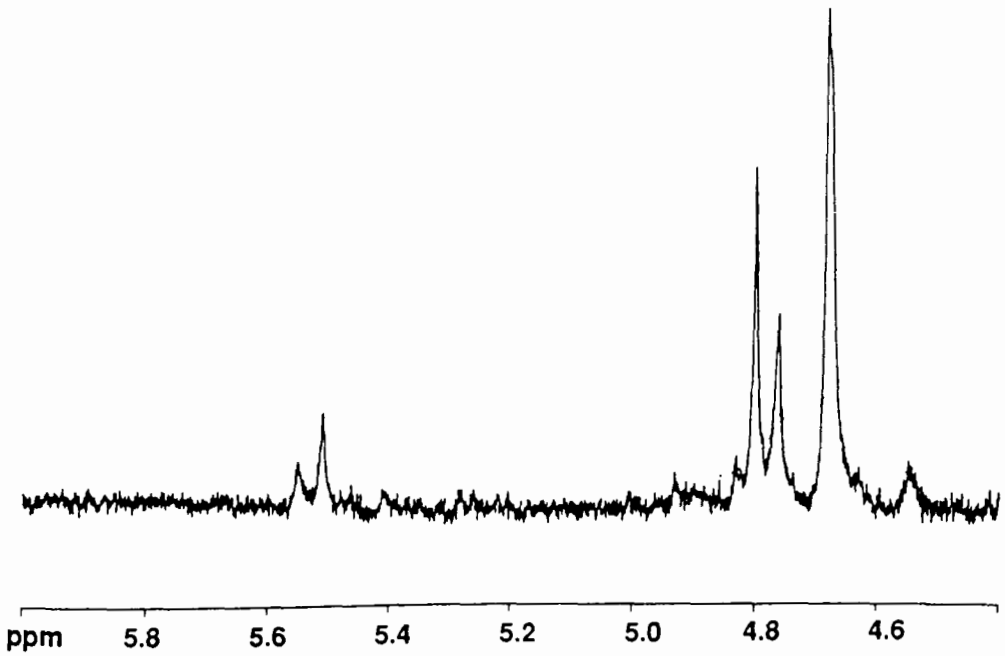


Figure I-2. Low temperature (-78 °C) ^{1}H-NMR spectrum of **5** + **6b** prepared in HMPA (4 equivalents).

I.2.2.3. Composition of Vinylcopper Intermediates

The ^1H NMR spectrum of solutions generated from the reaction of cuprate **6a** with **5** in THF solution at 0 °C showed one major signal in the vinyl region at 5.06 ppm ($^2J_{Sn-H}$: 100 Hz) (**Figure I-3a**). This was assigned to the vinyl hydrogen of **8a.** When this experiment was repeated using the same cuprate, prepared in THF containing 17 equivalents of HMPA (Table I-2, entry 3) two major signals were observed in the vinyl region (**Figure I-3b**). The signal at 5.01 ppm ($^2J_{Sn-H}$: 100 Hz) was assigned to the vinyl hydrogen of **8a** while the signal at 4.95 ppm ($^2J_{Sn-H}$: 103 Hz) was assigned to the vinyl hydrogen of a second species. These signals were reproducibly obtained in a ratio 6:4 when cuprate **8a** was prepared in solutions containing 17 equivalents of HMPA. In these HMPA containing solutions a second set of vinyl signals at 5.73 and 5.48 ppm ($^3J_{Sn-H}$: 180 Hz) was also observed (**Figure I-3b**). This latter set was attributed to intermediates regioisomeric with those exhibiting signals at 5.01 and 4.95 ppm. The two pairs of species were present in a ratio ~ 95:5.

Addition of HMPA to THF solutions resulting from reaction of **5** and **6a** at 0 °C shifted the signal attributable to the vinyl hydrogen of **8a** from 5.06 ppm to 5.01 ppm (17 equivalents of HMPA added, **Figure I-4**) but did not result in the appearance of a signal assignable to the vinyl hydrogen of the second species at 4.95 ppm. The broad signals observed upon addition of 2 and 4 equivalents of HMPA are characteristic of a rapid exchange.[49c] Thus, signals at 5.01 and 5.06 ppm are assigned to species **8a** coordinated and not coordinated with HMPA respectively.

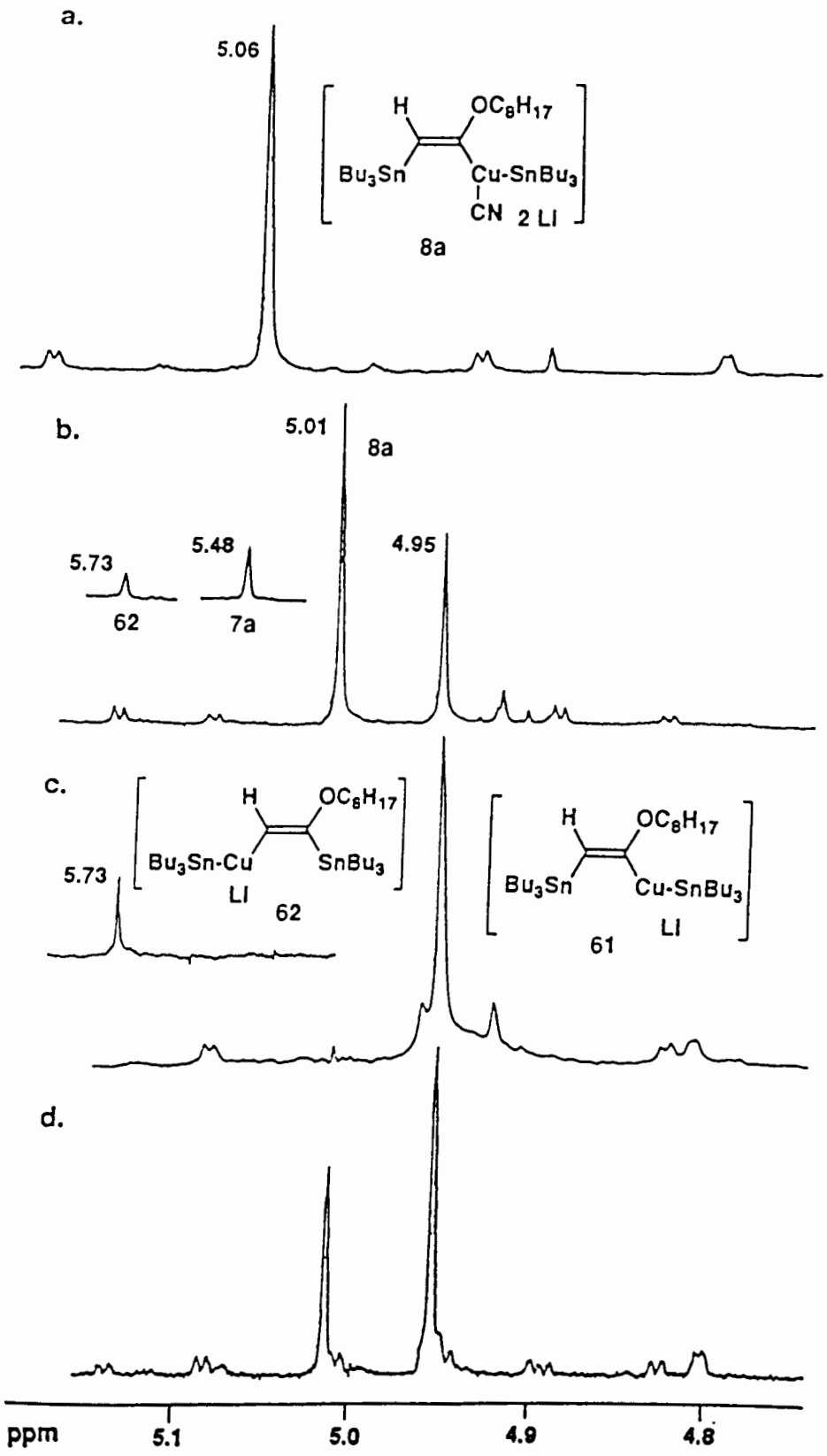


Figure I-3. Low temperature (0 °C) ^{1}H-NMR spectra of
a. **5** + **6a** in THF.
b. **5** + **6a** (prepared in the presence of HMPA).
c. **5** + **60** (prepared in the presence of HMPA).
d. solutions **I-2b** + **I-2c**.

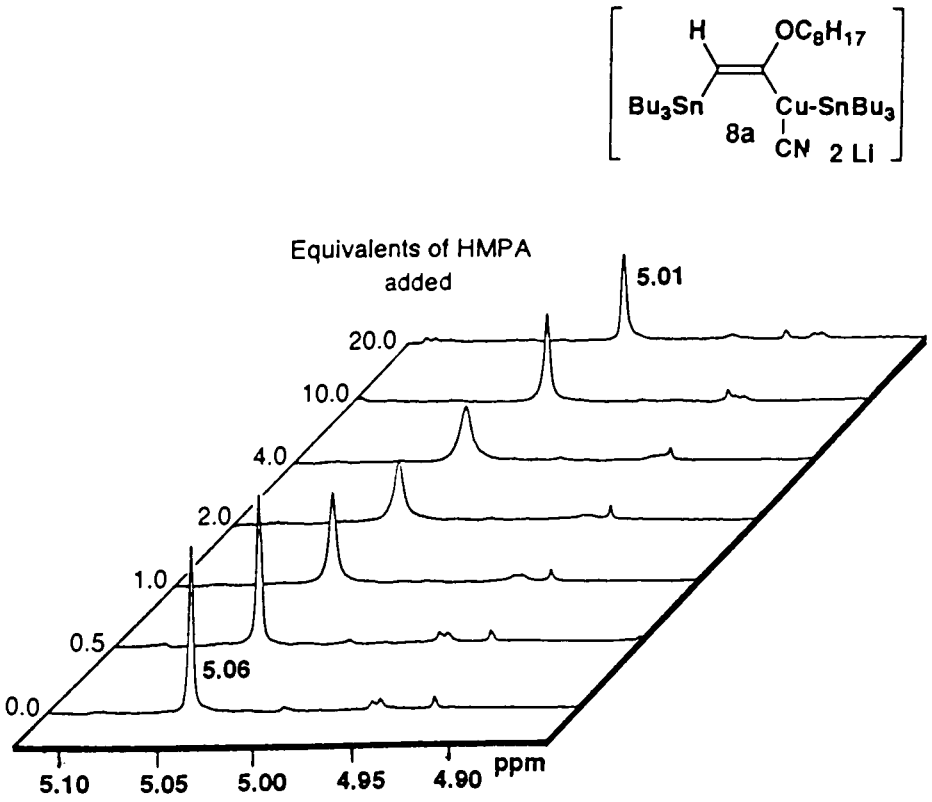


Figure I-4. Low temperature (0 °C) ^{1}H-NMR spectra of a THF solution of **8a** with successive additions of HMPA.

At intermediate concentrations of HMPA (2-4 equivalents, **Figure I-4**) a mixture of both species is probably present and the exchange is not rapid enough, on NMR time scale, to give sharp signals.

$$\mathbf{8a} + \text{HMPA} \rightleftharpoons \text{HMPA} \cdot \mathbf{8a}$$

Although HMPA coordinates with **8a** it does not promote its conversion to the second species at 0 °C. It is conjectured that the second species (4.95 ppm) could be the lower order form of **8a** lacking the tri-*n* -butyltin or cyano ligand on copper or a different aggregation state of **8a**.

It has been suggested[50] that in the presence of HMPA, the cyanide ligand in higher order alkylcyanocuprates $R_2Cu(CN)Li_2$ at -30 °C, is dissociated from copper.

To test the hypothesis that the signals at 5.01 and 4.95 ppm (**Figure. I-3b**) could be due to **8a** with and without cyanide, respectively, the Gilman cuprate $(Bu_3Sn)_2CuLi$, **60**, was prepared in THF by the addition of 2 equiv. of Bu_3SnLi to 1 equiv. of CuI in the presence of 17 equiv of HMPA. After the LiI that formed was removed by filtration[51] at -50 °C under argon, the resulting clear yellow solution was allowed to warm and reacted with **5** at 0 °C. The ^{1}H-NMR spectrum of the resulting solution showed a singlet at 4.95 ppm and a small singlet at 5.73 ppm, the latter was attributed to **62** (**Figure I-3c**). To determine if the signals at 4.95 ppm in reaction mixtures shown in **Figures I-3b** and **I-3c** were both due to **61**, equivalent amounts of these solutions were

mixed *via* canula, under argon and the spectrum recorded. One major singlet at 4.95 ppm (**Figure I-3d**) was observed. This is consistent with the hypothesis that **61** is formed from reaction of **5** and **60**, when **6a**, prepared in the presence of HMPA, is reacted with **5**.

Thus, ^{1}H-NMR analysis indicates that reaction of **5** with **6a** at 0 °C gives **8a** unless **6a** is prepared in the presence of HMPA, in which case both **8a** and **61** are formed. Adduct **61** was independently formed from reaction of **5** and lower order cuprate **60**. Because the addition of HMPA to solutions of **8a** does not convert it to **61** it is suggested that the formation of both **8a** and **61** from reaction of **5** and **6a**, prepared in the presence of HMPA, is due to the conversion of **6a** to mixtures of **6a** and lower order cuprate **60** prior to reaction with **5**.

If the ^{1}H-NMR signals at δ = 5.01 and 4.95 ppm in **Figure I-3b** are produced by **8a** and **61**, respectively, the ^{13}C signals due to the vinyl carbons bearing copper in these species should have different chemical shifts. Additionally, methanolysis of both intermediates should produce **10a.**

A ^{13}C-NMR study of these intermediates was facilitated by development of a new synthesis of acetylenic ethers which allowed preparation of 2-^{13}C-ethynyl octyl ether 2-^{13}C-**5** from commercially available 1-^{13}C-acetyl chloride (see **Scheme II-2, Chapter III**).

The ^{13}C-NMR spectrum of the reaction mixture of 2-^{13}C-**5** (**Figure I-5a**), with **6a**, under the conditions used in **Figure 3b** (THF, HMPA, 0 °C), exhibited two major peaks at δ= 213.4 and 208.6 ppm assigned to the vinylcopper intermediates **61** and **8a**, respectively. Two minor signals at 166.8 and 163.2 ppm were assigned to the regioisomeric intermediates **7a** and **62** respectively (**Figure I-5b**). The observation of tin satellites associated with the signals at δ = 166.8 (J_{Sn-C}= 772 Hz) and 163.2 ppm (J_{Sn-C}= 793 Hz) corroborate the structural assignments in so far that the tin must be bonded to the α-carbon in **7a** and **62**. Methanolysis of this reaction mixture at 0 °C resulted in the disappearance of the signals attributed to the vinylcopper intermediates and the emergence of two signals at δ = 156.3 and 173.1 ppm which are assigned to C-2 of **10a** and **9a**, respectively (**Figure I-5c**).

The regioisomers were obtained in a ratio of 92:8 (**10a**:**9a**). The observation that the signals at δ = 213.4 and 208.6 ppm underwent upfield shifts to 156.3 ppm when **61** and **8a** were hydrolyzed, supports the assignment of these low field signals to carbons bonded to copper. Presumably, the upfield shift is due to the greater electrophilic character of the copper cation compared to hydrogen. The presence of tin satellites (J_{C-Sn}= 475 Hz) associated with the signal at δ = 173.1 ppm further confirmed the structure of **9a** in which the labelled carbon giving rise to this signal is bonded to the tin of the tri-*n*-butylstannyl group. The signal at δ = 153.0 ppm corresponds to the α-carbon of octyl vinyl ether **15**, which is formed during the hydrolysis.

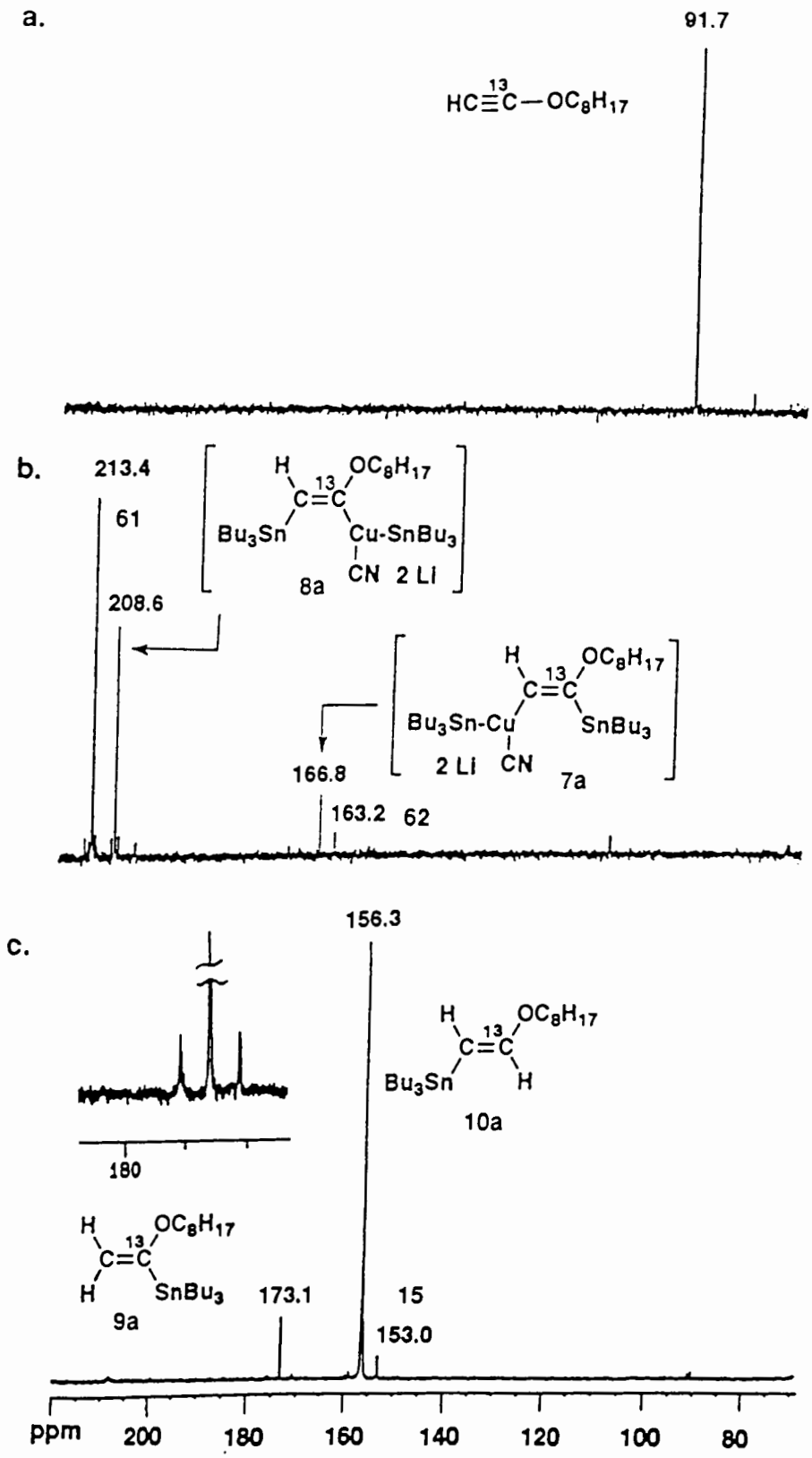
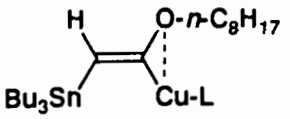


Figure I-5. Low temperature (0 °C) ^{13}C-NMR spectra of
a. 2-^{13}C-**5** in THF.
b. 2-^{13}C-**5** + **6a** (prepared in the presence of HMPA).
c. solution **I-4b** + MeOH.

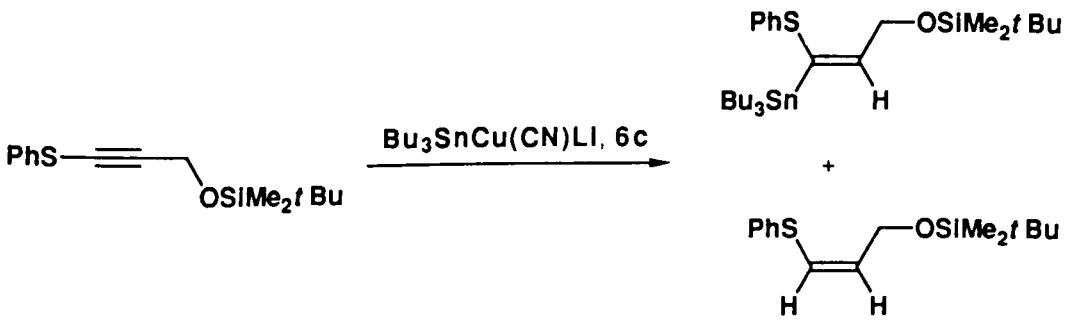
Thus, at 0 °C, reaction of **5** and **6a** in the presence of HMPA produces intermediates **6a** or **61**, respectively as the major (thermodymanic) intermediates. Subsequent methanolysis of these produces **10a** (thermodynamic product). Regioselective formation of **8a** or **61** under these conditions is presumed to be favoured by intramolecular interaction between the oxygen and copper as in **Scheme I-25**. Similar stabilization has been reported for 1-lithio-1-alkoxyvinyl species.[52]



Scheme I-25. Intramolecular interaction in intermediate 8.

To further confirm the identity of the species in **Figure I-5**, reaction of 2-^{13}C- **5**, with lower order cuprate $(Bu_3Sn)_2CuLi$, **60,** (prepared in the presence of HMPA) was performed at 0 °C. ^{13}C-NMR analysis revealed two principal signals at δ = 213.4 and 163.2 ppm which were assigned to intermediates **61** and **62**, respectively (**Figure I-6a**). Addition of LiCN (1 equivalent) to this solution resulted in the emergence of two signals at δ = 208.6 and 166.8 ppm, which had been previously observed (**Figure I-5b**), and corresponded to the higher order vinyl copper intermediates **8a** and **7a**, respectively (**Figure I-6b**). Methanolysis of this solution generated **9a** and **10a** as well as octyl vinyl ether, **15** (δ = 153.0) (**Figure I-6c**).

In situ generation of a Cu(I) hydride has been invoked in the generation of phenylthioalkenes during the stannylcupration of phenylthioalkynes by lower order stannylcuprate, **6c**[53] (**Scheme I-26**).



Scheme I-26. Formation of phenylthioalkenes in the stanylcupration of phenylthioalkynes.[53]

^{1}H and ^{13}C-NMR analysis of solutions arising from reaction of **5** and **6a** (or **60**) and of **23** with **6c** at 0 °C revealed that **15** and **22** respectively, were present only after hydrolysis (see **Figures I-5** and **I-6** for formation of **15**). These observations suggest the latter products are formed by hydrolytic and not hydride mediated processes.

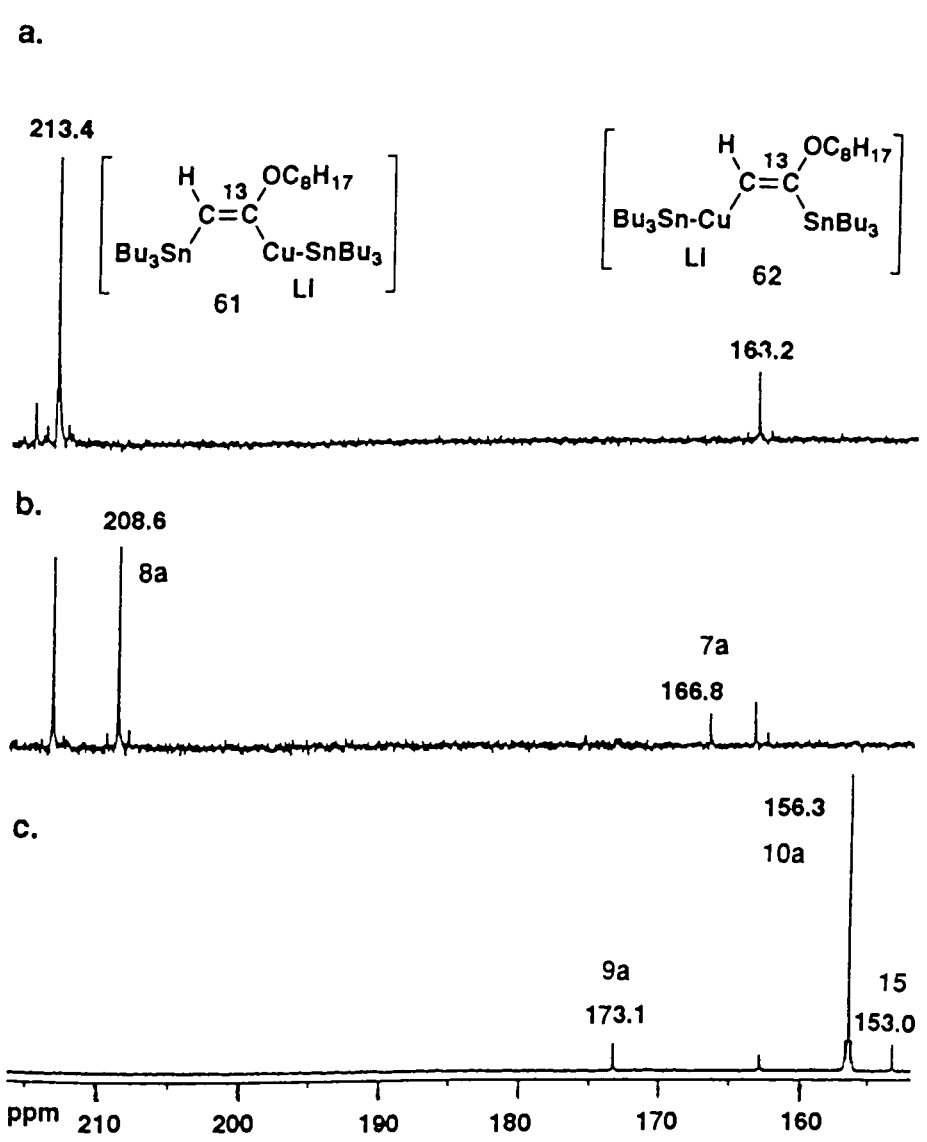


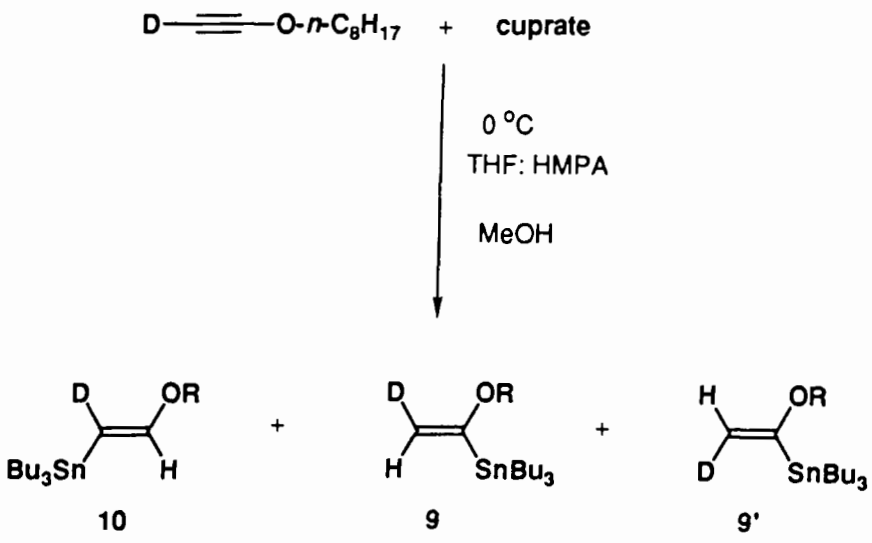
Figure I-6. Low temperature (0 °C) ^{13}C-NMR spectra of
a. 2-^{13}C-**5** + **60** (prepared in the presence of HMPA).
b. solution **I-5a** + LiCN (1 equivalent in HMPA).
c. solution **I-5b** + MeOH.

I. 2.2.4. Hydrolysis of Reaction Mixtures

To determine if (E), (Z)- isomerization was occurring during the hydrolysis of intermediates **7** and **8**, 1-^{2}H-**5** was prepared and reacted with **6a** and **6b** at 0 °C and hydrolyzed by addition of methanol. Surprisingly, reaction of 1-^{2}H-**5** with **6b** gave, after methanolysis, a mixture of (E) and (Z) isomers of regioisomer **9** (**Scheme I-27**).

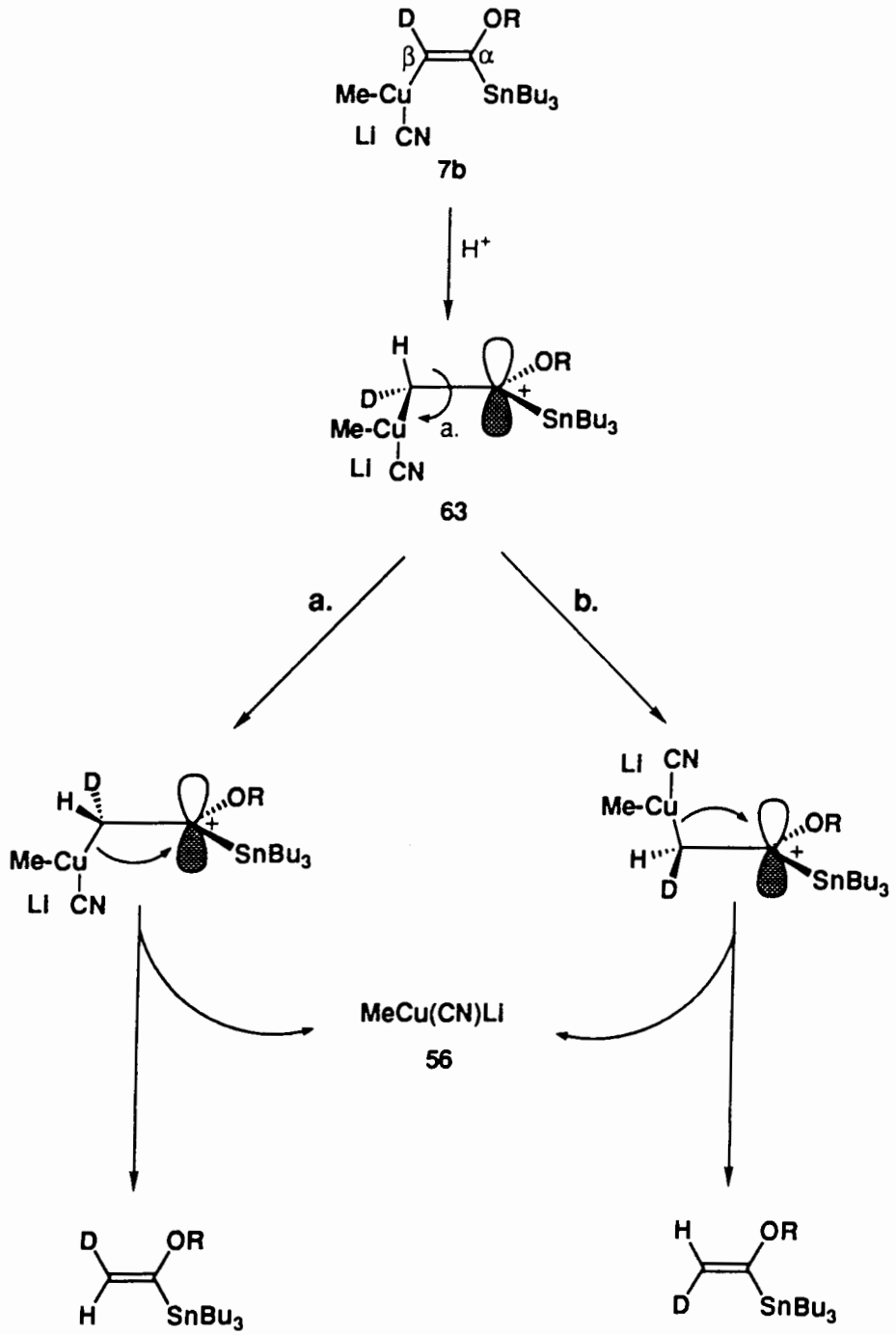
Noltes and co-workers[54] reported that (Z)-1,2-diarylpropenyl-copper compounds isomerized during hydrolysis to produce an (E):(Z) mixture of isomers. Application of the mechanism proposed by these investigators to the hydrolysis of **7b** involves protonation at the β-carbon to generate the stabilized cation, **63** (**Scheme I-28**). The latter could undergo rotation clockwise (a) or counterclockwise (b), about the Cα-Cβ bond to align the Cβ-Cu bond with the empty p-orbital on Cα. This could be followed by elimination of the lower order cuprate **56**. The formation of **56**, during methanolysis of the reaction of **5** with **6b**, was evidenced by low temperature ^{1}H-NMR analysis.

Reaction of 1-^{2}H **5** with **6a** followed by methanolysis at 0 °C gave regioisomers **9a** and **10a** (**Scheme I-27**). With this cuprate, regioisomer **9a** produced, contained only deuterium *trans* to the tri-*n*-butylstannyl group. Presumably, in the intermediate of type **63** (Me = Bu_3Sn), elimination of **56** occurs in a concerted fashion, giving the internal regioisomer containing only deuterium *trans* to the stannyl group (**9**, **Scheme I-27**).



	Ratio		
Cuprate	**10**	**9**	**9'**
6b :	70	15	15
6a :	90	10	--

Scheme I-27. Reaction of 1-^{2}H-5 with 6a and 6b.



Scheme I-28. Proposed isomerization of vinyl copper intermediate 7b during methanolysis

1.3. Conclusions

Conditions have been developed for the regioselective synthesis of stannylvinyl ethers **9** and **10** in very good yields. The key to high yields is the inclusion of HMPA in the reaction solution to stabilize **7a** against elimination of a lower order cuprate. Regioselectivity is a function of the reaction conditions. Vinylcopper intermediate **7a** and its subsequent products (**9**) are formed under conditions of kinetic control whereas products (**10**) arising from **8a** are formed under conditions of thermodynamic control. Spectroscopic and chemical data suggest that the ratios of vinyl stannane products (**9a**, **10a**) are proportional to the ratio of the vinyl copper intermediates (**7a**, **8a**).

Nuclear magnetic resonance analysis of solutions derived from reaction of **5** with higher order cuprate $(Bu_3Sn)_2Cu(CN)Li_2$, **6a**, prepared in the presence of HMPA, suggest that considerable amounts (~40%) of the Gilman reagent $(Bu_3Sn)_2CuLi$, **60**, are formed from **6a**, under these conditions. Presumably, in these solutions the HMPA is in competition with cyanide ligand for copper.

I-4. Experimental Section

I.4.1. General Methods. All glassware and syringes were dried in an oven overnight at 140 °C and flushed with argon immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All reactions were carried out under a positive pressure of argon. THF was refluxed and freshly distilled from potassium / benzophenone ketyl under argon atmosphere. Argon was passed trough a Drierite column (40 cmx 3 cm). HMPA was fractionally distilled under vacuum from calcium hydride, collected and stored over activated 4 A molecular sieves. Methanol was refluxed and distilled, under argon, from activated magnesium, collected and stored over activated 4 A molecular sieves. Methyllithium and butyllithium were purchased from Aldrich and titrated according to the method of Watson and Eastham.[55] Copper cyanide was purchased from Aldrich and transferred in a glove bag. Tributyltin hydride was purchased from Aldrich and used without further purification. Triphenylmethane was used as the internal standard for quantitative NMR analysis where indicated. Low resolution mass spectra were obtained on a Hewlett-Packard 5985B GC/MS operating at 70 eV. High resolution GC/MS spectra were obtained on a Kratos MS80 instrument. For compounds containing Bu_3Sn groups, molecular mass measurements are based on the ^{120}Sn (M^+-Bu) fragment. Gas chromatographic analyses were conducted on Hewlett-Packard 5892 instruments equipped with a flame-ionization detector and employing a fused silica capillary column (15 m X 0.25 mm ID) with DB-1 liquid phase. Dodecane was used as internal standard for quantitative GC analysis.

Low temperature ^{1}H-NMR Studies.

Low temperature ^{1}H-NMR spectra were recorded in *d8*-THF on a Bruker AMX-400 spectrometer. ^{1}H NMR and ^{13}C spectra were recorded at 400.13 MHz and 100.62 MHz, respectively and were referenced to THF, α= 68.33, β =26.53 ppm for ^{13}C NMR and α =3.72 ppm for ^{1}H NMR spectra. The Sn-H coupling constants (J_{Sn-H}) are given as an average of the ^{117}Sn and ^{119}Sn values. *d8* -THF was dried over activated 4 A molecular sieves.

Reaction mixtures were prepared following the procedures described below and an aliquot was transfered *via* canula under argon to dry 5 mm NMR tubes equipped with septa, previously flushed with argon and maintained at -78 °C or 0 °C.

Preparation of *n*-tributyltin lithium, Bu_3SnLi (12):

n-Butyllithium in hexanes 2.45 M (0.82 mL, 2.0 mmol) was added to a cold (-30 °C) solution of diisopropylamine (0.30 mL, 2 mmol) in THF (4 mL) and stirred at this temperature for 20 min. After this time, the temperature was lowered to -40°C and tri-*n*-tributylstannyl hydride (0.54 mL, 2.0 mmol) was added dropwise and the solution stirred at this temperature for 1 hr.

Preparation of $(Bu_3Sn)_2Cu(CN)Li_2$ (6a):

A THF solution of Bu_3SnLi (2.0 mmol), prepared as described above, was added, *via* canula under argon, to a cold (-40 °C) suspension of CuCN (0.090

g, 1.0 mmol) in 6 mL of THF (or 6 mL of a 1:1 mixture of THF:HMPA) and stirred at this temperature for 45 min. The resulting solution was cooled to -78 °C or warmed to 0 °C.

Preparation of $(Bu_3Sn)MeCu(CN)Li_2$ (6b):

Copper cyanide (0.090 g, 1.0 mmol) was suspended in 6 mL of THF at -35 °C and MeLi (0.71 mL, 1.0 mmol) added dropwise while stirring and the solution obtained stirred for 30 min at this temperature. To this mixture, a cold (-40 °C) solution of Bu_3SnLi (1.0 mmol), prepared as above, was added *via* canula and the resulting mixture stirred for 45 min at -35 °C then an additional 15 min at -78 °C.

Preparation of $Bu_3SnCu(CN)Li$ (6c).

A THF solution of tri-*n*-butyltin lithium (1.0 mmol), prepared as above, was added, *via* canula, to a THF (3 mL) suspension (or THF:HMPA 1:1) of CuCN (0.090 g, 1.0 mmol) at -40 °C and stirred at this temperature for 45 min. The resulting solution was cooled to -78 °C or warmed to 0 °C.

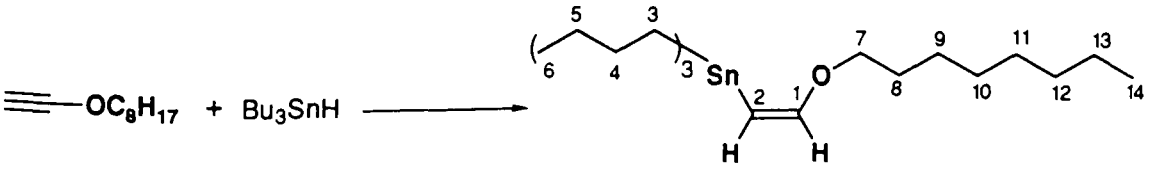
Reaction of $Bu_3SnAlEt_2$, 13, with 5:

A 1.0 M solution of Et_2AlCl in hexanes (2.0 mmol, 2.0 mmol) was added dropwise to a cold (-40 °C) THF solution of Bu_3SnLi (2.0 mmol) prepared as described before and stirred at this temperature for 30 min.* After this time, a solution of **5** (0.308 g, 2.0 mmol) in THF (2 mL) was added, followed by the

additon of CuCN (0.010 g) and stirred for 1 hr. The reaction was quenched by addition of MeOH (2 mL) and partitioned between water and ether. The extracts were dried ($MgSO_4$) and the extract concentrated *in vacuo*.

* In the reactions carried out at 0 °C, HMPA (3.0 ml) was added at this point and the solution warmed to 0 °C before addition of **5**.

Preparation of (*Z*)-Octyl 2-(Tributylstannyl)vinyl Ether (14)[41]:



1 4

Tributylstannyl hydride (0.54 mL, 2.0 mmol) was added to a solution of **5** (0.308 g, 2.0 mmol) and the resulting solution stirred for 3 hr. at 50 °C. The resulting mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The product was obtained in 88 % yield with a (GC) purity of 91%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84-0.95 (m, 18H,**H3**, **H6**, **H14**), 1.25-1.40 (m, 16H, **H4**,**H9**, **H10**, **H11**, **H12**, **H13**), 1.45-1.65 (m, 8H **H5**, **H8**), 3.70 (t, 2H, J = 7.0 Hz, **H7**), 4.46 (d, 1H, J = 8.0 Hz; $^2J_{Sn-H}$ = 46 Hz, **H2**), 6.77 (d, 1H, J = 8.0 Hz; $^3J_{Sn-H}$ = 100 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 10.1 (**C3**), 13.7 (**C6**), 14.0 (**C14**), 22.6 (**C13**), 26.0 (**C12**), 27.3 (**C4**), 28.9 (**C11**), 29.2 (**C5**), 29.4 (**C10**), 30.0 (**C9**), 31.8 (**C8**), 71.5 (**C7**), 97.2 (**C2**), 157.5 (**C1**); IR (film) 2960, 2925, 1605, 1100, 727 cm^{-1}.

Preparation of Octyl Vinyl Ether (15).

To a solution of octyl ethynyl ether, **5**, (0.200 g, 1.30 mmol) in tetrahydrofuran (5 mL) was added dropwise 2.5 mL of a 1.0 M hexanes solution of DIBAL-H (2.50 mmol) at 0 °C and the resulting solution was stirred at this temperature for 3 hr. After this time the reaction mixture was quenched by the addition of methanol (3 mL) and then water (3 mL) and the organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the product was purified using a short path microdistillation apparatus (ext. temp.70-75 °C/ 2.0 mm Hg) to give 1.09 g (84% yield) of **15.**

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, *J*= 7.0 Hz, **H10**), 1.20-1.35 (m, 10H, **H5**, **H6**, **H7**, **H8**, **H9**), 1.65 (m, 2H, **H4**), 3.66 (t, 2H, *J*= 6.5 Hz, **H3**), 3.96 (dd, 1H, *J*= 7.0, 2.0 Hz, **H2**), 4.16 (dd, 1H, *J*= 14.5, 2.0 Hz, **H2'**), 6.46 (dd, 1H, *J*= 14.5, 7.0 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (**C10**), 19.8 (**C9**), 22.6 (**C8**), 26.3 (**C7**), 29.2 (**C6**), 29.9 (**C5**), 31.8 (**C4**), 65.4 (**C3**), 99.7 (**C2**), 152.3 (**C1**); IR (film) 2926, 2856, 1635, 1610, 1320, 1203 cm^{-1}; GC/MS m/e (rel. intensity) 156 (M^+, 3), 141 (8), 83 (26), 71 (50), 57 (74), 43 (100).

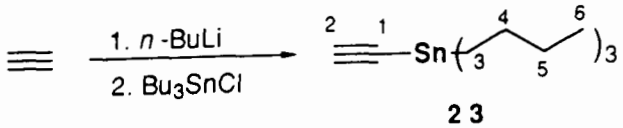
Reaction of 23 with 6c.

Bu_3SnLi (1.0 mmol) prepared as outlined above, was added to a suspension of CuCN (0.090 g, 1.0 mmol) in THF (6 mL) and stirred at -35 °C for 45 min. The solution was warmed to -20 °C and a THF solution (2 mL) of **23** (0.316 g, 1.0 mmol) was added dropwise. The reaction mixture was warmed to 0 °C over 1hr, quenched by addition of 1 mL of methanol and worked-up as usual.

Reaction of 23 with 56.

Methylithium (0.71 mL, 1.4 M solution, 1.0 mmol) was added to a suspension of CuCN (0.090 g, 1.0 mmol) in THF (6 mL) at -35 °C. The resulting solution was stirred 45 min, then warmed to -20 °C and a THF solution (2 mL) of **23** (0.316 g, 1.0 mmol) was added dropwise. The reaction was warmed to 0 °C over 1 hr, hydrolyzed and worked-up as above.

Preparation of Ethynyl tri-*n*-butyltin (23):



23

Purified acetylene (passed successively, through the following traps: cold trap at -78 °C, concentrated sulfuric acid, solid potassium hydroxide, Driedrite) was bubbled through cold THF (15 mL, -78 °C) until 0.7 g (27 mmol) of acetylene was dissolved. To this solution a 2.45 M solution *n*-butyllithium in hexanes

(6.12 mL, 15 mmol) was added dropwise and the solution was stirred at this temperature for 20 min. followed by the addition of tri-*n*-butyltin chloride (4.1 mL, 15 mmol). The reaction mixture was stirred at -78 °C for 30 min. then allowed to warm to room temperature. After the addition of water, the reaction was extracted with diethyl ether (3 x 20 mL) and the ethereal phase dried over anhyd. magnesium sulfate. Evaporation of the solvent was followed by purification of the product by bulb to bulb distillation (100-110 °C @ 0.025 mm Hg) to give 4.70 g, 94 %.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.8-1.0 (m, 15H, **H3**, **H6**), 1.2-1.9 (13H, **H2**, **H4**, **H5**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 11.1 (**C3**), 13.6 (**C6**), 26.9 (**C4**), 28.9 (**C5**), 88.9 (**C1**), 96.8 (**C2**); IR (film): 3272, 2931, 2872, 1990 and 1461 cm^{-1}; GC/MS (EI) *m/e* (rel. intensity) 259 (M^+ - Bu, 100), 203 (90), 145 (57). (Registry No. 994-89-8).

Preparation of *trans* -1,2-Bis (tri-*n* -butylstannyl) ethylene (19):

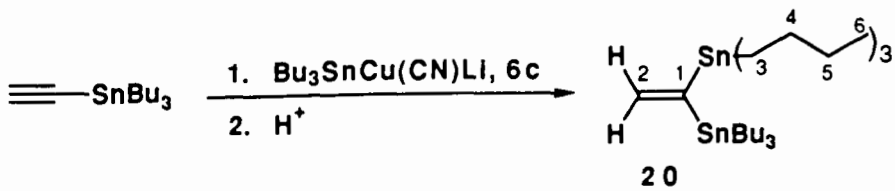
19

A neat mixture of 0.314 g (1 mmol) of ethynyl tri-n-butyltin **19**, 0.27 mL (1 mmol) of tri-n-butyltin hydride and azobisisobutyronitrile (AIBN, ~ 10 mg) was stirred and heated at 90 °C. After 4 hr, GC analysis showed consumption of 97 % of the starting material. The reaction was quenched by the addition of water (2 mL) and extracted with ether (10 mL). The ethereal phase was dried ($MgSO_4$)

and the solvent evaporated *in vacuo*. The product was obtained with a GC purity of 91%.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84-0.98 (m, 30 H, **H2**, **H5**), 1.24-1.38 (m, 12 H, **H3**), 1.42-1.64 (m, 12 H, **H4**), 6.87 (s, 2 H, $^2J_{Sn-H}$= 107 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.6 (**C2**), 13.7 (**C5**), 27.2 (**C3**), 29.2 (**C4**), 153.0 (**C1**); IR (film) 2956, 2871, 1522, 668 cm^{-1}; GC/MS (EI) *m/e* (rel. intensity) 606 (M^+, 9), 549 (97), 493 (26), 291 (63), 235 (56).(Registry No 14275-61-7).

Preparation of 1,1-Bis (tri-*n* -butylstannyl) ethylene (20):



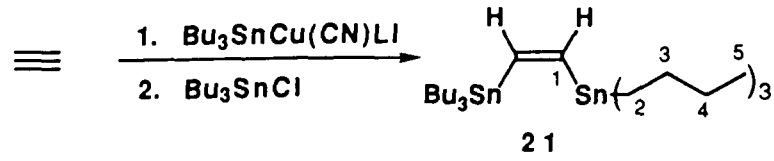
20

To a cold (-30 °C) THF solution of **6c** (1.0 mmol), prepared as described above, was added a solution of ethynyl tri-*n* -butyltin, **23**, (1.0 mmol) in THF (1 mL). The reaction mixture was stirred for 1 hr and quenched by the addition of water (2 mL) and extracted with ether. The extracts were dried ($MgSO_4$) and the mixture concentrated *in vacuo*. GC and ^{1}H-NMR analysis of the crude mixture showed the presence of **20** and **21** in 14 and 8 % yield, respectively (based on the amount of **23**) . Vinyl tri *n*-butyltin, **22**, was obtained in 12 %.

^{1}H-NMR of **20** ($CDCl_3$, 400 MHz) δ 0.80-0.98 (m, 30 H, **H3**, **H6**), 1.24-1.40 (m, 12 H, **H4**), 1.40-1.65 (m, 12 H, **H5**), 6.47 (s, $^3J_{Sn-H\ cis}$ = 112 Hz; $^3J_{Sn-H\ trans}$

=195 Hz, **H2**)[56] ; GC/MS (EI) *m/e* (rel. intensity) 291(M^+-$C_2H_2SnBu_3$, 24), 259 (M^+-$SnBu_3$, 19), 235 (38), 203 (29), 177 (100), 145 (33), 121 (71).

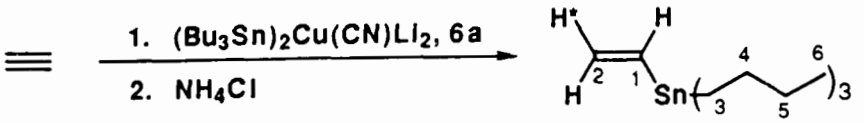
Preparation of *cis*-Bis (tri-*n* -butylstannyl) ethylene (21):[28b]



21

A THF solution of acetylene (5 mmol), prepared as described above, was added to a THF solution of cuprate **6b** (5 mmol) at -78 °C. After stirring at this temperature for 1 hr, tri-*n*-butylstannyl chloride (1.36 mL, 5 mmol) was added dropwise and the reaction allowed to warm to 0 °C in 2 hr. The reaction was quenched by addition of water (4 mL) and extracted with ether, the extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Analysis (GC, ^{1}H-NMR) of the crude reaction mixture showed that the product was obtained in 84 % yield. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85-0.95 (m, 30 H, **H2**, **H5**), 1.25-1.40 (m, 12 H, **H3**), 1.45-1.60 (m, 12 H, **H4**), 7.40 (s, 2 H, $^2J_{Sn-H}$ = 45 Hz, $^3J_{Sn-H}$ = 96 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 10.3 (**C2**), 13.6 (**C5**), 27.6 (**C3**), 29.1 (**C4**), 154.0 (**C1**); GC/MS *m/e* (rel intensity) 549 (M^+- Bu, 44), 493 (12), 467 (31), 413 (63), 353 (50), 291 (25), 235 (38), 177 (100), 121 (56).

Preparation of vinyl tri- *n* -butyltin (22):



22

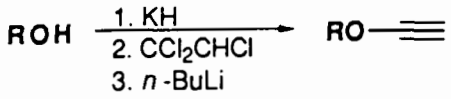
To a cold (-78 °C) THF solution of cuprate **6a** (4 mmol), prepared as described above, was added a THF solution of acetylene (5 mmol) and stirred at this temperature for 1 h. After this time the reaction was quenched by addition of NH_4Cl (4 mL, sat. solution) and allowed to warm to room temperature. The product was extracted with ether (3 X 15 mL) and the extracts dried ($MgSO_4$). After concentration*in vacuo* , the product was purified by high vacuum distillation using a short path microdistillation apparatus (ext. temp. 90-100 °C / 0.025 mm Hg) to give 0.91 g (72 % yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82-0.94 (m, 15 H, **H3**, **H6**), 1.22-1.38 (m, 6 H, **H4**), 1.45-1.62 (m, 6 H, **H5**), 5.65 (dd, 1 H, J = 20, .6 Hz; $^3J_{Sn\text{-}H\ cis}$ = 72 Hz, **H2**), 6.14 (dd, 1H, J = 14, 3.6 Hz; $^3J_{Sn\text{-}H\ trans}$ = 148 Hz, **H2***), 6.46 (dd, 1H, J = 20, 14 Hz, **H1**); ^{13}C-NMR (CDCl3, 100.6 MHz) δ 10.1 (**C3**), 13.6 (**C6**), 27.5 (**C4**), 29.1 (**C5**), 133.6 (**C2**), 147.1 (**C1**); IR (film) 2956, 2925, 2871, 1464, 668 cm^{-1}; GC/MS (EI) *m/e* (rel intensity) 261 (M^+-Bu, 76), 295 (100), 147 (52).

Preparation of 2-^{13}C-ethynyl octyl ether (2-^{13}C-1).

See **Chapter III**, Experimental Section.

General procedure for the preparation of acetylenic ethers.[57]

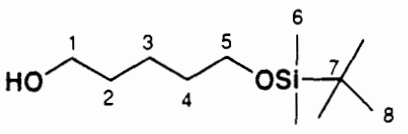


To a suspension of mineral oil free (washed 3 times with hexanes under argon) KH (2.1 g, 51 mmol), in 50 mL of THF was added dropwise a THF solution (50 mL) of the alcohol (25 mmol). After stirring for 1 h. at room temperature the reaction mixture was cooled to -50 °C and trichloroethylene (2.25 mL, 25 mmol) dissolved in THF (30 mL) was added dropwise. The solution was warmed to room temperature and stirred at this temperature for 1.5 hr. After this time the mixture was cooled to -78 °C and treated with a 2.45 M (hexanes) solution of *n* -BuLi (24.5 mL, 60 mmol). The reaction mixture was then warmed to -20°C and hydrolyzed by the addition of MeOH (3 mL) followed by a saturated solution of NH_4Cl. The crude mixture was extracted with ether, which was dried over $MgSO_4$ and concentrated *in vacuo*. Products were purified by bulb to bulb distillation or filtration through a silica gel pad (4 X 6 cm., pretreated with 3% Et_3N) (eluted with 10% diethyl ether in pentane).

Octyl Ethynyl Ether (5):

See **Chapter III**,.Experimental Section.

Preparation of 5-(*tert* -Butyl dimethylsiloxyl)-1-pentanol (36)[58] .



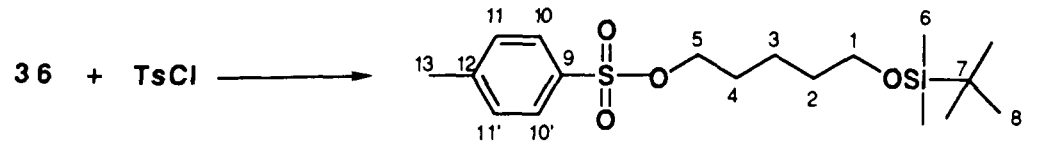
To a suspension of mineral oil free (washed 3 times with hexanes under argon) sodium hydride (1.37 g, 57 mmol) in THF (110 mL) 1,5-pentanediol (5.92 g, 57 mmol) was added dropwise at room temperature and stirred for 1 hr. After this time *tert* - butyldimethylsilyl chloride (8.59 g, 57 mmol) was added and stirring was continued for one aditional hour. The mixture was poured into ether (100 mL), which was separated, washed with 10 % K_2CO_3 (40 mL) and brine (40 mL) then dried (Na_2SO_4). The extract was concentrated *in vacuo*. The product was purified by column chromatography using ethyl acetate:hexanes (3:7) as eluant to give 10.48 g, (84 % yield). Spectroscopic data obtained for **36** are in agreement with those previously reported.[58]

^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.06 (s, 6 H, **H6**), 0.90 (s, 9 H, **H8**), 1.30-1.75 (m, 7 H, **H2**, **H3**, **H4**, **OH**), 3.50-3.75 (m, 4 H, **H1**, **H5**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.3 (**C6**), 18.4 (**C7**), 22.1 (**C3**), 26.0 (**C8**), 32.5 (**C2** + **C4**), 62.9 (**C5**), 63.1 (**C1**); IR (film) 3343, 2933, 2858, 1255, 1102, 836 and 775 cm^{-1}. Registry No 83067-20-3.

5-(*tert* -Butyl dimethylsiloxyl)pentyl Ethynyl Ether (37):

See **Chapter III**, Experimental Section.

Preparation of 5-(*p*-Toluensulfonyl)pentyl *tert* -butyldimethylsilyl ether (38):

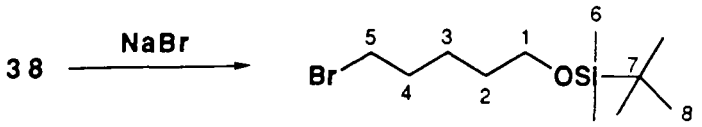


38

To a stirred solution of alcohol **36** (3.5 g, 16 mmol) and pyridine (4 mL, 50 mmol) in methylene chloride (90 mL) at 0°C was added *p*-TsCl (3.36 g, 17.6 mmol) and the resulting solution stirred overnight. The mixture was poured into ice-water (100 mL) and extracted with ether (3 X 50 mL). The organic extracts were washed with ice-cold 0.1 M HCl (2 X 50 mL), saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The oil obtained was filtered, *in vacuo*, through a silica Gel pad (4 X 8 cm) and eluted with hexanes:ether (9:1) to give 5.4 g of **38** (87 % yield) in a purity (GC) of 92%. The product was taken to the next step without further purification.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.03 (s, 6 H, **H6**), 0.87 (s, 9H, **H8**), 1.20-1.86 (m, 6H, **H2**, **H3**, **H4**), 2.45 (s, 3H, **H13**), 3.54 (t, 2H, 6.0 Hz, **H1**), 4.04 (t, 2H, 6.0 Hz, **H5**), 7.35 (m, 2H, **H10**, **H10'**), 7.80 (m, 2H, **H11**, **H11'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.4 (**C6**), 18.3 (**C7**), 21.5 (**C13**), 21.8 (**C3**), 25.9 (**C8**), 28.7 (**C2**), 32.0 (**C4**), 62.7 (**C1**), 70.5 (**C5**), 127.8 (**C10**, **C10'**), 129.7 (**C11**, **C11'**), 144.5 (**C9**); IR (film) 2931, 1362, 1178, 1098, 835 and 776 cm^{-1}.

Preparation of 5-bromopentyl *tert*-butyldimethylsilyl ether (39):

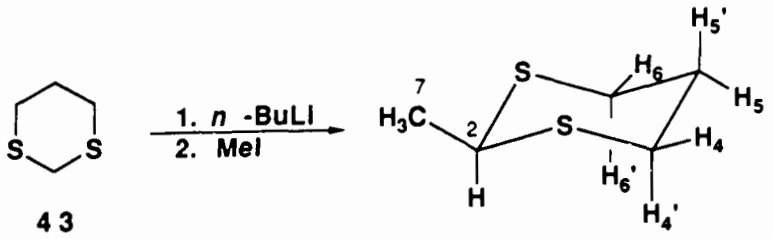


39

A solution of 5-(*p*-toluensulfonyl)pentyl *tert* -butyldimethylsilyl ether, **38** (4.70 g, 12.6 mmol) and lithium bromide (3.14 g, 36 mmol) in dry acetone (150 mL) was refluxed under argon for 3 hr. The reaction mixture was partitioned in a mixture water / ether and the organic phase dried over anhyd. $MgSO_4$. Purification of the crude product by column chromatography (silica Gel, ether:hexane, 1:1) gave 3.1 g (88 % yield) of **39**.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6H, **H6**), 0.90 (s, 9H, **H8**), 1.45-1.55 (m, 4H, **H3**, **H4**), 1.88 (t t, 2H, J = 7.0, 7.0 Hz, **H2**), 3.41 (t, 2H, J = 7.0 Hz, **H5**), 3.61 (t, 2H, 7.0 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.2 (**C6**), 18.3 (**C7**), 24.6 (**C3**), 26.0 (**C8**), 31.9 (**C4**), 32.6 (**C2**), 33.7 (**C5**), 62.8 (**C1**); IR (film) 2929, 2857, 1255, 1104, 835 and 775 cm^{-1}; GC/MS (EI) *m/e* (rel intensity) 281 (M^+, 3), 169 (52), 139 (57); Anal. Calcd. for $C_{11}H_{25}SiOBr$: C, 46.97; H, 8.96. Found: C, 47.09; H, 9.10.

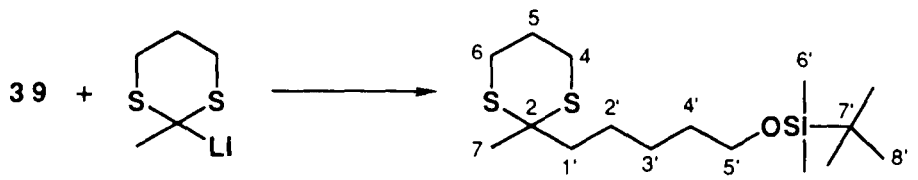
Preparation of 2-methyl-1,3-dithiane (44).[59] :



43 44

To a cold (-40°C) THF solution (65 mL) of 1,3-dithiane, **43**, (7.25 g, 60 mmol) was added dropwise *n*-BuLi (28 mL, 68 mmol). The solution was stirred for 1.5 hr. After this time the solution was cooled to -78 °C and MeI (4.60 mL, 74 mmol) in THF (20 mL) added dropwise. The solution was then allowed to warm to room temperature overnight. After addition of water (10 mL) the solution was extracted with ether (3 x 50 mL) and the extracts dried ($MgSO_4$). The extracts were concentrated *in vacuo* and the crude **44** purified by bulb to bulb distillation (40-46 °C / 0.025 mm Hg) to give7.33 g (91 % yield) of **44** .
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, 3H, 7.0 Hz, **H7**), 1.80 (m, 1H, **H5'**), 2.10 (m, 1H, **H5**), 2.80 (ddd, 2H, 15, 4, 4 Hz, **H4**, **H6**), 2.90 (ddd, 2H, 15, 15, 4 Hz, **H4'**, **H6'**), 4.10 (q, 1H, 7 Hz, **H2**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 21.2 (**C7**), 25.1 (**C5**), 30.6 (**C4**, **C6**), 42.0 (**C2**); IR 2965, 2897, 1422, 1275, 907 cm^{-1}.

Preparation of 2-[5'-(*tert* -butyldimethylsiloxyl)pentyl]-2-methyl-1,3-dithiane (40):

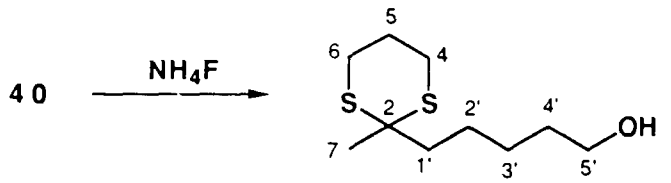


40

A solution of 2-methyl-1,3-dithiane, **44**, (0.95 g, 7.1 mmol) in THF (20 mL) was treated dropwise with *n* -BuLi (3.2 mL, 7.8 mmol), under argon, at -30 °C with stirring for 2.5 hr. After this time the temperature was lowered to -78 °C and a solution of 5-bromopentyl *tert* -butyldimethylsilyl ether, **39**, (2.0 g, 7.1 mmol) in THF (2 mL) added dropwise. The solution was then allowed to warmed to room temperature overnight. The reaction was quenched by addition of water (10 mL) and extracted with pentane (3 X 25 mL). The organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. The product was purified by column chromatography (silica Gel, hexanes : ether 9:1; 7:3) to give 2.20 g (93 % yield) of **40**.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H, **H6'**), 0.89 (s, 9H, **H8'**), 1.31-1.39 (m, 2H, **H3'**), 1.44-1.57 (m, 4H, **H2'**, **H4'**), 1.61 (s, 3H, **H7**), 1.82-1.98 (m, 4H, **H1'**, **H5**), 2.82-2.85 (m, 4H, **H4**, **H6**), 3.60 (t, 2H, J = 6.5 Hz, **H5'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) d -5.2 (**C6'**), 18.4 (**C7'**),24.3 (**C2'**), 25.4 (**C5**), 26.0 (**C8'**), 26.1 (**C3'**), 26.5 (**C4**, **C6**), 27.8 (**C7**), 32.7 (**C4'**), 41.8 (**C1'**), 49.3 (**C2**), 63.1 (**C5'**); IR (film) 2933, 2856, 1098 and 835 cm^{-1}; GC/MS (EI) *m/e* (rel intensity) 334 (M^+, 25),277 (88), 203 (12), 165 (94), 133 (31); Anal. Calcd. for $C_{16}H_{34}SiS_2O$: C, 57.43; H, 10.24. Found: C, 58.02; H, 10.40.

Preparation of 2-[5'-(hydroxy)pentyl]-2-methyl-1,3-dithiane (**41**):

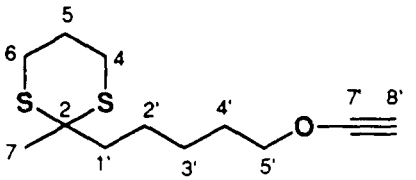


41

A solution of 2-[5'-(*tert* -butyldimethylsiloxy)pentyl]-2-methyl-1,3-dithiane, **40**, (2.10 g, 6.3 mmol) , in THF (12 mL), was cooled to 0 °C and a 1.0 M solution of Bu_4NF in THF (12.5 mL, 12.5 mmol) added dropwise and stirred at this temperature for 3.5 hr. The reaction was quenched by addition of water (5 mL) and extracted with ether (3 X 25 mL). The extracts were concentrated *in vacuo* and the concentrate purified by column chromatography (silica Gel, hexanes:ether 8:2, 6:4) to give 1.26 g (91 % yield) of **41**.

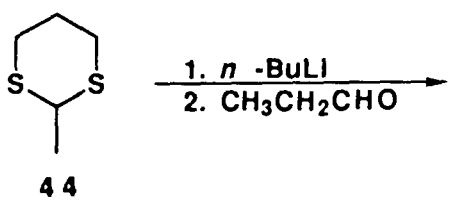
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.40 (m, 2H, **H3'**), 1.50 (m, 2H, **H2'**), 1.57 (m, 2H, **H4'**), 1.61 (s, 3H, **H7**), 1.93 (m, 4H, **H5**, **H1'**), 2.83 (m, 4H, **H4**, **H6**), 3.64 (t, 2H, J = 6.5 Hz, **H5'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 24.3 (**C2'**), 25.4 (**C5**), 26.0 (**C3'**), 26.5 (**C4**, **C6**), 27.8 (**C7**), 32.6 (**C4'**), 41.7 (**C1'**), 49.2 (**C2**), 62.8 (**C5'**); IR (film) 3375, 2935, 1276, 1048 cm^{-1}; GC/MS (EI) *m/e* (rel intensity) 220 (M^+, 24), 133 (100), 113 (14), 87 (9), 74 (43); Anal. Calcd. for $C_{10}H_{20}S_2O$: C, 54.50; H, 9.15. Found: C, 54.37; H, 9.28.

2-[5'-(Ethynyloxy)pentyl]-2-methyl-1,3-dithiane (42):

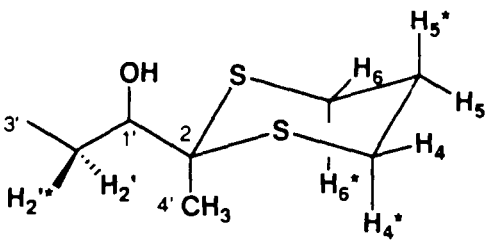


^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.40-1.46 (m, 2H, **H3'**), 1.48-1.56 (m, 2H, **H2'**), 1.52 (s, 1H, **H8'**), 1.61 (s, 3H, **H7**), 1.78 (tt, 2H, *J* = 7.0, 7.0 Hz, **H4'**), 1.88-2.00 (m, 4H, **H5**, **H1'**), 2.81-2.87 (m, 4H, **H4**, **H6**), 4.10 (t, 2H, *J* = 7.0 Hz, **H5'**); ^{13}C-NMR ($CDCl_3$, 100.6) δ 24.1 (**C2'**), 25.3 (**C5**), 25.5 (**C3'**), 26.2 (**C8'**), 26.5 (**C4**, **C6**), 27.9 (**C7**), 28.5 (**C4'**), 41.6 (**C1'**), 49.1 (**C2**), 78.8 (**C5'**), 91.1 (**C7'**); IR (film) 3310, 2939, 2861, 2149, 1462, 1422 and 1091 cm^{-1} ; GC/MS (EI) *m/e* (rel intensity) 244 (M^+, 5), 203 (2), 175 (38), 145 (24), 106 (52), 74 (100); Anal. Calcd. for $C_{12}H_{20}S_2O$: C, 58.97; H, 8.25. Found: C, 59.03: H, 8.41.

Preparation of 2-[1'-(Hydroxy)propyl]-2-methyl-1,3-dithiane (45)[59]:



44



45

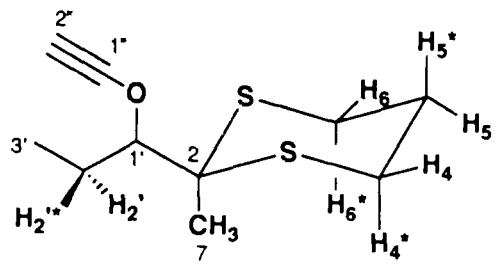
To a cold (-40 °C) THF solution (90 mL) of 2-methyl-1,3-dithiane, **44**, (4.02 g, 30 mmol) *n* -BuLi (13.5 mL, 33 mmol) was added dropwise and the solution stirred

for 1.5 hr. After this time the solution was cooled to -78°C and propanal (2.20 mL, 30 mmol) in THF (20 mL) added dropwise then the solution was warmed to room temperature overnight. The solution was poured into 60 mL of water and extracted with ether (50 mL), the aqueous phase was saturated with NaCl and extracted with ether (3 X 40 mL). The ethereal extracts were dried (K_2CO_3), concentrated *in vacuo* and the remaining 2-methyl-1,3-dithiane removed by distillation. Bul to bulb distillation (40-45 °C / 0.05 mm Hg) gave 5.02 g (87 % yield) of **45**.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, 3H, *J* = 7.0 Hz, **H3'**), 1.38 (s, 3H, **H7**), 1.36 (m, 1H, **H2'***), 1.85 (ddddd, 1H, *J* = 15, 12, 12, 3.5, 3.5 Hz, **H5***), 2.02 (dqd, 1H, *J* = 15, 7.0, 2.0 Hz, **H2'**), 2.09 (m, 1H, **H5**), 2.59 (ddd, 1H, *J* = 15, 3.5, 3.5 Hz, **H6**)#, 2.61 (ddd, 1H, *J* = 15, 3.5, 3.5 Hz, **H4**)#, 2.75 (br s, 1H, **OH**), 3.0 (m, 2H, **H4***, **H6***), 3.85 (dd, 1H, J = 10, 1.8 Hz, **H1'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 12.1 (**C3'**), 21.9 (**C4'**), 23.3 (**C2'**), 24.5 (**C5**), 25.6 (**C4**)#, 26.2 (**C6**)#, 54.2 (**C2**), 73.5 (**C1'**); IR (film) 3476, 2961, 2874, 1450, 1422, 1300, 1110, 1060, 974 cm^{-1}; GC *m/e* (rel intensity) 192 (M^+, 3), 133 (100), 59 (27).

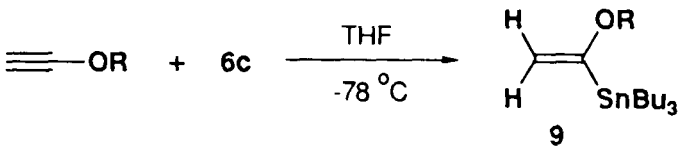
These Assigments are not definitive.

2-[1-(Ethynyloxy)propyl]-2-methyl-1,3-dithiane (46):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 3H, **H7**), 1.18 (t, 3H, *J* = 7 Hz, **H3'**), 1.61 (s, 1H, **H2"**), 1.76 (ddq, 1H, *J* = 15, 10, 7 Hz, **H2"***), 1.90 (ddddd, 1H, *J* = 15, 11, 11, 3.5, 3.5 Hz, **H5***), 2.08 (ddddd, 1H, *J* = 15, 3.0, 3.0, 3.0, 3.0 Hz, **H5**), 2.10 (ddq, 1H, *J* = 15, 7, 2 Hz, **H2'**), 2.68-2.75 (m, 2H, **H6**, **H4**), 3.00 (ddd, 1H, *J* = 15, 11, 3.0 Hz, **H4***), 3.11 (ddd, 1H, *J* = 15, 11, 3.0, Hz, **H6***), 4.24 (dd, 1H, *J* = 10, 2 Hz, **H1'**); ^{13}C-NMR ($CDCl_3$, 100.6) δ 11.4 (**C3'**), 23.2 (**C7**), 23.8 (**C2'**), 24.3 (**C5**), 26.1 (**C2"**), 26.6 (**C4**), 26.8 (**C6**), 51.4 (**C2**), 92.1 (**C1"**), 96.0; (**C1'**) IR (film) 3312, 2970, 2933, 2145, 1150, 1114 and 1088 cm^{-1}; MS, *m/e* (rel intensity) 216 (M^+, 13), 142 (12), 106 (100), 95 (83); Anal. Calcd. for $C_{10}H_{16}OS_2$: C, 55.52, H, 7.45. Found: C: 55.62, H, 7.49.

I.4.2. General Procedure for the Preparation of 1-tri-*n*-Butylstannyl Alkoxyvinyl Ethers 9.

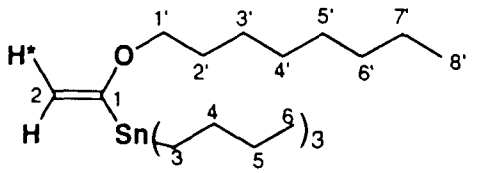


9

Tri-*n*-butyltin hydride (0.54 mL, 2.0 mmol) was added dropwise to a cold solution (-40 °C) of LDA (2.0 mmol) and stirred for 1 hr at this temperature. LDA was prepared at -30 °C, from diisopropylamine (0.30 mL, 2.0 mmol), dissolved THF (6 mL), and 2.45 M solution of *n*-BuLi in hexanes (0.82 mL, 2.0 mmol). Bu_3SnLi, prepared as above, was transferred *via* canula under argon to a cold (-35 °C) suspension of CuCN (0.180 g, 2.0 mmol) in 6 mL of THF and stirred at this temperature for 45 min. The resulting pale yellow solution was cooled to -78 °C and stirred for 15 min. then a precooled (-78 °C) solution of acetylenic ether (2.0 mmol) in 3 mL of dry MeOH / THF (1:1) was added dropwise. After 30 min. the reaction was allowed to warm to room temperature and partitioned between ether and water. The etheral extracts were dried over anhyd. $MgSO_4$. Concentration *in vacuo* gave an oily residue which was dissolved in hexanes and (in the cases were a dark oil was obtained) rapidly filtered under vacuum through a small pad of silica Gel (4 cm X 3 cm) to give a colorless solution. GC analysis gave purities of 85-90 %.

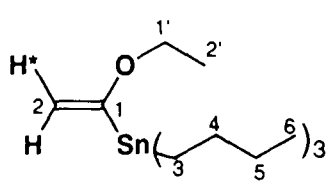
For the preparation of 1-tri-*n*-Butylstannyl Alkoxyvinyl Ethers, **9**, from reaction of acetylenic ethers with higher order cuprate **6a**, the same procedure was used. Cuprate **6a** was prepared as described above.

Octyl 1-(Tributylstannyl) vinyl Ether (9a):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85-0.95 (m, 18H, **H8'**,**H3**, **H6**), 1.25-1.40 (m, 16H, **H3'**, **H4'**, **H5'**, **H6'**, **H7'**, **H4**), 1.45-1.65 (m, 8H, **H5**, **H2'**), 3.62 (t, 2H, J = 7.0 Hz, **H1'**), 4.03 (d, 1H, J = 1.5 Hz; $^3J_{Sn-H}$ = 32 Hz, **H2**), 4.66 (d, 1H, J = 1.5 Hz; $^3J_{Sn-H}$ = 100 Hz, **H2***), ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.9 (**C3**), 13.7 (**C6**), 14.1 (**C8'**), 22.7 (**C7'**), 26.3 (**C6'**), 27.2 (**C4**), 27.5 (**C5'**), 29.0 (**C5**), 29.1 (**C4'**), 30.6 (**C3'**), 31.8 (**C2'**), 66.5 (**C1'**), 95.2 (**C2**), 173.2 (**C1**); IR (film) 3080, 2925, 2854, 1569, 1464 and 1180 cm^{-1}; MS (EI), *m/e* 389 (M^+-Bu, 24), 333 (38), 291 (19), 235 (48), 177 (100); Exact mass calcd for $C_{18}H_{37}OSn$ (M-Bu): 389.1866. Found: 389.1871.

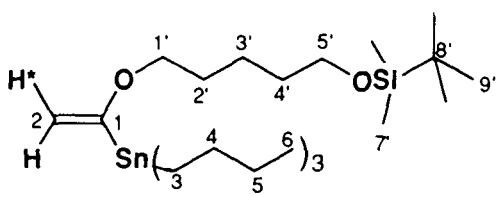
Ethyl 1-(Tributylstannyl)vinyl Ether (48):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 9H, 7.3 Hz, **H6**), 0.92 (t, 6H, J = 7.0 Hz, **H3**), 1.25 (t, 3H, J = 7.0 Hz, **H2'**), 1.31 (m, 6H, **H4**), 1.51 (m, 6H, **H5**), 3.68 (q, 2H, J = 7.0 Hz, **H1'**), 4.03 (d, 1H, 1.6 Hz; $^3J_{Sn-H}$ = 33 Hz, **H2**), 4.66 (d, 1H, J =

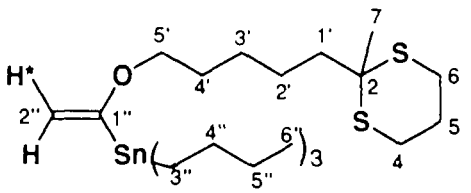
1.6 Hz; $^3J_{Sn-H}$ = 100 Hz, **H2***); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.8 (**C3**), 13.6 (**C6**), 14.5 (**C2'**), 27.2 (**C4**), 28.9 (**C5**), 62.0 (**C1'**), 95.4 (**C2**), 173.0 (**C1**); IR (film) 3080, 2956, 2853, 1570, 1464, 1182, 1045, 967 and 807 cm^{-1}; GC/MS (EI) *m/e* (rel intensity) 305 (M+-Bu, 73), 291 (40), 235 (100), 170 (100), 121 (33).

5'-(*tert* -butyldimethylsilyloxy)pentyl 1-(Tributylstannyl)vinyl Ether (50):



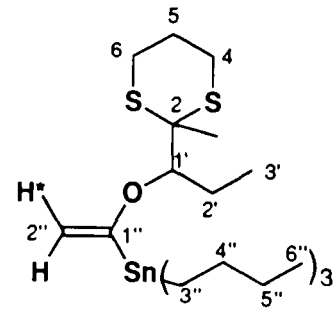
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6H, **H7'**), 0.89 (s, 9H, **H9'**), 0.86-0.93 (m, 15H, **H3**, **H6**), 1.31 (m, 6H, **H4**),1.40 (m, 2H, **H3'**), 1.52 (m, 8H, **H5**, **H4'**), 1.65 (m,2H, **H2'**), 3.61 (t, 2H, *J* = 6.7 Hz, **H5'**), 3.62 (t, 2H, *J* = 6.7 Hz, **H1'**), 4.03 (d, 1H, *J* = 1.5 Hz; $^3J_{Sn-H}$ = 32 Hz, **H2**), 4.66 (d, 1H, *J* = 1.5 Hz; $^3J_{Sn-H}$ = 100 Hz, **H2***); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.3 (**C7**), 9.8 (**C3**), 13.7 (**C6**), 18.4 (**C3'**), 22.6 (**C4'**), 26.0 (**C9'**), 27.2 (**C4**), 28.9 (**C5**), 32.7 (**C2'**), 63.2 (**C5'**), 66.4 (**C1'**), 95.2 (**C2**), 173.1 (**C1**); IR (film) 3100, 2928, 2856, 1568, 1463, 1255, 1178, 1098 and 836 cm^{-1};GC/MS (EI) *m/e* (rel intensity) 477 (M^+-Bu, 29), 291 (48), 249 (43), 193 (86), 177 (71), 101 (29); Exact mass calcd for $C_{21}H_{45}SiO_2Sn$: 477.2211. Found: 477.2213; Anal. Calcd for $C_{25}H_{54}SnSiO_2$: C, 56.15; H, 10.19. Found: C, 56.31; H, 10.21.

2-Methyl-2-{5'-[1''-(Tributylstannyl)vinyloxy]pentyl}-1,3-dihtiane (52):



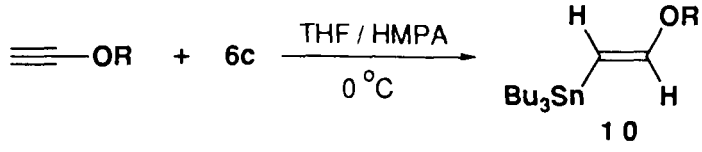
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 9H, *J* = 7.0 Hz, **H6''**), 0.94 (m, 6H, **H3''**), 1.26-1.36 (m, 6H, **H4''**), 1.40-1.75 (m, 12H, **H4'**, **H3'**, **H2'**, **H5''**), 1.62 (s, 3H, **H7**), 1.88-2.00 (m, 4H,**H1'**, **H5**), 2.82-2.87 (m, 4H, **H4**, **H6**), 3.63 (t, 2H, *J* = 6.3 Hz, **H5'**), 4.03 (d, 1H, *J* = 1.6 Hz; $^3J_{Sn-H}$ = 34 Hz, **H2''**), 4.66 (d, 1H, *J* = 1.6 Hz; $^3J_{Sn-H}$ = 99 Hz, **H2''***); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.8 (**C3''**), 13.7 (**C6''**), 24.3 (**C2'**), 25.4 (**C5**), 26.5 (**C4**, **C6**), 27.2 (**C4''**), 27.5 (**C3'**), 27.8 (**C7**), 28.9 (**C5''**), 29.1 (**C4'**), 41.6 (**C1'**), 49.2 (**C2**), 66.3 (**C5'**), 95.3 (**C2''**), 173.1 (**C1''**); IR (film) 3075, 2926, 2869,1568, 1463, 1178, 1072 and 865 cm^{-1}; GC/MS *m/e* (rel intensity) 479 (M^+-Bu, 24), 291 (14), 277 (71), 221 (100), 177 (86); Exact mass calcd. for $C_{20}H_{39}SnS_2O$: 479.1464. Found: 479.1478.

2-Methyl-2-{1'-[1''-(Tributylstannyl)vinyloxy]propyl}-1,3-dihtiane (54):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85-1.05 (m, 18 H), 1.25-1.35 (m, 6H), 1.40-1.50 (m, 6H), 1.57 (s, 3H), 1.80-2.05 (m, 4H), 2.68-2.70 (m, 2 H), 2.85-2.95 (m, 2H), 4.11 (d, 1H, J = 2.0 Hz; $^3J_{Sn-H}$ = 33 Hz), 4.44 (dd, 1H, J = 9.0, 3.0 Hz), 4.82 (d, 1H, J = 2.0 Hz; $^3J_{Sn-H}$ = 100 Hz); GC/MS (EI) *m/e* (rel intensity) 451 (M^+-Bu, 31), 409 (19), 341 (29), 291 (29), 235 (38), 217 (86), 175 (100); Exact mass calcd. for $C_{18}H_{35}S_2OSn$: 451.1151. Found: 451.1143.

I.4.3. General Procedure for the Preparation of 2-tri-*n*-Butylstannyl Alkoxy Vinyl Ethers 10.

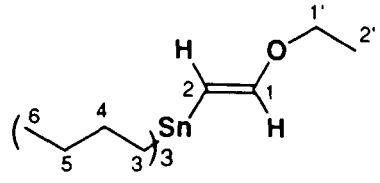


A solution of Bu_3SnLi (2.0 mmol), prepared in 5 mL of THF, as described above, was added *via* canula under argon atmosphere to a cold (-35°C) solution of

CuCN (0.180 g, 2.0 mmol) in 6 mL of THF:HMPA (1:1). After 45 min at -35 °C the solution was warmed to 0 °C over 15 min and a THF solution (2 mL) of acetylenic ether (2.0 mmol) added dropwise. After 40 min. at 0 °C the reaction was quenched by the addition of MeOH (2 mL) and worked-up as usual.

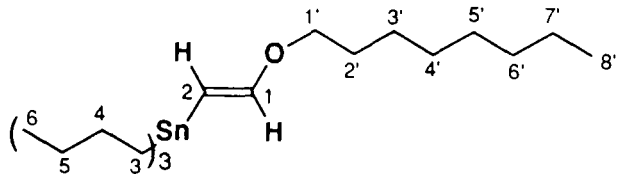
For the preparation of 2-tri-*n*-Butylstannyl Alkoxyvinyl Ethers, **10**, from reaction of acetylenic ethers with higher order cuprate **6a**, the same procedure was used. Cuprate **6a** was prepared as described above.

Ethyl 2-(Tributylstannyl)vinyl Ether (**49**).



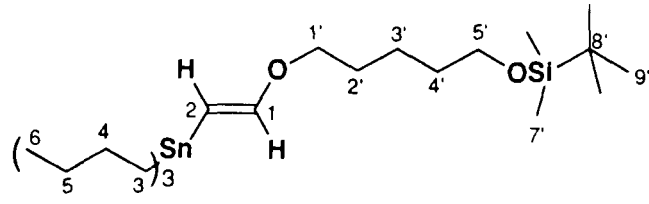
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84-0.90 (m, 15 H, **H3**, **H6**), 1.25-1.35 (m, 9H, **H4**, **H2'**), 1.44-1.52 (m, 6H, **H5**), 3.78 (q, 2H, J = 7.0 Hz, **H1'**), 4.62 (d, 1H, J = 15.6 Hz; $^2J_{Sn-H}$ = 52 Hz, **H2**), 6.21 (d, 1H, J = 15.6 Hz; $^3J_{Sn-H}$ = 51 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.8 (**C3**), 13.7 (**C6**), 14.7 (**C2'**), 27.3 (**C4**), 29.1 (**C5**), 62.9 (**C1'**), 92.0 (**C2**), 154.7 (**C1**); IR (film) 2956, 2871, 1579, 1602, 1463, 1128 and 1102 cm^{-1}; GC MS (EI) m/e (rel. intensity) 305 (M+-Bu, 71), 291 (39), 235 (96), 179 (100); Anal. Calcd. for $C_{16}H_{34}SnO$: C, 53.21; H, 9.49. Found: C, 53.40; H, 9.64.

Octyl 2-(Tributylstannyl) Ether (10a).



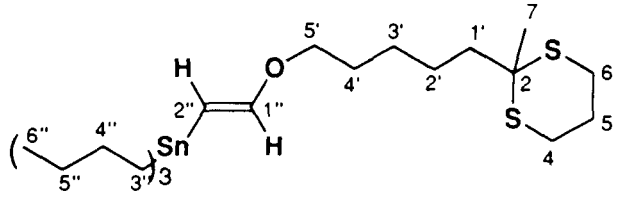
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85-1.00 (m, 18H, **H3**, **H6**, **H8'**), 1.25-1.40 (m, 16 H, **H4**, **H3'**, **H4'**, **H5'**, **H6'**, **H7'**), 1.44-1.52 (m, 6H,**H5**), 1.55-1.69 (m, 2H, **H2'**), 3.70 (t, 2H, J = 7.0 Hz, **H1'**), 4.60 (d, 1H, J = 16 Hz; $^2J_{Sn-H}$ = 52 Hz, **H2**), 6.22 (d, 1H, 16Hz; $^3J_{Sn-H}$ = 51 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.7 (**C3**), 13.6 (**C6**), 14.0 (**C8'**), 22.6 (**C7'**), 26.1 (**C6'**), 27.2 (**C4**), 27.5 (**C5'**), 27.8 (**C5**), 29.2 (**C4'**), 30.6 (**C3'**), 31.8 (**C2'**), 67.5 (**C1'**), 91.7 (**C2**), 154.9 (**C1**); IR (film) 2925, 2855, 1602, 1579 and 1117 cm^{-1}; MS (EI) *m/e* (rel. intensity) 389 (M^+- Bu, 57), 333 (14), 235 (76), 179 (100), 137 (38). Exact mass calculated for $C_{18}H_{37}OSn$: 389.1866. Found: 389.1853.

5-(*tert* -Butyldimethylsilyloxy)pentyl 2-(Tributylstannyl)vinyl Ether (51):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6H, **H7'**), 0.84-1.00 (m, 24H, **H9'**, **H3**, **H6**), 1.26-1.35 (m,6H, **H4**), 1.40-1.70 (m, 12H, **H2'**, **H3'**, **H4'**, **H5**), 3.61 (t, 2H, J = 7.0 Hz, **H5'**), 3.70 (t, 2H, J = 7.0 Hz, **H1'**), 4.60 (d, 1H, J = 15.8 Hz, $^2J_{Sn\text{-}H}$ = 56 Hz, **H2**), 6.22 (d, 1H, J = 15.8 Hz, $^3J_{Sn\text{-}H}$ = 51 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) d -5.3 (**C7'**), 9.7 (**C3**), 13.7 (**C6**), 15.3 (**C8'**), 18.3 (**C3'**), 22.4 (**C4'**), 26.0 (**C9'**), 27.2 (**C4**), 29.1 (**C5**), 32.6 (**C2'**), 63.1 (**C5'**), 67.3 (**C1**), 91.7 (**C2**), 154.8 (**C1**); MS (EI) *m/e* (rel intensity) 477 (M^+-Bu, 72), 291 (60), 249 (46), 177 (70), 101 (71). Exact mass calcd for $C_{21}H_{45}SiO_2Sn$: 477.2211. Found: 477.2242.

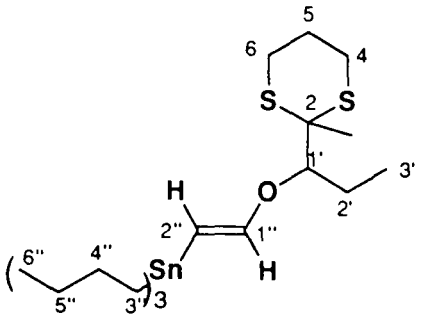
2-Methyl-2-{5'-[(*E*) 2''-(Tributylstannyl)vinyloxy]pentyl}-1,3-dihtiane (53).



^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.83-1.00 (m, 15H, **H3''**, **H6''**), 1.25-1.35 (m, 6H, **H4''**), 1.40-1.75 (m, 12H, **H4'**, **H3'**, **H2'**, **H5''**), 1.61 (s, 3H, **H7**), 1.88-2.00 (m, 4H, **H1'**, **H5**), 2.82-2.90 (m, 4H, **H4**, **H6**), 3.73 (t, 2H, J = 6.5 Hz, **H5'**), 4.61 (d, 1H, J = 16 Hz; $^2J_{Sn\text{-}H}$ = 56 Hz, **H2''**), 6.22 (d, 1H, J = 16Hz; $^3J_{Sn\text{-}H}$ =50 Hz, **H1''**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.8 (**C3''**), 13.6 (**C6''**), 24.3 (**C2'**), 25.4 (**C5**), 26.5 (**C4**, **C6**), 27.2 (**C3'**), 27.4 (**C4''**), 27.8 (**C7**), 29.0 (**C5''**), 29.1 (**C4'**), 41.7 (**C1'**), 49.2 (**C2**), 67.2 (**C5'**), 91.8 (**C2''**), 154.8 (**C1''**); IR (film) 2938,

2863, 1614, 1320, 1202 and 815 cm^{-1}. Exact mass calcd. for $C_{20}H_{39}SnS_2O$: 479.1464. Found: 479.1459.

2-Methyl-2-{1'-[(*E*)-2''-(tributylstannyl)vinyloxy]propyl}-1,3-dihtiane (55).



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85-1.05 (m, 18 H, **H3''**, **H6''**, **H3'**), 1.25-1.35 (m, 6H, **H4''**), 1.40-1.50 (m, 6H, **H5''**), 1.57 (s, 3H, **H7**), 1.80-2.05 (m, 4H, **H2'**, **H5**), 2.68-2.70 (m, 2 H, **H4**, **H6**), 2.95-3.05 (m, 2H, **H4**, **H6**), 3.90 (dd, 1H, J = 10.2, 1.7 Hz, **H1'**), 4.76 (d, 1H, J = 15.3 Hz; $^2J_{Sn-H}$ = 56 H, **H2''**), 6.10 (d, 1H, J = 15.3 Hz; $^3J_{S\ n-H}$ = 49 H, **H1''**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 9.9 (**C3''**), 11.3 (**C3'**), 13.8 (**C6''**), 24.5 (**C7**), 24.6 (**C5**), 24.9 (**C2'**), 26.8 (**C4**), 26.9 (**C6**), 27.3 (**C4''**), 29.1 (**C5''**), 52.8 (**C2**), 89.0 (**C2''**), 92.8 (**C1'**), 156.7 (**C1''**); IR (film) 2956, 2923, 2871, 1520, 1370, 1190 $cm.^{-1}$ Exact mass calcd. for $C_{18}H_{35}S_2OSn$: 451.1151. Found: 451.1154.

CHAPTER II

Effect of HMPA in the Composition of Higher Order Organocyanocuprates.

II.1. Introduction

One of the most basic reactions in organic chemistry is the formation of carbon-carbon single bonds. This can be achieved by the reaction of an organometallic reagent with an organic substrate possessing a polarized π or σ bond. One of the most widely used organometallics in C-C construction are those in which an organic anion is coordinated with copper (I). The use of organocuprates has expanded constantly since 1952 when Gilman *et al.* reported[60] the *in situ* preparation of the organocuprate, Me_2CuLi, **64**, from 2 equivalents of MeLi and 1 equivalent of CuI according to **Scheme II-1**.

$$2\ MeLi + CuI \longrightarrow \underset{\mathbf{64}}{Me_2CuLi} + LiI$$

Scheme II-1. Preparation of Gilman Cuprate 64.

Fourteen years after the preparation of Gilman's reagent Me_2CuLi, House[61] , and others[62] used cuprates, prepared from CuI, to achieve reactions not readily effected by organometallics based on lithium or magnesium which at

that time were two of the more common metals used for organic synthetic purposes.

The reactivity of diorganocopperlithium reagents was shown to be greater than that of the mono-organocopper reagents (**Scheme II-2**), whose low solubility and thermal instability have limited their use.[63]

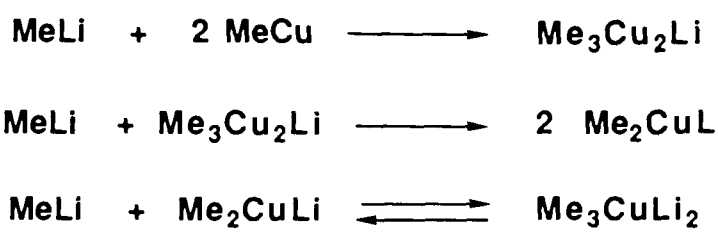
$$RLi + CuX \longrightarrow RCu + LiX$$

$$RLi + L\text{-}CuX \longrightarrow RCu\text{-}L + LiX$$

L: ligand (phosphines or sulfides).

Scheme II-2. Preparation of mono-organocopper reagents.

In 1977 Ashby reported[64] that several methyl copper species were formed from the mixing MeLi and MeCu in different stoichiometries. Thus, in Me_2O and THF, Me_3Cu_2Li and Me_2CuLi were found to exist when the MeLi:MeCu ratios were 1:2 and 1:1, respectively. When the ratio MeLi:MeCu was 2:1, Me_3CuLi_2 was formed as an equilibrium mixture with Me_2CuLi and MeLi (**Scheme II-3**).

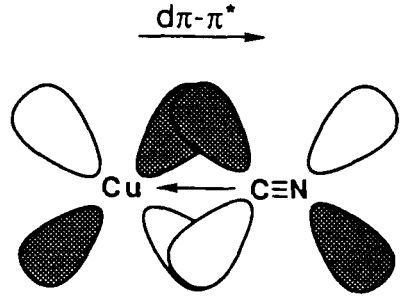


Scheme II-3. Methylcopper species present in different Me-Cu: MeLi ratios.

The presence of the species Me_3CuLi_2 is believed to be responsible for the higher stereoselectivity[65] and reactivity[66] observed in mixtures of MeLi and Me_2CuLi compared with MeLi or Me_2CuLi[67]. In this species, presumably, three methyl groups are bounded to copper, forming a Cu(I) dianionic salt.

In 1981 Lipshutz *et al.* reported[68] the formation of "higher order mixed cyanocuprates," prepared by the addition of 2 equivalents of an organolithium (RLi) to 1 equivalent of copper cyanide (CuCN). In these species one of the ligands of the previously reported cuprate Me_3CuLi_2 (**Scheme II-3**) was replaced by a non-transferable ("dummy") ligand: the cyano group. These "higher order organocyanocuprates" were assumed to be dianionic salts with three ligands on copper, one of them being the cyano group, $[R_2Cu(CN)Li_2]$, and were claimed to be differentiated from "lower order cuprates" in "that the cyanide ligand (negatively charged) on copper permits the build-up of a negative charge in the complex. Hence, they are formally Cu (I) dianionic salts."[69]

It has been shown that these new "higher order cuprates" tend to be more reactive toward displacements and epoxide openings and more stable than the Gilman-like cuprates. Higher order cuprates generally give higher yields than lower order cuprates[70]. Their higher stability has been attributed to backbonding from the filled d-orbital on copper into the empty π^*-orbital on the nitrile ligand (**Scheme II-4**).



Scheme II-4. d π-π^* Backbonding stabilization in "higher order" mixed cyano cuprates.

In recent years whether or not the cyanide ligand is bonded to copper in these cuprates has been a topic of controversy.[71,72] An alternative formulation for these reagents was proposed by Bertz[72] in which the cyano group is not covalently bonded to copper but is present as lithium cyanide co-ordinated to a Gilman-like species ($R_2CuLi \cdot LiCN$). Bertz proposed this formulation based on the observation that the ^{13}C-NMR chemical shifts obtained for cuprates prepared from the addition of 2 equivalents of an alkyl lithium RLi (R= Me, Et, Ph) to 1 equivalent of CuCN (higher order cuprates) were the same as those prepared by the addition of 2 equivalents of RLi to 1 equivalent of CuI (lower order cuprates) both before and after adittion of HMPA. Additional support in

favor of the Bertz formulation was the observation[73] that for higher order cuprates $R_2Cu(CN)Li_2$ (R= Me, Et) no $^2J\,^{13}C\text{-}^{13}CN$ couplings were observed between C-1 (in Me and Et groups) and ^{13}CN when the spectra were recorded at -78 and -100 °C with and without HMPA. Coupling of 21 Hz ($^2J\,^{13}C\text{-}^{13}C$) was observed between C-1 and ^{13}CN for the corresponding Gilman-like cuprates RCu(CN)Li (R= Me, Et) at -78 and -100 °C, establishing that in these "lower order" cuprates the cyanide ligand is bonded to copper. An alternative explanation for this observation is that rapid exchange of the cyanide ligand in higher order cuprates might be responsible for the absence of observable coupling in these species.[73]

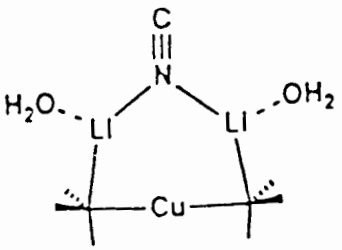
Lipshutz reported[71] that although the ^{13}C-NMR resonances for C-1 in cuprates prepared from CuCN ["$R_2Cu(CN)Li_2$"] and CuI ($R_2CuLi{\cdot}LiI$) are coincident when these species are examined in THF solutions, they are observed at significantly different locations (1.1 ppm, for R= Me) when examined in DMS solutions. Lipshutz also reported that addition of a HMPA solution of LiCN to cuprate Me_2CuLi, **64**, resulted in the complete formation of H.O. cuprate $Me_2Cu(CN)Li_2$, **65**, and postulated the later as the "thermodynamic sink for a Gilman reagent in the presence of cyanide ion".

Recent theoretical calculations suggested[74] that dianionic trivalent copper (I) is not a sufficiently stable species to represent the structure of "higher order cyanocuprates" as $R_2Cu(CN)Li_2$. One of the alternative formulations to emerge from theoretical studies consists in a Gilman reagent bridged by a Li_2CN moiety (**66**, **Scheme II-5**). Support for this structure is Bertz's failure to

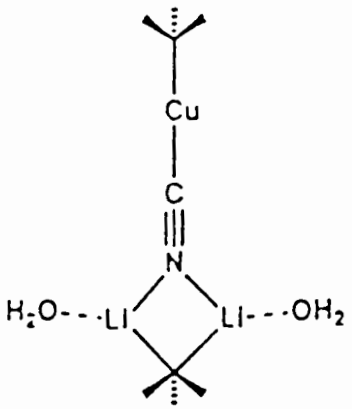
observe alkyl ^{13}C-^{13}CN NMR couplings for "higher order" species $[R_2Cu(^{13}CN)Li_2]$.

In the preceeding chapter, spectroscopic evidence was presented showing that, higher order stannylcyanocuprate **6a,** when prepared in the presence of HMPA, appreciably dissociated to the corresponding lower order (L.O.) stannylcuprate, **60**. To obtain further insight into the composition of H.O. cuprates in the presence of highly coordinating solvents (e.g.. HMPA), H.O. cuprates $(Bu_3Sn)_2Cu(CN)Li_2$, **6a**, and $Me_2Cu(CN)Li_2$, **65**, prepared with $Cu^{13}CN$, were studied by ^1H and ^{13}C NMR in THF and THF:HMPA solutions.

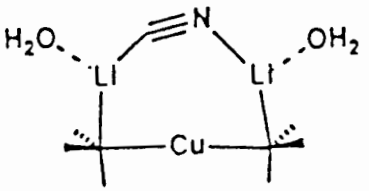
These results provide new evidence that "higher order cuprates", when prepared in the presence of HMPA, exist as mixtures of "higher order cuprates" and their corresponding Gilman-like cuprates.



66



67

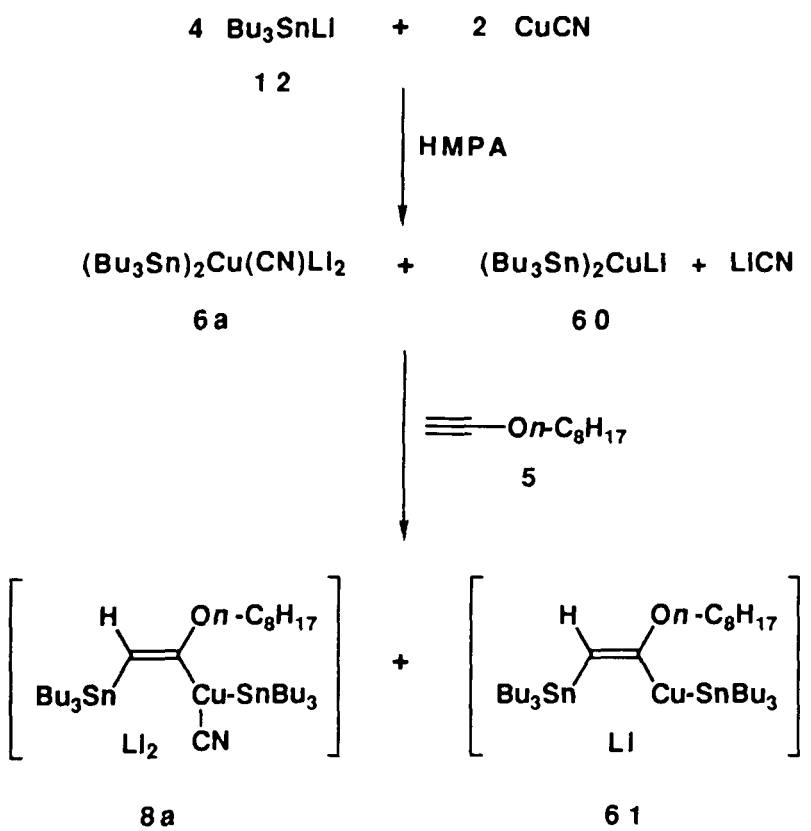


68

Scheme II-5. Alternative structures for higher order cyanocuprates.[74]

II.2. Results and Discussion

It was shown in Chapter I that when cuprate $(Bu_3Sn)_2Cu(CN)Li_2$, **6a**, prepared in the presence of HMPA, was reacted with acetylenic ether **5** at 0 °C, two major vinylcopper intermediates **8a** and **61** were formed. The latter was postulated to lack a cyano ligand (**Scheme II-6**). It was suggested that, when prepared in the presence of HMPA, higher order stannylcyanocuprate **6a** and lower order cuprate **60** were present and both of these cuprates reacted with **5** to form intermediates **8a** and **61** respectively.



Scheme II-6. Vinylcopper intermediates formed in the reaction of 5 with 6a, prepared in the presence of HMPA.

To demonstrate that the cyano ligand dissociates from copper in higher order cuprates, when prepared in the presence of HMPA, several NMR experiments were performed with these reagents, prepared from labeled $Cu^{13}CN$.

The ^{13}C-NMR spectrum of H.O. cuprate **6a**, prepared from 2 equivalents of Bu_3SnLi and 1 equiv. of $^{13}CuCN$ (**Figure II-1 a**) at 0 °C in the presence of HMPA (17 equiv.), exhibited very broad signals for the carbon of the cyano group (**Figure II-1 b**). This is attributed to rapid ligand interchange (possibly bonded and free cyano ligand). When this cuprate solution was reacted with 1 equivalent of acetylenic ether **5** and the ^1H-NMR taken, two major peaks at 5.01 and 4.95 ppm were observed for the vinylcopper intermediates **8a** and **61**, respectively in a ratio *ca.* 55:45. This is similar to the spectrum obtained in **Figure I-2b** (Chapter I, page 38). Because only one of these intermediates has a cyano ligand on copper (**8a**), only one peak should be observable for this group in the ^{13}C-NMR spectrum of this reaction mixture. Indeed, when the ^{13}C-NMR spectrum of this sample was recorded, only one major peak at 144.8 ppm was present (**Figure II-1 c**), this was assigned to the carbon of the cyano ligand of intermediate **8a**. Sharper signals than the ones obtained for cuprate **6a** (**Figure II-1 b**) were observed in this case, suggesting slower ligand exchange in intermediate **8a** as it, presumably, does in cuprate **6a**. This result is consistent with the previous observation that addition of HMPA to the vinylcopper intermediate **8a** did not result in the formation of intermediate **61** (**Figure I-3**, Chapter I, page 39). A small signal at 153.1 ppm was also present (**Figure II-1** c). This presumably corresponds to the carbon of free lithium

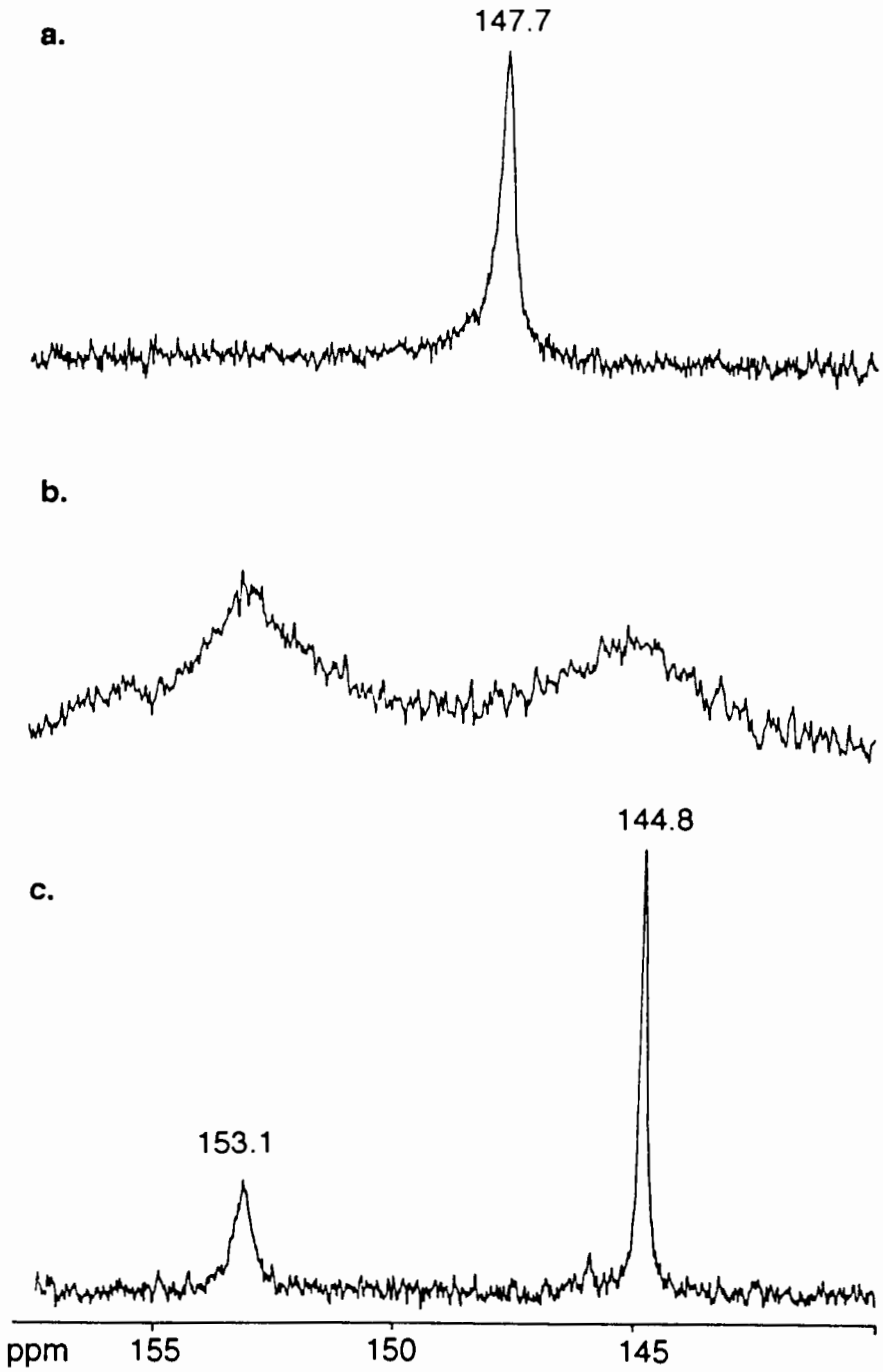


Figure II-1. Low temperature (0 °C) ^{13}C-NMR spectra of
a. $Cu^{13}CN$ in THF:HMPA (17 equivalents).
b. $Cu^{13}CN$ (HMPA, 17 equiv.) + 2 equivalents of Bu_3SnLi
c. $(Bu_3Sn)_2Cu(CN)Li_2$ + **5** (1 equivalent).

cyanide, whose chemical shift is dependent on the concentration of HMPA[71] and possibly the concentration of oxygen containing intermediates in the solution. These observations provide additional evidence that in the presence of HMPA stannylcyanocuprate, **6a**, exists as a mixture with lower order Gilman-like cuprate, **60**.

To determine if higher order dialkycyanocuprates behaved in the same manner as **6a** a similar experiment was performed using cuprate **65** [$Me_2Cu(^{13}CN)Li_2$]. Thus, when the later reagent was prepared by addition of 2 equivalents of MeLi to 1 equivalent of $Cu^{13}CN$ in the presence of HMPA (17 equivalents) at -40 °C and the ^{1}H-NMR spectrum taken, two major signals were observed at -1.31 and -1.39 ppm (**Figure II-2 a**), these were assigned to the higher order (**65**) and Gilman (**64**) cuprates respectively. To identify the species giving rise to these signals Gilman cuprate Me_2CuLi, **64**, was prepared by addition of 2 equivalents of MeLi to a cold (-40 °C) THF suspension of CuI (1 equivalent) containing HMPA (17 equivalents). After the LiI that formed was removed by filtration at low temperature under argon,[51] the spectrum was recorded. The low temperature (-40 °C) ^{1}H-NMR spectrum of this solution exhibited a singlet at -1.39 ppm (**Figure II-2 b**) identical with the one previously obtained from the higher order cuprate solution (**Figure II-2 a**). One equivalent of LiCN, dissolved in HMPA, was added to the Gilman cuprate **64** (**Figure II-2 b**) and after 25 min. at -40 °C the ^{1}H NMR spectrum was recorded. A signal at -1.31 ppm, assigned to the higher order species **65**, was evident (**Figure II-2 c**). More significantly, the former spectrum (**Figure II-2 a**) was reproduced. Addition of a second equivalent of LiCN (in HMPA) to the

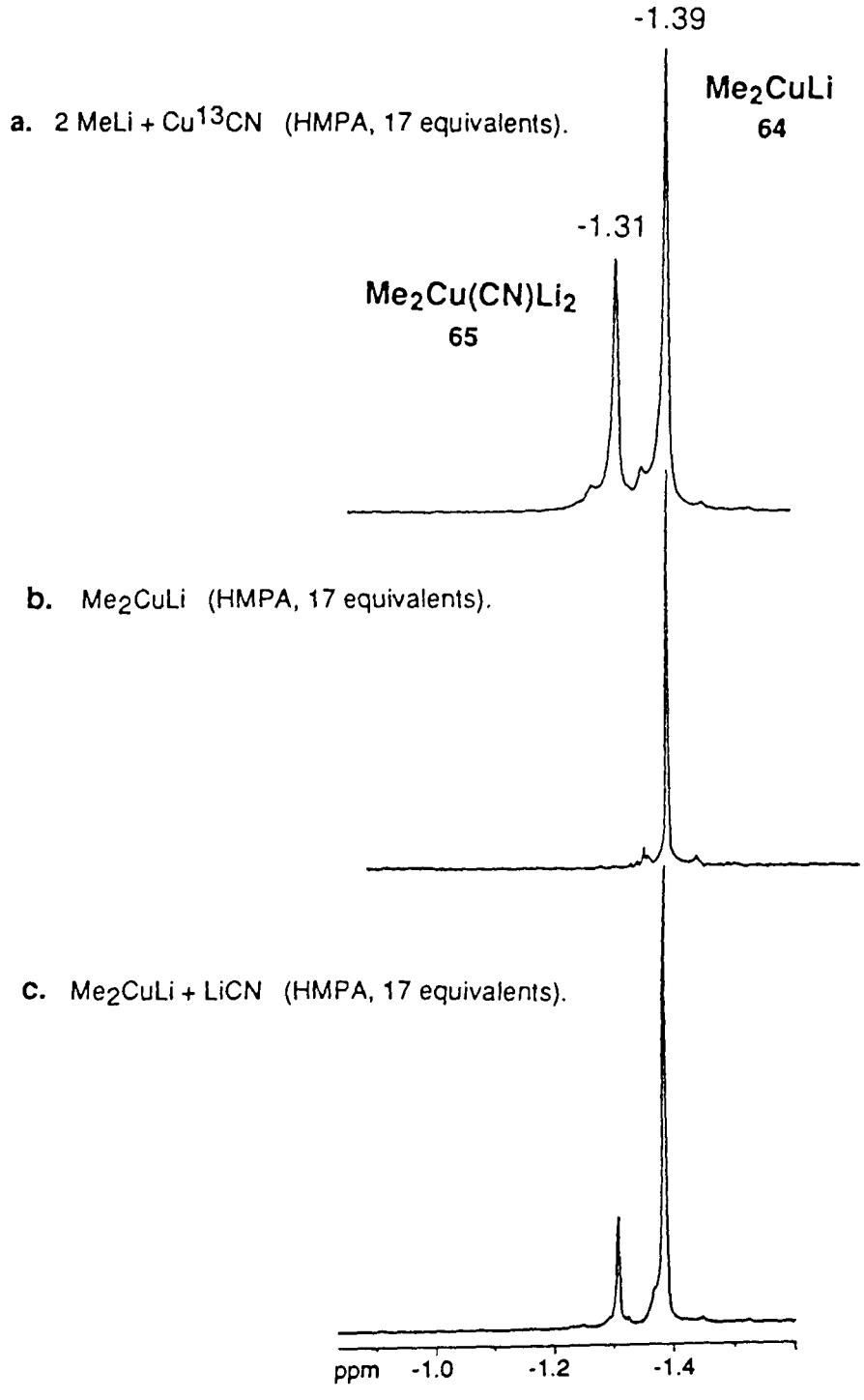


Figure II.2. Low temperature (-40 °C) ^{1}H-NMR spectra of
a. $Me_2Cu(CN)Li_2$ (prepared in the presence of HMPA).
b. Me_2CuLi (prepared in the presence of HMPA).
c. Me2CuLi (HMPA) + LiCN.

above solution did not result in an increase in intensity of the signal attributed to **65**. Gradually increasing the temperature from -40 to 20 °C resulted in an increase in the intensity of the signal attributable to **65** and the eventual disappearance of the signal attributable to **64**.

In a similar experiment 1 equivalent of LiCN was added to a THF:HMPA (17 equivalents of the latter) solution of Gilman cuprate Me_2CuLi, **64**, at -40 °C and the temperature gradually increased to 0 °C (**Figure II-3**). A ^{1}H-NMR signal at -1.31 ppm, assigned to the higher order species, **65**, gradually emerged at expense of a signal attributable to the lower order species, **64**. In this case the increase in the temperature did not result in complete formation of the higher order species. Lowering the reaction temperature of this sample (**Figure II-3 e**) to -40 °C did not affect the ratio of the two strongest signals and the original spectrum (**Figure II-3 a**, -40 °C) was not obtained. This result suggest that the reaction between Gilman cuprate Me_2CuLi, **64**, and LiCN is not reversible under these conditions.

The (-40 °C) ^{13}C-NMR spectrum of the THF solution of cuprate **65**, prepared from the addition of 2 equivalents of MeLi to 1 equivalent of $Cu^{13}CN$, in the presence of HMPA (17 equiv.), exhibited 3 principal signals at 146.5, 153.1 and 167.1 ppm (**Figure II-4 b**). The signal at 146 ppm was assigned to the cyano ligand of the higher order cuprate $Me_2Cu(^{13}CN)Li_2$, **65.** The signal at 167.1 ppm was assigned to free $Li^{13}CN$. To confirm this assignment, the ^{13}C-NMR spectrum of a LiCN sample in THF-HMPA (17 equivalents) was recorded (**Figure II-4 a**). The presence of free lithium cyanide in this sample

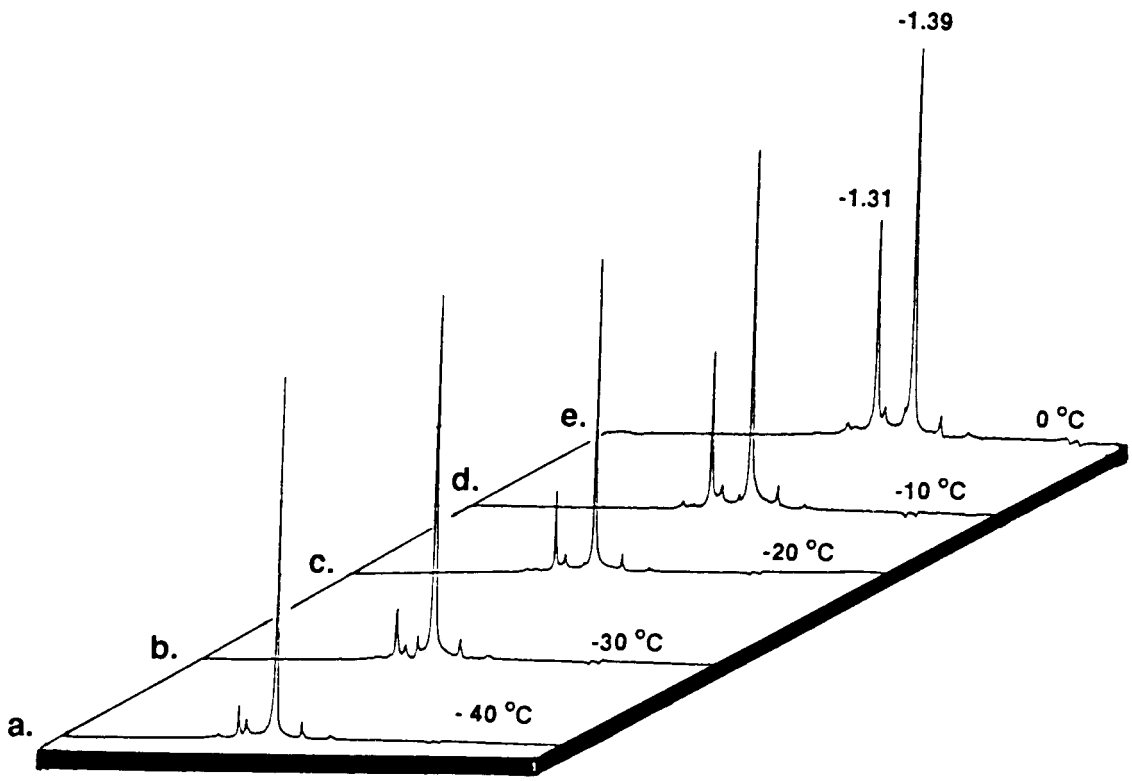


Figure II-3. Variable low temperature ^{1}H-NMR spectrum of a THF:HMPA solution of Gilman cuprate Me_2CuLi, **64**, and LiCN.

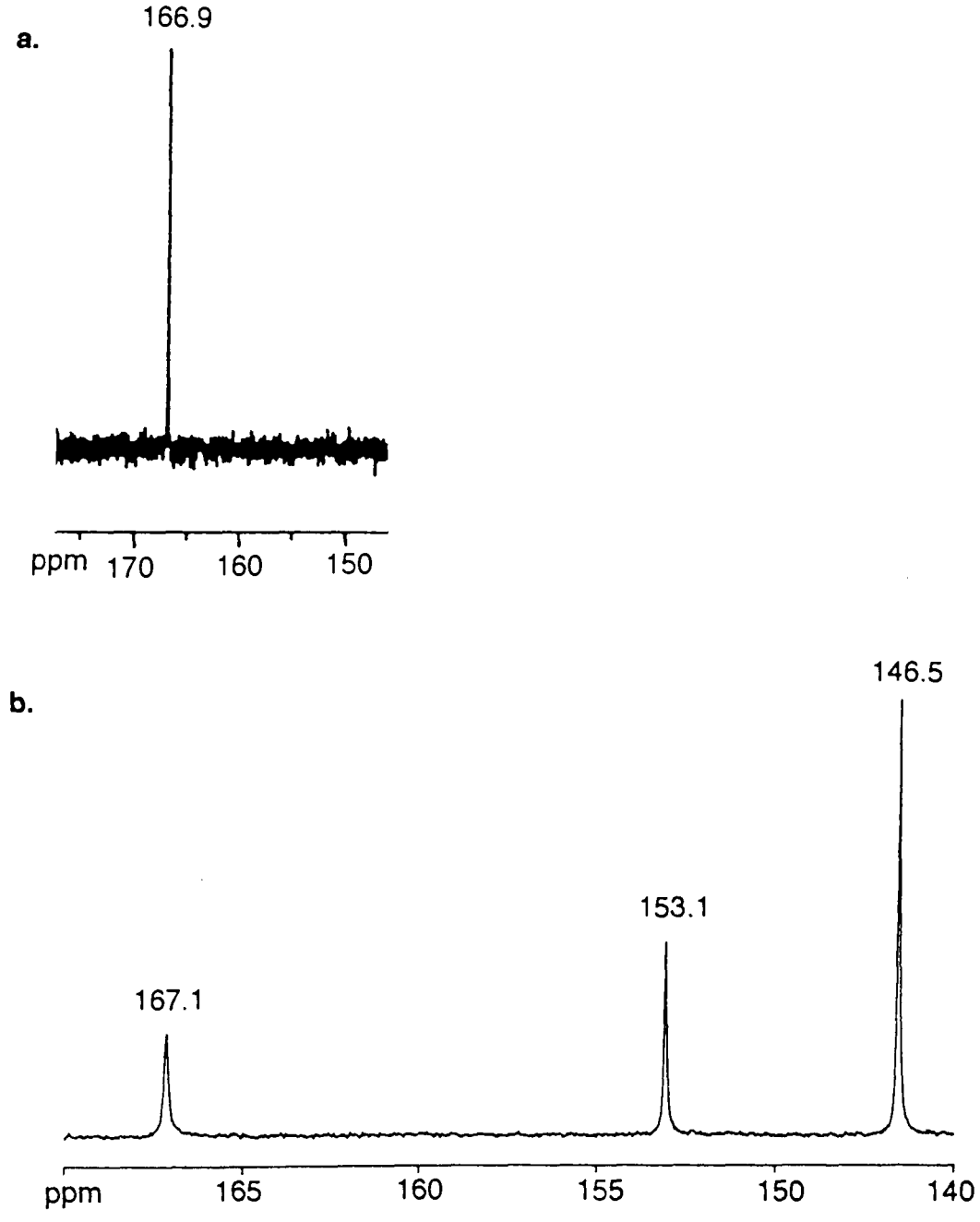


Figure II-4. **a.** ^{13}C-NMR spectrum of LiCN in THF/HMPA (17 equiv.).
b. Low temperature (-40 °C) ^{13}C-NMR spectrum of $Me_2Cu(CN)Li_2$ (prepared in the presence of HMPA (17 equiv.).

fully supports the idea that, when prepared in the presence of HMPA, higher order cuprates exist as mixtures with the corresponding Gilman cuprates and lithium cyanide. Increasing the temperature from -40 to 0 °C resulted in simplification of the spectrum (**Figure II-5**) with the signal at 146 ppm the only observable signal at 0 °C (**Figure II-5 e**). When the temperature of this (0 °C) sample was lowered to -40 °C the spectrum did not change and the original (-40 °C) spectrum (**Figure II-5 a**) was not obtained. These observations suggest again that coordination of cyanide with copper occurs when the temperature is increased but does not reverse upon lowering the temperature. Thus, Lipshutz is correct in formulating **65** as the thermodynamic sink resulting from reaction of **64** and LiCN. When a THF:HMPA solution of non-labelled **65** was stirred for 1.5 h at 0 °C the ^{1}H-NMR spectrum of this cuprate exhibited only a lone singlet at -1.31 ppm, assigned to the methyl groups **65**.

A similar ^{13}C-NMR spectrum (**Figure II-4 b**) was obtained by Lipshutz et al[12] for cuprate **65** when 1 equivalent of LiCN in HMPA was added to **64** (**Figure II-6**). However, in this case the signal at 162.8, as well as the one at 151.7 ppm, were both assigned to the **C**N carbon of **65** [$Me_2Cu(CN)Li_2$] and the assumption was that these signals corresponded to monomeric and dimeric species of this cuprate. It was also claimed that the original signal for LiCN (167 ppm) was no longer visible. This interpretation was construed as evidence for the covalent bond between the CN group and copper.[71] We suggest that the signal at 162.8 in Lipshutz's spectrum was due to LiCN. The change in chemical shift from 166.9 to 162.8 ppm for the LiCN is most likely due to dilution when the LiCN in HMPA was added to a THF solution of **64**. It is known that the

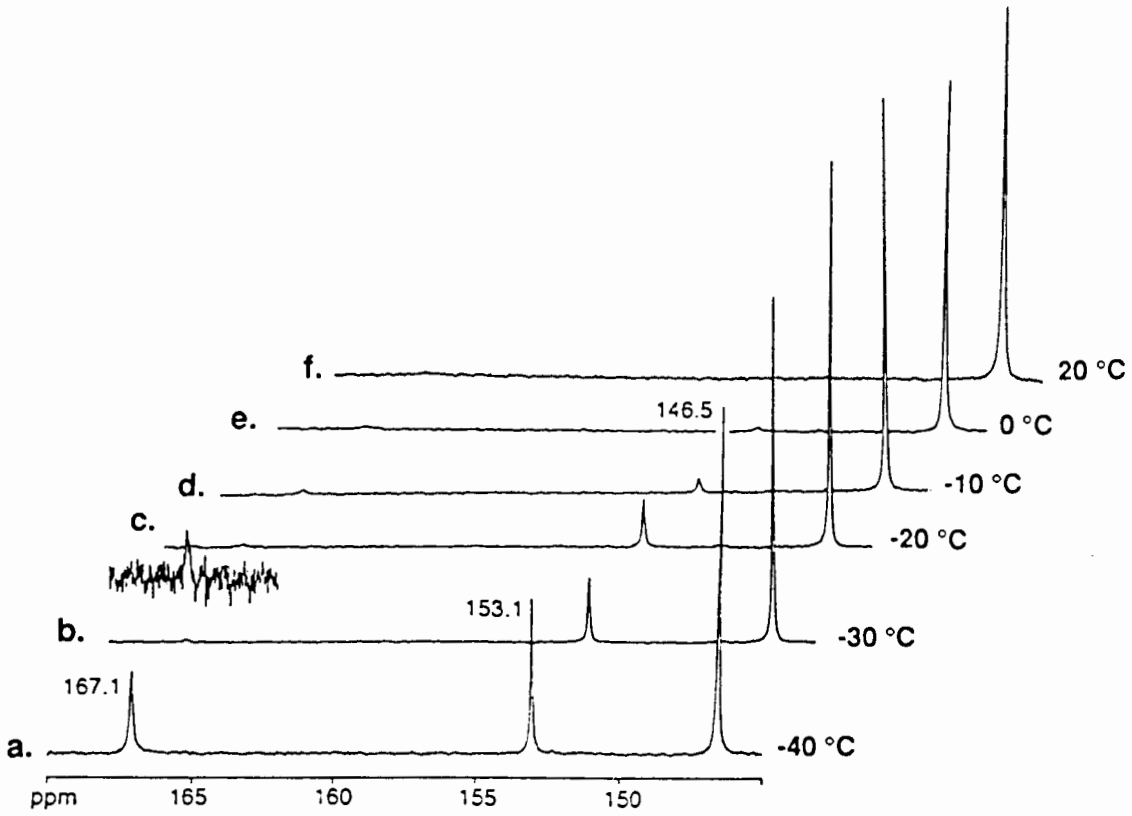


Figure II-5. Variable low temperature ^{13}C-NMR spectrum of $Me_2Cu(CN)Li_2$, **65**, (prepared in the presence of HMPA).

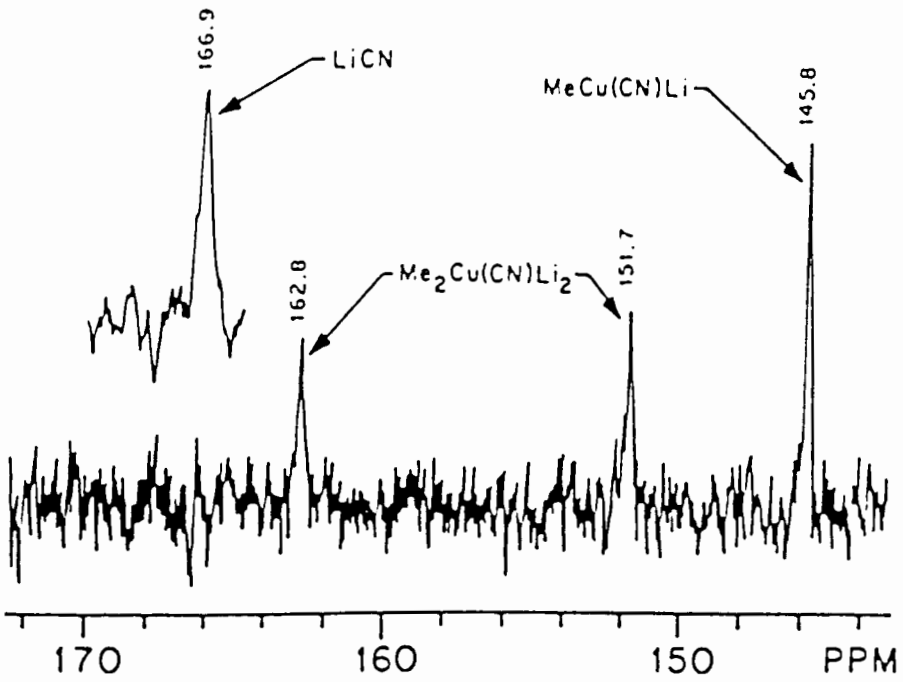


Figure II-6. ^{13}C-NMR spectrum of Me_2CuLi LiI + LiCN /HMPA (1 equiv.) in THF at -40 °C vs LiCN. (Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4032).

^{13}C-chemical shift for the cyano ligand depends of the concentration of HMPA in the medium.[71] Lipshutz also assigned the peak at 145.8 ppm to the lower order cuprate MeCu(CN)Li, **56**, arguing that this chemical shift corresponded to that of an independently prepared sample of **56**.

Because previous assignments and conclusions were different than those presently made from the data obtained in **Figures II-2**, **II-3**, **II-4** and **II-5** the previous experiments were repeated. Reagent **56**, MeCu(^{13}CN)Li, was prepared by the addition of 1 equivalent of MeLi to 1 equivalent of a cold (-40 °C) THF solution of Cu^{13}CN containing HMPA (17 equivalents) and analyzed spectroscopically. Indeed, the ^{13}C-NMR chemical shift obtained for this sample (**Figure II-7**) was identical with the one in **Figure II-4 b**: 146.5 ppm. However, when the ^{1}H-NMR of this sample was recorded (**Figure II-8**), the chemical shift (-1.43 ppm) did not correspond with any of the chemical shifts obtained for this H.O. cuprate sample in **Figure II-2 a**. In spite of the fact that the species with a chemical shift of 146.5 ppm in **Figure II-4b** and cuprate **56** exhibit identical ^{13}C-NMR, they do not exhibit the same ^{1}H-NMR spectra and it can be concluded that they are not the same species.

To further confirm the identity of the species giving rise to the signal at 146.5 ppm in **Figure II-4 b**, cuprate **65** [$Me_2Cu(^{13}CN)Li_2$], was prepared by addition of 2 equivalents of MeLi to a THF suspension of Cu^{13}CN (1 equivalent) at -40 °C, and after formation of the soluble cuprate (ca. 45 minutes) successive amounts of HMPA were added while both ^{1}H and ^{13}C-NMR spectra were recorded. The ^{13}C-NMR spectrum of the THF solution (0 equivalents of HMPA)

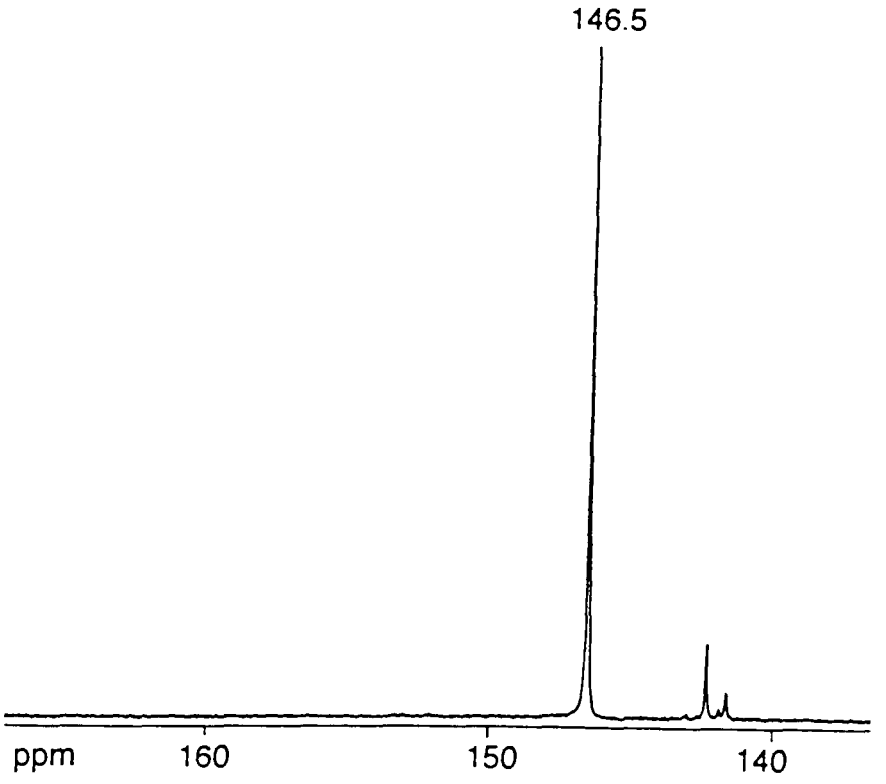


Figure II-7. Low temperature (-40 °C) ^{13}C-NMR spectrum of $MeCu^{13}CNLi$ (prepared in the presence of HMPA).

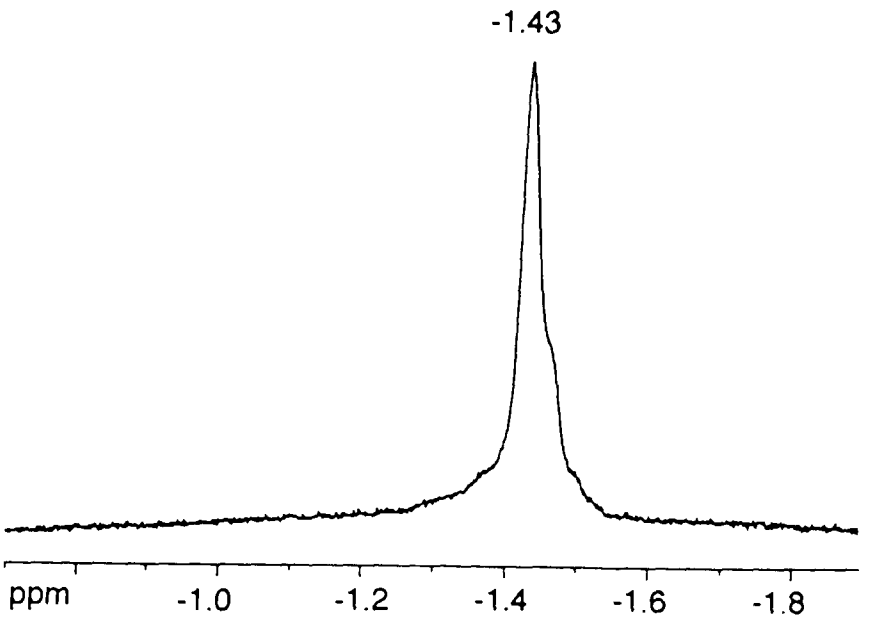


Figure II-8. Low temperature (-40 °C) ^{1}H-NMR spectrum of MeCu^{13}CNLi (prepared in the presence of HMPA)

of cuprate **65**, showed a signal with a chemical shift of 149.6 ppm (**Figure II-9 a**), but as the amount of HMPA was increased the signal shifted upfield. When 17 equivalents of HMPA had been added (**Figure II-9 e**) the chemical shift obtained corresponded with the signal at 146.5 ppm obtained in **Figure II-4b**. Similarly, the ^{1}H-NMR of the THF solution of **65**, presented a major signal at -1.27 ppm (**Figure II-10a**), but as HMPA was gradually added, it shifted to -1.31 ppm (17 equivalents) (**Figure II-10 e**), corresponding with the signal assigned to this higher order cuprate in **Figures II-2a**, **II-2c** and **II-3**. It can be concluded from these experiments, that the signal at 146.5 ppm in **Figure II-4b** (or 145.8 ppm in **Figure II-6**) corresponds to cuprate **65** and not to **56** as previously suggested.[71]

Addition of HMPA to higher order cuprate **65**, prepared in THF (**Figure II-9**), did not result in the development of strong signals at 153.1 or 167.1 ppm which were obtained when the same cuprate was prepared in the presence of HMPA. A very small peak at 153.1 ppm appeared, when 4.0 equivalents of HMPA had been added (**Figure II-9c**). Similar observations were made in Chapter I, for the addition of HMPA to the vinylcopper intermediate **8a** (**Figure I-3**). Thus, although the cyano group dissociates from copper when the higher order cuprate **65** is prepared in the presence of HMPA, it maintains its bonding to copper when prepared in THF solutions to which HMPA is added after the preparation. Presumably, the small ^{13}C-NMR signal at 153.1 ppm observed for cuprate **65** upon addition of HMPA (**Figures II-4b** and **II-9c**) could be due to a different aggregation state of this species in the presence of HMPA.

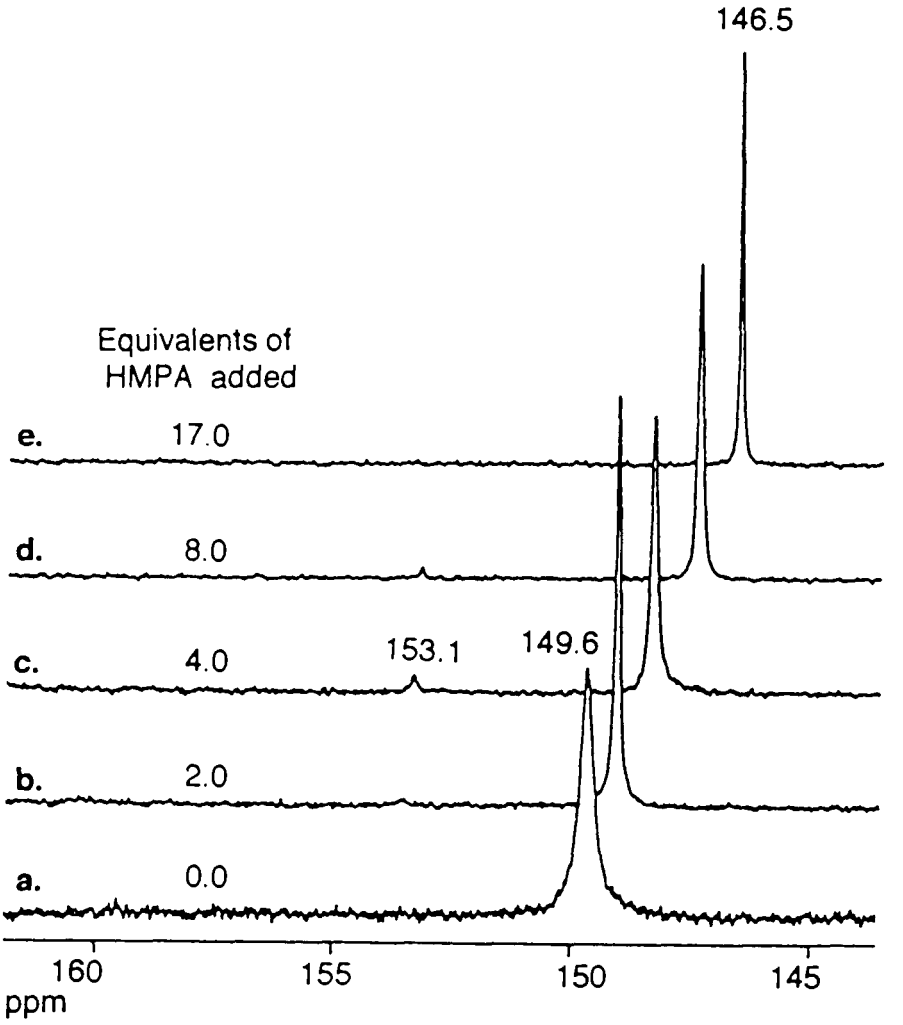


Figure II-9. Low temperature (-40 °C) ^{13}C-NMR spectra of a THF solution of $Me_2Cu(^{13}CN)Li_2$ with successive additions of HMPA.

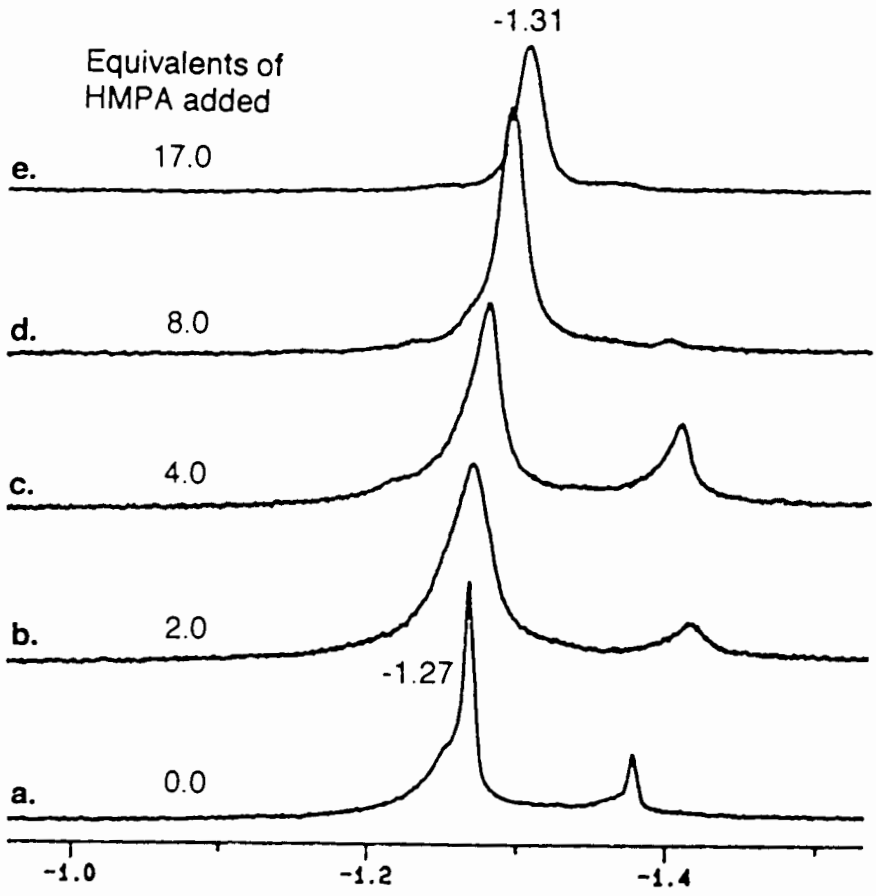


Figure II-10. Low temperature (-40 °C) ^{1}H-NMR spectra of a THF solution of $Me_2Cu(^{13}CN)Li_2$ with successive additions of HMPA.

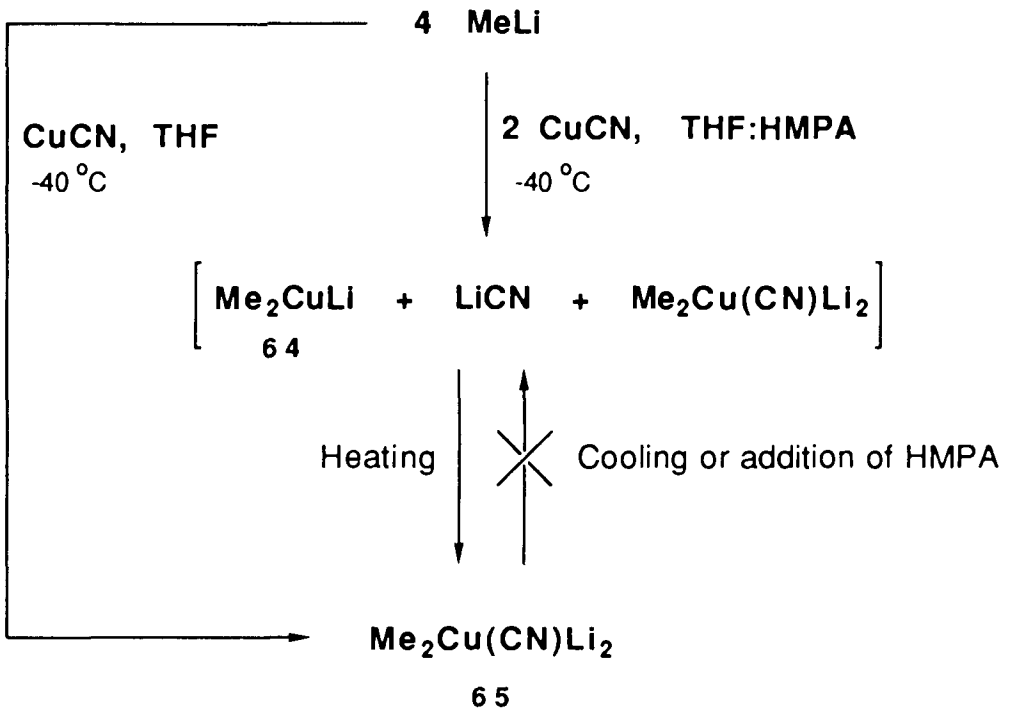
It has been proposed[74] that in lithium cuprates, because of the superior bridging capacity of Li^+ it is this ion rather than Cu (I) that is the determinant of structure. Formulations such as **66** and **68** (**Scheme II-5**) are alternative formulations for mixed higher order cyanocuprates that can rationalize the presence of Gilman cuprates and free lithium cyanide when higher order cuprates are prepared in the presence of HMPA. Initial capture of Li^+ by HMPA prior to cuprate formation may appreciably disrupt normal cuprate structure.

II.3. Conclusions

Detailed structural information was obtained through ^1H and ^{13}C NMR spectroscopic investigations of higher order cyanocuprates as well as the vinyl cyanocuprates obtained when these reagents are added to alkynes (Chapter I). It was revealed that both types of higher order cyanocuprates behave similarly with respect to coordination of the cyanide to copper when prepared in THF or THF containing HMPA.

If higher order cyanocuprates (or vinylcyanocuprates) are prepared in THF they are formed and exist with cyanide coordinated to copper. Addition of HMPA at this point does not displace the cyanide from copper.

When prepared in THF solutions containing HMPA higher order cuprates (and vinylcyanocuprates) exist as mixtures accompanied by the corresponding Gilman cuprates and free lithium cyanide (Bertz formulation, page 82). If the temperature of these solutions is increased, cyanide ligation to the copper occurs at the expense of the lower order cuprate. This process is not reversed when the temperature is lowered (**Scheme II-7**).



Scheme II-7. Formation of higher order cuprate 65, in THF and THF containing HMPA.

Thus, Professor Lipshutz is correct that higher order cyanocuprates are thermodynamic sinks of Gilman cuprates and lithium cyanide. HMPA can

interfere with the formation of higher order cyanocuprates if it is present during their formation.

II. 4. Experimental Section

II.4.1. General Methods (See also **Chapter I**)

MeLi was purchased form Aldrich and titrated according to the method of Watson and Eastham.[55] Labelled copper cyanide ($Cu^{13}CN$) was purchased from Cambridge Isotopes and transferred in a glove bag. THF-*d8* was purchased from Sigma and was dried over activated 3 A molecular sieves prior to use. The low temperature NMR spectra were recorded on a Bruker AMX-400 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded at 400.13 and 100.62 MHz, respectively and were referenced to THF, α= 68.4, β= 26.5 ppm for ^{13}C-NMR, and α= 3.75, β= 1.85 ppm for ^{1}H-NMR spectra.

Preparation of Me_2CuLi (64)

To a suspension of CuI (0.190 g, 1 mmol) in *d8*-THF (5 mL) at -40°C, was added dropwise a solution of MeLi (1.43 mL, 2 mmol) and stirred at this temperature for 45 min. After this time the CuI formed was removed by filtration through a fritted

glass filter at low temperature under argon using Schlenk techniques.[51] The clear yellow solution was cannulated into a dry 5 mm NMR maintained under argon at -40 °C and the spectra recorded.

Preparation of $Me_2Cu(^{13}CN)Li_2$ (65)

A 1.4 M solution of MeLi (1.43 mL, 2 mmol) was added dropwise to a cold (-40 °C) solution of $Cu^{13}CN$ (0.090 g, 1 mmol) in a 1:1 mixture (6 mL) of THF-HMPA (17 equivalents of HMPA) and stirred at this temperature for 1 hr. After this time an aliquot was transferred *via* cannula into a dry 5 mm NMR tube maintained at -40 °C under argon and the spectra recorded.

Preparation of $MeCu(^{13}CN)Li$ (56)

A 1.4 M solution of MeLi (0.72 mL, 1.0 mmol) was added dropwise to a solution of $Cu^{13}CN$ (0.090 g, 1 mmol) in a 1:1 mixture (6 mL) of THF-HMPA (17 equivalents of HMPA) maintained at -40 °C. After stirring at this temperature for 45 min. an aliquot was transferred *via* cannula into an NMR tube maintained at -40 °C under argon.

CHAPTER III

A New Method for the Synthesis of 1-Ethynyl Ethers.

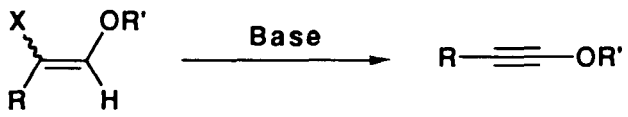
III.1. Introduction

During the study of stannylcupration of alkynyl ethers[75] (**Chapter I**) a ^{13}C labelled ethynyl ether (2-^{13}C-**5**) was required for mechanistic studies. A search of the literature revealed that this compound was not easily accessible by known procedures. Ethynyl ethers can be prepared[76] by dehydrohalogenation of halo vinyl ethers or haloacetals, addition-elimination procedures and 1,3- substitution of functionalized allenes.

A. Dehydrohalogenation

Base-induced elimination of hydrogen halide from 2-halo vinyl ethers[77] (**Scheme III-1**) or alcohol and hydrogen chloride from chloroacetals[78] (**Scheme III-2**) are the most common procedures for the preparation of alkynyl ethers. Commonly used bases are potassium hydroxide and sodium amide in liquid ammonia. When the former is used, the procedure involves relatively high temperatures which often cause decomposition of the desired product.[77b] Sodium amide in liquid ammonia is preferred for this dehydrohalogenation. Furthermore, sodium amide reacts with both the *cis* and the *trans* isomers of

the halo vinyl ethers, whereas potassium hydroxide does not react with the *trans* isomer.[77a,b]

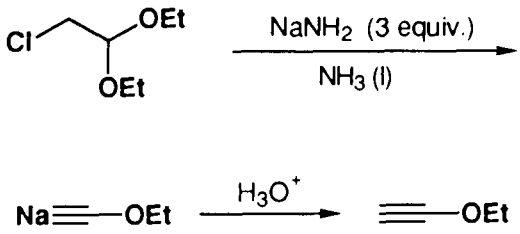


X: Cl. Br
R: H, alkyl, aryl
R': alkyl, vinyl, aryl

Base: KOH or $NaNH_2$ / NH_3 (l)

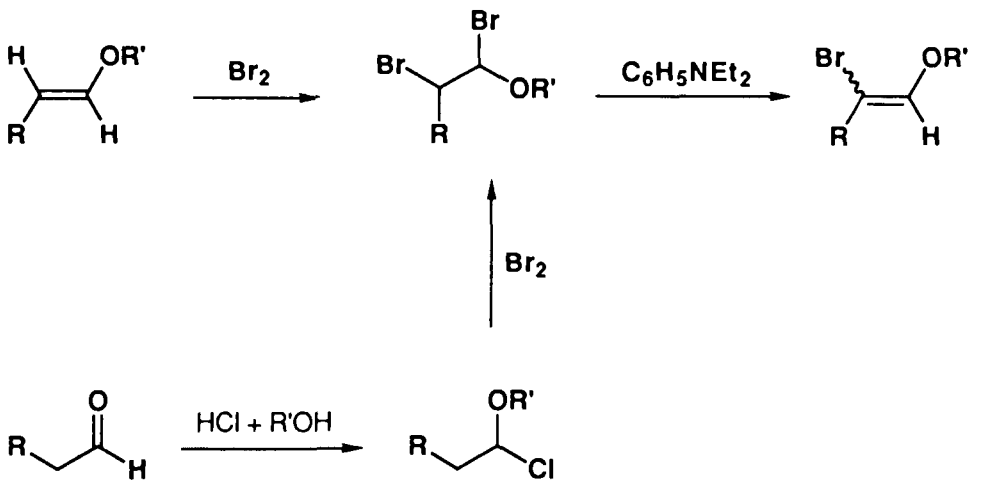
Scheme III-1. Preparation of acetylenic ethers by dehydrohalogenation of halo vinyl ethers.

Elimination of chloroacetals by sodium amide has been extensively used for the preparation of ethoxyethyne (**Scheme III-2**). In this procedure, acidification of the ethoxyacetylide intermediate must be done in the total absence of air because this derivative is pyrophoric. To avoid the hazard involved in this preparation, alternative procedures have been developed.[77e]

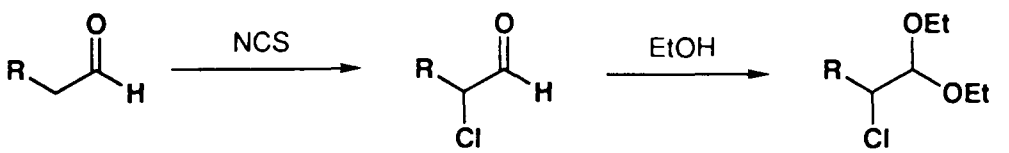


Scheme III-2. Preparation of acetylenic ethers by dehydrohalogenation of chloroacetals.

The principal routes for the preparation of the starting materials[79] for these dehydrohalogenations are represented in **Schemes III-3** and **III-4**. Halo vinyl ethers are usually obtained as a mixture of the *cis* and the *trans* isomers (**Scheme III-3**); because the isomer required for production of alkynyl ethers[76a] must have a *trans* relationship between the hydrogen and halogen to be abstracted (if KOH is used) (**Scheme III-1**), part of the precursor is wasted in this procedure.



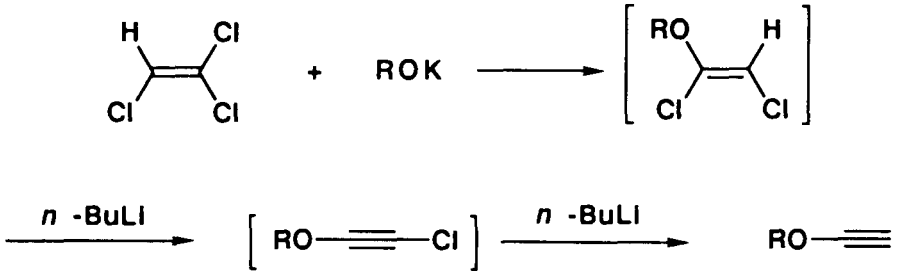
Scheme III-3. Preparation of 2-halo vinyl ethers .



Scheme III-4. Preparation of chloroacetals.

B. Addition-Elimination

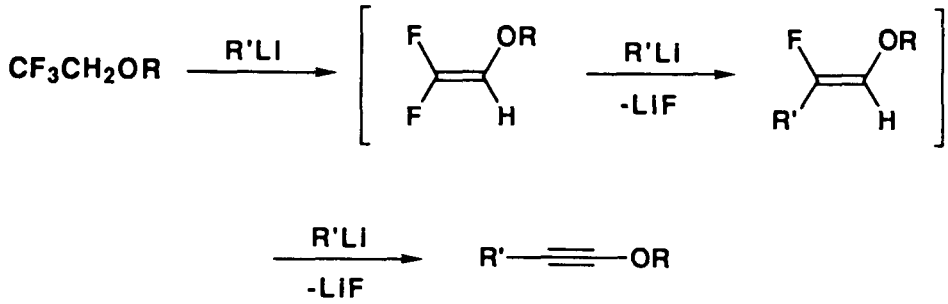
In the presence of potassium hydride alcohols react with trichloroethene to generate 1,2-dichloro vinyl ethers which can be converted to the corresponding alkoxyacetylides by butyllithium[80] (**Scheme III-5**). This method has the advantage that the procedure can be conducted as a "single-pot" reaction.



Scheme III-5. Preparation of 1-ethynyl ethers from trichloroethylene.[80]

In a similar process, phenylalkoxyacetylenes can be prepared from phenylacetylene and alkoxides.[81]

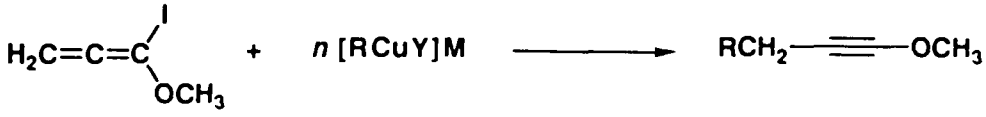
Substituted alkynyl ethers can be prepared by reaction of 2,2,2-trifluoroethyl ethers with alkyl lithiums. This involves an addition-elimination sequence[82] as described in **Scheme III-6**. This procedure is useful only for the synthesis of substituted alkynyl ethers and requires use of primary and secondary alkyllithiums.



Scheme III-6. Preparation of substituted alkynyl ethers from organofluorine reagents.[82]

C. 1,3-Substitution of allenes[83].

An alternative method for the preparation of substituted 1-alkynyl ethers is by reaction of 1-iodo-1-methoxypropadiene with cuprates. This organocopper (I)-induced 1,3-substitution reaction is useful for the preparation of alkynyl ethers with an alkenyl or alkynyl group in position 3 (**Scheme III-7**).



R = alkyl, vinyl, Ph, or C≡CR'
Y = Br (*n* = 1.0) or R (*n* = 0.5)
M = Li or MgX LiBr

Scheme III-7. Preparation of substituted alkynyl ethers from 1-iodo-1-methoxypropadiene.[83]

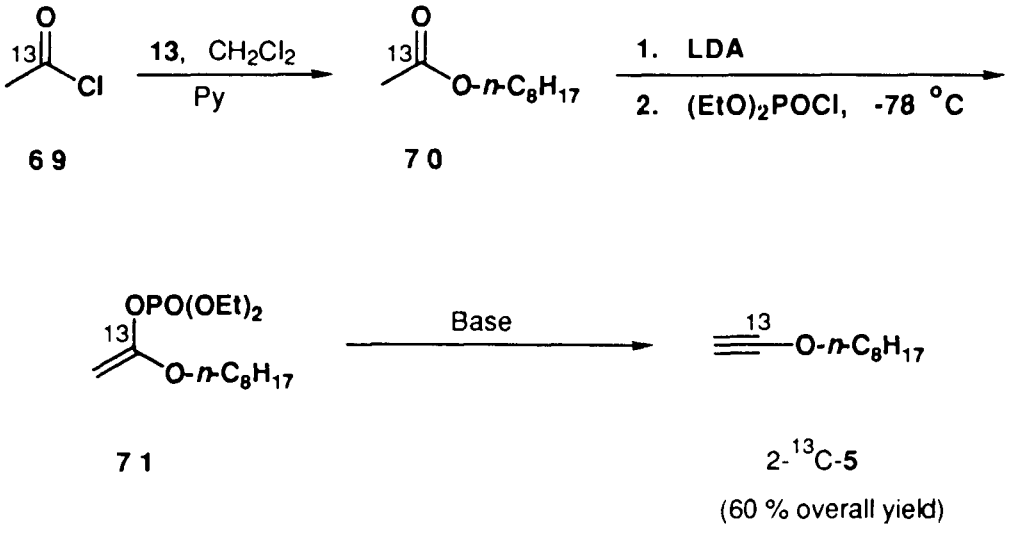
One of the limitations of the above procedures is that the strongly basic conditions precludes preparation of alkynyl ethers with labile functional groups (i.e. chlorides).

Application of any of these procedures for the synthesis of 1- or 2-^{13}C alkynyl ethers would require the stereo- and regiospecific preparation of any of the corresponding^{13}C-labelled starting materials which is cumbersome. Furthermore, the high cost of commercial sources of ^{13}C labelled materials requires shorter and more efficient procedures than those outlined above. For this reason a new and shorter procedure was investigated.

This chapter describes the development and optimization of a new method for the synthesis of 1-alkynyl ethers and its application to the preparation of ^{13}C labelled and functionalized alkynyl ethers that were not easily accessible *via* existing methodologies.

III.2. Results and Discussion

Due to the commercial availability of ^{13}C labelled acetyl chloride, **69**, the transformation of an acetate to an acetylenic ether was an attractive alternative for the preparation of a ^{13}C labelled alkynyl ether For this process, the transformation of an ester (**70**) to the corresponding enolphosphate (**71**) followed by *trans* -elimination was an obvious strategy which is analogous to Negishi's conversion of methyl ketones to terminal acetylenes[84] (**Scheme III-8**).



69 **70** **71**

2-^{13}C-**5**

(60 % overall yield)

Scheme III-8. Synthesis of 2-^{13}C- ethynyl octyl ether 5.

While the conversion of ketones or acetates to the corresponding enolphosphates are well known processes,[85] the presence of an alkoxy group in the latter (**71**) complicates the subsequent elimination reaction. Initial reactions involving treatment of octyl acetate **70**, with an equivalent of LDA followed by addition of diethylchlorophosphate in the presence of HMPA (1

equiv.) at -78 °C, gave the corresponding enol phosphate, **71**. "One-pot", reactions in which two more equivalents of LDA was added to **71** at -78 °C gave 70-80% of 1-octanol, **18**, and 10-20% of the desired octyl ethynyl ether, **5** (**Table III-1**, entry 3). Both products can be envisioned as arising from a 1,2-*trans* -elimination of **71** (**Scheme III-9**, paths **a** and **b**). It has been reported[86] that elimination of alkoxides from *trans* -β-lithio vinyl ethers is facile even at -100 °C.

When ester **70** was treated, at -78 °C, with 3 equiv of LDA, followed by addition of diethylchlorophosphate in HMPA (8 equiv.), the principal product, **72**, (58%), arose from 1,2-phosphate migration (**Scheme III-9**, path **c**) (**Table III-1**, entry 4). Interestingly, higher amounts of HMPA favour 1,2-migration over elimination in the corresponding *trans* -alkoxyvinyl lithium species. 1,2-Phosphate migration has been studied by Weimer in cyclic ketones,[87] lactones and α-substituted esters.[88] Reported yields for conversion of an ester to the corresponding β-carboalkoxy diethylphosphonate are in the range of 0-26 %. The use of KTMP or *t* -BuLi in the presence of HMPA offers significant advantages for promotion of this process (**Table III-1**, entries 5 and 6).

The effect of base structure on the course of the elimination was investigated. Sterically undemanding bases such as NaH and MeLi afforded only elimination of alkoxide (**Table III-1**, entries 1 and 2).

Sterically demanding bases such as LDA or *t* -BuLi preferentially abstracted the hydrogen *trans* to the alkoxy group, to afford alkoxide elimination or phosphate migration (**Table III-1**, entries 3-5). This might be promoted by a

Table III-1. Effect of Base on Efficiency of Conversion of Enolphosphate 71 to Alkynyl Ether 5.*

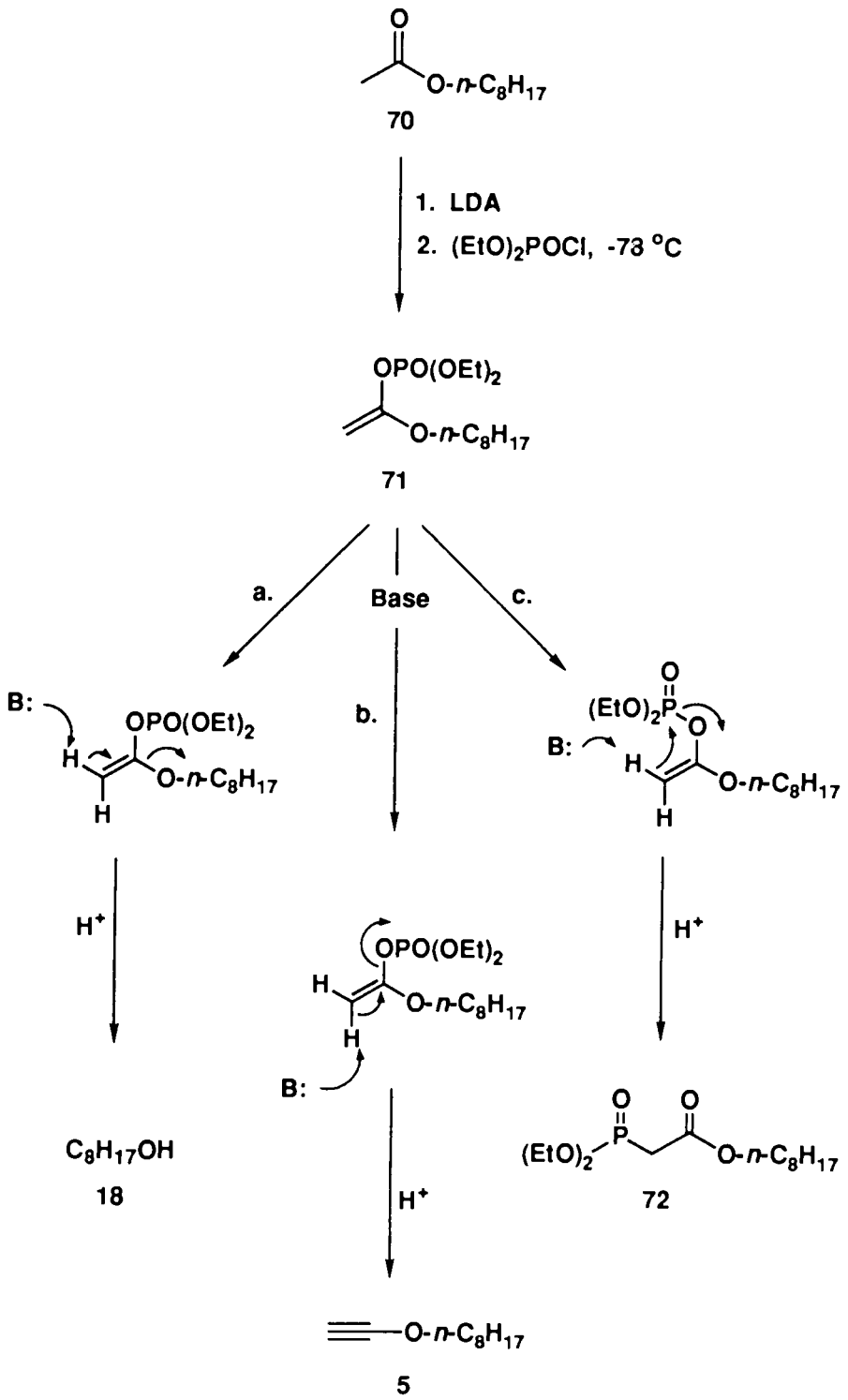
Entry	Base	Products (%)[a]		
		5	**18**	**72**
1	NaH	-	100	-
2	MeLi	-	100	-
3	LDA[b]	15	80	5
4	LDA/ HMPA[c]	24	-[d]	58
5	*t*-BuLi / HMPA[c]	16	10	74
6	KTMP / HMPA[c]	28	7	55
7	*t*- BuLi/ TMEDA	27	13	-[e]
8	*t*- BuLi/ HMPA	35	5	60
9	*t*-BuLi	40	45	5

* All reactions were performed in THF at -78 °C. Reactions in entries 3-5 were carried out in "one pot" procedure. In entries 1,2, 6-9 enolphosphate **71** was first isolated and then treated with two equivalents of base.

[a] Calculated by GC analysis. [b] 1 equiv.of HMPA was used in this reaction.

[c] 8 equiv. of HMPA were used . [d] Octyl acetate was produced in this reaction (24%).

[e] 60% of octyl acetate was produced.



Scheme III-9. Synthesis of 2-^{13}C- ethynyl octyl ether 5.

proximity effect involving co-ordination of the lithium base[89] with the phosphate oxygen (**Figure III-1**).

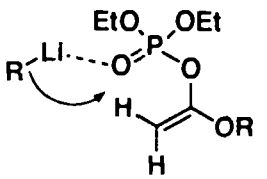


Figure III-1. Coordination of a lithium base RLi with phosphate group

Superior yields of **5** were obtained if enolphosphate, **71**, was first isolated, then treated with base (**Table III-1**, entries 8 and 9). Only in the case of *t*-BuLi in the absence of HMPA were reasonable yields of **5** obtained from **71** (**Table III-1**, entry 9). Lowering the temperature of the elimination from -78 °C to -100 °C in the *t*-BuLi promoted process further increased the yields (**Table III-2**, entry 2).

When pentane[90] was used as a solvent instead of THF, in the reaction of **71** with *t*-BuLi, the yield of **5** improved from 46 to 55 % (**Table III-2**, entry 3). It is possible that the presence of remanent LiCl, formed in the first step of the sequence, could promote the formation of a chelate[91], as depicted in **Figure III-2**, favoring for steric reasons abstraction of the proton *trans* to the alkoxy group . When enolphosphate, **71**, was dissolved in pentane some LiCl precipitated from the solution. At -100 °C it was required to have at least 10 % of THF in the reaction mixture to maintain **71** in solution, this co-solvent might have maintained some LiCl in solution.

Yields of **5** were marginally improved when LiCl was removed from enolphosphate, **71**, prior to treatment with *t* -BuLi (**Table III-2,** entry 4). This can be executed without chromatography by dissolution of the crude quenched reaction mixture (from the preparation of **71**) in pentane and filtration of the LiCl precipitate before subjecting **71** to elimination. When this procedure was executed prior to treatment of **71** with *t*-BuLi (2.2 equivalents) at -100 °C, followed by warming of the reaction mixture to -30 °C before quenching, yields of **5** increased from 55% to 65% (**Table III-2**, entries 3 and 4).

Table III-2. Effect of Solvent and Temperature on Conversion of Enol Phosphate 71 to Octyl Ethynyl Ether 5 with *t*-BuLi.

Entry	Temperature (°C)*	Solvent	% Yield[a]
1	-78	THF	40
2	-100	THF	46
3	-100	Pentane[b]	55
4	-100	Pentane[b,c]	65

* Internal temperature. [a] Yield of chromatographically isolated compound [b] 10% of THF was used in this case. [c] This sample was LiCl free

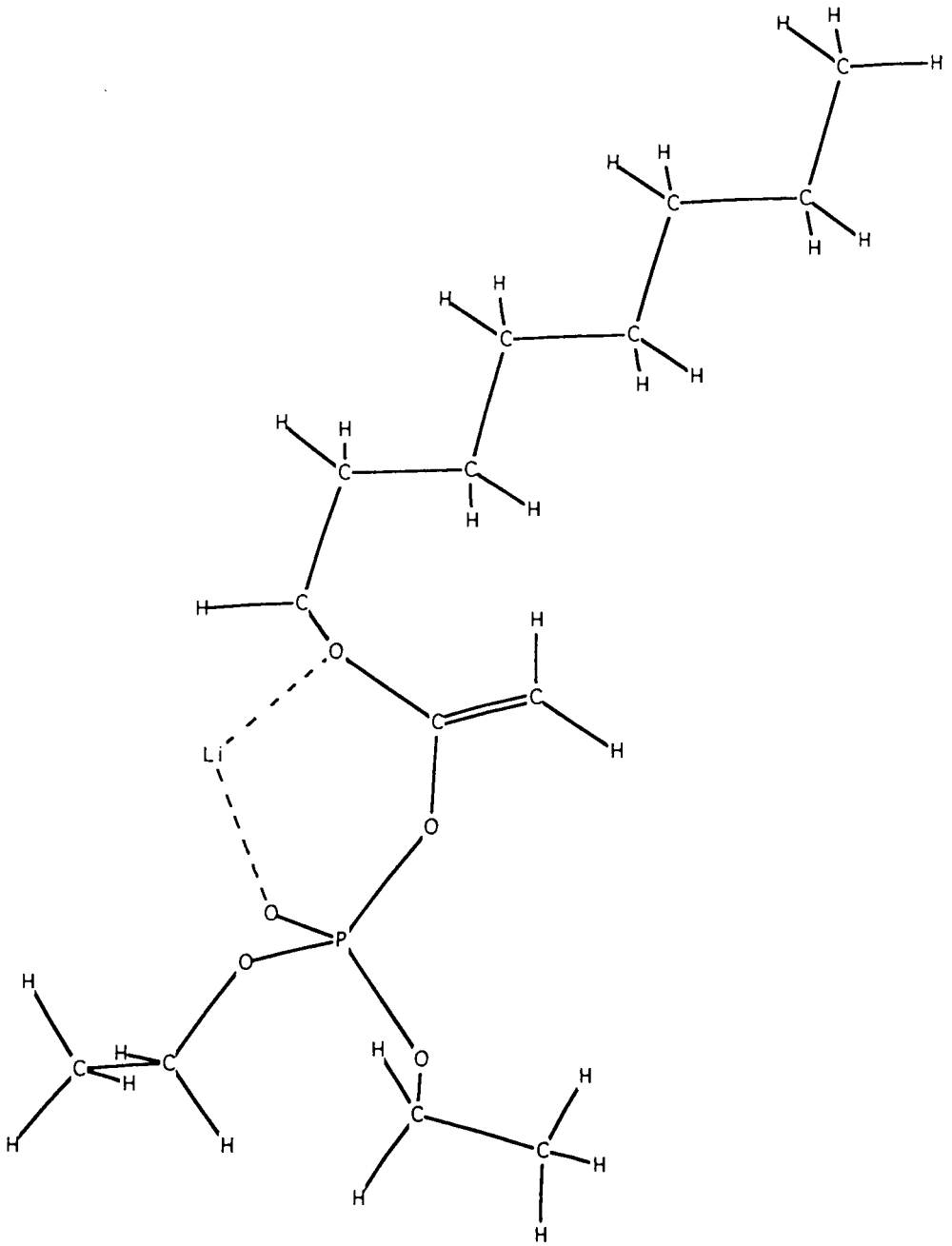
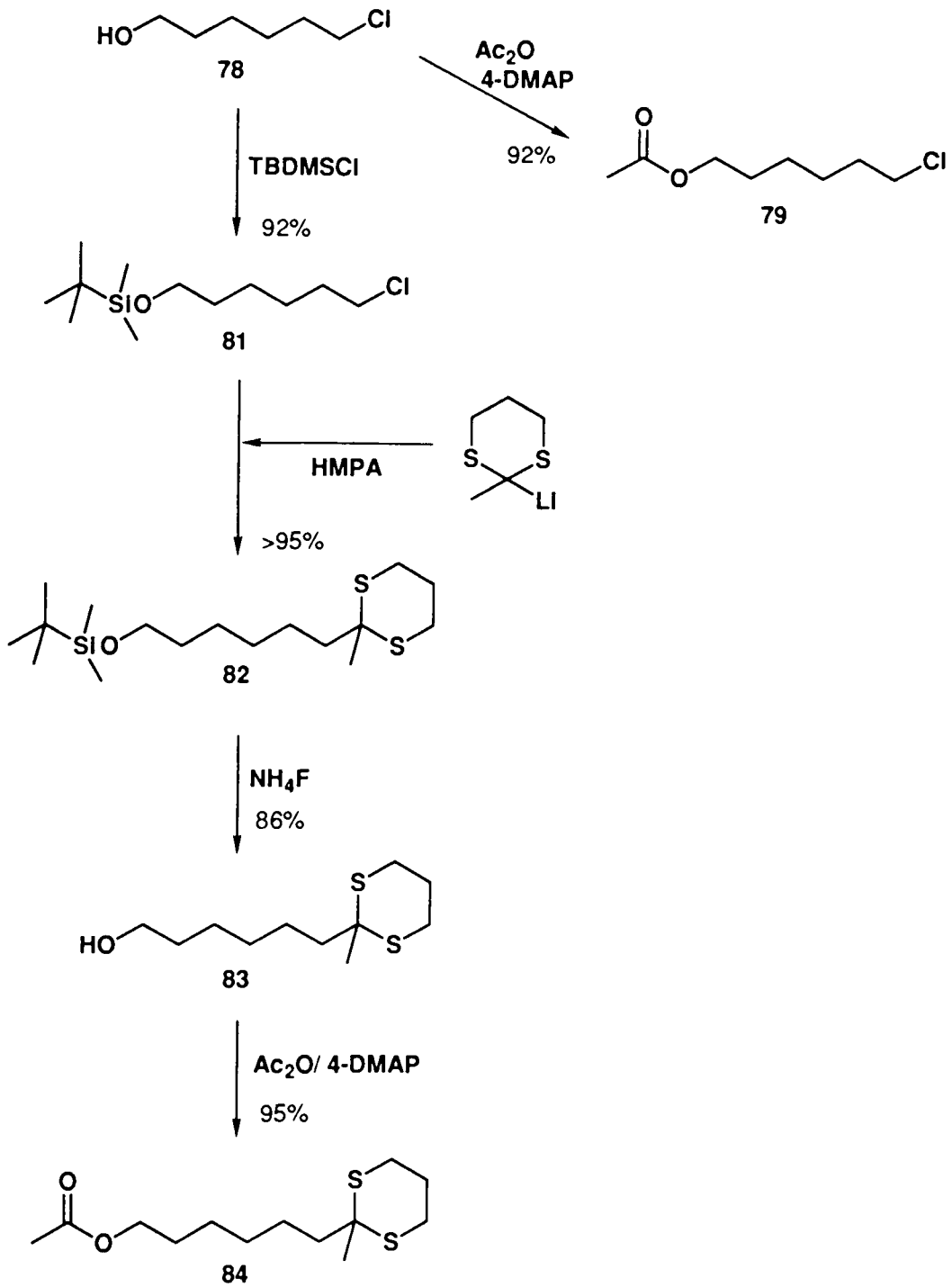


Figure III-2. Model of a chelate complex formed between enolphosphate **71** and LiCl.

To demonstrate that the method is applicable to a variety of substrates, the transformation of several esters into the corresponding alkynyl ethers was performed. Acetates were prepared from the corresponding alcohols by reaction with acetic anhydride and 4-dimethylaminopyridine, according to Steglich.[92] Acetates **79** and **84** were prepared according to **Scheme III-10**.

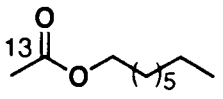
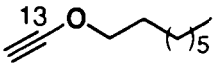
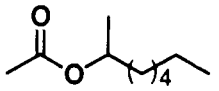
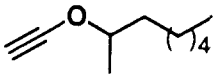
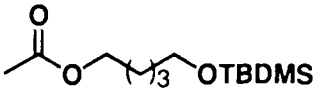
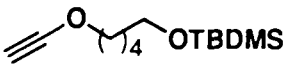
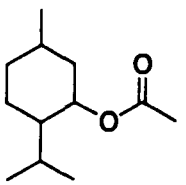
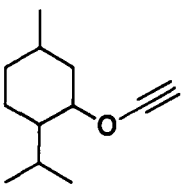
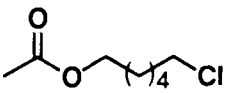
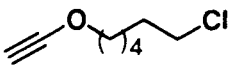
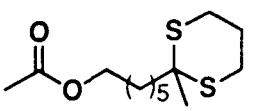
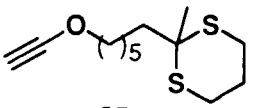
The method gave reproducible and high yields with the selection of substrates chosen (**Table III-3**). The yields obtained with this method were similar to those using reported procedures[57] [compare yields of compounds **5**, **37** and **85** (with **42**), **Table III-3** and **Scheme I-16**]

Several attempts to obtain alkynyl ether **80** by treatment of the corresponding enolphosphate of acetate **79** with *t*-BuLi (2.1 equiv) at -100 °C (internal temperature) followed by warming to -30 °C and treatment with *i*-PrOH resulted in an inseparable mixture (ca 8:2) of **80** and 7,7-dimethyl octyl ethynyl ether from nucleophilic displacement of the primary chloride of **80** by *t*-BuLi. Presumably, the later reaction was favoured by the increase in the reaction mixture temperature from -100 to -30 °C. Treatment of the enolphosphate of **79** with 1.8 equivalents of *t*-BuLi at -100 °C followed by treatment with *i*-PrOH at -85 °C (internal temperature) resulted in a clean formation of **80** (**Table III-3**, entry 5).



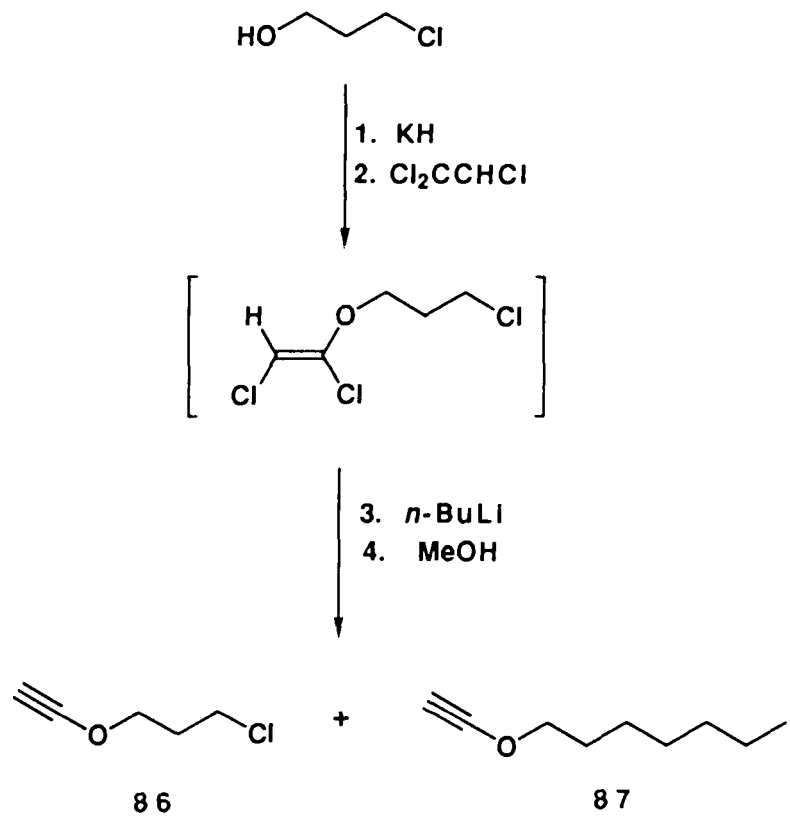
Scheme III-10. Preparation of Acetates 79 and 84.

Table III-3. Transformation of Acetates to Acetylenic Ethers

Entry	Acetate	Acetylenic Ether	% Yield[a]
1	 **70**	 **5**	65
2	 **73**	 **74**	68
3	 **75**	 **37**	63
4	 **76**	 **77**	64
5	 **79**	 **80**	55
6	 **84**	 **85**	57

[a] Isolated yield.

The developed procedure offers significant advantages over previously reported methods for the preparation of 1-ethynyl ethers. Thus, several attempts to obtain 3-chloropropyl ethynyl ether **86**, from the reaction of the corresponding alcohol with trichloroethylene, according to Moyano's procedure[57] (**Scheme III-5**), resulted in the formation of *n*-heptyl ethynyl ether **87** as the major product, obtained as a result of a substitution of the primary chloride by *n*-BuLi (**Scheme III-11**).



Scheme III-11.

III.3. Conclusion

This new method proved to be generally applicable to a variety of functionalized substrates offering access to alkynyl ethers that were not accessible by the existing procedures. It was possible to obtain ^{13}C-labelled alkynyl ethers (**5**) and 1-ethynyl ethers containing labile groups such as a primary chloride (**80**) in good yields (**Table III-3**, entries 1 and 5).

The ability to perform these syntheses as a "two-pot" procedure provides easier access to a variety of 1-alkynyl ethers compared to previously available procedures.

III.4. Experimental Section

III. 4. 1. General Methods (See Experimental Section **Chapter I**). Diethylchlorophosphate was purchased from Sigma and stored over activated 4 A molecular sieves. Diisopropylamine was freshly distilled from sodium under argon atmosphere.

Preparation of 2-^{13}C-octyl acetate (70).

2-^{13}C-Acetyl chloride (0.7 mL, 9.8 mmol) was added dropwise to a cold solution (0 °C) of octanol (1.6 g, 12 mmol) and pyridine (1.0 mL, 12 mmol) in CH_2Cl_2 (6 mL). After stirring at 0 °C for 3 h the solution was washed with dilute HCl, $NaHCO_3$ (sat) and water and the organic extracts dried over anhyd. $MgSO_4$. The product was purified by filtration through a silica Gel pad and eluted with CH_2Cl_2. After evaporation of solvent 1.64 g (97% yield) of product was obtained.

III.4.2. Typical Procedure. Preparation of 2-^{13}C-ethynyl octyl ether (5):

A solution of 2-^{13}C-octyl acetate (1.33 g., 7.7 mmol) in THF (2 mL) was added to a cold (-78°C) THF solution (5 mL) of LDA (prepared from 1.15 mL, 8.2 mmol of diisopropylamine and 3.27 mL, 8.0 mmol of *n*-BuLi, 2.45 M) and the mixture stirred for 45 min. A solution of diethylchlorophosphate (2.2 mL, 15.4 mmol) in HMPA (2 mL) was then added and the mixture stirred at this temperature for 3 h.

The reaction mixture was treated with 4 mL of a THF:water mixture (1:1), warmed to room temperature and extracted with ether (2 X 20 mL). The organic extracts were washed with water (2 X 10 mL), NaOH 0.3 M (2 X 10 mL), water (10 mL) and dried over anhyd. $MgSO_4$. After concentration *in vacuo* the remaining oil was dissolved in pentane (50 mL) and the LiCl removed by filtration through a fritted glass. This crude solution was used without further purification.

The pentane solution obtained (~40 mL) was cooled to -100°C (internal temperature) using a liquid nitrogen-ether bath and *tert* -BuLi (9.25 mL, 15.7 mmol, 1.7 M in pentane) was added dropwise. The temperature was allowed to rise to -30°C and the reaction mixture treated with isopropanol (2-3 mL) and water (2 mL). The mixture was extracted with ether (2 X 20 mL), the extracts washed with water (3 X 20 mL) and dried over anhyd. $MgSO_4$. After concentration *in vacuo* the crude product was dissolved in pentane and filtered through a silica Gel pad (pretreated with 2% Et_3N) and eluted with pentane. Concentration *in vacuo* affored 0.91 g of 2-^{13}C-**1** (60 % overall yield), b.p. 50-51 °C @ 1.75 mm Hg.

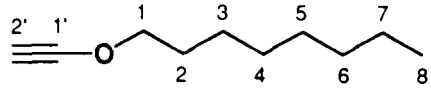
Acetylenic ethers were purified either by distillation or filtration through a silica Gel pad (2% Et_3N).

General Procedure for the Preparation of Acetates.[92]

To a cold (0 °C) THF solution (25 mL) of an alcohol (75 mmol) was sequentially added triethylamine (8.2 mL, 102 mmol), acetic anhydride (10.6 mL, 102 mmol) and 4-dimethylaminopyridine (0.73 g, 6 mmol) and stirred for 3-4 h. After this

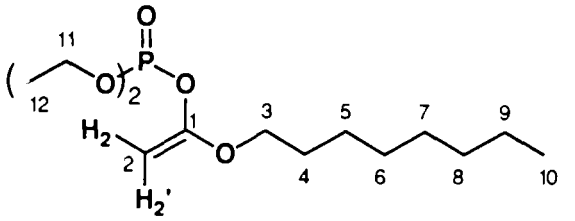
time the reaction mixture was quenched by the addition of water (10 mL) and extracted with ether (2 X 20 mL). The organic extracts were washed with water (2 X 15 mL), $NaHCO_3$ (saturated solution) water (10 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the product purified by distillation.

Octyl Ethynyl Ether (5):



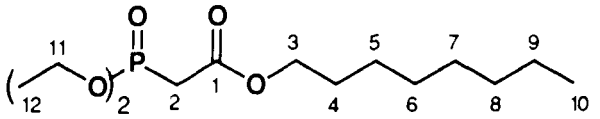
[B.p. 50-51 °C @ 1.75 mm Hg (bulb to bulb distillation)]; ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.88 (t, 3H, **H8**), 1.30 (br s, 10H, **H3**, **H4**, **H5**, **H6**, **H7**), 1.51 (s, 1H, **H2'**), 1.76 (m, 2H,**H2**), 4.07 (t, 2H, J = 7Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (**C8**), 22.6 (**C7**), 25.3 (**C6**), 26.0 (**C2'**), 28.6 (**C5**), 29.1 (**C3**, **C4**), 31.7 (**C2**), 79.0 (**C1**), 91.3 (**C1'**); IR (film) 3328, 2930, 2856, 2152, 1467, and 1094 cm^{-1}; MS (EI), *m/e* (rel. intensity) 112 (M^+-C_2H_2O, 3), 97 (4), 83 (15), 71 (94), 57 (100); Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.62; H, 11.82.

1-[(Diethoxyphosphinyl)oxyl]-vinyl octyl ether (71):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J = 7 Hz, **H10**), 1.20-1.32 (br s, 10H, **H5**, **H6**, **H7**, **H8**, **H9**), 1.35 (t, 6H, J = 7 Hz, **H12**), 1.70 (m, 2H, **H4**), 3.52 (d, 1H, J = 3.5 Hz, **H2**), 3.77 (t, 2H, J = 6.5 Hz, **H3**), 3.85 (dd, 1H, J = 3.5 Hz, $^4J_{P\text{-}H}$= 2.0 Hz, **H2'**), 4.19 (m, 4H, **H11**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (**C10**), 16.0 (**C12**), 22.6 (**C9**), 25.8 (**C8**), 28.6 (**C7**), 29.1 (**C6**), 29.2 (**C5**), 31.7 (**C4**), 64.5 (**C3**), 67.6 (**C2**), 69.3 (**C11**), 157.0 (**C1**); IR (film) 2928, 2856, 1669, 1243, 1166 and 1036 cm^{-1}; MS (CI) *m/e* (rel. intensity) 309 (M+1, 17), 197 (100), 155 (83).

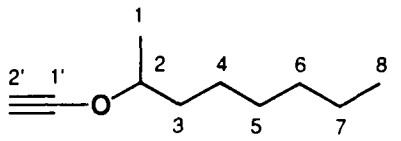
Octyl α-(Diethoxyphosphinyl)acetate (72):



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, 3H, J =7 Hz, **H10**), 1.15-1.27 (m, 10 H, **H5**, **H6**, **H7**, **H8**, **H9**), 1.30 (t, 6H, J =7 Hz, **H12**), 1.60 (m, 2H, **H4**), 2.95 (d, 2H, $^2J_{P\text{-}H}$ = 22 Hz, **H2**), 4.10 (t, 2H, J = 7 Hz, **H3**), 4.15 (dq, 4H, J = 7.0 Hz, $^3J_{P\text{-}H}$ = 7.0 Hz, **H11**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 13.9 (**C10**), 16.3 (**C12**), 22.5

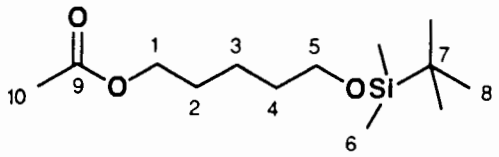
(**C9**), 25.8 (**C8**), 28.5 (**C7**), 29.1 (**C6**), 31.7 (**C5**), 33.7 (**C4**), 35.1 (**C2**), 62.6 (**C3**), 65.7 (**C11**), 165.8 (**C1**); IR (film) 2930, 2857, 1737, 1272 and 1027 cm^{-1}; MS (CI) *m/e* (rel intensity) 309 (M+1, 100).

2-Octyl Ethynyl Ether (74):



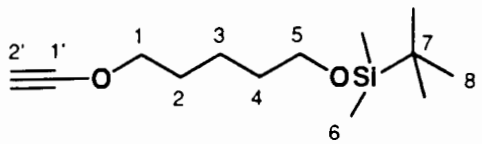
(Eluted with Hexanes); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, *J* =7.0 Hz, **H8**), 1.20-1.30 (m, 6H, **H5**, **H6**, **H7**), 1.36 (d, 3H, *J* =7.0 Hz, **H1**), 1.45-1.58 (m, 2H, **H4**), 1.54 (s, 1H, **H2'**), 1.70-1.80 (m, 2H, **H3**), 4.10-4.20 (m, 1H,**H2**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (**C8**), 19.1 (**C1**), 22.5 (**C7**), 25.1 (**C6**), 27.3 (**C2'**), 29.0 (**C5**), 31.7 (**C4**), 35.3 (**C3**), 85.7 (**C2**), 89.8 (**C1'**); IR (film) 3331, 2928, 2858, 2145 and 1105 cm^{-1}; MS (EI) *m/e* (rel. intensity) 112 (M^{+}-C_2H_2O, 29), 83 (56), 70 (100), 55 (67); Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.12; H, 12.00.

5-(*tert* -Butyldimethylsiloxy) Pentyl Acetate (75):



[B.p.= 87-90 °C @ 0.5 mm Hg (bulb to bulb distillation)]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H, **H6**), 0.87 (s, 9H, **H8**), 1.40 (m, 2H, **H3**), 1.54 (m, 2H, **H4**), 1.63 (m, 2H, **H2**), 3.60 (t, 2H, *J* = 6.5 Hz, **H5**), 4.05 (t, 2H, *J* = 6.7 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.3 (**C6**), 18.3 (**C7**), 20.9 (**C10**), 22.3 (**C3**), 25.9 (**C8**), 28.5 (**C4**), 32.4 (**C2**), 62.9 (**C5**), 64.5 (**C1**), 171.0 (**C9**); IR (film) 2930, 2858, 1743, 1240, 1098, 836, 776 cm^{-1}; MS *m/e* (rel. intensity) 261 (M^+, 3), 203 (39), 159 (26), 117 (100); Anal. Calcd. for $C_{13}H_{28}SiO_3$: C, 59.95; H, 10.84. Found, C, 60.06; H, 10.66.

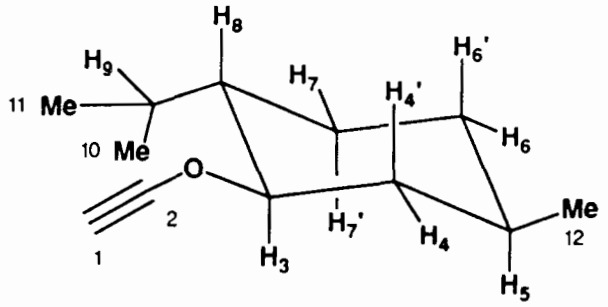
5-(*tert* -Butyldimethylsiloxy) Ethynyl Ether (37):



[B.p.= 67-74 °C @ 0.25 mm Hg (bulb to bulb distillation)]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H, **H6**), 0.86 (s, 9H, **H7**), 1.42 (m, 2H, **H3**), 1.50 (s, 1H, **H2'**), 1.54 (m, 2H, **H4**), 1.76 (m, 2H, **H2**), 3.60 (t, 2H, *J* = 7 Hz, **H5**), 4.05 (t, 2H, *J* = 7 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6) δ -5.3 (**C6**), 18.3 (**C7**), 21.7 (**C3**), 25.9 (**C8**), 26.1 (**C2'**), 28.4 (**C4**), 32.2 (**C2**), 62.8 (**C5**), 78.9 (**C1**), 91.2 (**C1'**); IR (film)

3330, 2954, 2858, 2153, 1256 and 1099 cm^{-1}; MS (EI), *m/e* (rel. intensity) 201(M^+-C_2H_2O, 1), 143 (37), 129 (17), 115 (11), 99 (56), 75 (100); Anal. Calcd. for $C_{13}H_{26}SiO_2$: C, 64.41; H, 10.81. Found: C, 64.28; H, 10.89.

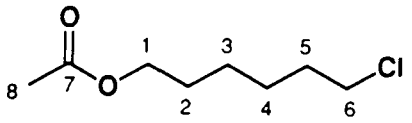
Menthyl Ethynyl Ether (77).



(Eluted with hexanes);^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, 3H, *J* =7.0 Hz, **H11**)*, 0.92 (d, 3H, *J* =7.0 Hz, **H10**)*, 0.96 (d, 3H, *J* =7.0 Hz, **H12**), 0.85-1.05 (m, 2H, **H6**, **H6'**), 1.20 (ddd, 1H, *J*=12, 12, 12 Hz, **H4'**),1.38-1.48 (m, 2H, **H8**, **H5**), 1.51 (s, 1H, **H1**), 1.63-1.72 (m, 2H, **H7**, **H7'**), 2.14 (qqd, 1H, *J*=7.0, 7.0, 3.0 Hz, **H9**), 2.28 (dddd, 1H, *J* =12.0, 4.0, 4.0, 2.0 Hz, **H4**), 3.86 (ddd, 1H, *J* =12.0, 12.0, 4..0 Hz, **H3**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 16.3 (**C11**)*, 20.5 (**C10**)*, 21.9 (**C12**), 23.5 (**C6**), 26.0 (**C5**)#, 27.1 (**C1**), 31.6 (**C9**)#, 34.0 (**C7**), 39.4 (**C4**), 46.8 (**C8**), 88.3 (**C3**), 89.8 (**C2**); IR (film) 3331, 2145 and 1102 cm^{-1}; MS (EI) *m/e* (rel. intensity) 138 (M^+-C_2H_2O, 42), 123 (27), 95 (100), 81 (81); Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.39; H, 11.73.

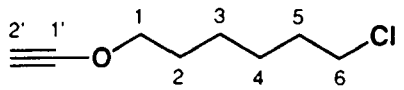
* # These Assigments are not definitive.

6-Chloro Hexyl Acetate (79):



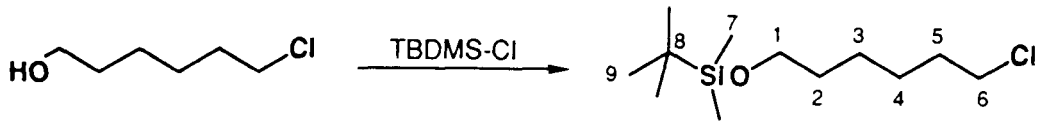
[92% Yield. B.p.= 60-68 °C @ 0.75 mm Hg (bulb to bulb distillation)]; ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 0.31-0.95 (m, 8H, **H2**, **H3**, **H4**, **H5**), 2.02 (s, 3H, **H8**), 3.54 (t, 2H, 7 Hz, **H6**), 4.05 (t, 2H, 7 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 20.9 (**C8**), 25.3 (**C4**), 26.5 (**C3**), 28.5 (**C5**), 32.5 (**C2**), 44.8 (**C6**), 64.3 (**C1**), 171.0 (**C7**); IR (film) 2940, 2862, 1738, 1243, 1050 cm^{-1}; Anal Calcd. for $C_8H_{15}O_2Cl$: C, 53.78; H, 8.46. Found: C, 53.77; H, 8.49.

6-Chloro Hexynyl Ethynyl Ether (80):



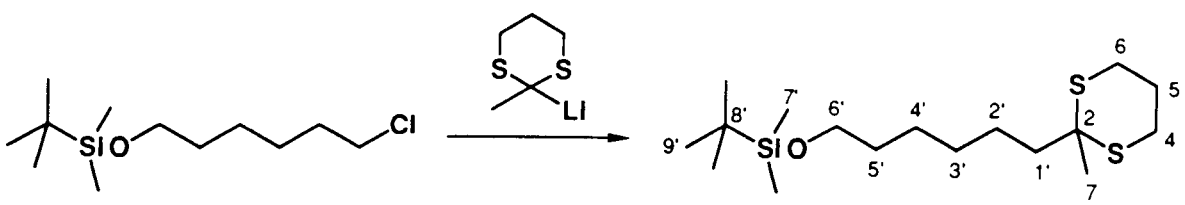
(Eluted with pentane); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.35-1.50 (m, 4H, **H3**, **H4**), 1.53 (s, 1H, **H2'**), 1.70-1.83 (m, 4H, **H2**, **H5**), 3.53 (t, 2H, *J* =7.0 Hz, **H6**), 4.07 (t, 2H, *J* =7.0 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 24.7 (**C4**), 26.2 (**C2'**), 26.4 (**C3**), 28.5 (**C5**), 32.4 (**C2**), 44.8 (**C6**), 78.7 (**C1**), 91.1 (**C1'**); IR (film) 3321, 2936, 2862, 2152, 1468, 1120 cm^{-1}; MS (EI) *m/e* (rel. intensity) 118 (M^{+}-C_2H_2O, 21), 82 (42), 69 (25), 55 (31), 43 (100); Anal Calcd. for $C_8H_{13}OCl$: C, 59.81; H, 8.16. Found: C, 59.97; H, 8.33.

Preparation of 6-Chlorohexyl *tert* -butyldimethylsilyl ether (81):



To a DMF solution (14 mL) of 6-chlorohexanol (4.5 g, 33 mmol) was added 5.6 g of imidazole (7.9 mmol) and 6 g of *tert*-butyldimethylsilylchloride (40 mmol) and stirred at room temperature overnight. The reaction mixture was quenched by addition of water (10 mL) and extracted with ether (2 X 25 mL). The organic extracts were dried over $MgSO_4$ and the mixture concentrated *in vacuo*. The concentrate was purified by distillation to give 7.6 g (92% yield) of product. [B.p.= 62-68 °C @ 0.6 mm Hg (bulb to bulb distillation)]; ^{1}H-NMR($CDCl_3$, 400 MHz) δ 0.03 (s, 6H, **H7**), 0.87 (s, 9H, **H9**), 1.30-1.55 (m, 6H, **H3**, **H4**, **H5**), 1.77 (m, 2H, **H2**), 3.53 (t, 2H, *J* =7.0 Hz, **H6**), 3.60 (t, 2H, *J* =7 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.3 (**C7**), 18.3 (**C8**), 25.2 (**C4**), 26.0 (**C9**), 26.7 (**C3**), 32.7 (**C2**, **C5**), 45.0 (**C6**), 63.0 (**C1**); IR (film) 2935, 2858, 1101, 836 and 775 cm^{-1}; Anal. Calcd. for $C_{12}H_{27}SiOCl$: C, 57.45; H, 10.85. Found: C, 57.67; H, 11.09.

Preparation of 2-[6'-(*tert* -Butyldimethylsiloxy)hexyl]-2-methyl-1,3-dithiane (82):



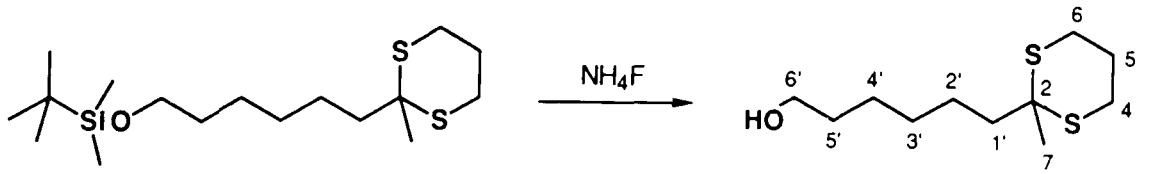
82

To a cold (-40 °C) THF solution (85 mL) of 2-methyl-1,3 dithiane, **44**, (4.03 g, 30 mmol) was added dropwise 13.4 mL of *n*-BuLi (32 mmol) and the reaction was allowed to warm to -15 °C over 2 h. After this time the mixture was cooled to -78 °C and 5.52 g (30 mmol) of 6-chlorohexyl *tert* -butyldimethylsilyl ether (**81**) in THF (10 mL) added dropwise, followed by the addition of HMPA (6 mL) after which the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of NH_4Cl (10 mL sat. solution) and extracted with ether (3 X 30 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 10.02 g of residue. GC analysis showed a purity of 100%. The product was taken to the next step without further purification.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H, **H7'**), 0.85 (s, 9H, **H9'**), 1.22-1.38 (m, 4H, **H3'**, **H4'**), 1.42-1.55 (m, 4H, **H2'**, **H5'**), 1.61 (s, 3H, **H7**), 1.78-1.98 (m, 4H, **H1'**, **H5**), 2.80-2.85 (m, 4H, **H4**, **H6**), 3.59 (t, 2H, J = 6.5 Hz, **H6'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ -5.2 (**C7'**), 25.7 (**C3'**)*, 25.5 (**C5**), 29.6 (**C4'**)*, 26.0 (**C9'**), 26.5 (**C4**, **C6**), 27.8 (**C7**), 24.5 (**C2'**),32.8 (**C5'**), 41.7 (**C1'**), 49.3 (**C2**), 63.2 (**C6'**); IR (film) 2932, 2857, 1255, 1099, 835 and 775 cm^{-1}; MS (EI) m/e (rel. intensity) 291 (M^+ - *t*-Bu, 38), 217 (19), 147 (24), 133 (67).

* These assignments are not definitive.

Preparation of 2-[6'-(Hydroxy)hexyl]-2-methyl-1,3-dithiane (83):



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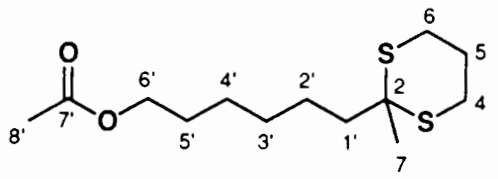
Same procedure as for preparation of compound **41** (Chapter I, pagX) was followed (86% yield) Purified by column chromatography (hexanes: ether, 8:2 to 6:4).

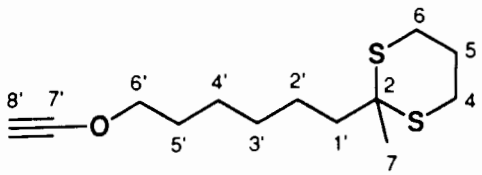
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.34-1.50 (m, 7H, **H2'**, **H3'**, **H4'**, OH), 1.57 (m, 2H, **H5'**), 1.60 (s, 3H, **H7**), 1.86-1.96 (m, 4H, **H1'**, **H5**), 2.83 (m, 4H, **H4**, **H6**), 3.63 (t, 2H, *J*= 7.0 Hz, **H6'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 24.4 (**C2'**), 25.4 (**C5**), 25.6 (**C3'**), 26.5 (**C4**, **C6**), 27.8 (**C7**), 29.6 (**C4'**), 32.7 (**C5'**), 41.7 (**C1'**), 49.3 (**C2**), 62.9 (**C6'**); IR (film) 3370, 2932, 1275, 1048 cm^{-1}; Anal. Calcd. for $C_{11}H_{22}S_2O$: C, 56.36; H, 9.46. Found: C, 56.30; H, 9.61

2-[6'-(Acetoxy) hexyl]-2-methyl-1,3-dithiane (84):



Purified (95% yield) by column chromatography, pentane:ether 8:2); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.30-1.42 (m, 4H, **H2'**, **H3'**), 1.43-1.53 (m, 2H, **H4'**), 1.61 (s, 3H, **H7**), 1.63 (m, 2H, **H5'**), 1.85-1.91 (m, 2H, **H1'**), 1.92-2.00 (m, 2H, **H5**), 2.05 (s, 3H, **H8'**), 2.80-2.90 (m, 4H, **H4**, **H6**), 4.05 (t, 2H, J = 7 Hz, **H6'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 20.9 (**C8'**), 24.3 (**C2'**), 25.4 (**C3'**), 25.8 (**C5**), 26.5 (**C4**, **C6**), 27.8 (**C4'**), 28.5 (**C7**), 29.4 (**C5'**), 41.7 (**C1'**), 49.2 (**C2**), 64.4 (**C6'**), 171.0 (**C7**); IR (film) 2935, 2858, 1738, 1237 and 1037 cm^{-1}; MS (EI) *m/e* (rel intensity) 276 (M^+, 20), 133 (100), 74 (47); Anal. Calcd. for $C_{13}H_{24}S_2O_2$: C, 56.48; H, 8.75. Found: C, 56.68; H, 8.96.

2-[6'-(Ethynyloxy) hexyl]-2-methyl-1,3-dithiane (85):



Purified (57% yield) by chromatography using pentane:ether 85:15 as eluant. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.32-1.56 (m, 6H, **H2'**, **H3'**, **H4'**), 1.52 (s, 1H, **H8'**), 1.61 (s, 3H, **H7**), 1.76 (m, 2H, **H5'**), 1.87-1.98 (m, 4H, **H1'**, **H5**), 2.83-2.86

(m, 4H, **H4**, **H6**), 4.07 (t, 2H, J = 6.5 Hz, **H6'**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 24.3 (**C2'**), 25.2 (**C3'**), 25.4 (**C5**), 26.1 (**C8'**), 26.5 (**C4**, **C6**), 27.8 (**C4'**), 28.5 (**C7**), 29.2 (**C5'**), 41.6 (**C1'**), 49.2 (**C2**), 78.9 (**C6'**), 91.2 (**C7'**); IR (film) 3312, 1458 and 1093 cm^{-1}; MS (EI) *m/e* (rel. intensity) 216 (M^+ - C_2H_2O, 19), 141 (46), 133 (100), 106 (25); Anal. Calcd. for $C_{13}H_{22}S_2O$: C, 60.42; H, 8.58. Found: C, 60.74; H, 8.76.

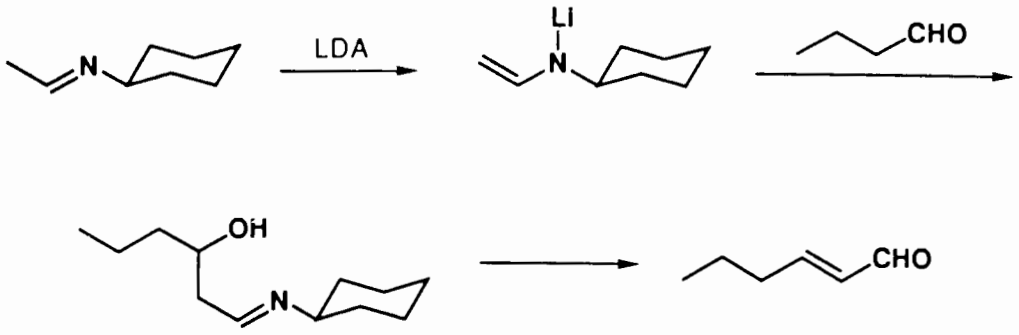
CHAPTER IV

Synthetic Application of α- and β-tri *n*-Butylstannyl Vinyl Ethers. Two-Carbon Homologation of Aldehydes.

IV.1. Introduction

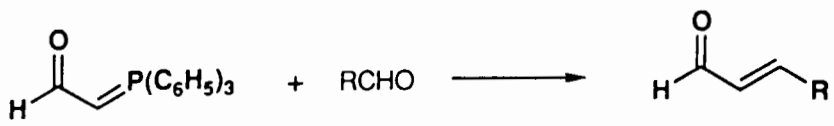
The transformation of aldehydes to their α, β-unsaturated analogs with two-carbon chain extension is a very useful reaction. The latter functionality is widely present in natural products including insect antifeedants and pheromones[1] which are of interest to this research group.

A simple approach for the synthesis of α, β-unsaturated aldehydes is the aldol condensation between an aldehyde and another carbonyl compound. This strategy is often complicated by competing self condensation reaction of the aldehyde[93]. A solution to this problem is the transformation of the aldehyde to a Schiff base. The latter can be metallated and reacted with carbonyl compounds to produce, after dehydration and hydrolysis, the corresponding unsaturated aldehyde[94] (**Scheme IV-1**). Several other groups have been successfully used to mask aldehydes during directed aldol condensations.[95]



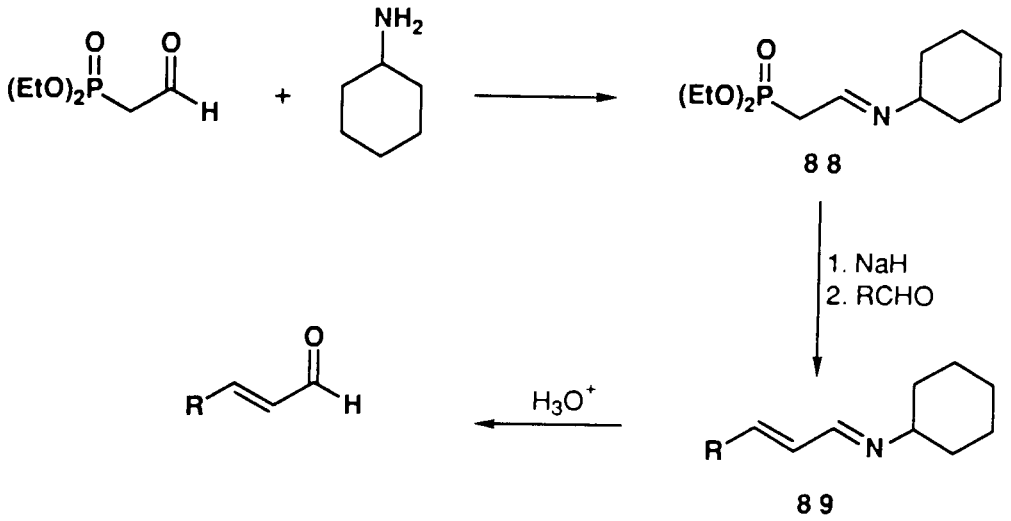
Scheme IV-1. Reaction of lithium ethylidenecyclohexylamine with aldehydes

Other methods for this transformation involve use of formylmethylenetriphenylphosphorane[96] in Wittig-type condensations (**Scheme IV-2**), or the reaction of 2-(cyclohexylimino)ethylphosphonate (**88**) with aldehydes[97] (**Scheme IV-3**). In the latter method, double bond isomerization has been reported during hydrolysis of the intermediate aldimines (**89**).



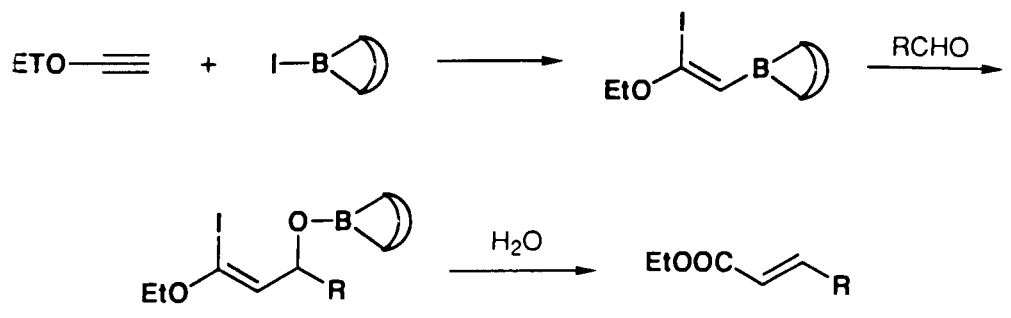
Scheme IV-2. Use of formylmethylenetriphenylphosphorane in Wittig-type condensations.

Additional methods involve addition of vinylmetallic reagents to aldehydes.[98]



Scheme IV-3. Use of cyclohexyliminophosphonates in the synthesis of α, β-unsaturated aldehydes.

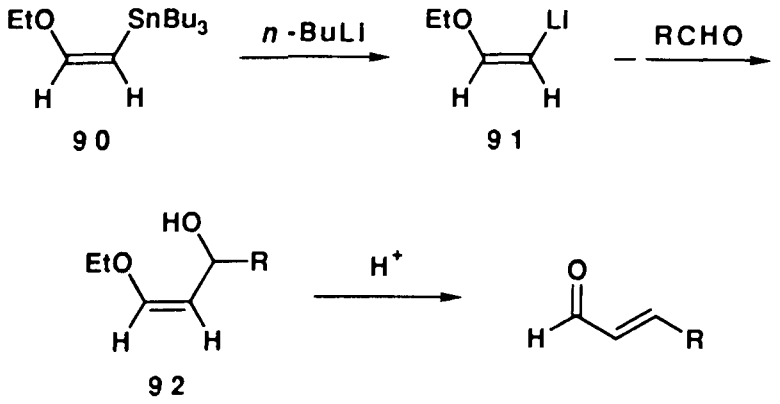
α, β-Unsaturated esters have been recently prepared by iodoborination of ethoxyethyne followed by condensation with aldehydes (**Scheme IV-4**).[99]



Scheme IV-4. Synthesis of α, β-unsaturated esters by iodoboration of ethoxy ethynyl ether.

cis-2-Ethoxyvinyllithium,**91**, obtained by transmetallation of *cis*-2-tributylstannylvinyl ethyl ether, **90**, has been used as acetaldehyde equivalent

in the synthesis of α,β-unsaturated aldehydes. Reaction of **91**, with carbonyl compounds results in formation of the γ-alkoxy allylic alcohols, **92**, further hydrolysis of which yields the corresponding α, β-unsaturated aldehyde (**Scheme IV-5**).[100]

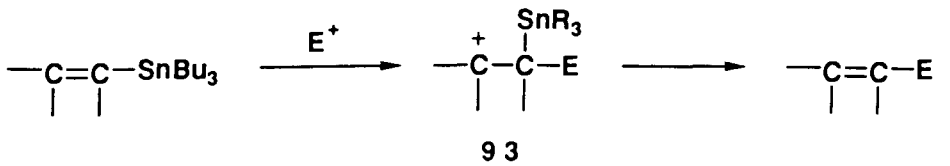


Scheme IV-5. Use of 91 as acetaldehyde equivalent.

In this chapter development of a new method for a "one-pot" transformation of an aldehyde to a homologous α, β-unsaturated aldehyde is described. In this procedure α- or β-tri-*n* -butylstannylvinyl ethers were used as acetaldehyde equivalents under Lewis acid catalysis.

IV.2. Results and Discussion

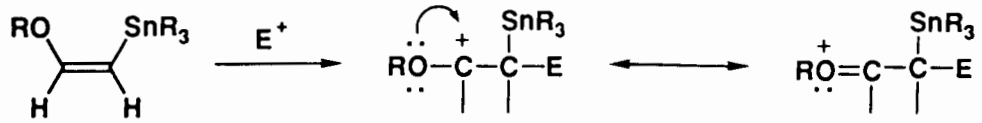
Because of their ability to act as a masked carbonyls, enol ethers are attractive equivalents of this functionality. Furthermore, it is known that vinylstannyl derivatives are highly reactive toward many electrophiles (i.e. Br_2, ICl, HX). These reactions proceed via stepwise addition of the electrophile to the double bond of the vinylstannane yielding intermediate **93** which undergoes elimination of the trialkylstannyl cation[101] (**Scheme IV-6**). The facility of these reactions is attributable to the stability of intermediates of type **93** which are strongly stabilized by the β-tin.[102]



93

Scheme IV-6. Intermediacy of β-stannylcarbocations in reactions of stannylvinyl compounds with electrophiles.

It was envisioned that, due to its electron-donating properties, the alkoxy group β to the tri *n*-butylstannyl moiety should further favor this type of reaction through stabilization of the carbocation intermediate (**Scheme IV-7**).

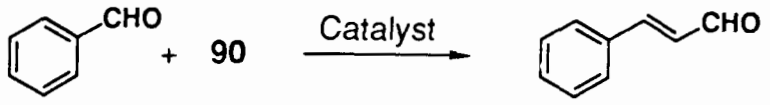


Scheme IV-7. Stabilization of β-stannylcarbocations in reactions of stannylvinyl ethers with electrophiles.

Thus, the reaction of **90** with aldehydes should be an attractive strategy for synthesis of α,β-unsaturated aldehydes. Initial reactions of *cis*-tributylstannylvinyl ethyl ether **90**, with benzaldehyde (**94**) at -78 or 0 °C gave no reaction (**Table IV-1**, entry 1). When the reaction was conducted at -78 °C, using Lewis acid catalysts the best yields were obtained with Et_2AlCl and boron trifluoride etherate (**Table IV-1**, entries 6 and 7). These reactions proceeded stereospecifically to yield *trans* -cinnamaldehyde, **95**, as the only detectable product.

When the *trans*- isomer **49** was reacted with benzaldehyde (**94**) under the same conditions used for the *cis* isomer **90**, *trans* -cinamaldehyde, **95**, was also obtained in a similar yield (**Scheme IV-8**).

Table IV-1. Use of Different Catalysts in the Homologation of Benzaldehyde (94)

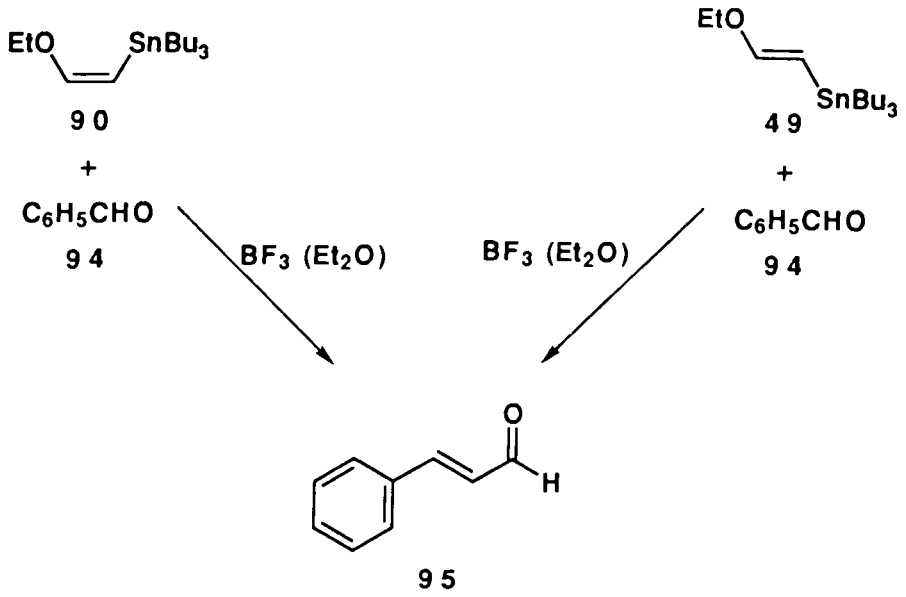


94 **95**

Entry	Catalyst	% Yield [a] of **95**
1	none	0
2	LiBr	0
3	$TiCl_4$ [b]	0
4	$Ti(i\text{-}PrO)_4$	0
5	$ZnCl_2$	10
6	Et_2AlCl	60
7	BF_3 (EtO_2)	91

[a] Calculated by G.C. analysis, based on the amount of **94** consumed.

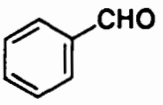
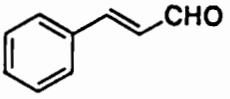
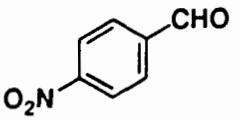
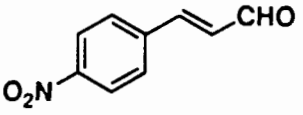
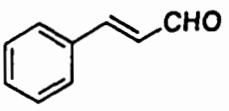
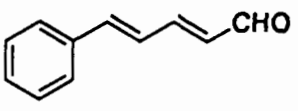
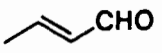
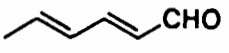
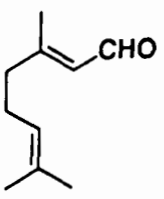
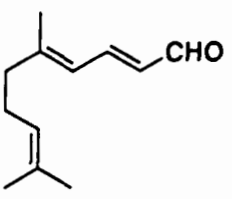
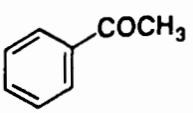
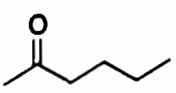
[b] In this case the vinylstannyl compound **90** was decomposed by the catalyst.



Scheme IV-8. Reaction of stannylvinyl ethers 49 and 90 with benzaldehyde.

The reaction proceeded smoothly with other aldehydes to give, the *trans* -isomer of the α,β-unsaturated aldehydic product (**Table IV-2**). No condensation products were obtained when the reaction was performed with aliphatic or aromatic ketones (**Table IV-2**, entries 6 and 7). Thus, this reaction is highly chemoselective.

Table IV-2. Synthesis of *trans* α, β - Unsaturated Aldehydes

Entry	Starting Material	Product	% Yield[a]
1	 **94**	 **95**	86
2	 **108**	 **109**	35
3	 **95**	 **110**	63
4	 **111**	 **112**	78
5	 **113**	 **114**	73
6		**N.R.**	–
7		**N.R.**	–

[a] Isolated yield.

IV.2.1. Mechanistic Considerations

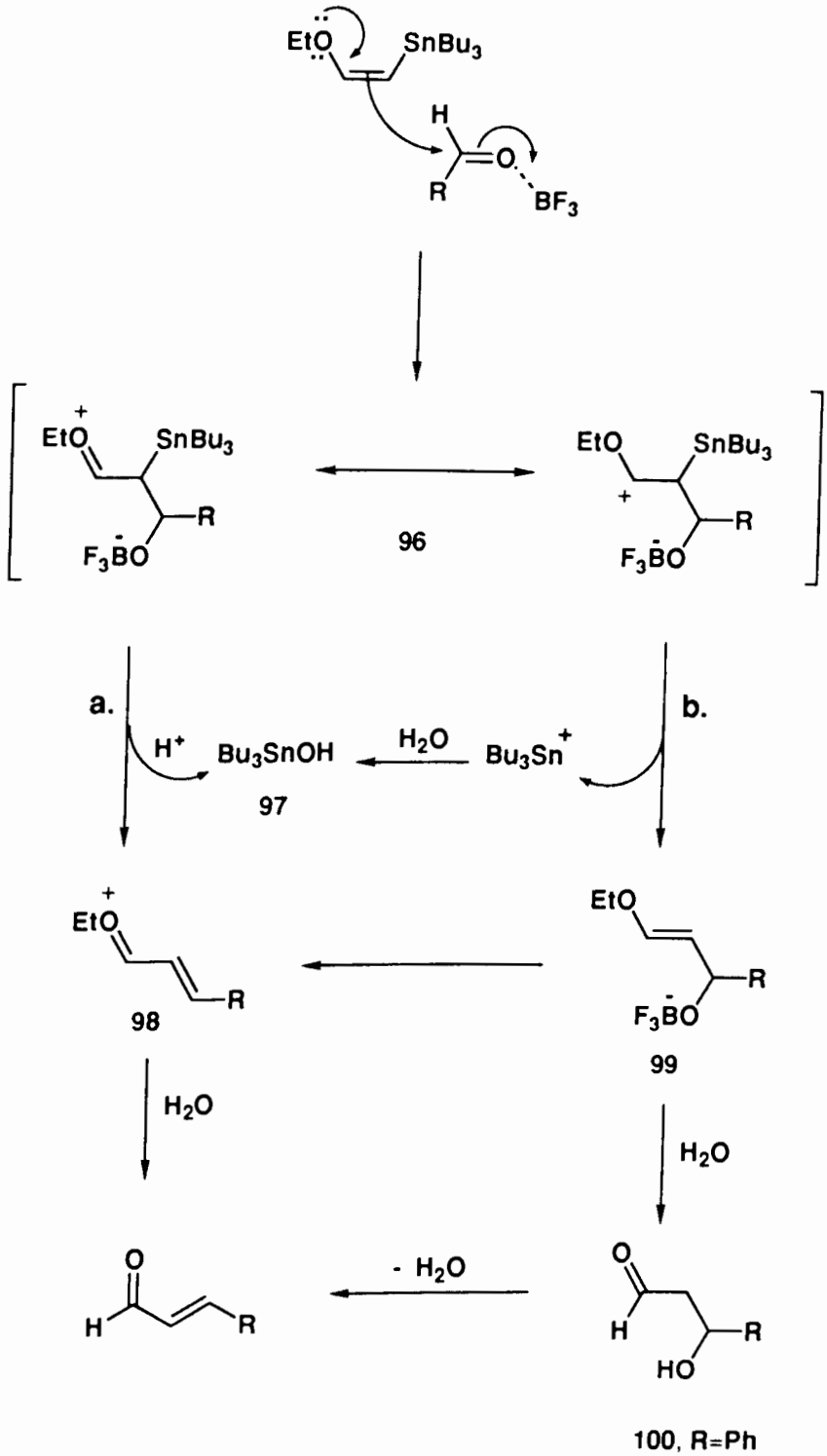
A mechanism for this transformation might involve nucleophilic attack of the π electrons of **90** (or **49**) on the Lewis acid activated carbonyl group of the aldehyde to form stabilized adduct **96** (**Scheme IV-9**). At this point two pathways are possible. Intermediate **96** could eliminate tributylstannylhydroxide, **97**, to generate a *trans* -double bond between the alkyl group (R) and the masked formyl group (**98**) (**Scheme IV-9**, path **a**). It is known that deoxystannylations are facile in β-hydroxy or alkoxy trialkylstannyl alkanes and they occur in a *trans* manner.[103] Hydrolysis of intermediate **98** would yield the corresponding *trans* -α, β-unsaturated aldehyde.

Alternatively, intermediate **96** could eliminate the tributylstannyl moiety to form vinyl ether **99** (**Scheme IV-9**, path **b**). It has been reported that β-stannyl carbocations undergo spontaneous elimination to form the corresponding alkenes.[101,104] Hydrolysis of ethyl vinyl ether **99** would give the corresponding β-hydroxyaldehyde which, after dehydration, could be converted to the unsaturated aldehyde. The latter step is most likely to be base-promoted and to occur at higher temperatures[105] than the ones used in this procedure.

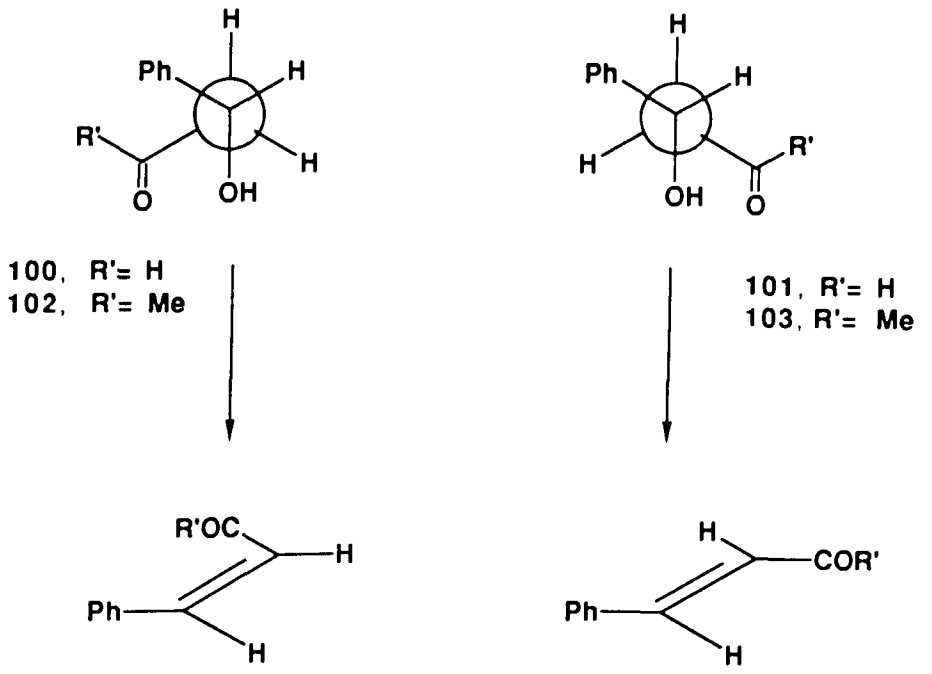
According to the latter mechanism (**Scheme IV-9**, path **b**) the stereochemistry should arise in the dehydration step which would suggest that a mixture of *cis* and *trans* isomers should be formed. Thus, in the reaction of benzaldehyde (**94**) ($R=C_6H_5$, **Scheme IV-9**) with **90**, in the dehydration step, there is not a significant steric interaction difference in the transition state

leading to the *cis* double bond (**100**, **Scheme IV-10**) when compared with the transition state leading to the *trans* isomer (**101**, **Scheme IV-10**) that would be expected to favour the latter. In this case a mixture of *cis* and *trans* isomers would have been obtained if path **b** (**Scheme IV-9**) were operating.

When a base promoted dehydration has been performed in similar compounds (**102**), the intermediate **102** (**Scheme IV-10**) becomes sterically more congested because of interactions between the methyl and phenyl groups.[106] Because this steric congestion is released in transition state **103**, the latter directs the course of the dehydration and the reaction has a preference (but not stereospecificity) for the formation of a *trans* double bond.[106] In this case, where the steric interaction difference between **102** and **103** is expected to be greater than in **100** and **101**, the reaction does not proceed sterospecifically. Since in the reaction between **90** and **94** only the *trans* isomer was detected, one suspects that path **a** (**Scheme IV-9**) is preferred. Thus, the mechanism proposed in path **a** (**Scheme IV-9**) gives a better description of this homologation reaction.

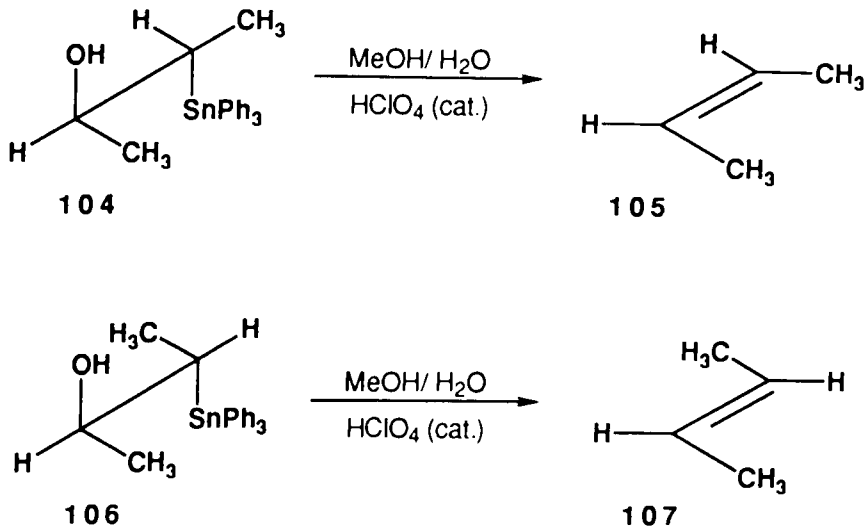


Scheme IV-9. Mechanism for 2-carbon homologation of aldehydes.



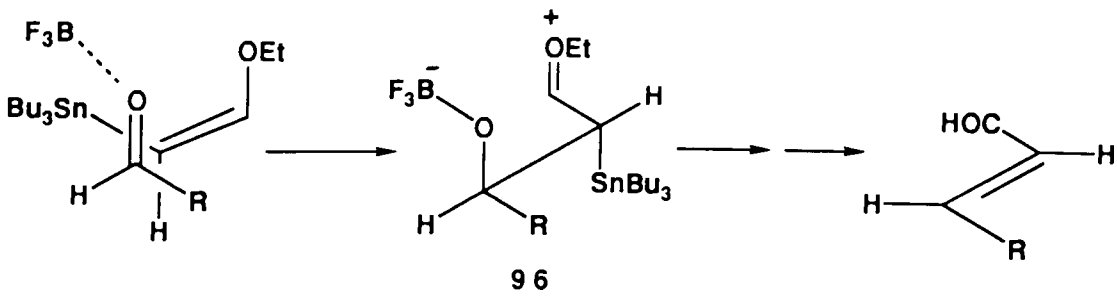
Scheme IV-10. Stereochemical course of dehydration in intermediates 100-103.

The stereochemical course of deoxystannylation reactions (**Scheme IV-9**, path **a**) has been demonstrated to occur in a *trans* fashion.[103] When *threo* -3-(triphenylstannyl)-2-butanol (**104**) was subjected to the elimination reaction conditions (25 °C, MeOH, water, catalytic amounts of $HClO_4$) *cis* -2 butene (**105**) was formed[103a] (**Scheme IV-11**). Furthermore, a 77:23 mixture of the *erythro* (**106**) and *threo* (**104**) alcohols gave a 77:23 mixture of the *trans*- (**107**) and *cis*- 2-butenes (**105**) respectively. Similar results were obtained with the corresponding β-tri *n* -butylstannyl alcohols,[103d] acetates[103c] and with β-trimethylsilyl alcohols and esters.[107]



Scheme IV-11. Stereochemical course of deoxystannylation in *threo*- and *erythro*-3-(triphenylstannyl)-2-butanols.[103]

Assuming that the deoxymetallation (**Scheme IV-9**, path **a**) occurs in a *trans*-fashion in intermediate **96**, the stereospecificity of the reaction might be explained by an acyclic transition state in which the tributylstannyl group occupies the least crowded site around the aldehyde[108] during the carbon-carbon bond formation step (**Scheme IV-12**). The corresponding *trans* -elimination in the intermediate thus obtained (**96**) followed by hydrolysis leads to the *trans* - α,β-unsaturated aldehyde.



Scheme IV-12. Deoxystannylation in intermediate 96.

IV.3. Conclusion

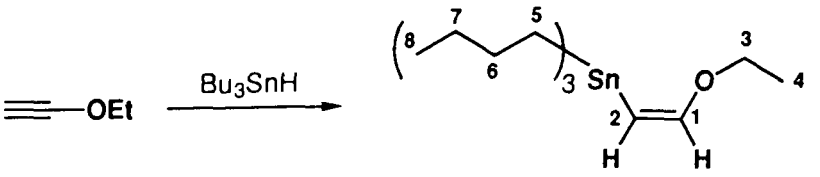
This method represents a new procedure for the homologation of aldehydes to α, β-unsaturated aldehydes with a two carbon chain extension. The stereospecificity as well as the chemoselectivity obtained makes it very attractive for stereospecific transformations of aldehydes in the presence of other carbonyl groups, such as ketones, without protection-deprotection procedures.

IV.4. Experimental Section

For general methods see Experimental Section Chapter I.

Dichloromethane was dried over activated 4A molecular sieves. Boron trifluoride ethereate was purchased from Aldrich and used without further purification. Ethoxy ethynyl ether was freshly distilled under argon prior to use.

Preparation of 2-*cis*-tri-*n*-butylstannylvinyl ethyl ether (90).

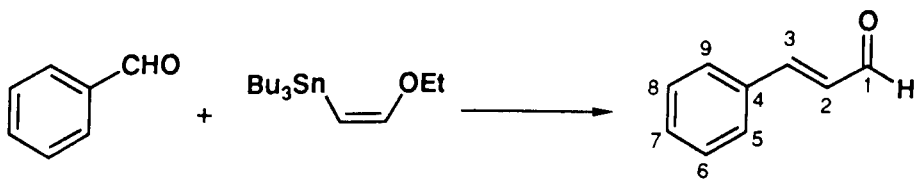


To a cold (0 °C) 50% hexanes solution of ethoxy ethynyl ether ,**47**, (4.5 g of solution, 32 mmol) was added 6.7 mL (25 mmol) of tri-*n*-butyltinhydride dropwise, under argon. After the addition the cold bath was removed, the solution allowed to warm to room temperature and then heated at 50 °C with stirring for 3 hr. After this time the reaction mixture was allowed to cool to room temperature and the mixture was concentrated *in vacuo*. GC analysis revealed consumption of all starting material. The product was obtained with a purity of 92%.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.88 (m, 15 H, H5, **H8**), 1.20 (t, 3H, J =7.0 Hz, **H4**), 1.30 (m, 6H, **H6**), 1.50 (m, 6H, **H7**), 3.75 (q, 2H, J =7.0 Hz, **H3**), 4.50 (d, 1H, J =7.0 Hz, $^2J_{Sn\text{-}H}$= 48 Hz, **H2**), 6.78 (d, 1H, J = 7.0 Hz, $^3J_{Sn\text{-}H}$=100 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 10.1 (**C5**), 13.7 (**C8**), 15.3 (**C4**), 27.3

(**C6**), 29.2 (**C7**), 66.7 (**C3**), 97.7 (**C2**), 157.1 (**C1**); IR (film) 2956, 2924, 2871, 1600, 1104 cm^{-1}; MS *m/e* (rel. intensity) 305 (M^+-Bu, 38), 279 (18), 235 (50), 179 (100), 135 (30), 121 (79).

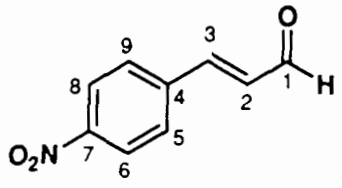
IV.4.1. Preparation of *trans* -cinnamaldehyde (95). General Procedure for Homologation of Aldehydes.



To a cold (-78 °C) dichloromethane solution (6 mL) of benzaldehyde (0.20 mL, 2 mmol) was added via syringe BF_3 (Et_2O) (0.25 mL, 2 mmol) and the solution stirred for 5 min. A solution of 2-cis- tributylstannyl ethyl ether (0.724 g, 2 mmol) in dichloromethane (3 mL) was added dropwise and the resulting mixture stirred at -78°C for 1 h. After this time a 1:1 mixture of MeOH:H_2O (3 mL) was added, the cooling bath removed and the solution was allowed to warm to room temperature. The organic phase was washed with water (2 X 5 mL) and dried ($MgSO_4$). The mixture was concentrated *in vacuo* and the product purified by column chromatography (hexanes:ether, 8:2) to give 0.24 g (91% yield).
^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.72 (dd, 1H, *J* = 15, 8 Hz, **H2**), 7.40-7.60 (m,6H, **H3**, **H5**, **H6**, **H7**, **H8**, **H9**), 9.70 (d, 1H, *J* = 8 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 128.5 (**C6**, **C8**), 128.7 (**C7**), 129.1 (**C5**, **C9**), 131.2 (**C2**), 134.1 (**C4**),

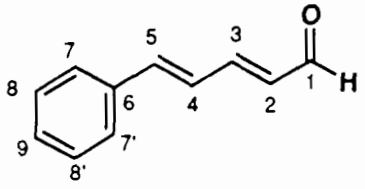
152.6 (**C3**), 193.5 (**C1**); MS (EI) *m/e* rel. intensity 132 (M^+, 52), 131 (100), 103 (44), 77 (38).

trans -p -nitrocinnamaldehyde (109)



(Eluted with hexanes:ether 7:3); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.80 (dd, 1H, J = 8, 15 Hz, **H2**), 7.55 (d, 1H, J = 15 Hz, **H3**), 7.73 (d, 2H, **H5**, **H9**), 8.30 (d, 2H, **H6**, **H8**), 9.78 (d, 1H, J = 8 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 124.3 (**C5**, **C9**), 129.0 (**C6**, **C8**), 130.4 (**C4**), 131.8 (**C2**), 140.0 (**C7**), 148.5 (**C3**), 192.5 (**C1**); IR (KBr) 3072, 2931, 1678, 1596, 1519, 1349, 1124, 865, 744 cm^{-1}; MS m/e (rel intensity) 177 (M^+, 23), 160 (80), 130 (87), 113 (15), 103 (53), 77 (100).

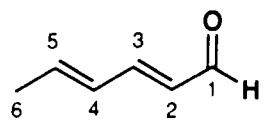
(2*E*, 4*E*)-5-Phenyl-2,4-Pentadienal (110)



(Silica Gel, hexanes:ethyl acetate 9:1); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.26 (dd, 1H, *J*= 15, 8 Hz, **H2**), 6.99- 7.10 (m, 2H, **H7**, **H7'**), 7.23-7.29 (m, 1H, **H9**), 7.34-7.41 (m, 3H, **H3**, **H4**, **H5**), 7.48-7.51 (m, 2H, **H8**, **H8'**), 9.61 (d, 1H, *J*=8Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 126.2 (**C2**), 127.5 (**C8'**, **C8**), 128.9 (**C7'**, **C7**), 129.7 (**C4**)*, 131.7 (**C5**)*, 135.7 (**C6**), 142.4 (**C9**), 151.8 (**C3**), 193.4 (**C1**); MS (EI) *m/e* rel. intensity 158 (M^+, 75), 157 (23), 129 (100), 77 (8).

* These assignments are not definitive

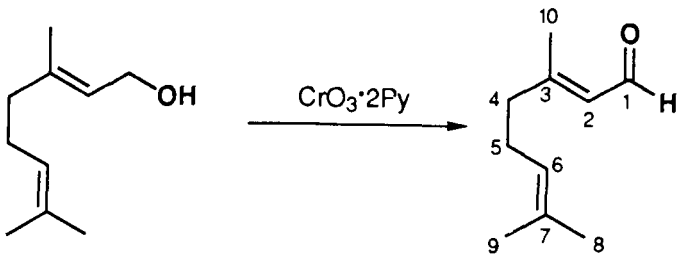
(2*E*, 4*E*)-2,4-Hexadienal (112)



^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.90 (d, 3H, *J* = 6 Hz, **H6**), 6.05 (dd, 1H, *J* = 8, 15 Hz, **H2**), 6.22-6.37 (m, 2H, **H4**, **H5**), 7.06 (dd, 1H, *J* = 10, 15 Hz, **H3**), 9.55 (d, 1H, *J* = 8 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 18.8 (**C6**), 129.9 (**C4**)*, 130.1 (**C5**)*, 141.7 (**C2**), 152.4 (**C3**), 193.8 (**C1**); IR (film) 3027, 2812, 1681, 1643, 1165, 1121, 1013 cm^{-1}; MS (EI) *m/e* rel. intensity 96 (M^+, 35), 95 (10), 81 (100), 67 (25), 53 (19).

* These assignments are not definitive.

Preparation of (2*E*)-3,7-Dimethyl-2,6-octadiene-al (113)[109]

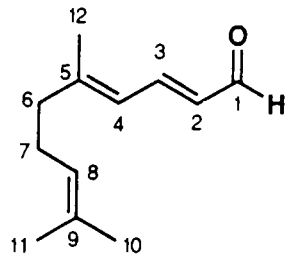


To a solution of pyridine (9.70 mL, 120 mmol) in dichloromethane (150 mL), was added, in portions, chromium trioxide (6.0 g., 60 mmol). After stirring at room temperature for 20 minutes a dichloromethane solution (4 mL) of geraniol (1.54 g, 10 mmol) was added in one portion and the mixture stirred at room temperature for 30 minutes. After this time the reaction mixture was diluted with diethyl ether (100 mL) and filtered through a small pad of silica Gel. After concentration *in vacuo* 1.13 g (74%) of product was obtained.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 3H, **H9**)*, 1.66 (d, 3H, *J* =1.0 Hz, **H8**)*, 2.15 (d, 3H, J= 1.2 Hz, **H10**), 2.17-2.22 (m, 4H, **H4**, **H5**), 5.03-5.08 (m, 1H, **H6**), 5.86 (dq, 1H, *J* = 8.1, 1.2 Hz, **H2**), 9.97 (d, 1H, *J* =8.1 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 17.5 (**C8**)#, 17.6 (**C9**)#, 24.9 (**C10**), 25.6 (**C5**), 40.6 (**C4**), 122.6 (**C6**), 127.4 (**C2**) 132.9 (**C7**), 163.4 (**C3**), 191.1 (**C1**).

*•# These assignments are not definitive.

(2*E*, 4*E*)-5, 9-Dimethyl-2, 4, 8-Decatriene-al (114)



(Eluted with hexanes: ether 8:2); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 3H, **H10**)*, 1.68 (s, 3H, **H11**)*, 1.93 (d, 3H, *J* =1.0 Hz, **H12**), 2.13-2.22 (m, 4H, **H6**, **H7**), 5.05-5.07 (m, 1H, **H8**), 6.07 (dd, 1H, *J* = 15.0, 8.1 Hz, **H2**), 6.13 (broad d, 1H, *J* =11.5 Hz, **H4**); 7.40 (dd, 1H, *J* = 15.0, 11.5 Hz, **H3**), 9.56 (d, 1H, *J* = 8.1 Hz, **H1**); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 17.6 (**C10**)#, 17.7 (**C11**)#, 25.6 (**C12**), 26.3 (**C7**), 40.5 (**C6**), 123.1 (**C8**), 123.8 (**C2**), 130.1 (**C4**), 132.5 (**C9**), 148.3 (**C3**), 152.8 (**C5**), 193.9 (**C1**); MS m/e (rel. intensity) 178 (M^+, 1), 110 (25), 95 (35), 81 (19), 69 (100).

* # These assignments are not definitive.

General Conclusions

Chemical and spectroscopic studies of the stannylcupration of acetylenic ethers show that this process kinetically produces vinylcopper intermediates containing a stannyl group on the carbon bearing the alkoxy group at -78 °C. These intermediates can be quenched with methanol at this reaction temperature to produce regioselectively α-stannylvinyl ethers in very good yields. If these intermediates are warmed above this reaction temperature they decompose by 1,2-elimination of the *trans* alkoxy and copper groups. This elimination can be retarded by the addition of HMPA to the stannylcupration reaction. If stannylcupration of acetylenic ethers is conducted in the presence of HMPA at 0 °C the thermodynamically more stable vinylcopper intermediate possessing the stannyl group *trans* to the alkoxyl group is obtained. Methanolysis at this point yields the corresponding β-stannylvinyl ethers in very good yields.

^{13}C and ^{1}H-NMR studies of the stannylcuprations of acetylenic ethers revealed that, when prepared in the presence of HMPA, bis(tributylstannyl)cyano cuprates exist as mixtures of cyano coordinated higher order cuprates with the corresponding Gilman cuprates and copper (I) cyanide. This behavior was confirmed for (dialkyl) cyano cuprates. Thus, when higher order cyanocuprates are prepared in THF the cyanide is fully coordinated and the reagents exist as dianionic copper (I) salts. When higher order cyanocuprates are prepared in THF containing HMPA these reagents exist as mixtures of the higher order cyano coordinated and lower order Gilman reagents and lithium (I) cyanide. Warming

of such (THF/HMPA) solutions irreversibly produces the higher order species. These observations have resolved a controversy concerning the coordination of cyanide to copper in the presence of two equivalents of trialkylstannyl or alkyl lithium.

The NMR study of the alkoxyvinylcopper intermediates obtained in the stannylcupration was facilitated by the development of a new procedure for the synthesis of acetylenic ethers. This method involved the 1,2-elimination of vinyl phosphonate esters which was optimized by proper choice of base and elimination of lithium phosphonates from the reaction solution. The method allowed regiospecific preparation of ^{13}C-labelled ethers from readily available ^{13}C-acetate. The procedure is applicable to the synthesis of functionalized acetylenic ethers carrying labile groups such as chlorides that were not previously easily accessible.

trans-Stannylvinyl ethers, obtained by stannylcupration of acetylenic ethers, as well as the *cis* isomers, were found to react with aldehydes in the presence of $BF_3(Et_2O)$ to give the corresponding (E)-2-carbon homologated α,β-unsaturated aldehydes. Unfortunately this method is limited to unsaturated aldehydes.

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