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Organotitanium-Aluminum Promoted Carbometalations of Alkynols: Substituent Effects

Nikola A. Nikolic
College of William & Mary - Arts & Sciences

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<https://dx.doi.org/doi:10.21220/s2-jn77-gm95>

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ORGANOTITANIUM-ALUMINUM PROMOTED CARBOMETALATIONS
OF ALKYNOLS: SUBSTITUENT EFFECTS

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A Thesis presented to the Graduate Faculty
of the College of William and Mary in Candidacy for the Degree of
Master of Science

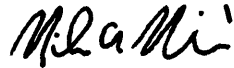
Department of Chemistry

The College of William and Mary
May 2008

APPROVAL PAGE

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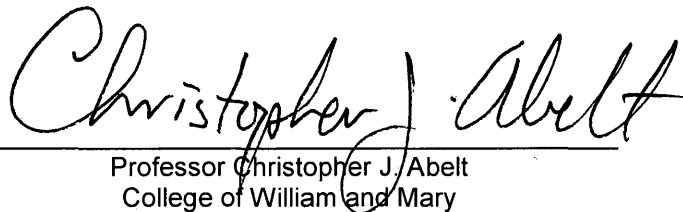


Nikola A. Nikolic

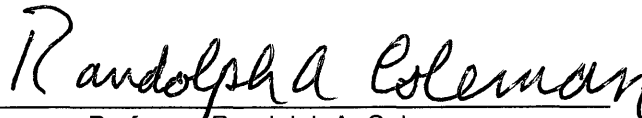
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DEDICATION

This thesis is dedicated to my father and teacher,

Dr. Nikola M. Nikolic

ACKNOWLEDGEMENTS

I would like to thank Dr. David W. Thompson for his outstanding guidance and support throughout the course of this project. I would also like to thank C. P. Desmond Longford for the helpful comments and suggestions which he contributed. Miss Susan D. Parker deserves a special thanks for the patience and understanding she exhibited during this endeavor.

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ORGANOTITANIUM-ALUMINUM PROMOTED CARBOMETALATIONS
OF ALKYNOLS: SUBSTITUENT EFFECTS

ABSTRACT

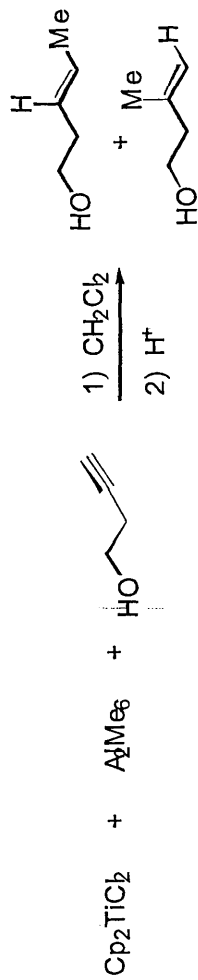
Homoallylic alcohols are useful intermediates in natural product synthesis, particularly in the construction of terpenoid carbon skeletons. Until recently, however, the synthesis of such alkenols has been somewhat cumbersome. In this investigation, homoallylic alcohols were synthesized in one pot *via* methylmethylation of homopropargyl alcohols with trimethylaluminum. A series of ring-substituted titanocene dichlorides were used as promoters of this process. The major focus of this study was to examine the effects of ring substitution on the regiochemistry of the methyl addition. Three ring-substituted titanocene promoters: $(\text{MeCp})_2\text{TiCl}_2$, $(\text{Me}_3\text{Cp})_2\text{TiCl}_2$, and $(\text{Me}_5\text{Cp})_2\text{Ti}_2\text{Cl}_2$ were investigated. Each of these promoters was used to methylate both an internal homopropargylic alcohol (*i.e.* 3-pentyn-1-ol) and a terminal homopropargyl alcohol (*i.e.* 3-butyne-1-ol). In these studies, an increase in the number of ring substituents on the titanocene promoter afforded an increase in regioselectivity of methylation of the substrates. Unfortunately, increased ring substitution also led to decreased yields of the methylated substrates. The addition of the methyl group occurred predominantly on the terminal acetylenic carbon of the 3-pentyn-1-ol substrate. Conversely, the methyl addition was predominantly internal for 3-butyne-1-ol. In both cases, the addition of the methyl-metal bond occurs in a *syn* fashion.

INTRODUCTION TO THE RESEARCH GOALS

The focus of this investigation is the adaptation of typical Ziegler-Natta catalyst systems to effect single-stage carbometallation reactions on the acetylenic functionality of alkynols. Since the early 1950's, it has been well known that Ziegler-Natta catalyst systems are powerful, repetitive carbometalating reagents for the production of polyolefins. However, only during the past decade has progress been made in utilizing the Ziegler-Natta chemistry in a manner of interest to non-macromolecular synthesis. Since the stereoselective construction of carbon skeletons is fundamental to organic synthesis, it is surprising that so little effort had been made in adapting the discoveries of Ziegler to these ends.

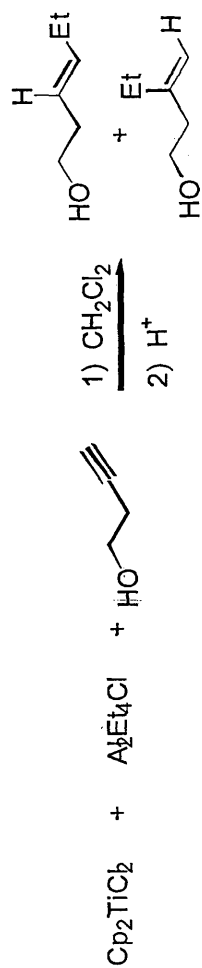
In the late 1970's, Thompson *et al.* published the results on the controlled single-stage carbometallations of homopropargyl alcohols using bis(η^5 -cyclopentadienyl)titanium dichloride-organoalane reagents, which are active Ziegler catalysts for the polymerization of ethylene. Representative results from these studies which are germane to the investigation reported herein are shown in Figures 1 and 2. Figure 3 illustrates a proposed pathway for these carbometalation reactions.

Figure 1. Methylation of alkynols with trimethylaluminum/titanocene dichlorides.



Alkynol	Titanocene Dichloride	Temperature (°C)	Time (min)	Molar Ratio	Products (Relative Ratio)
3-Butyn-1-ol	Cp_2TiCl_2	0	120	2 : 1	3-Methyl-3-buten-1-ol (85) (<i>E</i>)-3-Penten-1-ol (15)
3-Butyn-1-ol	$(\text{MeCp})_2\text{TiCl}_2$	0	120	2 : 1	3-Methyl-3-buten-1-ol (79) (<i>E</i>)-3-Penten-1-ol (21)
3-Butyn-1-ol	$(t\text{-BuCp})_2\text{TiCl}_2$	0	120	2 : 1	3-Methyl-3-buten-1-ol (80) (<i>E</i>)-3-Penten-1-ol (20)
3-Pentyn-1-ol	Cp_2TiCl_2	0	120	2 : 1	4-Methyl-3-penten-1-ol

Figure 2. Methylation of alkynols with diethylaluminum chloride/titanocene dichlorides.



Alkynol	Titanocene Dichloride	Temperature (°C)	Time (min)	Molar Ratio	Products (Relative Ratio)
3-Butyn-1-ol	Cp ₂ TiCl ₂	0	120	2 : 1	3-Ethyl-3-buten-1-ol (50) (E)-3-Hexen-1-ol (50)
3-Butyn-1-ol	(MeCp) ₂ TiCl ₂	0	120	2 : 1	3-Ethyl-3-buten-1-ol (46) (E)-3-Hexen-1-ol (54)
3-Butyn-1-ol	(<i>t</i> -BuCp) ₂ TiCl ₂	0	120	2 : 1	3-Ethyl-3-buten-1-ol (43) (E)-3-Hexen-1-ol (57)
3-Pentyn-1-ol	Cp ₂ TiCl ₂	0	240	2 : 1	4-Methyl-3-hexen-1-ol (93) 3-Ethyl-3-penten-1-ol (7)
3-Pentyn-1-ol	Cp ₂ TiCl ₂	0	240	2 : 1	4-Methyl-3-hexen-1-ol (95) 3-Ethyl-3-penten-1-ol (5)

Inspection of Figures 1 and 2 demonstrates that both bis(η^5 -cyclopentadienyl)titanium dichloride and bis(η^5 -methylcyclopentadienyl)titanium dichloride give carbometalated products in good yields with a

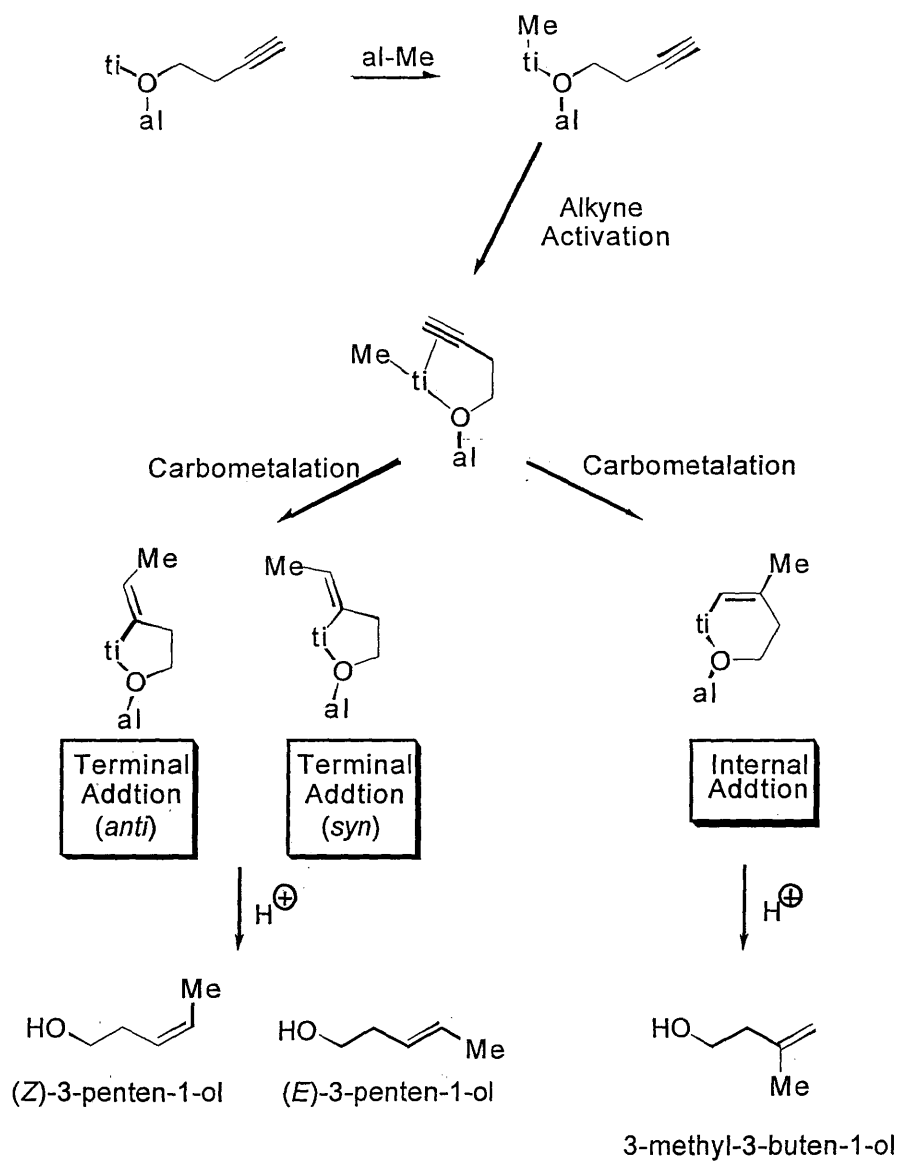


Figure 3. An approach to controlled carbometalation with Ziegler-Natta catalyst system.

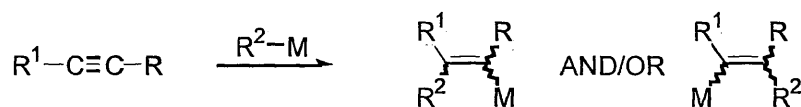
similar distribution of regioisomers. The lack of stereospecificity in most of these reaction was disappointing. It was surprising that the methyl substituent of the titanocene appeared to have no effect on the regioselectivity of this process as the carbometalation is almost certainly taking place at the titanium center (*cf.* Figure 3). Further work demonstrated that even a *t*-butyl substituent on the titanocene promoter does not give rise to pronounced effects on the regiochemical outcome of the carbometalation. In light of these observations, the first goal of our investigations was to examine the effects on the regioselectivity of the carbometalation reaction arising from multiply ring-substituted titanocene promoters (*e.g.* bis(η^5 -1,2,4-trimethylcyclopentadienyl)- and bis(η^5 -pentamethylcyclopentadienyl) titanium dichloride).

Thompson *et al.* have presented evidence^{1,2} that the carbometallation proceeds through a cyclic intermediate as illustrated in Figure 3. If this is the case for the formation of 3-methyl-3-buten-1-ol from the $\text{Cp}_2\text{TiCl}_2\text{-Me}_3\text{Al}$ catalyzed methylation of 3-buten-1-ol, then the carbometalation step appears to involve an *anti*-addition of the methyl-metal bond (*syn*-addition cannot occur to form a six-membered ring). To our knowledge, no documented cases of carbometalation with organotitanium-organoaluminum reagent in an *anti*-fashion have been established. Thus, the second goal of this research was to elucidate the stereochemistry of addition of the methyl-metal bond in the formation of 3-methyl-3-buten-1-ol from Cp_2TiCl_2 reagents.

Finally, the carbometalation of 3-butyne-1-ol with the cyclopentadienyl reagent systems gives a mixture of regioisomers with a slight tendency to favor internal alkylation. However, it was reported by Brown *et al.*² that 3-pentyne-1-ol ethylmetalates to afford greater than 93% of the terminally-alkylated product. This substituent effect is somewhat surprising given that the *t*-butylcyclopentadienyl titanocene promoter has little effect of the regioselectivity (*vide supra*). Thus, the third goal of this study was to investigate the change in regioselectivity on going from 3-butyne-1-ol to 3-pentyne-1-ol during ethylation.

CARBOMETALATION OF CARBON-CARBON MULTIPLE BONDS BY BIMETALLIC ZIEGLER-NATTA TYPE CATALYSTS: A SELECTIVE LITERATURE REVIEW

The addition of an R-M bond across an unsaturated carbon-carbon bond is known as carbometalation, and can generally be represented by Scheme 1.³ Since the goal of this investigation is the stereoselective



R, R¹, R² = Alkyl or Aryl; M = Metal

Scheme 1

carbometalation of alkynols, the primary focus of this review will be the carbometalation work of Negishi, *et al.* The topics to be covered in this review include: a description of the carbometalation systems; carbometalation of terminal acetylenes; carbometalation of internal acetylenes; the synthetic utility of carbometalated products, and; an examination of the carbometalation mechanism.

DESCRIPTION OF CARBOMETALATION SYSTEMS

According to the broad patent definition, a Ziegler-Natta catalyst is a mixture of a metal alkyl of Groups 1, 2 and 13 and a transition metal salt of Groups 4 through 8.⁴ Based on this description, the carbometalation systems used by Negishi, *et al.*, are of a Ziegler-Natta type. These systems are composed of bis(η^5 -cyclopentadienyl)zirconium chloride (or its titanium analog) and either organoalanes or organozincs. Chlorohydrocarbon solvents such as 1,2-dichloroethane,⁵ chlorobenzene⁶ and methylene chloride⁷ are generally employed; however, benzene⁶ can also be used. Ethereal solvents are not typically used since trialkylaluminums are strong Lewis Acids and coordinate with electron donors to form complexes.⁸

One of the advantages of the Negishi system is that a wide variety of organic groups can be added across the acetylenic functionality. It will be seen later that the system can add methyl,^{3,9,10,11} ethyl,^{12,13} *n*-propyl,^{3,13} allyl^{14,15} and crotyl¹⁵ groups with a high degree of stereo- and regioselectivity. It will also be seen that both internal and terminal acetylenes can be carbometalated.

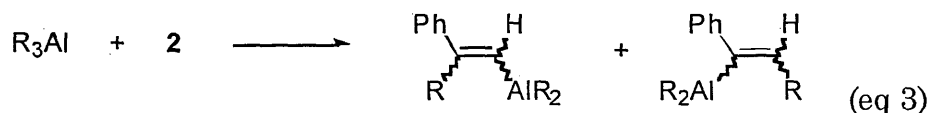
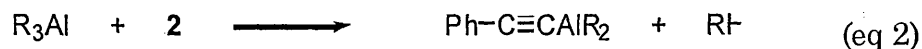
Another advantage of the carbometalations described herein is that they are compatible with alkyne substrates containing a number of different functional groups. Neither a conjugated nor an isolated alkenyl group interferes with the carbometalation sequence.¹¹ Heterofunctional groups such as hydroxyl,⁷ *t*-butyldimethylsilyl ether,⁷ trimethylsilyl,^{15,16} phenylthio ether,^{7,11} bromine,⁶ and iodine⁷ are compatible with this transformation. The

unsaturated portion of some organometallic compounds such as alkynylzinc chlorides,⁹ dialkylalkynylboranes,⁹ and dialkylalkynylalanes⁹ also undergo carbometalation. The ability to tolerate such a wide variety of functionalities greatly increases the synthetic utility of this methodology.

Fortunately, the carbometalation reaction is not complicated by the known hydrogen abstraction of terminal acetylenes with either organozirconium or organoaluminum compounds.³ In the case of organozirconium, dicyclopentadienyldimethylzirconium (1) was observed to react with phenylacetylene (2) to give both mono- and diacetylide (eq 1).¹⁷ On the other



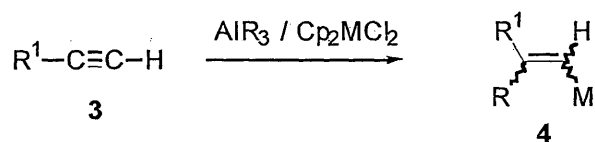
hand, organoaluminum compounds are known to react directly (eq 2), or add across carbon-carbon triple bonds (eq 3).⁸



CARBOMETALATION OF TERMINAL ACETYLENES

Organoalane-Transition Metal Systems

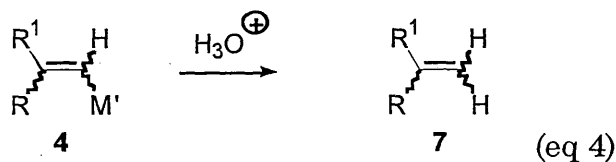
The first reported carbometalations of acetylenes were effected with an aluminum/zirconium catalyst.³ It was not long before the utility of an aluminum/titanium system was also recognized.⁹ The general transformation of terminal acetylenes **3** to the corresponding organometallic reagent **4** (Scheme 2) is analogous to that shown in Scheme 1 (*vide supra*).



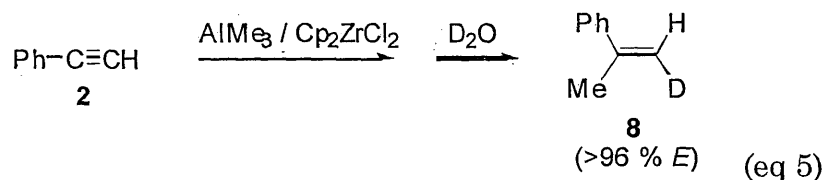
R & R¹ = ORGANIC GROUPS
M = Zr or Ti
M' = Metal Containing Group

Scheme 2

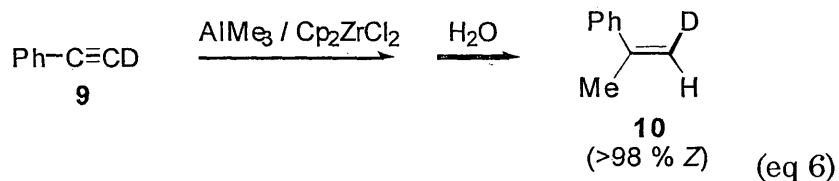
In this reaction, if one either omits zirconocene dichloride **5** or uses aluminum-free (Cp₂)MeZrCl **6**, no more than a trace of the carbometalated product is formed even after 24 h under otherwise comparable conditions, indicating that both Al and Zr (or Ti) are essential in observing the facile carbometalation reaction.³ The organometallic intermediate **4** can be hydrolyzed with dilute acid to afford a disubstituted olefin **7** (eq 4).



To establish the stereochemistry of these reactions, Negishi *et al.* performed two carbometalations. In the first reaction, phenylacetylene (**2**) was methylmetalated, and then quenched with D₂O (eq 5). Deuterolysis

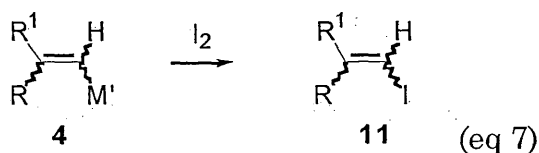


afforded *ca.* 96% of the (*E*)-isomer **8** as judged by ¹H NMR.³ The second reaction involved the methylmetalation of deuterophenylacetylene (**9**) (eq 6).



In this case, ¹H NMR was consistent with >98% of the (*Z*)-isomer **10** after protonolysis.³ From this work, and subsequent reactions, a *syn*-addition of the R-M moiety is indicated.

An interesting application of this methodology is the synthesis of vinyl iodides. Iodinolysis of carbometalation intermediate **4** affords a trisubstituted olefin **11** (eq 7). In the systems to be described, the ratio of



trimethylalane to acetylene has been typically 2 : 1 or 3 : 1 to ensure completion of the carbometalation reaction. Thus, the stoichiometric ratio of iodine to aluminum required for complete iodinolysis of all C-M bonds is 6 : 1 or 9 : 1. In practice however, the use of a 20-50 mol % excess is sufficient, indicating that the alkenyl group is considerably more reactive toward iodine than the methyl group.¹¹

A listing of the carbometalation-protonolysis (eqs 4 & 5) and iodinolysis (eq 7) is presented in Table I. A few features of this type of carbometalation bear some mention. In the $\text{R}_3\text{Al}/\text{Cp}_2\text{ZrX}_2$ system, represented by entry 2d, reaction with higher alanes containing β -hydrogen substituents leads to β -hydride elimination and loss of regioselectivity.¹⁸ Despite this observation, allylalanes (*cf.* Table I Entries 2-e, -f, -g; 3-b, -c; 12-a, -b and 13-a, -b) can effect allylalumination. In one such example, allyldiisobutyl-alane undergoes allylalumination with terminal acetylenes in the presence of Cp_2ZrCl_2 to produce exclusively *cis*-monomethylation products (>98% *Z*) as a *ca.* 75 : 25 mixture of two regioisomers.¹⁵ Such zirconium-catalyzed allylalumination reactions are >98% stereoselective as judged by ^{13}C and ^1H NMR.¹⁵ Furthermore, in reactions with allyldiisobutylalane, there is no indication of either addition of the *i*-Bu-Al bond or Zr-catalyzed

Table I. Carboalumination of terminal acetylenes.


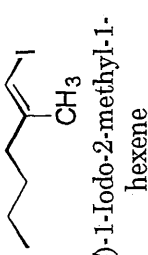



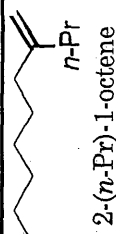

Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
1	 1-Hexyne	Cp_2ZrCl_2	AlMe_3	1.) DCE, 20-25 °C 2.) I_2 , THF, 0 °C	 (<i>E</i>)-1-Iodo-2-methyl-1-hexene	85	11
2a	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2	AlMe_3	1.) DCE, 20-25 °C, 3h 2.) H_3O^+	 2-Methyl-1-octene  (<i>E</i>)-2-Nonene	100 (95 : 5)	3
2b	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2TiCl_2	AlMe_3	1.) DCE, 20-22 °C 2.) H_3O^+	 2-Methyl-1-octene	25 ^b	9
2c	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2	$\text{Al}(n\text{-Pr})_3$	1.) DCE, 0 °C, 1h 2.) H_3O^+	 2-(<i>n</i> -Pr)-1-octene  (<i>E</i>)-4-undecene	75 (80 : 20)	3

Table I. Carboalumination of terminal acetylenes. (Cont'd)






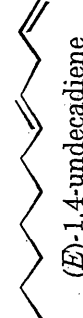
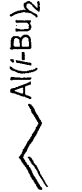

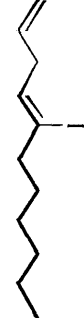
Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
2d	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2	$\text{Al}(n\text{-Pr})_3$	1.) DCE, 20-25 °C, 6h 2.) H_3O^+	 2-(<i>n</i> -Pr)-1-octene  (<i>E</i>)-4-undecene  1-Octene	29 8 47	13
2e	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2	 $\text{Al}(i\text{-Bu})_2$	1.) DCE, 20-25 °C, 1h 2.) H_3O^+	 2-Allyl-1-octene  (<i>E</i>)-1,4-undecadiene	99 (72 : 28)	15
2f	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2	 $\text{Al}(i\text{-Bu})_2$	1.) DCE, 20-25 °C 2.) I_2 , THF, 0 °C	 (<i>E</i>)-1-Iodo-2-allyl-1-octene  (1- <i>E</i> ,4- <i>Z</i>)-5-Iodo-1,4-decadiene	64 (98 : 2)	15

Table I. Carboalumination of terminal acetylenes. (Cont'd)






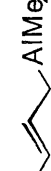

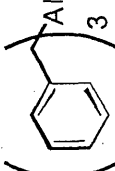
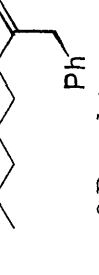

Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
2g	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2		1.) DCE, 20-25 °C, 1h 2.) H_3O^+	 2-Allyl-1-octene  (<i>E</i>)-1,4-undecadiene	98 (75 : 25)	15
2h	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2	$(n\text{-Pr})_2\text{AlCl}$	1.) DCE, 20-25 °C 2.) I_2	 (<i>E</i>)-1-Iodo-2-(<i>n</i> -Propyl)-1-octene  (<i>E</i>)-5-Iodo-4-undecene	61 (88 : 12)	15
2i	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2		1.) DCE, 20-25 °C 2.) I_2	 (1- <i>Z</i> ,4- <i>E</i>)-1-Iodo-2-hexyl-1,4-decadiene	61 (>98)	15
2j	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne	Cp_2ZrCl_2		1.) DCE, 60 °C 2.) H_3O^+	 2-Benzyl-1-octene  (<i>E</i>)-1-Phenyl-2-nonene	94 (70 : 30)	15

Table I. Carboalumination of terminal acetylenes. (Cont'd)

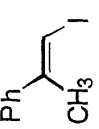
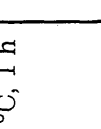
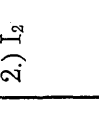

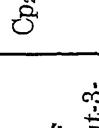
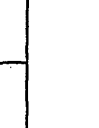

Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
3a	Ph-C≡CH Phenylacetylene	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C, 24h 2.) I ₂ , THF, 0 °C	 (E)-Iodo-2-phenyl-propene	73	11
3b	Ph-C≡CH Phenylacetylene	Cp ₂ ZrCl ₂		1.) DCE, 20-25 °C, 1 h 2.) H ₃ O ⁺	 2-Phenyl-1,4-butadiene	90 (>98 : 2)	15
3c	Ph-C≡CH Phenylacetylene	Cp ₂ ZrCl ₂		1.) DCE, 20-25 °C, 1 h 2.) I ₂	 (E)-1-Iodo-2-phenyl-1,4-pentadiene	86 (>98)	15
4	PhS(CH ₂) ₂ C≡CH 3-Thiophenoxy-1-propyne	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C, 3 h 2.) I ₂ , THF, 0 °C	 (E)-1-Iodo-2-methyl-3-(thiophenoxy)-1-propene	75 (>98)	11
5	 3-Methyl-but-3-ene-1-yne	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C 2.) I ₂ , THF, 0 °C	 (E)-1-Iodo-2,3-dimethylbutane	70	11

Table I. Carboalumination of terminal acetylenes. (Cont'd)


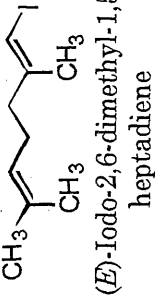
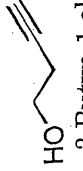
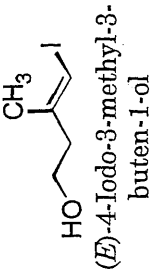
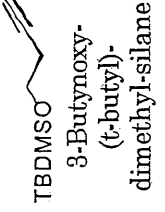
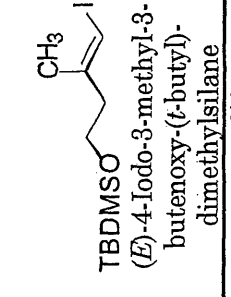
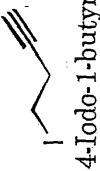
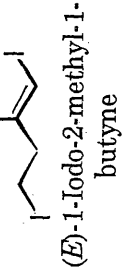
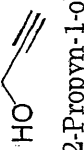
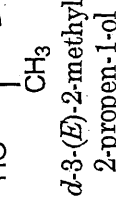
Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int. Term.)	Ref.
6	 2-Methylhept-2-ene-6-yne	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C 2.) I ₂ , THF, 0 °C	 (<i>E</i>)-Iodo-2,6-dimethyl-1,5-heptadiene	79	11
7	 HO-3-Butyn-1-ol	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C 2.) I ₂ , THF	 (<i>E</i>)-4-Iodo-3-methyl-3-buten-1-ol	85 (92 : 8)	7
8	 TBDMSO-3-Butynoxy-(<i>t</i> -butyl)-dimethylsilane	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C 2.) I ₂ , THF	 TBDMSO-4-Iodo-3-methyl-3-butenyloxy-(<i>t</i> -butyl)-dimethylsilane	52 (94 : 6)	7
9	 I-4-Iodo-1-butyne	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C 2.) I ₂ , THF	 (<i>E</i>)-1-Iodo-2-methyl-1-butyne	60	7
10	 HO-2-Propyn-1-ol	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-25 °C 2.) I ₂ , THF, 0 °C	 HO- <i>d</i> -3-(<i>E</i>)-2-methyl-2-propen-1-ol	41	7

Table I. Carboalumination of terminal acetylenes. (Cont'd)

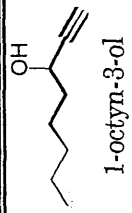
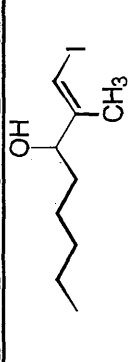
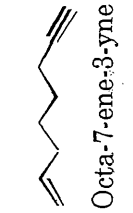

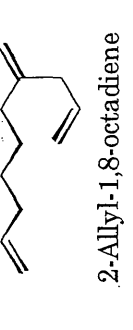

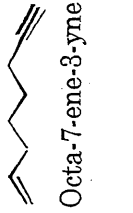

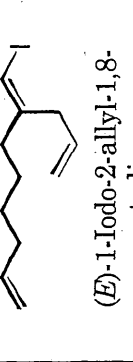
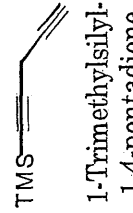

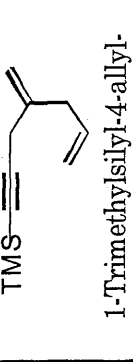
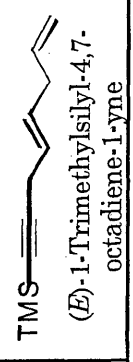



Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
11	 1-octyn-3-ol	Cp_2ZrI_2	AlMe_3	1.) DCE, 20-25 °C 2.) I_2 , THF	 (<i>E</i>)-Iodo-2methyl-1-octen-3-ol	77	7
12a	 Octa-7-ene-3-yne	Cp_2ZrCl_2		1.) DCE, 20-25 °C, 1 h 2.) H_3O^+	 2-Allyl-1,8-octadiene  (<i>E</i>)-1,4,10-undecatriene	95 (75 : 25)	15
12b	 Octa-7-ene-3-yne	Cp_2ZrCl_2		1.) DCE, 20-25 °C, 1 h 2.) I_2	 (<i>E</i>)-1-Iodo-2-allyl-1,8-octadiene	53 (98 : 2)	15
13a	 1-Trimethylsilyl-1,4-pentadiene	Cp_2ZrCl_2		1.) DCE, 20-25 °C, 2 h 2.) H_3O^+	 1-Trimethylsilyl-4-allyl-penta-4-ene-1-yne  TMS (<i>E</i>)-1-Trimethylsilyl-4,7-octadiene-1-yne	99 (65 : 35)	15

Table I. Carboalumination of terminal acetylenes. (Cont'd)

Entry	Alkyne	Cat.	Alane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
13b	 TMS-1-Trimethylsilyl-1,4-pentadiene	Cp_2ZrCl_2	 $\text{Al}(i\text{-Bu})_2$	1.) DCE, 20-25 °C, 2 h 2.) I_2 , THF	 TMS-5-Iodo-1-trimethylsilyl-4-allyl-penta-4-ene-1-yne	53 (>98)	15

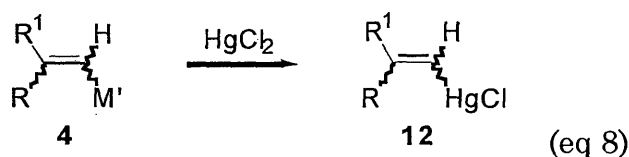
^a DCE = 1,2-dichloroethane

^b Some unidentified dimeric product was formed

hydroalumination.¹⁵ Entry 2-j demonstrates that benzylmetalation can be accomplished as well.¹⁹

The entries in Table I also indicate that a wide variety of functional groups can be tolerated. Alkynes containing conjugated and non-conjugated double bonds (*cf.* Entries 5 and 6), can be carbometalated. Similarly, heteroatom-containing acetylenes can be carbometalated (*cf.* Entries 4, 7, 8, 9 and 13). Although the regioselectivity in these reactions is high, it is somewhat dependent on the proximal heteroatoms.⁷

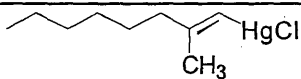
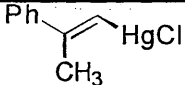
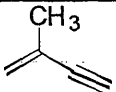
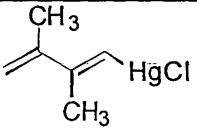
Alkenylmercuric chlorides represent a third class of compounds which can be accessed directly from the carbometalation reaction mixtures. Mercury(II) chloride reacts with the organometallic species **4** in anhydrous tetrahydrofuran to yield the organomercuric compound **12** (eq 8). Some



examples of these reactions are presented in Table II. Such compounds represent useful synthetic intermediates.²⁰ The products **12** were judged to be stereochemically pure (>98 %) by ¹³C NMR; an (*E*)-geometry was assigned on the basis of ¹⁹⁹Hg NMR.¹⁹ As before, the presence of a conjugated double bond

in the starting alkyne appeared to have no effect on either the carbometalation or the transmetalation step.




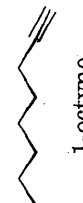




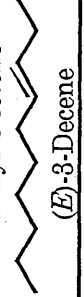


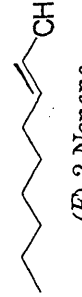
Table II. Conversion of terminal alkynes into alkenylmercuric chlorides via a trimethyl/cp₂zrcl₂ carbometalation.¹⁹

Entry	Alkyne	Product	Yield (%)	Stereochem. Purity (%)
1	$(n\text{-CH}_2)_6\text{-C}\equiv\text{CH}$ 1-Octyne		83	> 98
2	$\text{Ph-C}\equiv\text{CH}$ Phenylacetylene		81	ca. 95
3	 3-Methyl-but-3-ene-1-yne		75	> 98

Organozinc-Transition Metal Systems

Negishi, *et al.*, reported that organozinc compounds may be used in place of organoalanes in carbometalation reactions.¹⁸ As in the case of carboalumination, the organometallic intermediate 4 can be hydrolyzed with weak acid (eq 5) or iodinated (eq 7). A list of such reactions, specifically the ethyl- and methylation of 1-octyne is provided in Table III. In all cases reported, the formation of a single stereoisomer (>98 %) was observed, as established by ¹³C and ¹H NMR as well as by glc analysis.¹⁸ Entry 1-d shows that methylation has a higher regioselectivity than ethylation (Entry 1-a), under the same conditions.

Table III. Carbometalation of terminal acetylenes with organozincs.

Entry	Alkyne	Cat.	Organozinc	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
1-a	 1-octyne	Cp ₂ ZrI ₂	ZnEt ₂	1.) DCE, 20-22 °C, 3h 2.) H ₃ O ⁺	 2-Ethyl-1-octene  (E)-3-Decene	100 (76 : 24)	18
1-b	 1-octyne	Cp ₂ ZrI ₂	ZnEt ₂	1.) DCE, 20-22 °C, 3h 2.) I ₂	 (E)-Iodo-2-ethyl-1-octene  (Z)-4-Iodo-3-decene	100 (75 : 25)	18
1-c	 1-octyne	Cp ₂ ZrCl ₂	ZnEt ₂	1.) DCE, 50 °C, 48 h 2.) H ₃ O ⁺	 2-Ethyl-1-octene  (E)-3-Decene	56 (96 : 4)	18
1-d	 1-octyne	Cp ₂ ZrI ₂	ZnMe ₂	1.) DCE, 20-22 °C, 6 h 2.) H ₃ O ⁺	 2-Methyl-1-octene  (E)-2-Nonene	100 (95 : 5)	18

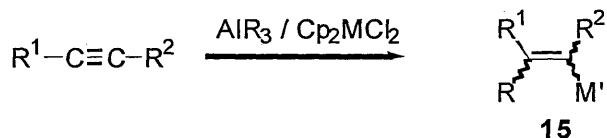
Ethylzinc chloride can replace diethylzinc without noticeable adverse effect in the carboalumination of 1-octyne. Other di-*n*-alkylzincs (e.g. *n*-Bu₂Zn) afford equally satisfactory results. Little or no β-elimination occurs with these reagents.¹⁸

One interesting aspect of the carbozincation is that Cp₂ZnI₂ **13** promotes reaction more effectively than its corresponding chloro- and bromo-analogs (*i.e.* Cp₂ZrCl₂ **5** and Cp₂ZrBr₂ **14**). This is demonstrated in Entries 1-b and 1-c of Table III. Although it has been reported that the reaction of alkynes with Me₂Zn and Cp₂ZnI₂ **13** is catalytic in the zirconocene, the reaction is very sluggish with less than one equivalent of **13**.¹⁸

CARBOMETALATION OF TERMINAL ALKYNES

Organoalane-Transition Metal Systems

As was the case with terminal acetylenes, internal acetylenes can also be stereoselectively carbometalated.³ The general equation for this transformation is analogous the Scheme 2, and is represented by Scheme 3.



R & R¹ = ORGANIC GROUPS

M = Zr or Ti

M' = Metal Containing Group

Scheme 3

For the most part, carbometalations of internal acetylenes are similar to the reactions of terminal acetylenes as described in the preceding section. These reactions exhibit the same compatibility with heterofunctional groups as well as conjugated and non-conjugated double bonds (*vide supra*). Some examples of this type of carbometalation are presented in Table IV.

That these reactions are stereoselective is evident in the methylation of 5-decyne (**16**) (Table IV, entry 1-a). The stereochemistry of the (*Z*)-5-methyl-5-decene (**17**) product has been established by ^{13}C NMR, and the stereoselectivity is > 98 %.³ Such is the also the case in the methylation of diphenylacetylene (**18**) (Table IV, entries 2-a & 2-b). It should be noted that the corresponding reaction of acetylene **18** with $\text{Me}_3\text{Al}/\text{Cp}_2\text{ZrCl}_2$ is much slower than with the corresponding titanocene analog. This zirconocene catalyst also affords the desired (*Z*)-1,2-diphenyl-1-propene (**19**) in lower yield (< 30 %), and is complicated by the formation of an unidentified by-product.

An interesting side reaction occurred in the methylation of 5-decyne (**16**) with an aluminum-titanium catalyst. Entry 1-b demonstrates that an allyene, 6-methyl-4,5-decadiene (**20**), was formed instead of the expected product (*Z*)-5-methyl-5-decene (**17**). The ^1H NMR spectrum of the reaction mixture was not informative due to the line broadening of the signals caused presumably by the presence of paramagnetic Ti species.⁹ Negishi, *et al.*, tentatively concluded that the carbometalation of alkyne **16** took place as

Table IV. Carbometalation of internal acetylenes.


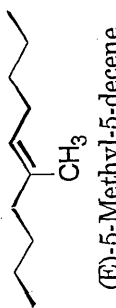

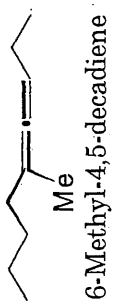
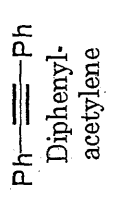
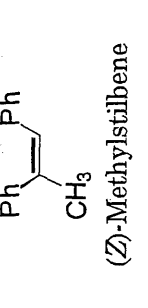
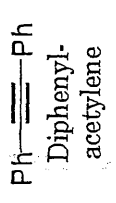
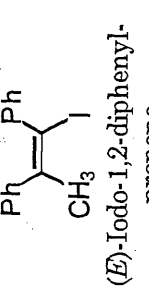
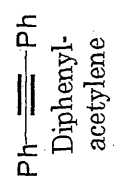
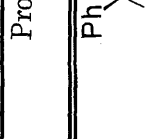

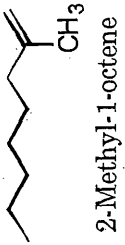

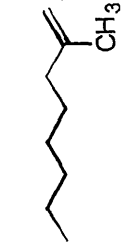
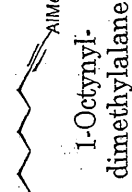
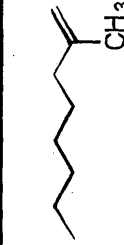
Entry	Alkyne	Cat.	Organoalane	Conditions ^a	Product(s)	Yield (Int. Term.)	Ref.
1-a	 5-Decyne	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 50 °C, 6h 2.) H ₃ O ⁺	 (E)-5-Methyl-5-decene	89 (> 98)	3
1-b	 5-Decyne	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 6-Methyl-4,5-decadiene	92	9
2-a	 Diphenyl- acetylene	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 (Z)-Methylstilbene	84 (> 98)	9
2-b	 Diphenyl- acetylene	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) I ₂	 (E)-Iodo-1,2-diphenyl- propene	75 (> 97)	9

Table IV. Carbometalation of internal acetylenes. (Cont'd)

Entry	Alkyne	Cat.	Organoalane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
2-c	 Diphenyl- acetylene	Cp ₂ ZrCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 (Z)-Methylstilbene	< 30 *	9
3-a	 1-Octynylzinc chloride	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 2-Methyl-1-octene	75	9
3-b	 1-Octynyl- dicyclohexyl borane	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 2-Methyl-1-octene	81 (> 98)	9
3-c	 1-Octynyl- dimethylalane	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 2-Methyl-1-octene	84	9

* Reaction Complicated by Formation of Byproduct

Table IV. Carbometalation of internal acetylenes. (Cont'd)

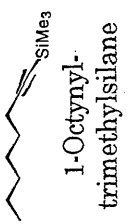
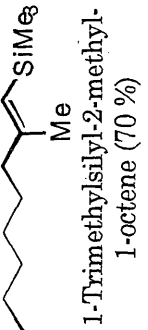
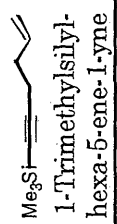
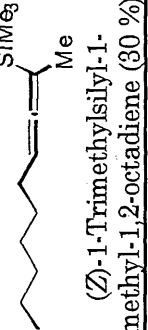
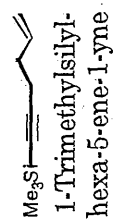
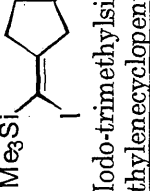
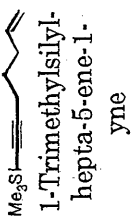
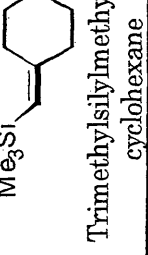
Entry	Alkyne	Cat.	Organoalane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
3-d	 1-Octynyl-trimethylsilyl silane	Cp ₂ TiCl ₂	AlMe ₃	1.) DCE, 20-22 °C, 12h 2.) H ₃ O ⁺	 1-Trimethylsilyl-2-methyl-1-octene (70 %)	80	9
4-a	 1-Trimethylsilyl-1-hexa-5-ene-1-yne	Cp ₂ ZrCl ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 20-22 °C, 18h 2.) H ₃ O ⁺	 (<i>Z</i>)-1-Trimethylsilyl-1-methyl-1,2-octadiene (30 %)	85	16
4-b	 1-Trimethylsilyl-1-hexa-5-ene-1-yne	Cp ₂ ZrCl ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 20-22 °C, 18h 2.) I ₂	 1-Iodo-1-trimethylsilyl-1-methylcyclopentane	68	16
5	 1-Trimethylsilyl-1-hepta-5-ene-1-yne	Cp ₂ ZrCl ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 20-22 °C, 18h 2.) H ₃ O ⁺	 1-Trimethylsilyl-1-methylcyclohexane	72	16

Table IV. Carbometalation of internal acetylenes. Cont'd

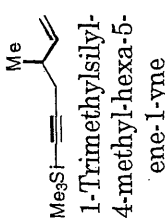
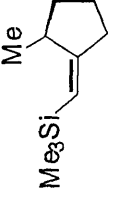
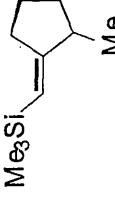
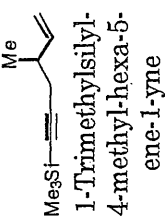
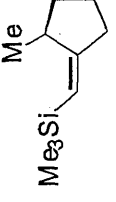
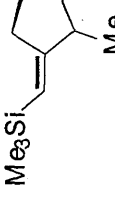


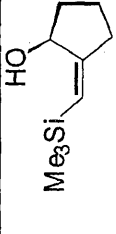
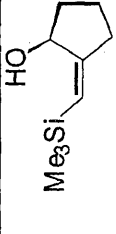


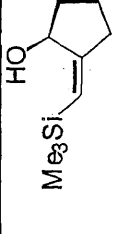
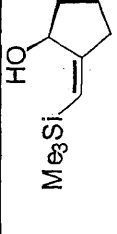
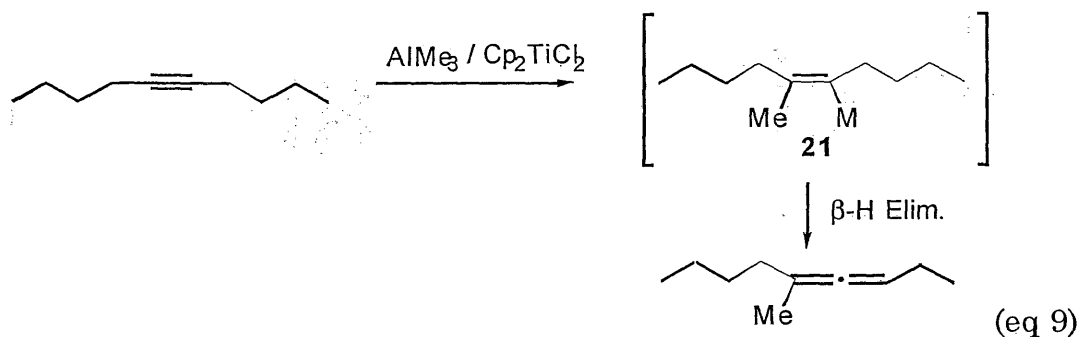
Entry	Alkyne	Cat.	Organoalane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
6-a	 <p>Me₃Si-1-Trimethylsilyl-4-methyl-hexa-5-ene-1-yne</p>	Cp ₂ ZrCl ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 20-22 °C, 18h 2.) H ₃ O ⁺	 <p>Me₃Si-<i>(Z)</i>-Trimethylsilyl-2-methylcyclopentane (50 %)</p>  <p>Me₃Si-<i>(E)</i>-Trimethylsilyl-2-methylcyclopentane (50 %)</p>	79	16
6-b	 <p>Me₃Si-1-Trimethylsilyl-4-methyl-hexa-5-ene-1-yne</p>	Cp ₂ ZrI ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 20-22 °C, 6h 2.) H ₃ O ⁺	 <p>Me₃Si-<i>(Z)</i>-Trimethylsilyl-2-methylcyclopentane (20 %)</p>  <p>Me₃Si-<i>(E)</i>-Trimethylsilyl-2-methylcyclopentane (80 %)</p>	71	16

Table IV. Carbometallation of internal acetylenes. (Cont'd)

Entry	Alkyne	Cat.	Organoalane	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
7-a	 <p>Me₃Si--1-Trimethylsilyl-4-hydroxy-hexa-5-ene-1-yne</p>	Cp ₂ ZrCl ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 20-22 °C, 4h 2.) 3 N NaOH	 <p>Me₃Si--HO (Z)-Trimethylsilyl-2-hydroxy-cyclopentane (90 %)</p>	82	16
7-b	 <p>Me₃Si--1-Trimethylsilyl-4-hydroxy-hexa-5-ene-1-yne</p>	Cp ₂ ZrI ₂	Al(<i>i</i> -Bu) ₃	1.) DCE, 60 °C, 6h 2.) H ₃ O ⁺	 <p>Me₃Si--HO (E)-Trimethylsilyl-2-hydroxy-cyclopentane (10 %)</p>	74	16

expected, but that the carbometalated intermediate **21** underwent dehydrometalation under the carbometalation conditions (eq 9).⁹



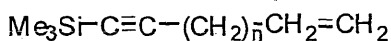
To overcome this allene formation, as well as the titanium-catalyzed dimerization of substrates illustrated in Table I, Entry 2-b, the carbometalation of metal-substituted alkynes was attempted. Entries 3-a, -b and -c demonstrate the successful methylation of these moieties in high yields. In no case was there any evidence for the formation of 2,3-nonadiene, the putative product formed *via* dehydrometalation.⁹ However, the reaction of the trimethylsilyl-substituted alkyne (Entry 3-d) did lead to the formation of an allenic product presumably arising from β -hydride elimination.⁹ Despite these findings, the compatibility of the carbometalation system with such metal-substituted alkynes was demonstrated.

Cyclization Reactions

An interesting case of the carbometalation of internal acetylenes involves selectively hydroaluminating the alkene functionality of suitably

structured enynes to access the alkynylalanes required for the cyclic carboalumination.¹⁶ It is known that diisobutylaluminum hydride (DIBAL) selectively reacts with alkynes in the presence of alkenes.¹¹ Indeed, the reaction of 1-octene and either 5-decyne (**16**) or 1-trimethylsilyl-1-octyne with one equivalent of DIBAL in hexane involves a selective hydroalumination of the acetylene. However, when a 1 : 1 mixture of 1-octene and 1-trimethylsilyl-1-octene was subjected to Zr-catalyzed hydroalumination with one equivalent of DIBAL and 10 mol % Cp₂ZrCl₂, *n*-octane was generated in high yield after 24 hours at room temperature followed by protonolysis.¹⁶ The results of this competition experiment demonstrate a methodology for selectively hydroalumination of a terminal alkyne in the presence of a trimethylsilylalkyne.¹⁶ Interestingly, the corresponding reaction of DIBAL and a catalytic amount of Cp₂ZrCl₂ with 1-octene does not proceed to any detectable extent (< 1-2 %) in 6 h at 0 °C.¹³

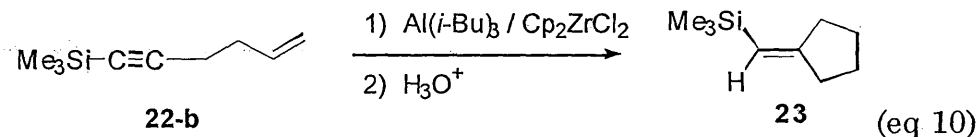
With this method in hand, Negishi and co-workers synthesized a series of trimethylsilyl-substituted enynes **22** and subjected them to carbometalation reaction conditions. Entry 4-a in Table IV shows that



$$n = 1 - 4$$

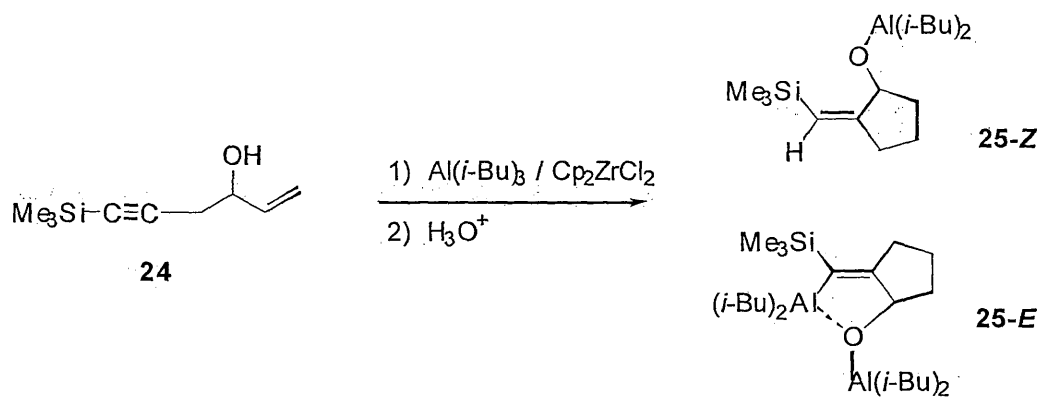
22

treatment of **22-b** ($n=2$) with 1.1 equivalents of triisobutylaluminum in the presence of 10 mol % of Cp_2ZrCl_2 in 1,2-dichloroethane for 18 hours cleanly affords, after protonolysis, the desired cyclic olefin **23** in 85 % yield (eq 10).

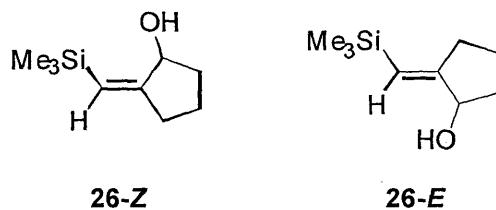


Similarly, entry 4-b shows that treatment of the reaction mixture with 1.25 equivalents of iodine affords the corresponding iodide in 68 % yield, indicating that the product before iodinolysis was an alkenylmetal species.¹⁶ The six-membered ring analog was produced in a similar manner for **22-c** ($n = 3$) in 72 % yield, however, efforts to prepare the four- and seven-membered ring *via* this route proved unsuccessful.¹⁶

An interesting effect was observed during an attempt to make use of the stereodirective effects of proximal polar substituents, such as hydroxyl, in the carbometalation of alkynes. It was surmised that an alane would react more strongly with an oxy functionality. A test substrate, 1-trimethylsilylhex-5-en-1-yn-3-ol **24** was prepared, and carbometalation of this alkyne under equilibrating conditions was expected to favor formation of the (*E*)-alkenylalane **25-E**. Under kinetic conditions (*cf.* Table IV, entry 7-a),



the substrate was carbometalated to afford (*Z*) : (*E*)-alkenols in a 90 : 10 ratio. However, when the reaction mixture was allowed to equilibrate at 60 °C before quenching, this ratio changed to favor the thermodynamic product **26-E** derived from the coordinatively-stabilized intermediate **25-E**. These



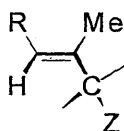
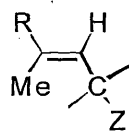
examples (Entries 7-a and -b) demonstrate the formation of products from kinetic and thermodynamic control respectively.¹⁶

Organozinc-Transition Metal Systems

In the carbometalations of internal alkynes, organozinc compounds may be substituted for organoalanes in the bimetallic catalyst system. A listing of such carbometalation systems is given in Table V. Although the examples are few in number, they demonstrate the ability of the system to add ethyl (Entry 1-a), allyl (Entries 1-b and -c), and (*E*)-crotyl groups (Entry 2) to internal acetylenes with good stereoselectivity.

SYNTHETIC UTILITY OF CARBOMETALATED PRODUCTS


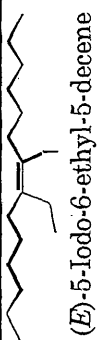


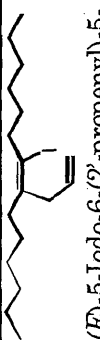
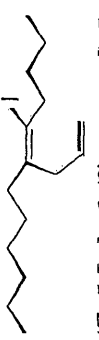


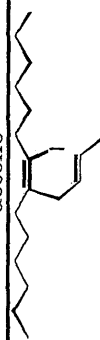
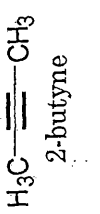

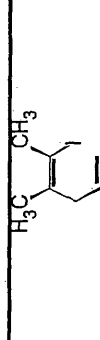
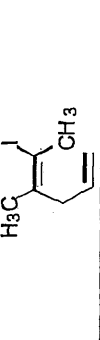
Many of the carbometalated products described thus far represent useful intermediates in the synthesis of natural products. For example, a wide variety of natural products, in particular terpenoids, are either represented by, or can be readily be accessed from, terminally functionalized (*E*)-2-methyl-2-alkenes **27** and/or (*E*)-3-methyl-2-alkenes **28**.¹⁰ Whereas

**27****28**

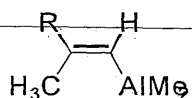
Z = HETEROFUNCTIONAL GROUP

various satisfactory methods for the synthesis of the former compounds **27** are now available, there are a limited number of highly stereoselective routes

Table V. Carbözirconation of internal acetylenes.

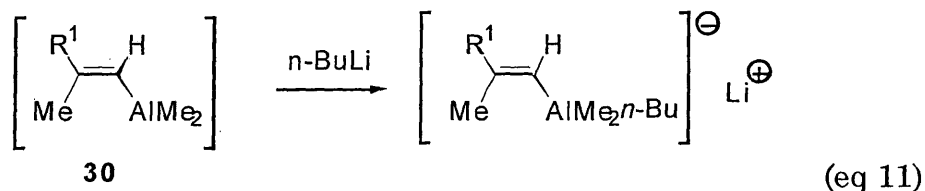
Entry	Alkyne	Cat.	Organozinc	Conditions ^a	Product(s)	Yield (Int.:Term.)	Ref.
1-a	 5-Decyne	Cp ₂ ZrCl ₂	ZnEt ₂	1.) DCE, 20-22 °C, 6h 2.) I ₂	 (E)-5-Iodo-6-ethyl-5-decene	88 (> 98 %)	18
1-b	 5-Decyne	Cp ₂ ZrCl ₂		1.) DCE, 20-22 °C, 6h 2.) I ₂	 (E)-5-Iodo-6-(2'-propenyl)-5-decene  (Z)-5-Iodo-6-(2'-propenyl)-5-decene	84 (96 : 4)	14
1-c	 5-Decyne	Cp ₂ ZrCl ₂		1.) DCE, 20-22 °C, 6h 2.) I ₂	 (E)-5-Iodo-6-((E)-2'-butenyl)-5-decene	92	14
2	 H ₃ C-C≡C-CH ₃ 2-butyne	Cp ₂ ZrCl ₂		1.) DCE, 20-22 °C, 18h 2.) I ₂	 (Z)-2-Iodo-3-methyl-2,6-hexadiene  (E)-2-Iodo-3-methyl-2,6-hexadiene	92 (80 : 20)	14

to the latter **28**.¹⁰ The finding of Negishi, *et al.*, that carbometalated products essentially consist of (*E*)-2-methylalkenyl alanes **XX** prompted the evaluation

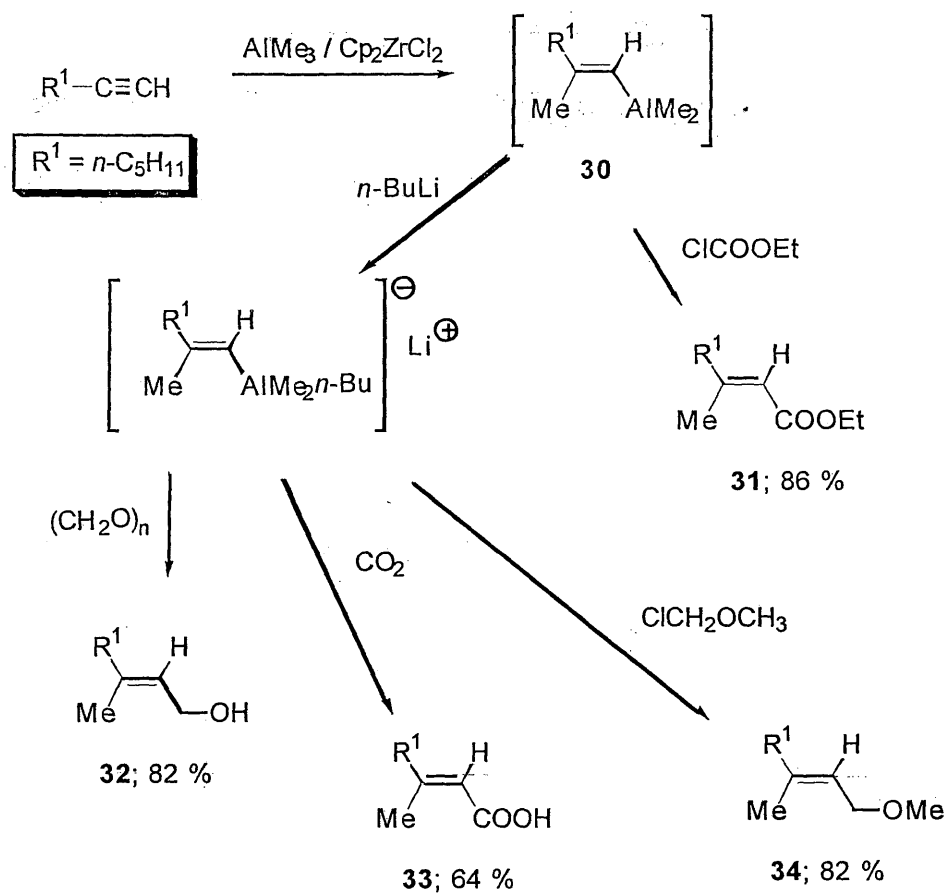


29

of converting **29** to **28** *via* known one-carbon homologation reactions of alkenylalanes.¹⁰ As a model system, 1-heptyne was carbometalated with an AlMe₃/Cp₂ZrCl₂ catalyst, and the resulting organoalane **30** was allowed to react with carbon-based electrophiles either directly, or after *in situ* conversion to the ate complex (eq 11). The experimental results obtained by

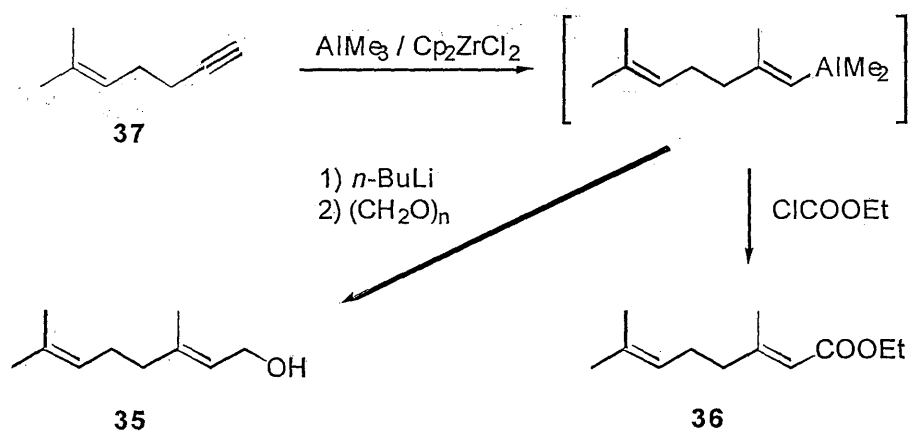


Negishi, *et al.*, are summarized in Scheme 4.¹⁰ The stereoselectivity in each case was > 98 % as judged by ¹H and ¹³C NMR and GLC.¹⁰ The one-carbon homologated products are not contaminated with any more than traces (< 2 %) of their regioisomers, except for ethyl-(*E*)-3-methyl-2-octonate (**31**) which was contaminated to the extent of *ca.* 5 %.¹⁰

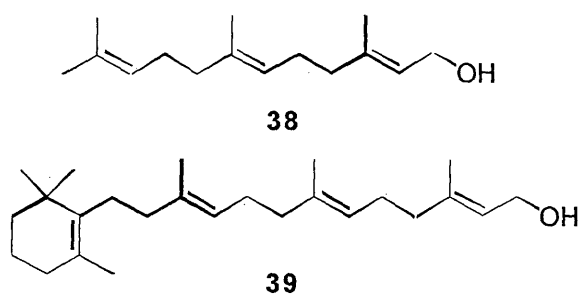


Scheme 4

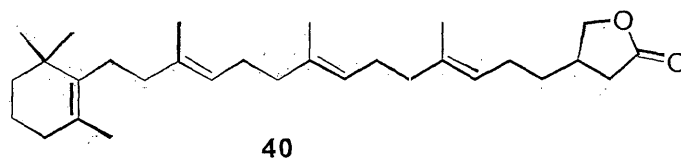
With this method in hand, Negishi, *et al.*, synthesized two natural products, geraniol (**35**) and ethyl geranate (**36**), in one step from 6-methyl-5-heptene-1-yne (**37**).¹⁰ The alcohol **35** was prepared in 87 % yield, and the ester **36** in 85 % yield by this method.¹⁰



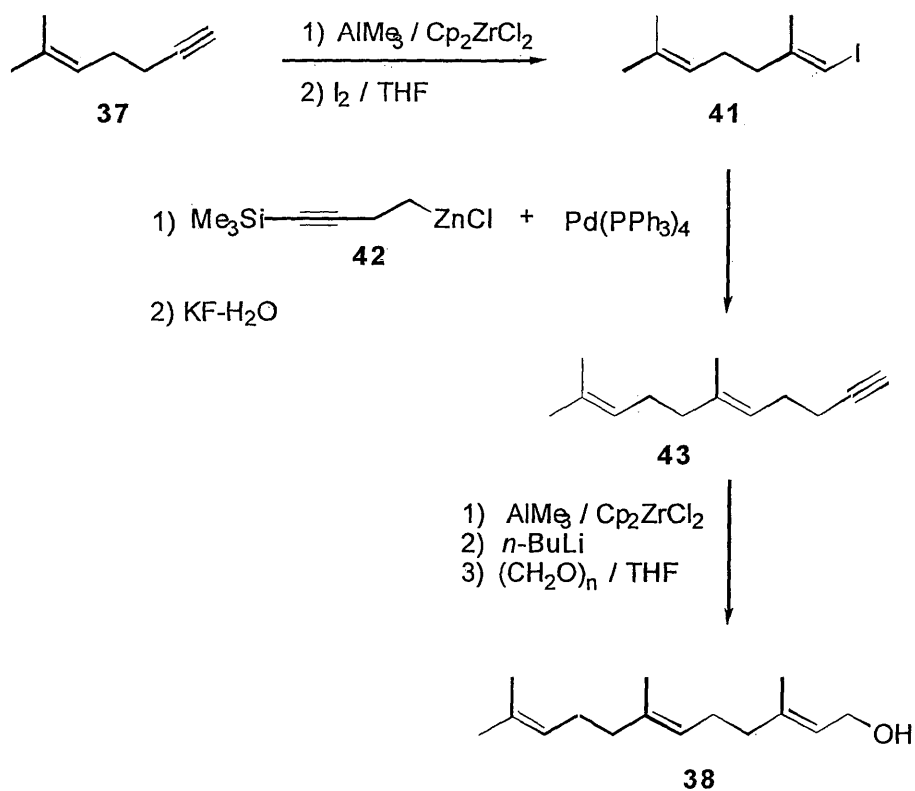
Multiple carbometalations, when combined with palladium-catalyzed cross-coupling and homologation reactions, can be used to synthesize long-chain terpenoids. Negishi, *et al.*, used a combination of these reactions to prepare sesquiterpenol (*E,E*)-farnesol (**38**), and a tetraenol **39**.²¹ The tetra-



enol **39** is a target intermediate in Sum and Weiler's synthesis of mokupalide (**40**), a hexaprene found in a Pacific marine sponge.²² The synthesis of



(*E,E*)-farnesol is given in Scheme 5. An appropriate alkyne, 6-methyl-hept-5-en-2-yne (**37**) was first carbometalated and then subjected to iodinolysis



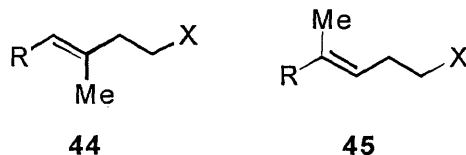
Scheme 5

to afford the iodide **41**. This iodide is then cross-coupled with the trimethylsilyl derivative of homopropargylzinc chloride **42** using tetrakis(triphenylphosphine)palladium (0).²³ The trimethylsilyl group is then

removed with potassium fluoride to afford the dienyne **43**. Without further purification, **43** was subjected to the second carbometalation followed by ate complexation and treatment with paraformaldehyde, as previously described.²¹ Examination of the unpurified product by GLC and ¹H NMR indicated the formation of *ca.* 95 % pure (*E,E*)-farnesol (**38**).²¹

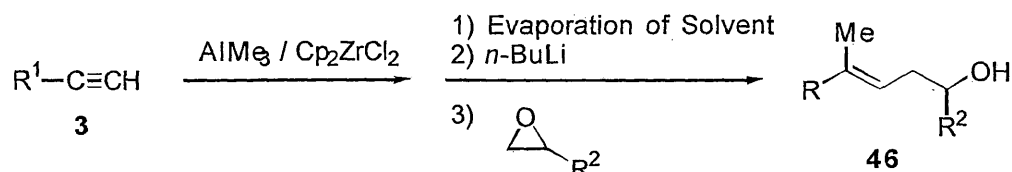
One distinctly attractive feature of this methodology is that the two-step cycle consisting of carbometalation-iodinolysis and cross-coupling can readily be repeated for the construction of long-chain 1,5-diene skeletons. Thus, no major difficulty was encountered in synthesizing tetraenol **39** by twice applying the two-step cycle. Here again, the overall process is estimated to be > 98 % stereoselective.²¹

Homoallylic derivatives, represented by **44** and **45**, are useful inter-



mediates for the synthesis of terpenoids. While the Julia-Johnson synthesis²⁴ is usually highly stereoselective (> 95 %) for the synthesis of alkene **44** (X = Br), its application to the synthesis of **45** typically leads to a *ca.* 75 : 25 mixture of *trans*- and *cis*-isomers.²⁵ Accordingly, Negishi, *et al.*, undertook to develop an efficient and selective route to compounds of the type **45** by

combining two reactions developed by them: 1.) The zirconium-catalyzed carboalumination of acetylenes, and; 2.) The reaction of alkenylaluminates with epoxides to form homoallylic alcohols.²⁶ With this method, homoallylic alcohols represented by **46** can be synthesized from terminal alkynes **3** (Scheme 6). In each case, the stereoselectivity of the overall process is > 98 %



Scheme 6

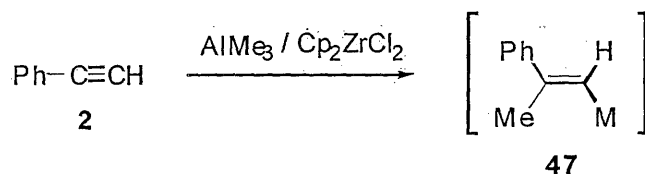
as determined by GLC analysis as well as by ¹H and ¹³C NMR spectroscopy.²⁵

A variety of other reactions resulting in synthetic intermediates is also possible. As was previously described, the organometallic compound **4** resulting from carboalumination (*cf.* Scheme 2) can lead to a number of trisubstituted olefins including iodides, alkenylmercuric chlorides and exocyclic silanes. The metal group in **4** can also be replaced with two- and multi-carbon groups such as hydroxyethyl, γ -oxoalkyl, alkyl, homoallyl, homobenzyl, homopropargyl, allyl, benzyl, aryl, alkenyl, alkynyl, heteroaryl, and acyl groups.⁶ Several proximal heterofunctional groups such as: Me₃Si, -OH, -OSi-*t*-BuMe₂, -SPh, -Br and -I can be tolerated in the propargylic and/or homopropargylic positions.⁶ The ability of the carbometalation reaction to

provide a pathway to all these derivatives makes it a potentially powerful synthetic tool.

THE MECHANISM OF CARBOMETALATION

One aspect of the carbometalation which remains to be addressed is that of the reaction mechanism. Since the carbometalation of alkynes requires the simultaneous presence of an organoalane and a zirconium-containing species, the reaction must involve an Al-assisted carbozirconation and/or a Zr-assisted carboalumination in the crucial carbon-carbon bond forming step.¹² The analogous process should hold true for organoalane/titanium systems. Unfortunately, NMR spectroscopy proved to be of limited value in the elucidation of the nature of the carbon-metal bond in the titanium-containing systems. Negishi, *et al.*, reported that attempts to elucidate the structure of these organometallic moieties were severely hampered by the formation of paramagnetic species under the reaction conditions.⁹ Despite this drawback, their investigation of zirconium-containing systems was more fruitful. The reaction of phenylacetylene (2) with AlMe_3 / Cp_2ZrCl_2 proceeds through a mixture of an (*E*)-2-phenylpropenylalane species 47 (*ca.* 95 %) with the remainder as the corresponding

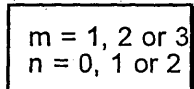


organozirconium species.³ This finding is consistent with the Zr-assisted carboalumination pathway.

Turning to the bimetallic catalyst system, Negishi, *et al.*, report that although the exact structure of the $\text{AlMe}_3 / \text{Cp}_2\text{ZrCl}_2$ reaction product has not been elucidated, the formation of an organozirconium species, which rapidly exchanges a methyl group with methylalanes, has been clearly indicated by ^1H NMR.³ An NMR study of such an Al-Zr system was performed in which the active species was quenched with THF. The chemical shifts and relative intensities indicate that the quenched mixture consisted of Cp_2ZrCl_2 , Cp_2MeZrCl , $\text{Me}_3\text{Al-THF}$, and $\text{Me}_2\text{AlCl-THF}$. The ratio of Cp_2ZrCl_2 : Cp_2MeZrCl was found to be 1 : 2, and no Cp_2ZrMe_2 was observed.³ In a later study, Negishi, *et al.*, examined the reagent system 48 and varied the ratio of the constituents \underline{m} and \underline{n} and measured the respective ^1H NMR spectra (from



48

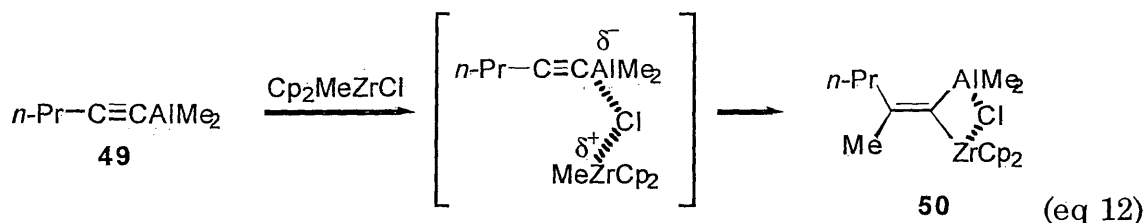


-50 to 80 °C) as well as their reaction with 1-heptyne.¹² The results indicated that Me-Cl exchange which is rapid on the NMR time scale at ambient temperature (*ca.* 25 °C) is observed only with the AlMe₃ / Cp₂ZrCl₂ system. And yet all four reagent systems undergo the desired carbometalation.¹² This finding indicates that Me-Cl exchange between the alane and zirconium moieties is unnecessary to effect carbometalation, further supporting the carboalumination pathway.

To probe the critical question of Al-assisted carbozirconation vs. Zr-assisted carbalumination, Negishi, *et al.*, allowed 1-heptyne to react with a mixture of AlEt₃ and Cp₂MeZrCl **6**. This reaction afforded a 70 :30 mixture of 2-ethyl-heptene and (*E*)-3-nonene in 93 % yield with only traces, if any, of the corresponding methylated alkenes. The results of this competition experiment are not only consistent with direct carboalumination, and is inconsistent with direct carbozirconation.¹²

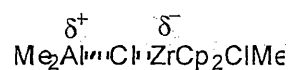
To rule out any effects arising from differences between the transfer of methyl and ethyl, the authors then reacted 1-heptyne with a 1 : 1 mixture of AlMe₃ and Cp₂(CD₃)ZrCl. The iodinolysis product obtained from this reaction mixture is stereochemically pure (> 98 %) (*E*)-iodo-2-methyl-1-heptene contaminated with a trace amount of (*Z*)-iodo-2-octene. The extent of deuterium incorporation was less than 4 %.¹²

A special case in which Al-assisted *carbozirconation* apparently takes place is the reaction of 1-alkynyl dimethylalane **49** with preformed Cp_2MeZrCl .⁶ These reagents in a 1 : 1 ratio afford cleanly and quantitatively the carbozirconated product **50**, thereby providing a clear-cut example of carbozirconation of alkynes (eq. 12).¹² Negishi concludes that the



Zr-catalyzed carbometalation of terminal alkynes, at least in some cases, proceeds through a Zr-assisted carboalumination. It is not unreasonable to conclude that the Al-Zr reagent systems may effect either carboalumination or carbozirconation of alkynes, depending on the reaction parameters involved.¹² The relationship between two coordinatively unsaturated species containing Al or Zr suggest that the electronegativities of these two metals are comparable. The Pauling electronegativity values for Al and Zr are 1.5 and 1.4 respectively.⁶ Indeed, the electronegativity value for Ti is also a comparable 1.5.²⁷

Finally, the presumed significance of polarization in reactive intermediates, such as **51**, was probed by examining the effect of solvent on



51

the rate of reaction. As would be expected for the case when such a polar intermediate was formed, the rate of reaction of phenylacetylene (2) with $\text{AlMe}_3 / \text{Cp}_2\text{ZrCl}_2$ in 1,2-dichloroethane (DCE, $\epsilon = 10.37$), chlorobenzene ($\epsilon = 5.61$), and benzene ($\epsilon = 2.27$) decreases as the dielectric constant of the solvent decreases.⁶

EXPERIMENTAL

Carbometalation System: Alkynol + $\text{AlR}_3 + (\eta^5\text{-C}_5\text{H}_5\text{-mMe}_m)_2\text{TiCl}_2$

REAGENTS

The alkynols, 4-pentyn-2-ol (Farchan Labs OA-545), 3-butyn-1-ol (Farchan Labs 1790-8), and 3-pentyn-1-ol (Aldrich 20,869-8), were stored over 5 Å molecular sieves (Aldrich 20,862-0), and were used without further purification. The organoalanes, trimethylaluminum (Aldrich 25,722-2) and diethylaluminum chloride (Ethyl Corp.), were stored under nitrogen and were used without further purification. Transfers of these compounds were made in a dry box owing to their pyrophoric nature. Two titanium complexes, $(\text{Me}_3\text{Cp})_2\text{TiCl}_2$ and $(\text{Me}_5\text{Cp})_2\text{TiCl}_2$, were synthesized for this study. Their syntheses are reported in this section (*vide infra*). The titanocene $(\text{MeCp})_2\text{TiCl}_2$ was donated by Hercules Inc., and was used without further purification. Dichloromethane was purified by distillation over phosphorous pentoxide (Aldrich 21,470-1) under an atmosphere of nitrogen. The saturated alcohols, 1-heptanol (Eastman 381) and 1-octanol, were used as internal standards to calculate yields. Both were stored over Linde 4 Å molecular sieves, and were used without further purification. D_2O (Aldrich 15,188-2) was used without further purification, and sodium deuterioxide (Aldrich 17,678-8) was used as a 40 wgt. % solution in D_2O .

GENERAL PROCEDURE FOR THE CARBOMETALATION OF ALKYNOLS

The following description is representative of a typical carbometalation reaction. In order to minimize the chance of contamination by either air or moisture, a special apparatus for these reactions was constructed (Figure 4).

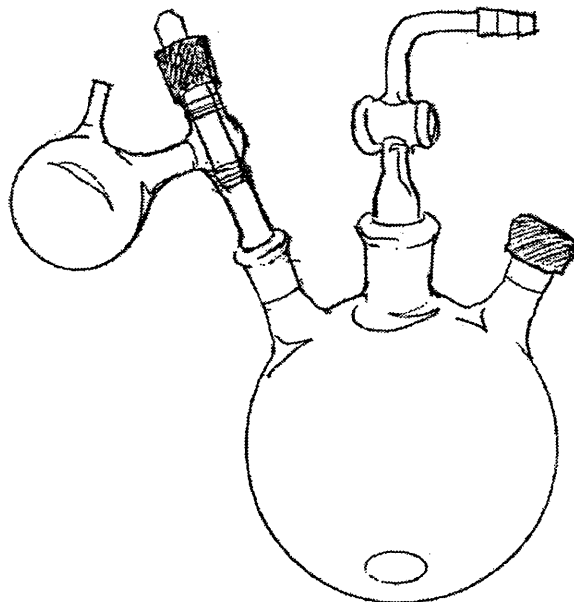


Figure 4. Carbometalation Apparatus

This apparatus was taken into a dry box where the bottom flask was charged with a measured amount of the titanium catalyst, anhydrous CH_2Cl_2 (20 mL) and a magnetic stirbar. The top bulb was charged with anhydrous CH_2Cl_2 (20 mL), the organoalane, and a magnetic stirbar. The apparatus was then sealed, removed from the dry box, and clamped in a hood under an atmosphere of dry nitrogen.

The top flask was cooled in an ice bath, and a measured amount of alkynol substrate was injected therein. The bottom flask was then cooled in an ice bath. At this point, the top flask was rotated so as to allow the organoaluminum solution to flow into the organotitanium solution in the bottom flask. Typically the resulting carbometalation mixture was allowed to stir for 2 h before the reaction was quenched. The reactions were quenched with either methanol or 1-deutromethanol (Aldrich 15,188-2), followed by 1*N* HCl (15 mL) in saturated salt solution.

CARBOMETALATION OF 3-BUTYN-1-OL

3-Butyn-1-ol was methylmetalated with $(\text{MeCp})_2\text{TiCl}_2$ and AlMe_3 in a 1 : 0.5 : 3 mol ratio of alkynol : titanocene : organoalane respectively. The reaction was carried out at 0 °C for 2 h, producing both internal and terminal methylation products (*i.e.* 3-methyl-3-buten-1-ol and (*E*)-3-penten-1-ol) in a 77 : 23 ratio respectively. When the reaction was carried out at 25 °C for 2 h with the same ratio of reactants, essentially the same ratio of products was observed.

The same alkynol was then methylmetalated with $(\text{Me}_3\text{Cp})_2\text{TiCl}_2$ and AlMe_3 in the same 1 : 0.5 : 3 mol ratio. After 2 h of reaction at 0 °C, a 95 : 5 ratio of internal : terminal products was obtained in 55 % yield.

3-Butyn-1-ol was methylmetalated with $(\text{Me}_5\text{Cp})_2\text{TiCl}_2$ and AlMe_3 in a 1 : 0.2 : 2 mol ratio. After 2 h of reaction at $-23\text{ }^\circ\text{C}$, essentially a single product isomer (presumably arising from internal addition) was obtained. The yield of this reaction, based on a 1-heptanol internal standard, was calculated to be 33 %.

CARBOMETALATION OF 3-PENTYN-1-OL

3-Pentyn-1-ol was methylmetalated with $(\text{MeCp})_2\text{TiCl}_2$ and AlMe_3 in a 1 : 0.25 : 2 mol ratio of alkynol : titanocene : organoalane respectively. The reaction was carried out at $0\text{ }^\circ\text{C}$ for 2 h, producing both internal and terminal methylation products (*i.e.* (*Z*)-3-methyl-3-penten-1-ol and 4-methyl-3-penten-1-ol) in a 97 : 3 ratio respectively. When the reaction was carried out with a 2 : 1 : 5 mol ratio of reactants at $25\text{ }^\circ\text{C}$ a product ratio of 9 : 1 was observed.

The same alkynol was then methylmetalated with $(\text{Me}_3\text{Cp})_2\text{TiCl}_2$ and AlMe_3 in a 1 : 0.25 : 3 mol ratio. After 2 h of reaction at $0\text{ }^\circ\text{C}$, a single product isomer was afforded in 6 % yield.

CARBOMETALATION OF 4-PENTYN-2-OL

4-Pentyn-2-ol was methylmetalated with $(\text{Me}_3\text{Cp})_2\text{TiCl}_2$ and AlMe_3 in a 1 : 0.5 : 3 mol ratio of alkynol : titanocene : organoalane respectively. The reaction was carried out at $0\text{ }^\circ\text{C}$ for 2 h, producing both internal and terminal

methylation products (*i.e.* 4-methyl-4-penten-2-ol and (*Z*)-4-hexene-2-ol) in a 98 : 2 ratio respectively. The reaction afforded 81 % yield, based on a 1-heptanol internal standard.

CARBOMETALATION OF 4,*O*-DIDEUTERO-3-BUTYN-1-OL

The labeled alkynol, 4,*O*-dideutero-3-butyn-1-ol, was prepared by stirring a solution of 3-butyn-1-ol (15 mL), D₂O (30 mL), and NaOD (*ca.* 0.125 mL) for 4 days. The solution was then extracted with ethyl ether (3 x 30 mL). The solvents were removed *in vacuo*, and a ¹H NMR spectrum was measured. The alkynol was subjected to methylmetalation with (MeCp)₂TiCl₂ and AlMe₃ in a 1 : 0.5 : 5 mol ratio of alkynol : titanocene : organoalane respectively. The reaction was carried out at 0 °C for 2 h. After this interval, the reaction was quenched with CH₃OD (2 mL) followed by D₂O (5 mL). A ¹H NMR spectrum confirmed that the carbometalation occurred *via* the *syn*-addition of the methyl-metal bond. The results of this study will be discussed in a later section.

CARBOMETALATION OF 3-BUTYN-1-OL QUENCHED WITH CH₃OD/D₂O

In order to verify further the *syn*-addition described in the preceding methylation, 3-butyn-1-ol was methylmetalated with (MeCp)₂TiCl₂ and Me₃Al in a 1 : 0.5 : 5 mol ratio of alkynol : titanium complex : organoalane.

The reaction was carried out for 2 h at 0 °C. At this time, the reaction was quenched with 2 mL of CH₃OD followed by 5 mL of D₂O. A ¹H NMR spectrum confirmed that the carbometalation occurred *via* the *syn*-addition of the methyl metal bond. The results of this study will be presented in a later section.

SYNTHESIS OF RING-SUBSTITUTED BIS-(η^5 -CYCLOPENTA- DIENYL) TITANIUM (IV) DICHLORIDE COMPOUNDS

SYNTHESIS OF BIS-(η^5 -1,3,4-TRIMETHYLCYCLOPENTADIENYL) TITANIUM (IV) DICHLORIDE

REAGENTS

Crotonic acid (Aldrich 11,301-8), 2-propanol (Fisher A-415), and polyphosphoric acid (Aldrich 20,821-3) were used without further purification. Diethyl ether (Anhydrous, Fisher, E-138) and tetrahydrofuran (Burdick and Jackson Labs.) were distilled over lithium aluminum hydride. Methylmagnesium iodide (Aldrich 25,436-3) was used as a 3.0 *M* solution in diethyl ether. Methyl lithium (Aldrich 19,734-3) was used as a 1.4 *M* solution also in diethyl ether. Titanium trichloride (Aldrich, 22,097-3) was used

without further purification as was concentrated hydrochloric acid (Fisher, A-144 °C).

PREPARATION OF ISOPROPYL CROTONATE

A 1-liter round-bottomed flask was charged with crotonic acid (96 g, 1.1 mol), 2-propanol (210 mL, 2.7 mol), concentrated H_2SO_4 (5 mL), and benzene (350 mL). The resulting solution was refluxed over a Dean-Stark trap overnight. A total of 29 mL of water was collected over this interval. The yellow-gold solution was allowed to cool, and was then diluted with lab grade ether (300 mL). The solution was washed with saturated NaHCO_3 (4 x 75 mL). The organics were dried over MgSO_4 and filtered. The solvents were removed in vacuo, and the residue was distilled (b.p. = 120-140 °C) to afford 112 g of the product ester (80 % yield).

PREPARATION OF 3,4-DIMETHYLCYCLPENT-2-EN-1-ONE

A 1-liter three-necked round-bottomed flask was set up under an overhead stirrer and was outfitted with a 250 mL addition funnel. The flask was charged with polyphosphoric acid (505 g), and this acid was subsequently heated to 85 °C. At this time, the addition funnel was charged with the isopropyl crotonate (112 g, 0.88 mol), and this was added to the acid slowly and with vigorous stirring. The suspension turned a burnt-orange, and an

exotherm was noted. The flask was cooled with an ice bath so as to keep the reaction mixture under *ca.* 110 °C. After 1 hour of reaction, the suspension was poured onto 1 kg of ice, and with vigorous mixing, the orange suspension was dissolved.

The resulting solution was saturated with ammonium chloride, and was then extracted with lab grade ether (6 x 150 mL). The organic phases were combined, dried over MgSO₄, and filtered. The solvents were removed in vacuo, and the residual oil was distilled under vacuum (bp = 98-116 °C @ 61 mm Hg) to afford 61 g of the ketone (63 % yield).

PREPARATION OF 1,3,4-TRIMETHYLCYCLOPENTADIENE

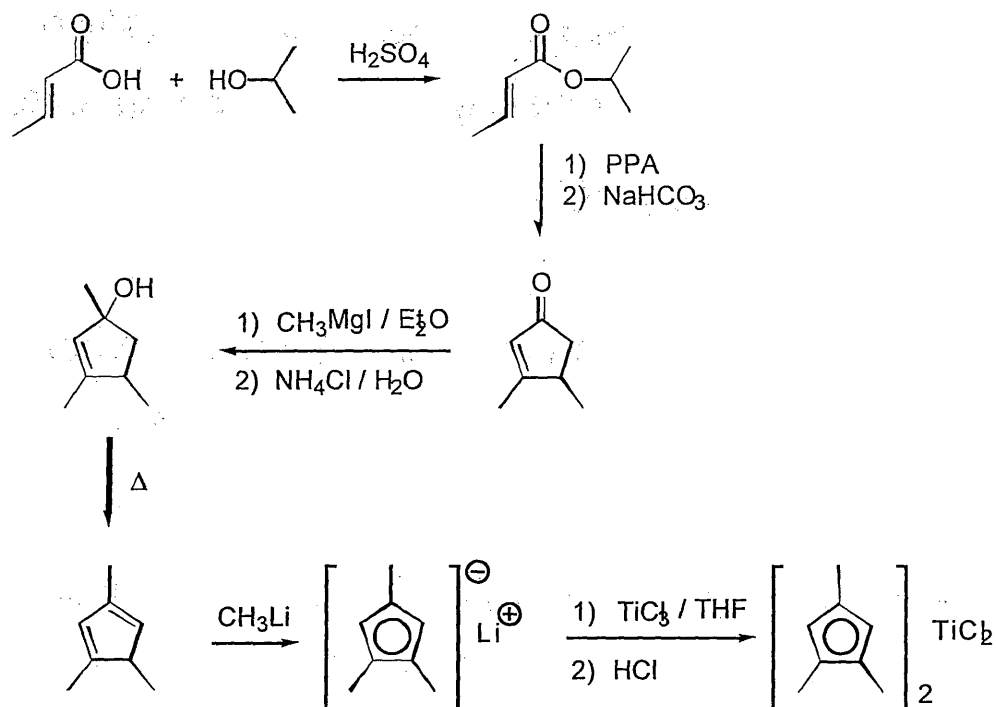
A 2-liter, three-necked round-bottomed flask was outfitted with a condenser, an N₂ inlet, and a 250 mL addition funnel. The system was purged with dry N₂ for 1.5 h, and was then charged with anhydrous ether (500 g). Methylmagnesium iodide (205 mL, 0.62 mol) was transferred into the ether *via* standard cannulation techniques. The dropping funnel was charged with anhydrous ether (100 mL) and the ketone (45 g, 0.41 mol). The Grignard solution was cooled to 0 °C, and the ketone solution was added dropwise. The reaction immediately became a clear yellow, and stirring was maintained for 1 hour at 0 °C.

After this interval, the reaction mixture was poured onto a mixture of ice (500 g) and ammonium chloride (30 g). The mixture was stirred until the ice was melted, and then the phases were partitioned. The organic phase was set aside, and the aqueous phase was extracted with freshly distilled ether (3 x 200 mL). (Acids and/or peroxide in ordinary lab grade ether then to cause the decomposition of the tertiary alcohol at this stage.) The organics were then combined, dried over MgSO_4 , and the solvents were removed *in vacuo*. The residual oil was immediately distilled resulting in a dehydration of the tertiary alcohol. The distillate was redistilled (b.p. = 120-138 °C) to afford 20 g of the cyclopentadiene (48 %).

PREPARATION OF BIS-(η^5 -1,3,4-TRIMETHYLCYCLOPENTADIENYL)

TITANIUM (IV) DICHLORIDE

The overall synthetic route to this ligand is presented in Scheme 7. A 500 mL, three-necked, round-bottomed flask was outfitted with a 250 mL addition funnel and an N_2 inlet. The flask was purged with dry N_2 for 2 h, at which time the flask was charged with anhydrous THF (250 mL) and



Scheme 7

trimethyl-cyclopentadiene (16 g, 150 mmol). The flask was then cooled to 0 °C, and the addition funnel was charged with methyllithium solution (225 mL, 320 mmol) using standard cannulation techniques. The methyllithium was added dropwise over a period of 15 minutes. The resulting white reaction mixture was allowed to stir for 1.5 h at 0 °C.

During this process, a 2-liter, three-necked, round-bottomed flask was taken into the dry box and charged with TiCl_3 (11.6 g, 75.3 mmol), and a magnetic stir bar. The flask was sealed, removed from the dry box, was outfitted with a condenser and N_2 inlet. The flask was then charged with anhydrous hexane (100 mL) and anhydrous THF (150 mL). The resulting dark purple suspension was stirred and cooled to 0 °C. The white suspension

of the lithium salt was then transferred into the TiCl_3 suspension using standard cannulation techniques. The resulting purple suspension was stirred at $0\text{ }^\circ\text{C}$ for 2 h. After this interval, the mixture was heated to reflux for 48 h

After this interval, the reaction vessel was cooled to $0\text{ }^\circ\text{C}$. The flask was outfitted with an addition funnel, and this was charged with 12 *N* HCl (320 mL). The acid was added dropwise to the reaction mixture over a period of 30 minutes. The suspension was allowed to stir for 2 h at which time the purple-red crystals were vacuum filtered and washed with deionized water (3 x 75 mL). Approximately 10.5 g (42 %) of the crystals were obtained. ^1H NMR (Figure 5): $\delta = 1.87$ (s), 1.93 (s), 5.95 (s); ^{13}C NMR (Figure 6): $\delta = 14.7$, 16.8, 123.5, 126.7, 133.0.

SYNTHESIS OF BIS-(η^5 -1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENYL) TITANIUM (IV) DICHLORIDE

REAGENTS

Pentamethylcyclopentadiene (Aldrich, 21,402-7) was used without further purification, as was titanium trichloride (Aldrich, 22,097-3). Methyllithium (Aldrich, 19,734-3) was used as a 1.4 *M* solution in diethyl ether. The solvents were prepared and stored as described in the preceding section.

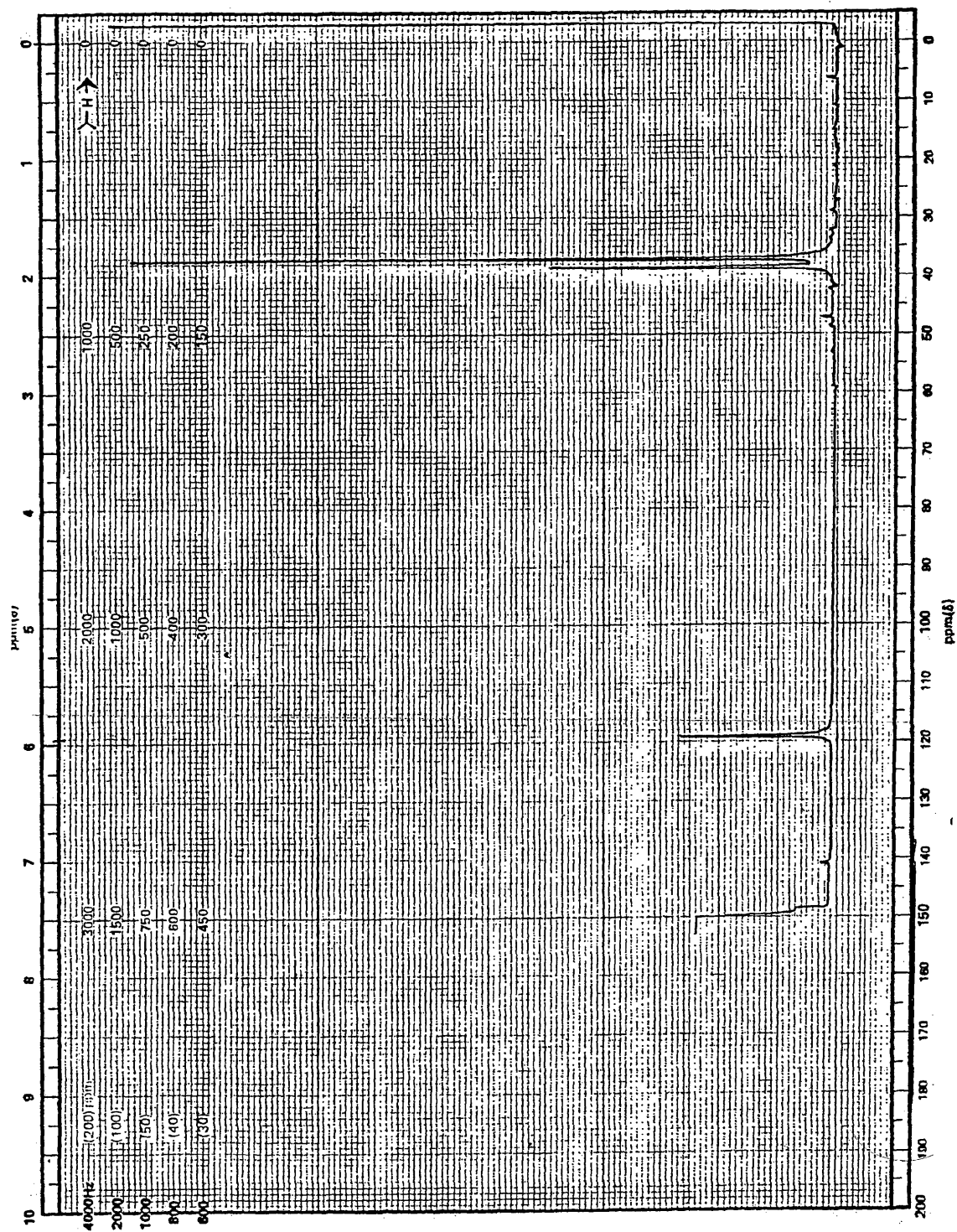


Figure 5. H-1 NMR spectrum of bis(1,2,4-trimethylcyclopentadienyl)titanium(IV) dichloride.

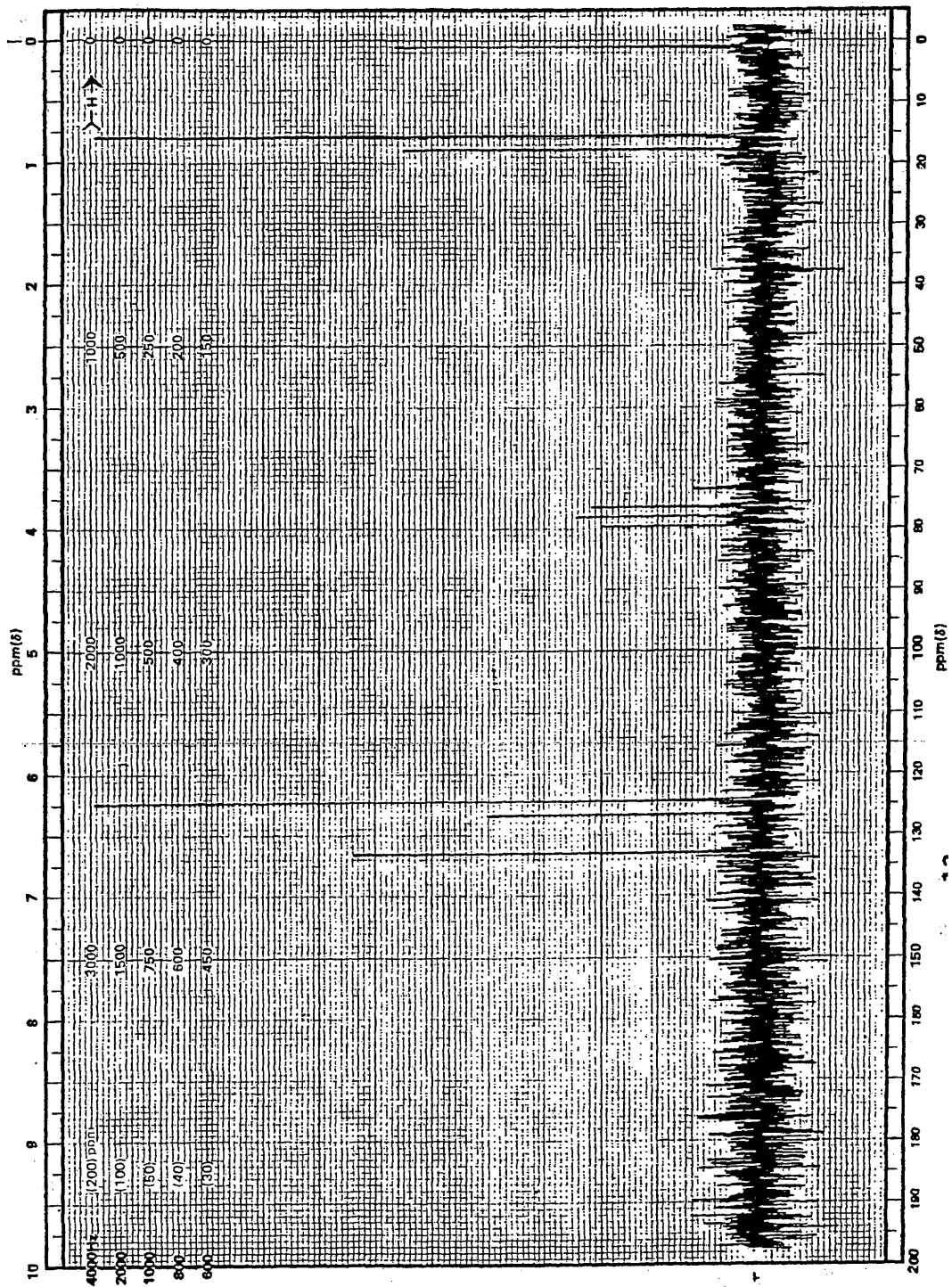


Figure 6. ^{13}C NMR spectrum of bis(1,2,4-trimethylcyclopentadieny)titanium(IV) dichloride.

PREPARATION OF BIS-(η^5 -1,2,3,4,5-PENTAMETHYLCYCLOPENTADIENYL) TITANIUM (IV) DICHLORIDE

A 1-liter, three-necked, round-bottomed flask was outfitted with a condenser, N₂ inlet and a 125 mL dropping funnel. The flask was then charged with anhydrous THF (200 mL) and pentamethylcyclopentadiene (12.2 g, 89.5 mmol). The flask was cooled to 0 °C, and the addition funnel was charged with the methyllithium solution (75 mL, 105 mmol) *via* standard cannulation techniques. The methyllithium solution was added dropwise to the diene over a period of 7 minutes, producing a milky-white slurry. This suspension was allowed to stir for 1 h at 0 °C.

During this process, a 2-liter, three-necked, round-bottomed flask was taken into the dry box and charged with TiCl₃ (5.3 g, 34 mmol), and a magnetic stir bar. The flask was sealed, removed from the dry box, was outfitted with a condenser and N₂ inlet. The flask was then charged with anhydrous hexane (50 mL) and anhydrous THF (75 mL). The resulting dark purple suspension was stirred and cooled to 0 °C. The white slurry of the lithium salt was then transferred into the TiCl₃ suspension using standard cannulation techniques. The resulting dark green suspension was heated to reflux for 41 h.

After this interval, the reaction vessel was cooled to 0 °C. The flask was outfitted with a 250 mL addition funnel, and this was charged with 12 N HCl (200 mL). The acid was added dropwise to the reaction mixture over a period of 25 minutes, causing a brown mass of crystals to precipitate. The crystals were vacuum filtered and set aside. Chloroform (125 mL) was added to the filtered solution, and the resulting organic phase was partitioned. The organics were removed *in vacuo*, and the brown residues were combined and subjected to Soxhlet extraction with hexane (200 mL) for 48 h. Approximately 11 g (28.2 mmol) of finely divided brown crystals were collected (83 % yield).

RESULTS AND DISCUSSION

CARBOMETALATION OF 3-BUTYN-1-OL--STEREOSELECTIVITY

All reports to date involving carbometalation of alkenes and alkynes with organoalane-group 4 metal systems are consistent with only *syn*-addition. This presents a problem for some observations made in these laboratories, in particular, if a cyclic intramolecular mechanism holds for the carbometalation of alkynols. We have observed that the methylation of 3-butyn-1-ol occurs predominantly to give internally methylated products. This requires an *anti*-addition if a cyclic intermediate is formed (*cf.* Figure 7) since *syn*-addition cannot be sterically tolerated to afford a six-membered titanocyclic intermediate. The early reports of this reaction by Thompson, *et al.*, did not address *syn*- or *anti*-addition for the system. Since there is good evidence for a cyclic intermediate, the investigation focused on the unprecedented case of *anti*-carbometalation.

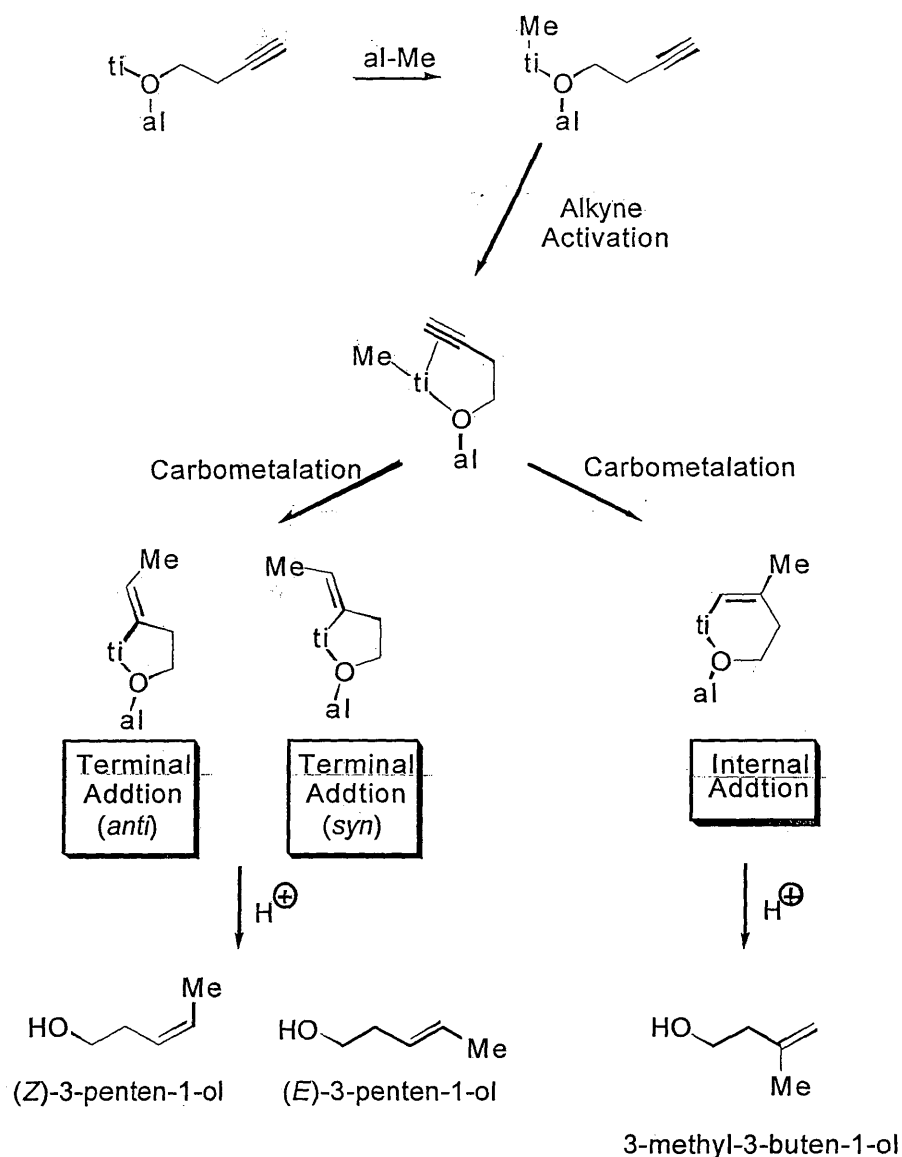
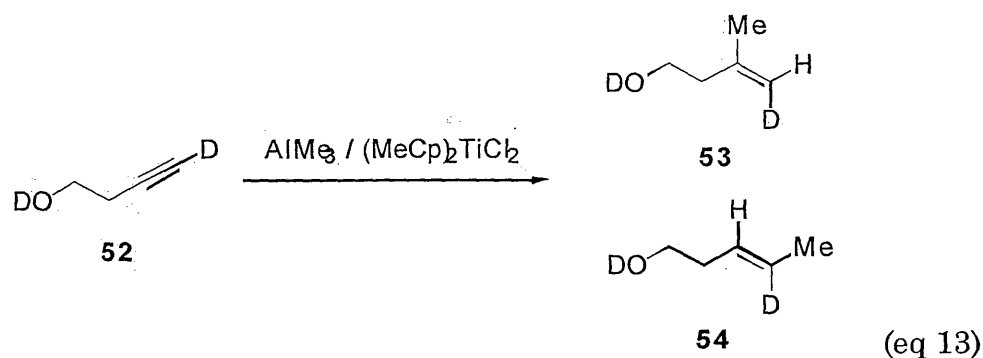


Figure 7. An approach to controlled carbometalation with Ziegler-Natta catalyst system.

In order to investigate the stereochemistry of the carbometalation reactions, a model alkyne, 4, O-dideutero-3-butyn-1-ol, was subjected to methylmetalation in a $\text{AlMe}_3 / (\text{MeCp})_2\text{TiCl}_2$ system as described in the experimental section (eq 13). The resulting regioisomeric products (*i.e.* 4, O-



dideutro-3-methyl-3-buten-1-ol and 4,*O*-dideutro-3-penten-1-ol) arising from internal and terminal addition respectively, were isolated in good purity via preparative GLC. The ratio of the alkenols was 95 : 5, in favor of the internal addition product. A ^1H NMR spectrum (Figure 8) of the major isomer showed a multiplet at $\delta = 4.80$ ($J = 1.5$ Hz), a triplet at $\delta = 3.60$ ($J = 5$ Hz), a multiplet at $\delta = 2.18$ ($J = 6$ Hz), and a multiplet at $\delta = 1.69$ ($J = 2$ Hz). The observed methyl doublet, arising from the interaction of the *cis*-vinylidene proton with the methyl group, is consistent with a *syn*-addition had taken place in the internal addition. The coupling constant from the corresponding *trans*-relationship of the aforementioned protons is expected to be *ca.* 0 Hz. No such interaction should arise between a *cis*-deuterium and a methyl group in

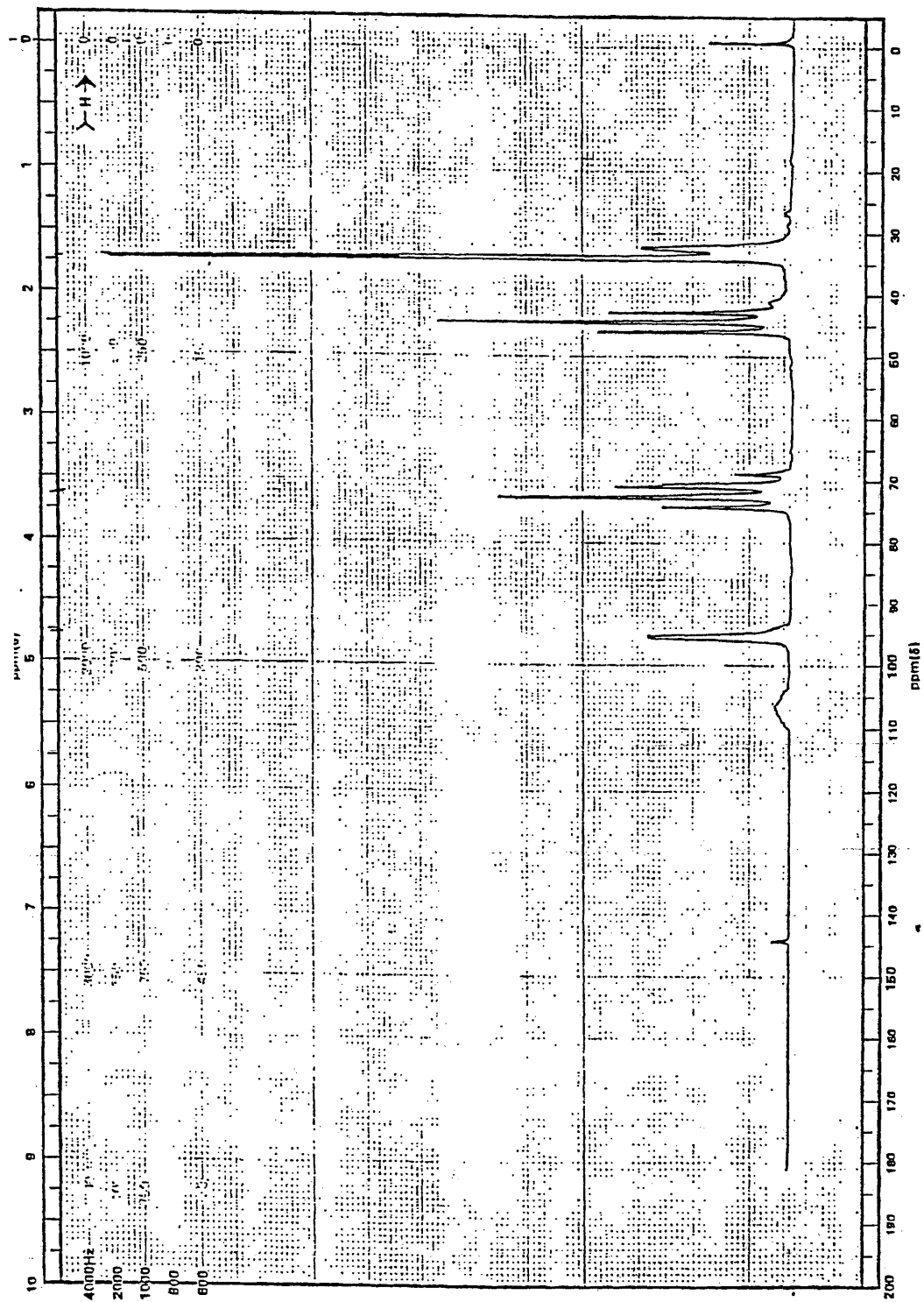
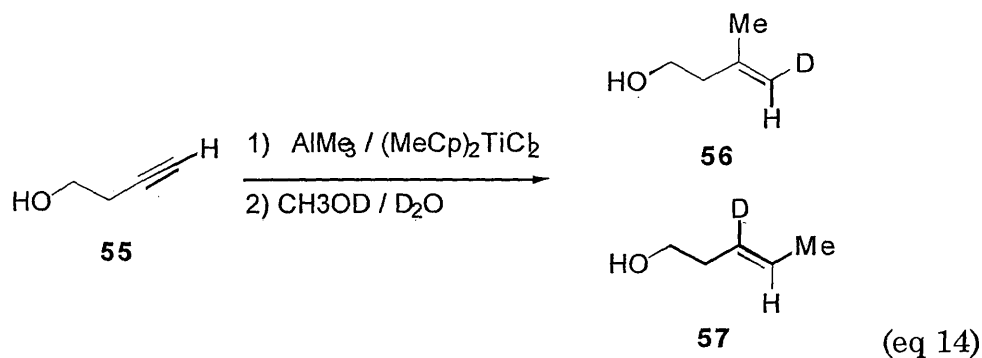


Figure 8. H-1 NMR spectrum of 4,0-dideuterio-3-butyn-1-ol methylmetalation products.

the case of trans-addition. Thus the major isomer is (*Z*)-4-deutero-3-methyl-3-buten-1-ol (**53**); the minor isomer had been previously characterized as (*Z*)-4-deutero-3-methyl-3-penten-1-ol (**54**).

As further evidence of a *syn*-addition, 3-butyn-1-ol was methylmetalated and then quenched with CH₃OD and D₂O as described in the experimental section (eq 14). The ¹H NMR spectrum (Figure 9) of the



purified product revealed that splitting patterns as described in the previous reaction (*cf.* eq 13 and Figure 8), were no longer present, and a new splitting interaction had emerged between the *cis*-vinylidene proton and the vicinal methyl group. This is consistent with a *syn*-addition of the methyl-metal bond. With these two pieces of evidence in hand, as well as reports of a ubiquitous *syn*-carbometalation pathway, it is apparent that a modification of the proposed carbometalation mechanism involving a six-membered titanocyclic intermediate is necessary.

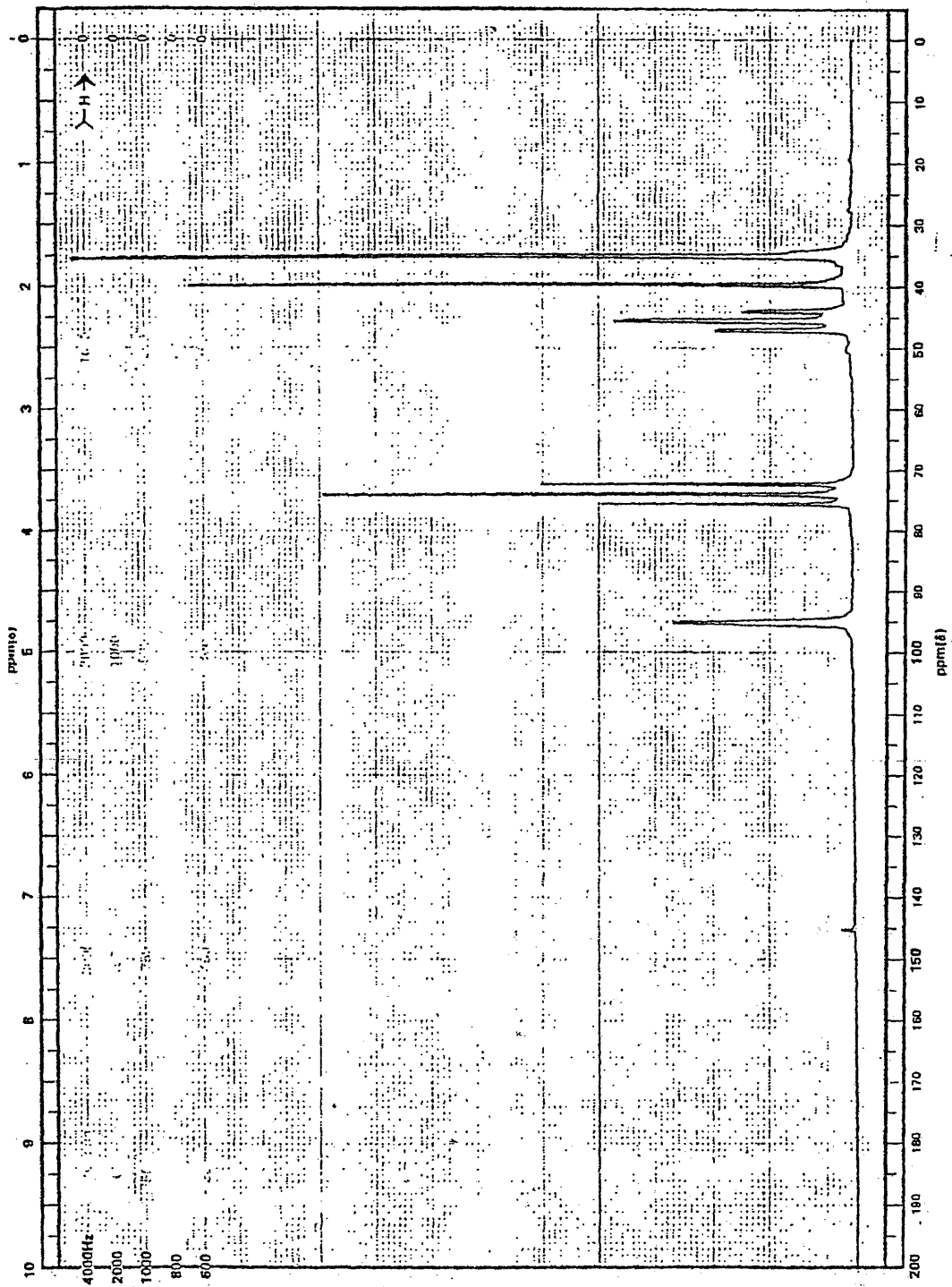


Figure 9. ^1H -1 NMR spectrum of 3-butyn-1-ol methylation products quenched with $\text{CH}_3\text{OD}/\text{D}_2\text{O}$.

In thinking about a modification of the previously presented mechanism of carbometalation (*cf.* Figure 7), one consideration is the effect of the oxygen in the substrate alkynol. That the presence of oxygen in carbometalation substrates does exert an effect is evident in the following observations. Based on the investigations by Negishi, *et al.*,⁹ carbometalation of internal alkynes such as 5-decyne (**16**) with a Cp_2TiCl_2 promoter should afford some allenic products as a result of β -hydride elimination (*vide supra*). Thompson, *et al.*, investigated the carbometalation of homopropargyl alcohols with Cp_2TiCl_2 or $(\text{MeCp})_2\text{TiCl}_2 / \text{Et}_2\text{AlCl}$ systems.² In this investigation, ethylation of terminal alkynes ethylated under these reaction conditions resulted in fair to poor regioselectivity. However, the internal alkyne, 3-pentyn-1-ol, afforded a 93 : 7 ratio of terminal to internal alkylation products in good yield. Interestingly, no allenic products were observed by Thompson, *et al.*, in these carbometalations.

These observations are consistent with an intramolecular mechanism in which a cyclic intermediate (*cf.* Figure 7) is formed prior to the addition of the metal-alkyl moiety. In this cyclic intermediate there are only endocyclic β -hydrogens which do not have a favorable dihedral angle for elimination. The carbometalation mechanism, along with its appropriate modifications accounting for the current observations, will be discussed later.

Under similar reaction conditions, 3-pentyn-1-ol was methylmetalated using three different ring-substituted titanocene / AlMe₃ systems. Even in the case of a (MeCp)₂TiCl₂ / AlMe₃ system, in which a high degree of reactivity and regioselectivity was observed, there was no evidence of the formation of allenic products. Far more surprising is the observation by Thompson, *et al.*, that in a TiCl₄ / AlMe₃ carbometalation system which is substantially less sterically demanding, there was no evidence of the formation of allenic products. These findings also are consistent with an intramolecular mechanism in which the oxygenated functionality of the substrate has an effect.

A final series of observations provide additional evidence consistent with the cyclic intermediate in Figure 3. It has been documented that terminal alkynes, including 1-butyne, will homopolymerize under Ziegler-Natta conditions.⁴ That this behavior occurs in carbometalation reactions is demonstrated in the findings of Negishi, *et al.*, who report that when 1-octyne is subjected to methylation *via* a Cp₂TiCl₂ / AlMe₃ system, some dimeric products are formed.⁹ Since 3-butyne-1-ol is sterically unhindered and contains a similar terminal alkyne functionality, it is plausible that this substrate should also exhibit some dimerization/oligomerization reactions under the carbometalation conditions. However, in this investigation, as well as previous findings by Thompson, *et al.*,^{1,2} there has been no evidence of the formation of such coupled products when the substrates contain oxygenated

functionality. These findings indicate that the oxygen does exert an influence on the mechanistic pathway.

CARBOMETALATION OF 3-PENTYN-1-OL

In a report by Thompson, et al., 3-pentyn-1-ol was ethylated (*cf.* Figure 2). In order to augment this investigation, 3-pentyn-1-ol was methylated with two ring-substituted titanocenes promoters, namely, $(\text{MeCp})_2\text{TiCl}_2$, and $(1,2,4\text{-Me}_3\text{Cp}_2)\text{TiCl}_2$. The synthesis of the latter complex is reported in the experimental section (*vide infra*). The regioselectivity of the $(\text{MeCp})_2\text{TiCl}_2 / \text{AlMe}_3$ methylation reaction was high. Despite the presence of an internal alkyne functionality in a Ziegler-Natta system, neither allenic (arising from β -hydride elimination), nor oligomers (resulting from sequential carbometalation) were formed. The $(1,2,4\text{-Me}_3\text{Cp}_2)\text{TiCl}_2 / \text{AlMe}_3$ methylation resulted in very low yields.

That the addition of the methyl-metal bond occurred at the terminal position for the $(\text{MeCp})_2\text{TiCl}_2 / \text{AlMe}_3$ system is evident from the ^1H NMR spectrum of the product (Figure 10). The observed splitting pattern of the multiplet at $\delta = 5.17$ is consistent with the splitting pattern of the multiplet at $\delta = 5.13$ in the spectrum of 6-methyl-5-heptene-3-ol (Figure 11). This compound was prepared by exclusive terminal methylation of 5-heptyne-3-ol with a $\text{TiCl}_4 / \text{AlMe}_3$ carbometalation system.

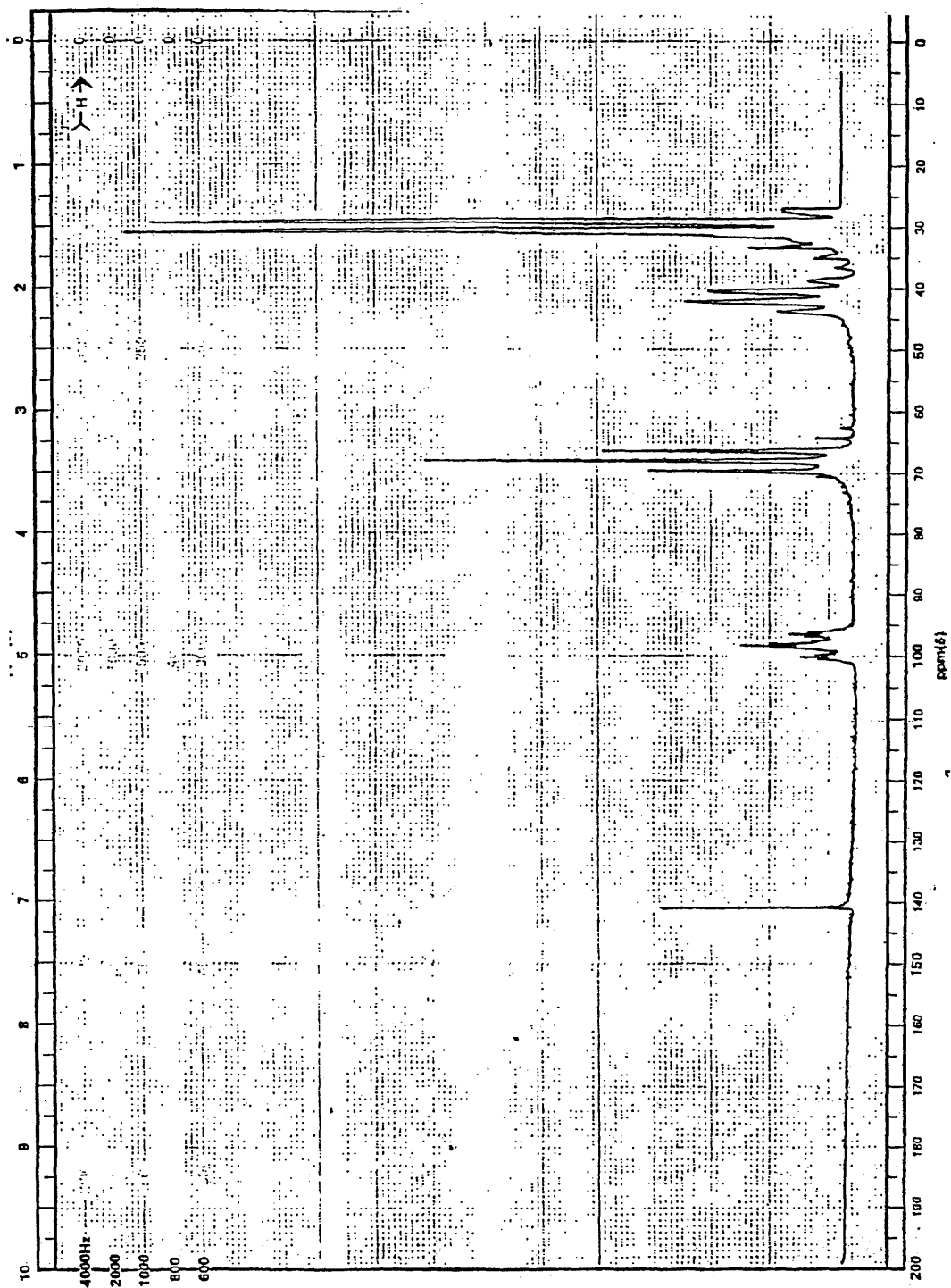


Figure 10. H-1 NMR spectrum of 3-pentyn-1-ol methylmetalation products.

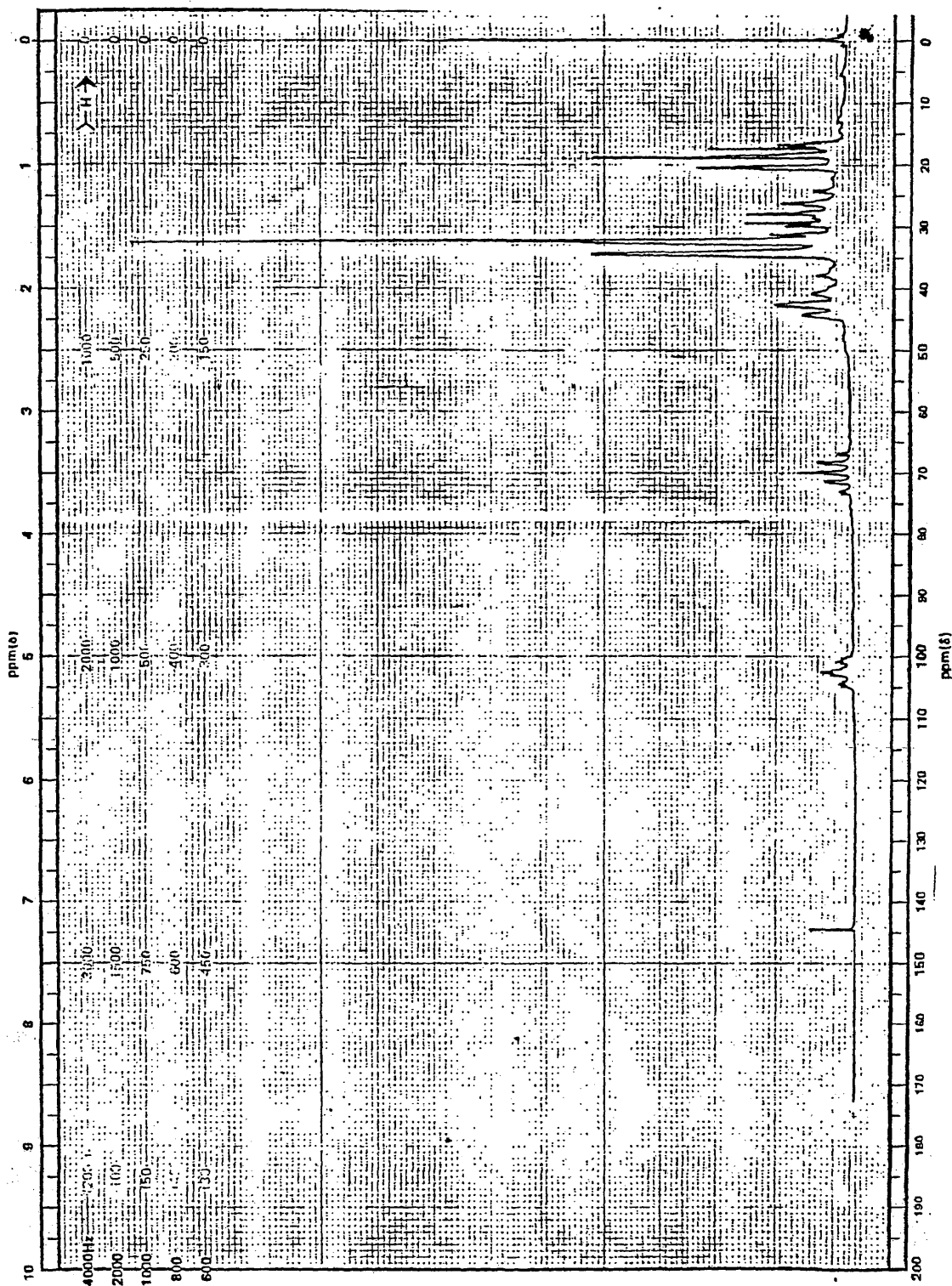


Figure 11. ^1H NMR spectrum of 6-methyl-5-hepten-3-ol.

The substrate, 3-pentyn-1-ol, was also ethylated with a $(\text{MeCp})_2\text{TiCl}_2 / \text{AlMe}_3$ system in order to confirm the regioselectivity of the previously reported reaction. In this instance, as in the methylation, alkylation at the terminal position was favored. A 76 : 24 ratio of terminal to internal ethylation products was observed (much less favorable than the 95 : 5 ratio previously reported). Again, no formation of oligomeric or allenic products were observed.

EFFECT OF RING SUBSTITUENTS

This investigation demonstrates that the ring substituents on the titanocene dichloride promoters have a significant effect on the regioselectivity of the carbometalation reaction (Table VI). The trend shows that, on going from a single methyl substituent on the cyclopentadienyl ring to five such substituents, there was an increase in the regioselectivity. In the case of the methylation of 3-butyn-1-ol (Table VI), the ratio of internal to terminal addition increased from 77 : 23 to 95 : 5 to greater than 98 : 2 for the mono-, tri- and pentamethyl titanocenes respectively. The methylation of 3-pentyn-1-ol strongly favors terminal addition for both the mono- and tri-methyl titanocene promoters. It is unclear at this time whether the propensity of terminal addition in the system arises from a ring substituent effect or an effect of the internal alkyne in the substrate.

Table VI. Carboalumination of alkynols.

Alkynol	Cat.	Alane	Ratio (ROH : Cat. : Alane)	Temp (°C)	Time (h)	Product(s)	Yield	Ratio (Int. : Term.)
3-Butyn-1-ol	Cp_2TiCl_2	AlMe_3	1 : 0.5 : 2	25	3	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	70	80 : 20
3-Butyn-1-ol	$(\text{MeCp})_2\text{TiCl}_2$	AlMe_3	1 : 0.5 : 3	0	2	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	--	77 : 23
3-Butyn-1-ol	$(\text{MeCp})_2\text{TiCl}_2$	AlMe_3	1 : 0.5 : 3	25	2	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	--	77 : 23
3-Butyn-1-ol	$(\text{MeCp})_2\text{TiCl}_2$	AlMe_3	1 : 0.25 : 2	0	2	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	56	79 : 21
3-Butyn-1-ol	$(\text{MeCp})_2\text{TiCl}_2$	AlMe_3	1 : 0.1 : 2	25	4	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	75	74 : 26
3-Butyn-1-ol	$(\text{Me}_3\text{Cp})_2\text{TiCl}_2$	AlMe_3	1 : 0.5 : 3	0	2	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	--	95 : 5
3-Butyn-1-ol	$(\text{Me}_3\text{Cp})_2\text{TiCl}_2$	AlMe_3	1 : 0.2 : 2	0	2	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	55	<96 : 4
3-Butyn-1-ol	$(\text{Me}_5\text{Cp})_2\text{TiCl}_2$	AlMe_3	1 : 0.2 : 2	-23	2	3-Methyl-3-butene-1-ol (<i>E</i>)-3-penten-1-ol	33	>98
3-Pentyn-1-ol	$(\text{MeCp})_2\text{TiCl}_2$	AlMe_3	1 : 0.25 : 2	0	2	4-Methyl-3-pentene-1-ol (<i>Z</i>)-3-Hexen-1-ol	--	3 : 97
3-Pentyn-1-ol	$(\text{Me}_3\text{Cp})_2\text{TiCl}_2$	AlMe_3	1 : 0.5 : 5	0	2	4-Methyl-3-pentene-1-ol (<i>Z</i>)-3-Hexen-1-ol	6	--
4-Pentyn-2-ol	$(\text{Me}_3\text{Cp})_2\text{TiCl}_2$	AlMe_3	1 : 0.5 : 3	0	2	4-Methyl-4-pentene-2-ol (<i>Z</i>)-4-Hexen-2-ol	81	98 : 2
4-Pentyn-2-ol	$(\text{Me}_3\text{Cp})_2\text{TiCl}_2$	AlMe_3	1 : 0.25 : 2.5	0	2	4-Methyl-4-pentene-2-ol (<i>Z</i>)-4-Hexen-2-ol	93	97 : 3

Unfortunately, as the number of methyl substituents present on the titanocene increased, there appeared to be a corresponding decrease in the total yield of the alkylation. Whether this trend is the result of a steric effect, or an effect of the electron-donating properties of the substituent methyl groups toward the titanium center is unclear at this time. Despite this drawback, each reaction proceeded cleanly with no indication of competing side-reactions. Thus, it is plausible to recover the unreacted starting material for subsequent carbometalations.

DISCUSSION OF THE MECHANISM

The results of this investigation, along with other reported data, is consistent with an alkynol carbometalation mechanism which is intramolecular in nature. Indeed, a intramolecular cyclic intermediate was proposed in which the titanium center was simultaneously coordinated with both the alkyne functionality and the oxygen of the substrate (*cf.* Figure 7). Such a cyclic intermediate accounts nicely for both the role of the oxygen in carbometalation as well as for the lack of β -hydride elimination products. However, the studies with deuterated alkynols is clearly consistent with a *syn*-addition of the methyl-metal bond. In such a circumstance, a cyclic intermediate is not sterically plausible.

Based on these findings, a new mechanistic pathway for carbometalations is proposed (Figure 12). In the first step, the oxygen of the substrate becomes coordinated with the aluminum and titanium species. Binuclear complexes with alkoxide ligands are well known in the chemistry of titanium (*e.g.* tetraalkoxides of titanium are highly associated). A methyl-chloride exchange then takes place between the aluminum and titanium to yield a methyl-titanium moiety. Next, a cyclic intermediate is formed as the

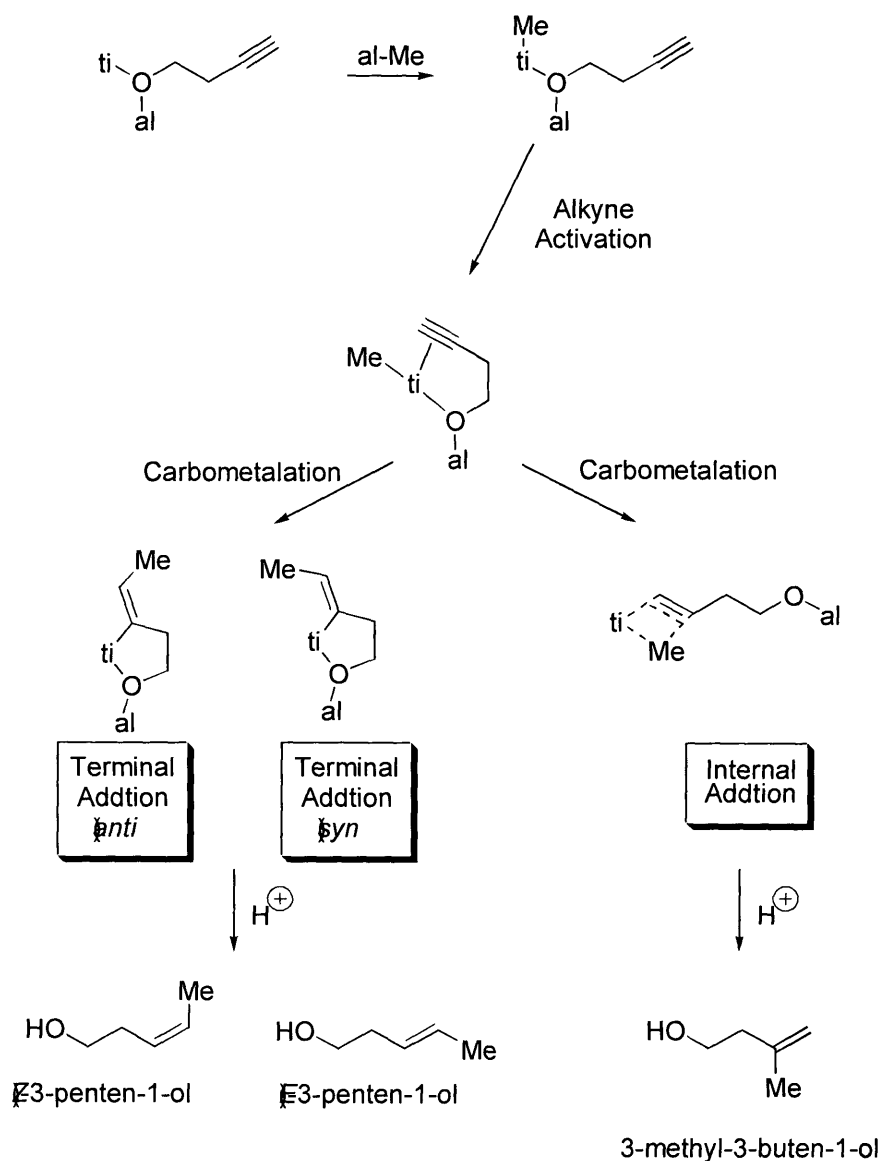


Figure 12. Modified carbometalation pathway.

titanium becomes coordinated to the electron density of the carbon-carbon triple bond. Then, in a single concerted step, the methyl addition takes place as the labile titanium-oxygen coordination is broken. Release of the ring-strain in the intermediate provides some driving force. For the 3-butyn-1-ol

system, as in all the terminal alkynols, no possibility of β -hydride elimination is possible since there are no hydrogens beta to the titanium center.

In conclusion, it appears that multiple ring substituents on the titanocene promoters give rise to steric effects on the regioselectivity of the carbometalation. Highly substituted cyclopentadienyl rings favor internal methylation of terminal alkynols as indicated by the 3-butyn-1-ol data (*cf.* Table VI). However, there is evidence that increasing substitutions on the cyclopentadienyl rings adversely affects conversion. At present it is also difficult to prepare cyclopentadienyl compounds. Thus, the synthetic utility of such promoters to organic chemistry is uncertain at this point.

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