The hydrometallation, carbometallation, and metallometallation of heteroalkynes

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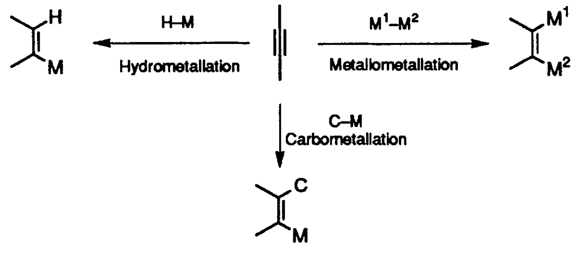
Reviewing the literature published up to the end of July 1994

1 Introduction

The hydrometallation and carbometallation of terminal and internal alkynes (**Scheme 1**) is a powerful method for generating alkenylmetals. The former proceeds well for Al, Zr, B, Sn, and Ge, while Cu and Al have proved useful for the latter.[1] More recently, metallometallation has emerged as a means of simultaneously generating two adjacent regio- and stereo-defined alkenylmetal bonds of differential reactivity. To date metallometallation has been used mainly to introduce Si or Sn in conjunction with Li, Mg, Al, Cu, B, or Zn. Unfortunately, poor regiocontrol detracts from many hydrometallations and metallometallations and in some cases stereocontrol is a problem too. Regio- and stereo-control in carbometallations exhibit a marked sensitivity to proximal heterofunctionalities. In this review we survey the valuable influence of heteroatoms (O, S, N) on the crucial issue of regio- and stereo-control in hydrometallations, carbometallations, and metallometallations of alkynes.

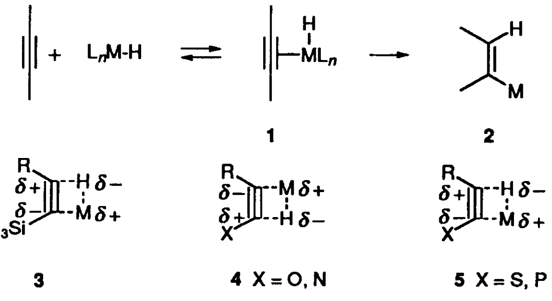


Scheme 1

2 Hydrometallation

The hydrometallation of alkynes offers the simplest and most direct route to alkenylmetals. There are over 50 potentially useful metals (including the lanthanides and actinides) which participate in the reaction, though in practice only a handful of metal hydrides have found general favour and these include B,[2-10] Al,[11-14] Zr,[15-23] and Sn.[24-30] In the case of Sn, Si,[31-38] Ge,[32,34,39] and Mg,[40-42] the reaction is best achieved under transition metal catalysis. The hydrometallation of unactivated terminal or internal alkynes generally proceeds with clean *cis*-stereoselectivity initially although isomerization can subsequently take place.

On a simplistic level, the *uncatalysed* hydrometallation of an alkyne involves two principal steps (**Scheme 2**): (i) reversible coordination of the alkyne to a vacant orbital on the metal atom and (ii) insertion of the coordinated metal-hydride bond into the alkyne π-bond. The overall rate of formation of **2** will be related to the product of the equilibrium and rate constants K and k. The concentration of intermediate **1** should decrease as the size of substituents attached to the unsaturated bond increase but the effect can be comparatively small since coordination takes place at the centre of the alkyne bond where steric effects are minimized. On the other hand, the concentration of **1** should increase as the electron density in the π-system increases; hence the



Scheme 2

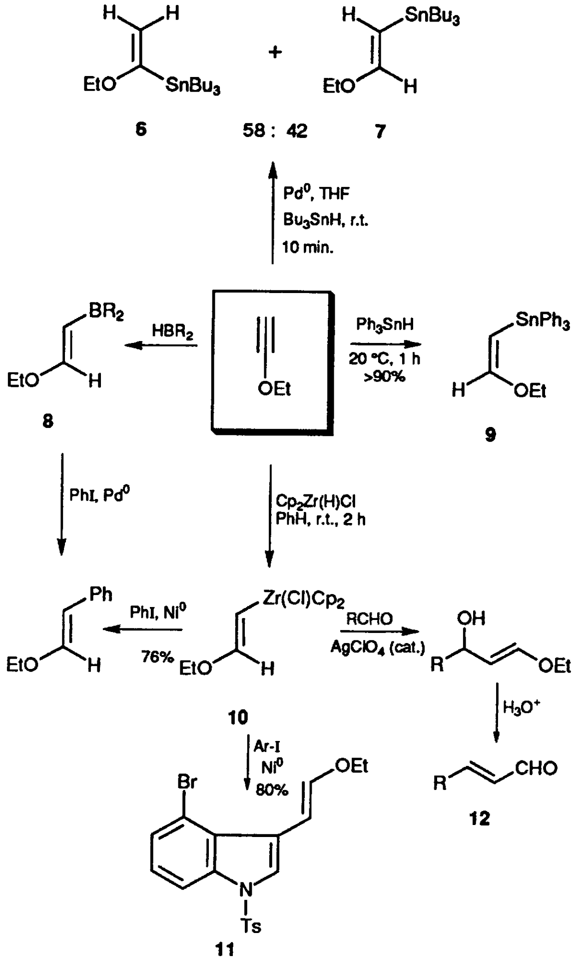
presence of electron-donating substituents should favour formation of the intermediate **1** and promote reaction. However, if intermediate **1** is too stable, the second step (insertion) may be slow or precluded altogether.[43]

The heteroatoms under consideration determine the regiochemistry of the hydrometallation by polarizing the alkyne bond. In the case of trialkylsilyl and other electron-releasing metal groups, polarization is governed by σ-bond hyperconjugation[44] resulting in stabilization of electron deficiency β to the M–C bond as in **3**; hence the metal is attracted to the carbon bearing the silyl group. In the case of mesomeric donors such as N or O, the metal is attracted to the electron-rich β-carbon as in **4**. Mesomeric donors with non-bonded electrons in the third shell show inverted regiochemistry relative to their second shell siblings. Thus, thio- and phospha-alkynes react as if they were polarized in the sense depicted in **5**. In the following sections we will consider in more detail the hydrometallation of 1-heteroalkynes $R^1\text{-C}\equiv\text{C-X-}R^2$ where X = O and S.

2.1 1-Alkoxy-1-alkynes

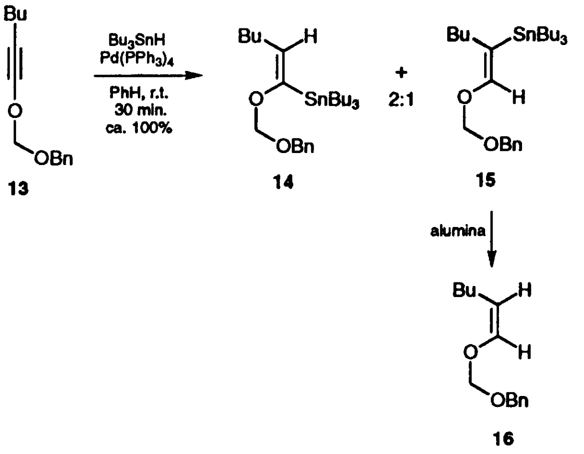
The benefits of increased functional diversity and improved rate and regiocontrol offered by dialkylamino and alkoxy substituents has hardly impinged on hydrometallation chemistry. No doubt one reason for the paucity of data is the comparative instability of 1-(dialkylamino)-1-alkynes and 1-alkoxy-1-alkynes, making them awkward compounds to handle and prepare. Information has mostly been gleaned from reactions with the only alkoxyalkyne which is commercially available: ethoxyethyne. Hydroboration,[2,3] hydrozirconation,[15,17,18] and uncatalysed hydrostannylation[24] of ethoxyethyne have all been accomplished and in every case the metal became attached to the distal carbon in accord with the electronic effects discussed above. Hydroalumination of somewhat more interesting alkoxyalkynes was investigated by Eisch and co-workers with the same regiochemical consequence.[13] An example which illustrates the improved opportunities for exploiting the heteroatom is shown in **Scheme 3**. Hydroboration of ethoxyethyne[3] with diborane gave trialkenylborane **8** which underwent Pd^0-catalysed coupling under basic conditions with iodobenzene. The significance of this transformation lies in the effective appendage of acetaldehyde to an *sp*^{2} centre—a reaction normally beyond the pale of traditional enolate chemistry. A similar transformation was accomplished using hydrozirconation followed by Ni^0-catalysed coupling.[17] A synthesis of the aurantioclavine precursor **11** attests to the synthetic utility of the sequence.[18] The β-alkoxy-alkenylzirconium derivative **10** of ethoxyethyne has also been employed in the two and four carbon homologation of aldehydes;[22] thus alkenylmetal **10** adds cleanly to an aldehyde in the presence of silver perchlorate and subsequent hydrolysis provides enal **12** in high yield and excellent (*E*)-selectivity.

In keeping with the vast store of precedent, hydrometallations of 1-alkoxy-1-alkynes adhere to the preference for *syn*-addition. An apparent exception is the uncatalysed hydrostannylation of ethoxyethyne (**Scheme 3**)[24] which gives the *anti*-adduct **9** in excellent yield contaminated with minor amounts of the *syn*-adduct **7**. However, once again this was no exception: the *syn*-adduct forms as the kinetic product which then easily isomerizes by addition–elimination of stannane. In the case of transition metal catalysed hydrostannylation, only *syn*-adducts are observed though with diminished regioselectivity. For example, Guibé and co-workers found that the Pd^0-catalysed hydrostannylation of ethoxyethyne produced regioisomers **6** and **7** in a 58:42 ratio.[25]



Scheme 3

The electronic bias in favour of β-metallation in the hydrometallation of ethoxyethyne amply demonstrated in **Scheme 3** is subverted in higher alkoxyalkynes: hydrostannylation of 1-(benzyloxymethoxy)-1-hexyne **13** (**Scheme 4**) occurs rapidly and efficiently on reaction with 1.1 eq. of Bu_3SnH in benzene at ambient temperature in the presence of 1 mol% of $Pd(PPh_3)_4$ to give an inseparable mixture of the α-regioisomer **14** and β-regioisomer **15** (**14**:**15** = 2:1). However, selective destruction of the β-regioisomer to the (*Z*)-enol ether **16** occurs on rapid passage of the mixture through a column of basic alumina allowing isolation of pure **14**. Hydrostannylation of a further nine alkoxyalkynes revealed that the preference for the α-regioisomer is general but the regioselectivity is strongly dependent on the size of the alkyl substituents.

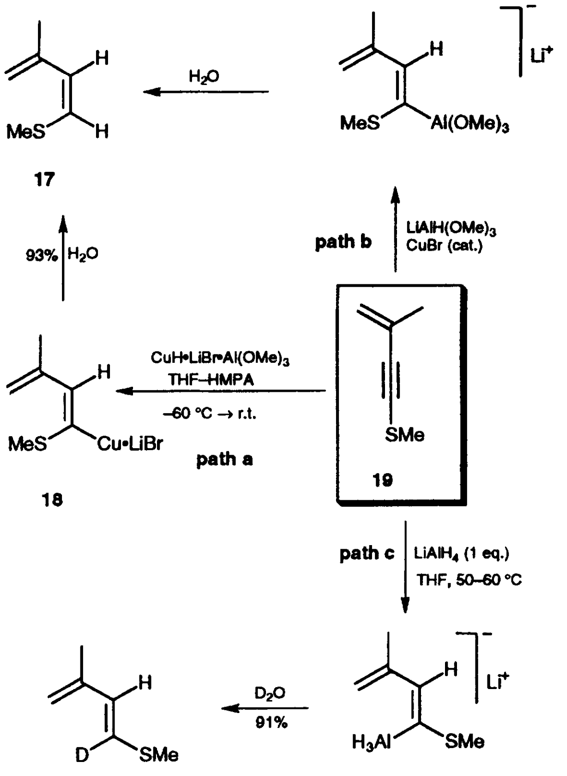


Scheme 4

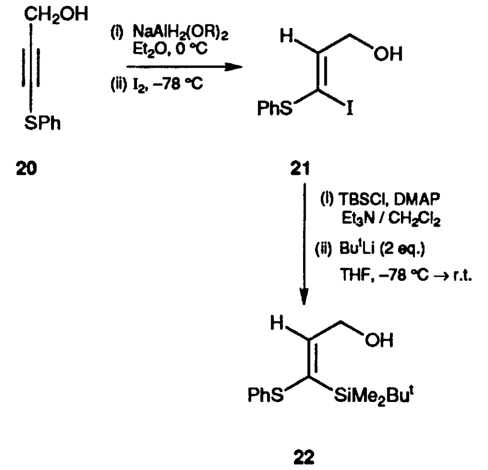
2.2 1-Phenylthio-1-alkynes

Thioalkynes are more stable than their oxygen counterparts in accord with diminished communication between the non-bonded $3p$ electron pairs on the sulfur atom and the π-system of the alkyne at level 2. Their improved stability and ease of preparation makes thioalkynes more practical substrates for hydrometallation studies. The phenylthio group is an electron sink and polarizes the alkyne in a sense opposite to that observed with alkoxyalkynes (see **Scheme 2**). The net reversal of polarization determines the regiochemistry of hydrometallation as shown in **Scheme 5**: there is a strong preference for attachment of the metal to the α-position. With a putative CuH reagent prepared by reaction of stiochiometric amounts of CuBr with LiAlH(OMe)$_3$, thioalkyne **19** undergoes *syn*-hydrocupration (path a) affording the diene **18**.[45,46] Furthermore, the same combination of reagents—but with CuBr present in catalytic amounts—accomplished the hydroalumination of alkyne **19** (path b), giving the diene product **17**. The regiochemistry of both reactions was determined by deuterolysis experiments. Complementary *anti*-stereochemistry can be obtained by hydroalumination of **19** with LAH (path c).

Kim and Magriotis[47] have prepared the (*Z*)-iodoalkene **21** in excellent yield by the hydroalumination of 1-phenylthio-1-propyn-3-ol **20**. In the example shown in **Scheme 6**, *anti*-hydroalumination was predominant (10:1). The (*Z*)-iodoalkene **21** served as a precursor to α-phenylthioalkenyl silane **22** via 1,4 O→C silyl migration of an alkenyl-lithium intermediate.



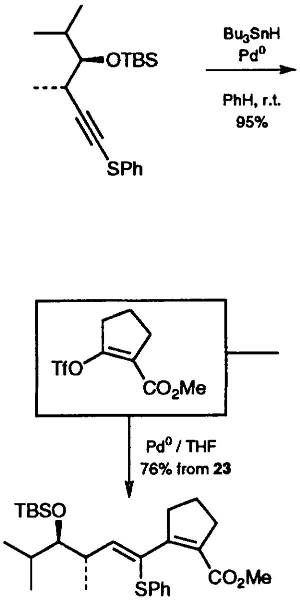
Scheme 5



Scheme 6

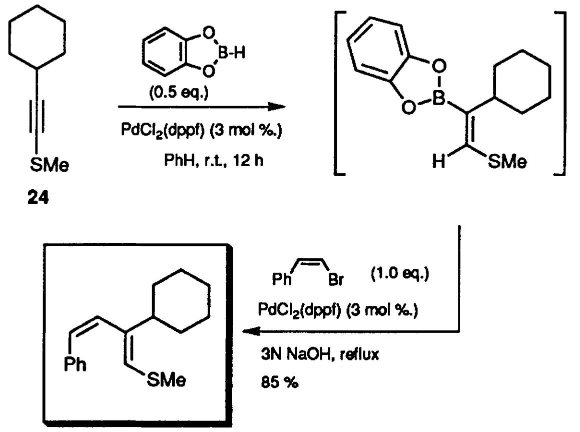
Two groups have recently shown that 1-phenylthio-1-alkynes undergo easy and efficient Pd^0-catalysed hydrostannylation.[28,48] **Scheme 7** illustrates the procedure and shows that the reaction is both regioselective and stereoselective. Stannane **23** does not participate readily in Pd^0-catalysed cross-coupling reactions but the corresponding α-(phenylthio)alkenyl zinc reagent **24** reacts with a wide variety of substrates under mild conditions, thus providing a significant enhancement to the cross-coupling chemistry of α-heteroalkenyl metals. Since α-(phenylthio)alkenes can be hydrolysed to ketones or cross-coupled with Grignard reagents in the presence of Ni^0 catalysts, reagent **24** serves as an exceptionally mild substrate for the nucleophilic acylation and alkylation of arenes and hetarenes.

The catalytic hydroboration of **24** with catecholborane provides the corresponding (*E*)-isomer with high regio- and stereo-selectivity



Scheme 7

(**Scheme 8**). The usual *syn* addition of the metal hydride occurs with the boron atom sited at the carbon β to the sulfur atom.[8] Cross-coupling reactions with aryl, alkynyl, and vinylic halides occurs with retention of configuration, thus providing a new method for the synthesis of stereodefined vinylic sulfides.

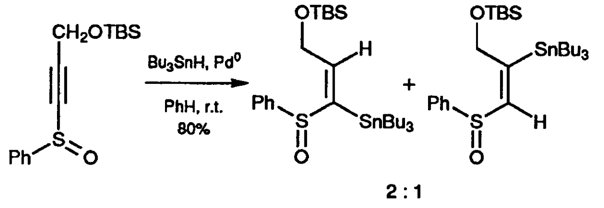


Scheme 8

Alkynes with sulfur substituents in higher oxidation states are also known to undergo hydrometallation. The enhanced polarization of the π-system should, if anything, reinforce the regiochemical preference for α-attachment of the metal. Hydroalumination of alkynyl sulfones behave as expected in a regiochemical sense but they give *anti*-adducts.[14] However, Pd^0-catalysed hydrostannylation of alkynyl sulfoxides has been reported[28] to give mixtures of regioisomers as exemplified in **Scheme 9**.

3 Carbometallation

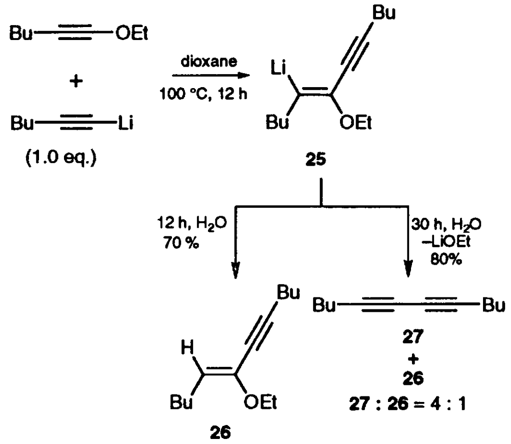
The addition of a C–M bond to an unactivated alkyne represents a significant advance in synthetic methodology. Such carbometallations are usually highly stereoselective and they are sufficiently mild in many cases to tolerate the presence of some functional groups. The resultant alkenylmetal can be further transformed in such a way that the overall result is the introduction of two new substituents in a *cis* manner. The kinetic and thermodynamic effects of proximate heteroatoms in directing carbometallation across C–C multiple bonds have been exploited in organic synthesis[49,50] and their virtues extolled in some of the extensive reviews on carbometallation reactions which are extant.[17,50–52] However, in this review we restrict attention to the activation and regiochemical advantages of heteroalkynes as substrates in carbometallation reactions.



Scheme 9

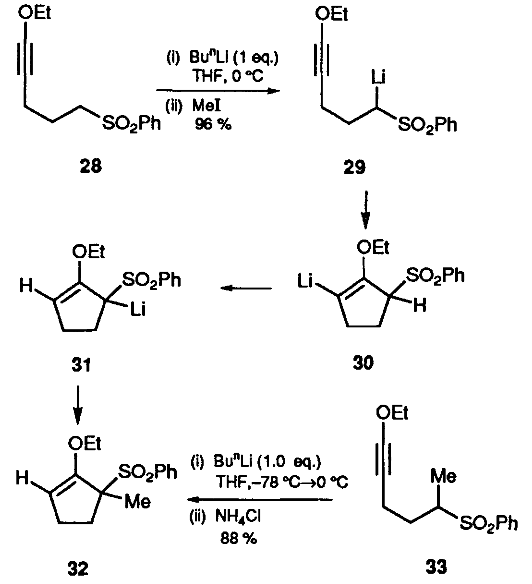
3.1. Organolithium reagents

Organolithium compounds are generally too strongly basic to be of appreciable synthetic utility in addition reactions to terminal and unactivated internal alkynes. There are some exceptions however. Kooyman and co-workers[53] showed that prolonged heating of a solution of ethoxyhexyne and hexynyllithium in dioxane at 100°C followed by hydrolysis of the adduct **25** afforded diyne **27** in addition to a small amount of the ether **26** (**Scheme 10**). The latter compound became the main product when the reaction time was shortened to 12 hours. Rapid *trans*-elimination of $LiOC_2H_5$ from the intermediates precluded the isolation of addition products of other alkynylation reactions.



Scheme 10

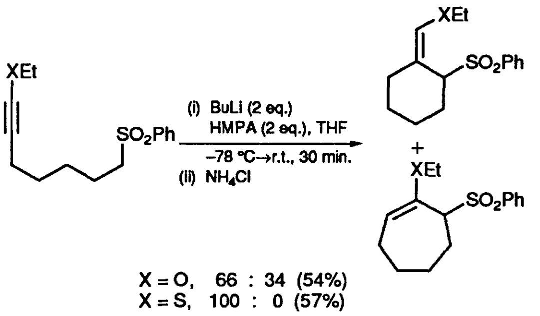
Perhaps the most cogent illustration of the powerful activating effect of heteroatoms on alkyne carbometallation was recently provided by Funk and co-workers[54] who discovered that alkylthio- and alkoxy-alkynes participate in cyclization reactions with a variety of *stabilized* lithio-carbanions to provide functionalized exocyclic and endocyclic enol and thioenol ethers. Thus, treatment of sulfone **28** with BuLi at 0°C, followed by a methyl iodide quench provided cyclopentene **32** in 96% yield (**Scheme 11**). The proposed mechanism for the transformation involves *trans*-carbometallation of alkoxyalkyne **29** by the α-phenylsulfonyl anion to afford the alkenyl anion **30** whose equilibration to **31** and regiospecific methylation with methyl iodide furnished **32**. The α-methylated sulfone **33** also cyclized smoothly to **32** suggesting that the cyclization reaction was not driven by the formation of stable anion **31**. However, attempts to trap the vinyl anion intermediates were unsuccessful owing to deprotonation of the solvent (THF) and *ortho*-metallation of the phenylsulfonyl moiety.



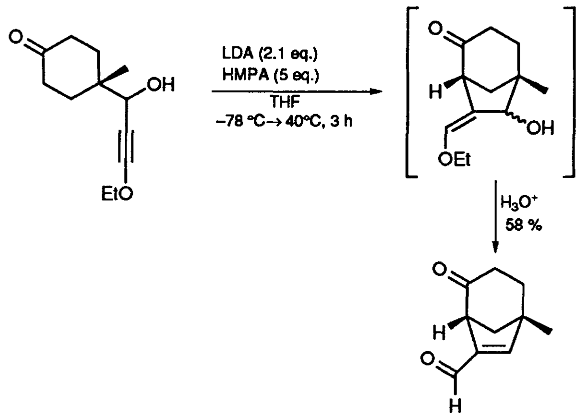
Scheme 11

High (*Z*)-stereoselectivity was observed in the formation of the *exo*-adducts, possibly due to an atypical *trans*-carbometallation reaction or, alternatively, to *cis*-carbometallation followed by equilibration of the intermediate allyl/α-phenylsulfonyl anion to the (*Z*)-stereoisomer as a result of stabilization by coordination of the lithium atom with the enol ether heteroatom. Preference for nucleophilic addition at the α-carbon of the alkoxyalkyne moiety was not sufficient to overcome a kinetically favoured attack at the β-carbon leading to a smaller ring system. However, the preferred site of intermolecular attack by nucleophiles on thioalkynes is at the β-carbon; consequently these cyclizations were completely regioselective (**Scheme 12**). Other carbanion stabilizing groups such as phosphorus ylides, ester and ketone enolates, and cyano-derivatives could be employed in the cyclization.

Scheme 13 provides a typical example of carbocyclic annulations highlighting the potential of the carbolithiation reaction in natural product synthesis.



Scheme 12



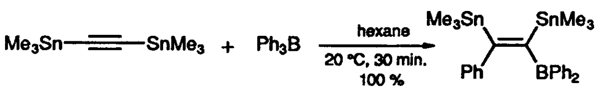
Scheme 13

3.2 Organoborane reagents

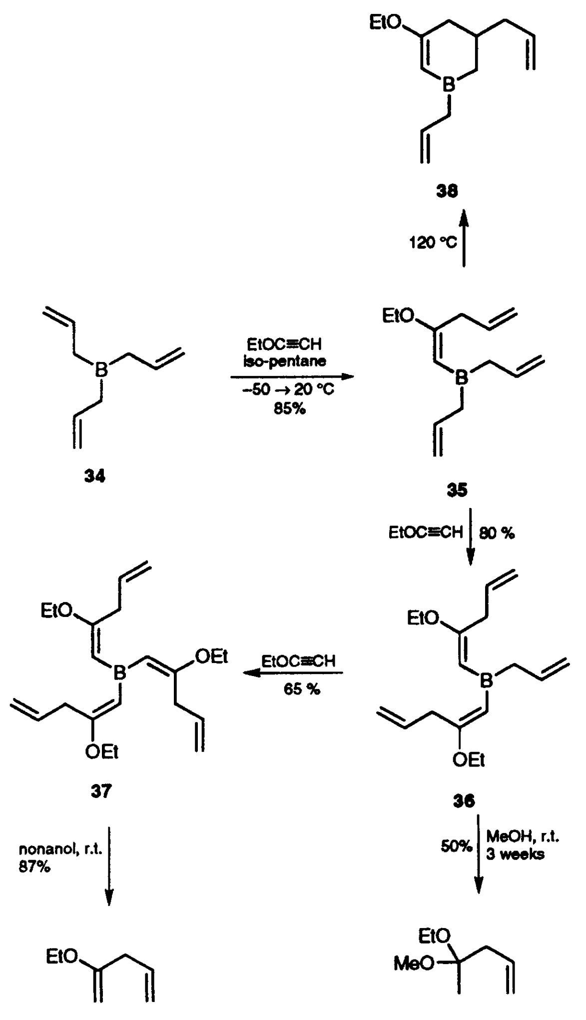
In contrast to boron hydrides, triorganoboron compounds do not readily add to alkynes unless exceptionally reactive substrates are employed. For example, 1,2-bis(trimethylstannyl)ethyne reacts quantitatively with triorganoboranes (**Scheme 14**).

Allylboranes, like other allylmetal reagents derived from zinc, boron, magnesium, and aluminium can add to alkynes *via* a six-centred transition state (metallo-ene reaction) leading to alkenylmetal adducts. However, with simple terminal alkynes allylmetallation is complicated by side-reactions such as hydrogen abstraction which accompanies the allylzincation of terminal alkynes;[17,51,55–57] and allylmetallation of internal alkynes fails altogether in the absence of electron-donating groups such as alkoxy substitutents. A case in point is the *cis*-addition of triallylborane **34** to 1-ethoxyethyne (**Scheme 15**)[58] which proceeds at – 50 → 20°C to provide adducts **35**, **36**, and **37** in 85, 80, and 65% yield respectively depending on the ratio of reagents. Cleavage of the B–C bond of compounds **35**–**37** with alcohols, water, and bases at 20–100°C gave 2-ethoxy-1,4-pentadiene and thermally-induced cyclization of adduct **35** occurred at 120°C to provide the boracycle **38**. Crotylboration of ethoxyethyne also occurs at room temperature to form stable adducts.[59]

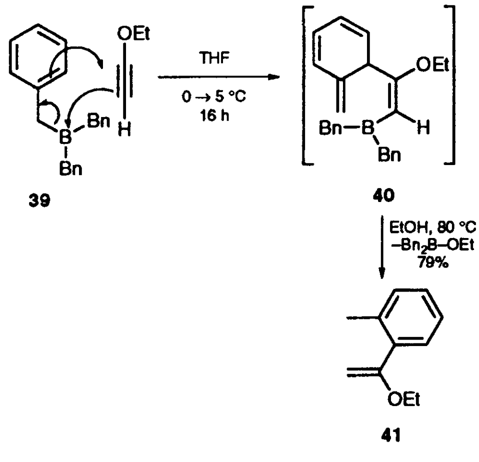
A metallo-ene reaction of tribenzylborane **39** with ethoxyethyne occurs in ether, THF, isopentane, or neat to provide intermediate **40** which ethanolyses to 1-ethoxy-1-*o*-tolylethylene **41** in 79% yield (**Scheme 16**).



Scheme 14

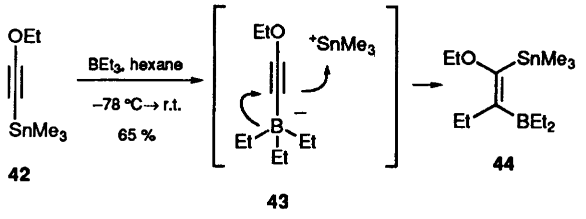


Scheme 15



Scheme 16

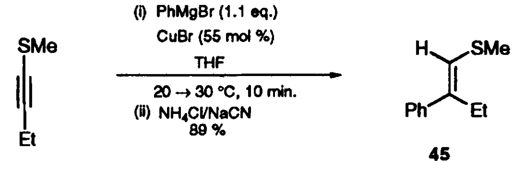
Wrackmeyer and co-workers[60] observed easy *cis*-addition of triethylborane to alkynylstannane **42** to give adduct **44** via rearrangement of alkynyl borate intermediate **43** (**Scheme 17**).



Scheme 17

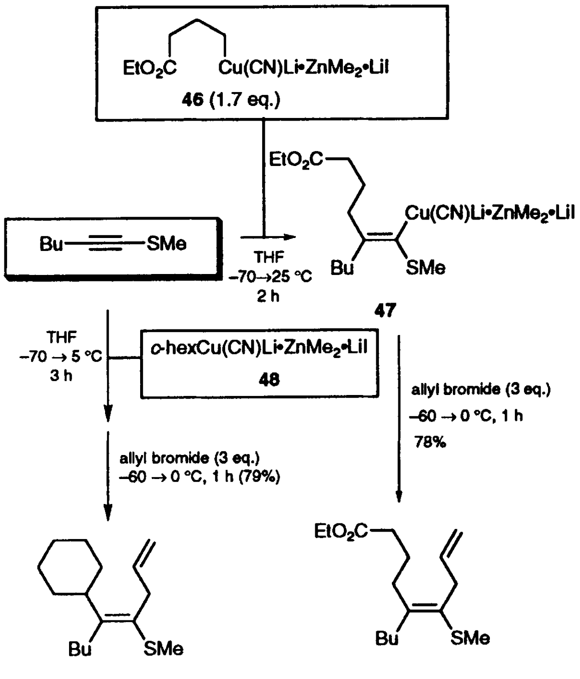
3.3 Organocopper reagents

Carbocupration of alkynes by lithium—and magnesium—derived copper reagents can be an efficient means of preparing stereoisomerically pure di- and tri- or tetra-substituted double bonds but the method has some synthetic limitations: (i) internal alkynes are usually inert towards carbocupration; (ii) aryl-, alkenyl-, and alkynyl-copper derivatives do not add to alkynes; (iii) methylcupration of alkynes is sluggish; and (iv) carbocupration of alkynes with secondary alkylcopper compounds has, in some cases, been found to be less regio- and stereo-selective.[61,62] Pioneering experiments on the carbocupration of various heteroalkynes carried out by the groups of Vermeer[63] and Normant[64] more than 20 years ago established that carbocupration of 1-heteroalkynes is much easier than simple terminal alkynes and that regioselectivity depends on the nature of the heteroatom and its influence on the polarity of the π-system. For example, in 1-alkylthioalkynes the complementary inductive effect of the β-alkyl substituent and electron-withdrawing effect of the S heteroatom causes location of the copper on the carbon atom adjacent to sulfur in adduct **45** (**Scheme 18**).[63] Improved yields and regioselectivity were achieved when THF was used instead of ether. In the absence of Cu^I salts, reaction of Grignard reagents with 1-thioalkynes can lead either to substitution at the sulfur group with the formation of alkynylmagnesium derivatives or proton removal to form allenic sulfides.



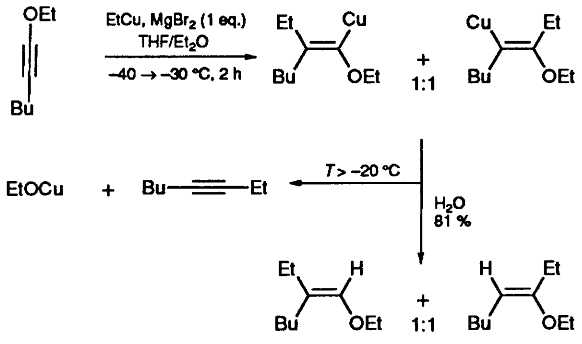
Scheme 18

A major limitation to the traditional methods for accomplishing carbocupration has been the incompatibility of most functional groups with the highly nucleophilic and basic organomagnesium and lithium reagents used to prepare the requisite cuprates. A significant extension of the synthetic utility of carbocupration with the stereoselective construction of tri- and tetra-substituted alkenes was recently achieved by the use of mixed clusters of copper, zinc, and lithium which are gentle enough to tolerate the presence of esters, nitriles, and chloride.[62] The method is illustrated (**Scheme 19**) by the regio- and stereo-selective addition of the cuprate **46** to 1-(methylthio)-1-hexyne leading to alkenylcopper derivative **47** which reacted with electrophiles such as water, iodine, allylic halides, and trimethyltin chloride to provide stereochemically pure tri- and tetra-substituted olefins in good yields (67–92%). Copper-zinc reagents such as **48** harbouring simple alkyl ligands are more reactive than their functionalized counterparts and add at lower temperature.

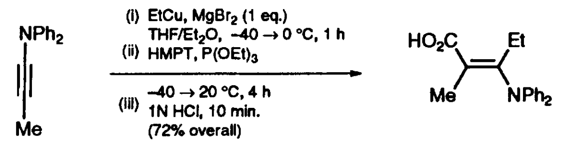


Scheme 19

Addition of the Gilman reagent EtCu to 1-ethoxy-1-hexyne and 1-diphenylamino-1-propyne, catalysed by magnesium bromide, illustrates the influence of mesomeric electron-donation on the regioselectivity of carbocupration. In the case of 1-ethoxy-1-hexyne, the reaction is not regioselective due to the conflicting inductive effect of the β-alkyl substituent and the mesomeric effect of the O atom (**Scheme 20**) whereas the analogous reaction with 1-diphenylamino-1-propyne is dominated by the donor properties of the amine substituent, giving rise to exclusive β-metallation (**Scheme 21**). Configurational stability at reflux in THF was observed for alkenylcuprates possessing a S heteroatom and at 20°C for the corresponding N intermediates. Alkoxyalkenyl cuprates, however, undergo facile *trans* elimination above − 20°C (**Scheme 21**).

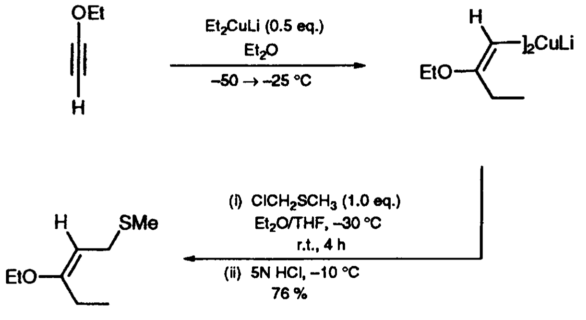


Scheme 20



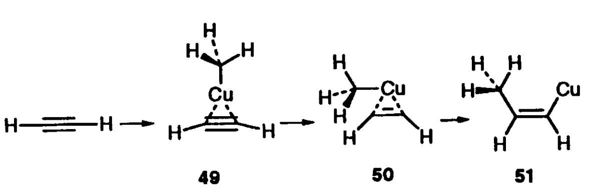
Scheme 21

Notwithstanding the less favourable regiocontrol and configurational stability exhibited by alkoxyalkynes compared to the sulfur and nitrogen analogues, Normant and co-workers[65] were able to utilize vinylcuprates, prepared via the *syn*-addition of lithium derived dialkylcuprates to ethoxyethyne, in the synthesis of stereochemically pure allylic sulfides as shown in **Scheme 22**.



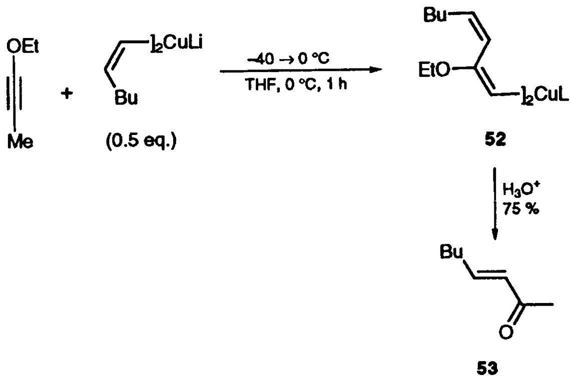
Scheme 22

Nakamura and co-workers studied the addition of MeLi, MeCu, and Me_2CuLi to heteroalkynes using *ab initio* molecular orbital calculations and found an excellent correlation between experimental regioselectivity and the calculated energies of the regioisomeric transition structures, indicating that the activation enthalpy is an important determinant of regioselectivity.[65(b)] They concluded that a heteroatom substituent controls the regiochemistry of carbometallation mainly by affecting the electron population of the alkyne fragment in the transition state. The addition of MeLi and MeCu to the alkyne were found to proceed through two stages involving the π-complex **49** and the transition structure **50** to the product **51** (**Scheme 23**). No indication of coordination between the heteroatom and the metal was found in any of the transition states, whereas some coordination was found in the products. In addition to their regiochemical influence, heteroatoms increased the rate of carbometallation while alkyl groups retarded the reaction.

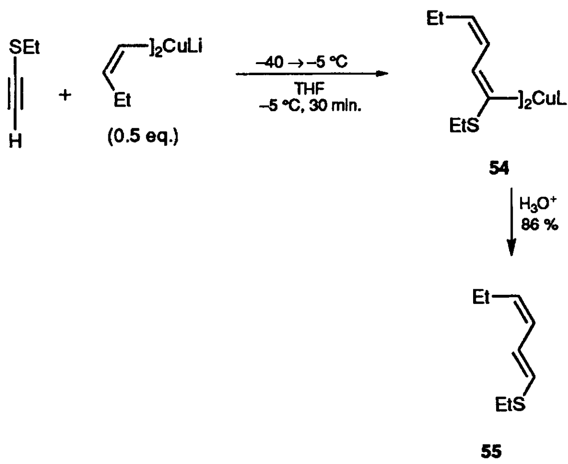


Scheme 23

The enhanced reactivity of 1-heteroalkynes allows addition of alkenyl cuprates which are generally less reactive than alkyl cuprates (**Schemes 24** and **25**).[65] Protonolysis of adduct **52** was accompanied by hydrolysis of the enol ether and isomerization of the double bond gave ketone **53** in 75% overall yield whereas protonolysis of adduct **54** gave the acid-stable 1-alkylthio-1,3-butadiene **55**.

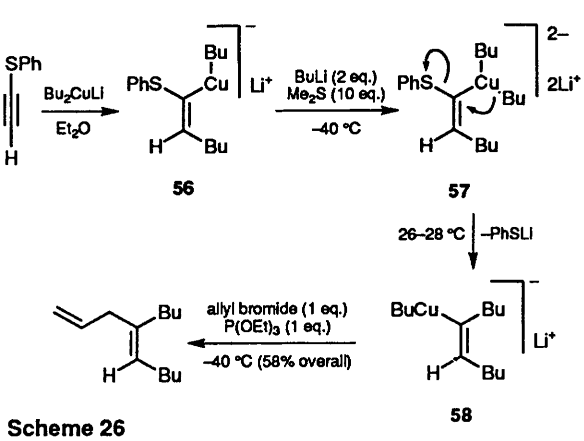


Scheme 24



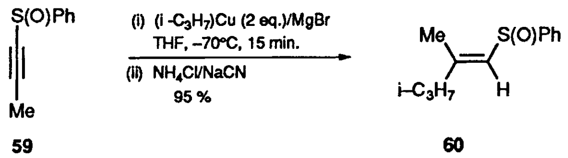
Scheme 25

Carbocupration of 1-(phenylthio)ethyne is the first step in a new stereoselective synthesis of trisubstituted alkenes (**Scheme 26**).[66] Addition of BuLi (2 eq.) to α-(phenylthio)alkenyl cuprate **56** generated a putative higher order cuprate **57** whose 1,2-metallate rearrangement occurred with inversion of configuration, leading to the alkenylcuprate **58** and thence to a variety of trisubstituted alkenes via reaction with electrophiles such as iodine, methyl propiolate, and allyl bromide.



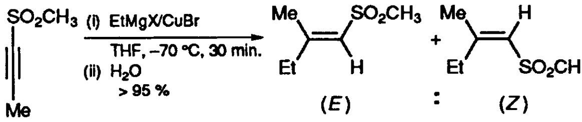
Scheme 26

Vermeer[67] and Truce[68] described the easy reaction of 1-alkynyl sulfoxides with organocopper(I) reagents. Reaction of Pr^{i}Cu—prepared from the corresponding Grignard reagent and 1 eq. of copper(I) bromide—with 1-propynylsulfoxide **59** provided *syn*-adduct **60** in almost quantitative yield (**Scheme 27**). Attack at sulfur rather than the triple bond occurs with some lithium dialkylcuprates. For example, lithium dimethylcuprate adds normally but the more reactive lithium di-n-butylcuprate gives appreciable quantities of n-butyl ethyl sulfoxide. Similarly, treatment of 1-alkynyl sulfoxides with Grignard reagents in THF at − 70°C results in attack on the sulfur atom.[67]



Scheme 27

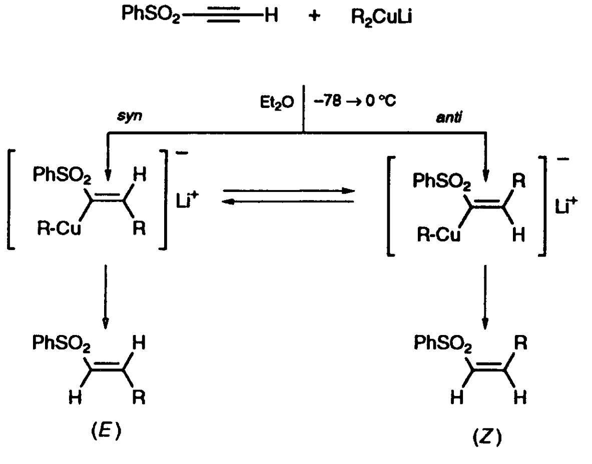
Mainly polymeric products are formed by the slow reaction of 1-alkynyl sulfones with Grignard reagents in THF at 0°C;[69] however, Vermeer and co-workers[70] found that Cu^I-catalyses addition to Grignard reagents to 1-alkynyl sulfones. The stereochemistry depends on the ratio of Grignard reagent to Cu^I with high concentrations of Cu^I forming the (*E*)-isomer—*i.e.*, *syn*-addition (**Scheme 28**). Similar results were observed for methylthioethyne. Discrepancies were also reported in the stereocontrol exhibited in the addition of monoalkylcopper(I) reagents and lithium dialkylcuprates to 1-alkynyl sulfones. Lithium di-n-butylcuprate provided an 81% yield of the *trans*-adduct when reacted with ethyl 1-propynyl sulfone whereas n-butylcopper gave a 90% yield of the *cis*-adduct.[68]



RMgX/CuBr	(*E*)		(*Z*)
1.0 / 0.1	75	:	25
1.0 / 0.5	88	:	12
1.0 / 3.0	99	:	1

Scheme 28

Naso and co-workers[71] observed that the stereochemistry of the addition of dialkyl- and diphenyl-cuprates to benzenesulfonylethyne depended on temperature, time allowed for equilibration, and the size of the ligands on the cuprates (**Scheme 29**). Up to 30% of the (*Z*)-isomer was isolated from the reaction of dimethyl- and diphenyl-cuprates at 0°C when the reaction was quenched immediately after mixing of the reagents (entry 2). Equilibration for 30 minutes provided the (*E*)-isomer exclusively (entry 1). With di-n-butyl and di-sec-butylcuprates 5–20% of the (*Z*)-isomer was isolated even after equilibration at 0°C. At − 78°C almost no stereoselectivity was observed (entry 4). Absolute stereocontrol was achieved with di-t-butylcuprate to form the (*Z*)-isomer even at lower temperatures (entries 5,6). Two possible explanations were cited for the inconsistent stereochemistry: the presence of two different reaction pathways with two different activation energies and/or isomerization of the two intermediates.

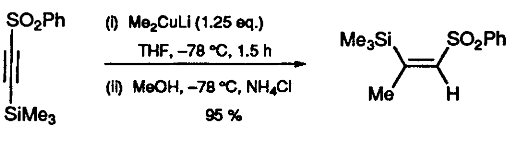


Entry	R	*T* °C	Time (min.)	(*Z*)	(*E*)
1	Me	0	30	–	100
2	Me	0	a	20–30	80–70
3	Bu^n	0	0.5	5	95
4	Bu^n	−78	0.5	42	58
5	Bu^t	−30	10	–	100
6	Bu^t	−78	0.5	–	100

a: reaction quenched immediately after mixing the reagents

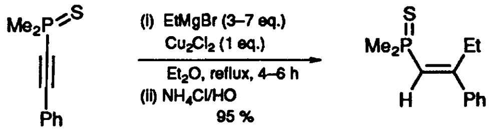
Scheme 29

Eisch and co-workers[14] were able to effect the *syn*-carbocupration of phenyl trimethylsilylethyl sulfone in high yield using lithium dialkylcuprates ($LiCuR_2$, R = Me, Ph, allyl) as illustrated in **Scheme 30**.



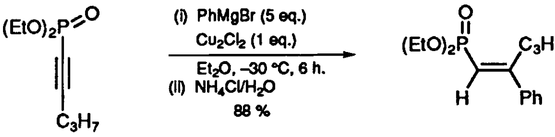
Scheme 30

Treatment of phospha- and thiophospha-alkynes with an excess of alkyl Grignard reagent in the presence of an equimolar amount of copper(I) chloride provides alkenylphosphine sulfides with excellent regio- and stereo-control.[72] (**Scheme 31**).



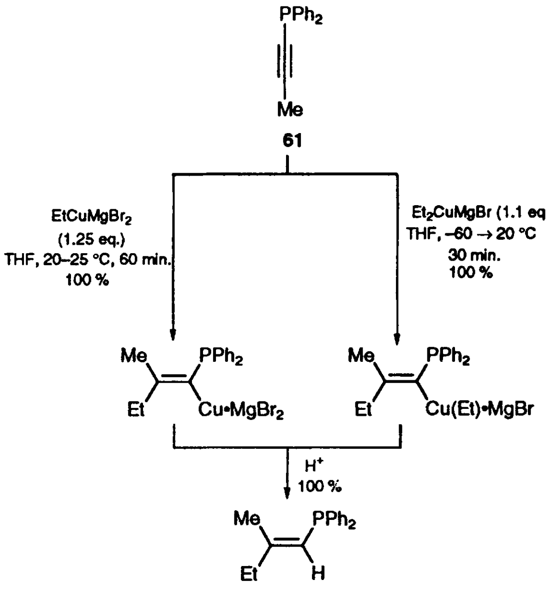
Scheme 31

Recently, a similar protocol was applied to *α*,*β*-alkynylphosphonates to form the corresponding disubstituted vinyl phosphonates in accordance with the well established *syn*-selectivity of addition and *β*-placement of the alkyl substituent[73] (**Scheme 32**).



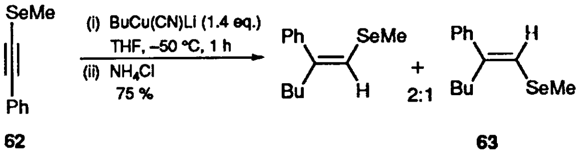
Scheme 32

Vermeer and co-workers investigated the behaviour of 1-alkynyldiphenylphosphines towards organocopper(I) compounds in THF and found that addition of **61** occurred in the presence of $R_2Cu{\cdot}MgBr$ or $RCu{\cdot}MgBr_2$ (**Scheme 33**).[69] Exclusive *syn* addition and high regiocontrol (exclusive attack of the R group at the *β*-C) was obtained. The transfer of only one of the two R groups from the homocuprate $R_2Cu{\cdot}MgBr$ to the alkynylphosphine is notable because, in similar additions to 1-alkynyl sulfides, both R groups are transferrable.



Scheme 33

The vicinal difunctionalization of acetylenes bearing an organoseleno group has recently been reported by Braga and co-workers.[74] Reaction of lithium butylcyanocuprate with **62** (**Scheme 34**), followed by capture of the intermediate alkenyl cuprate with several electrophiles led to di- and tri-substituted vinylic selenides in acceptable yields. In all the cases studied, only one regioisomer was obtained—a consequence of carbanion stabilization by the selenium atom. The major stereoisomer corresponded to *syn* addition of the organocuprate, although in some cases, an example of which is shown in **Scheme 34**, the product **63** derived from the *anti*-adduct could be detected.



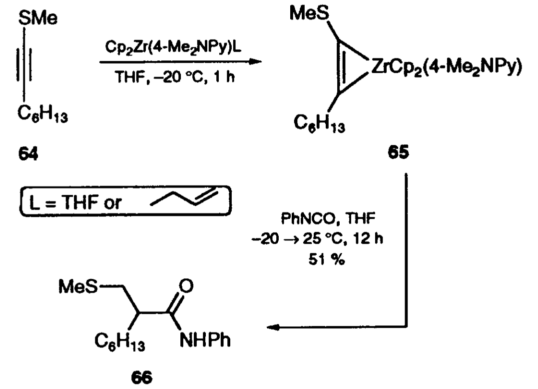
Scheme 34

3.4 Metallacycles

The formation of metallabicycles *via* intramolecular reductive coupling of enynes has received much attention in recent years.[75] Low-valent metallocenes (MPc_2, where M = Ti, Zr, Hf) form titana-, zircona- and hafna-cycles respectively. These metallabicycles are versatile intermediates which can be elaborated into a wide range of mono-and bi-cyclic organic compounds *via* protonolysis, iodinolysis, and carbonylation. Efficient cyclization is enhanced by the presence of a substituent boosting the alkene nucleophilicity, the most common being the silyl group, although tin, germanium, carbon, and hydrogen have been employed. Both electronic and steric effects control the regiochemistry of the reaction but insertion often occurs at the more sterically-hindered position, which highlights electronic control as being the dominant factor.[76]

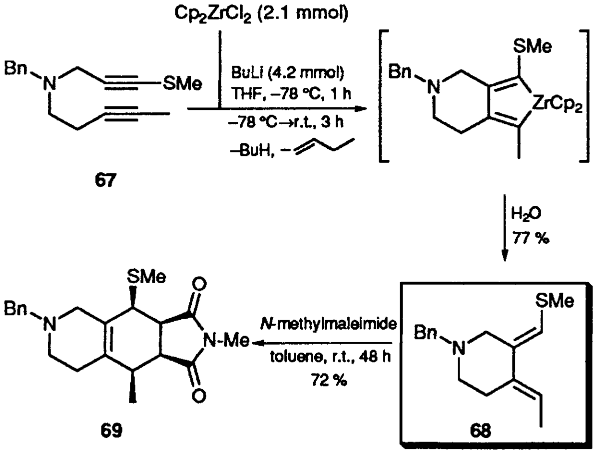
3.4.1 Zirconium-alkyne complexes

Alkyne autodimerization, a significant side-reaction in metallocylizations, is limited by the use of 1-trimethylsilylacetylenes, but additional difficulties arise from competitive displacement of the bulky silyl ligand prior to coupling.[77] Van Wagenen and Livinghouse[77] found that the complexation of strongly ligating 1-methylthioalkynes, *e.g.* **64** (**Scheme 35**), led to the generation of zirconacyclopropene **65** with a minimum (⩽ 3%) of dimer formation. Insertion of electrophiles, an example of which is shown in **Scheme 36**, followed by protonation provided the adduct **66** in good yield. The regiochemistry of the insertion is consistent with a transition state involving internal MeS → Zr complexation.



Scheme 35

Whitby and co-workers recently reported a zirconocene-mediated synthesis of 3,4-disubstituted piperidines and reduced isoquinolines using a methylthio activated alkyne (**Scheme 36**).[78] Reductive coupling of the diyne **67** and protolytic workup formed the piperidine **68** containing an (*E,E*)-exocyclic diene moiety which was further elaborated via cycloaddition chemistry to form **69**.



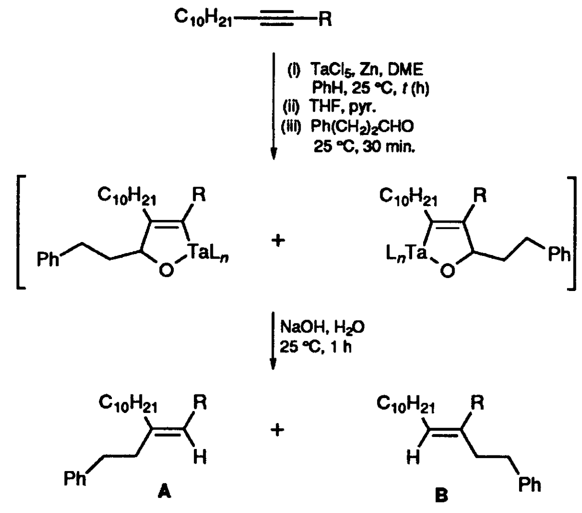
Scheme 36

3.4.2 Tantalum-alkyne complexes

Unsymmetrical tantalum-alkyne complexes react with carbonyl compounds to produce two regioisomeric allylic alcohols in varying ratio depending on which tantalum–carbon bond of the tantalacyclopropene inserts the carbonyl compound (**Scheme 37**).[75,76] The enhanced electron density imparted by the methylthio moiety gave exclusive reaction at the β-position of the methylthio substituent (entry a). In contrast, the reaction between the zirconocene-1-(methylthio)-1-alkyne complex and carbonyl compounds produced a 1:1 regioisomeric mixture.[77] The resonance effect of the phenyl group in phenylthioalkynes weakens the influence of the sulfur on regioselectivity (entry b). The proportion of α-adducts also increased when sulfonyl-substituted acetylenes were employed (entry c). Reactivity of alkynes toward the low-valent tantalum in the formation of tantalum-alkyne complexes was directly proportional to the electron density of the triple bond and decreased in the order: $R^1C\equiv CSR^2 > R^1C\equiv CR^2 > R^1C\equiv CSO_2R^2 \sim R^1C\equiv CCO_2R^2$.

3.4.3 Titanium-alkyne complexes

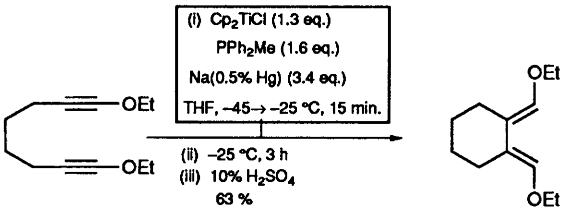
The cyclization of several heteroatom-containing diynes was investigated by Nugent and co-workers using both titanium and zirconium based reagents.[79]



Entry	R	t (h)	A : B	Yield (%)
a	SMe	0.2	99 : 1	73
b	SPh	0.5	77 : 23	85
c	SO_2Me	2.5	54 : 46	54

Scheme 37

Noteworthy, differences in selectivity were observed in the nominally isoelectronic reagents. In the case of the bis-alkoxyalkyne **70** (**Scheme 38**), the titanium reagent was found to be superior to the zirconium reagent with the desired cyclized product **71** produced in 63% yield.



70 **71**

Scheme 38

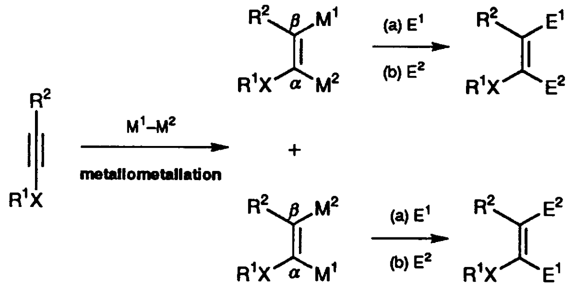
4 Metallometallation

Metallometallation of alkynes introduces two carbon–metal bonds in a single step thereby creating the opportunity for selective chain extension on adjacent carbons. Metallometallations usually involve bimetallic reagents of the type $R_3Si\text{-}MR_n$ or $R_3Sn\text{-}MR_n$ in which M = B, Al, Mg, Mn, Cu, Zn, Si, or Sn. A noteworthy feature of these reagents is their low basicity. In many cases metallometallations can be performed on substrates which contain functional groups such as hydroxyl, ester, amine, and halide. Metallometallation reactions can be divided into four categories depending on the nature of the bimetallic reagent:

- (i) stoichiometric metallo-cuprations:
  - Ge-Cu[26]
  - Sn-Cu[80–97]
  - Si-Cu;[84,92,94,96,98–102]
- (ii) metallometallations with Cu^I catalysis:
  - Sn-Zn[103–105]
  - Sn-Al[82,103,104,106–108]
  - Sn-Mg[82,103,104,108]
  - Sn-B[108–110]
  - Si-B[110]
  - Si-Al[41,106]
  - Si-Zn[41,106]
  - Si-Mg;[41,111]
- (iii) metallometallations with other transition metal catalysts:
  - Si-B/Co[110]
  - Sn-B/Co[110]
  - Si-Si/Mn[112]
  - SnSn/Mn[103]
  - Sn-Mg/Pd[123]
  - Sn-Al/Pd[103]
  - Sn-Zn/Pd[103]
  - Sn-Sn/Pd[82,106,111,113–117]
  - Si-Mg/Pd[106,111,117]
  - Si-Al/Pd[106,111,117]
  - Sn-Si/Pd[82,115,118,119]
  - Si-Si/Pd[31,36,120–126]
  - Ge-Ge/Pd[36]
  - B-B/Pt;[127]
- (iv) uncatalysed metallometallations:
  - Te-Te[128–131]
  - Si-Ti.[132]

Although terminal alkynes metallometallate with a high degree of regio- and stereo-control,[133] internal alkynes usually require the presence of some activating group such as CO_2R, to achieve useful control.[87,116,134] In addition to the inherent bias in the bimetallic reagent, the regio- and stereo-chemical outcome of the reaction may be influenced by the catalyst employed, reaction conditions, solvents, Lewis acids, and the presence of suitable functional groups on the substrate.[1,116] Unsymmetrical alkynes in which one of the substituents is a heteroatom (Si, O, S, N) present a potentially valuable method for controlling the regioselectivity of metallometallations through mesomeric, inductive, or coordination effects. A particularly attractive feature of the metallometallation of heteroalkynes is the opportunity for further elaboration to synthetically valuable heteroalkenes provided (a) the addition is regioselective and (b) the two C-metal bonds can be selectively and sequentially replaced by electrophiles as depicted in **Scheme 39**.

In the following sections the relatively small amount of data which describes the influence of Si, O, S, and N substituents on the regiochemistry of various metallometallation reactions are examined.

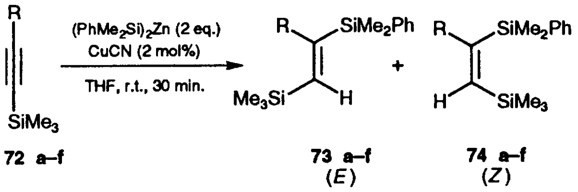


Scheme 39

4.1 1-Trimethylsilyl-1-alkynes

Oshima *et al.* investigated the Cu^I-catalysed reaction of 1-trimethylsilyl-1-alkynes with the silylzinc reagent $(PhMe_2Si)_2Zn$ (**Scheme 40**).[106] The reaction was highly regioselective and invariably gave 1,2-disilyl-1-alkenes regardless of the alkyne substituent. However, the stereochemistry depended on the presence of proximate hydroxyl groups. 1-(Trimethylsilyl)-1-octyne **72b** and 4-(2-tetrahydropyranyloxy)-1-(trimethylsilyl)-1-butyne **72e** gave *syn*-adducts which afforded the (*E*)-1,2-disilyl-1-alkenes **73b,e** on workup. However, 3-(trimethylsilyl)-2-propyn-1-ol **72c** and 4-(trimethylsilyl)-3-butyn-1-ol **72d** provided the *anti*-adducts which protonated to give the (*Z*)-isomers **74c,d**. The authors postulated that the initial addition proceeds with *syn*-stereochemistry but that isomerization later occurs driven by intramolecular coordination of the hydroxyl group to the zinc atom.

The chelation effect disappeared when the hydroxy group was separated from the alkyne by three carbons, **72f** leading to the expected *syn*-adduct exclusively.

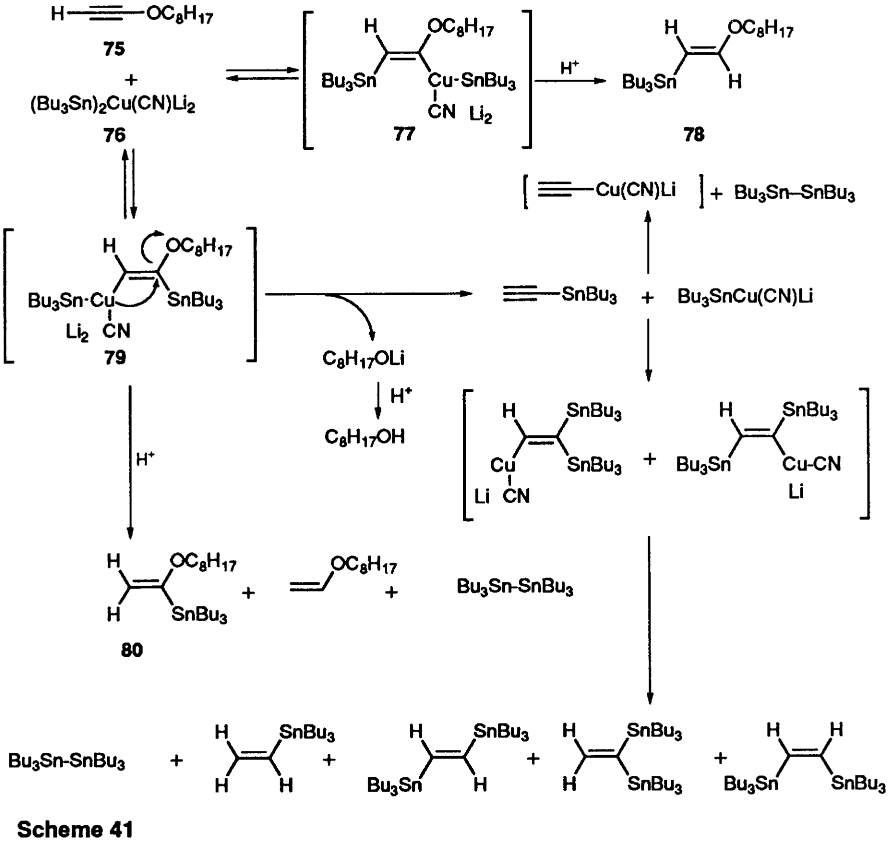


	R	(*E*) : (*Z*)	Yield
a	H	100 : 0	78%
b	n-C_6H_{13}	100 : 0	58%
c	CH_2OH	0 : 100	75%
d	CH_2CH_2OH	0 : 100	44%
e	CH_2CH_2OTHP	100 : 0	72%
f	$CH_2CH_2CH_2OH$	100 : 0	74%

Scheme 40

4.2 1-Alkoxy-1-alkynes

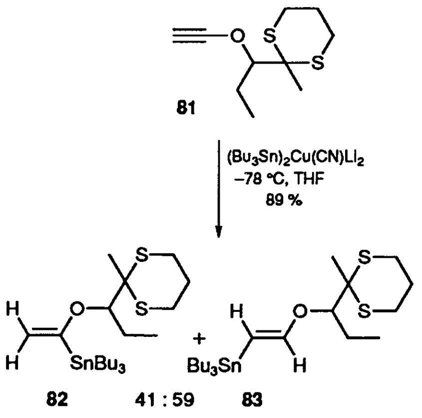
Scheme 41 outlines the stannylcupration of 1-alkoxy-1-alkynes which draws attention to one of its major limitations: reversibility. In principle the adducts **79** and **77** could be trapped *in situ* by a suitable electrophile, giving trisubstituted alkenyl stannanes as products. However, in practice, most electrophiles react preferentially with the bimetallic reagent rather than the adduct. Extensive chemical and NMR studies by Cabezas and Oehlschlager[85] on the stannylcupration of terminal alkoxyalkynes has finally



Scheme 41

provided conclusive evidence for the mechanism of the reaction, as well as an explanation for the presence of a number of by-products in the reaction. Reaction of **75** with **76** in THF at − 40°C followed by warming to 0°C and methanolysis gave a mixture of regioisomers **78** and **80** in a 4:6 ratio in 42% yield.

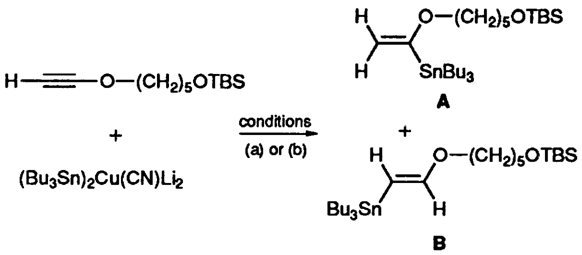
The kinetic product of addition at − 78°C corresponds to intermediate **79** which rapidly equilibrates with **77**. Addition of the alkoxyalkyne **75** in the presence of a protic source such as MeOH, to the higher order cuprate **76** at − 78°C results in protonolysis of intermediate **79** before equilibration with **77** is possible, thus providing regioisomer **80** in 95% yield. Selective protonation of the alkenylcopper intermediates **79** and **77** occurs because they are more basic than $Me_3Sn(L)CuLi$ thereby forcing the equilibrium to the right. Cox and Wudl[91] estimate the CuH conjugate acid of a stannylcuprate has a pK_a of about 5. When the reaction is performed at 0°C in the presence of HMPA and the absence of a proton source, a mixture of **78** and **80** were isolated in 94% yield with a regioselectivity of 95:5 in favour of **78**. Similar results were obtained in the reaction of $(Bu_3Sn)Cu(CN)Li$ with alkoxyalkynes, although the presence of HMPA was necessary to prevent decomposition of the copper reagent at 0°C. The regioselective formation of **77** under these conditions is presumed to be favoured by intramolecular interaction between the oxygen and the copper. In contrast, the reaction of the dithiane derivative **81** (**Scheme 42**) under kinetic conditions, provided **82** and **83** in a ratio of (41:59) in favour of **83**. The anomalous regioselectivity was attributed to coordination between Cu and S leading to preferential formation of regioisomer **83**.



Scheme 42

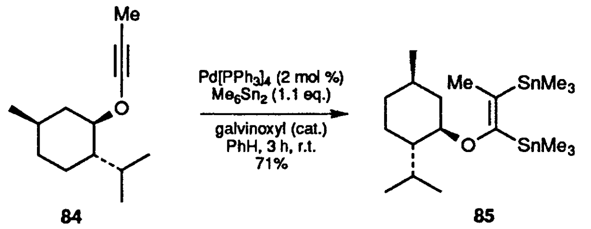
Despite the complexity of the stannylcupration reaction, the regiochemistry of the reaction can be tuned by deft manipulation of reaction conditions as illustrated in **Scheme 43**.

In order to avoid the problem of regioisomeric mixtures in reversible metallocupration reactions,[85] Casson[135] investigated the irreversible Pd^0-catalysed stannylstannylation of 1-alkoxy-1-alkynes under conditions which had already been established for simple terminal alkynes.[82,114] Stannylstannylation of 1-alkoxy-1-alkynes **84** (**Scheme 44**), for example, readily occurred on reaction with $Me_3Sn\text{-}SnMe_3$ in benzene in the presence of 2 mol% $Pd(PPh_3)_4$ and galvinoxyl (added to retard radical-induced isomerization) at ambient temperature to give *syn*-adduct **85** in good yield.



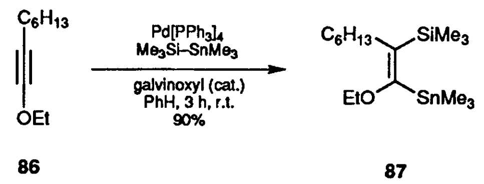
Conditions T (°C)	solvent	Ratio A : B	Yield (%)
(a) 0	THF/HMPA	10 : 90	91
(b) −78	THF	100 : 0	92

Scheme 43



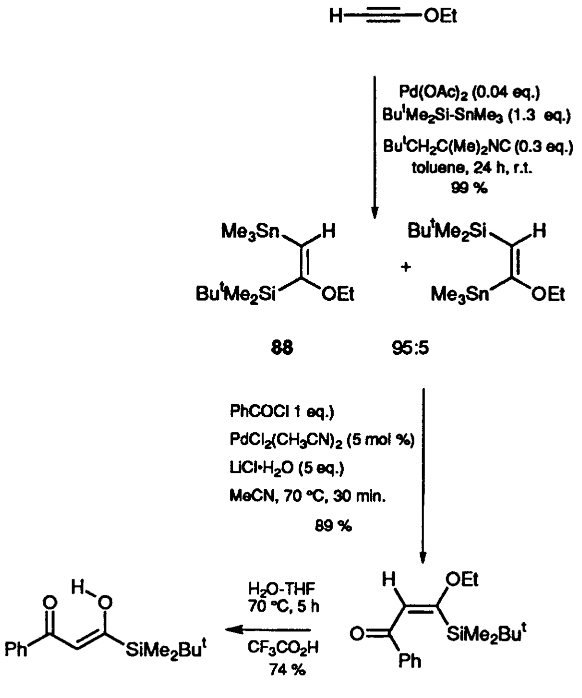
Scheme 44

The regioselectivity of silylstannylation was then examined in the hope that any regiochemical differentials could be amplified with more dissimilar metals. Surprisingly, alkoxyalkyne **86** (**Scheme 45**) reacts very easily with $Me_3Si\text{-}SnMe_3$ in benzene using $Pd(PPh_3)_4$ as the catalyst to give *syn*-adduct **87** as a single regioisomer in 90% yield in which the tin atom is located on the α-carbon adjacent to the oxygen substituent.



Scheme 45

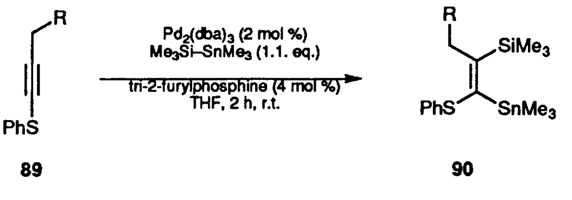
The results of Casson described above contrast sharply with those of Ito and co-workers[136] who showed that 1-ethoxy-1-propyne undergoes silylstannylation using $Pd(OAc)_2$ and 1,1,3,3-tetramethylbutyl isocyanide (**Scheme 46**) to give *syn*-adduct **88**, in which the tin atom is located on the β-carbon remote from the oxygen substituent, as the major product. Regioselectivity in excess of 95:5 is typical of reactions involving the bulky reagent t-$BuMe_2Si$-$SnMe_3$ whereas Me_3Si-$SnMe_3$ added with poor regiocontrol. The α-silylated enol ethers are amenable to further chemical manipulation as illustrated in **Scheme 46**. The complementary results observed by Ito and Casson suggests that the regioselectivity of other metallometallations might be tuned by simply varying the catalyst.



Scheme 46

4.3 1-(Phenylthio)-1-alkynes

Silylstannylation of 1-phenylthio-1-alkynes **89a–f** with Me_3Si–$SnMe_3$ in the presence of $Pd(PPh_3)_4$ occurs with the same regioselectivity as the alkoxy series described above but the reaction is more sluggish (**Scheme 47**).[135] Up to 30 h at reflux is required to produce the silylstannanes in yields of 11–58%. A substantial improvement can be obtained without sacrifice of regioselectivity by using $Pd_2(dba)_3$ (2 mol%) in the presence of tri-2-furylphosphine (4 mol%) in THF.[137] Now the reactions only require 2 h at r.t. and give the silylstannane adducts in 56–80% yield.

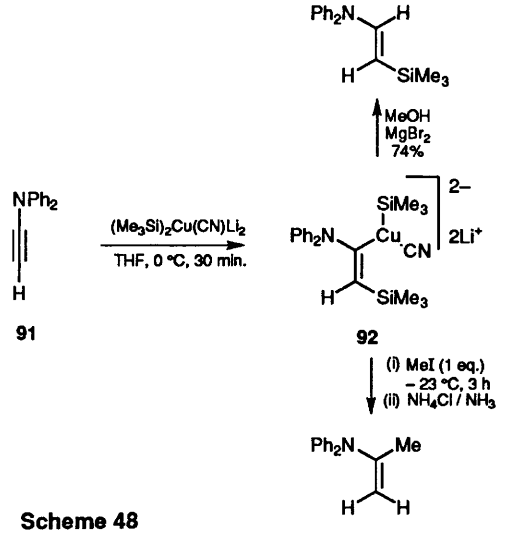


	R	Yield 90
a	OTHP	80%
b	OH	77%
c	$(CH_2)_2OH$	58%
d	OMe	78%
e	Pr^n	62%
f	p-$PhC_6H_4CO_2$	76%

Scheme 47

4.4 1-Amino-1-alkynes (ynamines)

Ricci and co-workers[102] recently described a highly regioselective silylcupration of *N,N*-diphenylaminoethyne **91** (**Scheme 48**) in which the copper atom is placed at the α-position next to the heteroatom—a result which appears to be opposite to the trend set by alkoxyalkynes. However, in this case it is likely that the regiochemistry is governed by internal coordination of the copper by the amino group in adduct **92**.



Scheme 48

5 Conclusion

In this review we have shown that heteroatoms both activate and control the regiochemistry of a wide variety of additions to alkynes leading to synthetically valuable heteroalkenylmetal derivatives. As the number and variety of participating metallic reagents increases, new opportunities for elaboration under very mild conditions will emerge.

6 References

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