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Metal mediated carbometallation of alkynes and alkenes containing adjacent heteroatoms

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Contents

1. Introduction

The first example of a carbometallation reaction appears to have been reported by Bähr and Ziegler in 1927.[1] Over the next 70 years, but particularly during the last decade, a broad cross-section of closely related families of reactions involving the addition of diverse organometallics to a variety of alkenes and alkynes have been developed. These accomplishments are summarized in several review articles.[2] In general, in the context of this review, carbometallation[3] describes a process in which an organometallic reagent reacts with an alkyne, alkene, allene, or related substrate to form an intermediate, that possesses a new carbon–carbon bond. Concomitantly, an alkenyl or alkyl metal species is also generated. A subsequent in situ reaction with an appropriate electrophile transforms this organometallic intermediate into the desired product(s).

The emphasis and common theme in this report, is placed on reactions, which involve an alkyne or alkene acceptor containing an allylic or homoallylic heteroatom. However, some recent representative examples of simple substituted acetylenes are also included. In general oxygen is the most useful substituent either as a free alcohol or ether. Some related examples of conjugated systems are also included for comparison, where appropriate. The literature coverage is selective (~5 years), in order to emphasize recent developments since the previous reviews. For ease of reference and comparison, despite the similarity and interrelationships of several organometallic transformations, the sections have been divided by the element employed rather than the synthetic transformation described.

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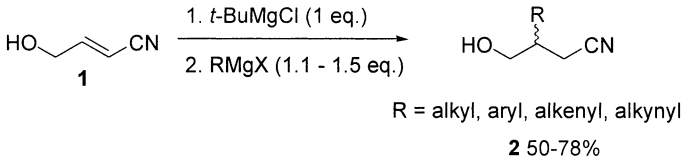


Scheme 1.

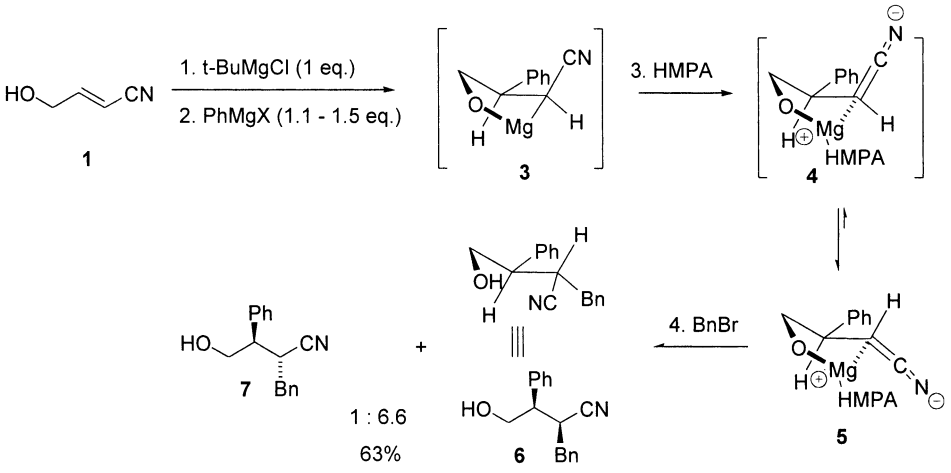
2. Magnesium

It is widely recognized, that conjugate additions of Grignard reagents to α,β-unsaturated nitriles is often more demanding, and troublesome, than the well established additions to conjugated enones.[4] A chelation controlled conjugate addition has been reported recently by Fleming and coworkers, which facilitates this process with α,β-unsaturated nitriles due to the presence of an allylic alcohol as illustrated in the transformation **1** to **2** in Scheme 1.[5]

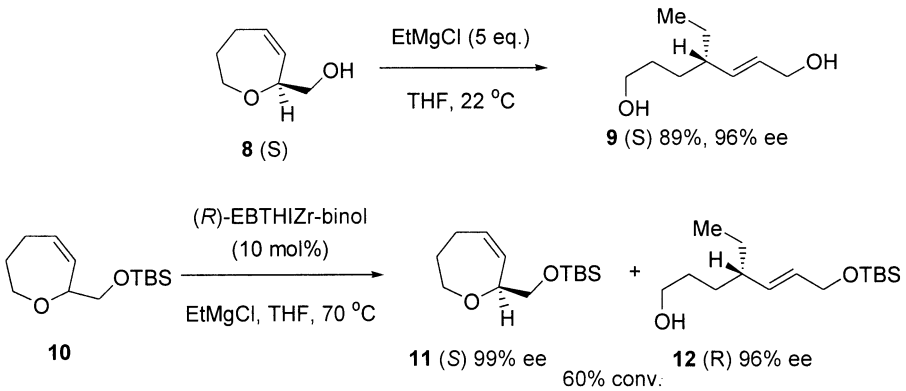
The scope of this reaction was extended to diastereoselective systems in which the intermediate anion, formed from addition to the conjugated nitrile, was quenched with a suitable electrophile in the presence of HMPA. Thus HMPA chelation appeared to weaken the carbon–magnesium bond[6] and allowed alkylation to occur smoothly. In addition, HMPA may aid the solvation of the complex, allowing more efficient equilibration between the two weakly coordinated keteniminate anions **4** and **5** (Scheme 2). Consequently, alkylation occurred preferentially on the less sterically hindered keteniminate **5**, via a backside approach to afford the nitrile **6**, whose structure was established by X-ray analysis.

Hoveyda and coworkers have developed a related heteroatom assisted alkylation of cyclic allylic ethers such as **8** with Grignard reagents, to provide a convenient route to enantiomerically pure allylic diols of type **9** (Scheme 3).[7] A range of Grignard reagents were employed and benzyl and alkyl ethers may replace the free alcohol. Modification of the reaction protocol by addition of a chiral zirconium complex resulted in a catalytically controlled kinetic resolution[8] to yield the enantiomerically pure carbocycle **11** and the ring opened product **12**.

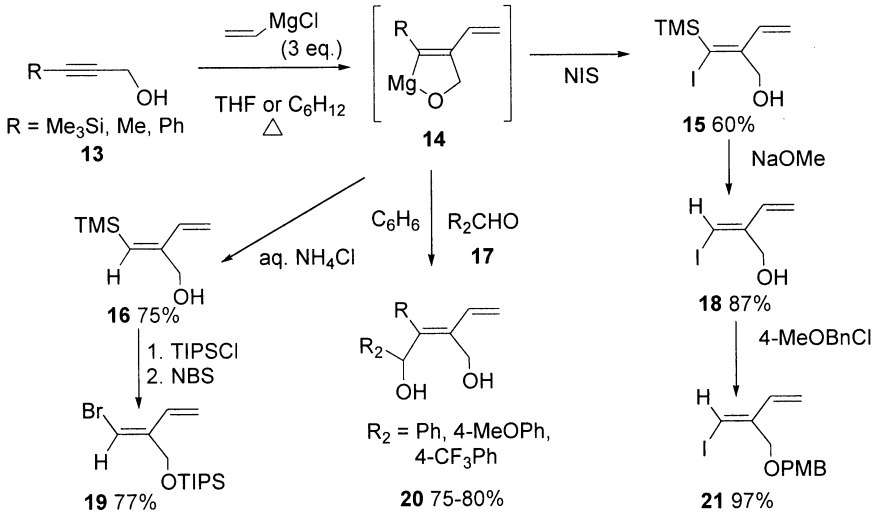
Several years ago Richey[9] and Eisch[10] and their respective co-workers independently demonstrated the general utility



Scheme 2.



Scheme 3.

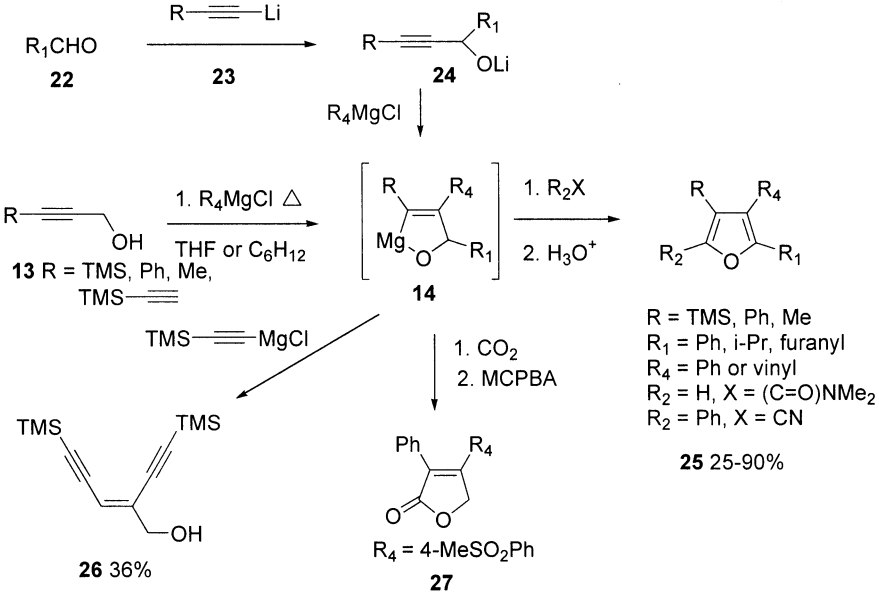


Scheme 4.

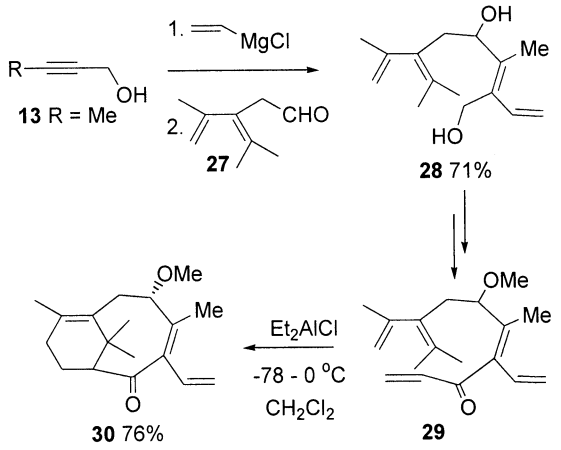
of the reactions of alkynyl alcohols with Grignard reagents (particularly allyl) to prepare dienes and butenolides. This pioneering work has been followed by several other studies.[11] Recently Fallis and co-workers have developed several related procedures for the magnesium mediated carbometallation of propargyl alcohols. Depending upon the synthetic objective, vinyl and related Grignard reagents may be manipulated to afford a variety of different unsaturated systems from a common pathway. As illustrated in Scheme 4, various propargyl alcohols **13** were reacted with vinylmagnesium chloride to generate the intermediate magnesium chelate **14**. Treatment of the silyl substituted intermediate (**14**, R=$SiMe_3$) with *N*-iodosuccinimide followed by desilylation and protection afforded the iodoether **21**. Alternatively, quenching **14** with a proton source provided **16**, which was converted to the bromide **19** upon reaction with *N*-bromosuccinimide (Scheme 4).[12]

Thus, both (*E*) and (*Z*) halodienes may be prepared in a regiospecific manner from a common precursor and condensed with various aldehydes (**17**) after metal–halogen exchange.[13] The use of a THF/cyclohexane solvent mixture permitted the direct reaction of **14** with aldehydes to generate the family of diene–diols **20**.[14] This avoided the sometimes troublesome, exchange reaction with the diene–halides.

The versatility and scope of this carbometallation protocol was extended to the synthesis of substituted furans **25**, when the intermediate **14** (Scheme 5) was reacted with either dimethylformamide or aryl nitriles. Alternatively, **14** was synthesized by addition of the alkynyl lithium salt **23** to an appropriate aldehyde **22** to form the lithium alkoxide **24**, followed by transmetallation with vinyl magnesium chloride accompanied by Grignard addition. Thus, the



Scheme 5.



Scheme 6.

judicious choice of the substrate, the carbometallating species, and the electrophile permitted the complete control of the substitution pattern about the furan ring. In some cases the yields are modest, however the sequence led directly to tetra-substituted furans in which five new bonds were generated during the reaction. In addition, the resulting oxygen heterocycles may be employed for a variety of synthetic objectives.

The reaction of trimethylsilylethynylmagnesium chloride with the diyne alcohol **13** (R=TMSCC) provided direct access to the enediyne synthon **26**. In a related manner, the reaction of the magnesium chelate with carbon dioxide yielded 2(5*H*)-furanones (butenolides) in a concise fashion.[15] Thus the new Merck anti-inflammatory drug Vioxx® was synthesized in a two step sequence, upon addition of 4-thiomethylphenylmagnesium chloride to **13** (R=Ph) to give **14** followed by a carbon dioxide quench and oxidation of the resulting sulfide with *meta*-chloroperoxybenzoic acid to afford **27**.

A recent extension of this one step sequence, played a key role in a carbometallation–intramolecular cycloaddition strategy for the synthesis of the AB-taxane ring system (Scheme 6).[16] Thus the tetraene–diol **28** was generated from the combination illustrated and converted via the diol **28** to the enone **29**, which cyclized readily to the desired bicyclo[5.3.1]undecene skeleton **30** at low temperature in the presence of diethylaluminum chloride. Thus, these magnesium mediated carbometallation protocols facilitate the direct preparation of a variety of different compounds with attractive attributes, and provide building blocks for more complex synthetic targets.

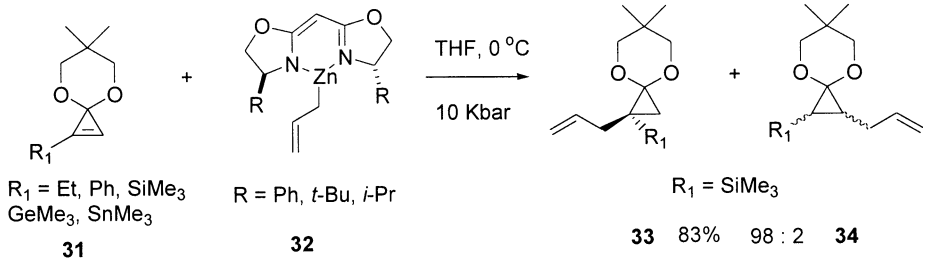
3. Zinc

The enantioselective construction of quaternary carbon centers is a challenge, which continues to receive attention. Nakamura and co-workers have reported an efficient method for the addition of an allylic zinc reagent bearing a chiral bisoxazoline ligand (BOX), to trisubstituted olefins.[17] The addition was regiospecific, as addition occurred exclusively at the more substituted carbon center of the olefin. High pressure experiments did not enhance the enantioselectivity or regioselectivity, but did accelerate the allylzincation reaction and improved the yield (Scheme 7).

The regioselectivity of the zinc addition to strained trisubstituted olefins of type **31** may be controlled by a combination of the choice of ligand for the zinc nucleophile, as well as the type of metal substituent (R_1=SiR_3, GeR_3 or SnR_3) selected. The regioselectivity was reversed when one of the metal substituents occupied the R_1 position. Thus, with allyl zinc bromide as the nucleophile, addition at the less substituted end of the olefin predominated to yield a metal stabilized anion alpha to the R_1 metal component corresponding to **34**. Conversely, addition of the bisoxazoline allylzinc reagent reversed the selectively to give addition preferentially at the more substituted end of the olefin to generate **33**. This was likely a consequence of the combined steric effect of the large metal substituent and the bisoxazoline ligand. Related studies established that the reaction could be catalyzed by the addition of ferric chloride in the case of magnesium and zinc reagents.[18] The enantioselective carbometallation of unactivated olefins continues to receive increased attention.[19]

The carbometallation of unactivated olefins with zinc-azaenolates, developed by Kubota and Nakamura, provided an attractive route to effect the three-component synthesis of carbonyl derivatives.[20] A key feature contributing to the success of this reaction was the use of the *t*-butyl zinc species generated in situ rather than bromo zinc reagent bromide, which otherwise resulted in an impractical, slow reaction (Scheme 8). Thus the intermediate hydrazone zinc salt **36** was added to the alkene to form the alkyl zinc species **37**, which was reacted with various electrophiles to provide the substituted ketones **39** after hydrolysis.

Knochel and co-workers have reported an efficient



R_1 = Et, Ph, $SiMe_3$, $GeMe_3$, $SnMe_3$

31

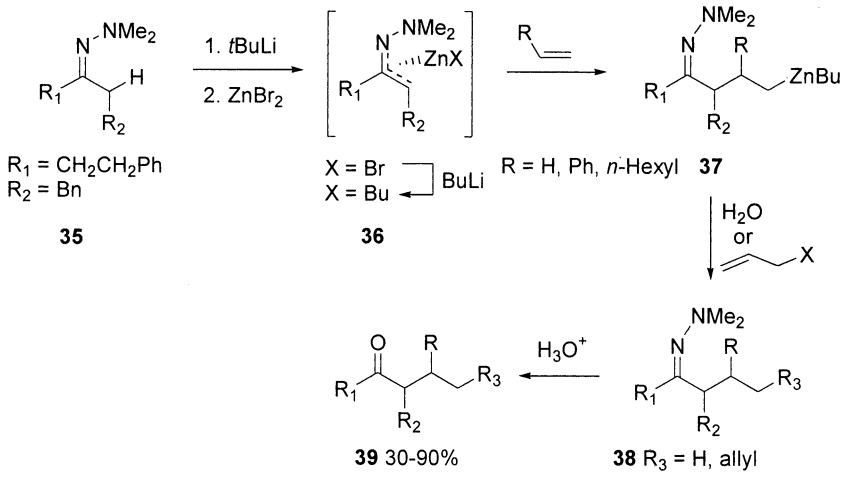
R = Ph, *t*-Bu, *i*-Pr

32

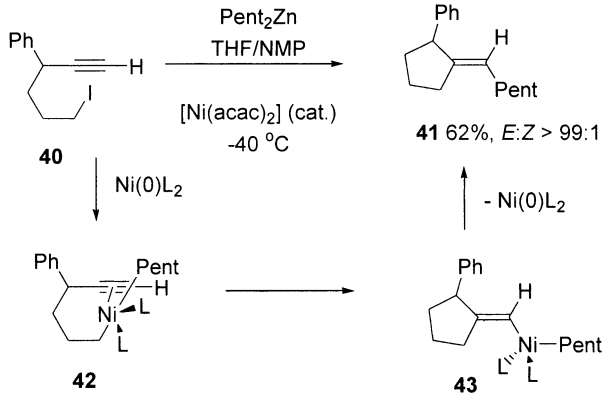
R_1 = $SiMe_3$

33 83% 98 : 2 **34**

Scheme 7.



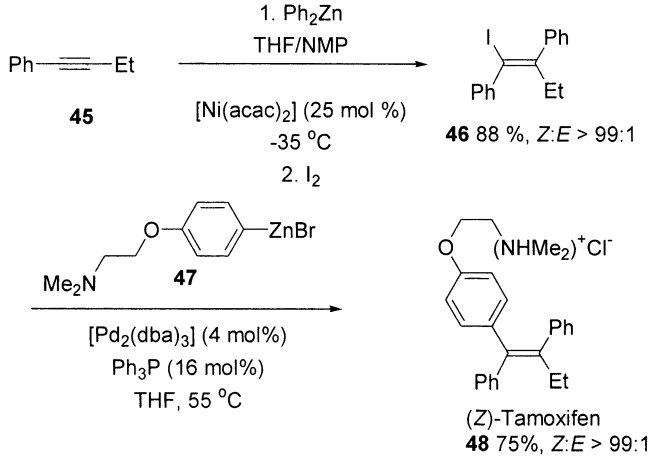
Scheme 8.



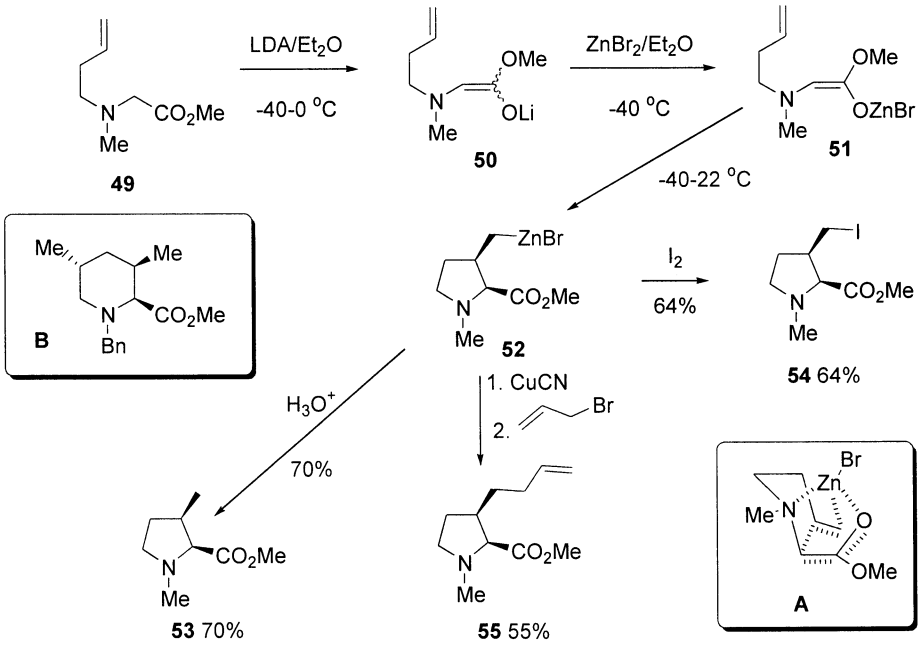
Scheme 9.

nickel-catalyzed carbozincation of unactivated alkynes.[21] The intramolecular reaction of **40** revealed a significant *syn* stereoselectivity (Scheme 9). The mechanism for the *syn* addition is believed to involve the insertion of nickel(0) (generated in-situ), into the carbon–iodine bond followed by transmetallation with the pentenyl zinc reagent ($Pent_2Zn$) to afford the nickel(II) complex **42**, which controlled the *syn* carbonickelation of the alkyne via formation of the alkenyl alkyl nickel(II) complex **43**. Reductive elimination then afforded the (*E*)-*exo*-alkylidenecyclopentane **41**. This *syn* selective procedure was extended to a direct two step synthesis of (*Z*)-tamoxifen (**48**) (Scheme 10). The addition of diphenylzinc to alkynes proceeded more readily than the reaction with dialkyzinc reagents. Therefore, the addition of diphenylzinc to 1-phenyl-1-butyne (**45**) was followed by an iodine quench to give the pure (*Z*)-alkene **46** in 88% yield. A subsequent zinc–palladium catalyzed coupling with the substituted phenyl zinc bromide **47** afforded the *anti*-estrogenic drug. Tamoxifen (**48**) and related estrogen receptor mimics are of interest for the treatment of breast cancer.[22]

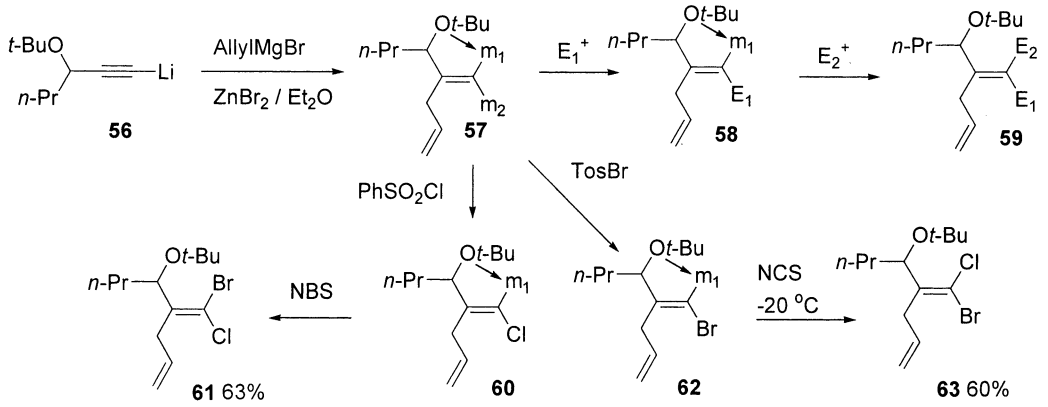
Normant and co-workers have developed a valuable method for the preparation of substituted pyrrolidines.[23] This sequence involved the diastereoselective generation of an amino-zinc-enolate **51**, formed from the initial lithium salt **50**. Intramolecular carbometallation onto the alkene afforded the heterocycle **52**, which was reacted with a selection of electrophiles to generate the compounds **53**, **54**, and **55**. The observed stereochemistry was consistent with the chair-like amino-zinc-enolate transition state **A**. It is noteworthy that this chemistry has also been extended to the



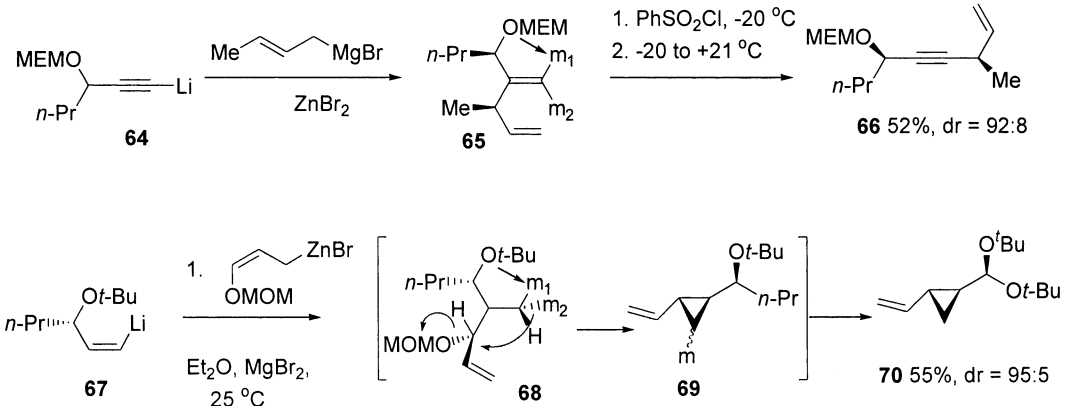
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

synthesis of the six membered ring piperidines, which are usually more difficult to prepare. Thus the single isomer **B** was generated in 62% yield upon quenching the corresponding zinc intermediate with ammonium chloride using a parallel reaction sequence (Scheme 11).[24]

4. Bismetallics

Normant and co-workers have also devised an excellent method to exploit the different reactivity of vinyl mixed metal 1,1-dianions such as **57**. These chelation-controlled reactions of propargyl ethers provided a direct route to stereodefined olefins, as illustrated in Scheme 12.[25] The versatility of this procedure is exemplified by the preparation of **61** and **63** from the common synthon **57** in which the reaction sequence and stereochemistry are controlled by chelation with the adjacent ether. Condensation of **57** with benzaldehyde in the presence of boron trifluoride etherate afforded trisubstituted allenes.

Additional investigations have resulted in modified sequences using these geminal-organobismetallics species in the Fritsch–Buttenberg–Wiechell[26,27] rearrangement in order to prepare disubstituted alkynes (Scheme 13).[28] This process provided the first example of the transfer of chirality in the Fritsch–Buttenberg–Wiechell rearrangement via zinc carbenoids. The migration occurred with retention of configuration. A further extension employed these *gem*-bismetallics for the preparation of 1,2-disubstituted cyclopropanes, such as **70**, in a highly diastereoselective manner.[29] An excellent review has been published describing the preparation and application of these mixed metal sp^2 anions.[30]

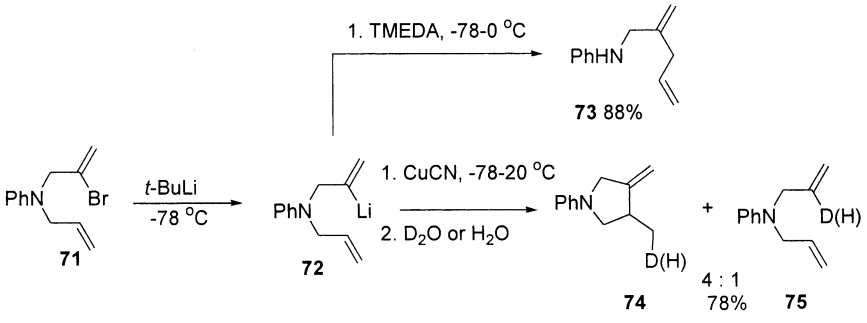
5. Copper

Barluenga and co-workers have developed an intramolecular carbometallation of olefins upon metal–metal lithium–copper(I) exchange with the lithium salt **72** to effect cyclization to **74**.[31] In the absence of copper, but with added TMEDA, the organometallic intermediate followed a different pathway. Allyl transfer took precedence to afford **73** via a 6-*endo* addition sequence (Scheme 14).[32]

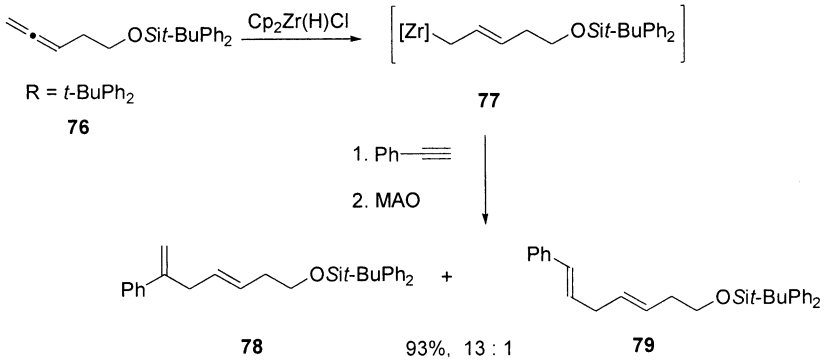
6. Zirconium

Yamanoi and co-workers discovered that hydrozirconation of allenes in the presence of methylaluminumoxane (MAO) effected the carbometallation of alkynes to provide a useful two-step method for the preparation of skipped dienes **78** and **79** in a regioselective manner.[33] The reaction failed in the absence of MAO and the regioselectivity was reduced to 9:1 from 13:1 when Et_3Al was employed instead of MAO (Scheme 15).

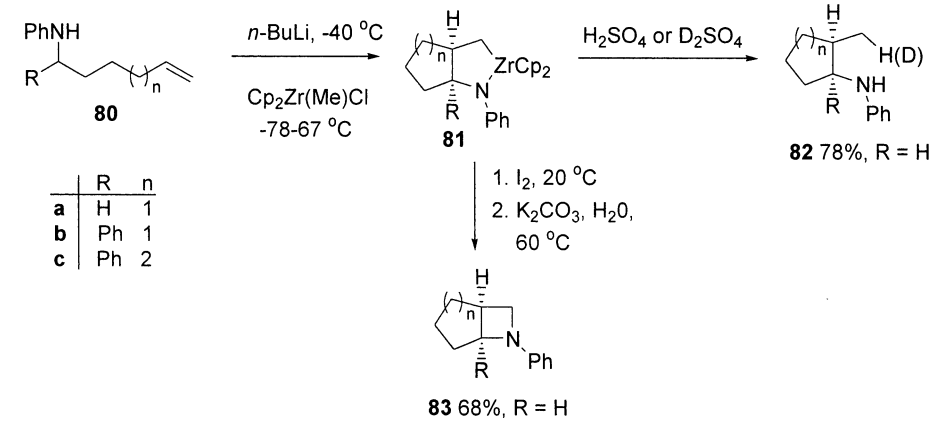
A related zirconium-mediated intramolecular coupling reaction of unsaturated alkyl anilines reported by Barluenga et al. afforded a versatile procedure for the synthesis of azetidines **83** from amino alkenes related to **80** (Scheme 16).[34] In a formal sense, this route to azetidines represents a regio- and diastereoselective [2+2] cycloaddition between an imine and an alkene. Related transformations to these



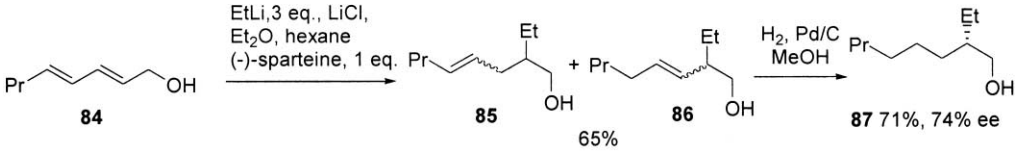
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

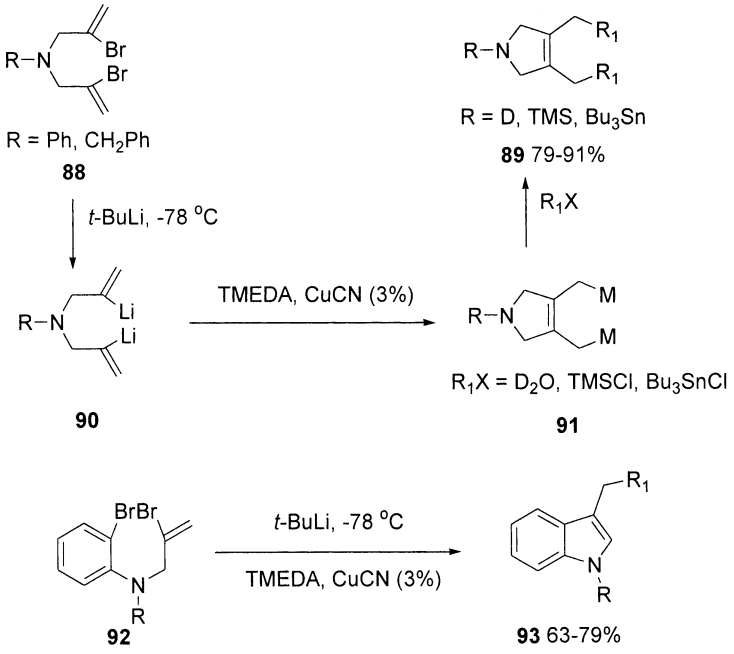
ring systems are usually difficult in the absence of activating groups.

7. Lithium

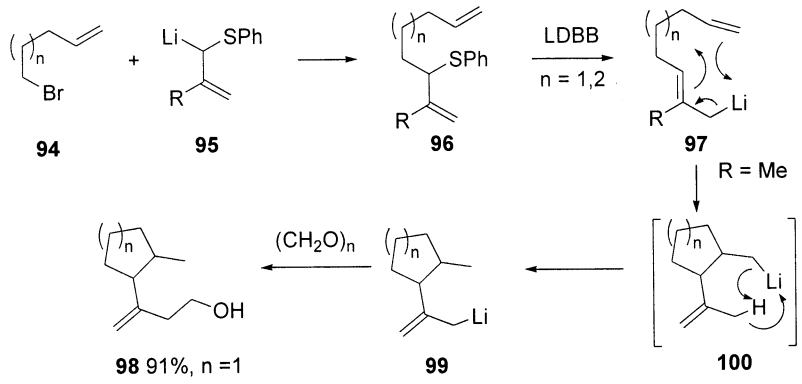
Normant and co-workers have examined the carbolithiation of allylic diene alcohols of type **84** in the presence of a molar equivalent of (−)-sparteine.[35] This enantio- and regioselective carbolithiation of dienols was accomplished in good yields with moderate enantioselectivity. Hexane is the preferred solvent due to diminished polymerization encountered compared to ether (Scheme 17).

Barluenga and co-workers have developed a new synthesis of dihydropyrroles **89** and functionalized indoles **93** by copper cyanide intramolecular coupling of the bis-vinyl lithium species **90** derived from the corresponding vinyl bromides (Scheme 18).[36]

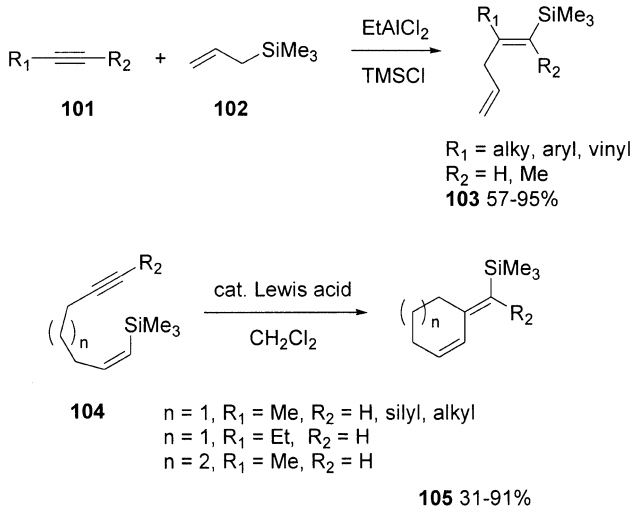
Cohen and co-workers have reported a carbometallation sequence, which involved intramolecular lithium-ene reactions. The reaction of bromoalkenes such as **94** with the



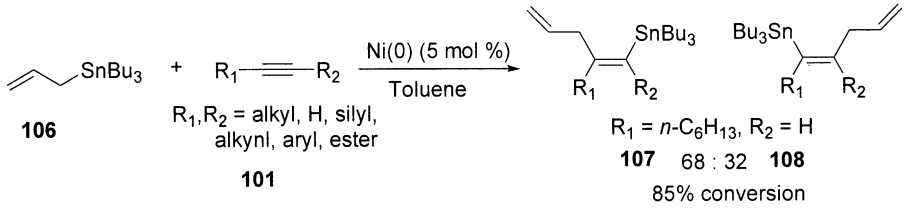
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

allyl-thio-lithium species **95** afforded the substituted cyclopentane **99** via the sequence illustrated in Scheme 19.[37] If no allylic protons were available in **97**, the rearrangement depicted failed due to competitive proton abstraction from the solvent.

8. Silicon

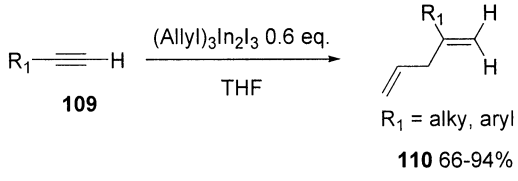
Yamamoto and colleagues have demonstrated that the *trans*-carbosilylation of a wide range of simple unactivated alkynes is accelerated in the presence of Lewis acid catalysts such as ethyl aluminum dichloride and hafnium tetrachloride (Scheme 20).[38] The relative ease of these reactions to the dienes **103** is interesting in view of the absence of activating or chelating groups.[39] This Lewis-acid catalyzed vinylsilylation of unactivated alkynes has been extended to intramolecular reactions for the preparation of cyclic olefins of type **105**.[40]

9. Tin

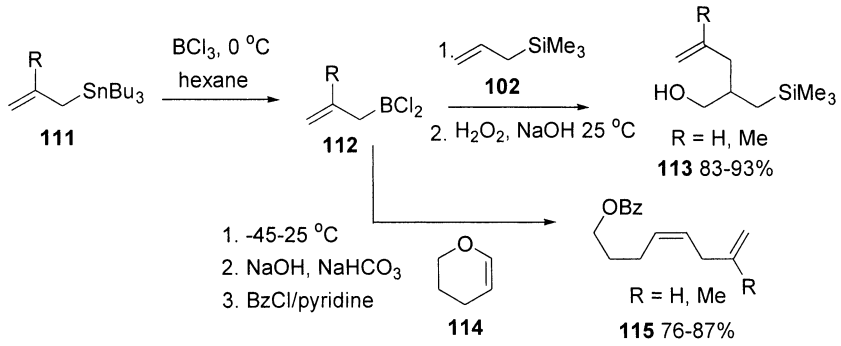
Carbostannylation of alkynes is a useful method for the generation of stereo- and regio- defined vinylstannanes based on the wide variety of palladium(0) mediated synthetic transformations that afford more complex products. Hiyama and co-workers have recently developed a nickel catalyzed carbostannylation of the acetylenes **101**, with allyl reactants of type **106**, which provided *cis* vinyl stannanes substituted with various allyl, acyl and alkynyl groups (Scheme 21).[41]

10. Indium

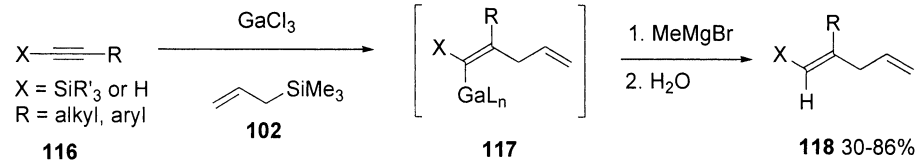
Research reported by Fujiwara and Yamamoto allowed allylation of either unactivated and/or functionalized alkynes with allyl or benzyl indium reagents to provide a versatile method for the preparation of a wide range of 1,4-dienes related to **110** (Scheme 22).[42] In the case in which the alkyne substituent R_1 was trimethylsilyl the reaction was slower and regiochemistry was reversed to afford the allylation product from the reaction on the terminal carbon. This indium mediated addition has been extended to nitriles



Scheme 22.



Scheme 23.



Scheme 24.

substituted with an electron-withdrawing group in the α-position to provide access to functionalized enamines.[43]

11. Boron

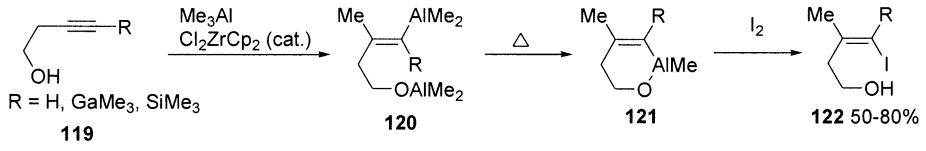
Singleton and co-workers have employed allylstannanes for the in situ generation of allylboranes in a reaction with allyl silanes (**102**) as a method for the formation of alkenols such as **113** (Scheme 23).[44] Enol ethers are also useful substrates for this protocol and the reaction with the allylborane **112** and dihydropyran (**114**) afforded the ring opened 1,4-diene ethers **115** upon elimination of the β-alkoxy-borane substituent.

12. Gallium

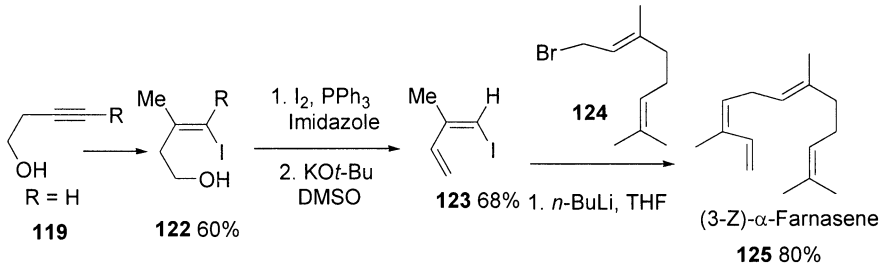
Yamaguchi and co-workers have utilized gallium intermediates to introduce allyl units in a versatile preparation of various 1,4-dienes (Scheme 24).[45] A wide variety of alkynes participate in this reaction, including primary and secondary aliphatic, and aromatic systems, although tertiary aliphatic alkynes were inert. In the case of silylalkynes related to **116**, the reaction with **102** occurs regioselectively at the β-carbon atom to provide the (*E*)-isomer **118**. The relationship between the silyl and allyl groups was confirmed by nOe experiments. The terminal alkynes gave a mixture of (*E*/*Z*) isomers, that was presumed to arise from the isomerization of the (*E*)- and (*Z*)-vinylgallium intermediates (**117**) based on their relative thermodynamic stability.

13. Aluminum

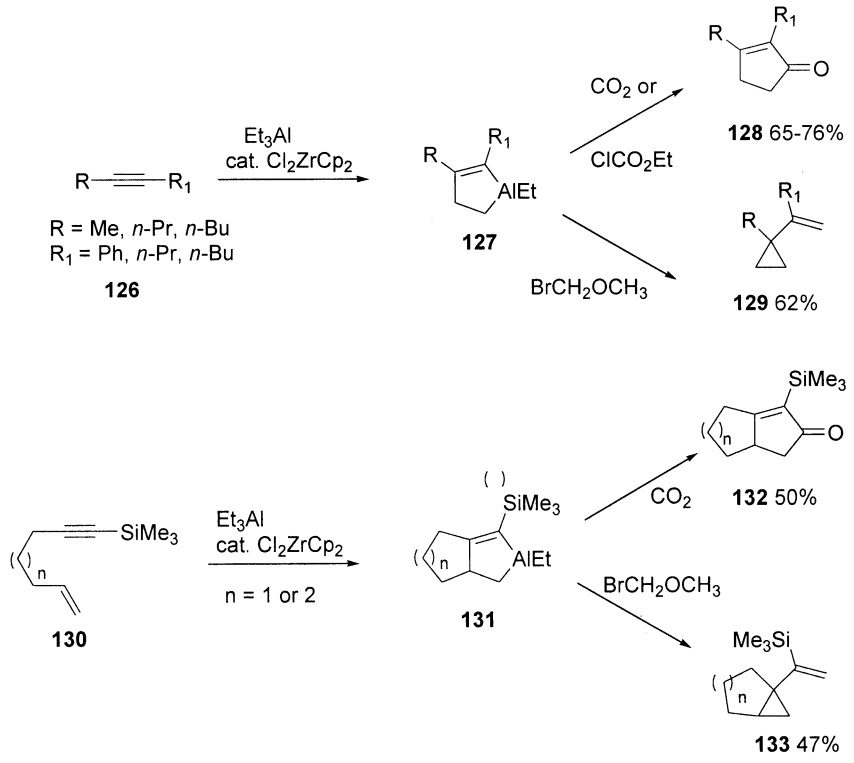
Negishi and co-workers have made significant contributions



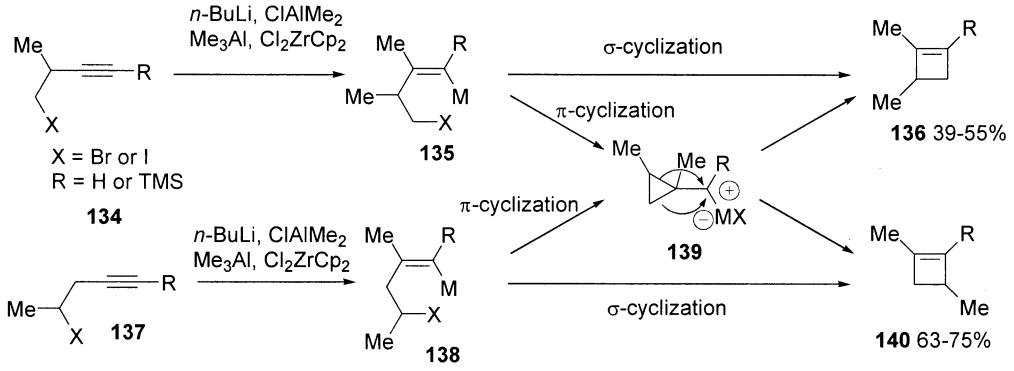
Scheme 25.



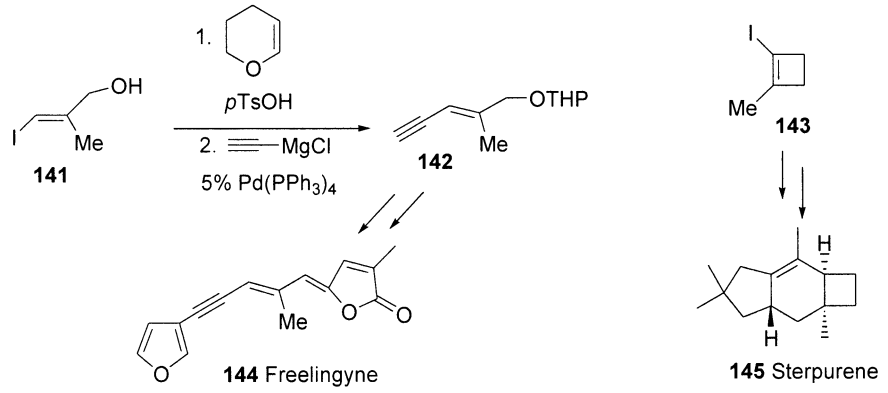
Scheme 26.



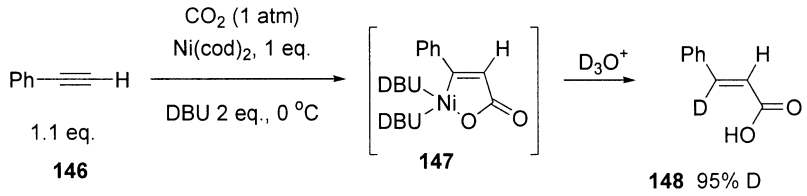
Scheme 27.



Scheme 28.



Scheme 29.



Scheme 30.

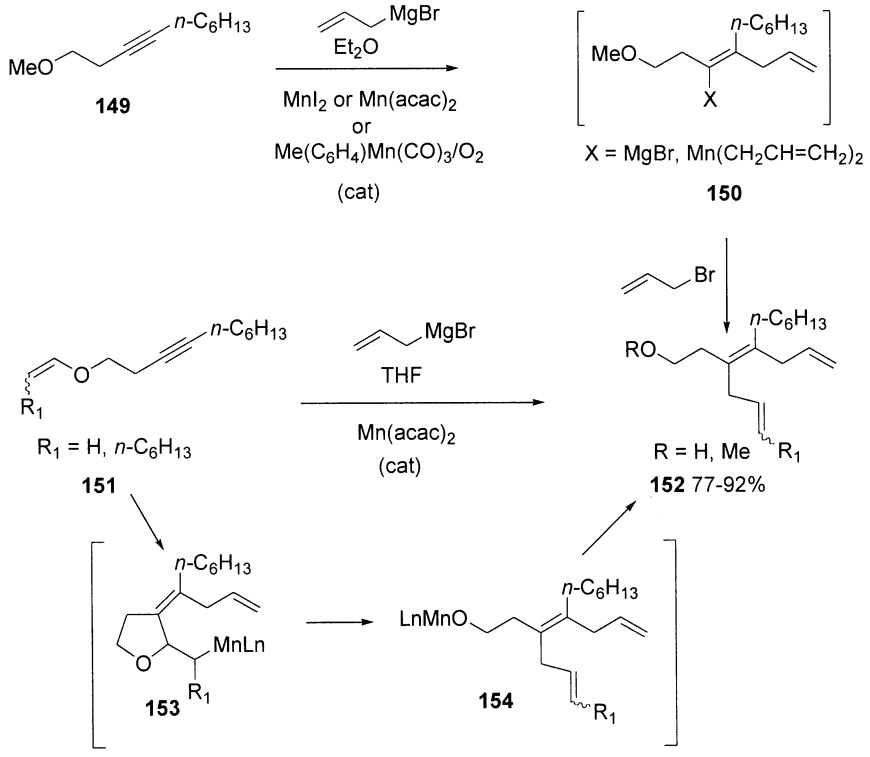
to the general area of zirconium-catalyzed carboalumination of alkynes and enynes. These protocols provide excellent routes to cyclic organic compounds in a concise fashion. The preparation of substituted alkynes by *anti*-carbometallation is frequently difficult but the selective formation of *Z* versus *E* olefins is extremely useful. This stereochemical result can be achieved by the chelation-controlled thermal isomerization of the initial *syn*-carbometallation product from the homopropargyl alcohols **119**. Thus the common intermediate **120** was isomerized to **121** and treated with an electrophile such as iodine to give **122** (Scheme 25).[46]

These concepts have been extended to a preparation of (3)-(*Z*)-α-farnesene (**125**). Commencing with the alcohol **119** (R=H), the procedure above afforded **122**. This was followed by functional group manipulation and a final coupling with the bromide **124** to afford the requisite (*Z*) isomer **125** with better than 95% (*Z*) selectivity (Scheme 26).

Simple acetylenes **126** are converted to the cyclic aluminum intermediate **127** to afford either cyclopentenones such as **128** or cyclopropanes related to **129** depending upon the synthetic objective. Related intramolecular combinations led to bicyclic structures of different ring combinations as illustrated by **132** and **133** (Scheme 27).[47]

A related method has been developed for the synthesis of regiodefined cyclobutenes of type **136** and **140** (Scheme 28).[48] These molecules are often difficult to prepare without employing a photochemical reaction. The metal systems employed in these sequences are either a mixture or $AlMe_3/Cl_2ZrCp_2$ (X=Br, R=TMS) or alternatively exposure to *n*-BuLi is followed by treatment with $AlClMe_2$ or $AlMe_3$ and Cl_2ZrCp_2. The four membered ring is generated directly or via a cyclopropanation rearrangement sequence as illustrated. The intermediate metallated olefins **135** and **138** can also be obtained directly from the metal–halogen exchange of the appropriate haloalkene to provide a more versatile choice of starting materials en route to the desired cyclobutenes.

The use of this metallation procedure, commencing with propargyl alcohol, was the initial step used to prepare **141**. This vinyl iodide was coupled with the acetylene Grignard as part of the total synthesis of freelingyne (**144**), a sesquiterpene from *Eremophila freelingii* (Scheme 29).[49]



Scheme 31.

The cyclobutene synthon **143**, which is closely related to those above, was used in an earlier total synthesis of sterpurene (**145**) by Gibbs and Okamura as indicated in Scheme 29.[50]

14. Nickel

Yamamoto and co-workers have developed a nickel-mediated route via **147** for the regio- and chemoselective carboxylation of alkynes in the presence of carbon dioxide (Scheme 30). This allows the direct synthesis of α,β-unsaturated carboxylic acids of type **148**.[51] The reaction displayed good selectivity when performed in the presence of two differentially substituted alkynes. The major product arose from the more rapid reaction of the less sterically hindered acetylenic carbon.

15. Manganese

Oshima and co-workers have established, that the treatment of homopropargylic ethers such as **149** with allyl magnesium bromide in the presence of a catalytic amount of manganese salts afforded a direct route to dienes and trienes. It was postulated, that with manganese diiodide as the catalyst, the intermediate vinyl Grignard intermediate **150** (X=MgBr) was formed to provide the monoallylated product upon workup. However, if allyl bromide was added to the reaction, the bisallyl-alkene **152** (R=Me, R_1=H) became the product. The authors suggested that when $MeC_5H_4Mn(CO)_3$ was employed as the catalyst followed by exposure to oxygen, the diallylmanganate **150** [$X=Mn(CH_2CH=CH_2)_2$] intermediate was involved *en route* to **152**. In a related experiment, the free alcohol **152** (R=H, R_1=*n*-C_6H_{13}) was formed from the vinyl ether **151** via the intermediates **153** and **154** when reacted in THF in the presence of allyl magnesium bromide and $Mn(ac)_2$. These methods provide an efficient route to 1,4,7-heptatrienes with good regio- and stereo- control (Scheme 31).[52]

16. Conclusion

The wide array of diverse chemistry that has resulted from the investigations summarized above confirms the future of this research area is filled with promise. From modest beginnings, undoubtedly encouraged by the rich chemical precedent provided by the various additions of organo-metallic compounds to carbonyl systems, the field of carbo-metallation chemistry has progressed at an exponential rate. This expansion and the rate of discovery will likely continue unabated. In the process, new studies will lead to increased mechanistic understanding, stimulate the development of novel transformations, new reagents, and synthetic proto-cols previously impossible. Thus, the arsenal of the synthetic organic chemist will continue to be augmented and enriched by new discoveries. This expanding knowledge will stimulate new applications to complex problems, whose innovative solutions will delight us all.

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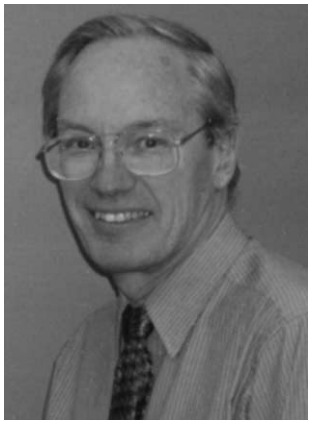
Biographical sketch



Alex Fallis was born in Toronto and received his BSc Hon. (1963), MA (1964), and PhD (1967) degrees from the University of Toronto with Professor Peter Yates. After an NRC Postdoctoral Fellowship at Oxford University with Professor E. R. H. Jones he joined the Department of Chemistry at Memorial University of Newfoundland in 1969. In 1988 he was appointed Professor in the Department of Chemistry at the University of Ottawa and was Director of the Ottawa-Carleton Chemistry Institute from 1990–1993. In 1996 he was awarded the Basic Science Research Award of the Ottawa Life Sciences Council, for 1997–2000 he received the Saunders-Matthey Foundation award for Breast Cancer Research, and was the recipient of the Alfred Bader Award of the Canadian Society for Chemistry for 1998.

Alex Fallis' research encompasses synthetic and medicinal organic chemistry, particularly intramolecular pericyclic reactions, including recent studies of organomagnesium and pentadienylindium based reagents. These aspects have been merged with the development of tether control groups for cycloaddition based approaches to taxoids. Earlier investigations with enediynes have evolved into new routes to helical cyclophanes with potential as liquid crystals, and the synthesis of related bridged and concave systems are under investigation for fullerenoids.

Pat Forgione was born in Brantford, Ontario Canada, and graduated from Honors Chemistry with his BSc (Co-Op) in 1996 from the University of Waterloo. His PhD thesis, completed in January 2001 at the University of Ottawa, described the carbometallation studies of propargyl alcohols to furans, taxoids, etc., summarized above. He received the BioMega Boehringinger Award for Graduate Research. Currently he is conducting postdoctoral research at the Ohio State University with L. A. Paquette.