

Synthesis and Reactivity of sp^2 Geminated Organobismetallic Derivatives

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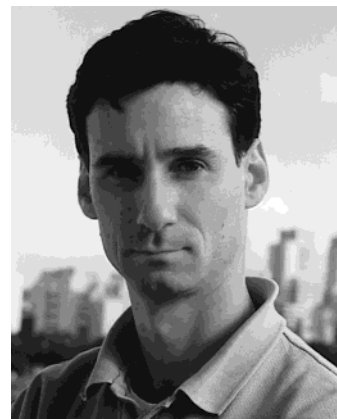
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I. Introduction

The development of new strategies in organic syntheses with a minimum of chemical steps is becoming more and more necessary for the efficient assembly of complex molecular structures.¹ So, the combination of multiple reactions in a single operation represents a particularly efficient approach. Among different strategies,² geminated organobismetallic derivatives (1,1-bisanions) are becoming



Ilan Marek (born in Haifa, Israel, in 1963) was educated in France and received his Ph.D. degree from the University Pierre et Marie Curie, Paris, in 1988 (Normant's laboratory). In 1989, he was a postdoctoral fellow with Professor Ghosez in Louvain-La-neuve, Belgium, and obtained a research position at the CNRS in 1990. After obtaining his Habilitation in Organic Chemistry at the University Pierre et Marie Curie in 1995, he moved to the Technion-Israel Institute of Technology at the end of 1997. His current interests include the development of new methodologies in organic synthesis pertaining to the diastereoselective and enantioselective carbometalation reaction of alkenes, the synthesis and reactivity of polymetalated species, and the reactivity of carbenoids.

more and more useful as demonstrated by the recent review on the synthesis and synthetic utilities of 1,1- sp^3 bismetallic derivatives.³

During the past decades, considerable effort has been made to find new routes for the preparation of geminated sp^2 bismetallic derivatives and for their selective reactions with several electrophiles. This review is intended to highlight the major results in this field.

Indeed, as they can be used, for example, as a source of polysubstituted carbon-carbon double bonds in a single-pot operation, their preparations are still challenging. We will concentrate on the chemistry of lithium, magnesium, boron, aluminum, copper, zirconium, titanium, gallium, indium, and zinc.⁴ However, the alkylidene carbene chemistry⁵ as well as groups 14 (such as tin or silicon) and 16 (such as Se and Te) elements will not be addressed in this review. In a similar way, the "anti-Van't Hoff/Le Bel" derivatives with a planar-tetracoordinate carbon atom and two metal substituents sharing an sp^2 orbital will also be not included in this review.⁶

As in few cases, the same metal can be presented in different subchapters; we have decided, as a general rule, to classify the corresponding bismetallic

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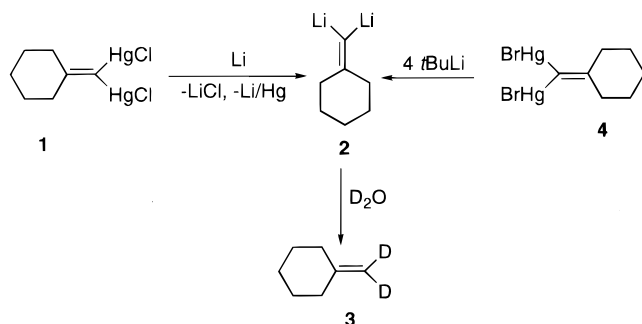
derivative in the chapter (or subchapter) in which the metal is held by the starting material. For example, the 1,1-borio-zincioalkene compound will be in the boron subchapter since the starting material is the α -iodoalkenylboronic ester.

II. 1,1-Dilithioalkene Reagents or Those Containing Lithio Species

1. 1,1-Dilithioalkene Reagents

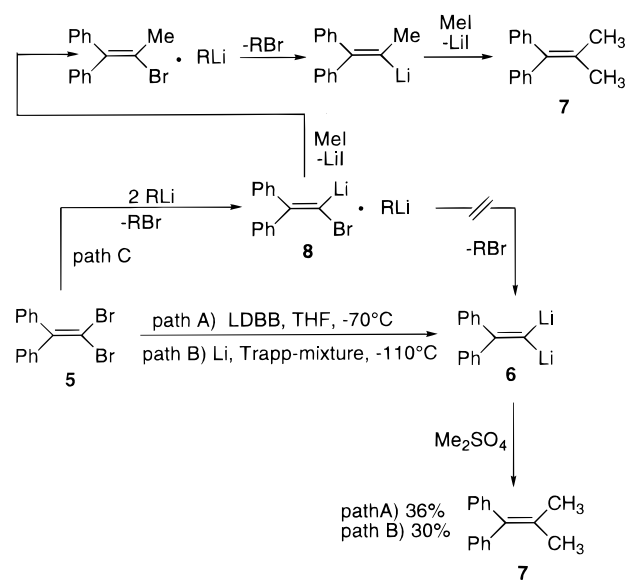
Among organopolylithium compounds, the 1,1-dilithioalkenes occupy the center of interest since, according to *ab initio* calculations on 1,1-dilithioethene,⁷ an orthogonal (perpendicular) double bond with a triplet ground state should be preferred. Furthermore, an extremely low value was calculated for the barrier of rotation to a planar double bond. As consequences, related molecules have been prepared. Indeed, the reaction of excess lithium vapor (700–800 °C) with several vaporized alkenes has been studied, and it has been found that substitution of hydrogen for lithium occurs to produce polyolithiated alkenes, albeit in very low yield.⁸ In this process, it seems likely that the first reaction of alkenes with lithium is the substitution of a vinylic hydrogen with subsequent replacement of both vinyl and alkyl hydrogens. A few years later, an alternative (and much more practical) method was developed by a mercury–lithium exchange; dilithiomethylenecyclohexane **2** was prepared by treatment of bis(chloromercurio)methylenecyclohexane **1** with lithium powder in diethyl ether.⁹ The resulting bislithio derivative was trapped with D₂O to form the pure dideuteriomethylenecyclohexane **3** in 51% yield as described in Scheme 1.

Scheme 1



The dilithioalkene **2** can also be obtained free of lithium amalgam and lithium halide if the bromomercury compound **4** is treated with *tert*-butyllithium⁹ (Scheme 1). On the other hand, when a solution of 1,1-dibromo-2,2-diphenylethene **5** is added slowly at low temperature to a radical anion lithium-*tert*-butylbiphenyl (LDBB) solution, the corresponding 1,1-dilithio-2,2-diphenylethene **6** is obtained in a moderate 36% yield¹⁰ (path A, Scheme 2). Nearly the same yield is obtained when the reaction of **5** is performed with lithium dust at –110 °C (path B, Scheme 2). The dilithio compound **6** was characterized by quenching with dimethyl sulfate to yield 2-methyl-1,1-diphenyl-1-propene **7**.

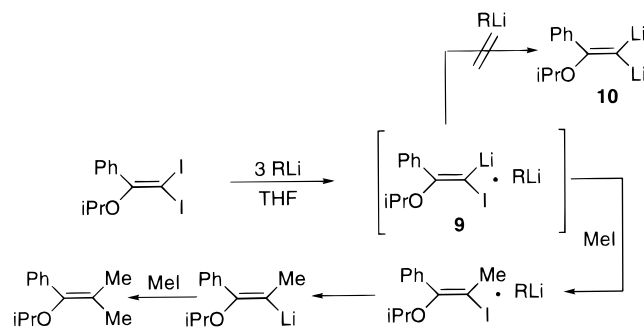
Scheme 2



However, only one halogen atom of 1,1-dihalo-1-alkenes can be replaced by lithium even with *tert*-butyllithium (path C). This was shown for aromatic as well as for aliphatic substituted geminal dihaloalkene.¹⁰ With 1,1-dibromo-2,2-diphenylethene **5**, a carbenoid complex **8** with the alkyl lithium compound is formed. However, this simulates the behavior expected of a geminal dilithioalkene, e.g., by reaction with methyl iodide or dimethyl sulfate (Scheme 2).¹⁰ The name “quasi dianion complex” (QUADAC) was coined for such species,¹⁰ which react as if they were “dianions”.

Despite the above statement (Scheme 2, path C), the supposed preparation of functionalized 1,1-dilithio-1-alkenes **10** was reported by treatment of the corresponding 1,1-diiodo-1-alkenes with alkyl lithiums (Scheme 3),¹¹ but few years later, evidence

Scheme 3



were presented that the reported 1,1-dilithio-2-isopropoxy-2-phenylethene **10**, in reality, is a carbenoid complexed with methyl lithium as **9**,¹² again a “QUADAC” simulating the existence of a geminal dilithioalkene.

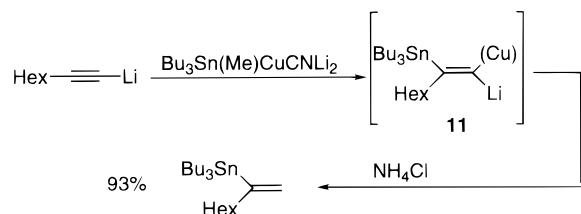
Finally, the preparation of 1,1-dilithiocumulenes by a double deprotonation reaction of allenes was also reported but, as these species are in metallotropic equilibrium with their corresponding isomers (1,3-dilithio species), they will be not considered as *sp*² geminated bimetallic derivatives.¹³

Unfortunately, all the predictions made by calculations 25 years ago are still not verified (no X-ray structure) by the actual syntheses which either are low yielding (but easy to handle, Scheme 2, path A or B) or use the mercury–lithium exchange (but are synthetically more difficult, Scheme 1).

2. 1,1-Lithio-cuprioalkene Reagents

Although the stannylcupration of various alkynes leads to the corresponding vinylcopper derivatives, two regioisomers are generally obtained. However, when the stannylcupration is performed on the corresponding lithium acetylide, the 1,1-lithio-cuprioalkene **11** is surprisingly obtained as a single isomer and in excellent yield (Scheme 4).¹⁴

Scheme 4

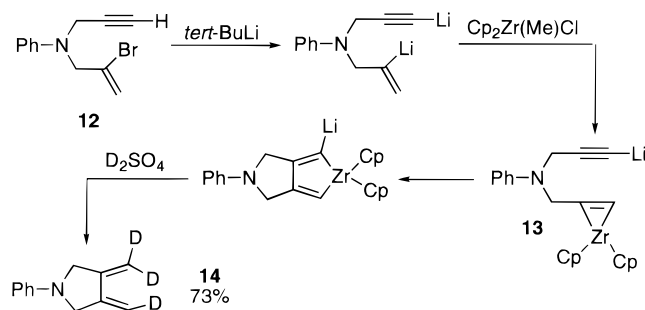


However, the reactivity of the 1,1-lithio-cuprioalkene derivative with electrophiles is yet to be established.

3. 1,1-Lithio-zirconioalkene Reagents

Treatment of *N*-(2-bromoallyl)-*N*-prop-2-ynylamines **12** with *tert*-butyllithium followed by reaction with zirconocene methyl chloride afforded, after addition of deuterated sulfuric acid, the trideuterated pyrrolidine **14** (Scheme 5).¹⁵ The formation of **14** can be

Scheme 5



understood by assuming an intramolecular insertion of the acetylide moiety, generated in the lithiation step, in the zirconacyclopentadiene **13** leading to the zirconacyclopentadiene which by deuteriolysis generates compound **14**.

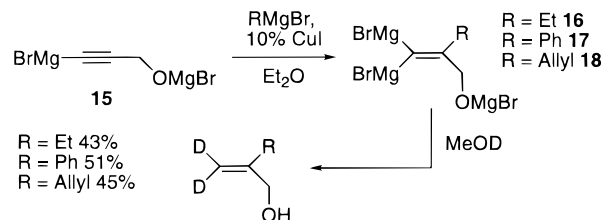
However, no attempt was made to differentiate the reactivity of the two metals with electrophiles.

III. 1,1-Dimagnesioalkene Reagents

Duboudin and Jousseume reported the only known example of 1,1-dimagnesioalkene.¹⁶ They observed a regioselective addition of organomagnesium com-

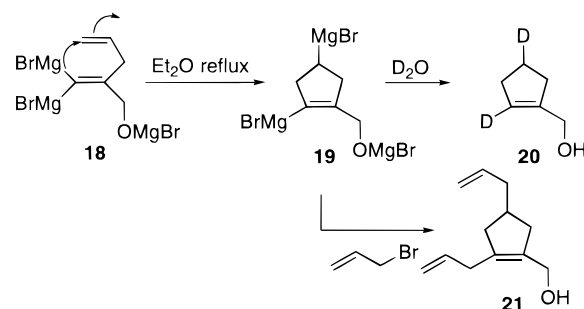
pounds to metalated propargylic alcoholates **15** in the presence of a catalytic amount of CuI. Geminal di-Grignard reagents **16–18** are obtained in moderate isolated yields after deuteriolysis (Scheme 6).

Scheme 6



Moreover, when **18** is heated under reflux for 5 h, an unusual 5-*endo*-trig¹⁷ cyclization reaction occurs to give the cyclic product **19**. The latter can be converted to deuterated hydroxymethylcyclopentene **20** or allylated to 2,4-diallyl-1-hydroxymethylcyclopentene **21** as described in Scheme 7.¹⁶

Scheme 7



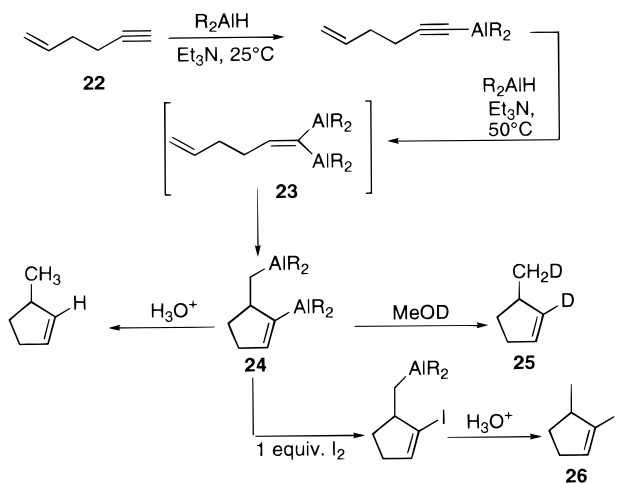
IV. 1,1-Dialuminioalkene Reagents or Those Containing Aluminum Species

1. 1,1-Dialuminioalkene Reagents

The hydroalumination of alk-1-yne can be controlled by the choice of solvent; mono-, di-, or trihydroalumination (formation of sp³ geminated trialuminioalkane) reactions are obtained by carrying out the reaction in hydrocarbon,¹⁸ ether or THF,¹⁹ or trialkylamine,²⁰ respectively. Thus, when the metalation was carried out in triethylamine at 25 °C using 1 mol equiv of R₂AlH per mol equiv of enyne **22**, followed by the slow addition of R₂AlH (1.2 mol equiv) at 50 °C,²¹ 3-methylcyclopentene was obtained, after hydrolysis, via a 5-*exo*-trig cyclization reaction of **23** in 79% yield.²² Deuteriolysis gave dideutero-3-methylcyclopentene **25** having one deuterium atom in the methyl group and the other one at the double bond as described in Scheme 8.

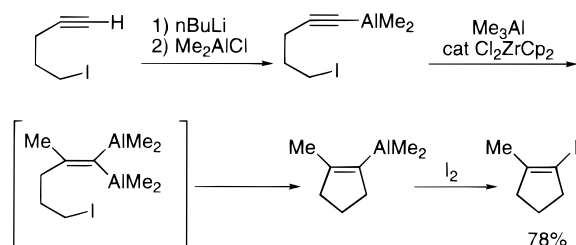
Moreover, selective iodination of the vinyl carbon–aluminum bond with 1 equiv of iodine at low temperature, followed by hydrolysis, gave only the vinyl iodide **26** (no trace of the iodomethyl iodocyclopentene was detected in the crude reaction mixture). However, although the precursor for the formation of **24** appears to be the 1,1-dialuminiohexa-1,5-diene **23**, a direct synthesis of **23** is still unknown. As a consequence, the intermolecular addition of electrophiles on 1,1-dialuminioalkenes is still unknown.

Scheme 8



If a leaving group is present in the carbon skeleton, the 1,1-bisaluminum derivative, generated by a zirconio-catalyzed methylalumination of alkynyl dimethylalane, undergoes a σ -cycloalkylation to lead to the cyclic five-membered ring product in high yield (Scheme 9).²³

Scheme 9

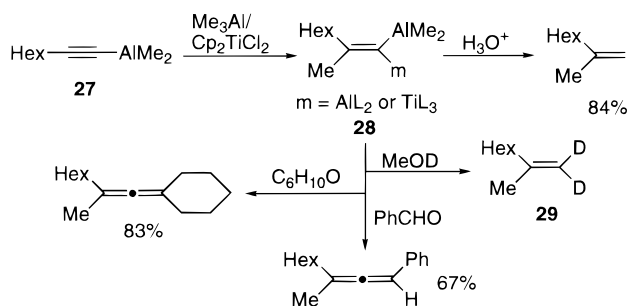


This new cyclization reaction of 1,1-polymetalated species containing aluminum derivatives was also applied to the synthesis of four-membered ring derivatives.²⁴

2. 1,1-Aluminio-titanioalkene Reagents

Octynyl dimethylalane **27** (generated by treatment of 1-octyne with Me_3Al at 85 °C) reacts smoothly with a 1:1 combination of $\text{Me}_3\text{Al}/\text{Cp}_2\text{TiCl}_2$ in methylene chloride at room temperature to lead to the corresponding sp^2 1,1-bismetallated derivative **28** in 84% yield after hydrolysis.²⁵ The intermediacy of the geminally dimetal-substituted alkenes²⁶ has been further supported by a NMR study²⁷ and by the formation of >95% pure 1,1-dideuterio-2-methyl-1-octene **29** as described in Scheme 10. These NMR

Scheme 10

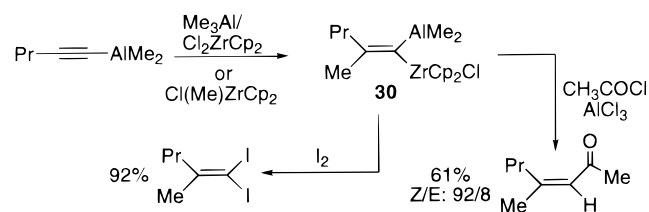


observations indicate that **28** is formed as a single stereoisomer which is probably the *E* isomer, based on the known stereochemistry of the carbometallation of simple acetylenes¹⁷ as well as the NMR spectral data. Then, **28** undergoes a relatively slow stereoisomerization leading to a ca. 60:40 mixture of the *E* and *Z* isomers. In the equilibrating mixture, however, no species other than the *E* and *Z* isomers of **28** appears to be present in readily detectable quantities. When cyclohexanone or benzaldehyde were added to the bismetallic derivative **28**, the expected allenenes were formed in, respectively, 83 and 67% yields.²⁷

3. 1,1-Aluminio-zirconioalkene Reagents

The carbometallation reaction of 1-pentynyl dimethylalane with either a 1:1 mixture of Me_3Al and Cl_2ZrCp_2 or $\text{Cl}(\text{Me})\text{ZrCp}_2$ was also studied.²⁵ The reaction produces the bismetallic derivatives **30** in high yield in both cases (Scheme 11). Despite the

Scheme 11



similarity in the mode of formation, **28** (Scheme 10) and **30** (Scheme 11) display a remarkable contrast. Unlike **28**, the reaction of **30** with cyclohexanone is sluggish and does not produce the allene. While the reaction of **28** with I_2 produces iodinated alkenes only in low yields (<20%), the corresponding reaction of **30** with 2 equiv of I_2 cleanly gives 1,1-diiodo-2-methyl-1-pentene in 92% yield. Attempts to differentiate the reactivity of the two metal groups were made. The reaction of **30** with acetyl chloride in the presence of AlCl_3 gives a 92:8 mixture of (*Z*)- and (*E*)-4-methyl-3-hepten-2-one in 61% yield (Scheme 11).²⁵ This reaction represents *the first example* where two different electrophiles were added intermolecularly on sp^2 bismetallic derivatives.

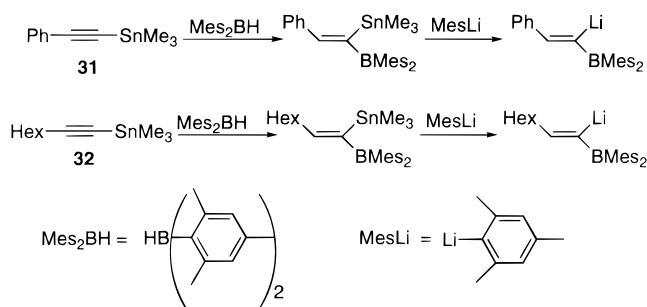
V. 1,1-Dimetalloalkene Reagents Containing Boron Species

1. 1,1-Borio-lithioalkene Reagents

As theoretical calculations indicate a high degree of stabilization of vinyl carbanion with an α -boron atom,²⁸ routes to boron-stabilized alkenyl carbanion have been established. As preliminary experiments to remove the α -proton directly from alkenylboranes met with little success,²⁸ the cleavage of geminal trialkylstannyl-boron species was investigated.²⁸ From these experiments, it was found that the less hindrance around the tin and the greater the hindrance around the boron the better the exchange. So, the combination of 1-trimethylstannyl-2-phenylethyne **31** or 1-trimethylstannyl-1-octyne **32** with dimesitylbo-

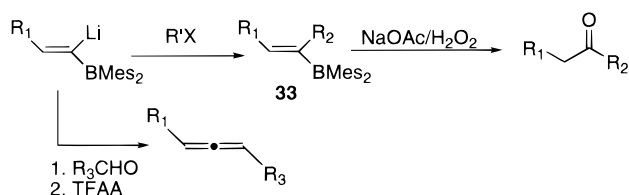
rane represents the highly efficient process for the conversion shown in Scheme 12.²⁸

Scheme 12



So long as the tin atom is bearing methyl groups, BuLi or MesLi can be used for the trialkylstannyl-lithium exchange. The α -borio-lithioalkene thus formed reacts with alkylating agents to give the single (*E*)-vinyl borane isomer **33** (Scheme 13). This

Scheme 13



stereospecific production of **33** is an interesting route to the stereochemically defined vinylborane which may not always be cleanly available by the direct hydroboration reaction of internal alkyne. On the other hand, the alkaline oxidation of these vinylboranes led to the corresponding ketones as described in Scheme 13.

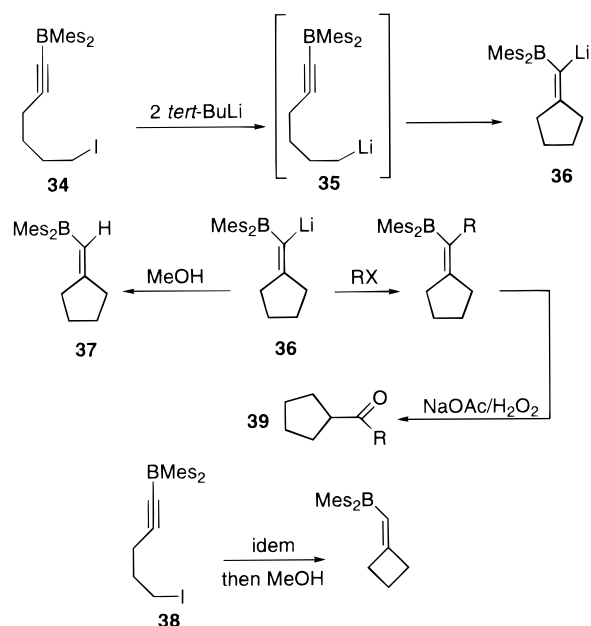
α -Borio-lithioalkenes also undergo a facile boron-Wittig-type reaction with aldehydes to give allenes (Scheme 13).²⁹ Successful intramolecular conjugate addition reactions of ω -lithio acetylenic dimesitylboranes were also described. Indeed, treatment of **34** in Et₂O with 2 equiv of ^tBuLi at -78 °C to 0 °C gave (through a rapid metal-halogen exchange into the linear organolithium derivative **35**) the cyclized boron-stabilized anion **36**.³⁰ Protonation of **36** with MeOH gave cyclic vinylborane **37** in 93% yield. Similarly, **38** was converted into cyclobutylidene derivative in 95% yield (Scheme 14).³⁰

Bismetallc **36** could also be trapped with a variety of alkylating agents and then after oxidation the corresponding ketones **39** were obtained (Scheme 14).³⁰

2. 1,1-Borio-zincioalkene and 1,1-Borio-cuprioalkene Reagents

The (*Z*)- α -iodoalkenylboronic ester **40** (prepared by the hydroboration of 1-iodoalkyne with HBBBr₂·Me₂S followed by the conversion into 1-iodoalkenylboronic acid and then esterification with pinacol) reacts with zinc dust in *N,N*-dimethylacetamide (DMA) to furnish the 1,1-boron, zinc alkenylbismetallic **41**.³¹ The zinc insertion to α -iodoalkenylboronic esters does not

Scheme 14



occur stereospecifically and the pure (*Z*)-**40** is converted to an *E/Z* mixture of alkenylzinc iodides **41** in a 82/18 ratio. Indeed, the iodolysis of **41** provides the parent compound but as a mixture of isomers in an *E/Z* ratio of 82/18. However, the transmetalation of **41** with CuCN and 2LiCl leads to the 1,1-borio-cuprio bismetallic reagent **42**. The different nature of the two metals present in compound **42**, or their different stereotopicity, can be used to make two new bonds successively (Scheme 15).³¹

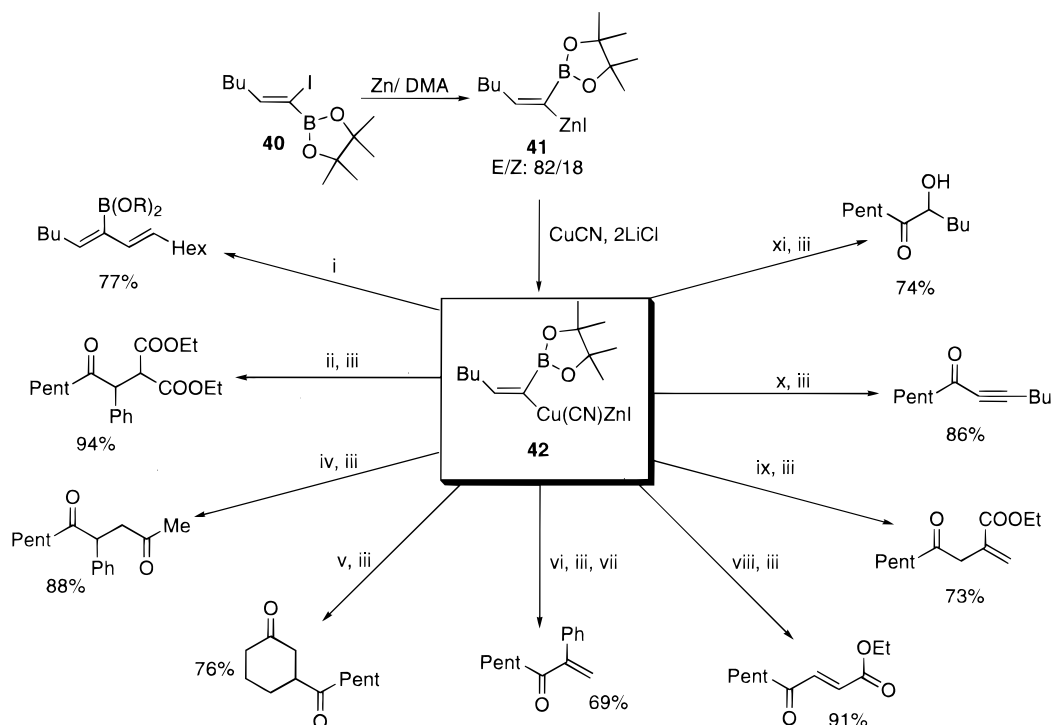
The polymetallic zinc reagent **44** was also prepared by treating the functionalized α -iodoalkenylboronic esters **43** with an excess of zinc dust in DMA (Scheme 16).³¹ After transmetalation to the copper compound and addition of ethyl α -(bromomethyl)acrylate followed by oxidation, the unsaturated ketodiester **45** was isolated in 59% yield (Scheme 16).³¹

3. 1,1-Borio-zirconioalkene Reagents

Hydrozirconation of 1-alkynyldioxaborolane with 1.2 equiv of HZrCp₂(Cl) in either THF or 1,4-dioxane proceeded readily by a syn addition to give essentially pure boryl zirconocene (*E*)-1,1-bismetallcs **46** (Scheme 17).³² As the carbon-zirconium bond is more reactive than the carbon-boron bond toward hydrolysis, a direct utility of **46** would be the preparation of (*Z*)-alkenyl boronates.

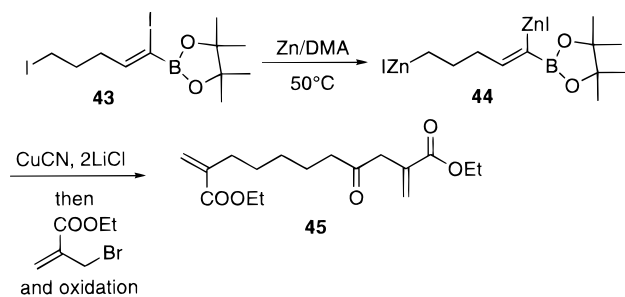
Moreover, since hydrozirconation is tolerant of many functional groups, several functionalized (*Z*)-vinylboronates were prepared by this way.³² Bismetallcs **46** were also reacted with various electrophiles and, as expected, the carbon-zirconium bond always reacts first as described in Scheme 18.³³ No dialkylated products were observed with 1 equiv of electrophile. The X-ray analysis of **46** confirmed the configuration of the four-coordinated Zr complex with two cyclopentadienyl rings.³³

As a demonstration of the scope of this emerging methodology, the synthesis of Tamarotene (retinoid),³⁴ Chokol A, and Chokol G (fungitoxic sesquiterpenoids)³⁵ were efficiently developed.

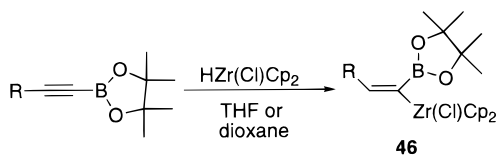
Scheme 15^a

^a Reaction conditions: (i) (*E*)-1-iodooctene, Pd(dba)₂ (1 mol %), PPh₃ (4 mol %); (ii) diethyl benzylidenemalonate, 25 °C, 8 h; (iii) H₂O₂ oxidation; (iv) benzylideneacetone, TMSCl –78 °C to 20 °C, 12 h; (v) cyclohexenone, TMSCl –78 °C to 20 °C, 12 h; (vi) nitrostyrene –78 °C to 0 °C, 1 h; (vii) DBU, flash chromatography; (viii) ethyl propiolate –78 °C to –40 °C, 1 h; (ix) ethyl α-(bromomethyl)acrylate –78 °C to 0 °C, 1 h; (x) 1-iodohexyne –30 °C, 18 h; (xi) pentanal, BF₃, Et₂O –10 °C, 15 h.

Scheme 16



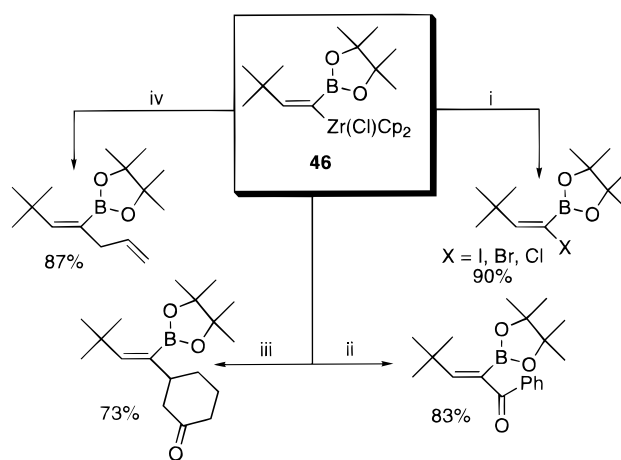
Scheme 17



Sequential addition of electrophiles is also possible. Thus, reaction of **47** with 2-bromopropene followed by coupling with phenyl iodide provided **48** (Scheme 19). The same starting material **47** leads to the isomeric product **48** by reversing the sequence of addition of electrophiles.³³

Cyclic borazirconocenes were also prepared by the reductive cyclization with Negishi's reagents³⁶ of 1-alkynyl-4-alkenyl diboronates **49** (see Scheme 20), but no attempt was made to isolate and characterize this borazirconocycles.³⁷

Only the hydrolysis with anhydrous HCl in Et₂O was performed to give the 1-alkenyl-4-alkyl diboronate **50** in 80% yield. The same reaction can be also applied for the formation of the six-membered ring.

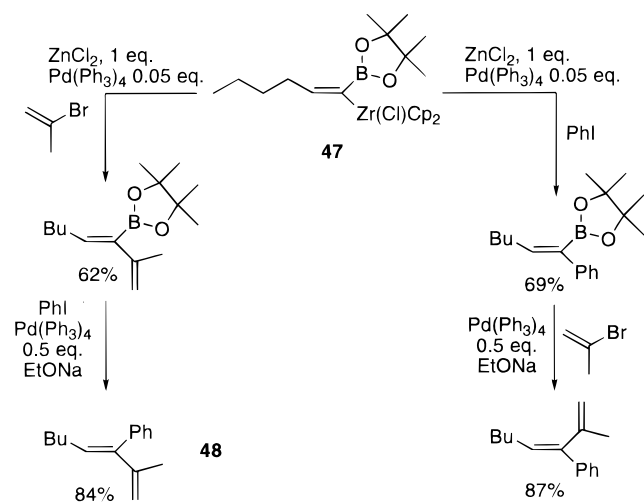
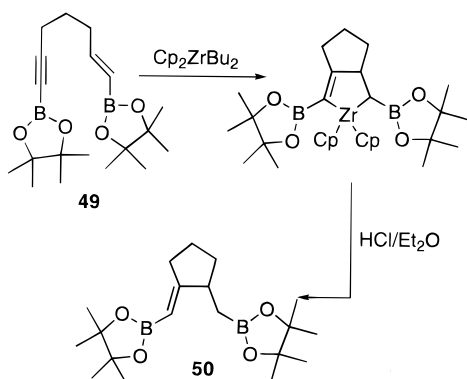
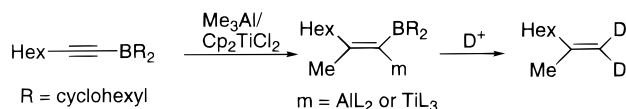
Scheme 18^a

^a Reaction conditions: (i) *N*-halogenosuccinimide; (ii) acid chloride, (1 equiv) CuBr, Me₂S, (0.1 equiv), THF, 1 h; (iii) cyclohexenone, CuBr, Me₂S (0.1 equiv), THF, 1 h; (iv) allylbromide, CuCN, THF, 12 h.

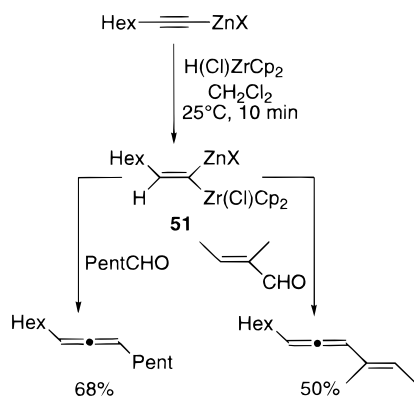
A Suzuki–Miyaura coupling of **50** with 1 equiv of aryl iodide occurred exclusively at the carbon-sp²–boron bond, and then the oxidation of the remaining carbon-sp³ carbon–boron occurs quantitatively in a second step, demonstrating that sequential transformation of the two boron moieties in **50** is feasible.

4. 1,1-Borio-aluminioalkene Reagents

Alkynyl dicyclohexylboranes were also successfully carbometalated by the combination of Me₃Al/Cp₂TiCl₂ to give the 1,1-borio-aluminioalkene derivatives (Scheme 21).²⁵

Scheme 19**Scheme 20****Scheme 21****VI. 1,1-Dizincioalkene Reagents or Those Containing Zincio Species****1. 1,1-Zincio-zirconioalkene Reagents**

Hydrozirconation of alkynylzinc halides by the Schwartz's reagent³⁸ afforded the zinc and zirconium 1,1-bimetallic reagents³⁹ as described in Scheme 22.

Scheme 22

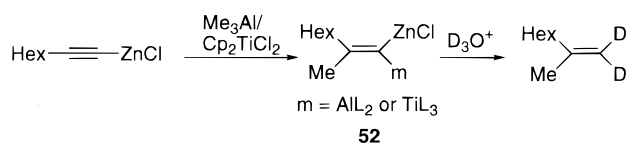
These dimetallioalkenes of type **51** react with aldehydes to provide the allenes in moderate yield.

The method seems to be well suited for the preparation of 1,2,4-trienes (see Scheme 22).

It is interesting to note that a typical reaction of dimetallioalkene is the addition of aldehyde; indeed, once the alcoholate is formed, the second carbon-metal bond undergoes a β -elimination to produce the allene. However, when the second carbon-metal bond is not reactive toward the β -elimination (as a carbon-boron bond) we have to activate the latter in order to generate the allene (compare Schemes 13 and 15).

2. 1,1-Zincio-aluminioalkene Reagents

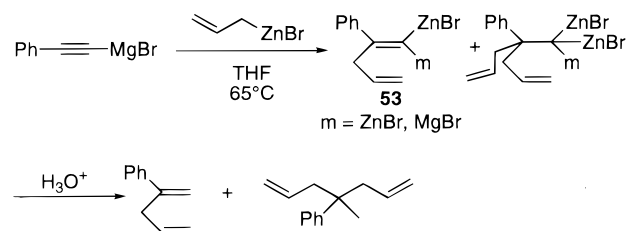
Alkynylzinc halide was also successfully carbo-metalated by the combination $\text{Me}_3\text{Al}/\text{Cp}_2\text{TiCl}_2$, as described in Scheme 23.²⁵

Scheme 23

The reactivity of the 1,1-zincio-aluminioalkene reagent **52** with different electrophiles is yet to be studied.

3. 1,1-Dizincioalkene Reagents

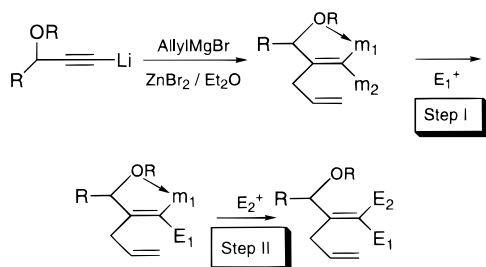
An elegant synthesis of 1,1-bimetallic derivatives has been found by Gaudemar⁴⁰ who reported that the addition of allylzinc bromide on alkynyl zinc bromide or alkynyl magnesium bromide in refluxing THF leads to the geminated bisanions **53** as the major product (Scheme 24).

Scheme 24

In a similar way, the reaction of 2-cyclohexenylzinc bromide with acetylenic Grignard reagent gives the products from single and double additions of the organozinc reagents to the carbon-carbon triple bond.⁴¹

As the allylmatalation reaction of alkynylmetals leads to a vinylic 1,1-organogembimetallic, a new strategy for effecting stereoselective synthesis of carbon-carbon double bonds was successfully described. This strategy requires a secondary propargylic substrate (the presence of a secondary substituent on the propargylic ether avoids the formation of the double addition) bearing a Lewis basic functional group as a propargylic ether, in order to differentiate the reactivity of the two metals toward electrophiles (Scheme 25).

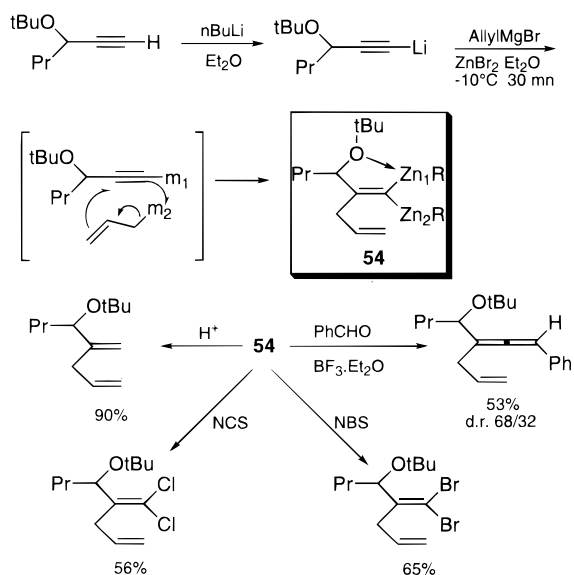
Scheme 25



Indeed, it has been recently described that an internal chelation (with a Lewis basic functional group) was able to differentiate the reactivity of the two metals of a 1,1-bimetalloalkane toward two electrophiles.⁴² The coordination of the oxygen atom to the metal m_1 decreases the reactivity of the latter toward the first electrophile, and thus the nonchelated metal m_2 reacts preferentially with this electrophile.

The allylmetalation step as described in Scheme 24 has been now performed under milder conditions in a less basic solvent such as Et_2O (-10°C , 30 min in Scheme 26 instead of 65°C in THF in Scheme 24),

Scheme 26

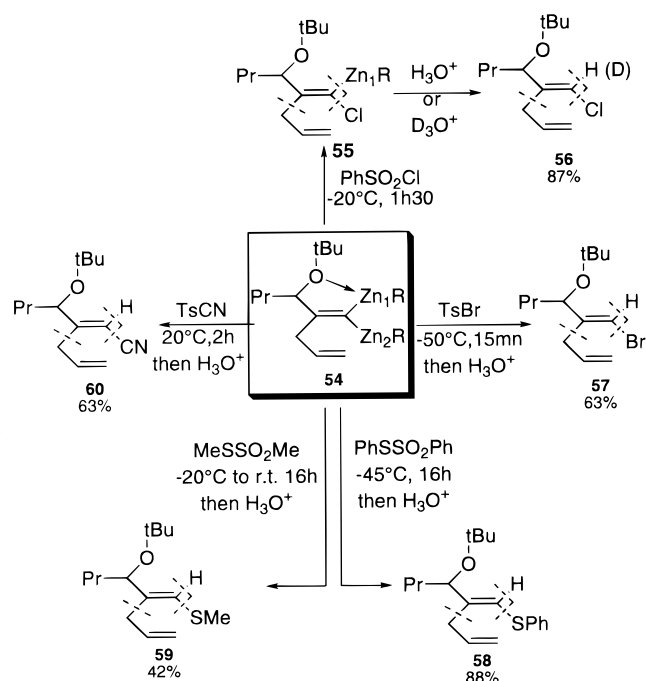


and the presence of the 1,1-dianionic species **54** has been proved by reaction of the latter with electrophiles (Scheme 26).⁴³

By titration of the metallic salts present in the solution it has been established that only the zinc element is present in the structure of the bismetallic,⁴⁴ and recent computational studies have also confirmed that only zinc was present in the bismetallic structure.⁴⁵ For the stereoselective reaction of the bismetallic **54** with different electrophiles (step I, Scheme 25), mild halogenating agents were chosen, such as phenylsulfonyl halides which are known to react selectively with sp^3 bismetallics.⁴⁶

Thus, addition of phenylsulfonyl chloride to **54** leads to the corresponding vinylic carbenoid **55**. The hydrolysis (or deuteriolysis) of the latter gives the unsaturated vinyl halide in good isolated yield as a unique isomer (Scheme 27).

Scheme 27

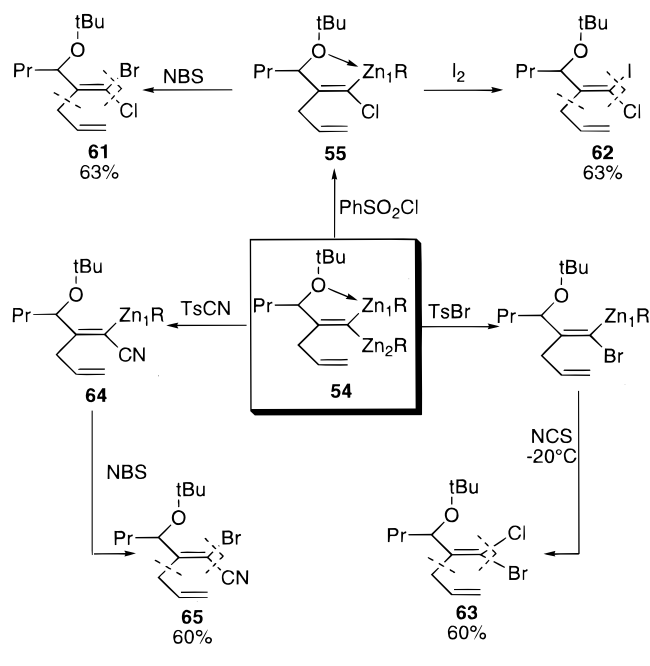
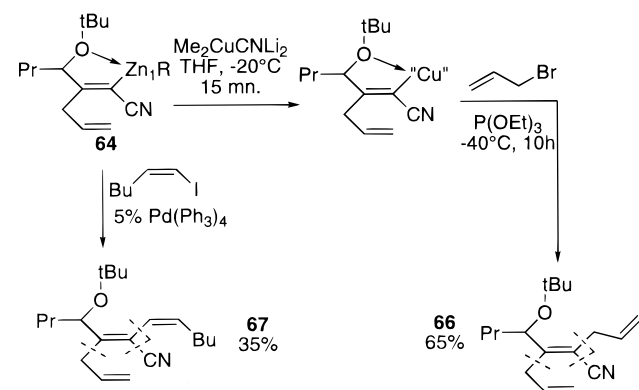


The stereochemistry was determined by the NOE effect between the vinylic and allylic hydrogens. This result reflects the chelation of the *tert*-butoxy group toward Zn_1R of **54**. Moreover, even an excess of PhSO_2Cl (4 equiv) does not lead to the vinylic gemdichloro derivative, and thus the resulting vinylic zinc **55** has a lower reactivity than the bismetallic **54**.⁴⁷ Taking advantage of the stereoselective reactivity of phenylsulfonyl chloride with **54**, other sulfonyl derivatives were tested (Scheme 27). In each case, only one stereoisomer was formed. Interestingly, the addition of *p*-toluenesulfonyl cyanide⁴⁸ leads to a unique metalated α,β -ethylenic nitrile. The chelation is absolutely necessary to discriminate the reactivity of the two metals toward the first electrophile. This was checked by the reaction with a substrate without internal chelation, and in this case the reaction described in Scheme 24 leads to the two geometrical isomers in equal amounts ($E:Z = 1:1$ after addition of phenylsulfonyl chloride).⁴⁷

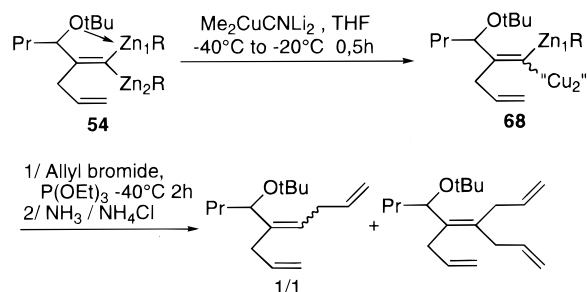
The remaining metal Zn_1R can also react with a stronger halogenating agent to give the polyhalogenated vinylic compound as a unique isomer. This reaction is of synthetic value for the obtention, at will, of the two geometrical isomers **61** and **63** starting from the same propargylic ether (Scheme 28).⁴⁷

In the case of an α -metalated vinyl cyanide **64**, the reactivity of the remaining metal Zn_1R can be increased by a transmetalation step with an organocuprate. The corresponding vinylic organocuprate derivative reacts with allyl bromide to give the skipped triene **66** as a unique isomer in good overall yield (starting from propargylic ether in a one-pot reaction, Scheme 29).⁴⁷ However, the coupling reaction of **64** with a vinyl iodide under palladium(0) catalyst gives the corresponding product **67** only in low yields.

When the transmetalation reaction is directly performed on the bismetallic **54** in order to obtain

Scheme 28**Scheme 29**

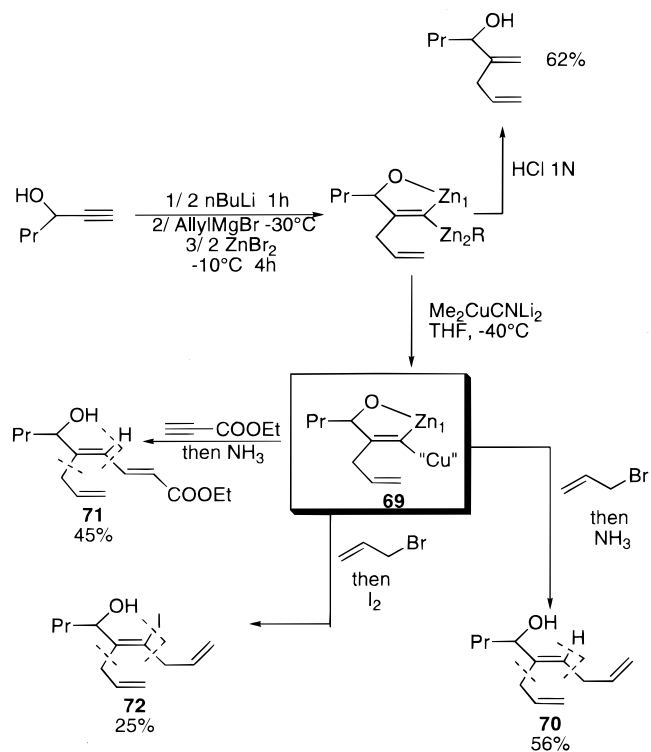
the corresponding Zn₁R/Cu₂-type bimetallic **68**, its reactivity is no more chemoselective as described in Scheme 30.⁴⁷

Scheme 30

Indeed, the addition of allyl bromide leads to a mixture of monoallylated (*E*:*Z* in a 1:1 ratio) and bisallylated product. So, the intramolecular chelation between the *tert*-butoxy group and Zn₁R is no more efficient to discriminate the reactivity of the two metals toward the *transmetalation step*.⁴⁷

To increase this stereodifferentiation of the bimetallic, the authors studied the allylmetalation of a secondary propargylic alcohol (instead of ether). In

this case, after the carbometalation reaction, a covalent metal–oxygen bond is formed, and the addition of an organocuprate leads only to a *transmetalation* of Zn₂R, namely the metal that is not chelated (Scheme 31).⁴⁷

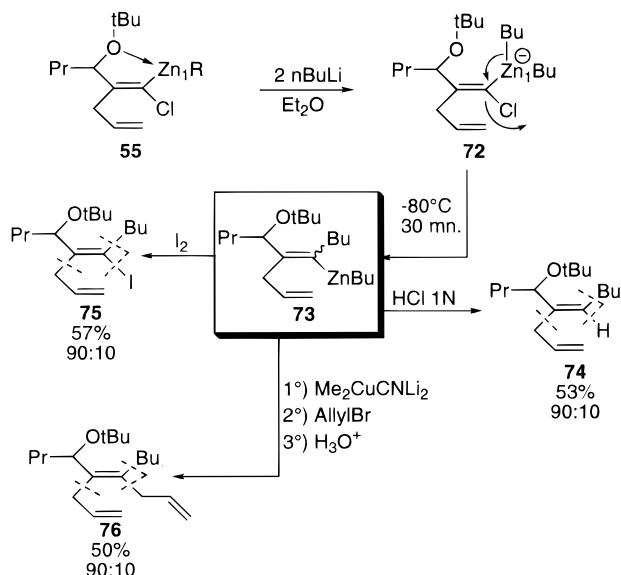
Scheme 31

The reaction of **69** with allyl bromide leads only to a monoallylated derivative **70** as a unique stereoisomer. The stereochemistry of the substituted double bond was determined by NOE effect and clearly shows that only the metal that is not attached by the oxygen moiety undergoes the *transmetalation* step. In a similar way ethyl propiolate leads to the triester **71**. The yields are moderate but the bisalkylation of a propargylic alcohol is carried out in a one-pot procedure. However, the reaction of **69** with cyclohexenone or chalcone does not lead to the 1,4-addition reaction. The reactivity of the second metal is lower than the reactivity of the first one, and iodination gives the tetrasubstituted olefin **72** as a single isomer in low yield (Scheme 31).⁴⁷

Thus, the alkylation of Zn₁R is synthetically useful in the case of the α -metalated α,β -ethylenic nitrile (see Scheme 29), but in the case of zinc halogenocarbenoid (as **55** in Scheme 28) the alkylation of Zn₁R is impossible since it requires higher temperature (degradation of the carbenoid). So, the chemistry of alkylidene chlorocarbenoids, which present an ambiphilic aspect, has been studied. Chlorocarbenoids can act as common nucleophiles (as in Scheme 28), but they can act as well as electrophiles toward organometallic nucleophiles. Indeed, the dropwise addition of *n*BuLi (2 equiv) to the α -chlorocarbenoid **55** at -78 °C leads to the formation of the zincate carbenoid **72** which undergoes a smooth intramolecular nucleophilic substitution reaction⁴⁹ to give the vinylic organozinc derivative **73**. The latter was

characterized by hydrolysis (**74**); iodolysis (**75**), and allylation (**76**) after a transmetalation step with **90**: **10** stereochemical purity as described in Scheme 32.⁴⁷

Scheme 32



By this 1,2-metalate rearrangement⁵⁰ Zn_1R is first alkylated via an *umpolung* reaction, and then Zn_2R reacts in a second step with different electrophiles.

A third possible reaction pathway of chlorocarbenoids (they can react as nucleophiles as described in Schemes 26 and 27 or as electrophiles toward nucleophiles as described in Scheme 31) has been known in the literature since 1894, namely the Fritsch–Buttenberg–Wiechell⁵¹ (FBW)⁵² rearrangement (Scheme 33). This rearrangement is known to

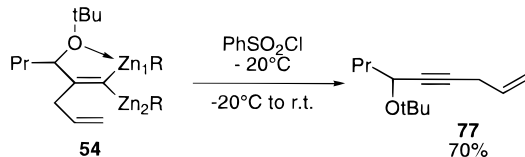
Scheme 33



be an efficient approach for alkyne synthesis when the migrating group (R_1 or R_2) is a hydrogen,⁵³ a heteroatom,⁵⁴ or an aryl moiety.⁵⁵ However, when R_1 and R_2 are alkyl groups, the yields in alkynes are very low (<10%) due to the competitive C–H insertion reaction to form cyclopentenones.⁵⁶

Interestingly, the alkylidene carbenoid **55**, generated from the 1,1-dizincioalkene **54**, rearranges cleanly in 70% yield, just by warming the reaction mixture to room temperature, into the disubstituted alkyne **77** (Scheme 34).⁵⁹ This first FBW rearrangement of

Scheme 34

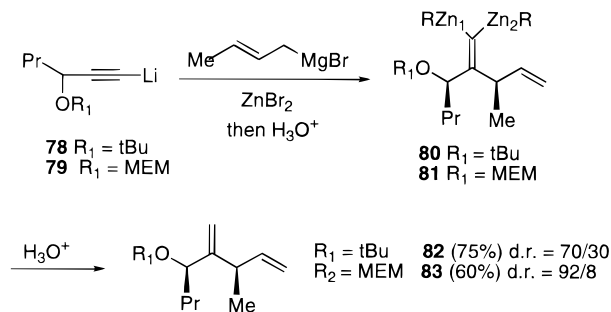


zincated species is in contradiction with the known results in lithio, sodio, and potassio analogues.⁵⁷ Indeed, when the same reaction is performed with the lithium carbenoid (generated from an iodine–lithium exchange on **62**, Scheme 28), a complex

mixture of products is obtained in which the alkyne is present *in less* than 10%.

The diastereoselectivity of this process was also studied by the addition of a substituted allylic organometallic derivative (namely crotylzinc bromide, *in situ* generated by the addition of crotylmagnesium bromide and zinc bromide) across the secondary metalated propargylic ether (Scheme 35).⁵⁸

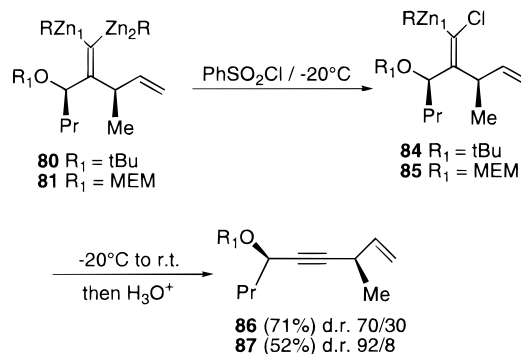
Scheme 35



Although a moderate diastereoselectivity is obtained for the crotylmetalation of **78** (formation of **82** after hydrolysis in a diastereomeric ratio of 70/30), the replacement of the *tert*-butyl ether into the methoxyethoxymethyl ether (OMEM) as in **79** raises the diastereoselectivity to 92/8 in 60% yield (see **83**, Scheme 35).⁵⁹ Via this strategy, two stereogenic centers and a bismetalated exomethylene moiety were created with a very good diastereomeric ratio.

The question of the fate of a chiral sp^3 carbon center as a migrating group in the FBW is then raised. To answer this interesting question, **80** is treated with $PhSO_2Cl$, as previously described in Scheme 27, and then the resulting carbenoid **84** (Scheme 36) is warmed to room temperature. A clean

Scheme 36



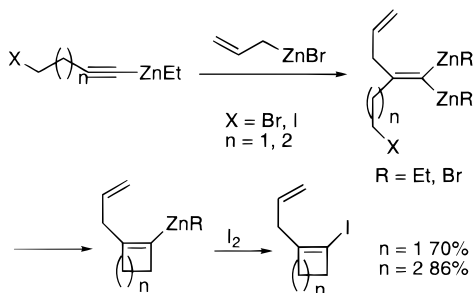
rearrangement takes place to lead to the enyne ether **86** with the same diastereoselectivity (70/30) as the one obtained for the intermediate **84** (or **82** after hydrolysis, see Scheme 34) as described in Scheme 36.⁵⁹

Starting from **81**, the obtained ether **87** displays a 92/8 diastereomeric ratio, similar to **83**.⁶⁰ Then, from these studies, it was shown that the migration occurs with a complete transfer of stereoselectivity (from 92/8 for **85** to 92/8 for **87**). Moreover, by chemical correlations, it was demonstrated that the FBW rearrangement occurs, via the zinc carbenoids, with a complete *retention of configuration at the migrating*

atom (the stereogenic centers in **80** or **81** with the one in **86** or **87** present the same diastereomeric ratios and the same absolute configurations). As described in this subchapter, the formation of sp² 1,1-dizincioalkene reagent represents a powerful tool for the preparation of the polysubstituted double bond via the successive addition of different electrophiles (up to three carbon-carbon bonds formed as unique isomer). Moreover, an interesting application is the synthesis of α,α' -chiral disubstituted alkynes from simple propargylic ether.

The allylmetalation of alkynylmetals were also used for the synthesis of metalated cyclobutenes²⁴ and cyclopentenes²³ as described in Scheme 37.

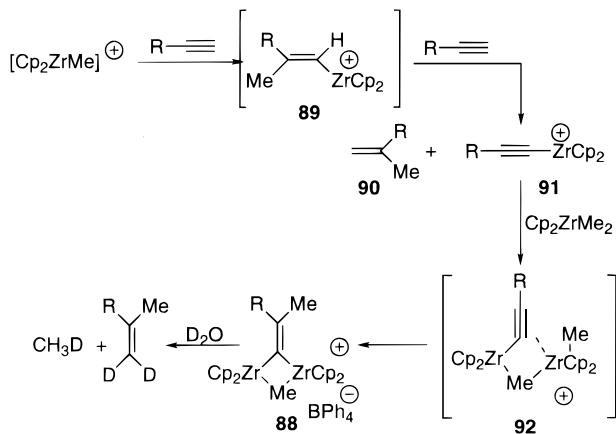
Scheme 37



VII. 1,1-Dizirconioalkene Reagents

Noncrowded alkynes react with [Cp₂ZrMe₂]/[PhMe₂-NH][BPh₄⁻] (2/1 ratio) at -30 °C to give complexes **88**-BPh₄⁻ in 70% yield.⁶¹ The possible mechanism for the formation of **88** is described in Scheme 38.

Scheme 38



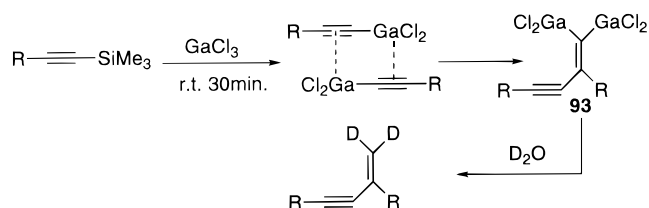
The likely first step is the alkyne insertion in [Cp₂⁻ZrMe(NMe₂Ph)]⁺, to give the alkenyl compounds **89**. Rapid σ -bond metathesis with the alkyne then liberates the olefin **90** (proven by NMR spectroscopy) and affords the transient alkyne complex **91**. Trapping of the unsaturated complex **91** by the Lewis base [Cp₂ZrMe₂] may give a transient dizirconocene intermediate, possibly the μ -alkynyl- μ -methyl complex **92**. The rapid insertion of the alkyne triple bond into a Zr-Me bond in **92** leads to the 1,1-dizirconioalkene derivatives **88**. The formation of the deuterated alkene and CH₃D after treatment of **88** with D₂O shows that complex **88** contains μ -methyl and μ -alk-

enylidene ligands which bridge the two Cp₂Zr fragments.

VIII. 1,1-Digallioalkene Reagents

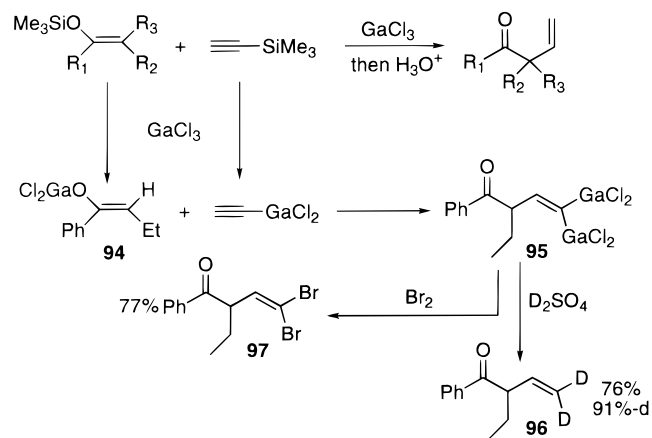
Treatment of alkynyltrimethylsilanes with GaCl₃ gave dimeric products via alkynyl digallioalkenes. Formation of the 1,1-dimetallo-1-buten-3-yne **93** was indicated by deuteration experiments (Scheme 39).⁶²

Scheme 39



In a similar way, trimethylsilylethyne and silyl enol ether were reacted with GaCl₃ to give the γ,γ -digallio- β -enone **95** as described in Scheme 40.⁶³

Scheme 40



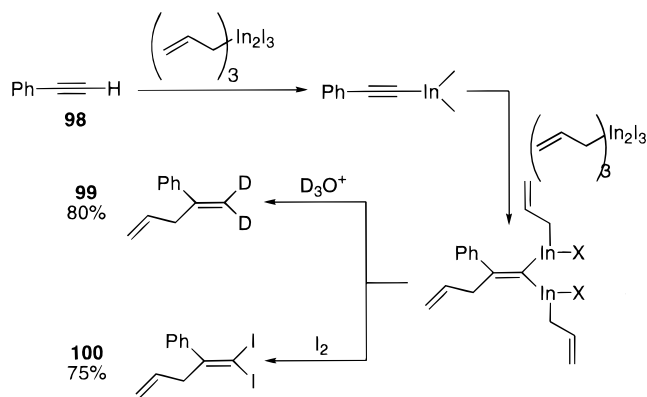
The mechanism of the reaction has been studied on a specific case and involved carbogallation⁶⁴ of the carbon-carbon triple bond by the gallium enolate **94**, generated by transmetalation of silyl enol ether with GaCl₃ (Scheme 40). Deuteriodegallation of **95** by the acidic workup with D₂SO₄ gave the ethenylated ketone **96**. The organodigallium can be also trapped by bromination of the C-Ga bond to give the γ,γ -dibromoethenylated ketones **97** in good yield. Interestingly, isomerization to the conjugated enone was not observed for these reactions.

IX. 1,1-Diindioalkene Reagents

Allylindium reagents, generated in situ by mixing In powder with allyl iodide in THF, react with alkynes to give the corresponding allylation products in good yields (Scheme 41).⁶⁵

In the case of the allylation of aromatic acetylenes **98** and with excess amounts of allylindium derivatives, the geminal diindation products were obtained, which produced **99-d₂** upon deuteration or produced diindinated **100** upon treatment with I₂.⁶⁶ However, when the same reaction was performed on aliphatic alkynes (with a less acidic acetylenic hydrogen), no

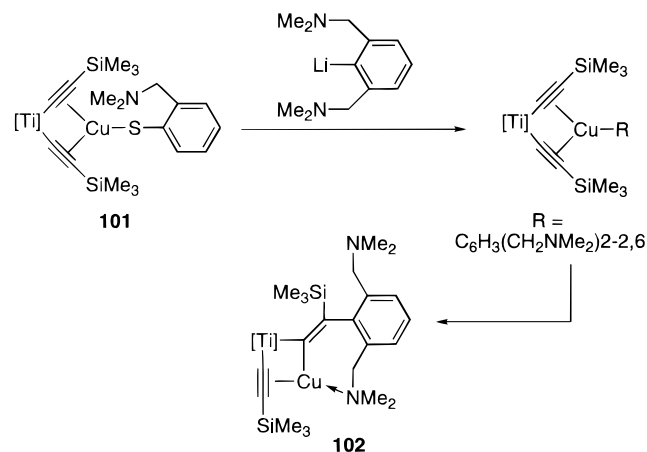
Scheme 41



1,1-diindioalkene derivatives were detected in the reaction mixture (no *premetalation* of the substrate).

X. 1,1-Cuprio-titanioalkene Reagents

The title derivatives **102** were achieved by reacting the monomeric copper arenethiolate complex **101** in a 2:1 molar ratio with $[\text{LiC}_6\text{H}_3(\text{CH}_2\text{NMe}_2)_2\text{-2,6}]_2$, and **102** has been isolated in 97% yield (Scheme 42).⁶⁷

Scheme 42^a

^a $(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}$ is abbreviated as [Ti].

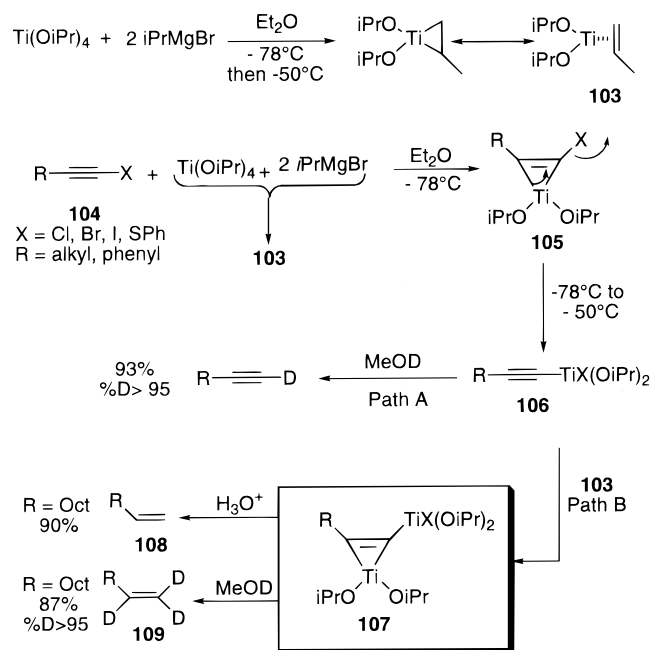
Compound **102** is an orange to red crystalline solid and is stable in air for several hours, and the solid-state structure was described.⁶⁷ However, the reactivity of **102** with electrophiles was not examined.

XI. 1,1,2-Trititanioalkene Reagents

Very recently, the diisopropoxy(η^2 -propene)titanium⁶⁸ **103**, readily generated by the reaction of $\text{Ti}(\text{O}^i\text{Pr})_4$ with 2 equiv of ${}^i\text{PrMgX}$ as described in Scheme 43, was reacted in situ with halogenoalkynes **104** to give, in a single-pot operation at -50°C , the titanio-titanacyclopropenes **107** in high chemical yields (Scheme 43).⁶⁹

A plausible mechanism for this reaction is shown in Scheme 43. The in situ formed diisopropoxy(η^2 -propene) titanium **103** reacts with halogenoalkyne **104**, via a ligand exchange,⁶⁸ to give as an unstable intermediate the halogeno-titanacyclopropene **105**. Then, **105** undergoes a very fast β -elimination at low temperature to give the alkynyltitanium derivative

Scheme 43



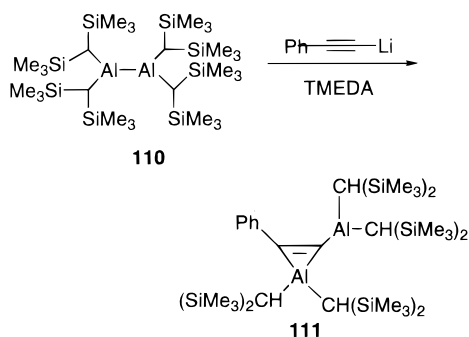
106.⁷⁰ Quenching the reaction with MeOD at -78°C proved the presence of the metalated alkyne **106** since the deuterioalkyne (Scheme 43, path A) was quantitatively obtained. When the reaction mixture is warmed to -50°C and stirred for 2 h, a second equiv of **103** reacts with **106** to give quantitatively the titanio-titanacyclopropene **107** (Scheme 43, path B). After hydrolysis, **108** is isolated in high yield. The presence of 3 carbon-metal bonds was proven by reaction with MeOD to give **109** ($>95\%$ *d* in 87% yield). The scope of this reaction is relatively large since various halogenoalkynes with $\text{X} = \text{Cl, Br, and I}$ as well as alkynyl thiophenyl ether give the trimetalated species in good to excellent yield (Scheme 43). Several chloroalkynes with an alkyl, phenyl, or homopropargylic ether group also lead to the product.⁶⁹ This strategy was also applied to the formation of 1,1,2-trizirconiaalkene derivatives by reaction of the *p*-tolylchloroacetylenes with zirconocene-(1-butene).⁶⁹

XII. 1,1,2-Trialuminioalkene Reagents

The dialuminum compound **110** reacts at room temperature with lithium phenyl ethynide in the presence of a small amount of the chelating Lewis base *N,N,N,N*-tetraethylethylenediamine (TMEDA) to give the crystalline compound **111** in a yield of about 50% (Scheme 44).⁷¹

The NMR spectroscopic characterization clearly showed an aluminacyclopropene structure with an additional exocyclic dialkylaluminum substituent.⁷¹ The structure was verified by a crystal analysis determination, and interestingly the Al-C distances in the ring differ by 10 pm. The shortest one is observed for the carbon atom bearing the phenyl group [195.1(3) pm], while the second bond which is attached to the exocyclic atom Al is lengthened to 205.2(3) pm. Moreover, the angle between the exocyclic aluminum and the double bond is almost linear (158.8°)!

Scheme 44



The reactivity of this compound with electrophiles is not yet studied.

XIII. Conclusions

The chemistry summarized in this review shows that various sp² geminated bismetals have been prepared and in some cases these derivatives are extremely useful synthons in a wide variety of carbon–carbon bond forming reactions. The success of these reactions is based on the intrinsic chemical knowledge of each metal and on its specific reactivity with different electrophiles. Their uses in organic synthesis have been particularly underlined in the case of *gem*-zincio-zirconio-, borio-zirconio-, and bis-zincioalkene derivatives. In many cases these bis donor reagents react with the more reactive carbon–metal bond whereas the less reactive one can be oxidized (i.e., C–B) or transmetalated (i.e., C–Zn) to a more efficient C–Cu bond. This relatively new field opened the way to many interesting synthetic transformations, and recent promising approaches were disclosed by the preparation of trismetallated double bonds.

XIV. Acknowledgments

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