

Synthesis and Reactivity of sp^3 -Geminated Organodimetallics

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Jean Normant (left) was born in Angers, France, in 1936. He received his Dr. from the Sorbonne (under Professor Prevost) and became associate professor in Reims (1963) then in Paris (1969), and was promoted to the rank of Professor in 1973 at the University Pierre et Marie Curie, Paris. His main interests are in the field of polar solvents; carbometalation of alkynes; alkenes; chemistry of copper, manganese, and zinc; fluoroorganometallics; and *gem*-dimetallic reagents.

the field of geminated dilithiated organic compounds really started only in the middle of the 1970s.⁶ As a consequence, theoretical modeling of monomeric and dimeric CH_2Li_2 molecules has been the subject of considerable interest.⁷ More recently, 1,1-dilithio-methane has been prepared by the reaction of lithium vapor with methylene chloride^{8a} or by the modified Ziegler synthesis.^{8b} Alternatively, higher homologs were prepared by reaction of bis(iodomercuro)-alkanes with lithium powder,⁹ by reaction of dichlorodiphenylmethane with a large excess of *t*-BuLi at low temperature¹⁰ or with lithium bis(4-di-*tert*-butylphenyl) (LiDBB)¹¹ and by reaction of bis(trimethylsilyl)dichloromethane with lithium vapor¹² or with LiDBB.¹³ This latter approach to *gem*-dilithioalkanes has been applied to the synthesis of unstabilized aliphatic geminal dilithium compounds, such as the dilithiomethane^{13a} or 7,7-dilithionorborene^{13b} (Scheme 1).

This organo *gem*-dilithio derivative **1** was quenched with electrophiles such as MeOD, CO₂ (followed by esterification with diazomethane), dimethyl sulfate, and even with ethylene to lead to a 1,3-dilithio derivative. Besides these reactions with different electrophiles, warming the dimetallic species **1** gave

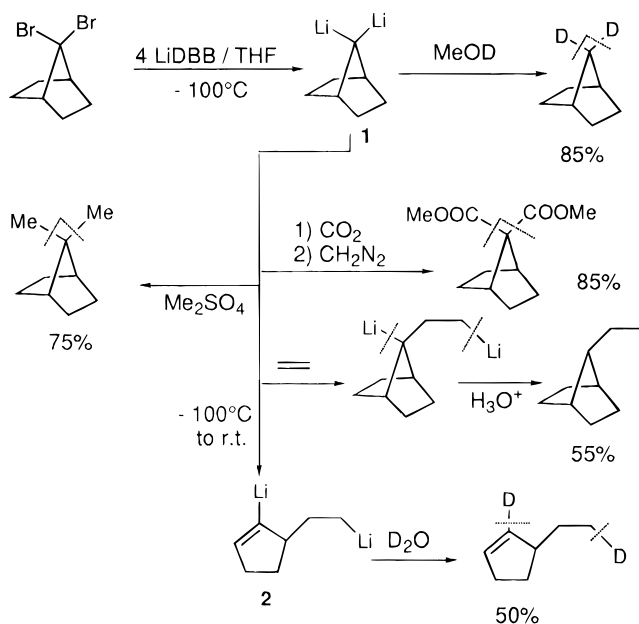
I. Introduction

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 Therefore, the combination of multiple reactions in a single operation represents a particularly efficient approach. Among different strategies,² the synthesis and reactivity of geminated organodimetallics has never been reviewed although its popularity for the synthesis of complex architectural molecules has been steadily increasing during the last decade.

This review is intended to highlight the use of geminated organodimetallic reagents (*gem*-dimetallics), but we will concentrate only on the chemistry of lithium, magnesium, boron, aluminum, copper, zirconium, and zinc. However, the reagents derived from titanium³ (such as Tebbe reagents³), group 14 elements such as tin or silicon and the chemistry of the bis-chromium derivatives⁴ will not be addressed.

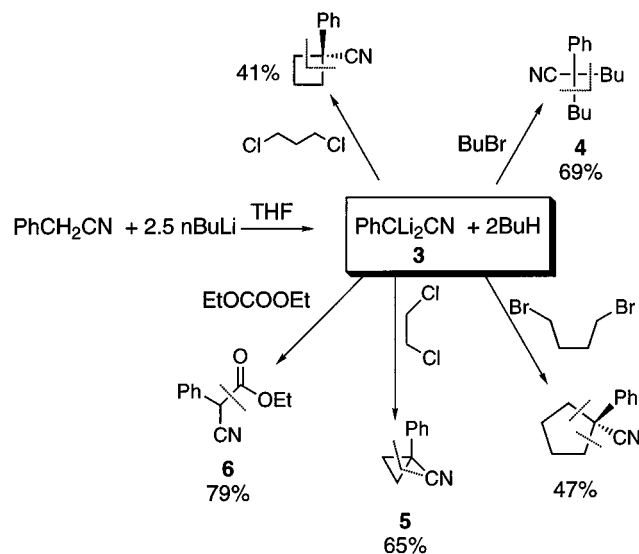
II. 1,1-Dilithioalkane Reagents

Since the first preparations of dilithiomethane in the pioneering works of Wittig, West, and Ziegler,⁵

Scheme 1

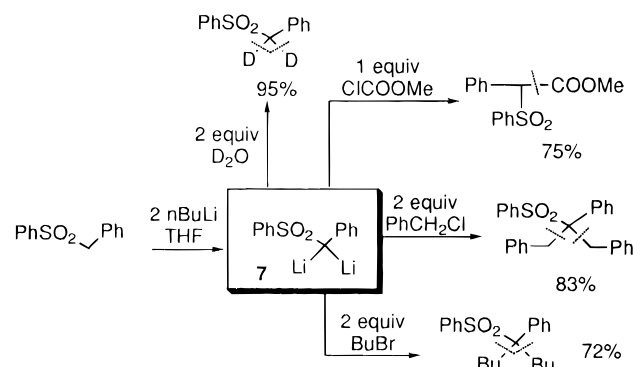
rise to ring opening, resulting in the lithio(lithioethyl)cyclopentene **2**, as shown by the formation of the corresponding dideuterated ethylcyclopentene.

However, the synthesis of *gem*-dilithioalkanes by metalation of derivatives containing acidic hydrogen atoms has been shown in recent years to possess great synthetic potential. In a seminal paper, Kaiser^{14a} reports that reaction of phenylacetonitrile with 2.5 equiv of *n*-BuLi produced butane in only slightly less than the calculated amount. Alkylation of the resulting dilithio species **3** with butyl bromide and ethylene dichloride afforded the dibutylated derivative **4** and the cyclic product **5** respectively in 69% and 65% yield (Scheme 2).

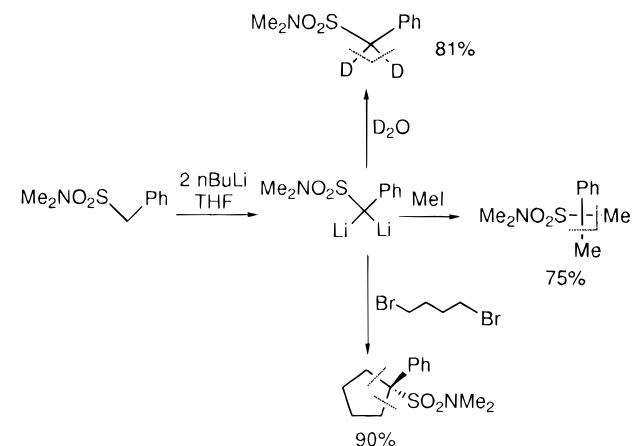
Scheme 2

Dilithiophenylacetonitrile **3** was also monoacylated with 1.25 equiv of diethyl carbonate to afford the cyano ester **6** in 79% yield^{14b} (an identical carboethoxylation of lithiophenylacetonitrile gave the same cyano ester in only 39% yield). Certain sulfur-containing compounds possessing labile α -hydrogens were also treated with *n*-BuLi in THF/hexane to

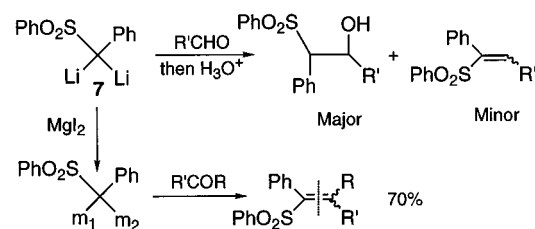
afford the corresponding *gem*-dilithio derivatives. For example, benzyl phenyl sulfone has been converted to the dilithio derivative **7** as suggested by infrared spectroscopy and condensation reactions^{14bc} (Scheme 3).

Scheme 3

Similar treatment of *N,N*-dimethyl- α -tolylsulfonamide gave the corresponding α,α -dilithio derivative,^{14b} which could also be quenched with different electrophiles (Scheme 4).

Scheme 4

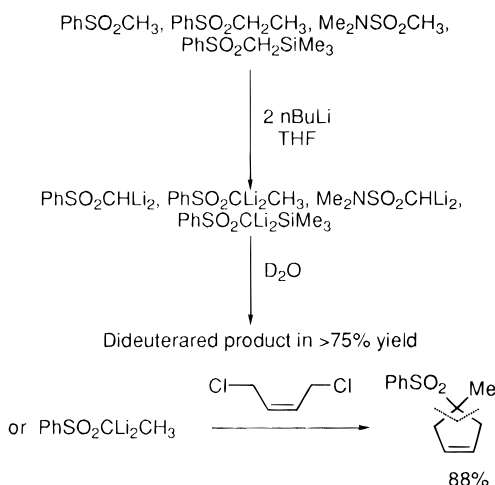
The same trend was observed with benzyl phenyl sulfide,^{14b} acetonitrile,¹⁵ 4-[(α -chloromethyl)sulfonyl]morpholine^{15b} and ferrocenyl methyl sulfone.^{15c} Formation of the dianion of benzyl phenyl sulfone **7** is also a method for obtaining various α,β -unsaturated phenyl sulfones from aldehydes and ketones¹⁶ (Scheme 5).

Scheme 5

Indeed, treatment of the α,α -dilithio derivative **7** with propionaldehyde at room temperature gives the expected α,β -unsaturated phenyl sulfone but in low yield, the main product being the hydroxy phenyl sulfone. This result was explained by the poor leaving group character of OLi. Since OMeX is

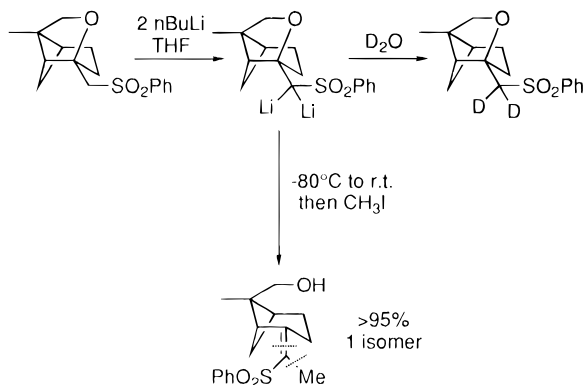
known to possess higher leaving group properties,¹⁷ the *gem*-dilithio derivative **7** was transmetalated with magnesium iodide¹⁸ and then treated with aldehydes or ketones to give the corresponding unsaturated phenyl sulfones in good yield (Scheme 5). This reaction has a wide applicability; saturated aliphatic and aromatic aldehydes including α,β -unsaturated carbonyl compounds can be employed. The synthesis of 1,1-dilithio derivatives is not restricted to benzyl phenyl sulfone, but can be also generalized to the alkyl phenyl sulfones,^{19a} to *N,N*-dimethylmethanesulfonamide,^{19b} and to (phenylsulfonyl)(trimethylsilyl)methane^{19c} (Scheme 6). Once again, the addition of magnesium iodide or the activation by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is necessary to obtain the corresponding olefination reaction in moderate chemical yield.^{19b} The synthesis of α -functionalized α,β -unsaturated sulfones (α -chloro or α -methoxy) from chloromethyl phenyl sulfone and methoxymethyl phenyl sulfone was also reported.^{19d}

Scheme 6



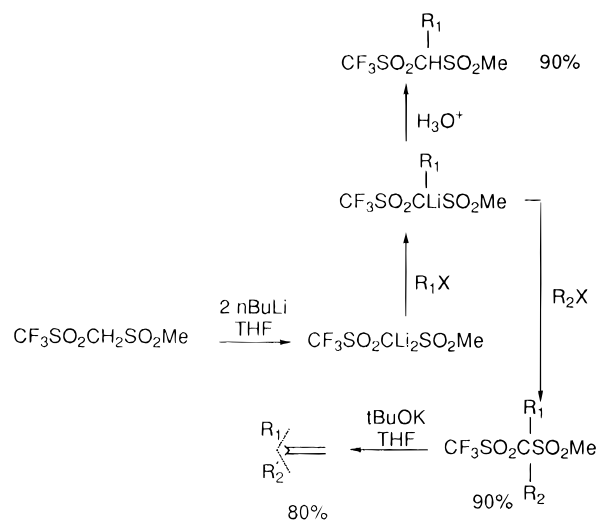
However, the use of an ether moiety instead of an alcoholate as a leaving group allows the quantitative formation of an olefinated product²⁰ via an E1CB mechanism (Scheme 7).

Scheme 7



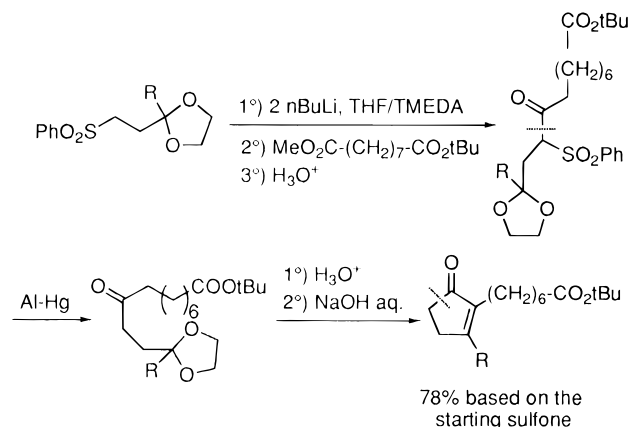
An alternative method has been recently developed²¹ for the synthesis of olefins via a double alkylation followed by a Ramberg-Bäcklund elimination (Scheme 8).

Scheme 8



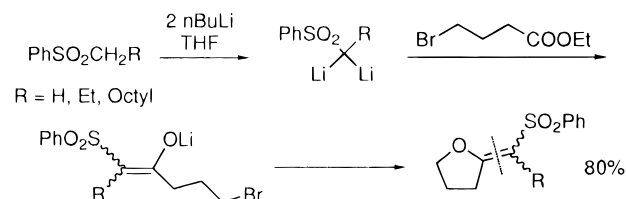
The second alkylation requires more reactive alkylating agents and higher temperatures than the first alkylation. An interesting point is that monoalkylation of the dianion gives a better result than the alkylation of the very stable monoanion.²² This observation has been extensively used for increasing the chemical yield of the acylation reaction. Indeed, the reaction of acid chlorides or esters with the monoanion of the sulfone is not rewarding. Once the keto sulfone is formed under these conditions, it is presumably rapidly deprotonated by any unreacted [(phenylsulfonyl)alkyl]lithium, therefore the maximum yield of β -keto sulfone would be 50%. Since the reaction of the sulfone dianion with an acylating reagent directly gives the enolate, this undesirable internal quenching is avoided^{22b} (Scheme 9).

Scheme 9



The enolate intermediate can also be directly functionalized in an intramolecular fashion^{22c,d} (Scheme 10).

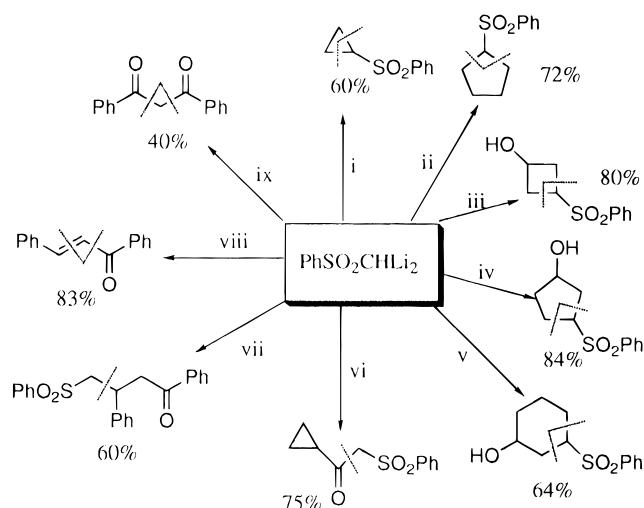
Scheme 10



The ring closure provides in a single-pot operation the expected vinyl ethers as a mixture of *E* and *Z* isomers.

Thus, the α,α -dianion reacts readily with a bifunctional organic substrate, such as ethyl 4-bromobutyrate or with other "bis-electrophiles" such as dihalides, halo epoxides, halocarbonyls, halonitriles, dicarbonyls, and α,β -unsaturated carbonyls to give carbocyclic and homologous derivatives in good yield^{23a} as described in Scheme 11.

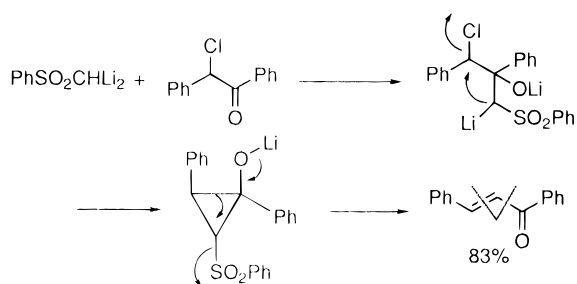
Scheme 11^a



^a Reagents: (i) 1,2-dichloroethane; (ii) 1,4-diodobutane; (iii) 3-chloro-1,2-epoxypropane; (iv) 4-bromo-1,2-epoxybutane; (v) 5-bromo-1,2-epoxypentane; (vi) 4-bromobutanenitrile; (vii) 1,3(*E*)-diphenyl-2-propen-1-one; (viii) 2-chloro-1,2-diphenyl-1-ethanone; (ix) benzil.

Some unusual homologations are described in this scheme, such as the reaction of α -chloro carbonyl derivatives (Scheme 11, path viii) which react first at the carbonyl center and then rearrange via a cyclopropanolate to the chalcone (Scheme 12).

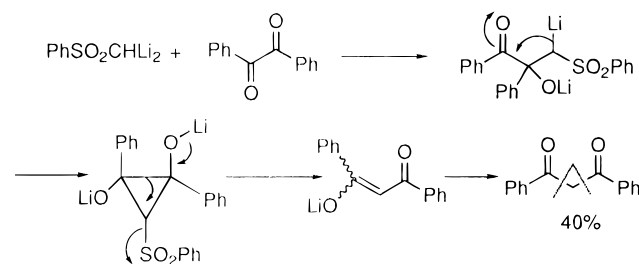
Scheme 12



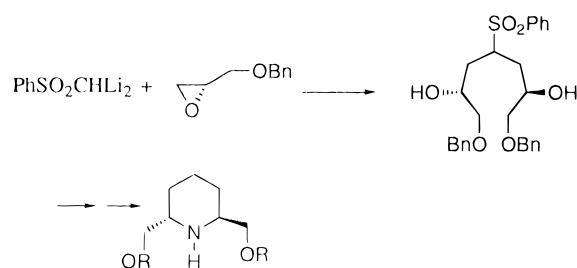
A similar cyclopropanediolate intermediate (Scheme 11, path ix) and its subsequent decomposition allows the interesting transformation of 1,2-diketones into 1,3-diketones via the mechanism described in Scheme 13.

3,3-Dilithio-1,1-dimethoxy-3-tosylpropane reacts as well with mono and dielectrophiles to give dialkylated products.^{23b} The methyl phenyl sulfone dianion can also be condensed with 2 equiv of (*S*)-[(benzyloxy)methyl]oxirane to produce the corresponding 1,7-bis-(benzyloxy)-4-(phenylsulfonyl)-(2*R*,6*R*)-heptanediol in 91% yield (Scheme 14), which is the precursor of the C_2 -symmetrical chiral piperidines.^{23c}

Scheme 13

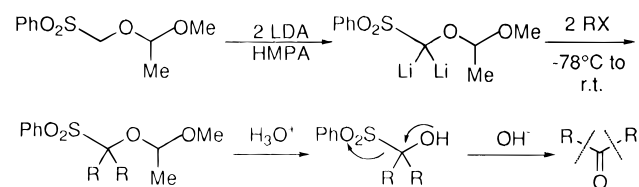


Scheme 14



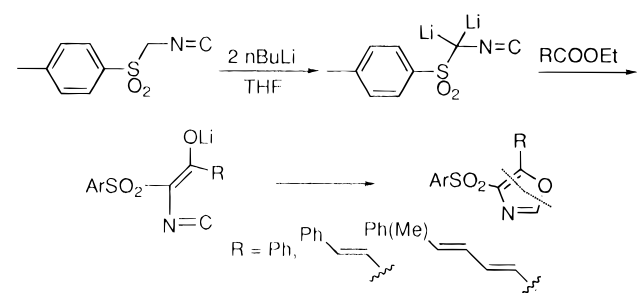
The dianion of the (1-ethoxymethoxy)methyl phenyl sulfone is also successfully generated by treatment with 2 equiv of LDA in THF in the presence of HMPA (Scheme 15). This dilithio species, considered as a double acyl anion equivalent, reacts with alkyl halides to give symmetrical ketones²⁴ in good yield.

Scheme 15



The dilithium derivative of tosylmethyl isocyanide²⁵ (TOSMIC) is also formed by treatment with 2 equiv of *n*-BuLi in THF at -70°C . Once again, the dilithio derivative is more stable and more reactive than the corresponding TOSMIC monoanion. For example, dilithio-TOSMIC smoothly converts esters to oxazoles in good yield (Scheme 16), whereas TOSMIC monoanion fails to react.

Scheme 16



Similarly, imidazole and imidazo derivatives are rapidly formed with the TOSMIC dianion (Scheme 17).

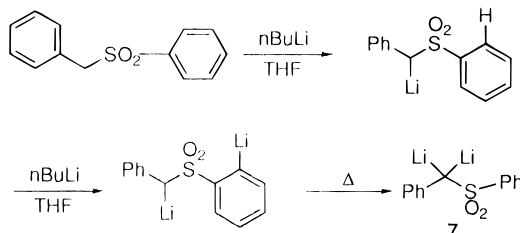
In summary, dilithio sulfones of different types represent potential dilithioalkane derivatives with a preparatively useful functional group and are therefore of particular synthetic interest. The first solid-state and solution structure of dilithium trimethyl-

Scheme 17



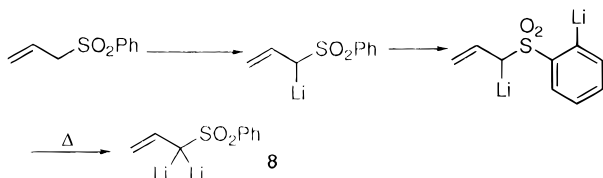
[(phenylsulfonyl)methyl]silane^{26a} was recently disclosed. This reagent was isolated and unequivocally characterized by ^{13}C and ^1H NMR spectroscopy.^{26b} The results of this investigation show that these dianions are true geminal dilithio compounds in the solid state as well as in solution. However, metalation of benzyl phenyl sulfone takes a different course at low temperature; highly selective ortho lithiation affords the ortho, α -dilithio sulfone. Transmetalation to the α,α -dilithio sulfone **7** takes place only at higher temperatures²⁷ (Scheme 18).

Scheme 18



The same translocation is observed in the dilithiation of phenyl allyl sulfone²⁷ (Scheme 19).

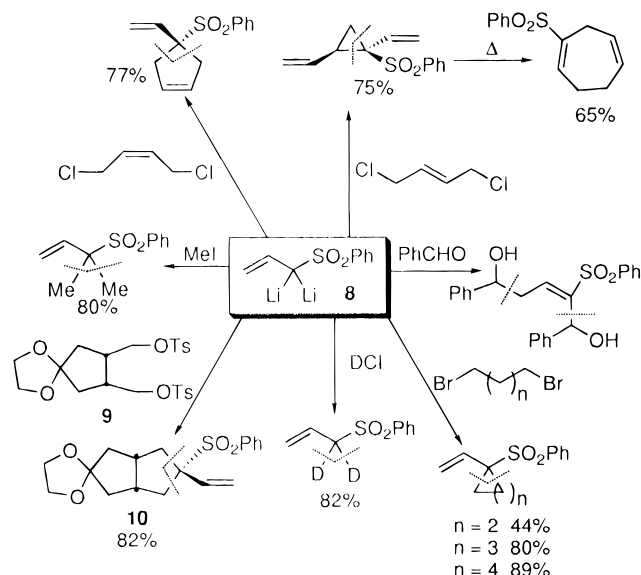
Scheme 19



These observations raised some doubt about the apparent geminal dianion structure of other dilithioalkyl aryl sulfones, and the formation of the latter should be viewed with caution, in the absence of NMR data, since the metalation of phenyl 2-propenyl sulfone proceeds via two distinct steps as described in Scheme 19.

Compound **8** (Scheme 20) is remarkably stable in THF and after 4 h at 50 °C, deuteration with $\text{DCI}/\text{D}_2\text{O}$ (0 °C) still afforded 82% of α,α -dideuterioallyl phenyl sulfone. The dialkylation of **8** with MeI proceeds regioselectively to give the 1,1-dimethyl allyl sulfone (80%). The same reactivity is observed for the cycloalkylation with 1, ω -dibromoalkanes to give carbocyclic compounds.²⁸ By geminal cycloalkylation of **8** with a ditosylate **9**, a new bicyclic **10** compound is synthesized in 82% yield with 90% dr. This compound is geminally substituted by a vinyl and a phenylsulfonyl group and has been converted by a $\text{S}_{\text{N}}2'$ reaction with an organocuprate into a carbaprostacyclin precursor.²⁹ When **8** is treated with an excess of *cis*-1,4-dichloro-2-butene, the corresponding cyclopentene³⁰ is obtained in 77% yield. Alternatively employing *trans*-1,4-dichloro-2-butene under identical conditions resulted in the exclusive formation of the divinylcyclopropane³⁰ in 75% yield, which is

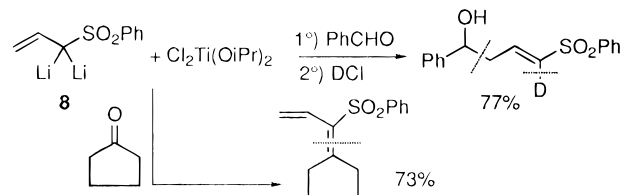
Scheme 20



smoothly converted into the 1,4-cycloheptadiene upon heating at 130 °C in xylene (Scheme 20).

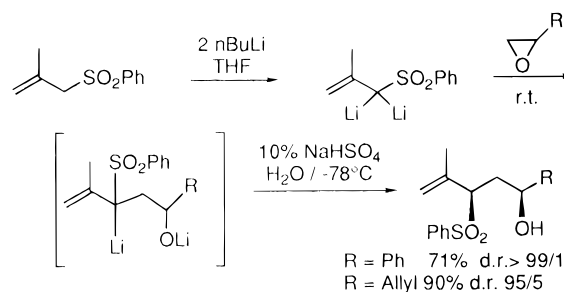
Compound **8** can be also transmetalated with 1 equiv of $(i\text{-PrO})_2\text{TiCl}_2$ to give the corresponding organotitanium²⁸ compound, which can react sequentially with aldehydes or ketones and then with $\text{DCI}/\text{D}_2\text{O}$ as described in Scheme 21. The reaction of this new organotitanium complex with cyclopentanone²⁸ gives the carbonyl olefination product in 73% yield.

Scheme 21



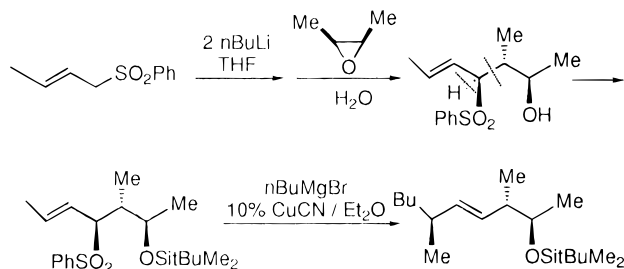
Alkylation of the methallyl phenyl sulfone dianion with styrene oxide leads to essentially a single (>99:1) γ -hydroxy sulfone after hydrolysis³¹ (Scheme 22).

Scheme 22

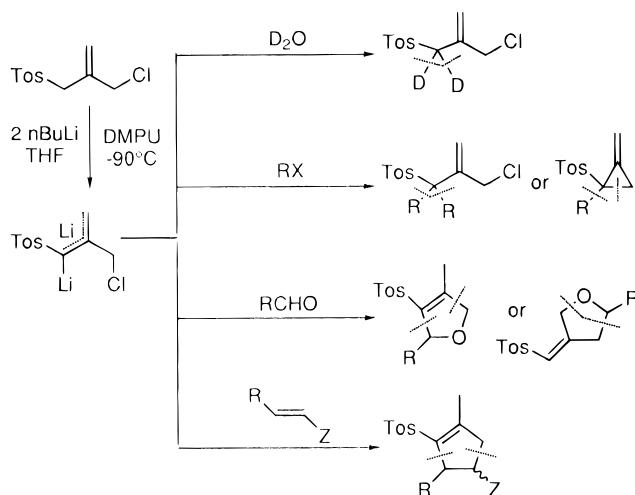


Other allylic dianions and epoxides have been studied and according to preferential kinetic or thermodynamic control, very high diastereoselectivities are obtained.³¹ For example, treatment of the dianion of crotyl sulfone with *cis*-butene oxide leads to virtually a single (>99:1) diastereomer in 71% yield as described in Scheme 23.

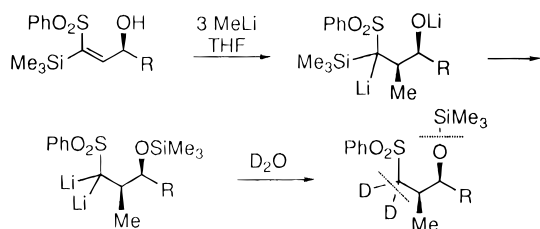
Thus, the use of the dilithiated sulfone allows the formation of only one β -hydroxy sulfone and then a stereoselective $\text{S}_{\text{N}}2'$ reaction follows (Scheme 23).

Scheme 23

Sulfolene,³² (*E*)-2-methoxy-1-(phenylsulfonyl)propene³³ and 2-(chloromethyl)-3-tosylpropene³⁴ can also be readily dilithiated. In the latter case, the dilithio intermediate is stable at low temperature and reacts with different electrophiles regioselectively, depending on the nature of the electrophilic reagent used³⁵ (Scheme 24).

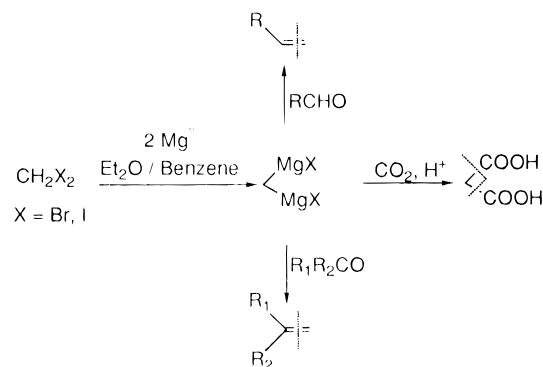
Scheme 24

An interesting alternative synthesis of sulfone dianions has also been described (Scheme 25) via a silyl migration from carbon to oxygen atoms.³⁶

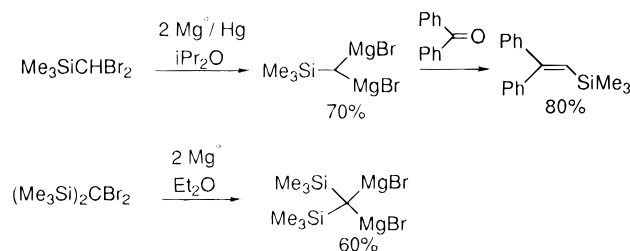
Scheme 25**III. 1,1-Dimagnesioalkane Reagents**

The preparation of the simplest member of the di-Grignard compounds, first described by Emschwiller³⁷ in 1926 (in 11% yield), was improved by Fidler^{38a} (in 50% yield) and latter by Cainelli^{38b} (60–70% yield) using dibromo- or diiodomethane and magnesium amalgam in a 1:1 mixture of ether and benzene. A colorless, stable solution³⁹ of organo-*gem*-dimagnesium compound is obtained, which reacts with aldehydes, ketones, and carbon dioxide to give the

corresponding products in moderate to good yield (Scheme 26).

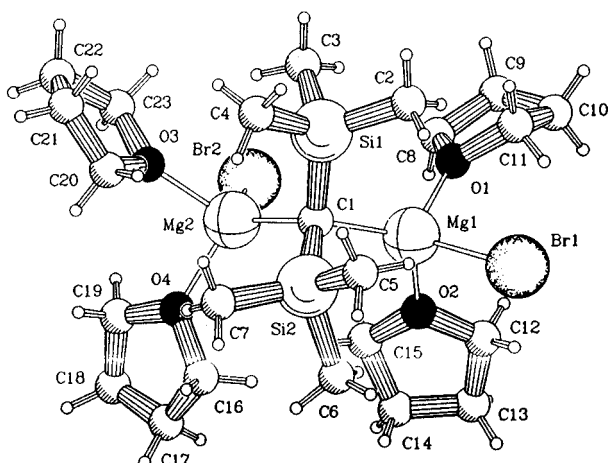
Scheme 26

The reaction with carbonyl compounds seems to have a wide range of applicability; saturated aliphatic and aromatic aldehydes and ketones including steroids can be employed.^{38b} Although, the synthesis was further improved by using diisopropyl ether as the solvent (80% yield)⁴⁰ and that the mechanism of the reaction of geminal dihalides with magnesium has been intensively studied,⁴¹ the preparation of 1,1-dimagnesium compounds cannot be extended to the synthesis of higher homologs in good yields. (Trimethylsilyl)dibromomethane^{42,43} has also been successfully converted to the di-Grignard reagent (Scheme 27).

Scheme 27

The bis(bromomagnesium)(trimethylsilyl)methane was treated with a non-enolizable ketone to give the corresponding olefinated product in good chemical yield. However, with cyclohexanone, the Wittig-type product was formed in only 13%. The bis(bromomagnesium)bis(trimethylsilyl)methane was obtained in diethyl ether⁴³ and isolated by crystallization (obtained from a saturated solution of THF/hexane). Its X-ray structure⁴⁴ shows the monomeric unit of the derivative with two THF ligands per magnesium in the crystal lattice and association measurements indicated that the monomeric state is retained in a THF solution. The central carbon atom is a slightly distorted tetrahedron with bond angles ranging from 104° to 116°. Moreover, all carbon–magnesium and carbon–silicon bonds are slightly shorter than usual: attachment of electropositive groups to the central carbon leads to accumulation of negative charge at this carbon and thus to electrostatic strengthening and shortening of the highly polar bonds. All these factors contribute to the low reac-

tivity of bis(bromomagnesium)bis(trimethylsilyl)methane toward classical electrophiles.

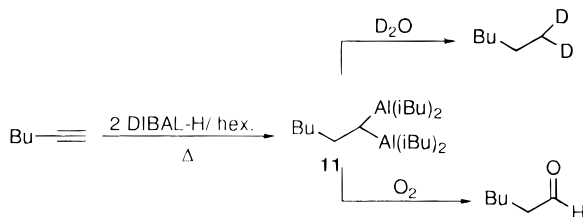


Particularly promising is the use of the methylene di-Grignard in the synthesis of 1,3-dimetallacyclobutanes, which have been recently reviewed.⁴⁵

IV. 1,1-Dialuminioalkane Reagents

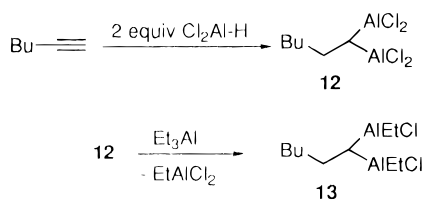
Bis-1,1-(diisobutylaluminio)alkanes **11** are readily accessible via double hydroalumination of 1-alkynes⁴⁷ and even from the double carboalumination of acetylene^{46a,47} (Scheme 28).

Scheme 28



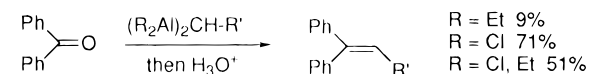
1,1-Bis(diethylaluminio)hexane⁴⁷ and 1,1-bis(dichloroaluminio)hexane⁴⁸ **12** were also prepared respectively by adding 2 mol equiv of Et₂AlH or Cl₂AlH to hexyne.⁴⁸ Treatment of **12** with Et₃Al (Scheme 29) afforded 1,1-bis(chloroethylaluminio)hexane⁴⁸ (**13**) in good yield.

Scheme 29



Benzophenone was allowed to react with these 1,1-bis(substituted aluminio)hexanes to give fair to good conversions to 1,1-diphenyl-1-heptene but with significant^{47,48} amounts of reduction (Scheme 30, R' = C₅H₁₁).

Scheme 30

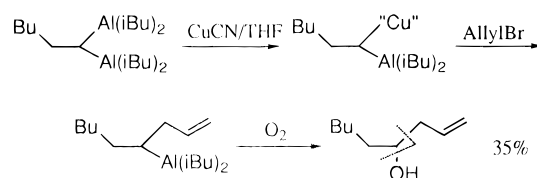


Even reagent **12** gave a 29% yield of the reduction product of benzophenone, whereas aliphatic ketones proved to be completely unsatisfactory in the Wittig-type reaction⁴⁸ (Scheme 30). With 1,1-bis(diisobutylaluminio)hexane **11**, extensive reduction of aromatic and aliphatic aldehydes and ketones resulted in the corresponding alcohols as the major products.⁴⁹

The geminal dialuminummethanes can be synthesized as well,^{48,50} their reactions with a wide variety of ketones including cyclohexanone, 4-*tert*-butylcyclohexanone, α -tetralone, dihydrocarvone, and 4-chromanone gave the methylenated products in 50% to 90% yield.⁴⁸

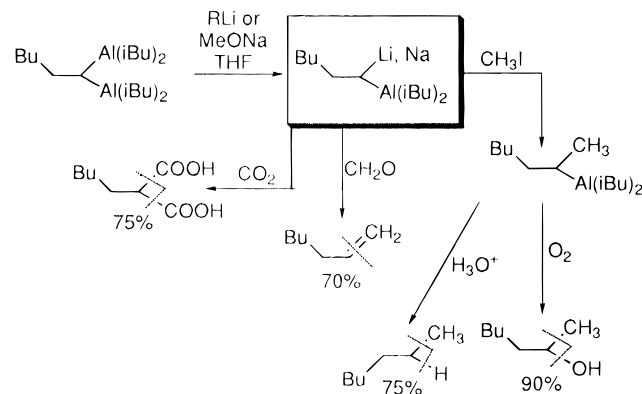
Transmetalation of the 1,1-bis(diisobutylaluminio)alkanes **11** with a copper salt gave a new mixed organo-*gem*-dimetallic, which can react selectively with allyl bromide and dry air to provide the corresponding alcohol in modest yield⁵¹ as described in Scheme 31.

Scheme 31



However, treatment of the 1,1-bis(diisobutylaluminio)hexane derivative with MeLi, BuLi, or MeONa in THF resulted in the formation of a new organo-*gem*-dimetallic (containing aluminum and sodium or aluminum and lithium on the terminal carbon atom⁵² or a new aluminum-aluminate complex, Scheme 32).

Scheme 32

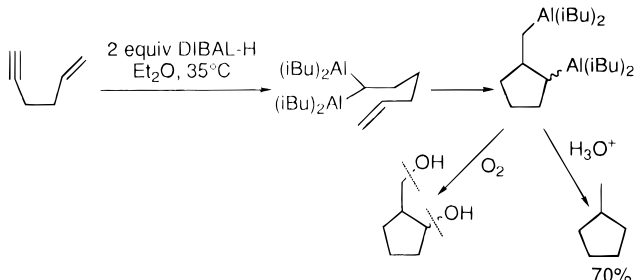


Addition of excess methyl iodide to this new organo-*gem*-dimetallic, followed by either hydrolysis or oxidation leads to the corresponding hydrocarbon or alcohol respectively. Direct carbonation or olefination of the dimetalloalkane gave the *n*-amylmalonic acid in 75% and 1-heptene in 70% yield respectively (Scheme 32).

Double hydroalumination of hex-1-en-5-yne with diisobutylaluminum hydride (2 mol equiv) in diethyl ether leads to the organo-*gem*-dialane, which then undergoes intramolecular Al-C bond addition to the double bond⁵³ to afford after hydrolysis, the corresponding methylcyclopentane in 70% yield (Scheme

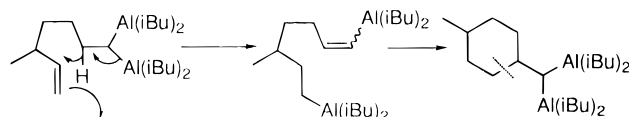
33). Alternatively, the reaction mixture can be treated with molecular oxygen to produce a mixture of *cis*- and *trans*-2-hydroxycyclopentylmethanol.

Scheme 33



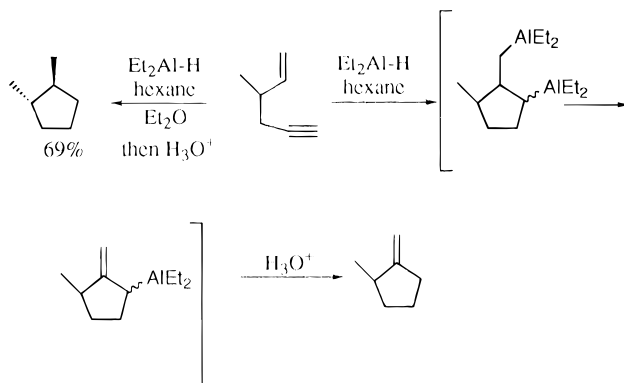
When a six-membered ring is created by carboalumination of a 1,1-dialumino-6-heptene in the absence of ether, the reaction proceeds via internal hydroalumination of the C=C bond followed by carboalumination of the resulting vinyl alane.⁵⁴ This is illustrated in Scheme 34 with 3-methyl-1-hepten-6-yne employed as the starting material.

Scheme 34



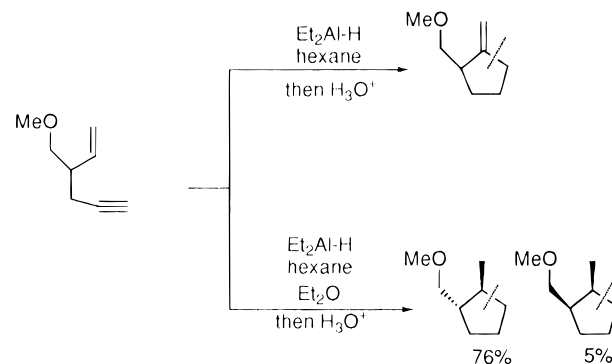
In the absence of ether, the cyclization of the organo-*gem*-dialanes to five-membered rings leads to an olefin,⁵⁵ while *trans*-1,2-dimethylcyclopentane results when the cyclization is performed in the presence of as little as 2 equiv of ether (Scheme 35). This is an indication of the stabilizing effect of ether as solvent in the preparation of organoalane derivatives.

Scheme 35



An appropriately located heteroatom can influence the course of the cyclizations of alkenylalanes. For example, the following enyne methyl ether (Scheme 36) was cyclized using 2 equiv of diethylaluminum hydride. In similarity to the previous case (see Scheme 35), a dehydroalumination product is the main product in the absence of added ether, while in its presence, *trans*-2-(methoxymethyl)-1-methylcyclopentane is obtained as the major product.

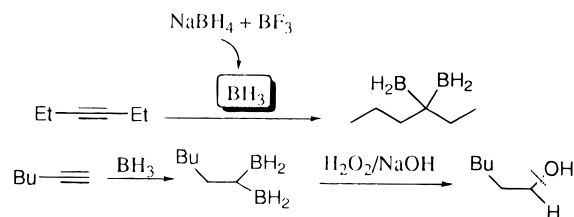
Scheme 36



V. 1,1-Diborioalkane and 1,1-Borio-lithioalkane Reagents

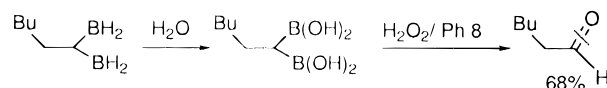
The double hydroboration of 1- and 3-hexyne was examined first with an excess of diborane,⁵⁶ but the oxidation of the product from dihydroboration of 1-hexyne yielded *surprisingly* 1-hexanol as the major product⁵⁷ (64% yield, Scheme 37).

Scheme 37



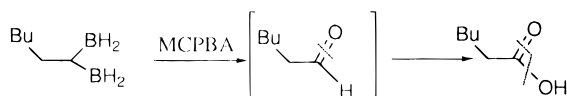
The only reasonable explanation for the high yield of primary alcohol is that the hydroboration product, whatever its structure, undergoes a rapid hydrolysis to lose one of the two boron-carbon bonds prior to oxidation. Since the alkaline hydrolysis involves an attack by a base on the electrophilic boron atom, these substituents which decrease the acidity of the boron atom should greatly reduce the hydrolytic stability of the 1,1-diborio derivative. So, the diborioalkane was hydrolyzed first and oxidized in a second step with alkaline hydrogen peroxide at pH 8, to give the aldehyde (Scheme 38) in 68% yield.⁵⁷

Scheme 38



The direct conversion of the 1,1-diborio compound into *n*-hexanal in 43% yield by oxidation with *m*-chloroperbenzoic acid was also described, but this reaction also yielded 18% of hexanoic acid⁵⁸ (Scheme 38). The formation of the acid can be rationalized by oxidation of hexanal by mCPBA. Confirmatory evidence that hexanal was indeed the precursor for the carboxylic acid was given by oxidation of the dihydroboration product with 3 mol equiv of *m*-chloroperbenzoic acid, which resulted in a 79% yield of the acid⁵⁸ (Scheme 39).

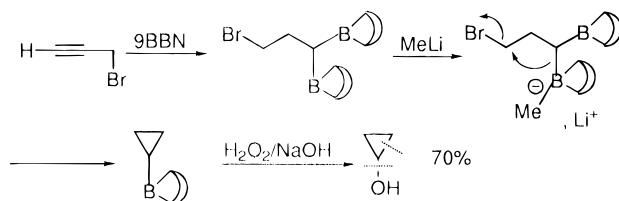
1,1-Bis(dibutoxyborio)ethane was easily prepared, as stable crystals, by the hydroboration of dibutyl eth-

Scheme 39

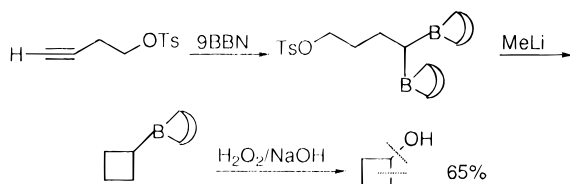
yleneboronate⁵⁹ followed by the addition of oxygen-free butanol.

1. Boriolithioalkanes from Diborio Compounds

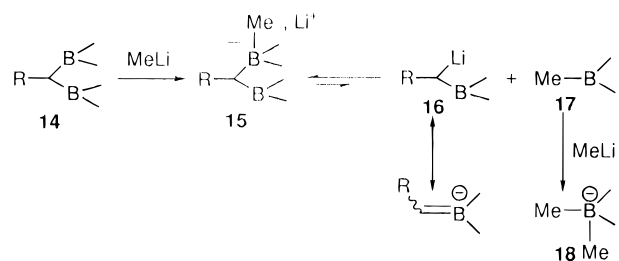
The synthesis of (diethylcyclopropyl)borane⁶⁰ or cyclopropyl-9-BBN⁶¹ was performed via the dihydroboration of either propargyl chloride or bromide, followed by the addition of methyllithium to the resulting 1,1-diborio compound (Scheme 40).

Scheme 40

In the case of the *B*-cyclobutyl-9-borabicyclo[3.3.1]nonane, tosylate was chosen as the leaving group⁶¹ (Scheme 41).

Scheme 41

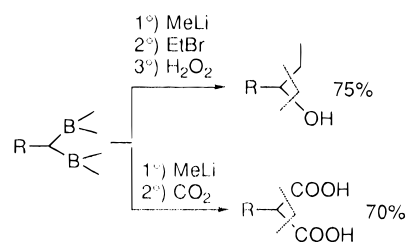
The strong influence of adding alkyl lithium on the reactivity of the 1,1-diborioalkanes with electrophiles was recently studied by NMR⁶² (Scheme 42). 1-Pen-

Scheme 42

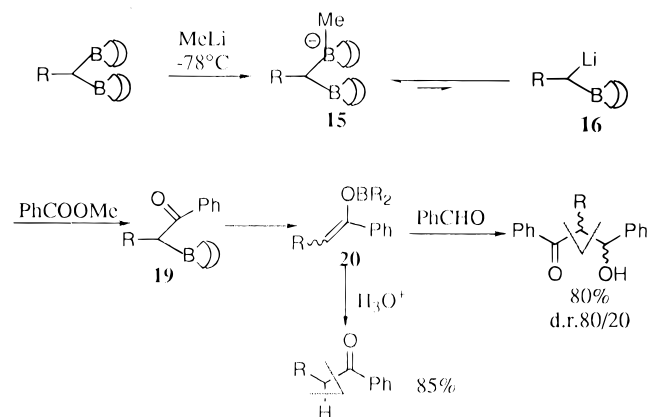
tyne was dihydroborated and then treated with 1 equiv of methyllithium in ether; the NMR spectra of the reaction mixture revealed the absence of free methyllithium in solution and the presence of two signals for the CH₃ protons. The data obtained can be interpreted in terms of the mechanism proposed in Scheme 42, whereby addition of methyllithium to the *gem*-diborioalkanes **14** gives the corresponding ate complex **15** which is the source of the high-field

CH₃ protons. The NMR data suggest that the ate complexes are only slightly dissociated into the boron-stabilized carbanions **16** and the corresponding methylboranes (some analogous results have been obtained in the case of 1-phenylborabenzene anion^{62b}).

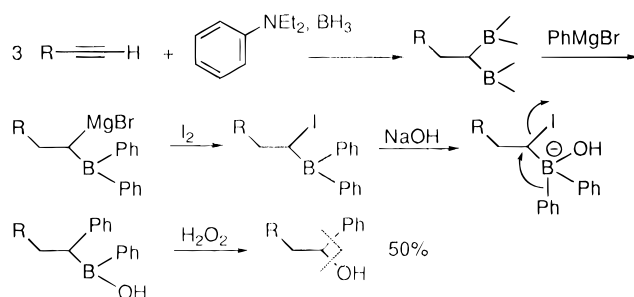
This conclusion is based on the fact that the intermediate **17** can compete with **14** for methyllithium to give the dimethyl borate **18**, which also exhibits the typical high-field CH₃ protons shift (Scheme 42). Addition of ethyl bromide to **15** or **16** followed by oxidation of the resulting intermediate with alkaline hydrogen peroxide or carbonatation gives the corresponding secondary alcohols^{62a,63} and malonic acids⁶⁴ respectively (Scheme 43).

Scheme 43

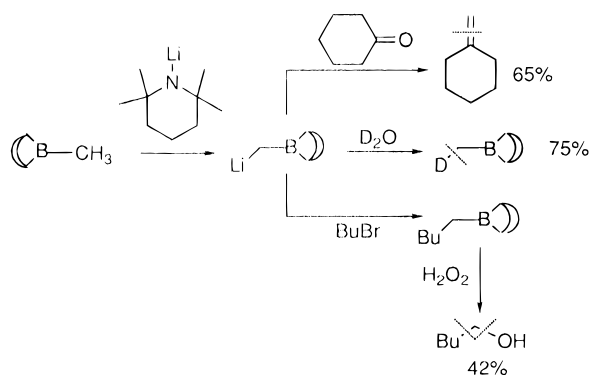
The intermediates **15** or **16** react with aldehydes or ketones to give the Wittig-type products in moderate yield⁶⁵ and also with acylating reagents to give α -boryl ketones **19**, which immediately isomerize to form (vinyloxy)boranes **20**. These latter products can either be hydrolyzed or reacted with a variety of aldehydes to afford the corresponding cross-aldol products in good yields as a mixture of two diastereomers⁶⁶ (Scheme 44).

Scheme 44

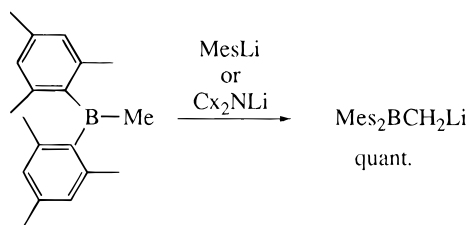
The α -boromagnesium halides can be prepared through the exchange reaction between a Grignard reagent and a 1,1-diborane, generated by double hydroboration of an alkyne with the *N,N*-diethylaniline-borane complex. Sequential treatment of the boromagnesium halide with iodine then NaOH/H₂O₂ leads to the corresponding alcohols⁶⁷ via 1,2-metalate rearrangement and oxidation (Scheme 45).

Scheme 45**2. Boriolithioalkanes from Metalation of Boranes**

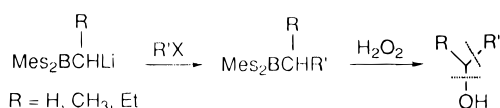
Addition of a base to an organoborane results in coordination of the base to the boron atom. This ate complex formation can be overcome by utilizing a base with large steric requirements that causes coordination to boron to be impossible. Indeed, lithium 2,2,6,6-tetramethylpiperidine furnishes the corresponding boriolithioalkanes⁶⁸ (Scheme 46).

Scheme 46

A different method involves attachment to boron of sterically encumbered groups which inhibit the formation of the ate complex.⁶⁹ Thus, methyldimesitylborane was chosen as the substrate and lithium dicyclohexylamide or mesityllithium act as excellent bases to yield quantitatively the desired carbanion.^{69d-f}



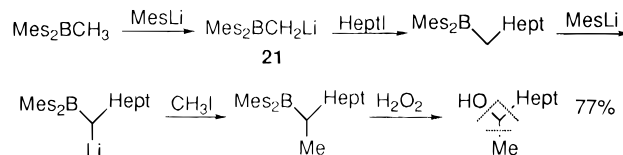
From whichever base the anion was produced, alkylations⁷⁰ proceeded satisfactorily (Scheme 47). However, the rates of alkylation were enhanced in the presence of dicyclohexylamine.

Scheme 47

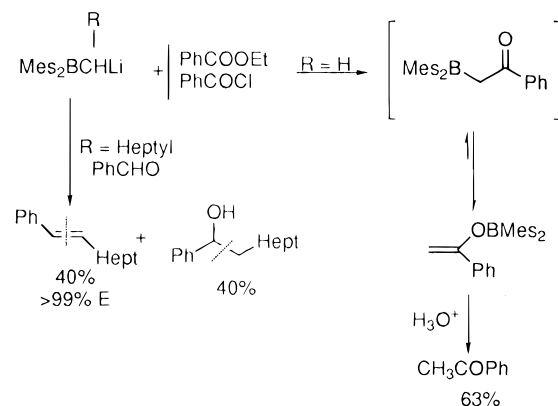
Primary alkyl iodides or bromides and benzyl iodide gave good chemical yields, whereas secondary halides and sulfonates led mainly to elimination rather than substitution. The synthesis of hetero-

atom-substituted (dimesitylborio)methanes such as Mes₂BCH₂Li + MR_nX → Mes₂BCH₂MR_n with M = (Si, Sn, S, Pb, Hg) is also described.^{70c,d}

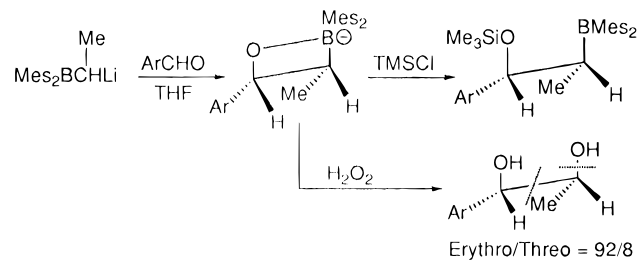
The reaction can proceed without isolation of the intermediate borane. So, **21** was alkylated first with heptyl iodide and then metalated again by addition of 1 equiv of mesityllithium followed by alkylation with methyl iodide to give a 77% yield of nonan-2-ol after oxidation as described in Scheme 48.

Scheme 48

The acylation of boron-stabilized carbanions is a potential route to boryl enolates,^{70b} and olefins⁷¹ from aromatic aldehydes and ketones (Scheme 49).

Scheme 49

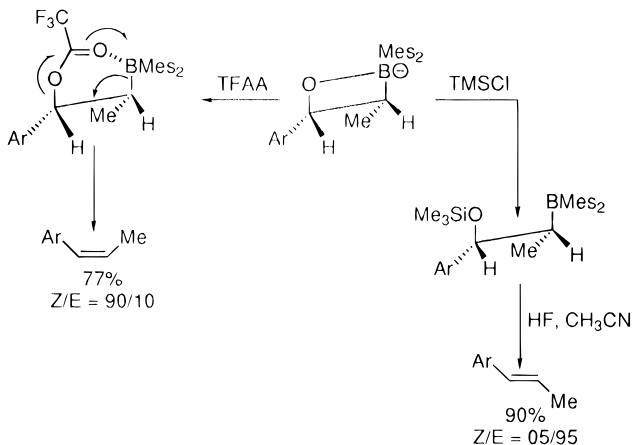
For example, the reaction of benzaldehyde with the anion of octyldimesitylborane, in refluxing chloroform for 2 h, leads to 1-phenylnon-1-ene in 40% yield with 99.9% *trans* stereoselectivity. However, a 40% yield of 1-phenylnonanol is also produced as a result of a cleavage of the boron-alkyl bond (Scheme 49). In order to understand the course of the boron Wittig-type reaction, the intermediate boroaxetane was trapped by silylation to give the *erythro* product, and by oxidation to give the corresponding diol⁷² (Scheme 50).

Scheme 50

The selective formation of the *E* olefin from the *erythro* intermediate is thus explained by an *anti*-elimination. The same stereoisomer is obtained by reaction of the silylated intermediate with HF in acetonitrile,⁷³ whereas trapping the alcoholate with TFAA produces the trifluoromethyl ester which che-

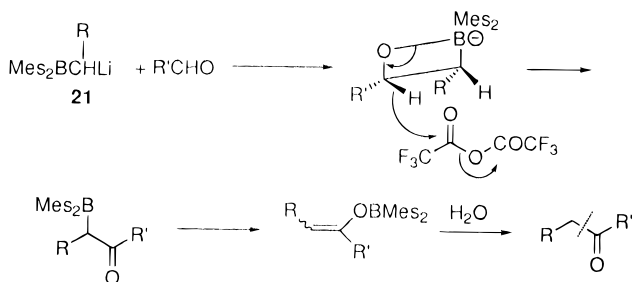
lates to the boron atom. Despite the unfavourable steric interactions, a *syn*-elimination process now leads mainly to the (*Z*)-alkene⁷³ (Scheme 51).

Scheme 51



The substituted borolithioalkanes also react as well, in the presence of TFAA with aliphatic aldehydes but afford ketones instead of the expected alkene⁷⁴ after elution through a silica gel column or exposure to aqueous acid. This surprising result was explained by a redox process in which TFAA acts as a hydride receptor (Scheme 52). Treatment with a good oxidant such as *N*-chlorosuccinimide also leads to the ketone in good yield. However, the unsubstituted $\text{Mes}_2\text{BCH}_2\text{Li}$ gives high yields of alkenes under the same conditions.^{74b}

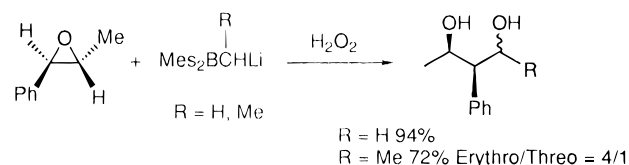
Scheme 52



If **21** ($R = \text{alkyl}$) is subjected to aliphatic aldehydes in the presence of acid instead of TFAA, the corresponding alkene is formed with no ketone.⁷⁵ In the presence of strong acids such as HCl or $\text{CF}_3\text{SO}_3\text{H}$, the products contain >90% of (*E*)-alkenes in all attended cases. (*Z*)-Alkenes may result predominantly^{75b} if acetic acid is used instead.

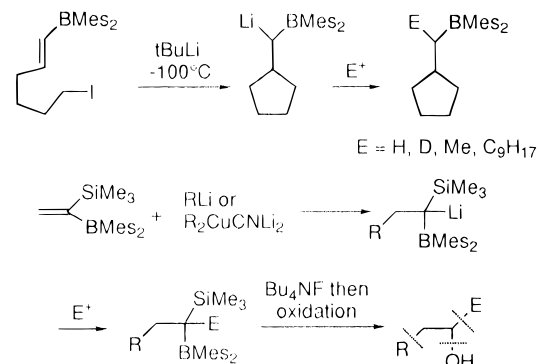
(Dimesitylborio)lithioalkanes also react with substituted oxiranes to give the corresponding products that can be oxidized to 1,3-diols.⁷⁶ The reactions are, in general, under steric rather than electronic control and proceed smoothly (Scheme 53).

Scheme 53



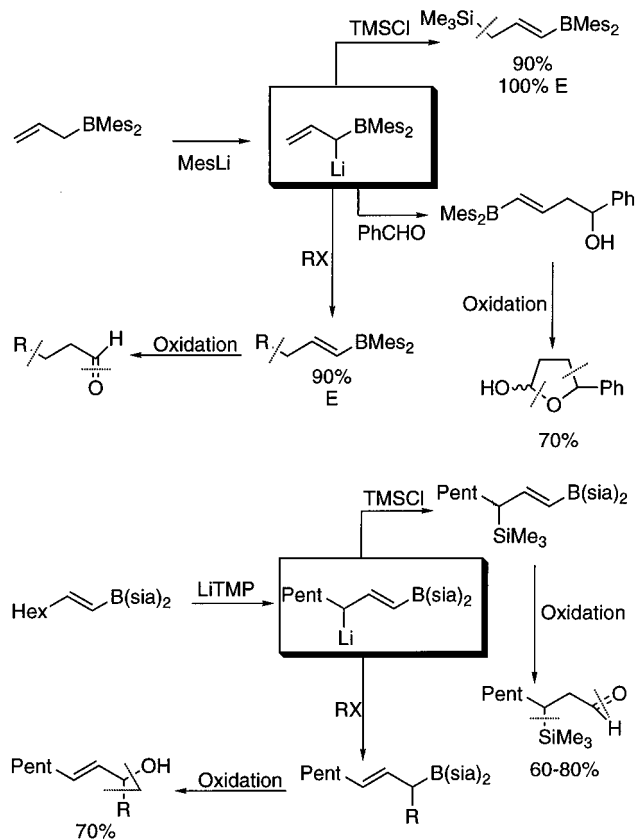
The suppression of ate complex formation by the use of dimesitylboron, allows possible boron-activated nucleophilic addition to olefins in an intramolecular or intermolecular fashion⁷⁷ (Scheme 54).

Scheme 54



Allyldimesitylborane⁷⁸ and 1-alkenyldisiamylborane⁷⁹ are deprotonated at the allylic position, resulting in allylic borolithioalkanes, which are attacked by electrophiles in a regio and stereospecific fashion (Scheme 55).

Scheme 55

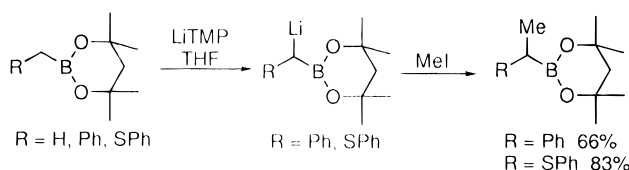


Thus, these anions possess the reactivity of an allylic metal, while maintaining the synthetic versatility associated with organoboron chemistry.

A very different strategy for the metalation α to boron involves the attachment of heteroatoms to boron which are capable of π -back-donation, that discourage ate complex formation.⁸⁰ Whereas 1,3-dimethylpentanediyl methylboronate ($R = \text{H}$) can not be deprotonated under classical conditions, 1,3-dimethylpentanediyl benzyl- and [(phenylthio)methyl]-

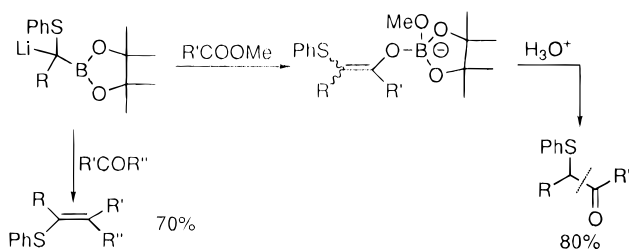
boronate ($R = \text{Ph, SPh}$) are readily deprotonated by LiTMP to form the corresponding borolithio compounds, which react with methyl iodide. In the former case, further oxidation yields 1-phenylethanol (Scheme 56).

Scheme 56



Acylation of the α -(phenylthio)borolithiomethane with methyl esters provides an efficient, regioselective general synthesis of α -(phenylthio) ketones⁸¹ (Scheme 57).

Scheme 57

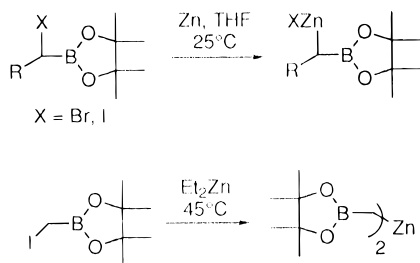


The same dimetallic reacts with aldehydes and ketones with elimination of boron to form ene thiol ethers in good yield⁸² (Scheme 57). Thus, 1,3-dimethylbutanediyli [(phenylthio)methyl] boronate, via its lithio derivative is a highly versatile connecting carbon for synthetic purposes. This reagent can react as a formyl anion equivalent, as a Wittig reagent, and also as a source of (trimethylsilyl)methyl ketones.⁸³ An alternative way for the preparation of these α -lithioboronic esters has also been described from α -(trimethylstannyl)boronic esters.⁸⁴

VI. 1,1-Borio-zincioalkane Reagents

The insertion of zinc dust into α -haloboronic esters proceeds smoothly to afford the $[\alpha$ -[(alkylenedioxy)boryl]alkyl]zinc halides,⁸⁵ whereas bis[(alkylenedioxy)boryl]methylzinc is obtained by the reaction of (iodomethyl)boronic ester with Et_2Zn ⁸⁶ (Scheme 58).

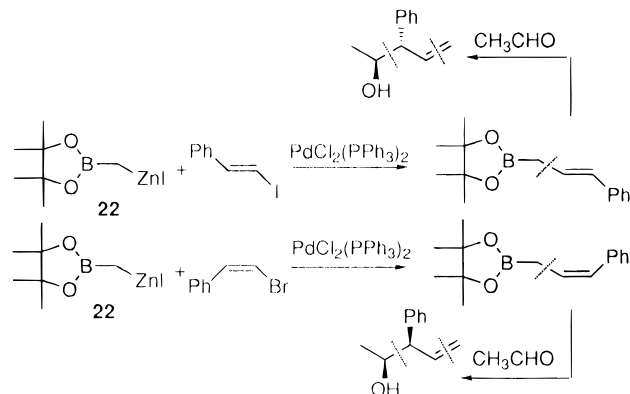
Scheme 58



The cross-coupling reaction of [(alkylenedioxy)methyl]zinc reagents (**22**, $R = \text{H}$) with (*E*)- or (*Z*)-1-halo-1-alkenes, under palladium catalysis, leads to the corresponding stereochemically pure allylboronic esters.⁸⁷ Sequential treatment with an excess of acetaldehyde provides the *threo* or *erythro* homo-

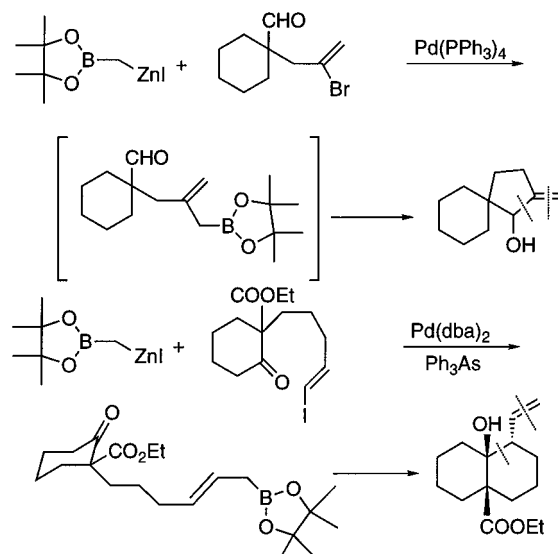
allylic alcohols in 61% and 57% yield respectively as described in Scheme 59.

Scheme 59



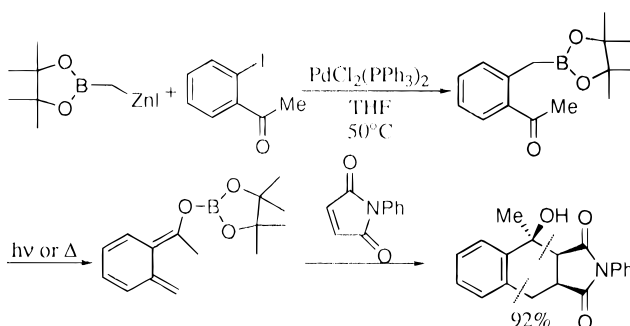
The potential versatility of this coupling reaction was illustrated by the application to intramolecular allylboration reactions^{87,88} (Scheme 60).

Scheme 60



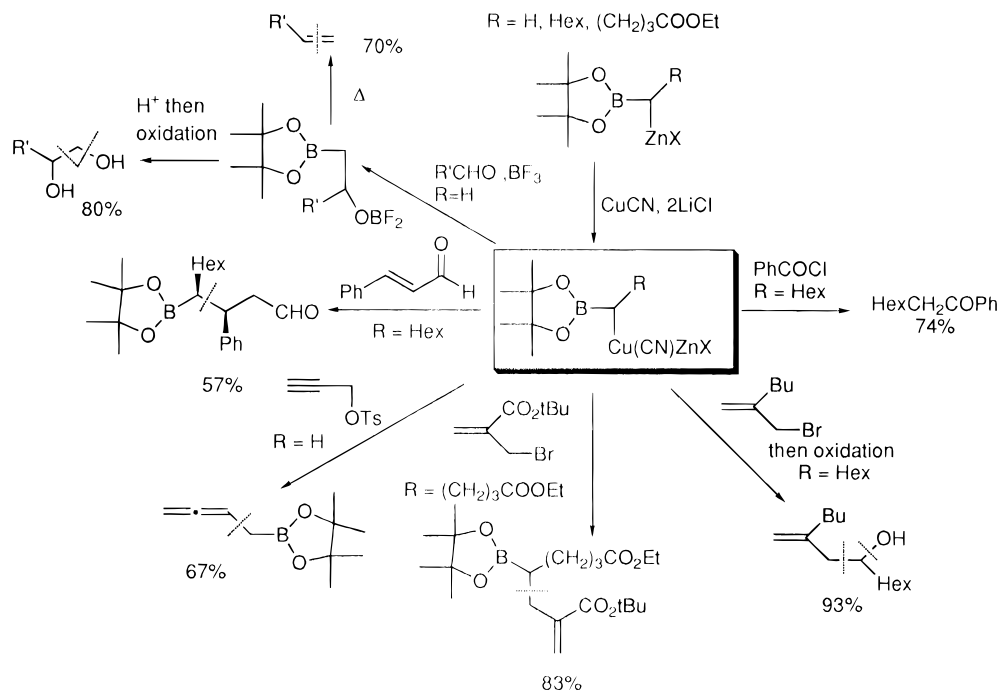
This cross-coupling with *o*-iodoacetophenone in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ affords benzylic boronates. Heating of the resulting mixture generates the *o*-quinodimethane which may be trapped *in situ* with different dienophiles⁸⁹ (Scheme 61).

Scheme 61



Addition of the THF-soluble copper salt $\text{CuCN} \cdot 2\text{LiCl}$ to the $[\alpha$ -[(alkylenedioxy)boryl]alkyl]zinc halides converts it to the more reactive copper deriva-

Scheme 62

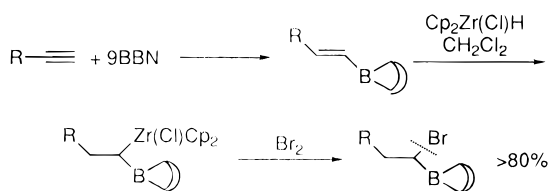


tive,^{85,90} which can react with a wide range of electrophiles in good yield (Scheme 62).

VII. 1,1-Borio-zirconioalkane Reagents

Hydrozirconation of various *B*-alkenylborabicyclo[3.3.1]nonanes (*B*-alkenyl-9-BBN) with Schwartz's reagent H(Cl)ZrCp₂⁹¹ proceeds smoothly to afford 1,1-dimetallics⁹² of boron and zirconium, which can react selectively with bromine to give the α-bromoboranes in high yields (Scheme 63).

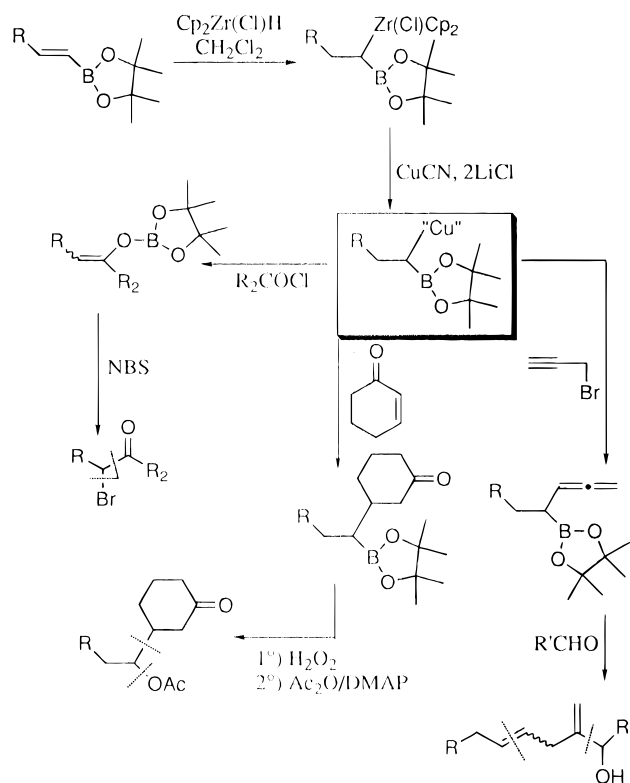
Scheme 63



Although this route offers an interesting method for the preparation of a new class of dimetallics, it suffers from the poor stability of these reagents which decompose fairly rapidly in CDCl₃. Hence, efforts to characterize and determine their structure have been unsuccessful. However, a new class of such dimetallic reagents have been prepared from boronic esters and zirconocene hydrochloride.⁹³ These boriozirconioalkenes were unambiguously characterized by ¹H-¹H double quantum filtered COSY NMR, ¹³C-¹H heteronuclear chemical shift correlation NMR spectroscopy⁹³ and X-ray analysis.⁹⁴ Once again, the zirconioboronic ester reacts with *N*-halosuccinimides to provide the corresponding α-haloboronic esters,⁹⁵ or it may be transmetalated into its organocopper reagent. The latter reagents can react either with propargyl bromide,⁹⁶ with a Michael acceptor in a 1,4-fashion,⁹⁷ or with acid chlorides,⁹⁸ leading to an enol

borate which can be trapped by addition of NBS to afford unsymmetrical α-bromo ketones (Scheme 64).

Scheme 64



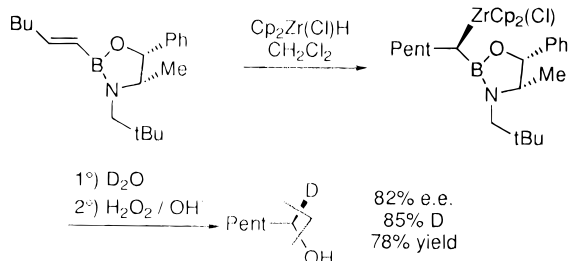
More recently, the stereoselective synthesis of racchokols A and G were described from these borazirconocene reagents.^{98b}

However, the hydrozirconation of substituted alkenylboronates leads to the migration of the boron⁹⁹ moiety.

The diastereoselective hydrozirconation of chiral vinylboranes provided optically active 1,1-dimetallics

and selective cleavage of the Zr–C bond with D₂O, followed by alkaline oxidation of the C–B bond afforded the optically active 1-deuterio primary alcohols¹⁰⁰ (Scheme 65).

Scheme 65

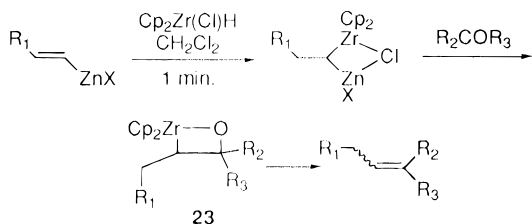


Thus, knowing that the cleavage of the carbon–boron¹⁰¹ and carbon–zirconium bond¹⁰² occurs with retention; the absolute configuration of optically active 1-deuterio-1-hexanol should correspond to the absolute configuration of the dimetallic.

VIII. 1,1-Zirconazincalkane Reagents

Hydrozirconation of alkenylzinc halides by Schwartz's reagent⁹¹ afforded the zinc and zirconium 1,1-dimetallic reagents, which are unstable and decompose after 10 min at 25 °C. However, once a carbonyl derivative is added immediately after their generation, an olefination reaction takes place to give the alkene in good yield¹⁰³ (Scheme 66).

Scheme 66

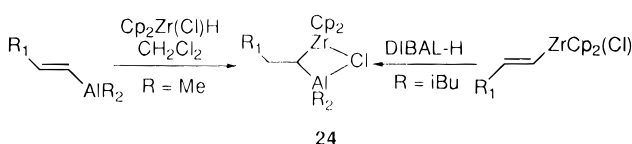


The hydrozirconation reaction displays a remarkable chemoselectivity, and functional groups such as a chloride, cyanide, or ester functionality are tolerated (R₁ = alkyl, (CH₂)₄Cl, (CH₂)₄CN, ester). Similar to the Wittig reaction, the first step of the reaction of the dimetallic with aldehydes involves the formation of a cyclic intermediate of type **23**, which then eliminates the zirconium moiety (Scheme 66). This elimination appears to be the rate determining step, since the aldehyde was consumed immediately after its addition.¹⁰⁴

IX. 1,1-Zirconioaluminioalkane Reagents

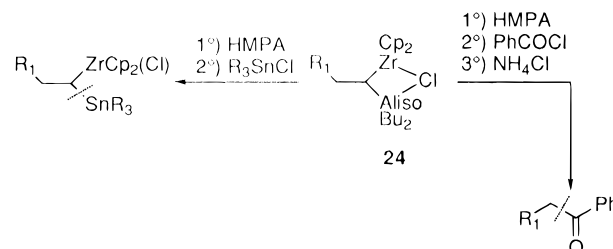
The hydroalumination of alkenylzirconium complexes or the hydrozirconation of the double bond of an alkenyl organoaluminum leads to a new dimetallic species^{103a,105} (Scheme 67).

Scheme 67



However, a Wittig-type reaction with this new reagent affords the olefin product in poor yield. Treatment of a solution of the zirconium–aluminum dimetallics **24** with 1 equiv of HCl results in the selective cleavage of the Zr–C bond, but coordination of a donor ligand such as HMPA to the Al atom of **24** (determined by low-temperature NMR analysis), followed by addition of 1 equiv of HCl results in specific cleavage of the C–Al bond to give Cp₂ZrR(Cl) and ClAl(*i*-Bu)₂(HMPA).¹⁰⁶ Ligand-based activation of the C–Al bond can also be used to initiate the reaction of **24** with benzoyl chloride in 25% yield, or with trialkyltin chloride¹⁰⁶ (Scheme 68).

Scheme 68

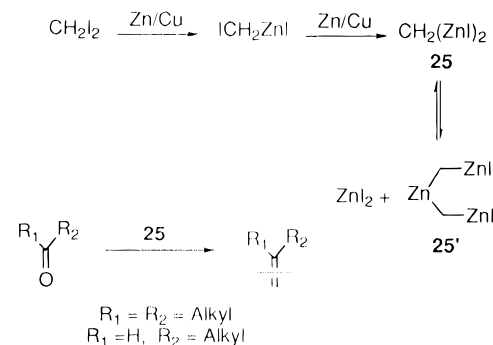


X. 1,1-Dizincio-, 1,1-Zincio-lithio-, 1,1-Zincio-magnesio-, and 1,1-Zincio-cuprioalkane Reagents

1. Synthesis via Zn⁰ Insertion

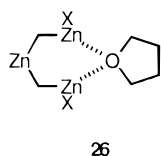
Zinc methylene–iodide complex obtained from zinc–copper couple and methylene–iodide react with olefinic double bonds to form cyclopropanes.¹⁰⁷ In contrast, in the presence of a large excess of zinc, another complex was formed.¹⁰⁸ The difference in the stoichiometry between the Simmons–Smith reagent¹⁰⁷ and this latter complex as well as the formation of methane measured by its alcoholysis are rationalized by the formation of an organo-*gem*-dizincio alkane¹⁰⁹ **25** (Scheme 69).

Scheme 69



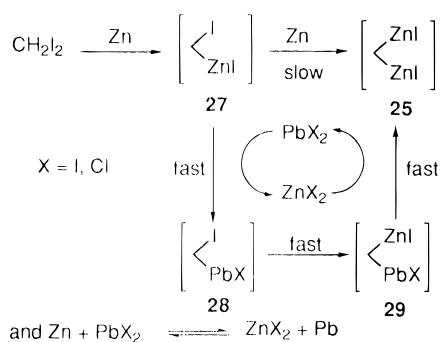
Olefination of aldehydes and ketones, even in the steroid cases by reagent **25**, is quite general.^{109b,110} However, in the absence of an excess of zinc metal, the aldehyde was recovered almost unchanged.¹¹¹ The separate preparation of the zinc–copper couple is not required; a mixture of zinc dust and cuprous chloride is also effective,¹¹² as well as the use of zinc metal, activated by formation of the lead–zinc couple. In the latter case, treatment of CH₂X₂ (X = Br, I) with

zinc–lead couple in THF leads to the methylenating agent **26** known as the Nysted reagent.¹¹³



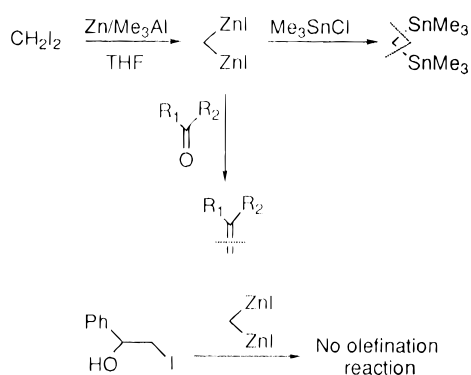
Compound **26** was used to convert ketosteroids to methylene derivatives in good yield. The tremendous catalytic effect of lead was recently investigated¹¹⁴ and explains the transformation of zinc carbenoid (ICH₂ZnI) to geminal dizinc compound CH₂(ZnI)₂ in the presence of zinc as described in Scheme 70.

Scheme 70



Transmetalation from the zinc carbenoid **27** with lead(II) produces lead carbenoid **28** which is readily reduced by zinc to give geminal lead–zinc compound **29**. Transmetalation from lead to zinc with zinc halide affords geminal dizinc compound **25** which is an excellent Wittig-type reagent.¹¹⁴ An analogous divalent species, known for the olefination reaction was also described by treatment of CH₂I₂ with Zn and Me₃Al¹¹⁵ (Scheme 71).

Scheme 71



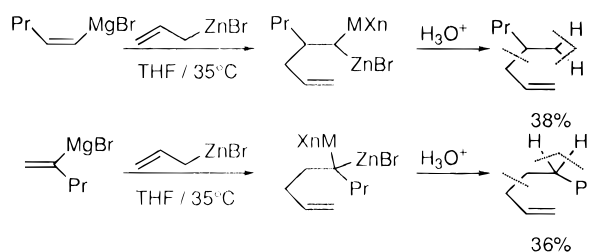
Although the role of Me₃Al is still not clear, the *gem*-dimetallic nature of the reagent has been further confirmed by the fact that preformed iodohydrin was practically unchanged after treatment with the reagent prepared as above.

2. Synthesis via Allylmatalation Reaction

In 1971, an elegant alternative for the synthesis of organo-*gem*-dimetallic has been found by Gaudemar¹¹⁶ who reported that the addition of allylzinc

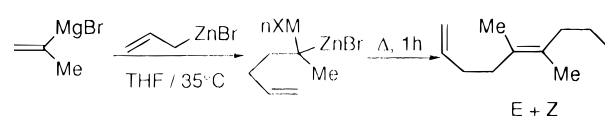
bromide on substituted vinyl Grignard reagents leads to the organo-*gem*-dimetallic species (Scheme 72).

Scheme 72

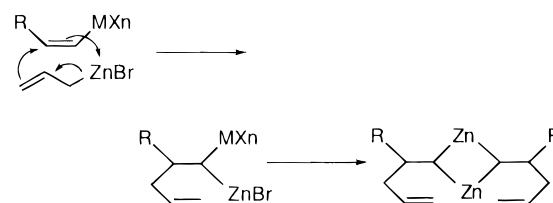


The latter, heated at reflux for 1 h, leads to the triene^{116c} (Scheme 73).

Scheme 73



Although these organometallic compounds were obtained in moderate chemical yields, this reaction allows an easy approach to the synthesis of *gem*-dimetallic reagents via the carbometalation reaction. Some years later, it was found that a wide range of 1,1-dimetallic compounds were available in high yields¹¹⁷ by carbometalation of alkenyl organometallics by allylic zinc bromide using reaction conditions similar to those described by Gaudemar.¹¹⁶ Although the exact mechanism of this reaction is still under study, different hypotheses have been taken into consideration. The addition of an allylic zinc bromide to a vinyl lithium or magnesium reagent leads to the *gem*-dimetallic by a carbometalation process, via a transition state corresponding to a zinca-ene reaction.¹¹⁸ It seems plausible that, especially in the case of MXn = Li, the coexistence of an organolithium with an organozinc bromide on the same carbon atom should lead to a dizincacyclobutane¹¹⁹ by a dimerization process¹²⁰ as described in the following equation.

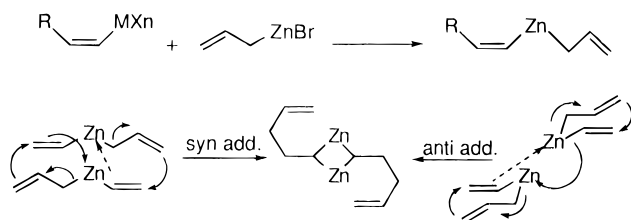


Instead of this suprafacial addition, one should also consider a possible *anti*-allylzincation of the vinyl metal, which recalls the *anti*-allylmagnesiumation of allylic alcohols as described by Felkin *et al.*¹²¹



But a preliminary formation of a mixed vinyl–allyl zinc derivative can also be considered, undergoing a

rearrangement akin to the Claisen rearrangement where zinc plays the role of oxygen.^{120,122}

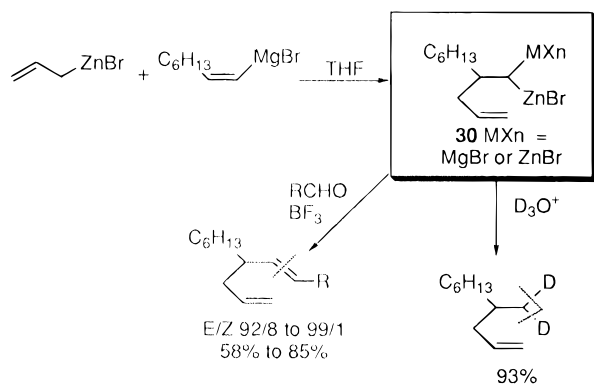


Various metals may be used on the vinylic part as $\text{MX}_n = \text{Li}, \text{Mg}, \text{B}, \text{Al}, \text{Cu}$ but the presence of zinc (or cadmium) is compulsory for the addition to proceed.¹²²

A. Reactivity

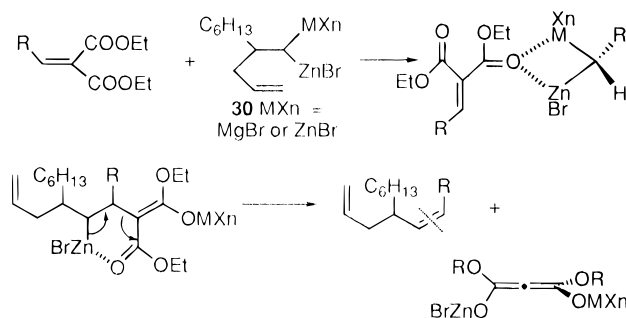
Treatment of the dimetallic compounds with D_3O^+ / D_2O or with aldehydes in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gives the corresponding 1,1-dideuterated alkenes (100% D) and olefinated product in good chemical yield¹¹⁷ (Scheme 74).

Scheme 74



The reaction shows a good chemoselectivity since ketones do not react. (*Z*-Olefins were also obtained with very high stereoselectivity by reaction of the organo-*gem*-dimetallics with alkylidenemalonates instead of aldehydes¹²³ (Scheme 75).

Scheme 75

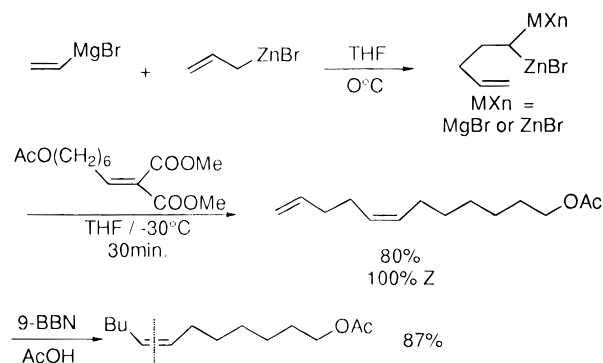


Thus, the reaction of alkylidenemalonates with 1,1-dimetallic reagents produces, very smoothly in 1 h at -20°C , the corresponding (*Z*)-olefins. A complexation of the dimetallic **30** with the least sterically hindered ethoxycarbonyl group may be responsible both for the rapid addition to the alkylidenemalonate and for the stereoselectivity observed¹²³ (Scheme 75).

Although a general trend was observed for the predominance of the *Z* isomer (*E/Z* = 20/80), a strong

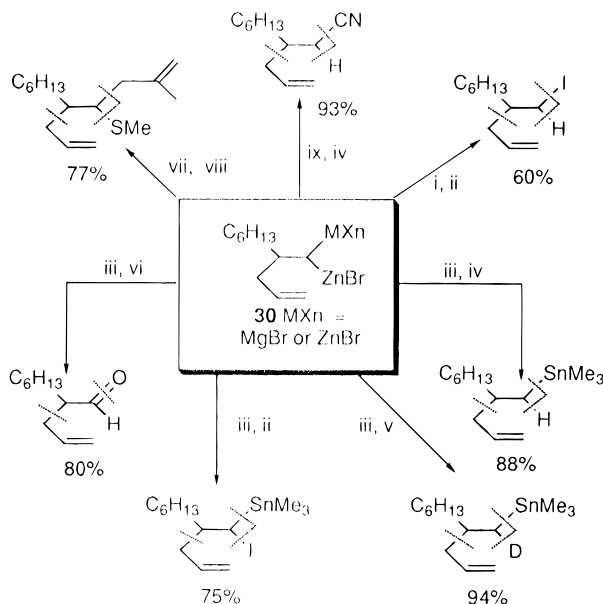
dependence upon the nature of the substituents R and of the ester alkyl group was observed. So, the *cis* stereoselectivity can be enhanced by increasing the size of the alkoxy group of the alkylidenemalonates. The use of dimethyl alkylidenemalonates provides the desired olefin with a *Z* stereoselectivity greater than 92%. As an application of this method, the synthesis of the cabbage looper moth pheromone (Scheme 76) was described in two steps from commercially available starting materials¹²³ in 70% overall yield.

Scheme 76



The different nature of the two metals present in compound **30**, or their different stereotopicity, can be used to make successively two new bonds^{124,125} (Scheme 77).

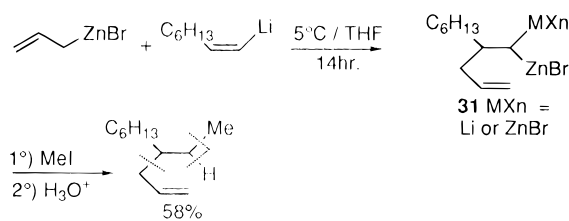
Scheme 77^a



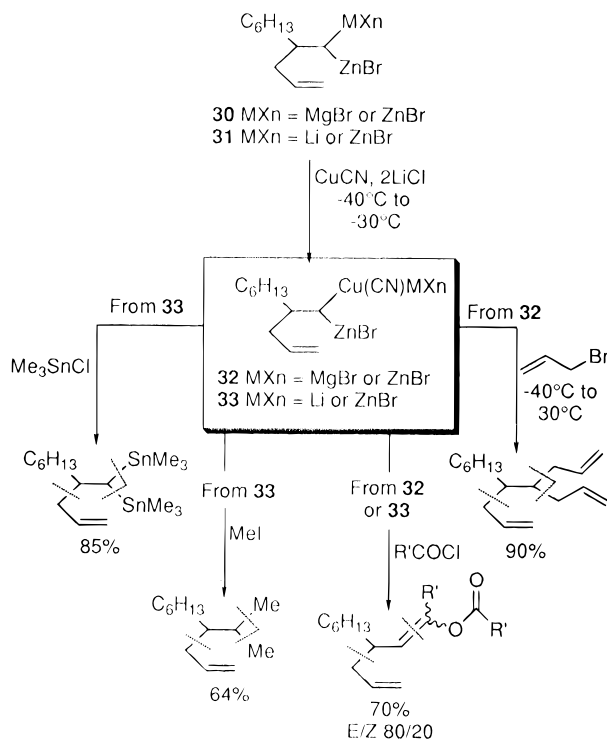
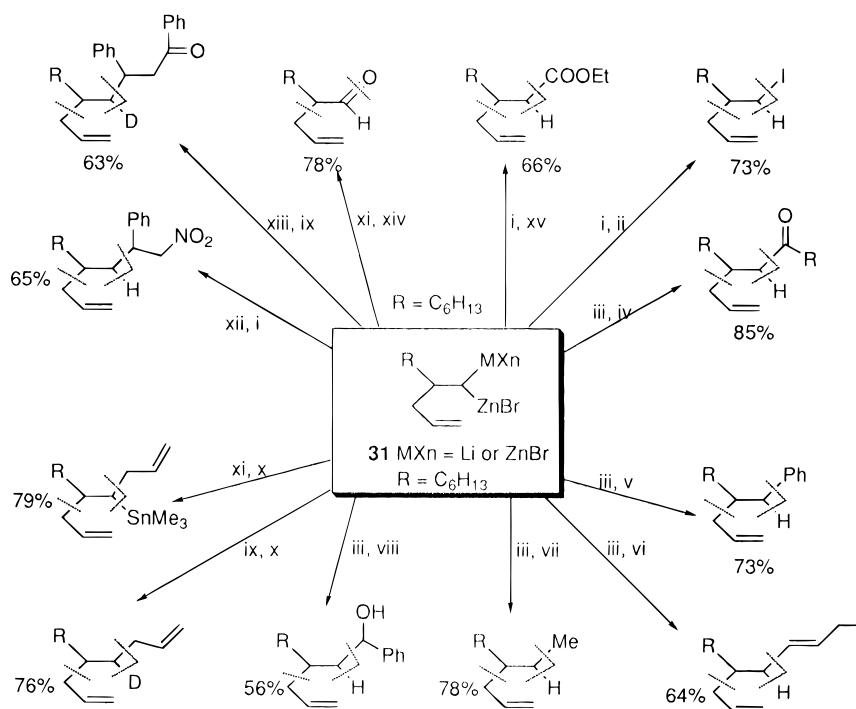
^a Reagents: (i) AcOH (1 equiv), 15 min; (ii) I_2 (1 equiv); (iii) Me_3SnCl (1 equiv); 45 min -25°C to -5°C ; (iv) H_3O^+ , -5°C to room temperature; (v) D_3O^+ , -5°C to room temperature; (vi) O_2 , TMSCl; (vii) MeSSMe; (viii) 5.5 equiv of methallyl bromide; (ix) TosCN.

The dimetallic **30** (considered as a d^1/d^1 multicoupling reagent¹²⁶) is then able to react selectively with two different electrophiles to give the corresponding product. Although **30** does not react with methyl iodide under various reaction conditions, the dimetallic **31** (Scheme 78) obtained from allylzincation of vinyl lithium, furnishes the monomethylated alkene¹²⁴ in 58% yield.

Scheme 78



Scheme 79

Scheme 80^a

^a Reaction conditions: (i) MeOH; (ii) I₂; (iii) *sec*-BuOH; (iv) RCOCl, 5% Pd(PPh₃)₄; (v) PhI, 5% Pd(PPh₃)₄; (vi) (*E*)-iodo-1-butene 5% Pd(PPh₃)₄; (vii) CuI then MeI; (viii) TiCl(O-*i*-Pr)₃ then PhCHO; (ix) MeOD; (x) CuCN then allyl bromide; (xi) Me₃SnCl; (xii) nitrostyrene; (xiii) benzal acetophenone; (xiv) O₂, TMSCl; (xv) ClCOOEt, 5% Pd(PPh₃)₄.

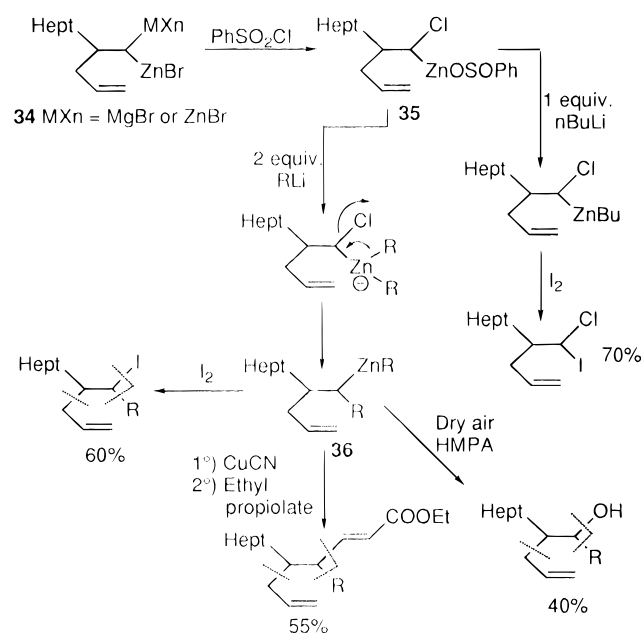
The reactivity of **30** and **31** can be increased toward alkylating or allylating electrophiles by a transmetalation reaction with copper cyanide into the corresponding 1,1-zinca cyanocuprates **32** and **33**. Addition of an excess of allyl bromide to **32** or methyl iodide to **33** leads to the corresponding bis-allylated or bis-methylated product in 90% and 64% yield¹²⁷ (Scheme 79).

The dimetallic species **32** or **33** react first with the electrophile to give the monoalkylated or allylated derivatives which, by a second transmetalation step with the same copper cyanide, furnish a new cyanocuprate derivatives which again react with the electrophiles leading to the corresponding bis-alkylated product.

The dimetallic compounds **32** and **33** react as well with acyl chlorides to give, as a mixture of stereoisomers the enol acylates in fair yields (Scheme 79). Moreover, the organo-*gem*-dimetallic **31** is more reactive than **30** toward electrophiles. So, this former derivative can be selectively monoprotonated, deuterated, stannylated, or alkylated, leading to highly functionalized secondary organozinc halides which can react with a second electrophile,¹²⁸ with or without a transmetalation step as described in Scheme 80.

Since the monoalkylation of the organo-*gem*-dimetallics **32** and **33** is, until now, impossible (the second step is competitive with the first one), a selective monoalkylation of organo-*gem*-dimetallics via an intramolecular nucleophilic substitution was recently described¹²⁹ (Scheme 81). In the case of the organo-*gem*-dimetallic **34**, the reaction with neat PhSO₂Cl at -80 °C gives the α-chlorozinc carbenoid **35**, which is stable below -60 °C in ether solution, or below -20 °C after adding THF. Addition of 1 equiv of *n*-BuLi

Scheme 81



followed by quenching with iodine leads to the expected α -chloro-iodo compound in 70% yield, but the addition of 2 equiv of alkyl lithium to the chloro carbenoid **35**, gives the α -chloro-triorganozincate which undergoes an 1,2-metalate rearrangement. The resulting organometallic **36** could react with iodine to give the secondary iodide in 60% yield, or could be oxidized by a slow absorption of dry air to give the secondary alcohol.¹³⁰

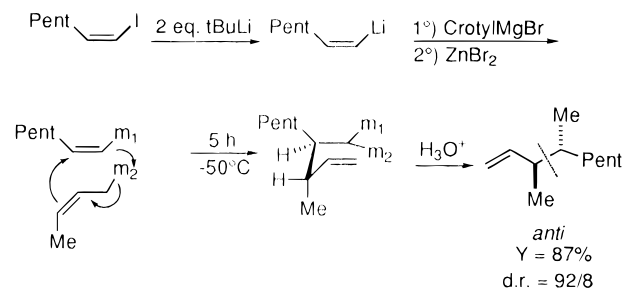
The scope of the intramolecular nucleophilic rearrangement is quite broad; primary, secondary and tertiary alkyl lithium reagents participate in this reaction as well as organomagnesium halides. Instead of quenching **36** with iodine, a transmetalation step from Zn to Cu increases the reactivity of the resulting organometallic¹²⁴ and the latter can react with ethyl propionate to yield the corresponding α,β -unsaturated ester¹²⁹ (Scheme 81). So, the monoalkylation of such organo-*gem*-dimetallics was realized by transforming a nucleophilic organometallic species into another one via an electrophilic carbenoid and thus, three carbon-carbon bonds were selectively created in a single-pot operation.

B. Diastereoselectivity

If we consider the carbometalation transition state, the addition of substituted allylic systems with a stereochemically pure alkenyl metal can generate at least three products according to the metallotropic rearrangements of the substituted allylic system.¹²⁰ Preliminary experiments were carried out by addition of 2-butenylzinc bromide to the pure 2-heptenyl lithium in THF,¹³¹ leading after hydrolysis to the alkene as a mixture of two diastereomers in a 1:1 ratio. This diastereoselection was improved by replacement of the 2-butenylzinc bromide by the 2-octenylzinc bromide.¹³² Since then, it was observed that the diastereoselection is highly dependent on the temperature and on the nature of the solvent. Thus, decreasing the Lewis basicity of the solvent, by switching from THF to ether, considerably speeds up the reaction and allows the addition to be carried out

at much lower temperatures. Under these conditions, crotylzinc bromide leads to a very high diastereoselection at -50°C within 5 h (Scheme 82).

Scheme 82

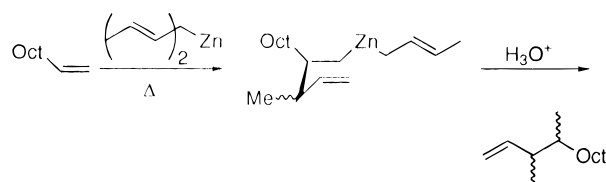


The (*Z*)-alkenyllithium reacts with crotylmagnesium bromide and zinc dibromide in ether to give the stable 1,1-dimetallic species via the postulated transition state involving a zinca-ene reaction. After acidic hydrolysis, *anti*-3(*S*^{*}),4(*R*^{*})-dimethylnon-1-ene was obtained in 87% yield with a diastereoselection of 92/8¹³³ (Scheme 82).

The high diastereoselectivity observed in the crotylmetalation of vinyl metals may be accounted for by a preferential or kinetically favored *Z* configuration of the crotylmetal species, if we consider a chair-like transition state.¹²⁰ The tremendous effect observed when using a metalated vinyl moiety (Scheme 82) instead of a mere alkene for the allylmetalation reaction is pointed out by comparison with the allylzincation of 1-octene at 50°C for 66–96 h as described by Lehmkuhl et al.¹³⁴ where 1-octene is the solvent.

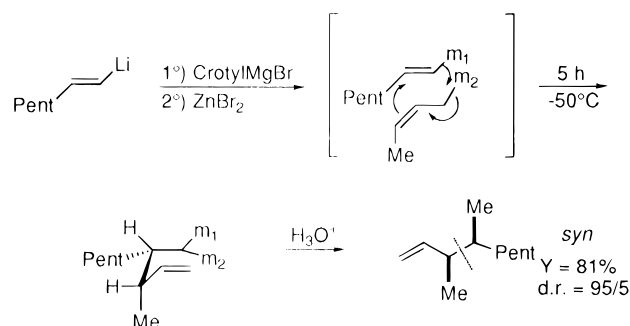
So, via the organo-*gem*-dimetallic pathway, the same product is obtained with better diastereoselectivity and chemical yield (which can be interpreted in terms of a good ability for zinc to bridge carbon atoms), and under milder conditions (-50°C in Scheme 82 instead $+50^\circ\text{C}$ in Scheme 83).

Scheme 83



The other diastereomer *syn*-3(*S*^{*}),4(*S*^{*})-dimethylnon-1-ene is obtained with a high diastereomeric purity, only by changing the stereochemistry of the starting vinyl lithium¹²⁰ (Scheme 84).

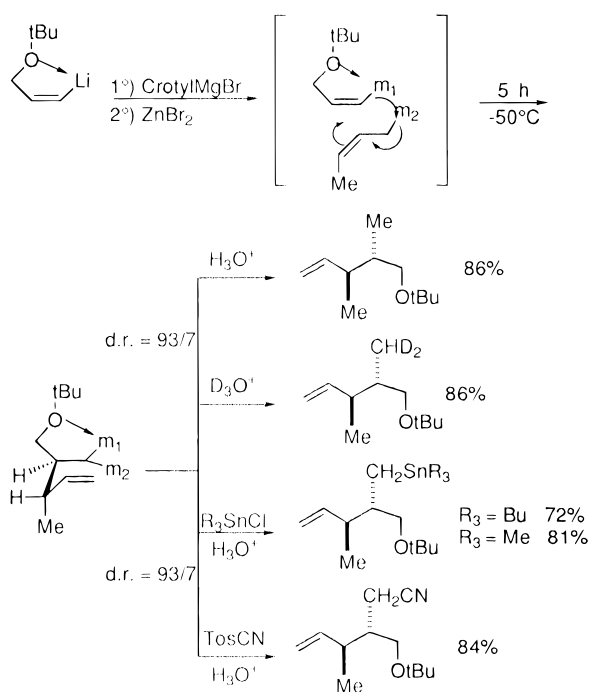
Scheme 84



As described above, decreasing the Lewis basicity of the solvent allows the crotylmetalation to proceed at lower temperatures and then with a better diastereoselection. So, the case of functionalized vinyl-lithiums was investigated in order to determine if a stronger intramolecular chelation of the zinc atom would still be favorable (if we consider the detrimental effect of THF as compared to ether).

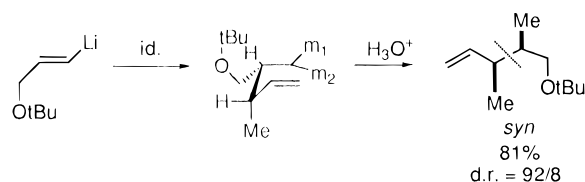
In spite of the chelation of the zinc atom by the *tert*-butoxy¹²⁰ or by the methoxy methyl group,¹³⁵ these substrates undergo the crotylmetalation at low temperature and with a high diastereoselectivity. The formation of the *gem*-dimetallic species has been proved by quenching the intermediate with various electrophiles as described in Scheme 85.

Scheme 85



The preparation of the corresponding (*E*)-vinyl-lithium leads, according to the same procedure, to the *syn* diastereomer (Scheme 86).

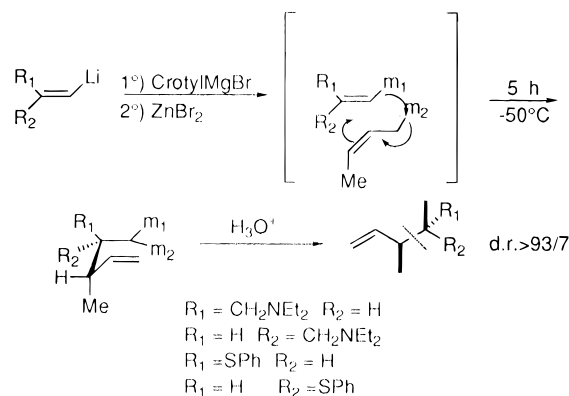
Scheme 86



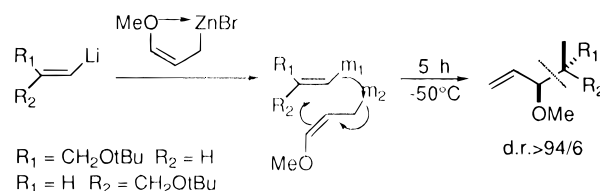
This methodology has been generalized to various functionalized molecules: (γ -amino-2-propenyl)- and [β -(alkylthio)vinyl]metals react diastereoselectively with crotylzinc bromide¹³⁶ (Scheme 87).

An allylzinc bromide bearing an alkoxy group can also be used; for example¹³² if one starts from the metalated allyl methyl ether and reacts it¹²⁰ with an *E* or *Z* functionalized vinyl lithium, the two diastereomers are selectively obtained (Scheme 88).

Scheme 87

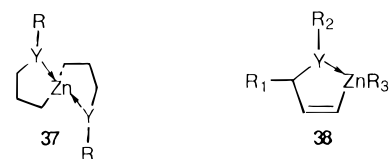


Scheme 88



The *syn* or *anti* product is obtained diastereoselectively in spite of the presence of heteroatoms. By this way, from two prochiral carbon atoms, two stereogenic centers were created with good diastereoselectivity.

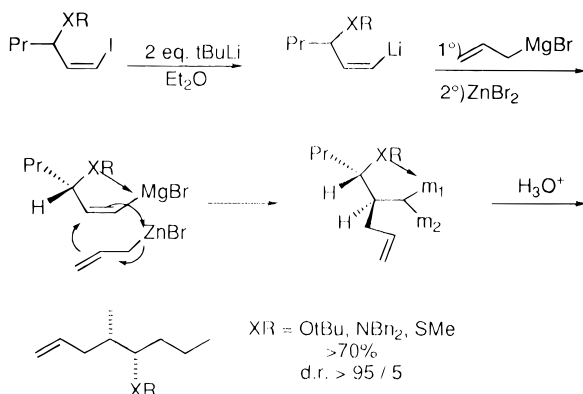
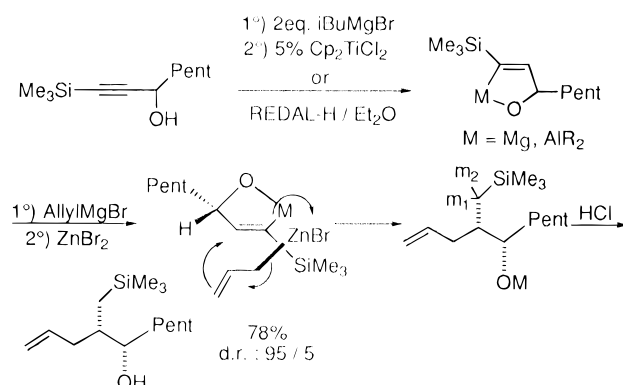
Knowing that the chelation between zinc and heteroatoms in ω -hetero-substituted dialkylzinc reagents has already been shown by NMR studies, the allylzincation of substituted γ -hetero-substituted vinyl metals was studied. Van der Kerk¹³⁷ established that dialkylzinc reagents **37** bearing heteroatoms at the γ position, such as Zn[(CH₂)₃ZR]₂ with Z = N, O, S are chelated, are monomeric in benzene solution, and display a spirostructure with nitrogen coordinating better than oxygen, and oxygen better than sulfur. If so, then the presence of a double bond in derivative **38** should increase this chelation, which will promote a difference between the two prochiral faces of the vinyl zinc moiety since one is shielded by the alkyl group.



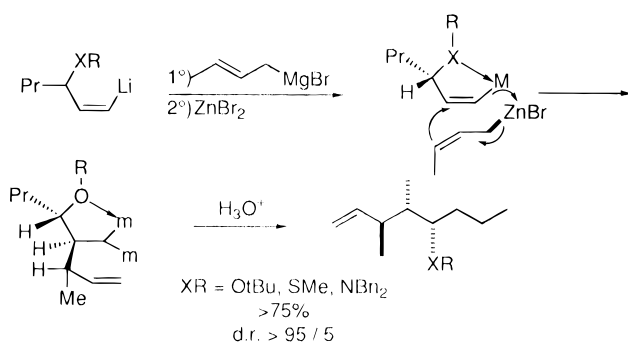
This hypothesis has been verified by using (*Z*)- γ -iodoallylic ethers,¹³⁸ amines,¹³⁶ and thio ethers,¹³⁶ easily accessible from a propargylic ether¹³⁹ or ethyl propiolate¹⁴⁰ as described in Scheme 89, as starting materials.

In each case, the heteroatom chelates the vinyl metal to form a rigid five-membered ring, and the allyl moiety approaches the vinyl part with a diastereofacial selectivity *anti* to the alkyl group.¹⁴¹

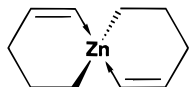
The same selectivity was obtained when the γ -trimethylsilyl propargylic alcohol was used directly as the starting material in a one-pot reaction¹³⁸ (Scheme 90).

Scheme 89**Scheme 90**

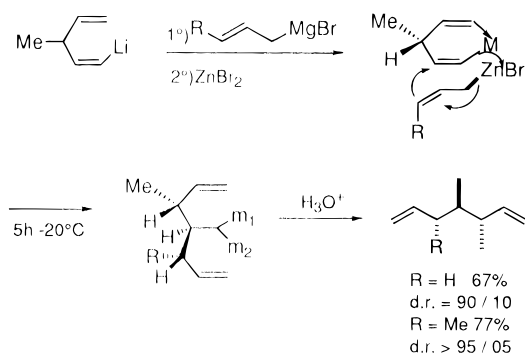
If this facial selectivity is combined with the selectivity arising from the use of a substituted allylzinc bromide, two new stereogenic centers are created out of a single starting one^{142,136} (Scheme 91).

Scheme 91

The chelation between zinc and heteroatoms allows a diastereoselective allyl or crotylzincation of secondary γ -hetero substituted vinyl metals. However, the intramolecular interactions between the metal center and a olefinic site was also described in the case of di-4-pentenylzinc.¹⁴³ This weak dipolar chelation is the result of the inherent polarity of the $\text{Zn}^{+\delta}-\text{C}^{-\delta}$ bond and the polarity of the double bond (partial negative charge on the terminal carbon). Such interactions were evidenced by NMR investigations and the spirostructure of di-4-pentenyl-zinc was postulated to interpret this phenomenon.

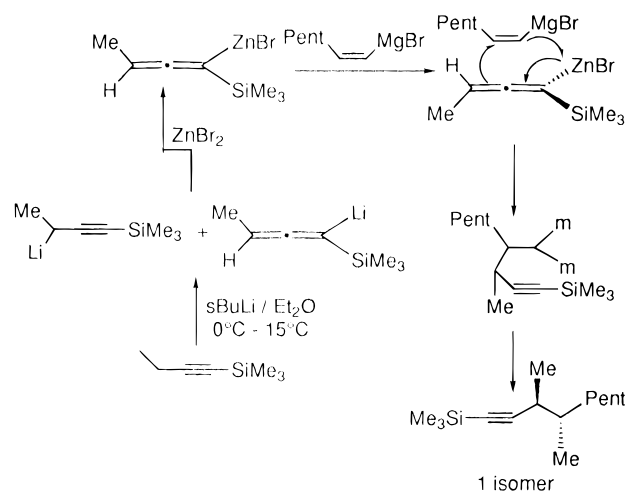


The oxygen chelation described in Scheme 89 is now replaced by a π -chelation between a vinyl organozinc and a ω -olefinic residue. Thus, treatment of 1-lithio-3-methyl-1,4-pentadiene by allylzinc bromide or crotylzinc bromide (Scheme 92) leads to the corresponding stereochemically substituted dienes with a good diastereoselectivity.¹⁴⁴

Scheme 92

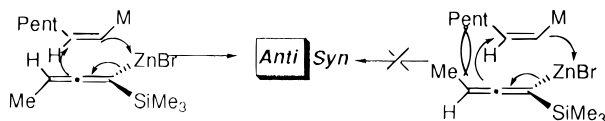
In these cases, the terminal vinyl moiety chelates the zinc atom to form a rigid five-membered ring complex and the allyl or crotyl reagent approaches the vinylzinc moiety *anti* to the methyl group (when the vinyl group is replaced by an ethyl group, two diastereomers are obtained in equal amount).¹⁴⁴

The carbometalation of vinylmetals can be also applied to the addition of substituted propargylzinc bromides¹³⁶ (Scheme 93).

Scheme 93

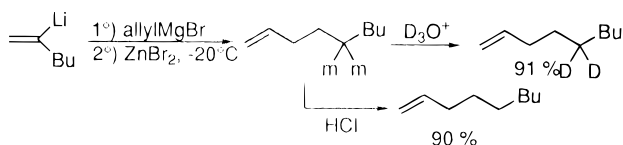
The addition of zinc salts to a propargyl/allenyl organolithium reagent leads quantitatively to the allenylzinc bromide,¹⁴⁵ and considering that this latter reacts with the vinyl metal moiety via a $\text{S}_{\text{E}}2'$ process,¹⁴⁶ the stereochemical result is explained by a minimum steric interaction between the methyl group located on an sp^2 carbon atom of the allenic system and the prochiral carbon atom of the vinyl metal moiety. The other transition state, leading to the *syn* isomer, is highly disfavored by the repulsion between the two alkyl groups¹³⁶ as described in Scheme 94.

The same diastereomer is obtained from the (*E*)-vinyl Grignard reagent,¹³⁶ and the scope of the reaction is quite broad: the use of functionalized

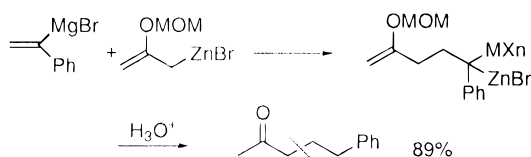
Scheme 94

vinyl metals as well as the introduction of an alkyl group (different from the methyl group) on the allenyl zinc bromide were shown to be possible without altering the diastereoselectivity.¹³⁶

The synthesis of disubstituted organo-*gem*-dimetallic was also described by reaction of an ethereal solution of 1-hexen-2-yl lithium and allylmagnesium bromide in the presence of zinc bromide¹⁴⁷ (Scheme 95).

Scheme 95

These organometallics are stable at $-20\text{ }^{\circ}\text{C}$, as evidenced by the fact that quenching of the reaction mixture with HCl or DCl afforded respectively the hydrogenated or deuterioalkenes in good yield. The same trend is also observed when starting from an α -styryllithium or -magnesium reagent.¹⁴⁸ Of special interest is the addition of a functionalized allylic zinc reagent such as [2-(methoxymethoxy)-2-propenyl]zinc bromide, since it allows a formal regiospecific addition of an acetyl moiety across styrene¹⁴⁸ (Scheme 96).

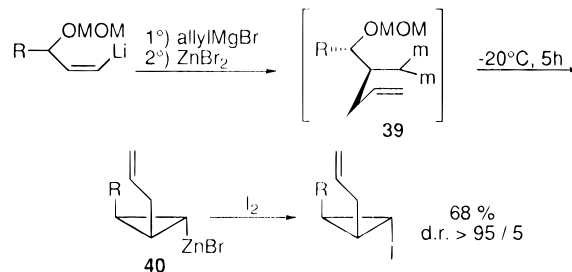
Scheme 96

However, such addition to β -substituted α -styryl-magnesium bromides like (1-phenyl-1-pentenyl)magnesium bromide does not proceed in THF even under forcing conditions.

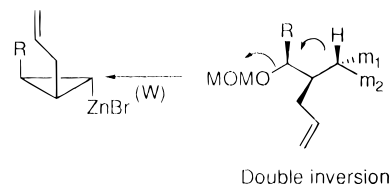
C. Diastereoselective Reactivity of the Organo-*gem*-dimetallics

a. Intramolecular Electrophile. As seen above, the addition of substituted allyl zinc bromides to γ -hetero-substituted vinyl metals ($\text{XR} = \text{O}-t\text{-Bu}$, NR_2 , SR) allows the creation of stereogenic centers (see Scheme 89). However, if the chelating moiety is a methoxy-methyl ether (MOM group) the formed dimetallic species is not stabilized but becomes thermally labile. Warming the mixture to room temperature promotes an internal nucleophilic substitution, leading to a metalated cyclopropane which can react with different electrophiles. This cyclization reaction corresponds to the reaction of the organo-*gem*-dimetallic with an intramolecular electrophile (the MOM group) followed eventually by the reaction of the configurationally stable cyclopropyl-

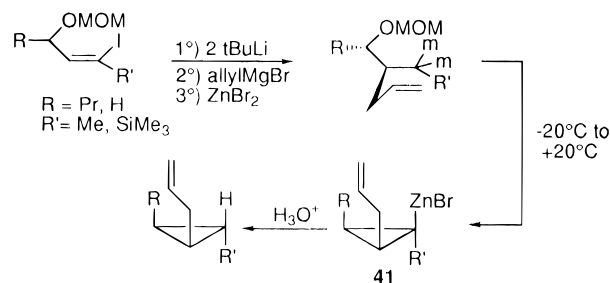
zinc bromide, thus formed, with an external electrophile¹⁴⁹ (Scheme 97).

Scheme 97

Since the alkyl and allyl groups in **39** were *anti* to each other and *syn* in the metalated cyclopropane **40**, this stereochemical outcome clearly shows that the internal nucleophilic substitution of the MOM group by one of the C–M bonds occurs with inversion of configuration at the electrophilic center, but also means that the chelation has to be broken for the reaction to proceed (Scheme 97). In order to explain the relative configuration of the metalated carbon, the mechanism involving an inversion–inversion (at both centers) in a W-shaped conformer was postulated¹⁵⁰ (Scheme 98).

Scheme 98

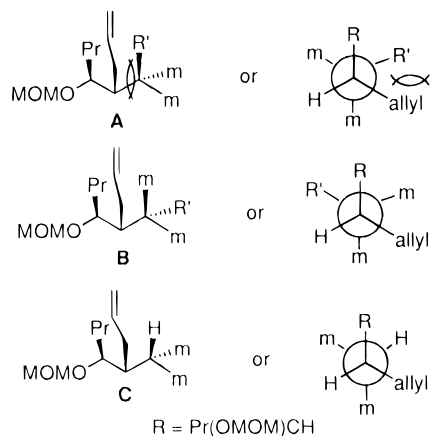
The diastereoselective synthesis of a tetrasubstituted zinccyclopropane can also be achieved according to the same procedure¹⁵⁰ (Scheme 99).

Scheme 99

In these cases, the resulting organozinc halide **41** displays a metal *syn* to the allyl and R groups, whereas in Scheme 97, the organometallic moiety was *trans* to the latter groups. In the W-shaped transition state **A** (Scheme 100), a gauche interaction exists between R' and the allyl moiety which is released when turning from **A** to **B**, whereas such hindrance was absent in the nonsubstituted (R' = H) case¹⁵⁰ **C**. Therefore, the trimethylsilyl or methyl groups R' are bulkier than the metal.

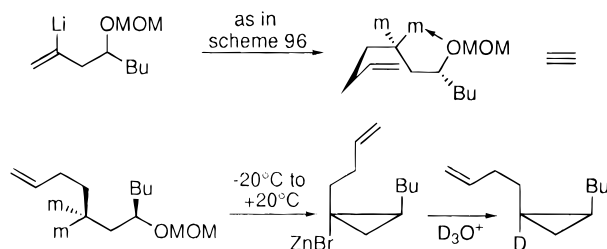
An alternative strategy to prepare tertiary cyclopropyl zinc derivatives is to start from *n,n*-organo-*gem*-dimetallic reagents, as already described in Scheme 95 and bearing an OMOM group β to the metalated carbon. When the latter reagent is submit-

Scheme 100



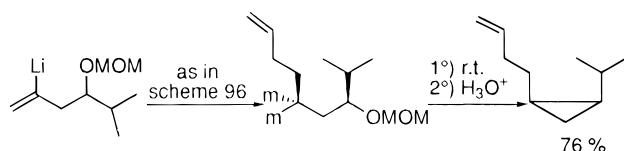
ted to the cyclopropanation reaction, by raising the temperature from $-20\text{ }^{\circ}\text{C}$ to $+20\text{ }^{\circ}\text{C}$, a single *syn* diastereomer is formed¹⁴⁷ (Scheme 101).

Scheme 101



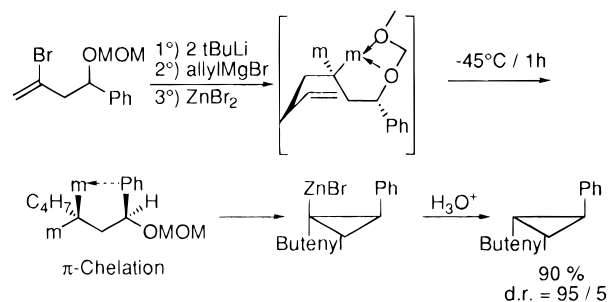
The tertiary cyclopropyl zinc halide can be also transmetalated to copper and then reacted with ethyl propiolate, allyl iodide, or an amino ether to give the corresponding functionalized cyclopropanes as a single diastereomer (one-pot creation of three carbon-carbon bonds).¹⁴⁷ The *syn* stereochemistry between the butenyl and butyl residues is explained by the W-shaped transition state. Then, in this case, the 1,3 steric interaction has no effect on the stereochemical outcome of this cyclization. The same trend is observed even with a bulkier group such as isopropyl instead of *n*-Butyl¹⁵⁰ (Scheme 102).

Scheme 102



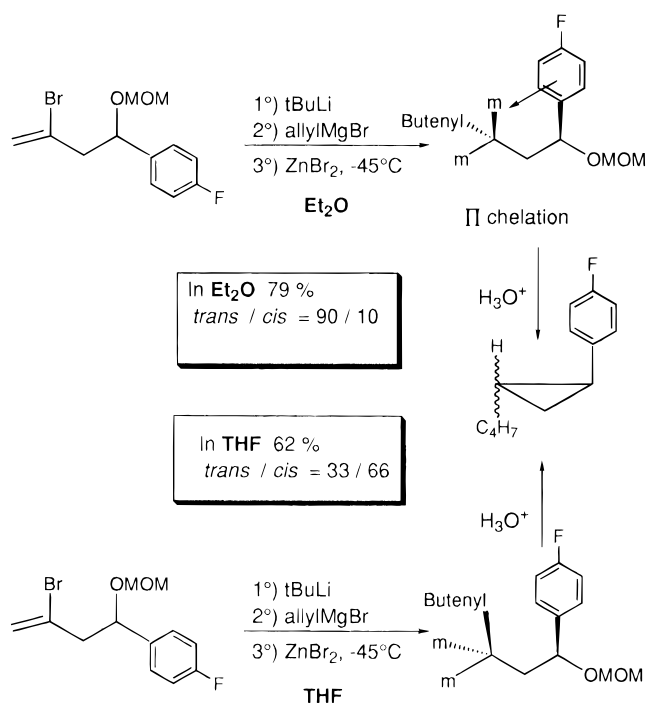
However, changing the alkyl group to a phenyl group also changes the stereochemical outcome of the cyclization reactions. Although the carbometalation is performed at lower temperatures, the organo-*gem*-dimetallic reagent cyclizes immediately to lead, after hydrolysis, to the *anti*-cyclopropane with a diastereomeric ratio of 95/5. This unexpected result led the authors¹⁵⁰ to consider a π -chelation between one metal and the phenyl group¹⁴³ (as already described in Scheme 92) in the W-shaped transition state (Scheme 103).

Scheme 103



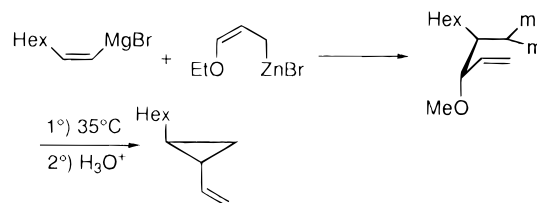
This holds true if the phenyl group is replaced by a vinyl group, whereas replacement of the phenyl by a pentafluoro phenyl group (less prone to π -chelate the metal), lowers the selectivity, and a 1/1 mixture of *cis* and *trans* isomers are then obtained. Also, use of a polar solvent (THF instead of ether) hampers this chelation¹⁵⁰ as shown in Scheme 104.

Scheme 104



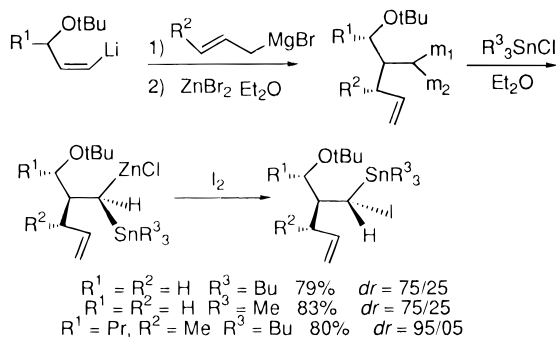
An alternative approach to 1-alkyl-2-vinylcyclopropanes from the cyclization of organo-*gem*-dimetallics has also been described.^{128b} Thus, the addition of (3-ethoxyallyl)zinc bromide to a vinyl Grignard reagent gives the organo-*gem*-dimetallic which undergoes a 1,3 elimination and leads after hydrolysis, to the corresponding cyclopropane (Scheme 105).

Scheme 105



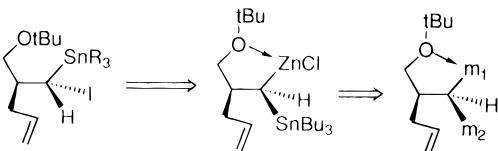
b. Intermolecular Electrophiles. The chelated organo-*gem*-dimetallics react with 1 equiv of R_3SnCl to give the $[\alpha$ -(trialkylstannyl)alkyl]zinc chlorides and then with 1 equiv of iodine to give the corresponding (α -iodoalkyl)trialkylstannanes with a fair to good diastereoselectivity and good chemical yield¹⁵¹ (Scheme 106).

Scheme 106



These results indicate clearly that the 1,1-dianions can react diastereoselectively with two different electrophiles to afford the functionalized α -iodo stannanes with one more asymmetric center. The relative configuration of this new asymmetric center was determined by chemical correlation and led the authors to consider that the intermediate α -stannylated organozinc halide¹⁵² is the contrathermodynamic product (trialkyltin *syn* to the allyl moiety in the chelated organometallic as described in Scheme 107).

Scheme 107

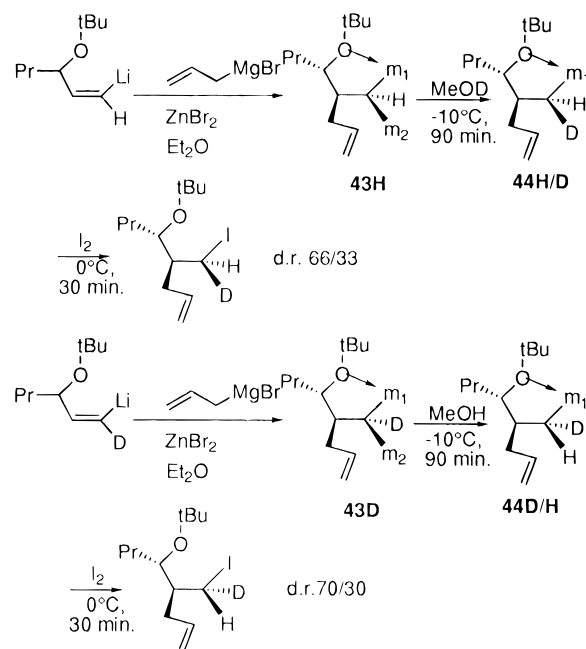


Whatever the mechanism of the formation of the organo-*gem*-dimetallic, the coordination of the oxygen atom to the metal m_1 is absolutely necessary to discriminate the reactivity of the two metals toward the first electrophile: without internal chelation, two diastereomers are obtained in approximately equal amounts.¹⁵¹

Other electrophiles can be introduced with a lower diastereoselectivity which corroborate however the configurational stability of these dimetallics. For example sequential treatment of the bis anion **43H** with deuteriomethanol and iodine leads to a predominant diastereomer, whereas the sequential treatment of the deuterated dianion **43D** with hydrogenomethanol and iodine leads to the opposite predominant diastereomer (Scheme 108).

The diastereoselection is not as good as it was in the Scheme 106 but it clearly shows an inversion of the ratio of the two products, exactly under the same experimental conditions. In this case, the two diastereomers **44H/D** and **44D/H** do not show interconversion under the experimental conditions. This result points to a configurational stability of these primary organozinc halides.^{151,153}

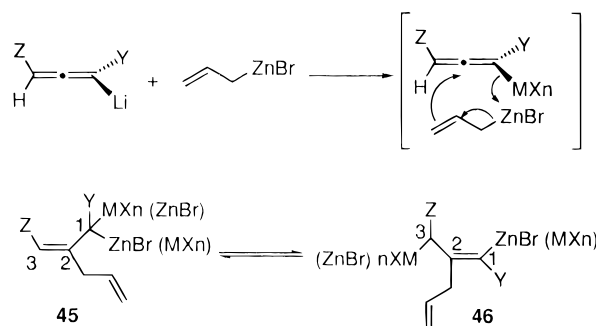
Scheme 108



D. Synthesis and Reactivity of Allylic Dimetallic Zinc Reagents

Allylic 1,1-dimetallic reagents, easily obtained from the allylzinc bromide addition to metalated allenes, are potential bis nucleophiles. However, they may react as geminated dimetals **45** or as vinylic-allylic dimetallic species **46**, so that the location of these two metals has to be taken into consideration (Scheme 109).

Scheme 109

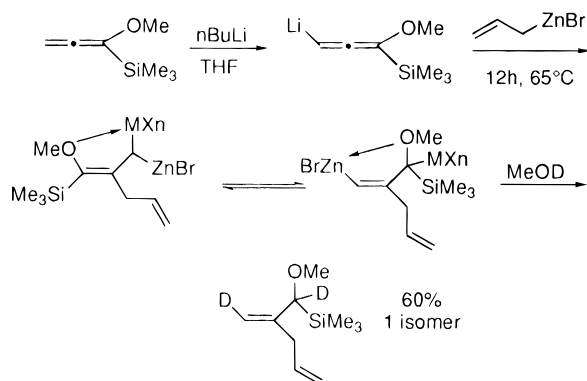
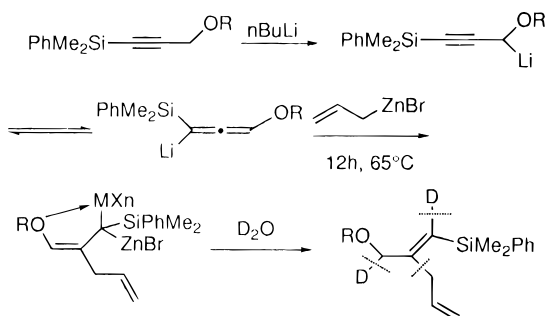


In the case where an oxygen atom is present, on a position γ relative to the lithium atom, deuteration of the reaction mixture shows that the reaction is regioselective.¹⁵⁴ Deuteration occurs exclusively on carbons 1 and 3 (Scheme 110).

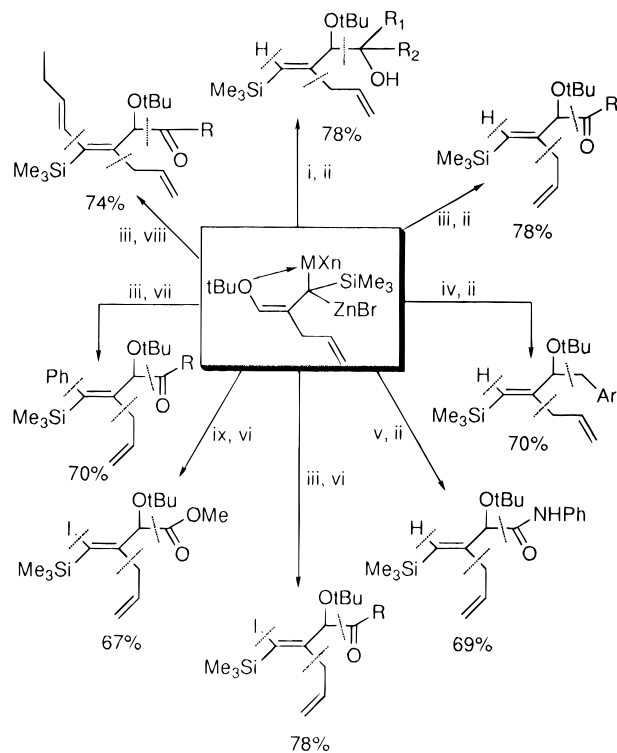
The metalation of a propargylic ether leads also, via its metallotropic equilibrium, to the corresponding allenylmetal which can react with allylzinc bromide.

In this case, after deuteration, a single isomer is obtained¹⁵⁴ (Scheme 111).

The high regio- and stereoselectivity is accounted for by a favored chelation of the dimetallic reagent. The latter can also react selectively with two different electrophiles: acyl chlorides, ketones, aldehydes, phenyl isocyanate, alkyl halide, amino ether, imines, and leads to the corresponding functionalized vinyl metals.¹⁵⁵ These latter then react with a second

Scheme 110**Scheme 111**

electrophile to give the multicoupled products in good yield as described in Scheme 112.

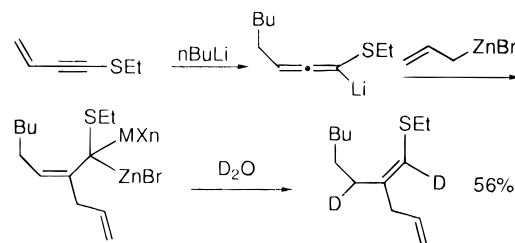
Scheme 112^a

^a Reagents: (i) R_1R_2CO ; (ii) MeOH; (iii) $RCOCl$; (iv) $ArCH_2Br$; (v) $PhNCO$; (vi) I_2 ; (vii) ArI , 5% $Pd(PPh_3)_4$; (viii) (*E*)-1-iodobutene 5% $Pd(PPh_3)_4$; (ix) $ClCOOMe$.

The reactivity of the second metal is lower than the reactivity of the first due to the vinylic character of the remaining metal and also to the intramolecular chelation by the heteroatom. However, it can be

deuterolyzed, iodolyzed, or coupled with a vinyl iodide under palladium catalysis in the presence of a stoichiometric amount of copper salt in DMA or DMF.¹⁵⁶

Metalated allenes can also be prepared by carbolithiation of activated enynes. In this case, the subsequent addition of allylzinc bromide followed by an acidic deuterolysis leads to a 88/12 mixture of geometric isomers¹⁵⁴ (Scheme 113).

Scheme 113

When the reaction is performed with nonsilylated or non-oxygenated educts, the dimetallic is protonated nonregioselectively¹⁵⁷ and can promote three consecutive rearrangements leading to cyclic polyorganometallic species with good stereoselectivity.¹⁵⁷

XI. Conclusion

In conclusion, this brief survey of *gem*-dimetallic reagents shows that these derivatives should not be considered as esoteric compounds any longer. Their use in organic synthesis has been particularly underlined in the case of α,α -dilithiosulfones, of *gem*-lithio-alanes and -boranes (or their ate complexes) which allow sequential alkylations and cyclizations, the resulting alane or borane being a source of hydroxy functions. *gem*-Boriozincioalkanes can be vinyllated to reactive allylboranes. In many cases these bis donor (d^2) reagents react via the more reactive alkaline C–M bond, whereas the less reactive one (i.e. C–Zn) can be transmetalated to a more efficient C–Cu bond.

Allylmetalation of vinylmetals leads directly to a *gem*-dimetallic compound, and various substituents on the two partners are located diastereoselectively on the linear chain thus obtained, or, via elimination, they can give way to metalated substituted cyclopropanes of unique geometry.

This field has opened the way to many new molecular constructions in few steps (one-pot reactions) from generally simple starting materials.

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XIII. References and Notes

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