

Synthesis and reactivity of geminated organobismetallic derivatives

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Résumé

Synthèse et réactivité des dérivés organobismmétalliques géminés

Comme la complexité synthétique des molécules organiques est toujours croissante, l'élaboration de nouvelles stratégies permettant la création efficace de liaisons carbone-carbone entre différentes entités fonctionnalisées est absolument nécessaire en synthèse organique. Pour répondre à ce besoin, le développement de nouveaux réactifs et intermédiaires organométalliques demeure continuellement une priorité en chimie organique. Dans ce contexte, la préparation et l'étude de la réactivité des dérivés bismmétalliques géminés (1,1-dianions) jouent un rôle majeur. Les exemples les plus récents et significatifs dans ce domaine sont décrits dans cette revue.

Mots-clés

Organobismmétalliques, dérivés zinciques, carbométallation, synthèse « one-pot », polyfonctionnalisation.

Key-words

Organobismetallics, zinc derivatives, carbometalation, one-pot synthesis, polyfunctionalization.

The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon-carbon bonds between functionalized moieties are needed. A serious limitation in practice is set by the mere number of steps accumulating in linear sequences and by the extensive protecting-group strategies used. Despite the tremendous progress in this area, a much larger panel of reactions achieving a significant increase in structural complexity per chemical steps is necessary. This is particularly true for transformations, which involve more than one bond-making event and particularly if functional groups are present in the carbon skeleton. Indeed, the need for preparing complex polyfunctional molecules requires the development of new selective organometallic reagents and catalysts for organic synthesis. Then the chemo-, regio- and even enantioselective creation of several functionalized carbon-carbon bonds in a one-pot reaction in lieu of multiple group manipulations will result in a better orchestration of retrosynthetic analysis. This relatively new topic of research was recently internationally boosted by the launching of a new journal, *Advanced Synthesis and Catalysis*, in which Prof. Ryoji Noyori, chairman of the editorial board and one of the last Wolf and Nobel prize winners in chemistry, stated: « *Despite the extraordinary masterworks of total synthesis in the last century, the development of practical and efficient synthetic methodologies is still in its infancy. The need for efficient and practical synthesis remains one of the greatest intellectual challenges with which chemists are faced in the 21st Century* ».

Among these different intellectual challenges, the preparations of geminated organobismetallic derivatives (1,1-bisanions) have a predominant role as demonstrated by the increasing number of scientific papers published in the last few years. One of the first questions which have to be solved is to define general, easy and straightforward methods for the preparation of molecules bearing two negatives charges on the same sp^3 or sp^2 carbon center.

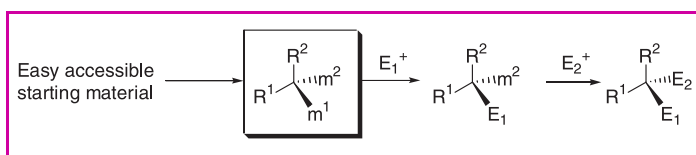


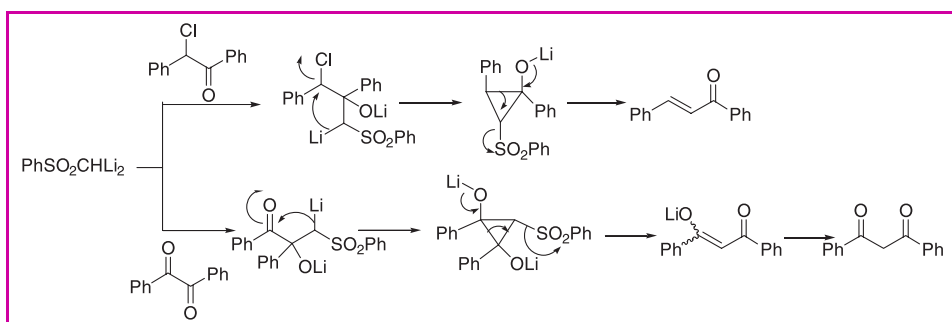
Figure 1.

Then, once we have in hands these new methodologies, the second problem that we have to address is the control of the reactivity of these two carbon-metal bonds towards two different electrophiles (*figure 1*). No doubt that simple strategies allowing the simultaneous creation of two carbon-carbon bonds in a stereo- and ultimately enantioselective manner on the same carbon center will have a tremendous impact in synthetic organic chemistry.

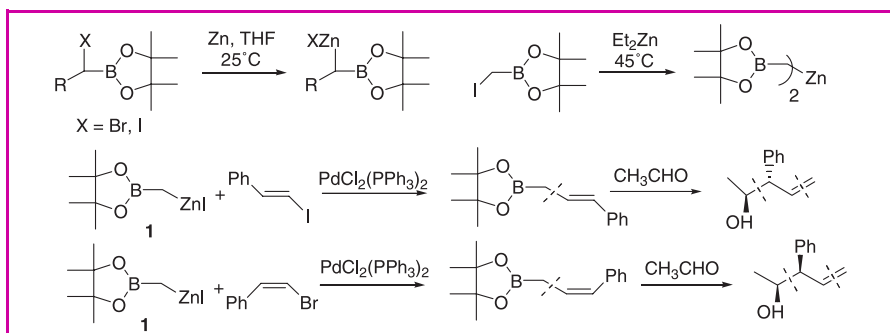
This article is intended to highlight the « state of the art » in this field [1].

Although the simplest member of this family, namely the 1,1-diGrignard reagent $CH_2C(Mg)_2$ was reported more than 75 years ago [2], the narrow scope and the low reactivity of this first dianion towards classical electrophiles have limited its application in synthetic organic chemistry [3]. On the other hand, the only example known to date of sp^2 1,1-bismagnesiated species was reported by Duboudin and Jousseume in France, and found several applications in the preparation of substituted allylic alcohols although the selective reactivity of the two carbon-metal bonds with two different electrophiles has still not been investigated [4]. The most convenient preparation of sp^3 gem-dithioalkane is by double metalation of derivatives containing acidic hydrogen atoms [1] (α to sulfoxides or sulfones) and has been shown in recent years to possess a great synthetic potential as described with the two examples in *scheme 1* [5].

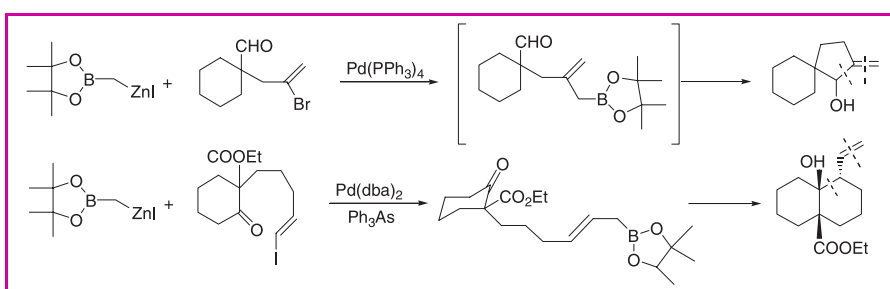
Although the chemistry of 1,1-bisolithio derivatives shows promising results, the major breakthrough came few years



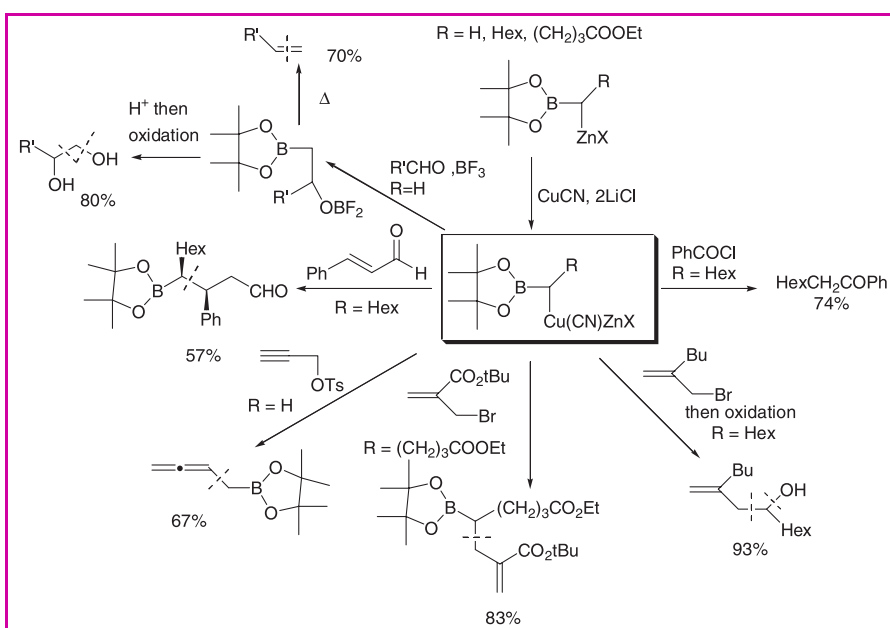
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

later with the development of the 1,1-borio-zincio-, 1,1-borio-zirconio- and the 1,1-bis-zincioalkanes and alkenes chemistry [1].

The insertion of zinc dust into α -haloboronic esters proceeds smoothly to afford the α -(dialkoxyboryl)alkyl zinc halides, whereas bis(dialkoxyboryl)methylzinc is obtained by the reaction of iodomethyl boronic ester with Et_2Zn (scheme 2) [6]. The cross-coupling reaction of (dialkoxyboryl)methylzinc reagents ($\text{R} = \text{H}$) with E

or Z 1-halo-1-alkenes under palladium catalysis, leads to the corresponding stereochemically pure allyboronic acids. Sequential treatment with an excess of acetaldehyde provides the *threo* or *erythro* homoallylic alcohols in 61% and 57% yield respectively as described in scheme 2 [7].

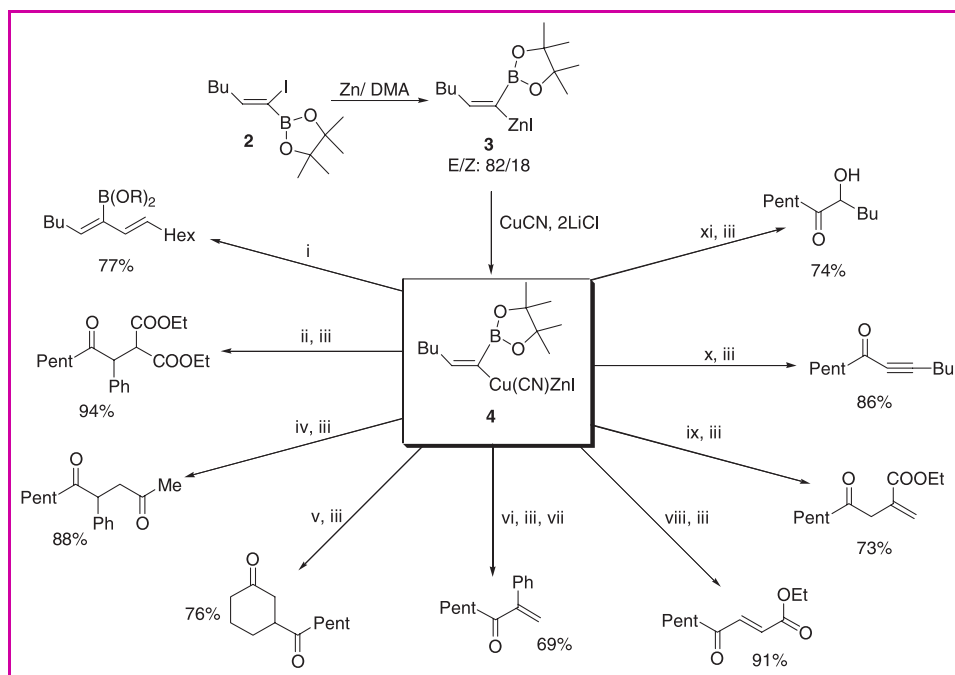
The potential versatility of this coupling reaction was illustrated by the application to intramolecular allylboration reactions (scheme 3) [8].

Addition of the THF soluble copper salt $\text{CuCN} \cdot 2\text{LiCl}$ to the α -(dialkoxyboryl)alkylzinc halides converts them to the more reactive copper derivatives, which can react with a wide range of electrophiles in good yields (scheme 4) [6, 9].

On the other hand, the (Z)- α -iodoalkenylboronic ester **2** (prepared by the hydroboration of 1-iodoalkyne with $\text{HBr}_2 \cdot \text{Me}_2\text{S}$ followed by the conversion into 1-iodoalkenylboronic acid and then esterification with pinacol) reacts with zinc dust in N,N-dimethylacetamide (DMA) to furnish the 1,1-boron-zinc-alkenylbismetallic **3** (scheme 5). [10]. The zinc insertion to α -iodoalkenylboronic esters does not occur stereospecifically and the pure (Z)-**2** is converted to an E/Z mixture of alkenylzinc iodides **3** in a 82/18 ratio. Indeed, the iodolysis of **3** provides the parent compound but as a mixture of isomers in a E/Z ratio of 82/18 [10]. However, the transmetalation of **3** with $\text{CuCN} \cdot 2\text{LiCl}$ leads to the 1,1-borio-cuprio bismetallic reagent **4**.

The different nature of the two metals present in compound **4**, or their different stereotopicity, can be used to make two new bonds successively (scheme 5) [10]. Hydrozirconation of 1-alkynyldioxaborolane with 1.2 equiv. of $\text{HZrCp}_2(\text{Cl})$ in either THF or 1,4-dioxane proceeded readily by a *syn* addition to give essentially pure boryl zirconocene (E)-1,1-bismetallics **5** (scheme 6) [11]. As the carbon-zirconium bond is more reactive than the carbon-boron bond towards hydrolysis, a direct utility of **5** would be the preparation of (Z)-alkenyl boronates [12].

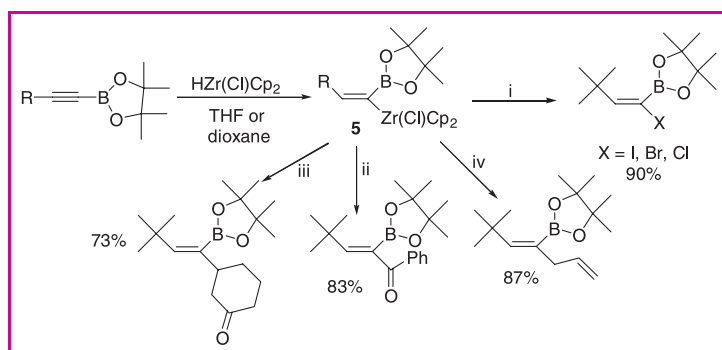
Moreover, since hydrozirconation is tolerant of many functional groups, several functionalized (Z)-vinylboronates were



Scheme 5.

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

prepared by this way. Bismetallics **5** were also reacted with various electrophiles and, as expected, the carbon-zirconium bond always reacts first as described in *scheme 6* [12]. No dialkylated products were observed with one equiv. of electrophile [13].



Scheme 6.

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

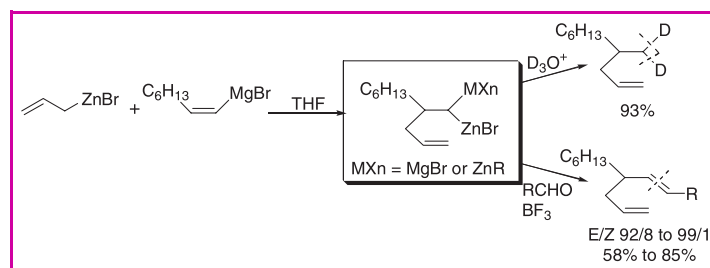
In 1971, an elegant alternative for the synthesis of organogembismetallics has been found by Gaudemar who reported that the addition of allylzinc bromide on substituted vinyl Grignard reagents leads to the organogembismetallic species (*scheme 7*) [14]. Although these organometallic compounds were obtained in moderate chemical yields, this reaction allows an easy approach to the synthesis of gembismetallic reagents *via* the carbometalation reaction [15]. Some years later, it was found that a wide range of 1,1-bismetallated compounds were available in high yields by carbometalation of alkenyl organometallics with allylic zinc bromide using reaction conditions similar to those described by Gaudemar [16].

The different nature of the two metals present in this bimetalated compounds or their different stereotopicity can be used to make successively two new bonds (*scheme 8*) [17]. More recently, computational studies have shown the zinc nature of the bimetalated species and thus, the different reactivity is most probably coming from the different reactivity of the biszincated species [18].

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 metalotropic rearrangements of the substituted allylic system. This 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, crotyl-zinc bromide leads to a very high diastereoselection at -50 °C within

5 h (*scheme 9*) [19]. The high diastereoselectivity observed in the crotylmatalation of vinyl metals may be accounted for by a preferential or kinetically favored Z configuration of the crotyl metal species, if we consider a chair like transition state [20].

This methodology has been generalized to various functionalized molecules: (γ-amino-2-propenyl), (γ-alkoxy-2-propenyl)- and [β-(alkylthio)vinyl]metals react diastereoselectively with crotyl zinc bromide, but also with an allylzinc bromide bearing an alkoxy group [19]. 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 to excellent diastereoselectivity. Knowing that the chelation between zinc and heteroatoms in ω-heterosubstituted dialkylzinc reagents has already been shown by NMR studies [21], the allylzincation of substituted γ-heterosubstituted vinyl metals was studied. This reaction has been studied starting from (Z)-γ-iodo allylic ethers [22], amines and thioethers [23] easily accessible from a propargylic ether or ethyl propiolate [24] as described in *scheme 10*. 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. The same



Scheme 7.

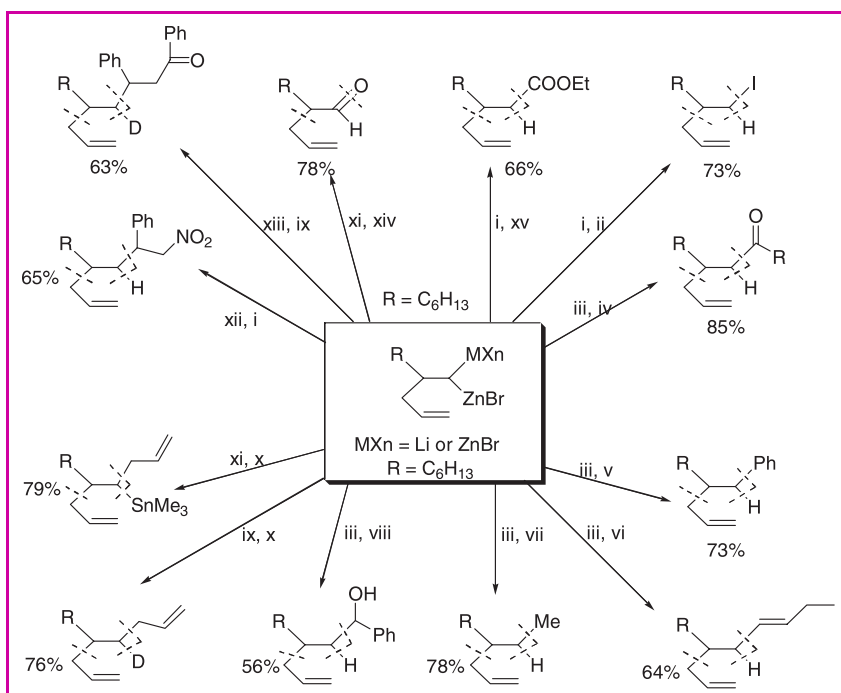
selectivity was obtained, starting directly from the γ -trimethylsilyl propargylic alcohol in a one-pot reaction. If this facial selectivity is combined with the selectivity arising from the use of a substituted allylzinc bromide, two new stereogenic centers are created out of a single starting one (scheme 10) [25].

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 an olefinic site was also described in the case of di-4-pentenylzinc [26]. This weak dipolar chelation is the result of the inherent polarity of the $Zn^{+\delta}-C^{-\delta}$ bond and the polarity of the double bond (partial negative charge on the terminal carbon).

Such interactions were evidenced by NMR investigations and the *spiro*-structure of di-4-pentenylzinc was postulated to interpret this phenomenon. The oxygen chelation described in scheme 10 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 11) leads to the corresponding stereochemically substituted dienes with a good diastereoselectivity [27].

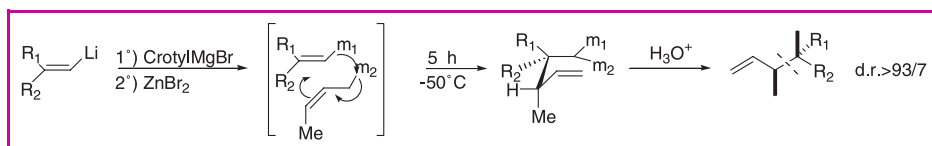
The carbometalation of vinyl metals can be also applied to the addition of substituted propargylzinc bromides [22]. The addition of zinc salts to a propargyl/allenyl organolithium reagent leads quantitatively to the allenyl zinc bromide and considering that this latter reacts with the vinyl metal moiety *via* a S_E2' process, 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 as described in scheme 12. The other transition state, leading to the *syn* isomer, is highly disfavored by the repulsion between the two alkyl groups [22].

As seen above, the addition of substituted allyl zinc bromides to γ -heterosubstituted vinyl metals

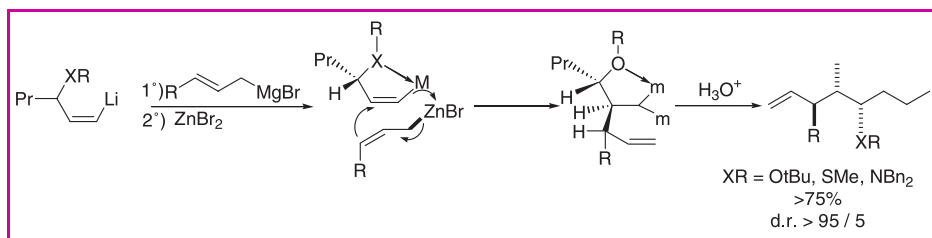


Scheme 8.

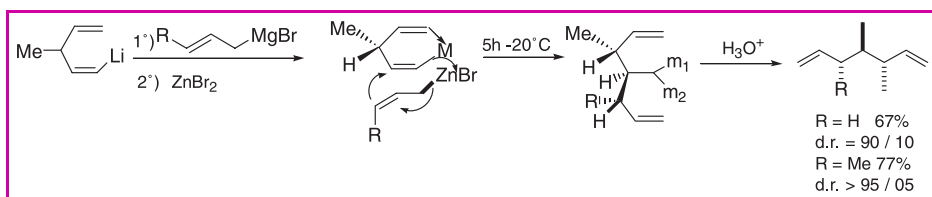
Reaction conditions: i) MeOH; ii) I_2 ; iii) $sBuOH$; iv) $RCOCl$, 5% $Pd(PPh_3)_4$; v) PhI , 5% $Pd(PPh_3)_4$; vi) (E)-iodo-1-butene; vii) CuI then MeI ; viii) $TiCl(OiPr)_3$ then $PhCHO$; ix) $MeOD$; x) $CuCN$ then allyl bromide; xi) Me_3SnCl ; xii) nitrostyrene; xiii) benzalacetophenone; xiv) O_2 , $TMSCl$; xv) $ClCOEt$, 5% $Pd(PPh_3)_4$.



Scheme 9.



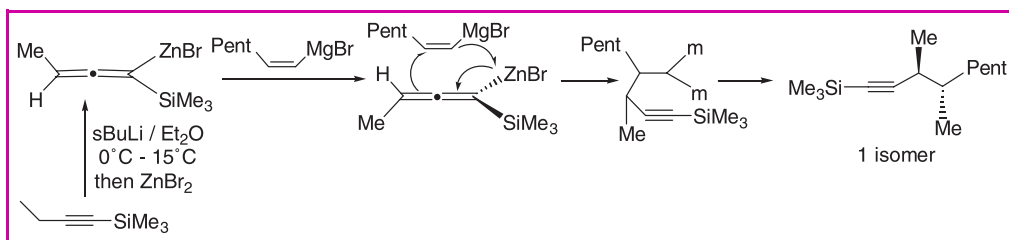
Scheme 10.



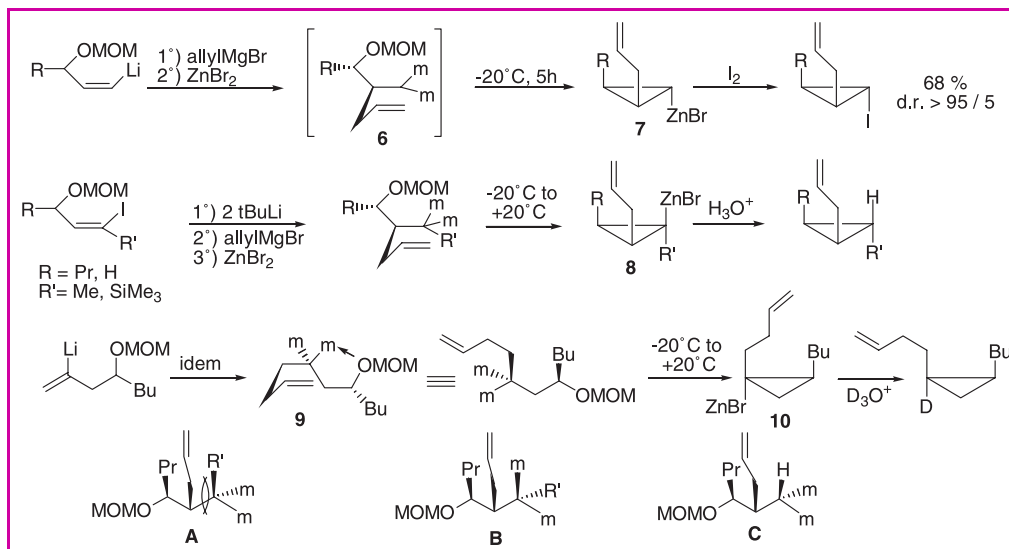
Scheme 11.

($XR = OtBu, NR_2, SR$) allows the creation of stereogenic centers (see scheme 10) [28]. However, if the chelating moiety is a methoxy methyl ether (MOM group), the formed bimetallic 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 [29]. This cyclization reaction corresponds to the reaction of the organogembimetallic with an intramolecular electrophile (the MOM group) followed eventually by the reaction of the configurationally stable cyclopropyl zinc bromide, thus formed, with an external electrophile (scheme 13) [30].

Since the alkyl and allyl groups in **6** were *anti* to each other (see scheme 10), and *syn* in the metalated cyclopropane **7**, 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 13) [31]. In order to explain the relative configuration of the metalated



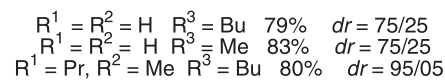
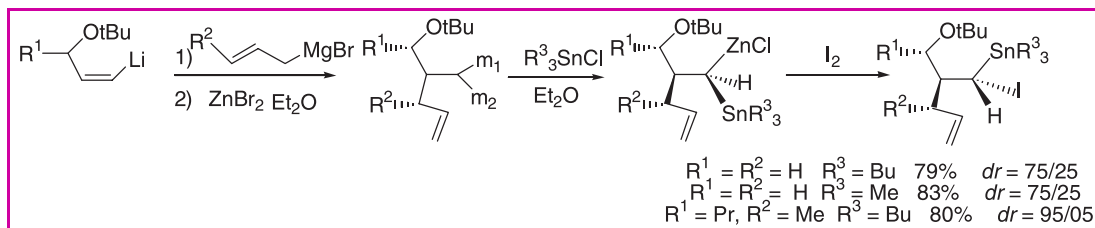
Scheme 12.



Scheme 13.

carbon, the mechanism involving an inversion-inversion (at both centers) in a w-shaped conformer [31]. The diastereoselective synthesis of a tetrasubstituted zinc-cyclopropane can also be achieved according to the same procedure (see **8**, *scheme 13*). In this case, the resulting organozinc halide **8** displays a metal *syn* to the allyl and R groups whereas in **7**, the organometallic moiety was *trans* to the latter groups. In the w-shaped transition state **A** (*scheme 13*), 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 non-substituted (R' = H) case **C**. Then, 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*-organogembimetallic reagents **9** bearing an OMOM group β to the metalated carbon. When the latter reagent is submitted to the cyclopropanation reaction, by raising the temperature from $-20\text{ }^\circ\text{C}$ to $+20\text{ }^\circ\text{C}$, a single *syn* diastereomer **10** is formed [31].

The chelated organogembimetallics react with 1 equiv of R_3SnCl to give the α -trialkylstannyl alkyl zinc chlorides and then with 1 equiv. of iodine to give the corresponding α -iodo alkyl trialkylstannanes with a fair to good diastereoselectivity and good chemical yield [32]. These results indicate



Scheme 14.

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 (*scheme 14*).

As the allylmethallation reaction of alkynyl metals leads also to a vinylic 1,1-organogembimetallic [14, 33], a new strategy for effecting stereoselective synthesis of carbon-carbon double bonds was successfully described. This strategy requires a secondary propargylic substrate (the presence of a secondary substituent on the propargylic ether avoids the formation of the double addition) bearing a Lewis basic functional group as propargylic ether, in order to differentiate the reactivity of the two metals towards electrophiles (*scheme 15*) [32].

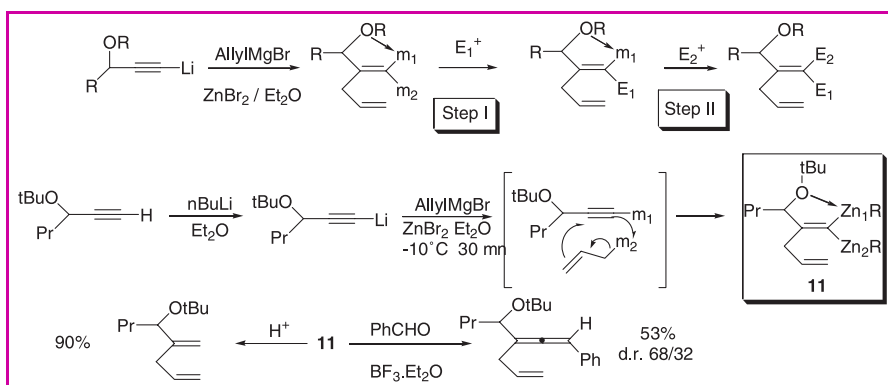
As previously described in *scheme 14*, the coordination of the oxygen atom to the metal m_1 decreases the reactivity of the latter toward the first electrophile, and thus, the non-chelated metal m_2 reacts preferentially with this electrophile.

The allylmethallation step has been performed under mild conditions in Et_2O ($-10\text{ }^\circ\text{C}$, 30 min) and the presence of the 1,1-dianionic species **11** has been proved by reaction of the latter with electrophiles (*scheme 15*) [34].

For the stereoselective reaction of the bismetallic **11** with different electrophiles (step I, *scheme 15*), it has been chosen mild halogenating agents such as phenylsulfonyl halides which are known to react selectively with sp^3 bismetallics [35].

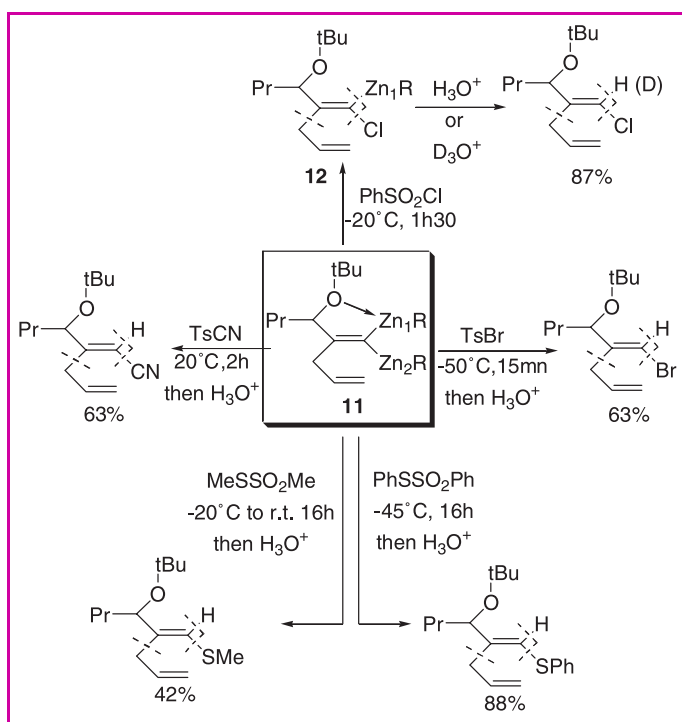
Thus, addition of phenylsulfonyl chloride to **11** leads to the corresponding vinylic carbenoid **12**. The hydrolysis (or deuteriolysis) of the latter gives the unsaturated vinyl halide in good isolated yield as a unique isomer (*scheme 16*) [34].

The stereochemistry was determined by NOE effect between the vinylic and allylic hydrogens. This result reflects the chelation of the *tert*-butoxy group toward Zn_1R of **11**. Moreover, even an excess of PhSO_2Cl (4 equiv.) doesn't lead to the vinylic gemdichloro derivative and thus, the resulting vinylic

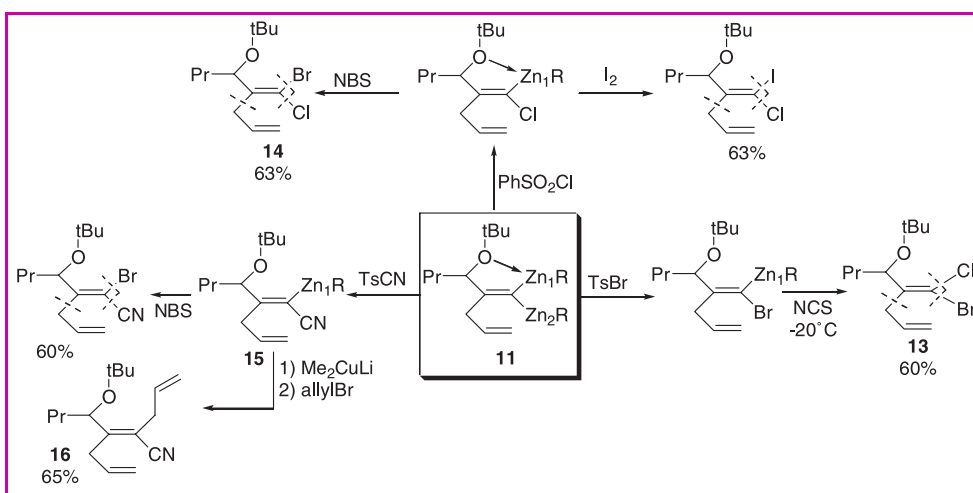


Scheme 15.

zinc **12** has a lower reactivity than the bis-metallic **11**. Taking advantage of the stereoselective reactivity of phenylsulfonyl chloride with **11**, other sulfonyl derivatives were tested (scheme 16) [36]. In each case, only one stereoisomer was formed. Interestingly, the addition of *p*-toluenesulfonyl cyanide leads to a unique metalated α,β -ethylenic nitrile. The chelation is absolutely necessary to discriminate the reactivity of the two metals toward the first electrophile. The remaining metal Zn_1R can also react with a stronger halogenating agent to give the polyhalogenated vinylic compound as a unique isomer. This reaction is of synthetic value for the obtention, at will, of the two geometrical isomers **13** and **14**



Scheme 16.



Scheme 17.

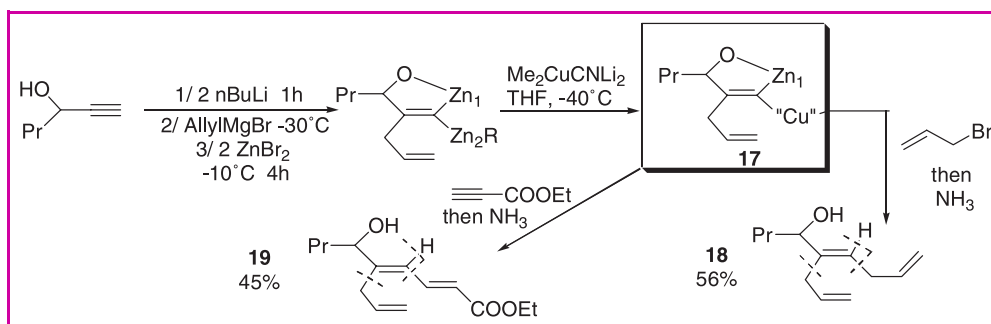
starting from the same propargylic ether (scheme 17) [36]. In the case of an α -metalated vinyl cyanide **15**, the reactivity of the remaining metal Zn_1R can be increased by a transmetalation step with an organocuprate. The corresponding vinylic organocuprate derivative reacts with allyl bromide to give the skipped triene **16** as a unique isomer in 65% overall yield (starting from propargylic ether in one-pot reaction, scheme 17).

In order to increase this stereodifferentiation of the bismetallic, the allylmetalation of a secondary propargylic alcohol (instead of ether) was also studied. In this case, after the carbometallation reaction, a covalent metal-oxygen bond is formed, and the addition of an organocuprate leads only to a transmetalation of Zn_2R namely the metal that is not chelated (scheme 18) [36].

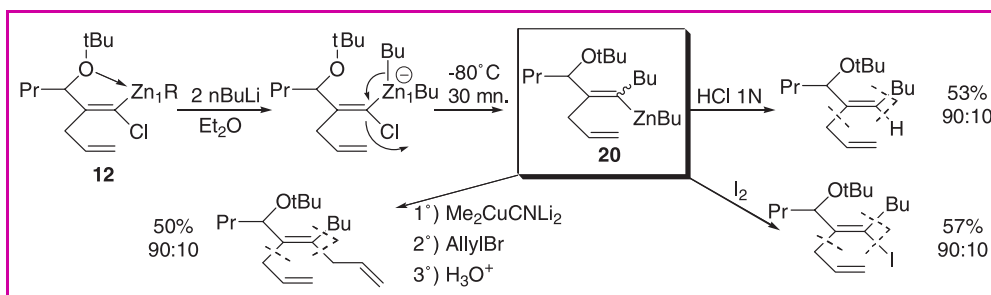
The reaction of **17** with allyl bromide leads only to a monoallylated derivative **18** as a unique stereoisomer. The stereochemistry of the substituted double bond was determined by NOE and clearly shows that only the metal that is not attached by the oxygen moiety undergoes the transmetalation step. In a similar way, ethyl propiolate leads to the triene-ester **19**. The yields are moderate but the bis-alkylation of a propargylic alcohol is carried out in a one-pot procedure [36].

Thus, the alkylation of Zn_1R is synthetically useful in the case of the α -metalated α,β -ethylenic nitrile (see scheme 17), but in the case of zinc halogenocarbene (as in scheme 16) the alkylation of Zn_1R is impossible since it requires higher temperature (degradation of the carbene)

(degradation of the carbene). So, the chemistry of alkylidene chlorocarbene **12**, which present an ambiphilic aspect, have been studied. Chlorocarbene can act as common nucleophiles (as in scheme 16) but they can act as well as electrophiles toward organometallic nucleophiles. Indeed, the dropwise addition of *n*-BuLi (2 equiv.) to the α -chlorocarbene **12** at -78°C leads to the formation of the zincate carbene, which undergoes a smooth intramolecular nucleophilic substitution reaction to give the vinylic organozinc derivative **20** [35]. The latter was characterized by hydrolysis, iodolysis and allylation after a transmetalation



Scheme 18.



Scheme 19.

step with 90:10 stereochemical purity as described in *scheme 19* [36].

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

A third possible reaction pathway of chlorocarbenoids is known in the literature since 1894, namely the Fritsch-Buttenberg-Wiechell (FBW) rearrangement (*scheme 20*) [37]. This rearrangement is known to be an efficient approach for alkyne synthesis when the migrating group (R_1 or R_2) is a hydrogen, an heteroatom or an aryl moiety. However, when R_1 and R_2 are alkyl groups, the yields in alkynes are very low (< 10%) due to the competitive C-H insertion reaction to form cyclopentenes [38].

Interestingly, the alkylidene carbenoid **12**, generated from the 1,1-dizincioalkene **11** rearranges cleanly in 70% yield, just by warming the reaction mixture to room temperature, into the disubstituted alkyne **21** (*scheme 20*) [39]. This first FBW rearrangement of zincated species is in contradiction with the known results in lithio-, sodio- and potassio analogs [40].

The diastereoselectivity of this process was also studied by the addition of a substituted allylic organometallic derivative (namely crotylzinc bromide, *in situ* generated by the addition of crotylmagnesium bromide and zinc bromide) across the secondary metallated propargylic ether (*scheme 20*) [39].

Although a moderate diastereoselectivity is obtained for the crotylmetallation of **22** (formation of **26** after hydrolysis in a diastereomeric ratio of

70/30), the replacement of the *tert*-butyl ether into the methoxyethoxymethyl ether (OMEM) as in **23** raises the diastereoselectivity to 92/8 in 60% yield (see **27**, *scheme 20*). Via this strategy, two stereogenic centers and a bismetallated exomethylene moiety such as in **25** were created with a very good diastereomeric ratio.

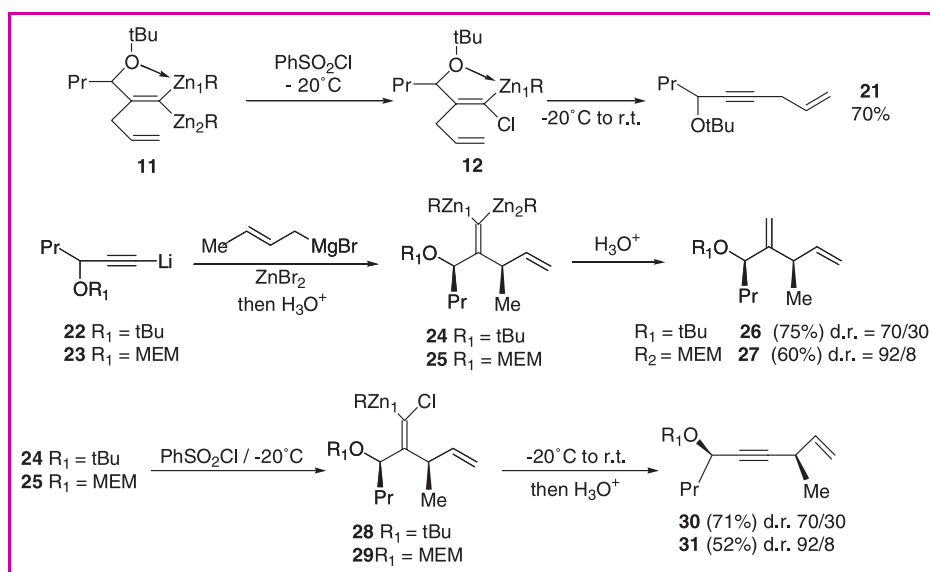
The question of the fate of a chiral sp^3 carbon center as a migrating group in the FBW is then raised. To answer to this interesting question, **24** and **25** were treated with $PhSO_2Cl$, and then the resulting carbenoids **28-29** were warmed to room temperature. A clean rearrangement takes place to lead to the enyne ethers **30-31** with the same diastereoselectivity as the one obtained for the intermediates **26-27**.

Then, from these studies, it

was shown that the migration occurs with a complete transfer of stereoselectivity (from 92/8 for **27** to 92/8 for **31**). Moreover, by chemical correlations, it was demonstrated that the FBW rearrangement occurs, *via* the zinc carbenoids, with a complete *retention of configuration at the migrating atom* (the stereogenic centers in **26** or **27** with the one in **30** or **31** present the same diastereomeric ratios and the same absolute configurations) [39, 41].

Conclusion

In summary, this field has opened the way to many new molecular constructions in few chemical steps (usually in a one-pot reaction) from generally simple starting materials. In many cases, the more reactive carbon-metal bond reacts



Scheme 20.

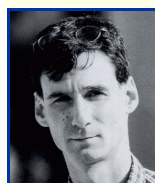
with the first electrophile, whereas the less reactive carbon-metal bond can be transmetalated to more efficient organometallic derivatives. Up to 4 stereogenic centers were easily created by using sp^3 gem-bismetallated species and the formation of sp^2 1,1-dizincioalkene reagents represent a powerful tool for the preparation of polysubstituted double bonds via the successive addition of different electrophiles (up to 3 carbon-carbon bonds formed as unique isomer). Moreover, an interesting application is the synthesis of α, α' -chiral disubstituted alkynes from simple propargylic ether. Considering the importance of these *polyreactions* in a single-pot-operation, these methods are highly useful in organic synthesis and the target of these coming years will be to render such a process asymmetric by a judicious combination of metals and chiral ligands [42]. No doubt that many further applications will appear in the future.

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