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Sp³ organozinc carbenoid homologation in organic synthesis

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1. Introduction

The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon–carbon bonds between functionalised moieties are needed. A seemingly trivial but rather serious limitation in practice is set by the mere number of steps accumulating in linear sequences.

Despite the tremendous progress in this area, a much larger panel of reactions achieving a significant increase in structural complexity per chemical step is necessary. This is particularly true for transformations which involve more than one bond-making event. Indeed, the need for preparing complex polyfunctional molecules requires the development of new selective organometallic reagents. The chemo- regio- and even enantioselective creation of several functionalised carbon–carbon bonds in a one-pot reaction in lieu of multiple group manipulations will then result in a better orchestration of retrosynthetic analysis.

To meet these challenging problems, new polyreactive intermediates, which are able to create consecutively the same number of carbon–carbon bonds as in a multistep process, but in a single-pot reaction, have to be prepared. Sp^3 carbenoids are excellent candidates for multiple reactions since their chemistry was shown to present an interesting ambiphilic aspect. They can act as a common nucleophiles but they can also act as electrophiles towards nucleophiles. Since the pioneering work of Kobrich,[1] the interest in carbenoids has not diminished.[2] Among all the possible carbenoids used in synthesis, organozinc carbenoid derivatives[3] such as (iodomethyl)zinc iodide[4] **1a** and bis(iodomethyl)zinc[5] **2a** are probably the most popular and were abundantly used for the cyclopropanation reactions of olefins.[4–6] Sp^3 carbenoids have also been used for different synthetic purposes, although much less frequently, such as the homologation reactions. The aim of this report is

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Keywords: organometallic reagents; carbenoids; carbon–carbon bond.

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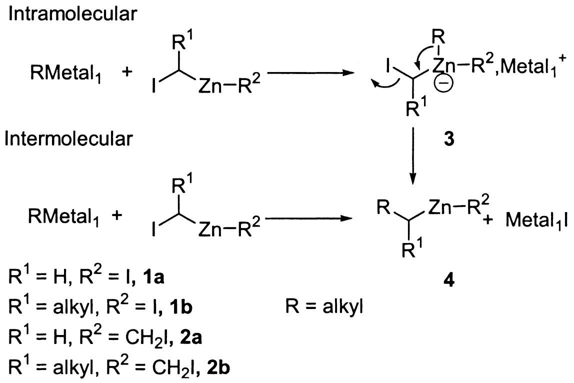
to review the synthetic applications of carbon–carbon bond-forming reactions involving sp^3 zinc carbenoids in which a carbon ligand R bound to the zinc **3** undergoes a 1,2-shift to an electrophilic carbon attached to the same metal to give a new sp^3 organozinc derivative **4** (intramolecular homologation reaction) as described in Scheme 1. The same final organozinc compounds **4** can also be obtained from the reaction between two different molecules (intermolecular homologation reaction).



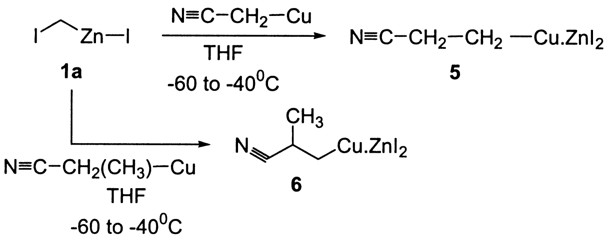
Scheme 1.

To be synthetically useful, the reactivity of the compound **4** has to be substantially lower than the reactivity of the nucleophile ($RMetal_1$) towards the carbenoids **1a**,**b** or **2a**,**b** in order to avoid polyhomologation.

2. Methylene homologation

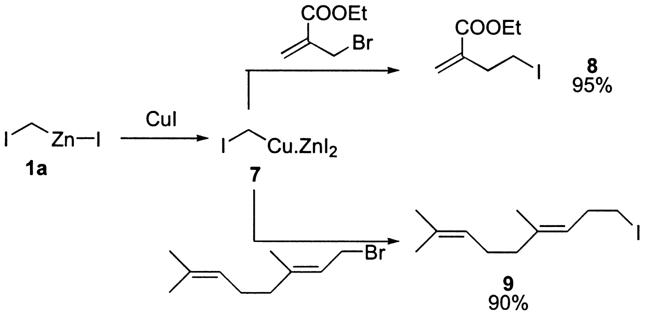
2.1. Methylene homologation of organocopper reagents

2.1.1. Homologation of cyanomethylcopper compounds. (Iodomethyl)zinc iodide **1a** allows the realisation of this synthetic operation in fair to good isolated yields using (cyanomethyl)copper and α-substituted (cyanomethyl)-copper derivatives to give the (2-cyanoethyl)copper analogues **5** and **6** as described in Scheme 2.[7] These resulting organocopper derivatives are then allylated or undergo Michael addition in satisfactory yields. **1a** can also be transmetallated to the reagent $ICH_2Cu\cdot ZnI_2$ **7**, which shows only a limited stability even at −78°C.



Scheme 2.

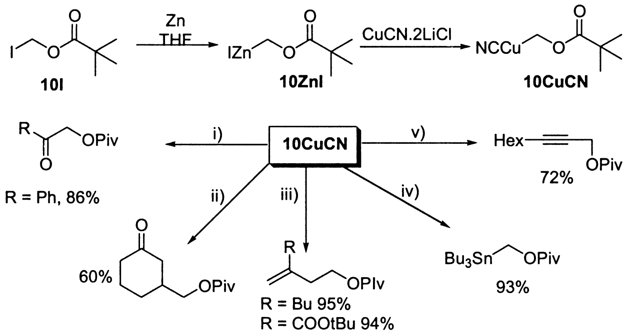
To be synthetically useful as a nucleophile, **7** has to be generated in the presence of an electrophile (Barbier conditions) and at a temperature where it reacts with its electrophile. Functionalised allylic bromide derivatives are therefore excellent electrophiles for this transformation and undergo the iodomethyl homologation reaction to give the functionalised homoallylic iodides **8** and **9** (Scheme 3).[8]



Scheme 3.

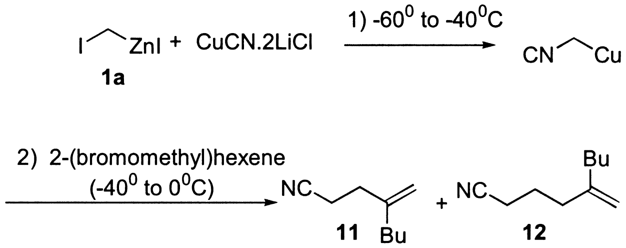
Other functionalised zinc carbenoids such as $tBuCOOCH_2ZnI$ **10ZnI** can be easily prepared from iodomethyl pivalate **10I** with activated zinc foil in over 85% yield.

The addition of **10ZnI** to $CuCN\cdot 2LiCl$ gives the copper derivative **10CuCN**, which reacts in fair to good yields with several classes of electrophiles. Indeed, its reactions with acyl chlorides, enones and allyl bromide, trialkyltin halide and alkynyl bromide derivatives give the corresponding functionalised compounds in good to excellent isolated yields (Scheme 4).[9]



Scheme 4. (i) RCOCl; (ii) cyclohexenone; (iii) allyl bromide derivatives; (iv) Bu_3SnCl; (v) bromoalkyne.

2.1.2. Homologation of copper-cyanide compounds. The methylene insertion also occurs with copper cyanides such as $CuCN\cdot 2LiCl$ (see Scheme 5).[7] The addition of **1a** to $CuCN\cdot 2LiCl$, however, furnished after allylation the double insertion product **12**, besides the desired insertion product **11** (**11**/**12** ratio 85:15). This double homologation was rationalised by assuming that **1a** may contain some bis(iodomethyl)zinc **2a** which is responsible for the double reaction. The addition of ZnI_2 to **1a** should considerably reduce the amount of **2a** present in equilibrium with **1a**. Indeed, by adding 1 equiv. of ZnI_2 to **1a**, it has been observed than CuCN (1 equiv.) undergoes a cleaner monohomologation, since after allylation with

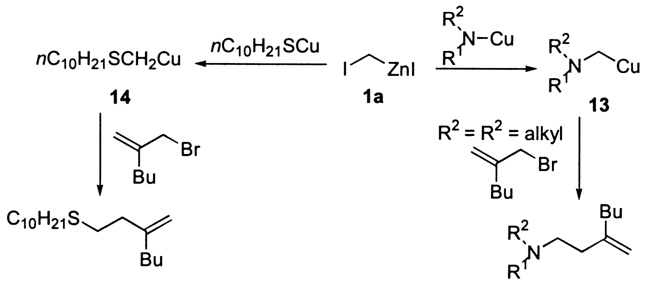


Scheme 5.

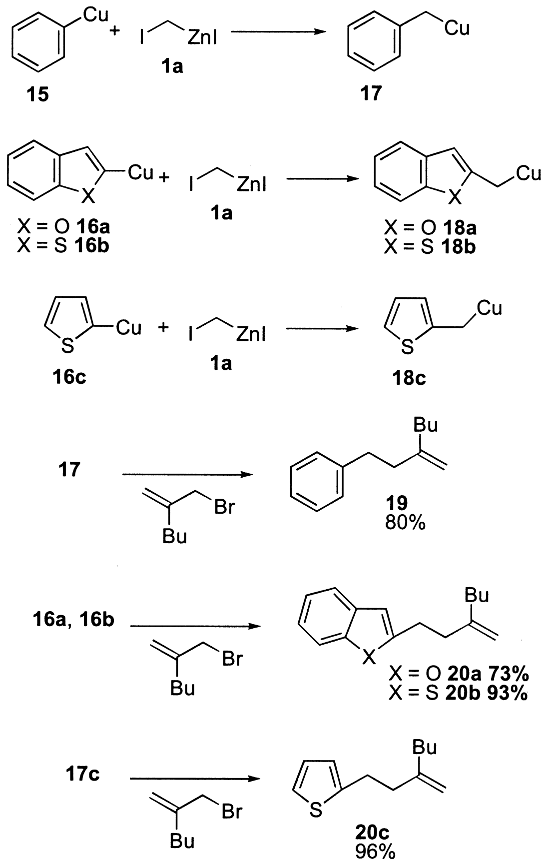
2-(bromomethyl)hexene the ratio of **11** and **12** is now 95:5. On the other hand, the addition of bis(iodomethyl)zinc **2a** to CuCN·2LiCl affords (after allylation) mainly the double methylene insertion product **12** (the **11**/**12** ratio is 9:91 in 95% yield).

The addition of ZnI_2 may, however, have more complex effects than just shifting the Schlenk equilibrium between **1a** and **2a**, since it also reduces the reactivity of the copper reagent and may therefore also affect the ratio of the two products **11** and **12** by modifying the reactivity of the organometallic intermediates.

2.1.3. Homologation of heterocopper compounds. Copper amide and copper thiolate compounds undergo the migration under the previously described reaction conditions (see Scheme 6).[7]



Scheme 6.



Scheme 7.

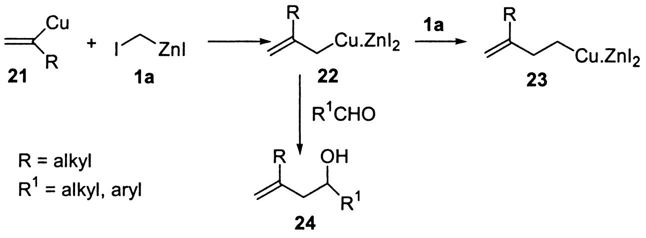
The low reactivity of the homologated products **13** and **14** allows only allylation reactions and provides homoallylic amines and thioethers in respectively 70 and 75% yields.

2.1.4. Homologation of aromatic and heteroaromatic copper compounds. Arylcopper **15** and heteroarylcopper **16a–c** derivatives can be homologated by (iodomethylzinc)iodide **1a** to furnish the benzylic organometallic derivatives **17** and **18a–c** accompanied by ca. 15% of the double homologated product. Since benzylic organometallics are usually more reactive than the resulting double homologated alkylcoppers, after addition of an electrophile (0.6 equiv.) only the benzylated or heteroaromatic compounds react to give **19** and **20a–c** (Scheme 7).[7]

Due to the presence of several equivalents of zinc salt, the reactivities of the benzylic copper derivatives **17** were reduced and only the most reactive electrophiles such as allylic halides, acid chlorides, benzaldehyde in the presence of BF_3·OEt_2 react with these copper–zinc compounds with a satisfactory yield. With the heteroarylcoppers **18a–c**, the acylation occurs on the aromatic ring affording 3-acyl-2-methyl-substituted heteroaromatic rings.[9]

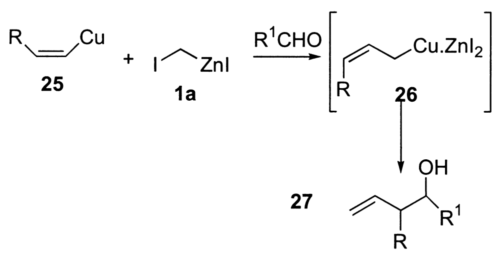
2.1.5. Homologation of unsaturated copper and zinc reagents

2.1.5.1. Homologation of alkenyl-copper and -zinc derivatives. The homologation reaction of alkenyl compounds **21** with (iodomethyl)zinc iodide **1a** represents an interesting and fast method for the direct conversion of alkenylcopper derivatives into allylic zinc–copper species **22** (Scheme 8). The resulting highly reactive allylic organometallics **22**, in the absence of any electrophiles, readily insert a further methylene unit, leading to the homoallylic copper reagents **23**. Therefore, here again, the reaction has to be performed in the presence of an electrophile such as an aldehyde or ketone in order to trap the intermediate **22**. Then, homoallylic alcohols **24** are obtained in good yields.[10]



Scheme 8.

Several substituents R can be used in this reaction (i.e. with benzaldehyde as internal electrophile, R^1=Ph) such as alkyl (94%), aryl (93%), acetal (96%), diethylaminomethyl (90%) and allylsilane (75%) groups. Aliphatic aldehydes and imines can also be used successfully in this transformation.[10] The presence of substituents in position 2 of the vinylcopper such as in **25** affords after the methylene homologation an unsymmetrical allylic organometallic derivative **26** (Scheme 9). Like classical allylic organometallic derivatives, the formation of the new carbon–carbon bond occurs preferentially on the more substituted end of the allylic system, leading to diastereomeric

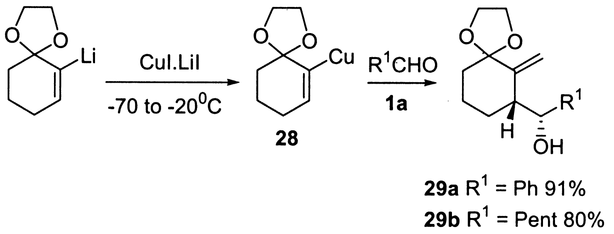


Scheme 9.

enriched homoallylic alcohols **27** (ratio typically being around 9:1).

If the substituent R is bulky or if the aldehyde is poorly reactive, however, the homoallylic alcohols **27** are formed as a mixture of diastereoisomers in variable ratios, depending on the *E*/*Z* isomerisation of the allylic zinc–copper reagents under these reaction conditions. The linear isomer can even be exclusively formed when R=*t*Bu.[9]

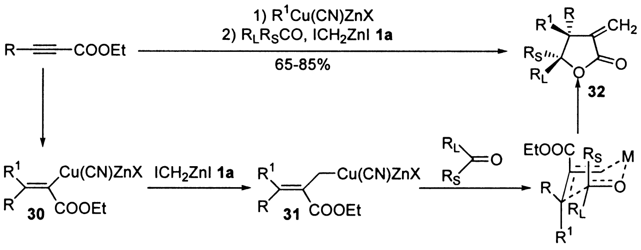
When the cyclohexenylcopper derivative **28** with a ketal functionality is treated with **1a** in the presence of aliphatic or aromatic aldehydes, the corresponding *lk* alcohols[11] **29a**,**b** are obtained with a complete regio- and diastereoselectivity in excellent yields (Scheme 10).[9]



Scheme 10.

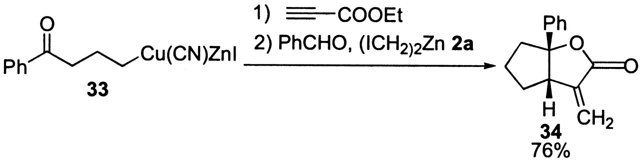
The methylene homologation can be extended to the one-pot preparation of highly functionalised α-methylene-γ-butyrolactones. Indeed, the carbocupration reaction[12] of acetylenic esters[13] with the organocopper reagent provides stereoselectively the alkenylcopper **30**. On addition of a carbonyl compound and (iodomethyl)zinc iodide **1a**, the in situ homologation reaction occurs to give the reactive polyfunctional allylic zinc–copper species **31**, which reacts stereoselectively with the carbonyl compound to give the α-methylene-γ-butyrolactones **32** (Scheme 11).[14]

The groups R of the alkyne, R^1 of the zinc–copper organometallic and R_L of the aldehyde can bear a wide range of functionalities (ester, nitrile, halide, triple bond), allowing a straightforward access to functionalise α-methylene-γ-butyrolactones **32**. A *cis* relationship is always found between the substituent R_L and R^1 in the major diastereoisomer of **32**, which is compatible with the chair-like transition state described in Scheme 11. The stereochemistry of the lactone **32** depends on the stereochemistry of the vinylcopper **30**. If the carbocupration can be performed at a low temperature (below −30°C), the resulting *syn*-adduct **30** is configurationally stable at this temperature and affords, after methylene homologation and reaction with a carbonyl compound, the *cis* lactone as the major diastereoisomer. If the alkenylcopper **30** is allowed to warm to −10°C, however, a mixture of the (*E*)- and (*Z*)-alkenylcopper is obtained and, after the same sequence of homologation-reaction with aldehyde, the butyrolactone is produced as a 75:25 *cis*/*trans* mixture of isomers.[9]



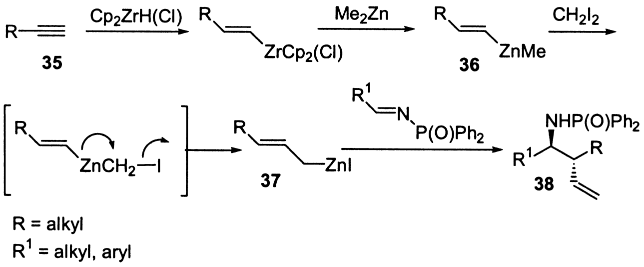
Scheme 11.

The intramolecular version of the reaction is also possible and the addition of the keto-substituted copper reagent[15] **33** to ethyl propiolate provides, after addition of **2a** and benzaldehyde, the bicyclic α-methylene lactone **34** in 76% yield (Scheme 12).[14]



Scheme 12.

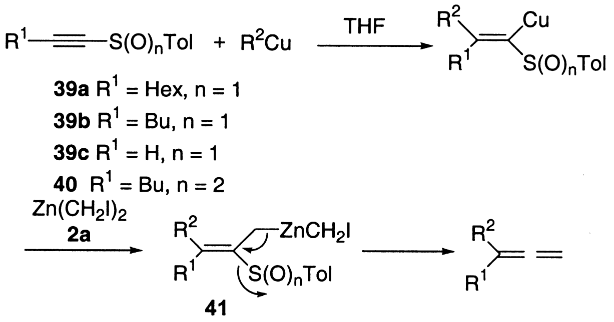
By using the same principle, homoallylic amines have recently been reported by a three-component coupling of aldimines, diiodomethane and alkenylzirconocenes in the presence of dimethylzinc (Scheme 13).[16]



Scheme 13.

The formation of homoallylic products is rationalised by the mechanism shown in Scheme 13. Hydrozirconation of the 1-alkyne **35** followed by transmetallation with Me_2Zn affords the vinylzinc intermediate **36**. The rapid reaction of **36** with CH_2I_2 gives, after the homologation reaction, the corresponding allylzinc **37**, which adds to aldimines to form the homoallylic amide **38**. Here again, a closed chair-like transition state is likely for this reaction, which explains the *anti*-relationship of the final product **38**.

This methodology of carbocupration–zinc carbenoid homologation was also successfully applied for a new synthesis of polysubstituted allenes,[17] without the possibility to have any side products such as alkynes, as obtained by using classical strategies.[18] This strategy is based on the carbocupration–zinc homologation of the alkynyl sulphoxides **39a–c** or the

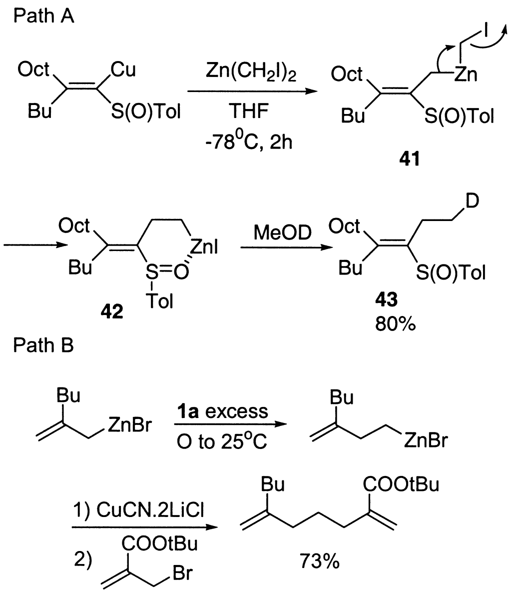


Scheme 14.

sulphone **40** to give the corresponding allylzinc derivatives **41**. A *syn* β-elimination reaction then occurs to lead to the desired allenes in excellent isolated yields (Scheme 14).[19]

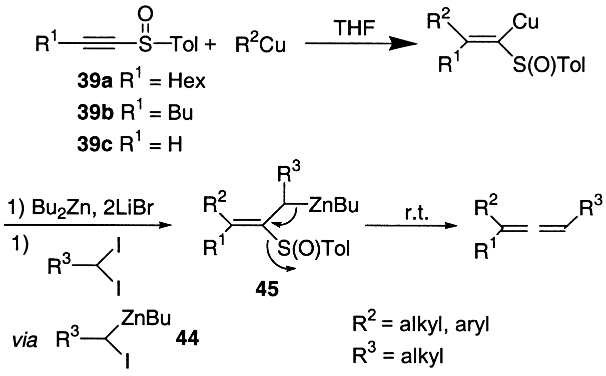
The scope of this reaction is broad since primary (Me, Bu and Oct) as well as secondary and even tertiary alkyl groups on the organocopper reagent (R^2) add cleanly to the alkynyl sulphoxides **39a–c** to lead to the corresponding vinylcopper. Via the homologation–β-elimination sequence, the allenes are then formed. Although the yield decreases slightly with the degree of substitution of the alkylcopper, the reaction proceeds smoothly in all cases. Even arylcoppers add cleanly to the hexenyl or ethynyl sulphoxides (**39a** and **39c**, respectively) to lead to the corresponding allenes in excellent yields. The alkynyl sulphones **40** also undergo this transformation. By using this strategy, functionalised allenes are prepared in quantitative yield.[19]

The homologation step with the carbenoid has to be performed between 0°C and room temperature in order to have a spontaneous β-elimination. At a lower temperature, the more reactive allylic organometallic derivative **41** (R^1=Bu, R^2=Oct, n=1) underwent a second homologation reaction (intra- or intermolecularly) to give the homoallylzinc **42** in good yield (the homoallylzinc derivative **42** is much less reactive than the parent allylzinc **41**). The presence of this organometallic derivative was proved by the isolation of **43** after reaction with MeOD (Scheme 15, path A). In a similar way, the treatment of 2-butyl-2-propenylzinc bromide with an excess of **1a** provides cleanly the homoallylic zinc (Scheme 15, path B). In this particular case, the insertion of a methylene unit in an allylic zinc bromide does not require the addition of copper(I) salts. The resulting homoallylic species is converted to the corresponding copper reagent and is allylated with *t*butyl-α-(bromomethyl)acrylate, leading to the corresponding ester in 73% isolated yield.[7]



Scheme 15.

Concerning the synthesis of 1,3-di- or 1,1,3-tri-substituted allenes, the use of a secondary carbenoid for the homologation reaction is necessary. Their uses in organic synthesis are, however, mainly limited[20] their in situ preparations for the cyclopropanation reactions.[21] The strategy was therefore designed in such a way that, as soon as the secondary zinc carbenoid is formed in the reaction mixture, it reacts with the vinylcopper (Scheme 16).[19]



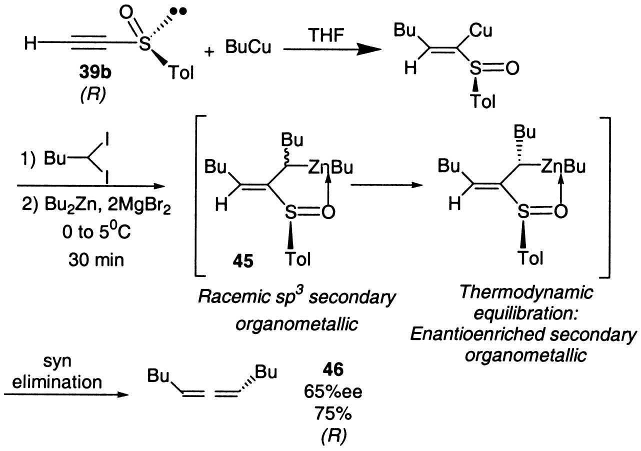
Scheme 16.

After the carbocupration reaction on **39a–c**, dibutylzinc (prepared by the reaction of 2 equiv. of nBuLi with $ZnBr_2$) is first added to the reaction mixture, followed by the 1,1-diiodoalkane at room temperature as described in Scheme 16.

A plausible mechanism for this reaction is as follows: the in situ-formed secondary carbenoid **44** (generated by the reaction between Bu_2Zn, 2LiBr and the diiodoalkane[22]) reacts with the vinylcopper to give the homologated product **45** as an unstable intermediate, which underwent an instantaneous β-elimination to furnish the corresponding allene in excellent yield.

Carbocupration–zinc homologation followed by β-elimination was also used for the asymmetric synthesis of allenes. In this case, the enantioselective step is the equilibration of the allylic sp^3 organometallic **45** before the *syn* β-elimination reaction (Scheme 17). In order to observe this equilibration, an intramolecular chelation between the zinc organometallic and the oxygen of **45** is necessary, and via a thermodynamic equilibration[23] (or deracemisation if related to an existing chiral center), an *anti* relationship between the tolyl and the alkyl groups is then more favourable.[24]

When the chiral propargylic sulphoxide **39c** of *R* configuration is reacted with BuCu·$MgBr_2$, followed by the zinc



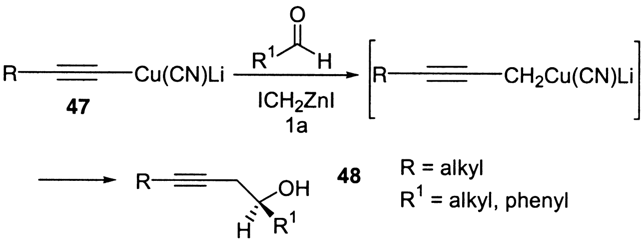
Scheme 17.

homologation–β-elimination conditions (described in Scheme 16), the optically active dibutylallene **46** of *R*configuration is obtained in good yield and in 51% enantiomeric excess. The absolute configuration of the starting material and of the final allene implies that the intermediate allylic zinc derivative **45** undergoes an epimerisation into the most stable intermediate in which the tolyl and the butyl groups are *anti* to each other, followed by a *syn* β-elimination as described in Scheme 17. The best enantiomeric excess (ee 65 and 75% yield) was obtained when the zinc carbenoid was prepared by treatment of the 1,1-diiodoalkane with $Bu_2Zn{\cdot}MgBr_2$ (by the reaction of $ZnBr_2$ with 2 equiv. of BuMgBr) and when the reaction mixture was stirred between 0 and 5°C during 30 min as described in Scheme 17.

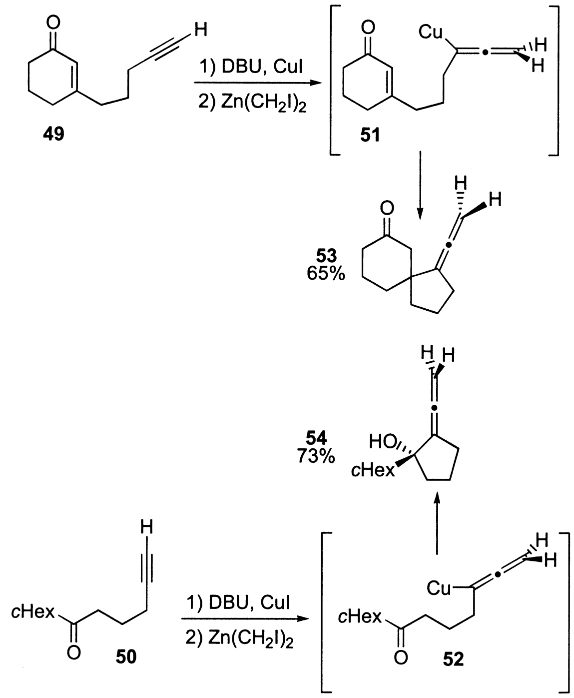
This magnesium salt effect on the enantioselectivity of the reaction indicates that further investigations are needed to elucidate completely the mechanism of this reaction as well as the exact nature of the allylic intermediate **45**.

2.1.5.2. Homologation of allenic and acetylenic copper derivatives. In common with alkenyl organometallic derivatives, acetylenic and propargylic reagents have very different reactivities, and this property can be exploited in performing a selective methylene homologation and selective trapping of the homologated organometallic. If the alkynylcopper **47** is treated with reactive aldehydes and an excess of (iodomethyl)zinc iodide **1a** at low temperature, the homopropargylic alcohol **48** is isolated in satisfactory to good yields (Scheme 18).

The intermediate organometallic reacts only at the propargylic position and no allene formation was observed. The homologation of copper acetylenides can be exploited to perform new types of cyclisation reactions. In this way, the functionalised terminal alkynes **49** and **50** can be deprotonated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and, by treatment with copper iodide, the corresponding copper acetylenides are formed. The copper acetylenides are then efficiently homologated with bis(iodomethyl)zinc **2a** providing the intermediate allenic copper reagents **51** and **52** which undergo a ring closure leading, respectively, to the spiroketone **53** and to the allenic alcohol **54** in good yields (Scheme 19).[9]



Scheme 18.

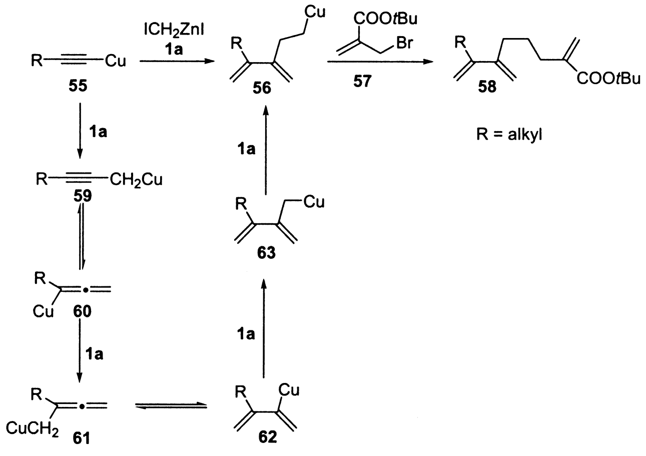


Scheme 19.

Here again, if an excess of (iodomethyl)zinc iodide **1a** is added to the copper acetylide **55** in the absence of an electrophile, a multiple methylene insertion is observed and the dienic zinc–copper reagent **56** is obtained.[25] After the addition of an allylic bromide such as *t*butyl-α-(bromomethyl)-acrylate **57**, the unsaturated ester **58** is obtained in good yield. The formation of the quadruple homologation products **56** can be explained by a first homologation of **55** with **1a** to give the propargylic zinc–copper reagent **59** (Scheme 20).

This propargylic organometallic is in equilibrium with the allenic copper derivative **60**, which can be further homologated by **1a** to the allylic reagent **61**. This species is in equilibrium with the dienic zinc–copper compound **62**, which after a third methylene homologation gives the allylic copper derivative **63**. As this derivative is extremely reactive towards **1a**, as discussed previously (path B, Scheme 15), **63** undergoes a fourth homologation providing the unsaturated alkylcopper derivative **56** which is now unreactive towards further homologations and can be trapped by the allylic bromide derivative (Scheme 20).

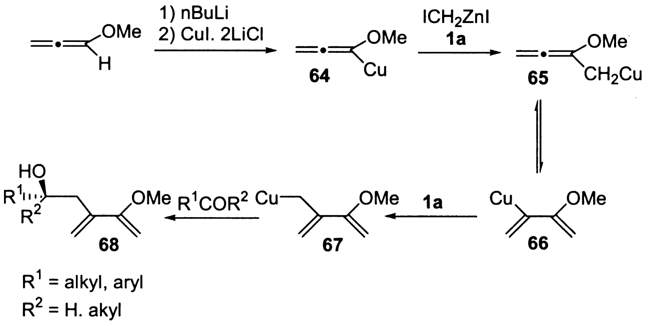
The allenic copper derivative **64** (an intermediate of type **60** from Scheme 20) can also be generated independently by metallation of methoxyallene with *n*BuLi,[26] followed by



Scheme 20.

a transmetallation reaction with CuI·2LiCl. As described previously, **64** reacts further with **1a** to furnish the allylic compound **65** which is in equilibrium with its dienyl form **66**.

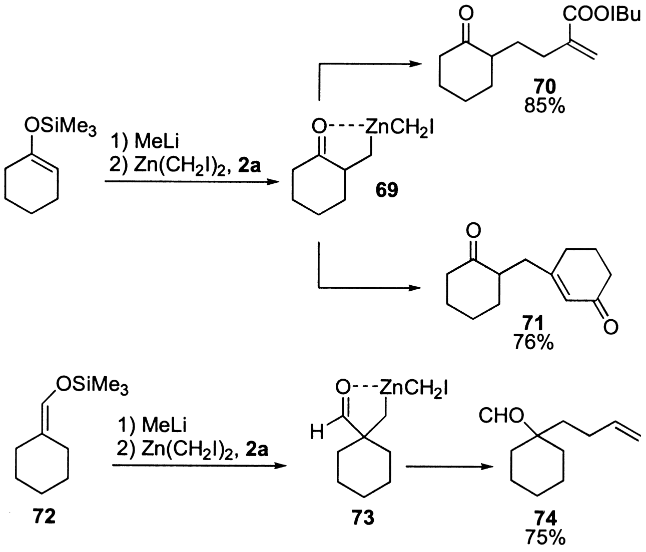
As vinylcopper is not a very reactive species towards aldehydes, a new homologation reaction now occurs to give the more reactive allylcopper species **67**, which can react in situ with the ketone to give the homoallylic diene **68** as described in Scheme 21.



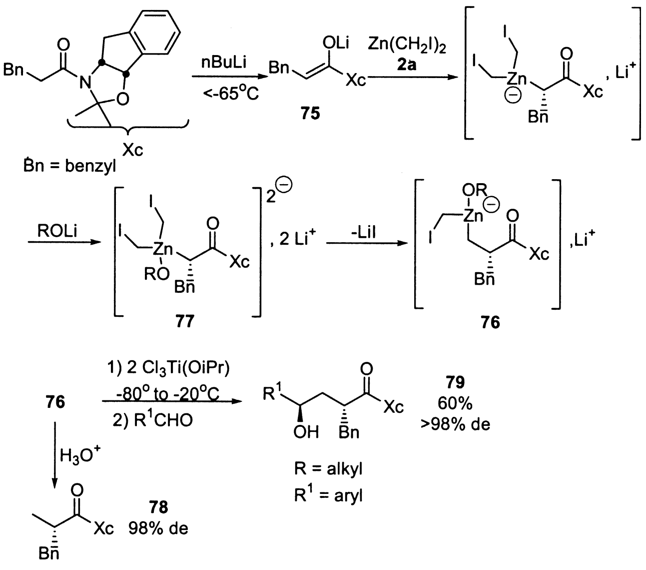
Scheme 21.

2.1.6. Homologation of enolate derivatives. Zinc organometallic derivatives bearing a carbonyl function at the β-position (homoenolates)[27] can be obtained by the homologation reaction of lithium enolates with bis(iodomethyl)zinc **2a**.[28] Treatment of the lithium enolate of cyclohexanone, generated from the silyl enol ether, with **2a** affords the homoenolate **69**, which can be allylated after transmetallation with CuCN·2LiCl to afford **70**. The homoenolate **69** can also be coupled with 3-iodocyclohexenone in the presence of a catalytic amount of Pd(dba)$_2$ and PPh$_3$ to afford **71** (Scheme 22).[29] Similarly, the silyl enol ether of cyclohexanecarboxaldehyde **72** was converted to the homoenolate **73** which was allylated with an excess of allyl bromide in the presence of CuCN·2LiCl, giving the aldehyde **74** in 75% yield (Scheme 22).[28]

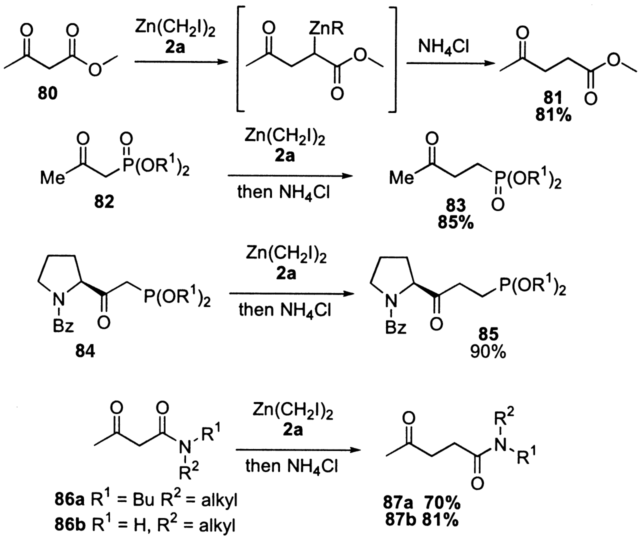
A more extensive exploration of the mechanism of the reaction between the chiral enolate **75** and bis(iodomethyl)zinc **2a** indicates that the yields are very dependent on the order of addition.[30] If the enolate **75** is added to 1.1 equiv. of **2a**, only 3% of the homologated product **76** is formed. If, however, the lithium enolate was added to a solution containing only 0.6 equiv. of **2a**, a 60% conversion to the homoenolate **76** was now produced. This study, coupled with in situ IR spectroscopy measurements led to the conclusion that the reaction proceeds through the higher order zincate **77**. Presumably, this species increases the electron density at the zinc centre, driving the 1,2-migration to **76** (Scheme 23). In order to reach the stage of the higher order zincate, which induces the homologation reaction, several alkoxides were therefore screened in this transformation. It was found that a lithium benzyl alkoxide (ROLi in Scheme 23) was the most appropriate alkoxide for this reaction and the 1,2-migration then occurs to give **76** in excellent yield and excellent diastereoselectivity (98% de) after hydrolysis (formation of **78**). Transmetallation of **76** with (*i*PrO)TiCl$_3$ followed by the reaction of the resulting homoenolate with aldehydes gives the homoaldol product **79** in 60% yield and with a diastereoselectivity higher than 98%.



Scheme 22.



Scheme 23.



Scheme 24.

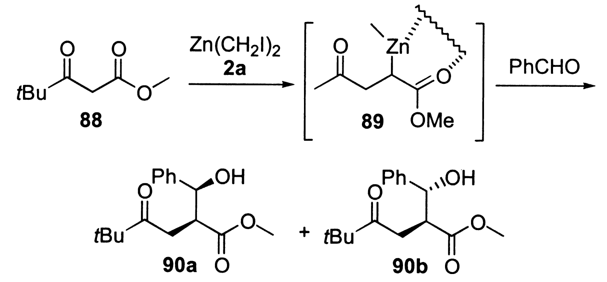
When the α-unsubstituted β-keto ester **80** is treated with an excess of **2a**, a clean and rapid formation of the γ-keto ester **81** is observed (Scheme 24).[31] The reaction is remarkably efficient with respect to the substitution pattern about the β-keto ester and substrates containing either electron-rich or electron-poor olefins underwent selective chain extension of the alkene in preference to cyclopropane formation. Substrates in which the ketone is incorporated into a small ring or which possess α-substitution of the β-keto ester react with diminished efficiency, although these limitations can most likely be overcome through prior formation of the trimethylsilyl enol ether.[32]

The intermediacy of a cyclopropyl alcoholate has been suggested as the reactive intermediate.[33] In a fashion similar to that observed with β-keto esters, treatment of the simple β-keto phosphonates **82** with **2a** provide also the corresponding γ-keto phosphonates **83**.[34] The most significant difference between the β-keto esters and the β-keto phosphonates is the rate with which the reaction proceeds. While the chain extension of **80** is typically complete within minutes, the chain extension of **82** required reaction times of the order of 2 h for complete consumption of the starting material. On the other hand, the presence of α-alkyl substituents, Lewis basic functionality, and modestly acidic NH protons in the R group is accommodated in substrates of the reaction of β-keto phosphonates.

As an example, the benzoyl-protected β-keto phosphonates **84** underwent an efficient transformation into their homologated products **85**.

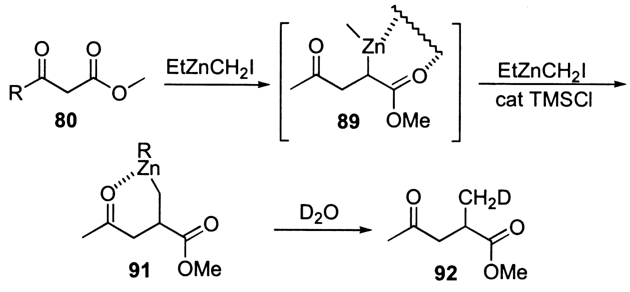
Finally, a large variety of α-unsubstituted tertiary β-keto amides are also easily transformed into their corresponding γ-keto amides in moderate to good yields as described in Scheme 24.[35] The effect of acidic hydrogen atoms on the amide was also tested and it was found that *N*-cyclohexyl-3-oxo-butanamide **86b** ($R^2{=}cC_6H_{11}$) reacted cleanly and provided the chain-extended product, *N*-cyclohexyl 4-oxo-pentanamide **87b** in excellent yield.[35]

As enolates are formed in this chain extension, a diastereoselective aldolisation reaction was then performed. This tandem chain extension-aldol reaction proceeds efficiently with β-keto ester and amides as starting materials.[36] For example, treatment of methyl pivaloylacetate **88** with diethylzinc and methylene iodide, followed by the addition of benzaldehyde, resulted in an isolated 95% yield of the two aldol products **90a** and **90b** in a *syn*/*anti* ratio of 12:1, via the intermediate species **99** (Scheme 25).



Scheme 25.

When an α-unsubstituted β-keto ester or an α-unsubstituted tertiary β-keto amide such as **80** (or **86a**, Scheme 24) is treated with $EtZnCH_2I$ in the presence of a catalytic amount of trimethylsilyl chloride, the corresponding α-methyl-β-keto ester (or amide) is formed in good yield (Scheme 26).



Scheme 26.

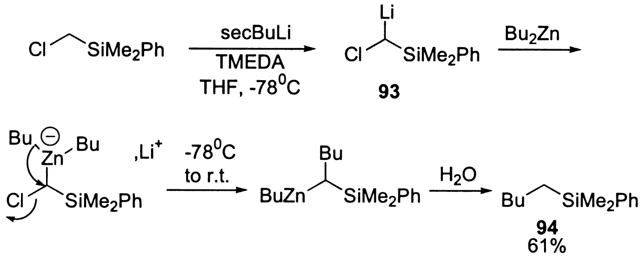
The trimethylsilyl group appears to promote the fragmentation of the possible dimeric species **89** and generation of an activated nucleophile **91** for the homoaldol reaction.[37]

3. 1,2-Organozincate rearrangement

1,2-Migration or 1,2-migratory insertion is, in principle, one of the most fundamental patterns for carbon–carbon and carbon–heteroatom bond formation. Indeed, the majority of carbon–carbon bond-forming reactions of organoboron compounds proceed via 1,2-migration.[38] In a similar way, carbonylation and related reactions of organotransition metals are representative examples of 1,2-migration reactions involving transition metals.[39]

3.1. 1,2-Migration reactions of dialkylzinc with α-halo-organolithium derivatives

The initial report of this 1,2-migration reaction of organozincate has been described when Bu_2Zn was added to $LiCH(Cl)SiMe_2Ph$ **93** at −78°C.[40] After hydrolysis, the



Scheme 27.

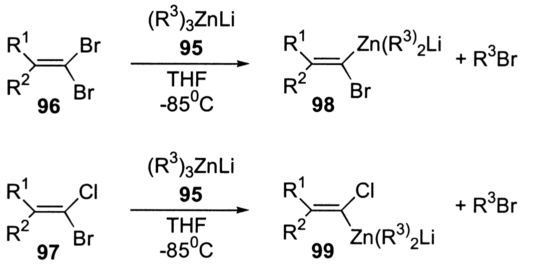
homologated product **94** was isolated in 61% yield (Scheme 27).

The above reaction can, in principle, proceed by various mechanisms. The three most likely paths are those involving: (i) 1,2-migration (Scheme 27), (ii) direct displacement as an S_N2 reaction on the carbenoid **93**, or (iii) carbene insertion after an α-elimination of **93**. The currently available data on the reaction pathway clearly favour the 1,2-migration reaction over the other two pathways.[40]

3.2. 1,2-Migration reactions of organozincate and dialkylzinc derivatives with 1,1-dihalo species

Although lithium carbenoids can be used as a method for the homologation reaction, its practical use is restricted unfortunately by the thermal instability of lithium carbenoids. Alternative approaches have then been described by reaction of organozincate with 1,1-dihalo derivatives.

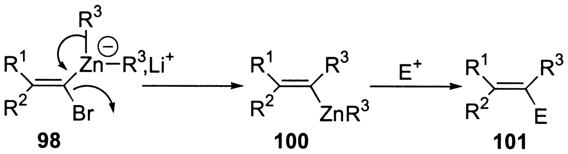
3.2.1. Reactions of 1,1-dihaloalkenes with triorganozincates. When lithium triorganozincates $[(R^3)_3ZnLi]$ **95** (easily prepared by the reaction of $ZnCl_2$ with 3 equiv. of the appropriate organolithium at 0°C in THF), are treated with 1,1-dihaloalkenes such as **96** or **97** at low temperature (usually around −85°C), the corresponding carbenoids **98** and **99** are formed via the corresponding halogen–metal exchange (Scheme 28).[41]



Scheme 28.

The exchange reaction can be carried out with various trioganozincates. The reactivities of the lithium zincates decreased roughly in the order R^3=*n*Bu, *s*BuLi>*t*Bu>Me≫Ph. No reaction proceeds with Me_3ZnLi at low temperature, but, at higher temperatures, the exchange reaction takes place with a simultaneous 1,2-migration of the resulting (1-haloalkenyl)zincate. On the other hand, no reaction is observed with Ph_3ZnLi, even at room temperature. Chloromagnesium zincate also undergoes the exchange reaction with **96** but the resulting carbenoid was less stable than the lithium zincate **98**. Both **98** and **99** are configurationally stable at −85°C and, therefore, the stereoselectivity in the Br/Zn exchange reaction is determined kinetically.[42] In general, the exchange reaction takes place preferentially at the more hindered bromine atom, although the level of selectivity is only moderate.[42] This observation is not compatible with a sterically demanding four-centred transition state or with a stepwise process initiated by a single electron process. The selectivity is most reasonably explained by a linear transition state of either anate complex[43] or an S_N2 reaction[44] where strain relief due to elongation of the carbon–bromine bond is expected in the reaction at the more hindered bromine atom.[42]

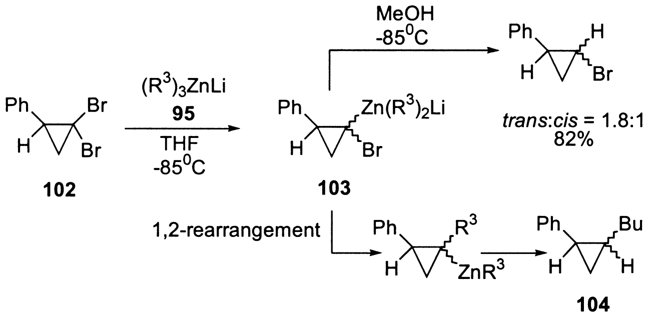
On warming, the (1-haloalkenyl)zincate **98** (or **99**) undergoes the 1,2-alkyl migration to generate the alkenyl species **100** (Scheme 29). A large variety of alkyl groups can be introduced via the corresponding zincates. The timing of carbon–halogen bond breaking and carbon–carbon bond formation plays an important role in determining the stereochemical outcome of the 1,2-alkyl migrations of zincate carbenoids. Without any unfavourable steric interactions, the stereoelectronically favoured alkyl migration with inversion take place synchronously with the breaking of the carbon–halogen bond. When the migration becomes sterically less feasible, the bond breaking may precede the migration and the alkyl migration proceeds less stereospecifically.



Scheme 29.

After the rearrangement, alkenylzinc species are formed in the reaction mixture and further reactions of these alkenylzincs with electrophiles are possible particularly under palladium(0) catalysis.[45]

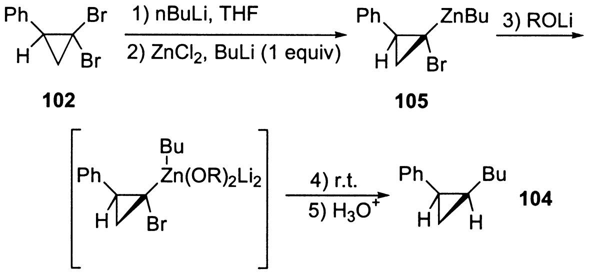
3.2.2. Reactions of 1,1-dibromocyclopropanes with triorganozincates. In a similar way, 1-bromocyclopropylzincates **103** can be readily generated in good yield by a bromide–zinc exchange reaction of the dibromocyclopropane **102** and trialkylzincates **95** in a modest isomeric ratio (*trans*/*cis*=1.8:1). The carbenoids **103** are stable at low temperature but undergo the 1,2-rearrangement by warming



Scheme 30.

to 0°C to give the corresponding 1-butyl-2-phenylcyclopropane **104** (R^3=Bu) in 86% yield after hydrolysis (Scheme 30).[46]

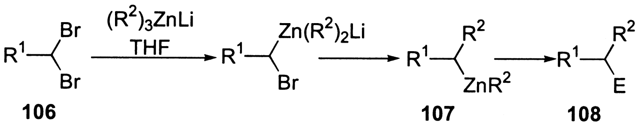
The low stereoselectivity observed in this 1,2-zincate rearrangement can be improved by generating the zincate carbenoid stereoselectively via the corresponding lithium carbenoid.[47] In order to avoid the excessive use of alkyl groups R^3 in this transformation (three R^3 groups for one cyclopropane), an interesting variant has been developed. Successive treatment of the lithium carbenoid generated from **102** with $ZnCl_2$ and 1 equiv. of BuLi at low temperature affords the stable zinc carbenoid **105**.[48] In the presence of metal alkoxides (2 equiv), **105** undergoes a similar 1,2-alkyl migration reaction to give stereoselectively *cis*-**104** after hydrolysis (Scheme 31).[47]



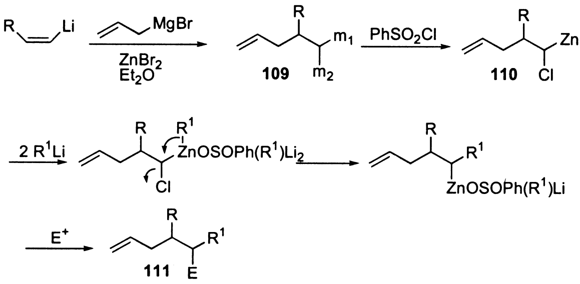
Scheme 31.

Once the cyclopropylzinc derivative **104** is formed, several electrophiles can be added[49] and particularly attractive is the metal-catalysed cross-coupling reaction.[50]

3.2.3. Reactions of 1,1-dibromoalkanes with triorganozincates. 1,1-Dibromoalkanes **106** exhibit lower reactivity in the Br/Zn exchange reaction in comparison with 1,1-dibromoalkenes and 1,1-dibromocyclopropanes (a rapid exchange at −85°C was observed, see Schemes 28 and 30). In contrast, the reaction of **106** with Bu_3ZnLi did not go to completion even at −40°C and gave the alkylated products **107** in only 27% yield with the recovery of **106**. In order to ensue a complete transformation, a large excess of the triorganozincate must therefore be used (5 equiv.) in the reaction mixture in order to have a good conversion of **107** into **108** (Scheme 32).[51]



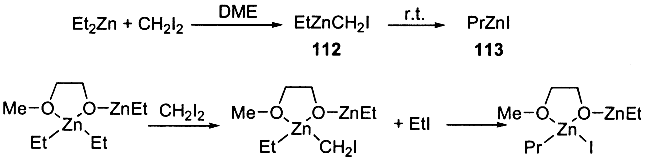
Scheme 32.



Scheme 33.

As an alternative approach, the selective chlorination of *gem*bismetallic derivatives **109** with benzenesulfonyl chloride leads to the chloro carbenoid **110**. When 2 equiv. of alkyl lithium are added to **110**, the corresponding zincate was formed which undergoes the intramolecular nucleophilic substitution to give the alkylated product **111** in good overall yield (Scheme 33).[20]

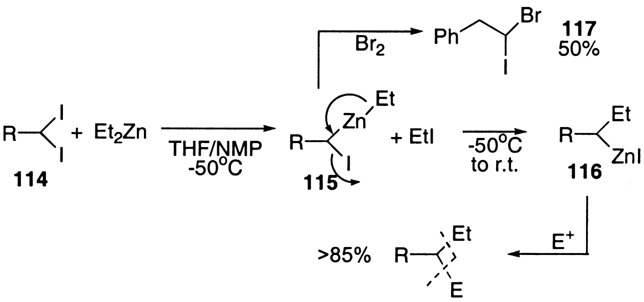
3.2.4. Reactions of 1,1-diiodoalkanes with dialkylzinc derivatives. When a carbenoid derivative is prepared using a 1:1 stoichiometry of Et_2Zn and CH_2I_2 in CD_2Cl_2 in the presence of an ether such as 1,2-dimethoxyethane (DME), an extremely rapid formation of the carbenoid $EtZnCH_2I$ **112** appears by analysis of ^1H NMR. This zinc carbenoid **112**, however, partly undergoes the 1,2-rearrangement at room temperature to produce PrZnI **113**.[52] This methylene insertion occurs in the absence of an olefin. To probe the effect of a zinc alkoxide on the rate of this methylene insertion, 2-methoxy-1-ethanol is treated with 2 equiv. of Et_2Zn followed by 1 equiv. of CH_2I_2. In this case, the rearrangement is even faster in the presence of a zinc alkoxide (Scheme 34).[53]



Scheme 34.

From the NMR experiment, it may be deduced that an external chelation from the solvent induces the rearrangement, most probably via a pseudo-zincate species.

As the use of polar cosolvents like *N*-methylpyrrolidinone (NMP) also increases the ionisation of the diorganozinc, providing a more reactive pseudozincate,[53] the 1,2-intramolecular rearrangement of sp^3 carbenoids in NMP was recently investigated.[54] Treatment of a 1,1-diiodoalkane[55] **114** with 1.2 equiv. of Et_2Zn in THF in the presence of NMP allows iodine–zinc exchange at −50°C to form the corresponding sp^3 secondary zinc carbenoid **115**. On warming the reaction mixture to room temperature, the carbenoid **115** undergoes an intramolecular nucleophilic rearrangement into the secondary organozinc iodide derivative **116** which can react with different electrophiles in good overall yields (Scheme 35).[55] In order to prove the stepwise mechanism, the intermediate zinc carbenoid **115** was trapped with Br_2 at −50°C into **117**. The α,α′-bromoiodo derivative **117** is isolated in only 50% yield, since minor

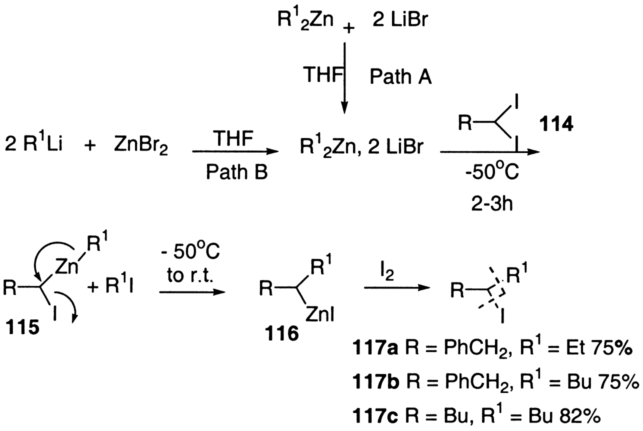


Scheme 35.

amounts of dibromoalkanes are always present in the crude reaction mixture (probably formed by degradation of the carbenoid **115** into carbene and subsequent reaction with Br_2).

The presence of NMP is absolutely necessary for the reaction to proceed since, in pure THF, no homologation was observed.

Moreover, as it was also reported recently that lithium halides may also modify the Lewis acid character of the zinc atom,[56] probably via a zincate species,[57] the behaviour of the combination of R_2Zn/LiBr in this intramolecular rearrangement was also checked. Addition of R^1_2Zn and 2LiBr in THF to **114** at −50°C also led to the formation of the carbenoid **115**, which rearranged cleanly into the secondary zinc iodide **116** and, after addition of iodine, **117** was isolated in 75% yield (path A, Scheme 36).



Scheme 36.

As the combination R^1_2Zn and 2LiBr was also successful for the intramolecular rearrangement, the direct preparation of this complex was performed by treatment of BuLi with $ZnBr_2$ in THF at 0°C to room temperature (path B, Scheme 36).

A solution of **114** was then added at −50°C and the reaction mixture was warmed to room temperature to furnish the homologated product, which was classically isolated as the iodide **117a–c** in excellent yields (Scheme 36).[55] The same result was obtained by the reaction of Bu_2Zn, $2MgBr_2$ (2BuMgBr with $ZnBr_2$) and **114** to furnish **117** in 75% yield. This new strategy allows not only the 1,2-zinc rearrangement but only 1 equiv. of the electrophile is necessary for the functionalisation of **116**.

4. Conclusions

Sp^3 zinc carbenoids such as (iodomethyl)zinc iodide or bis(iodomethyl)zinc have been successfully used for the diastereoselective and enantioselective cyclopropanation of olefins. The use of these carbenoids for different synthetic purposes, however, was much less frequent and the aim of this review is to demonstrate the potential of these derivatives for the selective creation of carbon–carbon bonds in a regio-, diastereo- and even enantioselective manner.

Acknowledgements

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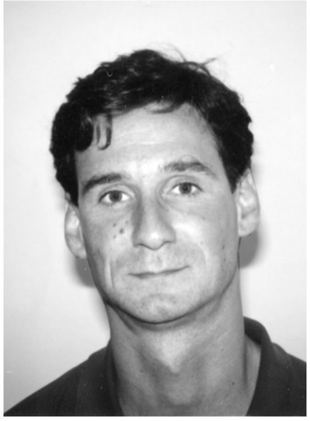
Biographical sketch



Ilan Marek was born in Haifa, Israel in 1963, educated in France and received his PhD degree from the University Pierre et Marie Curie, Paris in 1988 (Normant's laboratory). In 1989, he was posdoctoral fellow with Professor Ghosez in Louvain-La-neuve, Belgium and obtained a research position at the CNRS in 1990 (University Pierre et Marie Curie, Paris). After obtaining his Habilitation in Organic Chemistry at the University Pierre et Marie Curie in 1995, he moved to the Technion-Israel Institute of Technology at the end of 1997 where he holds an Associate Professor position. His current interests include the development of new methodologies in Organic Synthesis as the diastereoselective and enantioselective carbometallation reaction of alkenes, the synthesis and reactivity of polymetallated species, the reactivity of sp^3 carbenoids, the development of new preparation of vinylic and dienyl organometallic derivatives. He was awarded the first French Chemical Society-Acros Price for young Organic Chemist in 1997, the Japan Society for the Promotion of Science Visiting Professor Award (also in 1997), the Yigal Alon Fellowship (1998), the Salomon Simon Mani Award for excellence in Teaching (2002) and very recently the Michael Bruno Memorial Award from the Rotschild Foundation (2002).