

The chemistry of polyfunctional organozinc and copper reagents

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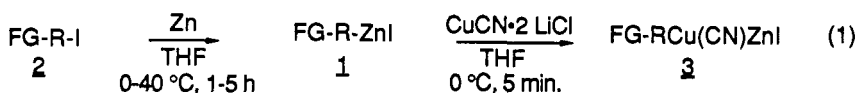
Abstract - Recent developments of the chemistry of polyfunctional organozinc and copper reagents applied to organic synthesis are presented.

INTRODUCTION

Functionalized organometallics are very useful intermediates allowing the rapid construction of polyfunctional molecules without the need of protection/deprotection steps and functional group interconversion steps. In the recent years, organozinc reagents were shown to tolerate the presence of most organic functionalities. In this review, we wish to report our recent progress in this field. Especially, we will demonstrate that polyfunctional zinc reagents can be used to perform highly chemo- and stereoselective transformations.

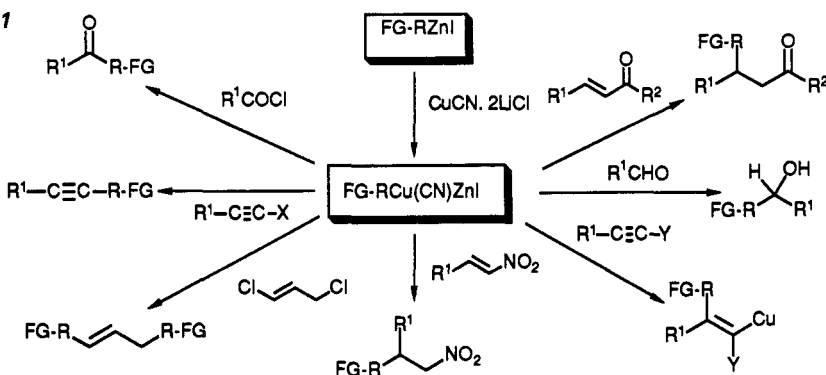
NEW PREPARATION OF ORGANOZINC REAGENTS

Organozinc halides **1** are generally prepared by the insertion of zinc dust to primary or secondary iodides **2** in THF (ref. 1). The reaction is usually complete within a few hours at temperatures between 0 °C - 40 °C (depending on the nature of the substrate (equation 1)) The alkyl halide can bear almost all organic functionalities (COOR, CN, COR, P(O)(OEt)₂, enoate, enone, NH₂, NHR, Si(OR)₃, SOR, SO₂R, SR, SCOPh, OCOR, CHO) (ref. 1). This high functional group compatibility implies that the zinc organometallics



1 have a very low reactivity toward most classes of organic electrophiles. However the addition of the THF soluble copper salt CuCN·2 LiCl affords the corresponding copper derivatives **3** which now display a good reactivity with electrophiles such as enones, and acid chlorides, allylic, alkynyl and alkenyl halides (ref. 1,2), activated alkynes (ref. 3), nitro olefins (ref. 4) and aldehydes (ref. 5); see Scheme 1.

Scheme 1



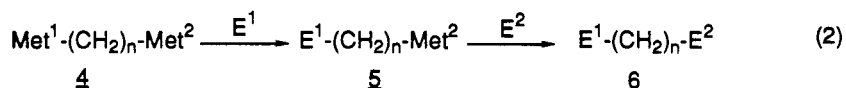
Alkyl bromides or chlorides can only be used under special conditions for the preparation of organozinc reagents (ref. 6). We have now found that the addition of catalytic amounts of an alkali iodide (MI; M = Li, Na, Cs; 0.2 equiv.) to a solution of a primary alkyl bromide in DMA (N,N-dimethylacetamide) containing zinc dust at 70 °C leads to a smooth formation of the corresponding organozinc bromide in high yields. Similarly the treatment of polyfunctional alkyl chlorides with a mixture of an alkali bromide (1.0 equiv.), an alkali iodide (0.2 equiv.) and zinc dust in DMA (ref. 7), leads to the corresponding organozinc halide. The addition of CuCN·2 LiCl followed by an electrophile affords the desired products in excellent yields (entries 1-3 of Table I). In strong contrast to Grignard reagents, it is also possible to insert zinc dust into primary mesylates and tosylates leading to new classes of organozinc reagents (RZnOTs and RZnOMs) which were found to display the usual reactivity toward electrophiles after the addition of CuCN·2 LiCl (entries 4-7 of Table I). Interestingly, the reaction can be extended to the preparation of benzylic and allylic zinc sulfonates (20 mol% LiI, DMA, 35 °C, 12 h; entries 8-10 of Table I). Remarkably, *no homo-coupling product* was observed in these reactions in contrast to benzylic and allylic bromides which under non-optimized conditions furnish variable amounts (5-100%) of Wurtz coupling products. These procedures allow a very practical and economical preparation of polyfunctional zinc and copper reagents both for a laboratory and industrial scale (ref. 7).

TABLE 1. Products obtained from the reaction of FG-RX (X = Cl, Br, OMs, OTs) with zinc, followed by the addition of CuCN·2LiCl and an electrophile

Entry	Product	FG-RX, Electrophile, Reaction Conditions for Zn Insertion and Yield	Entry	Product	FG-RX, Electrophile, Reaction Conditions for Zn Insertion and Yield
1		From EtO ₂ C(CH ₂) ₄ Br and nitro-styrene; LiI (0.25 eq.) in DME/DMSO, 80°C, 2.5 h; 85% yield	6		From 4-chlorobutylmesylate and 2-ethylthionitrocyclohexene; LiI (0.2 eq.), LiBr (1 eq.) in DMPU, 50°C, 12 h; 85% yield
2		From EtO ₂ C(CH ₂) ₃ Cl and ethyl 2-(bromomethyl)acrylate; CsI (0.2 eq.) in DMPU, 90°C, 36 h; 89% yield	7		From 4-chlorobutylmesylate and nitropentene; LiI (0.2 eq.), LiBr (1 eq.) in DMPU, 50°C, 12 h; 82% yield
3		From EtO ₂ C(CH ₂) ₃ Cl and 2-phenylsulfonylnitroethylene; NaI (0.2 eq.), NaBr (1.0 eq.) in DMPU, 75°C, 12 h; 78% yield	8		From benzyl mesylate and 3-iodo-2-cyclohexenone; LiI (0.2 eq.) in DMPU, 35°C, 12 h; 95% yield.
4		From citronellyl tosylate and ethyl propiolate; LiI (0.2 eq.), LiBr (1.0 eq.) in DMA, 60°C, 12 h; 81% yield	9		From benzyl mesylate and diethyl benzyldienemalonate; LiI (0.2 eq.) in DMA, 35°C, 12 h; 82% yield.
5		From citronellyl tosylate and 3-iodo-cyclohexenone; LiI (0.2 eq.), LiBr (1.0 eq.) in DMA, 60°C, 12 h; 85% yield	10		From 2-butylallyl mesylate and an aldehyde; LiI (0.2 eq.) in DMA, 35°C, 12 h; Barbier conditions R = Ph : 88% yield R = c-Hex : 85% yield R = Pent : 81% yield

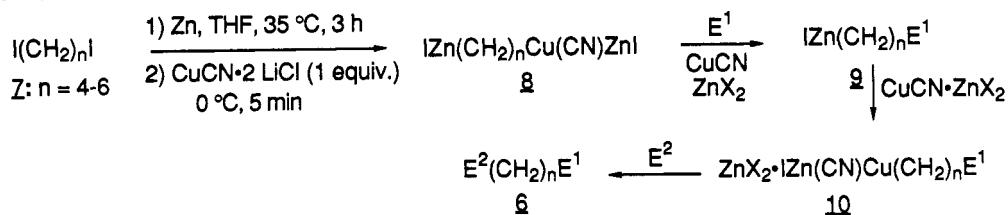
1,N-BIMETALLICS OF ZINC AND COPPER AS SELECTIVE MULTI-COUPLING REAGENTS

Mixed bimetallic reagents of type **4** bearing two carbon-metal bonds of different reactivity (C-Met¹ and C-Met²) can in principle react successively with two different electrophiles E¹ and E² giving the multi-coupling products **6**. The electrophile E¹ reacting first with the most reactive carbon-metal bond affords an intermediate functionalized organometallic **5** which can then react with a different second electrophile E² leading to the products of type **6** (equation 2). We found that this reaction scheme can be efficiently realized by using mixed bimetallic reagents of zinc and copper (ref. 8). Thus the addition of zinc dust to a 1,n-diiodide (n = 4-6) of



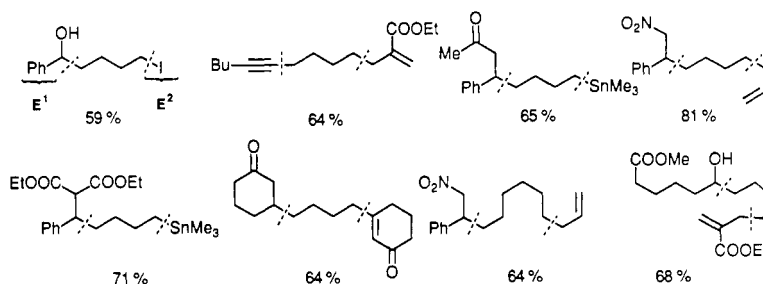
type **7** in THF at 35 °C (3 h) affords a bis-zinc organometallic which was treated with CuCN·2 LiCl (1equiv.) leading to the mixed bimetallic reagent **8**. Remarkably, the treatment of **8** with various types of electrophiles E¹ (aldehydes, enones, 1-iodoalkynes, nitro olefins, alkylidenemalonates) gives with high selectivity the mono-coupling products. The most reactive carbon-copper bond reacts with E¹ leading first to a functional-

Scheme 2



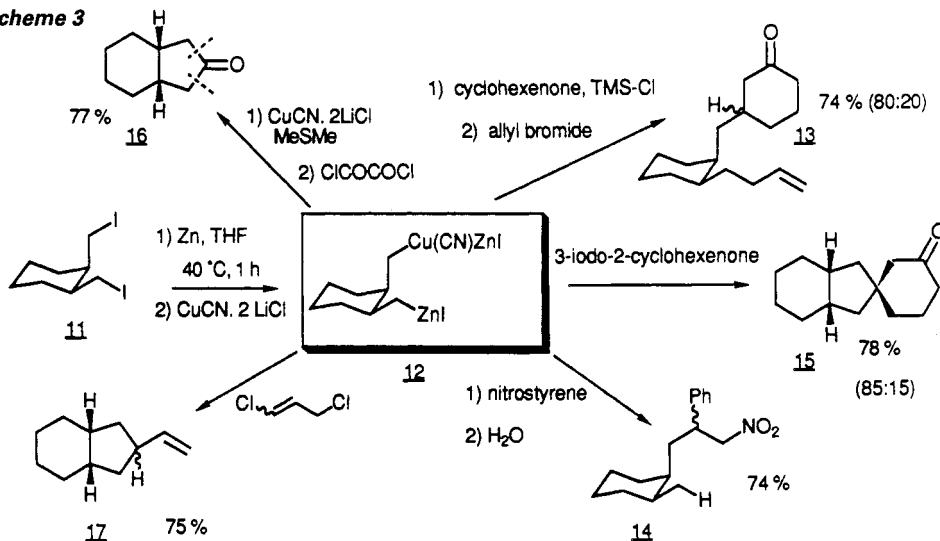
ized organozinc iodide **9**, liberating CuCN (1 equiv.) and ZnX₂ (1 equiv.). The zinc organometallic **9** will rapidly react with CuCN·ZnX₂ affording a new copper cluster **10** containing an extra equivalent of zinc salt (ZnX₂). The presence of an excess of zinc halide was shown in related studies to lower the reactivity of copper-zinc reagents and explains the observed good selectivity (less than 5% of symmetrical bis-coupling product E¹-(CH₂)_n-E¹ was formed). The reaction of **10** with a more reactive electrophile E² (iodine, allylic halides, water, 3-iodocyclohexenone, Me₃SnCl) leads to a wide range of highly functionalized molecules

Table 2. Products of type **6** obtained by the selective bis-coupling of two different electrophiles with the mixed copper, zinc bimetallics **8**.



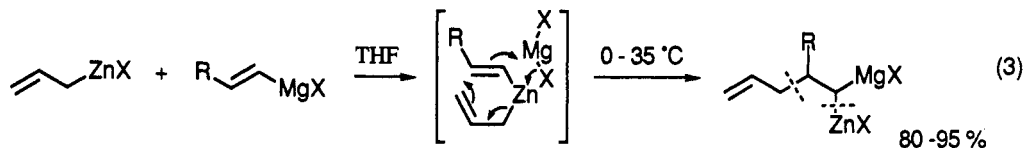
of type **6** (Scheme 2). This one-pot synthesis proceeds in 55-81% overall yields (Table 2). The reaction can be extended to structurally more complex bis-iodides. Thus, *cis*-1,2-bis(iodomethyl)cyclohexane **11** was converted to the bimetallic **12** and reacted selectively with successively cyclohexenone and allyl bromide giving the ketone **13** in 74% yield or nitrostyrene and water providing the nitroalkane **14** in 74% overall yield. Cyclization reactions with **12** can be readily performed; its reaction with 3-iodocyclohexenone gives the spiro-ketone **15** in 78% yield. Interestingly, the reaction of **12** with oxalyl chloride in the presence of an extra equivalent of CuCN·2 LiCl and Me₂S as co-solvent provides the bicyclic ketone **16** in 77% yield whereas the double substitution of 1,3-dichloropropene furnishes the bicyclic compound **17** in 75% yield (Scheme 3).

Scheme 3

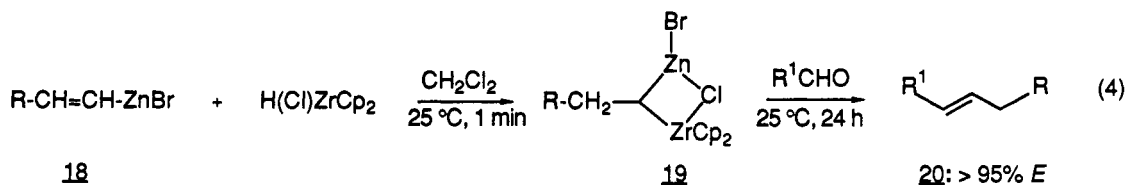


1,1-BIMETALLIC COMPOUNDS OF ZINC AND ZIRCONIUM AS SELECTIVE OLEFINATION REAGENTS

Some years ago, we reported the interesting chemical behavior of 1,1-bimetallic alkanes of zinc and magnesium of type **17** which were obtained via an allylzincation of alkenylmagnesium halides with allylic zinc



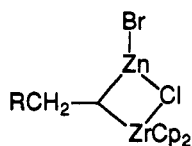
bromides (equation 3, ref. 9). These reactions proceed in high yields and under mild reaction conditions. However, they suffer from a structural uniformity, and many interesting carbon skeletons cannot be prepared via this route. In the search of a more general preparation of bimetallic reagents, we noticed the work of J. Schwartz (ref. 10), who showed that alkenylzirconium derivatives can be hydroaluminated affording 1,1-bimetallics of aluminum and zirconium which then reacted with aldehydes affording olefins with modest stereoselectivity. Similarly, we treated the readily available alkenylzinc halides **18** with $\text{H}(\text{Cl})\text{ZrCp}_2$ in CH_2Cl_2 (25°C , 1 min.) and obtained the 1,1-bimetallic reagents of zinc and zirconium tentatively formulated as **19** (equation 4). The reaction **19** with aldehydes (R^1CHO) gives (*E*)-olefins with a very high stereoselec-



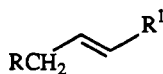
tivity (> 95% *E*) and in good yields (Table 3). A wide range of different structural bimetallics of type **19** can be prepared, and remarkably, the presence of functional groups such as an ester, nitrile or chloride is tolerated in these reagents (see the reagents **19c-e** of Table 3).

Ketones react with similar yields, affording in the case of cyclohexanone only exo-alkylidene cyclohexanes (**20h-20i**). The hydrozirconation of alkenylzinc halides gives 1,1-bimetallic alkylidenes (ref. 11) of type **21** which react with aldehydes (R^1CHO) leading to allenes **22** in 68-71% yield (equation 5).

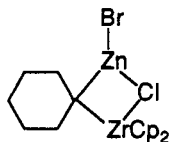
TABLE 3. 1,1-Bimetallics of zirconium and zinc of type **19** and polyfunctional (*E*)-olefins of type **20** prepared by the reaction of aldehydes with the bimetallics **19**



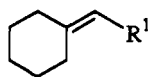
19a: R = Hex
19b: R = Ph
19c: R = $(\text{CH}_2)_3\text{Cl}$
19d: R = $(\text{CH}_2)_3\text{CN}$
19e: R = $(\text{CH}_2)_3\text{CH}(\text{Bu})\text{CH}_2\text{CO}_2\text{Et}$



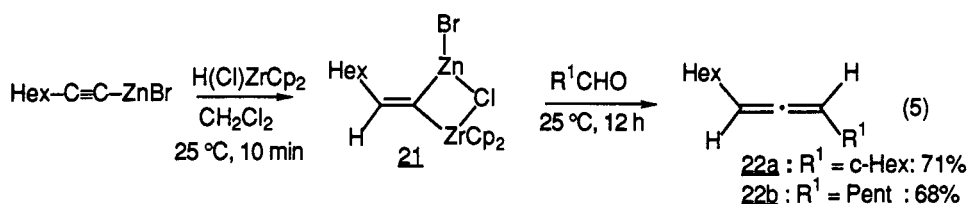
20a: R = Hex; R^1 = c-Hex : 83%; 100% *E*
20b: R = Hex; R^1 = Pent : 73%; 100% *E*
20c: R = Hex; R^1 = $(\text{CH}_2)_4\text{CO}_2\text{Me}$: 46%; 100% *E*
20d: R = Ph; R^1 = c-Hex : 86%; 100% *E*
20e: R = $(\text{CH}_2)_3\text{Cl}$; R^1 = c-Hex : 64%; 100% *E*
20f: R = $(\text{CH}_2)_3\text{CN}$; R^1 = c-Hex : 57%; *E*:*Z*, 94:6
20g: R = $(\text{CH}_2)_3\text{CH}(\text{Bu})\text{CH}_2\text{CO}_2\text{Et}$; R^1 = c-Hex : 68%; *E*:*Z*, 97:3



19f

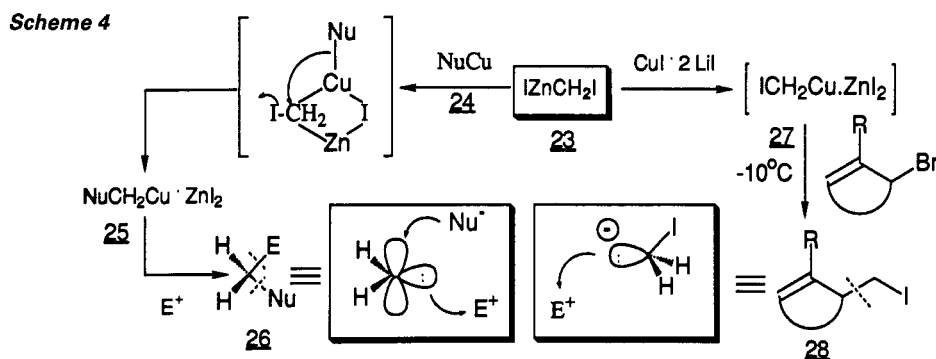


20h: R^1 = Ph: 83%
20i: R^1 = c-Hex: 76%

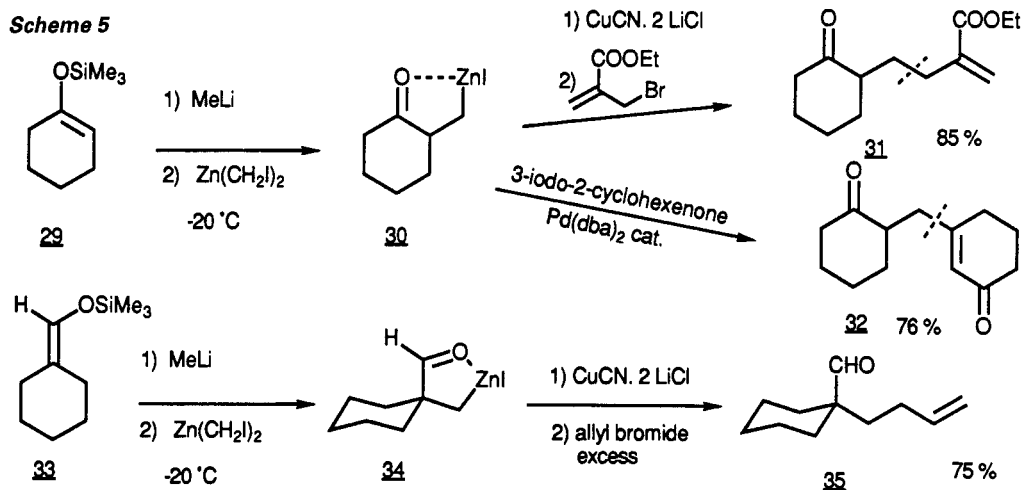


SELECTIVE METHYLENE HOMOLOGATION REACTIONS

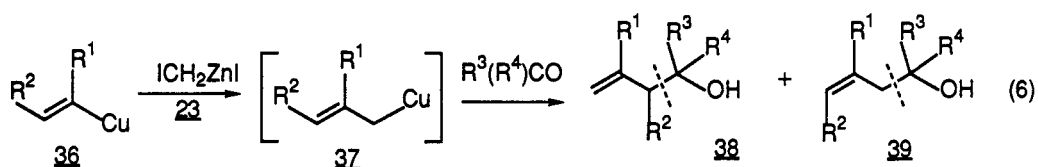
Iodomethylzinc iodide **23** which is prepared in high yield (ref. 12) by the direct insertion of zinc to diiodomethane (zinc foil, 25 °C, 3 h, 85% yield) was found to be an efficient synthetic equivalent of a carbene(CH₂). It allows very selective mono- and polymethylene insertion reactions into the carbon-copper bond of a wide range of organocopper reagents (ref. 13). The addition of NuCu **24** to ICH₂ZnI leads to a 1,2 migration of the group Nu from copper to zinc with a simultaneous substitution of the iodide; this process affords a new methylene homologated copper reagent **25** which can in a second step react with various electrophiles affording products of type **26** in which a nucleophile and an electrophile have been formally attached to a methylene unit. If copper iodide is the copper salt added, then a very reactive species ICH₂Cu·ZnI₂ **27** is formed which can be efficiently trapped with allylic halides affording homoallylic iodides **28** in high yields. In this case, iododomethylzinc iodide **23** plays the role of a synthetic equivalent of an anion at the alpha position to iodine (Scheme 4).



Lithium enolates can be efficiently homologated by a methylene unit by using (ICH₂)₂Zn prepared by the reaction of diiodomethane with diethylzinc. Thus the treatment of the lithium enolate of cyclohexanone generated from the corresponding silylenol ether **29** with (ICH₂)₂Zn affords the homo-enolate **30** which can be allylated after its transmetalation with CuCN·2 LiCl or coupled with 3-iodo-2-cyclohexenone in the presence of Pd(dba)₂ and PPh₃ (1 and 4 mol % respectively) leading to the products **31** and **32** in 85% and 76% yield. Similarly, the silylenol ether of cyclohexanecarboxaldehyde **33** was converted to the corresponding homo-enolate **34** which was allylated with an excess of allyl bromide in the presence of CuCN·2 LiCl affording the aldehyde **35** in 75% yield (Scheme 5).

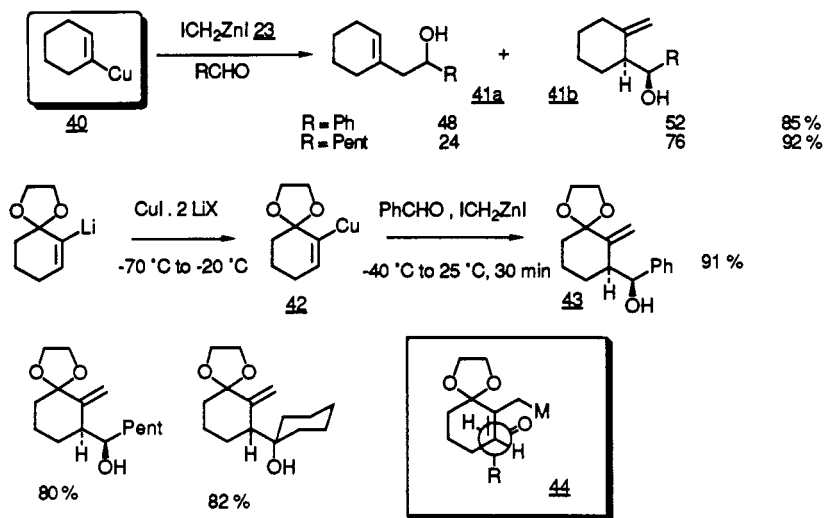


Of special interest is the direct conversion of alkenylcoppers **36** to allylic copper reagents **37** (equation 6). If the reaction is performed in the presence of a carbonyl derivative (aldehyde, ketone, imine, ethyl formate) the



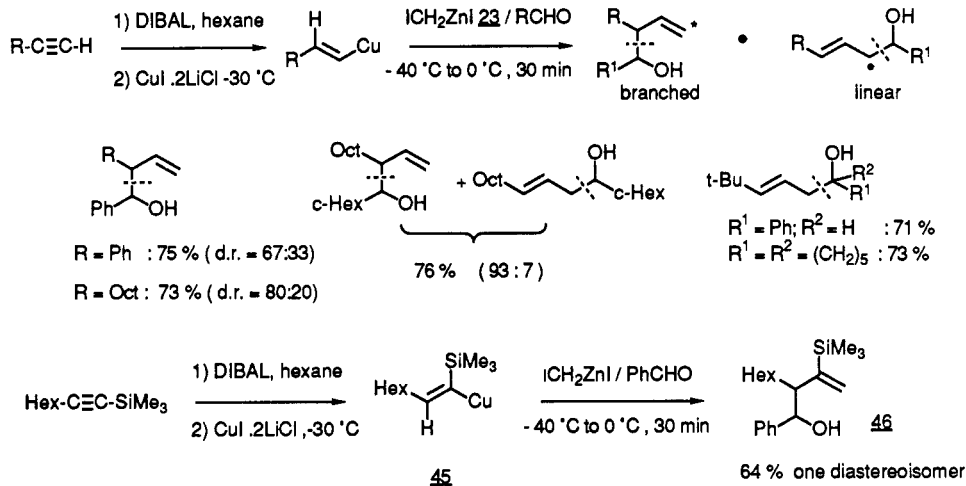
very reactive allylic organometallic **37** is trapped *in situ* and provides in the case of aldehydes or ketones, homoallylic alcohols of type **38** and **39** in high yields (equation 6). Thus, cyclohexenylcopper **40** reacts with aldehydes in the presence of iodomethylzinc iodide **23** and furnishes a mixture of the two regioisomers **41a** and **41b** in variable ratios (Scheme 6).

Scheme 6

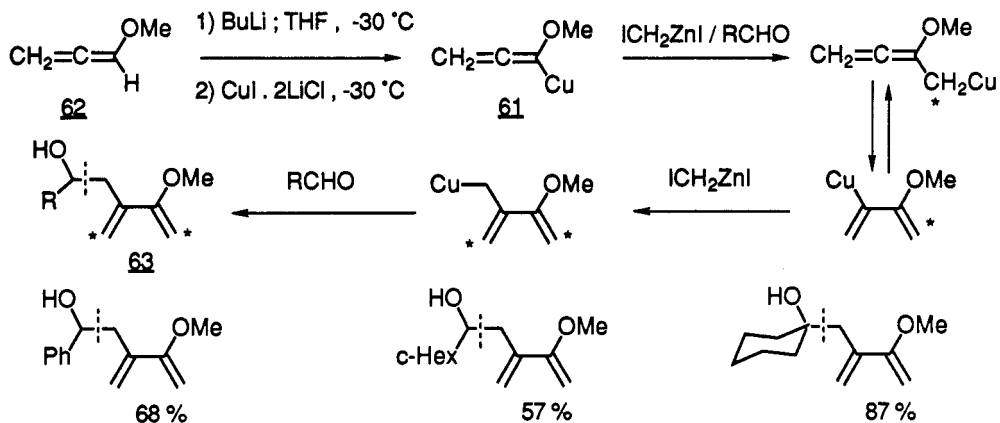


Interestingly, the regioisomer formed by the addition of the most substituted end of the intermediate allylic organometallic to the aldehyde is formed as only one diastereoisomer. The use of the cyclohexenylcopper **42** makes the reaction both regio- and diastereospecific and only the alcohol **43** is formed. This diastereoselectivity can be rationalized by assuming a cyclic transition state of type **44** (Scheme 6). We found that alkenylcopper reagents prepared by the hydroalumination of alkynes, followed by a transmetalation with $\text{CuI} \cdot 2 \text{LiCl}$ undergo the desired homologation reaction with **23** providing the expected homoallylic alcohols (Scheme 7). Especially promising is the generation of the (*E*)-1-sila-alkenylcopper **45** formed by the

Scheme 7

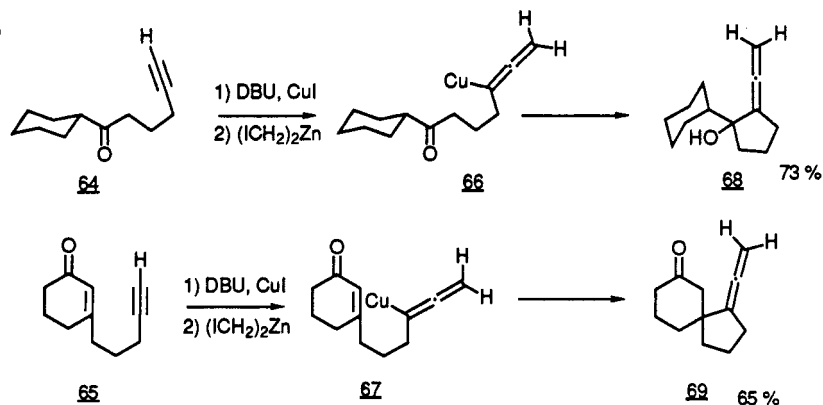


Scheme 9



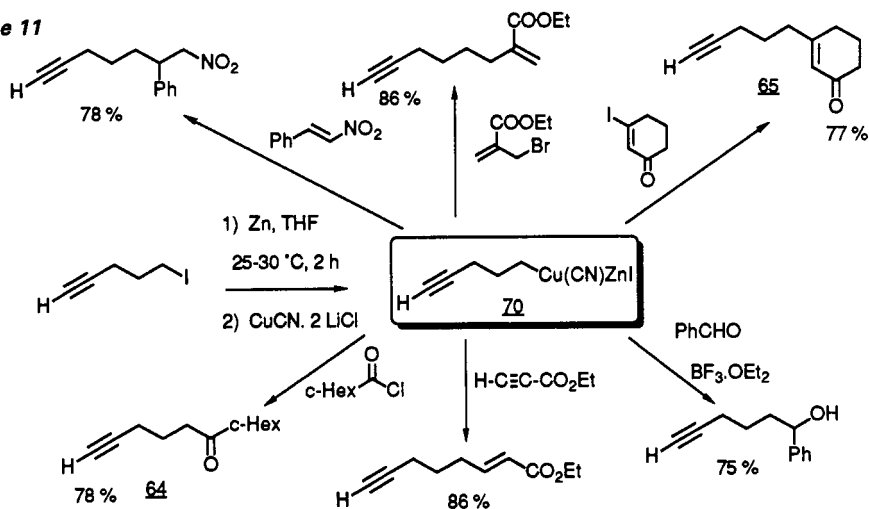
Novel ring closures are also possible and the treatment of the acetylenic ketones **64** and **65** with CuI in the presence of DBU (THF, 30 °C, 24 h) leads to an alkynylcopper which can be efficiently homologated by bis-(iodomethyl)zinc furnishing the intermediate polyfunctional allenyl copper compounds **66** and **67** which undergo a cyclization reaction (ref. 14) and give the functional allenes **68** and **69** (Scheme 10). The acetylenic

Scheme 10



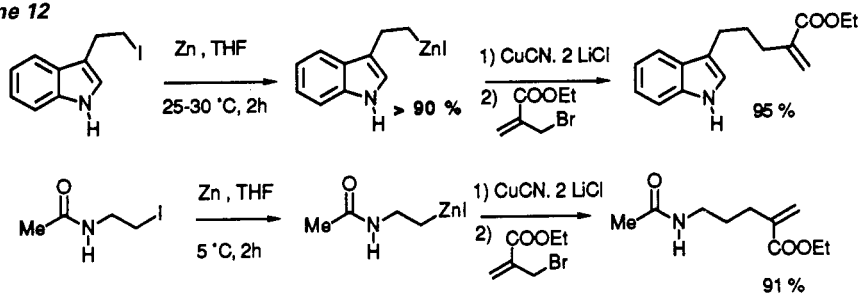
ketones **64** and **65** were prepared using the acetylenic copper derivative **70** which bears a terminal acetylenic hydrogen. The terminal acetylenic hydrogen of **70** reagent does not need to be protected in strong contrast to the corresponding magnesium or lithium compound and the reagent **70** can be used for the preparation of a variety of highly functionalized acetylenes (Scheme 11)

Scheme 11



A more general study showed that organozinc reagents bearing several classes of acidic hydrogens such as primary and secondary amines and amides can be readily prepared and used for the formation of new carbon-carbon bonds as shown for example in Scheme 12 (ref. 15).

Scheme 12



CONCLUSION

We have shown that polyfunctional zinc reagents allow unique chemoselective and stereoselective transformations. The high functional group compatibility as well as their good ability to form new carbon-carbon bonds should make these organometallics essential intermediates in organic synthesis.

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