Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis

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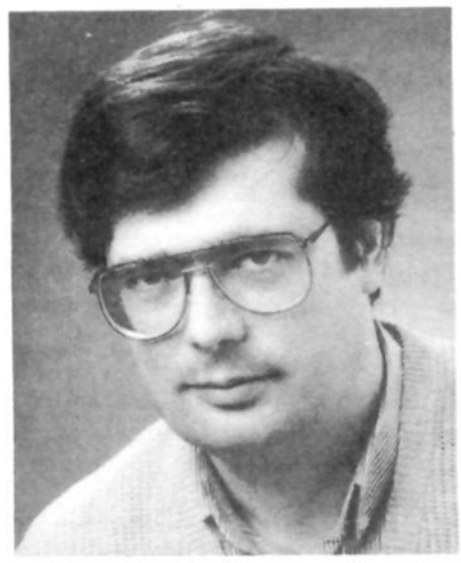
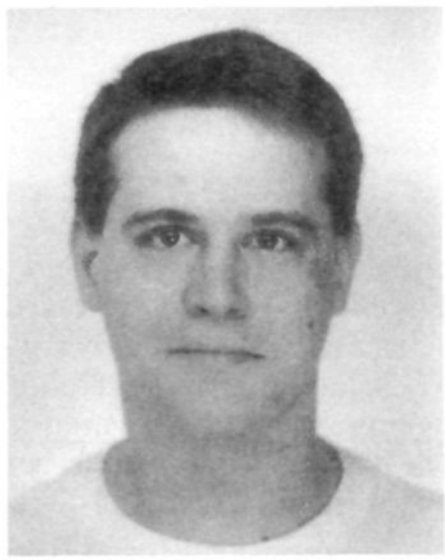
Contents



Paul Knochel, born in 1955 in Strasbourg, France, completed his Ph.D. under the supervision of Professor Dieter Seebach in 1982 (ETH Zürich, Switzerland). He joined the CNRS in Paris and worked in the laboratory of Professor Jean Francois Normant until 1986. After a year of post-doctoral research at the Princeton University with Professor Martin F. Semmelhack, he became assistant professor at the University of Michigan in Ann Arbor and full professor in 1991. He was awarded an Alfred P. Sloan fellowship and received the Berthelot Medal of the Academie des Sciences, Paris, France, in 1992. He then moved back to Europe and accepted a C4-professor position at the Philipps-University in Marburg, Germany. His research is focused on the use of organometallic reagents for the development of new synthetic methodologies.



Robert Douglas Singer was born at Halifax, Canada, on September 16, 1964. He received his B.Sc. Honours from Saint Mary's University, Halifax, Nova Scotia, and his Ph.D. from Simon Fraser University, Burnaby, British Columbia, in 1992 under Professor A. C. Oehlschlager. His thesis work involved spectroscopic and chemical investigations of alkyl-, (trialkylsilyl)-, and (trialkylstannyl)-cuprates. He is currently an Alexander von Humboldt Fellow engaged in postdoctoral research in the laboratory of Professor Paul Knochel at Philipps-University in Marburg, Germany. His research interests include the development of new organometallic methods in organic synthesis.

I. Introduction

Most organic target molecules are polyfunctional compounds requiring, in a retrosynthetic analysis,[1] the reaction between a functionalized carbon electrophile and a functionalized carbon nucleophile. Many carbon nucleophiles are organometallic reagents, and the highly reactive nature of the carbon–metal bond often pre-

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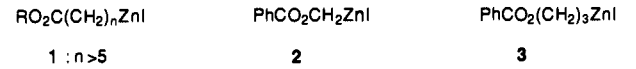
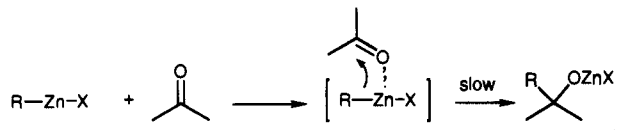
cludes having functional groups present in these reagents. Thus, the development of methods allowing the preparation of functionalized organometallic compounds is of great importance. These reagents will be very useful in the preparation of complex organic molecules since they will allow shorter synthetic routes by avoiding, for example, the use of protection–deprotection steps as well as functional group interconversions. The use of functionalized organometallics may also lead to the discovery of new reactivity patterns, especially if the carbon–metal bond can interact with an organic functionality in close proximity. This type of interaction may change both the chemical behavior of the functional group and of the carbon–metal bond leading to new synthetic applications. If the carbon chain linking the carbon–metal bond to the functional group has the appropriate length, then new ring closure reactions can be performed. Finally, if the functional group contains a chiral moiety, then new types of asymmetric synthesis will become possible.

A reactivity problem may, however, occur if functionalized organometallics are used. As a general rule, an organometallic reagent which tolerates the presence of a broad range of functional groups will display a low reactivity toward these organic functions and, in general, will also be relatively unreactive toward many organic electrophiles. The apparent contradiction of having a reactive organometallic bearing functionalities can be realized if two metals, M^1 and M^2, are used instead of one. The role of the first metal, M^1, will be to convert a highly functionalized organic substrate FG-RX into a relatively stable (and unreactive) organometallic FG-RM^1. This reagent is then transmetalated by the second metal, M^2, to a more reactive organometallic reagent, FG-RM^2, which can then react efficiently with an electrophile. A large part of this review will be devoted to the demonstration of the synthetic utility of this approach using Zn as M^1 and Cu, Pd, or Ti as M^2. Thus, after a section describing the various preparations of functionalized organozinc reagents, we will examine their reactivity toward electrophiles after transmetalation or in the presence of other metallic salts. Applications of the use of functionalized zinc–copper organometallics in natural product synthesis will be presented. Only the preparation and reactivity of organometallics bearing relatively reactive functionalities will be discussed. The chemistry of organometallic species bearing an ether, acetal, or ketal functionality will generally not be covered in this review. Only reactions in which organozinc compounds are clearly reaction intermediates will be discussed in detail.

Organozinc compounds (R_2Zn and RZnX) are one of the first classes of main-group organometallic compounds prepared.[2] Frankland discovered, in 1849 at Marburg, that the heating of ethyl iodide with zinc produces highly pyrophoric diethylzinc. Amazingly, hydrogen gas was used as protective atmosphere in this preparation.[3,4] A systematic study of the carbon–carbon-bond-forming ability of these reagents with typical organic electrophiles such as acid chlorides,[5] aldehydes, ketones,[6,7] or esters had been completed before 1880.[8] These popular organometallic reagents were, however, replaced at the turn of the century by the more reactive organomagnesium compounds. Only the Reformatsky reaction[9] (addition of zinc ester enolates to aldehydes) has remained in use by organic chemists. The reasons for this lack of interest were due to the very low reactivity of dialkylzincs toward most organic electrophiles and to the moderate yields obtained.[2] This low reactivity presents a potential advantage for the preparation of functionalized zinc reagents. This was first recognized in 1936 by Hunsdiecker who prepared several organozinc iodides **1** bearing an ester functionality by the direct insertion of zinc into the corresponding alkyl iodides in boiling ethyl acetate.[10] More than 30 years later, Wittig and Jautelat reported the preparation of [(benzoyloxy)methyl]zinc iodide **2** in ether (reflux, 4 h, 82% yield) and [3-(benzoyloxy)propyl]zinc iodide **3** in dioxane (90 °C, 2.5 h, 65% yield).[11]

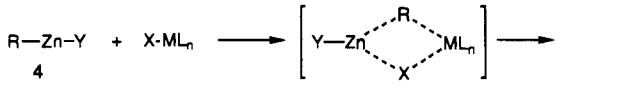


In these reports, no reactivity studies of these reagents were made. The reagent **2**[11,12] as well as ICH_2ZnI[12–15] were used as precursors of a carbene in cyclopropanation reactions. Only a few other reactions using ICH_2ZnI for forming new carbon–carbon bonds have been reported.[16,17] The low reactivity of organozincs is a result of the high covalent character of the carbon–zinc bond (comparable to the carbon–tin bond).[18] Also, the Lewis acidity of Zn(II) is not sufficient to activate carbonyl groups toward addition reactions (eq 1). On the other



(1)

hand, the empty low-lying p orbitals of zinc allow many transmetalation reactions with metallic salts to proceed as long as they are thermodynamically favored (eq 2). This excellent transmetalation ability permits the conversion of organozinc reagents **4** into a variety of new organometallics **5**.

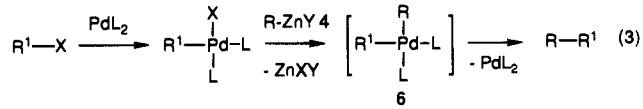


Y = R, halide...
M = Ti, Mo, Ta, Nb, V, Pd, Ni, Pt, Cu...

RML_n + ZnXY (2)

5

Especially interesting for synthetic applications are compounds **5** in which M is a transition metal, since these metals can mediate reaction pathways not available for main-group metals. Thus it has been shown, first by Negishi, that intermediate organopalladium(II) **6** can readily be formed from organozinc compounds **4**, and after reductive elimination, various cross-coupling products are obtained[20–25] (eq 3).



(3)

6

The process is catalytic in palladium and allows efficient cross-coupling reactions of various unsaturated

halides or acid chlorides with organozinc reagents.[20-25] Similarly, a transmetalation of 4 to copper organometallics using CuBr·SMe_2[26-27] in ether/HMPA, CuCN,[28] or CuCN·2LiCl[29] in THF are also possible (eq 4). The THF soluble copper salt CuCN·2LiCl is especially convenient, leading to functionalized copper reagents which react with various classes of electrophiles.

$$\underset{4}{R\text{—}Zn\text{—}Y} \xrightarrow{CuX} R\text{—}Cu \xrightarrow{E^+} R\text{—}\overset{+}{C}u\text{—}E \xrightarrow{-Cu^+} R\text{—}E \qquad (4)$$

Some of these reactions (allylation, acylation) can be performed using catalytic amounts of copper(I) salts.[28,29] Finally, the reactivity of the carbon–zinc bond toward aldehydes can be improved by the presence of various Lewis acids, and efficient asymmetric catalysis can be developed if chiral Lewis acid complexes are used.[30]

II. Preparation of Functionalized Organozinc Reagents

A. Preparation by a Direct Insertion of Zinc Metal

The rate of zinc insertion into the carbon–halide bond of organic halides depends strongly on the nature of the organic moiety, the halide, the reaction conditions (solvent, concentration, temperature), and the zinc activation. In 1962, Gaudemar reported that alkyl iodides insert zinc rapidly using zinc foil (electrolytic quality >99.9% purity) in THF under relatively mild conditions[31] (50 °C, for primary iodides, 25 °C for secondary iodides). This procedure proved to be very general. Zinc foil can be replaced by zinc dust from various sources (Aldrich, Fluka, Riedel-de Häen).[32] If the zinc dust is activated successively with 1,2-dibromoethane (4–5 mol %)[29,33] and chlorotrimethylsilane (1 mol %)[29,33,34] prior to the addition of the organic halide, then fast reaction rates are observed. Thus if the alkyl iodide (i.e. butyl iodide) is added as a 2.5–3.0 M THF solution, the zinc insertion is complete within 2–3 h between 35 and 40 °C. Secondary iodides react even faster, and a complete conversion to the alkylzinc iodide is usually observed after 0.5–1 h at 25 °C.[29] The zinc insertion shows a remarkable functional group tolerance and most common organic functional groups (i.e. ester,[29,35-52] ketone,[29,35] cyanide,[29,35-43,47,49-52,54] halide,[29,35,43,48,50,52] *N,N*-bis(trimethylsilyl)amino group,[55] primary and secondary amino groups,[56] amide and phthalimide,[25,56,57] trialkoxysilyl group,[58] sulfoxide,[59] sulfide,[59] sulfone,[59,60] thioester,[60] boronic ester,[46,48,50] enone,[40,53] and phosphate[39,61]) can be present during the organozinc formation (eq 5). Only hydroxyl groups (deprotonation) or nitro and azide functionalities (inhibition of the zinc insertion) cannot be present in the alkyl iodide.

$$FG\text{-}RX + Zn \xrightarrow[5\text{-}45\ ^\circ C]{THF} \underset{>85\%}{FG\text{-}RZnX} \qquad (5)$$

X = I, Br; FG = CO_2R, enoate, CN, enone, halide, $(RCO)_2N$, $(TMS)_2Si$, RNH, NH_2, RCONH, $(RO)_3Si$, $(RO)_2P(O)$, RS, RS(O), RSO_2, PhCOS; R = alkyl, aryl, benzyl, allyl.

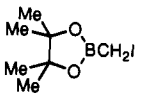
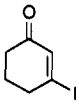
The structure of the alkyl halide is very important for predicting the zinc insertion rate. Thus, allylic and benzylic groups considerably facilitate the formation of the zinc reagent and these reactions occur between 5 and 10 °C allowing the less active organic bromides[31] (or even chlorides[36,37]) to be used. The presence of a polar functional group in the α or β position to the halide in an alkyl chain also strongly enhances the zinc insertion rate. Thus, whereas butyl iodide reacts in THF at 40 °C, the presence of a cyano group[54,55] at the β position to the halide allows zinc insertion at 25–30 °C. The presence of a polar phosphonate moiety in the organic halide enables successful zinc insertion under very mild conditions. Thus, diethyl 2-*bromo*ethylphosphonate[61] is converted to the corresponding zinc reagent at 30 °C (10 h; >85% yield). The exact reason for such a rate enhancement is not clear. Since the addition of equimolar quantities of acetonitrile to butyl iodide does not enhance the rate of zinc insertion in this reaction, the observed rate enhancement mentioned above cannot only be due to more efficient solvation of the zinc reagent or more efficient displacement of the newly formed organometallic from the zinc surface. The close proximity of the polar group to the carbon–iodine bond is also important. Hence, the rate of the zinc insertion to the iodides of type $NC(CH_2)_nI$ decreases as n increases and reaches a comparable rate to the zinc insertion into butyl iodide when $n = 4$. Thus, the polar group may facilitate the zinc insertion by accepting an electron from the zinc surface. This electron may then be transferred in a second step into the σ^*(C–X) orbital. These successive electron transfer reactions between closer energy levels should proceed at a faster rate than the direct electron transfer from the zinc surface to the σ^*(C–X) orbital.[62] Interestingly, the presence of a nitro or azide functionality in the molecule completely inhibits zinc insertion. In these cases, the electron from the zinc surface seems to be transferred reversibly to the NO_2 or N_3 group (no reduction product is observed under aprotic conditions in THF), and no further transfer to the σ^*(C–X) seems to occur. Also, pinacol (iodomethyl)boronate, which has a low empty nonbonding orbital centered at boron, inserts zinc very rapidly (20 °C, 0.1 h, >90% yield).[46] The presence of a phenylthio group, which is also a good electron acceptor,[63] allows smooth zinc insertion into the *carbon–chlorine* bond in chloromethyl phenyl thioether (THF, 25 °C, 1 h).[59,60] Alkenyl and aryl iodides having a stronger Csp^2–I bond (compared to Csp^3–I) do not insert zinc in THF and react only in polar solvents at elevated temperatures with zinc metal (DMF, 70 °C, 14 h).[35] However, a vinylic iodide conjugated with a carbonyl group such as 3-iodo-2-cyclohexen-1-one is converted to (3-oxo-1-cyclohexenyl)zinc iodide in THF under quite mild conditions (25–50 °C, 0.5 h; >85% yield).[53] Some typical reaction conditions for the preparation of organozinc halides are summarized in Table 1.

The preparation of alkylzinc halides can also be performed in mixtures of benzene and DMA or HMPA using a zinc–copper couple.[21-25,28b,c] It is possible to generate *in situ* very reactive zinc metal by the reduction of zinc chloride with lithium naphthalenide in THF (eq 6).[64-67] This type of zinc reacts with alkyl *bromides*

$$ZnCl_2 + Li\text{•}Naphthalene \longrightarrow Zn^* \xrightarrow[THF,\ 25\text{-}60\ ^\circ C]{FG\text{-}RX} FG\text{-}RZnX \qquad (6)$$

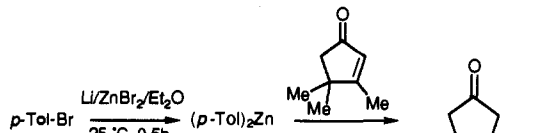
X = Cl, Br, I

Table 1. Reaction Conditions for the Preparation of Organozinc Halides from the Corresponding Organic Halides (Added as 2.5–3.0 M Solution)

organic halide	T (°C)	t (h)	solvent
n-BuI	45–50	3–4	THF
c-HexI	25–30	2	THF
$NC(CH_2)_2I$	20	2	THF
$(EtO)_2(O)P(CH_2)_2Br$	30	10	THF
	20	0.1	THF
$PhSCH_2Cl$	25	1	THF
Hex(H)C=CHI (E or Z)	70	14	DMF
	25–50	0.5	THF
benzyl bromide	0–5	2	THF
allyl bromide	10	4–5	THF

in THF at 25 °C in a few hours and with aromatic *bromides* at reflux, in THF, affording the corresponding organozinc bromides in excellent yields. After a transmetalation to the copper reagent by the addition of the THF soluble copper(I) salt CuCN·2LiBr,[29] various electrophiles (i.e. acid chlorides, enones, and allylic or propargylic halides) react with these organometallics in excellent yields. The addition of an aromatic bromide or iodide bearing an electron-withdrawing group to the zinc reagent in the presence of $Pd(PPh_3)_4$ (5 mol %) also produces the desired coupling products.[64] The reaction was shown to tolerate various functional groups (i.e. ester, nitrile, aromatic ketone, or halide)[64–67] and should be especially useful for the preparation of polyfunctional aromatic zinc compounds.

A potentially very promising preparation of dialkyl- and diarylzinc reagents is the direct reaction of alkyl, alkenyl, and aromatic bromides with lithium metal and zinc chloride under sonication.[68–72] The reaction proceeds under mild conditions and affords reactive diorganozincs which undergo 1,4-addition reactions with enones in the presence of nickel(II) salts (eq 7). The sonication of an alkyl iodide and a zinc–copper couple in the presence of an enone in an aqueous medium provides the 1,4-adduct in excellent yield (eq 8).[68,71]



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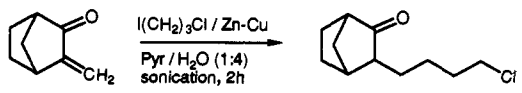
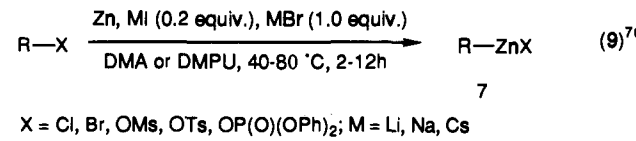


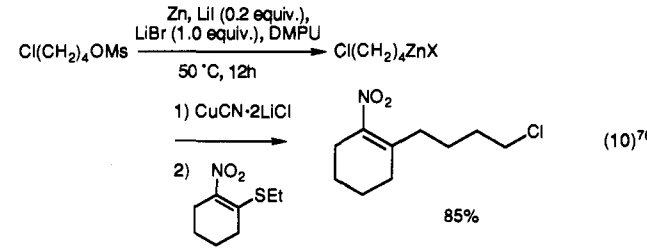
(8)

It is, however, questionable if the reaction proceeds through the intermediate of a zinc or copper organometallic while the radical nature of the reactive species is very probable.[73] Remarkably, this Barbier reaction[74] can be performed with alkyl iodides bearing a halide or a hydroxy functionality.[68] The use of polar solvents such as *N*,*N*-dimethylacetamide (DMA) or *N*,*N*-dimethylpropylene urea (DMPU)[75] in the presence of a catalytic amount of LiI allows the use of primary alkyl chlorides, sulfonates, phosphates, or bromides as precursors for the formation of organozinc compounds **7** (eq 9).[76]



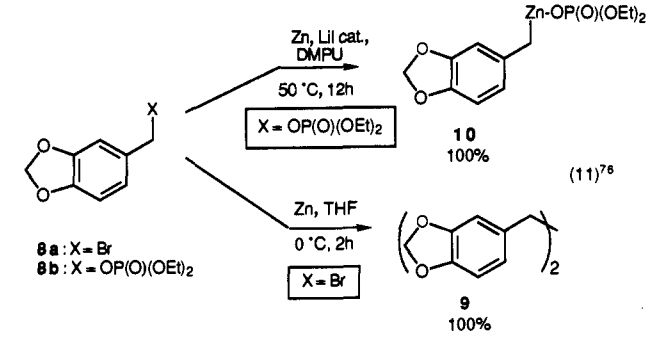
(9)[76]

Various functional groups are tolerated such as an ester, cyanide, or chloride. After the addition of CuCN·2LiCl,[29] these zinc reagents are readily converted to the corresponding copper derivatives and react well with various electrophiles (eq 10).[76]



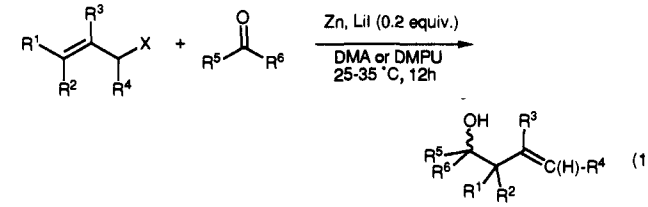
(10)[76]

Remarkably, the reaction can be extended to the preparation of benzylic and allylic zinc reagents. These reactions proceed without the formation of Wurtz-coupling products. Thus, for example, an electron-rich benzylic bromide such as **8a** (X = Br) furnishes, with zinc under typical reaction conditions (THF, 5 °C, 2 h), only the Wurtz-coupling product **9**. However, the reaction of the corresponding phosphate **8b** [X = OP(O)(OEt)$_2$], which is obtained in quantitative yield from the corresponding benzylic alcohol,[77] reacts with zinc in DMPU in the presence of LiI (0.2 equiv) to produce, after 12 h at 50 °C, the desired zinc reagent **10** without the formation of *any* self-coupling product **9** (eq 11).



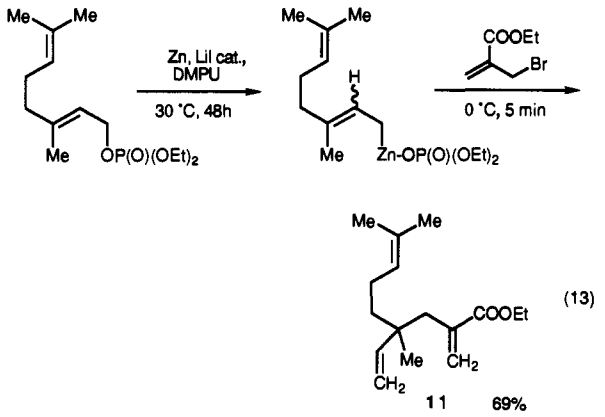
(11)[76]

Allylic mesylates and phosphates react under Barbier conditions in the presence of an aldehyde or ketone, LiI (0.2 equiv), and zinc in DMA or DMPU to furnish homoallylic alcohols in excellent yields (25–35 °C, 12 h, 78–95% yield, eq 12).[76]



(12)

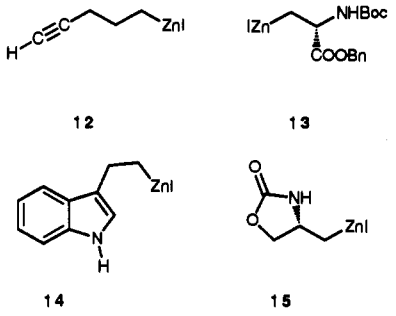
The reaction proceeds well, even with highly substituted allylic mesylates or phosphates (i.e. no Wurtz coupling). It is also possible to generate the zinc organometallic first and to couple it in a second step with a reactive allylic bromide such as ethyl α-(bromomethyl)acrylate[78] to obtain the cross-coupling product 11 in 69% yield (eq 13).[76]



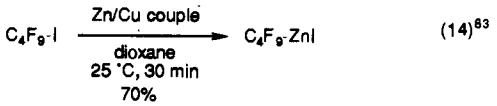
(13)

It should be mentioned that allylic or benzylic phosphates are far more stable than the corresponding bromides, tosylates, or mesylates and thus, are particularly convenient precursors for the preparation of allylic or benzylic organozinc reagents.[77]

Relatively acidic protons are tolerated during the preparation of organozinc halides in strong contrast to the preparation of organomagnesium or lithium compounds. Thus, 5-iodopentyne can readily be converted to the zinc reagent **12** (THF, 25–30 °C, 2 h) with less than 5% deprotonation.[56,79] Similarly, zinc reagents bearing NH and NH_2 groups of amines or amides can be obtained, and the reagents **13**,[80,81] **14**,[56] and **15**[95] can be easily prepared and reacted with electrophiles in the presence of Cu(I) or Pd(0) complexes.[56,80,81]

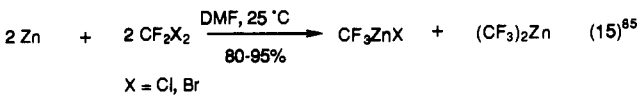


Remarkably the reagent **13** does not show any tendency to undergo a β-elimination reaction, and other zinc reagents bearing a potential leaving group in the β-position such as $NCCH_2CH_2ZnI$[54] and $(EtO)_2P(O)CH_2CH_2ZnI$[61] do not undergo an elimination under the usual reaction conditions. Fluorinated organozinc reagents have also been prepared by the direct insertion of zinc metal. Thus polyfluoroalkyl iodides are cleanly converted to the corresponding zinc reagents under mild conditions in solvents such as dioxane or THF[82,63] (eq 14). These compounds have a low reactivity,[84] and



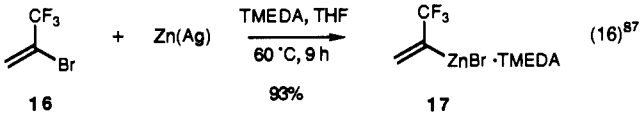
(14)[63]

transmetalations to the corresponding copper reagents have been performed to increase their reactivity. If difluorodihalomethanes, such as CF_2Cl_2 or CF_2Br_2, are submitted to zinc insertion in DMF, a complex reaction occurs[85] and produces a mixture of bis(trifluoromethyl)zinc and a trifluoromethylzinc halide in high yield (eq 15).[85,86]



(15)[85]

The presence of a trifluoromethyl group close to the carbon–halide bond in vinyl halides facilitates the formation of the organozinc reagents[87–89] and 2-bromotrifluoropropene **16** can be converted to (trifluoroisopropenyl)zinc bromide **17** in THF (60 °C, 9 h, 93% yield; eq 16).[87]

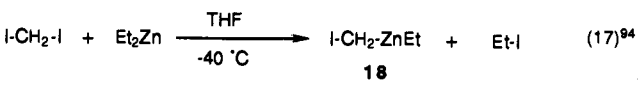


(16)[87]

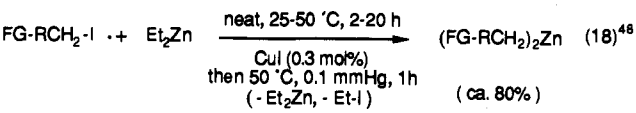
Finally, electrochemical methods[90] or the use of metal vapors[91] of Zn can also be used to prepare fluorinated organozinc reagents.

B. Preparation of Functionalized Dialkylzincs by an Iodine–Zinc Exchange Reaction

The preparation of diorganozinc compounds is of special importance due to the utility of these reagents for catalytic asymmetric additions to aldehydes.[92,93] Furukawa described in 1966 that diiodomethane readily reacts with diethylzinc affording ethyl(iodomethyl)zinc (**18**) and ethyl iodide in quantitative yield[94] (eq 17). This reaction can be greatly extended to a variety of functionalized primary iodides (eq 18).[48,95]



(17)[94]

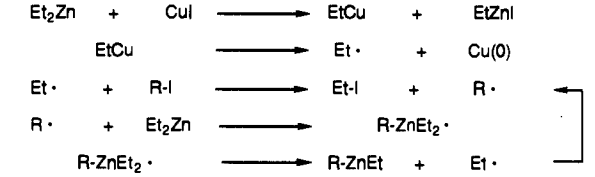


(18)[48]

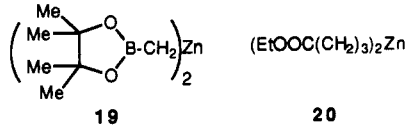
The exchange reaction can be catalyzed by transition-metal salts, and it was found that the addition of CuI (0.3 mol %) allows the reduction of both the reaction time (by half) and the excess of Et_2Zn used (1.5 equiv instead of 5 equiv). A possible mechanism for the catalytic effect of CuI is given in Scheme 1.

The reaction of Et_2Zn with CuI first produces EtCu which decomposes under the reaction conditions (50 °C) giving an ethyl radical and copper(0). A copper mirror is observed at the end of the reaction. The ethyl radical undergoes a radical substitution reaction with

Scheme 1



the alkyl iodide, and the newly produced radical, R•, adds to diethylzinc providing an organozinc radical Et_2-(R)Zn• which then fragments and gives a new ethyl radical which continues the catalytic cycle. The yields are good, and a wide range of new functionalized dialkylzincs (**19–22**) are obtained by this method. Interestingly, other transition-metal catalysts such as $PdCl_2(dppf)$[96] or $Ni(acac)_2$ catalyze these reactions even more effectively. However, in these cases the corresponding alkylzinc iodide is obtained instead of the dialkylzinc (eq 19).[95]



19

$(EtOOC(CH_2)_3)_2Zn$

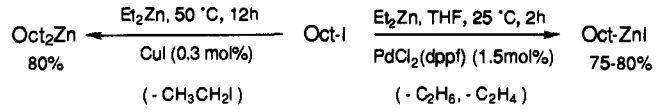
20

$(NC(CH_2)_3)_2Zn$

21

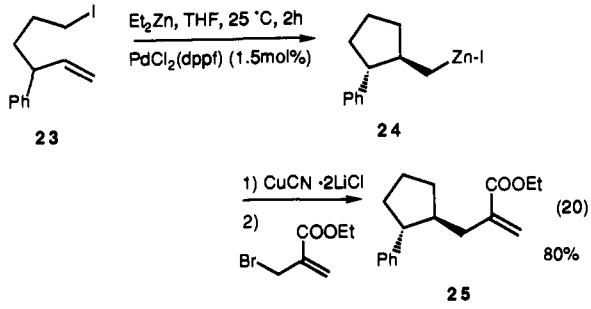
$(Cl(CH_2)_4)_2Zn$

22



(19)

The mechanism of this reaction is currently under investigation[95,97] and seems to be of radical nature. The reaction of the 5-hexenyl iodide **23** with Et_2Zn, in the presence of a catalytic amount of $PdCl_2(dppf)$ or $Ni(acac)_2$ in THF, produces with an excellent selectivity (ca. 20:1) the cyclized organozinc **24**. Transmetalation of **24** with CuCN·2LiCl[29] followed by reaction with ethyl α-(bromomethyl)acrylate[78] affords the cyclopentylmethyl derivative **25**[95] (eq 20, Scheme 8 and Table 20).



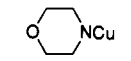
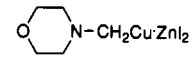
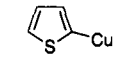
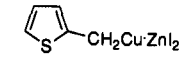
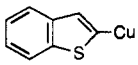
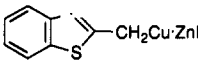
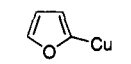
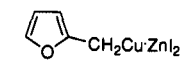
23 **24** **25** (20)

Whereas, the Pd-catalyzed reaction allows carbozincation to be performed under mild conditions (section C.4), the copper(I)-catalyzed preparation of functionalized dialkylzincs provides a unique source of zinc reagents for the catalytic asymmetric addition to aldehydes[48] (section V). Polyfluorinated iodides such as CF_3I or CF_6F_5I react with dialkylzincs in the presence of a Lewis base to give $(CF_3)_2Zn$ and $(C_6F_5)_2Zn$ complexes.[98] The extension of the reaction to higher polyfluorinated iodides does not proceed cleanly.[98]

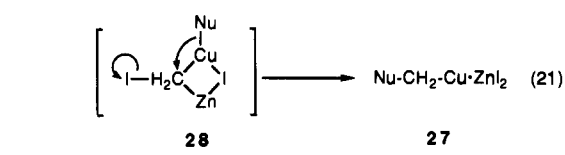
C. Preparation of Functionalized Organozinc–Copper Reagents by Using Insertion Reactions

The oxidative addition of zinc metal to organic halides represents the most widely used preparation method of functionalized organozinc halides. However, a recently described selective methylene homologation[44,99–101]

Table 2. Zinc–Copper Organometallics 27 Obtained by the Reaction of a Copper Reagent with Iodomethylzinc Iodide

copper reagent **26**	homologated reagent **27**	yield (%)
CuCN	$NC\text{-}CH_2Cu\cdot ZnI_2$	84
$NCCH_2Cu$	$NC\text{-}(CH_2)_2Cu\cdot ZnI_2$	91
$NC(CH_3)CHCu$	$NC\text{-}CH(CH_3)CH_2Cu\cdot ZnI_2$	69
$PhCH_2(CH_3)NCu$	$PhCH_2(CH_3)NCH_2Cu\cdot ZnI_2$	68
		64
		96
		93
		74

of organocopper compounds using ICH_2ZnI allows the conversion of a variety of copper derivatives Nu–Cu (**26**) into $NuCH_2Cu\cdot ZnI_2$ (**27**) in good to excellent yields (eq 21).[14,16,94]

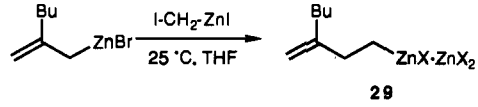


26 **28** **27**

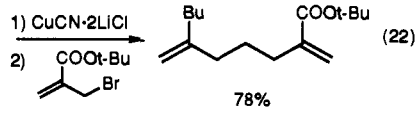
Nu : CN, CH(R)CN, NR_2, S-alkyl, Ar, 2- thienyl, alkynyl, alkenyl

The copper nucleophile Nu–Cu (**26**) can be CuCN, a cyanoalkylcopper, a copper amide, an aryl- or heteroarylcopper, or an alkenyl- or an alkynylcopper[99–101] (Table 2).

The tentative mechanism for this reaction involves a 1,2-migration of the nucleophile Nu from copper to carbon with the simultaneous expulsion of an iodide ion (see **28**, eq 21). The copper reagent formed, **27**, is intimately associated with ZnI_2 as shown by its reactivity and is best considered as being a mixed zinc–copper cluster.[99–101] In strong contrast to organocopper compounds, Grignard reagents, organozincs, or organolithiums do not undergo the methylene homologation cleanly.[102] Only the reactive allylic zinc bromides react directly with ICH_2ZnI, affording homoallylic zinc halides of type **29**, which after transmetalation to the corresponding copper reagent[30] can be allylated in good yields (eq 22).[103]



29

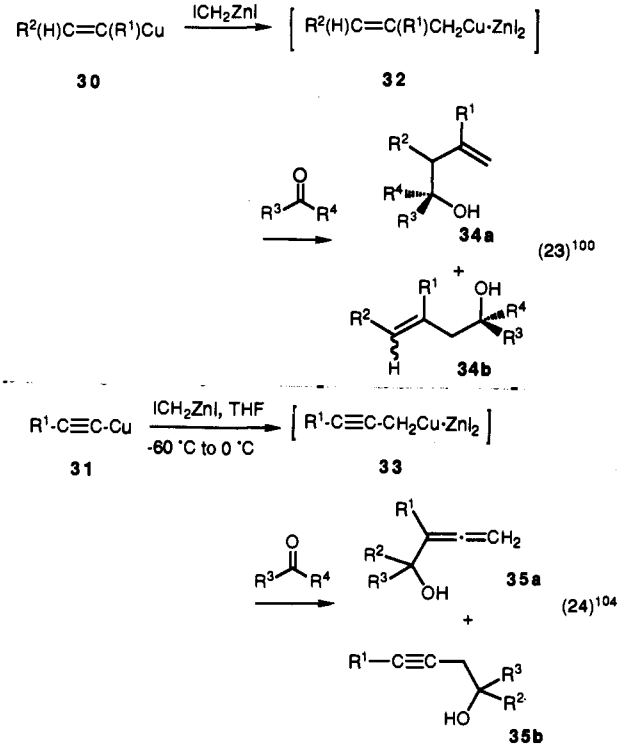


(22)

Interestingly alkenyl- and alkynylcopper reagents **30** and **31** can be cleanly converted respectively to allylic and propargylic copper–zinc reagents of type **32** and **33**. The reactive organometallics **32** and **33** undergo

further reaction with ICH_2ZnI if no other reaction partner is present in the reaction mixture.

However, if an electrophile such as an aldehyde, ketone, imine, or formate is added to **30** prior to the addition of ICH_2ZnI, then the intermediate allylic reagent **32** is trapped by this electrophile and high yields of homoallylic alcohols of type **34a,b** are obtained.[100] A similar reaction of the propargylic intermediate **33** with an aldehyde or a ketone provides the allenic and/or homopropargylic alcohols **35a** and **35b** (eqs 23 and 24).[101]



The method is especially well suited for the preparation of functionalized allylic organometallics not readily available by standard methods. Thus, the alkenylcopper reagents **36** and **37** are readily homologated by a methylene unit, affording the allylic reagents **38** and **39** bearing an allylsilane[104] and an allylic amine functionality, respectively. Trapping **38** or **39** with an aldehyde or a ketone provides the expected functionalized homoallylic alcohols **40** and **41a,b** in good yields (eqs 25 and 26).[100]

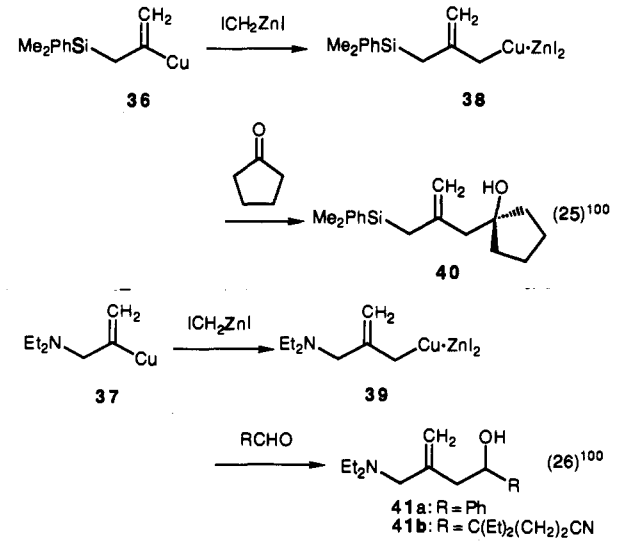
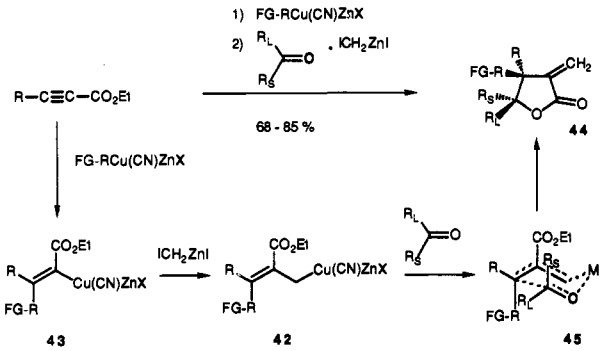


Table 3. α-Methylene-γ-Butyrolactones 44 Prepared by the Reaction of an Acetylenic Ester, FG-RCu(CN)ZnX, a Carbonyl Compound, and Iodomethylzinc Iodide

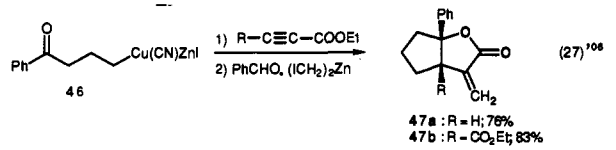
R	FG-R	R_L	R_S	cis-trans ratio	yield (%)
H	Bu	c-Hex	H	80:20	76
H	$PhCH_2$	Ph	H	92:8	78
H	$NC(CH_2)_3$	Ph	H	90:10	75
H	$Bu-C\equiv C(CH_2)_2$	Ph	H	95:5	76
H	$EtO_2C(CH_2)_3$	Ph	H	95:5	85
H	$EtO_2C(CH_2)_3$	$(CH_2)_5$	H		68
H	$Cl(CH_2)_4$	Ph	CH_3	100:0	82
EtO_2C	$EtO_2C(CH_2)_3$	$PhCH_2CH_2$	H	85:15	86
EtO_2C	$NC(CH_2)_3$	c-Hex	H	95:5	93
Bu	c-Hex	Ph	H	75:25	60
c-Hex	Bu	Ph	H	98:2	67
Bu	Ph	Ph	H	60:40	78
Ph	Bu	Ph	H	98:2	85

Scheme 2

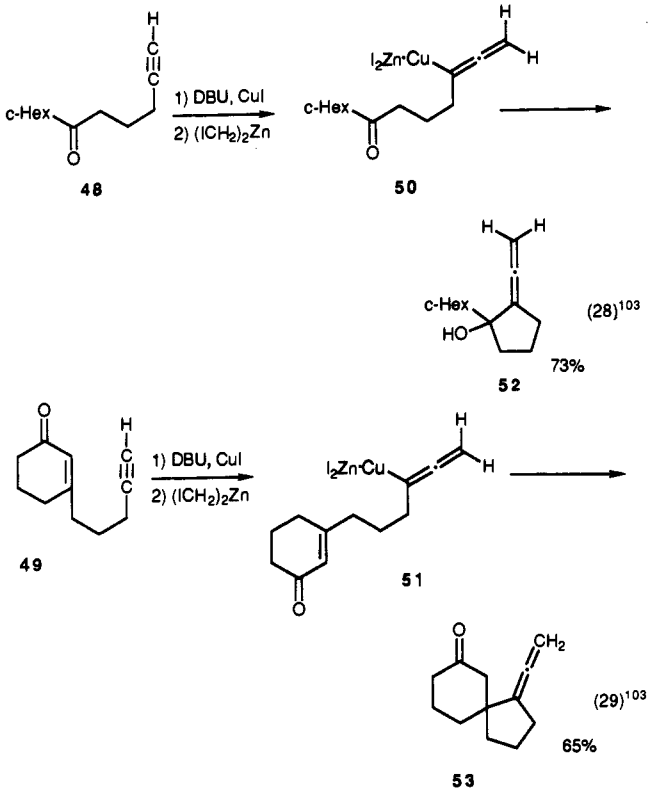


Furthermore, a one-pot preparation of functionalized α-methylene-γ-butyrolactones can be realized using an allylic organometallic intermediate of type **42**[105] bearing an ester functionality in position 2 (Scheme 2 and Table 3).[103,106] Thus, the carbocupration of acetylenic esters with a functionalized copper–zinc reagent, FG-RCu(CN)ZnI, provides a functionalized alkenylcopper of type **43** which inserts ICH_2ZnI and gives a *cis*-α-methylene-γ-butyrolactone **44** stereoselectively in the presence of an aldehyde or ketone. The stereochemistry of this transformation can be rationalized by a transition state of type **45**[106] (Scheme 2).

The addition of a zinc–copper reagent bearing a keto group at the γ-position[24b] such as **46** allows a direct construction of the bicyclic γ-butyrolactones **47**[106] (eq 27).[103]

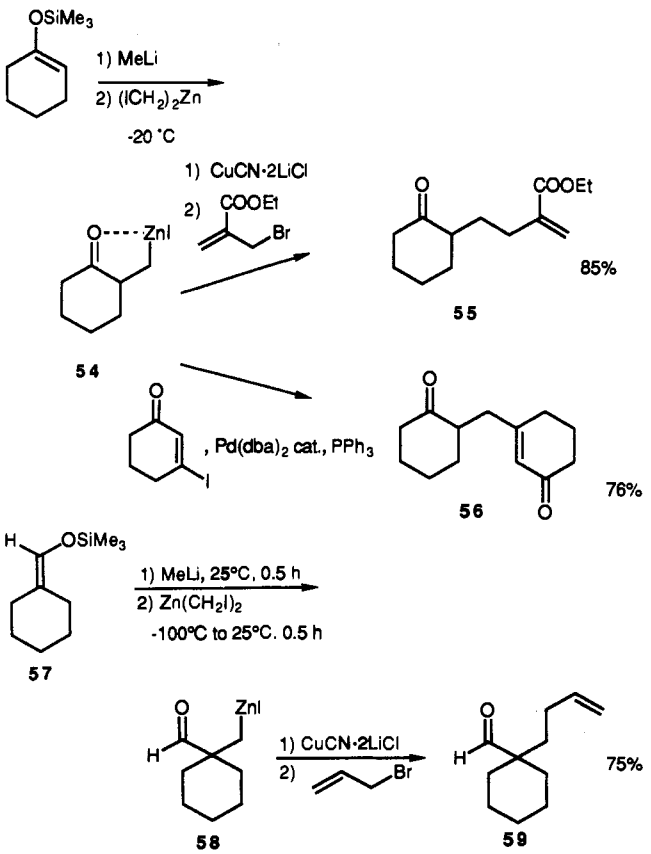


An extension of this method to the functionalized copper acetylenides **48** and **49** permits the preparation of polyfunctional allenic organometallics such as **50** and **51**. Intramolecular trapping of **50** and **51** in a 1,2- or 1,4-addition leads to the cyclized products **52** and **53** in good yields (eqs 28 and 29).[49a,103] Zinc organometallics bearing a carbonyl function at the β-position (homoenolate)[26-28] can be obtained by the homologation of lithium enolates with bis(iodomethyl)zinc.[14b] Thus, the treatment of the lithium enolate of cyclohexanone generated from the silylenol ether, with $(ICH_2)_2Zn$

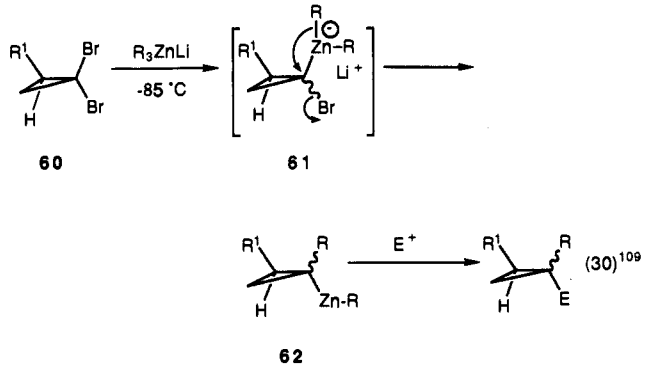


affords the homoenolate **54** which can be allylated after its transmetalation with CuCN·2LiCl to afford **55**.[49a] Homoenolate **54** can also be coupled with 3-iodocyclohexenone in the presence of catalytic amounts of $Pd(dba)_2$[107] and PPh_3 to afford **56** (Scheme 3).

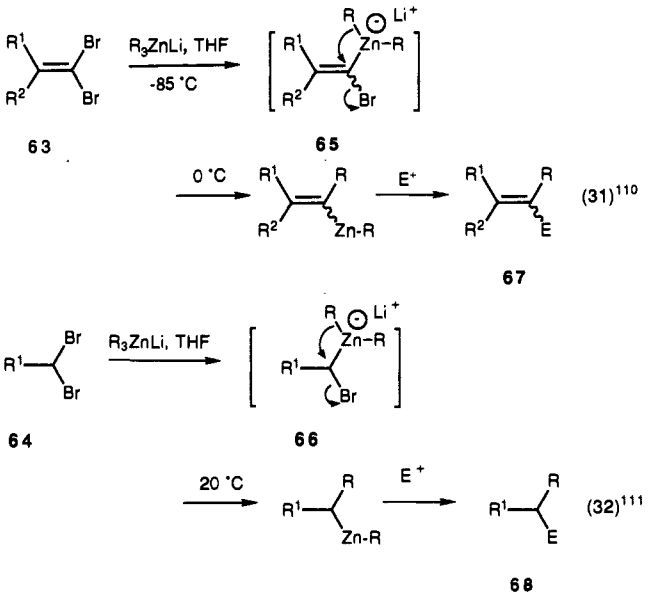
Scheme 3



Similarly, the silylenol ether of cyclohexanecarboxaldehyde **57** was converted to the homoenolate **58** which was allylated with an excess of allyl bromide in the presence of CuCN·2LiCl, giving the aldehyde **59** in 75% yield (Scheme 3).[49a,103] Geminal dibromocyclopropanes **60** bearing some functionalities react with lithium zincates (R_3ZnLi) leading to cyclopropanic zinc carbenoids **61** which undergo a 1,2-migration[108] leading to substituted mixed dialkylzincs **62** (eq 30).[109]

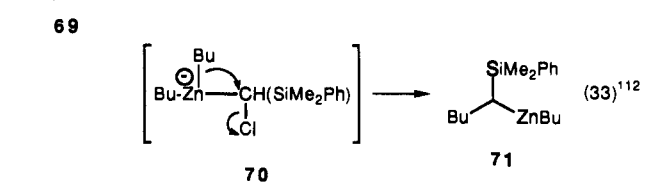


This reaction pattern is quite general, and 1,1-dibromoalkenes **63**[110] as well as 1,1-dibromoalkanes **64**[111a] undergo a bromine–zinc exchange reaction with the zincates R_3ZnLi, providing the corresponding zinc carbenoids **65** and **66** which after the 1,2-migration and reaction with an electrophile (H^+, acyl chloride, alkenyl, and aryl halide) furnish products of type **67** and **68** in good yields (eqs 31 and 32).[110,111]



R^1 = Oct, $PhCH_2CH_2$, $THPO(CH_2)_4$; E^+ = RCOCl, ArBr, alkenyl-Br

The reaction of silicon-substituted carbenoids like **69** with dialkylzincs provides the same type of intermediate zincates **70** and after 1,2-migration leads to the interesting zinc and silicon 1,1-bimetallics **71** (eq 33).[112-114] Polyfluorinated copper reagents such as **72**

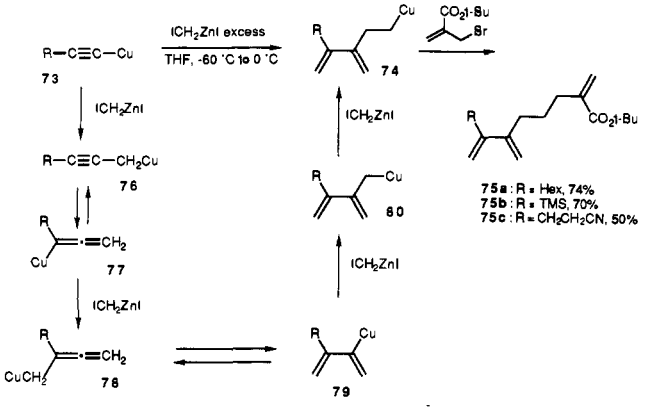


can be obtained formally by a double insertion reaction of a (trifluoromethyl)zinc halide with a phenylcadmium halide in the presence of CuBr (eq 34).[115]

$$PhCdX + 2\,CF_3ZnX \xrightarrow[25\,^\circ C]{CuBr,\ DMF} C_6F_5CF_2CF_2Cu \quad (34)^{115}$$
72

Selective poly*methylene* insertions can also be performed very efficiently.[49a,99,101,103] Thus, alkynylcopper reagents like **73** selectively insert, in the absence of an electrophile, four methylene units leading to dienylcopper–zinc reagents **74** which after allylation give the unsaturated esters **75a–c** in 74–50% yield (Scheme 4).[103]

Scheme 4

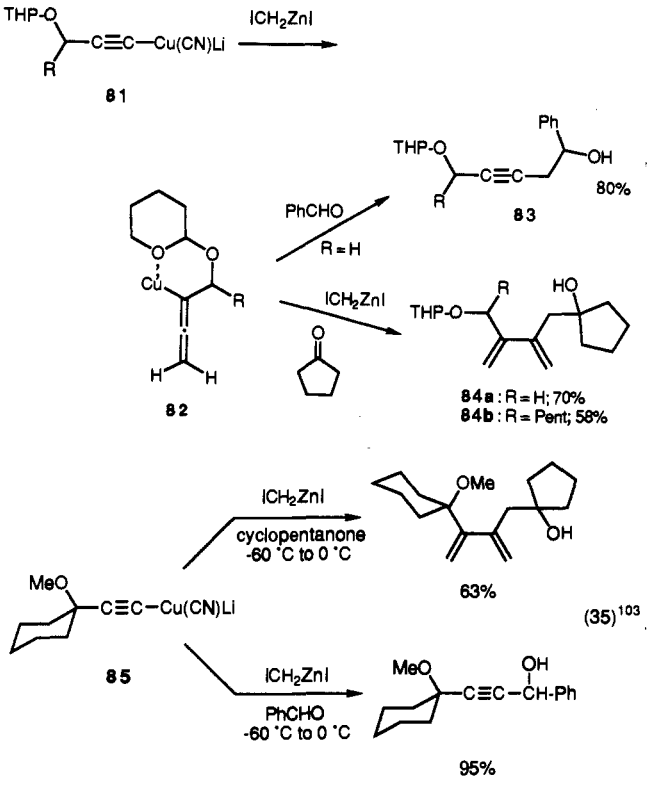


The first methylene insertion converts the alkynyl copper **73** into a propargylic organometallic **76** which is in equilibrium with the allenic from **77**. The insertion of a new methylene unit leads to the allylic reagent **78** which is in equilibrium with the dienic organocopper **79**. The methylene homologation of **79** by ICH_2ZnI furnishes the relatively reactive allylic reagent **80** which readily inserts another molecule of ICH_2ZnI, providing the alkylzinc–copper **74** which under the reaction conditions does not insert another methylene group and can be allylated cleanly (Scheme 4).

Alkynylcoppers, bearing an alkoxy group in the propargylic position, display a reactivity pattern which depends on the nature of the electrophile. Thus the tetrahydropyranyl ether **81** is readily homologated by ICH_2ZnI in the presence of a carbonyl compound, giving the chelation stabilized allenic copper compounds **82**. In the presence of a reactive electrophile such as benzaldehyde, the polar addition reaction proceeds and the homopropargylic alcohol **83** is isolated as the only product. In the presence of a less reactive electrophile such as cyclopentanone, further homologation of **82** is faster than the addition to the electrophile and it is only when the homologation process produces a reactive allylic intermediate (of type **80**, Scheme 4) that the reaction with cyclopentanone occurs. The hydroxydienes **84a,b** are then obtained in 58–70% yields (Scheme 5). The same type of reactivity is observed with the propargylic ether **85** (eq 35).[101,103]

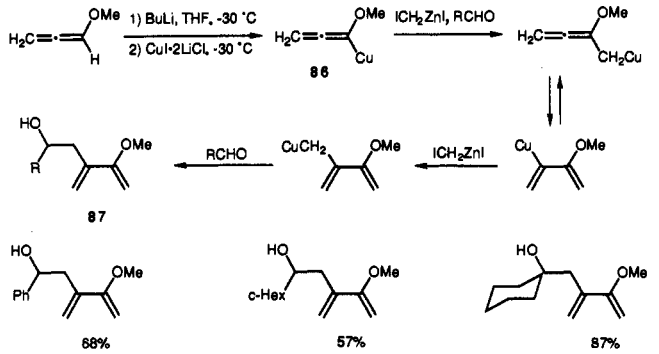
The functionalized allenic copper reagent **86**, obtained by the metalation of methoxyallene, is also an excellent precursor for a selective double methylene homologation. Its reaction with ICH_2ZnI in the presence of an aldehyde or a ketone provides functionalized dienols of type **87** in fair to good yields (Scheme 6).[103]

Scheme 5



(35)[103]

Scheme 6

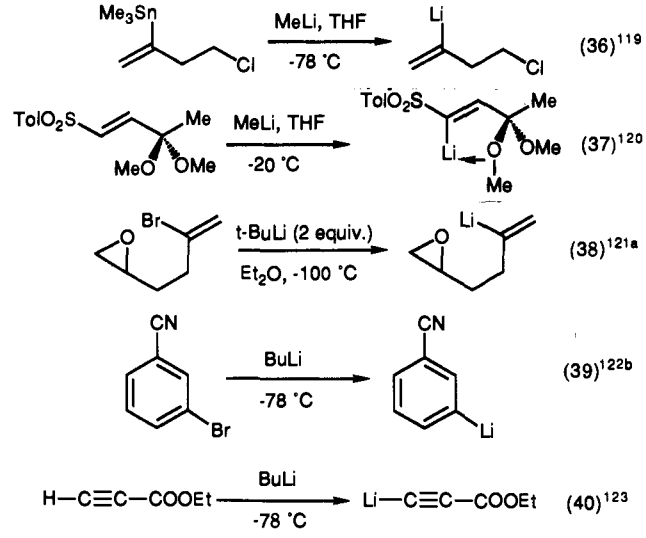


The insertion reaction described in this section allow unique and very efficient preparations of various types of functionalized zinc and copper organometallic reagents. The novel aspects of this chemistry certainly increases the synthetic potential of carbenoic reagents[15,116] and should lead to useful applications in synthesis.

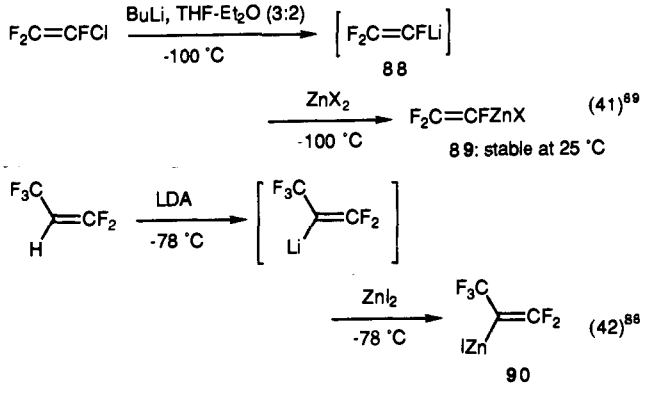
D. Preparation of Functionalized Organozinc Reagents Obtained from Reactive Organolithiums by a Lithium–Zinc Transmetalation

Organolithium reagents are considered to be too reactive to tolerate most functionalities.[18,117,118] However, the polar character and the reactivity of a carbon–metal bond depends not only on the nature of the metal, but also on the hybridization of the carbon atom attached to this metal and on the structure and aggregation of this organometallic.[18,117,118] Alkenyl- and aryllithiums are known to be less reactive than their alkyl counterparts and several electrophilic functions can be present in these organometallics [i.e. a halide (eq 36),[119] a sulfone (eq 37),[120] an epoxide (eq 38),[121a] or even in the case of aryl[126] and acetylenic[123] lithiums, an

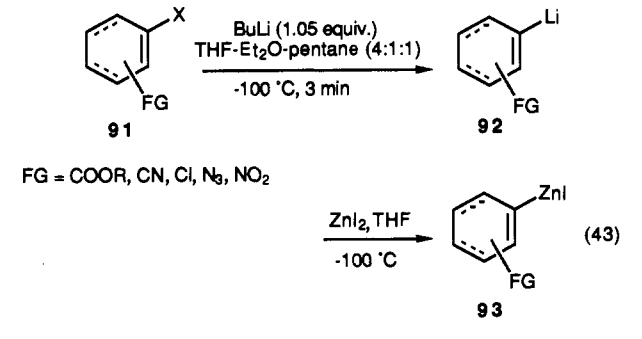
ester, a nitro or a cyano group (eqs 39 and 40)]. However, most of these organometallics are very unstable and react only with selected electrophiles. The stability of these polyfunctional lithium derivatives can be greatly improved by performing a transmetalation with zinc(II) salts.



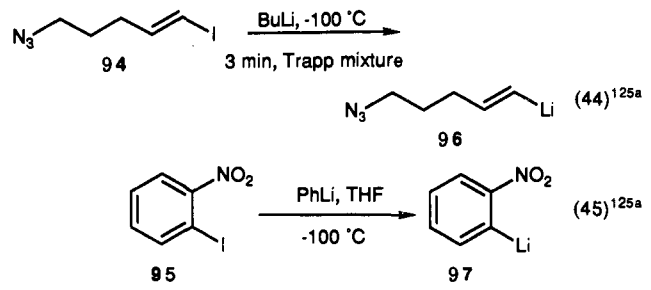
Thus, Sauvêtre and Normant showed that, whereas (1,2,2-trifluoroethenyl)lithium (88) is a very unstable carbenoid (stable only at −100 °C), its addition to ZnX_2 furnishes a very stable zinc reagent **89** which has considerable synthetic utility (eq 41).[89,124] Similarly, 2-hydropentafluoropropene can be converted to the corresponding polyfluorinated organozinc compound **90** (eq 42).[88]



It is also possible to extend these reactions to the preparation of alkenylzinc halides and arylzinc halide (eq 43).[124-126] The reaction of alkenyl iodides of type



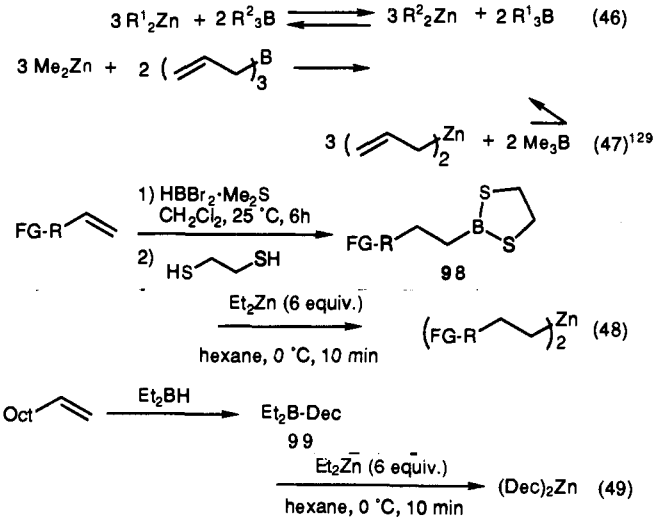
91 with BuLi in a Trapp mixture[127] at ca. −100 °C provides the corresponding functionalized lithium derivatives **92**. The iodine–lithium exchange is complete within 3 min at −100 °C.[128] After the addition of ZnI_2 (−100 °C), the zinc reagents **93** are obtained. They can be handled at 25 °C without decomposition. This method allows access to functionalized organozincs which cannot be prepared by direct zinc insertion. Although the presence of an azide or nitro group both inhibit direct zinc insertion, the iodine–lithium exchange reaction can be performed on the unsaturated azide **94** or on the aromatic nitro compound **95**[122i,j] furnishing the desired lithium compounds **96** and **97** which can subsequently be cleanly transmetalated to the corresponding zinc (or copper) reagent (eqs 44 and 45).[122i,j,125]



E. Diverse Preparations of Organozinc Reagents

1. Via a Boron–Zinc Exchange Reaction

Organoboranes can be converted to diorganozincs under appropriate conditions (eq 46).[2] This reaction has been used to prepare diallylzinc and dibenzylzinc in excellent yields.[129,130] The driving force of the reaction is the formation of the very volatile BMe_3 (bp −20 °C; eq 47). More recently, this transmetalation



has been used to prepare bis(alkenyl)zincs for a highly diastereo- and enantioselective preparation of trisubstituted allylic alcohols.[131] This very efficient and very fast transmetalation proceeds in hexane and leads within a few minutes at 0 °C to unexpectedly reactive di(alkenyl)zincs.[131b] A related transmetalation using readily prepared functionalized 2-alkyl-1,3-dithia-2-borolanes (**98**) and diethylzinc (hexane, 0 °C, 10 min) provides functionalized dialkylzincs (eq 48).[132] The reaction must proceed through an intermediate dieth-

ylalkylborane of type **99** since this reagent undergoes the transmetalation under the same conditions (eq 49).

2. Via a Mercury–Zinc Exchange Reaction

The transmetalation reaction between diorganomercurials and zinc metal was discovered by Frankland in 1864.[133] This reaction allows the preparation of various functionalized dialkylzincs (eq 50) and has found applications in the preparation of optically active secondary alcohols.[50] The reaction is complete within

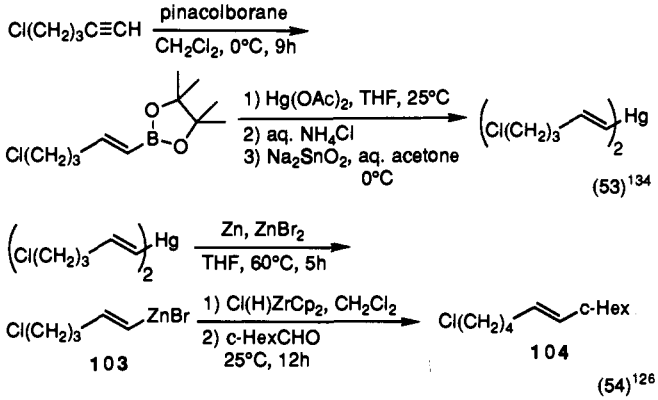
$$(FG\text{-}R)_2Hg + Zn \xrightarrow[110\ ^\circ C,\ 3\text{-}5h]{toluene} (FG\text{-}R)_2Zn + Hg(0) \quad (50)^{50}$$
>80%

a few hours at 110 °C in toluene. Catalysis by the addition of ZnX_2 is also possible; in this case, the transmetalation is complete in THF within 2 h at 60 °C. The polyfunctional mercurials used in these reactions can be prepared either by performing a substitution reaction between functionalized copper–zinc reagents **100** and bis(iodomethyl)mercury **101** leading to methylene homologated diorganomercurials **102** (eq 51) or by using a new transmetalation reaction between functionalized organozinc halides and mercurous chloride Hg_2Cl_2 in THF (−50 to 20 °C, 2 h; eq 52). Both

$$\underset{\mathbf{100}}{FG\text{-}RCu(CN)ZnI} + \underset{\mathbf{101}}{(ICH_2)_2Hg} \xrightarrow[\substack{-60\ ^\circ C,\ 15h\\(74\text{-}98\%)}]{DMF/THF} \underset{\mathbf{102}}{(FG\text{-}RCH_2)_2Hg} \quad (51)^{50}$$

$$\underset{+}{FG\text{-}RZnI}\ \underset{Hg_2Cl_2}{} \xrightarrow[\substack{2h\\61\text{-}89\%}]{THF,\ -50\ ^\circ C\ to\ 20\ ^\circ C} \underset{+}{(FG\text{-}R)_2Hg} \underset{Hg(0)}{} + 2\ ZnX_2 \quad (52)^{50}$$

reactions proceed in good yields and represent very convenient and general preparations of functionalized diorganomercurials.[50] The synthesis of functionalized alkenylzinc halides such as **103** is also possible and can be applied to a highly selective preparation of functionalized (*E*)-olefins like **104** (eqs 53 and 54).[50,126,134]



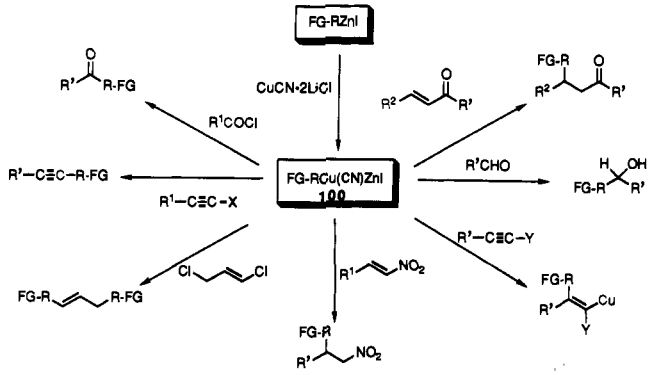
A related transmetalation of bis(trifluoromethyl)-mercury with dimethylzinc in pyridine produces the complex of bis(trifluoromethyl)zinc and pyridine in 82% yield.[135]

III. Reactions of Functionalized Organozincs Mediated by Copper(I) Salts

A. General

As mentioned in previous sections, organozinc halides and even diorganozincs are relatively unreactive organometallic reagents and their transmetalation to more reactive organometallic species is required for most reactions with electrophiles.[2] Organocoppers derived from organolithiums or Grignard reagents react in excellent yields with a wide range of electrophiles and hence constitute a major class of organometallic reagents for organic synthesis.[136] It is possible to prepare organocopper reagents derived from organozinc halides and dialkylzincs.[137] The most efficient copper salts for performing this transmetalation are the THF soluble, CuCN·*n*LiX (X = Cl, Br, I; *n* = 1–2).[29] Their reactions with either FG-RZnX or $(FG\text{-}R)_2Zn$ at 0 °C for 5 min furnish the corresponding copper reagents **100**[29] and **105**[48] (eqs 55 and 56).

Scheme 7



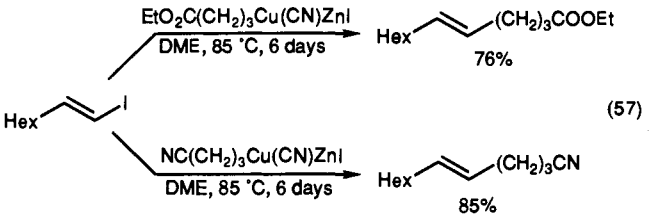
$$FG\text{-}R + CuCN\cdot nLiX \xrightarrow[0°C,\ 5\ min]{THF} \underset{\mathbf{100}}{FG\text{-}RCu(CN)ZnX\cdot nLiX} \quad (55)^{29}$$

$$(FG\text{-}R)_2Zn + CuCN\cdot nLiX \xrightarrow[0°C,\ 5\ min]{THF} \underset{\mathbf{105}}{FG\text{-}RCu(CN)Zn(FG\text{-}R)\cdot nLiX} \quad (56)^{48}$$

X = Cl, Br, I; n = 1,2

The exact nature of the structures of **100** and **105** are not known; however, an EXAFS spectra of CuCN·2LiCl indicates that this species is not monomeric but contains oligomeric units of $(CuCN)_n$ ($n > 2$) and that in the complex **100** the cyanide ligand is still attached to the copper center.[138] These reagents should be considered as being mixed clusters of copper and zinc. It was noted that the addition of increasing amounts of zinc salts to the reagent **100** considerably decreases its reactivity, suggesting that even in **100** some of the FG-R groups could still be attached to a zinc center. The use of lithium halides to solubilize CuCN was found to facilitate the transmetalation (i.e. to form the copper reagents **105** rapidly and under mild conditions). The new copper compounds **100** and **105** present a significant advantage compared to classical copper reagents since most organic functional groups can be contained in these copper derivatives. Their reactivity is somewhat reduced compared to lithium or magnesium-based reagents, and for example, epoxides do not react with **100** or **105**. Also the substitution reactions with alkyl halides proceed well only with primary alkyl iodides and need to be performed in polar solvents. Nevertheless, they react with a wide range of electrophiles as shown in Scheme 7 and display a remarkable thermal stability. Thus primary alkyl zinc–copper compounds **100** can be heated in refluxing 1,2-dimethoxyethane for several

hours without appreciable decomposition (eq 57).[139] The



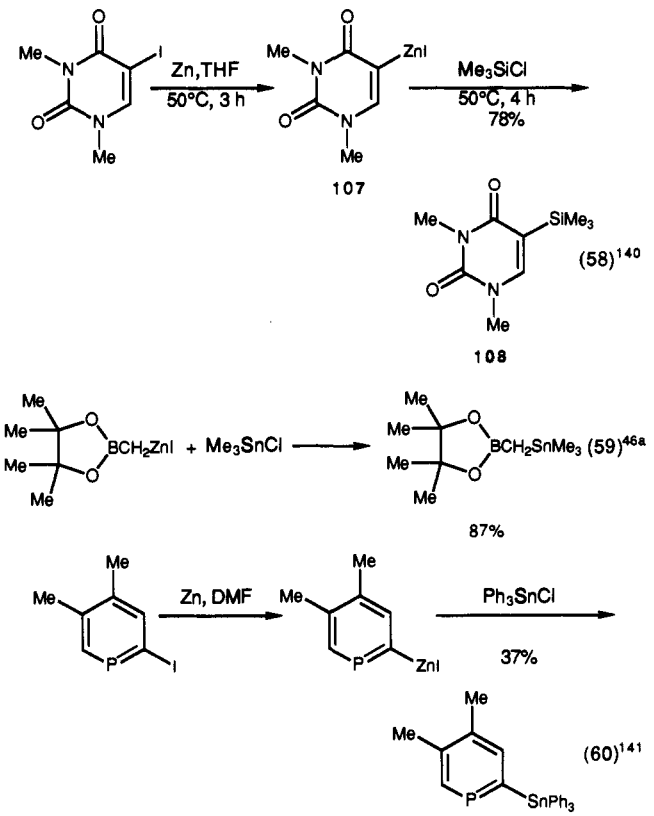
(57)

reactivity of **100** toward different classes of electrophiles is described in detail in the following sections.

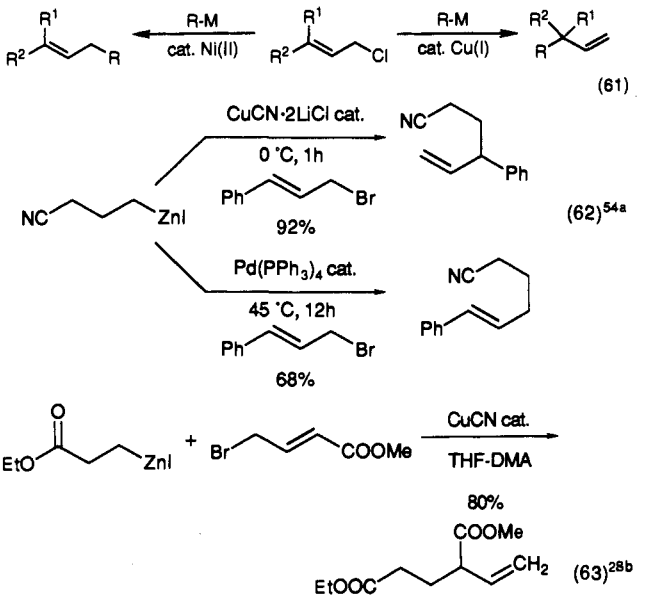
B. Substitution Reactions

1. Coupling with Reactive Halides

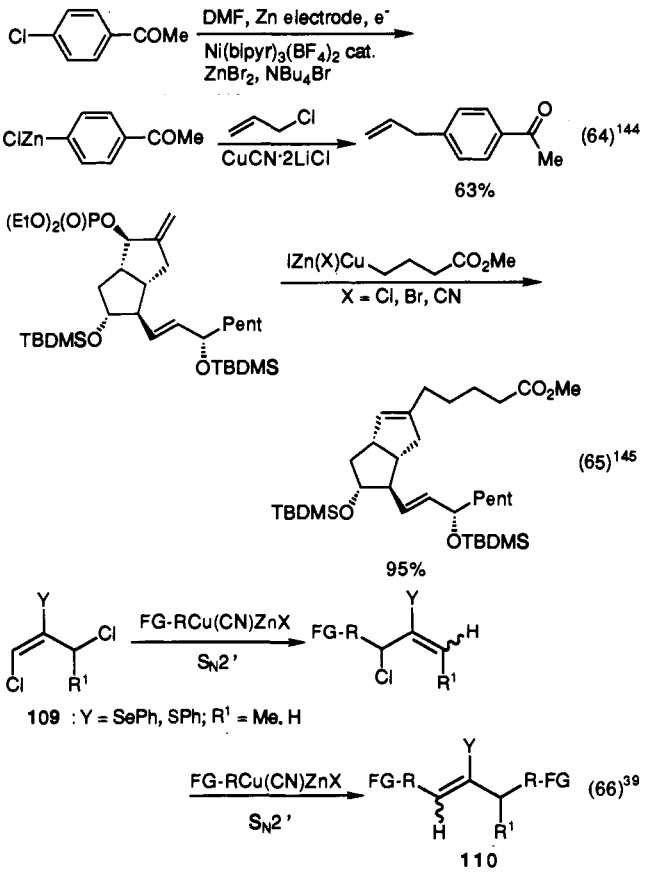
Metallic halides of the type MX_n react differently with zinc–copper reagents (Table 4). Thus, Me_3SiCl does not react with most zinc–copper compounds, although the direct reaction of the zinc reagent **107** with Me_3SiCl furnishes the silylated heterocycle **108** in good yields (eq 58).[140] However, R_3SnCl reacts with **100** or **105** in very high yields (eq 59). This reaction can be used to prepare stannylated phosphabenzenes directly from the aromatic zinc reagent (eq 60).[141]



The reaction of organozinc halides or diorganozincs with allylic halides in the presence of copper(I) salts (catalytic or stoichiometric amounts) occurs with a very high S_N2' selectivity.[27,28b,30,64,142] In contrast, Ni(0)- or Pd(0)-catalyzed reactions of organozincs with allylic halides produce preferentially the S_N2 substitution product (eq 61)[27,142] and (eq 62).[54a] 3-Carbomethoxy-2-propenyl bromide gives the S_N2' product with complete selectivity (eq 63),[28,143] whereas most allylic halides (chlorides or bromides)[27,28b,29,64] react with regioselectivity (S_N2'/S_N2) of ca. 95–80/5–20 (Tables 5–7).

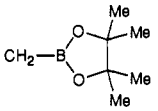
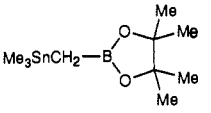
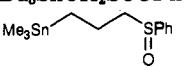
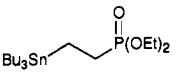
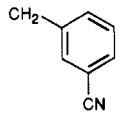
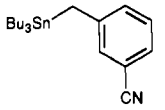
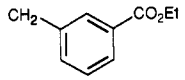
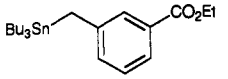
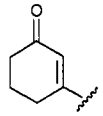
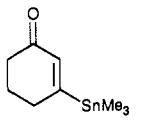
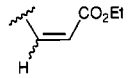
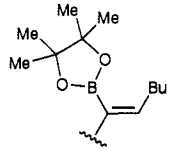
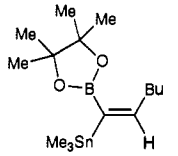
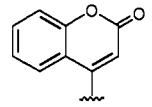
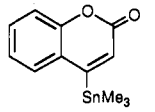
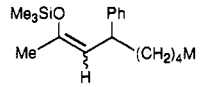
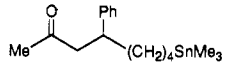
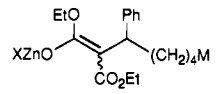
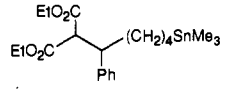


Aromatic organozinc reagents generated electrochemically using a sacrificial zinc anode can be allylated after transmetalation with CuCN·2LiCl in satisfactory yields (eq 64).[144] This allylation procedure can be applied to a short preparation of isocarbacyclins (eq 65).[145] The 1,3-dichloropropenes of type **109** (Y = SPh, SePh) react with almost complete S_N2' selectivity[39] with RCu(CN)ZnI and give 1,3-disubstituted propenes **110** in excellent yields (eq 66 and Tables 5–7).[11]

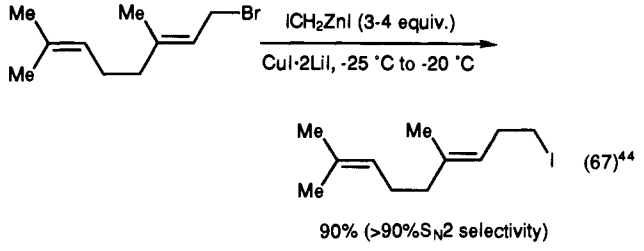


In strong contrast to most functionalized copper–zinc reagents ICH_2Cu (**100**), an unstable copper carbenoid which is generated *in situ* in the presence of an allylic halide by the addition of ICH_2ZnI[16] to CuI·2LiI,

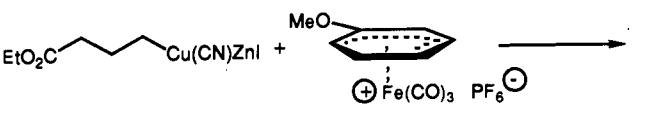
Table 4. Functionalized Stannanes Obtained by the Reaction of Functionalized Zinc–Copper Reagents with Trialkyltin Chlorides

FG-RCu(CN)ZnX (FG-R)	chlorotrialkylstannane	product	yield (%)	ref(s)
CH_2OPiv	Bu_3SnCl	Bu_3SnCH_2OPiv	93	44
	Me_3SnCl		87	46a
CH_2SCOPh	Bu_3SnCl	Bu_3SnCH_2SCOPh	64	60
$(CH_2)_3S(O)Ph$	Me_3SnCl		90	59,60
$CH_2CH_2P(O)(OEt)_2$	Bu_3SnCl		81	61
$CH(Pr)CH_2P(O)(OMe)_2$	Me_3SnCl	$Me_3SnCH(Pr)CH_2P(O)(OMe)_2$	67	61
$(CH_2)_3COPh$	Bu_3SnCl	$Bu_3Sn(CH_2)_3COPh$	65	24b
	Bu_3SnCl		86	37
	Bu_3SnCl		88	37
	Me_3SnCl		93	53
 *E/Z* (11:89)	Me_3SnCl	 *E/Z* (0:100)	95	53
	Me_3SnCl	 *E/Z* (82:18)	89	46b
	Me_3SnCl		69	53
	Me_3SnCl		65	49b
	Me_3SnCl		74	49b

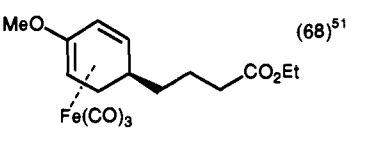
reacts with very high S_N2 selectivity (eq 67 and Table 5).[44] The reaction of FG-RCu(CN)ZnI with propargylic halides or tosylates provides allenes or dienes (Table 8).[28b,65,80d]



Cationic pentadienyliron and pentadienylmolybdenum complexes such as 111 also react under very mild conditions (23 °C, 2 h) with FG-RCu(CN)ZnX (100), providing several types of functionalized iron dienes 112 (Table 9, eq 68).[51,80f]



111



112

Table 5. Products Obtained from the Reaction of Functionalized Aliphatic Organozinc–Copper Reagents with Allylic Halides or Tosylates

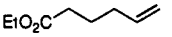
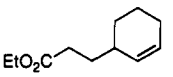
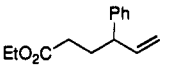
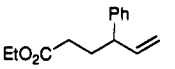
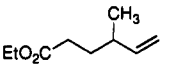
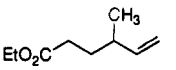
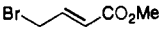
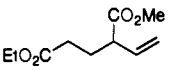
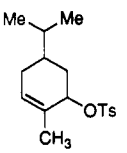
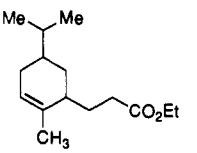
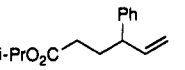
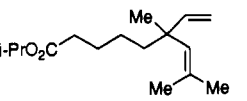
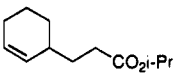
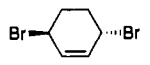
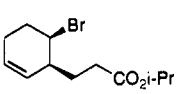
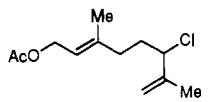
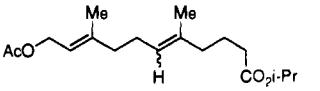
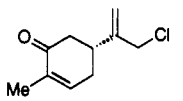
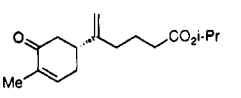
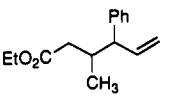
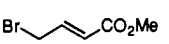
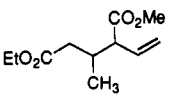
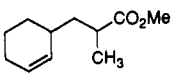
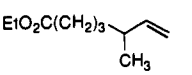
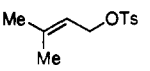
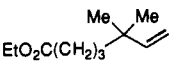
RCu(CN)ZnX (R)	allylic electrophile	product	S_N2'/S_N2 ratio	yield (%)	ref(s)
$CH_2CH_2CO_2Et$	allyl tosylate			89	28b
$CH_2CH_2CO_2Et$	2-cyclohexenyl tosylate			82	28b
$CH_2CH_2CO_2Et$	cinnamyl tosylate		87:13	80	28b
$CH_2CH_2CO_2Et$	cinnamyl bromide		88:12	93	28b
$CH_2CH_2CO_2Et$	cinnamyl chloride		87:13	99	28b
$CH_2CH_2CO_2Et$	α-methallyl tosylate		72:28	50	28b
$CH_2CH_2CO_2Et$			100:0	80	28b
$CH_2CH_2CO_2Et$				89	28b
$CH_2CH_2CO_2i$-Pr	cinnamyl chloride		96:4	97	27
$CH_2CH_2CO_2i$-Pr	geranyl chloride		88:12	81	27
$CH_2CH_2CO_2i$-Pr	2-cyclohexenyl bromide			93	27
$CH_2CH_2CO_2i$-Pr			85:15	79	27
$CH_2CH_2CO_2i$-Pr			100:0	72	27
$CH_2CH_2CO_2i$-Pr				87	27
$CH(CH_3)CH_2CO_2Et$	cinnamyl bromide		86:14	85	29b
$CH(CH_3)CH_2CO_2Et$			100:0	79	29b
$CH_2CH(CH_3)CO_2Me$	2-cyclohexenyl bromide			59	27
$(CH_2)_3CO_2Et$	crotyl tosylate		78:22	68	29b
$(CH_2)_3CO_2Et$			73:27	95	29b

Table 5. (Continued)

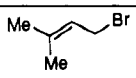
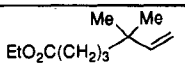
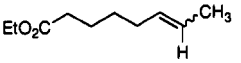
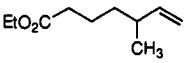
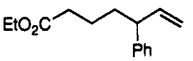
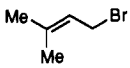
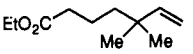
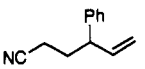
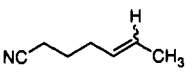
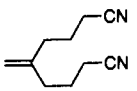
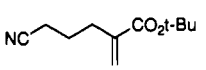
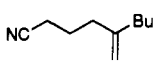
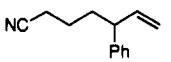
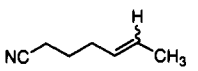
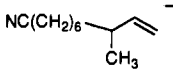
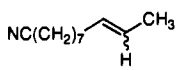
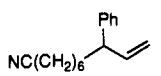
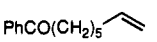
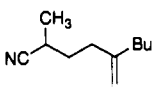
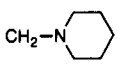
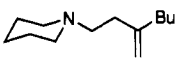
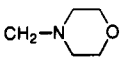
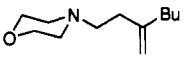
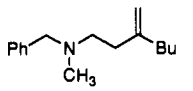
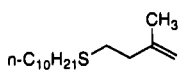
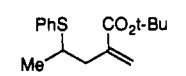
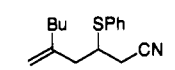
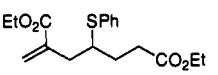
RCu(CN)ZnX (R)	allylic electrophile	product	S_N2/S_N2' ratio	yield (%)	ref(s)
$(CH_2)_3CO_2Et$			83;17	91	29b
$(CH_2)_3CO_2Et$	3-chloro-1-butene		100:0	87	64
$(CH_2)_3CO_2Et$	1-chloro-2-butene		96:4	83	64
$(CH_2)_3CO_2Et$	cinnamyl chloride		97:3	86	64
$(CH_2)_3CO_2Et$			98:2	88	64
CH_2CH_2CN	cinnamyl bromide		100:0	92	54a
CH_2CH_2CN	3-chloro-1-butene		100:0	84	54a
CH_2CH_2CN	2-chloromethyl-1-propene			83	54a
CH_2CH_2CN				95	54a
CH_2CH_2CN	2-(bromomethyl)hexene			84	99
$(CH_2)_3CN$	cinnamyl bromide		96:4	88	30
$(CH_2)_3CN$	3-chloro-1-butene		97:3	85	30
$(CH_2)_6CN$	1-chloro-2-butene		97:3	91	64
$(CH_2)_6CN$	3-chloro-2-butene		97:3	87	64
$(CH_2)_6CN$	cinnamyl chloride		98:2	88	64
$(CH_2)_4COPh$	allyl chloride			70	24b
$CH_2CH(CH_3)CN$	2-(bromomethyl)hexene			69	99
	2-(bromomethyl)hexene			76	99
	2-(bromomethyl)hexene			68	99
$CH_2N(CH_3)CH_2Ph$	2-(bromomethyl)hexene			64	99
$CH_2SC_{10}H_{21}$				75	99
$CH(CH_3)SPh$				87	59,60
$CH(SPh)CH_2CN$	2-(bromomethyl)hexene			75	60
$CH(SPh)(CH_2)_2CO_2Et$				92	59,60

Table 5. (Continued)

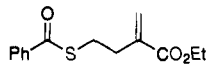
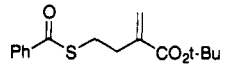
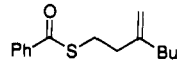
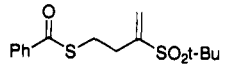
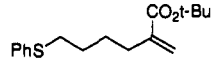
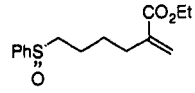
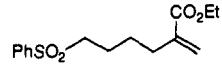
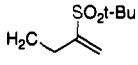
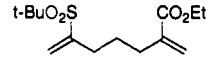
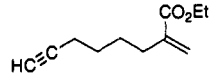
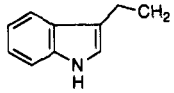
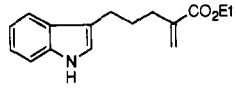
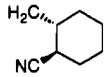
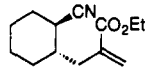
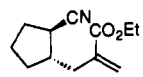
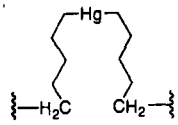
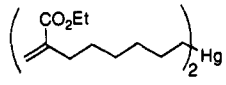
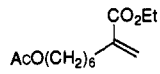
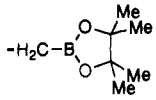
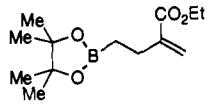
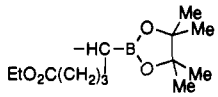
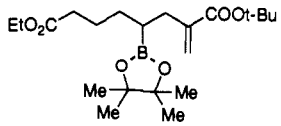
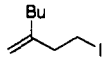
RCu(CN)ZnX (R)	allylic electrophile	product	S_N2/S_N2 ratio	yield (%)	ref(s)
CH_2SCOPh				95	60
CH_2SCOPh				89	60
CH_2SCOPh	2-(bromomethyl)hexene			75	60
CH_2SCOPh				70	60
$(CH_2)_3SPh$				87	59,60
$(CH_2)_3S(O)Ph$				76	59,60
$(CH_2)_3SO_2Ph$				88	60
				90	60
$(CH_2)_3C{\equiv}CH$				86	56
				95	56
		 cis:trans (18:82)		95	54b
		 cis:trans (14:86)		86	54b
				80	50
$(CH_2)_5OAc$				88	48
				90	46a,48
				86	46a
CH_2I	2-(bromomethyl)hexene			90	44
CH_2I				89	44
CH_2I				95	44
CH_2I				96	44

Table 5. (Continued)

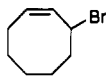
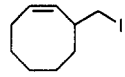
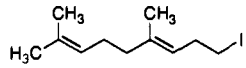
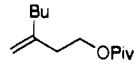
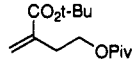
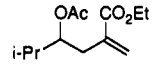
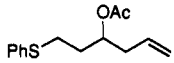
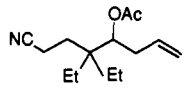
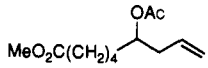
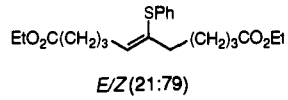
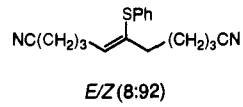
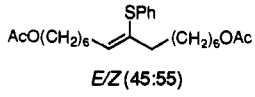
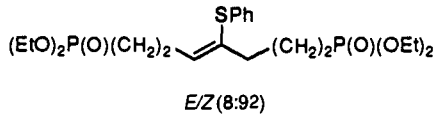
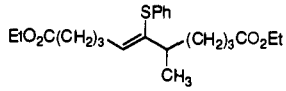
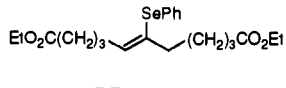
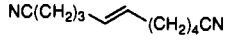
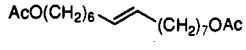
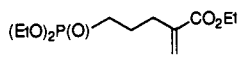
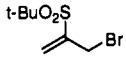
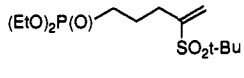
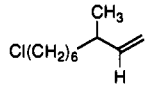
RCu(CN)ZnX (R)	allylic electrophile	product	S_N2/S_N2' ratio	yield (%)	ref(s)
CH_2I				79	44
CH_2I	geranyl bromide			90	44
CH_2OPiv	2-(bromomethyl)hexene			95	44
CH_2OPiv				94	44
$CH(OAc)CH(CH_3)_2$				95	45
$CH(OAc)CH_2CH_2SPh$	allyl bromide			86	45
$CH(OAc)C(Et)_2CH_2CH_2CN$	allyl bromide			69	45
$CH(OAc)(CH_2)34CO_2Me$	allyl bromide			95	45
$(CH_2)_3CO_2Et$		 *E/Z* (21:79)	>97:3	88	39
$(CH_2)_3CN$		 *E/Z* (8:92)	>97:3	85	39
$(CH_2)_6OAc$		 *E/Z* (45:55)	>97:3	76	39
$(CH_2)_2P(O)(OEt)_2$		 *E/Z* (8:92)	>97:3	90	39
$(CH_2)_3CO_2Et$		 *E/Z* (11:89)	>97:3	89	39
$(CH_2)_3CO_2Et$		 *E/Z* (20:80)	>97:3	89	39
$(CH_2)_3CN$	1,3-dichloropropene	 *E/Z* (87:13)	>97:3	88	39
$(CH_2)_6OAc$	1,3-dichloropropene	 *E/Z* (70:30)	>97:3	80	39
$(CH_2)_2P(O)(OEt)_2$				92	61
$(CH_2)_2P(O)(OEt)_2$				79	61
$(CH_2)_6Cl$	1-chloro-2-butene		98:2	94	64

Table 5. (Continued)

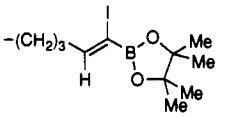
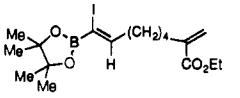
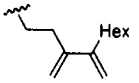
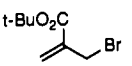
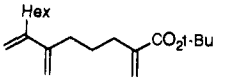
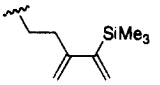
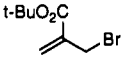
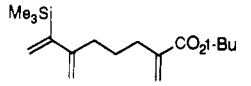
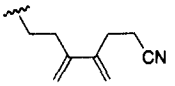
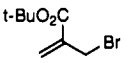
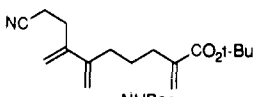
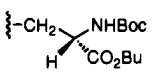
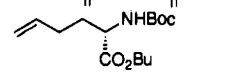
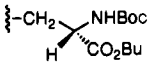
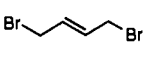
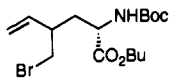
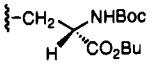
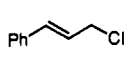
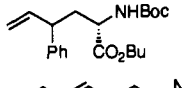
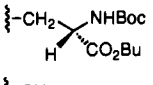
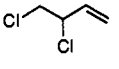
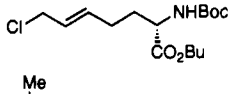
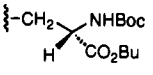
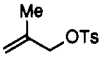
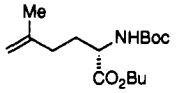
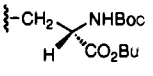
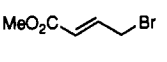
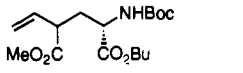
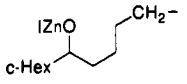
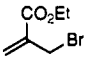
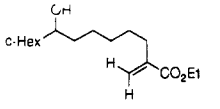
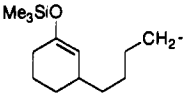
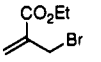
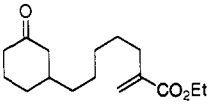
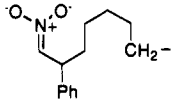
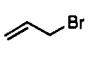
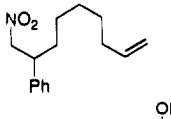
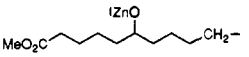
RCu(CN)ZnX (R)	allylic electrophile	product	S_N2/S_N2' ratio	yield (%)	ref(s)
				83	46b
				74	101
				70	101
				50	80d
				65	80d
				48	80d
				48	80d
				55	80d
				56	80d
				51	80d
				62	49b
				70	49b
				81	49b
				68	49b
				67	49b
				59	49b
				64	49b
				74	49b
				75	49b

Table 6. Products Obtained by the Reaction of Functionalized Benzylic Zinc–Copper Reagents with Allylic Halides

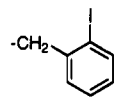
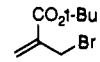
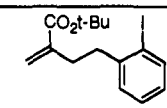
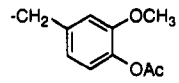
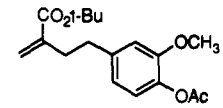
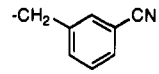
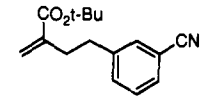
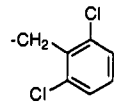
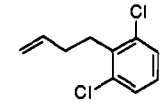
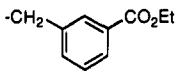
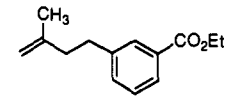
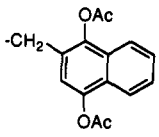
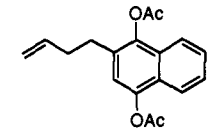
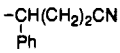
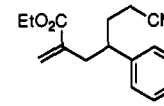
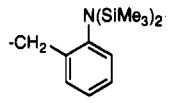
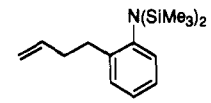
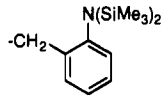
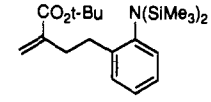
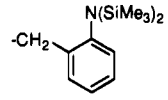
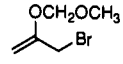
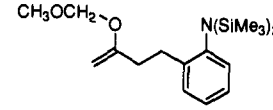
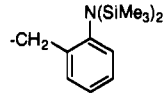
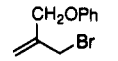
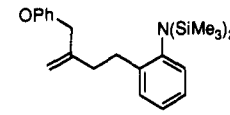
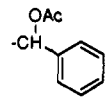
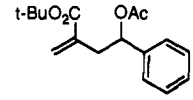
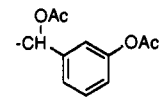
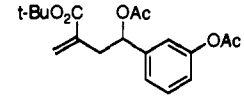
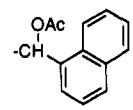
FG-RCu(CN)ZnX (FG-R)	allylic halide	product	yield (%)	ref(s)
			95	36
			98	36
			97	37
			96	37
			87	37
			82	37
			92	37,54b
			86	55
			84	55
			81	55
			93	55
			91	45
			89	45
			71	45
			96	99
			93	99
			74	99

Table 6 (Continued)

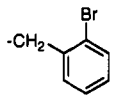
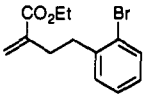
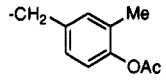
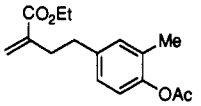
FG-RCu(CN)ZnX (FG-R)	allylic halide	product	yield (%)	ref(s)
			86	76
			82	76

Table 7. Products Obtained by the Reaction of Functionalized Alkenyl and Aromatic Zinc–Copper Reagents with Allylic Halides

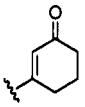
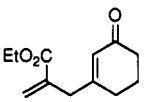
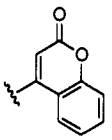
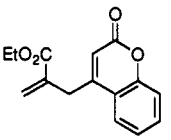
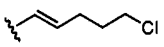
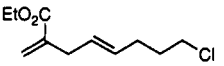
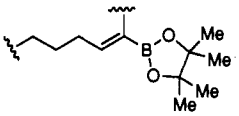
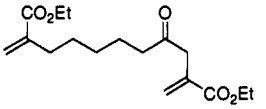
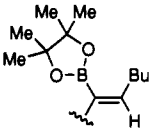
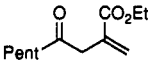
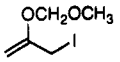
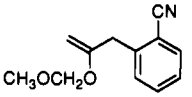
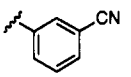
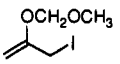
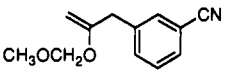
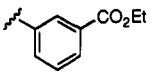
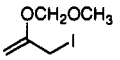
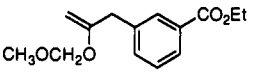
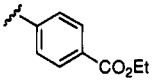
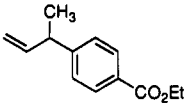
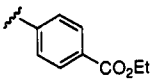
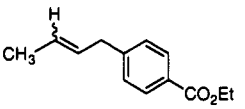
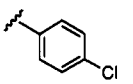
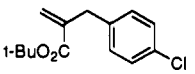
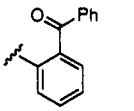
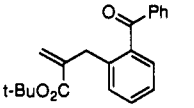
FG-RCu(CN)ZnX (FG-R)	allylic halide	product	S_N2'/S_N2	yield (%)	ref
				83	53
				71	53
				81	125a
				59	46b
				69	46b
				72	35
				91	35
				72	35
	1-chloro-2-butene		80:20	86	64
	3-chloro-1-butene		100:0	93	64
				83	35
				83	35
				72	35
				79	125

Table 7 (Continued)

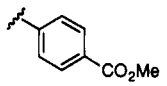
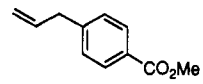
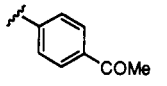
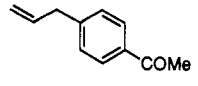
FG-RCu(CN)ZnX (FG-R)	allylic halide	product	S_N2'/S_N2	yield (%)	ref
	allyl chloride			41	144
	allyl chloride			63	144

Table 8. Preparation of Dienes or Allenes by the Reaction of Propargylic Halides or Tosylates with Organozinc–Copper Reagents

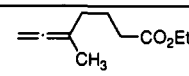
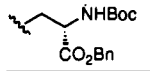
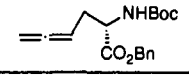
FG-RCu(CN)ZnX (FG-R)	propargylic electrophile	product	yield (%)	ref
$(CH_2)_3CO_2Et$	$HC{\equiv}CCH_2OTs$			28b
				
$(CH_2)_3CN$	$ClCH_2C{\equiv}CCH_2Cl$	R = $(CH_2)_3CN$	84	65
$(CH_2)_3CO_2Et$	$ClCH_2C{\equiv}CCH_2Cl$	R = $(CH_2)_3CO_2Et$	95	65
$(CH_2)_8Cl$	$ClCH_2C{\equiv}CCH_2Cl$	R = $(CH_2)_6Cl$	92	65
CH_2-C_6H_4-*p*-CN	$TsOCH_2C{\equiv}CCH_2OTs$	R = CH_2-C_6H_4-*p*-CN	93	65
C_6H_4-*p*-COMe	$TsOCH_2C{\equiv}CCH_2OTs$	R = C_6H_4-*p*-COMe	93	65
C_6H_4-*p*-CN	$TsOCH_2C{\equiv}CCH_2OTs$	R = C_6H_4-*p*-CN	97	65
	$HC{\equiv}CCH_2Br$		55	80d

Table 9. Functionalized Iron and Molybdenum Diene Complexes Obtained by the Reaction of Cationic Iron or Molybdenum Complexes with Functionalized Zinc–Copper Reagents

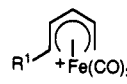
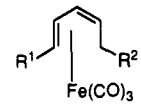
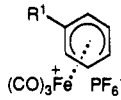
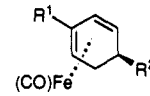
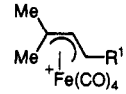
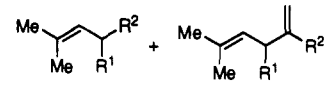
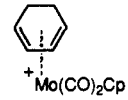
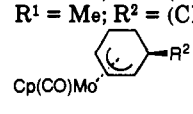
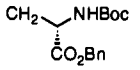
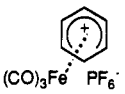
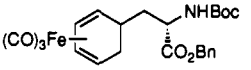
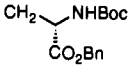
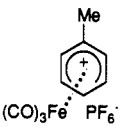
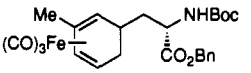
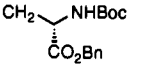
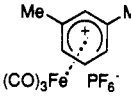
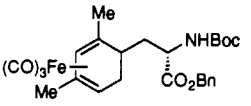
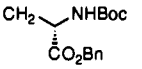
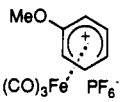
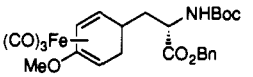
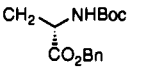
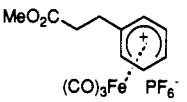
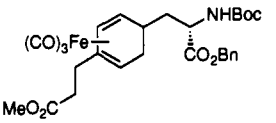
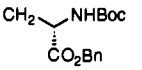
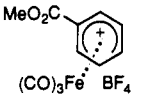
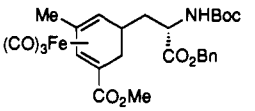
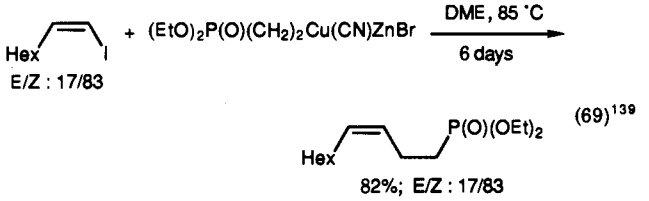
FG-R^2Cu(CN)ZnX (FG-R^2)	cationic complex	product	yield (%)	ref
				
$(CH_2)_2CN$		R^1 = H; R^2 = $(CH_2)_2CN$	84	51a
$(CH_2)_3CN$		R^1 = H; R^2 = $(CH_2)_3CN$	90	51a
$(CH_2)_3CO_2Et$		R^1 = H; R^2 = $(CH_2)_3CO_2Et$	97	51a
$(CH_2)_3CN$		R^1 = Me; R^2 = $(CH_2)_3CN$	75	51a
				
$(CH_2)_2CN$		R^1 = H; R^2 = $(CH_2)_2CN$	78	51a
$(CH_2)_3CN$		R^1 = H; R^2 = $(CH_2)_3CN$	75	51a
$(CH_2)_3CO_2Et$		R^1 = H; R^2 = $(CH_2)_3CO_2Et$	83	51a
$(CH_2)_4OAc$		R^1 = H; R^2 = $(CH_2)_4OAc$	60	51a
$(CH_2)_3CO_2Et$		R^1 = OMe; R^2 = $(CH_2)_3CO_2Et$	76	51a
				
		A : B	A:B	
$(CH_2)_3CO_2Et$		R^1 = H; R^2 = $(CH_2)_3CO_2Et$	57:0	51b
$(CH_2)_4OAc$		R^1 = H; R^2 = $(CH_2)_4OAc$	68:0	51b
$(CH_2)_3CN$		R^1 = H; R^2 = $(CH_2)_3CN$	65:0	51b
$(CH_2)_2CN$		R^1 = H; R^2 = $(CH_2)_2CN$	45:0	51b
$(CH_2)_3CO_2Et$		R^1 = Me; R^2 = $(CH_2)_3CO_2Et$	28:23	51b
$(CH_2)_4OAc$		R^1 = Me; R^2 = $(CH_2)_4OAc$	15:43	51b
$(CH_2)_2CN$		R^1 = Me; R^2 = $(CH_2)_2CN$	20:36	51b
				
$(CH_2)_4CO_2Et$		R^2 = $(CH_2)_4CO_2Et$	90	51c
$(CH_2)_3CO_2Et$		R^2 = $(CH_2)_3CO_2Et$	90	51c
$(CH_2)_2CO_2Et$		R^2 = $(CH_2)_2CO_2Et$	33	51c
$(CH_2)_4CN$		R^2 = $(CH_2)_4CN$	58	51c
$(CH_2)_3CN$		R^2 = $(CH_2)_3CN$	41	51c
$(CH_2)_4OAc$		R^2 = $(CH_2)_4OAc$	51	51c

Table 9 (Continued)

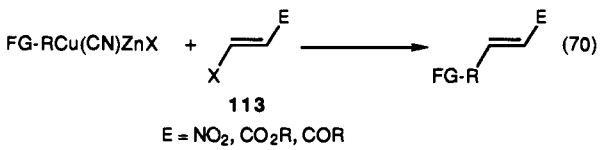
FG-R²Cu(CN)ZnX (FG-R²)	cationic complex	product	yield (%)	ref
$(CH_2)_4OCOPh$		$R^2 = (CH_2)_4OCOPh$	57	51c
			68	80f
			59	80f
			57	80f
			64	80f
			52	80f
			31	80f

2. Coupling with Alkynyl, Alkenyl, and Alkyl Halides

Organocopper reagents are well known to undergo coupling reactions with alkenyl halides.[136] The copper reagents derived from organozinc halides, RCu(CN)ZnI, react only under harsh conditions with alkenyl halides[139] (several days, reflux in DME); however, the reactions produce functionalized olefins in a stereocontrolled fashion (eqs 57 and 69).

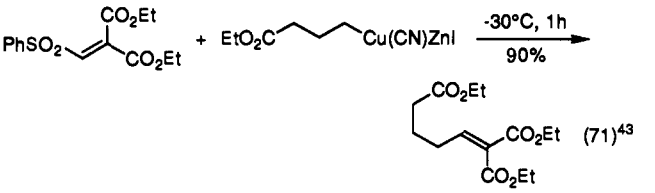


The presence of an electron-withdrawing substituent at the β-position considerably facilitates the substitution reaction since an addition–elimination mechanism can take place. Various reagents of type **113** react with zinc–copper organometallics in high yields (eq 70 and Table 10).

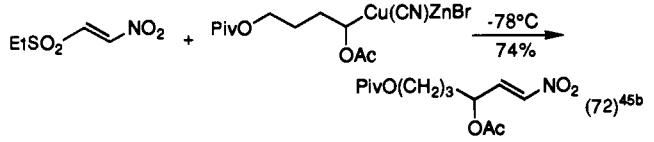


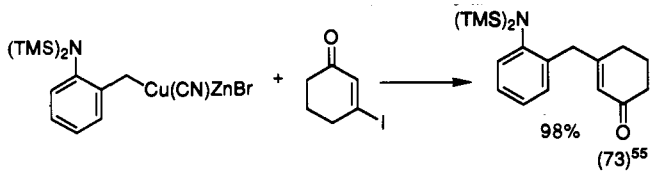
The reaction can be used to prepare a variety of β-substituted alkylidenemalonates by the addition of various zinc–copper reagents FG-RCu(CN)ZnX to a [(phenylsulfonyl)methylidene]malonate (eq 71).[43]

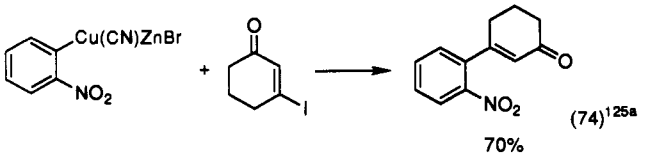
A unique access to γ-acetoxy nitro olefins **114** is also possible by this approach. Thus, the addition of an α-acetoxyalkylzinc–copper reagent to (*E*)-2-(ethylsulfonyl)-1-nitroethylene provides the pure (*E*)-acetoxy



nitro olefin **114** in good yields (eq 72).[45b] The addition of FG-RCu(CN)ZnX to 3-iodocyclohexenone usually proceeds very well and leads to highly functionalized 3-substituted cyclohexanones (eqs 73 and 74 and Table







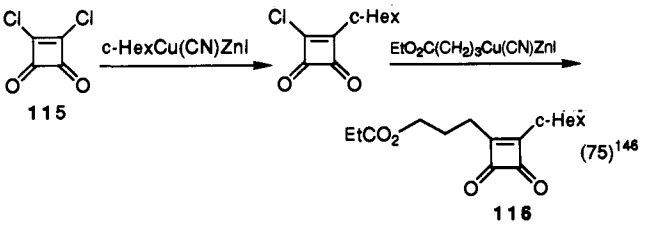


Table 10. Reaction of Alkenyl Halides and Related Compounds with Zinc–Copper Organometallics Leading to Functionalized Olefins

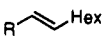
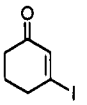
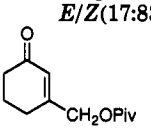
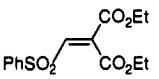
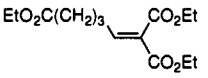
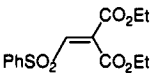
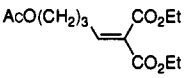
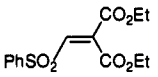
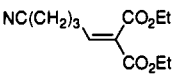
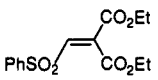
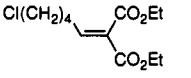
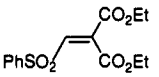
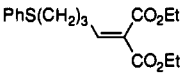
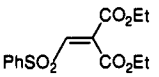
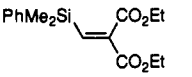
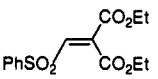
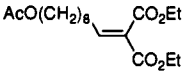
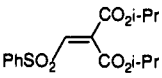
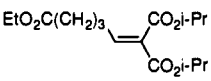
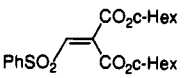
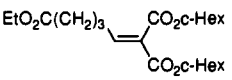
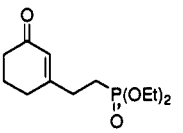
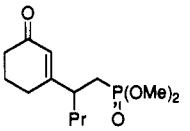
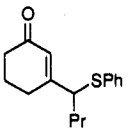
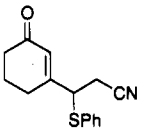
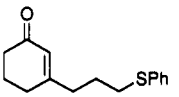
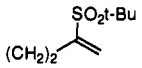
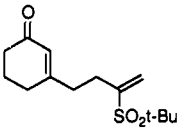
FG-RCu(CN)ZnI	alkenyl iodide	product	yield (%)	ref(s)
				
$(CH_2)_3CN$	(E)-octenyl iodide	R = $(CH_2)_3CN$ (100% E)	85	139
$(CH_2)_3CO_2Et$	(E)-octenyl iodide	R = $(CH_2)_3CO_2Et$ (100% E)	76	139
$(CH_2)_2P(O)(OEt)_2$	(*E*/*Z*)-1-octenyl iodide *E*/*Z*(17:83)	R = $(CH_2)_2P(O)(OEt)_2$ *E*/*Z*(17:83)	82 97	139 44
CH_2OPiv			97	44
$(CH_2)_3CO_2Et$			90	43
$(CH_2)_3OAc$			88	43
$(CH_2)_3CN$			83	43
$(CH_2)_4Cl$			84	43
$(CH_2)_3SPh$			74	43
$SiMe_2Ph$			40	43
$(CH_2)_6OAc$			88	43
$(CH_2)_3CO_2Et$			82	43
$(CH_2)_3CO_2Et$			74	43
$CH_2CH_2P(O)(OEt)_2$	3-iodo-2-cyclohexenone		86	61
$CH(Pr)CH_2P(O)(OMe)_2$	3-iodo-2-cyclohexenone		95	61
CH(Pr)SPh	3-iodo-2-cyclohexenone		88	59,60
$CH(SPh)CH_2CN$	3-iodo-2-cyclohexenone		86	59,60
$(CH_2)_3SPh$	3-iodo-2-cyclohexenone		85	59,60
	3-iodo-2-cyclohexenone		93	60

Table 10 (Continued)

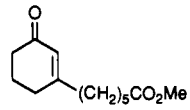
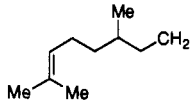
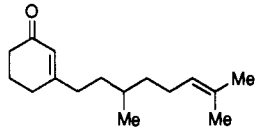
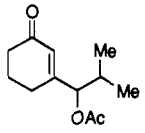
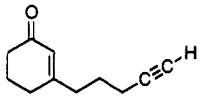
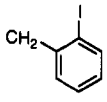
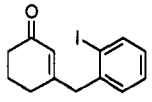
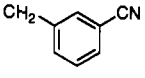
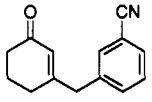
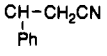
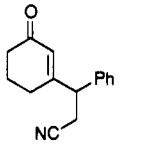
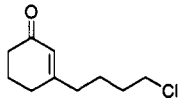
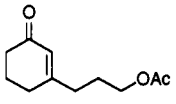
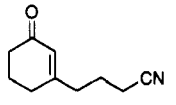
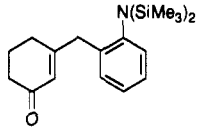
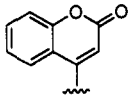
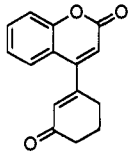
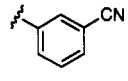
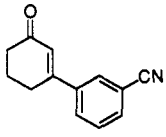
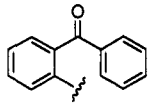
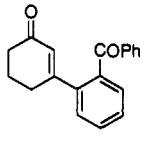
FG-RCu(CN)ZnI	alkenyl iodide	product	yield (%)	ref(s)
$(CH_2)_5CO_2Me$	3-iodo-2-cyclohexenone		86	76
	3-iodo-2-cyclohexenone		85	76
$CH(OAc)CH(CH_3)_2$	3-iodo-2-cyclohexenone		95	45
$(CH_2)_3—C\equiv C—H$	3-iodo-2-cyclohexenone		88	56
	3-iodo-2-cyclohexenone		85	37
	3-iodo-2-cyclohexenone		84	36,37
	3-iodo-2-cyclohexenone		89	54b
$(CH_2)_4Cl$	3-iodo-2-cyclohexenone		84	38,48
$(CH_2)_3OAc$	3-iodo-2-cyclohexenone		79	38
$(CH_2)_3CN$	3-iodo-2-cyclohexenone		89	38
	3-iodo-2-cyclohexenone		97	55
	3-iodo-2-cyclohexenone		70	53
	3-iodo-2-cyclohexenone		64	35
	3-iodo-2-cyclohexenone		71	35

Table 10 (Continued)

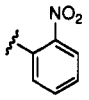
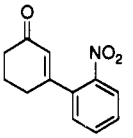
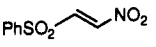
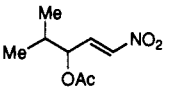
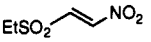
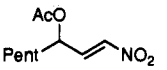
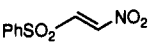
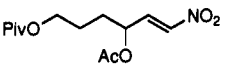
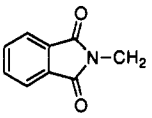
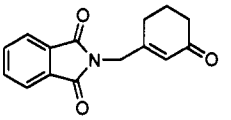
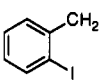
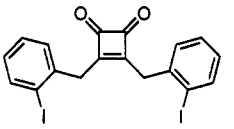
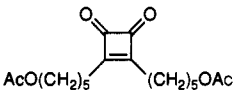
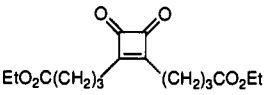
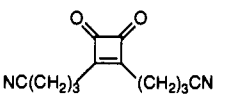
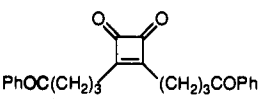
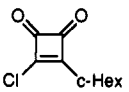
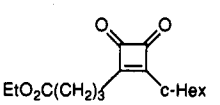
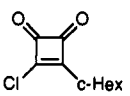
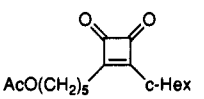
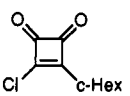
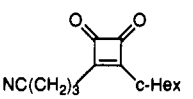
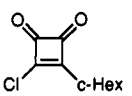
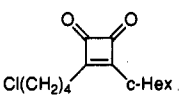
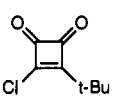
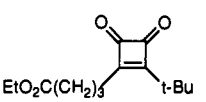
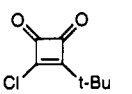
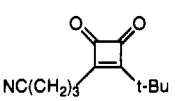
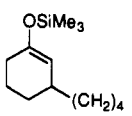
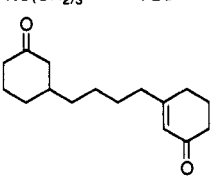
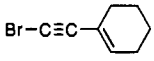
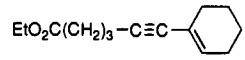
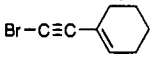
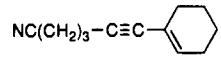
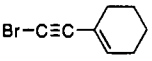
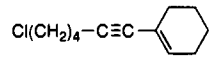
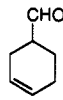
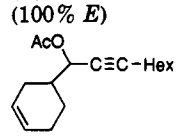
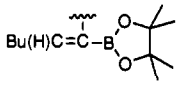
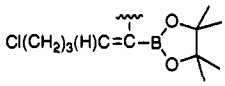
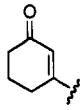
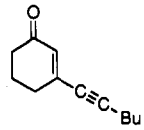
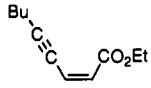
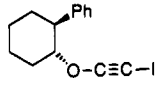
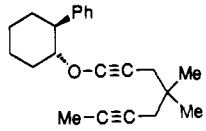
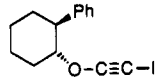
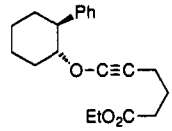
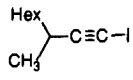
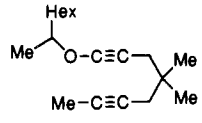
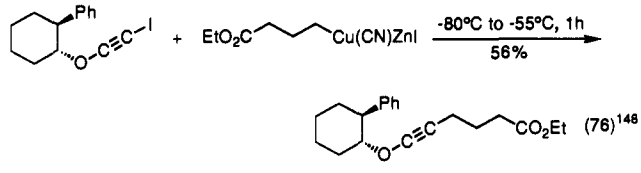
FG-RCu(CN)ZnI	alkenyl iodide	product	yield (%)	ref(s)
	3-iodo-2-cyclohexenone		70	125a
$CH(OAc)\text{-}CH(CH_3)_2$			74	45b
CH(OAc)Pent			80	45b
$CH(OAc)(CH_2)_3OPiv$			74	45b
	3-iodo-2-cyclohexenone		72	45b
			79	146
$(CH_2)_5OAc$			89	146
$(CH_2)_3CO_2Et$			83	146
$(CH_2)_3CN$			83	146
$(CH_2)_3COPh$			72	146
$(CH_2)_3CO_2Et$			74	146
$(CH_2)_5OAc$			67	146
$(CH_2)_3CN$			65	146
$(CH_2)_4Cl$			57	146
$(CH_2)_3CCO_2Et$			81	146
$(CH_2)_3CN$			77	146
	3-iodo-2-cyclohexenone		64	49b

Table 11. Functionalized Alkynes Obtained by the Reaction of Zinc–Copper Organometallics with 1-Haloalkynes

FG-RCu(CN)ZnX (FG-R)	alkynyl halide	product	yield (%)	ref(s)
CH_2OPiv	1-bromooctyne	$PivOCH_2C{\equiv}CHex$	72	44
$(CH_2)_3CO_2Et$	$BrC{\equiv}CCH_2OTHP$	$EtO_2C(CH_2)_3C{\equiv}CCH_2OTHP$	74	147e
$(CH_2)_3CO_2Et$	1-bromooctyne	$EtO_2C(CH_2)_3C{\equiv}CHex$	78	41
$(CH_2)_3CO_2Et$	1-bromo-2-phenylacetylene	$EtO_2C(CH_2)_3C{\equiv}CPh$	71	41
$(CH_2)_3CO_2Et$			74	41
$(CH_2)_3CN$	1-bromooctyne	$HexC{\equiv}C(CH_2)_3CN$	81	41
$(CH_2)_3CN$			79	41
$(CH_2)_3CH(OPiv)CH_3$	1-iodooctyne	$CH_3CH(OPiv)(CH_2)_3C{\equiv}CHex$	75	41
$(CH_2)_4Cl$			81	41
$(CH_2)_3C{\equiv}CPent$	$BrC{\equiv}CPh$	$PentC{\equiv}C(CH_2)_3C{\equiv}CPh$	73	41
$CH_2CH_2P(O)(OEt)_2$	1-bromooctyne	$(EtO)_2P(O)CH_2CH_2C{\equiv}CHex$	89	61
CH_2SPh	1-bromooctyne	$PhSCH_2C{\equiv}CHex$	70	59,60
$(CH{=}CH)Hex\text{-}(E)$	1-iodohexyne	$(E)\text{-}BuC{\equiv}CCH{=}CHHex$ (100% E)	77	50
	1-bromooctyne		86	45
$(CH_2)_3C{\equiv}CH$	1-iodohexyne	$BuC{\equiv}C(CH_2)_3C{\equiv}CH$	60	56
CH_2OPiv	1-iodohexyne	$BuC{\equiv}CCH_2OPiv$	74	45
$(H)C{=}C(H)(CH_2)_3OPiv\text{-}(E)$	1-iodohexyne	$(E)\text{-}BuC{\equiv}CCH{=}CH(CH_2)_3OPiv$	66	125a
	1-iodohexyne	$PentCOC{\equiv}CBu$	86	46b
	1-iodohexyne	$Cl(CH_2)_4COC{\equiv}CBu$	87	46b
	1-iodohexyne		92	53
$(H)C{=}(H)CO_2Et$	1-iodohexyne		81	53
$CH_2C(CH_3)_2CH_2C{\equiv}CMe$			61	148
$(CH_2)_3CO_2Et$			56	148
$CH_2C(CH_3)_2CH_2C{\equiv}CMe$			56	148

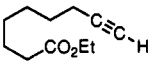
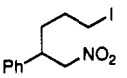
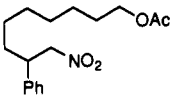
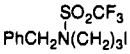
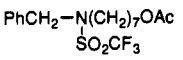
10). A selective double addition–elimination on 3,4-dichlorocyclobutene-1,2-dione (**115**) provides a range of functionalized 3,4-disubstituted cyclobutene-1,2-diones **116** (eq 75).[146]

Lithium- and magnesium-derived organocopper reagents are known to react under mild conditions with 1-halogenoalkynes.[147] Similarly, it was found that the functionalized copper–zinc reagents FG-RCu(CN)ZnX (**100**) undergo a smooth coupling reaction with 1-iodo or 1-bromoalkynes. This provides an excellent synthesis of functionalized alkynes (Table 11) and has been used to prepare functionalized acetylenic ethers **117** (eq 76).[148]

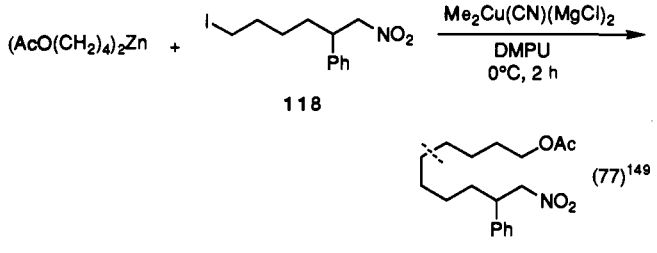


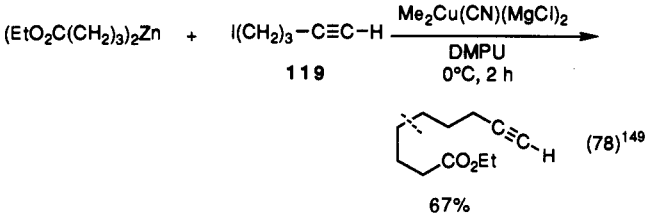
117

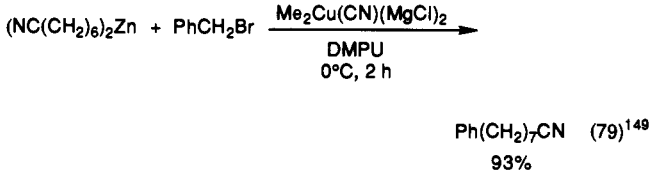
Table 12. Coupling Reaction between Functionalized Alkylzinc Reagents and Polyfunctional Electrophiles in DMPU[149]

$(FG\text{-}R)_2Cu(MgX)\cdot Me_2Zn$ (FG-R)	alkyl halide	product	yield (%)
$AcO(CH_2)_5$	OctI	$AcO(CH_2)_{12}CH_3$	80
$AcO(CH_2)_5$	$EtO_2C(CH_2)_3I$	$AcO(CH_2)_8CO_2Et$	74
$AcO(CH_2)_5$	$NC(CH_2)_3I$	$AcO(CH_2)_8CN$	81
$EtO_2C(CH_2)_3$	OctI	$EtO_2C(CH_2)_{10}CH_3$	72
$EtO_2C(CH_2)_3$	$I(CH_2)_3C{\equiv}CH$		71
$AcO(CH_2)_4$			83
$AcO(CH_2)_4$			87
$PhCH_2N(SO_2CF_3)(CH_2)_3$	$NC(CH_2)_3I$	$PhCH_2N(SO_2CF_3)(CH_2)_6CN$	77
$NC(CH_2)_6$	$PhCH_2Br$	$NC(CH_2)_7Ph$	93

The lower reactivity of copper–zinc reagents compared to the corresponding lithium or magnesium copper derivatives becomes especially apparent in alkylation reactions. However, it was found that the treatment of *dialkylzincs* with 1 equiv of a lithium or magnesium dimethylcuprate provides a reagent which is able to alkylate primary alkyl iodides and benzylic bromides in polar solvents such as DMPU or NMP under relatively mild conditions (0 °C, 2 h).[149] Less than 5% of methyl transfer was observed under these conditions. This reaction shows a remarkable functional group tolerance, and an iodide bearing a primary nitroalkane (**118**) or a terminal acetylene functionality (**119**) reacts to provide the expected mixed coupling product (Table 12 and eqs 77–79). This is one of the few methods allowing cross-coupling reactions between functionalized substrates to be performed.

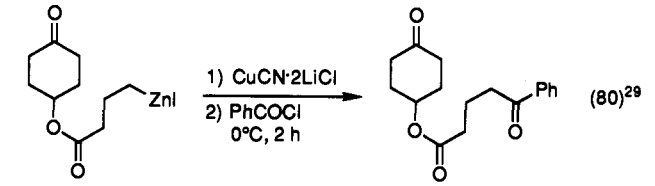


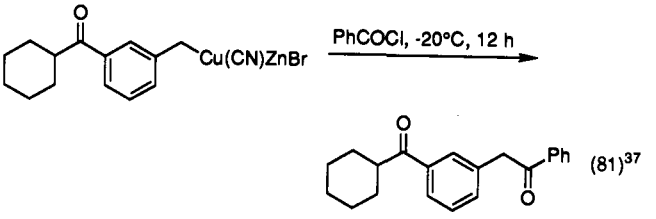


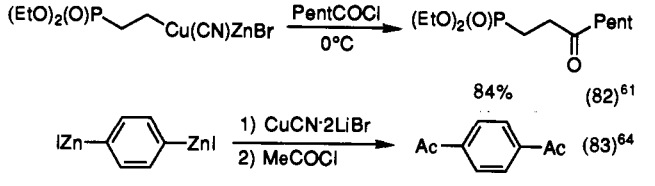


3. Coupling with Acid Chlorides

Acid chlorides react only slowly with alkylzinc halides, and the reaction is further complicated by zinc(II)-catalyzed THF ring opening. In contrast, the corresponding organocopper reagents **100** react smoothly with acid chlorides at 0 °C (2–12 h) and provide polyfunctional ketones in excellent yields. Alkyl, aryl, or benzylic zinc–copper reagents can be used with equal success (eqs 80–83 and Table 13). In the case of α-oxygenated organometallics, it was shown that the corresponding copper–cadmium organometallics react with acid chlorides in better yields.[45]







C. Addition Reactions

1. Additions to Aldehydes and Related Reagents

The direct addition of alkyl, aryl, or alkenyl zinc reagents to aldehydes is usually relatively inefficient.[2] However, it has been shown that alkenylzinc chlorides which seem to be more reactive than their alkyl

Table 13. Preparation of Polyfunctional Ketones by the Addition of Zinc–Copper Reagents to Acid Chlorides

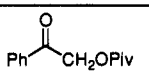
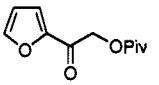
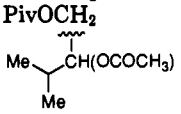
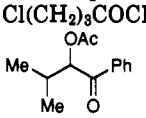
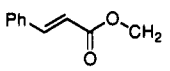
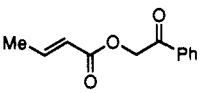
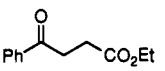
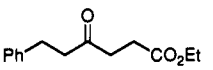
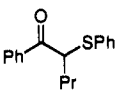
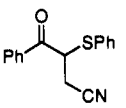
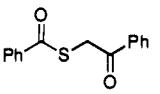
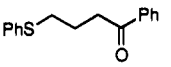
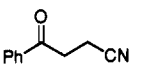
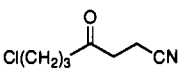
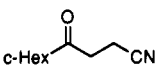
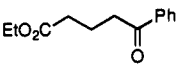
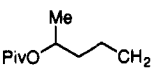
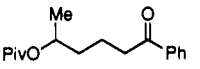
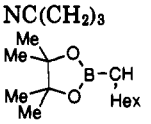
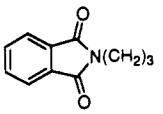
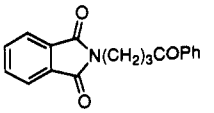
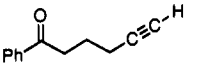
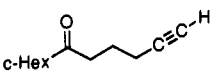
FG-RCu(CN)ZnX (FG-R)	RCOCl (R)	product	yield (%)	ref(s)
$PivOCH_2$	Ph		81	44,45
$PivOCH_2$			90	44,45
$PivOCH_2$	c-Hex	$PivOCH_2COc\text{-}Hex$	66	44,45
$PivOCH_2$	$Cl(CH_2)_3$	$Cl(CH_2)_3COCH_2OPiv$	42	44,45
	Ph		82	45
	Ph		93	45
$EtO_2CCH_2CH_2$	Ph		76	27a
$EtO_2CCH_2CH_2$	$Ph(CH_2)_2$		89	27a
$PrCH(SPh)$	Ph		93	59,60
$NCCH_2CH(SPh)$	Ph		79	59,60
$PhCOSCH_2$	Ph		85	60
$PhS(CH_2)_3$	Ph		87	59,60
$NC(CH_2)_2$	Ph		83	54a
$NC(CH_2)_2$	$Cl(CH_2)_3$		77	54a
$NC(CH_2)_2$	c-Hex		79	54a
$EtO_2C(CH_2)_3$	Ph		87	29
	Ph		93	29
$NC(CH_2)_3$	Ph	$NC(CH_2)_3COPh$	93	29
	Ph	HeptCOPh	74	46a
	Ph		74	57
$HC{\equiv}C{-}(CH_2)_3$	Ph		68	56
$HC{\equiv}C{-}(CH_2)_3$	c-Hex		67	56
$(EtO)_2(O)P(CH_2)_2$	Ph	$PhCO(CH_2)_2P(O)(OEt)_2$	96	61
$(EtO)_2(O)P(CH_2)_2$	c-Hex	$c\text{-}HexCO(CH_2)_2P(O)(OEt)_2$	86	61
$(EtO)_2(O)P(CH_2)_2$	Pent	$PentCO(CH_2)_2P(O)(OEt)_2$	84	61
$AcO(CH_2)_5$	Ph	$OhCO(CH_2)_5OAc$	87	48

Table 13 (Continued)

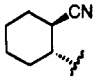
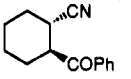
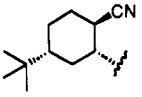
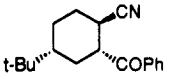
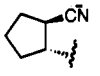
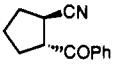
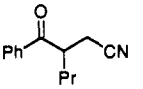
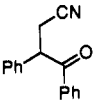
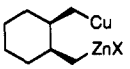
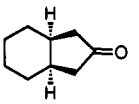
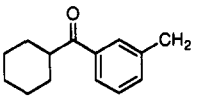
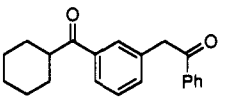
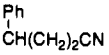
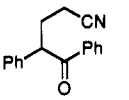
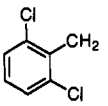
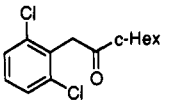
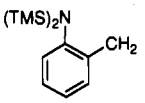
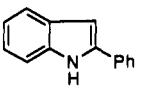
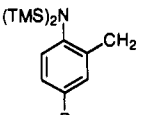
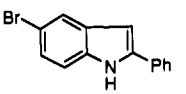
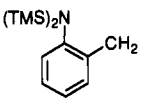
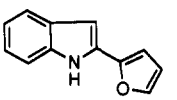
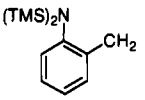
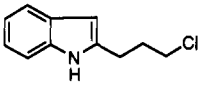
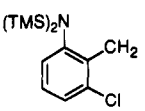
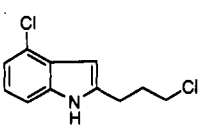
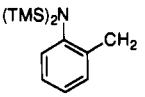
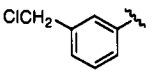
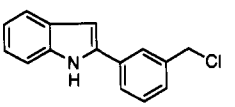
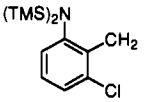
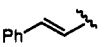
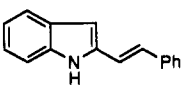
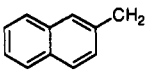
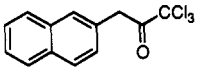
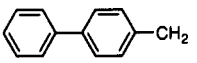
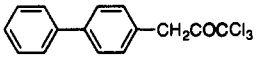
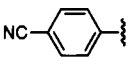
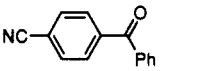
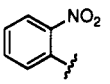
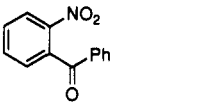
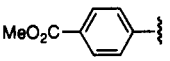
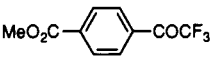
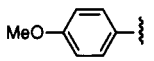
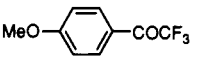
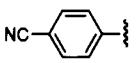
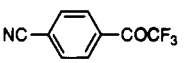
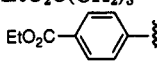
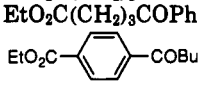
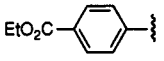
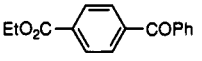
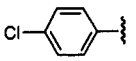
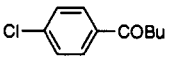
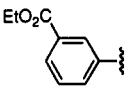
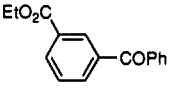
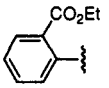
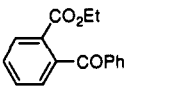
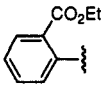
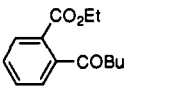
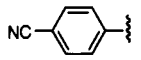
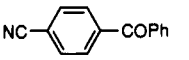
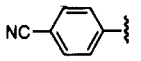
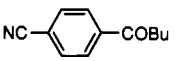
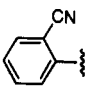
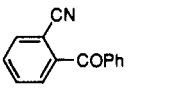
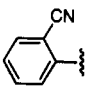
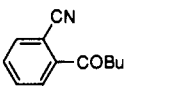
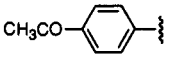
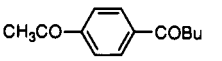
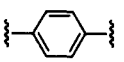
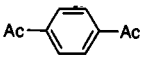
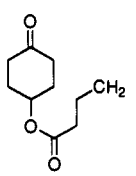
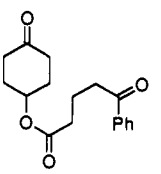
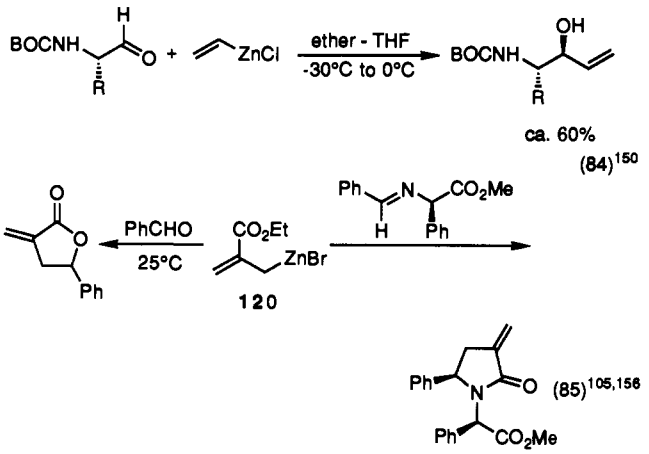
FG-RCu(CN)ZnX (FG-R)	RCOCl (R)	product	yield (%)	ref(s)
	Ph	 *cis/trans* (1:4)	89	54b
	Ph	 *cis/trans* (<1:>99)	67	54b
	Ph	 *cis/trans* (<1:>99)	68	54b
$PrCH(CH_2CN)$	Ph		81	54b
$PhCH(CH_2CN)$	Ph		82	54b
	ClCOCOCl		77	49
	Ph		90	36,37
$PhCH(CH_3)$	c-Hex	$PhCH(CH_3)COc\text{-}Hex$	93	36,37
	Ph		83	37
	c-Hex		92	36
	Ph		94	55
	Ph		75	55
			78	55
	$Cl(CH_2)_3$		80	55
	$Cl(CH_2)_3$		73	55
			76	55
			53	55

Table 13 (Continued)

FG-RCu(CN)ZnX (FG-R)	RCOCl (R)	product	yield (%)	ref(s)
	Cl_3C		82	70b
	Cl_3C		85	70b
	Ph		82	125
	Ph		75	125
	CF_3[a]		52	144
	CF_3[a]		32	144
	CF_3[a]		50	144
$NC(CH_2)_6$	Ph	$NC(CH_2)_6COPh$	94	64
$Cl(CH_2)_6$	Ph	$PhCO(CH_2)_6Cl$	85	64
$EtO_2C(CH_2)_3$	Bu	$EtO_2C(CH_2)_3COBu$	91	64
$EtO_2C(CH_2)_3$	Ph	$EtO_2C(CH_2)_3COPh$	95	64
	Bu		83	64
	Ph		88	64
	Bu		90	64
	Ph		83	64
	Ph		92	64
	Bu		94	64
	Ph		73	64
	Bu		71	64
	Ph		98	64
	Bu		97	64
	Bu		80	64
	CH_3		76	64
	Ph		80	29
	Ph		75	125a

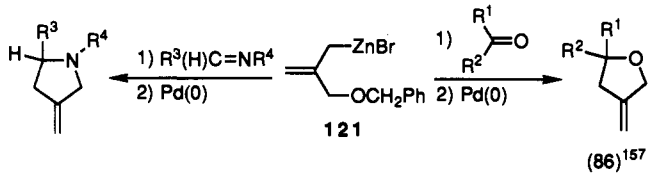
[a] $(CF_3CO)_2O$ was used.

counterparts,[131b] add to α-amino aldehydes in acceptable yields,[150] providing unsaturated 1,2-amino alcohols stereoselectively (eq 84). Allylic zinc reagents, which are highly reactive, add to a wide range of carbonyl functionalities (Table 14).[151-156] For example, the functionalized 2-carboethoxyallylzinc bromide **120** reacts well with aldehydes, ketones or imines[105,156] (eq 85



and Table 14) leading to α-methylene-γ-butyrolactones or α-methylene-γ-butyrolactams.[156]

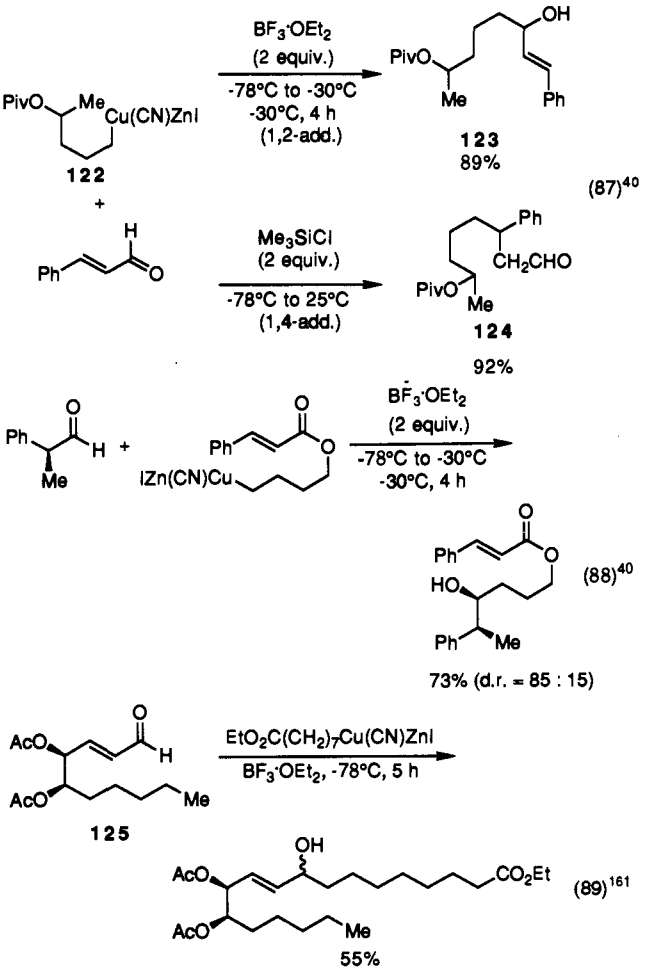
The zinc reagent **120** is prepared in high yield (>90%) from the corresponding bromide in THF if the reaction temperature is maintained between 17 and 20 °C during the addition and if zinc having a granulometry of 30 mesh is used (Table 14).[105] The allylic zinc compound **121** formally allows (3 + 2) cyclization reactions to be performed,[157] and its addition to aldehydes or imines furnishes, after a Pd(0)-catalyzed ring closure, 3-methylenetetrahydrofurans and 3-methylenepyrrolidines (eq 86).[157]



(86)157

In the presence of Lewis acids such as $Ti(OiPr)_nCl_{4-n}$,[158-159] Me_3SiCl, or $BF_3{\cdot}OEt_2$,[40] the addition of functionalized organozinc halides to aldehydes proceeds satisfactorily. An excellent chemoselectivity is observed; thus, the reaction of cinnamaldehyde with the zinc–copper reagent **122** produces in the presence of $BF_3{\cdot}OEt_2$ (2 equiv) the 1,2-adduct **123** in 89% yield (Table 14), whereas in the presence of Me_3SiCl (2 equiv) the same organometallic reagent undergoes a 1,4-addition leading to the aldehyde **124** (92% yield; eq 87).[40] As is the case for organotitanium reagents,[162-163] the organometallics FG-RCu(CN)ZnI add, in the presence of $BF_3{\cdot}OEt_2$, with good diastereoselectivity to α-chiral aldehydes (eq 88).[40] Oxygenated metabolites of unsaturated fatty acids can be prepared using the addition of a functionalized zinc–copper reagent to the unsaturated polyfunctional aldehyde **125** (eq 89).[161]

The direct addition of organozinc halides to aromatic aldehydes is possible in the presence of $BF_3{\cdot}OEt_2$, but the use of the corresponding copper compounds is mandatory for other classes of aldehydes (Table 15). Interestingly, it was found that functionalized (bromomethyl)oxazoles of type **126** can be readily converted to the corresponding zinc reagents **127** and be added under very mild reaction conditions (0 °C, 2 h) to aldehydes and ketones *in the absence of copper salts* (eq 90).[164] This high reactivity can be explained by the



enolate character of the zinc compounds **127**, and it is well known that zinc enolates display usually a good reactivity toward carbonyl compounds (Reformatsky reaction).[9] In contrast, a benzylic zinc halide requires the transmetalation to the copper reagent **128** to add to aldehydes (eq 91).

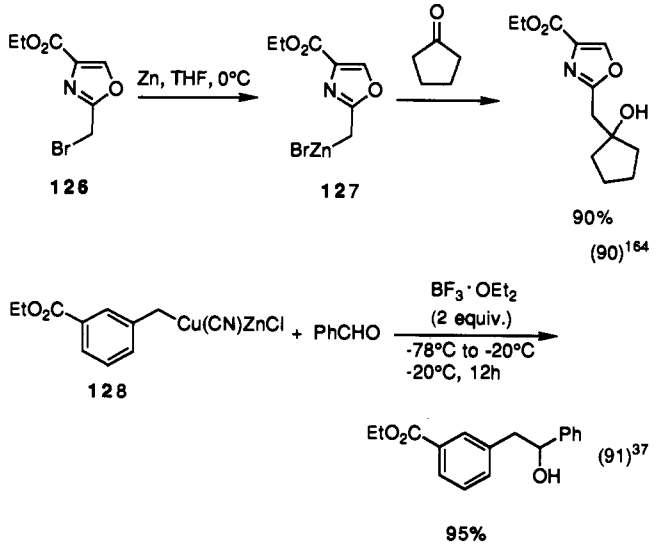


Table 14. Preparation of Polyfunctional Secondary Alcohols by the Addition of Allylic Organozinc or Organozinc–Copper Reagents to Aldehydes, Ketones, and Imines

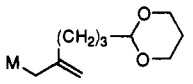
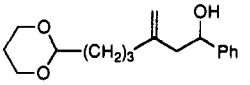
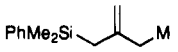
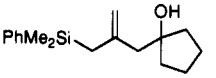
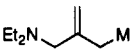
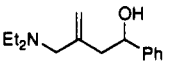
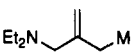
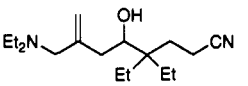
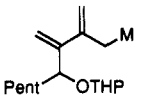
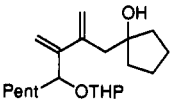
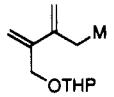
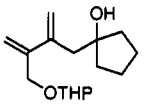
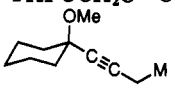
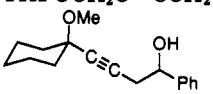
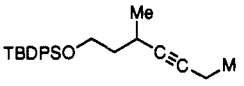
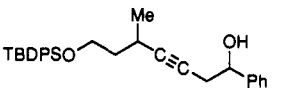
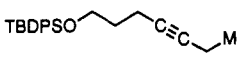
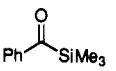
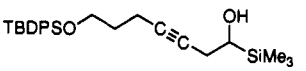
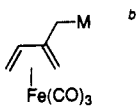
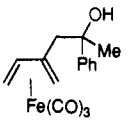
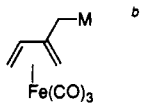
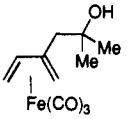
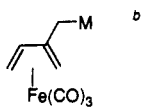
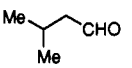
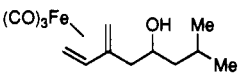
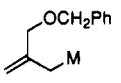
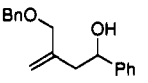
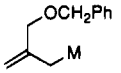
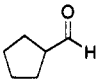
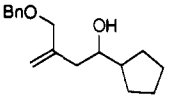
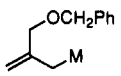
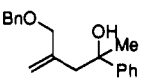
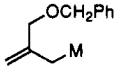
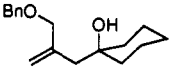
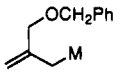
FG-RM[a] M = Cu(CN)ZnI	carbonyl compound	product	yield (%)	ref
	PhCHO		96	100
			71	100
	PhCHO		90	100
	$NC(CH_2)_2C(Et)_2CHO$		75	100
			58	101a
			70	101a
$THPOCH_2C{\equiv}CCH_2M$	PhCHO	$THPOCH_2C{\equiv}CCH_2CH(OH)Ph$	80	101a
	PhCHO		95	101a
	PhCHO		46	101b
			64	101b
 [b]	PhCOMe		37	151c
 [b]	MeCOMe		20	151c
 [b]			64	151c
	PhCHO		95	157c
			92	157c
	PhCOMe		100	157c
			100	157c
			98	157c
			90	157c

Table 14 (Continued)

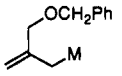
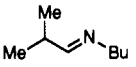
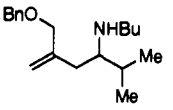
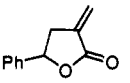
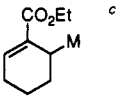
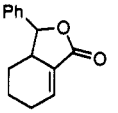
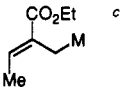
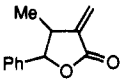
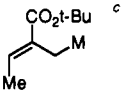
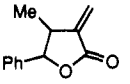
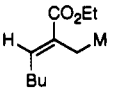
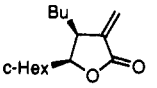
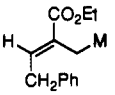
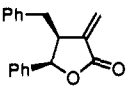
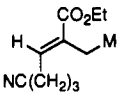
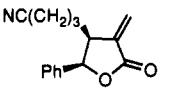
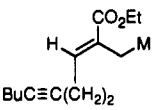
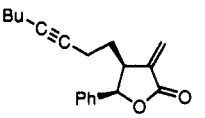
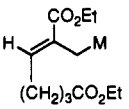
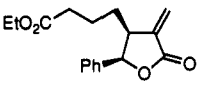
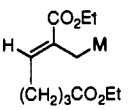
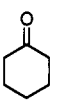
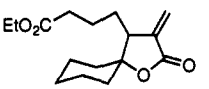
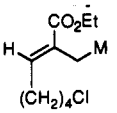
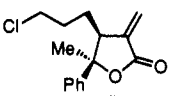
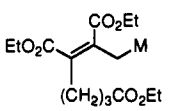
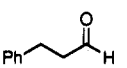
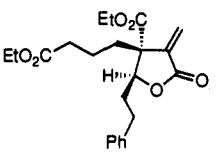
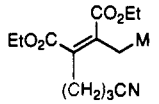
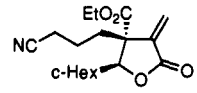
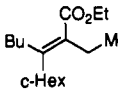
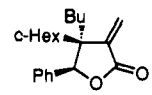
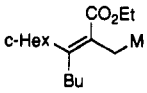
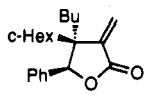
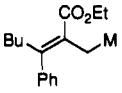
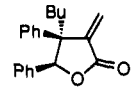
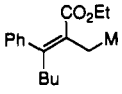
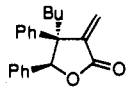
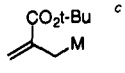
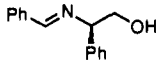
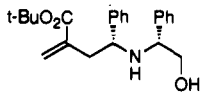
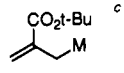
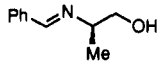
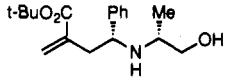
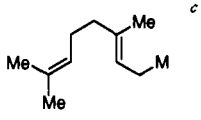
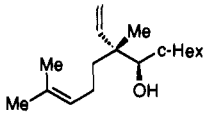
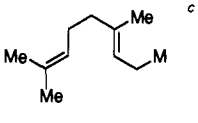
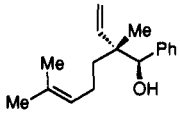
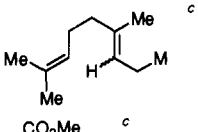
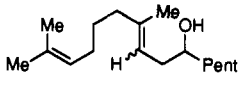
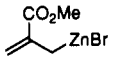
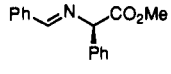
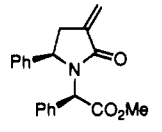
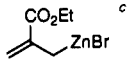
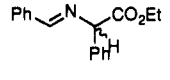
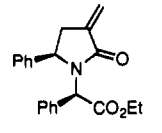
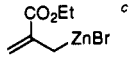
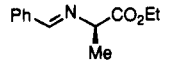
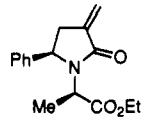
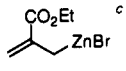
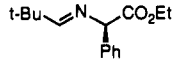
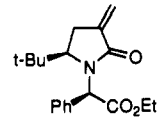
FG-RM[a] M = Cu(CN)ZnI	carbonyl compound	product	yield (%)	ref
			91	157c
	PhCHO		88	105b
 [c]	PhCHO		33	105b
 [c]	PhCHO		87	105b
 [c]	PhCHO		89	105b
	c-HexCHO	 *cis/trans* (80:20)	76	106
	PhCHO	 *cis/trans* (92:8)	78	106
	PhCHO	 *cis/trans* (90:10)	75	106
	PhCHO	 *cis/trans* (95:5)	76	106
	PhCHO	 *cis/trans* (95:5)	85	106
			68	106
	PhCOMe	 *cis/trans* (100:0)	82	106
		 *cis/trans* (85:15)	86	106

Table 14 (Continued)

FG-RM[a] M = Cu(CN)ZnI	carbonyl compound	product	yield (%)	ref
	c-HexCHO	 *cis/trans* (95:5)	93	106
	PhCHO	 *cis/trans* (75:25)	60	106
	PhCHO	 *cis/trans* (98:2)	67	106
	PhCHO	 *cis/trans* (60:40)	78	106
	PhCHO	 *cis/trans* (98:2)	85	106
 [c]			85	156a
 [c]			77	156a
 [c]	c-HexCHO	 (dr = 9:1)	78	76
 [c]	PhCHO	 (dr = 4:1)	95	76
 [c]	$PentCOSiMe_3$		78	155
 [c]			70	156b
 [c]			85	156b
 [c]			78	156b
 [c]			75	156b

[a] Prepared by the methylene homologation of the corresponding alkenylcopper (or alkynylcopper) using iodomethylzinc iodide. [b] Prepared by metalation. [c] Prepared by direct zinc insertion.

Table 15. Preparation of Polyfunctional Secondary Alcohols Obtained by the Addition of Organozinc or Organozinc–Copper Reagents to Aldehydes, Ketones, Imines, or Immonium Ions in the Presence of Lewis Acids

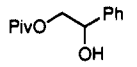
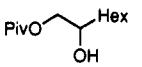
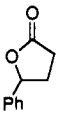
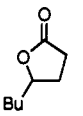
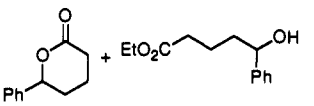
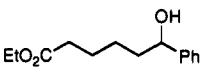
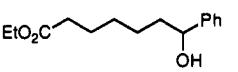
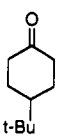
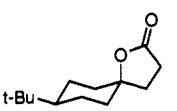
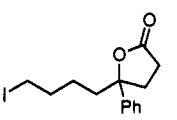
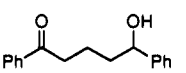
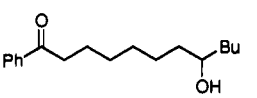
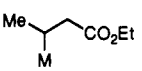
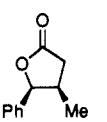
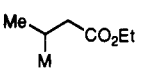
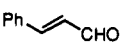
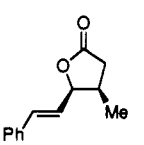
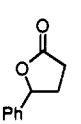
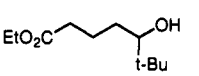
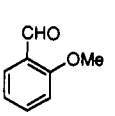
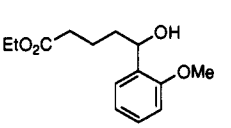
FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
$PivOCH_2M$	PhCHO		89	44,45b
$PivOCH_2M$	HexCHO		73	44,45b
$PhSCH_2M$	PhCHO	$PhSCH_2CH(OH)Ph$	71	59,60
$EtO_2C(CH_2)_2M$	PhCHO		95	158
$EtO_2C(CH_2)_2M$	BuCHO		100	158
$EtO_2C(CH_2)_3M$	PhCHO		78	158
$EtO_2C(CH_2)_4M$	PhCHO		80	158
$EtO_2C(CH_2)_5M$	PhCHO		95	158
$EtO_2C(CH_2)_2M$			88	158
$EtO_2C(CH_2)_2M$	$I(CH_2)_4COPh$		95	158
$PhCO(CH_2)_3M$	PhCHO		76	158
$PhCO(CH_2)_5M$	BuCHO		75	158
	PhCHO	 *cis/trans* (>99:1)	94	158
		 *cis/trans* (83:17)	95	158
$EtO_2C(CH_2)_2M$	PhCHO		95	160
$EtO_2C(CH_2)_3M$	t-BuCHO		40	160
$EtO_2C(CH_2)_3M$			97	160

Table 15 (Continued)

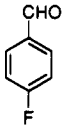
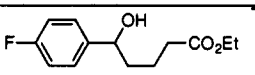
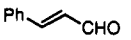
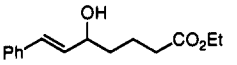
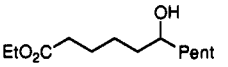
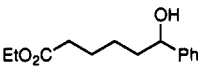
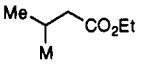
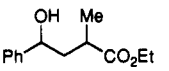
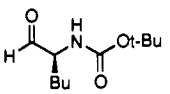
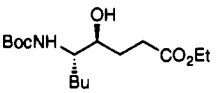
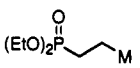
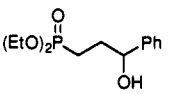
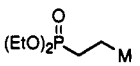
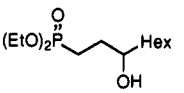
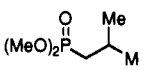
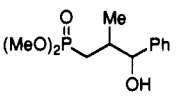
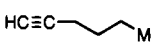
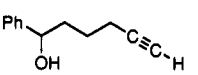
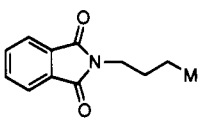
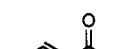
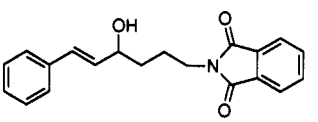
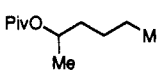
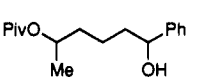
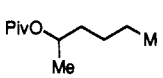
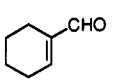
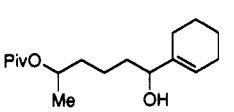
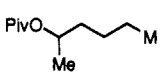
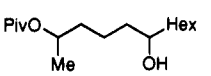
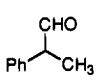
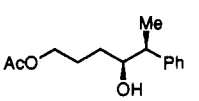
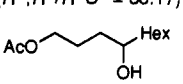
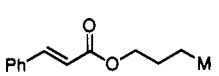
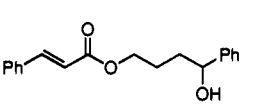
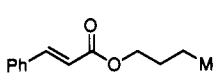
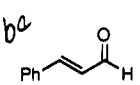
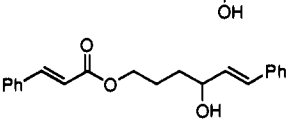
FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
$EtO_2C(CH_2)_3M$			88	160
$EtO_2C(CH_2)_3M$			68	160
$EtO_2C(CH_2)_4M$	PentCHO		22	160
$EtO_2C(CH_2)_4M$	PhCHO		80	160
	PhCHO		70	160
$EtO_2C(CH_2)_2M$			32	159
	PhCHO		96	61
	HexCHO		88	61
	PhCHO		81	61
	PhCHO		75	56
			65	57
	PhCHO		80	40
			84	40
	HexCHO		77	40
$AcO(CH_2)_3M$			77	40
		($R^*,R^*/R^*S^*$ = 83:17)		
$AcO(CH_2)_3M$	HexCHO		91	40
	PhCHO		93	40
			79	40

Table 15 (Continued)

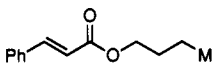
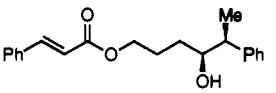
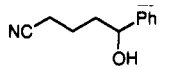
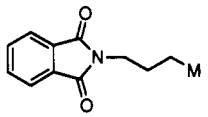
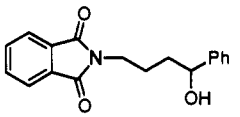
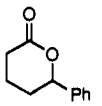
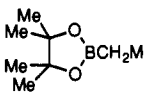
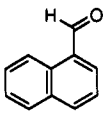
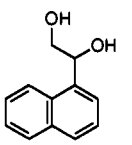
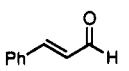
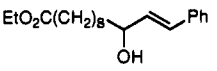
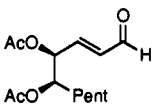
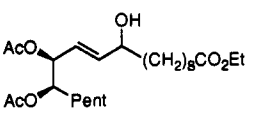
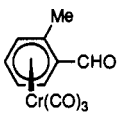
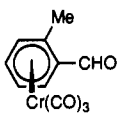
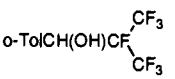
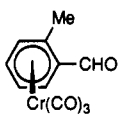
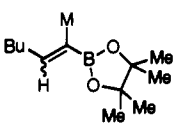
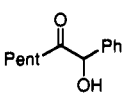
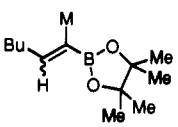
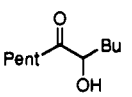
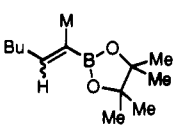
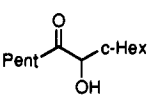
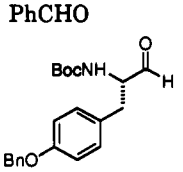
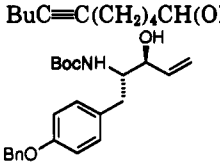
FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
		 ($R^*,R^*/R^*S^*$ = 85:15)	73	40
$NC(CH_2)_3M$	PhCHO		85	40
	PhCHO		89	40
$EtO_2C(CH_2)_3M$	PhCHO		72	40
			93	46a
$EtO_2C(CH_2)_3M$			80	161
$EtO_2C(CH_2)_8M$			55	161
C_2F_5M		*o*-Tol-CH(OH)C_2F_5	85	176
i-C_3F_7M			100	176
$C_6F_{13}M$		*o*-TolCH(OH)C_6F_{13}	80	176
	PhCHO		76	46b
	BuCHO		74	46b
	c-HexCHO		87	46b
$BuC{\equiv}C(CH_2)_4M$ 	PhCHO 	$BuC{\equiv}C(CH_2)_4CH(OH)Ph$  (dr = 8:1)	64 >60	49b 150

Table 15 (Continued)

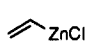
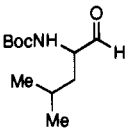
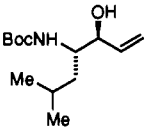
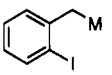
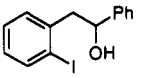
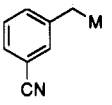
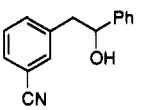
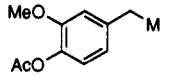
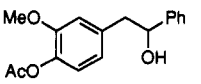
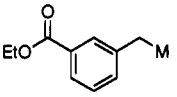
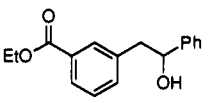
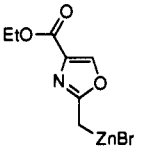
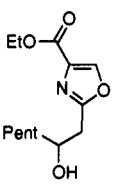
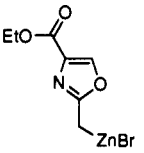
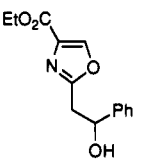
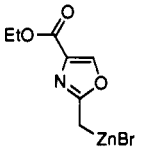
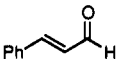
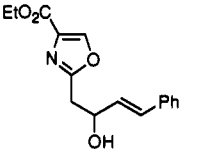
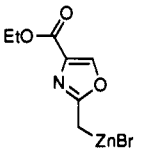
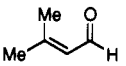
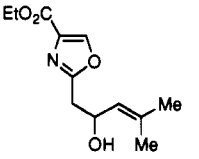
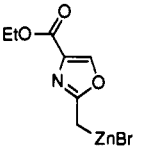
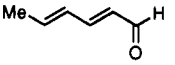
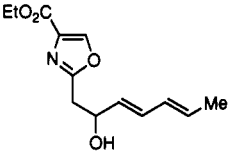
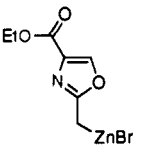
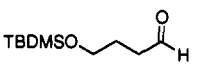
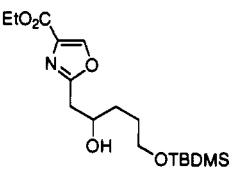
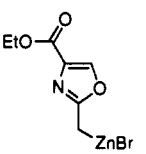
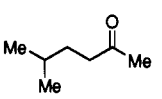
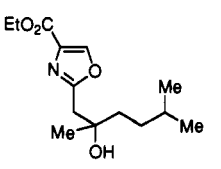
FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
		 (dr = 8:1)	>60	150
	PhCHO		93	36,37
	PhCHO		94	36,37
	PhCHO		85	36,37
	PhCHO		97	37
	PhCHO		92[b]	164
	PhCHO		96[b]	164
			97[b]	164
			62[b]	164
			40[b]	164
			62[b]	164
			39[b]	164

Table 15 (Continued)

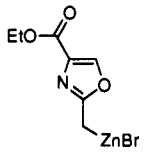
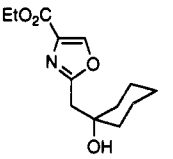
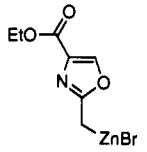
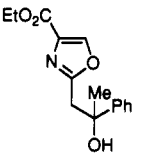
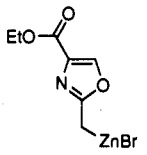
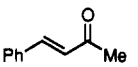
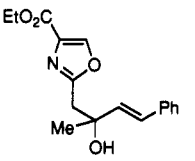
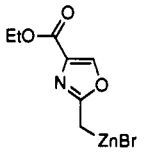
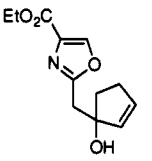
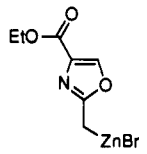
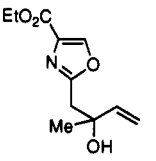
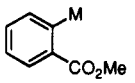
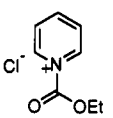
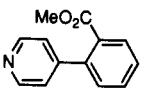
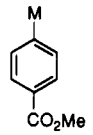
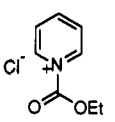
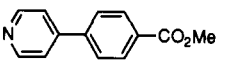
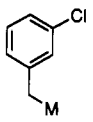
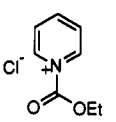
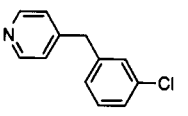
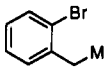
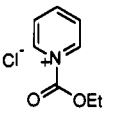
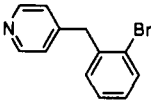
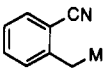
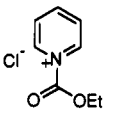
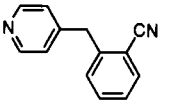
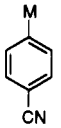
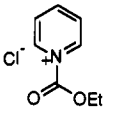
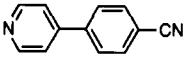
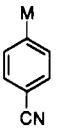
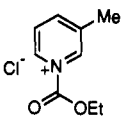
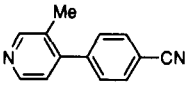
FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
			49[b]	164
	PhCOMe		47[b]	164
			93[b]	164
			90[b]	164
			52[b]	164
			50[b]	170
			57[b]	170
			56[b]	167
			43[b]	167
			40[b]	167
			50[b]	169
			46[b]	169

Table 15 (Continued)

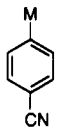
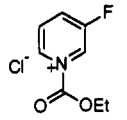
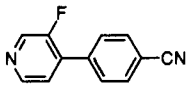
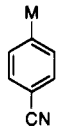
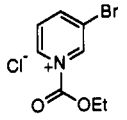
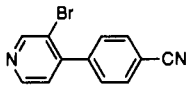
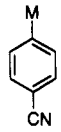
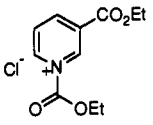
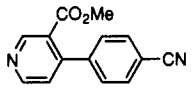
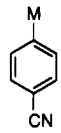
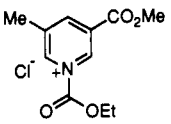
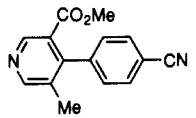
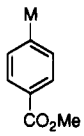
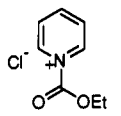
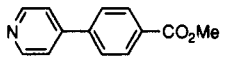
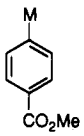
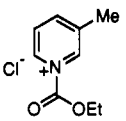
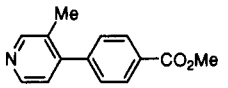
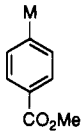
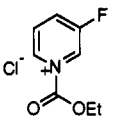
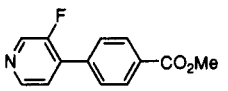
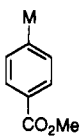
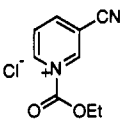
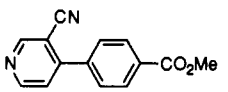
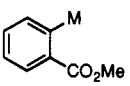
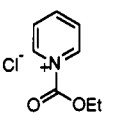
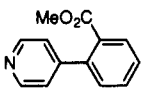
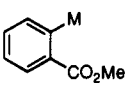
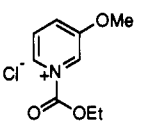
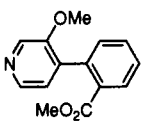
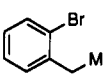
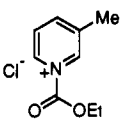
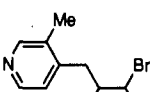
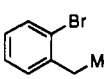
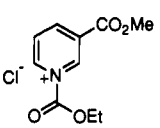
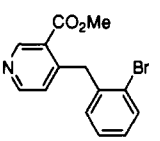
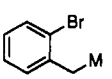
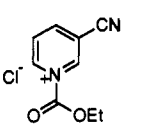
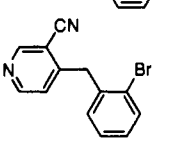
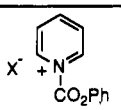
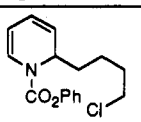
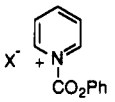
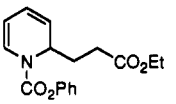
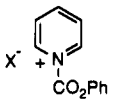
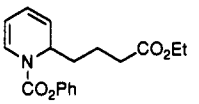
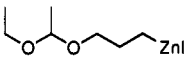
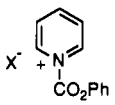
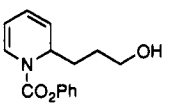
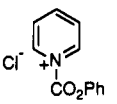
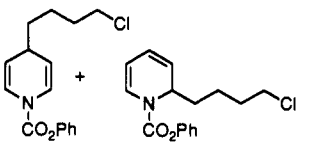
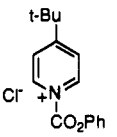
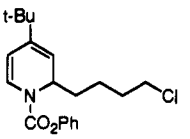
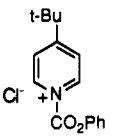
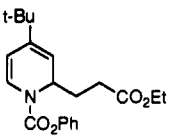
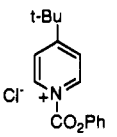
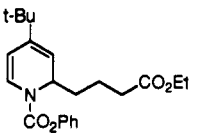
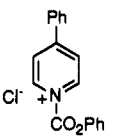
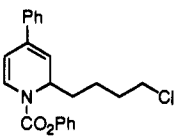
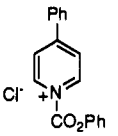
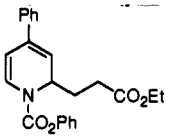
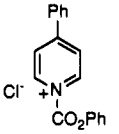
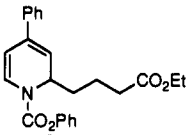
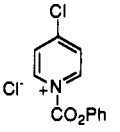
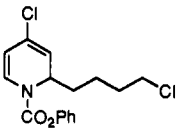
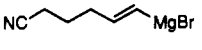
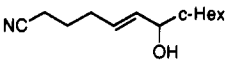
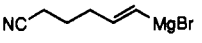
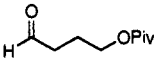
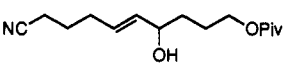
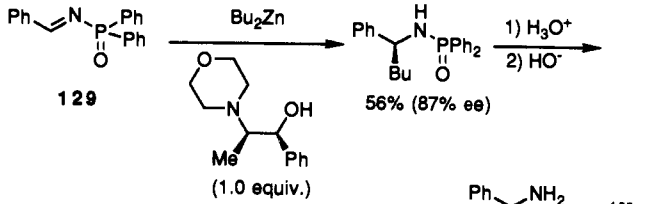
FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
			60[b]	169
			44[b]	169
			45[b]	169
			43[b]	169
			57[b]	169
			46[b]	169
			38[b]	169
			29[b]	169
			50[b]	169
			41[b]	169
			61[b]	168
			39[b]	168
			66[b]	168

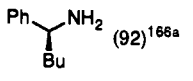
Table 15 (Continued)

FG-RM[a]	carbonyl compound	product	yield (%)	ref(s)
$Cl(CH_2)_4ZnI$			77[b]	172
$EtO_2C(CH_2)_2ZnI$			97[b]	172
$EtO_2C(CH_2)_3ZnI$			82[b]	172
			64[b]	172
$Cl(CH_2)_4ZnI$		 68 : 32	70[b]	171
$Cl(CH_2)_4ZnI$			81[b]	171
$EtO_2C(CH_2)_2ZnI$			46[b]	171
$EtO_2C(CH_2)_3ZnI$			35[b]	171
$Cl(CH_2)_4ZnI$			57[b]	171
$EtO_2C(CH_2)_2ZnI$			66[b]	171
$EtO_2C(CH_2)_3ZnI$			47[b]	171
$Cl(CH_2)_4ZnI$			66[b]	171
	c-HexCHO		71[b]	125a
			77[b]	125a

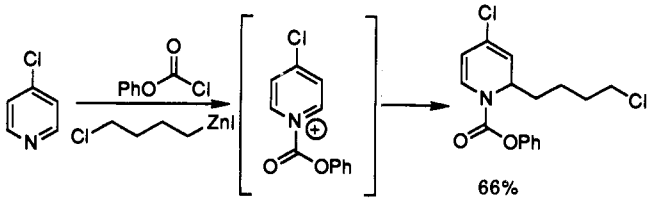
[a] M = Cu(CN)ZnX. [b] Prepared in the absence of Lewis acid.

Nonactivated imines do not react with organozinc reagents; however, the addition of some dialkylzincs to α-diimines proceeds quantitatively.[165] The addition of dialkylzincs to *N*-diphenylphosphinoylimines **129** in the presence of a catalytic or a stoichiometric amount of chiral β-amino alcohols provides chiral amines of type **130** with excellent enantioselectivity (75–98% ee; eq 92).[166a]

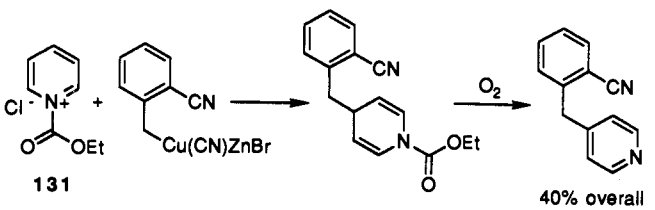




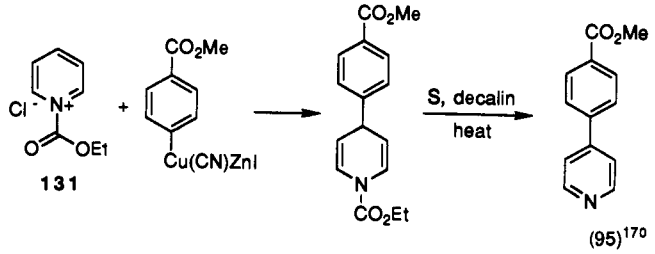
(92)[166a]



(93)[171]

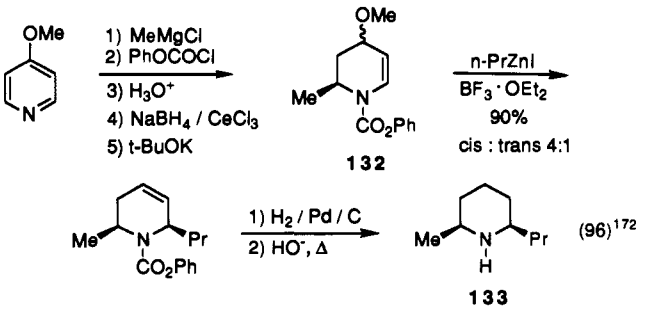


(94)[167]



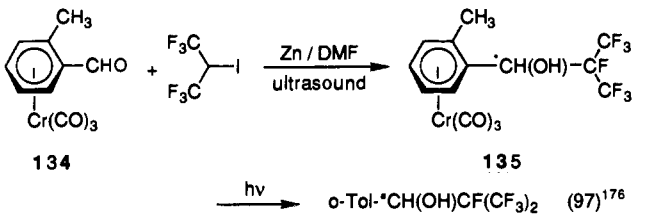
(95)[170]

Pyridinium salts **131**[167–171] or unsaturated piperidines[172] **132** react with various organozincs or with the corresponding copper reagents and provide an expeditive preparation of various polyfunctional heterocycles (eqs 93–95).[167–171] This reaction has been applied to a synthesis of (±)-dihydropinidine **133** (eq 96).[172] A new synthesis of chiral amino acids using the addition of dialkylzincs to chiral oxazolidines has been reported. The extension of the reaction to functionalized dialkylzincs seems straightforward and would allow an easy access to chiral polyfunctional amino acids.[173–175]



(96)[172]

The diastereoselective addition of perfluoroalkylzinc iodides to chiral arene–chromium complexes **134** has been exploited to prepare (perfluoroalkyl)arylcarbinols **135** in 30–66% ee (eq 97).[176]

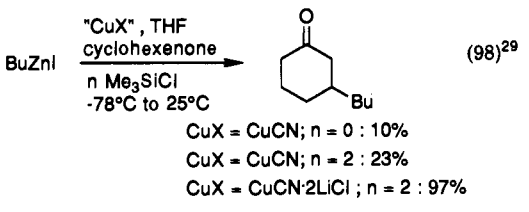


(97)[176]

The low reactivity of organozinc compounds in addition reactions makes these organometallics ideal reagents for catalyzed reactions, and a number of highly efficient catalytic systems have been developed for performing selective additions of diethylzinc to aldehydes.[30,92,93] Recently, the reaction has been extended to functionalized diorganozincs using a chiral titanium catalyst (see section V).[48]

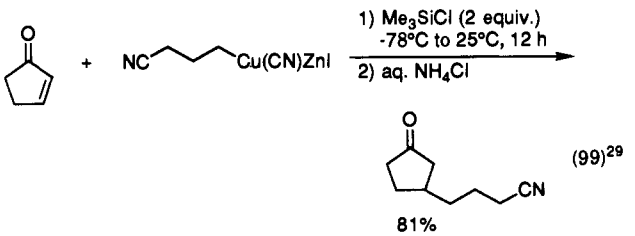
2. 1,4-Additions to α,β-Unsaturated Carbonyl Compounds

One of the most useful synthetic properties of organocopper compounds derived from lithium or magnesium organometallics is their ability to readily undergo 1,4-addition reactions. As expected the zinc copper reagents FG-RCu(CN)ZnI react under the appropriate reaction conditions with several types of α,β-unsaturated carbonyl compounds. The use of a soluble copper salt was found to be mandatory.[29] The addition of CuCN (1 equiv), which is insoluble in THF, to butylzinc iodide in the presence or absence of Me_3SiCl[177–180] leads only to low yields of 3-butylcyclohexanone (10–23%; eq 98 and Table 16), whereas the use of the THF soluble copper salt CuCN·2LiX, in the presence of Me_3SiCl, provides the desired Michael adduct in 97% isolated yield![29]



(98)[29]

Clearly the rate of the transmetalation from zinc to copper is faster if a soluble copper salt is used. With CuCN·2LiCl, various functionalized organozinc halides can be added to β-monosubstituted enones in the presence of Me_3SiCl (2 equiv; eqs 99–101 and Table



(99)[29]

Table 16. Michael Additions of Functionalized Zinc–Copper Reagents to Enones and Related Carbonyl Compounds

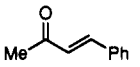
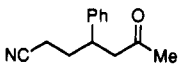
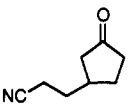
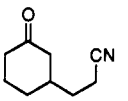
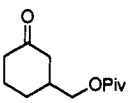
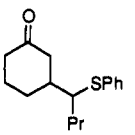
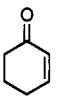
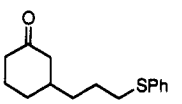
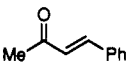
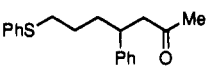
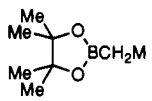
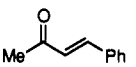
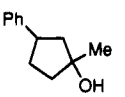
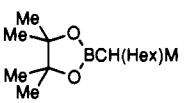
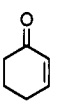
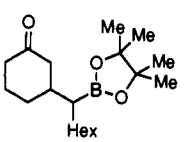
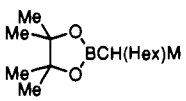
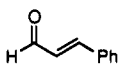
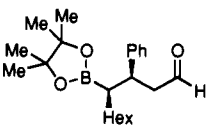
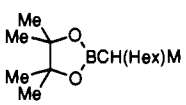
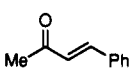
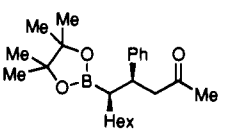
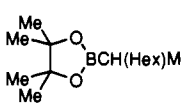
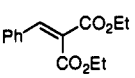
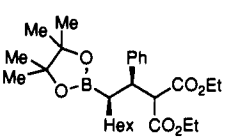
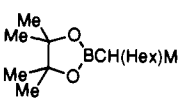
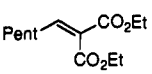
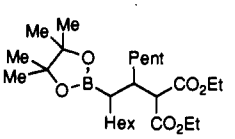
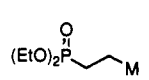
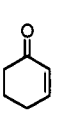
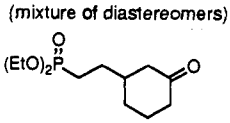
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref(s)
$NCCH_2CH_2M$			95	54a,99
$NCCH_2CH_2M$			65	54a
$NCCH_2CH_2M$			86	54a
$PivOCH_2M$			59	44,45b
PhSCH(Pr)M			78	59,60
$PhS(CH_2)_3M$			84	59,60
$PhS(CH_2)_3M$			81	60
			67	46a
			74	46a
			57	46a
		(1 diastereomer)		
			79	46a
		(1 diastereomer)		
			95	46a
		(1 diastereomer)		
			86	46a
		(mixture of diastereomers)		
			71	61

Table 16 (Continued)

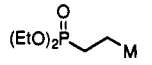
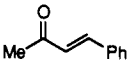
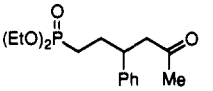
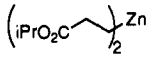
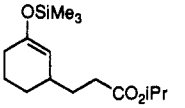
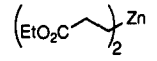
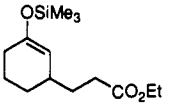
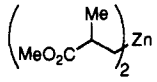
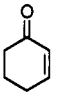
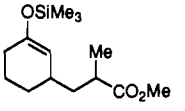
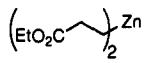
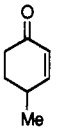
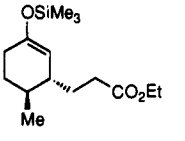
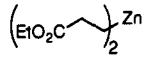
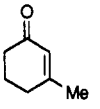
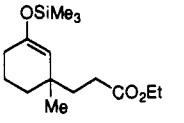
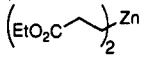
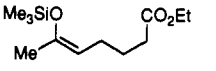
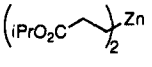
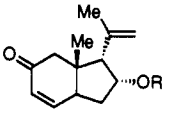
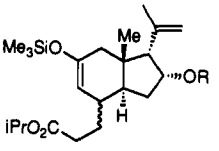
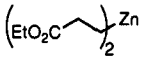
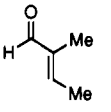
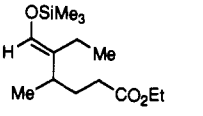
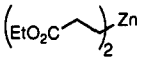
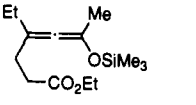
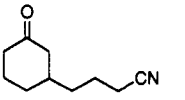
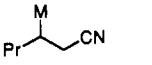
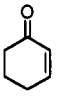
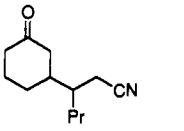
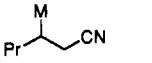
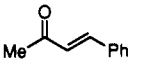
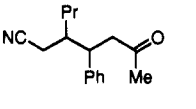
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref(s)
			88	61
			93	27a
			76	27a
			91	27a,28b
		 (dr = 72:28)	78	27a
			92	27a
		 *E/Z* (24:76)	75	27a
	 R = Me_3Sn, Ac, MOM	 (dr = 1:1)	85–95	27a
			75	27a
	EtC≡CCOMe		73	27a
$(NC(CH_2)_3)_2Zn$			83	48
		 (dr = 67:33)	84	54b
		 (dr = 76:24)	83	54b

Table 16 (Continued)

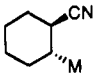
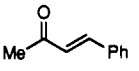
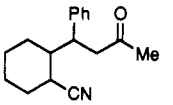
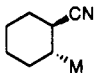
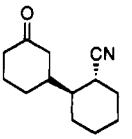
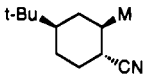
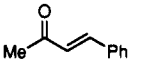
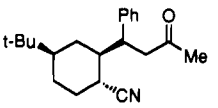
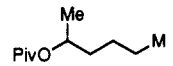
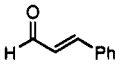
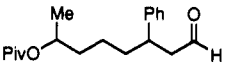
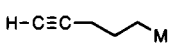
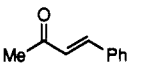
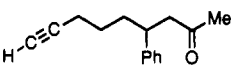
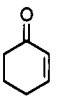
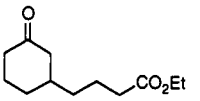
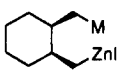
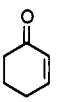
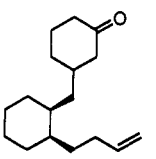
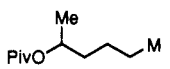
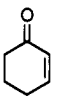
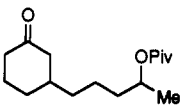
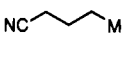
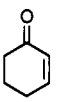
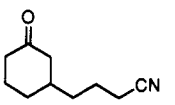
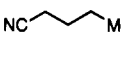
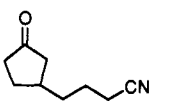
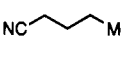
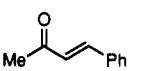
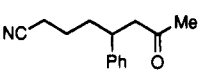
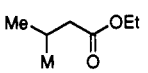
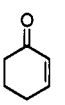
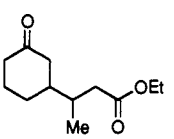
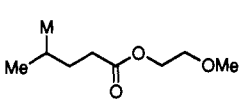
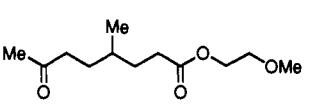
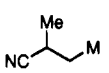
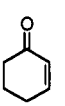
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref(s)
			76	54b
		 (dr = 83:17)	62	54b
			86	54b
			92	40
			95	56
$EtO_2C(CH_2)_3M$			95 (55,64)	29 (64,28b)
	 (then allyl bromide)	 (dr = 80:20)	74	49
			94	29
			97	29
			81	29
			99	29
			78	28b
			76	28b
			70	28b

Table 16 (Continued)

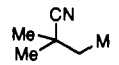
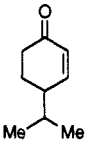
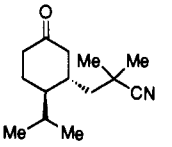
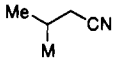
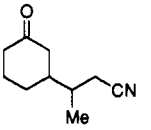
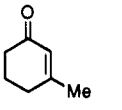
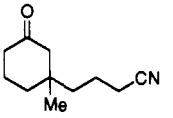
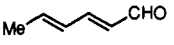
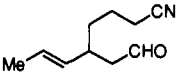
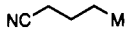
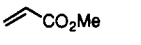
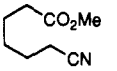
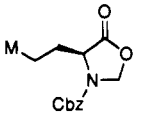
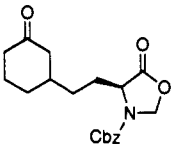
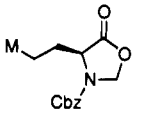
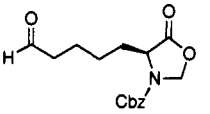
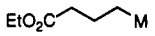
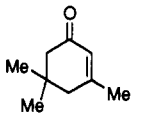
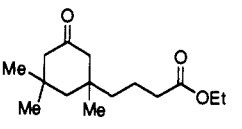
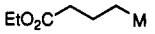
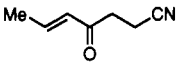
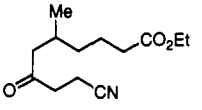
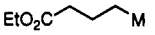
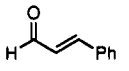
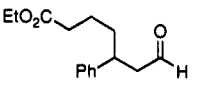
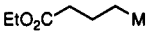
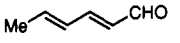
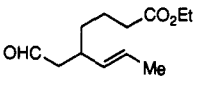
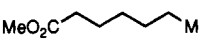
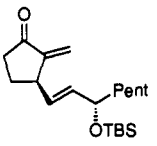
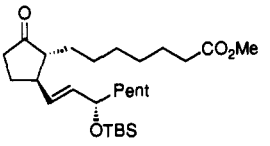
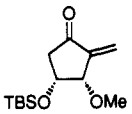
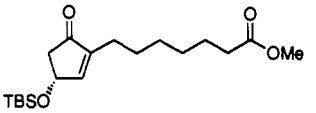
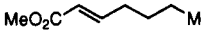
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref(s)
			54	28b
			62	28b
			70	28b
			95	28b
			59	28b
			71	28b
			70	28b
			77	28b
			77	28b
			94	28b
			73	28b
			86	185
			88	185
			83	185

Table 16 (Continued)

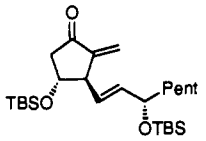
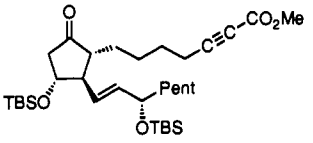
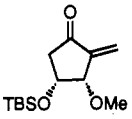
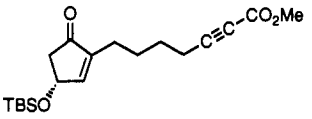
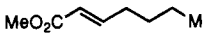
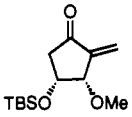
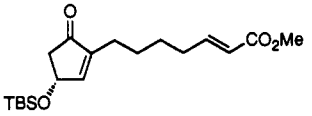
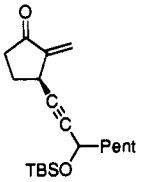
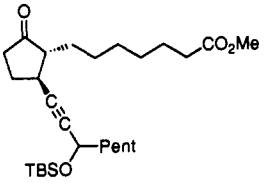
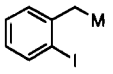
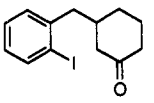
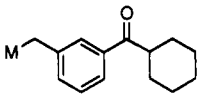
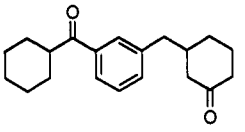
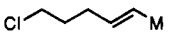
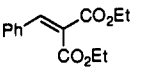
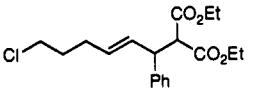
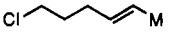
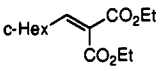
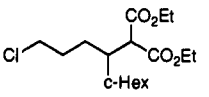
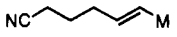
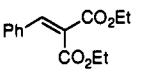
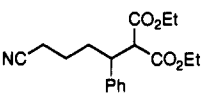
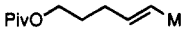
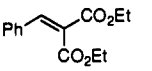
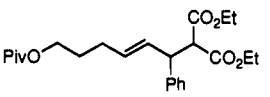
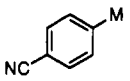
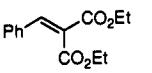
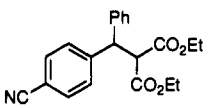
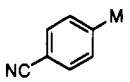
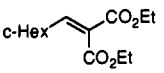
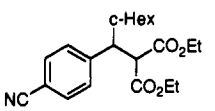
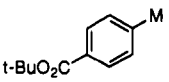
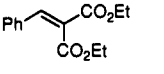
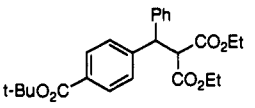
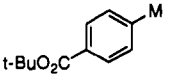
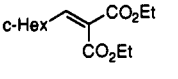
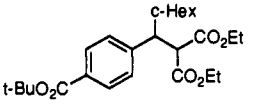
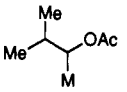
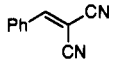
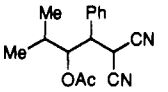
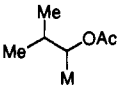
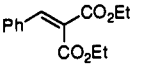
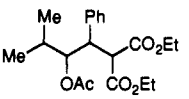
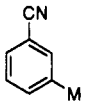
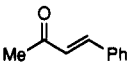
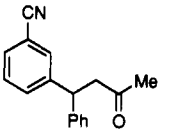
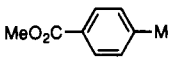
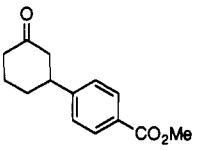
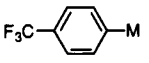
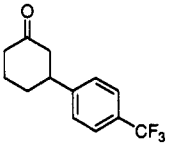
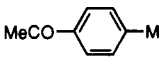
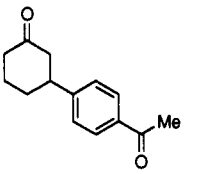
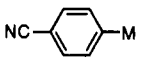
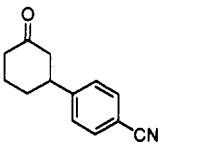
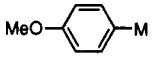
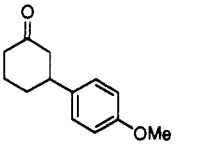
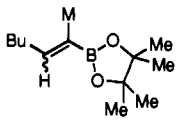
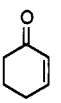
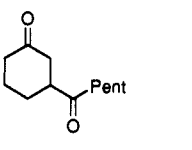
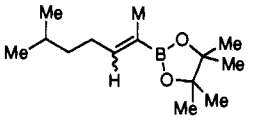
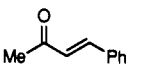
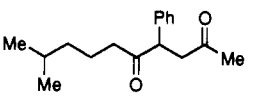
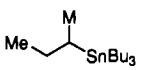
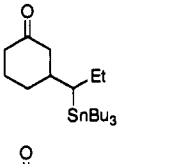
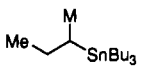
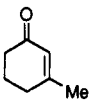
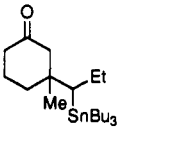
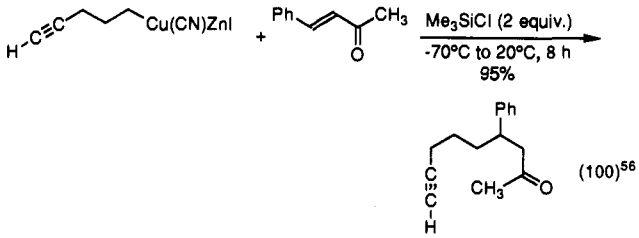
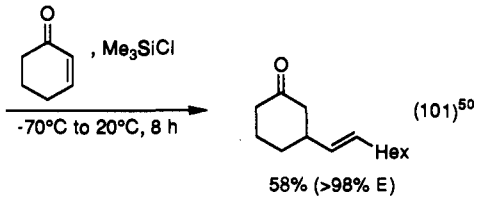
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref(s)
$MeO_2CC{\equiv}C(CH_2)_3M$			75	185
$MeO_2CC{\equiv}C(CH_2)_3M$			95	185
			75	185
$MeO_2C(CH_2)_5M$			78	186
			93	36,37
			95	36,37
			80	125b
			71	125b
			82	125b
			76	125b
			90	125b
			92	125b
			85	125b
			79	125b

Table 16 (Continued)

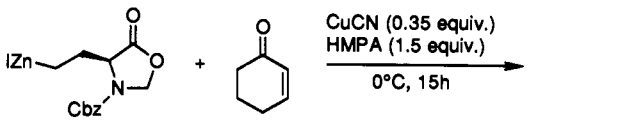
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref(s)
			89	45
			86	45
			61	35
			44	144
			52	144
			54	144
			35	144
			54	144
			76	46b
			73	46b
			66	216
			38	216

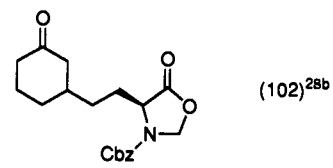
[a] M = Cu(CN)ZnX.

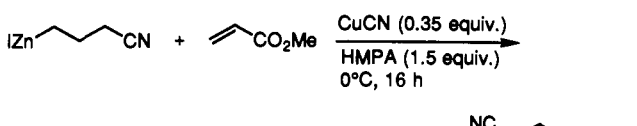


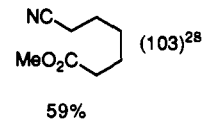


16). However, under these conditions *β-disubstituted* enones or unsaturated esters do not react. The use of a polar solvent such as HMPA circumvents this problem and allows the addition of organozinc reagents to both β-mono and β-disubstituted enones as well as to ethyl acrylate to proceed (eqs 102 and 103).[28b] Another way

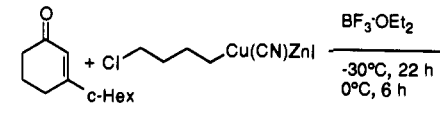


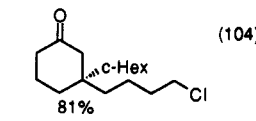


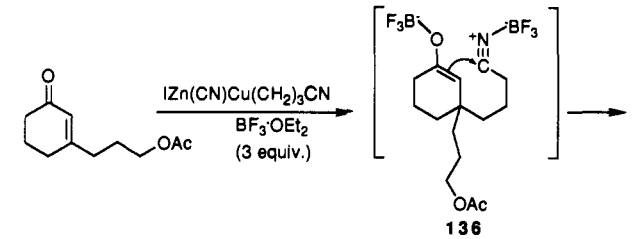


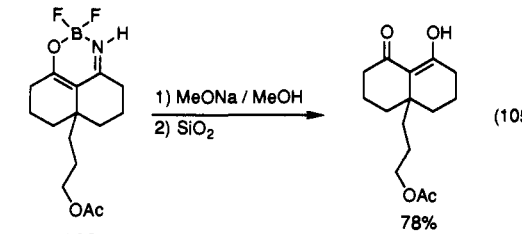


to extend the scope of the reaction is to use a Lewis acid or Me_3SiX[180] to activate the unsaturated carbonyl moiety. The reaction of *β-disubstituted* enones with various functionalized zinc–copper reagents occurs well under these conditions (eqs 104 and 105 and Table 17).[38] Interestingly, if a cyano substituent is present or introduced on the side chain at the appropriate position, as in **136**, a ring closure occurs affording a stable difluoroboron enolate **137** which can be purified by flash-chromatography and was characterized by its X-ray structure.[38] The Michael addition can also be performed with functionalized arylzinc reagents prepared by an electroreduction of the corresponding chloride or bromide using a sacrificial zinc electrode (eq 106).[144] Dialkylzincs like **138** can be used advan-

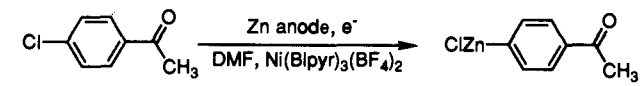


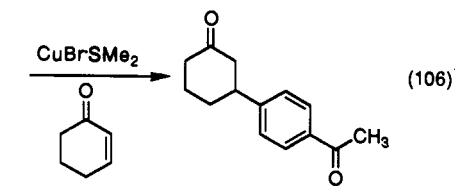


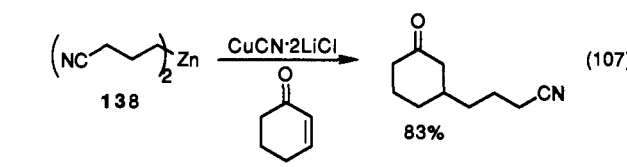


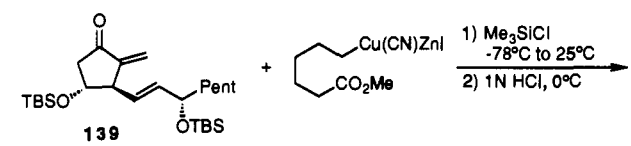


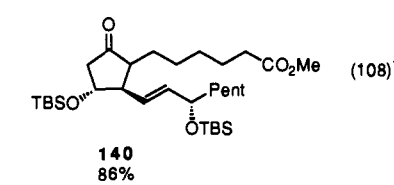
tageously in Michael additions, and their transmetalation with CuCN·2LiCl affords a copper species which reacts readily with enones (eq 107).[48] It should be noted





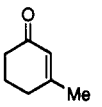
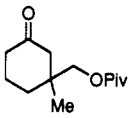
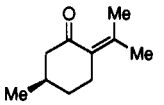
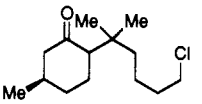
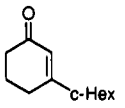
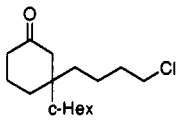
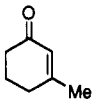
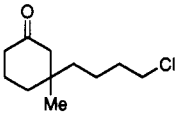
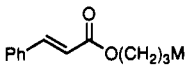
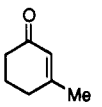
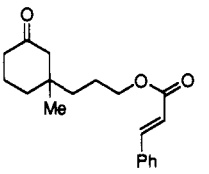
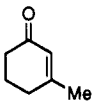
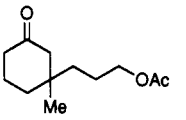
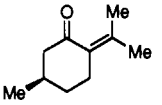
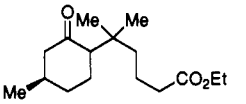
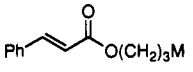
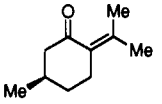
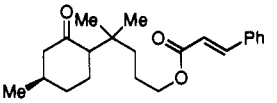
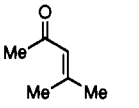
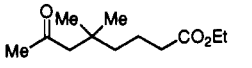
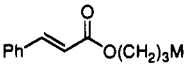
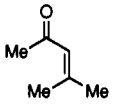
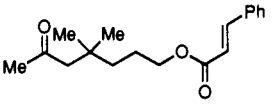
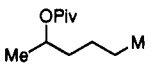
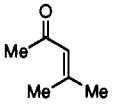
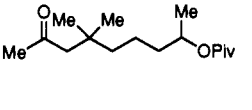
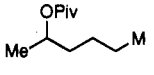
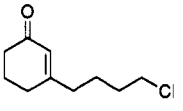
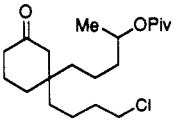
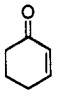
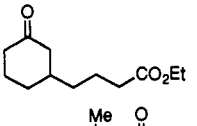
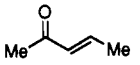
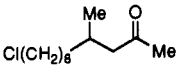
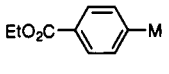
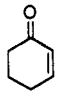
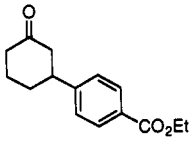






that unfunctionalized dialkylzincs (Et_2Zn) can also be added enantioselectively in a 1,4-fashion to chalcone in the presence of Ni(II) salts and chiral ligands[181,182] or

Table 17. Michael Additions of Functionalized Zinc–Copper Reagents to β-Disubstituted Enones in the Presence of BF_3·OEt_2

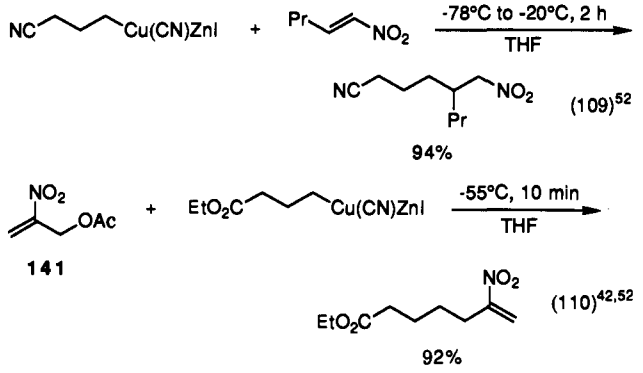
FG-RM[a]	α,β-unsaturated carbonyl compound	product	yield (%)	ref
$PivOCH_2M$			71	44
$Cl(CH_2)_4M$			94	38
$Cl(CH_2)_4M$			81	38
$Cl(CH_2)_4M$			88	38
			98	38
$AcO(CH_2)_3M$			87	38
$EtO_2C(CH_2)_3M$			94	38
			84	38
$EtO_2C(CH_2)_3M$			88	38
			88	38
			88	38
			86	38
$EtO_2C(CH_2)_3M$			74	64
$Cl(CH_2)_6M$			77	64
			68	64

[a] M = Cu(CN)ZnI.

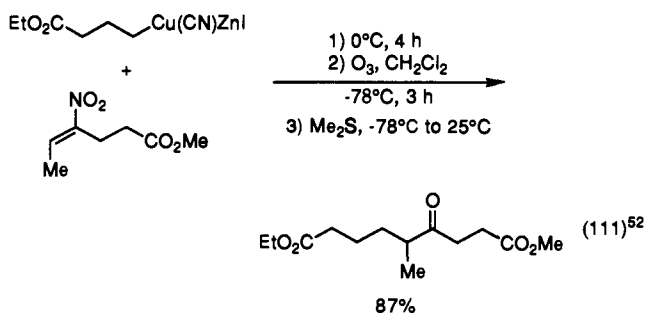
by using a chiral copper(I) catalyst.[183,184] The Michael addition of functionalized zinc–copper organometallics has been extensively applied to the synthesis of prostacyclins, prostaglandins, and related molecules.[185,186] Thus, the α-methylenecyclopentanone **139** reacts in excellent yields with various types of polyfunctional reagents (FG-R)Cu(CN)ZnI providing the desired prostaglandin **140** (eq 108).

3. Michael Additions to Nitro Olefins and Related Reagents

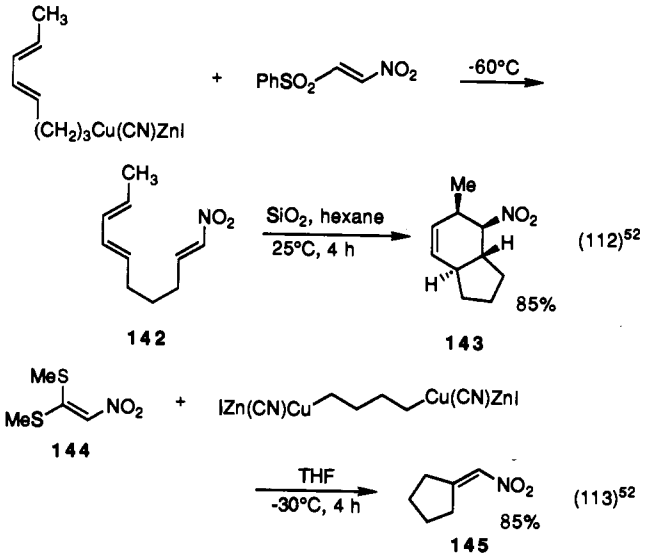
Nitro olefins are excellent Michael acceptors and add a wide range of nucleophiles providing functionalized nitroalkanes which are important intermediates in synthesis. They can be readily converted to amines by reduction or carbonyl compounds by a Nef reaction.[187] Interestingly, the addition of lithium or magnesium cuprates to nitrostyrene does not occur cleanly. This may be due to electron-transfer side reactions and to the fact that the magnesium and lithium nitronates obtained after addition can themselves add to nitro olefins and hence lead to polymerization products.[188,189] In strong contrast, copper reagents derived from organozinc compounds add cleanly and in high yields to various types of nitro olefins.[42,47,52] The reaction proceeds at −20 °C for aliphatic nitro olefins, whereas conjugated aromatic nitro olefins, such as nitrostyrene, react only at 0 °C (eq 109 and Table 18). Unsaturated nitro compounds bearing a leaving group in the β-position,[190] such as 2-nitro-1-acetoxy-2-propene, (**141**), react under milder conditions (−55 °C, 10 min) and provide new nitro olefins which are susceptible to addition of a second different nucleophile (multicoupling reagent)[190] (eq 110). The intermediate nitronates



obtained after the addition of FG-RCu(CN)ZnX can be directly submitted to an oxidative Nef reaction (O_3, CH_2Cl_2, −78 °C, 3 h) and converted into polyfunctional ketones in good overall yields (eq 111).[52] Finally, an



interesting addition–elimination reaction of **100** to nitro olefins bearing a leaving group in the β-position (SR or SO_2R) produces pure (*E*)-nitro olefins.[47,52] The reaction has been applied to the preparation of the nitro triene **142** which undergoes a highly stereoselective Diels–Alder reaction on silica gel[191] leading to the nitro compound **143** (eq 112)[47,52,192] The addition of RCu(CN)ZnI to 2,2-bis(methylthio)-1-nitroethylene (**144**) provides the *exo*-(nitromethylidene)cyclopentane (**145**) in 85% yield. No migration of the double bond is observed under the mild reaction conditions used (eq 113).[52]



4. Carbocupration Reactions

The addition of organometallics to unactivated alkynes represents a unique method for the stereoselective preparation of (*E*)- or (*Z*)-trisubstituted alkenes.[193,194] As expected only highly reactive zinc reagents such as allylic zinc compounds are able to add to unactivated alkynes. These reactions have been elegantly applied to the synthesis of 1,5-annelated 4-methylenecyclopentenes. Thus, the zinc reagent **146** undergoes a smooth cyclization (THF, 25 °C, 2 h) leading to the alkenyl zinc **147**. Treatment of **147** with a catalytic amount of $Pd(PPh_3)_4$ (5 mol %) provides the bicyclic diene **148** in 84% GC yield (eq 114 and

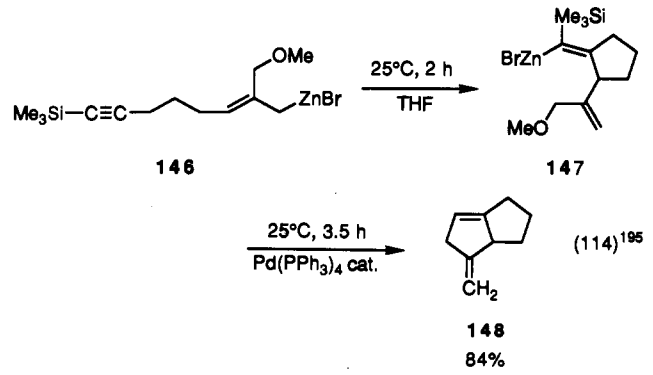


Table 19).[195] Several classes of mixed zinc–copper organometallics are able to add to activated and some nonactivated alkynes. Ethyl propiolate reacts at −60 to −50 °C with FG-RCu(CN)ZnI and provides the *syn*-addition product **149** with high stereoselectivity. By performing the reaction at higher temperature and

Table 18. Preparation of Polyfunctional Nitroalkanes by the Addition of Polyfunctional Zinc–Copper Reagents to Nitro Olefins

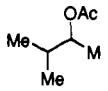
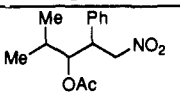
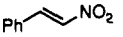
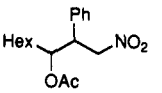
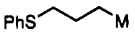
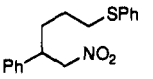
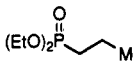
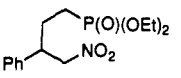
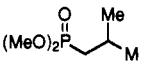
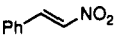
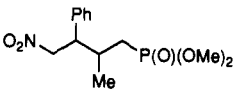
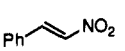
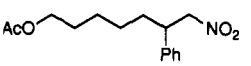
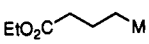
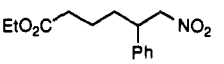
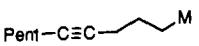
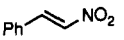
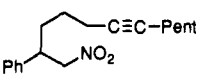
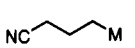
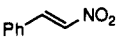
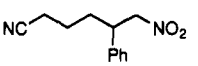
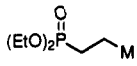
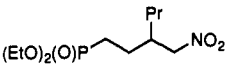
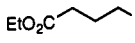
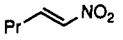
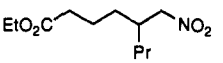
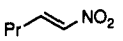
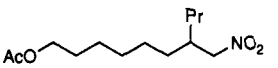
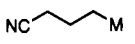
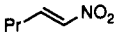
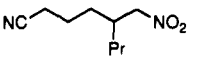
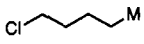
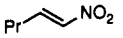
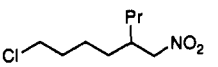
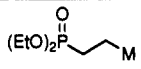
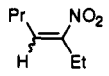
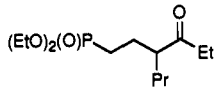
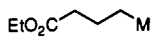
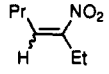
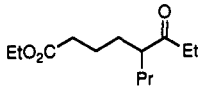
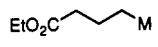
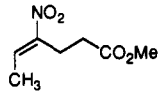
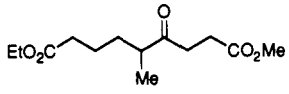
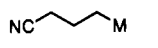
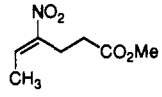
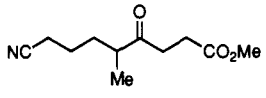
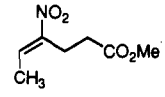
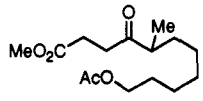
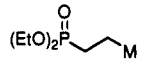
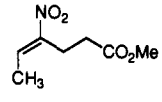
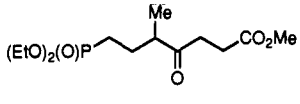
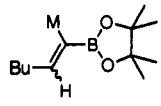
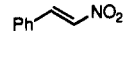
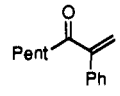
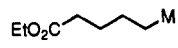
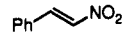
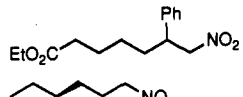
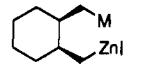
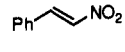
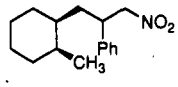
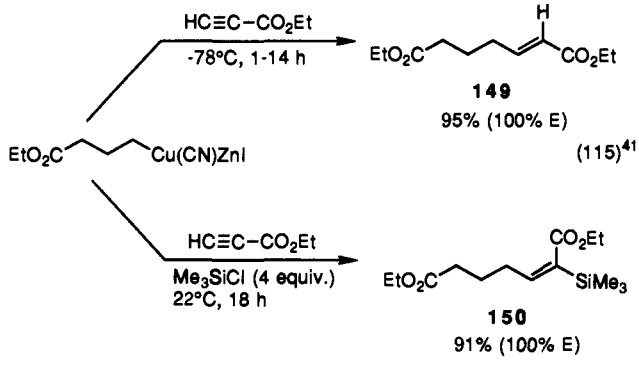
FG-RM[a]	nitro olefin	product	yield (%)	ref(s)
			72	45
			68	45b
			83	60
			81	61
			91	61
$AcO(CH_2)_5M$			82	48
			90	42,52,56
			77	42,52
			84	42,52
			80	61
			94	42,52
$AcO(CH_2)_6M$			76	42,52
			94	42,52
			90	42,52
			81	42,52
			75	42,52
			92	42,52
$AcO(CH_2)_6M$			88	42,52
			72	42,52
			82[b]	42,52
			76[b]	42,52
$AcO(CH_2)_6M$			71[b]	42,52

Table 18 Preparation of Polyfunctional Nitroalkanes by the Addition of Polyfunctional Zinc–Copper Reagents to Nitro Olefins

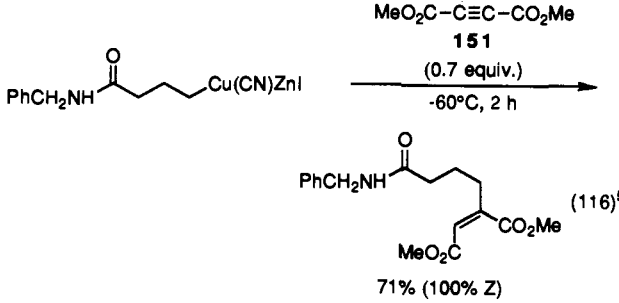
FG-RM[a]	nitro olefin	product	yield (%)	ref(s)
			70[b]	61
			85[b]	52
			87[b]	52
			74[b]	52
$AcO(CH_2)_8M$			75[b]	52
			78[b]	52
			69[b]	46b
			85	76
			74	49b

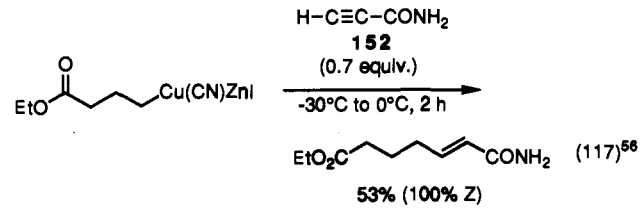
[a] M = Cu(CN)ZnI. [b] Yield after oxidative Nef reaction.

in the presence of an excess of Me_3SiCl, an (*E*)-α-silylated acrylic ester of type **150** is obtained (eq 115).[41]



Dimethyl acetylenedicarboxylate (**151**)[27a,56] and propiolamide (**152**)[56] react in satisfactory yield with FG-RCu(CN)ZnX. The presence of relatively acidic N–H protons does not interfer with the addition reaction (eqs 116 and 117). In the case of substituted propiolic





esters the addition proceeds only at −30 to −20 °C resulting in a partial isomerization of the intermediate alkenylcopper leading to a mixture of (*E*)- and (*Z*)-acrylic esters **153** (eq 118).[41] If the addition is performed

in HMPA using (2-carbethoxyethyl)zinc chloride (**154**), a cyclization reaction occurs leading to a highly functionalized cyclopentenone **155** (eq 119).[196]

The zinc–copper reagents FG-RCu(CN)ZnI (**100**) do not add to unactivated alkynes; however, the treatment

Table 19. Additions of Zinc or Zinc–Copper Reagents to Alkynes

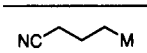
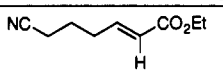
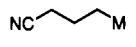
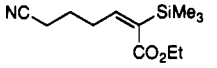
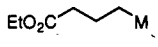
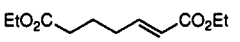
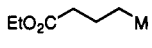
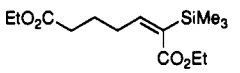
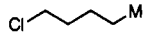
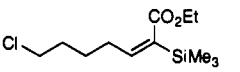
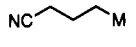
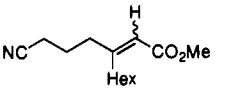
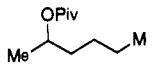
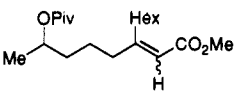
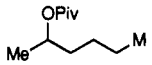
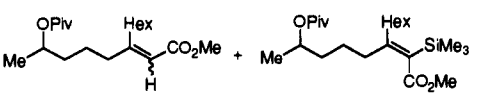
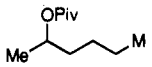
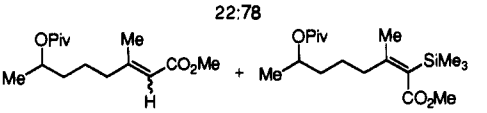
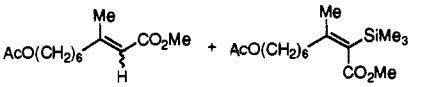
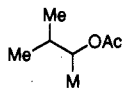
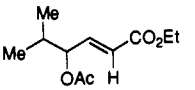
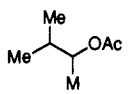
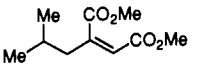
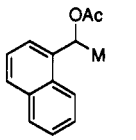
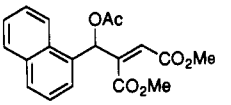
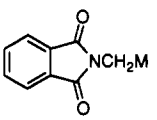
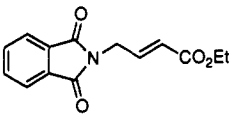
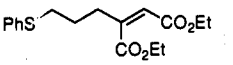
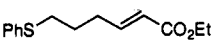
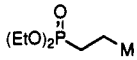
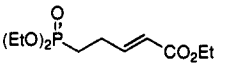
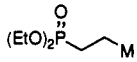
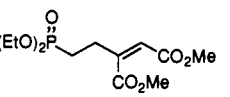
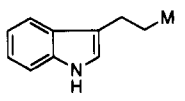
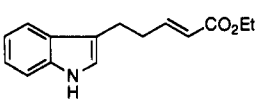
FG-RM	alkyne	product	*E*/*Z* ratio	yield (%)	ref(s)
	$HC{\equiv}CCO_2Et$		97:3	83	41
	$HC{\equiv}CCO_2Et$		>99:1	84[a]	41
	$HC{\equiv}CCO_2Et$		>99:1	99	41,76
	$HC{\equiv}CCO_2Et$		>99:1	91[a]	41
	$HC{\equiv}CCO_2Et$		>99:1	85[a]	41
	$HexC{\equiv}CCO_2Me$		mixture	82	41,48
	$HexC{\equiv}CCO_2Me$		mixture	77	41
	$HexC{\equiv}CCO_2Me$	 22:78	mixture	73[a]	41
	$MeC{\equiv}CCO_2Me$	 12:88	mixture	78[a]	41
$AcO(CH_2)_6M$	$MeC{\equiv}CCO_2Me$	 17:83	mixture	76[a]	41
	$HC{\equiv}CCO_2Et$		>96:4	91	45
	$MeO_2CC{\equiv}CCO_2Me$		>97:3	93	45
	$MeO_2CC{\equiv}CCO_2Me$		>98:2	77	45b
	$HC{\equiv}CCO_2Et$		98:2	69	45b
$PhS(CH_2)_3M$	$EtO_2CC{\equiv}CCO_2Et$		100:0	87	60
$PhS(CH_2)_3M$	$HC{\equiv}CCO_2Et$		100:0	95	60
	$HC{\equiv}CCO_2Et$		100:0	85	61
	$MeO_2CC{\equiv}CCO_2Me$		100:0	91	61
	$HC{\equiv}CCO_2Et$		>95.5:0.5	92	56

Table 19 (Continued)

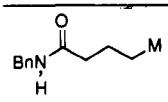
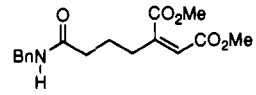
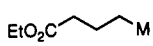
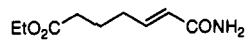
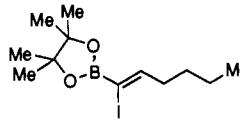
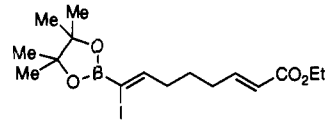
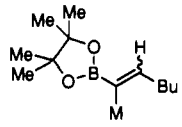
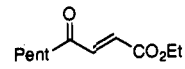
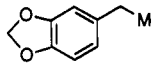
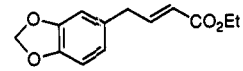
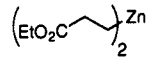
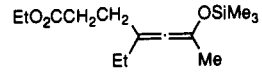
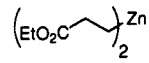
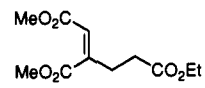
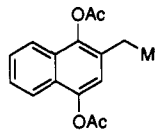
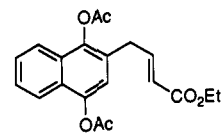
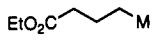
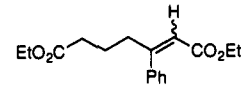
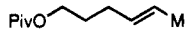
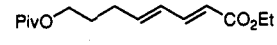
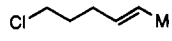
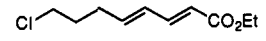
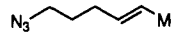
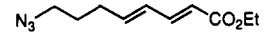
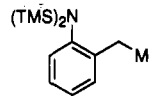
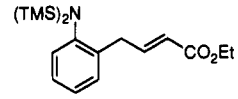
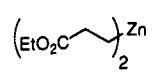
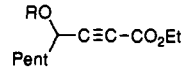
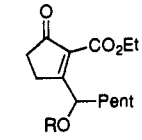
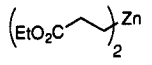
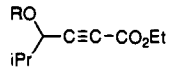
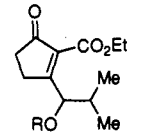
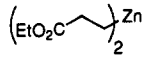
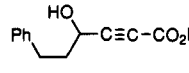
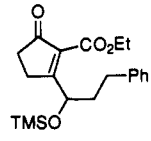
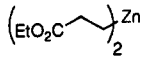
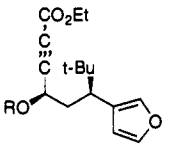
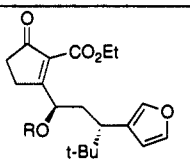
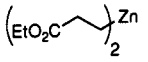
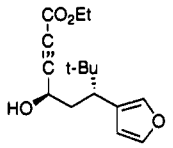
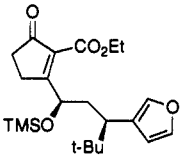
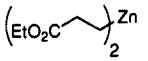
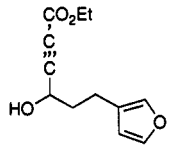
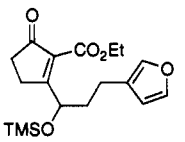
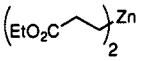
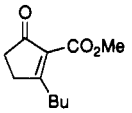
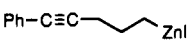
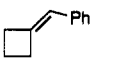
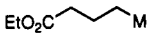
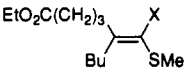
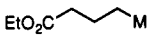
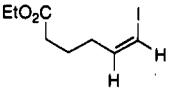
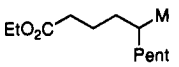
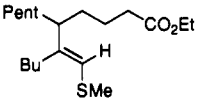
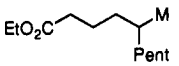
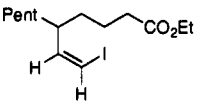
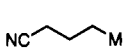
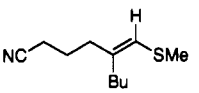
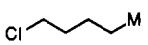
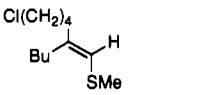
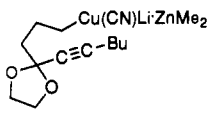
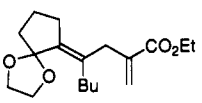
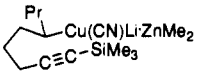
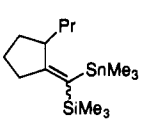
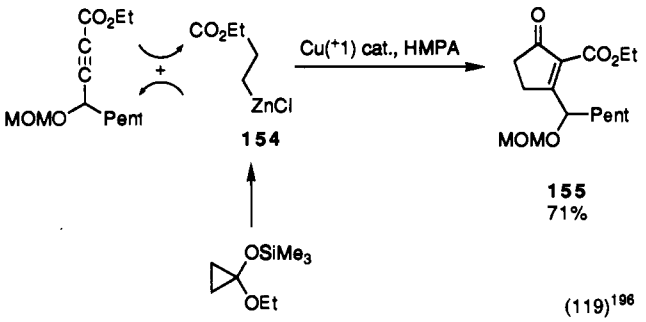
FG-RM	alkyne	product	*E*/*Z* ratio	yield (%)	ref(s)
	$MeO_2CC{\equiv}CCO_2Me$		100:0	71	56
	$HC{\equiv}CCONH_2$		100:0	53	56
	$HC{\equiv}CCO_2Et$		100:0	72	46b
	$HC{\equiv}CCO_2Et$		100:0	91	46b
	$HC{\equiv}CCO_2Et$		100:0	84	76
	$EtC{\equiv}CCOMe$			73	27a
	$MeO_2CC{\equiv}CCO_2Me$		92:8	63	27a,196
	$HC{\equiv}CCO_2Et$		95:5	79	37
	$PhC{\equiv}CCO_2Et$			70	28b
	$HC{\equiv}CCO_2Et$		>98:2	68	125a
	$HC{\equiv}CCO_2Et$		>98:2	70	125a
	$HC{\equiv}CCO_2Et$		>98:2	81	125a
	$HC{\equiv}CCO_2Et$		97:3	85	55
					
		R = MOM		71	196
		R = Ac		50	196
				70	196
		R = MOM		72	196
		R = Ac		49	196
		R = TMS, H		70	196
				65	196

Table 19 (Continued)

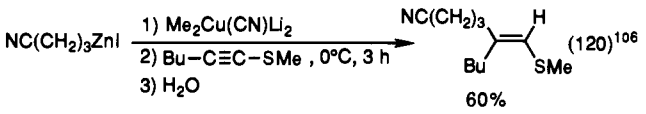
FG-RM	alkyne	product	*E*/*Z* ratio	yield (%)	ref(s)
					
		R = MOM		65	196
		R = TMS, H		82	196
				83	196
				65	196
	BuC≡CCO$_2$Me			65	196
				55[b]	198
	BuC≡CSMe				
		X = H	95:5	92	106
		X = allyl	95:5	70[c]	106
		X = I	95:5	75[d]	106
	HC≡CH		<1:99	26[d]	106
	BuC≡CSMe		<1:99	75	106
	HC≡CH		1:99	66[d]	106
	BuC≡CSMe		99:1	60	106
	BuC≡CSMe		99:1	66	106
			99:1	60[e]	106
			74:26	63[f]	106

[a] Reaction performed in the presence of excess TMSCl. [b] Addition of Cp_2TiCl_2. [c] The reaction mixture was trapped with allyl bromide. [d] The reaction mixture was trapped with iodine. [e] The reaction mixture was trapped with ethyl α-(bromomethyl)acrylate. [f] The reaction mixture was trapped with Me_3SnCl.



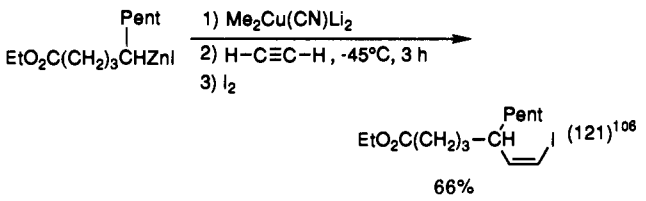
(119)[196]

of an alkylzinc iodide with $Me_2Cu(CN)Li_2$ provides a copper reagent, tentatively represented as FG-$RCu(CN)Li\cdot Me_2Zn\cdot LiI$, which adds smoothly to alkynyl thioethers (25 °C, 2–6 h) leading stereospecifically, after the trapping of the intermediate alkenylcopper with an electrophile, to tri- or tetrasubstituted olefins (eq 120 and Table 19).[106] The addition of these copper



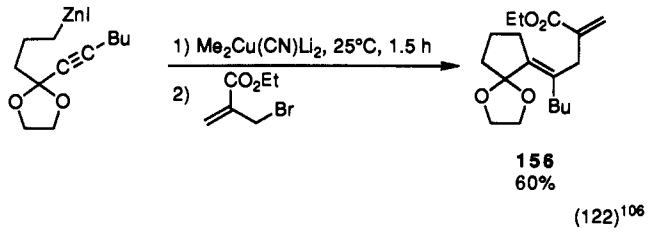
(120)[106]

derivatives to acetylene itself proceeds well if secondary alkylcopper reagents are used; with primary organozinc–copper reagents only low yields are obtained (eq 121).[106]

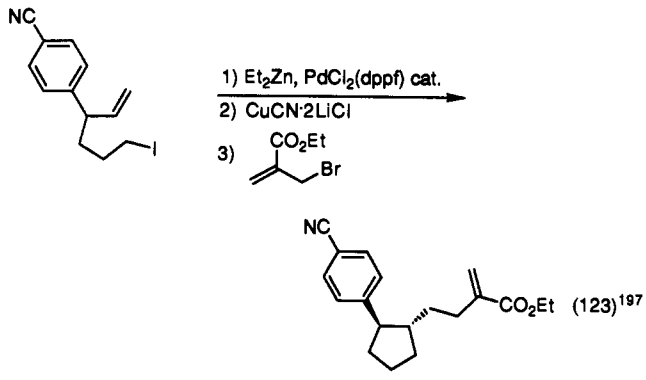


(121)[106]

The intramolecular version of these carbometalation reactions produces highly functionalized *exo*-alkylidenecyclopentanone derivatives of type **156** in satisfactory overall yields (eq 122).[106] The addition of



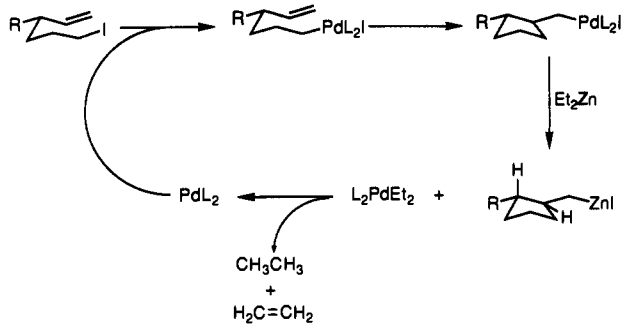
(122)[106]



(123)[197]

functionalized organozincs to alkenes is difficult to realize; however, in the presence of catalytic amounts of $PdCl_2$(dppf), an intramolecular addition occurs providing a new stereoselective route to polyfunctional

Scheme 8

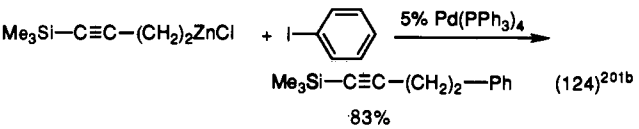


cyclopentanes (eq 123 and Table 20).[197] The tentative mechanism for the Pd-catalyzed ring closure is described in Scheme 8. Some radical cyclizations of organozinc derivatives have been described.[41,198]

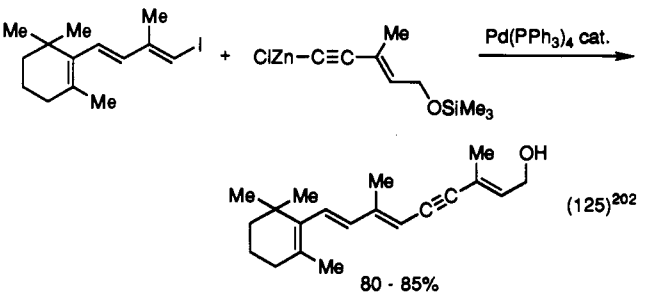
IV. Reactions of Functionalized Organozincs Catalyzed by Palladium(0) Complexes

A. Cross-Coupling Reactions with Alkenyl and Aryl Halides

Organozinc halides readily undergo transmetalation reactions with palladium(II) salts[20] (or nickel(II) salts).[199] The resulting organometallics display a rich and unique chemistry. Cross-coupling reactions with alkenyl and aromatic halides as well as acylation reactions (section IV.B) have been especially well studied.[200] In 1977, Negishi showed that organozinc halides react with alkenyl iodides in the presence of catalytic amounts of $Pd(PPh_3)_4$[201-202] (eqs 124 and 125). The reaction has

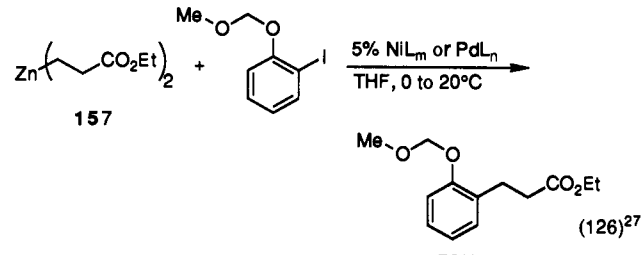


(124)[201b]



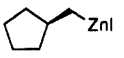
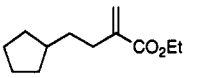
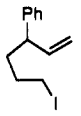
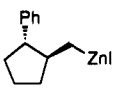
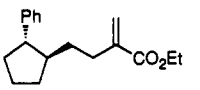
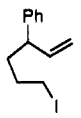
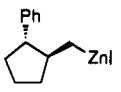
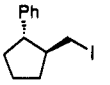
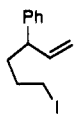
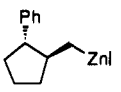
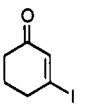
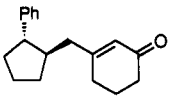
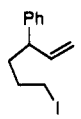
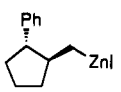
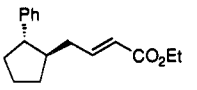
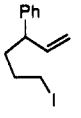
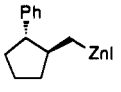
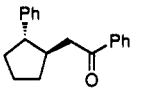
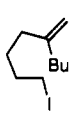
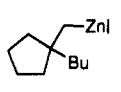
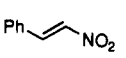
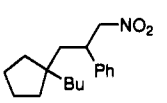
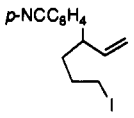
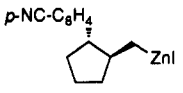
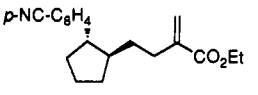
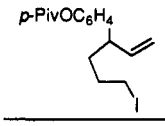
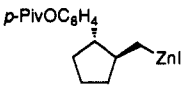
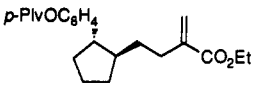
(125)[202]

been extended to highly functionalized organozinc compounds. For example, zinc homoenolates such as **157** undergo selective cross-coupling reactions with a wide range of aromatic or vinylic halides in the presence of 5% of a nickel or palladium catalyst (Table 21 and eq 126).[27] The reaction can be further extended to a

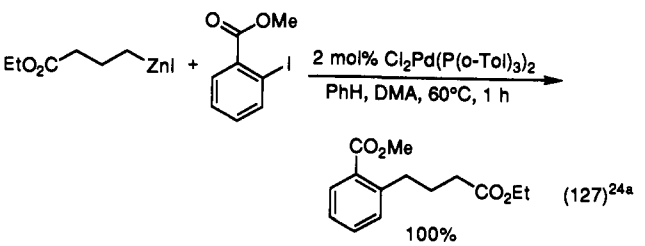


(126)[27]

Table 20. Intramolecular Carbozincation of Alkenes Catalyzed by $PdCl_2(dppf)$[197]

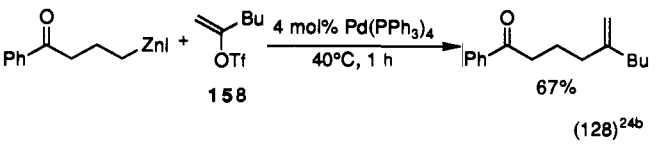
iodide	intermediate zinc derivative	electrophile	product	yield (%)
				80
				73
		I_2		90
				80
		$HC{\equiv}CCO_2Et$		64
		PhCOCl		76
				78
				83
				62

wide range of ester or ketone substituted organozinc compounds (Table 21 and eq 127). Interestingly,



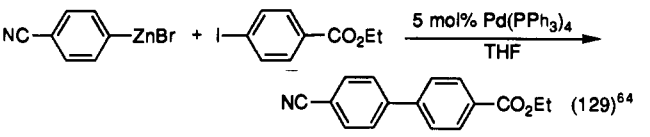
(127)[24a]

alkenyl triflates such as **158** can also be used under the same reaction conditions (eq 128).[24] The use of

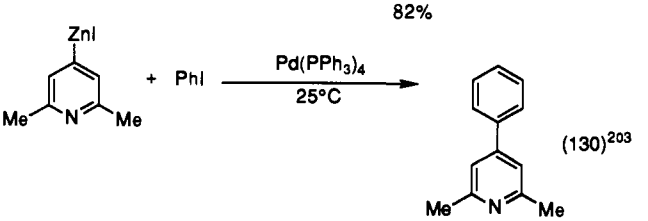


(128)[24b]

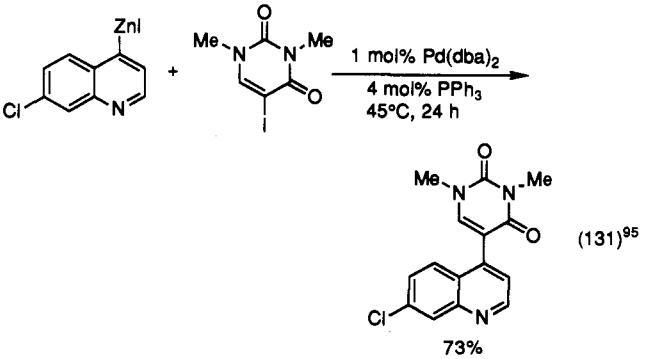
functionalized aromatic zinc halides allows easy access to polyfunctional aromatic and heteroaromatic compounds (eqs 129–131).[64,203,95] The remarkable aspect of this cross-coupling reaction is its high functional group tolerance.[204] Hence, a wide range of amino acids



(129)[64]



(130)[203]



(131)[95]

Table 21. Palladium-Catalyzed Cross-Coupling Reaction between Alkenyl and Aryl Halides or Triflates and Functionalized Organozincs

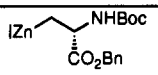
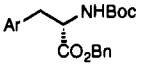
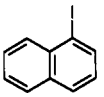
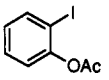
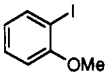
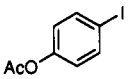
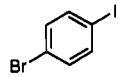
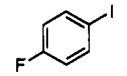
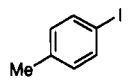
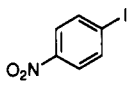
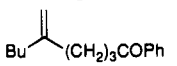
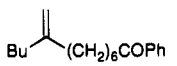
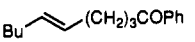
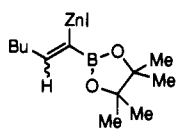
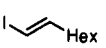
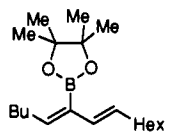
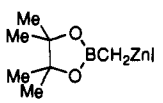
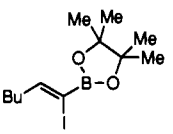
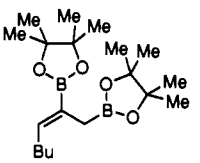
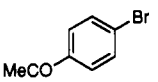
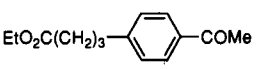
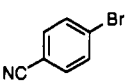
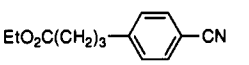
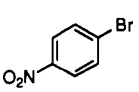
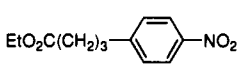
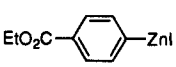
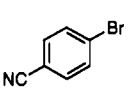
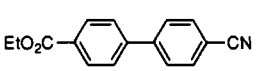
FG-RZnX	organic halide	product	yield (%)	ref(s)
				
	PhI	Ar = Ph	55	80,81
		Ar = 1-naphthyl	64	80,81
		Ar = 2-AcOC$_6$H$_4$	13	80,81
		Ar = 2-MeOC$_6$H$_4$	50	80,81
		Ar = AcOC$_6$H$_4$	53	80,81
		Ar = 4-BrC$_6$H$_4$	67	80,81
		Ar = 4-FC$_6$H$_4$	36	80,81
		Ar = 4-MeC$_6$H$_4$	50	80,81
		Ar = 4-NO$_2$C$_6$H$_4$	61	80,81
PhCO(CH$_2$)$_3$ZnI	PhI	PhCO(CH$_2$)$_3$Ph	99	24b
PhCO(CH$_2$)$_3$ZnI			67	24b
PhCO(CH$_2$)$_6$ZnI			74	24b
PhCO(CH$_2$)$_3$ZnI			77	24b
			77	46b
			86	46a
EtO$_2$C(CH$_2$)$_3$ZnBr			86	64
EtO$_2$C(CH$_2$)$_3$ZnBr			93	64
EtO$_2$C(CH$_2$)$_3$ZnBr			90	64
			80	64

Table 21 (Continued)

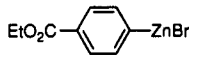
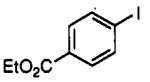
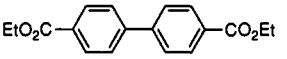
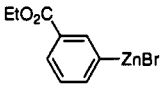
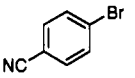
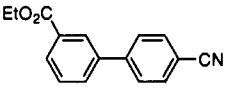
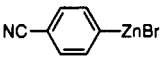
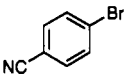
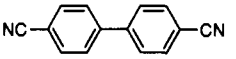
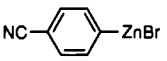
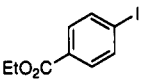
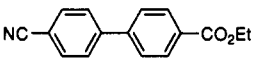
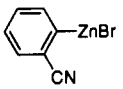
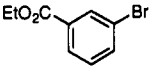
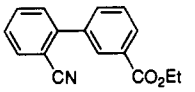
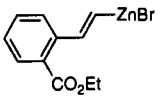
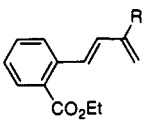
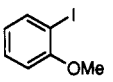
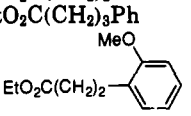
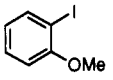
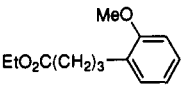
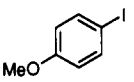
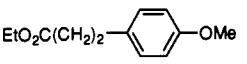
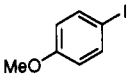
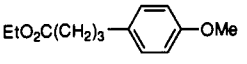
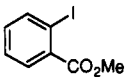
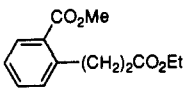
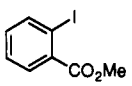
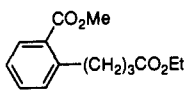
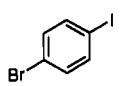
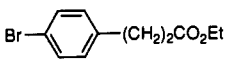
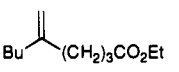
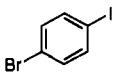
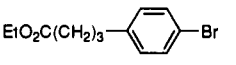
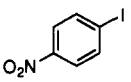
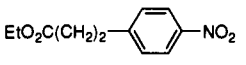
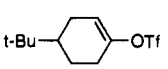
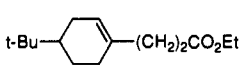
FG-RZnX	organic halide	product	yield (%)	ref(s)
			94	64
			82	64
			95	64
			82	64
			93	64
				
		R = H	95	64
		R = Me	93	64
$EtO_2C(CH_2)_2ZnI$	PhI	$EtO_2C(CH_2)_2Ph$	90	24a,27a
$EtO_2C(CH_2)_3ZnI$	PhI	$EtO_2C(CH_2)_3Ph$	90	24a
$EtO_2C(CH_2)_2ZnI$			90	24a
$EtO_2C(CH_2)_3ZnI$			95	24a
$EtO_2C(CH_2)_2ZnI$			96	24a
$EtO_2C(CH_2)_3ZnI$			75	24a
$EtO_2C(CH_2)_2ZnI$			95	24a
$EtO_2C(CH_2)_3ZnI$			100	24a
$EtO_2C(CH_2)_2ZnI$			67	24a
$EtO_2C(CH_2)_3ZnI$			75	24a
$EtO_2C(CH_2)_3ZnI$			78	24a
$EtO_2C(CH_2)_2ZnI$			80	24a
$EtO_2C(CH_2)_2ZnI$			74	24a
$EtO_2C(CH_2)_3ZnI$			87	24a

Table 21 (Continued)

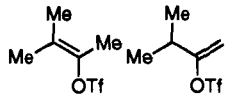
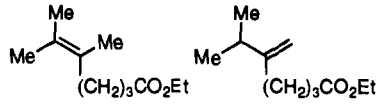
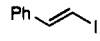
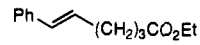
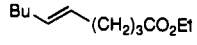
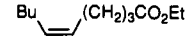
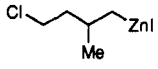
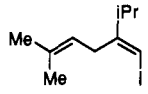
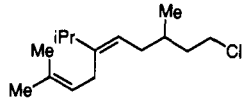
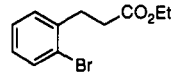
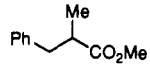
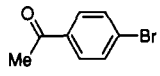
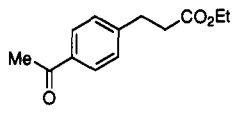
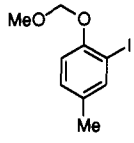
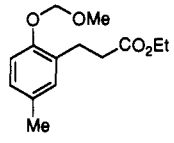
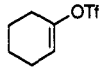
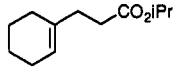
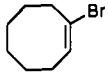
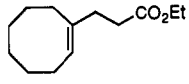
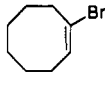
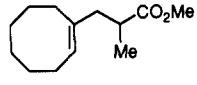
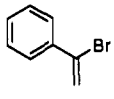
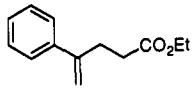
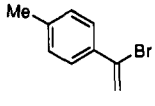
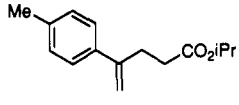
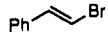
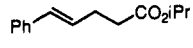
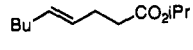
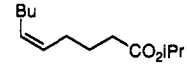
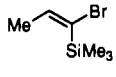
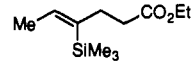
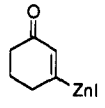
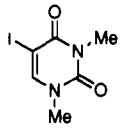
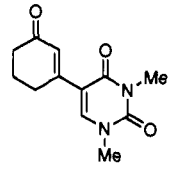
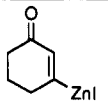
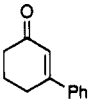
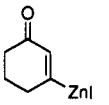
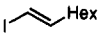
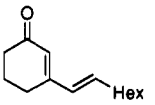
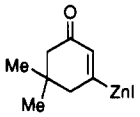
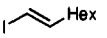
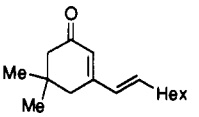
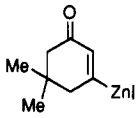
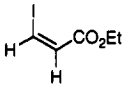
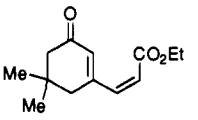
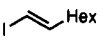
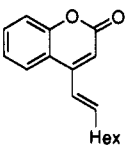
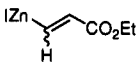
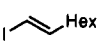
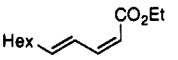
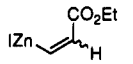
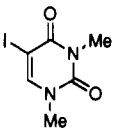
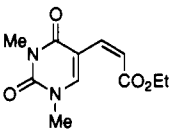
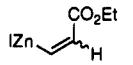
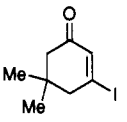
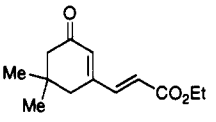
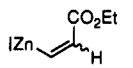
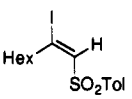
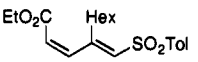
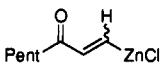
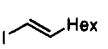
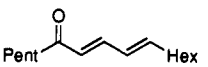
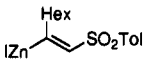
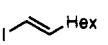
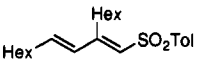
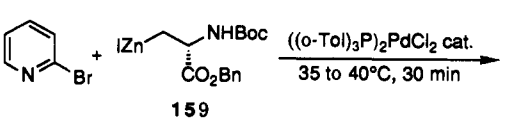
FG-RZnX	organic halide	product	yield (%)	ref(s)
$EtO_2C(CH_2)_3ZnI$	 9:1	 9:1	83	24a
$EtO_2C(CH_2)_3ZnI$			79	24a
$EtO_2C(CH_2)_3ZnI$			71	24a
$EtO_2C(CH_2)_3ZnI$			89	24a
			42	201c
$(EtO_2CCH_2CH_2)_2Zn$			83	27a
$(MeO_2CCH(Me)CH_2)_2Zn$	PhI		79	27a
$(EtO_2CCH_2CH_2)_2Zn$			49	27a
$(EtO_2CCH_2CH_2)_2Zn$			73	27a
$(i\text{-}PrO_2CCH_2CH_2)_2Zn$			55	27a
$(EtO_2CCH_2CH_2)_2Zn$			79	27a
$(MeO_2CCH(Me)CH_2)_2Zn$			85	27a
$(EtO_2CCH_2CH_2)_2Zn$			85	27a
$(iPrO_2CCH_2CH_2)_2Zn$			76	27a
$(iPrO_2CCH_2CH_2)_2Zn$			76	27a
$(iPrO_2CCH_2CH_2)_2Zn$			90	27a
$(iPrO_2CCH_2CH_2)_2Zn$			76	27a
$(EtO_2CCH_2CH_2)_2Zn$			87	27a
			97	53

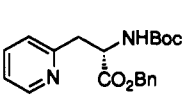
Table 21 (Continued)

FG-RZnX	organic halide	product	yield (%)	ref(s)
	PhI		71	53b
			73	53b
			82	53b
			93	53b
		E/Z (5:95)		
			71	53b
			81	53b
E : Z (11 : 89)		100% 2*Z*,4*E*		
			87	53b
		100% *Z*		
			88	53b
		E/Z (88:12)		
			87	53b
		E/Z (4:96)		
			55	53b
		100% E,E		
			40	53b

can be prepared by the palladium(0)-catalyzed cross-coupling reaction of the β-aminozinc reagent **159** with aromatic or heteroaromatics (eq 132).[80,81] The choice of the catalyst is important for many of these reactions and $[(o\text{-Tol})_3P]_2PdCl_2$ has been found to be the most effective in many cases.[24,80,81] A variety of fluorinated olefins and dienes have been obtained by this method.[87,89,124]



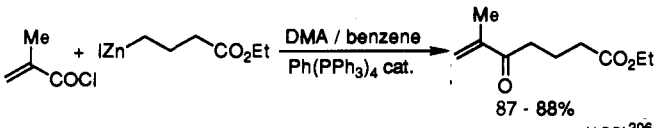
159



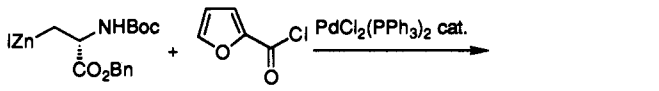
(132)[80]

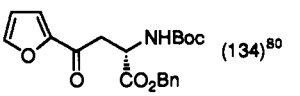
B. Acylation Reactions

Although several types of organometallics can be acylated with acid chlorides, organomanganese(II) halides are the reagents of choice for performing such reactions.[205] However, the palladium-catalyzed acylation reaction[20] using organozincs has the advantage that numerous functionalities can be present in the organometallic species. Several types of ester or ketone containing alkylzinc halides can be acylated by a wide range of acid chlorides (eqs 133[206] and 134,[80,81] Table 22). Interestingly, the direct acylation of organozinc halides with carbon monoxide and an allylic benzoate in the presence of 5 mol % of $Pd(PPh_3)_4$ provides δ-keto esters, **160**, in high yields (eq 135).[207]



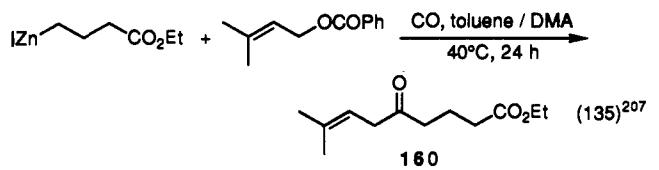
(133)[206]





(134)[80]

90%

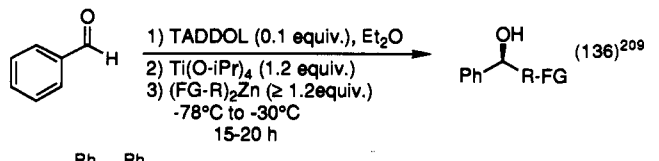


(135)[207]

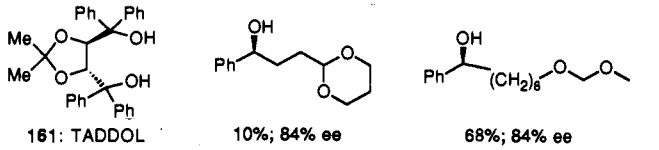
160
100%

V. Asymmetric Addition of Functionalized Organozincs to Aldehydes Catalyzed by Chiral Titanium(IV) Complexes

The transmetalation of organozinc reagents to organocopper reagents or intermediate organopalladium(II) complexes considerably increases the synthetic potential of organozinc halides. The synthetic utility of functionalized dialkylzincs can be extended through the titanium-catalyzed addition of functionalized dialkylzincs to aldehydes. The direct addition of zinc organometallics to aldehydes is very sluggish and requires the use of a catalyst.[2,5-8,40] In the presence of a chiral titanium catalyst, dialkylzincs add with high enantioselectivity to aldehydes.[30,92,93,48,208,209] For example, some functionalized dialkylzincs, obtained from the corresponding dialkylmagnesium derivatives,[209] add to benzaldehyde with excellent enantioselectivity in the presence of catalytic amounts of TADDOL (**161**, α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) (eq 136).[209]



(136)[209]

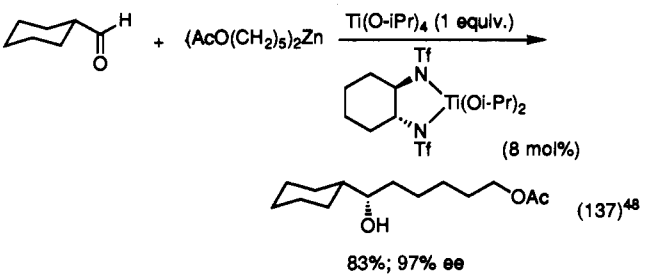


161: TADDOL

10%; 84% ee

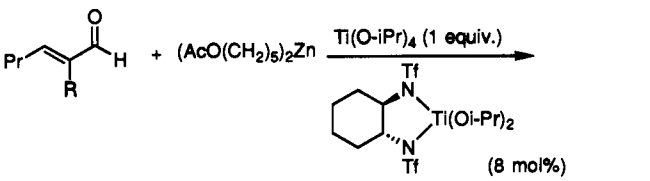
68%; 84% ee

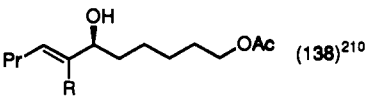
The iodine–zinc exchange reaction allows the preparation of a wide range of functionalized dialkylzincs.[48] A number of these functionalized organometallics add with excellent enantioselectivity to aromatic and aliphatic aldehydes (eq 137 and Table 23) in the presence of catalytic amounts of *trans*-1(*R*),2(*R*)-bis(trifluoromethanesulfonamido)cyclohexane[208] (8 mol %) and $Ti(Oi\text{-}Pr)_4$ (2 equiv).[48] The reaction can be extended to α,β-unsaturated aldehydes, and it was found that the presence of a substituent in α-position to the aldehyde function leads to a substantially higher enantiomeric excess (eq 138).[210]



(137)[48]

83%; 97% ee

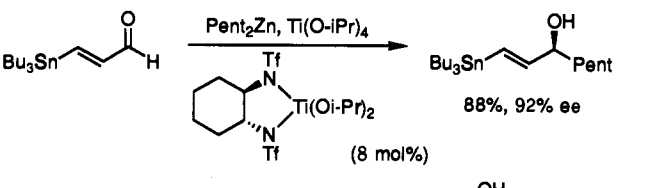




(138)[210]

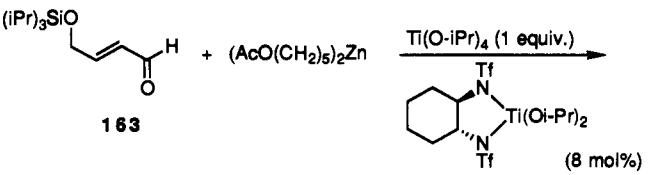
R = H : 75%; 83% ee
R = Br : 95%, 94% ee

This reaction has been applied to the preparation of the prostaglandin side chain **162** in excellent yield and high enantioselectivity (eq 139).[211,212] This reaction also allows an enantioselective synthesis of protected 1,4-diols of type **164** (eq 140)[210] using the γ-oxygenated α,β-unsaturated aldehyde **163**.[213] Finally, the addition

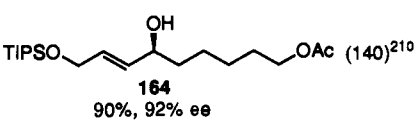


(139)[211]

162
98%



163



(140)[210]

164
90%, 92% ee

Table 22. Palladium-Catalyzed Acylation Reactions between Acid Chlorides or Related Reagents and Functionalized Organozincs

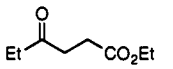
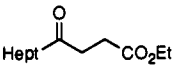
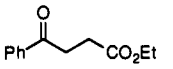
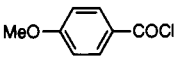
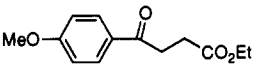
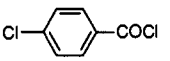
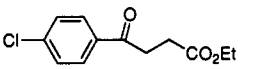
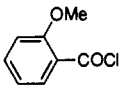
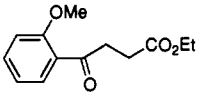
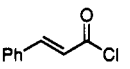
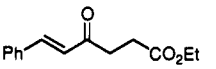
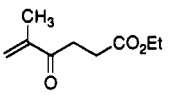
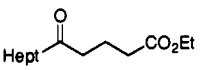
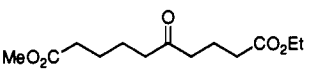
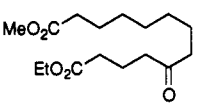
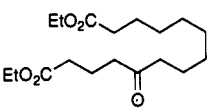
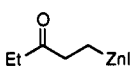
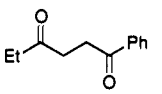
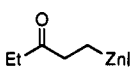
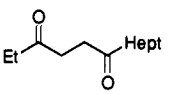
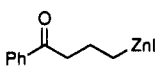
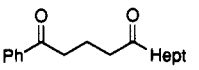
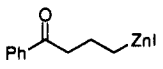
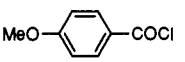
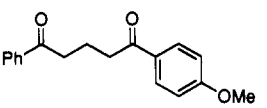
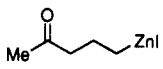
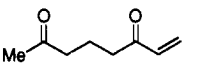
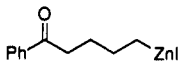
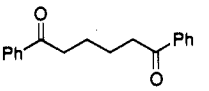
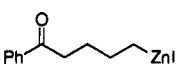
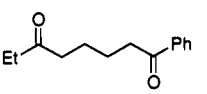
FG-RZnI	acid chloride	product	yield (%)	ref(s)
$EtO_2C(CH_2)_2ZnI$	EtCOCl		84	22
$EtO_2C(CH_2)_2ZnI$	HeptCOCl		100	22
$EtO_2C(CH_2)_2ZnI$	PhCOCl		100	22,27
$EtO_2C(CH_2)_2ZnI$			94	22
$EtO_2C(CH_2)_2ZnI$			100	22
$EtO_2C(CH_2)_2ZnI$			81	22
$EtO_2C(CH_2)_2ZnI$			92	22
$EtO_2C(CH_2)_2ZnI$			90	22
$EtO_2C(CH_2)_3ZnI$	HeptCOCl		94	22
$EtO_2C(CH_2)_3ZnI$	$MeO_2C(CH_2)_4COCl$		90	22
$EtO_2C(CH_2)_3ZnI$	$MeO_2C(CH_2)_7COCl$		89	22
$EtO_2C(CH_2)_3ZnI$	$EtO_2C(CH_2)_8COCl$		72	22
	PhCOCl		53	24b
	HeptCOCl		62	24b
	HeptCOCl		80	24b
			90	24b
			85	24b
	PhCOCl		76	24b
	EtCOCl		77	24b

Table 22 (Continued)

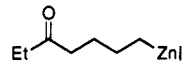
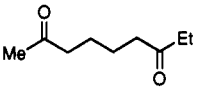
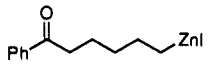
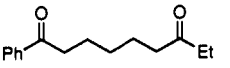
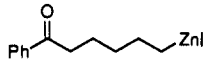
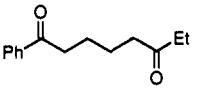
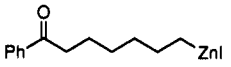
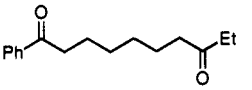
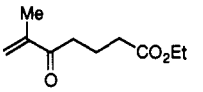
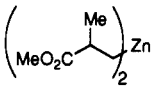
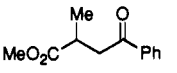
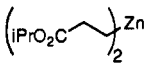
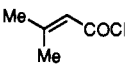
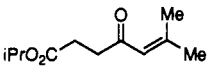
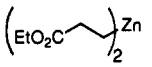
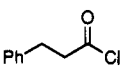
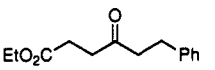
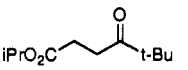
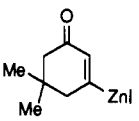
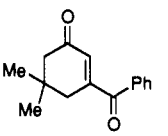
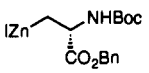
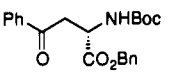
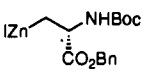
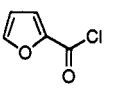
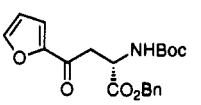
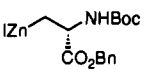
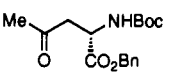
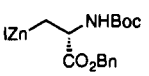
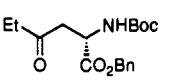
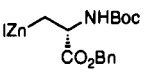
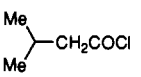
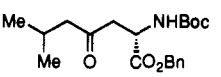
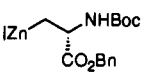
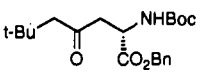
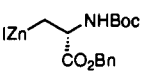
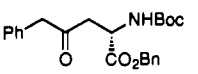
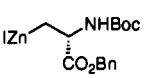
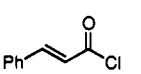
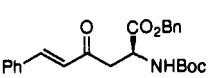
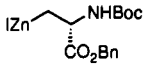
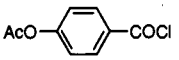
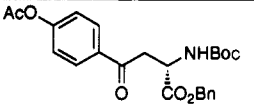
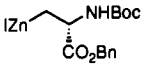
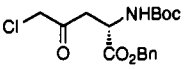
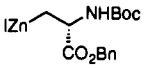
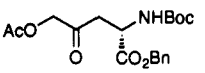
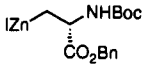
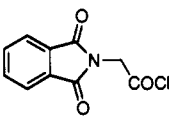
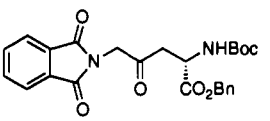
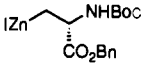
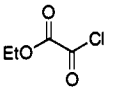
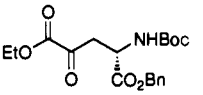
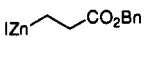
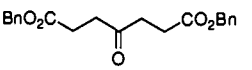
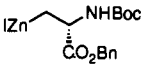
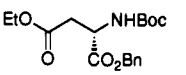
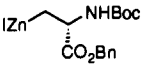
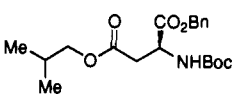
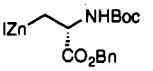
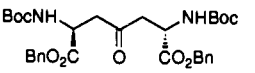
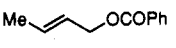
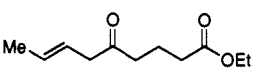
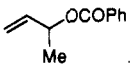
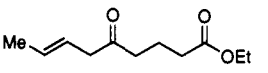
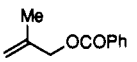
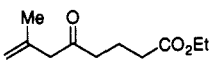
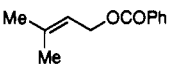
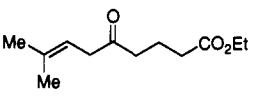
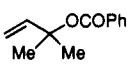
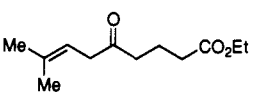
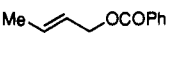
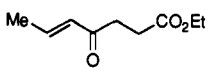
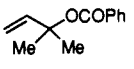
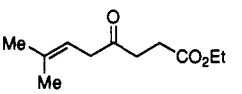
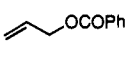
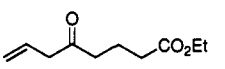
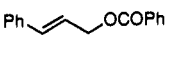
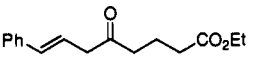
FG-RZnI	acid chloride	product	yield (%)	ref(s)
	MeCOCl		74	24b
	EtCOCl		85	24b
	EtCOCl		63	24b
	EtCOCl		91	24b
$EtO_2C(CH_2)_3ZnI$			88	206
	PhCOCl		93	27a
			81	27a
			89	27a
$(i\text{-}PrO_2C(CH_2)_2)_2Zn$	t-BuCOCl		50	27a
	PhCOCl		72	53b
	PhCOCl		70	80,81
			90	80,81
	MeCOCl		80	80,81
	EtCOCl		83	80,81
			76	80,81
	$t\text{-}BuCH_2COCl$		84	80,81
	$PhCH_2COCl$		41	80,81
			72	80,81
			43	80,81

Table 22 (Continued)

FG-RZnI	acid chloride	product	yield (%)	ref(s)
			63	80,81
	$ClCH_2COCl$		39	80,81
	$AcOCH_2COCl$		64	80,81
			53	80,81
			61	80e
	ClCOOPh		41	80e
	$ClCO_2Et$		10	80e
	$i\text{-}PrCH_2OCOCl$		10	80e
	PhOCOCl		45	80e
$EtO_2C(CH_2)_3ZnI$			87[a]	207
$EtO_2C(CH_2)_3ZnI$			85[a]	207
$EtO_2C(CH_2)_3ZnI$			85[a]	207
$EtO_2C(CH_2)_3ZnI$			100[a]	207
$EtO_2C(CH_2)_3ZnI$			100[a]	207
$EtO_2C(CH_2)_2ZnI$			35[a]	207
$EtO_2C(CH_2)_2ZnI$			44[a]	207
$EtO_2C(CH_2)_3ZnI$			28[a]	207
$EtO_2C(CH_2)_3ZnI$			78[a]	207

[a] Reaction performed under a CO atmosphere.

Table 23. Enantioselective Addition of Functionalized Dialkylzinc Reagents to Aldehydes in the Presence of Catalytic Amounts of 1(*R*),2(*R*)-Bis(trifluoromethanesulfonamido)cyclohexane

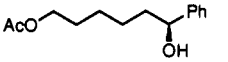
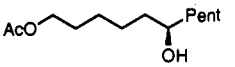
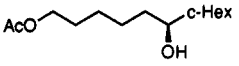
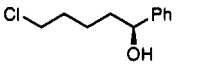
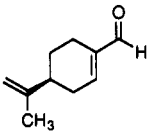
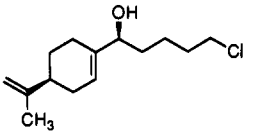
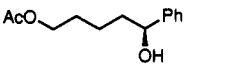
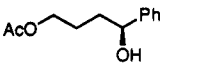
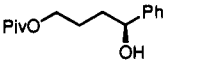
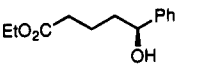
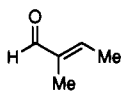
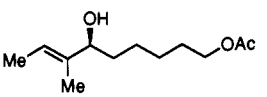
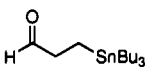
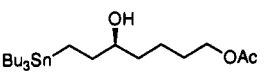
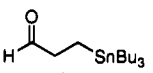
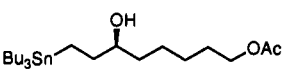
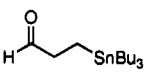
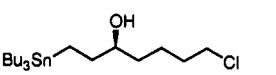
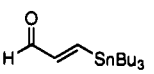
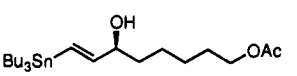
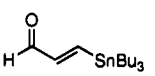
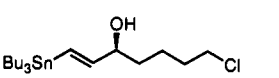
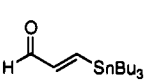
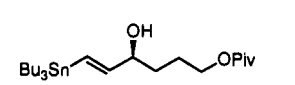
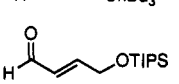
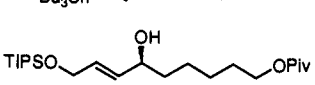
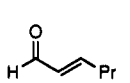
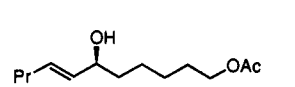
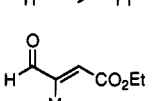
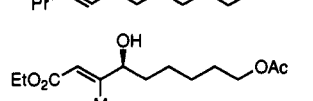
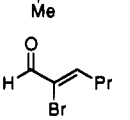
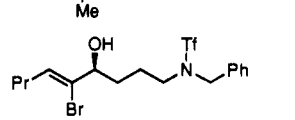
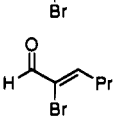
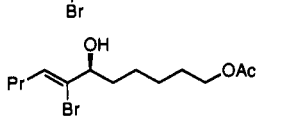
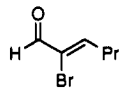
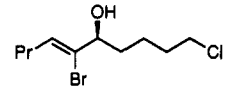
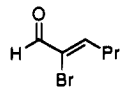
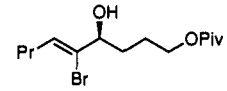
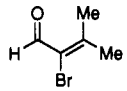
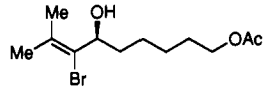
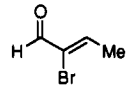
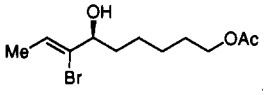
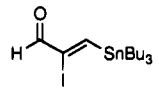
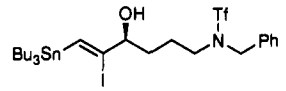
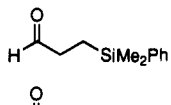
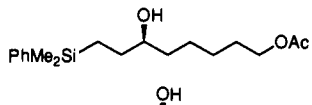
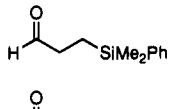
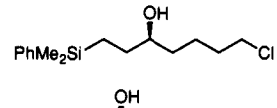
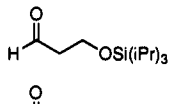
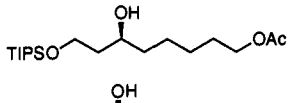
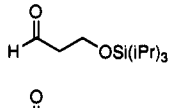
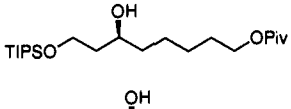
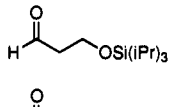
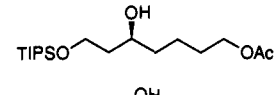
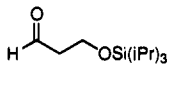
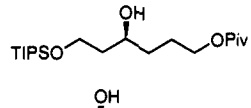
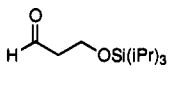
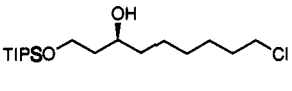
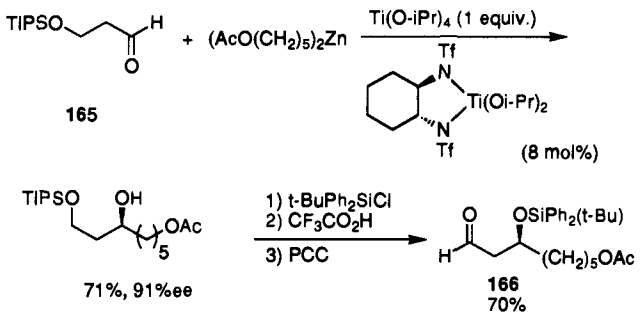
$(FG\text{-}R)_2Zn$ (FG-R)	aldehyde	product	enantiomeric excess (% ee)	yield (%)	ref
$AcO(CH_2)_5$	PhCHO		93	79	48
$AcO(CH_2)_5$	PentCHO		97	62	48
$AcO(CH_2)_5$	c-HexCHO		97	83	48
$Cl(CH_2)_4$	PhCHO		93	95	48
$Cl(CH_2)_4$			97	95	48
$AcO(CH_2)_4$	PhCHO		92	72	48
$AcO(CH_2)_3$	PhCHO		86	75	48
$PivO(CH_2)_3$	PhCHO		92	90	48
$EtO_2C(CH_2)_3$	PhCHO		60	75	48
$AcO(CH_2)_5$			98	70	48
$AcO(CH_2)_4$			93	85	211
$AcO(CH_2)_5$			92	81	211
$Cl(CH_2)_4$			95	79	211
$AcO(CH_2)_5$			91	75	211
$Cl(CH_2)_4$			95	69	211
$PivO(CH_2)_3$			90	67	211
$PivO(CH_2)_5$			92	90	210
$AcO(CH_2)_5$			75	83	210
$AcO(CH_2)_5$			80	78	210
$PhCH_2(Tf)N(CH_2)_3$			86	56	210
$AcO(CH_2)_5$			94	95	210

Table 23 (Continued)

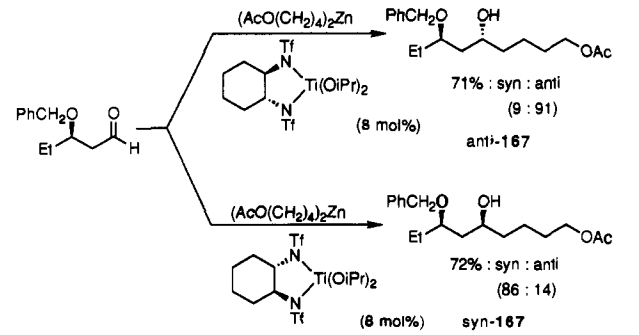
(FG-R)$_2$Zn (FG-R)	aldehyde	product	enantiomeric excess (% ee)	yield (%)	ref
$Cl(CH_2)_4$			95	68	210
$PivO(CH_2)_3$			95	68	210
$AcO(CH_2)_5$			68	68	210
$AcO(CH_2)_5$			80	77	210
$PhCH_2(Tf)N(CH_2)_3$			82	62	210
$AcO(CH_2)_5$			96	70	210
$Cl(CH_2)_4$			96	70	214
$AcO(CH_2)_5$			91	71	214
$PivO(CH_2)_5$			91	72	214
$AcO(CH_2)_4$			99	62	214
$PivO(CH_2)_3$			40	55	214
$Cl(CH_2)_6$			66	59	214

of functionalizied dialkylzincs to β-(silyloxy)propionaldehyde **165** provides 1,3-diol derivatives which can be converted to aldol products of type **166** (eq 141).[214] The



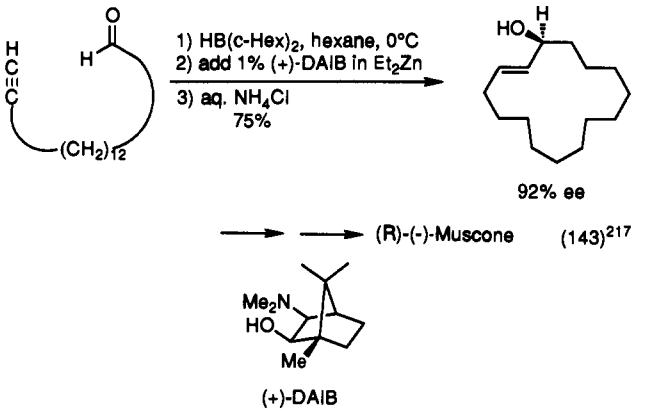
(141)[214]

enantioselective addition of a diorganozinc to these carbonyl compounds selectively provides *syn*- or *anti*-1,3-diols **167**, depending on the configuration of the catalyst used (eq 142).[214,215] Functionalized mixed alkenyl(alkyl)zincs can be readily prepared from the corresponding boranes.[131] Their addition to aldehydes



(142)[214]

in the presence of a chiral catalyst proceeds with high enantioselectivity.[131b] It should be noted that the alkenyl group is transferred preferentially to the alkyl group. This method has been elegantly applied to a synthesis of (*R*)-(−)-muscone (eq 143).[217] Clearly, this approach will allow the preparation of a wide range of chiral polyfunctionalized building blocks with a high enantioselectivity.



VI. Conclusions and Perspectives

Organozinc compounds have been considered for a long time as unreactive organometallics with limited applications in organic synthesis. It has become clear within recent years that this opinion has to be revised. In fact, the low reactivity of the carbon–zinc bond can be exploited for the preparation of a wide range of polyfunctionalized zinc reagents. The good transmetalation ability of organozinc derivatives with soluble copper salts such as CuCN·2LiX[29] or palladium(II) complexes[20] allows the *in situ* preparation of highly reactive organometallic species. The reaction pathways which are now available for these transition-metal intermediates allow reactions with numerous carbon electrophiles in excellent yields. The addition of functionalized dialkylzincs to aldehydes in the presence of chiral titanium catalysts provides a general enantioselective preparation to polyfunctional secondary alcohols and considerably extends the synthetic utility of diorganozincs. Their excellent functional group tolerance, their high chemoselectivity and excellent stereoselectivity in many reactions makes organozincs ideal organometallic intermediates for the construction of complex polyfunctional molecules.

VII. Acknowledgments

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