Pergamon

Tetrahedron 54 (1998) 8275–8319

TETRAHEDRON

Tetrahedron report number 459

Organozinc Mediated Reactions

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Dedicated to Prof. Dr. Dieter Seebach for his great scientific contributions and communicative enthusiasm for chemistry

Received 1 April 1998

Contents

1. Introduction

Organozinc reagents have been known for more than 150 years [1], however, their applications to organic synthesis was limited to very specific reactions like cyclopropanation [2] and the aldol reaction [3] due to the moderate reactivity of organozinc compounds. These reagents were soon replaced by the more reactive organomagnesium and organolithium reagents which found broad applications in organic synthesis due to their increased reactivity . However, it became clear that this high reactivity had some drawbacks, such as a low chemoselectivity and it only allows introduction of R groups bearing relatively few functionalities. The polar carbon-magnesium or carbon-lithium bonds preclude the presence of many organic functionalities in these organometallics. The first solutions to these problems were found between 1970 and 1980, by performing transmetalation reactions of organomagnesiums and organolithiums with copper [4] or titanium [5] salts leading to highly chemoselective reagents. Unfortunately, since these transition metal organometallics were prepared from the corresponding lithium or magnesium reagents, still no "highly" functionalized titanium or copper organometallics could be made. However, it was noticed that organozincs, although very unreactive with most organic electrophiles undergo smoothly transmetalations [6, 7] with a variety of transition metal salts or complexes leading to new transition metal compounds. The resulting organometallics react with a range of

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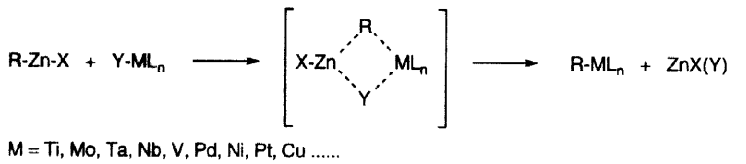
PII: S0040-4020(98)00318-4

organic electrophiles, due to the presence of *d*-orbitals at the metal which allows new reaction pathways not available to the main-group metal zinc (Scheme 1) [6, 7].



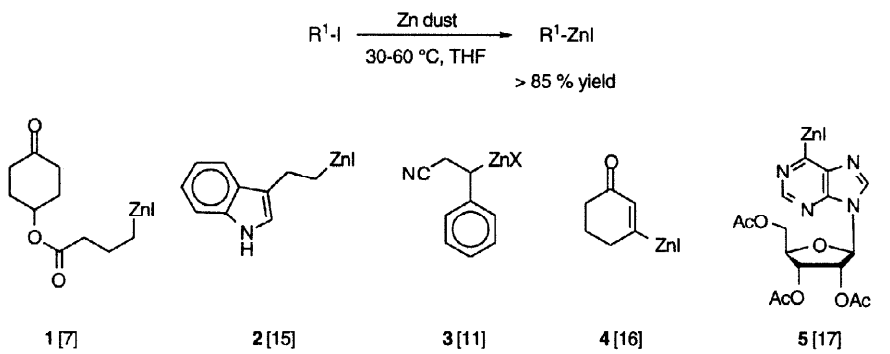
Scheme 1

After a short description of the preparation methods of organozinc halides (RZnX) and diorganozincs (R_2Zn), the utility of these reagents for forming new carbon-carbon bonds will be developed. Emphasis will be placed on reactions having a good generality and high synthetic potential. First, the uncatalyzed reactions of zinc organometallics will be discussed, followed by the transition metal (Cu, Co, Fe, Mn, Pd, Ni) catalyzed reactions. A section will be devoted to asymmetric reactions involving zinc organometallics, especially, the asymmetric addition of diorganozincs to aldehydes and the enantioselective cyclopropanation reaction will be presented in some detail.

2. Preparation of organozinc reagents

2.1. Preparation of organozinc halides

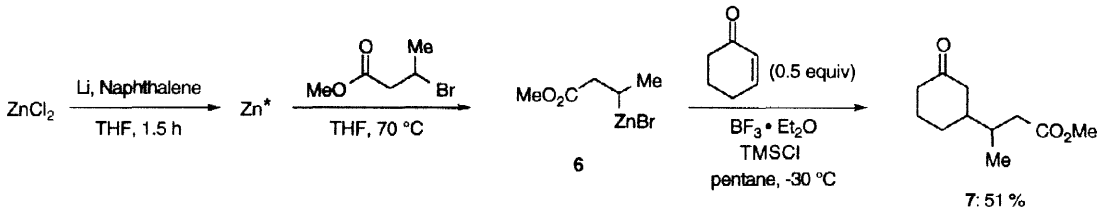
Polyfunctional organozinc halides are best prepared by the direct insertion of zinc into alkyl iodides. This method allows the preparation of organozinc iodides bearing almost all organic functionalities. With primary alkyl iodides, the insertion reaction is usually performed by adding a concentrated solution (3M) of the alkyl iodide in THF to a suspension of zinc dust (*ca.* 3 equiv) in THF at 40 °C. The zinc dust is treated with a few mol% of 1,2-dibromoethane and TMSCl prior to addition of the halide [7-10]. Secondary alkyl iodides react with zinc dust even at 25 °C [11, 12], whilst benzylic and allylic bromides undergo an optimal insertion reaction at 0 °C [13]. The insertion of zinc into Csp^2-I bonds is usually less straightforward and may require longer reaction times, higher temperature or the use of a polar solvent or cosolvent [14]. Thus, the polyfunctional zinc reagents **1-5** have been prepared in high yield using this procedure (Scheme 2).



Scheme 2

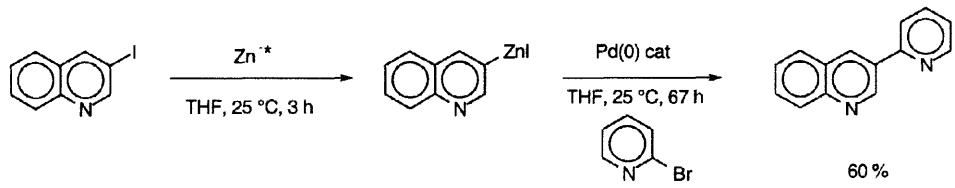
Alternatively, more activated zinc (Rieke zinc), prepared by the reduction of zinc halides, can be used for reactions with less reactive aryl iodides or bromides, also secondary and tertiary alkyl bromides [18-20]. Thus, the treatment of zinc chloride with finely cut lithium in the presence of naphthalene produces, within 1.5 h of stirring, highly reactive zinc (Rieke-zinc) which reacts, for example, with methyl 3-bromobutyrate in refluxing THF (2 h reaction time) providing the corresponding secondary organozinc compound **6**. This zinc reagent

undergoes a smooth addition to cyclohexenone in the presence of $BF_3 \cdot OEt_2$ leading to the desired Michael-adduct **7** in 51 % yield (Scheme 3) [20].



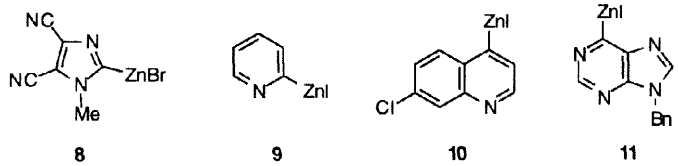
Scheme 3

Various π-deficient heteroaryl iodides undergo the oxidative addition of Rieke-zinc leading to heteroarylzinc iodides in THF (25 °C, a few hours). They can be further coupled with aromatic or heteroaromatic halides in the presence of a palladium(0) catalyst in satisfactory yield (Scheme 4) [21].



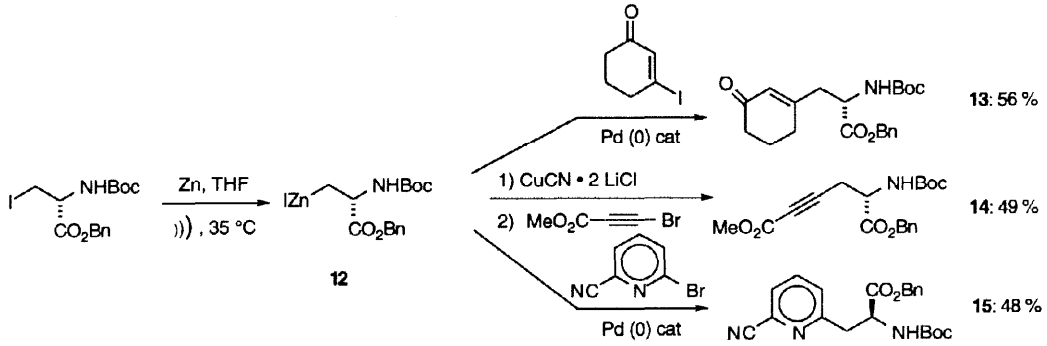
Scheme 4

Many heterocyclic iodides or even heteroaryl bromides are reactive enough to react directly with commercially zinc powder making the preparation of heteroarylzinc reagents like **8-11** very practical (Scheme 5) [22].



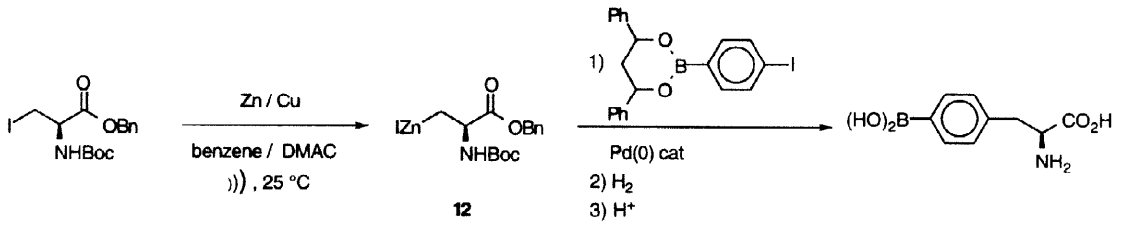
Scheme 5

The direct zinc insertion also proves to be very useful for the preparation of the zincated serine derivative **12** which constitutes a useful reagent for the synthesis of various enantiomerically pure amino acids such as **13-15** (Scheme 6) [23].



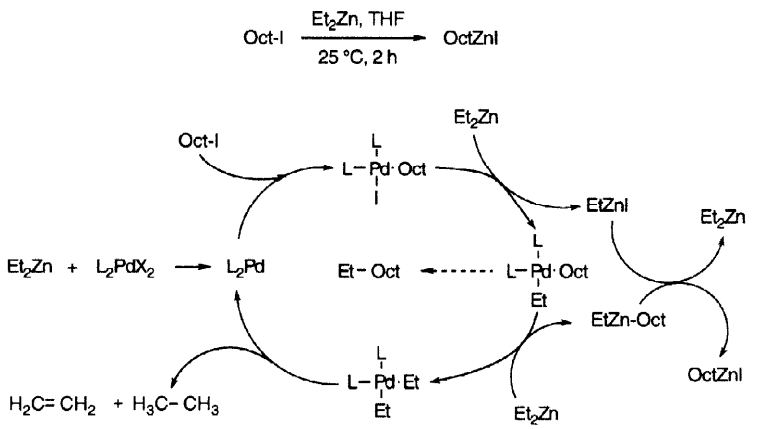
Scheme 6

This methodology has recently been applied to the preparation of 4-borono-*L*-phenylalanine (used in boroneutrotherapy) using a Zn / Cu couple in benzene / *N,N*-dimethylacetamide (DMAC) and sonication (Scheme 7) [24].



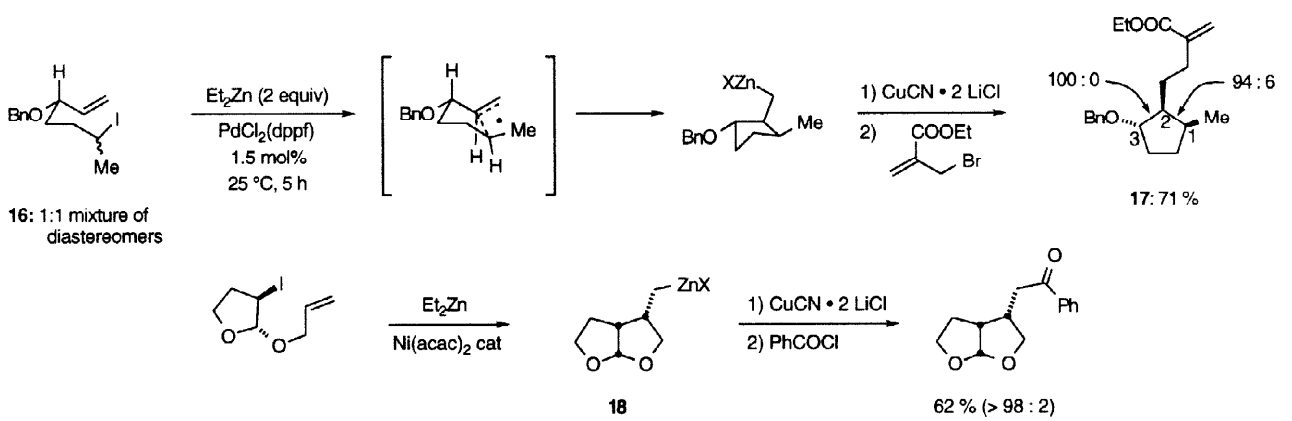
Scheme 7

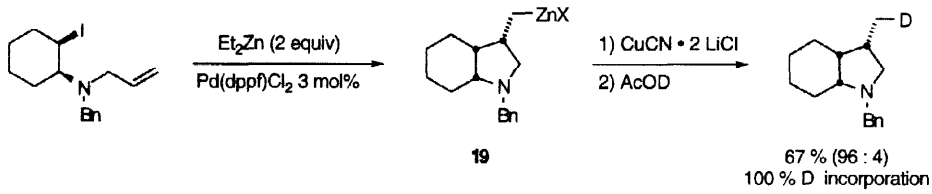
The preparation of organozinc halides can also be achieved with Et_2Zn using a transition metal (palladium or nickel) catalysis [25-30]. In this case, the insertion reaction proceeds by the formation of an intermediate palladium(II)-species which undergoes a transmetalation affording an organozinc halide (Scheme 8).



Scheme 8

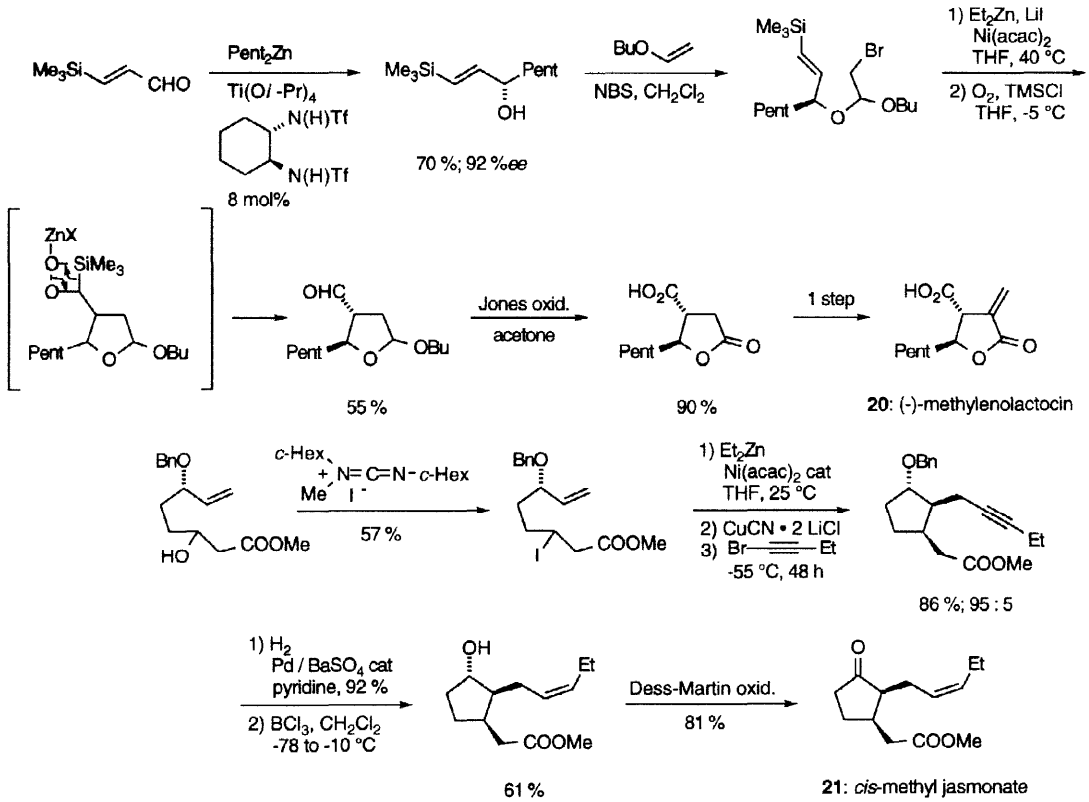
The palladium insertion proceeds *via* a radical insertion mechanism allowing radical cyclizations to be performed. These reactions are stereoconvergent and a mixture of diastereomers **16** produces the cyclopentane derivate **17** with an excellent stereocontrol of 3 contiguous chiral centers [26]. This cyclization reaction can also be used to prepare heterocyclic organozinc halides such as **18** and **19** (Scheme 9) [27, 30].





Scheme 9

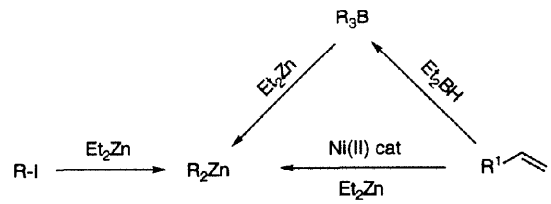
Applications of these reactions for the preparation of natural products such as (-)-methylenolactocin **20** [28] and *cis*-methyl jasmonate **21** [29] have been developed (Scheme 10).



Scheme 10

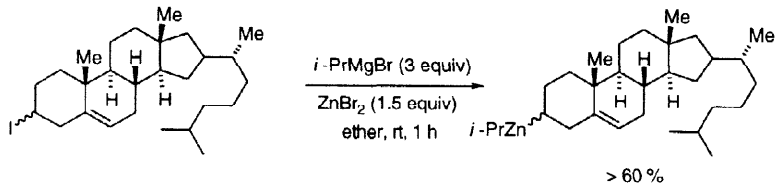
2.2. Preparation of diorganozincs

Diorganozincs (R_2Zn) are more reactive than organozinc halides [31] and undergo transmetalation reactions more readily. They are important for performing catalytic asymmetric additions to aldehydes, allowing the preparation of polyfunctional secondary alcohols with high enantioselectivity [32, 33]. Three methods have been developed recently for the synthesis of these reagents (Scheme 11) [31].



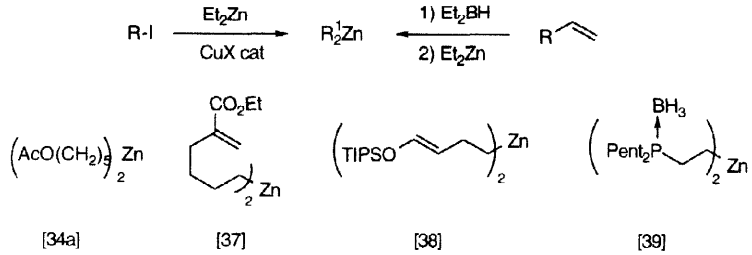
Scheme 11

The first method involves an iodine-zinc exchange reaction [34]. This reaction is suitable for primary or secondary alkyl iodides. It requires Et_2Zn or *i*-Pr_2Zn as reagents and a catalytic amount of a copper(I) salt. With Et_2Zn, the exchange reaction requires temperatures of 50 °C and reaction times between 3 h and 12 h [34]. Milder reaction conditions can be applied using *in situ* generated *i*-Pr_2Zn, prepared *via* the reaction of *i*-PrMgBr with $ZnBr_2$ (0.5 equiv). With such a reagent the iodine-zinc exchange reactions proceed very rapidly (25 °C, 1 h) and allow the preparation of complex secondary diorganozincs (Scheme 12) [35].



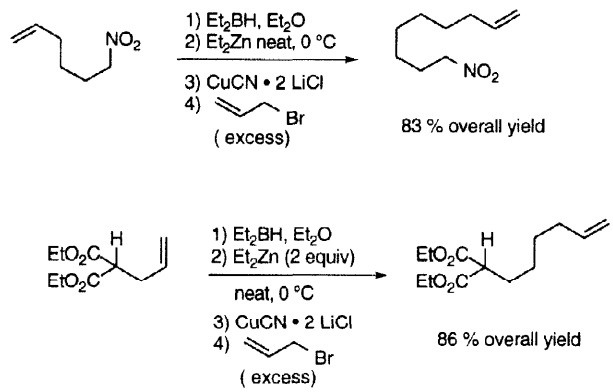
Scheme 12

The second method involves a boron-zinc exchange and uses functionalized olefins as starting materials. After hydroboration with Et_2BH [36, 37], the resulting organoboranes are treated with Et_2Zn or *i*-Pr_2Zn [35]. A wide range of polyfunctional diorganozincs can be prepared in this way (Scheme 13).



Scheme 13

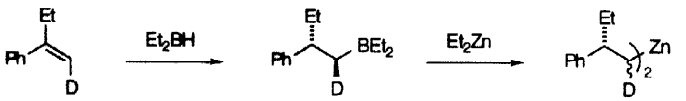
Remarkably, substrates bearing acidic hydrogen like primary nitroalkanes or alkylidenemalonates are readily converted into the corresponding zinc reagents and are allylated in good yields (Scheme 14) [40].



Scheme 14

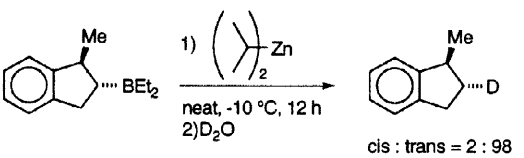
The boron-zinc exchange proceeds under significantly milder conditions (0 °C instead of 50 °C) for primary alkyl derivatives and requires only a few minutes compared to several hours which are necessary in the case of the iodine-zinc exchange. Nevertheless, the boron-zinc exchange reaction using Et_2Zn has some drawbacks and does not proceed rapidly with hindered secondary alkyldiethylboranes. Also a 1:1 mixture of diastereomeric

zinc reagents is produced with diastereomerically pure alkylboranes (Scheme 15) [40]. Generally it was observed that β-branched organoboranes undergo a slow exchange reaction with Et_2Zn.



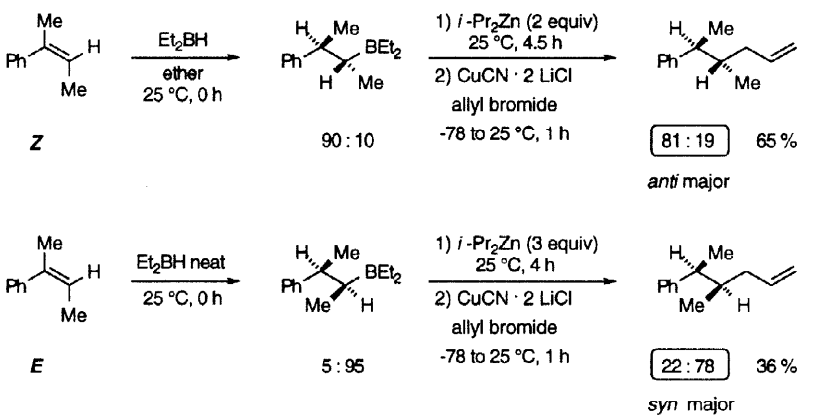
Scheme 15

Remarkably, it was found that *i*-Pr_2Zn undergoes the boron-zinc and iodine-zinc exchange with primary and *secondary* substrates rapidly, allowing the preparation of secondary dialkylzincs. By performing the boron-zinc exchange reaction at low temperature (-10 °C) retention of the configuration [41] is observed with several systems, allowing for the first time, a diastereoselective synthesis of non-stabilized secondary alkyl organometallics (Scheme 16) [42].



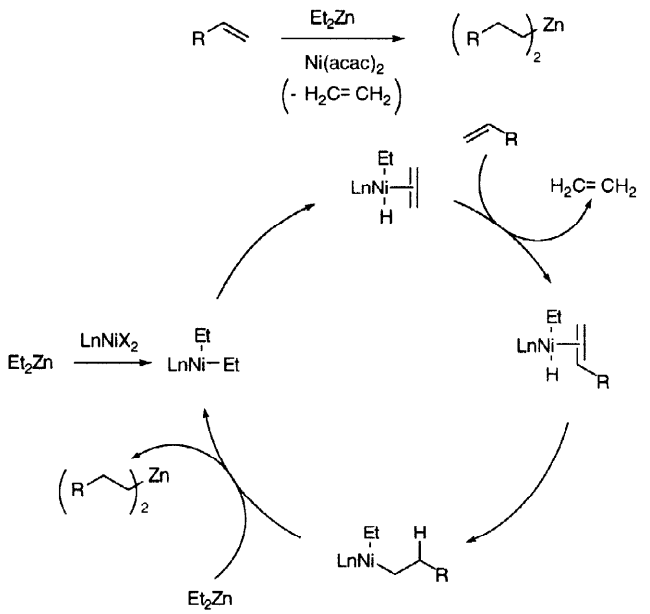
Scheme 16

This reaction can also be extended to open-chain systems and demonstrates well the stereoselectivity of the boron-zinc exchange (Scheme 17) [43].

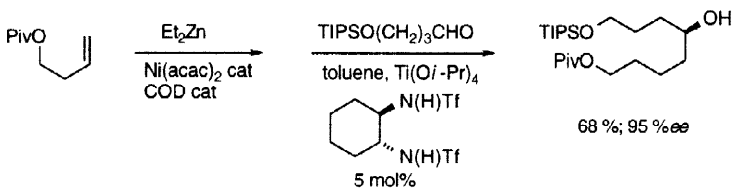


Scheme 17

In the third method, diorganozincs can also be obtained by a nickel catalyzed hydrozincation reaction. A tentative reaction mechanism is described in Scheme 18. This reaction has found applications in the asymmetric synthesis of polyfunctional alcohols (Scheme 19) [44].



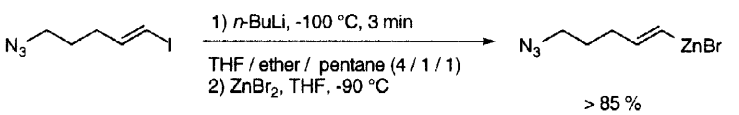
Scheme 18



Scheme 19

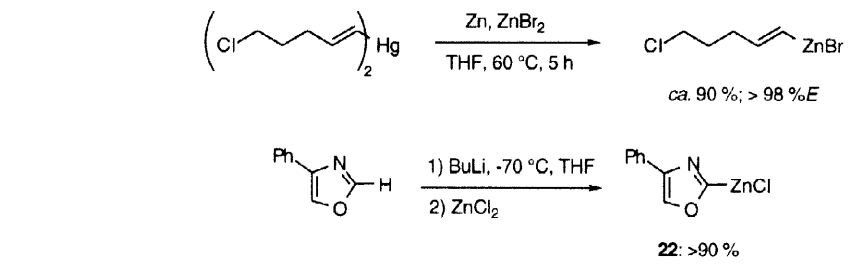
2.3. Other preparation methods

A few less general methods are available for the preparation of zinc organometallics. Thus, organozinc halides can also be obtained from the alkyl mesylates in the presence of sodium bromide and iodide in *N,N*-dimethylpropyleneurea (DMPU) [45] using zinc dust [46] or by an iodine-lithium exchange performed on functionalized alkenyl or aryl iodides followed by a transmetalation with zinc bromide (Scheme 20) [47] .



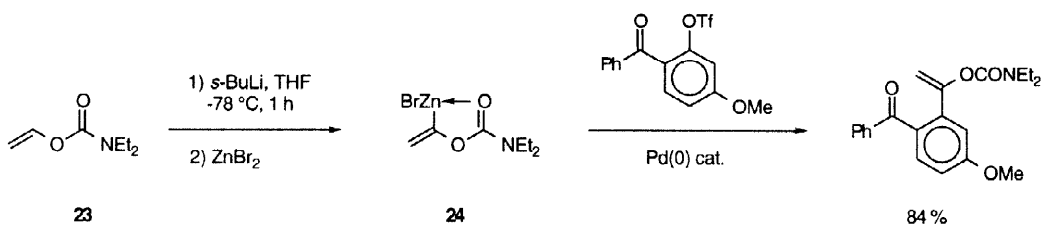
Scheme 20

A less general preparation of organozinc halides involves the treatment of diorganomercurials with zinc dust in the presence of zinc bromide (Scheme 21) [48]. Interestingly, it is also possible to prepare oxazol-2-ylzinc chloride **22** by transmetalation from the corresponding oxazol-2-yllithium compound. This transmetalation solves the problem of the well-known tendency of 2-lithiated oxazoles to undergo a ring-opening to the tautomeric isonitriles. Thus, the treatment of 4-phenyloxazole with *n*-BuLi (-70 °C, 0.5 h), followed by the addition of $ZnCl_2$ produces the corresponding zinc reagent **22** which undergoes high yield cross-coupling reactions with various functionalized triflates or iodides in the presence of a palladium(0) catalyst (Scheme 21) [49].



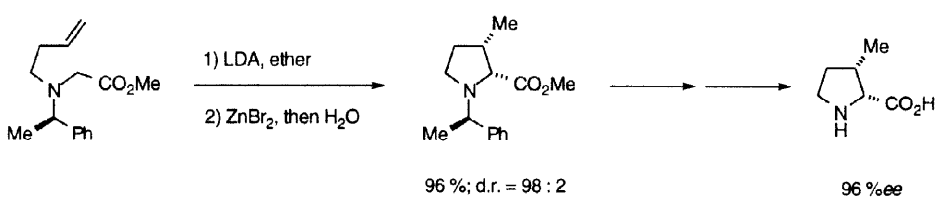
Scheme 21

O-vinyl carbamate **23** leads after lithiation with *s*-BuLi and zincation with zinc bromide, to the functionalized alkenylzinc **24**, which undergoes smooth cross-coupling reactions with various aryl or heteroaryl bromides or triflates (Scheme 22) [50].



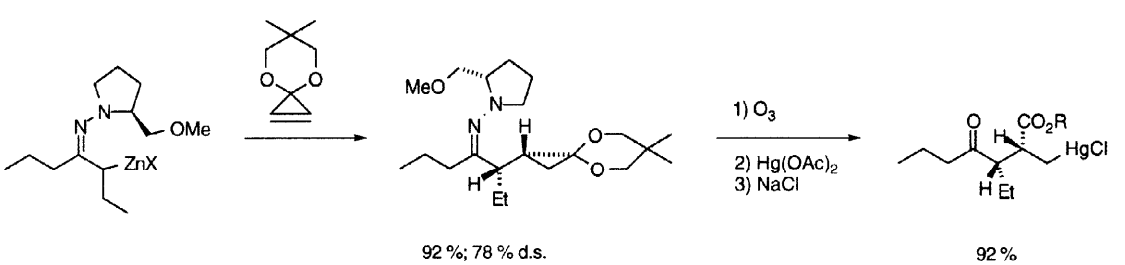
Scheme 22

Although zinc enolates have a moderate reactivity, they are able to add intramoleculary to an alkene furnishing the carbometalation product in high yield. The cyclisation proceeds with high diastereoselectivity (Scheme 23) [51].



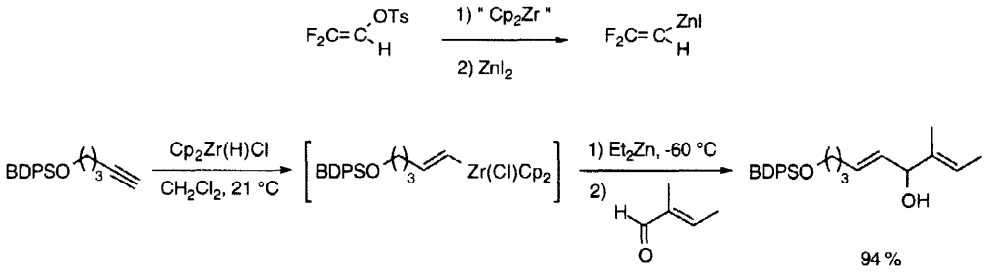
Scheme 23

An intermolecular version of this reaction has also been recently reported by Nakamura. Using a strained cyclopropene ring, it is possible to add zincated amide, ester or hydrazone enolates extending the scope of zinc enolate chemistry. The cyclopropane ring can be further opened allowing the stereoselective preparation of polyfunctional open-chain dicarbonyl compounds (Scheme 24) [52]. Addition to relatively unactivated olefins like ethylenes or styrenes is also possible [53].



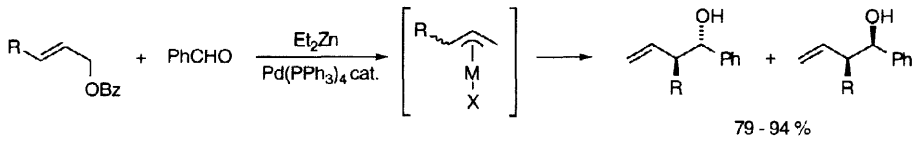
Scheme 24

Zinc organometallics can also be prepared by transmetalation from organozirconium compounds. This method has been elegantly applied by Ichikawa and Minami to prepare difluorovinylzinc intermediates and to use them in palladium catalyzed cross-coupling reactions. Likewise, Wipf has used this chemistry in an intermediate step during the total synthesis of (+)-curacin A (Scheme 25) [54].



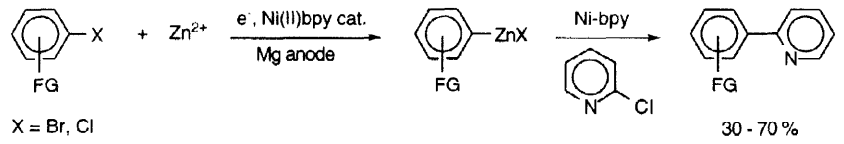
Scheme 25

Tamaru has utilised the transmetalation reaction of π-allyl palladium compounds to diethylzinc so as to develop a new procedure for the preparation of substituted allyl zinc reagents [55]. Treatment of substituted allyl benzoates with an aldehyde, $Pd(PPh_3)_4$ and diethylzinc results in first formation of a π-allyl palladium compound and then an allyl zinc reagent. These reagents give high selectivity depending on the substitution pattern of the allyl benzoate (Scheme 26) [55].



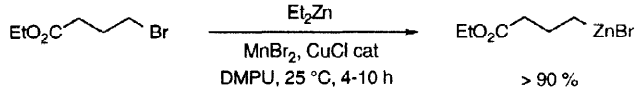
Scheme 26

Gosmini has recently obtained arylzinc compounds by means of an electrochemical reduction of aryl bromides or chlorides using a nickel-bipyridine complex in the presence of $ZnBr_2$. The resulting arylzinc halides were coupled with 2-chloropyridine in the presence of the same nickel catalyst in reasonable yields (Scheme 27) [56].



Scheme 27

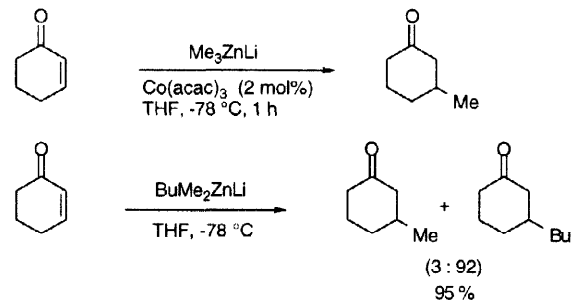
Finally some transition metals like manganese salts catalyze iodine- or bromine- zinc exchange reactions using Et_2Zn. This constitutes an excellent preparation of organozinc bromides starting from functionalized alkyl bromides (Scheme 28) [57].



Scheme 28

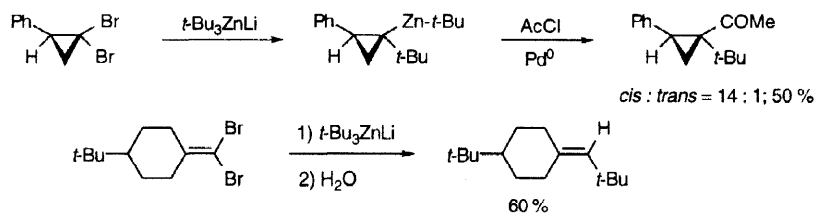
2.4. Preparation and reactions of organozincates

Lithium triorganozincates (R_3ZnLi) are prepared by the reaction of an alkyllithium (3 equiv) with zinc chloride or by treatment of a dialkylzinc with an alkyllithium (1 equiv) in ether or THF [58]. Lithium or magnesium trialkylzincates readily undergo 1,4-addition reactions to α,β-unsaturated ketones. The nature of the lithium salts present strongly influences the yield of the reaction [59]. Lithium trimethylzincates is one of the least reactive triorganozincates and the methyl group is usually transferred with moderate yield [58], however, methylation with Me_3ZnLi can be catalyzed by cobalt complexes (Scheme 29) [58]. The low transfer ability of a methyl group has been exploited and mixed alkyldimethylzincates selectively transfer the alkyl group in Michael-additions (Scheme 29) [58, 60].

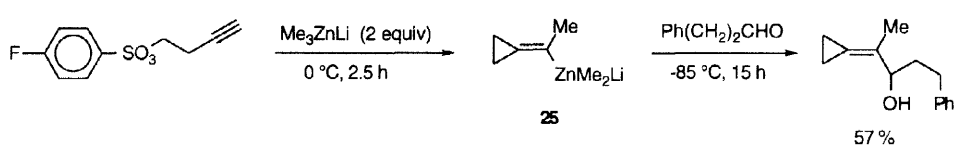


Scheme 29

Related mixed heterozincates $R_2(t\text{-BuO})ZnMgBr \cdot TMEDA$ prepared from RMgX (2 equiv), $ZnCl_2 \cdot TMEDA$ and *t*-BuOK react readily with enones providing the 1,4-adducts with satisfactory yields. By using chiral nitrogen-chelating ligands asymmetric 1,4-additions can be achieved with moderate enantioselectivity [61]. The addition of Bu_3ZnLi to nitrostyrene in a chiral solvent mixture of pentane and (*S,S*)-1,4-dimethylamino-2,3-dimethoxybutane (DDB) affords an optically enriched nitroalkane [62]. Triorganozincates also undergo halogen-zinc exchange reactions with a range of 1,1-dibromoalkenes or -alkanes (Scheme 30) [63-66]. The preparation of new cyclopropylidenealkylzinc reagents of type **25** is possible using Me_3ZnLi (Scheme 31) [67].

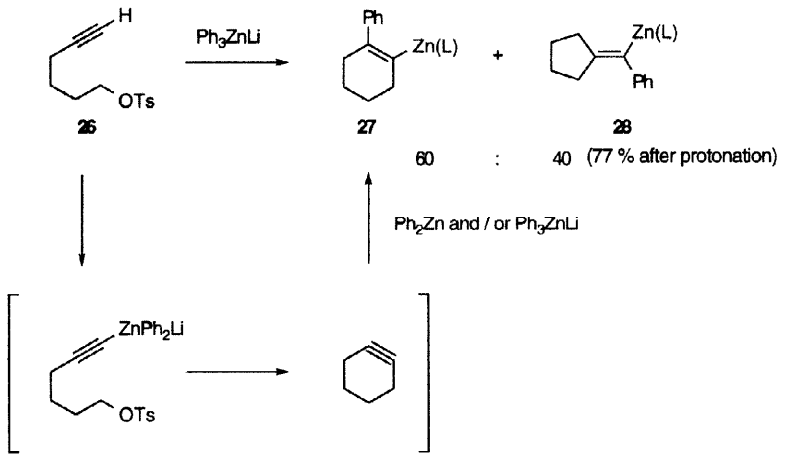


Scheme 30



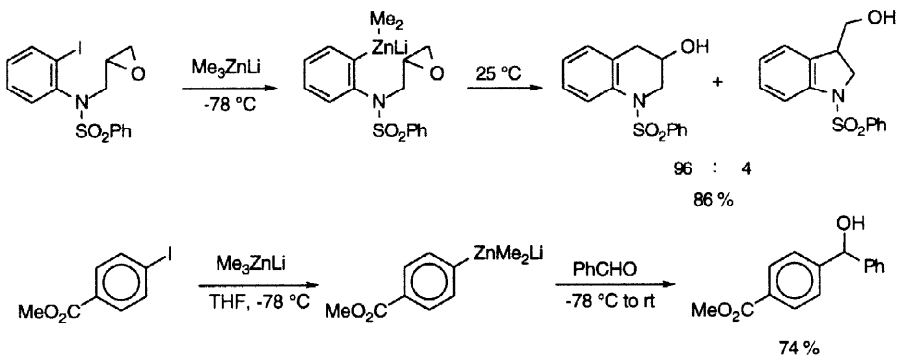
Scheme 31

Alkynyl zincates undergo also a new type of *endo*-cyclisation *via* a cyclohexyne intermediate. Thus, treatment of tosylate **26** with Ph_3ZnLi furnishes a mixture of *endo*-**27** and *exo*-**28** cyclisation products in a 60 : 40 ratio. The formation of **27** is explained *via* the formation of a cyclohexyne intermediate (Scheme 32) [68].



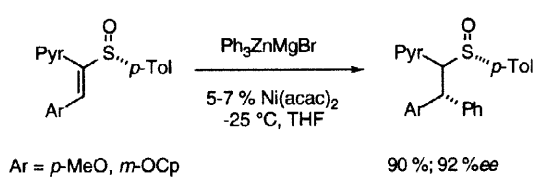
Scheme 32

Interestingly, lithium triorganozincates can be used for performing iodine-zinc exchange reactions. This provides a new method for the generation of arylzinc reagents (Scheme 33) [69].



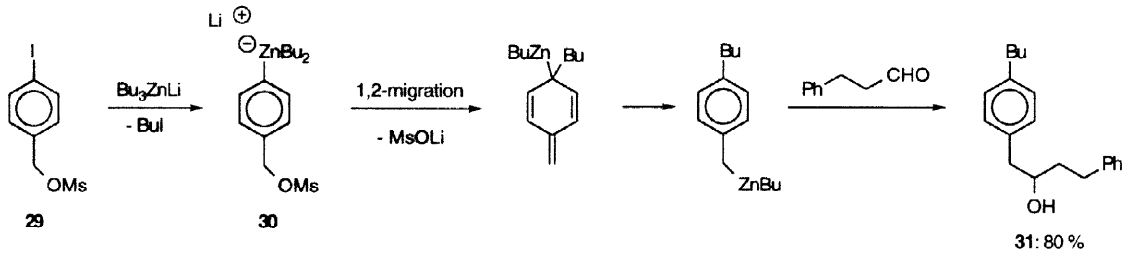
Scheme 33

Lithium and magnesium zincates have also been added with excellent enantioselectivity to α,β-unsaturated sulfoxides in the presence of catalytic amount of $Ni(acac)_2$ (Scheme 34) [70].



Scheme 34

A new method for preparing benzylic reagents has been found by Harada making use of triorganozincates. Thus, the reaction of *p*-iodobenzyl mesylate **29** with Bu_3ZnLi affords the intermediate **30**, which undergoes a 1,2-migration of the butyl group, furnishing after quenching with 3-phenylpropionaldehyde the expected product **31** (Scheme 35) [71].

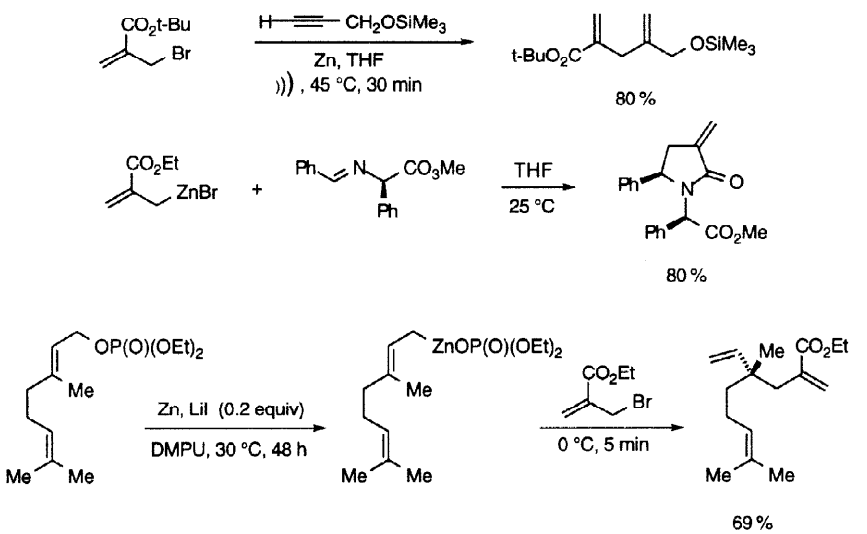


Scheme 35

3. Reactions of organozinc reagents

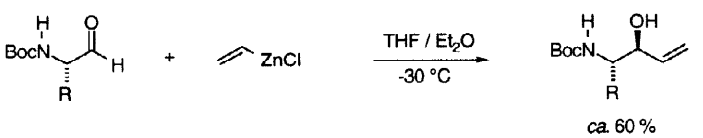
3.1. Uncatalyzed reactions

Many organozinc species are too unreactive to undergo addition reactions to carbonyl derivates or to double bonds. This is generally not true for allylic zinc reagents and to some extent propargylic zinc compounds which react smoothly with several electrophiles like carbonyl derivates [72-74], nitriles [75, 76] or triple bonds [77] (Scheme 36). Also, addition of allylic reagents to imines can occur with very high diastereoselectivity (Scheme 36) [78, 79]. Allylic zinc reagents undergo cross-coupling reactions with reactive halides leading to 1,5-dienes. Usually the new carbon-carbon bond is formed from the more substituted end of the allylic system (Scheme 36) [46].



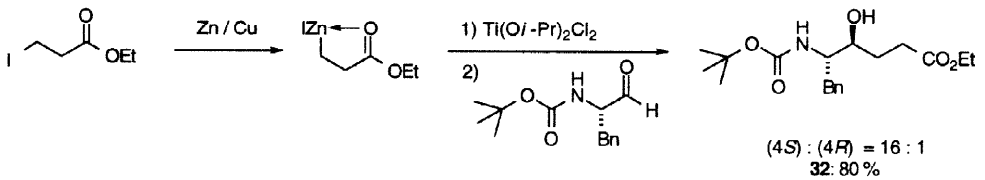
Scheme 36

Propargylic zinc derivatives do not react selectively with aldehydes or ketones and often give a mixture of allenic and homopropargylic alcohols [80, 81]. The regioselectivity depends strongly on the nature of the substituents. 1-Trimethylsilylpropargyl zinc reagents add to aldehydes with excellent regioselectivity and diastereoselectivity leading to *anti*-homopropargylic alcohols [82]. Alkylzinc derivatives react slowly with aldehydes, however, an alkenylzinc chloride has been added to a protected α-aminoaldehyde in satisfactory yield (Scheme 37) [83].



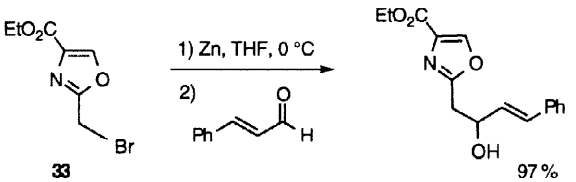
Scheme 37

The rate of addition can be improved by performing the reaction in the presence of a Lewis acid. Interesting results have been reported using chlorotrimethylsilane or titanium alkoxides [9, 84]. Under these conditions, zinc homoenolates have also been added to aldehydes furnishing medicinally important hydroxyester intermediates such as **32** (Scheme 38) [84].



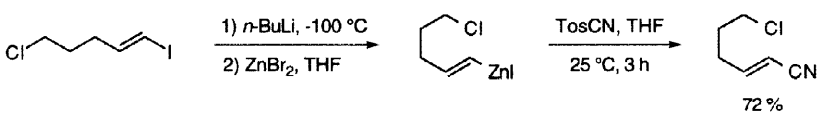
Scheme 38

2-Bromomethyloxazoles such as **33** can be easily converted to the corresponding zinc reagents. The enolate character of these reagents results in a high reactivity, and their additions to various aldehydes or ketones proceeds with excellent yields (Scheme 39) [85].



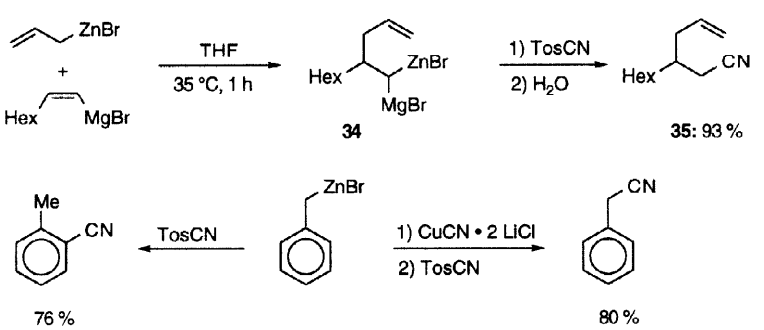
Scheme 39

A very reactive and selective carbon electrophile, tosyl cyanide (TosCN) reacts with various organozinc halides affording polyfunctional nitriles in good yields (Scheme 40) [86].



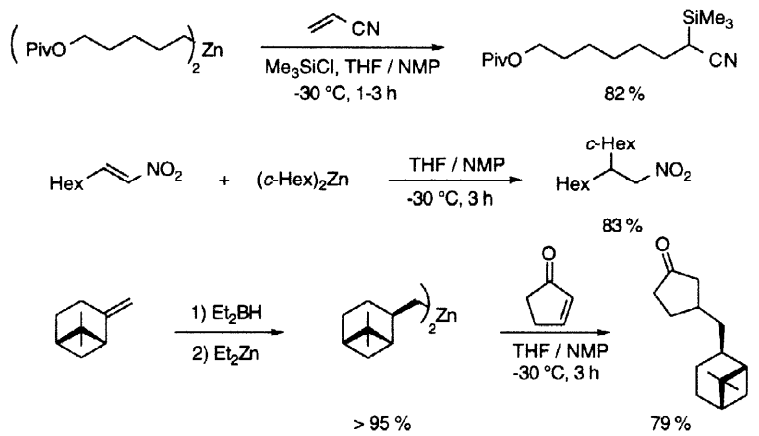
Scheme 40

The reaction can be used to convert 1,1-bimetallic reagents of zinc and magnesium, like **34**, to unsaturated nitriles, like **35** [86]. The regioselectivity of the reaction of benzylic zinc organometallics with TosCN affords *o*-methylbenzonitrile derivatives, whereas the reaction of the corresponding zinc-copper derivative provides a benzylic cyanide (Scheme 41) [86].



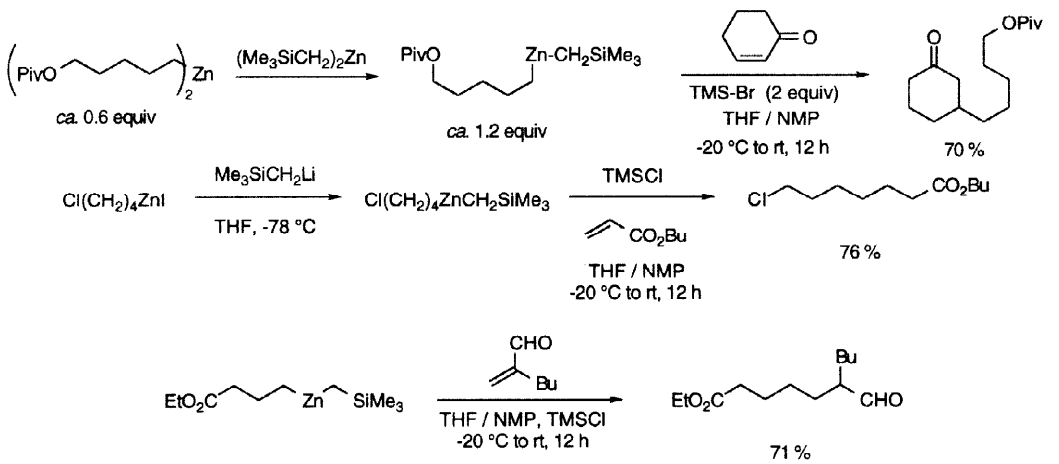
Scheme 41

The reactivity of diorganozincs can be increased by performing the reaction in a polar solvent, or by the addition of various Lewis acids. Thus, it was found that *N*-methylpyrrolidinone (NMP) is especially well suited and allows Michael-addition reactions to be performed with a variety of double bonds bearing electron-withdrawing groups like enones, alkylidenemalonates or nitroolefins (Scheme 42) [87]. One equivalent of NMP is sufficient to promote the addition reaction but the presence of Me_3SiCl is necessary. A range of β-monosubstituted enones can be used for this addition, however β-disubstituted enones undergo the Michael-addition only reluctantly.



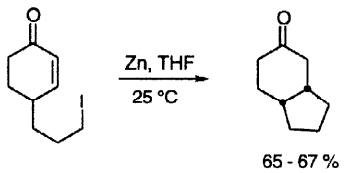
Scheme 42

Only one of the two R groups is transferred to the enone using diorganozincs of type R_2Zn. However mixed diorganozincs of type $R\text{-}ZnCH_2SiMe_3$ allow a selective transfer of the R group [88]. The Me_3SiCH_2 group is not transferable, and this method avoids the waste of an organic rest R (Scheme 43) [88]. Addition to α,β-unsaturated aldehydes furnish with high selectivity the 1,4-adduct, whilst the reaction with acrylates gives the Michael-addition product and no polymerisation products (Scheme 43) [89].



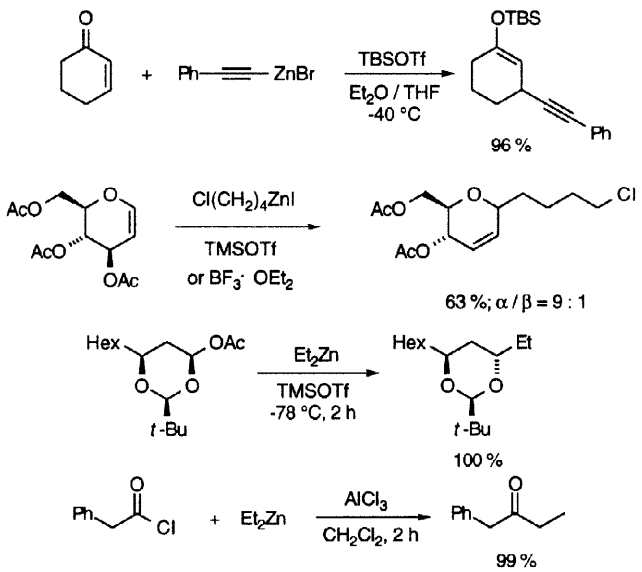
Scheme 43

The intramolecular 1,4-addition of an organozinc allows the preparation of bicyclic ketones (Scheme 44) [90].



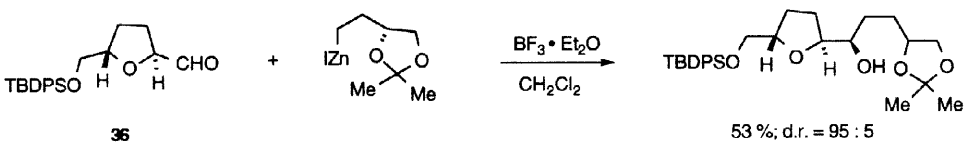
Scheme 44

Alkynylzinc halides undergo 1,4-addition to enones in the presence of *tert*-butyldimethylsilyl triflate [91]. In the presence of TMSOTf or $BF_3 \cdot OEt_2$, the addition of organozinc halides to glycals furnishes preferentially the α-substitution product [92]. TMSOTf has also been used in the highly stereoselective preparation of protected *anti*-1,3-diols by addition of dialkylzinc derivatives to 4-acetoxy-1,3-dioxanes [92]. A similar activation of acid chlorides with $AlCl_3$ allows acylation with Et_2Zn or Me_2Zn under mild conditions in CH_2Cl_2 (Scheme 45) [93].



Scheme 45

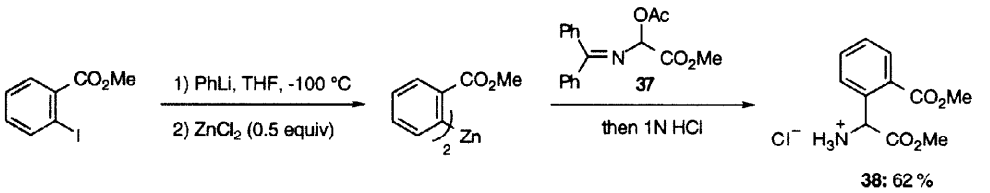
By using non-complexing solvents such as dichloromethane, alkylzinc iodides react directly with activated α-oxygenated aldehydes such as **36** leading to the addition product with excellent diastereoselectivity in the "matched" case (Scheme 46) [94].



36

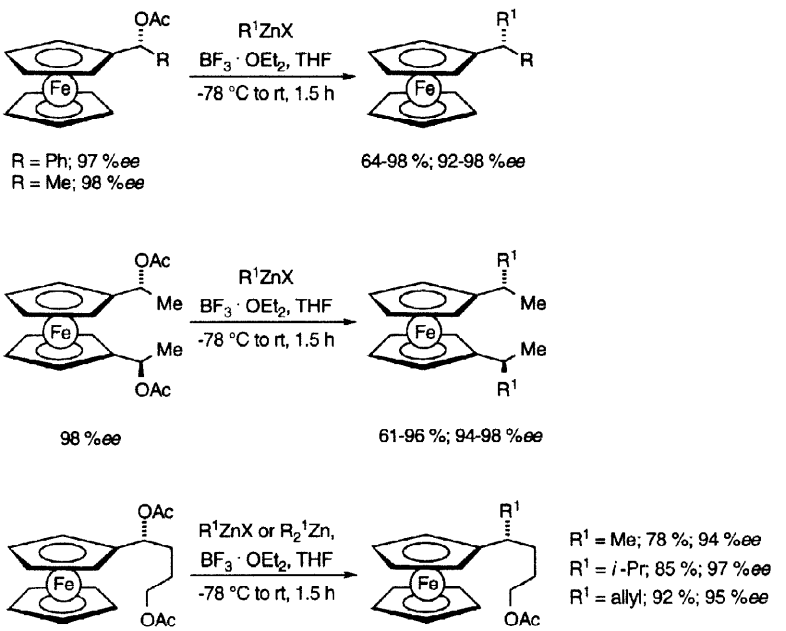
Scheme 46

In DMF, it is possible to add functionalized diarylzincs to the reactive Schiff base **37** leading to α-aryl-α-amino ester **38** in good yield. The diarylzinc has been prepared *in situ* by an iodine-lithium exchange at low temperature followed by a transmetallation with $ZnCl_2$ (Scheme 47) [95].



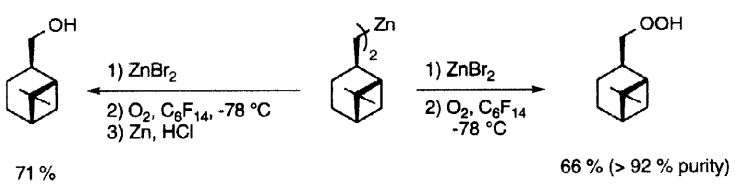
Scheme 47

The substitution of ferrocenyl acetates with various organozinc halides provides an enantioselective preparation of polyfunctional chiral ferrocenes in optically pure form (Scheme 48) [96].



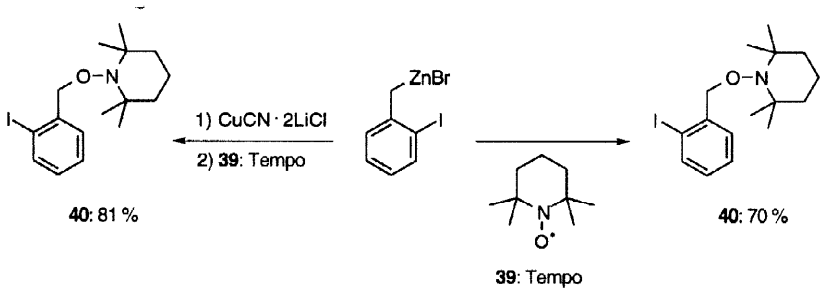
Scheme 48

Organozincs react rapidly with oxygen or air and this reaction has been used to prepare alcohols or hydroperoxides depending on the reaction conditions [97]. The use of perfluorohexane as solvent has proved to be especially attractive (Scheme 49) [98].



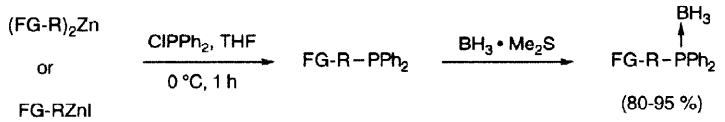
Scheme 49

The chemoselective oxidation of benzylic zinc reagents has also been performed under mild conditions using 2,2,6,6-tetramethylpiperidin-1-oxyl (Tempo) **39** leading to the adduct **40**. By carrying out a transmetalation of the zinc reagent with CuCN · 2LiCl, a better yield is obtained (Scheme 50) [99].



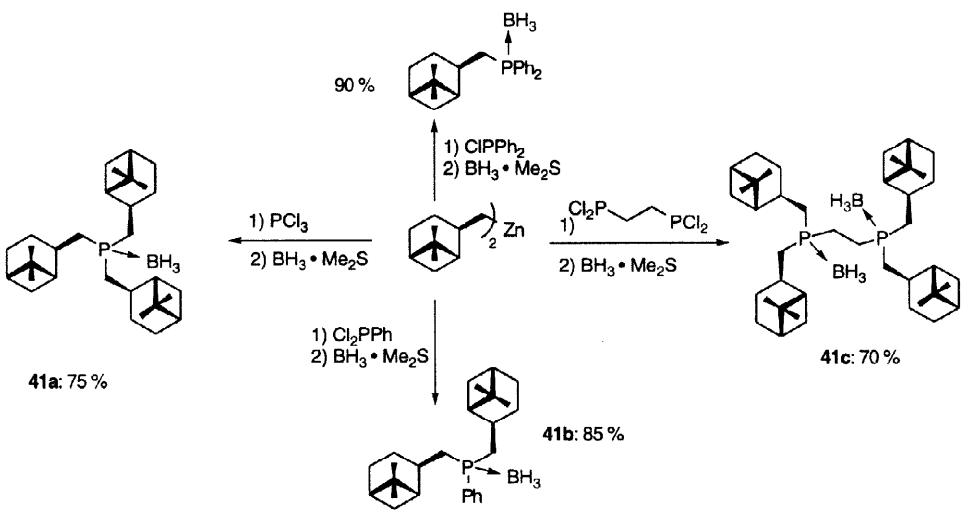
Scheme 50

Organozinc halides rarely react with electrophiles in the absence of a metal catalyst, however, chlorophosphines undergo smooth substitution reactions with various functionalized organozinc halides or diorganozincs furnishing polyfunctional phosphines in good to excellent yields (Scheme 51) [100].



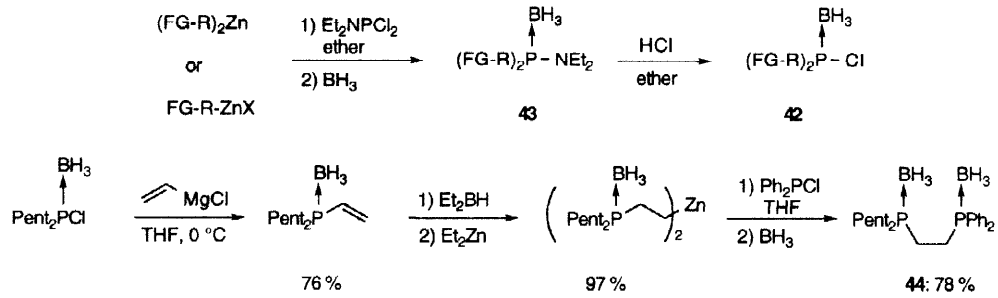
Scheme 51

This method gives a direct access to a range of polyfunctional phosphines of great interest for coordination chemistry. The preparation of chiral phosphines is readily achieved starting from terpenes. The hydroboration of β-pinene with $BH_3 \cdot Me_2S$ gives *tris*-myrtanylborane which by treatment with Et_2Zn gives *bis*-myrtanylzinc in quantitative yield. This zinc reagent undergoes substitution reactions with various chlorophosphines affording the chiral phosphines **41a-c** (Scheme 52). The chelating ability of the phosphine **41c** makes this compound of potential interest as chiral ligand for catalytic asymmetric reactions [101].



Scheme 52

The preparation of polyfunctional chlorophosphines like **42** was achieved by reaction of diethylaminodichlorophosphine with zinc organometallics. After protection with BH_3, the readily isolated borane-aminophosphines complexes **43** were obtained. Treatment with HCl in ether provides the desired borane protected chlorophosphines **42** in excellent overall yield (Scheme 53) [39]. As an application, the mixed diphosphine **44** was prepared (Scheme 53).

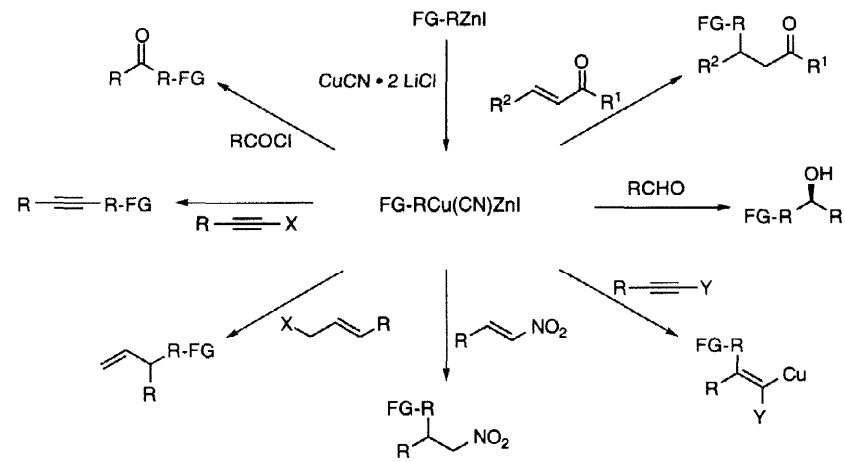


Scheme 53

3.2. Transition metal catalyzed reactions

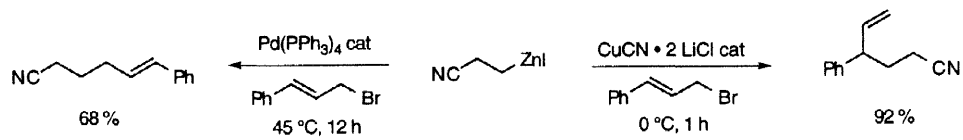
3.2.1. Copper catalyzed reactions

The reactivity of organozinc halides can be dramatically increased by the addition of copper salts like the THF soluble copper salt CuCN · 2LiCl [7, 102]. Although, the exact nature of the resultant organometallic species is not known, the new copper reagents are tentatively described as RCu(CN)ZnI. These reagents have a similar reactivity as lithium or magnesium derived copper derivatives and react with the same electrophiles (Scheme 54) [9].



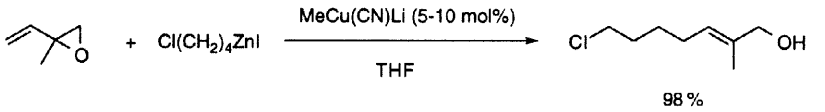
Scheme 54

Cross-coupling reactions with allylic halides are especially high yield reactions. They occur with high S_N2' selectivity, in contrast to the corresponding palladium or nickel catalyzed coupling-reactions (Scheme 55) [103-105].



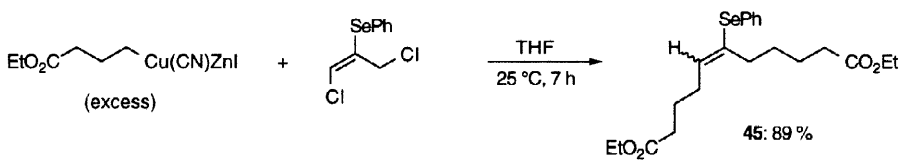
Scheme 55

Although organozinc reagents do not open epoxides, it is possible to alkylate allylic epoxides with functionalized organozinc compounds in the presence of a catalytic amount of a cyanocuprate (Scheme 56) [106].



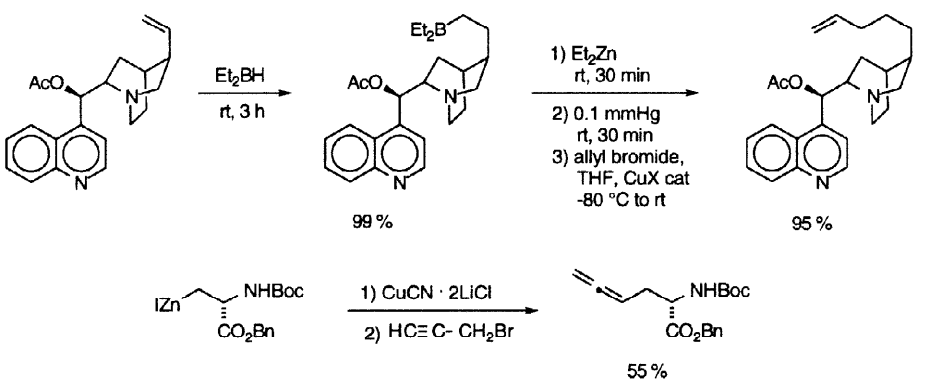
Scheme 56

The high S_N2' selectivity of organozinc derived cuprates allows multiple allylic substitution reactions to be performed with excellent results. Thus, the reaction of various 2-substituted-1,3-dichloropropenes with organozinc-copper compounds provides only products like **45** obtained after two successive S_N2' reactions (Scheme 57) [107].



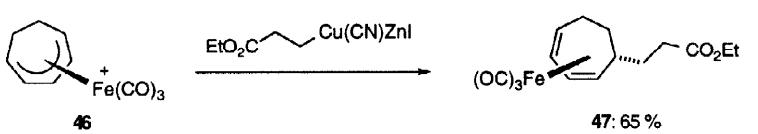
Scheme 57

Bimetallic reagents can be smoothly allylated under mild conditions leading to polyfunctional products [108, 109]. Polyfunctional natural products bearing a double bond can be allylated *via* a hydroboration, boron-zinc exchange and copper(I) catalyzed allylation (Scheme 58) [110]. Besides allylic halides, propargylic halides or sulfonates display a similar reactivity to these zinc copper reagents leading to allenes (Scheme 58) [111].



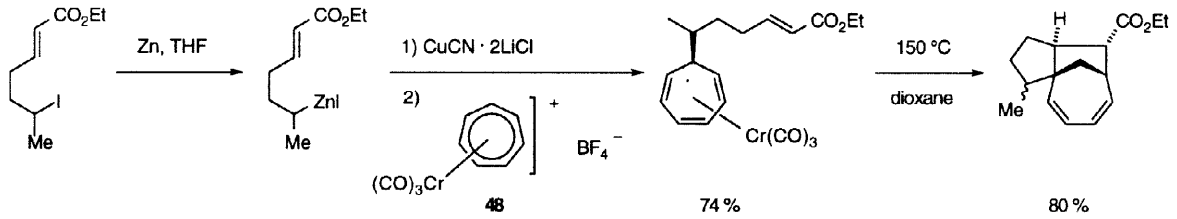
Scheme 58

Zinc-copper reagents add to the readily available cationic η^5-cycloheptadienyliron complex **46** leading to the polyfunctional iron-diene complexes **47** in satisfactory yield (Scheme 59) [112].



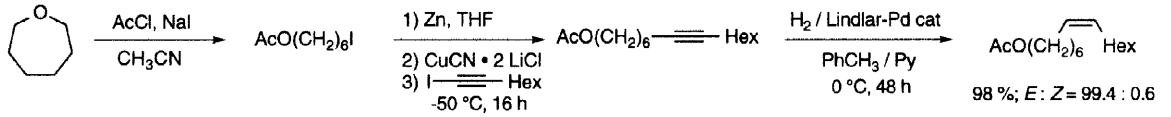
Scheme 59

A related alkylation of the tropylium cation complex **48** furnish an important intermediate for the synthesis of β-cedrene (Scheme 60) [113].



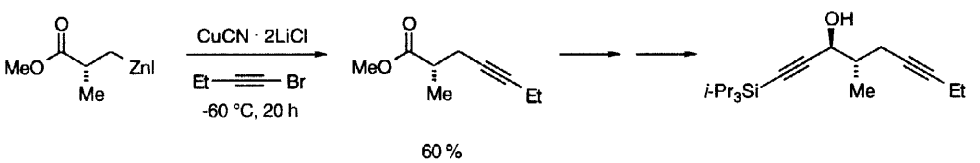
Scheme 60

Polyfunctional zinc-copper reagents react efficiently with 1-bromo or 1-iodoalkynes furnishing functionalized alkynes in good yields. The reaction proceeds at low temperature (-65 °C to -55 °C) and has been applied to the preparation of pheromones (Scheme 61) [114] and polyfunctional acetylenic ethers [115].



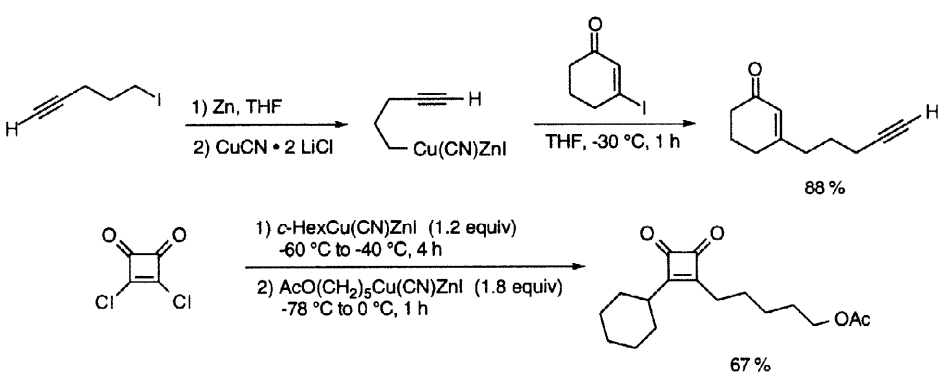
Scheme 61

This alkynylation has been recently used by Corey for the preparation of a key intermediate in the synthesis of the side chain of Cicaprost™, a drug used for the treatment of primary pulmonary hypertension (PPH) (Scheme 62) [116].



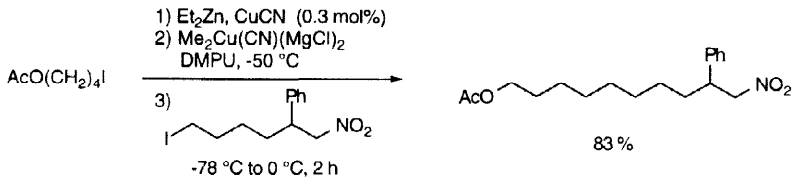
Scheme 62

The extension of this cross-coupling to iodoalkenes is also possible. Two cases should be distinguished, in the first the iodo-, bromo- or chloro-alkene is further conjugated with an electron-withdrawing group, a facile substitution is observed. Typically, 3-iodo-2-cyclohexenone [117] reacts with a zinc-copper reagent furnishing the expected cross-coupling product (Scheme 63) [15]. This addition-elimination reaction can be applied to the preparation of squaric acid derivatives. Thus, the treatment of 3,4-dichlorocyclobutene-1,2-dione with two different zinc-copper reagents furnishes polyfunctional squaric acid derivatives (Scheme 63) [118].



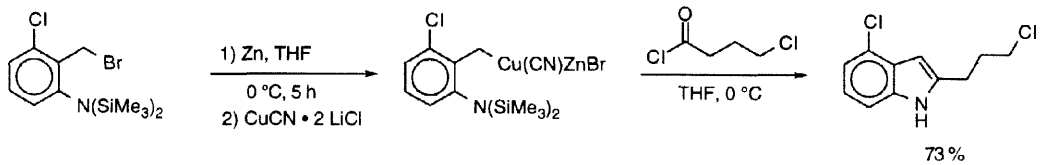
Scheme 63

The second case is the cross-coupling reaction with non-activated iodoalkenes, this requires a polar solvent like NMP or DMPU and elevated reaction temperatures (60 °C, 12 h). These reaction conditions demonstrates the remarkable thermal stability of zinc-copper organometallics. These cross-coupling reactions proceed with complete retention of configuration of the double bond and allow the stereospecific synthesis of highly functionalized alkenes [119]. Alkyl halides are unreactive towards zinc-copper reagents under standard reaction conditions. However, by using a polar solvent like DMPU and a new copper species [$R_2Cu(CN)(MgX)_2 \cdot Me_2Zn$] obtained by the reaction of magnesium derived cuprate [$Me_2Cu(CN)(MgCl)_2$] and a diorganozinc, a smooth coupling reaction is observed at 0 °C [120]. This method tolerates the presence of many functional groups and can be extended to couplings with benzylic bromides [120]. It displays a high chemoselectivity and allows coupling of substrates bearing a primary nitro group leading to the expected polyfunctional nitroalkane, without the formation of appreciable amounts of zinc nitronate despite the presence of acidic hydrogens atoms at the α-position of the nitro group (Scheme 64) [120].



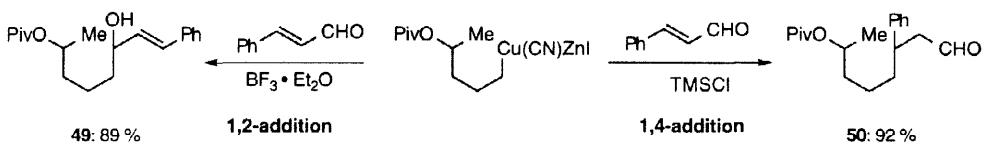
Scheme 64

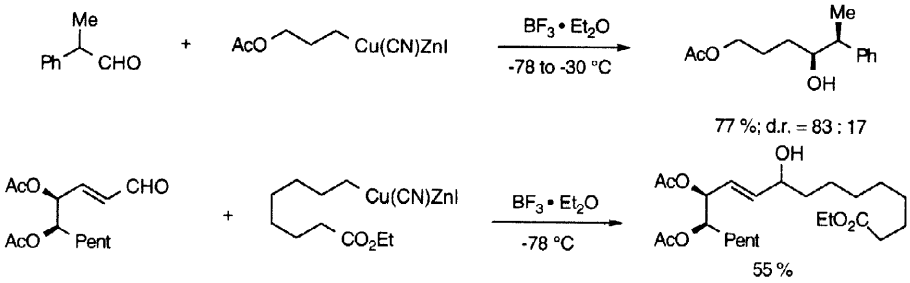
The reaction of zinc-copper reagents with acid chlorides has a remarkable generality and has found many applications in synthesis (Scheme 65) [9, 121-126]. The treatment of silyl-protected *o*-aminated benzylic zinc-copper derivatives with an acid chloride leads to 2-substituted indole [125]. Aromatic and heterocyclic zinc compounds provide polyfunctional aromatic or heterocyclic ketones (Scheme 65).



Scheme 65

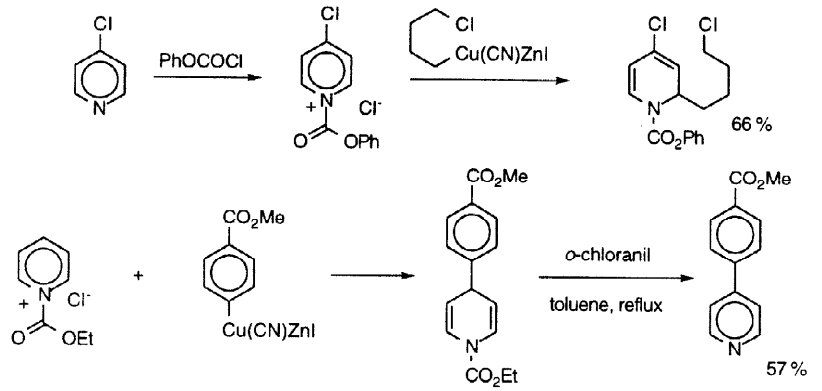
The rate of addition to aldehydes can be improved in the presence of a Lewis acid like chlorotrimethylsilane, titanium alkoxides or boron trifluoride etherate [9, 84, 127]. With a conjugated unsaturated aldehyde such as cinnamaldehyde, the nature of the addition product depends strongly on the nature of the catalyst used. With boron trifluoride etherate only the 1,2-addition product **49** is obtained, whereas in the presence of chlorotrimethylsilane the selective formation of the 1,4-addition product **50** is observed (Scheme 66) [127]. The addition of zinc-copper reagents to aldehydes bearing a chiral center at the α-position proceeds with a diastereoselectivity similar to that observed with organotitanium reagents [127-130]. Synthetic applications reported include the preparation of polyoxygenated metabolites of unsaturated fatty acids (Scheme 66) [131] and (perfluoralkyl)arylcarbinols [132].





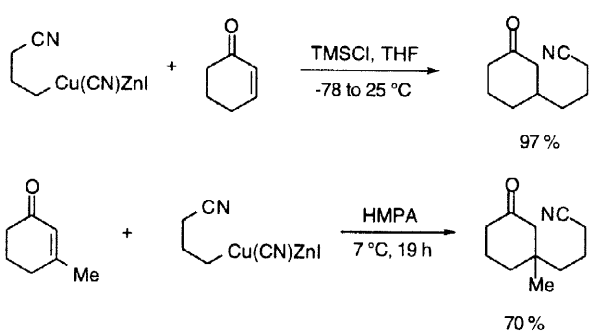
Scheme 66

Most alkylzinc halides do not add to ketones, even in the presence of a Lewis acid catalyst [2,10]. Similarly, the addition to imines is difficult and can be achieved only with particularly reactive substrates [133-138], but the *N*-acylation of imine derivatives leads to immonium salts which readily add zinc- or zinc-copper reagents (Scheme 67) [139-149].



Scheme 67

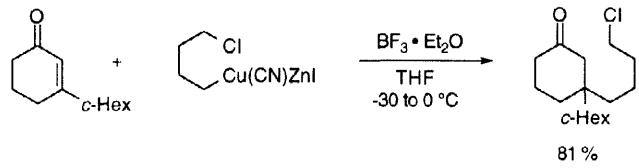
Lithium- and magnesium-derived organocopper reagents add to various activated double bonds (Michael addition) in excellent yield and regioselectivity [150-152]. It has been shown that zinc-copper reagents prepared by the transmetalation of organozinc reagents with CuCN · 2LiCl add to β-monosubstituted enones in the presence of chlorotrimethylsilane [153-163] leading selectively to the 1,4-adduct (Scheme 68) [7].



Scheme 68

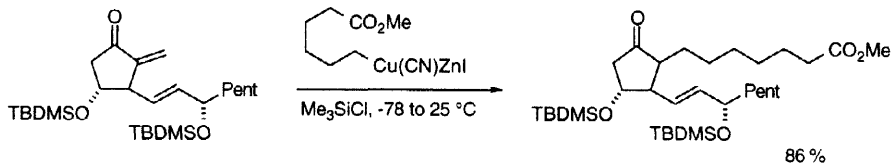
The addition to β-disubstituted enones does not proceed under these conditions. However, the use of a polar solvent facilitates the addition to these hindered Michael-acceptors. In such solvents, 3-methylcyclohex-2-enone gives the expect Michael-adduct (Scheme 68) [164]. Instead of using a polar solvent, it is also possible to

activate sterically hindered enone through the addition of boron trifluoride etherate. In the presence of this Lewis acid, the 1,4-addition can be performed in THF with satisfactory yields (Scheme 69) [165].



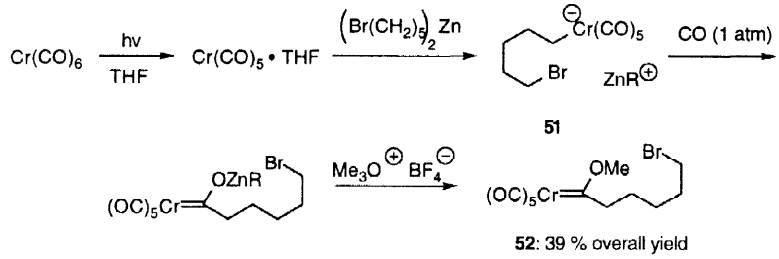
Scheme 69

The conjugated addition of functionalized zinc-copper reagents has found several applications in the field of natural products chemistry [166-168] as illustrated by the synthesis of prostaglandin derivatives (Scheme 70) [166].



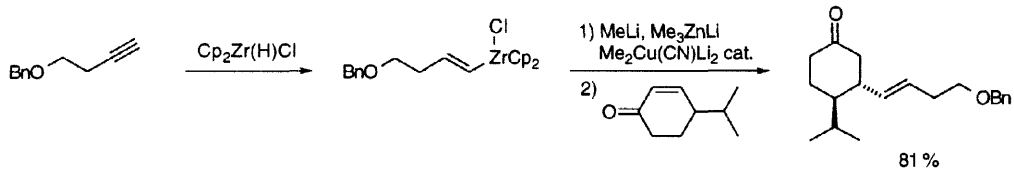
Scheme 70

Whereas the direct addition of zinc-copper reagents to carbon monoxide does not occur, the addition of polyfunctional dialkylzincs to chromium pentacarbonyl-tetrahydrofuran complex (Scheme 71) produces an alkylchromium intermediate **51** [169-172] which undergoes a 1,2-migration leading to an acyl-metalate. Trapping this with a Meerwein salt in dichloromethane furnishes a Fischer carbene complex **52** in 39 % overall yield. This reaction sequence allows the preparation of a range of new polyfunctional chromium-carbene complexes [172].



Scheme 71

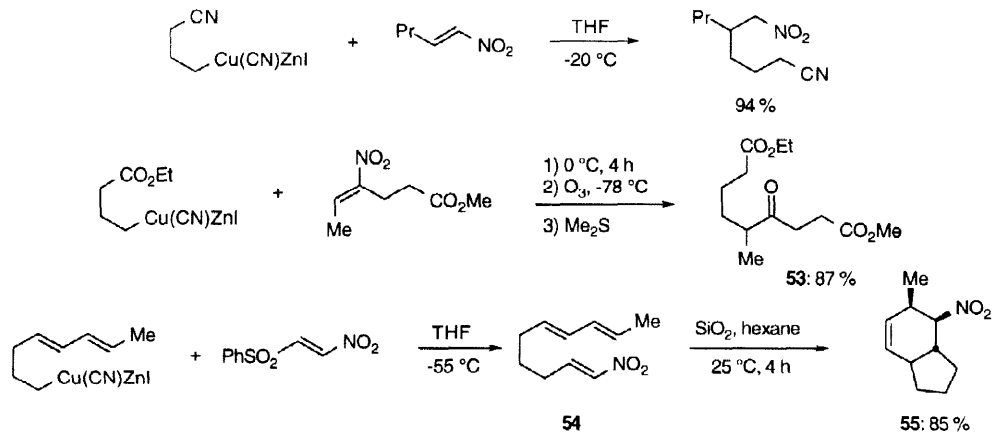
Alkenylcoppers prepared from alkenylzirconium derivatives can be added to enones. The transmetalation from zirconium to zinc and copper is performed by using lithium trimethylzincates, a soft but highly reactive transmetalating agent (Scheme 72) [173].



Scheme 72

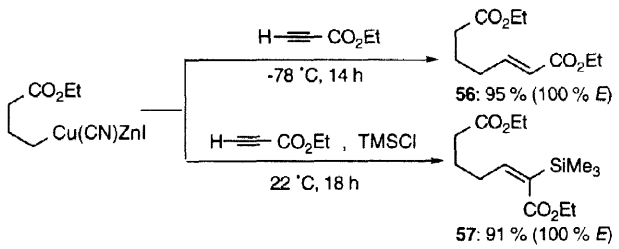
Dialkylzincs add to enones in the presence of copper(I)-*N*-monosubstituted sulfonamide combined catalyst system. The resulting zinc enolates can be further used for aldol reactions or palladium(0)-catalyzed reactions

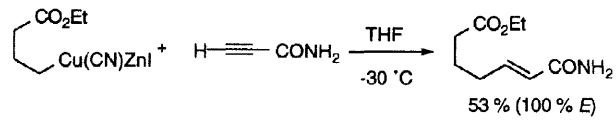
with allyl acetate [174]. Although the Michael addition of zinc-copper organometallics to unsaturated esters occurs only slowly, the addition to alkylidenemalonates proceeds smoothly [175]. Nitroolefins are excellent Michael-acceptors and react with many types of nucleophilic reagents. Although alkyllithiums can be added to some nitroolefins with satisfactory yields [176-178] the addition of lithium cuprates has been far less successful [179, 180]. This may be due to the high reactivity of the resulting lithium nitronates obtained after addition, which polymerizes the starting nitroolefin. In strong contrast, copper-zinc organometallics add to a range of nitroolefins affording polyfunctional nitro compounds with excellent yields. Interestingly, the intermediate zinc-copper nitronates can be readily oxidized with ozone, affording polyfunctional ketones, such as **53** [181]. The presence of a leaving group in the β-position relative to the nitro group allows the preparation of nitroolefins (Scheme 73) [181]. A rapid synthesis of the nitrotriene **54** can be achieved by the addition of a dienyl zinc-copper reagent to β-phenylsulfonylnitroethylene, this compound is efficiently cyclised on silica gel to provide stereospecifically the bicyclic nitro derivative **55** (Scheme 73) [181]. β-Disubstituted nitroolefins are difficult to prepare by a nitro-aldol reaction due to the reversibility of this reaction, however, Denmark has developed an ingenious synthesis of these molecules using the addition of polyfunctional zinc-copper organometallics to a nitroolefin followed by a phenylselenation and oxidative elimination [182].



Scheme 73

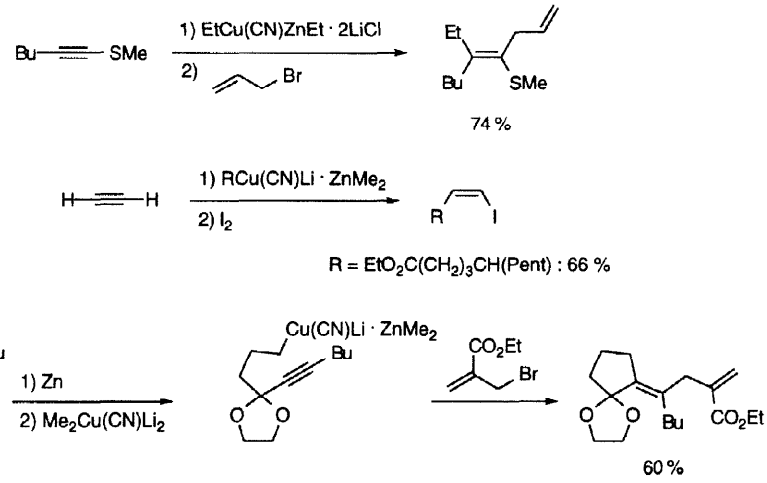
Acetylenic esters are excellent Michael-acceptors and zinc-copper reagents add efficiently. By performing the addition to ethyl propiolate at low temperature, only the (*E*)-unsaturated esters are obtained, e. g. **56** (Scheme 74). On warming up, a loss of the stereochemistry of the intermediate α-carbethoxyalkenylcopper is observed. By performing the reaction in the presence of chlorotrimethylsilane a stereochemically pure α-silylated unsaturated ester, such as **57**, is obtained [114]. The addition to higher acetylenic esters does not proceed at low temperature and the reaction mixture must be allowed to warm up. This usually results in isomerization of the alkenylcopper and produces a mixture of unsaturated *E* / *Z* esters [114]. Other acetylenic carboxylic derivatives, such as dimethyl acetylenedicarboxylate or propiolamide, similarly add zinc-copper compounds (Scheme 74) [15].





Scheme 74

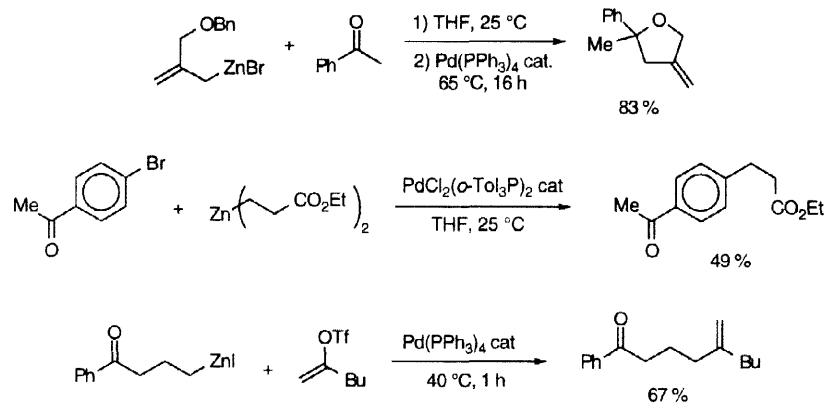
By performing the addition of *bis*-(2-carbethoxyethyl)zinc to an acetylenic ester in a solvent mixture containing HMPA, a cyclization occurs after addition to the alkyne, providing a 2-carbethoxycyclopentenone [183-186]. This new cyclization method has been applied by Crimmins to prepare a precursor of (±)-bilobalide [185]. The addition of functionalized copper-zinc reagents to less activated alkynes can be achieved by treating the zinc species with $Me_2Cu(CN)Li_2$ [186-187]. Thus, the addition to 1-thiomethylalkynes produces polyfunctional trisubstituted alkenylthioethers [186]. The addition to non-activated alkynes is not possible, but acetylene itself adds *secondary* polyfunctional zinc-copper reagents and after iodolysis affords (*Z*)-alkenyl iodides in fair yield (Scheme 75) [186]. By performing the reaction intramolecularly, the addition to a disubstituted alkyne can be achieved, this allows the steroselective preparation of cyclopentane derivatives in a satisfactory yield [186]. Substituted zinc malonates can be added to non-activated alkynes providing β,γ-unsaturated malonates [188].



Scheme 75

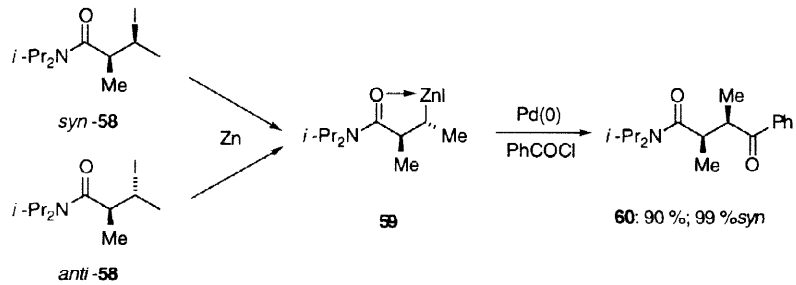
3.2.2. Palladium and nickel catalyzed reactions

Negishi demonstrated 20 years ago that various organozinc derivatives can be coupled with aryl, heteroaryl, alkenyl, and acyl halides in the presence of catalytic amounts of palladium(0) salts [189-194]. This cross-coupling reactions combines the reasonable reactivity of the zinc organometallic with a broad functional group tolerance and has found numerous synthetic applications. Polyfunctional zinc reagents [189-208] bearing groups such as a silylated acetylene [194], alkenylsilane [196-205], allylsilane [205], 1-alkoxy-acetylene [197] polythiopene [198], various substituted aromatic rings [199, 204] or heterocyclic rings [200-203], ester [189, 208], nitrile, ketone, protected α-aminoester, stannane [208] or boronic ester [209-211] have been used. Polyfunctional allylic zinc compounds have been used in elegant preparations of a range of heterocyclic and carbocyclic compounds (Scheme 76) [212-216]. The cross-coupling of zinc homoenolates with aromatic or alkenyl halides proceeds well using *bis*-(tri-*o*-tolylphosphine)palladium(II) dichloride as a catalyst (Scheme 76) [217]. Recently, some other catalysts such as $PdCl_2$(dppf) [218] and *bis*-(tri-*o*-furylphosphine)palladium(II) dichloride [219] have been reported. These new complexes having loosely bound phosphines ligands give excellent results. Besides unsaturated halides, alkenyl and aryl triflates can be used [220, 221]. This is especially advantageous when the starting triflate is readily available [61].



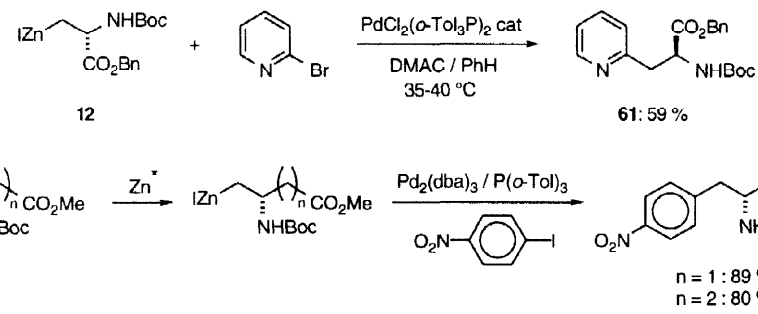
Scheme 76

The reaction of *syn*- or *anti*-3-iodo-2-methylbutanamide **58** with zinc furnish the same zinc reagent **59** which reacts diastereoselectively with aldehydes affording either C2-C3-*anti* products in the presence of TMSI, whereas after a transmetalation to a titanium(IV)-species, C2-C3-*syn* products are obtained. Acylation of **59** with acid chlorides in the presence of a palladium(0) catalyst gives the C2-C3-*syn* products of type **60** (Scheme 77) [222].



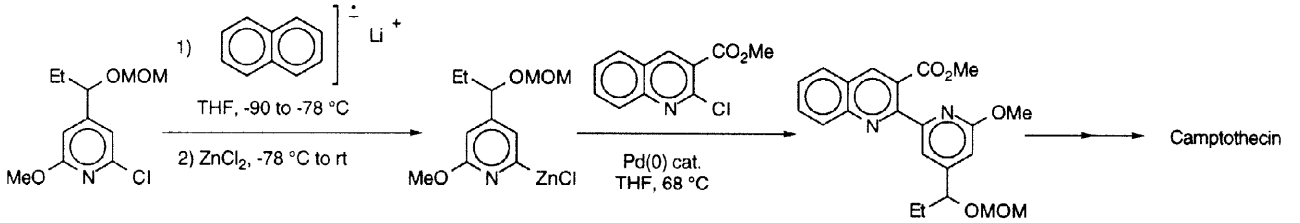
Scheme 77

New α-amino acids, such as **61**, have been prepared using a serine derived organozinc iodide (Scheme 78) [23, 105]; β- and γ-aminoacids have also been prepared starting from iodides derived from protected aspartic and glutamic acids. Zinc insertion in the carbon-iodine bond followed by palladium(0) catalyzed coupling with aromatic iodides furnished the expected β- and γ-aminoacids (Scheme 78) [223].



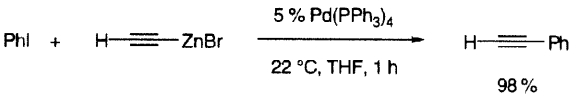
Scheme 78

Functionalized heteroaromatic zinc reagents have also been used for the preparation of complex molecules, like camptothecin, by a palladium catalyzed cross-coupling reaction (Scheme 79) [224].



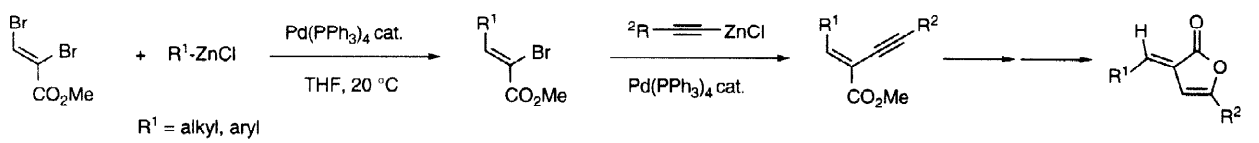
Scheme 79

The problem of a direct synthetic route to terminal alkynes *via* palladium catalyzed cross couplings has been overcome by Negishi, who has developed a procedure for coupling ethynyl zinc halides to aryl and alkenyl iodides (Scheme 80) [225].



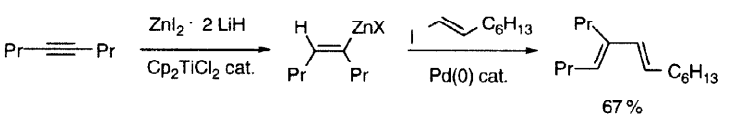
Scheme 80

Recently, Rossi has made use of the cross-coupling reaction of (*Z*)-2,3-dibromopropenoates and alkylzinc chlorides catalyzed by palladium(0). The resulting products are precursors of 5-substituted (*E*)-3-ylidene-3*H*-furan-2-ones *via* a palladium-catalyzed cyclisation (Scheme 81) [226].



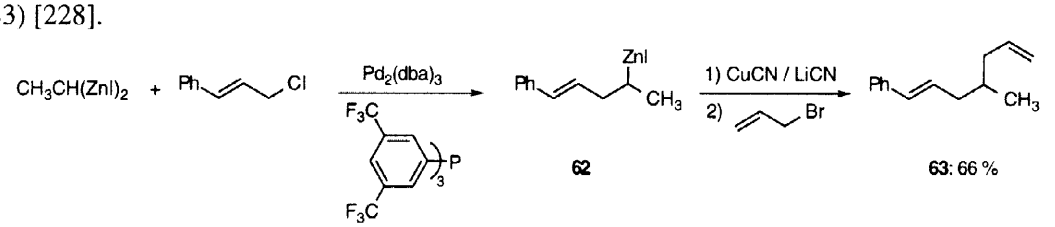
Scheme 81

Alkenylzinc reagents prepared by a titanium catalyzed hydrozincation undergo palladium cross-coupling reactions with various aryl or alkenyl iodides (Scheme 82) [227].



Scheme 82

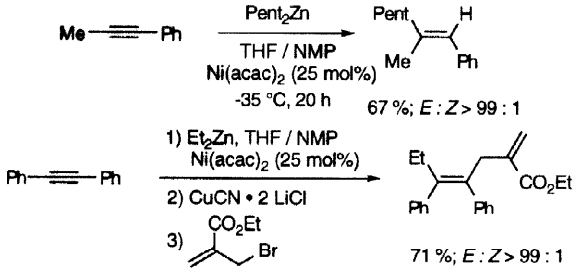
A novel use of geminal bimetallic reagents has been described by Utimoto and Matsubara, whereby *bis*(iodozinc)methane is able to undergo two sequential couplings with different electrophiles [228]. For instance, $CH_3CH(ZnI)_2$ can react under palladium catalysis with cinnamyl chloride to give the alkyl zinc iodide reagent **62**. Subsequent transmetallation to copper and reaction with allyl bromide gives diene **63** in 66 % yield (Scheme 83) [228].



Scheme 83

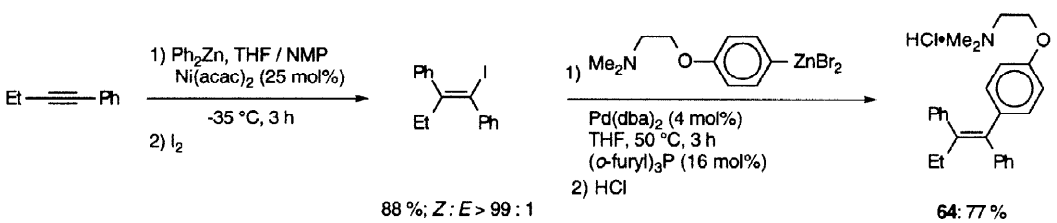
The addition of organometallics to internal alkynes seldom occurs and usually proceeds with moderate stereoselectivity. In the presence of $Ni(acac)_2$, it is possible to add diorganozincs to substituted

phenylacetylenes. The reaction occurs with high stereoselectivity (>99 % *syn*-addition) and is in many cases highly regioselective. The resulting alkenylzinc organometallics can be trapped with several types of electrophiles (Scheme 84) [229].



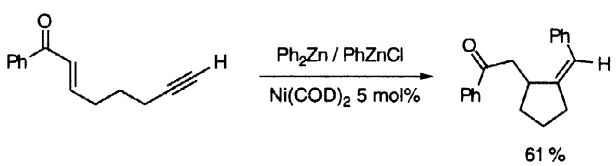
Scheme 84

Remarkably, this carbozincation procedure works well at low temperature and allows efficient addition of the relatively unreactive Me_2Zn. It was soon found that diarylzincs add even more readily and this reaction has been used to prepare Z-Tamoxifen **64** which is an antitumor drug (Scheme 85) [229].



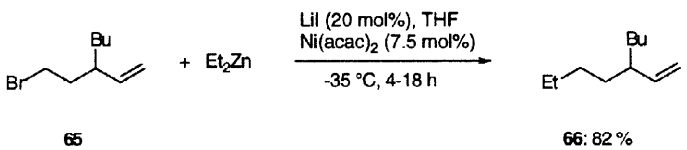
Scheme 85

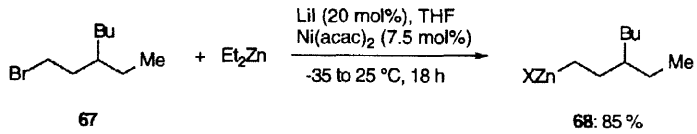
In the presence of catalytic amount of nickel(0) catalyst, organozinc halides add to alkynes and undergo a subsequent conjugate addition to an enone (Scheme 86) [230].



Scheme 86

One problem remaining to be solved in organic synthesis is an efficiently method for Csp^3-Csp^3 cross-coupling reactions using catalytic amounts of a transition metal. Whereas, organocuprates allow cross-couplings with stoichiometric amount of copper(I) organometallics, the use of catalytic amounts of a transition metal salt for performing these reactions remains a challenge. The difficulty is the reductive coupling step, which is slow with saturated organometallic intermediates such as R^1-M-R^2. By removing electron density from the metal center, such a reductive elimination should be easier [231-233]. It was observed that whereas the unsaturated alkyl bromide **65** undergoes a smooth cross-coupling reaction with Et_2Zn in the presence of $Ni(acac)_2$ leading to **66**, the corresponding saturated alkyl bromide **67** does not undergo the cross-coupling reaction but instead produces the bromide-zinc exchange product **68** (Scheme 87) [234].

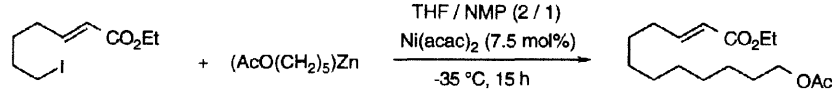




67 68: 85 %

Scheme 87

This behaviour can be rationalized by assuming that the remote double bond coordinates to the nickel center. Although a double bond bounded to a metal center behaves as a π-donor, it acts also as a π-acceptor and therefore removes electron density from the metal center facilitating the reductive coupling reaction. If the coordination of the double bond is too loose or prohibited by steric hindrance, the reductive elimination does not occur, but instead a ligand exchange reaction occurs leading to the transmetalation product [227]. The synthetic applications can be extended by using the polar cosolvent *N*-methylpyrrolidinone (NMP) which allows a variety of polyfunctional zinc organometallics to be coupled with alkyl iodides bearing a remote double bond, like **69**, giving the desired cross-coupling products (Scheme 88) [234].

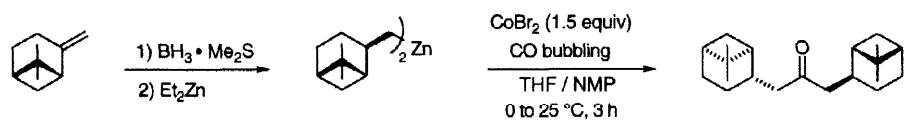


69 87 %

Scheme 88

3.2.3. Cobalt, iron and manganese catalyzed reactions

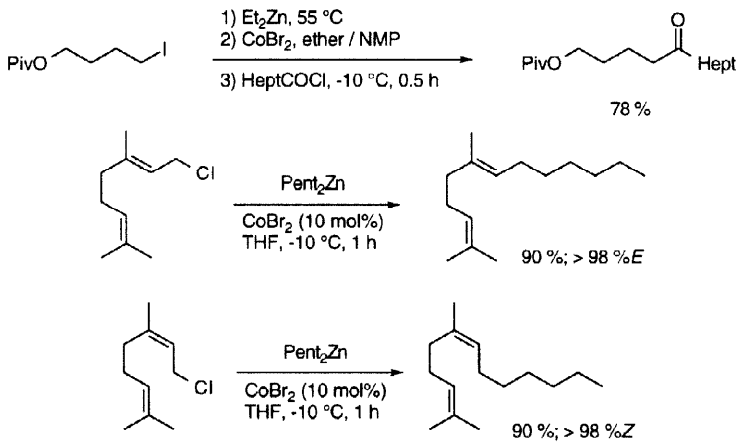
The reaction of cobalt(II) salts with organolithiums or -magnesiums leads to a fast decomposition even at low temperature giving homo-coupling products. These transmetalations have therefore found limited applications in organic synthesis [235]. It was recently found that the reaction of organozinc compounds with cobalt(II) bromide in mixtures of ether and NMP produces blue solutions of organocobalt intermediates which have a half-life time of *ca.* 40 min at -10 °C. Similarly, the reaction of iron(III) chloride with diorganozincs furnishes a grey solution of an organometallic species having an even longer half-life time (2.5 h at -10 °C). These new transition metal organometallics have interesting synthetic properties and organocobalt species prepared in this way undergo a smooth carbonylation at 25 °C furnishing symmetrical ketones in moderate to good yields [236]. Thus, starting from β-pinene, a C_2-symmetrical ketone is obtained in 48 % overall yield (Scheme 89) [236].



β-pinene > 95 % 48 %

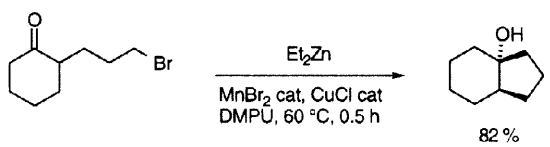
Scheme 89

Not only are stoichiometric reactions mediated by $CoBr_2$ possible but catalytic reactions can be also performed. The acylation of diorganozincs with acid chlorides in the presence of $CoBr_2$ (10 mol %) is a very rapid reaction in NMP / ether mixtures furnishing unsymmetrical ketones (Scheme 90) [237]. Allylic chlorides react with organozinc halides or diorganozincs in the presence of catalytic amounts of $CoBr_2$ [237]. These reactions lead to the S_N2-cross-coupling product with retention of the stereochemistry of the double bond. The reaction proceeds equally well with allylic phosphates (Scheme 90) [237].



Scheme 90

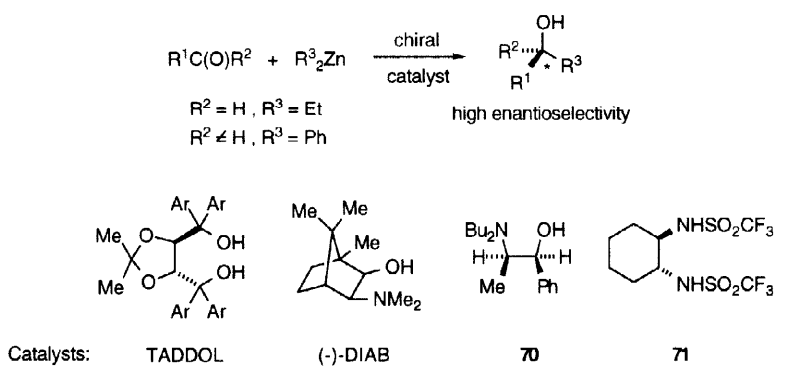
The transmetalation of zinc organometallics with manganese(II) salts does not produce functionalized organomanganese compounds. However, unsaturated alkyl bromides in the presence of Et_2Zn and a mixed metal salt system made of copper(I) chloride / manganese(II) bromide [238], give cyclization products in satisfactory yields (Scheme 91) [57, 239].



Scheme 91

4. Asymmetric reactions mediated by zinc organometallic reagents

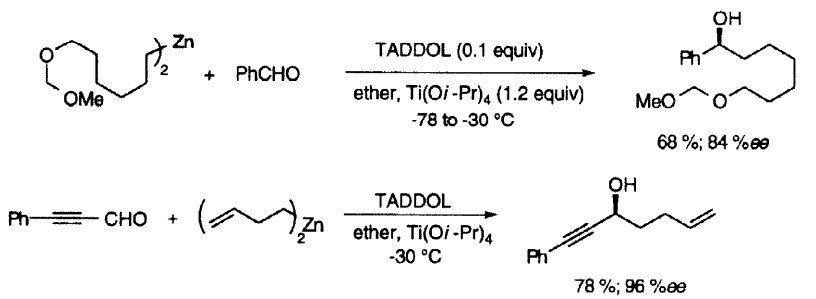
It has been shown that diethylzinc can be added to aldehydes in the presence of chiral catalysts with high enantioselectivity (Scheme 92) [32, 240-260]. Fu has also recently reported the high enantioselective catalytic asymmetric addition of diphenylzinc to ketones (Scheme 92) [261].



Scheme 92

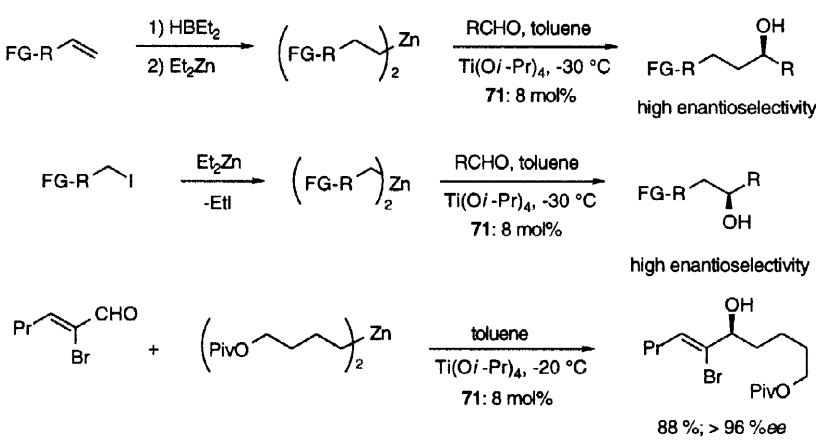
The addition of diorganozincs other than diethylzinc, especially functionalized organometallics, to carbonyl compounds is of great synthetic interest. Since diethylzinc is among the most reactive organozinc reagents, the use of a very active catalyst is essential if higher dialkylzincs or functionalized zinc reagents are to be used. Yoshioka and Ohno [241] and Seebach [242-260] found that the addition of titanium alkoxides to chiral ligands produces titanium complexes of very high catalytic activity which allow the addition of diethylzinc to various

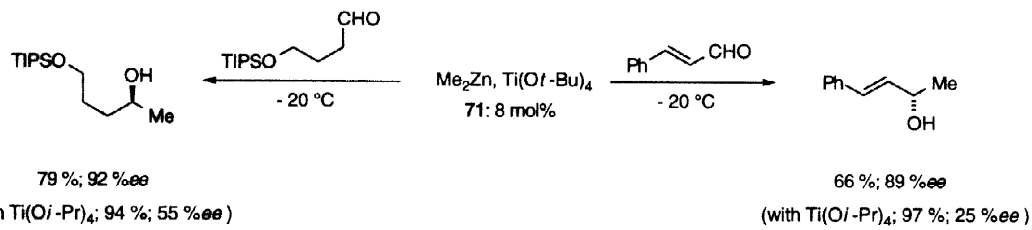
aldehydes with high enantioselectivity and very mild conditions. These active catalysts also allow the addition of higher dialkylzincs or polyfunctional zinc reagents. Seebach found that the transmetalations of alkenyl magnesium halides with zinc chloride in ether followed by the addition of 1,4-dioxane constitutes a convenient method for preparing higher salt-free dialkylzincs [246]. A few functionalized dialkylzincs can be obtained by this method and have been added to aldehydes in the presence of TADDOL with high enantioselectivity (Scheme 93) [246]. Functionalized propargylic alcohols with high optical purity can be prepared by the addition of *bis*-(3-butenyl)zinc to acetylenic aldehydes using this catalyst (Scheme 93) [248]. Interestingly, lithium and magnesium reagents can also be directly converted to trialkoxytitanium organometallics. This approach allows a more efficient transfer of the organic moiety to the aldehyde, since by using dialkylzincs no more than one of the two organic groups is transferred to the aldehyde [249].



Scheme 93

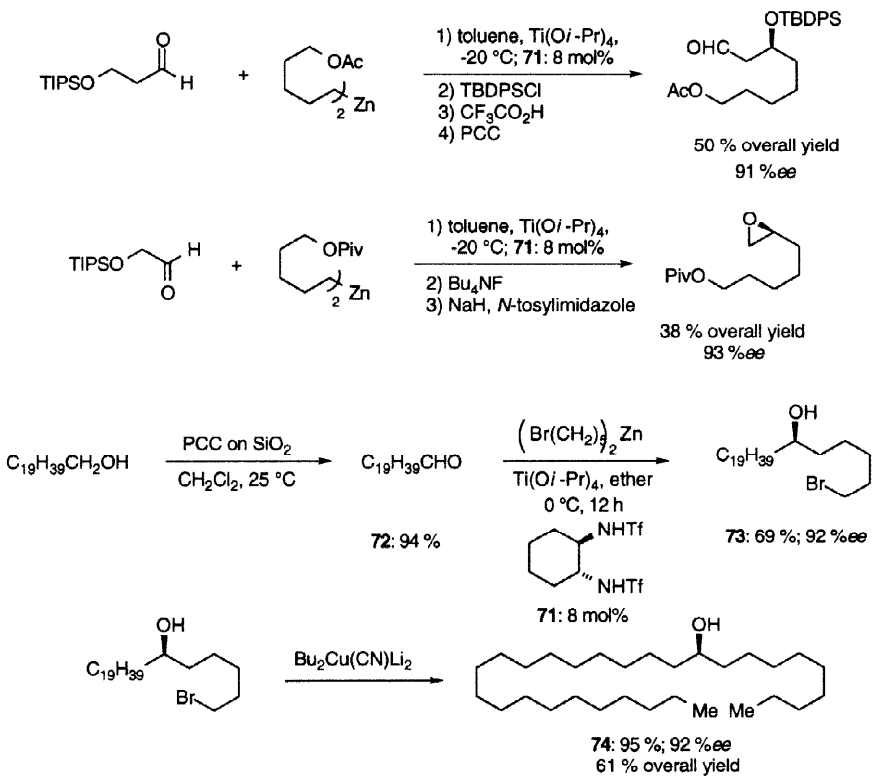
The iodine-zinc exchange reaction and the boron-zinc transmetalation are very general methods for preparing polyfunctional zinc organometallics. The reagents obtained in this way have found extensive applications in asymmetric additions to aldehydes (Scheme 94) [256-260, 262-267]. The *bis*-triflamide **71** is an excellent catalyst for these reactions and allows large structural variations of the substrates. The enantioselectivities are good for aromatic or aliphatic aldehydes. α,β-Unsaturated α-bromoaldehydes react well and allow the preparation of a broad range of polyfunctional allylic alcohols with high enantioselectivity (Scheme 94) [266]. In the absence of the α-bromine, it is possible to obtain excellent enantioselectivities by replacing the cocatalyst Ti(O*i*-Pr)4 by Ti(O*t*-Bu)4 [257].





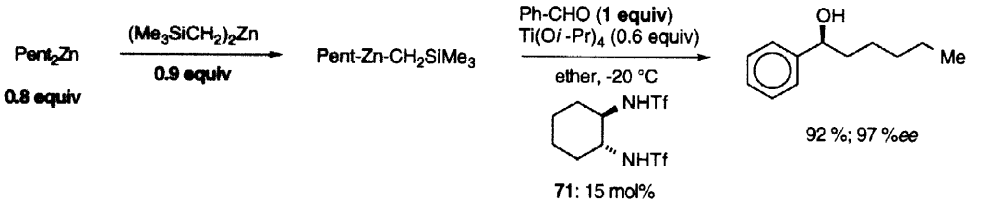
Scheme 94

By using α-alkoxyaldehydes, epoxides can be obtained with good enantioselectivities (Scheme 95) [262]. Applications to the synthesis of natural products have been reported. Thus, the addition of *bis*-(5-bromopentyl)zinc prepared *via* a boron-zinc transmetalation to the long-chain aldehyde **72** provides the bromo-alcohol **73** with 92 % *ee* (Scheme 95). Alkylation of this bromide with $Bu_2Cu(CN)Li_2$ produces 10-nonacosanol (ginnol, **74**) in three steps (61 % yield and 92 % *ee*) [37, 110].



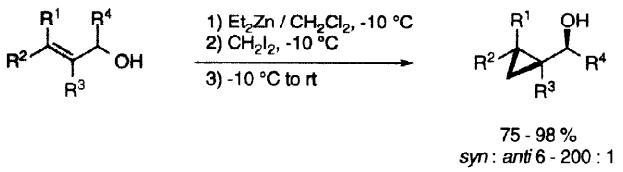
Scheme 95

A drawback of this last method is the requirement of large amounts of the functionalized diorganozinc (2-3 equiv). This problem can be solved by using the mixed zinc reagents FG-R-$ZnCH_2SiMe_3$. In this case only a small excess (0.8 equiv of $(FG\text{-}R)_2Zn$; 1.6 equiv of FG-R-groups) is necessary and high enantioselectivities are still obtained (Scheme 96) [88].



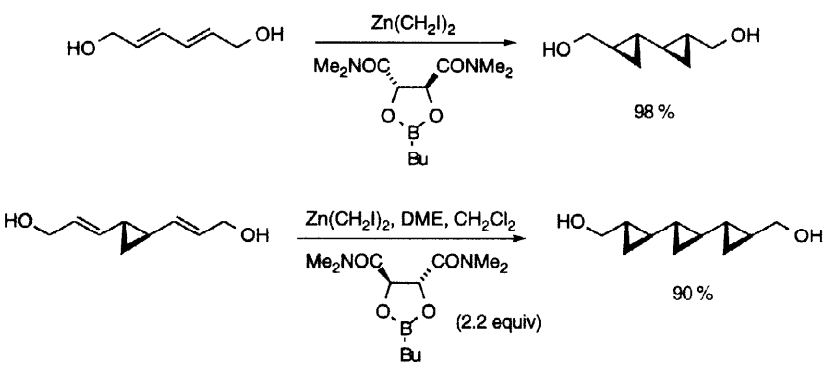
Scheme 96

Recently, the Simmons-Smith reagent has found renewed interest, either for conversion of β-keto esters to γ-keto esters [268], or in the stereoselective cyclopropanation of allylic alcohols. Thus, the cyclopropanation of allylic alcohols with zinc carbenoids ($Zn(CH_2I)_2$) has made significant progress [269] and has found useful applications in natural product synthesis (Scheme 97) [270].



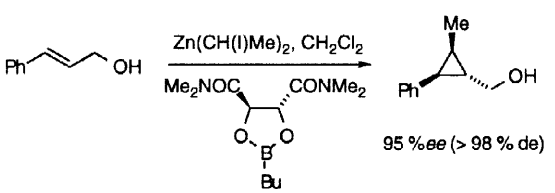
Scheme 97

This highly enantioselective method has been used to prepare chiral polycyclopropanic compounds which are important intermediates for the preparation of biologically active molecules, in the presence of a chiral dioxaborolane ligand (Scheme 98) [271].



Scheme 98

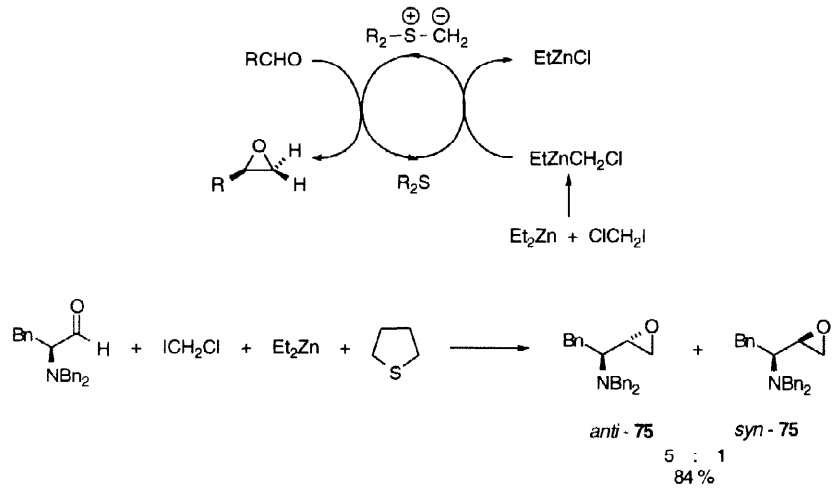
The method has been extended to other zinc carbenoids like $(CH_3CHI)_2Zn$ allowing the diastereo- and enantioselective preparation of cyclopropanes (Scheme 99) [272].



Scheme 99

Recently Aggarwal has utilised the Simmons-Smith reagent in a novel epoxidation procedure [273]. Treatment of $EtZnCH_2Cl$ with tetrahydrothiophene and an aldehyde results in formation of a sulfur ylid *in situ*, this in turn

reacts with a variety of aldehydes giving epoxides in good to excellent yields. Unsaturated aldehydes are also tolerated without any competing cyclopropane formation (Scheme 100) [273].



Scheme 100

The epoxide **75** derived from phenylalanine is extremely important as it is a key intermediate in the synthesis of many HIV protease inhibitors. In this case, this novel methodology avoids the previously reported racemization that occurs in the ylide epoxidation process.

5. Conclusion

The reactions between various polyfunctional organozinc derivatives and organic electrophiles provides an expeditive access to numerous polyfunctional molecules. The high functional group compatibility allows a unique diversity for zinc organometallic reagent. After transmetalation by the addition of catalytic quantities of transition metal salts like Cu(I), Pd(II), Ni(II), Co(II), Co(III), Fe(III), Mn(II) smooth reactions can usually be obtained. The applications of organozinc compounds range from asymmetric synthesis, the preparation of biologically relevant molecules and new materials to combinatorial chemistry. It can be predicted that a broader range of applications will be developed in the future.

Acknowledgements

The authors thank the Leibniz programm for generous financial support and Mrs. Birgit Schmidt for typing this manuscript. Juan J. Almena Perea thanks the Alexander von Humbolt Foundation for a fellowship. Philip Jones thanks the Royal Society for an award under the European Science Exchange Program.

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Paul Knochel, born in 1955 in Strasbourg, France, completed his Ph.D. under the supervision of Prof. Dieter Seebach in 1982 (ETH Zürich). He joined the CNRS in Paris and worked in the laboratory of Prof. Jean-François Normant until 1986. After a year of postdoctoral research at Princeton University with Prof. Martin F. Semmelhack, he became assistant professor at the University of Michigan, Ann Arbor (USA) and full professor in 1991. In 1992, he moved back to Europe and accepted a professorship at the Philipps-Universität Marburg (Germany). In 1994, he was awarded the Thieme-IUPAC prize in Synthetic Organic Chemistry, in 1995, the Otto-Bayer prize and in 1996 the Leibniz prize. He is the author of ca. 200 research publications and runs a research group of 15-18 members. His research is focused on the use of organometallic reagents for the development of new synthetic methodologies in organic synthesis. New research topic involve the development of new asymmetric metal catalyzed reactions, the performance of reactions in perfluorinated solvents and reactions on the solid phase for combinatorial chemistry.

Juan J. Almena Perea was born in Alicante, Spain, in 1969. He completed his Ph.D. under the supervision of Professor Miguel Yus and Dr. Francisco Foubelo in Alicante. Since February 1997 he is making a post-doctoral stay in the group of Professor Paul Knochel at Philipps-Universität in Marburg. He is currently an Alexander von Humboldt Fellow. His research interests include the use of functionalized organometallic reagents in organic synthesis and the synthesis of phosphine ligands with a ferrocene basis.

Philip Jones, was born in Chatham, England, in 1971 and obtained his BSc from the University of Southampton in 1993. He then moved to the University of Nottingham where he completed his Ph.D. in 1996 under the supervision of Prof. G. Pattenden, F. R. S., working on radical cascades directed towards polycycle construction. Since 1997 he has been working as a Royal Society European Science Exchange Fellow with Prof. P. Knochel on the application of organozinc reagents to organic synthesis.