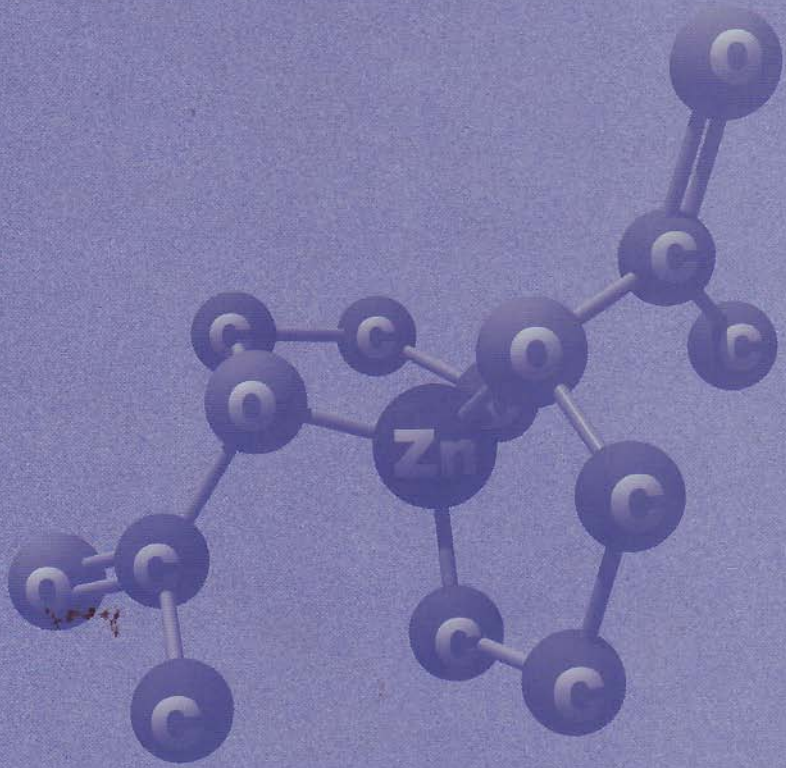
PRACTICAL APPROACH IN CHEMISTRY

ORGANOZINC REAGENTS

A PRACTICAL APPROACH

PAUL KNOCHEL AND PHILIP JONES



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Organozinc Reagents

A Practical Approach

Edited by

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Preface

Despite the widespread use of organometallic reagents in modern day organic synthesis, there exists a perception that these reagents are incompatible with many functional groups that are required for targeting current synthetic endeavours. While this is true, in part, of organolithium and Grignard reagents, organozinc reagents by no means hold to this classification, and will indeed tolerate a wide spectrum of functionality. The aim of this volume is to show the synthetic opportunities offered by these extremely versatile reagents. Numerous applications of organozinc reagents have appeared in the literature over the last 10 years giving these 150-year-old organometallics a real renaissance. We have concentrated on the most general and useful procedures, involving the synthesis and reactivity pattern of organozinc reagents, in this volume.

This book continues the tradition established by preceding volumes in the *Practical Approach in Chemistry* series by providing insight of what can be achieved using these resourceful reagents, but also, and very importantly, the Protocols required to achieve the desired end result.

The individual chapters are written by leading authorities in that field, who themselves know and have passed on the 'tricks of the trade' to ensure the success of the Protocols described. The layout of the volume is such as to first illustrate the numerous methods for preparing organozinc reagents, and then to demonstrate the potential afforded by these mild and highly selective reagents. Hopefully, this volume will convince the reader that organozinc reagents offer an efficient and elegant opportunity for organic synthesis, by providing an concise synthetic route to a target molecule without the need for a highly laborious and costly protection–deprotection sequence, typically associated with classical methods.

A project of this size is not possible without the co-operation and enthusiasm of numerous people. We would like to thank all the contributors to this book for sharing their knowledge and experience, and for providing such stimulating accounts of their own and others' research. Particular thanks are due to Mrs. Birgit Schmidt and Mrs. Ina Pinnschmidt for their valuable assistance, especially with our own chapters. Finally, we would also like to acknowledge the Royal Society for providing a fellowship to enable P. J. to work in Marburg.

Marburg P. K.
June 1998 P. J.

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Abbreviations

acac	acetylacetonate
AN	acetonitrile
bpy	2,2′-bipyridine
DMA	*N*,*N*-dimethylacetamide
DMF	dimethylformamide
GC	gas chromatography
NMP	*N*-methylpyrrolidinone
PFH	perfluorohexanes
rt	room temperature
TG	triglyme
THF	tetrahydrofuran
TLC	thin-layer chromatography

1

Organozinc chemistry: an overview and general experimental guidelines

PAUL KNOCHEL, PHILIP JONES, and FALK LANGER

1. Introduction

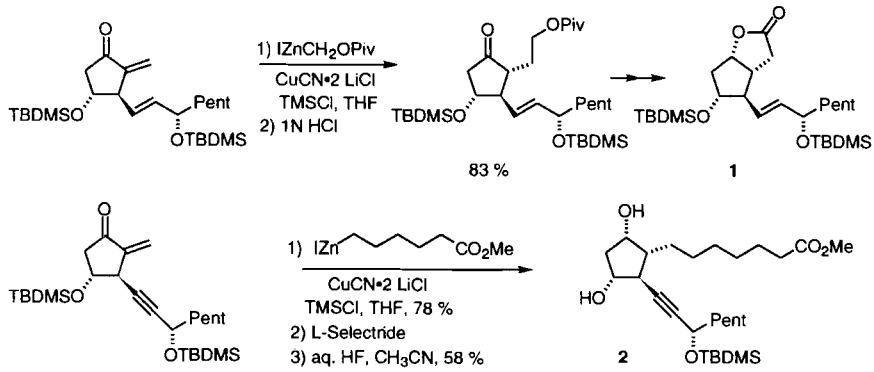
Zinc is found in a relatively low abundance in nature, but has been known for a long time due to the ease with which it is isolated from its ores. Despite the low occurrence, the ease of isolation results in today, zinc metal and zinc salts being available at low cost from the usual chemical suppliers.

Zinc is a relatively non-toxic metal and is an essential element for humans and all forms of plant and animal life, and a large number of diseases and congenital disorders have been traced to zinc deficiency. Among the metalloproteins and metalloenzymes,[1] zinc species constitute the largest category and their biological functions are diverse and important, including carboxypeptidases, carbonic anhydrase, and metallothioneins. Small amounts of zinc salts are also essential for the growth of animals and plants.

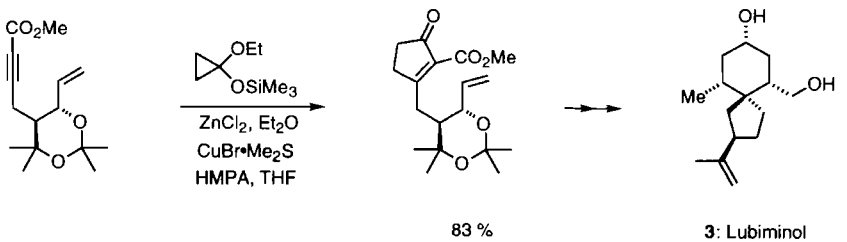
Although almost ignored for more than 100 years after their discovery, organozinc compounds are today one of the most useful class of organometallic reagents for organic and organometallic synthesis. The combination of their easy preparation, high functional group compatibility, and excellent reactivity in the presence of the appropriate catalyst, means, organozincs have found numerous applications in organic and organometallic chemistry. These attributes are clearly illustrated in the preparation of prostaglandin intermediates **1** and **2** (Scheme 1.1),[2] whereby functionalized zinc reagents react chemoselectively and in excellent yield with highly advanced synthetic intermediates.

A further example of the effectiveness of these reagents is demonstrated in the synthesis of the complex spiroventivane phytoalexin-lubiminol **3** (Scheme 1.2).[4] Generation *in situ* of a zinc homoenolate, $EtO_2C(CH_2)_2ZnCl$,[3] allows formation of the functionalized cyclopentenone intermediate, essential for the synthesis.

The excellent reactivity of organozinc reagents in the presence of the

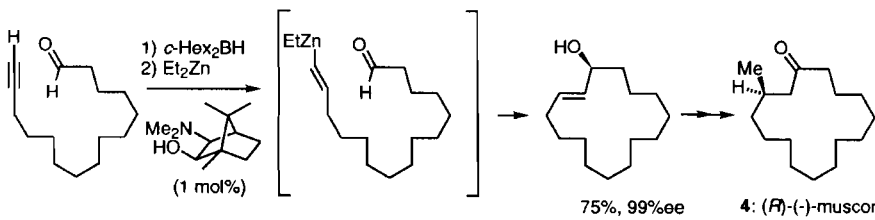


Scheme 1.1



Scheme 1.2

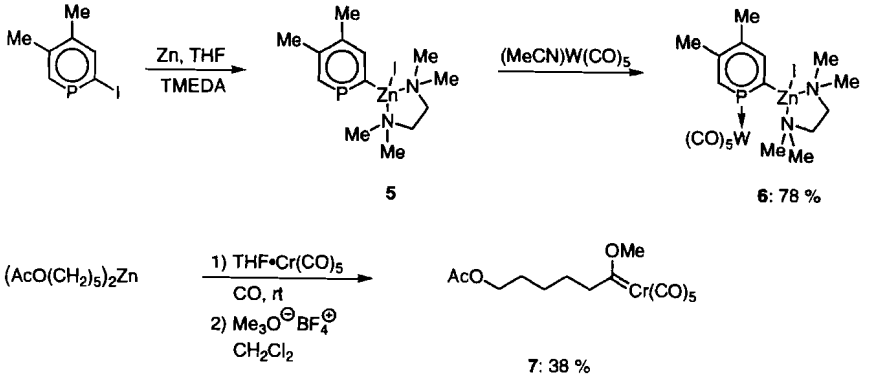
appropriate catalyst has resulted in these reagents being used extremely successfully for catalytic asymmetric reactions.[5] In these reactions, diorganozincs (R_2Zn) have proved to have tremendous synthetic potential, clearly illustrated in the enantioselective synthesis of (*R*)-muscone **4** using a mixed alkenyl(ethyl)zinc reagent (Scheme 1.3).[6]



Scheme 1.3

A further asset of this class of reagents is the covalent character of the zinc–carbon bond, this allows these organozinc reagents to undergo transmetallation reactions smoothly and cleanly with a wide variety of transition metal salts. Thus, the zincated phosphine **5** can be reacted with (acetonitrile)

pentacarbonyltungsten ($CH_3CN{\bullet}W(CO)_5$) furnishing the complex **6** in 78% yield.[7] Similarly, a one-pot preparation of polyfunctional chromium carbene complexes, such as **7**, is possible although in moderate overall yield (Scheme 1.4).[8]



Scheme 1.4

These few examples demonstrate the broad range of the synthetic potential of organozinc compounds and provide a foretaste of what can be achieved with these highly effective and synthetically valuable reagents.

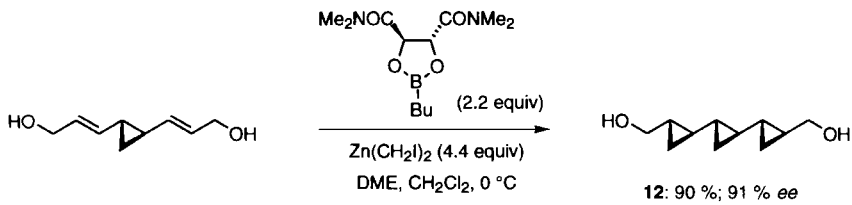
2. Historical perspective

Historically, organozinc chemistry starts with the birth of organometallic chemistry. Nearly 150 years ago Frankland, whilst working on the search for the preparation of ethyl radicals at the Philipps-Universität in Marburg, Germany in 1849, discovered that the heating of ethyl iodide with zinc powder gives highly pyrophoric diethylzinc. This colourless liquid (b.p. 27 °C/30 mmHg) reacts violently with water and explodes in oxygen. Amazingly, hydrogen gas was used by Frankland as a protective atmosphere for this reaction.[9,10] The reactivity of these organozinc compounds towards organic electrophiles like acid chlorides, aldehydes, or esters, was examined in a systematic way before 1880.[11] However, the low reactivity observed, together with the moderate yields obtained in many of these reactions, consequently led to their replacement at the turn of the century by the more reactive organomagnesium reagents.[11,12] During the first-half of this century zinc reagents found few synthetic applications and only zinc enolates (Reformatsky reaction)[13] were routinely used. Despite the synthetic potential of zinc reagents as a source of polyfunctional organometallic reagents being described in the patent literature, it was not until 1942 that Hunsdiecker prepared several functionalized zinc reagents.[14] By the insertion of zinc powder into various alkyl iodides bearing an ester

function at a remote position, Hunsdiecker was able to prepare reagents of type **8**.

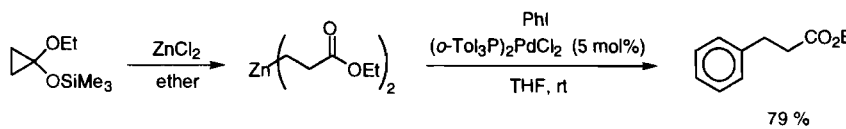
$RO_2C(CH_2)_nZnI$	$PhCO_2CH_2ZnI$	$PhCO_2(CH_2)_4ZnI$	ICH_2ZnI
8: n > 5	**9**	**10**	**11**

20 years later, Wittig and Jautelat reported the preparation of new functionalized zinc reagents **9** and **10**. The zinc carbenoid **9**[15,16] and the related iodomethylzinc iodide **11** proved to be very useful reagents in cyclopropanation reactions (Simmons–Smith reaction).[17] Recently, the asymmetric version of this reaction has been developed, and its use has led to the impressive preparation of polycyclopropanated materials, like **12** an intermediate necessary for the total synthesis of natural product (+)-U-106305 (Scheme 1.5).[18]



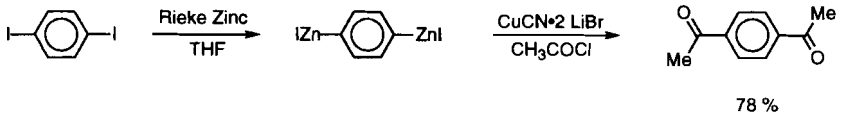
Scheme 1.5

Further advances in the field of organozinc chemistry were made by harnessing the chemistry of homoenolates pioneered by Nakamura and Kuwajima,[3] together with Negishi's discovery that palladium(0) complexes are able to catalyse the cross-coupling reaction of organozincs with unsaturated organic halides.[19] These revelations opened the way to modern organozinc chemistry (Scheme 1.6).[3]



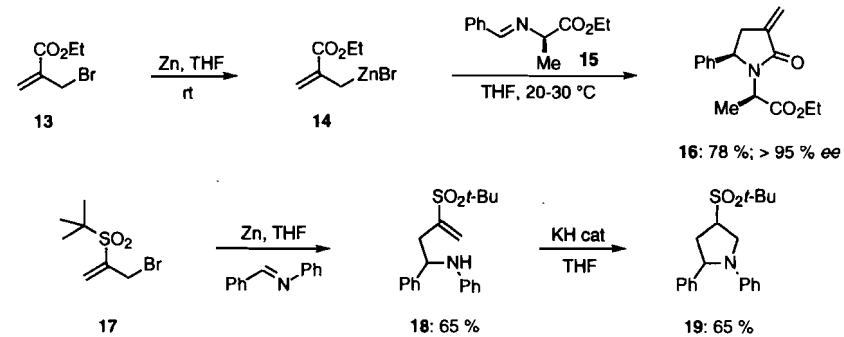
Scheme 1.6

At this time the applicability of organozinc chemistry had been limited to those zinc reagents that could be prepared by insertion of zinc powder into the corresponding alkyl iodide.[20] Further developments, notable the use of highly reactive zinc (Rieke zinc), obtained by the reduction of zinc halides with lithium naphthalenide, allowed the preparation of zinc reagents from otherwise unreactive organic substrates, such as aryl iodides and aryl bromides (Scheme 1.7).[21]



Scheme 1.7

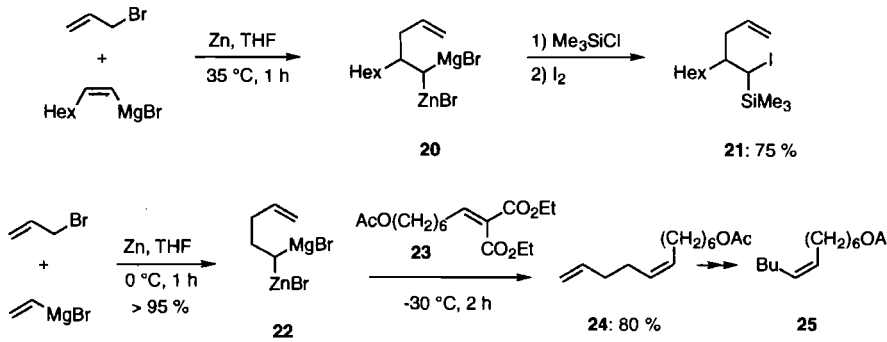
Gaudemar was also able to prepare allylic zinc reagents in high yield.[22] These reagents constitute an ideal source of a nucleophilic allylic anion, because preparation of the corresponding allylic lithium and magnesium compounds is normally accompanied by a significant amount of the homo-coupled compound. The preparation of functionalized allylic zinc reagents is possible and accordingly has been exploited in organic synthesis (Scheme 1.8).[23–26] Thus, the reaction of zinc dust with ethyl (α-bromomethyl)acrylate **13**[23] in THF at room temperature provides the zinc reagent **14** in > 80% yield. Subsequent reaction with the chiral imine **15** furnishes only one diastereomeric lactam **16**.



Scheme 1.8

In some cases, such as with the allylic bromosulfone **17**, the best reaction conditions to add to imines are obtained under Barbier conditions, reaction in this manner gives the unsaturated aminosulfone **18**. Treatment with catalytic potassium hydride, results in a 5-*endo*-trig cyclization to form the pyrrolidine **19** in 65% yield (Scheme 1.8).[25,26]

Further work by Gaudemar has shown that allyl zincation of alkenyl magnesium species allows the preparation of novel 1,1-bimetallic reagents of type **20**, bearing both zinc and magnesium.[27] The different reactivities of the two metals can be exploited, and a stepwise reaction with two different electrophiles can be achieved to furnish products of type **21**.[28] The potential of this chemistry has recently been shown in pheromone synthesis (Scheme 1.9).[29] Thus, the 1,1-bimetallic species **22** undergoes an olefination reactions with the alkylidenemalonate **23** leading stereospecifically to the (*Z*)-diene **24** in 80% yield. Hydrogenation of the terminal double bond furnishes the pheromone **25** in excellent overall yield.

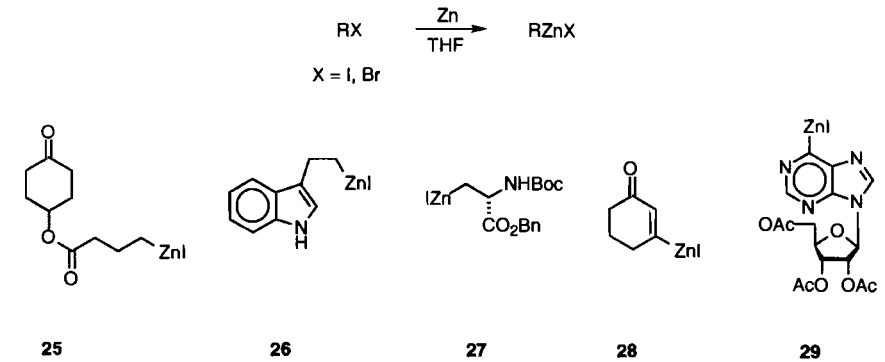


Scheme 1.9

3. Scope of organozinc chemistry

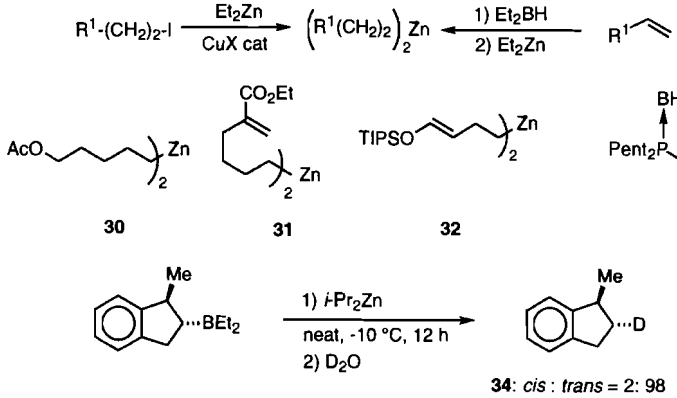
3.1 Nature of the organozinc reagents

There are three main classes of organozinc compounds: organozinc halides ($RZnX$); diorganozincs (R_2Zn); and lithium or magnesium zincates ($M^+R_3Zn^-$; M = Li or MgX). These bear in turn one, two, or three organic groups attached to the zinc metal centre. Organozinc halides are readily available by the direct insertion of zinc dust into organic halides.[20] This synthetic approach is very general and allows the preparation of a broad range of polyfunctional zinc reagents, such as **25–29** (Scheme 1.10).[31–35]



Scheme 1.10

Diorganozinc reagents (R_2Zn) require different methods of preparation and recently the iodine–zinc exchange and the boron–zinc exchange reactions have been developed.[30] These methods are applicable to primary[30] and secondary[36,37] diorganozinc species (Scheme 1.11).[38–41]

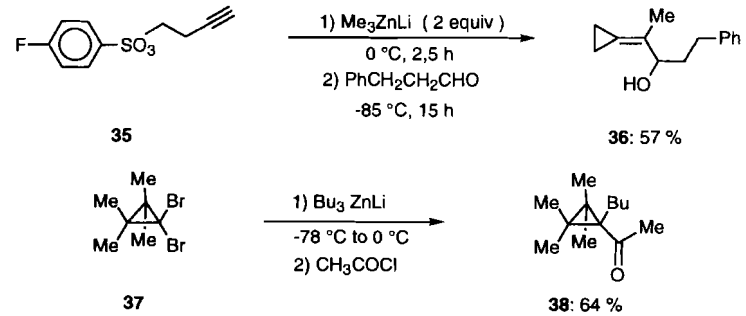


Scheme 1.11

Remarkably, by utilizing *i*-Pr_2Zn for the boron–zinc exchange reaction, configurational well defined secondary dialkylzinc reagents, like **34**, have been prepared for the first time (Scheme 1.11).[37]

Diorganozinc reagents display an enhanced chemical reactivity compared to alkylzinc halides and furthermore, they are better suited for applications in asymmetric synthesis.[38,39]

More reactive than diorganozincs are lithium or magnesium zincates which are readily prepared by transmetallation reactions from the corresponding magnesium or lithium reagents.[42–46] These highly reactive organozinc species are well suited for iodine–zinc exchange reactions.[45,46] They also undergo synthetically useful 1,2-migration reactions (Scheme 1.12).[47,48]



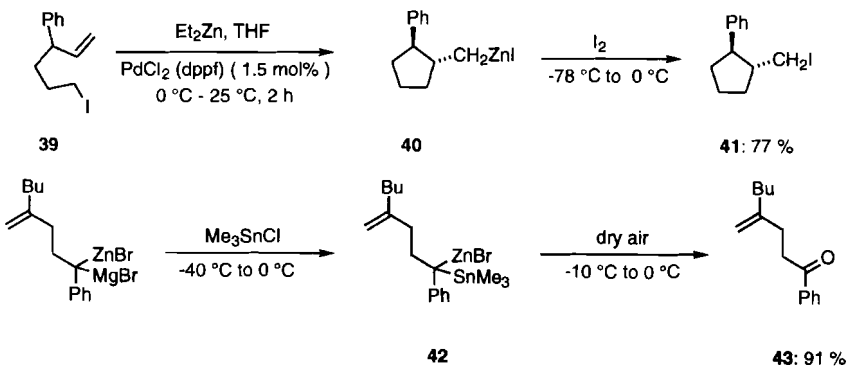
Scheme 1.12

The zincation of the acetylenic sulfonate **35** furnishes an intermediate lithium alkynylzincate which undergoes a 1,2-migration of a methyl group, followed by a cyclization, leading to a cyclopropylidenylzinc derivative. This intermediate can then be quenched with an aldehyde, resulting in the allylic

alcohol **36** in 57% overall yield.[47] Similarly, the 1,1-dibromocyclopropane **37** was converted to the ketone **38** after acylation of the intermediate zinc reagent.[48]

3.2 Uncatalysed reactions of organozinc reagents

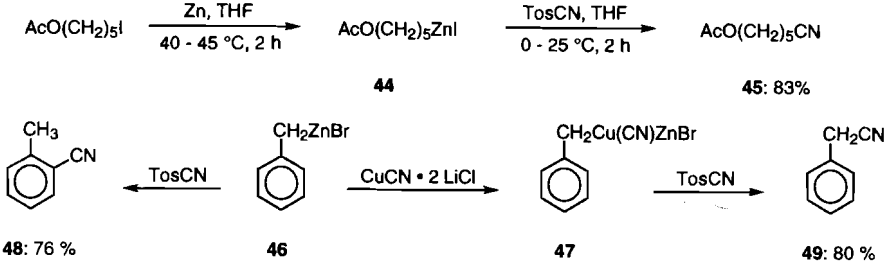
As mentioned above, organozinc reagents show a moderate reactivity towards many organic electrophiles, however, reactions such as halogenation,[49] oxidation,[50] cyanation,[51] phosphorylation,[52] and in some cases stannylation[53] and silylation[35] proceed even in the absence of any catalyst. Thus, the treatment of the unsaturated alkyl iodide **39** with Et_2Zn in the presence of catalytic amounts of dichloro(1,1′-*bis*(diphenylphosphino)ferrocene)palladium(II) ($PdCl_2$(dppf))[54] furnishes the cyclized *trans*-cyclopentylmethylzinc iodide **40**. This cyclization proceeds by a radical mechanism and affords a stereochemically well defined organozinc reagent (**40**).[55] The organozinc halide is then cleanly converted to the corresponding alkyl iodide **41** by treatment with iodine (–78°C to 0°C; 77% yield). Similarly, the oxidation of zinc organometallics is a very fast and efficient reaction, for example, the bimetallic reagent of tin and zinc **42** is oxidized by dry air and gives the ketone **43** in 91% yield via a peroxozinc intermediate[56] (Scheme 1.13).



Scheme 1.13

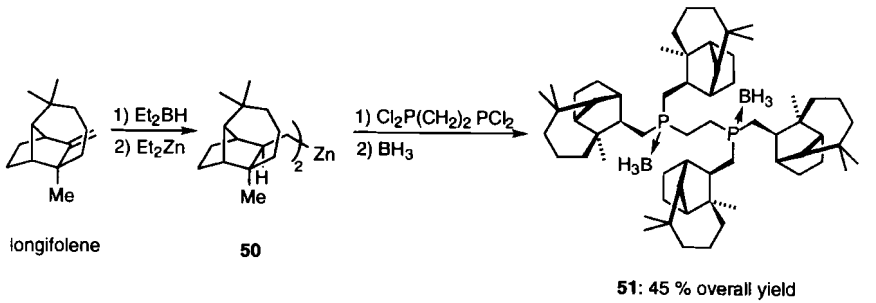
Normally tosyl cyanide reacts with the functionalized zinc reagents, such as **44**, to provide the expected nitrile **45** (0°C to 25°C, 2 h). However, the benzylic zinc reagent **46** and the corresponding copper–zinc reagent **47** react with tosyl cyanide differently. Whilst the zinc reagent furnishes the S_E2' substitution product **48** (functionalization at the ortho position of the phenyl ring), the zinc–copper compound leads to the direct (S_E2) substitution product **49** (Scheme 1.14).[51]

The direct phosphorylation of zinc organometallics provides an efficient



Scheme 1.14

and general way to polyfunctional phosphines. The hydroboration of longifolene furnishes, after boron–zinc exchange the *bis*-longifolylzinc **50**, this then reacts in a one-pot procedure with $Cl_2P(CH_2)_2PCl_2$. After borane protection, the chiral diphosphine–borane complex **51** is obtained in 45% overall yield (Scheme 1.15).

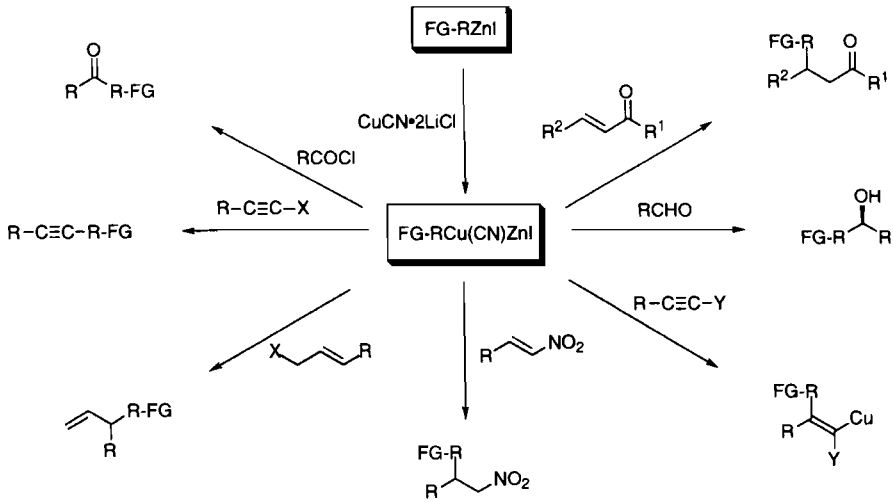


Scheme 1.15

3.3 Catalysed reactions of organozinc reagents

By far the most widely used reaction of organozinc compounds is transmetallation and subsequent reaction. The transmetallation of zinc organometallics with most transition metal salts occurs readily, leading to reactive transition metal intermediates, which can undergo new carbon–carbon bond formations with a range of organic electrophiles. Despite nearly all transition metals reacting, interestingly no transmetallation could be achieved with MnX_2 or $CeCl_2$. In the presence of a palladium(0) catalyst, cross-coupling reactions with unsaturated halides or tosylates proceed readily (Negishi reaction).[19] Whilst, in the presence of stoichiometric, or in some cases catalytic amounts of a copper(I) salt, preferentially the THF soluble salt CuCN•2LiCl, new organocopper intermediates are formed. These copper–zinc reagents, tentatively formulated as RCu(CN)ZnI, react with the same electrophiles as the copper species derived from lithium or magnesium reagents under the

appropriate reaction conditions (Scheme 1.16).[20] A considerable advantage over the lithium- or magnesium-derived copper compounds, is that the organozinc precursor can be heavily functionalized. These methods then provide an access to reactive polyfunctional copper organometallic reagents.

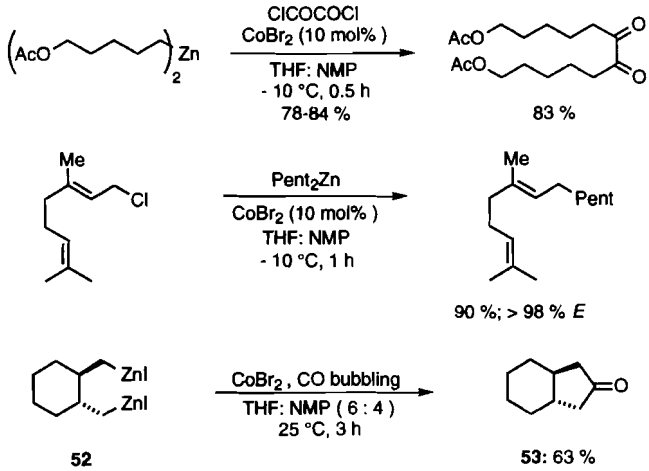


Scheme 1.16

Occasionally, under the appropriate conditions zinc organometallics can undergo monoelectron transfer reactions making these reagents suitable for transmetallation with late transition metal complexes. Thus, in the presence of catalytic amount of cobalt(II) or iron(III) chlorides, acylations and highly regioselective allylations can be performed.[57] The carbonylation of organozinc halides is also possible under mild conditions (atmospheric pressure, 25 °C).[58] In the case of an organo *bis*-zinc halide, like **52**, cyclization reactions can be undertaken, in this instance the chiral C_2-symmetrical cyclopentanone **53** is produced in satisfactory yield (Scheme 1.17). Palladium catalysed carbonylation can also be carried out using zinc organometallics.[59]

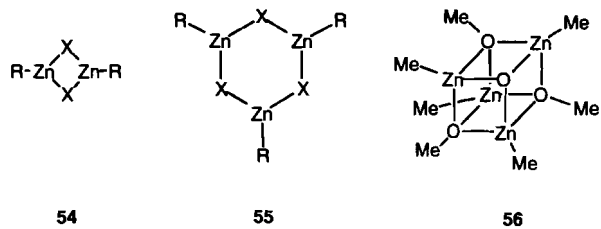
3.4 Structures and physical properties of organozinc reagents

The structure of organozinc reagents has been well studied and the complex forming ability of organozinc reagents is well known.[60] Diorganozincs (R_2Zn) are, with the exception of dialkynylzincs, always monomeric compounds, therefore the lower dialkylzincs are volatile liquids, whereas the higher dialkylzincs are oils or solids. On the other hand, organozinc halides (RZnX) form dimers or higher associates via halogen bridges, like **54** or **55**



Scheme 1.17

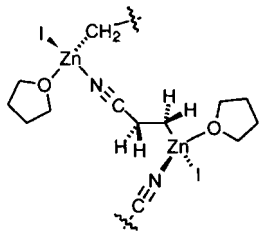
(Scheme 1.18). More complex structures have been observed with organozinc alcoholates like **56**.[61]



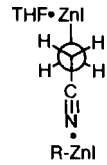
Scheme 1.18

Functionalized organozinc iodides, like 2-cyanoethylzinc iodide **57**, lead to polymeric structures where the functional group (cyano group) coordinates to the zinc centre (Scheme 1.19).[62] In the compound **57**, the carbon–zinc bond length is 2 Å and there is almost a perfect antiperiplanar arrangement between the C–ZnI bond and the C–CN bond, **57a**. A relatively long C–CN bond (1.5 Å compared to 1.44 Å) reflects the tendency of this zinc reagent to eliminate the β-CN group.[62]

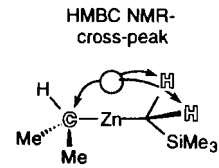
Under the appropriate conditions diorganozincs rapidly exchange their ligands and the mixing of two different diorganozincs R^1_2Zn and R^2_2Zn results in the formation of mixed dialkylzincs.[63] This rapid exchange reaction has been recently used to prepare mixed diorganozincs $RZnCH_2SiMe_3$ in which the Me_3SiCH_2 group plays the role of a non-transferable ligand. The proof of the existence of the mixed species has been established by 2D NMR experiments



57



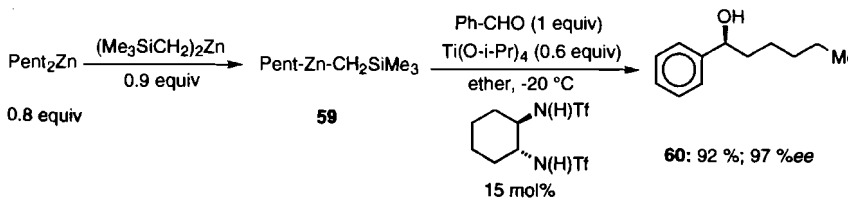
57a



58

Scheme 1.19

on compound **58** (Scheme 1.19).[64] The selective transfer of the group R compared to Me_3SiCH_2 allows to make the enantioselective addition reaction of diorganozincs to aldehydes more economical (Scheme 1.20).[64] Whereas, this asymmetric addition usually requires the addition of six equivalents of the R groups for one equivalent of aldehyde in order to obtain good yields, by using a mixed diorganozinc like **59** only 1.6 equivalents are required, leading to the desired chiral alcohol **60** in 92% yield and 97% *ee*.[64]



Scheme 1.20

4. General experimental guidelines

4.1 Introduction

In this section, general experimental information will be given concerning the preparation, handling, and storage of organozinc reagents. More detailed experimental procedures will be found in the following chapters.

4.2 Zinc as starting material

The nature of the zinc (dust, foil, or shots) is important for the success of the formation of an organozinc halide by oxidative addition. Usually, the use of zinc dust (–325 mesh) from Aldrich or Riedel de Haen gives the best results. In some cases, such as for the preparation of allylic zinc halide reagents,[22,28] iodomethylzinc iodide,[65] or benzylic zinc halides,[66] the use of zinc foil (0.1 mm or 0.25 mm thick, Aldrich or Merck) may be advantageous or even essential.

The activity of zinc dust can be increased by its treatment with 5 mol% of 1,2-dibromoethane and 1 mol% of TMSCl (Protocol 1). This activation is sufficient for allowing the zinc insertion into primary and secondary alkyl iodides, and benzylic bromides, and most aromatic iodides. More active zinc powders are obtained by the reduction of zinc halides with lithium naphthalenide according to Rieke.[21,67–69] In this case, even aromatic bromides,[21] secondary and tertiary alkyl bromides,[67,68] or alkyl chlorides [69] are converted to the corresponding zinc reagents. Other activation procedures involving the use of potassium graphite[70] or sodium dispersed on TiO_2[71] are also possible.

Protocol 1.
Activation of zinc dust in THF with 1,2-dibromoethane and trimethylsilyl chloride

Equipment

- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

- Zinc dust (FW 65.4), 3.27 g, 50 mmol
- 1,2-dibromoethane (FW 187.9), 0.47 g, 2.5 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.05 g, 0.5 mmol — **flammable, corrosive**
- Dry THF — **irritant, flammable, hygroscopic**

1. Weigh the zinc dust into the three-necked flask, add THF (20 mL), and flush the flask with argon.
2. Add 1,2-dibromoethane and heat gently with a heat gun allowing boiling of THF. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.

4.3 Handling of organozinc halides and diorganozincs

THF solutions of organozinc halides are usually stable for several months at room temperature under a nitrogen atmosphere and can be stored indefinitely under these conditions. Notable exceptions to this behaviour are reactive allylic, propargylic, and benzylic zinc halides, as well as zinc carbenoids like ICH_2ZnI, which should be prepared before use and can be stored at 0 °C for only a few days. The titration of organozinc halides or diorganozincs is best performed by a gas chromatographical (GC) analysis of the hydrolysis and iodolysis products derived from these organometallics (Protocol 2). Standardization procedures involving acid–base titrations as used for magnesium and

lithium compounds are not precise due to difficulties of determining the final colour change.

Protocol 2.
Gas chromatographical analysis of a zinc organometallic

The organozinc reagent formation and concentration is best determined by performing an iodolysis and a hydrolysis of a reaction aliquot. These experiments allow an accurate estimate of the organozinc reagent concentration.

1. Add a small amount of an internal standard (decane or undecane, *ca.* 2–5 mol% compared to the alkyl iodide) to the starting iodide. Determine the initial ratio A_0 between the integration of the alkyl iodide and the internal standard by GC analysis. Now start the zinc insertion reaction as described elsewhere. After completion of the reaction, perform a hydrolysis and iodolysis of a reaction sample.
2. For the hydrolysis, take an aliquot of the reaction mixture (*ca.* 0.1 mL) with a syringe, and add it to a vial containing ether (1 mL) and aqueous NH_4Cl (1 mL). Determine the new ratio A_t (ratio between the integration of the remaining alkyl iodide and the internal standard). The ratio A_t/A_0 leads to the conversion of the reaction.
3. For the iodolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe, and add it to a vial containing a solution of iodine (*ca.* 50 mg) in dry ether (1 mL). Mix well, decolorize the brown solution with a saturated aqueous solution of $Na_2S_2O_3$ (*ca.* 0.5 mL), and take the supernatant ether phase for GC analysis. Determine the ratio A_1 between the integration of the recovered alkyl iodide and the internal standard. The ratio between A_1 and A_0 allows the yield (± 3%) of the preparation of the zinc reagent (concentration of zinc reagent) to be determined precisely.

The hydrolysis of THF solutions of organozinc halides is a mild exothermic reaction and the disposal of solutions of organozinc halides does not require special precautions. On the other hand, neat diorganozincs are far more reactive and the lower compounds (R_2Zn, R = Me, Et, Pr, *i*-Pr, Bu) are highly reactive compounds which spontaneously ignite in air. The disposal of large amounts of these diorganozincs is best performed by dilution in dry cyclohexane, THF, CH_2Cl_2, or DME followed by the slow addition of ethanol at 0°C. Diethylzinc reacts explosively with pure oxygen even at low temperature. Due to the hazards involving the work with neat diethylzinc, alternatives have been searched and the use of complexes of diethylzinc with ethers was investigated. Thus, the treatment of diethylzinc with dibutyl ether (*ca.* two volumes) leads to a reagent $Et_2Zn{\bullet}Bu_2O$ which is far more convenient to handle. It does not ignite spontaneously in air but displays a similar reactivity as neat Et_2Zn (Protocols 4 and 5).

Protocol 3.
Preparation a stock solution of $Et_2Zn{\bullet}Bu_2O$

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.

Equipment

- One Schlenk flask (100 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

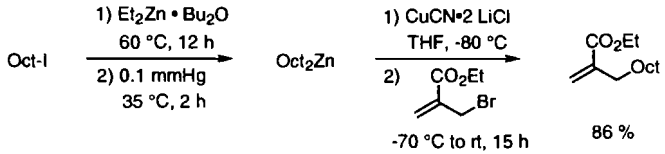
Materials

- Diethylzinc (FW 123.5), 15 mL, 150 mmol — **flammable and pyrophoric liquid**
- Dry dibutyl ether (FW 130.2), 30 mL — **flammable**

1. Charge the flame dried and argon flushed Schlenk flask with dibutyl ether and add diethylzinc (Caution!).
2. This stock solution of $Et_2Zn{\bullet}Bu_2O$ has a concentration of *ca.* 3.75 mol L^{-1} and can be stored for several months without decomposition at rt in the dark.

Protocol 4.
Preparation of dioctylzinc by iodine–zinc exchange and its copper-mediated coupling with an electrophile: preparation of ethyl 2-nonylacrylate

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- Two Schlenk flasks (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Protocol 4. *Continued*

Materials

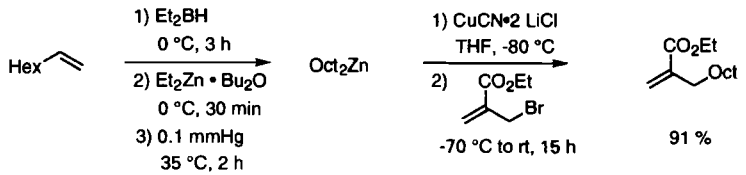
• 1-octyl iodide (FW 240.1), 2.4 g, 10 mmol	**irritant**
• $t_2Zn{\cdot}Bu_2O$ (c = 3.75 mol L^{-1}), 4 mL, 15 mmol	**flammable liquid**
• CuCN (FW 89.6), 0.9 g, 10 mmol	**toxic**
• LiCl (FW 42.4), 0.85 g, 20 mmol	**irritant, hygroscopic**
• Ethyl (2-bromomethyl)acrylate (FW 193), 1.74 g, 9 mmol	**flammable, harmful, lachrymator**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge the flame dried and argon flushed Schlenk flask with octyl iodide and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 60°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 60°C for 12 h (overnight).
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (35°C, 2 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis of a reaction sample. For the iodolysis, take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing a solution of iodine (*ca.* 50 mg) in dry ether (1 mL). Mix well, decolorize the brown solution with a saturated aqueous solution of $Na_2S_2O_3$ (*ca.* 0.5 mL), and take the supernatant ether phase for GLC analysis. For the hydrolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe, and add it to a vial containing ether (1 mL) and aqueous NH_4Cl (1 mL). Mix well and take the supernant ether phase for GLC analysis. These experiments allow an accurate estimate of the organozinc reagent concentration.
6. Dissolve the resulting oil of dioctylzinc in dry THF (3 mL) at rt and transfer the solution to the three-necked flask.
7. Weigh the CuCN and the LiCl into the second Schlenk flask. Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
8. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl at rt in dry THF (10 mL). A slight exothermic reaction is observed and a light yellow/green solution is formed.
9. Cool the dioctylzinc solution to –80°C and add slowly the CuCN•2LiCl solution.
10. Warm to 0°C for 1 min and recool to –70°C. Add the ethyl (2-bromomethyl)acrylate.
11. Allow the reaction mixture to warm slowly to rt overnight.
12. Add a saturated aqueous NH_4Cl solution (20 mL) to the reaction mixture and stir for 10 min at rt. Pour into an Erlenmeyer containing ether (200 mL) and aqueous NH_4Cl (100 mL) and filter over Celite®.

13. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash with brine (50 mL), dry over $MgSO_4$, and evaporate the solvent.
14. Purify the crude residue by flash chromatography using hexanes:ether (19:1). Pure ethyl 2-nonylacrylate (1.75 g, 86%) is obtained as a colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 5.
Preparation of dioctylzinc by boron–zinc exchange and its copper-mediated coupling with an electrophile: preparation of ethyl 2-nonylacrylate

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- Two Schlenk flasks (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

• 1-octene (FW 112.1), 1.12 g, 10 mmol	
• Triethylborane (FW 98), 0.65 g, 6.66 mmol	**flammable and pyrophoric liquid**
• Borane–methyl sulfide complex (FW 76), 0.25 g, 3.33 mmol	**toxic, stench**
• 1,5-cyclooctadiene (FW 108.2), 0.05 mL, 0.5 mmol	**flammable, harmful**
• $Et_2Zn•Bu_2O$ (c = 3.85 mol L^{-1}), 4 mL, 15 mmol	**flammable liquid**
• CuCN (FW 89.6), 0.9 g, 10 mmol	**toxic**
• LiCl (FW 42.4), 0.85 g, 20 mmol	**irritant, hygroscopic**
• Ethyl (2-bromomethyl)acrylate (FW 193), 1.74 g, 9 mmol	**flammable, harmful, lachrymator**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge the flame dried and argon flushed three-necked flask with 1-octene. Cool to 0°C, add triethylborane, and slowly the borane–methyl sulfide complex.

Protocol 5. *Continued*

2. Stir for 3 h at 0°C, then connect to vacuum (0.1 mmHg, 30 min), and remove all volatiles.
3. Add the diethylzinc solution (Caution!). Replace the septum cap with a glass stopper.
4. Stir for 30 min at 0°C.
5. Remove the triethylborane formed and the excess diethylzinc under vacuum (35°C, 2 h, *ca.* 0.1 mmHg).
6. Confirm the formation of the dialkylzinc compound as described in Protocol 2.
7. Dissolve the resulting oil of dioctylzinc in dry THF (3 mL) at rt and transfer the solution into the three-necked flask.
8. Weigh the CuCN and the LiCl into the second Schlenk flask. Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
9. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl at rt in dry THF (10 mL). A slight exothermic reaction is observed and a light yellow/green solution is formed.
10. Cool the dioctylzinc solution to –80°C and add slowly the CuCN•2LiCl solution.
11. Warm to 0°C for 1 min and recool to –70°C. Add ethyl (2-bromomethyl)acrylate.
12. Allow the reaction mixture to warm slowly to rt overnight.
13. Work-up as described in Protocol 4.
14. Purify the crude residue by flash chromatography using hexanes:ether (19:1). Pure ethyl 2-nonylacrylate (1.86 g, 91%) is obtained as a colourless oil. Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

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2

Active zinc in organic synthesis

REUBEN D. RIEKE and MARK V. HANSON

1. Introduction

In 1849, Frankland prepared diethylzinc from the reaction of zinc metal with ethyl iodide.[1] Since then, organozinc reagents have proven to be useful tools in organic synthesis.[2] The expansion of Frankland's method was hampered by the lack of reactivity of bulk zinc metal in the preparation of organozinc reagents directly from organohalides. This limitation is due primarily to oxide coating of the zinc surface, and an inherently small surface area. These factors can be alleviated by forming the zinc metal in an anhydrous, aprotic solvent, under an inert atmosphere, by the chemical reduction of anhydrous zinc salts. This chemical reduction produces a highly dispersed form of zinc metal, which is free of metal oxide, and has a dramatically increased surface area. This zinc metal displays an inherently higher reactivity towards organic halides than that of bulk zinc metal, commercial zinc dust, or zinc activated by standard entrainment methods.

In 1973, the direct potassium metal reduction of zinc salts was reported.[3] This active zinc powder reacted with alkyl and aryl bromides to form the alkyl- and arylzinc bromides under mild conditions.[4] The reduction of anhydrous zinc salts by alkali metals can be facilitated through the use of electron carriers. Lithium and sodium naphthalenide reduce zinc salts to give highly reactive metal powders under milder and safer conditions. Graphite[5] and liquid ammonia[6] have also been employed as electron carriers in producing zinc powders. A highly dispersed reactive zinc powder was formed from the sodium metal reduction of zinc salts on titanium dioxide.[7]

2. Active zinc: preparation and reactivity

Early preparations of active zinc utilized the potassium or sodium metal reduction of anhydrous zinc salts in refluxing THF or DME (Protocol 1).[3,8] These highly divided zinc powders displayed high reactivity towards organic halides in oxidative addition. Alkyl iodides and bromides reacted with the zinc powders at room temperature. Even aryl bromides and iodides would react to form the corresponding arylzinc iodides or bromides at refluxing

temperatures. The use of this active form of zinc allowed the Reformatsky reaction (Protocol 2) to be performed below or at room temperature in near quantitative yields (Scheme 2.1).[8]

Protocol 1.
Active zinc prepared from the potassium reduction of zinc chloride

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.

Equipment

- Two-necked, round-bottomed flask (100 mL)
- Condenser
- Gas adapter (with stopcock)
- Egg-type stirring bar
- Rubber septum
- Heating mantle
- Magnetic stirring plate
- Drybox or glove bag with an argon or nitrogen atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon or nitrogen manifold system
- Glass syringe with stainless steel needle

Materials

- Potassium metal (FW 39.1), 5.47 g, 0.14 mol — **flammable solid, moisture-sensitive**
- Dry zinc chloride (FW 136.28), 9.54 g, 0.07 mol — **corrosive, toxic**
- Dry, distilled tetrahydrofuran — **flammable liquid, irritant**

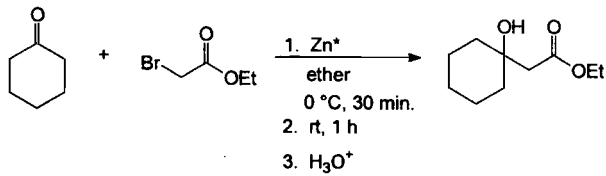
1. Using a drybox or a glove bag with an argon or nitrogen atmosphere, charge an oven-dried, two-necked, round-bottomed flask (100 mL), containing a magnetic stirring bar, with anhydrous zinc chloride (9.54 g, 0.07 mol) and thinly cut potassium metal (5.47 g, 0.14 mol). Fit the flask with a condenser capped with a gas adapter (with stopcock). Close the stopcock, and cap the side-neck with a rubber septum.
2. Remove the apparatus from the drybox or glove bag, and connect it to a vacuum/argon or nitrogen manifold. Before opening the stopcock to the inert atmosphere from the manifold, evacuate the system (5 min) and refill with argon or nitrogen (1 min) in three cycles.
3. Open the stopcock, and add freshly distilled THF (40 mL) through the septum inlet using a glass syringe.
4. The mixture is heated without stirring until the zinc chloride visibly reduces at the surface of the potassium. The heating is then stopped, and the vigorous exothermic reduction of the zinc chloride proceeds. At this point cooling in a water- or ice-bath may be required to moderate the progress of the reaction. After the reduction subsides, the mixture is refluxed for 2.5 h with rapid stirring. The active zinc is then ready for use.

The early potassium or sodium metal approach in the preparation of active zinc did not utilize an electron carrier to facilitate the reduction of the zinc salts. Initially, it was thought that the presence of an electron carrier in the

reaction pot would not be widely accepted due to complications in the isolation of the organic products. However, the reduction of zinc salts in anhydrous DME or THF using stoichiometric lithium naphthalenide (Protocol 3),[10] or lithium and catalytic naphthalene as a two-pot procedure (Protocol 4),[11] produced an active zinc of higher reactivity and under milder conditions than the potassium or sodium reduction. The electron carrier can be easily removed by washing the settled zinc with fresh, dry THF or DME before the zinc is to be used as a reagent.

Protocol 2.
Active zinc in the Reformatsky reaction

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Scheme 2.1

Equipment

- Three two-necked, round-bottomed flasks (100 mL)
- Round-bottomed flask (25 mL)
- Three gas adapters (with stopcock)
- Three egg-type stirring bars
- Rubber septa
- Two magnetic stirring plates
- Drybox or a glove with a nitrogen or argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon or nitrogen manifold system
- Glass syringe with stainless steel needle
- Cannula
- Glass distillation apparatus

Materials

- Active zinc (Protocol 1) (FW 65.39), 4.6 g, 70.3 mmol — **pyrophoric, moisture-sensitive**
- Ethyl bromoacetate (FW 167.01), 10.02 g, 60 mmol — **corrosive, lachrymator**
- Dry, diethyl ether — **flammable liquid, irritant**
- Cyclohexanone (FW 98.15), 5.65 g, 57.6 mmol — **corrosive, toxic**
- 2 N HCl
- Saturated sodium bicarbonate solution
- Anhydrous magnesium sulfate

1. Prepare active zinc (4.6 g, 70.3 mmol) according to Protocol 1 in a two-necked, round-bottomed flask (100 mL). Allow the active zinc to settle, and remove the THF by cannula. Remove the residual THF under vacuum. Add dry, distilled diethyl ether (40 mL) using a dry, glass syringe. Cool the flask in an ice-bath.
2. Transfer ethyl bromoacetate (10.02 g, 60 mmol) and cyclohexanone (5.65 g,

Protocol 2. *Continued*

57.6 mmol) to an oven-dried, round-bottomed flask (25 mL), containing a stirring bar, and fitted with a septum, and under positive argon or nitrogen pressure.

3. Add the mixture of ethyl bromoacetate and cyclohexanone dropwise using a cannula to the stirring slurry of active zinc over a 30 min period.
4. Warm the reaction mixture to room temperature, and stir vigorously for 1 h.
5. Quench the reaction mixture by pouring into a 2 N HCl (30 mL) solution, and stir for 15 min. Extract the aqueous layer with diethyl ether (3 × 20 mL). Wash the combined organic phases with saturated sodium bicarbonate solution (2 × 10 mL) and water (2 × 10 mL). Dry the combined ether extracts over anhydrous magnesium sulfate, filter, and concentrate. Isolate the product from the crude by vacuum distillation to obtain the β-hydroxyester[9] (10.4 g, 97%) as a colourless liquid.

Protocol 3.
Active zinc prepared from the stoichiometric lithium naphthalenide reduction of zinc chloride

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.

Equipment

- Two two-necked, round-bottomed flasks (50 mL)
- Two gas adapters (with stopcock)
- Two egg-type stirring bars
- Rubber septa
- Two magnetic stirring plates
- Drybox or glove bag with an argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon manifold system
- Scissors
- Cannula
- Glass syringe with stainless steel needle

Materials

- Lithium ribbon (FW 6.94), 0.213 g, 30.6 mmol — **flammable, corrosive**
- Naphthalene (FW 128.17), 3.99 g, 31.2 mmol — **cancer suspect agent, flammable**
- Anhydrous zinc chloride (FW 136.28), 2.09 g, 15.4 mmol — **corrosive, toxic**
- Dry, distilled THF — **flammable, irritant**

1. Using a drybox or glove bag with an argon atmosphere, charge an oven-dried, two-necked, round-bottomed flask (50 mL), containing a magnetic stirring bar, with anhydrous zinc chloride (2.09 g, 15.4 mmol). Secure a gas adapter (with stopcock) to the flask, and cap the side-neck with a septum. Charge a second, dry, two-necked, round-bottomed flask (50 mL) containing a magnetic stirring bar with thinly cut lithium metal (0.213 g, 30.6 mmol) and naphthalene (3.99 g, 31.2 mmol). Fit the flask with a gas adapter (with stop-

cock), and secure a septum to the side-neck. Close the stopcocks before removing the flasks from the drybox or glove bag.

2. Remove the flasks from the drybox or glove bag, and connect them to a vacuum/argon manifold. Before opening the stopcocks to the inert atmosphere from the manifold, evacuate the system (5 min) and refill with argon or nitrogen (1 min) in three cycles. Open the stopcocks to positive argon pressure.
3. Add dry, freshly distilled THF (15 mL) through the septum inlet using a glass syringe to the flask containing the lithium metal and naphthalene. The stirring mixture will turn green within 30 sec, and the stirring should be continued for 2 h at room temperature until the lithium metal is totally consumed. Add freshly distilled THF (20 mL) through the septum inlet using a dry, glass syringe to the flask containing the zinc chloride. Perform this addition with rapid stirring.
4. Transfer the zinc chloride solution to the flask containing the stirring lithium naphthalenide solution, using a cannula, dropwise, over a period of 15 min. The resulting black slurry of active zinc is ready for use.

Protocol 4.
Active zinc prepared from the lithium reduction of zinc chloride using catalytic naphthalene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.

Equipment

- Two two-necked, round-bottomed flasks (50 mL)
- Two gas adapters (with stopcock)
- Two egg-type stirring bars
- Rubber septa
- Two magnetic stirring plates
- Drybox or glove bag with an argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon manifold system
- Scissors
- Cannula
- Glass syringe with stainless steel needle

Materials

• Lithium ribbon (FW 6.94), 0.11 g, 16 mmol	**flammable, corrosive**
• Naphthalene (FW 128.17), 0.2 g, 1.6 mmol	**cancer suspect agent, flammable**
• Anhydrous zinc chloride (FW 136.28), 1.09 g, 8 mmol	**corrosive, toxic**
• Dry, distilled THF	**flammable, irritant**

1. Using a drybox or glove bag with an argon atmosphere, charge an oven-dried, two-necked flask (50 mL), containing a magnetic stirring bar, with anhydrous zinc chloride (1.09 g, 8 mmol). Secure a gas adapter (with stopcock) to the flask, and cap the side-neck with a septum. Charge a second, dry, two-necked, round-bottomed flask (50 mL) containing a magnetic stir bar, with thinly cut lithium metal (0.11 g, 1.6 mmol) and naphthalene (0.20 g,

Protocol 4. *Continued*

1.6 mmol). Fit the flask with a gas adapter (with stopcock), and secure a septum to the side-neck. Close the stopcocks before removing the flasks from the drybox or glove bag.

2. Remove the flasks from the drybox or glove bag, and connect them to a vacuum/argon manifold. Before opening the stopcocks to the inert atmosphere from the manifold, evacuate the system (5 min) and refill with argon or nitrogen (1 min) in three cycles. Open the stopcocks to positive argon pressure.
3. Add dry, freshly distilled THF (15 mL) through the septum inlet using a glass syringe to the flask containing the lithium metal and naphthalene. The stirring mixture will turn green in less than 30 sec. Add freshly distilled THF (20 mL) through the septum inlet using a dried glass syringe to the flask containing the zinc chloride. This addition should be performed with rapid stirring.
4. Transfer the stirring zinc chloride solution to the flask containing the stirring green mixture of lithium and naphthalene in THF, using a cannula, dropwise, over a period of 1.5 h. Perform the addition slowly enough so that the green colour of lithium naphthalenide persists. If the mixture becomes clear during the addition of the zinc chloride, stop the addition, and allow the mixture to stir until the green colour returns before resuming the addition of the zinc chloride solution. When addition of the zinc chloride is complete, stir the mixture until all the residual lithium is consumed. The resulting black slurry of active zinc is then ready for use. The rate of addition of the zinc chloride solution is crucial. If the addition of zinc chloride is performed over a period of four or more hours, the active zinc formed may not settle completely from the THF solution. The reduction of the zinc chloride in approx. 1.5–2 h produces a mossy form of active zinc which rapidly settles.
5. If the presence of naphthalene or lithium chloride (from the reduction) is not desired in the active zinc, they can be removed at this point by repeated washing with dry THF. After the reduction is complete, turn the stir plate off, and allow the active zinc to settle (1–2 h). Monitor the progress of the settling by shining a strong light through the slurry by use of a flashlight. Remove the THF solution, by cannula, down to the surface of the settled zinc. Tip the flask slightly to facilitate the removal of the last portion of THF. Add freshly distilled THF (25 mL), and stir for several minutes. Turn off the stirring, and allow the zinc to settle for a few minutes, and remove the supernatant by cannula. Repeat the washing cycle two additional times.

This form of active zinc prepared in the presence of an electron carrier can readily form arylzinc iodides at room temperature from aryl iodides. Aryl bromides reacted far more efficiently with reduced reaction times at refluxing temperatures. The newer two-pot lithium reduction procedures for the preparation of active zinc requires 3–4 h for a total preparation time. Whilst the old one-pot preparation of active zinc from the reduction of zinc salts with lithium

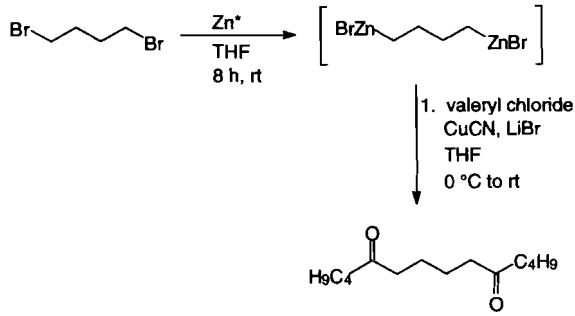
metal using catalytic amounts of electron carrier were plagued by long reduction times of 10–15 h.[4a] This was a consequence of the zinc metal plating the lithium and inhibiting further zinc reduction. As a general strategy in the formation of alkylzinc bromides or iodides, a slight excess of active zinc is used, usually 1.1–1.5 equivalents of active metal to the alkyl halide. The reaction proceeds readily at room temperature, and depending upon the alkyl halide substrate, the reaction is complete in 15 min to up to 6–8 h. Usually, the presence of an activating group within close proximity to the carbon–halogen bond facilitates the oxidative addition of zinc into the carbon–halogen bond.[2] Substrates containing an ester, nitrile, or amide functionality in close proximity to the carbon–halogen bond react very quickly to form the alkylzinc bromide or iodide. Remotely functionalized or unfunctionalized alkyl halides require longer reaction times. Primary, secondary, or tertiary alkyl bromides or iodides can be used to form the corresponding alkylzinc halide reagents.[10,11] For example, active zinc reacts with 1,4-dibromobutane to give the corresponding dimetallic reagent (Scheme 2.2) which cross-couples with valeryl chloride in the presence of a copper(I) catalyst[12] (Protocol 5).

Secondary and tertiary alkyl bromides react with active zinc at ambient temperature. However, the reaction time for the oxidative addition can be shortened by heating the reaction mixture at reflux in THF. Methyl 3-bromobutyrate gives the organozinc bromide intermediate upon reaction with active zinc and reacts with 2-cyclohexen-1-one to afford the 1,4-addition product (Protocol 6, Scheme 2.3).[14]

Alkyl chlorides react only sparingly, and alkyl fluorides are inert. However, reactive substrates, such as, benzylic bromides give high yields of the benzylzinc bromides (Protocol 7, Scheme 2.4).[15]

Protocol 5.
Preparation of 5,10-tetradecadione

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Scheme 2.2

Protocol 5. *Continued*

Equipment

- Three two-necked, round-bottomed flasks (50 mL)
- Three gas adapters (with stopcock)
- Three egg-type stirring bars
- Rubber septa
- Two magnetic stirring plates
- Drybox or glove bag with an argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon manifold system
- Glass syringe with stainless steel needle
- Cannula

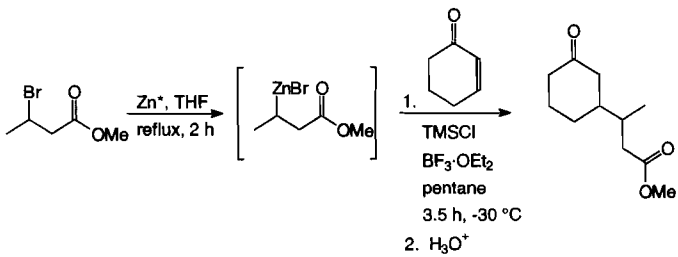
Materials

- Active zinc (Protocol 3) (FW 65.39), 1 g, 15.3 mmol — **flammable, moisture-sensitive**
- 1,4-dibromobutane (FW 215.93), 1.19 g, 5.51 mmol — **lachrymator, irritant**
- Valeryl chloride (FW 120.58), 1.4 g, 11.6 mmol — **flammable, corrosive**
- Copper(I) cyanide (FW 89.56), 0.1 g, 1.1 mmol — **highly toxic, irritant**
- Lithium bromide (FW 86.85), 0.11 g, 1.3 mmol — **hydroscopic**
- 3 N hydrochloric acid
- Saturated sodium bicarbonate
- Brine
- Anhydrous magnesium sulfate

1. Prepare active zinc (1 g, 15.3 mmol), in THF (20 mL), in a two-necked, round-bottomed flask (50 mL) according to Protocol 3.
2. To the stirring mixture of active zinc, add 1,4-dibromobutane (1.19 g, 5.5 mmol) and stir for 8 h at rt. Then allow the excess zinc to settle overnight.
3. Charge a two-necked, round-bottomed flask (50 mL) with copper(I) cyanide (0.1 g, 1.1 mmol), lithium bromide (0.11 g, 1.3 mmol), and a stirring bar. Fit the flask with a gas adapter (with stopcock) and a septum. Connect the flask to a vacuum/inert atmosphere manifold, and subject it to three pump/refill cycles. Add dry, distilled THF (15 mL) to the flask by use of a dry, glass syringe. Stir this mixture, and then cool it in an ice-bath.
4. Transfer the supernatant from step 2 by cannula to the copper(I) cyanide/lithium bromide solution. Once the transfer is complete, add valeryl chloride (1.4 g, 11.6 mmol) and allow the reaction mixture to warm to room temperature as it stirs overnight.
5. Quench the reaction mixture by addition to 3 M HCl (30 mL). Extract with ether (3 × 20 mL). Wash the combined organics with saturated sodium bicarbonate solution (30 mL), water (30 mL), and brine (30 mL). Dry the organics over magnesium sulfate, filter, and concentrate. Isolate the product[13] from the crude on silica (ethyl acetate:hexanes, 1:4, v/v).

Protocol 6.
The preparation of methyl 3-(3′-oxocyclohexyl)butanoate

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Scheme 2.3

Equipment

- Three two-necked, round-bottomed flasks (50 mL)
- Three gas adapters (with stopcock)
- Condenser
- Three egg-type stirring bars
- Rubber septa
- Two magnetic stirring plates
- Drybox or glove bag with an argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon or nitrogen manifold system
- Glass syringe with stainless steel needle
- Controlled temperature bath
- Cannula

Materials

• Active zinc (Protocol 3) (FW 65.39), 1.61 g, 11.8 mmol	**flammable, moisture-sensitive**
• Methyl 3-bromobutyrate (FW 181.03), 1.37 g, 7.59 mmol	**corrosive, lachrymator**
• 2-cyclohexen-1-one (FW 96.13), 0.398 g, 4.14 mmol	**highly toxic**
• Boron trifluoride diethyl etherate (FW 141.93), 1.5 g, 11 mmol	**corrosive, moisture-sensitive**
• Chlorotrimethylsilane (FW 108.64), 1.6 g, 15 mmol	**flammable, corrosive**
• Dry, distilled pentane	**flammable, irritant**
• Dry, distilled THF	**flammable, irritant**
• Saturated ammonium chloride	
• Diethyl ether	**flammable, toxic**
• Anhydrous magnesium sulfate	

1. Prepare active zinc (1.61 g, 11.8 mmol) in THF (30 mL) according to Protocol 3 in a two-necked, round-bottomed flask (50 mL), fitted with a condenser and a gas adapter (with stopcock). Wash the active zinc with dry, distilled THF (3 × 25 mL) according to Protocol 3, step 5. When the portion of THF is removed by cannula, add dry, distilled THF (10 mL) to the flask.
2. Add methyl 3-bromobutyrate (1.37 g, 7.59 mmol), to the stirring mixture of active zinc, and reflux the mixture for 2 h. Cool the reaction mixture to room temperature without stirring, and allow the zinc to settle.
3. Fit an oven-dried, two-necked, round-bottomed flask (100 mL), containing a

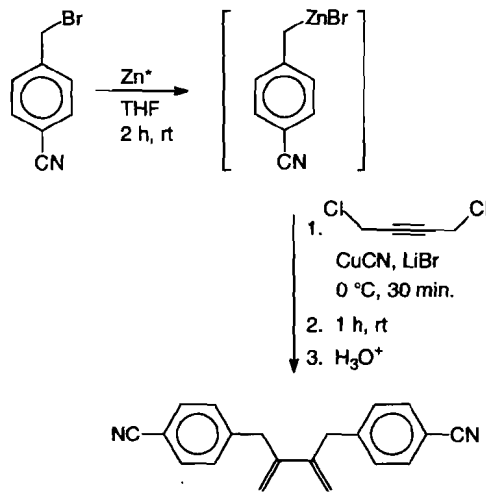
Protocol 5. *Continued*

stirring bar, with a gas adapter (with stopcock) and a septum. Connect the flask to a manifold system, and subject the flask to three evacuation/inert gas refill cycles. Under a blanket of argon, charged the flask with dry, distilled pentane (90 mL). Cool the flask to –30°C using a controlled temperature bath. To the cooled pentane, add 2-cyclohexen-1-one (0.4 g, 4.1 mmol), $BF_3.OEt_2$ (1.5 g, 11 mmol), and TMSCl (1.6 g, 15 mmol).

4. Add the alkylzinc bromide reagent dropwise to the cyclohexenone mixture over 20 min. Stir the heterogeneous reaction mixture for 3.5 h at –30°C.
5. Quench the reaction mixture by addition to saturated NH_4Cl (30 mL), and take the organics up in ether (20 mL). Separate and extract the aqueous layer with ether (2 × 20 mL). Wash the combined organics sequentially with water (20 mL), and brine (20 mL), then dry over $MgSO_4$ and concentrate. Isolate methyl 3-(3'-oxocyclohexyl)butanoate[14] (2.1 mmol, 51%) from the crude reaction mixture by flash chromatography (silica gel, hexanes:ethyl acetate).

Protocol 7.
Preparation of 2,3-di(*p*-cyanobenzyl)-1,3-butadiene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Scheme 2.4

Equipment

- Two two-necked, round-bottomed flasks (50 mL)
- Two-necked, round-bottomed flask (25 mL)
- Two-necked, round-bottomed flask (100 mL)
- Three gas adapters (with stopcock)
- Three egg-type stirring bars
- Rubber septa
- Two magnetic stirring plates
- Drybox or a glove bag with an argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon manifold system
- Glass syringe with stainless steel needle
- Cannula

Materials

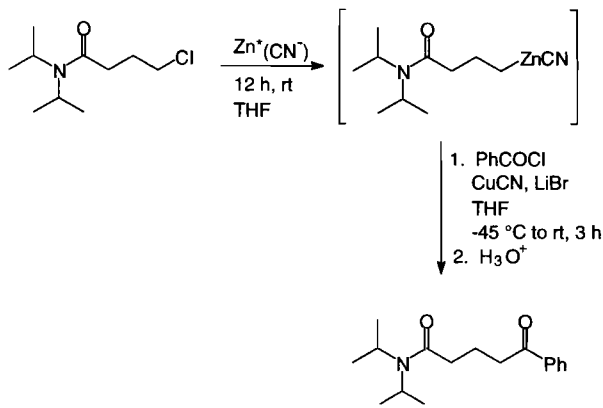
• Active zinc (Protocol 3) (FW 65.39), 3.3 g, 50 mmol	**flammable, moisture-sensitive**
• 4-cyanobenzyl bromide (FW 196.05), 4.3 g, 35 mmol	**corrosive, lachrymator**
• Copper cyanide (FW 89.56), 3.1 g, 35 mmol	**highly toxic, irritant**
• Lithium bromide (FW 86.85), 3 g, 35 mmol	**hygroscopic**
• 1,4-dichloro-2-butyne (FW 122.98), 1.84 g, 15 mmol	**lachrymator, irritant**
• Saturated ammonium chloride solution	
• Anhydrous magnesium sulfate	
• Dry, distilled THF	**flammable, irritant**
• Diethyl ether	**flammable, irritant**

1. Prepare active zinc (50 mmol) in a two-necked, round-bottomed flask (50 mL) fitted with a gas adapter (with stopcock) according to the procedures of Protocol 3 in THF (25 mL).
2. Charge an oven-dried, round-bottomed flask (25 mL), containing a stirring bar, with 4-cyanobenzyl bromide (4.3 g, 35 mmol). Seal the flask with a rubber septum, and subject it to three pump/inert atmosphere refill cycles. While maintaining a blanket of argon, add THF (10 mL) and stir until the 4-cyanobenzyl bromide is completely dissolved. Transfer the resulting solution by cannula to the active zinc. Stir the reaction mixture at rt for 2 h. Stop the stirring, and allow the active zinc to settle overnight.
3. Charge an oven-dried, two-necked, round-bottomed flask (100 mL), containing a stirring bar, with CuCN (3.1 g, 35 mmol) and LiBr (3 g, 35 mmol). Fit the flask with a gas adapter (with stopcock) and a septum. Connect the flask to a manifold system and subject it to three evacuation/inert gas refill cycles. Add dry, distilled THF (15 mL) and stir the mixture until the salts dissolve. Cool the solution to –20°C.
4. Transfer the supernatant, from step 2, by cannula, to the CuCN/LiBr solution at –20°C. Stir the solution for 15 min, and then warm to 0°C. Add 1,4-dichloro-2-butyne (1.84 g, 15 mmol) . Stir the solution for 30 min, and then at room temperature for 1 h.
5. Quench the reaction mixture by pouring into a saturated ammonium chloride solution (20 mL). Extract the aqueous layer with diethyl ether (3 × 20 mL), then dry the combined organic layers over $MgSO_4$, filter, and concentrate under reduced pressure. Isolate the product from the crude reaction mixture by flash chromatography (ethyl acetate:hexanes, 1:5, v/v); 2,3-di(*p*-cyanobenzyl)-1,3-butadiene[15] is obtained in 93% yield.

The zinc(II) halide salt used in the preparation of the active zinc can have a dramatic effect on the subsequent oxidative addition. If zinc iodide is used, alkyl chlorides can be effectively used as substrates towards oxidative addition. It is assumed that the alkyl chloride undergoes halogen exchange to form an alkyl iodide *in situ* which rapidly inserts zinc into the carbon–iodine bond.[10,16] The effect of cyanide ion has a dramatic effect upon the reactivity of active zinc. The lithium reduction of zinc cyanide in THF using a catalytic amount of naphthalene produces a very highly reactive zinc powder.[17] This zinc powder readily reacts with alkyl chlorides directly to give the corresponding alkylzinc halides (Protocol 8, Scheme 2.5). The enhancement of reactivity could result from the reduction of the zinc's work function in the vicinity of the absorbed cyanide ion, or the cyanide ion is acting as a conduction path for the transfer of electrons to the alkyl chloride. For example, this type of active zinc reacts with *N,N*-diisopropyl-3-chlorobutamide to give the alkylzinc halide, and effectively couples with benzoyl chloride using copper cyanide/lithium bromide complex[12] as a catalyst.

Protocol 8.
Active zinc from the lithium reduction of zinc cyanide: preparation of 5-oxo-5-phenyl-(*N,N*-diisopropyl)pentamide

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Scheme 2.5

Equipment

- Two two-necked, round-bottomed flasks (50 mL)
- Two gas adapters (with stopcock)
- Condenser
- Two egg-type stirring bars
- Rubber septa
- Magnetic stirring plate
- Drybox or a glove bag with an argon atmosphere
- Oven (110–130°C) or Bunsen burner
- Vacuum/argon manifold system
- Glass syringe with stainless steel needle
- Cannula

Materials

- Lithium (FW 6.94), 0.18 g, 16 mmol — **flammable, corrosive**
- Zinc cyanide (FW 117.41), 1.49 g, 12.7 mmol — **highly toxic**
- Naphthalene (FW 128.17), 0.333 g, 2.6 mmol — **cancer suspect agent, flammable**
- *N,N*-diisopropyl-3-chlorobutamide (FW 205.73), 0.853 g, 4.15 mmol
- Copper cyanide (FW 89.56), 0.232 g, 2.6 mmol — **highly toxic, irritant**
- Lithium bromide (FW 86.85), 0.225 g, 2.6 mmol — **hygroscopic**
- Dry, distilled THF — **flammable, irritant**
- Benzoyl chloride (FW 140.57), 0.408 g, 2.9 mmol — **corrosive, toxic**
- Saturated ammonium chloride solution
- Diethyl ether — **flammable, irritant**
- Brine
- Anhydrous magnesium sulfate

1. In a drybox or a glove bag with an argon atmosphere, charge an oven-dried, two-necked, round-bottomed flask (50 mL), containing a stirring bar, with finely cut lithium (0.18 g, 16 mmol), zinc cyanide (1.49 g, 12.7 mmol), and naphthalene (0.33 g, 2.6 mmol). Fit the flask with a condenser and gas adapter (with stopcock). Cap the side-neck with a septum, and close the stopcock.
2. Remove the apparatus from the drybox or glove bag, and connect it to a vacuum/argon or nitrogen manifold. Before opening the stopcock to the inert atmosphere from the manifold, evacuate the system (5 min) and refill with argon or nitrogen (1 min) in three cycles.
3. Add freshly distilled THF (20 mL) to the flask and stir the mixture vigorously for 5 h at room temperature under argon.
4. Add *N,N*-diisopropyl-3-chlorobutamide (0.85 g, 4.2 mmol) to the resulting black slurry of active zinc at rt. Stir the mixture for 12 h at rt. Then allow the excess zinc to settle for *ca.* 4 h.
5. Charge an oven-dried, two-necked, round-bottomed flask with copper(I) cyanide (0.23 g, 2.6 mmol), lithium bromide (0.22 g, 60 mmol), and a stirring bar. Cap the flask with a gas adapter (with stopcock) and a septum. Connect the flask to a manifold system and subject it to three evacuation/inert gas refill cycles. To the flask, add THF (10 mL) with stirring. Cool the flask to –45 °C.
6. Transfer the clear supernatant from step 4 to the copper(I) cyanide solution from step 5, by cannula. A gummy white precipitate immediately forms in the reaction mixture. Stir the resulting mixture for 10 min, and then add benzoyl chloride (0.41 g, 2.9 mmol). Allow the bath temperature to warm to room temperature over 3 h.
7. Quench the reaction mixture by addition to a saturated ammonium chloride solution (40 mL) and extract the aqueous layer with ether (3 × 20 mL). Wash the combined organic layers with water (20 mL) and brine (20 mL), dry over anhydrous magnesium sulfate, and concentrate. Isolate pure 5-oxo-5-phenyl-(*N,N*-diisopropyl)pentamide[17] (1.78 mmol, 61%) from the crude residue by flash chromatography (ethyl acetate:hexanes, 4:6).

The formation of arylzinc bromides or iodides from aryl iodides or bromides is accomplished by using a large excess of active zinc (two to four equivalents). The concentration of active zinc should be high when performing the oxidative addition, approx. 0.5–1 M. Difficult aryl bromides or iodides should not be refluxed more than several hours when reacting with active zinc as decomposition of the arylzinc reagent may occur. Aryl iodides are generally good substrates towards oxidative addition. Aryl bromides with an electron withdrawing group in the ring *para-* and especially *ortho-* to the carbon–bromine bond work well. *meta*-Substituted electron withdrawing groups to the carbon–bromine bond or electron donating groups on the ring greatly increase the difficulty of the oxidative addition of active zinc, and usually result in lower yields of the arylzinc bromide.

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3

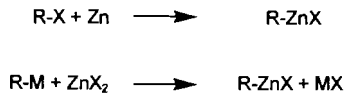
Preparation and use of organozinc halides

RICHARD F. W. JACKSON

1. Introduction

Organozinc halides have a very significant place in the development of organic synthesis. Ethylzinc iodide was first prepared by Edward Frankland in work reported in 1849,[1] and the preparation and use of simple organozinc compounds (organozinc halides and diorganozincs) was explored during the latter half of the 19th century. However, the discovery of Grignard reagents, which possessed higher reactivity and (at that time) were easier to prepare, pushed organozinc compounds into the background. It was very much later that it was realized that the lower reactivity of organozinc halides might be a significant advantage, and raised the possibility of incorporating reactive functional groups into the zinc reagent.[2]

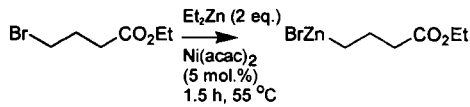
There are two basic methods for the preparation of organozinc halides. The most direct simply involves treatment of an organic halide with suitably activated zinc metal,[3] by analogy with the formation of Grignard reagents. As an alternative, treatment of certain alkylmetal derivatives with a zinc salt can be used to be prepare alkylzinc halides. For example, reaction of an organolithium reagent with anhydrous zinc iodide generates the corresponding organozinc iodide. Use of very low temperatures for the formation of the organolithium does allow the preparation of functionalized organozinc reagents,[4] although this procedure, whilst useful in some cases, does have less broad scope than the direct zinc insertion method. For this reason, this chapter will concentrate on methods for the preparation of organozinc halides by direct reaction of organic substrates with metallic zinc.



Scheme 3.1

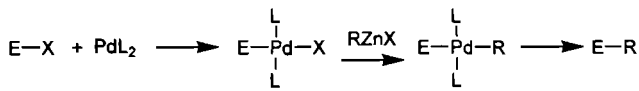
It has also been shown recently that it is possible to prepare organozinc halides by transition metal promoted exchange reactions between commercially

available diethylzinc and organic halides. For example, treatment of the ethyl 4-bromobutanoate with diethylzinc (two equivalents) in the presence of catalytic $Ni(acac)_2$ gives the corresponding functionalized alkylzinc bromide.[5]



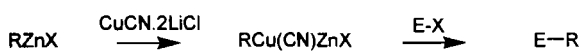
Scheme 3.2

The great kinetic unreactivity of organozinc halides towards organic electrophiles was overcome when it was realized that it was possible to transfer the organic fragment from zinc to another metal to generate a new organometallic reagent with higher reactivity, provided that this process was thermodynamically favourable. Transmetallation can be carried out both in a catalytic sense, and in a stoichiometric sense. The most significant breakthrough came with Negishi's discovery that organozinc halides were very well suited to the role of nucleophilic partner in palladium catalysed cross-coupling reactions.[6] This allowed the reaction of organozinc halides with a range of unsaturated electrophiles and acid chlorides.



Scheme 3.3

Subsequent developments indicated that transmetallation to copper was also possible in both catalytic and stoichiometric senses, with the use of the THF soluble copper salt CuCN.2LiCl being especially convenient.[7] The formation of these functionalized copper reagents has allowed a substantial increase in the range of products which may be prepared from organozinc halides.[8]



Scheme 3.4

2. Methods for zinc activation

The most significant obstacle to be overcome in the preparation of organozinc halides by direct insertion of zinc metal into an organic halide is the intrinsic lack of reactivity of commercially available zinc metal. This is primarily due to a surface coating, for example of zinc oxide, which prevents direct reaction with an organic substrate. The success of attempts to insert zinc metal into an organic halide is entirely dependent upon the care with which the zinc metal is

activated in the first place. One of the first tactics used to tackle this problem was to prepare a zinc/copper couple, as employed by Simmons and Smith for generating iodomethylzinc iodide for use in their cyclopropanation reaction.[9] Zinc/copper couple is prepared by treating zinc dust with hydrochloric acid, and then aqueous copper sulfate, before thorough washing and drying. Zinc/copper couple has the advantage that it can be prepared on a large scale, and stored safely for some months in a dry atmosphere. The most reactive, routinely available, source of zinc is Rieke zinc, which is generally prepared by reduction of a suitable zinc salt (for example, $ZnCl_2$) in an inert solvent,[10] and detailed protocols for its use are discussed in Chapter 2.

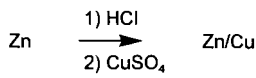
As a good compromise between preformed zinc/copper couple which is very easy to prepare on large scale, but not especially reactive, and very reactive Rieke zinc, it is possible to activate commercially available zinc dust (Aldrich –325 mesh) by treatment first with 1,2-dibromoethane and then with chlorotrimethylsilane.[7] This process, which is routinely carried out *in situ*, is a reliable and quick method for the preparation of zinc which is sufficiently reactive for many purposes.

3. Preparation of organozinc halides using zinc/copper couple

The first generally applicable method for the formation of functionalized alkylzinc iodides was developed by Yoshida and co-workers, who prepared the zinc reagents derived from ethyl 3-iodopropanaote and ethyl 4-iodobutanoate by reaction with zinc/copper couple, and then used these in subsequent palladium catalysed coupling reactions.[11] As a route to the preparation of 4-oxo esters, the coupling of the zinc reagent derived from ethyl 3-iodopropanaote with an acid chloride under palladium catalysis has much to recommend it over more traditional malonate alkylation chemistry. Protocol 1 describes how to prepare zinc/copper couple, and Protocol 2 is a typical example of the use of zinc/copper couple for the preparation of a functionalized alkylzinc iodide, and its subsequent coupling with an acid chloride under palladium catalysis.[12]

Protocol 1.
Preparation of zinc/copper couple

Caution! Chemically-resistant gloves and safety glasses should be worn.



Scheme 3.5

Protocol 1. *Continued*

Equipment

- Hotplate stirrer
- Magnetic stirrer bar
- Erlenmeyer flask (500 mL)
- Filter funnel with sinter
- Buchner flask to fit the sinter above (500 mL)
- Vacuum desiccator

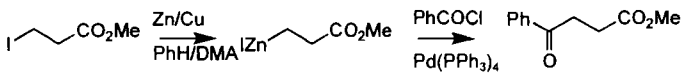
Materials

- Zinc powder (FW 65.4), 49.2 g, 0.75 mol — **flammable solid**
- 1 M HCl, 4 × 40 mL — **corrosive**
- $CuSO_4$, 2 × 75 mL, 2% (w/v)
- Distilled water
- Ethanol, 400 mL
- Diethyl ether, 500 mL — **flammable, irritant**
- P_2O_5 for vacuum desiccator — **corrosive**

1. Place the powdered zinc into the Erlenmeyer flask, containing the magnetic stirrer bar.
2. Add one portion of the HCl (40 mL) to the zinc in the Erlenmeyer flask and stir rapidly for 1 min, and then decant the supernatant. Repeat this process with the three additional portions of HCl.
3. Add distilled water (100 mL) to the zinc in the Erlenmeyer flask and stir rapidly, and then decant the supernatant. Repeat this process four more times.
4. Add aqueous copper(II) sulfate solution (75 mL) to the zinc in the Erlenmeyer flask and stir rapidly for 1 min, and then decant the supernatant. Repeat this process one more time.
5. Repeat step 3.
6. Set-up the sinter glass funnel and the Buchner flask.
7. Add ethanol (100 mL) to the zinc in the Erlenmeyer flask and stir, and then decant the supernatant directly onto the sintered funnel, and apply a vacuum. Repeat this process three more times. Discard the filtrate from the Buchner flask.
8. Add diethyl ether (100 mL) to the zinc in the Erlenmeyer flask and stir, and then decant the supernatant directly onto the sintered funnel. Repeat this process four more times. On the last occasion, transfer all the zinc/copper couple to the sintered funnel and dry under suction until room temperature is reached. Discard the filtrate from the Buchner flask.
9. Dry the zinc/copper couple in a vacuum desiccator over phosphorus pentoxide for several days before use.

Protocol 2.
Preparation of 2-carbomethoxyethylzinc iodide: preparation of methyl 4-phenyl-4-oxobutanoate

Caution! Benzene is a cancer suspect agent. All procedures should be carried out in an efficient fume-hood. Chemically-resistant gloves and safety glasses should be worn.



Scheme 3.6

Equipment

- Hotplate stirrer, fitted with contact thermometer
- Oil-bath
- Source of dry nitrogen
- Source of vacuum
- Two-necked round-bottomed flask (25 mL), reflux condenser fitted with three-way tap, rubber septum
- Syringes (250 μL, 1 mL, 5 mL)
- Needles for syringes (20 gauge)
- Beaker and watch glass for TLC developing
- Thin-layer chromatography plates (silica) and spotters
- Medium sintered glass funnel and Buchner flask
- Filter papers, fluted
- Separating funnel (125 mL)
- Rotary evaporator
- Chromatography column (20 cm × 2 cm)
- Desiccator

Materials

- Methyl 3-iodopropanoate[a] (FW 214), 331 mg, 1.55 mmol — **light-sensitive**
- Zinc/copper couple (FW ~ 65.4), 166 mg, ~ 2.54 mmmol — **flammable solid**
- *Tetrakis*(triphenylphosphine)palladium (FW 1155.6), 49 mg, 0.04 mmol — **toxic**
- *N,N*-dimethylacetamide,[b] 0.2 mL — **irritant**
- Benzene,[b,c] 5 mL — **cancer suspect agent, flammable**
- Benzoyl chloride (FW 140.5), 0.115 mL, 1 mmol — **causes burns**
- EtOAc — **flammable, irritant**
- Petroleum ether (40–60) — **flammable, irritant**
- 1 M NH_4Cl
- 1 M $NaHCO_3$
- Saturated brine
- Sodium sulfate
- Silica gel for chromatography — **irritating**

1. Clean all the glassware and syringes, and dry overnight in a hot oven before use. Allow the glassware to cool in a desiccator.
2. Clamp the 25 mL two-necked flask, and fit the condenser to the flask. Fit the three-way tap to the top of the condenser and the suba seal to the side-arm. Attach the side-arm of the three-way tap to a source of dry nitrogen, and the vertical arm to a source of vacuum. Evacuate the reaction system, and then fill it with nitrogen.

Protocol 2. *Continued*

3. Quickly place methyl 3-iodopropanoate into the flask, followed by zinc/copper couple (0.09 g), see Protocol 1.
4. Evacuate the flask and then fill it with nitrogen. Repeat this process twice more. Add dry benzene (5 mL) and dry dimethylacetamide (0.20 mL) using a syringe.
5. Stir the mixture vigorously at ambient temperature for 1 h, and then warm the reaction mixture using the oil-bath to 60°C (oil-bath temperature), and continue to stir at this temperature for 4 h.
6. Remove the reaction vessel from the heating bath. Add *tetrakis*(triphenylphosphine)palladium as a solution in benzene (1 mL), followed by a solution of freshly distilled benzoyl chloride (0.087 mL, 0.75 mmol) in benzene (0.2 mL). After an initial vigorous reaction, stir the mixture for a further 30 min by which point the reaction mixture has cooled to ambient temperature.
7. Add diethyl ether (50 mL) and filter the mixture through a Celite pad on a medium sintered glass funnel under suction. Wash the filter cake with more diethyl ether (50 mL), and transfer the combined filtrate to a separating funnel. Wash the filtrate with aqueous NH_4Cl solution (10 mL, 1 M), aqueous $NaHCO_3$ solution (5 mL), and aqueous NaCl (10 mL), dry over $MgSO_4$, filter, and remove the solvent on a rotary evaporator.
8. Purify the residue using flash chromatography over silica gel using EtOAc: petroleum ether (40–60) (1:4), to give methyl 4-oxo-4-phenylbutanoate as an oil (180 mg, 93%).

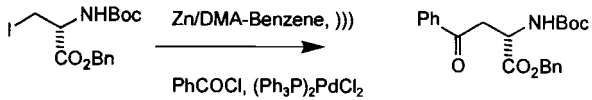
[a] Methyl 3-iodopropanoate was prepared by esterification of commercially available 3-iodobenzoic acid (Aldrich) with absolute methanol using catalytic concentrated sulfuric acid at ambient temperature.
[b] Dry benzene and dry dimethylacetamide were obtained from the Aldrich Chemical Company in Sure/Seal™ bottles and were both used as received.
[c] In general, benzene may effectively be replaced by an identical volume of toluene, thus reducing substantially the hazards associated with the procedure.

The procedure described in Protocol 2 is very effective for similar monofunctionalized alkyl iodides. In the case of somewhat more sensitive zinc reagents, the ability to prepare the zinc reagent more quickly under milder conditions is a substantial advantage.[13] Ultrasonication is an excellent method for increasing the rate of heterogeneous reactions, and it may be applied to the preparation of organozinc reagents.[14] The main challenge is concerned with ensuring that sonication is a reproducible process, which crucially depends on the choice of ultrasonic cleaning bath and with flask placement.[15] Sonication was achieved using a Pulsatron 95 cleaning bath (frequency 38 kHz ± 10%), available from Kerry Ultrasonics Limited, Hitchin, UK. The Pulsatron 95 is a rectangular-shaped bath with two transducers in the base. Other ultrasonic baths have also proved satisfactory, although those which

incorporate a frequency sweep feature (and therefore tend to be more expensive) are less effective. The procedure for carrying out the preparation of a highly functionalized organozinc iodide in Protocol 3 illustrates the process. In this protocol, an excess of the electrophilic reagent (benzoyl chloride) over the iodo precursor to the alkylzinc iodide is used. This is most appropriate in situations where the electrophile is the less valuable reagent. In cases where the electrophile is more valuable, higher yields based on the amount of electrophile used may often be obtained by using an excess of the organozinc iodide (see, for example, Protocol 7).

Protocol 3.
Use of an organozinc reagent for amino acid synthesis under sonochemical conditions

Caution! This procedure should be carried out in an efficient fume-hood to minimize exposure to benzene. Chemically-resistant gloves and safety glasses should be worn.



Scheme 3.7

Equipment

- Ultrasonic cleaning bath
- Source of dry nitrogen
- Source of vacuum
- Two-necked round-bottomed flask (25 mL), fitted with three-way tap and rubber septum• Additional empty two-necked round-bottomed flask (25 mL)
- Syringes (100 μL, 1 mL, 5 mL)
- Needles for syringes (20 gauge)
- Thin-layer chromatography plates (silica) and spotters
- Beaker and watch glass for TLC developing
- Filter papers, fluted
- Separating funnel (125 mL)
- Rotary evaporator
- Chromatography column (20 cm × 2.5 cm)

Materials

• *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine benzyl ester (FW 405), 304 mg, 0.75 mmol	**light-sensitive**
• Zinc/copper couple (FW ~ 65.4), 90 mg, ~ 1.38 mmol	**flammable solid**
• *Bis*(triphenylphosphine)palladium dichloride (FW 701.9), 28 mg, 0.04 mmol	**toxic**
• *N,N*-dimethylacetamide,[a] 0.2 mL	**irritant**
• Benzene,[a,b] 3 mL	**cancer suspect agent, flammable**
• Benzoyl chloride (FW 140.5), 87 μL, 0.75 mmol	**causes burns**
• EtOAc	**flammable, irritant**
• Petroleum ether (40–60)	**flammable, irritant**
• 1 N HCl	**corrosive, toxic**
• Brine	
• Distilled water	
• Sodium sulfate	
• Silica gel for chromatography	**irritating**

Protocol 3. *Continued*

1. Clean all the glassware and syringes, and dry overnight in a hot oven before use. Allow the glassware to cool in a desiccator over phosphorus pentoxide.
2. Clamp the 25 mL two-necked flask, and fit the three-way tap to the central neck and the suba seal to the side-arm. Attach the side-arm of the three-way tap to a source of dry nitrogen, and the vertical arm to a source of vacuum. Evacuate the flask, and then fill it with nitrogen.
3. Quickly place *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine benzyl ester[c] in the flask, followed by zinc/copper couple (0.09 g) (see Protocol 1).
4. Evacuate the flask and then fill it with nitrogen. Repeat this process twice more. Add dry benzene (3 mL) and dry dimethylacetamide (0.2 mL) using a syringe.
5. Fill the ultrasonic cleaning bath with cold (< 20°C) water to the correct level (indicated by an internal lip).
6. Place the reaction flask in the ultrasonic bath above one of the transducers, and place the second empty flask in the bath, as indicated in Fig. 3.1. Switch the bath on and 'tune' it by altering the positions of both flasks until a standing wave is achieved. This is indicated when the surface of the water in the bath is stationary. At this point degradation of ultrasound to audible frequencies should be minimal. The reaction mixture at this stage should start to foam slightly. Check the bath at regular intervals throughout the experiment and re-tune in a similar fashion whenever necessary.
7. Sonicate for 30 min until no starting material remained (as judged by TLC),[d] during which time the bath temperature rises from 22°C to 35°C.
8. Add *bis*(triphenylphosphine)palladium dichloride,[e] followed by freshly distilled benzoyl chloride (87 μL, 0.75 mmol), and sonicate the mixture for a further 30 min, after which a final bath temperature of 42°C was recorded.
9. Add EtOAc (50 mL) and filter the mixture into a separating funnel using a filter funnel and fluted filter paper. Wash the filtrate with aqueous hydrochloric acid (20 mL, 0.1 M) and distilled water (3 × 20 mL), dry the organic extract over anhydrous sodium sulfate, filter, and remove the solvent on a rotary evaporator.
10. Purify the residue using flash chromatography over silica gel using EtOAc:petroleum (1:20, increasing to 1:10). Analytically pure benzyl 2-(*S*)-(*tert*-butoxy carbonyl)amino-4-oxo-4-phenylbutanoate (0.2 g, 70% overall yield) is obtained as a yellow/brown oil.

Data

m.p. 82–83°C. $[\alpha]^{23}_{D}$ +24.7° (c 1.0 in $CHCl_3$); δ_H (300 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.44 (9H, s), 3.56 (1H, dd, $2J_{AB}$ = 16 Hz and $3J_{AX}$ = 3 Hz), 3.79 (1H, dd, $2J_{AB}$ = 16 Hz and $3J_{BX}$ = 3 Hz), 4.76 (1H, m), 5.20 (2H, s), 5.68 (1H, d, J = 4 Hz), 7.32 (5H, m), 7.49 (2H, dd, J = 9, 9 Hz), 7.60 (1H, d, J = 9 Hz), and 7.95 (2H, d, J = 9 Hz).

[a] Dry benzene and dry dimethylacetamide were obtained from Aldrich Chemical Company in Sure/Seal™ bottles and were both used as received.
[b] In general, benzene may effectively be replaced by an identical volume of toluene, thus reducing substantially the hazards associated with the procedure.
[c] *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine benzyl ester is available from Aldrich Chemical Company, or can be prepared by the literature procedure.[13]
[d] The starting iodide is much more sensitive to staining reagents than the protonated material (protected alanine). On balance, it is preferable to have small amounts of unconverted iodide, rather than to prolong sonication which results in degradation of the zinc reagent to protected alanine in the reaction mixture.
[e] *Bis*(triphenylphosphine)palladium dichloride was obtained from Aldrich Chemical Company and was used as received.

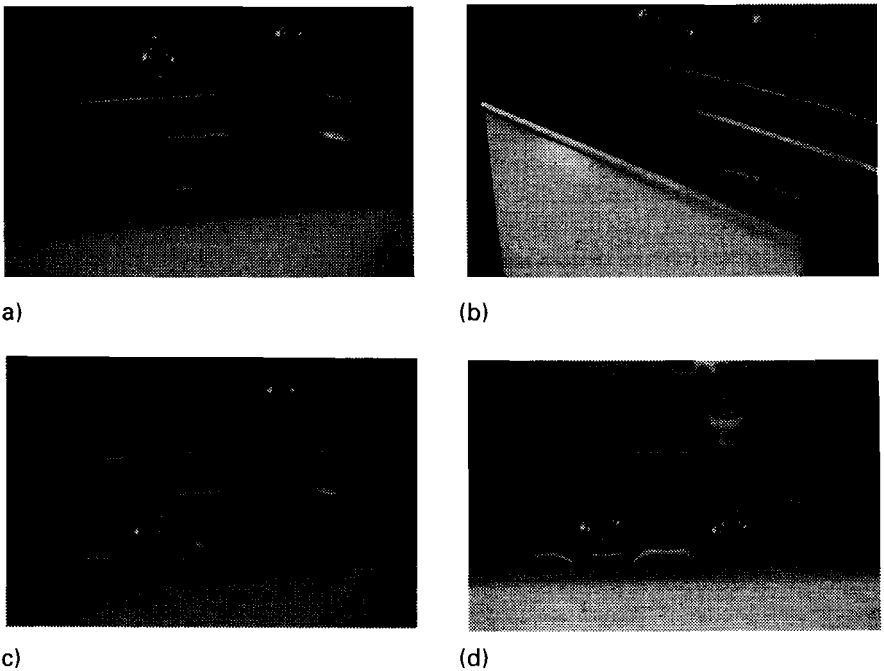
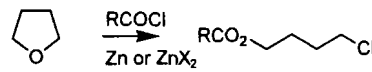


Fig. 3.1 Setting-up and tuning an ultrasonic bath for use in zinc insertion. (a) The ultrasonic bath immediately after switching on. Note the intense disturbance above each of the two transducers. (b) At this point, the surface of the water has settled, but the two positions of maximum agitation are still distinct. (c) Placing the empty flask in the bath results in a smooth water surface, apart from the point immediately above the second transducer. (d) Optimum conditions for ultrasonic zinc insertion are shown here, with a perfectly smooth water surface, and significant frothing in the reaction flask.

4. Preparation of organozinc halides using *in situ* activated zinc

The realization that zinc dust can be activated by treatment, sequentially, with 1,2-dibromoethane and chlorotrimethylsilane, has had a significant impact on

the ease of preparation of organozinc halides. The insertion reactions of zinc activated by this process will often occur efficiently in THF as solvent, which represents a significant improvement in convenience. The only major drawback with the use of THF as solvent is that palladium catalysed reactions of alkylzinc iodides with acid chlorides are often unsuccessful, due to zinc (or zinc salt) induced reaction of the acid chloride with THF.[16] Transmetallation from zinc to copper, and subsequent reaction with an acid chloride, is a good alternative under most circumstances, due to the milder nature of the conditions under which zinc/copper reagents react with acid chlorides.[7]



Scheme 3.8

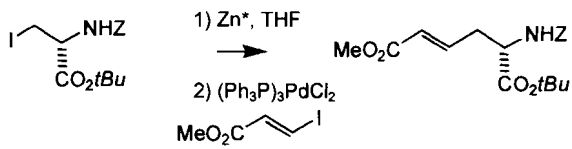
However, for other palladium catalysed reactions of organozinc iodides with electrophiles, THF is a good choice of solvent. The incompatibility of THF and acid chlorides at ambient temperature can also be overcome, in some cases, by the use of a carbonylative cross-coupling in which an iodobenzene derivative is used as the precursor.[17]

The application of organozinc iodides prepared in THF is illustrated in Protocols 4 and 5, which describe the palladium catalysed cross-coupling of a serine-derived organozinc iodide with a vinyl iodide, and the palladium catalysed carbonylative cross-coupling of another serine-derived organozinc iodide with a functionalized aromatic iodide. In the reaction with the vinyl iodide, it is important to transfer the solution of the organozinc iodide from the residual zinc, since this can react unproductively with the electrophile. In the case of the carbonylative coupling with the functionalized aromatic iodide, such a transfer is unnecessary, since the zinc does not react with the electrophile under the reaction conditions. These two protocols also illustrate how to conduct such reactions on different scales.

Protocol 4.
Preparation of a serine-derived organozinc iodide in THF, and coupling with methyl 3-iodopropenoate

Caution! This procedure should be carried out in an efficient fume-hood. Chemically-resistant gloves and safety glasses should be worn.

Equipment



Scheme 3.9

Materials

- Hotplate stirrer, fitted with contact thermometer
- Two magnetic stirrer bars
- Heat gun
- Oil-bath
- Source of dry nitrogen
- Source of vacuum
- Two-necked round-bottomed flask (100 mL), reflux condenser fitted with three-way tap and rubber septum
- Two-necked round-bottomed flask (250 mL), fitted with three-way tap and rubber septum
- Single-neck round-bottom flask (25 mL), fitted with three-way tap
- Syringes (100 μL, 250 μL, 5 mL, 10 mL, 20 mL)
- Needles for syringes (20 gauge)
- Thin-layer chromatography plates (silica) and spotters
- Beaker and watch glass for TLC developing
- Filter papers, fluted
- Separating funnel (1000 mL)
- Rotary evaporator
- Chromatography column (20 cm × 5 cm)

- *N*-(benzyloxycarbonyl)-3-iodo-L-alanine *tert*-butyl ester[a] (FW 405.23), 3.24 g, 8 mmol — **light-sensitive**
- Zinc dust (FW 65.4), –325 mesh, 3.2 g, 24 mmol — **flammable solid**
- 1,2-dibromoethane (FW 187.8), 213 μL, 2.47 mmol — **toxic, cancer suspect agent**
- Me_3SiCl (FW 108.6), 64 μL, 0.5 mmol — **flammable, corrosive**
- Dry tetrahydrofuran[b] — **flammable, irritant**
- *Bis*(triphenylphosphine)palladium dichloride (FW 701.9), 256 mg, 0.36 mmol — **toxic**
- (*E*)-methyl 3-iodopropenoate[c] (FW 211.98), 2.26 g, 10.7 mmol
- EtOAc — **flammable, irritant**
- Petroleum ether (40–60) — **flammable, irritant**
- 1 N HCl — **corrosive**
- Magnesium sulfate
- Silical gel for chromatography — **irritating**

1. Clean the glassware, stirrer bars, and syringes, and dry them overnight in a hot oven before use. Allow the glassware to cool in a desiccator.
2. Clamp the 100 mL two-necked flask, add the stirrer bar, fit the three-way tap to the central neck and the suba seal to the side-arm. Attach the side-arm of the three-way tap to a source of dry nitrogen, and the vertical arm to a source of vacuum. Evacuate the flask, and then fill it with nitrogen.
3. Place the zinc dust into the flask. Quickly evacuate the flask and then fill it with nitrogen using the three-way tap. Repeat this process three times.
4. Add the 1,2-dibromoethane and dry tetrahydrofuran (3.6 mL), and heat the mixture gently at 65°C for 5 min.
5. Allow the mixture to cool to room temperature, and add the trimethylsilyl chloride. Stir the mixture vigorously for 15 min.
6. Weigh the *N*-(benzyloxycarbonyl)-3-iodo-L-alanine *tert*-butyl ester into a dry 25 mL round-bottomed flask, fit a three-way tap, evacuate the flask and fill it with nitrogen, and then add anhydrous THF (8 mL) by syringe. Transfer this solution to the flask containing the activated zinc using a syringe. Warm the mixture to 35°C and stir vigorously under nitrogen until all of the iodide has been converted into the zinc reagent, as determined by TLC using toluene:EtOAc (10:1) as eluent, typically 1 h.
7. Set-up the 250 mL two-necked flask with a three-way tap and septum cap in the same way as described in step 2.
8. Add anhydrous THF (50 mL) to the stirred mixture in the 100 mL flask and

Protocol 4. *Continued*

allow the residual zinc to settle. Transfer the supernatant liquid by syringe to the 250 mL flask, and then add additional anhydrous THF (50 mL) to the residual zinc. Transfer this liquid to the second flask and warm the resulting mixture to 50 °C.

9. Add *bis*(triphenyl)phosphine palladium(II) chloride and (*E*)-methyl 3-iodoprop-2-enoate. Stir the mixture at 50 °C for 2.5 h.
10. Allow the mixture to cool to room temperature, and pour the reaction mixture into EtOAc (400 mL) in a separating funnel. Wash the organic phase with 1 M HCl (200 mL), water (3 × 200 mL), then dry it ($MgSO_4$), and evaporate under reduced pressure to give a brown oil.
11. Purify the residue by flash chromatography on silica gel using petroleum ether (40–60):EtOAc (10:1) as eluent to give the product as an oil (1.96 g, 5.4 mmol, 68%).

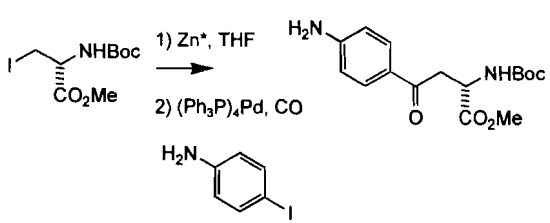
Data

$[\alpha]_D^{21}$ +41.9 (c 0.8 in CH_2Cl_2); δ_H (200 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.45 (9H, s, ^tBu), 2.53–2.85 (2H, m, C(3)H), 3.73 (3H, s, CH_3), 4.33–4.52 (1H, m, C(2)H), 5.11 (2H, s, PhCH_2), 5.39 (1H, d, J = 8.1 Hz, NH), 5.88 (1H, d, J = 15.5 Hz, C(5)H), 6.83 (1H, dt, J = 15.5 and 8 Hz, C(4)H) and 7.31–7.45 (5H, m, Ph); δ_C (125 MHz, $CDCl_3$): 28.0, 35.4, 51.6, 53.3, 67.0, 82.9, 89.9, 124.5, 128.1, 128.2, 128.6, 136.2, 142.6, 155.6, 166.2 and 170.

[a] *N*-(benzyloxycarbonyl)-3-iodo-L-alanine *tert*-butyl ester was prepared by the literature method.[18]
[b] THF was dried by distillation from potassium benzophenone ketyl.
[c] (*E*)-methyl 3-iodopropenoate was prepared by esterification of (*E*)-3-propenoic acid, itself prepared by addition of HI to propiolic acid.

Protocol 5.
Preparation of a serine-derived organozinc iodide in THF, and carbonylative coupling with 4-aminoiodobenzene

Caution! Carbon monoxide is a highly toxic, flammable gas. All procedures should be carried out in an efficient fume-hood. Chemically-resistant gloves and safety glasses should be worn.



Scheme 3.10

Equipment

- Hotplate stirrer, fitted with contact thermometer
- Magnetic stirrer bar
- Hot water (~ 65°C) in a small crystallizing dish
- Source of dry nitrogen
- Source of vacuum
- Two-necked round-bottomed flask (25 mL), reflux condenser fitted with greased glass three-way tap, and rubber septum
- Single-neck round-bottom flask (10 mL), fitted with three-way tap
- Syringes (100 μL × 2, 1 mL)
- Needles for syringes (20 gauge)
- Thin-layer chromatography plates (silica) and spotters
- Beaker and watch glass for TLC developing
- Filter papers, fluted
- Separating funnel (125 mL)
- Rotary evaporator
- Chromatography column (20 cm × 1 cm)

Materials

- *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester[a] (FW 329.13), 247 mg, 0.75 mmol — **light-sensitive**
- Zinc dust (FW 65.4), –325 mesh, 0.3 g, 4.6 mmol — **flammable solid**
- 1,2-dibromoethane (FW 187.8), 19.4 μL, 0.225 mmol — **toxic, cancer suspect agent**
- Me_3SiCl (FW 108.6), 6 μL, 0.046 mmol — **flammable, corrosive**
- Dry tetrahydrofuran — **flammable, irritant**
- *Tetrakis*(triphenylphosphine)palladium (FW 1155.6), 43 mg, 0.04 mmol
- Carbon monoxide — **highly toxic gas, flammable**
- 4-iodoaniline (FW 219), 0.219 g, 1 mmol — **toxic**
- EtOAc — **flammable, irritant**
- Petroleum ether (40–60) — **flammable, irritant**
- 1 M HCl — **corrosive**
- Magnesium sulfate
- Silical gel for chromatography — **irritating**

1. Clean the glassware, stirrer bar, and syringes, and dry them overnight in a hot oven before use. Allow the glassware to cool in a desiccator.
2. Clamp the 25 mL two-necked flask, and fit the three-way tap to the central neck and the suba seal to the side-arm. Attach the horizontal side-arm of the three-way tap to a source of dry nitrogen, and the vertical arm to a source of vacuum. Evacuate the flask, and then fill it with nitrogen.
3. Place the zinc dust into the flask. Quickly evacuate the flask and then fill it with nitrogen using the three-way tap. Repeat this process three times.
4. Add the 1,2-dibromoethane and anhydrous tetrahydrofuran (0.34 mL), and heat the mixture repeatedly using a hot water-bath at 65°C.
5. Allow the mixture to cool to room temperature, and add the trimethylsilyl chloride. Stir the mixture vigorously for 15 min.
6. Weigh the *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester into a dry 10 mL round-bottomed flask, fit a three-way tap, evacuate the flask and fill it with nitrogen, and then add anhydrous THF (0.34 mL) by syringe. Transfer this solution to the flask containing the activated zinc using a syringe. Warm the mixture to 35°C and stir the mixture until no starting material remains as determined by TLC using toluene:EtOAc (10:1) as eluent, typically 15–30 min, and then allow the mixture to cool to room temperature.

Protocol 5. *Continued*

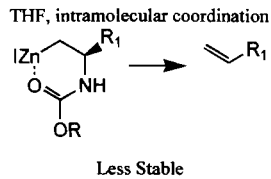
7. Add the 4-iodoaniline and $Pd(Ph_3P)_4$.
8. Fit a balloon filled with carbon monoxide to the vertical arm of the three-way tap, and then attach a source of vacuum to horizontal arm of the three-way tap. Evacuate the reaction flask briefly, and then replace the nitrogen atmosphere by carbon monoxide from the balloon. Repeat this process of evacuation and refilling to ensure that the nitrogen atmosphere is completely replaced with carbon monoxide. Stir the reaction mixture for 30 h at room temperature.
9. Allow the remaining carbon monoxide to vent in the fume-cupboard, and then filter the reaction mixture through fluted filter paper, and partition it between EtOAc (25 mL) and water (25 mL). Wash the organic extracts with brine (25 mL), dry them ($MgSO_4$), and then filter and concentrate to give the crude product.
10. Purify the crude product by flash chromatography with petroleum ether (40–60):EtOAc as eluent to give the pure ketone (135 mg, 58%) as a brown oil.

Data

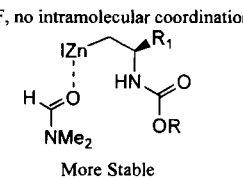
$[\alpha]_D$ +3.0 (c = 0.15, in dichloromethane). δ_H (200 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.4 (s, 9H), 3.3–3.7 (m, 2H), 3.7 (s, 3H), 4.6 (m, 1H), 5.6 (d, 1H, J = 8.2 Hz), 6.6 (m, 2H), 7.4–7.8 (m, 4H).

[a] *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester is available from Aldrich Chemical Company.

Recently it has become clear that organozinc halides can also be formed in more polar solvents than tetahydrofuran, for example in dimethylformamide.[19] Organozinc halides with a urethane protected β-amino group appear to be much more stable in polar solvents. This increased stability is due to the inhibition of intramolecular coordination by the urethane carbonyl to the zinc atom, which in turn can lead to facile β-elimination.[20]



Scheme 3.11



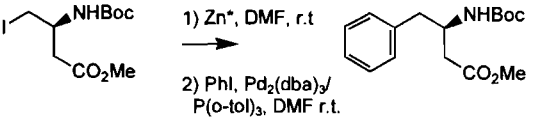
Scheme 3.12

The value of this process is illustrated by the preparation of the β-amino acid analogue of phenylalanine. This process is particularly convenient because both the zinc insertion reaction, and the subsequent palladium catalysed

coupling with iodobenzene, occur at room temperature. Attempts to perform this coupling in THF result in very much lower yields.

Protocol 6.
Preparation of an aspartic acid-derived organozinc iodide in DMF, and its coupling with iodobenzene

Caution! This procedure should be carried out in an efficient fume-hood. Chemically-resistant gloves and safety glasses should be worn.



Scheme 3.13

Equipment

- Hotplate stirrer
- Magnetic stirrer bar
- Hot water (~ 65°C) in a small crystallizing dish
- Source of dry nitrogen
- Source of vacuum
- Two-necked round-bottomed flask (50 mL), three-way tap and rubber septum
- Single-neck round-bottom flask (10 mL), fitted with three-way tap
- Syringes (100 μL × 2, 1 mL)
- Needles for syringes (20 gauge)
- Thin-layer chromatography plates (silica) and spotters
- Beaker and watch glass for TLC developing
- Filter papers, fluted
- Separating funnel (125 mL)
- Rotary evaporator
- Chromatography column (20 cm × 1 cm)

Materials

- Methyl 2(*S*)-(*tert*-butoxycarbonyl)amino-4-iodobutanonate[a] (FW 343.16), 257 mg, 0.75 mmol — **light-sensitive**
- Zinc dust (FW 65.4), –325 mesh, 294 mg, 4.5 mmol — **flammable solid**
- 1,2-dibromoethane (FW 187.8), 19.4 μL, 0.23 mmol — **toxic, cancer suspect agent**
- Me_3SiCl (FW 108.6), 6 μL, 0.05 mmol — **flammable, corrosive**
- Dry DMF[a,b] — **flammable, irritant**
- *Tris*(dibenzylideneacetone)dipalladium (FW 915.7), 22.8 mg, 0.025 mmol
- Tri-*o*-tolylphosphine (FW 304.38), 30.4 mg, 0.1 mmol
- Iodobenzene (FW 204), 110 μL, 1 mmol — **harmful, irritating to eyes**
- EtOAc — **flammable, irritant**
- Petroleum ether (40–60) — **flammable, irritant**
- Brine
- Magnesium sulfate

1. Clean the glassware, stirrer bar, and syringes, and dry them overnight in a hot oven before use. Allow the glassware to cool in a desiccator.
2. Clamp the 50 mL two-necked flask, and fit the three-way tap to the central neck and the suba seal to the side-arm. Attach the horizontal side-arm of the three-way tap to a source of dry nitrogen, and the vertical arm to a source of vacuum. Evacuate the flask, and then fill it with nitrogen.

Protocol 6. *Continued*

3. Place the zinc dust into the flask. Quickly evacuate the flask and then fill it with nitrogen using the three-way tap. Repeat this process three times.
4. Add the 1,2-dibromoethane and anhydrous DMF (0.5 mL), and heat the mixture using a hot water-bath at 65°C for 20 min, and then allow it to cool to room temperature.
5. Add Me_3SiCl and stir the mixture vigorously for 30 min.
6. Weigh the methyl 2(*S*)-(*tert*-butoxycarbonyl)amino-4-iodobutanonate into a dry 10 mL round-bottomed flask, fit a three-way tap, evacuate the flask and fill it with nitrogen, and then add anhydrous DMF (0.5 mL) by syringe. Transfer this solution to the flask containing the activated zinc using a syringe. Stir the mixture at room temperature until no starting material remains as determined by TLC using petroleum ether (40–60):EtOAc, 2:1 as eluent, typically 15 min.
7. Add iodobenzene by syringe, and the *tris*(dibenzylideneacetone)dipalladium and tri-*o*-tolylphosphine as solids successively to the reaction mixture.
8. Stir the reaction mixture at room temperature for 3 h, transfer it to a separating funnel, and then dilute it with EtOAc (50 mL). Wash the solution with brine, dry it ($MgSO_4$), and remove the solvent.
9. Purify the product by flash column chromatography over silica using petroleum ether (40–60):EtOAc, 6:1 as eluent to give the protected 4-aryl-β-amino acid (0.18 g, 75%), isolated as a white solid.

Data

m.p. 48–50°C. $[\alpha]_D$ +20.8 (c 1.28 in MeOH). δ_H (500 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.46 (9H, s), 2.49 (1H, dd, J = 6 and 16 Hz), 2.56 (1H, dd, J = 5.5 and 16 Hz), 2.86 (1H, J = 8.0, 13.5), 2.96–2.98 (1H, m), 3.73 (3H, s), 5.12 (1H, br d, J = 6.7 Hz) and 7.23–7.38 (5H, m); δ_C (125 MHz, $CDCl_3$, Me_4Si) 28.17, 37.46, 40.30, 48.72, 51.53, 79.26, 126.51, 128.44, 129.30, 137.65, 155.05 and 172.06.

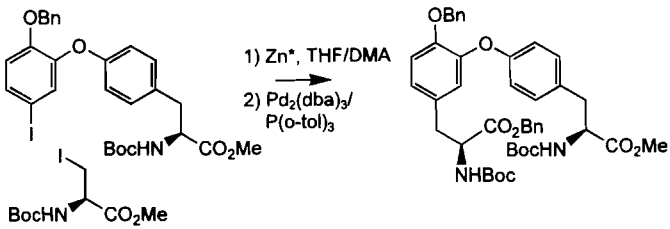
[a] Prepared by treatment of *N*-Boc-aspartic acid β-methyl ester with *N*-hydroxysuccinimide in the presence of *N,N*-dicyclohexylcarbodiimide,[21] reduction with $NaBH_4$ in aqueous THF, and conversion into the iodide using PPh_3, I_2, and imidazole.[22]

[b] DMF was dried by distillation under reduced pressure from CaH_2, and stored over 4 Å molecular sieves.

As a final illustration of the tremendous functional group compatibility of alkylzinc iodides, the preparation of a protected *iso*-dityrosine derivative is described in Protocol 7.[23] This procedure is noteworthy in the that it illustrates the possibility of inserting zinc selectively into an aliphatic carbon–iodine bond in the presence of an aromatic carbon–iodine bond. This stands in sharp contrast to the situation described in Protocol 4 where excess zinc can react with the electrophile, and must therefore be removed. The selectivity of

this process described in Protocol 7 is probably enhanced by the highly electron-rich nature of the aromatic iodide. The detailed procedures for the cleaning the glassware before the experiment reflect the need to maximize the yield of product from a valuable starting material. The procedures for carrying out the reaction under argon, and in a single-neck flask, show how the reaction can be successfully achieved on a very small scale.

Protocol 7.
Synthesis of protected *iso*-dityrosine



Scheme 3.14

Equipment

- Hotplate stirrer
- Oil-bath
- Round-bottomed flask (10 mL)
- Rubber septum
- Teflon-covered magnetic stirring bar (flea size)
- Syringes (10 μL × 2, 1 mL × 2, 2 mL)
- Needles for syringes (20 gauge)
- Heat gun
- Thin-layer chromatography plates (silica) and spotters
- Beaker and watch glass for TLC developing
- Source of dry argon with needle adapter
- Tygon tubing
- Oil bubbler
- Microscale filter: Pasteur pipette, cotton, sand, Celite (optional)
- Filter papers, fluted
- Separating funnel (125 mL)
- Rotary evaporator
- Chromatography column (20 cm × 1 cm)

Materials

- *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine benzyl ester (FW 405), 195 mg, 0.48 mmol — **light-sensitive**
- Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-[5-iodo-2-(phenylmethoxy)phenyl] tyrosinate (FW 603), 145 mg, 0.24 mmol
- Zinc dust, –325 mesh, oven-dried (FW 65.4), 94 mg, 1.44 mmol — **flammable solid, moisture-sensitive**
- 1,2-dibromoethane (FW 187.9), 6.2 mL, 72 mmol — **toxic**
- Me_3SiCl (FW 109), 1.8 mL, 14 mmol — **corrosive, toxic**
- *Tris*(dibenzylideneacetone)dipalladium(0) (FW 1035), 12 mg, 12 mmol
- Tri-*o*-tolylphosphine (FW 304.4), 15 mg, 48 mmol — **irritant**
- Dry tetrahydrofuran — **flammable, irritant**
- Dry *N,N*-dimethylacetamide — **irritant**
- EtOAc — **flammable, irritant**
- Dry diethyl ether — **flammable, toxic**
- Dichloromethane — **toxic, irritant**

Protocol 7. *Continued*

- Hexanes — **flammable, irritant**
- 1 M HCl — **corrosive, toxic**
- Saturated brine
- Distilled water
- Magnesium sulfate

1. Clean the round-bottomed flask and stir bar by soaking overnight in *aqua regia* (1:3, HNO_3:HCl), followed by treatment in a base bath (KOH:isopropanol) overnight, before rinsing with distilled water and reagent grade acetone. These materials, along with the syringes and needles, were dried overnight in an oven before use.
2. Weigh the oven-dried zinc dust into the oven-dried, round-bottomed flask containing a stirrer bar and then quickly fit the hot flask with a rubber septum.
3. Clamp the flask above the hotplate stirrer. Flush the flask with argon by piercing the septum with a needle from the argon source and a second needle for venting. Allow the gas to flow through the flask for a minute. Reduce the gas pressure and attach the venting needle to a gas bubbler.
4. Zinc activation: using a syringe for each, add THF (0.2 mL) and 1,2-dibromoethane to the flask. Warm the resulting mixture briefly with a heat gun until the solvent begins to boil, then stir vigorously for a few minutes. Repeat this procedure five times. Use an oil-bath to bring the flask to 35 °C before adding Me_3SiCl using a syringe. Stir the zinc suspension vigorously for 30 min.
5. Using a syringe, add dropwise a solution containg both the aryl iodide, methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*O*-[5-iodo-2-(phenylmethoxy)phenyl] tyrosinate, and *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine benzyl ester dissolved in 1:1 THF:*N*,*N*-dimethylacetamide (2 mL). Follow the zinc insertion reaction by TLC analysis (eluent 1:4 diethyl ether:hexanes). Note the disappearance of the iodoalanine starting material (R_f = 0.38) and the appearance of the corresponding alanine derivative which indicates the presence of the quenched zinc reagent (R_f = 0.24); the insertion should be complete within 15–30 min. To minimize exposure to the atmosphere while collecting TLC samples, the septum can be pierced with a one inch segment of a wide bore needle, through which the TLC capillary spotters can be introduced.
6. Once the zinc insertion is complete, briefly remove the septum and quickly add the $Pd_2(dba)_3$ and P(*o*-tol)$_3$. Flush the flask with argon as before. Heat the resulting mixture at 55 °C for 2 h.
7. Dilute the dark green reaction mixture with 10 mL EtOAc and filter through a Pasteur pipette packed with a cotton plug and a layer of sand (and layer of Celite, optional). Direct the filtrate into a separating funnel charged with 1 M

HCl (10 mL) and EtOAc (15 mL). After washing with acid and removing the aqueous layer (bottom), wash the organic layer (top) successively with distilled water (3 × 10 mL) and brine. Dry the organic layer over $MgSO_4$, filter to remove the drying agent, and remove the solvents on a rotary evaporator.

8. Purify the product by flash column chromatography (eluent 5–10% diethyl ether in dichoromethane).
9. Remove the solvent on a rotary evaporator, and then place under high vacuum. The product is isolated as a colourless oil (136 mg, 0.18 mmol, 75% yield).

Data

$[\alpha]_D$ +29.5 (c = 2.0, $CHCl_3$). δ_H (400 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.40 (9H, s), 1.42 (9H, s), 2.96 (1H, dd, *J* = 14.1, 5.9 Hz), 3.02 (1H, m), 3.04 (2H, m), 3.67 (3H, s), 4.56 (2H, m), 4.99 (2H, m), 5.03 (2H, s), 5.07 (2H, s), 6.76 (2H, m), 6.82 (2H, d, *J* = 8.5 Hz), 6.88 (1H, m), 7.03 (2H, d, *J* = 8.5 Hz), 7.18 (2H, br d, *J* = 6.6 Hz), 7.37–7.22 (8H, m).

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4

Fluorinated organozinc reagents

CHARLES R. DAVIS and DONALD J. BURTON

1. Introduction

Fluorinated organometallic reagents provide a general method for the introduction of fluorine into organic molecules and the chemistry of fluorinated vinyl, alkynyl, benzyl, allyl, propargyl, and aryl organometallics[1] as well as the chemistry of perfluoroalkyl and functionalized perfluoroalkyl organometallics[2] has been recently reviewed. The synthetic utility of many of these organometallic reagents, particularly the fluorinated lithium and Grignard reagents, has been impeded by their limited thermal stability. In recent years, however, significant progress has been made in the preparation and application of diverse fluorinated organozinc reagents which exhibit superior thermal stability. This chapter focuses on the practical aspects of preparation, handling, and application of salient fluorinated vinyl, alkynyl, allyl, Reformatsky, and dialkoxyphosphinylzinc reagents which typify the expanding utility of fluorinated organozinc reagents in organic synthesis.

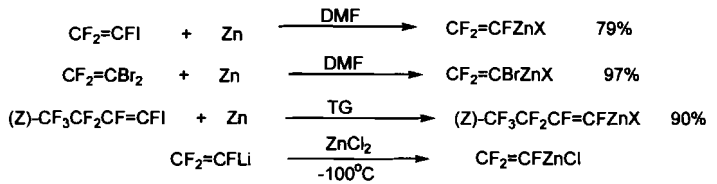
2. Fluorinated vinylzinc reagents

Fluorinated vinylzinc reagents have been prepared by two methods:

(a) Capture of the corresponding vinyllithium reagent at low temperatures with a zinc salt.[3]

(b) Direct insertion of zinc into the carbon–halogen bond of a vinyl halide.[4]

The latter method involves treatment of fluorovinyl iodides and bromides with activated zinc. Typical examples are illustrated in Scheme 4.1.[3,4]



Scheme 4.1

The corresponding vinyl chlorides are less reactive in the insertion of zinc but may be utilized in the first method to provide vinyllithium reagents. Although the starting iodides and bromides are typically more expensive, the direct metallation procedure is straightforward, and has the advantage of avoiding low temperatures. Fluorovinyl iodides give the zinc reagents at room temperature while the flourovinyl bromides react at room temperature to 60 °C.[4] Induction periods vary from a few seconds to one hour but are generally fastest with the iodides. A variety of solvents can be employed in preparation of vinylzinc reagents from the vinyl iodides (THF, DMF, DMAC, TG = triglyme, CH_3CN), whereas the vinyl bromides require more polar solvents such as DMF or DMAC.[4] The zinc reagents are formed as mono/bis mixtures; the ratio varies with the structure of the vinyl halide and solvent. The mono/bis reagents are distinguishable by ^{19}F NMR analysis. Upon addition of the appropriate zinc halide, the signals for the mono reagent increase at the expense of the signals for the bis reagent according to the Schlenk equilibrium (Equation 4.1):

$$R_f(CF{=}CF)_2Zn + ZnX_2 \rightleftharpoons 2\,R_fCF{=}CFZnX \qquad (4.1)$$

The fluorinated vinylzinc reagents exhibit excellent thermal stability.[4] A sample of (Z)–$CF_3CF{=}CFZnX$ in triglyme (TG) showed no loss of activity after three days at room temperature and only 10% of the zinc reagent decomposed after 36 days at room temperature. A 25% loss of activity was observed after the sample was heated at 65 °C for 36 days. Preparation of the zinc reagents is amenable to both small and molar scales. As a consequence of the thermal stability it is practical to generate the zinc reagents on a large scale, determine the molarity by ^{19}F NMR, and utilize aliquots in synthetic transformations over an extended time period. When Zn serves as the limiting reagent in these direct metallations, the excess vinyl halide can be removed from the reaction mixture under reduced pressure. In the case of the more expensive vinyl halides, it is prudent to utilize excess Zn to consume as much of the vinyl halide as possible. In cases where the excess Zn is incompatible with reagents employed in subsequent transformations, the Zn is readily removed by filtration.

Protocol 1.
Preparation of a fluorovinylzinc reagent by direct metallation of a fluorovinyl halide: preparation of 1,2,2-trifluoroethenylzinc bromide[4,5]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.

$$CF_2{=}CFBr + Zn \xrightarrow{DMF} CF_2{=}CFZnX$$

Equipment

- Oven-dried, 1 L round-bottomed, three-necked flask equipped with a magnetic stir bar, thermometer adapter, N_2 inlet, and dry ice condenser
- Vacuum source
- Dry N_2 source
- Ice water-bath

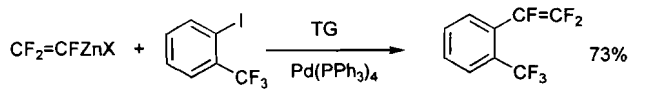
Materials

- Acid washed Zn,[a] 81.7 g, 1.25 mol — **irritant**
- Dry DMF,[b] 500 mL — **irritant, harmful by inhalation**
- Bromotrifluoroethylene,[c] 188 g, 1.2 mol — **pyrophoric, harmful**
- Dry ice — **avoid skin contact**

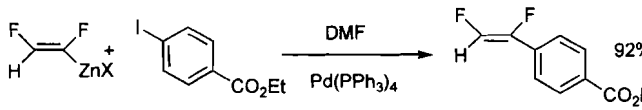
1. Assemble the apparatus as described above. Maintain a slight positive N_2 pressure throughout the course of the reaction. Add the acid washed Zn and DMF to the reaction flask.
2. Attach the bromotrifluoroethylene cylinder to the condenser with rubber tubing and condense approx. 20 g (0.1 mol) of the bromotrifluoroethylene into the reaction flask. Stir the mixture at room temperature until the reaction initiates, as evidenced by an exotherm and formation of a dark brown coloured mixture. If initiation does not occur within 1 h at room temperature, warm the flask gently to 50–60 °C with a heat gun to initiate metallation.
3. Place the solution into an ice-bath and condense the remaining bromotrifluoroethylene (168 g, 1.04 mol) into the flask at a rate such that the temperature remains at 40–50 °C. After the addition is complete, remove the ice-bath and stir for an additional 1 h at room temperature.
4. Remove any unreacted bromotrifluoroethylene under reduced pressure (< 5 mmHg, room temperature, 20 min).
5. Store the CF_2=CFZnBr/DMF solution in the stoppered flask at room temperature. Characterize by ^{19}F NMR analysis of the mixture and determine the molarity by relative integration versus internal $PhCF_3$ standard. Aliquots for subsequent reactions are conveniently drawn out via syringe. ^{19}F NMR (DMF, versus internal $CFCl_3$, mono/bis ~ 90:10): mono reagent –96.3 (dd, 1F, *cis*-CF=CF_2, F_a); –130.4 (dd, 1F, *trans*-CF=CF_2, F_b); –194.7 (dd, 1F, CF=CF_2, F_c) (J_{ab} = 93 Hz, J_{ac} = 33 Hz, J_{bc} = 105 Hz) p.p.m.

[a] Place 100 g of Zn powder and 0.9 L of water into a 1 L Erlenmeyer flask equipped with a stir bar. With stirring, add 10 mL concentrated HCl over 1 min. Stir the slurry for 20 min and decant the water. Wash the metal with water (3 × 250 mL), acetone (3 × 150 mL), and diethyl ether (2 × 100 mL). Transfer the metal to a flask equipped with vacuum take-off and dry under full vacuum for 3 h.
[b] DMF is distilled from CaH_2 under reduced pressure.
[c] Commercially available.

Fluorinated vinylzinc reagents readily undergo coupling with aryl iodides in the presence of catalytic $Pd(PPh_3)_4$ to afford the corresponding vinyl arenes in good yield (Equations 4.2 and 4.3).[5,6]

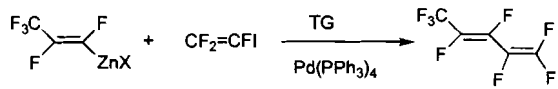


(4.2)

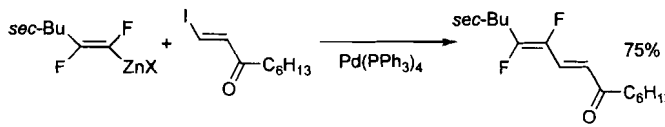


(4.3)

Similar coupling occurs with both fluorovinyl[7,8] and non-fluorovinyl[3,9] iodides, and is particularly useful for the preparation of fluorinated polyenes (Equations 4.4 and 4.5).



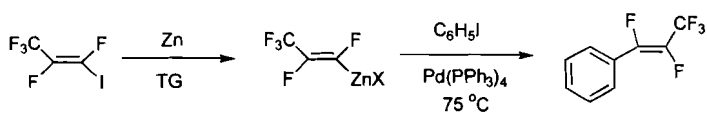
(4.4)



(4.5)

Protocol 2.
$Pd(PPh_3)_4$ catalysed coupling of a fluorovinylzinc reagent: preparation of 1,2,3,3,3-pentafluoro-1-phenylprop-1-ene[5]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, two-necked, 100 mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and cold water condenser topped with a glass N_2 tee
- Dry N_2 source
- Oil-bath heater
- Liquid N_2 flask

Materials

• Acid washed Zn,[a] 5 g, 76 mmol	**irritant**
• (*Z*)-$CF_3CF{=}CFI$,[b] 12.9 g, 50 mmol	**irritant, harmful by inhalation**
• Dry triglyme (TG),[c] 40 mL	**teratogen**
• Iodobenzene, 8.2 g, 40 mmol	**irritant**
• $Pd(PPh_3)_4$,[d] 0.3 g, 0.26 mmol	**air-sensitive, irritant**
• Liquid N_2	**avoid skin contact**

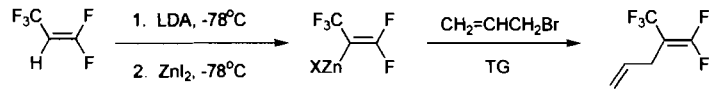
1. Assemble the apparatus as described above. Maintain a slight positive N_2 pressure throughout the course of the reaction.
2. Add the Zn to the flask, then the TG, followed by the (Z)–$CF_3CF{=}CFI$. Stir the mixture for 1 h at room temperature, during which time exothermic formation of the zinc reagent will result in a dark coloured reaction mixture.
3. Verify formation of the (Z)–$CF_3CF{=}CFZnX$ (X = I, $CF{=}CFCF_3$, mono/bis ~ 70:30) by ^{19}F NMR and determine the ^{19}F NMR yield (typically > 95%). ^{19}F NMR (TG, versus internal $CFCl_3$): –67.6 (two overlapped dd, 3F, $CF_3CF{=}CFZnX$); –148.0 (two overlapped dq, 1F, $CF_3CF{=}CFZnX$), –180.8 (two overlapped dq, 1F, $CF_3CF{=}CFZnX$) p.p.m.
4. Add the iodobenzene to the zinc reagent/TG solution, followed by the $Pd(PPh_3)_4$. Heat and stir the mixture at 75°C for 4 h.
5. Flash distill the reaction mixture (1 mmHg, oil-bath temperature 70°C) into a liquid N_2 cooled receiver.
6. Pour the distillate into iced-water (200 mL) and remove the organic layer with a pipette. Wash the organic layer twice with ice-water and dry over P_2O_5. Purify by distillation through a 6 inch Vigreaux column (b.p. 52–53°C, 15 mmHg) to obtain 6.6 g (80%, based on iodobenzene) of (*E*)-$C_6H_5CF{=}CFCF_3$ as a clear liquid of > 98% GLPC purity. ^{19}F NMR (TG versus internal $CFCl_3$): –68.0 (dd, J = 22, 10 Hz, 3F), –145.7 (dq, J = 132 , 22 Hz, 1F), –171.1 (dq, J = 132, 10 Hz, 1F); ^1H NMR ($CDCl_3$): 7.6 (s); MS (m/e): 208 (M^+, 100), 189 (23.9), 169 (32.1), 158 (69.8), 139 (22.4), 138 (21.1), 119 (24.5); IR: 1710 (w), 1430 (w), 1340 (s), 1265 (m), 1160 (s), 1070 (s), 845 (w), 740 (w), 670 (w) cm^{-1}.

[a] See Protocol 1.
[b] (*Z*)-$CF_3CF{=}CFI$ is prepared from $CF_3CF{=}CF_2$ according to the literature procedure.[10]
[c] TG is distilled from Na/benzophenone ketyl under reduced pressure.
[d] Although $Pd(PPh_3)_4$ is commercially available, best results are obtained when this catalyst is prepared according to the literature procedure,[11] with the one modification that the catalyst is dried under vacuum for 8 h instead of under a slow stream of nitrogen.

Generation of $(CF_3)ZnXC{=}CF_2$ (Protocol 3) serves as an example of zinc reagent preparation by capture of vinyllithium reagents with Zn halides and as an example of an internal vinylzinc reagent. $(CF_3)ZnXC{=}CF_2$ has also been prepared via a novel one-pot dehalogenation of $CF_3CBr_2CF_3$.[12] $(CF_3)ZnXC{=}CF_2$ participates in $Pd(PPh_3)_4$ catalysed coupling reactions[13] and undergoes allylation in the absence of a copper(I) halide catalyst.[13]

Protocol 3.
Generation and functionalization of a fluorovinylzinc reagent prepared by capture of a vinyllithium reagent: preparation of 1,1-difluoro-2-trifluoromethylpenta-1,4-diene[13]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, 500 mL, three-necked round-bottomed flask equipped with a magnetic stir bar, rubber septum, low temperature thermometer adapter, and a dry ice/IPA condenser with a N_2 inlet
- Liquid N_2 flask
- Oil-bath heater
- Vacuum source
- Dry N_2 source

Materials

- 2-hydropentafluoropropene,[a] 13.2 g, 100 mmol — **flammable, harmful**
- *t*-BuLi, 1.7 M in pentane, 95 mmol — **pyrophoric, moisture-sensitive**
- Diisopropylamine, 10.6 g, 105 mmol — **flammable, corrosive**
- Dry diethyl ether, 200 mL — **flammable**
- ZnI_2/THF solution[b] — **flammable**
- Dry TG,[c] 75 mL — **teratogen**
- Allyl bromide, 2.4 g, 20 mmol — **highly toxic, flammable**
- Liquid N_2 — **avoid skin contact**
- Dry ice — **avoid skin contact**

1. Assemble the reaction apparatus and place in an empty N_2 bath. Maintain a slight positive N_2 pressure throughout the course of the reaction.
2. Add the diethyl ether and diisopropylamine. With stirring cool the solution to –78°C by placing a liquid N_2/petroleum ether mixture in the liquid N_2 bath.
3. To the cooled solution, add the *t*-BuLi dropwise via syringe, maintaining the temperature at –78°C. After addition is complete, stir the solution at –78°C for 10 min, and then allow to warm to room temperature over 30 min.
4. Recool the resultant lithium diisopropylamide (LDA) solution to –78°C with the liquid N_2/petroleum ether bath. Condense the 2-hydropentafluoropropene into the stirred LDA solution slowly, so as to maintain a temperature of –78°C to –80°C. After addition is complete, continue stirring the orange coloured solution of $CF_3(Li)C{=}CF_2$ for 30 min at –78°C.
5. Add the ZnI_2/THF solution via syringe, maintaining the temperature at –75°C. Care must be taken to maintain consistent stirring as precipitate will

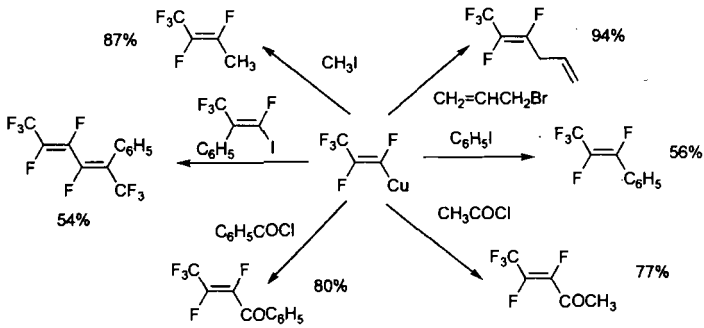
form. After addition is complete, stir for 1 h at –78°C, and then allow to warm to room temperature to give a brown coloured solution.

6. Replace the condenser with a flash distillation apparatus fitted with a 500 mL receiver cooled in a dry ice/IPA bath. Flash distill all of the volatile material from the reaction flask under vacuum at room temperature. When transfer of volatile materials is no longer observed, add the TG to the reaction mixture via syringe and heat the mixture with an oil-bath to 70°C. When the TG begins to flash distill, remove the heat source but allow the mixture to remain under full vacuum for 2.5 h at room temperature.
7. Verify formation of $CF_3(ZnX)CF{=}CF_2$ by ^{19}F NMR and determine the molarity and ^{19}F NMR yield (typically 90%). Store the stoppered reagent solution under N_2 for subsequent reactions. ^{19}F NMR (TG, versus internal $CFCl_3$): –48.9 (dd, 3F, CF_3, F_a); –61.1 (dq, 1F, *cis*-$CF{=}CF_2$, F_b); –72.3 (m, 1F, *trans*-$CF{=}CF_2$, F_c) (J_{ab} = 17 Hz, J_{ac} = 12 Hz, J_{bc} = 34 Hz) p.p.m.
8. Assemble a dry, 50 mL, two-necked round-bottomed flask apparatus equipped with a magnetic stir bar, and cold water condenser topped with a N_2 inlet. Transfer an aliquot of the $CF_3(ZnX)C{=}CF_2$/TG solution (22.5 mmol) to the flask via syringe.
9. With stirring, add the allyl bromide via syringe. Stir the mixture for 12 h at room temperature.
10. Flash distill the reaction mixture (room temperature, 1 mmHg) into a dry ice/IPA cooled receiver.
11. Purify the flash distillate by redistillation through a 6 cm Vigreaux column (b.p. 55–57°C, 760 mmHg) to obtain 3 g (87%) of 1,1-difluoro-2-trifluoromethyl-1,4-pentadiene as a colourless liquid of > 99% GLPC purity. ^{19}F NMR ($CDCl_3$ versus internal $CFCl_3$): –62.3 (dd, J = 22, 10 Hz, 3F), –78.9 (dq, J = 22, 22 Hz, 1F), –83.7 (dq, J = 22, 10 Hz, 1F); ^1H NMR ($CDCl_3$): 2.89 (ddd, J = 6, 1, 1 Hz, 2H), 5.10 (ddt, J = 10, 1, 1 Hz, 1H), 5.14 (ddt, J = 17, 1, 1 Hz), 5.76 (ddt, J = 17, 10, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$): 123.7 (qdd, J = 271, 13, 6 Hz), 156.9 (ddq, J = 303, 291, 5 Hz), 86.0 (qdd, J = 33, 28, 9 Hz), 132.9 (s), 117.6 (s), 27.6 (s); MS (m/e): 172 (M^+, 100), 163 (61.6), 162 (74.4), 151 (74.5), 145 (27.9), 131 (29.3), 103 (60.5); IR (CCl_4): 1749 (s), 1718 (w), 1440 (w), 1362 (s), 1360 (s), 1314 (m), 1298 (m), 1139 (s), 1128 (s) 1006 (s) cm^{-1}.

[a] Commercially available.
[b] Add I_2 (1 equiv) slowly to acid washed Zn (1 equiv) in dry THF with stirring. Stir for 2 h at room temperature and remove the THF under vacuum.
[c] TG is distilled from Na/benzophenone ketyl under reduced pressure.

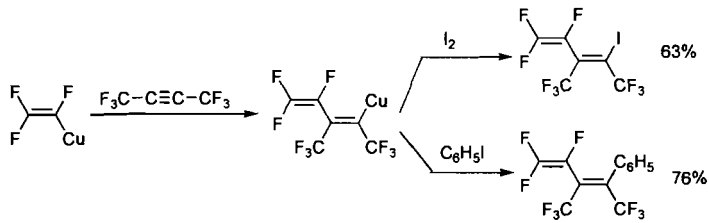
Although there are several exceptions, perfluorinated vinylzinc reagents react only slowly with allyl or acyl halides. Transmetallation of the vinyl zinc reagents to copper(I) halides provides high yields of vinylcopper reagents

which readily undergo coupling reactions with allyl, vinyl, acyl, methyl, and aryl halides (Scheme 4.2).[14]



Scheme 4.2

Trifluorovinylcopper also adds stereospecifically to perfluoroalkynes.[15] Quenching of the intermediate affords *syn* addition products (Equation 4.6).[15,16]

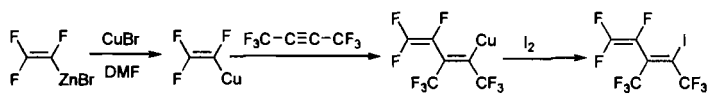


(4.6)

In the absence of oxygen and moisture, the fluorovinylcopper reagents are stable at room temperature but decomposition increases at 50°C.[15] The sequence of direct metallation with zinc, metathesis with copper halide, and functionalization of the intermediate copper reagent is amenable to a one-flask procedure.

Protocol 4.
Copper halide transmetallation of a fluorovinylzinc reagent and refunctionalization of the copper reagent: preparation of (*Z*)-1,1,2,5,5,5-hexafluoro-4-iodo-3-trifluoro methylpenta-1,3-diene[15,16]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, three-necked, 1 L round-bottomed flask equipped with a dry ice/IPA condenser, dry N_2 inlet, rubber septum, and magnetic stir bar
- Oil-bath heater
- Ice water-bath
- Oven-dried, three-necked, 250 mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, dry N_2 inlet, and thermometer adapter
- Dry N_2 source
- Liquid N_2 flask

Materials

- $F_2C{=}CFZnBr$/DMF solution, 186 mmol — **irritant, harmful by inhalation**
- CuBr, 29.4 g, 192 mmol — **irritant, hygroscopic**
- Perfluoro-2-butyne,[a] 33 g, 206 mmol — **flammable**
- I_2, 6.6 g, 26 mmol — **toxic, harmful vapour**
- Liquid N_2 — **avoid skin contact**

1. Assemble the 1 L apparatus. Maintain a slight positive N_2 pressure throughout the course of the reaction.
2. Add the CuBr. Transfer an aliquot of $F_2C{=}CFZnBr$/DMF solution (prepared as outlined in Protocol 1) to the reaction flask. Stir for 20 min at room temperature and verify formation of $CF_2{=}CFCu$ by ^{19}F NMR analysis of the reaction mixture. ^{19}F NMR yields are typically quantitative. ^{19}F NMR (DMF, versus internal $CFCl_3$): –96.1 (dd, 1F, *cis*-CF=CF_2, F_a); –131.3 (dd, 1F, *trans*-CF=CF_2, F_b); –182.8 (dm, 1F, CF=CF_2, F_c) (J_{ab} = 100 Hz, J_{ac} = 32 Hz, J_{bc} = 100 Hz).
3. With stirring, condense the perfluoro-2-butyne into the $CF_2{=}CFCu$/DMF solution. After addition is complete, stir the mixture at room temperature for 3 h. Verify formation of the $CF_2{=}CF{-}C(CF_3){=}C(CF_3)Cu$ by ^{19}F NMR analysis. Store the dienylcopper reagent at room temperature under N_2. ^{19}F NMR (DMF, versus internal $CFCl_3$): –53.5 (bs, 3F, CF_3, F_a); –58.2 (q, 3F, CF_3, F_b); –102.5 (dd, 1F, *cis*-CF=CF_2, F_c); –115.8 (dd, 1F, *trans*-CF=CF_2, F_d); –158.5 (dd, 1F, CF=CF_2, F_e) (J_{cd} = 73 Hz, J_{ce} = 28 Hz, J_{de} = 117 Hz) p.p.m.
4. Assemble the 250 mL apparatus. Maintain a slight positive N_2 pressure throughout the course of the reaction.
5. Transfer an aliquot of the $CF_2{=}CF{-}C(CF_3){=}C(CF_3)Cu$/DMF solution to the flask via syringe.
6. Add the I_2 in small portions, cooling the flask periodically in an ice-bath so as to maintain a temperature of ~ 30°C.
7. Replace the thermometer and rubber septum with glass stopcocks and flash distill the reaction mixture (oil-bath temperature 60°C, 0.2 mmHg) into a liquid N_2 cooled receiver.
8. Wash the distillate in a separatory funnel with an equal volume of cold water to remove DMF. Remove the lower product layer, dry over $MgSO_4$, and purify by distillation (b.p. 73°C, 746 mmHg) through a short path apparatus into a liquid N_2 cooled receiver to obtain 6.1 g (63%) of (*Z*)-1,1,2,5,5,5-hexafluoro-4-iodo-3-trifluoromethyl-1,3-penta diene of 97% GLPC purity. ^{19}F NMR ($CDCl_3$, versus internal $CFCl_3$): –58.0 (q, 3F, CF_3, Fa), –58.8 (q, 3F, CF_3,

Protocol 4. *Continued*

Fb), –97.1 (dd, 1F, *cis*-CF=CF_2, Fc), –110.3 (dd, 1F, *trans*-CF=CF_2, Fd), –172.3 (dd, 1F, –C*F*=CF_2, Fe) (J_{ab} = Hz, J_{cd} = 58 Hz, J_{ce} = 34 Hz, J_{de} = 119 Hz); ^{13}C NMR ($CDCl_3$): 153.1 (ddd, –CF=*C*F_2, ^1J = 296, 282 Hz, ^2J = 45 Hz), 134.9 (qd, Cl(CF_3)=*C*(CF_3)–CF=, ^2J = 39 Hz, ^2J = 17 Hz), 127.6 (ddd, –*C*F=CF_2, ^1J = 238 Hz, ^2J = 54, 25 Hz), 120.2 (q, *C*F_3, ^1J = 272 Hz), 119.5 (q, *C*F_3, ^1J = 278 Hz), 113.1 (q, *C*l(CF_3)=C(CF_3)–, ^2J = 40 Hz); MS (m/e): 370 (M^+, 0.7), 243 (M^+–I, 2.1), 224 (1.4), 193 (1.5), 174 (1.1), 155 (1.7), 143 (1.3), 124 (1.8), 59 (26), 45 (100); HRMS (C_6F_9I): obs., 369.8889 (calc., 369.8901); IR (CCl_4): 1790 (w), 1718 (w), 1550 (m), 1360 (w), 1312 (w), 1255 (m), 1241 (m), 1219 (m), 1196 (m), 1006 (w), 979 (w), 810 (s), 775 (s), 772 (s), 743 (s) cm^{-1}.

[a] Commercially available.

3. Perfluoroalkynylzinc reagents

Perfluoroalkynylzinc reagents have been prepared by three methods:

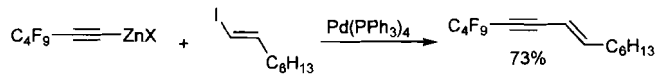
(a) Capture of perfluoroalkynyllithium reagents with $ZnCl_2$ in THF.[17]

(b) Direct reaction of 1-iodoperfluoro-1-alkynes with Zn in DMF or TG.[18]

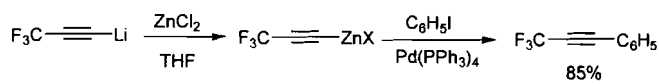
(c) Dehalogenation of 1,1,1,2,2-pentachloroperfluoroalkanes in DMF.[19]

The perfluoroalkynylzinc reagents exhibit good thermal stability.[18] For example, $C_4F_9C{\equiv}CZnX$ in DMF showed only a 4% loss of activity after 36 days at room temperature. Decomposition occurred upon heating to 100°C.

Like their vinyl counterparts, these perfluoroalkynylzinc reagents undergo $Pd(PPh_3)_4$ catalysed coupling with aryl iodides and vinyl iodides or bromides to afford the corresponding aryl alkynes[17,20] and enynes[20] (Equations 4.7 and 4.8).

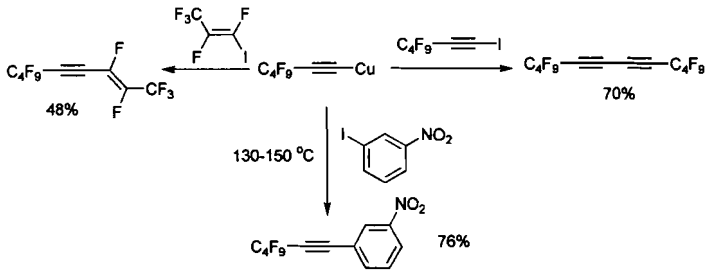


(4.7)



(4.8)

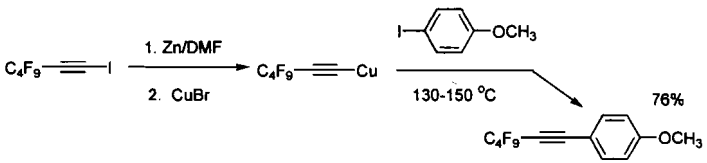
Although they do not generally undergo direct allylation or acylation, the synthetic utility of the perfluoroalkynylzinc reagents is extended via quantitative transmetallation with copper(I) halides in DMF to give versatile perfluoroalkynylcopper reagents.[18] The pre-generated perfluoroalkynylcopper reagents are thermally stable from room temperature to 65°C although perfluorohexynylcopper has been utilized at significantly higher temperatures.[18] The copper reagents couple with aryl iodides, vinyl iodides, allyl halides, and 1-iodoperfluoroalkynes (Scheme 4.3).[18]



Scheme 4.3

Protocol 5.
Transmetallation of a fluoroalkynylzinc reagent to copper bromide and cross-coupling: preparation of 1-(4-methoxyphenyl)-1-perfluorohexyne[18]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, three-necked, 250 mL round-bottomed flask equipped with a magnetic stir bar, glass stopper, rubber septum, and N_2 inlet
- Dry N_2 source

Materials

• 1-iodo-1-perfluorohexyne,[a] 7.4 g, 20 mmol	**irritant, harmful by inhalation**
• Acid washed Zn,[b] 1.63 g, 25 mmol	**irritant**
• Dry DMF,[c] 20 mL	**irritant, harmful by inhalation**
• CuBr, 2.9 g, 20 mmol	**irritant, hygroscopic**
• *p*-iodoanisole, 3.5 g, 15 mmol	**irritant, light-sensitive**

1. Assemble the apparatus and maintain a slight positive N_2 pressure throughout the course of the reaction.
2. Add the Zn and DMF to the reaction flask.
3. Add half of the 1-iodo-1-perfluorohexyne (3 g) to the Zn/DMF mixture via syringe with stirring. After induction is evidenced by a temperature increase (typically less than 5 min), add the remaining alkyne dropwise over 10 min.
4. Add the CuBr to the resultant $C_4F_9C{\equiv}CZnX$/DMF solution followed by *p*-iodoanisole. Heat the mixture to 150°C (oil-bath temperature) for 1.5 h.

Protocol 5. *Continued*

5. Cool the mixture to room temperature. Steam distill the reaction mixture and collect ~ 300 mL of distillate. Remove the lower layer of the steam distillate to give 5 g of product (95% GLPC purity).
6. Purify further on SiO_2 column chromatography (petroleum ether) to obtain 4 g (76%) of 1-(4-methoxyphenyl)-1-perfluorohexyne as an oil of > 99% GLPC purity. ^{19}F NMR ($CDCl_3$): -81.5 (tt, J = 9.8 Hz, 3F), -97.3 (m, 2F), -123.9 (m, 2F), -125.9 (m, 2F); ^1H NMR ($CDCl_3$): 7.5 (d, J = 9 Hz, 2H), 6.9 (d, J = 9 Hz, 2H), 3.8 (s, 3H); MS (m/e): 350 (M^+, 11.1), 351 (M^+ + 1, 1.5), 182 (11.1), 181 (100), 169 (11.5), 166 (13.4), 138 (33.1), 119 (6.9), 69 (12.9); IR (neat): 3013 (w), 2968 (w), 2906 (w), 2243 (s), 1607 (s), 1513 (s), 1297 (m), 1237 (s), 1207 (s), 1136 (s), 1110 (m), 1033 (m), 885 (m), 736 (m).

[a] $C_4F_9C{\equiv}CFI$ is prepared from $C_4F_9CCl_2CCl_3$.[18]
[b] See Protocol 1.
[c] DMF is distilled from CaH_2 under reduced pressure.

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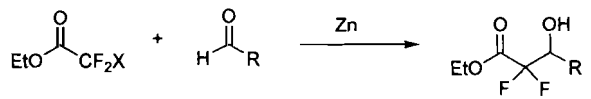
4. Functionalized fluoroalkylzinc reagents

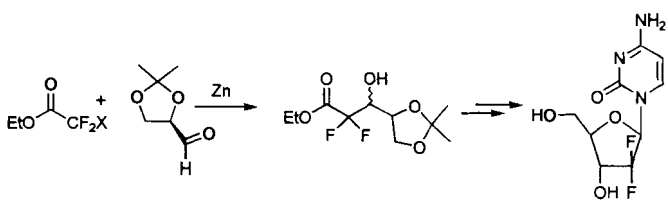
Reaction of halodifluoroacetates with carbonyl compounds in the presence of zinc gives α,α-difluoro-β-hydroxyesters (Equation 4.9).[21–23] The intermediate zinc reagent is typically trapped *in situ* with aldehydes (Barbier conditions).



X = I, Br, Cl

(4.9)

The α,α-difluoro Reformatsky reagent has been applied extensively to the preparation of compounds containing the $-CF_2C(O)-$ group and its derivatives,[2] since this functionality often confers enhanced biological activity. Typical examples include the preparation of selectively fluorinated thromboxane A_2 analogues[24] and the preparation of a difluoro-γ-lactone intermediate which was subsequently converted to 1-(2-deoxy-2,2-difluororibofuranosyl) pyrimidine nucleosides (Equation 4.10).[25]



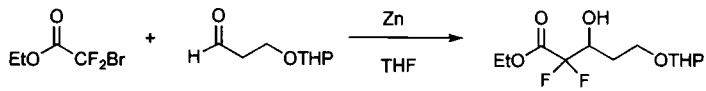
(4.10)

When the intermediate Reformatsky reagent is generated from iododifluoroacetates, a variety of solvents may be employed (THF, dioxane, DMF, DME,

and CH_3CN) although the best results are generally obtained with CH_3CN.[26] THF has been employed extensively with bromodifluoroacetates.[24,25] Lang demonstrated that the cheapest precursor, ethyl chlorodifluoroacetate, could also be converted to a Reformatsky reagent in DMF as ethereal solvents were ineffective.[23]

Protocol 6.
Generation and functionalization of a α,α-difluoro Reformatsky reagent: preparation of ethyl 2,2-difluoro-3-hydroxy-5-(tetrahydropyranyloxy)pentanoate[27]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, two-necked, 100 mL round-bottomed flask equipped with a magnetic stir bar, pressure-equalizing addition funnel, and cold water condenser topped with a glass N_2 tee
- Oil-bath heater
- Dry N_2 source

Materials

- Acid washed Zn,[a] 2.31 g, 35.3 mmol — **irritant**
- Dry THF,[b] 63 mL — **flammable**
- Ethyl bromodifluoroacetate,[c] 5.67 g, 28 mmol — **flammable**
- 3-tetrahydopryanyloxy-1-propanal,[d] 4 g, 25 mmol — **toxic, flammable**

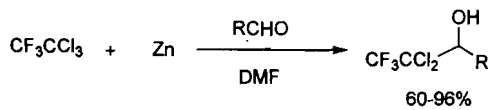
1. Assemble the apparatus and maintain a slight positive N_2 pressure throughout the reaction.
2. Add the Zn and THF (30 mL). Bring the mixture to reflux.
3. Add the ethyl bromodifluoroacetate and THF (33 mL) to the pressure-equalizing addition funnel. With stirring, add the ethyl bromodifluoroacetate/THF solution dropwise. After addition is complete, continue to stir the mixture at reflux for 3 h.
4. Allow the reaction mixture to cool to room temperature and transfer the contents to a 250 mL Erlenmeyer flask. Rinse the reaction flask with diethyl ether (75 mL) and combine with the reaction mixture. Add saturated aqueous NH_4Cl (75 mL). Stir the mixture and remove any solids by suction filtration through Celite.
5. Transfer the filtrate to a separatory funnel and separate the aqueous phase. Extract the aqueous phase with diethyl ether (2 × 50 mL). Wash the combined organic phases with brine (50 mL), dry over $MgSO_4$, and concentrate by rotary evaporation.

Protocol 6. *Continued*

6. Purify the crude residue by SiO_2 column chromatography (hexane:EtOAc, 5:1 to 2:1) to obtain 4.07 g (57%) of ethyl 2,2-difluoro-3-hydroxy-5-(tetrahydropyranyloxy)-pentanoate as an oil. ^{19}F NMR ($CDCl_3$): –50.9 and –51.1 (2 dd, 1F, J = 259.4, 7.5 Hz), –61.2 (2 dd, 1F, J = 259.4, 6.8 Hz); ^1H NMR ($CDCl_3$): 1.35 (t, J = 7.5 Hz, 3H), 1.2–2.1 (m, 8H), 2.1 (s, 1H), 3.4–4.2 (m, 5H), 4.4 (q, J = 7.5 Hz, 2H), 4.7 (br 1H); MS (m/e): 283 (M^+ + 1); IR (CCl_4): 3510, 2950, 2880, 1780, 1763.

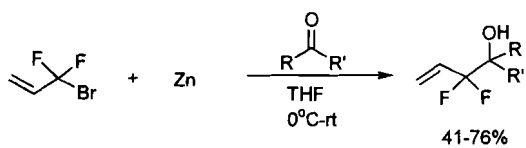
[a] See Protocol 1.
[b] THF is distilled from $LiAlH_4$ or Na/benzophenone ketyl under N_2.
[c] Commercially available.
[d] Prepared from 1,3-propanediol.[27]

The procedures utilized with the α,α-difluoro Reformatsky reagents are similar to those applied in the zinc-mediated additions of CF_3CCl_3[28] and $CH_2{=}CHCF_2Br$[29] to carbonyl compounds. 1,1-dichlorotrifluoroethylzinc chloride, CF_3CCl_2ZnCl, has received significant attention due to its ease of preparation and utility in the synthesis of industrially important compounds.[2,28] Although the CF_3CCl_2ZnCl has been pre-generated, the reagent adds most efficiently under Barbier conditions to aldehydes, α-ketoesters, but not to ketones, to give carbinols in good yields (Equation 4.11).[28,30,31]



(4.11)

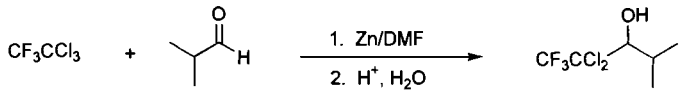
Similarly, preparation of α,α-difluorohomoallylic alcohols has been achieved by zinc-mediated addition of $CH_2{=}CHCF_2Br$ to carbonyl compounds.[29] The reaction is successful with dialkyl ketones as well as aliphatic and aromatic aldehydes (Equation 4.12). The allylation products are particularly useful since the alkene may be oxidized to an aldehyde,[32] epoxide,[33] or converted to a δ-lactone[34] via hydroformylation.



(4.12)

Protocol 7.
Zinc-mediated addition of CF_3CCl_3 to an aldehyde: preparation of 4-methyl-2,2-dichloro-1,1,1-trifluoro-3-pentanol[28]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Dry, 250 mL, two-necked flask equipped with a magnetic stir bar, rubber septum, and argon inlet
- Argon source

Materials

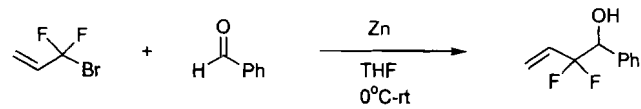
• Distilled 2-methylpropionaldehyde, 7.2 g, 0.1 mol	**flammable, irritant**
• 1,1,1-trichloro-2,2,2-trifluoroethane,[a] 20.6 g, 0.11 mol	**harmful**
• Acid washed Zn,[b] 8.17 g, 0.125 mol	**irritant**
• Dry DMF,[c] 180 mL	**irritant, harmful**

1. Assemble the apparatus and maintain a slight positive Ar pressure throughout the reaction.
2. Add the DMF, Zn, CF_3CCl_3, and 2-methylpropionaldehyde to the reaction flask and stir at room temperature for 48 h. After a 30–60 min induction period, a moderate exotherm will be observed and dissolution of the Zn will begin.
3. Pour the reaction mixture onto stirred ice-water (125 mL). Slowly add 10% aqueous HCl (40 mL). Stir for 10 min and transfer the contents to a separatory funnel.
4. Extract the aqueous/DMF solution with diethyl ether (3 × 75 mL).
5. Wash the combined ether phases with 2% aqueous HCl (40 mL), brine (40 mL), and dry over $MgSO_4$.
6. Concentrate the residue *in vacuo* at 0 °C.
7. Purify by distillation (b.p. 55–60 °C, 20 mmHg) to give 18 g (80%) of 4-methyl-2,2-dichloro-1,1,1-trifluoro-3-pentanol as a colourless oil. ^1H NMR ($CDCl_3$): 4.07 (d, J = 3 Hz, 1H), 2.9 (br, 1H), 2.4 (m, 1H), 1.1 (2d, J = 7 Hz, 6H); IR (neat): 3480 (br), 2960 (m), 2930 (w), 2880 (w), 1470 (w), 1395 (w), 1290 (w), 1255 (s), 1200 (s), 1020 (m), 1000 (w), 920 (m), 870 (s), 702 (s) cm^{-1}.

[a] Commercially available.
[b] See Protocol 1.
[c] DMF is distilled from CaH_2 under reduced pressure.

Protocol 8.
Zinc-mediated *gem*-difluoroallylation of a carbonyl compound: preparation of 2,2-difluoro-1-phenyl-3-buten-1-ol [29]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, two-necked, 50 mL round-bottomed flask equipped with a magnetic stir bar, glass N_2 tee, and pressure-equalizing addition funnel (25 mL)
- Ice water-bath
- Dry N_2 source

Materials

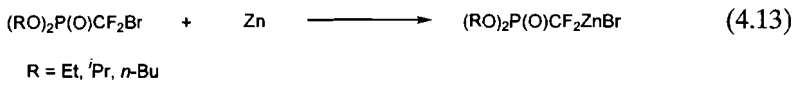
- Acid washed Zn,[a] 2.6 g, 40 mmol — **irritant**
- Distilled benzaldehyde, 2.1 g, 20 mmol — **toxic, cancer suspect agent**
- Dry THF,[b] 30 mL — **flammable, irritant**
- 3-bromo-3,3-difluoropropene,[c] 3.3 g, 21 mmol — **toxic, flammable**

1. Assemble the apparatus and maintain a slight positive N_2 pressure throughout the reaction.
2. Add the Zn, THF (20 mL), and benzaldehyde to the reaction flask. Stir and cool the mixture to 0 °C in the ice-bath.
3. Add the 3-bromo-3,3-difluoropropene and THF (10 mL) to the addition funnel. Add the contents of the addition funnel dropwise to the stirred, heterogeneous reaction mixture.
4. After complete addition, allow the reaction mixture to warm to room temperature and continue stirring overnight.
5. Add 5% aqueous HCl (30 mL) to the reaction mixture. Stir for 5 min and then remove any excess Zn by suction filtration. Wash the filtered solids with diethyl ether (30 mL).
6. Transfer the filtrate to a separatory funnel and separate the ether phase. Extract the aqueous phase with diethyl ether (2 × 50 mL). Wash the combined organic phases with saturated $NaHCO_3$ (50 mL), water (2 × 50 mL), and dry over $MgSO_4$.
7. Concentrate under reduced pressure and purify the residue by distillation through a short path apparatus (b.p. 56–57 °C, 0.5 mmHg) to give 2.5 g (67%) of 2,2-difluoro-1-phenyl-3-buten-1-ol of > 99% GLPC purity. ^{19}F NMR ($CDCl_3$ versus internal $CFCl_3$): –107.3 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1F), –110.7 (dt,

$^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1F); ^{1}H NMR ($CDCl_3$): 7.34 (s, 5H), 5.82–5.33 (m, 3H), 4.83 (t, $^3J_{F,H}$ = 10 Hz, 1H), 2.84 (br, 1H); FTIR (CCl_4): 3619 (s), 3033 (s), 1653 (w), 1150 (s), 1060 (s), 997 (s), 983 (s) cm^{-1}.

[a] See Protocol 1.
[b] THF is distilled under N_2 from $LiAlH_4$ or Na/benzophenone ketyl.
[c] Commercially available from Japan Halon Co.

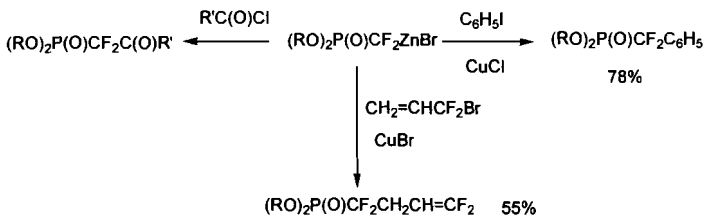
Treatment of dialkyl bromodifluoromethylphosphonates with zinc gives the dialkoxy phosphinyldifluoromethylzinc reagents in good yields (Equation 4.13).[35] A variety of solvents (THF, glymes, DMF) can be employed.



(4.13)

These zinc reagents provide a useful entry into compounds containing the dialkoxyphosphinyldifluoromethyl group.[36] Introduction of this moiety into organic molecules has attracted attention due to biological properties exhibited by these derivatives as compared to their non-fluorinated analogues.[37]

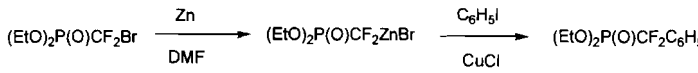
The thermal stability of these zinc reagents parallel their vinyl and alkynyl counterparts.[35] For example, only 49% of dibutoxyphosphinyldifluoromethylzinc decomposed on heating to 100 °C for 4 h. Although the dialkoxyphosphinyldifluoromethylzinc zinc reagent is not as reactive as the corresponding lithium reagent, it is the method of choice when either of the reagents can be employed, particularly on larger scales, as low temperatures are avoided. The reactivity of the zinc reagent is enhanced by addition of copper(I) halides, as the intermediate dialkoxyphosphinyldifluoromethylcopper reagents are more readily trapped by electrophiles. Typical applications are as follows (Scheme 4.4):[36,38,39]



Scheme 4.4

Protocol 9.
Generation and functionalization of a dialkoxyphosphinyldifluoromethylzinc reagent: preparation of diethyl-α,α-difluorobenzylphosphonate[40]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and safety glasses.



Equipment

- Oven-dried, 50 mL, two-necked round-bottomed flask equipped with a magnetic stir bar, rubber septum, and cold water condenser topped with a N_2 inlet
- Dry N_2 source

Materials

• Diethyl bromodifluoromethylphosphonate,[a] 2.67 g, 10 mmol	**toxic**
• Acid washed Zn,[b] 0.72 g, 11 mmol	**irritant**
• Dry DMF,[c] 10 mL	**irritant, harmful**
• CuCl, 0.69 g, 7 mmol	**irritant**
• Iodobenzene, 1.23 g, 6 mmol	**irritant**

1. Assemble the apparatus and maintain a slight positive N_2 pressure throughout the reaction.
2. Add the Zn and DMF to the reaction flask and then the diethyl bromodifluoromethyl phosphonate. Stir the mixture for 1 h at room temperature.
3. Remove unreacted Zn by filtration through a medium fritted funnel under a N_2 atmosphere.
4. Transfer the filtrate to a dry 50 mL round-bottomed flask equipped with a magnetic stir bar and N_2 inlet. Add the CuCl and iodobenzene to the filtrate and stir at room temperature for 3 h.
5. Add diethyl ether (100 mL) to the reaction mixture and remove the precipitated solids by filtration. Wash the filtered precipitate with ether (50 mL).
6. Wash the combined ether solutions with aqueous NH_4Cl and water. Dry over $MgSO_4$ and concentrate by rotary evaporation.
7. Purify by SiO_2 column chromatography (CH_2Cl_2:EtOAc, 15:1) to obtain 1.24 g (78%) of diethyl-α,α-difluorobenzylphosphonate as an oil. ^{19}F NMR ($CDCl_3$ versus internal $CFCl_3$): −108.9 (d, J = 116 Hz); ^1H NMR ($CDCl_3$): 1.30 (t, J = 7 Hz, 6H), 4.19 (m, 4H), 7.47 (m, 3H), 7.62 (m, 2H); ^{13}C NMR ($CDCl_3$): 16.3 (d, J = 6 Hz), 64.8 (d, J = 7 Hz), 118.1 (td, J = 263, 218 Hz), 126.3 (td, J = 7, 2 Hz), 128.5 (s),

130.8 (s), 132.7 (td, J = 22, 14 Hz); ^{31}P NMR ($CDCl_3$): 6.34 (t, J = 116 Hz); GCMS (m/e) 264 (M^+, 2.2), 127 (100), 137 (5.6), 109 (37.6), 77 (30.3).

[a] Diethyl bromodifluoromethylphosphonate may be prepared according to the literature procedure.[41]
[b] See Protocol 1.
[c] DMF is distilled from CaH_2 under reduced pressure.

In conclusion, the reagents and procedures described herein typify the expanding utility of fluorinated organozinc reagents as building blocks for the preparation of fluorine-containing organic molecules.

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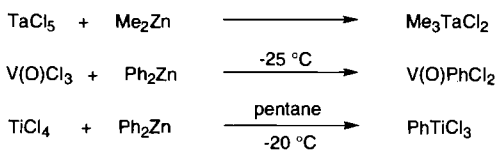
5

Preparation methods of diorganozincs

PAUL KNOCHEL, PHILIP JONES, and FALK LANGER

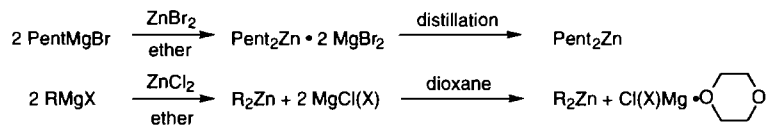
1. Introduction

Diorganozincs (R_2Zn) are an important class of zinc organometallic reagents because of their synthetic applications in organic synthesis[1] and asymmetric synthesis.[2] Compared to organozinc halides (RZnX), they usually display a higher reactivity, but as a drawback, they often transfer only one of the two organic groups to the electrophilic reagents. Diorganozincs have also found numerous applications in organometallic chemistry and dimethylzinc or diethylzinc are very useful reagents for the preparation of alkyl transition metals (Scheme 5.1).[3]



Scheme 5.1

Although, diorganozincs have been known since 1848,[4] their preparation has been limited to lower unfunctionalized dialkylzincs[5] and diphenylzinc.[6] These reagents have been synthesized by the reaction of organomagnesium halides with zinc bromide, followed by distillation of the crude reaction mixture (Scheme 5.2).[5] This procedure is only possible with lower diorganozincs up to dihexylzinc, since higher homologues decompose partially during distillation.



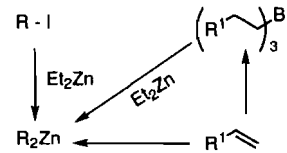
Scheme 5.2

Alternatively, it is possible to prepare almost salt-free diorganozincs in solution by the precipitation of the magnesium salts with 1,4-dioxane.[7] However, the preparation of functionalized diorganozincs is generally not possible using these methods and accordingly new methods have recently been developed for such preparations, utilizing:

(a) An iodine (or bromine)–zinc exchange reaction.[8,9]

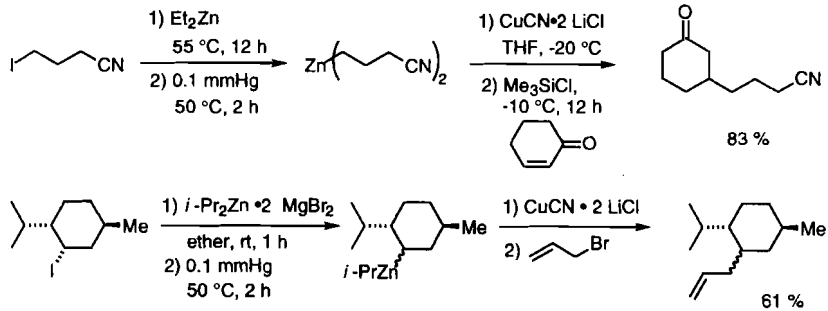
(b) A boron–zinc exchange reaction.[10–12]

(c) A nickel catalysed hydrozincation reaction[13,14] (Scheme 5.3).



Scheme 5.3

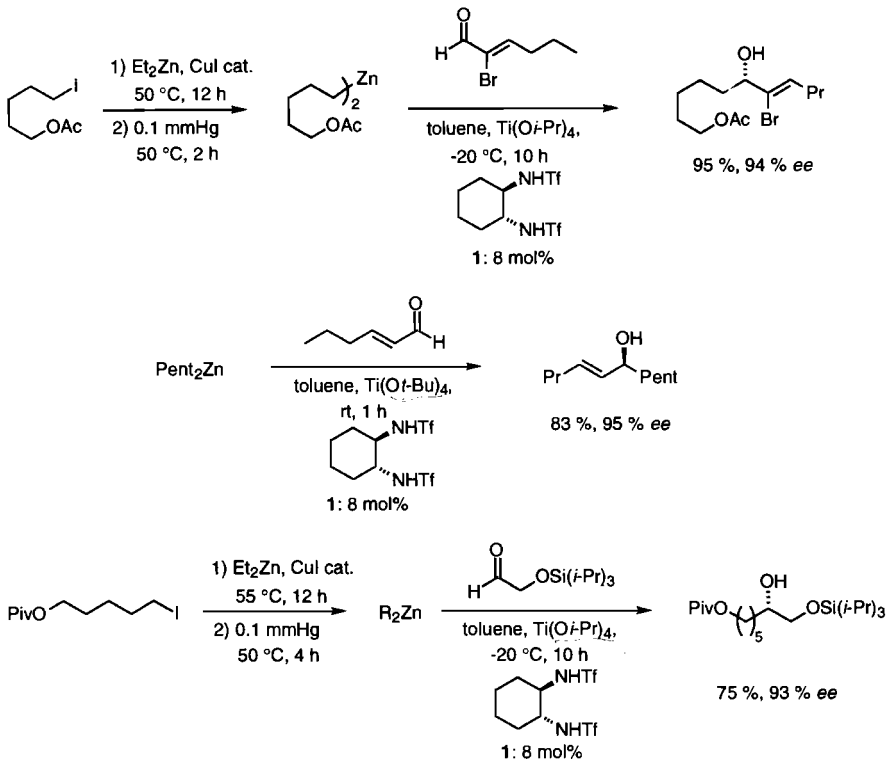
The iodine–zinc exchange reaction allows conversion of primary alkyl iodides to diorganozincs by the treatment with Et_2Zn.[4] This reaction proceeds via a radical mechanism[9,15] and is catalysed by the addition of small amounts of Cu(I) salts. It is run in the absence of a solvent, at a temperature of 50 °C, and requires between 1.5–3 equivalents of Et_2Zn. The reaction is complete after reaction times of between 2–10 h.[1] This exchange reaction provides a very general preparation of functionalized diorganozincs bearing ester, ether, halide, or cyanide functional groups (Scheme 5.4).



Scheme 5.4

Interestingly, secondary alkyl iodides also undergo iodine–zinc exchange reactions in the presence of *i*-Pr_2Zn. The best method consisting of generating *i*-Pr_2Zn *in situ* from *i*-PrMgBr and $ZnBr_2$.[16] The presence of magnesium salts considerably facilitates the iodine–zinc exchange (Scheme 5.4).[16] One major application of diorganozincs is their asymmetric addition to aldehydes in the presence of a chiral catalyst.[2] Especially effective is the chiral catalyst **1** (1,2-

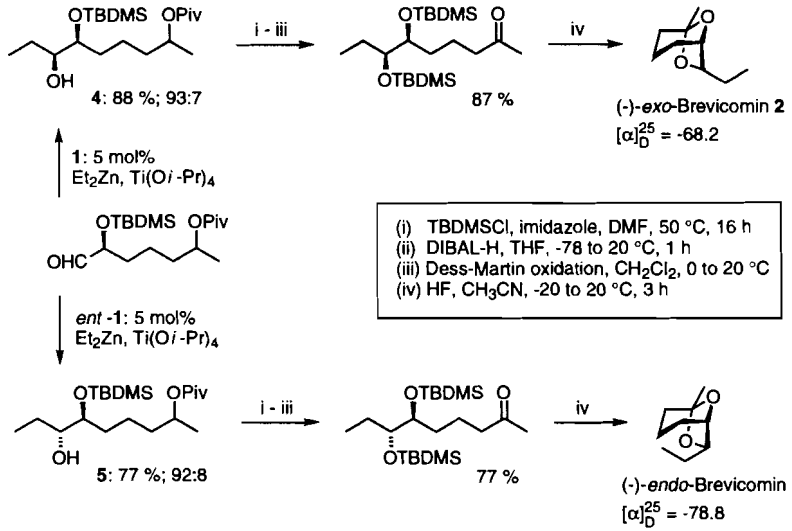
bis(trifluormethanesulfonamido)cyclohexane)[2,17] which in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ as co-catalyst leads to a highly enantioselective addition of diorganozincs to aliphatic α,β-unsaturated and aromatic aldehydes (Scheme 5.5).[9] The stereoselectivity can in many cases be improved by changing the nature of the titanium alkoxides (Scheme 5.5).[18]



Scheme 5.5

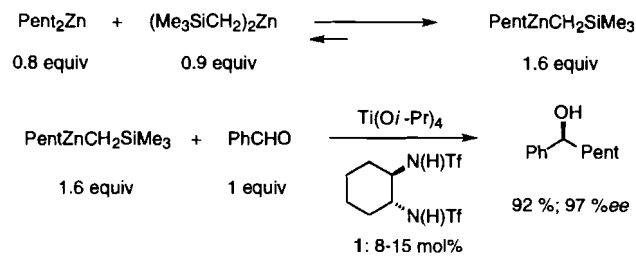
The addition of diorganozinc reagents to α-alkoxyaldehydes furnishes selectively protected 1,2-diols.[19] Applications toward the synthesis of pheromones like (–)-*exo*- and (–)-*endo*-brevicomin **2** and **3** exploits the catalytic nature of the stereochemical induction, e.g. the newly formed chiral centre depends only on the configuration of the chiral catalyst **1**.

The catalyst **1** furnishes the *syn*-diol derivative **4**, whereas the enantiomeric catalyst *ent*-**1** furnishes the *anti*-diol derivative **5** (Scheme 5.6).[20] In order to avoid the use of an excess of diorganozinc in these asymmetric reactions, mixed diorganozincs of the type $RZnCH_2SiMe_3$ have been prepared simply by mixing the diorganozincs with $(Me_3SiCH_2)_2Zn$. The use of these mixed diorganozinc reagents allows the excess of diorganozinc to be reduced from



Scheme 5.6

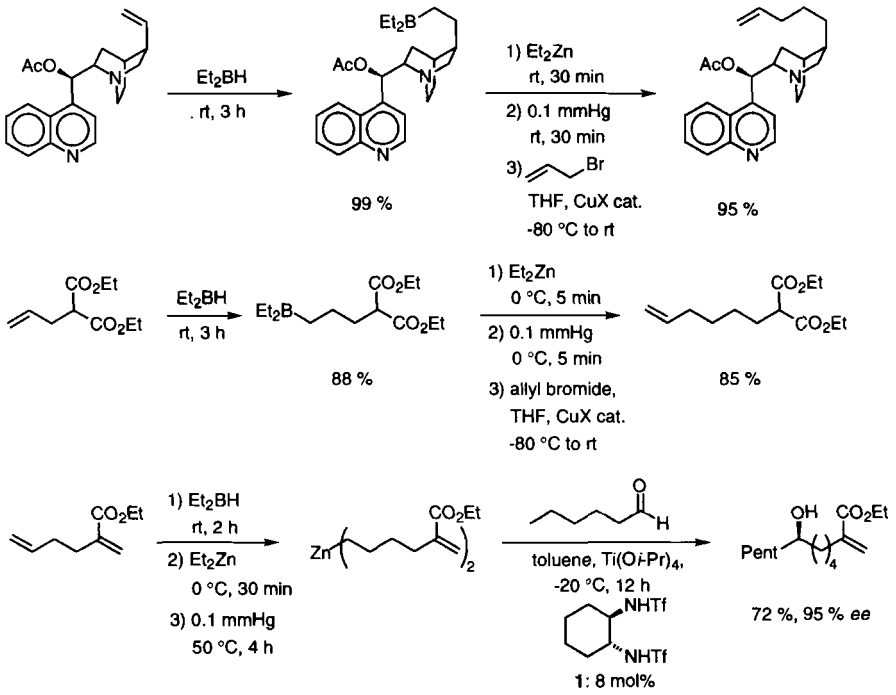
between 2–3 equivalents to 0.8 equivalents. The Me_3SiCH_2 group is playing the role of a non-transferable group (Scheme 5.7).[21]



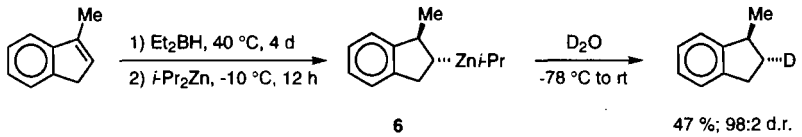
Scheme 5.7

Besides the iodine–zinc exchange reaction, the boron–zinc exchange reaction proves to be an excellent method for preparing a broad range of polyfunctional diorganozincs (Scheme 5.8). The exchange reaction for primary diethylalkyl boranes proceeds at room temperature and is complete within a few minutes.

Secondary diethylalkylboranes require longer reaction times.[10–12] In these cases, i-Pr_2Zn should be used instead of Et_2Zn. This procedure allows the preparation of mixed secondary diorganozincs like **6** having a defined configuration[22] (Scheme 5.9). The preparation of configuration defined diorganozincs requires the use of salt-free i-Pr_2Zn.



Scheme 5.8

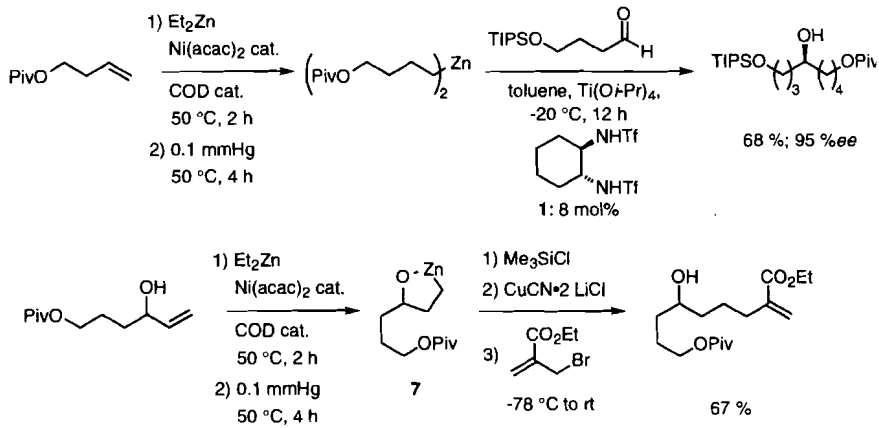


Scheme 5.9

The direct hydrozincation of olefins[14] is possible using Et_2Zn in the presence of catalytic amount of $Ni(acac)_2$ and 1,5-cyclooctadiene (COD). The resulting diorganozincs can be used for asymmetric additions to aldehydes. The best hydrozincation reactions are obtained with allylic alcohols or amines. In these cases the raction is driven to completion by the formation of a zinc-heterocycle of type **7** (Scheme 5.10).

2. General

The solvents used (THF, ether, toluene) were dried and distilled over Na/K under argon. Diethylzinc was purchased from Witco (Bergkamen, Germany). CuCN was used as received (Degussa, Germany). All lithium and zinc halides



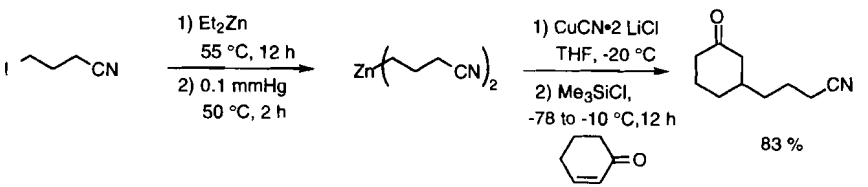
Scheme 5.10

were purchased as anhydrous salts (Aldrich, Merck, or Riedel de Haën), and were always dried for 1–2 h at 120–150°C under vacuum (*ca.* 0.1 mmHg) before use. Me_3SiCl, $Ti(Oi\text{-}Pr)_4$, $Ti(Ot\text{-}Bu)_4$, and all organic electrophiles were distilled before use. Argon (99.998%) was used without any purification.

3. Protocols

Protocol 1.
Preparation of *bis*(3-cyanopropyl)zinc by iodine–zinc exchange and its copper-mediated coupling with an electrophile: preparation of 3-(3-cyanopropyl)-cyclohexanone[8]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

- 4-iodobutyronitrile (FW 195), 1.2 g, 6 mmol — **irritant**
- Diethylzinc (FW 123.5), 3 mL, 30 mmol — **flammable, pyrophoric**
- CuCN (FW 89.6), 0.27 g, 3 mmol — **highly toxic**
- LiCl (FW 42.4), 0.26 g, 6 mmol — **irritant, hygroscopic**
- Me_3SiCl (FW 108.6), 0.76 g, 7 mmol — **flammable, corrosive**
- 2-cyclohexenone (FW 96.1), 0.34 g, 3.5 mmol — **flammable, toxic**
- Dry THF — **irritant, flammable, hygroscopic**

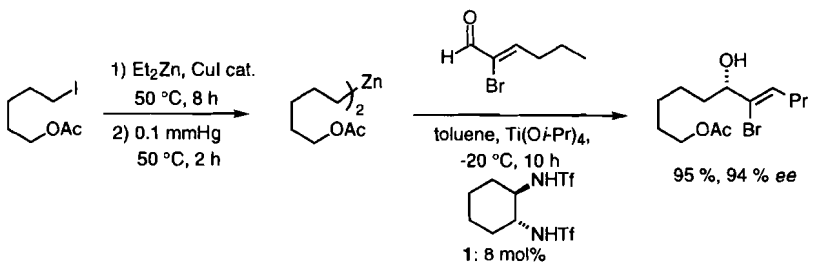
1. Charge the flame dried and argon flushed Schlenk flask with 4-iodobutyronitrile and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 55°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 55°C for 12 h.
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50°C, 2 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis of a reaction sample. For the iodolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing a solution of iodine (*ca.* 50 mg) in dry ether (1 mL). Mix well, decolorize the brown solution with an saturated aqueous solution of $Na_2S_2O_3$ (*ca.* 0.5 mL), and take the supernatant ether phase for GLC analysis. For the hydrolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing ether (1 mL) and aqueous NH_4Cl (1 mL). Mix well and take the ether phase for GLC analysis. These experiments allow an accurate estimate of the organozinc reagent concentration.
6. Dissolve the *bis*(3-cyanopropyl)zinc in dry THF (3 mL) at rt.
7. Meanwhile weigh the CuCN and the LiCl into the three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
8. Flush with argon, cool to rt, and then dissolve the CuCN•2LiCl in dry THF (6 mL). A slight exothermic reaction is observed and a light yellow/green solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –20°C.
9. Add the *bis*(3-cyanopropyl)zinc to the CuCN•2LiCl solution and then cool the resulting light green solution to –78°C.
10. Add Me_3SiCl and then 2-cyclohexenone. Replace the septum cap with a glass stopper.
11. Allow the reaction mixture to warm slowly to –10°C overnight.
12. Add a saturated aqueous NH_4Cl solution (20 mL) to the reaction mixture and stir for 10 min at rt. Pour into an Erlenmeyer containing ether (200 mL) and aqueous NH_4Cl (100 mL) and filter over Celite®.

Protocol 1. *Continued*

13. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic extracts and wash with brine (50 mL), dry over $MgSO_4$, filter, and evaporate the solvent.
14. Purify the crude residue by flash chromatography using hexanes:EtOAc (7:3). Pure 3-(3-cyanopropyl)cyclohexanone (0.48 g, 83%) is obtained as a light yellow oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 2.
Preparation of *bis*(5-acetoxypentyl)zinc by iodine–zinc exchange and its enantioselective addition to an aldehyde: preparation of (6*S*)-5-bromo-6-hydroxy-11-acetoxyundec-4-ene[9]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (100 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

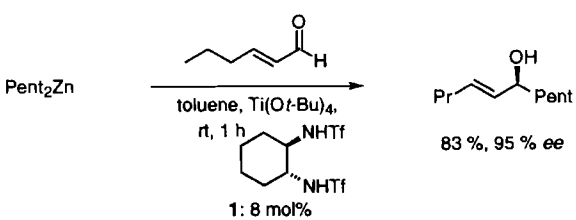
- 5-iodopentyl acetate (FW 256.1), 4.1 g, 16 mmol — **irritant**
- Diethylzinc (FW 123.5), 2 mL, 20 mmol — **flammable, pyrophoric**
- CuI (FW 190.4), 2 mg, 0.01 mmol
- $Ti(Oi\text{-}Pr)_4$ (FW 284.2), 2.4 mL, 8 mmol — **flammable, irritant**
- (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane (FW 346.3), 0.12 g, 0.3 mmol
- (*Z*)-2-bromo-2-hexenal (FW 177), 0.71 g, 4 mmol — **irritant**
- Dry toluene — **flammable**

1. Charge the flame dried and argon flushed Schlenk flask with CuI, 5-iodopentyl acetate, and diethylzinc (Caution!).

2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 50°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 50°C for 8 h.
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50°C, 2 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and hydrolysis as described in Protocol 1.
6. Dissolve the *bis*(5-acetoxypentyl)zinc in dry toluene (8 mL) at rt.
7. Meanwhile charge the three-necked flask with dry toluene (3 mL), Ti(O*i*-Pr)$_4$, and (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane.
8. Heat the three-necked flask to 45°C for 30 min and then cool to –60°C. The catalyst is now ready for use.
9. Add *bis*(5-acetoxycyclopentyl)zinc to the solution at –60°C, and then add slowly (*Z*)-2-bromo-2-hexenal. Warm to –20°C and stir the resulting mixture for 10 h.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 9:1) to afford the desired product (1.15 g, 95%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = +2.71°$ (c = 3.32, benzene).
11. Prepare the derivatives of the product with (*S*)-(–)-*O*-acetylmandelic acid and (+/–)-*O*-acetylmandelic acid, and compare their ^{1}H NMR spectra to determine the enantiomeric excess of the product (94% *ee*).

Protocol 3.
Preparation of dipentylzinc and its enantioselective addition to an aldehyde: preparation of (6*S*)-6-hydroxyundec-4-ene[18]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Protocol 3. *Continued*

Equipment

- One three-necked, round-bottomed flask (500 mL) equipped with an argon inlet, a dropping funnel, a septum cap, and a magnetic stirring bar
- One two-necked, round-bottomed flask (250 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Dry, gas-tight syringes, steel needles, and a double-ended needle
- One two-necked, round-bottomed flask (500 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet

Materials

- Magnesium (FW 24.3), 3.39 g, 345 mmol **flammable**
- Pentyl bromide (FW 151.1), 47.4 g, 314 mmol **flammable**
- Dry zinc(II) bromide (FW 225.2), 35.4 g, 157 mmol **corrosive**
- $Ti(O\textit{t}\text{-}Bu)_4$ (FW 340.3), 3.51 g, 10.3 mmol **flammable, irritant**
- (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane (FW 346.3), 0.14 g, 0.37 mmol
- (*E*)-2-hexenal (FW 98.1), 0.45 g, 4.58 mmol **irritant**
- Dry ether **flammable**
- Dry toluene **flammable**

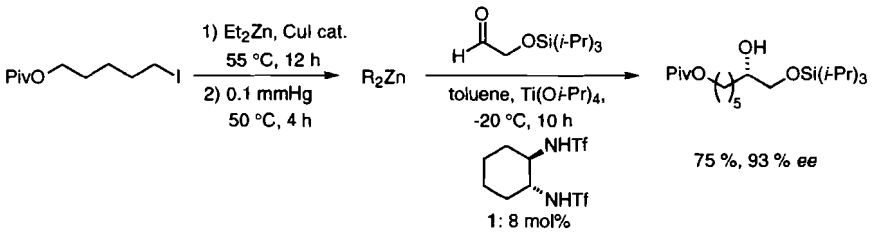
1. Charge the first three-necked flask with magnesium and ether (50 mL) and flush with argon.
2. Add the pentyl bromide in ether (200 mL) at such a rate that the ether is gently refluxing. Stir for 3 h at rt.
3. Meanwhile, weigh the zinc(II) bromide into the first two-necked flask. Dry the salt by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 140°C for 2 h, flush with argon, and dissolve in ether (150 mL).
4. Transfer the Grignard solution into the second two-necked flask via a double-ended needle. Cool to 0°C and add the zinc(II) bromide solution. Warm to rt and stir overnight.
5. Distill off the solvent under argon.
6. Distill the dipentylzinc under vacuum (b.p. 60°C, 0.1 mmHg). Yield: 26.5 g, 80%.
7. Charge the second three-necked flask with dry toluene (10 mL), $Ti(O\textit{t}\text{-}Bu)_4$, and (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane.
8. Heat this three-necked flask to 50°C for 30 min and then cool to rt. The catalyst is now ready for use.
9. Add dipentylzinc (2.49 g, 12 mmol) to the freshly prepared catalyst and then stir for 30 min. Finally add slowly the (*E*)-2-hexenal and stir for 1 h.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 4:1) to afford the desired product (0.65 g, 83%). Characterize the product by

^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = +0.55°$ (c = 7.3, benzene).

11. Prepare the derivatives of the product with (*S*)-(–)-*O*-acetylmandelic acid and (+/–)-*O*-acetylmandelic acid, and compare their ^{1}H NMR spectra to determine the enantiomeric excess of the product (95% *ee*).

Protocol 4.
Preparation of *bis*(5-pivaloxypentyl)zinc by iodine–zinc exchange and its enantioselective addition to an aldehyde: preparation of (6*S*)-6-hydroxy-7-(triisopropylsiloxy)heptyl pivalate[19]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

- 5-iodopentyl pivalate (FW 298.2), 7.4 g, 24 mmol — **irritant**
- Diethylzinc (FW 123.5), 3.6 mL, 36 mmol — **flammable, pyrophoric**
- CuI (FW 190.4), 14 mg, 0.3 mmol — **harmful**
- Ti(O*i*-Pr)$_4$ (FW 284.2), 2.4 mL, 8 mmol — **flammable, irritant**
- (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane (FW 346.3), 0.12 g, 0.3 mmol
- 2-(triisopropylsiloxy)acetaldehyde (FW 216.4), 0.86 g, 4 mmol — **flammable**
- Dry toluene — **flammable**

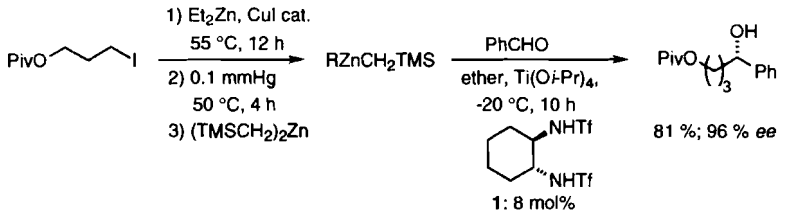
1. Charge the flame dried and argon flushed Schlenk flask with CuI, 5-iodopentyl pivalate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 55°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 55°C for 12 h.

Protocol 4. *Continued*

4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50 °C, 4 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(5-pivaloxypentyl)zinc at rt in dry toluene (8 mL).
7. Charge the three-necked flask with dry toluene (2 mL), $Ti(O\textit{i}\text{-}Pr)_4$, and (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane.
8. Heat the three-necked flask to 50 °C for 30 min and then cool to –40 °C. The catalyst is now ready for use.
9. Add *bis*(5-acetoxypentyl)zinc and stir for 25 min. Finally add 2-(triisopropylsiloxy)-acetaldehyde, warm to –20 °C, and then stir for 10 h at –20 °C.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 4:1) to afford the desired product (1.17 g, 75%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = +0.64°$($c = 4.71$, benzene).
11. Prepare the derivatives of the product with (*S*)-(–)-*O*-acetylmandelic acid and (+/–)-*O*-acetylmandelic acid, and compare their ^1H NMR spectra to determine the enantiomeric excess of the product (93% *ee*).

Protocol 5.
Preparation of 3-pivaloxypropyl-(trimethylsilylmethyl)zinc by iodine–zinc exchange, formation of a mixed diorganozinc and its enantioselective addition to an aldehyde: preparation of (*S*)-(–)-4-hydroxy-4-phenylbutyl pivalate[23]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

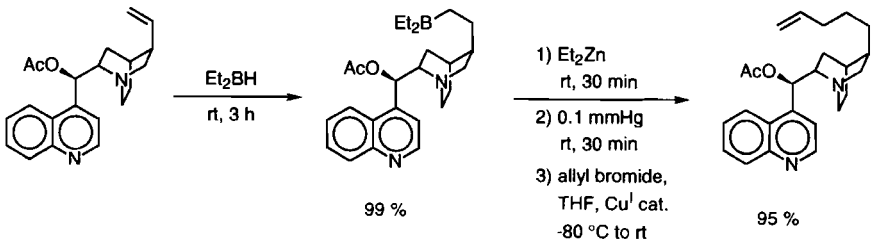
Materials

- 3-iodopropyl pivalate (FW 270.1), 1.49 g, 5.5 mmol — **irritant**
- Diethylzinc (FW 123.5), 3.6 mL, 36 mmol — **flammable, pyrophoric**
- *Bis*(trimethylsilylmethyl)zinc (FW 239.8), 0.57 g, 2.4 mmol — **flammable, pyrophoric**
- CuI (FW 190.4), 57 mg, 0.3 mmol — **harmful**
- $Ti(O\textit{i}\text{-}Pr)_4$ (FW 284.2), 0.36 mL, 1.2 mmol — **flammable, irritant**
- (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane (FW 346.3), 0.061 g, 0.18 mmol
- Benzaldehyde (FW 106.1), 0.21 g, 2 mmol — **harmful**
- Dry diethyl ether — **flammable**

1. Charge the flame dried and argon flushed Schlenk flask with CuI, 3-iodopropyl pivalate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 55°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 55°C for 12 h.
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50°C, 4 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(3-pivaloxypropyl)zinc at rt in dry diethyl ether (1.5 mL).
7. Add the *bis*(trimethylsilylmethyl)zinc to the *bis*(3-pivaloxypropyl)zinc solution at rt.
8. Meanwhile, charge the three-necked flask with dry diethyl ether (2 mL), $Ti(O\textit{i}\text{-}Pr)_4$, and (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane. Heat at 50°C for 30 min. The catalyst is now ready for use.
9. Add (3-pivaloxypropyl) (trimethylsilylmethyl)zinc to the catalyst and then stir for 25 min. Finally add benzaldehyde and stir for 26 h at −20°C.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 4:1) to afford the desired product (0.379 g, 81%, 96% *ee*). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = -19.8°$ ($c = 2.93$, benzene).
11. Determine the enantiomeric excess by chiral HPLC analysis; Chiracel OD, heptane:isopropanol, 90:10; flow 0.6 ml/min; retention time 12.6 (major) and 15.3 (minor enantiomer) min.

Protocol 6.
Preparation of *bis*((*S*)-1-acetoxy-1-((1*S*,2*S*,4*S*,5*S*)-5-(4-pentenyl)-1-azabicyclo[2.2.2]oct-2-yl)methyl)zinc by boron–zinc exchange and its copper catalysed allylation: preparation of 4-((*S*)-1-acetoxy-1-((1*S*,2*S*,4*S*,5*S*)-5-(4-pentenyl)-1-azabicyclo[2.2.2]oct-2-yl)methyl)quinoline[12]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (100 mL) equipped with an argon inlet and a septum cap
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- Two two-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar

Materials

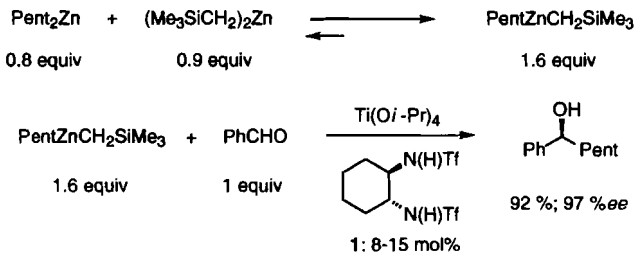
• *O*-acetyl quinidine (FW 200), 1.35 g, 4 mmol	**flammable, toxic**
• Triethylborane (FW 98), 261 mg, 2.66 mmol	**flammable, pyrophoric**
• Borane–methyl sulfide complex (FW 76), 101 mg, 1.33 mmol	**toxic, stench**
• Diethylborane (FW 70), 280 mg, 4 mmol	**flammable, pyrophoric**
• Diethylzinc (FW 123.5), 0.8 mL, 8 mmol	**flammable, pyrophoric**
• CuCN (FW 89.6), 36 mg, 0.4 mmol	**highly toxic**
• LiCl (FW 42.4), 34 mg, 0.8 mmol	**irritant, hygroscopic**
• Allyl bromide (FW 140.6), 4.84 g, 40 mmol	**flammable, toxic**
• Dry ether	**flammable**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge one flame dried and argon flushed two-necked flask with triethylborane and add borane–methyl sulfide complex at rt. Dilute with ether (1 mL). The stock solution of diethylborane is now ready for use.
2. Charge the second flame dried and argon flushed two-necked flask with *O*-acetyl quinidine, dissolve in ether (8 mL), and cool to 0°C.
3. Slowly add diethylborane. Allow to warm to rt and then stir for 12 h at 40°C.

4. Connect to vacuum (0.1 mmHg) and remove all volatiles at 40°C for 6 h to afford the crude hydroboration product (1.63 g, 99%) as a white solid.
5. Dissolve in CH_2Cl_2 (5 mL), cool to 0°C, and add diethylzinc (Caution!).
6. Replace the septum with a glass stopper. Stir for 30 min.
7. Remove the triethylborane formed and the excess diethylzinc in vacuum (rt, 2 h, *ca.* 0.1 mmHg).
8. Repeat steps 5–7 to ensure complete conversion to the diorganozinc compound.
9. Evaporate twice with toluene (5 mL) and finally with CH_2Cl_2 (5 mL) in vacuum (40°C, 2 h, 0.1 mmHg) to remove all diethylzinc.
10. Add THF (8 mL) and cool to –80°C.
11. Add allyl bromide, CuCN, and LiCl (dried and dissolved in 1 mL THF, see Protocol 1). Slowly warm to rt (3.5 h).
12. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (ether:THF, 4:1) to afford the desired product (1.44 g, 95%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 7.
Preparation of *bis*(4,4-dicarbethoxybutyl)zinc by boron–zinc exchange and its copper catalysed allylation: preparation of diethyl 5-hexen-1-ylmalonate[12]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (100 mL) equipped with an argon inlet and a septum cap
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- Two two-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar

Protocol 7. *Continued*

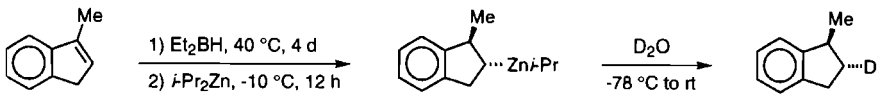
Materials

• Diethyl allylmalonate (FW 200), 1.05 g, 5.26 mmol	**flammable**
• Triethylborane (FW 98), 9.8 g, 100 mmol	**flammable, pyrophoric**
• Borane–methyl sulfide complex (FW 76), 3.8 g, 50 mmol	**toxic, stench**
• Diethylborane (FW 70), 1.18 g, 5.26 mmol	**flammable, pyrophoric**
• Diethylzinc (FW 123.5), 0.9 mL, 9 mmol	**flammable, pyrophoric**
• CuCN (FW 89.6), 41 mg, 0.46 mmol	**highly toxic**
• LiCl (FW 42.4), 39 mg, 0.92 mmol	**irritant, hygroscopic**
• Allyl bromide (FW 140.6), 6 g, 50 mmol	**flammable, toxic**
• Dry ether	**flammable**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge one flame dried and argon flushed two-necked flask with triethylborane, cool to 0 °C, add borane–methyl sulfide complex, and dilute with ether (15 mL). Stir for 5 min at 0 °C, the stock solution of diethylborane is now ready for use.
2. Charge the second flame dried and argon flushed two-necked flask with diethyl allylmalonate and cool to 0 °C.
3. Slowly add diethylborane to the diethyl allylmalonate. Allow to warm to rt and stir for 3 h.
4. Connect to vacuum (0.1 mmHg) and remove all volatiles at rt for 1 h to afford the crude hydroboration product (1.25 g, 88%) as a colourless liquid.
5. Cool to 0 °C and add diethylzinc (Caution!).
6. Replace the septum with a glass stopper. Stir for 30 min at 0 °C.
7. Remove the triethylborane formed and the excess diethylzinc in vacuum (0 °C, 3 h, *ca.* 0.1 mmHg).
8. Add THF (5 mL) to the *bis*(4,4-dicarbethoxybutyl)zinc and cool to –80 °C.
9. Add CuCN•2LiCl in THF (prepared according to Protocol 1). Warm to 0 °C and immediately cool back to –80 °C.
10. Add allyl bromide, warm to 0 °C, and stir for 1 h.
11. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 9:1) to afford the desired product (1.09 g, 85%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 8.
Preparation of *trans*-isopropyl(1-methyl-3H-indan-2-yl)zinc by boron–zinc exchange and deuterolysis: preparation of *trans*-2-deuterio-1-methyl-3H-indan[22]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diisopropylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



47 %; 98:2 d.r.

Equipment

- One two-necked, round-bottomed flask (100 mL) equipped with an argon inlet and a septum cap
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- Two two-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar

Materials

- 1-methyl-3H-indene (FW 130.2), 1 g, 7.68 mmol — **flammable**
- Triethylborane (FW 98), 30.3 g, 310 mmol — **flammable, pyrophoric**
- Borane–methyl sulfide complex (FW 76), 11.4 g, 150 mmol — **toxic, stench**
- Diethylborane (FW 70), 2.13 g, 23 mmol — **flammable, pyrophoric**
- Diisopropylzinc (FW 151.6), 2.33 mL, 15 mmol — **flammable, pyrophoric**
- Deuterium oxide (FW 20), 3 g, 150 mmol — **toxic**
- Dry THF — **irritant, flammable, hygroscopic**

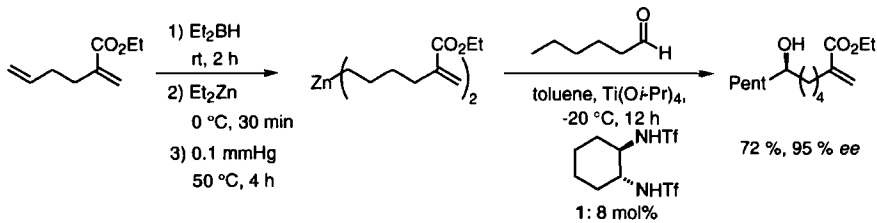
1. Charge one flame dried and argon flushed two-necked flask with triethylborane and add borane–methyl sulfide complex at rt. The stock solution of diethylborane is now ready for use.
2. Charge the second flame dried and argon flushed two-necked flask with 1-methyl-3H-indene and cool to 0 °C.
3. Add diethylborane to the indene. Allow to warm to rt and stir for 4 d at 40 °C.
4. Connect to vacuum and remove all volatiles at rt for 1 h to afford the crude hydroboration product.
5. Cool to −10 °C and add diisopropylzinc (Caution!).
6. Replace the septum with a glass stopper. Stir for 12 h at −10 °C.
7. Remove the triethylborane formed and the excess diisopropylzinc in vacuum (rt, 3 h, *ca.* 0.1 mmHg).
8. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.

Protocol 8. *Continued*

9. Add THF (5 mL) to the *trans*-isopropyl(1-methyl-3H-indan-2-yl)zinc and cool to –80 °C.
10. Add dropwise deuterium oxide, stir for 15 min, and then allow to warm to rt.
11. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes) to afford the desired product (0.48 g, 47%). Characterize the product by ^{1}H NMR, ^{2}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 9.
Preparation of *bis*(5-carbethoxy-5-hexen-1-yl)zinc by boron–zinc exchange and its enantioselective addition to an aldehyde: preparation of (6*R*)-ethyl 7-hydroxy-2-methylenedodecanoate[11]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- Two two-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (100 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

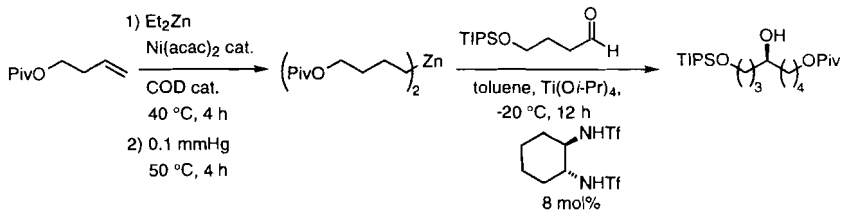
Materials

- Ethyl 2-methylene-5-hexenoate (FW 154.2), 1.4 g, 9.1 mmol — **flammable**
- Triethylborane (FW 98), 30.3 g, 310 mmol — **flammable, pyrophoric**
- Borane–methyl sulfide complex (FW 76), 11.4 g, 150 mmol — **toxic, stench**
- Diethylborane (FW 70), 0.83 g, 9 mmol — **flammable, pyrophoric**
- Diethylzinc (FW 123.5), 2 mL, 19.5 mmol — **flammable, pyrophoric**
- Ti(O*i*-Pr)$_4$ (FW 284.2), 0.8 g, 2.8 mmol — **flammable, irritant**
- (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane (FW 346.3), 42 mg, 0.11 mmol
- Hexanal (FW 100.2), 0.14 g, 1.4 mmol — **irritant**
- Dry toluene — **flammable**

1. Charge one flame dried and argon flushed two-necked flask with triethylborane and add borane–methyl sulfide complex at rt. The stock solution of diethylborane is now ready for use.
2. Charge the second flame dried and argon flushed two-necked flask with ethyl 2-methylene-5-hexenoate and cool to –10°C.
3. Slowly add diethylborane over a period of 15 min. Allow to warm to rt and stir for 2 h.
4. Connect to vacuum (0.1 mmHg) and remove all volatiles at rt for 1 h to afford the crude hydroboration product (1.72 g, 85%) as a colourless liquid.
5. Cool to 0°C and add diethylzinc (Caution!).
6. Replace the septum with a glass stopper. Stir for 30 min.
7. Remove the triethylborane formed and the excess diethylzinc in vacuum (50°C, 4 h, *ca.* 0.1 mmHg).
8. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
9. Dissolve the resulting oil of *bis*(5-carbethoxy-5-hexen-1-yl)zinc at rt in dry toluene (2 mL).
10. Charge the three-necked flask with dry toluene (1 mL), $Ti(O\textit{i}\text{-}Pr)_4$, and (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane.
11. Heat to 50°C for 30 min and then cool to –60°C. The catalyst is now ready for use.
12. Add *bis*(5-carbethoxy-5-hexen-1-yl)zinc at –60°C to the catalyst, then warm to –20°C, and after 20 min add hexanal. Stir for 12 h at –20°C.
13. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 5:1) to afford the desired product (0.26 g, 72%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = +0.3°$ ($c = 4.71$, $CHCl_3$).
14. Prepare the derivatives of the product with (*S*)-(–)-*O*-acetylmandelic acid and (+/–)-*O*-acetylmandelic acid, and compare their ^1H NMR spectra to determine the enantiomeric excess of the product (95% *ee*).

Protocol 10.
Preparation of *bis*(4-pivaloxybutyl)zinc by hydrozincation and its enantioselective addition to an aldehyde: preparation of (4*S*)-1-(triisopropylsiloxy)-4-hydroxy-8-pivaloxyoctane[13]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

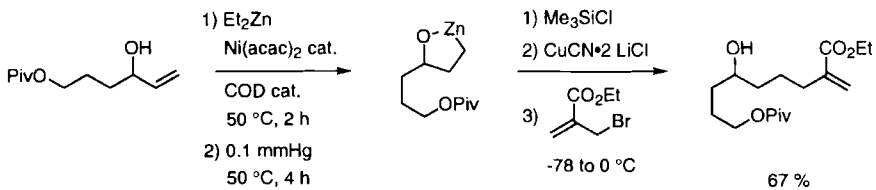
- 4-butenyl pivalate (FW 156.2), 3.91 g, 25 mmol — **flammable**
- Diethylzinc (FW 123.5), 1.5 mL, 15 mmol — **flammable, pyrophoric**
- $Ni(acac)_2$ (FW 256.9), 64 mg, 0.25 mmol — **harmful**
- 1,5-cyclooctadiene (FW 108.2), 54 mg, 0.5 mmol — **flammable, harmful**
- $Ti(Oi\text{-}Pr)_4$ (FW 284.2), 1.2 mL, 4 mmol — **flammable, irritant**
- (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane (FW 346.3), 61 mg, 0.18 mmol
- 4-(triisopropylsiloxy)butanal (FW 244.4), 0.49 g, 2 mmol — **flammable**
- Dry toluene — **flammable**

1. Charge the flame dried and argon flushed three-necked flask with 4-butenyl pivalate, 1,5-cyclooctadiene, and $Ni(acac)_2$, and cool the suspension to –78 °C.
2. Add diethylzinc (Caution!). Replace the septum cap with a glass stopper.
3. Warm the reaction mixture to 40 °C and stir for 4 h.
4. Remove the excess diethylzinc in vacuum (50 °C, 5 h, *ca.* 0.1 mmHg).
5. Confirm the formation of the zinc species by performing an iodolysis and hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(4-pivaloxybutyl)zinc at rt in dry toluene (2 mL).

7. Charge the three-necked flask with dry toluene (1 mL), Ti(O*i*-Pr)$_4$, and (1*R*, 2*R*)-1,2-*bis*(trifluoromethanesulfamido)cyclohexane.
8. Heat the catalyst to 50°C for 30 min and then cool to –60°C. The catalyst is now ready for use.
9. Add *bis*(4-pivaloxybutyl)zinc, warm to –10°C, and after 45 min add 4-(triisopropylsiloxy)butanal. Stir for 12 h at –10°C.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 4:1) to afford the desired product (0.54 g, 68%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = +0.8°$ (c = 15.7, benzene).
11. Prepare the derivatives of the product with (*S*)-(–)-*O*-acetylmandelic acid and (+/–)-*O*-acetylmandelic acid, and compare their ^{1}H NMR spectra to determine the enantiomeric excess of the product (95% *ee*).

Protocol 11.
Preparation of 3-(3-pivaloxypropyl)-1-zinca-2-oxacyclopentane by hydrozincation and its copper-mediated addition to an electrophile: preparation of ethyl 2-(4-hydroxy-7-pivaloxy)acrylate[13]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

- 4-hydroxy-5-hexenyl pivalate (FW 200.3), 0.5 g, 5 mmol
- 1,5-cyclooctadiene (FW 108.2), 0.05 mL, 0.5 mmol — **flammable, harmful**
- Ni(acac)$_2$ (FW 256.9), 60 mg, 0.25 mmol — **harmful**
- Diethylzinc (FW 123.5), 1.1 mL, 11 mmol — **flammable, pyrophoric**

Protocol 11. *Continued*

• Me_3SiCl (FW 108.6), 1.2 mL, 10 mmol	**flammable, corrosive**
• CuCN (FW 89.6), 0.89 g, 10 mmol	**highly toxic**
• LiCl (FW 42.4), 0.84 g, 20 mmol	**irritant, hygroscopic**
• Ethyl (2-bromomethyl)acrylate (FW 193), 1.25 g, 6.5 mmol	**irritant, lachrymator**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge the flame dried and argon flushed three-necked flask with 4-hydroxy-5-hexenyl pivalate, 1,5-cyclooctadiene, and $Ni(acac)_2$, and cool the suspension to –78°C.
2. Add diethylzinc (Caution!). Replace the septum cap with a glass stopper.
3. Slowly warm the reaction mixture to 40°C and stir for 4 h.
4. Remove the excess diethylzinc in vacuum (rt, 4 h, *ca.* 0.1 mmHg).
5. Dissolve the residual solid of 3-(3-pivaloxypropyl)-1-zinca-2-oxacyclopentane in THF (5 mL).
6. Confirm the formation of the zinc species by performing an iodolysis and a hydrolysis as described in Protocol 1.
7. Cool to –78°C and add Me_3SiCl. Allow to warm to rt overnight.
8. Meanwhile prepare a THF solution (10 mL) of CuCN•2LiCl in the two-necked flask (see Protocol 1).
9. Cool the zinc compound to –60°C and add the CuCN•2LiCl solution. Warm to 0°C and stir for 30 min.
10. Cool to –78°C and then add ethyl (2-bromomethyl)acrylate. Allow to warm to 0°C and stir for 30 min.
11. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 5:1) to afford the desired product (0.99 g, 67%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

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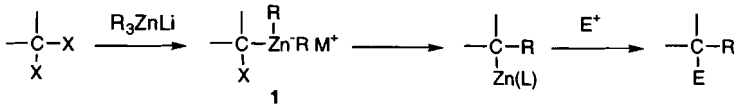
6

Preparation and reaction of triorganozincates

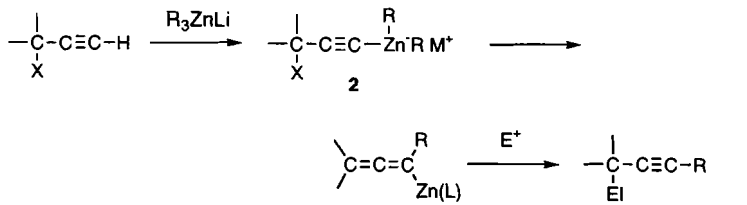
TOSHIRO HARADA and AKIRA OKU

1. Introduction

Reaction of diorganozincs with organolithium or Grignard reagents produces a thermally stable ate complexes R_3ZnM (M = Li, MgX) called organozincates.[1,2] Organozincates are generally more reactive than organozinc halides and diorganozincs, undergoing 1,2-addition to aldehydes and ketones and 1,4-addition to conjugate enones.[3] The latter reaction has been studied rather extensively and proved to be an alternative method to the use of cuprates as demonstrated in three-component coupling approach to prostaglandins.[4] Like other ate complexes, zincates bearing a leaving group at a proper position rearrange with 1,2-migration to give homologated organozincs[5,6] (Equations 6.1 and 6.2). Zincates are reactive enough to undergo halogen–zinc exchange with certain organic halides and to metalate carbon acids as terminal alkynes. The higher reactivities allows generation of intermediate zincate carbenoid **1** and alkynylzincate **2** directly from the corresponding *gem*-dibromo compound and alkyne, respectively. In addition, homologated organozincs, thus produced, can be trapped with a range of electrophiles (E^+). The overall reaction serves as a powerful tool for construction of carbon frameworks by a one-pot operation.



(6.1)



(6.2)

2. Preparation of zincates

In addition to the reaction of diorganozinc (Equation 6.3), a variety of zincates (R = alkyl, alkenyl, aryl, silyl[3c,g,h,7]) can be prepared also by transmetallation of Zn(II) salts (usually $ZnCl_2$) with three equivalents of organolithium or Grignard reagents (Equation 6.4). Although LiCl or MgX_2 is formed concurrently by this method, one can use the resulting mixture without any differences in reactivity compared to salt-free zincates. Mixed zincates $R^1(R^2)_2ZnLi$ are prepared either from $(R^2)_2Zn$ and R^1Li or by successive addition of R^2Li (2 equiv) and R^1Li (1 equiv) to $ZnCl_2$.[3c,d] Organic halides such as *gem*-dibromo and -bromochloro compounds,[5,8,9] iodoarenes,[10] iodoalkenes, and bromoalkynes[11] react with lithium trialkylzincates to give the corresponding mixed zincates (Equation 6.5). The reactivity of the zincates for halogen–zinc exchange decreases roughly in the order *n*-Bu ≈ *s*-Bu > *t*-Bu> Me. No reaction was observed for Ph_3ZnLi. For *gem*-diboromoalkenes, the exchange reaction generally accomplishes within 0.5 h at –85 °C except for Me_3ZnLi, which requires higher temperatures.[5b] Iodoarenes with a nitro or an ester group react with Me_3ZnLi to generate the corresponding functionalized aryldimethylzincates, which can be trapped by electrophiles like aldehydes.[10] Recently, tetracoordinated zincates $Me_3Zn(Y)Li_2$ (Y = CN, SCN), exhibiting higher reactivity, have been reported.[12]

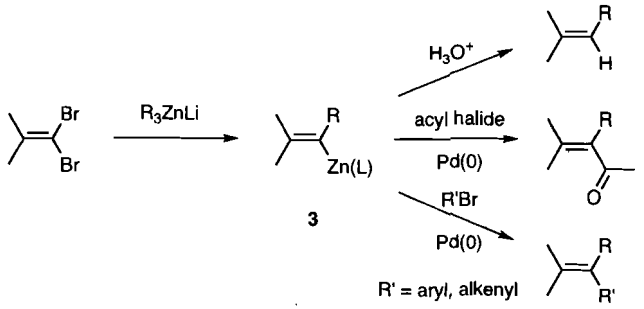
$$R_2Zn + RM \longrightarrow R_3ZnM \qquad (6.3)$$

$$ZnCl_2 + 3\,RM \longrightarrow R_3ZnM + 2\,MCl \qquad (6.4)$$

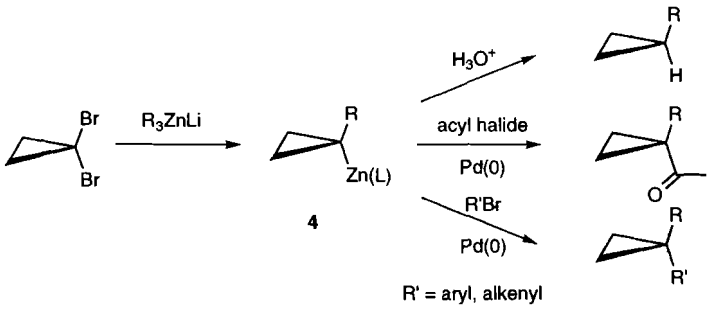
$$R^1X + (R^2)_3ZnLi \longrightarrow R^1(R^2)_2ZnLi + R^2X \qquad (6.5)$$

3. Generation of homologated organozincs via 1,2-migration of zincate carbenoids

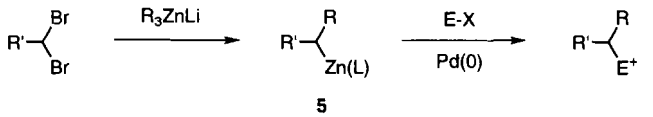
Reaction of *gem*-dibromoalkenes with zincates affords homologated alkenylzincs **3** via 1,2-migration of carbenoid intermediates (Scheme 6.1).[5] Similarly, cyclopropylzincs **4** can be prepared with carbon–carbon bond formation starting from *gem*-dibromocyclo propanes (Scheme 6.2).[8] A variety of alkyl groups, including sterically demanding *tert*-butyl group, can be introduced by using the corresponding lithium zincates (Protocol 1). Reactions are generally carried out in THF by using slight excess (1.25 equiv) of zincates. For *gem*-dibromoalkenes, it is necessary to perform the initial bromine/zinc exchange at the low temperature before warming up the resulting zincate carbenoids for 1,2-migration while the reaction of dibromocyclopropanes can be carried out at 0 °C (Protocol 2). It is also possible to generate *sec*-alkylzincs **5** starting from the corresponding *gem*-dibromoalkanes (Equation 6.6).[9]



Scheme 6.1



Scheme 6.2

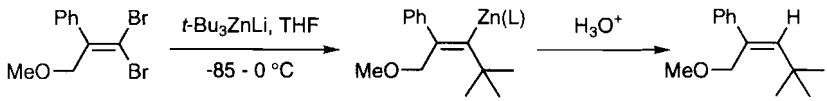


(6.6)

Protonation of the homologated organozincs gives the corresponding alkylation products (Protocol 1). On the other hand, palladium(0) catalysed cross-coupling reaction[13] of the resulting organozincs **3–5** with acyl chlorides, haloarenes, and halo-alkenes furnishes polysubstituted, functionalized products in one-pot reaction (Protocol 2). It should be noted that excess electrophiles (*ca.* 3 equiv) are required because a part of the alkyl group derived from the starting zincates also participates in the coupling reaction.

Protocol 1.
Alkylation of a 1,1-dibromoalkene with a zincate: synthesis of 1-methoxy-4,4-dimethyl-2-phenyl-2-pentene (Structure 8)[5b]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



6 7 8

Z:*E* = 1.5:1

Equipment

- Two-necked, round-bottom flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Vial (5 mL) with a septum cap
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)[a]
- Cooling bath[a]
- Dry, gas-tight syringes and needles

Materials

- $ZnCl_2$[a] (FW 136.3), 0.142 g, 1.04 mmol — **toxic**
- *t*-Butyllithium in pentane, 1.7 M, 1.84 mL, 3.12 mmol — **pyrophoric**
- Dibromoalkene **6**[b] (FW 204.3), 0.25 g, 0.818 mmol
- Dry, distilled THF — **flammable**

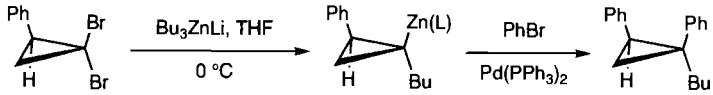
1. Assemble the reaction apparatus while hot and dry under vacuum. Fill the flask with nitrogen[c] through several vacuum cycles.
2. Remove the three-way stopcock and quickly weigh $ZnCl_2$ into the flask. Attach the stopcock and refill the flask with nitrogen (or argon) through several vacuum cycles.
3. Add dry THF (3.6 mL) with a syringe. Cool the solution at 0°C with stirring.
4. Add *t*-BuLi with a syringe. Stir at this temperature for 15 min.
5. Cool the flask to –85°C, add a solution of dibromoalkene **6** in THF (1 mL), prepared in a vial flushed with nitrogen, with a syringe over *ca.* 5 min. Stir for 2 h at this temperature and then warm up slowly to room temperature over 2.5 h to prepare alkenylzinc **7**.
6. Add water (1 mL) at room temperature. Pour the mixture into 1 N HCl (20 mL). Extract three times with ether and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over $MgSO_4$ and concentrate under reduced pressure.
7. Purify of the crude residue by flash chromatography on silica gel using pentane:Et_2O (96:4) as eluent to obtain pure 1-methoxy-4,4-dimethyl-2-phenyl-2-

pentene (**8**, *Z*:*E* = 1.5:1) (0.14 g, 84%) as a clear oil. Characterize the product by ^{1}H NMR, ^{13}C NMR, IR, MS spectroscopy, and elemental analysis.

[a] General comments on Protocols 1–7. A thick wall, natural latex rubber balloon (*ca.* 2 L) is used. A cryocool system is used for cooling. Commercial anhydrous $ZnCl_2$ is dried under high vacuum at 100 °C for 10 h over P_2O_5. This can be stored for use for at least ten days.
[b] Prepared by the reaction of α-methoxyacetophenone with PPh_3 and CBr_4 in refluxing benzene: Hessig, R.; Seebach, D.; Siegel, H. *Chem. Ber.* **1984**, *117*, 1877.
[c] Use of heavy argon in this step may cause difficulty in weighing of $ZnCl_2$.

Protocol 2.
Disubstitution of a *gem*-dibromocyclopropane: synthesis of 1-butyl-1,2-diphenylcyclopropane (Structure 9)[8c]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



9 **10** **11**; *cis*:*trans* = 2.7:1

Equipment

- One two-necked, round-bottom flask (50 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- One two-necked, pear-shaped flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Vial (5 mL) with a septum cap
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)
- Cooling bath
- Dry, gas-tight syringes and needles
- Kugelrohr apparatus

Materials

- $ZnCl_2$ (FW 136.3), 0.191 g, 1.4 mmol — **hygroscopic, corrosive, toxic**
- Triphenylmethane (FW 244.3), *ca.* 1 mg
- Butyllithium in hexane, 1.6 M, 2.63 mL, 4.20 mmol — **flammable**
- Dibromocyclopropane **10**[a] (FW 276), 0.31 g, 1.12 mmol
- *Bis*(triphenylphosphine)palladium(II) chloride (FW 701.9), 0.077 g, 0.11 mmol — **moisture-sensitive**
- Diisobutylaluminium hydride in hexane, 1 M, 0.22 mL, 0.22 mmol — **pyrophoric, moisture-sensitive**
- Bromobenzene (FW 157), 0.47 mL, 4.5 mmol — **irritant**
- Dry, distilled THF — **flammable, irritant**

1. Assemble a flask (50 mL) and other apparatus while hot and dry under vacuum. Fill the flask with nitrogen through several vacuum cycles.
2. Remove the three-way stopcock, quickly weigh $ZnCl_2$ into the flask, and add triphenylmethane. Attach the stopcock and refill the flask with nitrogen (or argon) through several vacuum cycles.

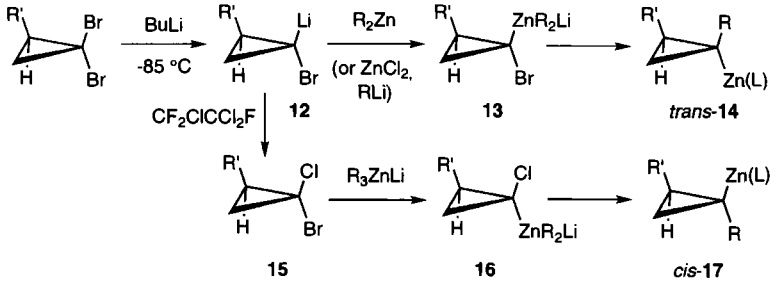
Protocol 2. *Continued*

3. Add dry THF (4.9 mL) with a syringe. Cool the solution to 0°C with stirring. Add BuLi with a syringe until a red colour appears.[b] Stir for 15 min at this temperature.
4. Add a solution of dibromocyclopropane **9** in THF (1 mL), prepared in a vial flushed with nitrogen, with a syringe. Stir at this temperature for 30 min to prepare cyclopropylzinc **10**.
5. During this time, place $PdCl_2(PPh_3)_2$ in another flask (20 mL). Fill the flask with nitrogen through several vacuum cycles. Add dry THF (8 mL) with a syringe and cool the resulting suspension to 0°C. Add diisobutylaluminium hydride with a syringe and stir for 15 min at 0°C.
6. Add thus prepared dark brown solution of $Pd(PPh_3)_2$ with a syringe to the solution of cyclopropylzinc **10** at 0°C. Add bromobenzene with a syringe and stir for 14 h at room temperature.
7. Pour the mixture into 1 N HCl (40 mL). Extract three times with ether and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over $MgSO_4$ and evaporate the solvents. Remove volatile by-products by vacuum distillation of the residue using a Kugelrohr at 150°C/10 mmHg.
8. Purify the crude product by flash chromatography on silica gel using hexane as an eluent to obtain pure 1-butyl-1,2-diphenylcyclopropane (**11**; *cis*:*trans* = 2.7:1) (0.23 g, 82%) as a clear oil. Characterize the product by ^1H NMR, IR, MS spectroscopy, and HRMS spectroscopy.

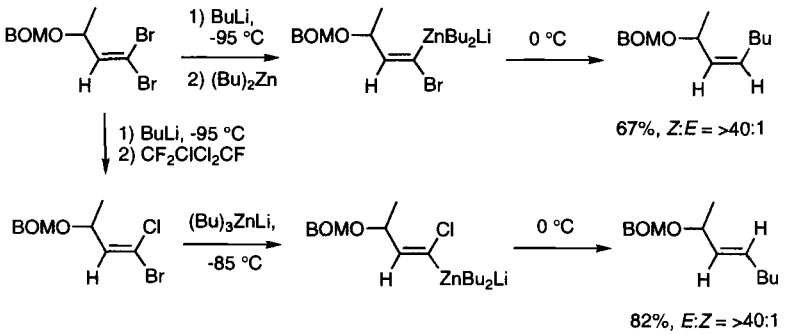
[a] Prepared by the reaction of the corresponding alkene with dibromocarbene generated from $CHBr_3$ and *t*-BuOK: Parham, W. E.; Schweizer, F. E. *Org. React.* **1963**, *13*, 55.
[b] Triphenylmethane can be used as an indicator[3a] for lithium *n*-butyl and *s*-butylzincates, but not for *t*-butylzincate and Grignard-derived zincates.

1,2-migration of zincate carbenoids generally proceeds with inversion of the carbenoid carbon. Because halogen–zinc exchange of *gem*-dibromoalkenes and -cyclopropanes proceeds with low stereoselectivity,[14] the organozincs produced via 1,2-migration are a mixture of stereoisomers. However, both *trans*- and *cis*-cyclopropylzincs can be prepared stereoselectively by generating intermediate zincate carbenoids **13** and **16** in a stereocontrolled manner (Scheme 6.3).[8] *Trans*-bromocyclopropyllithium **12** can be generated with high stereoselectivity (> 10:1) under thermodynamically controlled conditions.[14,15] Successive treatment of **12** with R_2Zn (or with $ZnCl_2$ and RLi) generates zincate carbenoid **13**, which rearranges to give *trans*-**14** stereoselectively (Protocol 3). On the other hand, chlorination of **12** with 1,1,2-trichlorotrifluoroethane gives bromochlorocyclopropane **15**. Halogen–zinc exchange by zincates takes place exclusively on the bromine atom with retention of the stereochemistry and *cis*-cyclopropylzinc **17** is formed via 1,2-migration of the resulting carbenoid **16** (Protocol 4). Palladium(0) catalysed coupling reaction

of the cyclopropylzincs proceeds without loss of the stereochemical integrity. Therefore, one can obtain desired stereoisomer of the substituted cyclopropanes by one-pot reaction. Lithium carbenoids derived from dibromoalkenes are generally less stable and prone to rearrange to alkynes.[16] However, in some instances, stereocontrolled preparation of alkenylzincs is possible by using a similar methodology (Scheme 6.4).[5b]



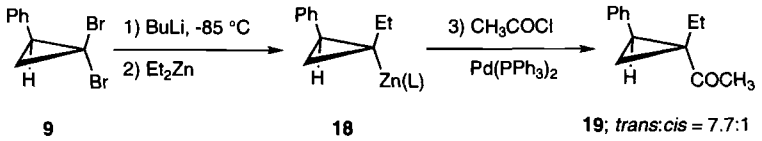
Scheme 6.3



Scheme 6.4

Protocol 3.
Cis-selective alkylation of a *gem*-dibromocyclopropane via a zincate carbenoid: synthesis of *r*-1-acetyl-1-ethyl-*t*-2-phenylcyclopropane (Structure 19)[8c]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Protocol 3. *Continued*

Equipment

- One two-necked, round-bottom flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)
- One two-necked, pear-shaped flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Cooling bath
- Dry, gas-tight syringes and needles

Materials

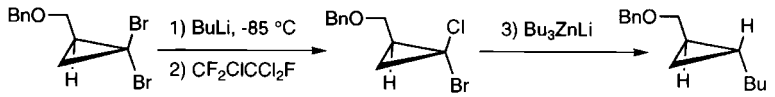
- Butyllithium in hexane, 1.6 M, 0.43 mL, 0.69 mmol — **flammable, moisture-sensitive**
- Dibromocyclopropane **10**[a] (FW 276), 0.189 g, 0.685 mmol
- Diethylzinc in hexane, 1 M, 0.69 mL, 0.69 mmol — **flammable, moisture-sensitive**
- *Bis*(triphenylphosphine)palladium(II) chloride (FW 701.9), 0.048 g, 0.069 mmol — **moisture-sensitive**
- Diisobutylaluminium hydride in hexane, 1 M, 0.14 mL, 0.14 mmol — **pyrophoric, moisture-sensitive**
- Acetyl chloride (FW 78.5), 0.146 mL, 2.06 mmol — **flammable, corrosive**
- Dry, distilled THF — **flammable, irritant**

1. Assemble a round-bottom flask and other apparatus while hot and dry under vacuum. Fill the flask with nitrogen through several vacuum cycles.
2. Remove the three-way stopcock and weigh dibromocyclopropane **9** into the flask. Attach the stopcock and refill the flask with nitrogen (or argon) through several vacuum cycles. Add dry THF (2.4 mL) with a syringe and cool to –85 °C.
3. Slowly add BuLi over 5 min with a syringe and stir for 15 min at this temperature.
4. Slowly add Et_2Zn over 5 min with a syringe and stir for 15 min at this temperature. Remove the cooling bath and stir for 30 min at room temperature to prepare cyclopropylzinc **18**.
5. During this time, prepare a THF (4.5 mL) solution of $Pd(PPh_3)_2$ in another flask as described in Protocol 2.
6. Add thus prepared solution of $Pd(PPh_3)_2$ to the solution of cyclopropylzinc **18** with a syringe at 0 °C. Stir at room temperature for 8 h.
7. Pour the mixture into 1 N HCl (20 mL). Extract twice with ethyl acetate and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over Na_2SO_4 and evaporate the solvents.
8. Purify of the crude residue by flash chromatography on silica gel using petroleum ether:ethyl acetate (98:2) as eluent to obtain pure *r*-1-acetyl-1-ethyl-*t*-2-phenylcyclo propane (**19**; *trans*:*cis* = 7.7:1) (0.103 g, 80%) as a clear oil. Characterize the product by ^1H NMR, IR spectroscopy, and HRMS spectroscopy.

[a]See footnote *a* of Protocol 2.

Protocol 4.
Trans-selective alkylation of dibromocyclopropanes via a bromochlorocyclopropane: synthesis of *trans*-1-butyl-2-[(phenylmethoxy)methyl]cyclopropane (Structure 22)[8c]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



20 **21** **22**; *trans*:*cis* = 15:1

Equipment

- One two-necked, round-bottom flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)
- One two-necked, pear-shaped flask (10 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Cooling bath
- Dry, gas-tight syringes and needles

Materials

- Butyllithium in hexane, 1.6 M, 0.625 mL, 1 mmol, and 2.34 mL, 3.75 mmol — **flammable, moisture-sensitive**
- Dibromocyclopropane **21**[a] (FW 320), 0.32 g, 1 mmol
- 1,1,2-Trichlorotrifluoroethane (FW 187.4), 0.12 mL, 1 mmol
- $ZnCl_2$ (FW 136.3), 0.17 g, 1.25 mmol — **toxic**
- Dry, distilled THF — **flammable, irritant**

1. Prepare a THF (3.5 mL) solution of the lithium carbenoid in a round-bottom flask at –85°C as in Protocol 3.
2. Add 1,1,2-trichlorotrifluoroethane at –85°C with a syringe. Stir at this temperature for 30 min and then at 0°C for 10 min to prepare bromochlorocyclopropane **21**.
3. During this time, prepare a solution of Bu_3ZnLi (1.25 mmol) in THF (4.4 mL) in another flask as described in Protocol 2.
4. Cool the flasks to –85°C and add the solution of Bu_3ZnLi with a syringe over *ca.* 5 min. Warm up slowly to room temperature over 3 h and stir further for 0.5 h.
5. Pour the mixture into 1 N HCl (20 mL). Extract three times with ether and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over $MgSO_4$ and concentrate under reduced pressure.
6. Purify the crude residue by flash chromatography on silica gel using hexane: ethyl acetate (98:2) as eluent to obtain pure *trans*-1-butyl-2-[(phenyl-

Protocol 4. *Continued*

methoxy)methylcyclopropane (**22**; *trans*:*cis* = 15:1) (0.152 g, 70%) as a clear oil. Characterize the product by ^{1}H NMR, IR, MS spectroscopy, and HRMS spectroscopy.

[a]See footnote *a* of Protocol 2.

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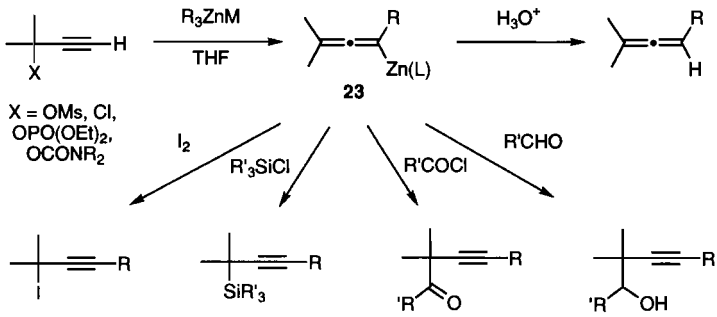
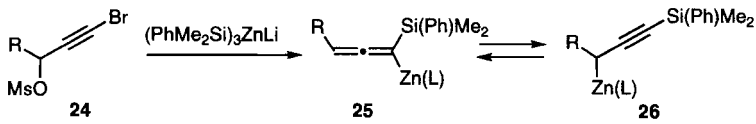
4. Generation of allenic zincs via 1,2-migration of alkynylzincates

Cuprates are known to react with propargylic derivatives to give allenes.[17] Zincates, on the other hand, afford allenic zincs **23**, which can be utilized further in the reaction with electrophiles (Scheme 6.5).[11,18] Allenic zincs are produced through a mechanism involving initial metallation of the terminal alkyne followed by 1,2-migration of the resulting alkynylzincate (Equation 6.2). Reactions are generally carried out by using two equivalents of zincates in THF at the temperature from –85 to 0 °C. Lithium or chloromagnesium trialkylzincates can be used for preparing the corresponding homologated allenic zinc. Allenic zinc bearing alkenyl and aryl groups can also be prepared by using the corresponding lithium zincates (Protocol 5). Secondary mesylates (X = OMs) and tertiary chlorides (X = Cl) are common propargylic substrates while phosphates and carbamates can be used as well. For the less basic zincates such as Me_3ZnLi and $(TMSCH_2)_3ZnLi$, better results are obtained by using carbamates (X = $OCONPh_2$). Silylzincates react with propargylic substrates to give directly α-silylallenes but not the corresponding organozincs. However, α-silylallenic zinc **25** can be generated as an equilibrating mixture with propargylic zinc **26** by the reaction of bromopropargyl mesylate **24** with $(PhMe_2Si)_3ZnLi$ (Equation 6.7).

Hydrolysis of allenic zinc **23** affords substituted allenes as in the reaction of cuprates while successive treatment of **23** with electrophiles, such as aldehydes, acyl chlorides, chlorosilanes, and iodine, regioselectively furnishes the propargylic products in which the R and E groups are introduced at the 1,3-positions of the substrates. As the allenic moiety on **23** reacts preferentially, excess electrophiles are not required except for iodination. Protocol 6 illustrates the utility of the reaction for preparation of functionalized alkynylsilanes. Direct reaction of the resulting allenic zincs with aldehydes gives a mixture of diastereomeric adducts non-stereoselectively. However, one can obtain *anti*-adduct **28** with high selectivity when allenic zincs is converted to allenic chlorozinc **27**[19] by treatment with $ZnCl_2$ (Equation 6.8). Thus, a wide range of *anti*-homopropargylic alcohols can be stereo- and regioselectively prepared from propargylic substrates, zincates, and aldehydes in a convergent manner (Protocol 5).



Scheme 6.5



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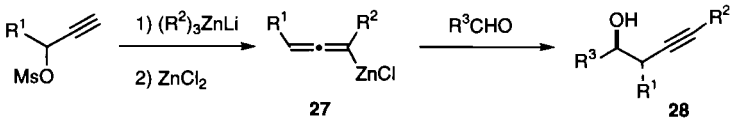
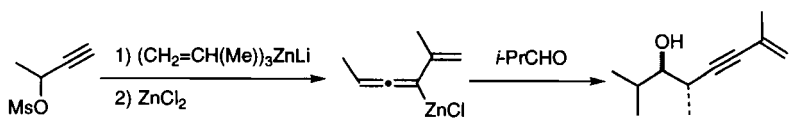


(6.8)

Protocol 5.
Generation of an allenic zinc and its reaction with an aldehyde: synthesis of (3*R**,4*S**)-2,4,7-trimethyloct-7-en-5-yn-3-ol (Structure 31)[11]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two two-necked, round-bottom flasks (50 mL) each with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Two-necked, pear-shaped flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Vial (5 mL) with a septum cap
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)
- Cooling bath
- Dry, gas-tight syringes and needles
- Cannula
- Syringe pump

Protocol 5. *Continued*

Materials

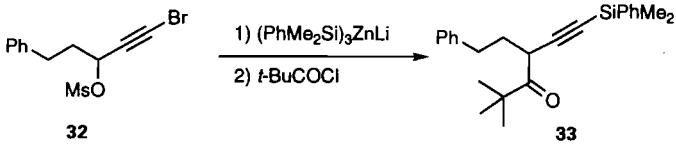
- 2-Bromopropene (FW 121), 0.76 mL, 8.5 mmol — **flammable, irritant**
- *t*-Butyllithium in pentane, 1.7 M, 10 mL, 17 mmol — **pyrophoric, moisture-sensitive**
- $ZnCl_2$ (FW 136.3), 0.382 g, 2.8 mmol and 0.572 g, 4.2 mmol — **corrosive, toxic**
- Mesylate **29**[a] (FW 148.2), 0.207 g, 1.40 mmol
- Distilled 2-methylpropanal (FW 72.1), 0.19 mL, 2.2 mmol — **flammable, irritant**
- Dry, distilled THF — **flammable, irritant**

1. Add 2-bromopropene and THF (8.5 mL) to a flask (50 mL) that has been vacuum dried and charged with argon, cool to –85 °C and add *t*-BuLi with a syringe, and stir for 1 h at this temperature. Warm the resulting suspension of *iso*-propenyllithium to 0 °C.
2. In the second flask (50 mL), prepare a solution of $ZnCl_2$ (2.8 mmol) in THF (2.4 mL) under argon, and cool at 0 °C as described in Protocol 1. Cannulate *iso*-propenyl lithium and stir at this temperature for 15 min. Cool the resulting solution of the alkenylzincate to –85 °C.
3. In the third flask (20 mL), prepare a solution of $ZnCl_2$ (4.2 mmol) in THF (4.1 mL) under argon as described in Protocol 1.
4. Add a solution of mesylate **29** in THF (1 mL), prepared in a vial under argon, to the alkenylzincate at –85 °C. Stir at this temperature for 15 min and then at 0 °C for 5 min.
5. Cool the flask to –85 °C. Slowly add the solution of $ZnCl_2$ over 15 min using a syringe pump, and then stir at this temperature for 1 h to prepare allenic zinc **30**.
6. Add 2-methylpropanal with a syringe. Slowly warm up the mixture to 0 °C over 2 h.
7. Pour the mixture into 1 N HCl (50 mL). Extract three times with ether and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over $MgSO_4$ and evaporate the solvents.
8. Purify of the crude residue by flash chromatography on silica gel using pentane:ether (85:15) as eluent to obtain pure (3*R**,4*S**)-2,4,7-trimethyloct-7-en-5-yn-3-ol (**31**; *anti*:*syn* = 98.6:1.4) (0.147 g, 63%) as a clear oil (b.p. 75 °C/8 mmHg; Kugelrohr). Characterize the product by ^1H NMR, ^{13}C NMR, IR, MS spectroscopy, and elemental analysis.

[a] Prepared by the reaction of 1-butyn-3-ol with CH_3SO_2Cl and Et_3N in CH_2Cl_2: Katsuhira, T.; Harada, T.; Oku, A. *J. Org. Chem.* **1994**, *59*, 4010.

Protocol 6.
Generation of an α-silylallenic zinc and its reaction with an acyl halide: synthesis of 6-(dimethylphenylsilyl)-2,2-dimethyl-4-(2-phenylethyl)-5-hexyn-3-one (Structure 33)[11]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



32 **33**

Equipment

- Two-necked, round-bottom flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Vial (5 mL) with a septum cap
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)
- Cooling bath
- Dry, gas-tight syringes and needles

Materials

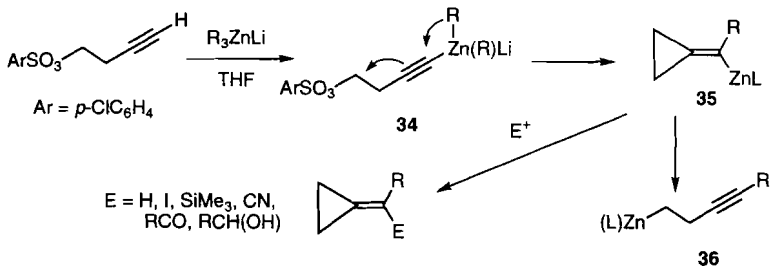
- $ZnCl_2$ (FW 136.3), 0.099 g, 0.73 mmol — **corrosive, toxic**
- $PhMe_2SiLi$[a] 0.37 M in THF, 5.84 mL, 2.16 mmol — **flammable, moisture-sensitive**
- Bromopropargyl mesylate **32**[b] (FW 317.2), 0.119 g, 0.6 mmol
- Pivaloyl chloride (FW 120.6), 0.11 mL, 0.9 mmol — **corrosive**
- Dry, distilled THF — **flammable, irritant**

1. Quickly weigh $ZnCl_2$ into a vacuum dried flask and charge with argon through several vacuum cycles.
2. Add dry THF (2.4 mL) with a syringe. Cool the solution to 0°C with stirring and add $PhMe_2SiLi$ with a syringe. Stir for 15 min at this temperature.
3. Cool the flask to –85°C. Add a solution of bromopropargyl mesylate **32** in THF (2.6 mL), prepared in a vial under argon, and stir at this temperature for 15 min.
4. Add pivaloyl chloride with a syringe at –85°C and stir at –75°C for 1 h.
5. Pour the mixture into 1 N HCl (20 mL). Extract three times with hexane and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over $MgSO_4$ and evaporate the solvents.
6. Purify of the crude residue by flash chromatography on silica gel using hexane:ethyl acetate as eluent (gradient elution from 98:2 to 90:10). Pure 6-(dimethylphenylsilyl)-2,2-dimethyl-4-(2-phenylethyl)-5-hexyn-3-one (**33**) (0.141 g, 65%) as a clear oil. Characterize the product by ^1H NMR, IR, MS spectroscopy, and elemental analysis.

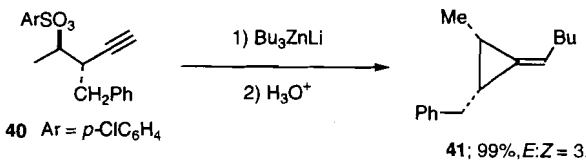
[a] Prepared by the reaction of $PhMe_2SiCl$ and Li in THF: George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403.
[b] Prepared in 68% overall yield by bromination of 5-phenyl-1-pentyn-3-ol (BuLi and then Br_2) followed by mesylation ($MeSO_2Cl$, Et_3N).[11]

5. Generation and reaction of 1-(cyclopropylidene)-alkylzincs

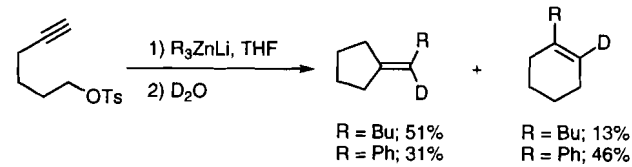
Methylenecyclopropanes exhibit unique reactivity in ring-opening reactions, cycloadditions, and transformations to cyclopropanes.[20] Zincates reacts with a homopropargylic *p*-chlorobenzenesulfonate to give 1-(cyclopropylidene) alkylzinc **35** via 1,2-migration/cyclization of alkynylzincate **34** (Scheme 6.6).[21] Alkyl- and arylzincates can be employed. The organozinc **35**, thus generated, serves as a versatile reagent for the preparation of functionalized methylenecyclopropanes (Protocol 7). Control of the reaction temperature is important because the organozinc **35** undergoes ring-opening reaction to homopropargylic zinc **36** at higher temperatures (*ca.* 0 °C). *p*-chloro- or *p*-fluorobenzenesulfonates, rather than tosylates, are recommended as substrates because the corresponding alkynylzincate intermediates are more reactive and cyclize below 0 °C. Formation of the *cis*-product **41** in the reaction of *anti* homopropargylic sulfonate **40** demonstrates that the cyclization proceeds with inversion of stereochemistry at the electrophilic carbon (Equation 6.9). Interestingly, *exo*- and *endo*-cyclization proceeds competitively in the reaction of a homologous substrate (Equation 6.10).[22]



Scheme 6.6



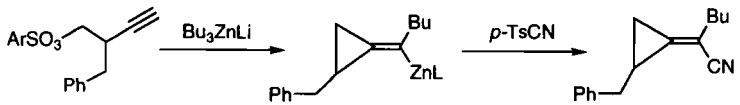
(6.9)



(6.10)

Protocol 7.
Generation and reaction of a 1-(cyclopropylidene)alkylzinc: synthesis of 1-[2-(phenylmethyl)cyclopropylidene]pentanenitrile (Structure 39)[21]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



37 Ar = *p*-ClC_6H_4 **38** **39**; *Z*:*E* = 2.1:1

Equipment

- Two-necked, round-bottom flask (20 mL) with a magnetic stirrer bar, septum cap (8 mm), and three-way stopcock, connected to a vacuum/nitrogen (or argon) source
- Two vials (5 mL) each with a septum cap
- Vacuum/inlet gas source (gas source may be a nitrogen or argon balloon)
- Cooling bath
- Dry, gas-tight syringes and needles

Materials

- $ZnCl_2$ (FW 136.3), 0.107 g, 0.785 mmol — **corrosive, toxic**
- Butyllithium, 1.6 M in hexane, 1.47 mL, 2.34 mmol — **flammable, moisture-sensitive**
- Triphenylmethane (FW 244.3), *ca.* 1 mg
- *p*-Chlorobenzenesulfonate **37**[a] (FW 334.8), 0.131 g, 0.392 mmol
- *p*-Toluenesulfonyl cyanide (FW 181.2), 0.142 mg, 0.785 mmol — **toxic**
- Dry, distilled THF — **flammable, irritant**

1. Prepare a solution of Bu_3ZnLi in THF (2.4 mL) as described in Protocol 2 and cool to –85°C.
2. Add a solution of *p*-chlorobenzenesulfonate **1** in THF (2 mL), prepared in a vial under argon. Stir for 6 h at –20°C to prepare cyclopropylidenealkylzinc **38**.
3. Cool the flask to –85°C. Add a solution of TsCN in THF (1 mL), prepared in a vial under argon, and stir at this temperature for 15 h.
4. Pour the mixture into 1 N HCl (20 mL). Extract twice with ether and wash the combined organic layers with 5% $NaHCO_3$. Dry the extract over $MgSO_4$ and evaporate the solvents.
5. Purify of the crude residue by flash chromatography on silica gel using hexane: ethyl acetate (96:4) to obtain pure 1-[2-(phenylmethyl)cyclopropylidene]pentanenitrile (**39**; *Z*:*E* = 2.1:1) (0.064 g, 73%) as a clear oil. Characterize the product by ^1H NMR, IR, MS spectroscopy, and HRMS spectroscopy.

[a] Prepared by the reaction of the corresponding homopropargyl alcohol with BuLi and *p*-chlorobenzenesulfonyl chloride: Brown, H. C.; Bernheimer, R.; Kim. C. J.; Sheppele, S. E. *J. Am. Chem. Soc.* **1967**, *89*, 370.

References

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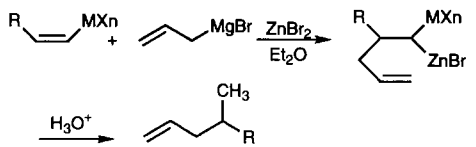
7

Preparation and reactions of 1,n-bismetallic reagents

ILANE MAREK and JEAN F. NORMANT

1. Introduction

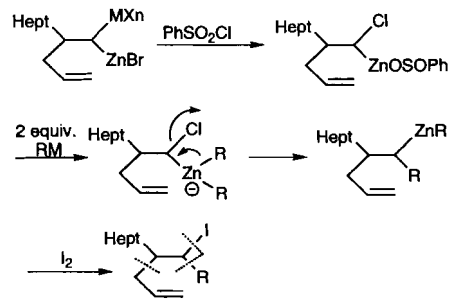
The story of the 1,1-organogembismetallic synthesis by allylmetallation, has originally started by the discovery of Gaudemar,[1] who reported that the addition of allylzinc bromide to vinyl or alkynyl Grignard reagents leads to the corresponding organogembismetallic species. Although these organometallic compounds were obtained in moderate chemical yields, this reaction now allows an easy approach to the synthesis of gembismetallic reagents[2] in high yield via a carbometallation reaction (Equation 7.1 and Protocol 1).



(7.1)

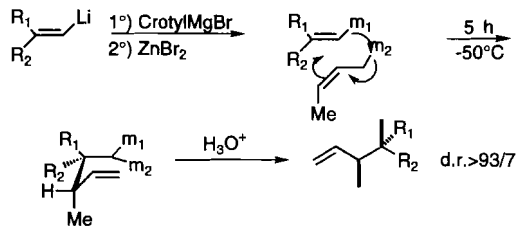
Various metals may be used on the vinylic part as MXn = Li, MgX, Al, B, Cu but the presence of zinc (or cadmium) is compulsory for the addition to proceed.[2] These bismetallic derivatives can be seen as stereoselective alkenylating reagents to give the *E*- (see Protocol 2) or *Z*-olefins,[3,4] but can be also considered as d^1/d^1 multicoupling reagents.[5] Indeed, they can be selectively monoprotonated,[3] deuterated,[3] and stannylated[6–8] leading to highly functionalized secondary organozinc halides which can react with a second electrophile[3,6–8] (see Protocol 3), with or without a transmetallation step into an organocopper derivative.[9] Since the monoalkylation of the organogembismetallic is rather difficult (even after a transmetallation reaction, in this case the second step is competitive with the first one), a selective monoalkylation of organogembismetallics via an intramolecular nucleophilic substitution was recently described[10] (Equation 7.2 and Protocol 4).

The diastereoselectivity of the carbometallation reaction was also investigated and it was observed that the diastereoselection is highly dependent on the temperature and on the nature of the solvent.[11] Thus, decreasing the Lewis



(7.2)

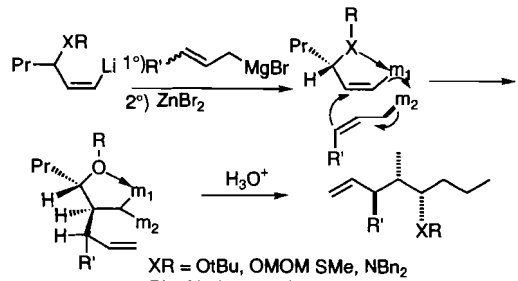
basicity of the solvent considerably speeds up the reaction and allows the addition to be carried out at much lower temperatures. Under these conditions, a substituted allylzinc bromide adds stereoselectively to the *Z*- or *E*-vinyl lithiums and leads respectively to the *anti* or *syn* diastereomers[11–13] (Equation 7.3 and Protocol 5).



(7.3)

R_1 = Alkyl, CH_2NEt_2, OtBu, OMOM, SPh R_2 = H
R_1 = H R_2 = Alkyl, CH_2NEt_2, OtBu, OMOM, SPh

By this way, from two prochiral vinylic carbon atoms, two stereogenic centres were created with good diastereoselectivity. Knowing that the chelation between zinc and heteroatoms in ω-heterosubstituted dialkylzinc reagents has already been shown by NMR studies,[14] the allylzincation of substituted γ-heterosubstituted vinyl metals has been studied.[13,15] In all cases, the chelation promotes a difference between the two prochiral faces of the vinyl moiety since one is shielded by the alkyl group, and then the allyl[13,15,16] or the substituted allylmetal[13,15,17] (Equation 7.4 and Protocol 6) reacts diastereoselectively.

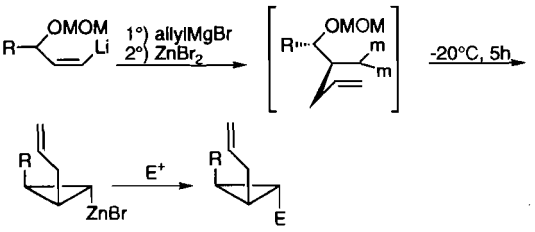


(7.4)

XR = OtBu, OMOM SMe, NBn_2
R' = H d.r. > 95 / 5, yield>70%.
XR = OtBu, OMOM SMe, NBn_2
R' = Me d.r. > 95 / 5, yield>75%.

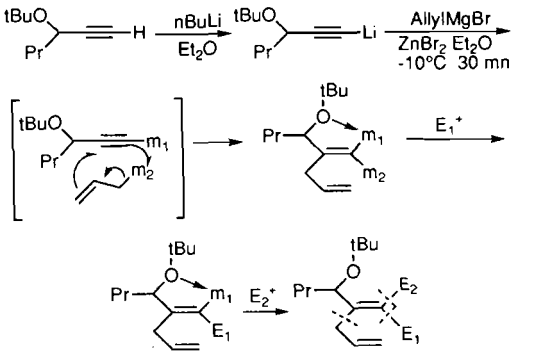
The same trend is observed for the allylmetallation of δ-heterosubstituted vinyl metals,[18] of a metallated pentadiene[19] (see Protocol 7) or in the propargylmetallation of vinyl metals[13] (see Protocol 8).

The allylmetallation of vinyl metals, γ-heterosubstituted with a methoxymethyl ether as the chelating group, leads to the corresponding gembismetallic derivatives,[20] but now, warming the reaction mixture to room temperature promotes an internal nucleophilic substitution, leading to a metallated cyclopropane which can react with different electrophiles[21] (Equation 7.5 and Protocol 9).



(7.5)

The allylmetallation of an alkynyl metal leads to a vinylic 1,1-organogembismetallic derivative,[22] and the stereoselective reaction of this latter with different electrophiles gives a new access to the synthesis of stereodefined polysubstituted olefins, as single stereoisomers[23] (Equation 7.6 and Protocol 10).



(7.6)

Some other sp^3 organogembismetallic compounds were reported as the synthesis of 1,3 dizinc derivatives using the boron–zinc exchange[24] (Protocol 11), or the synthesis of 1,n-heterobimetallic reagents.[25] In the latter case, the reactivity of these derivatives is mainly the same as that of the monometallic compound.

2. General

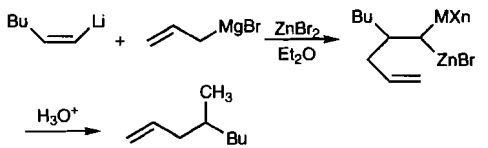
The solvents used (ether, THF) were dried and distilled over sodium benzophenone ketyl. Allylmagnesium or crotylmagnesium bromide were prepared

by standard methods.[26] Zinc bromide was purchased from Merck or Fluka and was melted under a stream of nitrogen and handled as 1 M ethereal solutions.

3. Protocols

Protocol 1. Allylmetallation of vinyl lithium derivatives: preparation of 4-methyloctene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

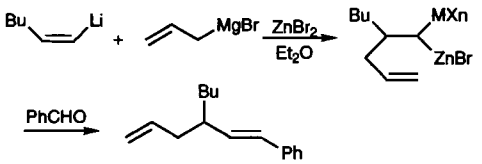
Materials

- 1-iodohexene[27] (FW 210), 1.05g, 5 mmol — **irritant**
- *t*BuLi, 1.7 M solution in pentane, 5.88 mL, 10 mmol — **pyrophoric, flammable**
- Allylmagnesium bromide, 1 M solution in ether, 10 mL, 10 mmol — **pyrophoric,flammable**
- $ZnBr_2$, 1 M solution in ether, 10 mL, 10 mmol — **irritant**
- Et_2O, 30 mL — **flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 1-iodo-1-hex-1-ene (1.05 g, 5 mmol) and Et_2O (30 mL).
2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (5.88 mL, 10 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add dropwise allylmagnesium bromide at –20°C (10 mL, 10 mmol) to the reaction mixture.
4. Add dropwise zinc bromide (10 mL, 10 mmol) at –20°C and then stir the mixture for 3 h at –20°C under nitrogen.
5. Hydrolyse at –20°C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane). The yield is 500 mg, 80%.

Protocol 2.
Allylmetallation of vinyl lithium derivatives and alkenylation of the resulting bismetallics: preparation of (*E*)-1-phenyl-3-butyl-1,5-hexadiene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80 °C to 30 °C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

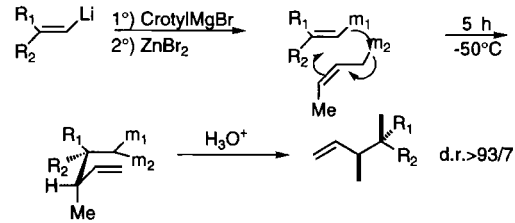
Materials

- 1-iodohexene[27] (FW 210), 1.05g, 5 mmol — **irritant**
- *t*BuLi, 1.7 M solution in pentane, 5.88 mL, 10 mmol — **pyrophoric, flammable**
- Allylmagnesium bromide, 1 M solution in ether, 10 mL, 10 mmol — **pyrophoric, flammable**
- $ZnBr_2$, 1 M solution in ether, 10 mL, 10 mmol — **irritant**
- Benzaldehyde (FW 106.12), 1.06 g, 10 mmol — **harmful**
- Et_2O, 40 mL — **flammable**

1. Prepare the organogembismetallic derivative following Protocol 1.
2. Add one portion of freshly distilled benzaldehyde (1.06 g, 10 mmol) in Et_2O (10 mL) at –40 °C, then stir the mixture for 2 h at –20 °C, and slowly warm to room temperature over 3 h.
3. Hydrolyse at –20 °C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer twice Et_2O (2 × 20 mL). The combined organic phases are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane). The yield is 770 mg, 72%.

Protocol 3.
Selective reaction of the organogembismetallic derivatives with two different electrophiles: preparation of 1-iodo-1-tributylstannyl-2-*tert*-butoxymethyl-4-pentene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



R_1 = Alkyl, CH_2NEt_2, OtBu, OMOM, SPh R_2 = H
R_1 = H R_2 = Alkyl, CH_2NEt_2, OtBu, OMOM, SPh

Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

Materials

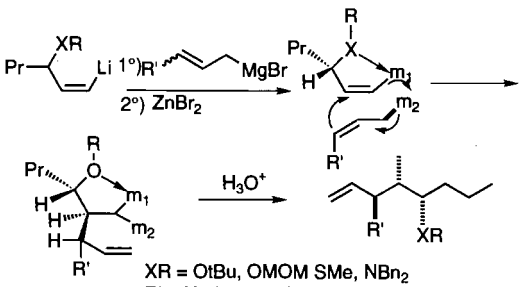
• 1-(*Z*)-iodo-3-*tert*-butoxyprop-1-ene[28] (FW 240), 500 mg, 2.1 mmol	**irritant**
• *t*BuLi, 1.7 M solution in pentane, 2.4 mL, 4.2 mmol	**pyrophoric, flammable**
• Allylmagnesium bromide, 1 M solution in ether, 4.2 mL, 4.2 mmol	**pyrophoric, flammable**
• $ZnBr_2$, 1 M solution in ether, 4.2 mL, 4.2 mmol	**irritant**
• Bu_3SnCl (FW 325.49), 1.36 g, 4.2 mmol	**toxic, harmful**
• I_2 (FW 254), 1.06 g, 4.2 mmol	**harmful**
• Et_2O, 60 mL	**flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 1-(*Z*)-iodo-3-*tert*-butoxyprop-1-ene (500 mg, 2.1 mmol) and Et_2O (30 mL).
2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (2.4 mL, 4.2 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add allylmagnesium bromide (4.2 mL, 4.2 mmol) at –20°C to the reaction mixture.
4. Add zinc bromide (4.2 mL, 4.2 mmol) at –20°C and then stir the mixture for 3 h at –20°C under nitrogen.
5. Add Bu_3SnCl (1.36 g, 4.2 mmol) in Et_2O (10 mL) at –20°C and stir the reaction mixture at this temperature for 2 h.
6. Cool the monometallic compound solution to –50°C, then add dropwise a solution of iodine (1.06 g, 4.2 mmol) in Et_2O (20 mL). Let the mixture warm to room temperature over 1 h.

7. Hydrolyse at –20°C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are washed with a solution of $Na_2S_2O_3$ (2 × 10 mL) and the resulting clear organic phase are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane:ethyl acetate, 98:2). The yield is 946 mg, 79% as two diastereomers, 75:25 ratio.

Protocol 4.
Selective monoalkylation of organogembismetallics via an intramolecular nucleophilic substitution: preparation of 4-allyl-3-iodo-2-methyl-undecane

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



XR = OtBu, OMOM SMe, NBn_2
R' = H d.r. > 95 / 5, yield>70%.
XR = OtBu, OMOM SMe, NBn_2
R' = Me d.r. > 95 / 5, yield>75%.

Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

Materials

- 1-(*Z*)-iodo-non-1-ene[27] (FW 251.9), 455 mg, 2 mmol — **irritant**
- *t*BuLi, 1.7 M solution in pentane, 2.9 mL, 5 mmol — **pyrophoric, flammable**
- Allylmagnesium bromide, 1 M solution in ether, 2 mL, 2 mmol — **pyrophoric, flammable**
- $ZnBr_2$, 1 M solution in ether, 2 mL, 2 mmol — **irritant**
- $PhSO_2Cl$ (FW 176.62), 0.27 mL, d = 1.384, 2 mmol — **corrosive**
- *i*PrMgCl, 0.96 M solution in THF, 5.2 mL, 5 mmol — **pyrophoric, flammable**
- I_2 (FW 254), 2 g, 8 mmol — **harmful**
- Et_2O, 40 mL — **flammable**
- THF, 10 mL — **flammable**

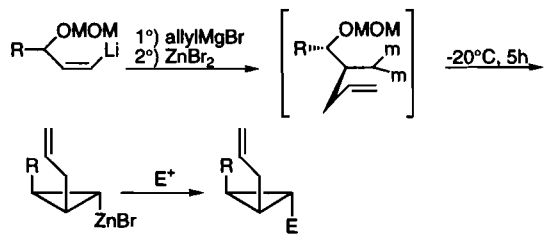
1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 1-(*Z*)-iodo-non-1-ene (455 mg, 2 mmol) and Et_2O (30 mL).

Protocol 4. *Continued*

2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (2.9 mL, 5 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add allylmagnesium bromide at –50°C (2 mL, 2 mmol) to the reaction mixture.
4. Add zinc bromide at –50°C (2 mL, 2 mmol) and then stir the mixture for 3 h at –30°C under nitrogen.
5. Cool to –80°C and add neat $PhSO_2Cl$ (0.27 mL, 2 mmol), stir the reaction mixture at this temperature for 30 min.
6. Add *i*PrMgCl (5.2 mL, 5 mmol) at –80°C and warm slowly to –40°C. Stir at –40°C for 1 h, followed by 1 h at –10°C.
7. Add a solution of iodine (2 g, 8 mmol) in THF (10 mL) at –20°C and warm slowly to room temperature.
8. Hydrolyse at –20°C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are washed with a solution of NaOH (2 × 10 mL) and the resulting clear organic phase is treated with a few crystals of $Na_2S.9H_2O$ overnight. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (pentane). The yield is 342 mg, 51% as two diastereomers, 50:50 ratio.

Protocol 5.
Crotylmetallation of vinyl lithium derivatives: preparation of (2*S**,3*S**)-dimethyl-1-*tert*-butoxypent-4-ene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

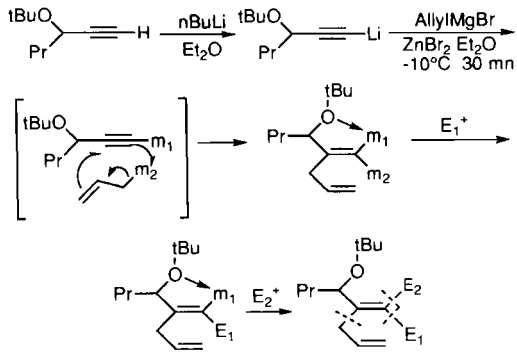
Materials

- 1-(*Z*)-iodo-3-*tert*-butoxyprop-1-ene[28] (FW 240), 500 mg, 2.1 mmol — **irritant**
- *t*BuLi,1.7 M solution in pentane, 2.4 mL, 4.2 mmol — **pyrophoric, flammable**
- Crotylmagnesium bromide, 1 M solution in ether, 4.2 mL, 4.2 mmol — **pyrophoric, flammable**
- $ZnBr_2$, 1 M solution in ether, 4.2 mL, 4.2 mmol — **irritant**
- Et_2O, 40 mL — **flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 1-(*Z*)-iodo-3-*tert*-butoxyprop-1-ene (500 mg, 2.1 mmol) and Et_2O (30 mL).
2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (2.4 mL, 4.2 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add crotylmagnesium bromide dropwise at –50°C (4.2 mL, 4.2 mmol) to the reaction mixture.
4. Add zinc bromide dropwise at –50°C (4.2 mL, 4.2 mmol) and then stir the mixture for 5 h at –50°C under nitrogen. The quantitative formation of the adduct is checked by GC.
5. Hydrolyse at –50°C with 1 M HCl (20 mL). Separate the two layers, and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane:ethyl acetate, 98:2). The yield is 303 mg, 86% in a 93:7 diastereomeric ratio.

Protocol 6.
Crotylmetallation of γ-heterosubstituted vinyl lithium derivatives: preparation of (3*R**,4*S**,5*S**)-3,4-dimethyl-5-*tert*-butoxy-oct-1-ene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Protocol 6. *Continued*

Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

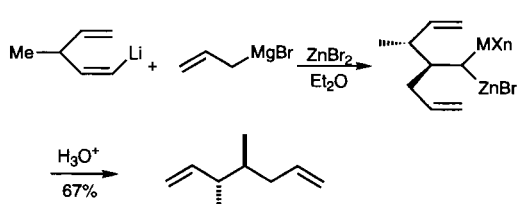
Materials

- 1-(*Z*)-iodo-3-(*tert*-butoxy)hex-1-ene[28] (FW 282), 500 mg, 1.77 mmol — **irritant**
- *t*BuLi, 1.7 M solution in pentane, 2.1 mL, 3.5 mmol — **pyrophoric, flammable**
- Crotylmagnesium bromide, 1 M solution in ether, 3.5 mL, 3.5 mmol — **pyrophoric, flammable**
- $ZnBr_2$, 1 M solution in ether, 3.5 mL, 3.5 mmol — **irritant**
- Et_2O, 40 mL — **flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 1-(*Z*)-iodo-3-(*tert*-butoxy)hex-1-ene (500 mg, 1.77 mmol) and Et_2O (30 mL).
2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (2.1 mL, 3.5 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add crotylmagnesium bromide dropwise at –50°C (3.5 mL, 3.5 mmol) to the reaction mixture.
4. Add zinc bromide dropwise at –50°C (3.5 mL, 3.5 mmol) and then stir the mixture for 5 h at –20°C under nitrogen. The quantitative formation of the adduct is checked by GC.
5. Hydrolyse at –50°C with 1 M HCl (20 mL). Separate the two layers, and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane:ethyl acetate, 98:2). The yield is 280 mg, 75% in a 95:5 diastereomeric ratio.

Protocol 7.
Allylmetallation of pentadienyl lithium derivatives: preparation of (3*R**,4*S**)-dimethyl-1,6-heptadiene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

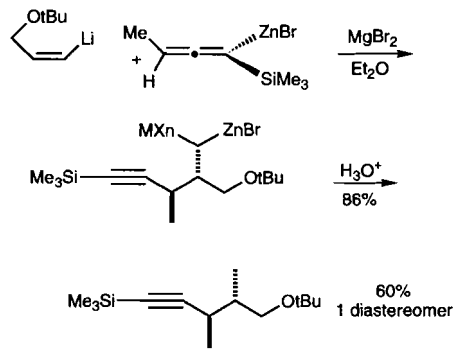
Materials

- 1-(*Z*)-iodo-3-methyl-1,4-pentadiene[19] (FW 208), 500 mg, 2.4 mmol — **irritant**
- *t*BuLi, 1.7 M solution in pentane, 2.8 mL, 4.8 mmol — **pyrophoric, flammable**
- Allylmagnesium bromide, 1 M solution in ether, 4.8 mL, 4.8 mmol — **pyrophoric, flammable**
- $ZnBr_2$, 1 M solution in ether, 4.8 mL, 4.8 mmol — **irritant**
- Et_2O, 30 mL — **flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature, add 1-(*Z*)-iodo-3-methyl-1,4-pentadiene (500 mg, 2.4 mmol) and Et_2O (30 mL).
2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (2.8 mL, 4.8 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add allylmagnesium bromide dropwise at –30°C (4.8 mL, 4.8 mmol) to the reaction mixture.
4. Add zinc bromide dropwise at –30°C (4.8 mL, 4.8 mmol) and then stir the mixture for 5 h at –50°C under nitrogen. The quantitative formation of the adduct is checked by GC.
5. Hydrolyse at –50°C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (pentane). The yield is 200 mg, 67% in a 90:10 diastereomeric ratio.

Protocol 8.
Propargylmetallation of vinyl lithium derivatives: preparation of (3*R**,4*S**)-dimethyl-1-trimethylsilyl-5-*tert*-butoxy-pent-1-yne

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Two-necked, round-bottomed flask (50 mL) fitted with a septum, a nitrogen inlet, and a magnetic stirring bar
- Dry glass syringes and needles
- Cannula

Materials

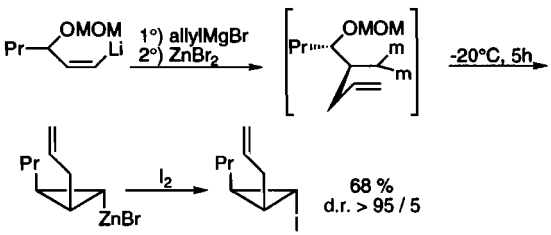
• 1-(*Z*)-iodo-3-*tert*-butoxyprop-1-ene[28] (FW 240), 480 mg, 2 mmol	**irritant**
• *t*BuLi, 1.7 M solution in pentane, 2.35 mL, 4 mmol	**pyrophoric, flammable**
• 1-trimethylsilyl-but-1-yne (FW 126), 504 mg, 4 mmol	**flammable**
• *s*BuLi, 1.3 M solution in hexane, 4 mL, 5.2 mmol	**pyrophoric, flammable**
• Magnesium bromide (FW 184.1), 736 mg, 4 mmol	**irritant**
• $ZnBr_2$, 1 M solution in ether, 5.2 mL, 5.2 mmol	**irritant**
• Et_2O, 50 mL	**flammable**

1. Flame dry the three-necked, round-bottomed flask (100 mL) and accessories under nitrogen. After cooling to room temperature add 1-(*Z*)-iodo-3-*tert*-butoxyprop-1-ene (480 mg, 2 mmol) and Et_2O (30 mL).
2. Cool the solution to –80°C (nitrogen bath), and add dropwise *t*BuLi (2.35 mL, 4 mmol) via a syringe. The reaction mixture is slowly warmed to –50°C and the halogen–metal exchange is checked by GC.
3. Add $MgBr_2$ (736 mg, 4 mmol) at –50°C and stir for 30 min.
4. Flame dry the two-necked, round-bottomed flask (50 mL) and accessories under nitrogen. After cooling to room temperature add 1-trimethylsilyl-but-1-yne (504 mg, 4 mmol) and Et_2O (20 mL).

5. Cool the solution to –10°C and add dropwise *s*BuLi (4 mL, 5.2 mmol) via a syringe. The reaction mixture is slowly warmed to 10°C and the metallation is checked by GC.
6. Add zinc bromide (5.2 mL, 5.2 mmol) dropwise to the allenyllithium at 0°C and then stir the mixture for 30 min at room temperature under nitrogen.
7. Cool both solutions to –25°C, transfer the allenyl zinc bromide solution to the stirred vinyl magnesium bromide using a cannula, and stir the reaction mixture at –20°C for 4 h. The quantitative formation of the adduct is checked by GC.
8. Hydrolyse at –20°C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane:ethyl acetate, 98:2). The yield is 304.7 mg, 68% as single diastereoisomers.

Protocol 9.
Allylmetallation of γ-heterosubstituted vinyl lithium derivatives and cyclopropanation reaction: preparation of 1-(S*)-iodo-2-(S*)-(2-propenyl)-3-(R*)-propylcyclopropane

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

Protocol 9. *Continued*

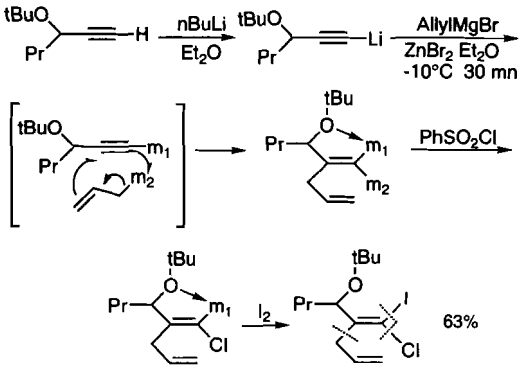
Materials

• 1-(*Z*)-iodo-3-(methoxymethoxy)-hex-1-ene[29] (FW 270), 594 mg, 2.2 mmol	**irritant**
• *t*BuLi, 1.7 M solution in pentane, 2.58 mL, 4.4 mmol	**pyrophoric, flammable**
• Allylmagnesium bromide, 1 M solution in ether, 4.4 mL, 4.4 mmol	**pyrophoric, flammable**
• $ZnBr_2$, 1 M solution in ether, 4.4 mL, 4.4 mmol	**irritant**
• I_2 (FW 254), 1.27 g, 5 mmol	**harmful**
• Et_2O, 40 mL	**flammable**
• THF, 10 mL	**flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 1-(*Z*)-iodo-3-(methoxymethoxy)-hex-1-ene (594 mg, 2.2 mmol) and Et_2O (40 mL).
2. Cool the solution to –80 °C (nitrogen bath), and add dropwise *t*BuLi (2.58 mL, 4.4 mmol) via a syringe. The reaction mixture is slowly warmed to –50 °C and the halogen–metal exchange is checked by GC.
3. Add allylmagnesium bromide dropwise at –50 °C (4.4 mL, 4.4 mmol) to the reaction mixture.
4. Add zinc bromide dropwise at –50 °C (4.4 mL, 4.4 mmol) and then stir the mixture for 5 h at –20 °C under nitrogen. The quantitative formation of the adduct is checked by GC.
5. Warm the reaction mixture to room temperature overnight.
6. Add a solution of iodine (1.27 g, 5 mmol) in THF (10 mL) at –10 °C and warm slowly to room temperature.
7. Hydrolyse at –20 °C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are washed with a solution of $Na_2S_2O_3$ (2 × 10 mL) and the resulting clear organic phase is treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (cyclohexane:ethyl acetate, 98:2). The yield is 357 mg, 65%.

Protocol 10.
Allylmetallation of γ-heterosubstituted acetylenic lithium derivatives and reaction with different electrophiles: preparation of (*Z*)-2-allyl-3-(*tert*-butoxy)-1-chloro-1-iodohex-1-ene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three-necked, round-bottomed flask (100 mL) equipped with a low temperature thermometer (–80°C to 30°C), a stirring bar, a gas inlet for nitrogen, and a septum
- Cooling bath
- Dry glass syringes and needles

Materials

• 3-(*tert*-butoxy)hex-1-yne (FW 154), 309 mg, 2 mmol	**flammable**
• *n*BuLi, 1.6 M solution in hexane, 1.6 mL, 2.6 mmol	**pyrophoric, flammable**
• Allylmagnesium bromide, 1 M solution in ether, 2.6 mL, 2.6 mmol	**pyrophoric, flammable**
• $ZnBr_2$, 1 M solution in ether, 2.6 mL, 2.6 mmol	**irritant**
• $PhSO_2Cl$ (FW 176.6), 650 mg, 2.6 mmol	**corrosive**
• I_2 (FW 254), 660 mg, 2.6 mmol	**harmful**
• Et_2O, 40 mL	**flammable**
• THF, 10 mL	**flammable**

1. Flame dry the reaction vessel and accessories under nitrogen. After cooling to room temperature add 3-(*tert*-butoxy)hex-1-yne (309 mg, 2 mmol) and Et_2O (40 mL).
2. Cool the solution to 0°C and add dropwise *n*BuLi (1.6 mL, 2.6 mmol) via a syringe. The reaction mixture is slowly warmed to room temperature and stirred for 1 h to yield a pale yellow suspension.
3. Add allylmagnesium bromide dropwise at –30°C (2.6 mL, 2.6 mmol) to the reaction mixture and warm to –10°C.
4. Add zinc bromide dropwise at –10°C (2.6 mL, 2.6 mmol) and then stir the

Protocol 10. *Continued*

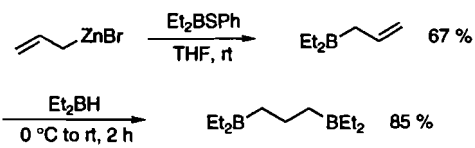
mixture for 30 min at –10°C under nitrogen. The quantitative formation of the adduct is checked by GC.

5. Cool the solution to –20°C, add $PhSO_2Cl$ (650 mg, 2.6 mmol), and stir the reaction mixture for 1.5 h at –20°C. The quantitative formation of the adduct is checked by GC.
6. Add a solution of iodine (660 mg, 2.6 mmol) in THF (10 mL) at –50°C, warm slowly to room temperature, and stir at this temperature for 1 h.
7. Hydrolyse at –20°C with 1 M HCl (20 mL). Separate the two layers and extract the aqueous layer with Et_2O (2 × 20 mL). The combined organic phases are washed with a solution of $Na_2S_2O_3$ (2 × 10 mL) and the resulting clear organic phase are treated with a few crystals of $Na_2S.9H_2O$ for 5 h. These are then removed by filtration, the organic solution washed with brine, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue is purified by chromatography on silica gel (pentane). The yield is 448 mg, 63%.

Protocol 11.
Preparation of 1,3-dizinc compounds and its *bis*-allylation

A. *Preparation of 1,3-*bis*(diethylboryl)propane*

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

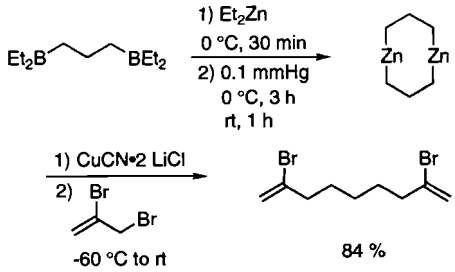
- Two Schlenk flasks (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

- Allylzinc bromide[1] (FW 186.35), 2.24 g, 12 mmol — **flammable**
- Diethylborane[31] (FW 68.94), 0.83 g, 12 mmol — **flammable**
- Diethylthiophenylborane[30] (FW 178.1), 2.14 g, 12 mmol — **flammable**

1. Prepare the allylzinc bromide and the diethylthiophenylborane like described in the literature (see above).
2. Add the diethylthiophenylborane (2.14 g, 12 mmol) at room temperature to the allylzinc bromide (2.24 g, 12 mmol).
3. Remove the product by distillation at 150°C oil-bath temperature. Pure diethylallylborane (0.88 g, 67%) is obtained as a colourless liquid (air-sensitive!).
4. Add the diethylborane (0.83 g, 12 mmol) at 0°C to the diethylallylborane and stir for 2 h at room temperature.
5. Connect to vacuum (0.1 mmHg) at 0°C for 15–20 min. Pure 1,3-*bis*(diethylboryl)propane (1.23 g, 85%) is obtained as a colourless liquid (air-sensitive!).

B. *Preparation of 1,5,-dizincacyclooctane by boron–zinc exchange and its copper catalysed allylation: preparation of 2,8-dibromo-1,8-nonadiene*



Caution ! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.

Equipment

- Two Schlenk flasks (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

- 1,3-*bis*(diethylboryl)propane (FW 179.9), 0.88 g, 4.89 mmol — **flammable**
- 2,3-dibromopropene (FW 199.8), 2.93 g, 16.67 mmol — **lachrymator**
- Diethylzinc (FW 123.5), 2 mL, 20 mmol — **pyrophoric, flammable**
- CuCN (FW 89.6), 0.88 g, 9.78 mmol — **toxic**
- LiCl (FW 42.4), 0.83 g, 19.56 mmol — **irritant**
- THF

Protocol 11. *Continued*

1. Charge the flame dried and argon flushed three-necked flask with 1,3-*bis* (diethylboryl)propane (0.88 g, 4.89 mmol). Cool to 0°C and add diethylzinc (2 mL, 20 mmol) (Caution!).
2. Stir for 30 min at 0°C.
3. Remove the triethylborane formed and the excess diethylzinc in vacuum (0.1 mmHg, 0°C, 3 h and rt, 1 h).
4. Dissolve the resulting oil in dry THF (8 mL) at room temperature and transfer the solution in a three-necked flask.
5. Weigh the CuCN (0.88 g, 9.78 mmol) and the LiCl (0.83 g, 19.6 mmol) into the second Schlenk flask. Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
6. Flush with argon and dissolve the CuCN•2LiCl dry THF (12 mL) at room temperature. A slight exothermic reaction is observed and a light yellow/green solution is formed.
7. Cool the zinc solution to –60°C and add slowly the CuCN•2LiCl solution.
8. Add slowly the 2,3-dibromopropene (2.93 g, 16.7 mmol) at –60°C.
9. Allow the reaction mixture to warm to room temperature.
10. Pour the reaction mixture into an Erlenmeyer containing saturated aqueous NH_4Cl (70 mL) and ether (70 mL).
11. Separate the organic and aqueous layers. Extract the aqueous layer with ether (3 × 30 mL). Combine the organic layers, dry over $MgSO_4$, and evaporate the solvents.
12. Purify the crude residue by flash chromatography using hexanes:ether (19:1). Pure 2,8-dibromo-1,8-nonadiene (1.16 g, 84%) is obtained as a light yellow liquid.

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8

Electrochemical generation and reaction of zinc reagents

JACQUES PÉRICHON, CORINNE GOSMINI, and YOLANDE ROLLIN

1. Introduction

The formation of organozinc compounds by reaction of zinc metal with organic halides often requires both the activation of Zn metal and the use of reactive organic halides, i.e. iodides or activated bromides. The alternative transmetallation method between a zinc salt and an organomagnesium or -lithium compound is incompatible with the presence of sensitive functional groups on the organic moiety. Then the electrochemical approach may offer a useful alternative to the conventional chemical routes. Indeed, the electroreduction of a zinc salt at between –0.8 and –1.4 V/SCE, depending of the nature of the organic solvent, generates a divided nascent zinc. This electrolytic zinc, however, only reacts with organic halides which are easily reduced, so the reaction (Equation 8.1) is restricted to reactive organic halides, such as α-bromoesters, or allyl or benzyl bromides.

$$Zn^{2+} + 2e^- \xrightarrow[\text{organic solvent}]{} Zn \xrightarrow{RX} RZnX \qquad (8.1)$$

We can alternatively envision the reduction of the organic halide in the presence of Zn(II) (Equation 8.2).

$$RX + 2e^- \longrightarrow R^- + X^- \xrightarrow{Zn^{2+}} RZnX \qquad (8.2)$$

However most organic halides are less easily reduced than Zn(II). So such a process can only be applied if one is able to catalyse the electroreduction of RX. This can be achieved by electrochemically formed zerovalent nickel complexes. Thus Ni(II)-2,2′-bipyridine (Ni-bpy) compounds can catalyse the electroreduction of alkyl and aryl halides[1] at potential more positive than

that of the Zn(II)/Zn system and the overall reaction (Equation 8.3) can be conducted in one step in DMF.[2]

$$RX + Zn^{2+} + 2e^- \xrightarrow[DMF]{Ni^{(II)}\text{-bpy cat}} RZnX \qquad (8.3)$$

A number of constraints can be set forth against the electrochemical method, such as the need of a counter-reaction, here an anodic one, or the requirement of a large amount of a salt as supporting electrolyte, usually an ammonium salt, to ensure a good conductivity of the medium. These constraints have been removed by the use of the sacrificial anode process, which, in addition, is the only one which is compatible with the running of reactions in aprotic organic solvents on a preparative scale.[3] For the above reactions (Equations 8.1 and 8.3) the cathodic reduction is combined with the anodic oxidation of an easily oxidized metal used as the anode, e.g. Mg, Al. The derived ions Mg^{2+} or Al^{3+}, which are reduced at low potential, do not interfere with the reduction process and allow a good conductivity. When the anode is made of zinc, the generated Zn^{2+} ions can be used to produce the organozinc, according to Scheme 8.1.

at the anode : $Zn - 2e^- \longrightarrow Zn^{2+}$

at the cathode : $RX + Zn^{2+} + 2e^- \longrightarrow RZnX$

Scheme 8.1

2. Electrochemical device and general reaction conditions

The undivided electrochemical glass cell and other equipment commonly used in the laboratory for many reactions described below are shown in Fig. 8.1.[3] The anode is a rod of magnesium or zinc; it is held by an open-top cap equipped with a joint and screwed on the top of the glass cell. The cathode is concentric and made of a grid of stainless steel or of carbon fibre, or a plate of zinc, or a foam of nickel. The apparent cathode surface is 10–20 cm^2. The electrodes are connected by stainless steel wires to the DC power supply which can provide up to 1 A current intensity. Side-arms equipped with screw caps allow the introduction of solvent (usually 30–50 mL), the reagents, as well as a permanent supply of an inert gas (N_2 or Ar), and for the connection of the cathode. Dipolar aprotic solvents are used, mainly dimethylformamide (DMF) and acetonitrile (AN), or their mixture with dichloromethane, and distilled before use though a quite high dryness is not required. A low concentration (0.01–0.02 M) of tetrabutylammonium salt, bromide, iodide, or tetrafluoroborate, is added to the medium to ensure a good initial conductivity.

However if the electrolysis is conducted in the presence of Zn(II) (either $ZnBr_2$ or $ZnCl_2$) added to the medium the ammonium salt is unnecessary. Electrolyses are usually conducted under argon, at 0–50°C under constant current density of 0.5–5 A/dm^2 of cathode. Under these reaction conditions current electrolyses allows preparation of 1–10 millimoles of product.

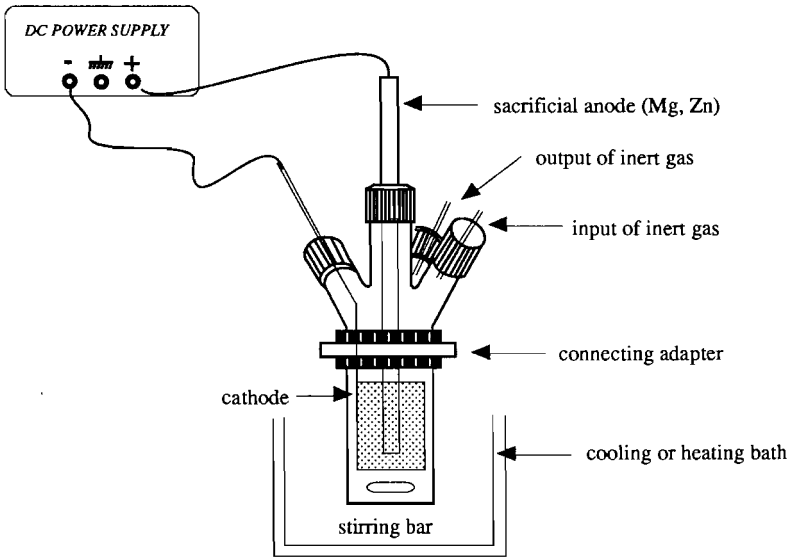


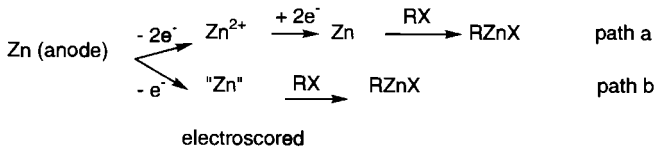
Fig. 8.1 'Electrochemical cell' used at laboratory scale for the electrosynthesis of zinc reagents.

3. Electrochemical activation of zinc: use for the formation of zinc reagents and for coupling reactions involving reactive halides

All reactions described in this part were run in the presence of a Zn sacrificial anode. Two processes involving the anode can occur:

(a) The Zn(II) ions produced by electro-oxidation of the anode are reduced at the cathode to produce a reactive zinc (Scheme 8.2, path a).

(b) The electroscoring of the anode makes it reactive towards the reagent (Scheme 8.2, path b).

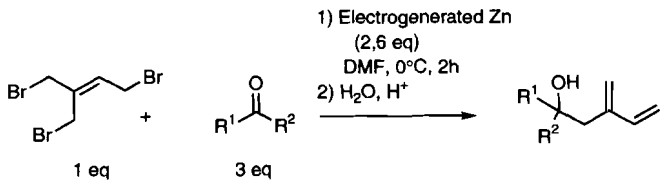


Scheme 8.2

These two processes can occur at the same time, their relative importance being related the experimental conditions: solvent, temperature, current density... They can only involve active organic halides like benzylic or allylic halides, α-bromoesters, or CF_3Br.

3.1 Reactions involving electrogenerated active zinc

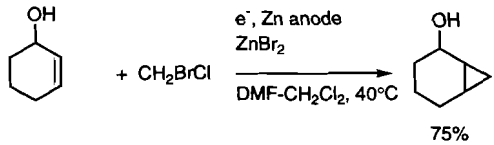
This procedure was used in the isoprenylation of aldehydes and ketones[4] (Equation 8.4):



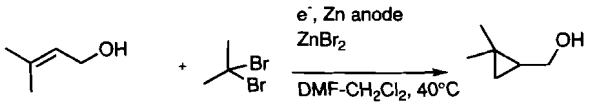
(8.4)

The active zinc was obtained by electrolysis at constant current in a one-compartment cell in DMF containing Et_4NClO_4 using a Zn/Pt anode/cathode system. The isoprenylation of isovaleraldehyde led to the product in 68% isolated yield, higher than with a conventional procedure using zinc dust in DMF or in refluxing THF.

A similar procedure was used in the cyclopropanation reaction[5] with CH_2Br_2 (Protocol 1), CH_2BrCl (Equation 8.5), or $(CH_3)_2CBr_2$ (Equation 8.6).



(8.5)

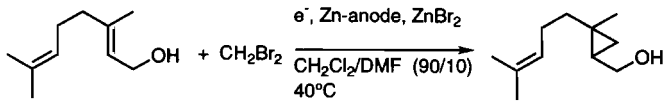


(8.6)

The solution of the gem-dihalide and the olefin in DMF:CH_2Cl_2 (v/v = 1:9) containing Bu_4NX (X = I, Br) was electrolysed at 40 °C with a zinc anode and a carbon fibre or a nickel foam cathode. The method compares favourably with the usual route involving CH_2I_2 and Cu/Zn.

Protocol 1.
Cyclopropanation of geraniol[5]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL) described previously, a magnetic stirring bar, a cylindrical rod of zinc as the anode surrounded by a nickel foam cathode
- Argon supply and inlet
- Power supply
- Reflux condenser

Materials

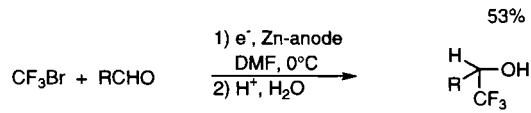
• Dry DMF, 4 mL	**toxic**
• Dry dichloromethane, 40 mL	**harmful**
• Zinc bromide (FW 225.2), 4.5 g, 20 mmol	**irritant**
• Geraniol (FW 154.2), 1.08 g, 1.21 mL, 7 mmol	**irritant**
• Tetrabutylammonium bromide (FW 322.3), 419 mg, 1.3 mmol	**irritant, harmful**
• Tetrabutylammonium iodide (FW 369.4), 185 mg, 0.5 mmol	**irritant, harmful**
• Dibromomethane (FW 173.8), 3.16 g, 1.28 mL, 18.2 mmol	**harmful**
• Ammonium chloride solution, 5%	**corrosive**
• Ether for extraction	**flammable**
• Brine	
• Anhydrous magnesium sulfate, 10 g	
• Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g	**irritant dust**
• Mixture of pentane and ether (4:1) for chromatography	**flammable, irritant**

1. Introduce into the cell dry DMF (4 mL) and CH_2Cl_2 (40 mL), purge with argon, add tetrabutylammonium bromide (419 mg, 1.3 mmol), tetrabutylammonium iodide (185 mg, 0.5 mmol), geraniol (1.08 g, 1.21 mL, 7 mmol), zinc bromide (4.5 g, 20 mmol), and dibromomethane (3.16 g, 1.28 mL, 18.2 mmol). Stir and heat the reaction mixture to reflux (40°C).
2. Connect the anode (zinc rod) to the positive pole of the power supply and the cathode (nickel foam) to the negative pole of the power supply, set the current intensity at 200 mA for 7 h 40 min (5500 C).
3. Add the reaction mixture to an Erlenmeyer containing a saturated aqueous NH_4Cl solution (75 mL) and ether (50 mL), and stir for 10 min at room temperature.
4. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, filter, and evaporate the solvent.

Protocol 1. *Continued*

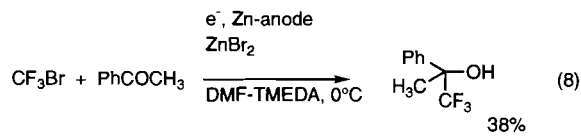
5. Purify the crude product by chromatography using pentane:ether (4:1). Pure *trans*-1-(hydroxymethyl)-2-methyl-2-(4-methyl-3-pentenyl)cyclopropane is obtained as a colourless oil (940 mg, 80%). Characterize the product by ^1H and ^{13}C NMR.

The trifluoromethylation of aldehydes from CF_3Br[6] can also be well conducted electrochemically in DMF in the presence of a zinc anode (Equation 8.7, Protocol 2). Again yields are higher than those obtained using activated zinc.



(8.7)

Using the same reaction conditions only non-enolizable aromatic ketones can be trifluoromethylated in good yields.[6] With enolizable ketones a DMF: tetramethylenediamine (TMEDA) solvent mixture allows trifluoromethylated alcohols to be obtained in 25–40% yields (Equation 8.8).

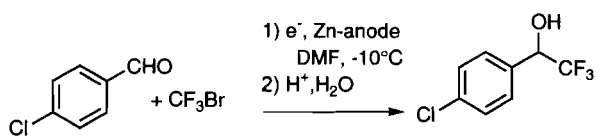


(8.8)

Organozincs $(CF_3)_2Zn$ and CF_3ZnBr are reported in the literature and have been found to have a low reactivity towards carbonyl compounds, thus indicating that a coordinated anion « $CF_3^-...Zn^{2+}$ » rather than an organozinc is the real intermediate.

Protocol 2.
Electrochemical trifluoromethylation of 4-chlorobenzaldehyde: preparation of 2,2,2-trifluoro-1-(4-chlorophenyl)ethanol[6]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL) described previously, a magnetic stirring bar, a cylindrical rod of zinc as the anode surrounded by a nickel foam cathode
- Argon and bromotrifluoromethane gas supply and inlet
- Power supply
- Cooling bath

Materials

- Dry DMF, 40 mL — **toxic**
- Tetrabutylammonium bromide (FW 322.3), 322 mg, 1 mmol — **irritant, harmful**
- Bromotrifluoromethane gas — **irritant, harmful, explosive**
- 4-chlorobenzaldehyde (FW 140.6), 2.81 g, 20 mmol — **irritant, harmful**
- Solution HCl, 6 mol/L — **corrosive**
- Ether for extraction — **flammable, irritant**
- Brine
- Anhydrous magnesium sulfate, 10 g
- Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g — **irritant dust**
- A mixture of pentane and ether (4:1) for chromatography — **flammable, irritant**

1. Introduce into the cell dry DMF (40 mL), purge with argon, add tetrabutylammonium bromide (322 mg, 1 mmol), 4-chlorobenzaldehyde (2.81 g, 20 mmol), and stir the mixture.
2. Immerse the cell in a cooling bath at −10 °C to ensure sufficient solubility of CF_3Br.
3. Bubble CF_3Br at atmospheric pressure through the solution.
4. Connect the anode (zinc rod) to the positive pole and the cathode (nickel foam) to negative pole of the power supply. Set the intensity at 300 mA for 4 h (4300 C).
5. Add the reaction mixture to an Erlenmeyer containing HCl solution (75 mL) and ether (50 mL), and stir for 10 min at room temperature.
6. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, filter, and evaporate the solvent.
7. Purify the crude product by chromatography using pentane:ether (4:1). Pure 2,2,2-trifluoro-1-(4-chlorophenyl)ethanol is obtained (3.79 g, 90%) and characterized by ^1H and ^{13}C NMR.

3.2 Activation of solid zinc by electroscoring

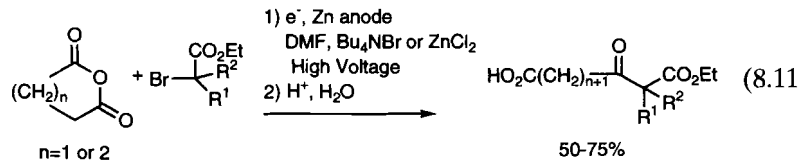
Trifluoromethylzinc compounds can be prepared by electrolysis of CF_3Br in DMF between a zinc anode and a stainless steel cathode.[7] Faradaic yields are higher than 100%, thus indicating the occurrence of a chemical route (Equation 8.10) at the surface of the anode along with the electrochemical process (Equation 8.9).

$$Zn^{2+} + 2e^- + CF_3Br \xrightarrow{DMF} CF_3ZnBr + (CF_3)_2Zn \qquad (8.9)$$

$$\text{Zn anode (electroscorred)} + CF_3Br \xrightarrow{\text{DMF}} CF_3ZnBr + (CF_3)_2Zn \qquad (8.10)$$

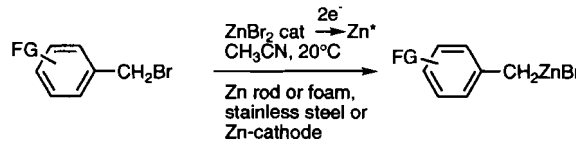
It was found, in keeping with this, that the lower the current density, the greater the chemical attack at the anode. For example, at the low 5 mA cm^{-2} current density the faradaic yield of the formation of trifluoromethylzinc compounds is higher than 300%. This chemical process only takes place during electrolysis.

Similar phenomena are observed in electrolysis in DMF at high voltage of mixtures of alkyl 2-bromoalkanoates and succinic or glutaric anhydride[8] (Equation 8.11).



(8.11)

In acetonitrile or CH_2Cl_2:acetonitrile mixture solid zinc becomes very reactive towards α-bromoesters, or allylic or benzylic bromides when being in the presence of catalytic amounts of zinc formed by electroreduction of ZnX_2 (X = Br, Cl). Stable benzylzinc compounds are thus obtained from benzylbromides (Equation 8.12, Protocol 3).[9]

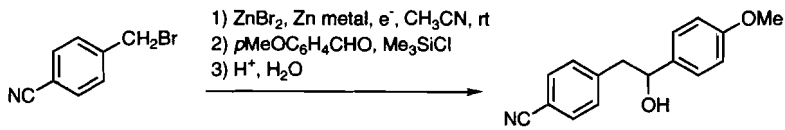


(8.12)

The rate of the reaction is increased with a low current intensity being applied during the reaction between the Zn rod or foam and the cathode.

Protocol 3.
Electrochemical preparation of a functionalized benzylic zinc reagent and its coupling with a functionalized aromatic aldehyde: preparation of 2-(4-cyanophenyl)-1-(4-methoxyphenyl)ethanol[9]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL) described previously, a magnetic stirring bar, a cylindrical rod of zinc as the anode surrounded by a nickel foam cathode
- Argon supply and inlet
- Power supply
- A syringe

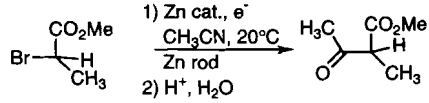
Materials

- Dry acetonitrile, 40 mL — **flammable, toxic**
- Tetrabutylammonium tetrafluoroborate (FW 329.3), 66 mg, 0.2 mmol — **irritant**
- Zinc bromide (FW 225.2), 450 mg, 2 mmol — **irritant**
- 4-methoxybenzaldehyde (FW 136.2), 1.36 g, 10 mmol — **harmful irritant**
- 4-cyanobenzyl bromide (FW 196), 1.96 g, 10 mmol — **irritant**
- Chlorotrimethylsilane (FW 108.6), 1.09 g, 1.27 mL, 10 mmol — **harmful**
- Ammonium chloride solution, 5% — **corrosive**
- Ether for extraction — **flammable, irritant**
- Brine
- Anhydrous magnesium sulfate, 10 g
- Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g — **irritant dust**
- A mixture of pentane and ether (4:1) for chromatography — **flammable, irritant**

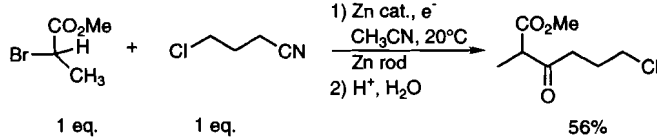
1. Introduce into the cell dry acetonitrile (40 mL), purge with argon, add Bu_4NBF_4 (66 mg, 0.2 mmol), and $ZnBr_2$ (450 mg, 2 mmol), then stir at room temperature. It is not necessary that all $ZnBr_2$ be dissolved to start the electrolysis.
2. Connect the anode (zinc rod) to the positive pole and the cathode (zinc sheet) to the negative pole of the power supply.
3. Set the current intensity at 100 mA for 33 min (200 C).
4. Add 4-cyanobenzyl bromide (1.96 g, 10 mmol).
5. Set the current intensity at 100 mA for 30 min. All benzyl bromide is converted into the corresponding organozinc.
6. Add 4-methoxybenzaldehyde (1.36 g, 1.22 mL, 10 mmol).
7. Add chlorotrimethylsilane with a syringe (100 μL/5 sec) (1.27 mL, 10 mmol).
8. Add the reaction mixture to an Erlenmeyer containing a saturated aqueous NH_4Cl solution (100 mL) and ether (50 mL), and stir for 10 min at room temperature.
9. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, filter, and evaporate the solvent.
10. Purify the crude residue by chromatography using pentane:ether (4:1). Pure 2-(4-cyanophenyl)-1-(4-methoxyphenyl)ethanol is obtained as a beige solid (1.87 g, 74%). Characterize the product by ^1H and ^{13}C NMR.

The organozinc reagents obtained by the same method from α-bromoesters react readily with the solvent CH_3CN (Equation 8.13) or with a nitrile as

reagent in CH_2Cl_2 (Equation 8.14) to give β-ketoesters in good yields after hydrolysis of the imine intermediate.[10]

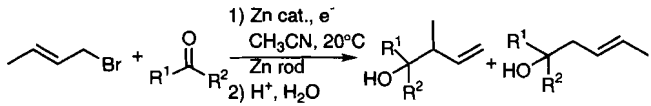


(8.13)



(8.14)

If the reaction is conducted with allylic bromides or α-bromoesters in acetonitrile containing aldehydes or ketones, homoallylic alcohols[11] (Equation 8.15) or β-hydroxy esters[12] are respectively obtained.

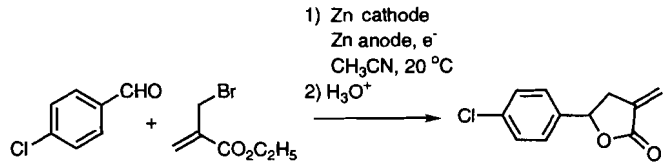


(8.15)

Yields are high (70–80%) except in the case of sterically hindered ketones (*t*-$BuCOCH_3$). In all cases, the branched versus linear alcohol ratio is at least 95:5. α-methylen-γ-lactones are prepared from ethyl 2-(bromomethyl)acrylate and carbonyl compounds using the same procedure (Protocol 4) with yields depending on the steric environment of the carbonyl compound.[11]

Protocol 4.
Electrochemical synthesis of α-methylene-γ-lactone: preparation of 5-(4-chlorophenyl)-4,5-dihydro-3-methylene(3H)-furanone[11]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL) described previously, a magnetic stirring bar, a cylindrical rod of zinc as the anode surrounded by a zinc sheet as the cathode
- Argon supply and inlet
- Power supply

Materials

• Dry acetonitrile, 40 mL	**flammable, toxic**
• Tetrabutylammonium tetrafluoroborate (FW 329.3), 66 mg, 0.2 mmol	**irritant**
• Zinc bromide (FW 225.2), 450 mg, 2 mmol	**irritant**
• 4-chlorobenzaldehyde (FW 140.6), 1.41 g, 10 mmol	**harmful irritant**
• Ethyl-2-(bromomethyl)acrylate (FW 193), 1.4 mL, 10 mmol	**irritant**
• Ammonium chloride solution, 5%	**corrosive**
• Ether for extraction	**flammable, irritant**
• Brine	
• Anhydrous magnesium sulfate, 10 g	
• Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g	**irritant dust**
• A mixture of pentane and ether (4:1) for chromatography	**flammable, irritant**

1. Introduce into the cell dry acetonitrile (40 mL), purge with argon, add nBu$_4$NBF$_4$ (66 mg, 0.2 mmol), and $ZnBr_2$ (450 mg, 2 mmol). Stir the reaction mixture at room temperature. It is not necessary that all $ZnBr_2$ be dissolved to start the electrolysis.
2. Connect the anode (zinc rod) to the positive pole and the cathode (zinc sheet) to negative pole of the power supply.
3. Set the current intensity at 100 mA for 33 min (200 C). Turn off the current.
4. Add 4-chlorobenzaldehyde (1.41 g, 10 mmol).
5. Add ethyl-2-(bromomethyl)acrylate (1.93 g, 1.4 mL, 10 mmol).
6. Monitor the reaction by GC analysis after treatment of an aliquot (0.2 mL) of the reaction mixture with 2 mL of HCl and extraction with 2 mL of ether. Reaction time is 1–2 h.
7. Add the reaction mixture to an Erlenmeyer containing a saturated aqueous NH_4Cl solution (100 mL) and ether (50 mL), and stir for 10 min at room temperature.
8. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, filter, and evaporate the solvent.
9. Purify the crude product by chromatography using pentane:ether (4:1). Pure 5-(4-chlorophenyl)-4,5-dihydro-3-methylene(3H)-furanone (1.87 g, 90%) is obtained and characterized by ^{1}H and ^{13}C NMR.

These methods of zinc activation complement the known chemical methods and are useful efficient alternatives, since no excess of halide or reducing agent is required, and the electrochemical setting is very simple. They are unfortunately not preparatively convenient for aromatic halides. Such a reaction (Equation 8.16) has been reported,[13] but the yields of arylzinc reagent are quite low when expressed on the basis of the starting aryl halide instead of the amount of zinc dissolved.

$$\text{PhX} \xrightarrow[\substack{\text{30-40V}\\ \text{MeCN, } C_6H_6\text{, bpy}}]{\text{e}^-\text{, Zn anode}} \text{PhZnX, bpy} \qquad (8.16)$$

4. Nickel catalysis in the electrosynthesis of aryl- and heteroarylzinc reagents, and in the electrochemical Reformatsky and allylation reactions using alkyl chlorides

4.1 Aromatic and heteroaromatic reagents

$Ni^0(bpy)_n$ complexes, with n = 1 or 2, formed by electroreduction of $NiX_2(bpy)_n$ in DMF rapidly add oxidatively to aryl halides.

$$ArX + 2e^- + NiX_2(bpy)_n \longrightarrow ArNiXbpy + 2X^- + n\text{-}1\ bpy \qquad (8.17)$$

So the overall reaction (Equation 8.17) occurs at a redox potential close to that of the Ni^{II}/Ni^0 system, i.e. at –1.1 V/SCE, whereas Zn^{II} ions are reduced at *ca.* –1.4 V/SCE in DMF, and aryl halides are reduced at between –2 and –2.7 V/SCE. In addition, apart from NO_2, sensitive functional groups can be present on the ring. σ-arylnickel compounds are reducibly converted into Ar–Ar (para- or meta-substituted compounds) or into Ar–H (ortho-substituted compounds).

If the reaction is run in the presence of a zinc salt ($ZnBr_2$ or $ZnCl_2$), an Mg or Zn anode, and excess bipyridine, compared to the nickel catalyst, the arylzinc halide is the major product (Equation 8.18).[2]

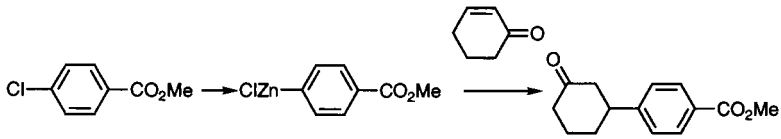
$$ArX + ZnBr_2 \xrightarrow[\text{bpy 0.2 eq, DMF, 20°C}]{\text{e}^-\text{, Mg or Zn-anode; Ni(BF}_4)_2\text{bpy}_3\ 0.1\ \text{eq}} ArZnX \qquad (8.18)$$

Bipyridine, when used in excess, is very likely responsible for the success of this reaction. Indeed, its more favourable coordination to Ni(II) than to Zn(II) enables the metal exchange (Equation 8.19), whereas, with only one bipyridine per nickel no transmetallation occurs.

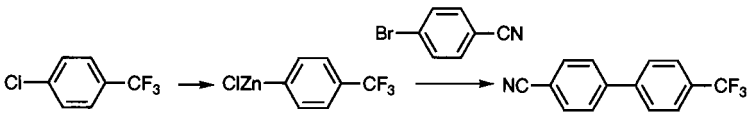
$$ArNiXbpy + ZnBr_2 \xrightarrow{bpy} ArZnX + NiX_2(bpy)_n \qquad (8.19)$$

In the case of ortho-substituted aryl halides, which are less reactive towards $Ni^0(bpy)_n$ the formation of the arylzinc intermediate likely involves the occurrence of a Ni^0–bpy–Zn(II) complex, which by reduction leads directly to the oxidative addition–transmetallation process. According to this, the nickel catalyst is $NiBr_2bpy$, without extra bipyridine. It is thus possible to prepare arylzinc halides from not easily reduced 2-chlorotoluene or 2-chloroanisole, but also, more importantly, from aryl bromides or chlorides bearing reactive functional groups (COR, CO_2R, CN). These compounds can then be added

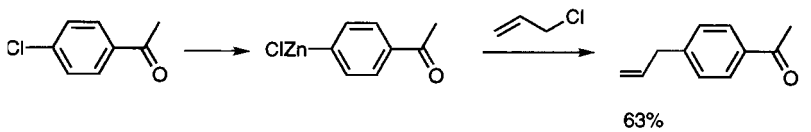
to enones[2] (Equation 8.20) or coupled with aryl halides (Equation 8.21 and Protocol 5) or allylic halides[2] (Equation 8.22).



(8.20)



(8.21)

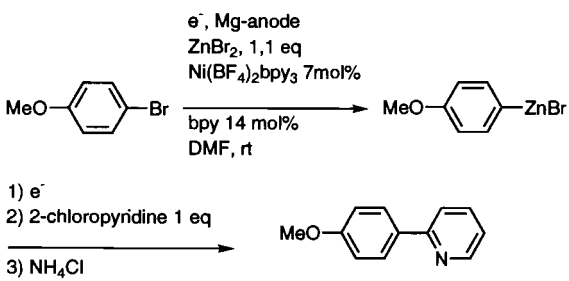


(8.22)

The method can be applied to heterocyclic compounds like 2- and 3-chloropyridine or 2- and 3-bromothiophene[14,15] (Protocol 6).

Protocol 5.
Electrochemical preparation of an arylzinc bromide and its coupling with 2-chloropyridine: synthesis of 2-(4-methoxyphenyl)pyridine

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL) described previously, a magnetic stirring bar, a cylindrical rod of magnesium as the anode surrounded by a nickel foam cathode
- Argon supply and inlet
- Power supply

Protocol 5. *Continued*

Materials

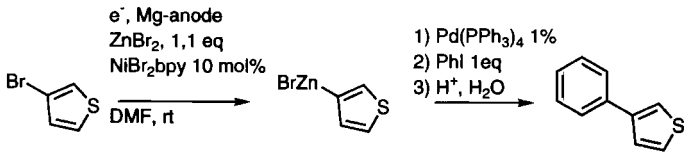
• Dry DMF, 40 mL	**toxic**
• $Ni(BF_4)_2(2,2'\text{-bipyridine})_3$[a] (FW 700), 350 mg, 0.5 mmol	**toxic**
• 2,2'-bipyridine (FW 156.2), 156 mg, 1 mmol	**toxic**
• 4-bromoanisole (FW 187), 1.4 g, 939 μL, 7.5 mmol	**flammable**
• Zinc bromide (FW 225.2), 1.8 g, 8 mmol	**irritant**
• 2-chloropyridine (FW 113.5), 851 mg, 710 μL, 7.5 mmol	**toxic**
• Ammonium chloride solution, 5%	**corrosive**
• Brine	
• Anhydrous magnesium sulfate, 10 g	
• Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g	**irritant dust**
• A mixture of pentane and ether (4:1) for chromatography	**flammable, irritant**

1. Introduce into the cell dry DMF (40 mL), purge with argon, add $Ni(BF_4)_2$ bpy_3 (350 mg, 0.5 mmol),[a] $ZnBr_2$ (1.8 g, 8 mmol), 2,2'-bipyridine (156 mg, 1 mmol), and 4-bromoanisole (1.4 g, 939 μL, 7.5 mmol). Stir the mixture for 10 min.
2. Connect the anode (magnesium rod) to the positive pole and the cathode (nickel foam) to the negative pole of the power supply; set the intensity at 200 mA. Monitor the reaction by GC analysis after treatment of an aliquot (0.2 mL) of the reaction mixture with iodine.
3. After 2 h 10 min (1500 C) at the intensity of 200 mA, the organozinc compound is formed.
4. Continue the electrolysis (200 mA) for 8 min (100 C) to generate Ni(0).
5. Stop the current.
6. Add 2-chloropyridine (851 mg, 710 μL, 7.5 mmol) with a syringe and stir the reaction mixture for 2 h at room temperature.
7. Add the reaction mixture to an Erlenmeyer containing a saturated aqueous NH_4Cl solution (100 mL) and ether (50 mL), and stir for 30 min at room temperature.
8. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, filter, and remove the solvent under reduced pressure, and then at 1 mmHg to eliminate DMF.
9. Purify the crude product by chromatography using pentane:ether (4:1). Pure 2(4-methoxyphenyl)pyridine is obtained as a white solid (764 mg, 55%) and characterized by ^1H and ^{13}C NMR.

[a] Preparation of the complex $Ni(BF_4)_2bpy_3$: place $Ni(BF_4)_2.6H_2O$ (3.4 g, 10 mmol) into an Erlenmeyer containing ethanol (20 mL) and stir the reaction mixture for 2 h at room temperature. Add 2,2'-bipyridine (4.7 g, 30 mmol) and stir for 12 h; separate the rose precipitate by filtration. Dry the precipitate under vacuum in the presence of P_2O_5.

Protocol 6.
Electrochemical synthesis of 3-thienylzinc bromide and its coupling with iodobenzene: synthesis of 3-phenylthiophene

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL) described previously, a magnetic stirring bar, a cylindrical rod of magnesium as the anode surrounded by a nickel foam cathode
- Argon supply and inlet
- Power supply

Materials

- Dry DMF, 40 mL — **toxic**
- $NiBr_2$ 2,2'-bipyridine[a] (FW 374.7), 281 mg, 0.75 mmol — **toxic**
- 3-bromothiophene (FW 163), 1.22 g, 702 μL, 7.5 mmol — **flammable**
- Zinc bromide (FW 225.2), 1.8 g, 8 mmol — **irritant**
- *Tetrakis*(triphenylphosphine)palladium(0) (FW 1155.6), 86 mg, 0.075 mmol
- Iodobenzene (FW 204), 1.53 g, 8.39 μL, 7.5 mmol — **irritant, harmful**
- 1 M HCl — **corrosive**
- Brine
- Anhydrous magnesium sulfate, 10 g
- Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g — **irritant dust**
- A mixture of pentane and ether (4:1) for chromatography — **flammable, irritant**

1. Introduce into the cell dry DMF (40 mL), purge with argon, add $NiBr_2$bpy (281 mg, 0.75 mmol), $ZnBr_2$ (1.8 g, 8 mmol), and 3-bromothiophene (1.22 g, 702 μL, 7.5 mmol). Stir the mixture for 10 min.
2. Connect the anode (magnesium rod) to the positive pole and the cathode (nickel foam) to the negative pole of the power supply.
3. Set the intensity at 200 mA for 2 h 10 min (1500 C) and stop the current. Monitor the reaction by GC analysis after treatment of an aliquot (0.2 mL) of the reaction mixture with iodine.
4. Add *tetrakis*(triphenylphosphine)palladium(0) (86 mg, 0.075 mmol), and iodobenzene (1.53 g, 839 μL, 7.5 mmol) with a syringe, stir the reaction mixture for 2 h at room temperature.
5. Add the reaction mixture to an Erlenmeyer containing 1 M HCl solution (100 mL) and ether (50 mL), and stir for 10 min at room temperature.

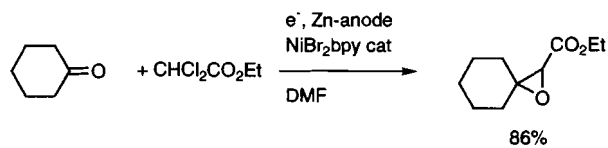
Protocol 6. *Continued*

6. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, and evaporate the solvent.
7. Purify the crude residue by chromatography using pentane:ether (9:1). Pure 3-phenyl thiophene is obtained as a yellow oil (972 mg, 81%). Characterize the product by ^1H NMR and ^{13}C NMR.

[a] Preparation of the complex $NiBr_2$.bpy complex: place $NiBr_2.3H_2O$ (2.725 g, 10 mmol) in an Erlenmeyer containing ethanol (20 mL) and stir the reaction mixture for 2 h at room temperature. Add 2,2'-bipyridine (1.56 g, 10 mmol) and stir for 24 h. Separate the green precipitate by filtration. Dry the precipitate under vacuum in the presence of P_2O_5.

4.2 Reformatsky and allylation reactions using alkyl chlorides

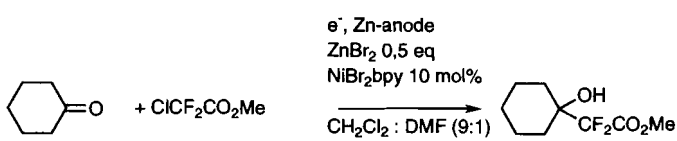
The electroreduction of a mixture of α-chloroester, or allylic chloride, or α-chloronitrile and a carbonyl compound in DMF, in the presence of catalytic amounts of $NiBr_2$bpy and a sacrificial zinc anode leads to the corresponding alcohol in good to high yields[16,17] (Protocol 7). Starting from a α,α-dichloroester one obtains the epoxide[16] (Equation 8.23). The occurrence of an alkylzinc intermediate in these reactions has been postulated.



(8.23)

Protocol 7.
Electrochemical synthesis of methyl 2,2-difluoro-2-(1-hydroxycyclohexyl)ethanoate[18]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- A four-necked electrochemical cell (50 mL), a magnetic stirring bar, a rod of zinc as the anode surrounded by a nickel foam cathode
- Argon supply and inlet
- Power supply
- Reflux condenser

Materials

• Dry DMF, 4 mL	**toxic**
• Dry dichoromethane, 40 mL	**harmful**
• Tetrabutylammonium bromide (FW 322.3), 322 mg, 1 mmol	**irritant, harmful**
• $NiBr_2$ 2,2′-bipyridine[a] (FW 374.7), 375 mg, 1 mmol	**toxic**
• Cyclohexanone (FW 98.2), 980 mg, 10 mmol	**flammable**
• Zinc bromide (FW 225.2), 1.13 g, 5 mmol	**irritant**
• Methyl-2-chlorodifluoroacetate (FW 144.5), 2.9 g, 20 mmol	**flammable, irritant**
• 1 M HCl	**corrosive**
• Ether for extraction	**flammable, irritant**
• Brine	
• Anhydrous magnesium sulfate, 10 g	
• Silica gel (Merck Kieselgel 60, 70–230 mesh), 60 g	**irritant dust**
• A mixture of pentane and ether (4:1) for chromatography	**flammable, irritant**

1. Introduce into the cell dry DMF (4 mL) and dichloromethane (40 mL), purge with argon, add $NiBr_2$bpy (375 mg, 1 mmol), $ZnBr_2$ (1.13 g, 5 mmol), cyclohexanone (980 mg, 1.04 mL, 10 mmol), and methyl 2-chloro-2,2-difluoroacetate (2.9 g, 20 mmol). Stir the mixture for 10 min.
2. Connect the anode (zinc rod) to the positive pole and the cathode (nickel foam) to the negative pole of the power supply.
3. Set the intensity at 200 mA for 7 h (5040 C) and stop the current. Monitor the reaction by GC analysis after treatment of an aliquot (0.2 mL) of the reaction mixture with 2 mL HCl 1 N and 2 mL ether.
4. Add the reaction mixture to an Erlenmeyer containing 1 M HCl solution (100 mL) and ether (50 mL), and stir for 10 min at room temperature.
5. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash the organic phase with brine (50 mL), dry over $MgSO_4$, filter, and evaporate the solvent.
6. Purify the crude product by chromatography using pentane:ether (9:1). Pure methyl-2,2-difluoro-2-(1-hydroxycyclohexyl)ethanoate is obtained as a colourless oil (1.25 g, 60%). Characterize the product by ^1H and ^{13}C NMR.

[a] Preparation of the $NiBr_2$.bpy complex: place $NiBr_2.3H_2O$ (2.725 g, 10 mmol) into an Erlenmeyer containing ethanol (20 mL) and stir the reaction mixture for 2 h at room temperature. Add 2,2′-bipyridine (1.56 g, 10 mmol) and stir for 24 h. Separate the green precipitate by filtration. Dry the precipitate under vacuum in the presence of P_2O_5.

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9

Uncatalysed reactions of zinc organometallics

PAUL KNOCHEL, PHILIP JONES, and FALK LANGER

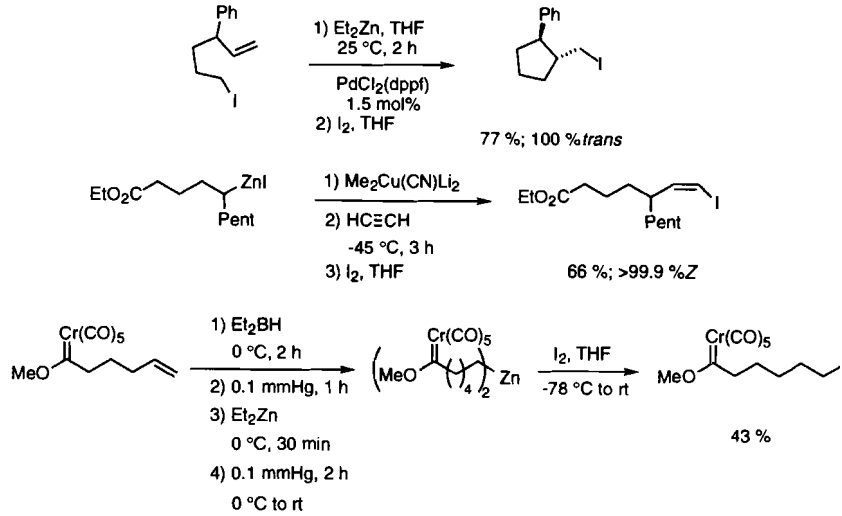
1. Introduction

Compared to organolithiums and Grignard reagents, organozincs have a relatively covalent carbon–metal bond resulting in a moderate reactivity compared to more polar organometallics. Already experiments from last century[1] show that the addition of dialkylzincs to aldehydes is a sluggish reaction providing secondary alcohols in moderate yields. Only reactive classes of organozinc reagents like allylic zinc halides[2] and zinc enolates[3] efficiently undergo these addition reactions to carbonyl compounds. Whilst a few classes of highly reactive electrophilic reagents or radical reagents directly react with zinc organometallics. This chapter will cover these reactions with a special emphasis of those having synthetic utility and broad applicability. The reaction of organozinc halides or diorganozincs with halogens (Cl_2, Br_2, or I_2)[1] or equivalent sources of bromonium, chloronium, or iodonium ions are high yielding reactions and consequently have been used to titrate organozinc compounds.[1] A range of polyfunctional organozinc compounds have been trapped by iodine in THF. All these reactions are rapid and furnish alkenyl or alkyl iodides in excellent yields (Scheme 9.1).[4–6]

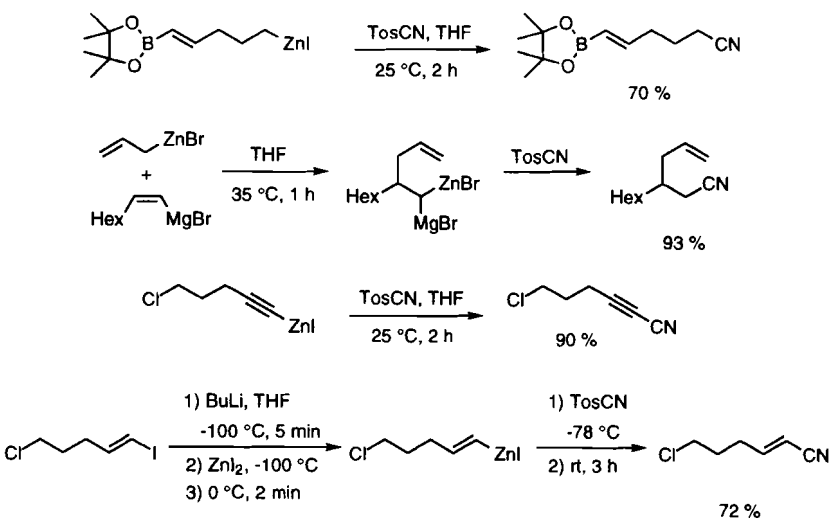
Pseudohalogens like tosyl cyanide (TosCN), react with various diorganozincs and organozinc halides to provide nitriles (Scheme 9.2).[7] Interestingly, the cyanation of 1,1-bimetallic reagents of zinc and magnesium selectively furnishes mononitriles. The reaction with alkynylzinc iodides affords polyfunctional alkynyl cyanides whereas the cyanation of arylzinc bromides provides ring-substituted nitriles.

Functionalized chromium carbene complexes can be prepared by the reaction of polyfunctional diorganozincs with photochemically generated $Cr(CO)_5$.THF. The resulting intermediate ate complexes furnish under 1 atm of carbon monoxide an acyl complex which can be treated with Meerwein salt (Me_3O^+ BF_4^- in dry CH_2Cl_2) at –30 °C to give a chromium carbene complex (Scheme 9.3).

Polyfunctional phosphines can be prepared by the reaction of functional-



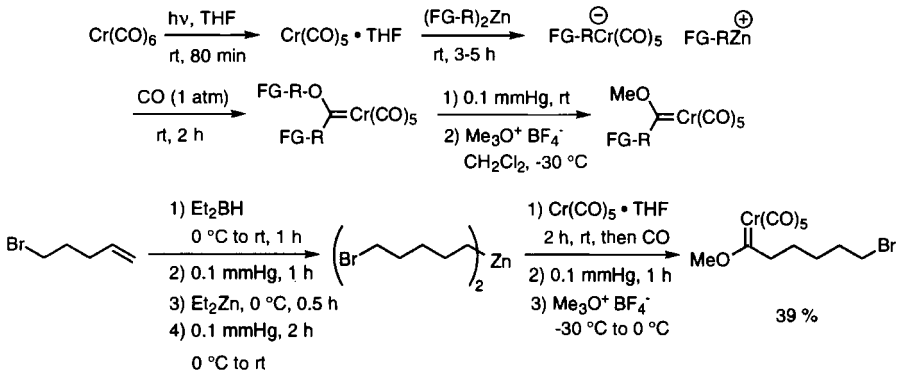
Scheme 9.1



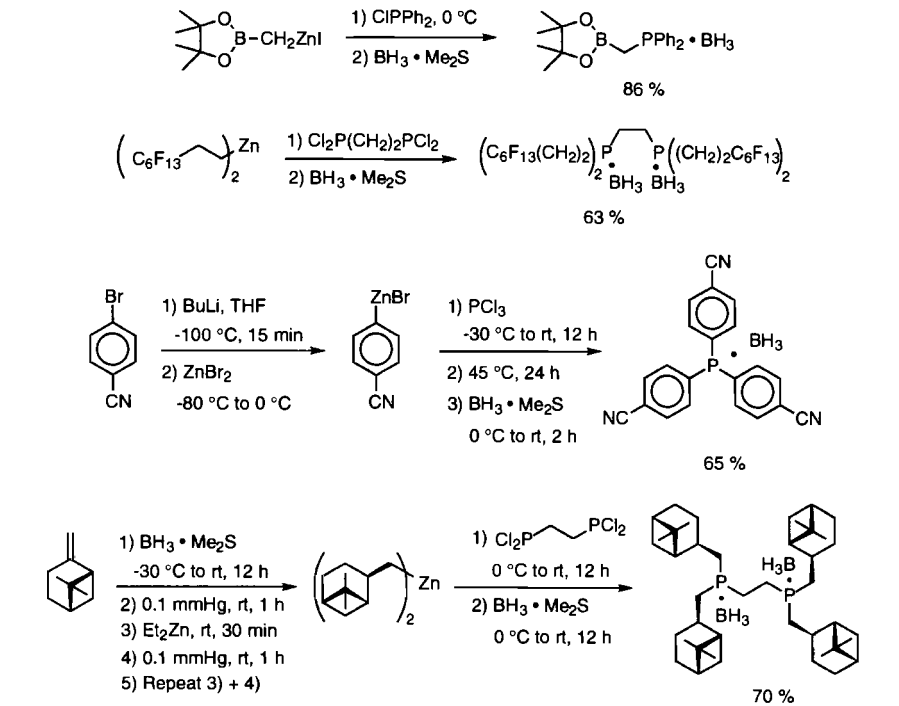
Scheme 9.2

ized diorganozincs or organozinc halides with chlorophosphines under mild conditions.[8,9] This method is ideally suited for the preparation of highly functionalized phosphines without the need of using multi-step synthesis (Scheme 9.4).

By using chiral diorganozincs, it is possible to obtain chiral phosphines or diphosphines of interest as ligand for metal catalysed asymmetric synthesis.



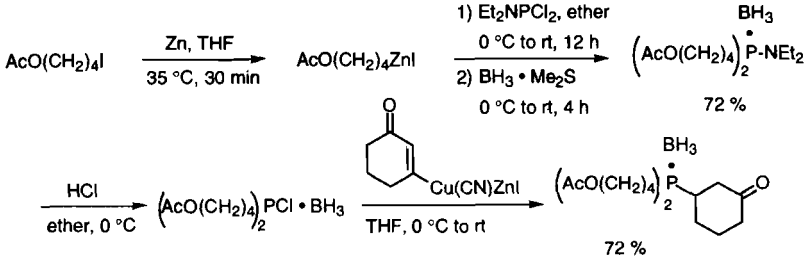
Scheme 9.3



Scheme 9.4

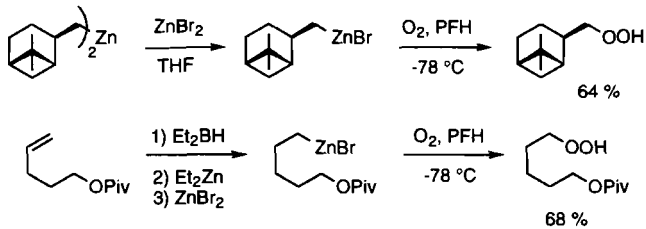
The selective preparation of various chlorophosphines used as building blocks for the preparation of polyfunctional phosphines is achieved using dichloro (diethylamino)phosphine (Et_2NPCl_2). Alkylation of this phosphine with organozinc halides furnishes, after borane treatment, protected aminodiorganophosphines. These in turn can be converted to the corresponding

chloro-diorganophosphine borane complexes by treatment with HCl in ether[10] (Scheme 9.5). This methodology has been applied to the preparation of new chiral phosphines.[11]



Scheme 9.5

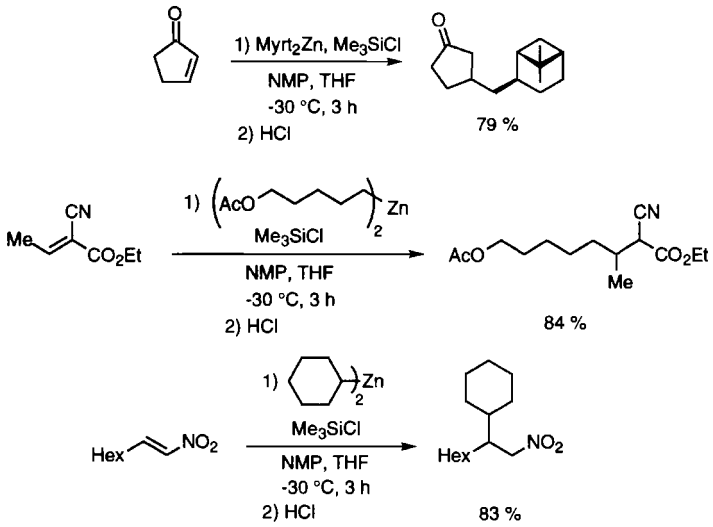
The oxidation of organozinc halides and diorganozincs is a facile radical reaction.[1] It provides usually a mixture of hydroperoxides and alcohols,[12,13] but through careful control of the reaction conditions it allows preparation of either new hydroperoxides or by working under reductive conditions solely alcohols.[14,15] Thus, the treatment of myrtanylzinc bromide with oxygen in perfluorohexanes[12,13] at –78 °C affords the desired hydroperoxide with high selectivity. This method is well suited for the preparation of polyfunctional hydroperoxides (Scheme 9.6).



Scheme 9.6

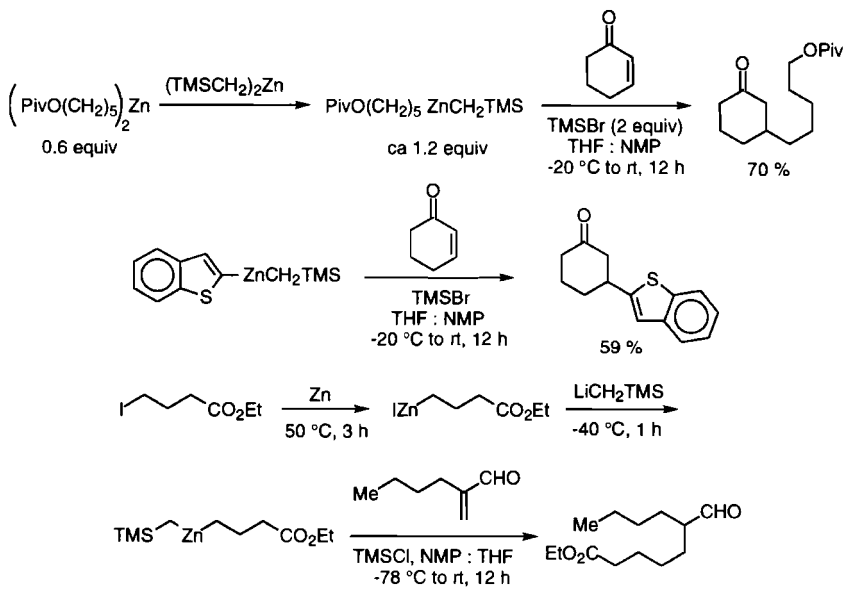
The Michael-addition of zinc organometallics to enones can be catalysed by transition metals like copper[16–21] or nickel.[22–25] However, by using a polar co-solvent like *N*-methylpyrrolidinone (NMP) in the presence of TMSCl or TMSBr, Michael-additions can be achieved at low temperature and good yields without the need for another metal (Scheme 9.7).

The same experimental procedure can be used with alkylidenemalonate and other related Michael-acceptors, as well as nitroolefins.[26] However, under these reaction conditions only one of the two R groups of R_2Zn is transferred to the enone. This problem can be solved by using mixed diorganozincs of the



Scheme 9.7

type $RZnCH_2SiMe_3$.[27,28] By using these reagents, only a slight excess of the organozinc reagents are required. This procedure allows only the transfer of thienyl and benzothienyl groups, these organic groups cannot be transferred using organocopper chemistry (Scheme 9.8).



Scheme 9.8

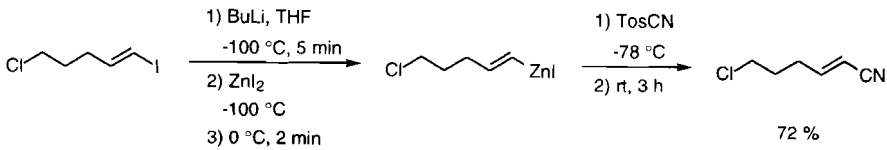
2. General

The solvents used (THF, ether, toluene) were dried and distilled over Na/K under argon. Diethylzinc was purchased from Witco (Bergkamen, Germany). CuCN was used as received (Degussa, Germany). All lithium and zinc halides were purchased as anhydrous salts (Aldrich, Merck, or Riedel de Haën) were always dried for 1–2 h at 120–150°C under vacuum (*ca.* 0.1 mmHg) before use. Me_3SiCl, $Ti(O\textit{i}\text{-}Pr)_4$, $Ti(O\textit{t}\text{-}Bu)_4$, and all organic electrophiles were distilled before use. Argon (99.998%) was used without any purification.

3. Protocols

Protocol 1.
Preparation of 5-chloro-1-pentenylzinc iodide by transmetallation and its cyanation: preparation of (*E*)-6-chloro-2-hexenenitrile[7]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two two-necked, round-bottomed flasks (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

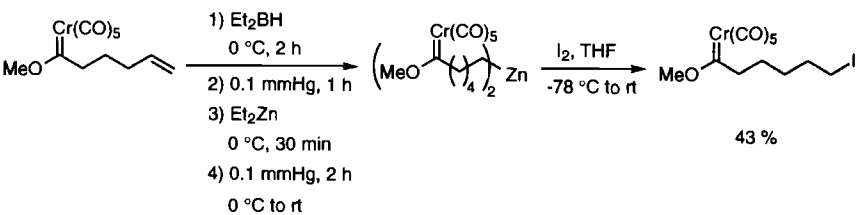
- (*E*)-5-Chloro-1-iodo-1-pentene (FW 230.5), 1.38 g, 6 mmol — **irritant**
- *n*-BuLi solution (1.6 M in hexane), 3.9 mL, 6.3 mmol — **flammable**
- Zinc(II) iodide (FW 319.2), 1.91 g, 6 mmol — **corrosive**
- *p*-Toluenesulfonyl cyanide (FW 181.2), 0.9 g, 5 mmol — **corrosive, harmful**
- Dry THF — **irritant, flammable, hygroscopic**

1. Weigh the zinc(II) iodide into the first two-necked flask, flush with argon, and dissolve in THF (5 mL).
2. Weigh the *p*-toluenesulfonyl cyanide into the second two-necked flask, flush with argon, and dissolve in THF (5 mL).
3. Charge the flame dried and argon flushed three-necked flask with (*E*)-5-chloro-1-iodo-1-pentene and THF (5 mL).
4. Cool the iodopentene solution to –100°C (liquid nitrogen/ether bath) and add BuLi dropwise over 4 min.

5. Stir for 3 min at –100 °C and then add the zinc(II) iodide solution.
6. Warm up to 0 °C for 2 min and then recool back to –78 °C.
7. Confirm the formation of the organozinc iodide by performing an iodolysis and a hydrolysis of a reaction sample. For the iodolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing a solution of iodine (*ca.* 50 mg) in dry ether (1 mL). Mix well, decolorize the brown solution with a saturated aqueous solution of $Na_2S_2O_3$ (*ca.* 0.5 mL), and take the supernatant ether phase for GLC analysis. For the hydrolysis, take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing ether (1 mL) and aqueous NH_4Cl (1 mL). Mix well and take the supernatant ether phase for GLC analysis. These experiments allow an accurate estimate of the organozinc reagent concentration.
8. Add the *p*-toluenesulfonyl cyanide solution to the solution of the organozinc halide at –78 °C.
9. Allow the reaction mixture to warm to rt and stir for 3 h.
10. Add a saturated aqueous NH_4Cl solution (20 mL) to the reaction mixture and stir for 10 min at rt. Pour into an Erlenmeyer containing ether (200 mL) and aqueous NH_4Cl (100 mL) and filter over Celite®.
11. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash with brine (50 mL), dry over $MgSO_4$, and evaporate the solvent.
12. Purify the crude residue by flash chromatography using hexanes:ether (10:1). Pure (*E*)-6-chloro-2-hexenenitrile (0.47 g, 72%) is obtained as a clear oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 2.
Preparation of *bis*(5-(methoxy(pentacarbonylchromium(0) carbene))pentyl) zinc and its iodolysis: preparation of pentacarbonyl ((5-iodopentyl)methoxycarbene) chromium(0)[6]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Protocol 2. *Continued*

Equipment

- Two two-necked, round-bottomed flasks (10 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

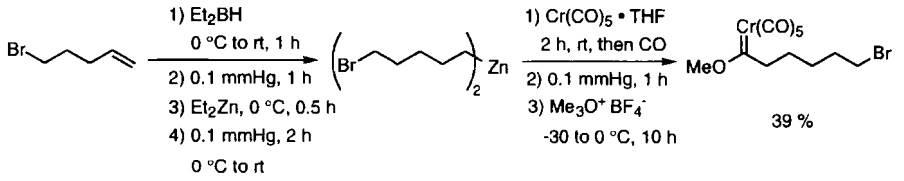
Materials

- Pentacarbonyl(methoxy(4-pentenyl)carbene)chromium(0) (FW 304.2), 230 mg, 0.76 mmol
- Diethylborane solution, 3 M in ether, 0.26 mL, 0.78 mmol — **flammable**
- Diethylzinc (FW 123.5), 0.16 mL, 1.6 mmol — **flammable, pyrophoric**
- Iodine (FW 253.8), 139 mg, 0.55 mmol — **corrosive, harmful**
- Dry THF — **irritant, flammable, hygroscopic**

1. Charge the first flame dried and argon flushed two-necked flask with pentacarbonyl-(methoxy(4-pentenyl)carbene)chromium(0).
2. Cool to 0°C and add diethylborane.
3. Stir for 2 h at 0°C.
4. Connect to vacuum (0.1 mmHg) and remove all volatiles at rt for 1 h to afford the crude hydroboration product.
5. Cool to 0°C and add diethylzinc (Caution!).
6. Replace the septum with a glass stopper. Stir for 30 min.
7. Remove the triethylborane formed and the excess diethylzinc in vacuum (0°C to rt, 2 h, *ca.* 0.1 mmHg).
8. Dissolve the resulting *bis*[5-(methoxy(pentacarbonylchromium(0)carbene)) pentyl]zinc in THF (3 mL) and cool to –78°C.
9. Charge the second two-necked flask with the iodine, flush with argon, and dissolve in THF (5 mL).
10. Add the iodine solution to the dialkylzinc. Decolorize the reaction mixture with diethylzinc (0.03 mL).
11. Filter the reaction mixture through a silica gel pad and evaporate the solvents.
12. Purify the crude residue by radial chromatography (hexanes) to afford the desired product (127 mg, 43%) as an orange oil. Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 3.
Preparation of *bis*(5-bromopentyl)zinc and its reaction with chromium pentacarbonyl•THF: preparation of pentacarbonyl ((5-bromopentyl)methoxycarbene) chromium(0)[6]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- High-pressure mercury lamp, Pyrex (Leybold Heraeus)
- One Schlenk flask (250 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

• 5-bromo-1-pentene (FW 149), 1.2 g, 8.05 mmol	**toxic**
• Diethylborane solution, 3 M in ether, 2.7 mL, 8.05 mmol	**flammable**
• Diethylzinc (FW 123.5), 1.6 mL, 16 mmol	**flammable, pyrophoric**
• $Cr(CO)_6$ (FW 220.1), 0.44 g, 2 mmol	**toxic**
• Carbon monoxide (FW 28)	**highly toxic**
• $Me_3O^+ BF_4^-$ (FW 147.9), 1.11 g, 8.4 mmol	**corrosive**
• Dry THF	**irritant, flammable, hygroscopic**
• Dry CH_2Cl_2	**harmful**

1. Charge the flame dried and argon flushed two-necked flask with 5-bromo-1-pentene.
2. Cool to 0 °C and add diethylborane at once.
3. Stir for 30 min at 0 °C and for 30 min at rt.
4. Connect to vacuum (0.1 mmHg) and remove all volatiles at rt for 1 h to afford the crude hydroboration product.
5. Cool to 0 °C and add diethylzinc (Caution!).
6. Replace the septum with a glass stopper. Stir for 30 min.
7. Remove the triethylborane formed and the excess diethylzinc in vacuum (rt, 2 h, *ca.* 0.1 mmHg).
8. Dissolve the resulting *bis*(5-bromopentyl)zinc in THF (5 mL) and confirm

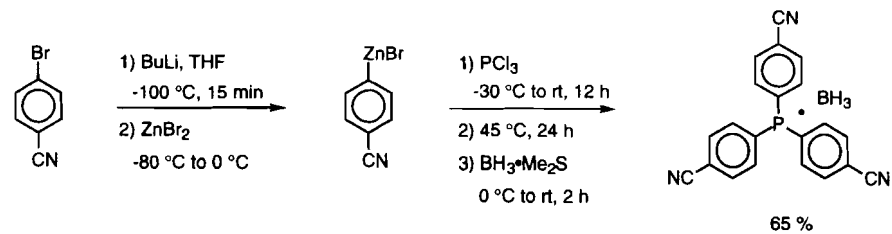
Protocol 3. *Continued*

the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.

9. Charge the flame dried and argon flushed Schlenk flask with the $Cr(CO)_6$ and dissolve in THF (180 mL).
10. Irradiate the solution of $Cr(CO)_6$ for 90 min at rt and confirm the formation of the $Cr(CO)_5$•THF complex by IR spectroscopy.
11. Add the dialkylzinc solution. Stir for 2 h at rt.
12. Slowly pass carbon monoxide through the deep red coloured reaction mixture. Monitor the completion of the reaction by IR spectroscopy.
13. Stir for 2 h at rt and then remove the solvent under reduced pressure (0.1 mmHg, rt, 1 h).
14. Dissolve the residue in CH_2Cl_2 (10 mL), cool to –30 °C, and add Me_3O^+ BF_4^-. Warm to 0 °C and stir for 10 h.
15. Filter the reaction mixture through a silica gel pad and evaporate the solvents.
16. Purify the crude residue by radial chromatography (hexanes) to afford the desired product (297 mg, 39%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 4.
Preparation of 4-cyanophenylzinc bromide by transmetallation and its reaction with phosphorus trichloride: preparation of tris (4-cyanophenyl)phosphine–borane complex[8]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



65 %

Equipment

- One two-necked, round-bottomed flask (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

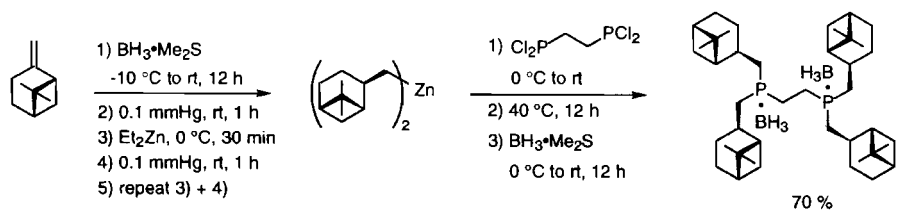
Materials

• 4-bromobenzonitrile (FW 182), 2.46 g, 13.5 mmol	**toxic**
• *n*-BuLi solution, 1.6 M in hexane, 8.4 mL, 13.5 mmol	**flammable**
• Dry zinc(II) bromide (FW 225.2), 3.04 g, 13.5 mmol	**corrosive**
• Phosphorus trichloride (FW 137.3), 0.69 g, 4 mmol	**irritant, corrosive**
• Borane–methyl sulfide complex (FW 76), 0.38 g, 5 mmol	**toxic, stench**
• Dry THF	**irritant, flammable, hygroscopic**

1. Weigh the zinc(II) bromide into the first two-necked flask, flush with argon, and dissolve in THF (7 mL).
2. Charge the flame dried and argon flushed three-necked flask with 4-bromobenzonitrile and dissolve in THF (12.5 mL).
3. Cool to –100 °C (liquid nitrogen/ether bath) and add BuLi dropwise over 5 min.
4. Stir for 15 min at –100 °C, warm to –80 °C, and add the zinc(II) bromide solution.
5. Allow to warm up to 0 °C. Two phases are formed.
6. Confirm the organozinc halide formation by performing an iodolysis and a hydrolysis as described in Protocol 1 of an aliquot of the lower phase.
7. Recool to –30 °C and add the phosphorus trichloride. Warm to rt and stir for 12 h at rt, then stir at 45 °C for 24 h.
8. Cool to 0 °C and add the borane–methyl sulfide complex. Warm to rt and stir for 2 h.
9. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (9:1) to afford the desired product (0.91 g, 65%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 5.
Preparation of dimyrtanylzinc and its addition to 1,2-*bis*(dichlorophosphino)ethane: preparation of 1,2-*bis*(dimyrtanylphosphino)ethane–diborane complex[8]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



70 %

Protocol 5. *Continued*

Equipment

- One two-necked, round-bottomed flask (100 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar

Materials

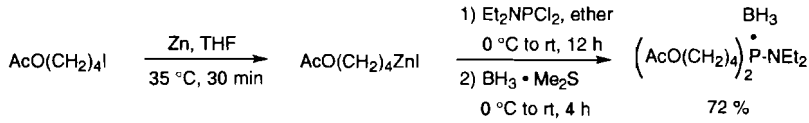
- (1*S*)-(–)-β-pinene (FW 136.24), 13.62 g, 100 mmol — **flammable**
- Borane–methyl sulfide complex (FW 76), 2.28 g, 30 mmol — **toxic, stench**
- Diethylzinc (FW 123.5), 2 × 6 mL, 2 × 60 mmol — **flammable, pyrophoric**
- 1,2-*bis*(dichlorophosphino)ethane (FW 213.8), 0.46 g, 2 mmol — **corrosive**
- Borane–methyl sulfide complex, 1 molar in CH_2Cl_2, 6 ml, 6 mmol — **toxic, stench**
- Dry THF — **irritant, flammable, hygroscopic**
- Dry ether — **flammable**
- Dry hexanes — **flammable**

1. Charge the first flame dried and argon flushed two-necked flask with (1*S*)-(–)-β-pinene and cool to –10°C. Add borane–methyl sulfide complex. After 10 min a thick precipitate will form. Dissolve in ether (15 mL) and stir at 0°C for 2 h.
2. Warm to rt and stir for a further 8 h.
3. Remove the solvent and excess pinene under reduced pressure (0.1 mmHg, rt, 1 h) to give the tri-*cis*-myrtanyl-borane as a white solid (12.5 g, 99%).
4. Add hexanes (12 ml) and cool to 0°C.
5. Add diethylzinc to the mixture (Caution!), and then stir at 0°C for 30 min.
6. Remove the solvent and excess diethylzinc under reduced pressure (0.1 mmHg, rt, 1 h).
7. Repeat steps 4–6.
8. Heat at 40°C for 4 h under reduced pressure (0.1 mmHg) to ensure removal of all excess diethylzinc.
9. Cool to rt and dissolve in THF (45 mL). Confirm the formation of the dialkylzinc by performing an idolysis and a hydrolysis as described in Protocol 1. (This THF solution can be stored for several months at 0°C.)
10. Add the dimyrtanylzinc solution (6 mL) to the second flame dried argon flushed two-necked flask and cool to 0°C.
11. Add 1,2-*bis*(dichlorophosphino)ethane slowly (Caution! exothermic reaction).
12. Warm slowly to rt and then heat at 40°C overnight.
13. Recool to 0°C and add the borane–methyl sulfide solution.
14. Warm to rt and stir at rt overnight.
15. Work-up as described in Protocol 1 using CH_2Cl_2 (400 mL).

16. The residue obtained after evaporation of the solvents was purified by flash chromatography (hexanes:ether:CH_2Cl_2, 17:1:2) affording the phosphine–borane complex as a white solid (0.93 g, 70%). Characterize the product by ^1H NMR, ^{13}C NMR, ^{31}P NMR, IR spectroscopy, mass spectrometry, elementary analysis, and determine the optical rotation. $[\alpha]_D^{25} = -38.2°$ ($c = 3.55$, $CHCl_3$).

Protocol 6.
Preparation of 4-acetoxybutylzinc iodide and its addition to dichloro(diethylamino)phosphine: preparation of di(4-acetoxybutyl) (diethylamino)-phosphine–borane complex[10]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Dry, gas-tight syringes and steel needles

Materials

- Zinc dust (FW 65.4), 2.62 g, 40 mmol
- 1,2-dibromoethane (FW 187.9), 0.3 g, 1.6 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.17 g, 1.6 mmol — **flammable, corrosive**
- 4-iodobutyl acetate (FW 242.1), 3.19 g, 13.2 mmol — **toxic, stench**
- Dichloro(diethylamino)phosphine (FW 174), 0.98 g, 5.6 mmol — **corrosive**
- Borane–methyl sulfide solution, 1 M in CH_2Cl_2, 5.6 mL, 5.6 mmol — **toxic, stench**
- Dry THF — **irritant, flammable, hygroscopic**
- Dry ether — **flammable**

1. Weigh the zinc dust into the three-necked flask, add THF (13.2 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and heat gently with a heat gun to boil the THF. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl slowly, whilst warming with the heat gun, and then stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Add slowly the 4-iodobutyl acetate at such a rate that the reaction temperature remains between 35–40 °C. Stir the reaction mixture at 35 °C and monitor the

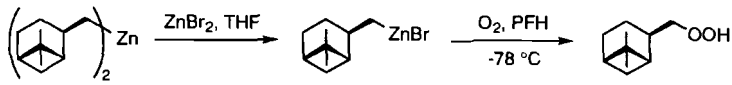
Protocol 6. *Continued*

insertion reaction by performing an iodolysis and a hydrolysis as described in Protocol 1.

5. Add THF (5 mL) and stop the stirring. Allow the zinc suspension to settle for 15 min.
6. Charge the two-necked flask with dichloro(diethylamino)phosphine and ether (5 mL) and cool to 0°C.
7. Add the solution of the 4-acetoxybutylzinc iodide over 5 min. Stir at 0°C for 2 h and then at rt overnight.
8. Cool to 0°C and add the borane–methyl sulfide solution. Stir at rt for 4 h. Monitor the protection reaction by GLC analysis of hydrolysed reaction aliquots.
9. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (4:1) to afford the desired product (1.40 g, 72%). Characterize the product by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 7.
Oxidation of dimyrtanylzinc with oxygen in perfluorohexanes: preparation of myrtanyl hydroperoxide[12]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



64 %

Equipment

- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (250 mL) equipped with an argon inlet, a gas outlet (bubbler), a septum cap, and a magnetic stirring bar

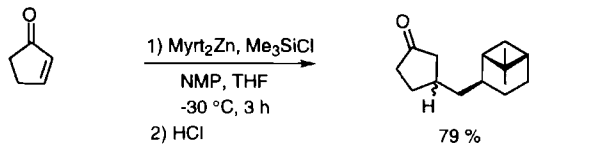
Materials

- Dimyrtanylzinc (FW 339.9), 1.7 g, 5 mmol (see Protocol 5) — **hygroscopic**
- Dry zinc(II) bromide (FW 225.2), 1.12 g, 5 mmol — **corrosive**
- Oxygen (FW 16)
- Dry THF — **irritant, flammable, hygroscopic**
- Perfluorohexanes (PFH)

1. Charge the flame dried and argon flushed two-necked flask with zinc(II) bromide, dissolve in ether, and cool to 0°C. Slowly add the dimyrtanylzinc and stir for 10 min. The myrtanylzinc bromide solution is now ready for use.
2. Add perfluorohexanes (50 mL) to the three-necked flask, cool to –78°C, and bubble oxygen through the solvent for 2 h.
3. Rapidly inject the myrtanylzinc bromide solution into the oxygen saturated PFH. Stir for 4 h at –78°C and then allow to warm to rt.
4. Add a 2 N HCl solution (6 mL) and separate the PFH layer for recycling.
5. Work-up the aqueous phase as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (9:1) to afford the desired product (1.08 g, 64%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 8.
Conjugate addition of dimyrtanylzinc to an enone in *N*-methylpyrrolidinone (NMP): preparation of 3-myrtanylcyclopentanone[26]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



79 %

1 : 1 mixture of diastereoisomers

Equipment

- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

- Dimyrtanylzinc (FW 339.9), 1.7 g, 5 mmol (see Protocol 5) — **hygroscopic**
- Me_3SiCl (FW 108.6), 0.54 g, 5 mmol — **flammable, corrosive**
- 2-cyclopenten-1-one (FW 82.1), 0.41 g, 5 mmol — **flammable**
- Dry NMP — **irritant**
- Dry THF — **irritant, flammable, hygroscopic**

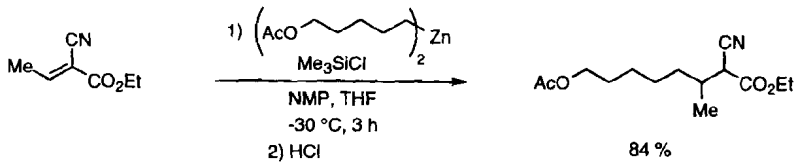
1. Charge the flame dried and argon flushed three-necked flask with THF (2 mL), NMP (3 mL), and 2-cyclopenten-1-one.

Protocol 8. *Continued*

2. Cool to –30°C, add Me_3SiCl and dimyrtanylzinc, and stir at –30°C for 3 h.
3. Dilute with THF (20 mL) and pour into an aqueous 10% HCl solution (10 mL). Stir for 15 min.
4. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (19:1) to afford the desired product (0.87 g, 79%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 9.
Conjugate addition of *bis*(5-acetoxypentyl)zinc to a Michael-acceptor in *N*-methylpyrrolidinone (NMP): preparation of ethyl 8-acetoxy-3-methyl-2-cyano-octanoate[26]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



84 %

Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

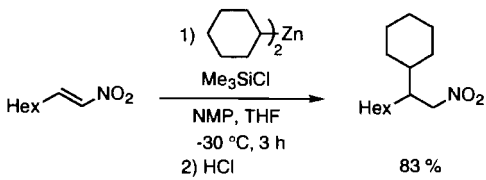
- 5-iodopentyl acetate (FW 256.1), 1.79 g, 7 mmol — **irritant**
- Diethylzinc (FW 123.5), 1.4 mL, 14 mmol — **flammable, pyrophoric**
- CuI (FW 190.4), 4 mg, 0.02 mmol
- Me_3SiCl (FW 108.6), 0.32 g, 3 mmol — **flammable, corrosive**
- Ethyl 2-cyanocrotonate (FW 139.1), 0.42 g, 3 mmol — **irritant, harmful**
- Dry NMP — **irritant**
- Dry THF — **irritant, flammable, hygroscopic**

1. Charge the flame dried and argon flushed Schlenk flask with CuI, 5-iodopentyl acetate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.

3. Slowly heat the Schlenk flask to 50°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 50°C for 8 h.
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50°C, 2 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(5-acetoxypentyl)zinc at rt in THF (2 mL).
7. Charge the flame dried and argon flushed three-necked flask with THF (2 mL), NMP (1 mL), and ethyl 2-cyanocrotonate.
8. Cool to –30°C, add Me_3SiCl, and then *bis*(5-acetoxypentyl)zinc slowly over a period of 10 min. Stir at –30°C for 3 h.
9. Dilute with THF (20 mL) and pour into an aqueous 10% HCl solution (10 mL). Stir for 15 min.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (9:1) to afford the desired product (0.68 g, 84%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 10.
Conjugate addition of dicyclohexylzinc to a nitro olefin in *N*-methylpyrrolidinone (NMP): preparation of 2-cyclohexyl-1-nitrooctane[26]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Protocol 10. *Continued*

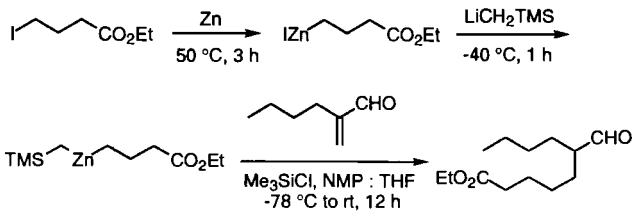
Materials

• Cyclohexene (FW 82.1), 0.99 g, 12 mmol	**flammable**
• Borane–methyl sulfide complex (FW 76), 0.27 g, 3.5 mmol	**toxic, stench**
• Diethylzinc (FW 123.5), 2 mL, 20 mmol	**flammable, pyrophoric**
• Me_3SiCl (FW 108.6), 0.54 g, 5 mmol	**flammable, corrosive**
• 1-nitro-1-octene (FW 157.2), 0.79 g, 5 mmol	
• Dry ether	**flammable**
• Dry hexanes	**flammable**
• Dry NMP	**irritant**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge the flame dried and argon flushed two necked flask with cyclohexene and ether (5 mL) and cool to 0°C.
2. Add the borane–methyl sulfide complex. Allow to warm to rt and stir for 3 h at rt.
3. Connect to vacuum and remove the solvent and the excess olefin (rt, 1 h, *ca.* 0.1 mmHg).
4. Suspend the remaining solid of tricyclohexylborane in hexanes (1 mL) and add diethylzinc (Caution!). Carefully protect the reaction flask from light.
5. Stir the reaction mixture at rt for 3 h.
6. Remove the triethylborane formed and the excess diethylzinc in vacuum (rt, 3 h, *ca.* 0.1 mmHg).
7. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
8. Dissolve the resulting oil of dicyclohexylzinc in THF (3 mL) at rt.
9. Charge the flame dried and argon flushed three-necked flask with THF (2 mL), NMP (2 mL), and 1-nitro-1-octene.
10. Cool to –30°C, add Me_3SiCl, and then dicyclohexylzinc slowly over a period of 10 min. Stir at –30°C for 3 h.
11. Dilute with THF (20 mL) and pour into an aqueous 10% HCl solution (10 mL). Stir for 15 min.
12. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (19:1) to afford the desired product (1 g, 83%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 11.
Conjugate addition reaction of a mixed dialkylzinc reagent to an unsaturated aldehyde: preparation of ethyl 6-(oxomethyl)decanoate[28]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Three three-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

• Zinc dust (FW 65.4), 1.57 g, 24 mmol	
• 1,2-dibromoethane (FW 187.9), 0.2 mL, 2.3 mmol	**toxic**
• Me_3SiCl (FW 108.6), 0.2 mL, 1.6 mmol	**flammable, corrosive**
• Ethyl 4-iodobutanoate (FW 240.1), 1.45 g, 6 mmol	**irritant, lachrymator**
• Trimethylsilylmethyllithium, 1 mol dm^{-3} in pentane, 6 mL, 6 mmol	**flammable, corrosive**
• 2-butylacrolein (FW 112.17), 0.53 mL, 4 mmol	**lachrymator, flammable**
• Me_3SiCl (FW 108.6), 1.02 mL, 8 mmol	**flammable, corrosive**
• Dry NMP	**irritant**
• Dry THF	**irritant, flammable, hygroscopic**

1. Weigh the zinc dust into the first three-necked flask, add THF (6 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and heat gently with a heat gun to boil the THF. Allow to cool to rt. Repeat the heating–cooling process four more times.
3. Add Me_3SiCl dropwise, gently warming the flask with the heat gun to boil the solvent. The zinc dust is now activated and ready for use.
4. Add slowly the ethyl 4-iodobutanoate dropwise over 5 min. Upon complete addition, warm the reaction mixture to 50°C and heat at this temperature for 3 h. Monitor the insertion reaction by performing an iodolysis and hydrolysis as described in Protocol 1.
5. Cool to rt and stop stirring. Allow the zinc suspension to settle for 15 min.
6. Transfer the solution of the organozinc iodide to the second three-necked flask and cool to –78°C. Add the solution of trimethylsilylmethyllithium in pentane dropwise over 5 min and then stir for 1 h, slowly warming to –40°C.

Protocol 11. *Continued*

7. Meanwhile in the third three-necked flask prepare a solution of 2-butylacrolein, trimethylsilyl chloride in THF (3 mL), and NMP (1 mL) at –78°C.
8. Add the solution of the mixed dialkylzinc to the 2-butylacrolein solution over 10 min and then stir overnight, slowly warming to rt.
9. Pour the mixture into an aqueous saturated ammonium chloride solution (50 mL) and extract with diethyl ether (3 × 50 mL). Wash the combined ethereal extracts with brine (50 mL) and dry ($MgSO_4$). Add silica (10 g) and stir for 1 h to hydrolyse the silyl enol ether, monitor by GC. Filter and concentrate the filtrate under reduced pressure.
10. Purify the crude residue obtained after evaporation of the solvent by flash column chromatography using 15% diethyl ether:hexanes to afford the desired product (650 mg, 71%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectroscopy, and elementary analysis.

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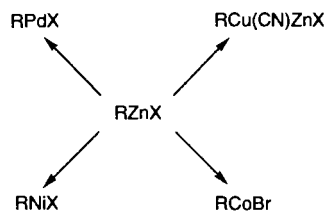
10

Transition metal catalysed reactions of zinc organometallics

PAUL KNOCHEL, PHILIP JONES, and FALK LANGER

1. Introduction

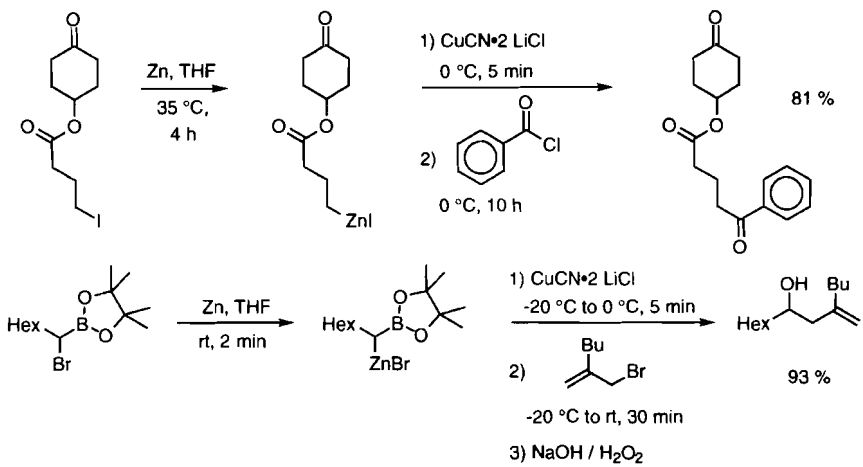
The low reactivity of zinc organometallic reagents can be dramatically increased by adding a transition metal catalyst. Many transition metal salts undergo transmetallation with organozinc halides or diorganozincs producing intermediate transition metal organometallics which display an enhanced reactivity toward many organic electrophiles due to the presence of *d*-orbitals. This increased reactivity allows many reactions not possible with conventional main group organometallic compounds to be carried out.[1] The moderate activity of zinc organometallics is an essential factor for the success of these transmetallations, since it avoids the transfer of several organic groups to the same metal centre and therefore reduces the decomposition pathways available of these transition metal organometallic intermediates. Thus, whereas the treatment of BuLi or BuMgBr with $CoBr_2$ or $FeCl_3$ at very low temperature leads to an instantaneous decomposition, the reaction of $Pent_2Zn$ with $CoBr_2$ or $FeCl_3$ in THF:NMP produces organometallic species processing reasonable stability at –30 °C. In this chapter, transmetallation reactions with practical applications in organic synthesis will be extensively discussed. Mostly copper, cobalt, palladium, and nickel catalysed reactions of zinc organometallics will be presented (Scheme 10.1).



Scheme 10.1

2. Copper catalysed reactions of zinc organometallics

The THF soluble copper salt CuCN•2LiCl[2,3] combines a good chemical stability with a good transmetallation ability. Added in stoichiometric amount, it converts organozinc halides into zinc–copper reagents, tentatively represented as RCu(CN)ZnX.[2,4] These copper–zinc reagents show a similar reactivity to organocopper species, derived from organolithiums or Grignard reagents. The copper–zinc compounds RCu(CN)ZnI react with acid chlorides in THF (0 °C, 4–12 h) providing polyfunctional ketones[2] (Scheme 10.2). Allylation reactions with allylic chlorides or bromides are performed under very mild conditions (0–25 °C, 0.5–1 h) and afford the S_N2' substitution product with high regioselectivity.[5–8]

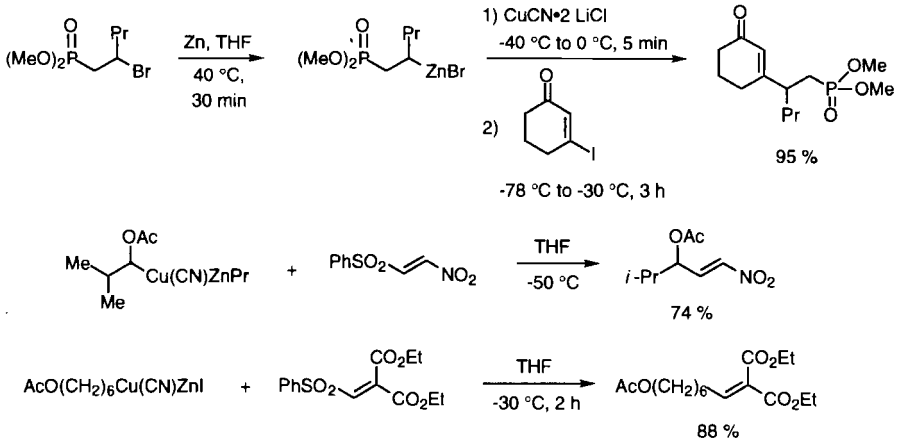


Scheme 10.2

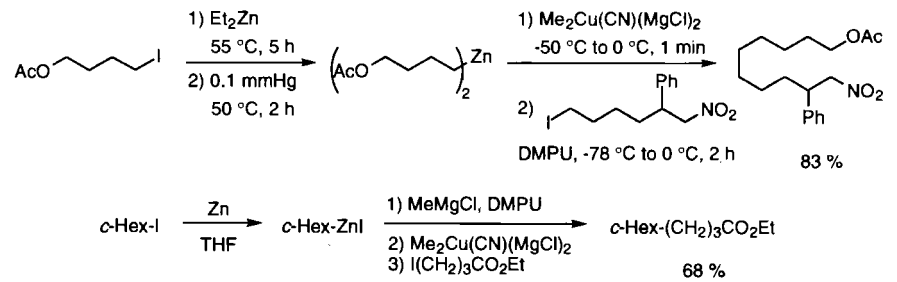
Copper catalysed substitution reactions require high reaction temperatures and polar solvents like NMP.[9] With activated alkenyl iodides bearing electron-withdrawing groups, copper–zinc reagents react readily leading to addition-elimination products.[10,11] This method can be used to prepare a range of polyfunctional unsaturated molecules (Scheme 10.3).[10–12]

Cross-coupling reactions between C_{sp3}- centres are possible using reagents prepared from diorganozincs R_2Zn with 2MeMgCl•CuCN.[12] The resulting copper reagents, tentatively formulated as $R_2Cu(CN)(MgX)_2$•Me_2Zn, undergo nucleophilic substitution reactions in DMPU.[13] Secondary organozinc halides can be converted to mixed diorganozincs by the reaction with MeMgCl and used for nucleophilic substitution reactions after formation of the corresponding copper reagent (Scheme 10.4).

Michael-addition reactions can be performed with various zinc/copper reagents derived from organozinc halides. β-Monosubstituted enones react in



Scheme 10.3

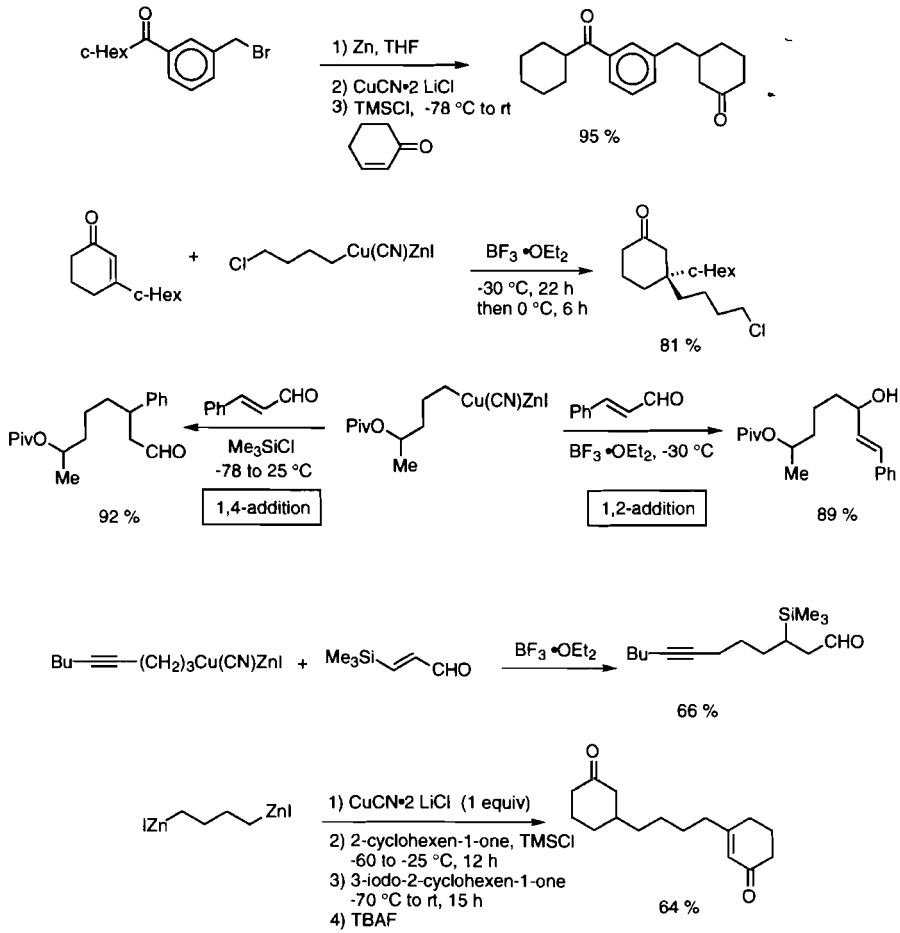


Scheme 10.4

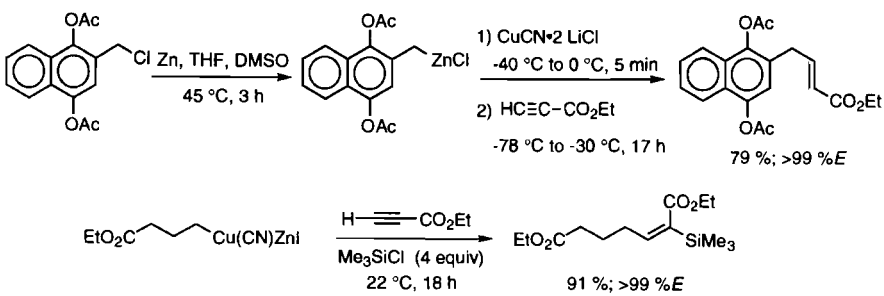
the presence of TMSCl[2,14] whilst BF_3•OEt_2 is necessary for β-disubstituted.[15] With α,β-unsaturated aldehydes, the nature of the product (1,2- versus 1,4-addition) depends on the reaction conditions[16] and on the nature of the aldehyde. Thus, 3-trimethylsilylacrolein shows a high propensity to furnish the 1,4-adduct even in the presence of a strong Lewis acid like BF_3•OEt_2.[17] 1,n-organodizincs can be converted to mixed copper–zinc 1,n-bimetallics by adding only one equivalent of CuCN•2LiCl.[18] A selective stepwise reaction with two different electrophiles is possible in many cases by the proper choice of the reaction conditions (Scheme 10.5).

Additions to activated triple bonds,[14] like ethyl propiolate, provide a simple entry to (*E*)-unsaturated esters. In the presence of TMSCl, incorporation of the TMS group in the product is observed (Scheme 10.6).[19]

Addition reaction of zinc–copper reagents to nitro olefins is a versatile method for preparing polyfunctional nitroalkanes.[20] A direct ozonolysis of the intermediate zinc nitronate furnishes the corresponding ketone (Nef-reaction).[20]

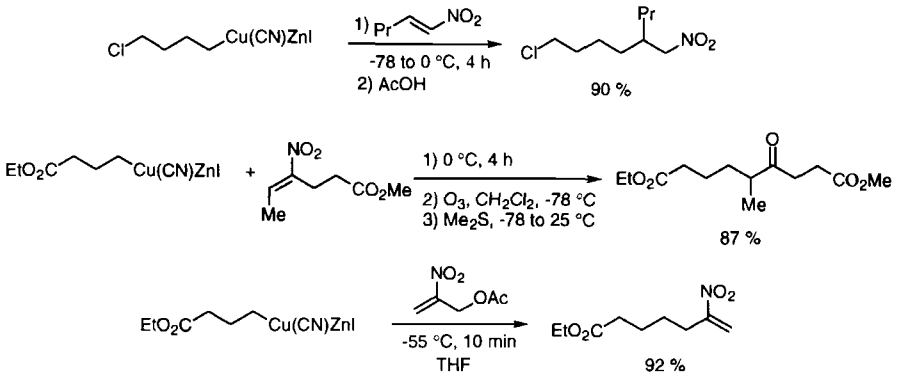


Scheme 10.5



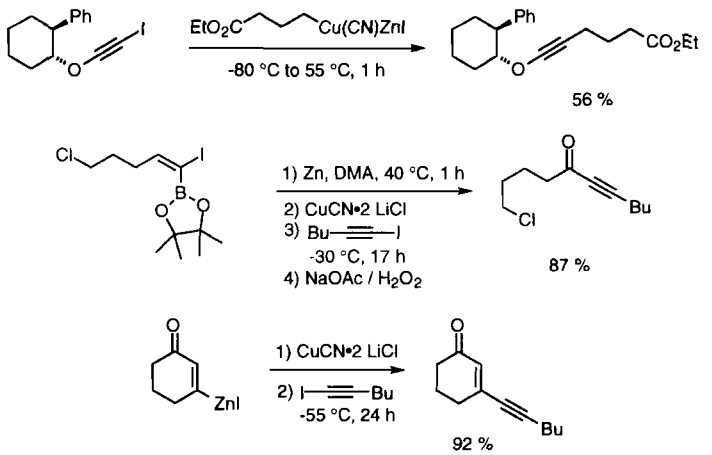
Scheme 10.6

The addition of zinc–copper reagents to an activated nitro olefin like 2-nitro-3-acetoxypropene is complete within a few minutes at –55 °C (Scheme 10.7).[21]



Scheme 10.7

Cross-coupling reactions with 1-bromo- and 1-iodoalkynes[19,22] provides an easy access to polyfunctional alkynes (Scheme 10.8).[23,24]

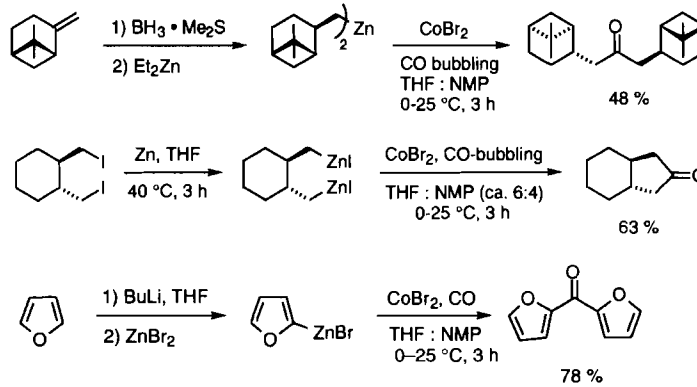


Scheme 10.8

3. Cobalt catalysed reactions of zinc organometallics

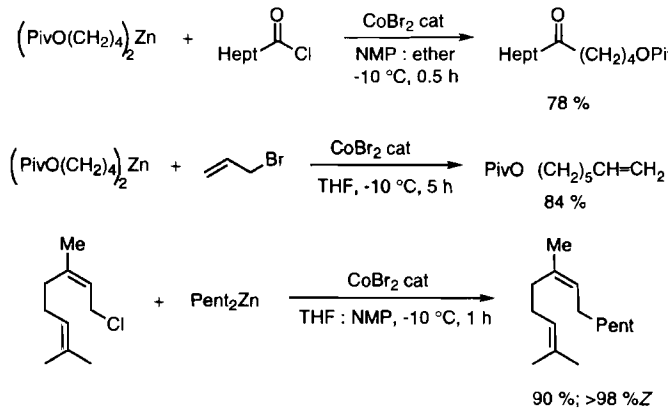
The treatment of diorganozincs or organozinc halides with cobalt bromide in THF:NMP mixtures provides blue solutions of organocobalt reagents, which have a half-life of several hours at –20 °C.[25,26] Carbonylation reactions with these new cobalt reagents proceed well simply by bubbling carbon monoxide

through the THF:NMP solution of these reagents leading to symmetrical ketones (Scheme 10.9).[25–27]



Scheme 10.9

Organozinc halides and diorganozincs can be successfully acylated and allylated using catalytic ammounts of transition metal salts like $CoBr_2$, $FeCl_3$.[25] With trisubstituted double bonds, the substitution reaction occurs with S_N2 selectivity and complete retention of the double bond geometry (Scheme 10.10).[25]

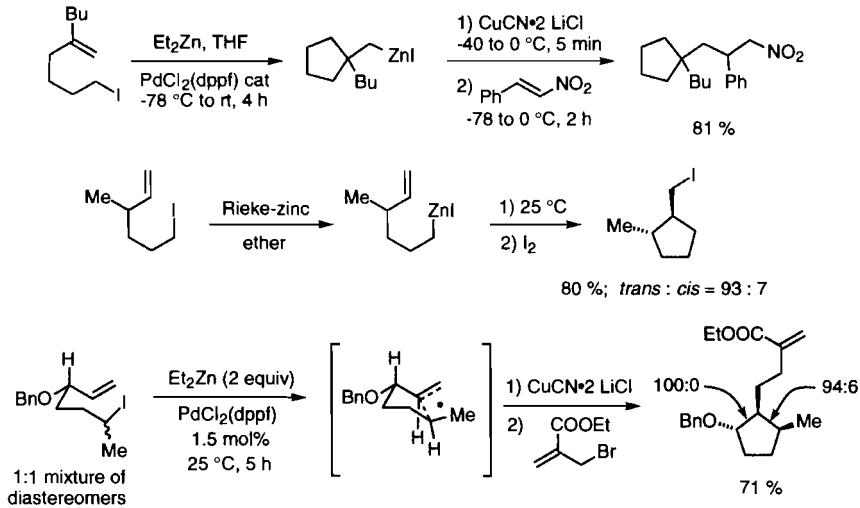


Scheme 10.10

4. Palladium and nickel catalysed reactions

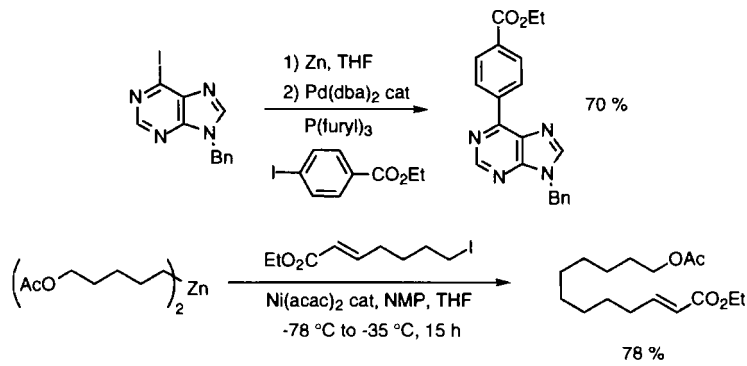
Radical cyclization reactions can be carried out by treating an unsaturated alkyl iodide or bromide with Et_2Zn in the presence of palladium(II) or nickel(II) complexes.[28] Under these conditions, an intermediate Pd(0) or Ni(0) complex is formed which initiates a radical chain reaction providing a new cyclized zinc cyclopentylmethyl derivative which can be trapped with various electrophiles in the presence of a copper catalyst. A related cyclization can be

realized in ether, in the absence of a transition metal catalyst, but by using highly activated Rieke-zinc for generating the uncyclized zinc reagent. In this case, the ring closure is believed to proceed via a carbozincation pathway.[29] These reactions can be used advantageously for the stereoselective preparation of various substituted cyclopentane derivatives. The radical cyclization is stereoconvergent and an epimeric mixture of secondary alkyl iodides can be cyclized via a chair transition state, the bulkiest substituents occupying a pseudo-equatorial position.[30] This cyclization reaction can also be used to prepare oxygen and nitrogen heterocycles (Scheme 10.11).[30,31]



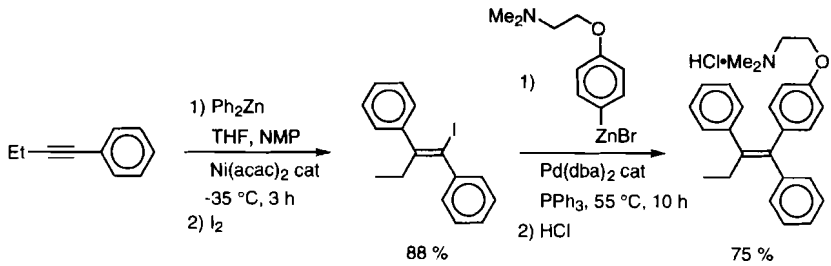
Scheme 10.11

Finally, various palladium(0) (Negishi-reaction)[32] and Ni(0) catalysed reactions can be used to perform cross-couplings between highly functionalized substrates (Scheme 10.12).[33,34]



Scheme 10.12

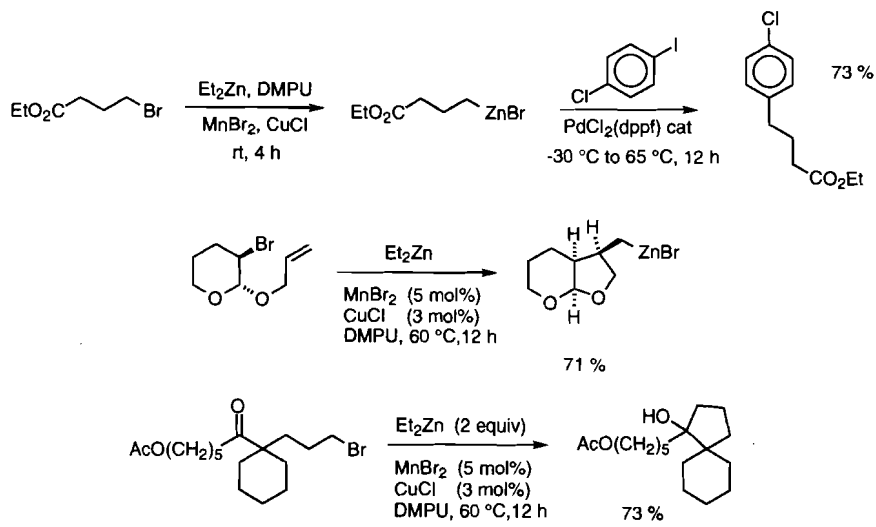
Diorganozincs add to substituted phenylacetylenes with high regioselectivity and complete stereoselectivity (*syn*-addition).[35] This methodology has been recently used to prepare the anti-cancer drug (*Z*)-Tamoxifen (Scheme 10.13).[35]



Scheme 10.13

5. Manganese catalysed reactions

Organomanganese halides have found numerous applications in organic synthesis in most cases as demonstrated by pioneering work of Cahiez.[36–41] Although organozinc halides cannot be transmetallated[42] to organomanganese intermediates, it was recently shown that a mixed metal catalyst (manganese(II) and copper(I)) allows preparation of organozinc compounds directly from alkyl bromides using Et_2Zn for performing the bromine–zinc exchange.[43] The mechanism of these reaction is radical in nature and can be used to perform cyclization reactions. Cyclizations onto carbonyl groups, like aldehydes or ketones, also proceed well (Scheme 10.14).[44]



Scheme 10.14

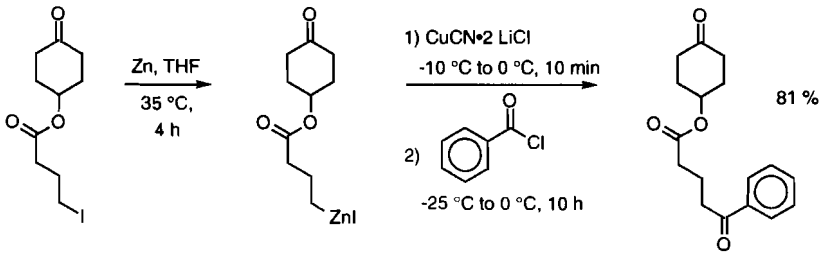
6. General

The solvents used (THF, ether, toluene) were dried and distilled over Na/K under argon. Diethylzinc was purchased from Witco (Bergkamen, Germany). CuCN was used as received (Degussa, Germany). All lithium and zinc halides were purchased as anhydrous salts (Aldrich, Merck or Riedel de Haën) and were always dried for 1–2 h at 120–150°C under vacuum (*ca.* 0.1 mmHg) before use. Me_3SiCl, $Ti(O\textit{i}\text{-}Pr)_4$, $Ti(O\textit{t}\text{-}Bu)_4$, and all organic electrophiles were distilled before use. Argon (99.998%) was used without any purification.

7. Protocols

Protocol 1.
Copper-mediated addition of a functionalized alkylzinc iodide to an acid chloride: preparation of 4-oxocyclohexyl 5-phenyl-5-oxopentanoate[2]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two three-necked, round-bottomed flasks (25 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

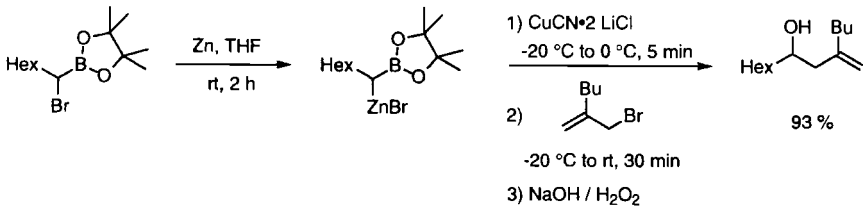
• Zinc dust (FW 65.4), 1.62 g, 25 mmol	
• 1,2-Dibromoethane (FW 187.9), 0.37 g, 2 mmol	**toxic**
• Me_3SiCl (FW 108.6), 0.22 g, 2 mmol	**flammable, corrosive**
• 4-Oxocyclohexyl 4-iodobutanoate (FW 309.9), 3.1 g, 10 mmol	**harmful**
• CuCN (FW 89.6), 0.9 g, 10 mmol	**highly toxic**
• LiCl (FW 42.4), 0.84 g, 20 mmol	**irritant, hygroscopic**
• Benzoyl chloride (FW 117.1), 0.88 g, 7.5 mmol	**irritant, harmful**
• Dry THF	**irritant, flammable, hygroscopic**

Protocol 1. *Continued*

1. Weigh the zinc dust into the first three-necked flask, add THF (2 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and heat gently with a heat gun to gently boil the THF. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Add slowly a solution of 4-oxocyclohexyl 4-iodobutanoate in THF (10 mL) at such a rate that the reaction temperature remains between 35–40 °C. Stir the reaction mixture at 35 °C and monitor the insertion reaction by performing an iodolysis and a hydrolysis, approx. 4 h. For the iodolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing a solution of iodine (*ca.* 50 mg) in dry ether (1 mL). Mix well, decolorize the brown solution with a saturated aqueous solution of $Na_2S_2O_3$ (*ca.* 0.5 mL), and take the supernatant ether phase for GLC analysis. For the hydrolysis take a reaction aliquot (*ca.* 0.1 mL) with a syringe and add it to a vial containing ether (1 mL) and aqueous NH_4Cl (1 mL). Mix well and take the supernatant ether phase for GLC analysis. These experiments allow an accurate estimate of the organozinc reagent concentration.
5. Cool to rt and stop the stirring. Allow the zinc suspension to settle for 15 min.
6. Meanwhile weigh the CuCN and the LiCl into the second three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150 °C for 2 h.
7. Cool to rt and flush with argon. Dissolve the CuCN•2LiCl in dry THF (10 mL) at rt. A slight exothermic reaction is observed and a light yellow/green solution is formed. Cool the solution to –10 °C.
8. Add the solution of the alkylzinc bromide to the CuCN•2LiCl solution rapidly. Allow to warm to 0 °C, stir for 10 min, and cool the resulting light green solution to –25 °C.
9. Add the benzoyl chloride slowly and then allow the reaction mixture to warm to 0 °C. Stir overnight.
10. Add a saturated aqueous NH_4Cl solution (20 mL) to the reaction mixture and stir for 10 min at rt. Pour into an Erlenmeyer containing ether (200 mL) and aqueous NH_4Cl (100 mL), and filter over Celite®.
11. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash with brine (50 mL), dry over $MgSO_4$, and evaporate the solvent.
12. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (9:1) to afford the desired product (1.51 g, 81%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 2.
Copper catalysed allylation of a boron stabilized secondary alkylzinc bromide: preparation of 2-butyl-1-decen-4-ol[8]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two three-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

- Zinc dust (FW 65.4), 1.5 g, 23 mmol
- 1,2-Dibromoethane (FW 187.9), 0.2 g, 1.1 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.11 g, 1 mmol — **flammable, corrosive**
- Pinacol 1-bromoheptane-1-boronate (FW 305.1), 2.26 g, 7.4 mmol — **harmful**
- CuCN (FW 89.6), 0.72 g, 8 mmol — **highly toxic**
- LiCl (FW 42.4), 0.68 g, 16 mmol — **irritant, hygroscopic**
- 2-(Bromomethyl)-1-hexene (FW 163.1), 0.88 g, 5 mmol — **toxic**
- NaOH solution, 6 N in water — **corrosive**
- H_2O_2 solution, 35% in water, 4 mL — **corrosive**
- Dry THF — **irritant, flammable, hygroscopic**
- Ethanol — **toxic, flammable**

1. Weigh the zinc dust into the first three-necked flask, add THF (4 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and heat with a heat gun to gently boil the solvent. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Add slowly a solution of the pinacol 1-bromoheptane-1-boronate in THF (4 mL) at such a rate that the reaction temperature remains between 20–25 °C. Stir the reaction mixture at rt and monitor the insertion reaction, approx. 2 h, by performing an iodolysis and a hydrolysis as described in Protocol 1.
5. Stop the stirring and allow the zinc suspension to settle for 30 min.
6. Meanwhile, weigh the CuCN and the LiCl into the second three-necked flask

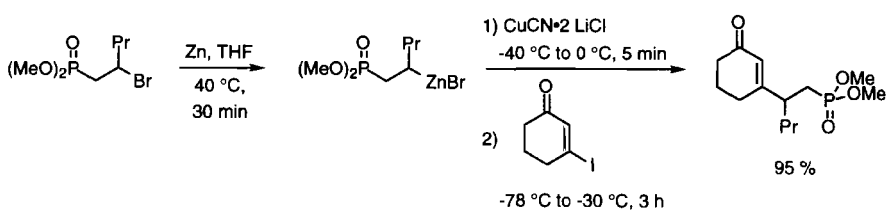
Protocol 2. *Continued*

(equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.

7. Cool to rt and flush with argon. Dissolve the CuCN•2LiCl in dry THF (10 mL) at rt. A slight exothermic reaction is observed and a light yellow/green solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –20°C.
8. Add the solution of the alkylzinc bromide to the CuCN•2LiCl solution. Allow to warm to 5°C, stir for 5 min, and then cool the resulting light green solution to –20°C.
9. Add the 2-(bromomethyl)-1-hexene and allow the reaction mixture to warm to rt. Stir for 30 min.
10. Add a saturated aqueous NH_4Cl solution (20 mL) to the reaction mixture and stir for 10 min at rt. Pour into an Erlenmeyer containing ether (200 mL) and aqueous NH_4Cl solution (100 mL), and filter over Celite®.
11. Separate the organic and aqueous layers. Extract the aqueous layer with ether (2 × 50 mL). Combine the organic layers and wash with brine (50 mL), dry over $MgSO_4$, and evaporate the solvent.
12. Dissolve the resulting yellow oil in THF (10 mL) and ethanol (10 mL). Add the NaOH solution (3.3 mL) and cool to 0°C. Carefully add the H_2O_2. An exothermic reaction occurs. Monitor the reaction by GC analysis.
13. Evaporate the solvents under reduced pressure and dilute with ether (150 mL).
14. Work-up as described above. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (9:1) to afford the desired product (0.99 g, 93%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 3.
Copper catalysed addition of a β-zincated phosphonate to an electrophile: preparation of dimethyl 2-(cyclohex-1-en-3-on-1-yl)pentanephosphonate[10]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two three-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

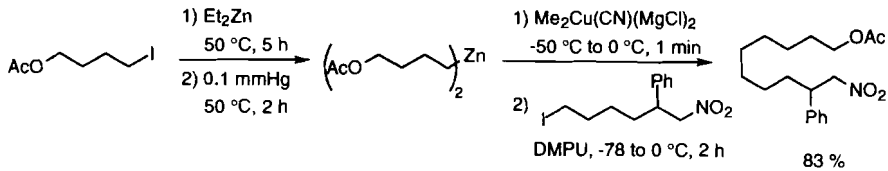
Materials

- Zinc dust (FW 65.4), 1.96 g, 30 mmol
- 1,2-Dibromoethane (FW 187.9), 0.19 g, 1 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.11 g, 1 mmol — **flammable, corrosive**
- Dimethyl 2-bromopentanephosphonate (FW 259.1), 2.59 g, 10 mmol — **irritant**
- CuCN (FW 89.6), 0.72 g, 8 mmol — **highly toxic**
- LiCl (FW 42.4), 0.68 g, 16 mmol — **irritant, hygroscopic**
- 3-Iodo-2-cyclohexenone (FW 222), 1.33 g, 6 mmol — **light-sensitive, irritant, harmful**
- Dry THF — **irritant, flammable, hygroscopic**

1. Weigh the zinc dust into the first three-necked flask, add THF (5 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and heat with a heat gun to gently boil the THF. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Add slowly a solution of the dimethyl 2-bromopentanephosphonate in THF (5 mL) at such a rate that the reaction temperature remains between 40–45 °C. Stir the reaction mixture at rt and monitor the insertion reaction by performing an iodolysis and a hydrolysis as described in Protocol 1.
5. Stop the stirring and allow the zinc suspension to settle for 30 min.
6. Meanwhile, weigh the CuCN and the LiCl into the second three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150 °C for 2 h.
7. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl at rt in dry THF (8 mL). A slight exothermic reaction is observed and a light yellow/green solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –40 °C.
8. Add the solution of the alkylzinc bromide to the CuCN•2LiCl solution. Allow to warm to 0 °C, stir for 5 min, and cool the resulting light green solution to –78 °C.
9. Add a solution of the 3-iodo-2-cyclohexenone in THF (2 mL) slowly. Allow the reaction mixture to warm to –30 °C and stir at this temperature for 4 h.
10. Work-up as described in Protocol 1 using EtOAc instead of ether. Remove the excess dimethyl pentane phosphonate by distillation (b.p. 52 °C at 0.03 mmHg). Purify the crude residue by flash chromatography using CH_2Cl_2:MeOH (19:1) to afford the desired product (1.56 g, 95%). Characterize the product by ^1H NMR, ^{13}C NMR, ^{31}P NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 4.
Copper-mediated cross-coupling between an dialkylzinc and an alkyl halide: preparation of 10-nitro-9-phenyldecyl acetate[12]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

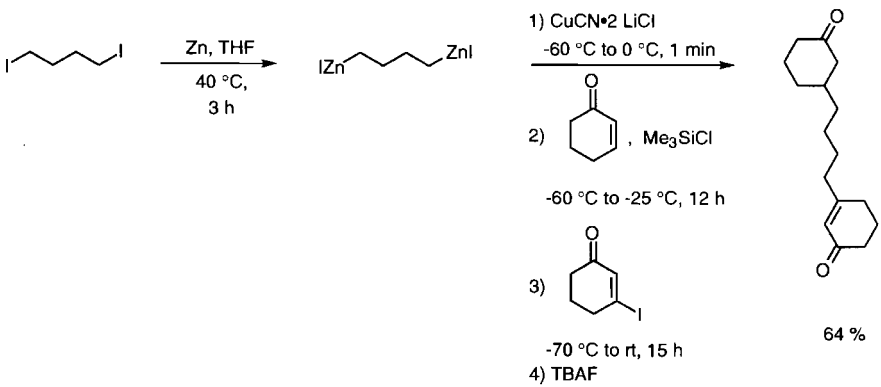
• 4-Iodobutyl acetate (FW 65.4), 2.42 g, 10 mmol	**irritant**
• CuCN (FW 89.6), 5 mg, 0.6 mmol	**highly toxic**
• Diethylzinc (FW 123.5), 2 mL, 20 mmol	**flammable, pyrophoric**
• $Me_2Cu(CN)$ $(MgCl_2)$ solution, 1 M in THF, 5 mL, 5 mmol	**hygroscopic**
• 6-Iodo-1-nitro-2-phenylhexane (FW 333.2), 1 g, 3 mmol	**harmful**
• Dry THF	**irritant, flammable, hygroscopic**
• Dry DMPU	**harmful, irritant**

1. Charge the flame dried and argon flushed Schlenk flask with CuCN, 4-iodobutyl acetate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 50°C with an oil-bath, close the argon inlet, and stir the reaction mixture at 50°C for 5 h.
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50°C, 2 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(4-acetoxybutyl)zinc in THF (5 mL) at rt.
7. Allow the suspension to settle for 3 h at rt.
8. Meanwhile prepare the solution of $Me_2Cu(CN)$ $(MgCl)_2$ in the three-necked flask by mixing MeMgCl (2 equiv) with CuCN (1 equiv) at 0°C. Cool to –50°C.
9. Add the *bis*(4-acetoxybutyl)zinc solution to the $Me_2Cu(CN)$ $(MgCl)_2$ solution. Allow to warm to 0°C, stir for 1 min, and then recool to –78°C.

10. Add DMPU (5 mL), and 6-iodo-1-nitro-2-phenylhexane, and allow the reaction mixture to warm to 0 °C. Stir for 2 h at 0 °C.
11. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (4:1) to afford the desired product (0.8 g, 83%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 5.
Copper catalysed addition of a 1,4-organodizinc reagent to an electrophile: preparation of 4-(3-oxocyclohexyl)-1-(3-oxocyclohex-1-enyl)butane[18]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two three-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

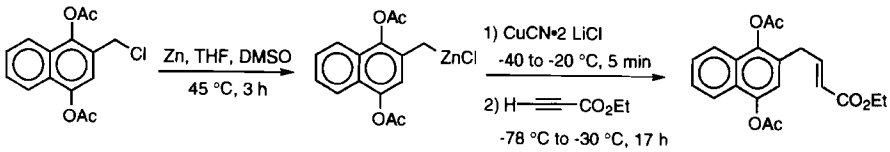
- Zinc dust (FW 65.4), 2.62 g, 40 mmol
- 1,2-Dibromoethane (FW 187.9), 0.38 g, 2 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.22 g, 2 mmol — **flammable, corrosive**
- 1,4-Diiodobutane (FW 309.9), 3.1 g, 10 mmol — **irritant**
- CuCN (FW 89.6), 0.9 g, 10 mmol — **highly toxic**
- LiCl (FW 42.4), 0.84 g, 20 mmol — **irritant, hygroscopic**
- 2-Cyclohexen-1-one (FW 96.1), 0.68 g, 7 mmol
- Me_3SiCl (FW 108.6), 1.62 g, 15 mmol — **flammable, corrosive**
- 3-Iodo-2-cyclohexenone (FW 222), 3.33 g, 15 mmol — **light-sensitive, irritant**
- Bu_4NF solution, 1 M in THF — **hygroscopic**
- Dry THF — **irritant, flammable, hygroscopic**
- Pentane — **flammable**

Protocol 5. *Continued*

1. Weigh the zinc dust into the first three-necked flask, add THF (3 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and heat gently with a heat gun to gently boil the THF. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Add slowly a solution of the 1,4-diiodobutane in THF (10 mL) at such a rate that the reaction temperature remains between 40–45 °C. Warm the reaction mixture to 40 °C and stir for approx. 3 h. Monitor the insertion reaction by performing an iodolysis and a hydrolysis as described in Protocol 1.
5. Cool to rt and stop stirring. Allow the zinc suspension to settle for 30 min.
6. Meanwhile weigh the CuCN and the LiCl into the second three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150 °C for 2 h.
7. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl in dry THF (10 mL) at rt. A slight exothermic reaction is observed and a light yellow/green solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –60 °C.
8. Add the solution of the organodizinc to the CuCN•2LiCl solution. Allow to warm to 0 °C, stir for 1 min, and then recool to –60 °C.
9. Add pentane (10 mL), 2-cyclohexenone, and Me_3SiCl, and allow the reaction mixture to warm to –25 °C. Stir for 12 h at –25 °C.
10. Cool to –70 °C and add 3-iodo-2-cyclohexenone. Allow to warm to rt and stir for 15 h.
11. Work-up as described in Protocol 1 using ether (250 mL). Evaporate the solvents and dissolve the resulting oil in THF (10 mL). Add the Bu_4NF solution (15 mL) and stir for 30 min.
12. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:EtOAc (7:3) to afford the desired product (1.11 g, 64%). Characterize the product by ^1H NMR, ^{13}C NMR, ^{31}P NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 6.
Copper catalysed addition of a functionalized benzylic organometallic to an electrophile: preparation of 2-(3-carbethoxy-2-propenyl)-1,4-diacetoxynaphthalene[14]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



79 %

Equipment

- Two three-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

- Zinc dust (FW 65.4), 2.55 g, 39 mmol
- 1,4-Diacetoxy-2-(chloromethyl)naphthalene (FW 287.7), 3.74 g, 13 mmol
- CuCN (FW 89.6), 1.16 g, 13 mmol **highly toxic**
- LiCl (FW 42.4), 1.1 g, 26 mmol **irritant, hygroscopic**
- Ethyl propiolate (FW 98.1), 1.02 mL, 10 mmol
- Dry THF **irritant, flammable, hygroscopic**
- Dry DMSO

1. Weigh the zinc dust into the first three-necked flask, add THF (3 mL), and flush the flask with argon.
2. Add slowly a solution of the 1,4-diacetoxy-2-(chloromethyl)naphthalene in THF (11 mL) and DMSO (3 mL) at such a rate that the reaction temperature remains between 40–45°C. Stir the reaction mixture at 45°C for 3 h and monitor the insertion reaction by performing an iodolysis and a hydrolysis as described in Protocol 1.
3. Add THF (5 mL) and stop the stirring. Allow the zinc suspension to settle for 30 min.
4. Meanwhile weigh the CuCN and the LiCl into the second three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
5. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl in dry THF (13 mL) at rt. A slight exothermic reaction is observed and a light yellow/green

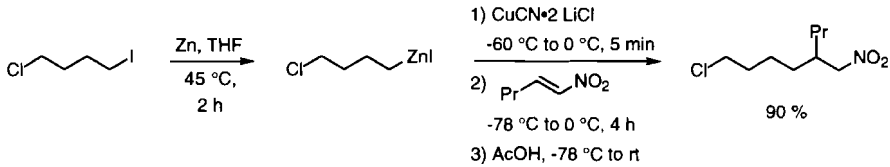
Protocol 6. *Continued*

solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –40 °C.

6. Add the solution of the alkylzinc chloride to the CuCN•2LiCl solution. Allow to warm to –20 °C, stir for 5 min, and cool the resulting light green solution to –78 °C.
7. Add the ethyl propiolate, warm to –50 °C, and stir for 14 h at –50 °C. Allow the reaction mixture to warm to –30 °C. Stir for 3 h.
8. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:EtOAc (3:1) to afford the desired product (2.55 g, 79%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 7.
Copper-mediated conjugate addition of an alkylzinc iodide to a nitro olefin: preparation of 1-chloro-5-(nitromethyl)octane[20]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two three-necked, round-bottomed flasks (25 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

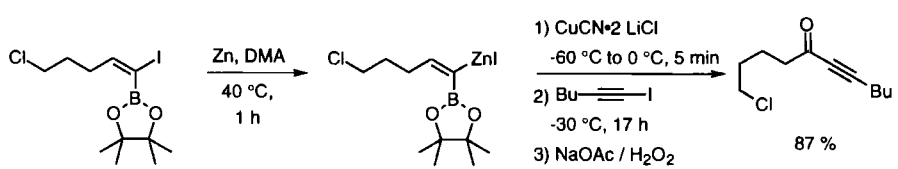
• Zinc dust (FW 65.4), 1.62 g, 25 mmol	
• 1,2-Dibromoethane (FW 187.9), 0.37 g, 2 mmol	**toxic**
• Me_3SiCl (FW 108.6), 0.22 g, 2 mmol	**flammable, corrosive**
• 1-Chloro-4-iodobutane (FW 218.5), 2.47 g, 12 mmol	**irritant**
• CuCN (FW 89.6), 0.9 g, 10 mmol	**highly toxic**
• LiCl (FW 42.4), 0.84 g, 20 mmol	**irritant, hygroscopic**
• 1-Nitropentene (FW 117.1), 0.86 g, 7.5 mmol	**irritant, harmful**
• Acetic acid (FW 60.1), 2 mL, 33 mmol	**corrosive**
• Dry THF	**irritant, flammable, hygroscopic**

1. Weigh the zinc dust into the first three-necked flask, add THF (10 mL), and flush the flask with argon.

2. Add the 1,2-dibromoethane and heat gently with a heat gun to gently boil the THF. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Add slowly the 1-chloro-4-iodobutane at such a rate that the reaction temperature remains between 35–40 °C. Warm the reaction mixture to 45 °C and stir at this temperature for approx. 2 h. Monitor the insertion reaction by performing an iodolysis and a hydrolysis as described in Protocol 1.
5. Cool to rt, add THF (10 mL), and stop stirring. Allow the zinc suspension to settle for 30 min.
6. Meanwhile weigh the CuCN and the LiCl into the second three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150 °C for 2 h.
7. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl in dry THF (10 mL) at rt. A slight exothermic reaction is observed and a light yellow/green solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –60 °C.
8. Add the solution of the alkylzinc iodide to the CuCN•2LiCl solution. Allow to warm to 0 °C, stir for 5 min, and cool the resulting light green solution to –78 °C.
9. Add 1-nitropentene dropwise and then allow the reaction mixture to warm to 0 °C. Stir for 4 h at this temperature.
10. Add THF (5 mL), cool to –78 °C, and add acetic acid (2 mL) in THF (5 mL). Finally warm to rt.
11. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (20:1) to afford the desired product (1.4 g, 90%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 8.
Copper-mediated reaction of a 1,1-zinc, boron alkenyl bimetallic with an electrophile: preparation of 1-chloro-5-oxo-6-undecyne[23]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Protocol 8. *Continued*

Equipment

- Two three-necked, round-bottomed flasks (25 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

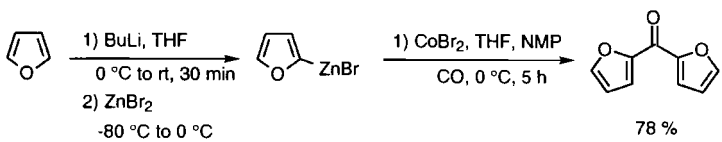
- Zinc dust (FW 65.4), 0.9 g, 13.5 mmol
- 1,2-Dibromoethane (FW 187.9), 0.3 g, 1.5 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.1 g, 1 mmol — **flammable, corrosive**
- (*Z*)-Pinacol 5-chloro-1-iodo-1-pentenylboronate (FW 356.4), 1.92 g, 5.4 mmol
- CuCN (FW 89.6), 0.48 g, 5.4 mmol — **highly toxic**
- LiCl (FW 42.4), 0.46 g, 10.8 mmol — **irritant, hygroscopic**
- 1-Iodohexyne (FW 208), 0.68 g, 3.25 mmol — **irritant**
- NaOAc solution, saturated in water — **corrosive**
- H_2O_2 solution, 35% in water — **corrosive**
- Dry DMA (*N*,*N*-dimethylacetamide) — **harmful, irritant**
- Dry THF — **irritant, flammable, hygroscopic**
- Dry ethanol — **toxic, flammable**

1. Weigh the zinc dust into the first three-necked flask, add DMA (5 mL), and flush the flask with argon.
2. Add the 1,2-dibromoethane and gently heat with a heat gun to 80°C. Allow to cool to rt. Repeat this heating–cooling process four more times.
3. Add Me_3SiCl and stir the reaction mixture for 15 min at rt. The zinc dust is now activated and ready for use.
4. Slowly add a solution of the (*Z*)-pinacol 5-chloro-1-iodo-1-pentenylboronate in DMA (1 mL). Stir the reaction mixture at 40°C for 1 h and monitor the insertion reaction by performing an iodolysis and a hydrolysis as described in Protocol 1.
5. Cool to rt and add THF (10 mL). Stop the stirring and allow the zinc suspension to settle for 1 h.
6. Meanwhile weigh the CuCN and the LiCl into the second three-necked flask (equipped with two glass stoppers, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
7. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl in dry THF (5 mL) at rt. A slight exothermic reaction is observed and a light yellow/green solution is formed. Replace the two glass stoppers by a low temperature thermometer and a septum cap. Cool the solution to –60°C.
8. Add the solution of the bimetallic reagent to the CuCN•2LiCl solution at –60°C. Allow to warm to 0°C, stir for 5 min, and cool the resulting light green solution to –30°C.
9. Add the 1-iodohexyne and stir for 17 h at –30°C.

10. Work-up as described in Protocol 1. Evaporate the solvents and dissolve the residue in EtOH (10 mL) and THF (10 mL). Cool to 0 °C.
11. Add the NaOAc solution (5 mL) and then dropwise H_2O_2 (Caution: exothermic reaction!). Stir for 10 min at rt.
12. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (9:1) to afford the desired product (0.57 g, 87%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 9.
Cobalt-mediated carbonylation of 2-furylzinc bromide: preparation of *bis*(2-furyl)ketone[25]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- One two-necked, round-bottomed flask (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- One three-necked, round-bottomed flask (50 mL) equipped with a gas inlet, a dropping funnel, a gas outlet, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

Materials

- Furan (FW 68.1), 1.7 g, 25 mmol — **harmful, flammable**
- *n*-BuLi solution, 1.6 M in hexane, 12.5 mL, 20 mmol — **flammable**
- Dry zinc(II) bromide (FW 225.2), 4.5 g, 20 mmol — **corrosive**
- Dry cobalt(II) bromide (FW 218.8), 4.38 g, 20 mmol — **harmful, irritant**
- Carbon monoxide — **toxic**
- Dry THF — **irritant, flammable, hygroscopic**
- Dry NMP — **irritant**

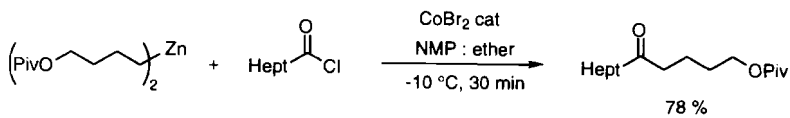
1. Weigh the zinc(II) bromide into the two-necked flask. Dry the salt by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 140 °C for 2 h. Cool to rt, flush with argon, and then dissolve in ether (15 mL).
2. Charge the first flame dried and argon flushed three-necked flask with furan and dissolve in THF (10 mL).
3. Cool to 0 °C (liquid nitrogen/ether bath) and add BuLi dropwise over 5 min.

Protocol 9. *Continued*

4. Stir for 30 min at rt, cool the resulting solution to –80 °C, and then add the zinc(II) bromide solution. Allow to warm up to 0 °C.
5. Meanwhile charge the second three-necked flask with cobalt(II) bromide and dissolve in THF (5 mL) and NMP (15 mL). Cool to 0 °C.
6. Bubble carbon monoxide through the cobalt bromide solution using a pipette and then add the 2-furylzinc bromide solution dropwise with the dropping funnel.
7. Stir for 3 h at 0 °C with continuous bubbling of carbon monoxide through the reaction mixture.
8. Stop the carbon monoxide stream and stir for an additional 2 h.
9. Pour into an Erlenmeyer containing hexanes (200 mL) and stir for 2 h to decompose the intermediate cobalt–carbonyl complexes.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography using hexanes:ether (19:1) to afford the desired product (1.26 g, 78%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 10.
Cobalt catalysed acylation of a primary dialkylzinc: preparation of 5-oxododecyl pivalate[25]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One Schlenk flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

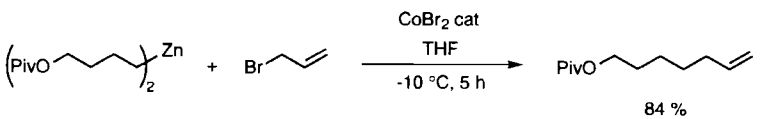
Materials

• 4-Iodobutyl pivalate (FW 284.2), 8.52 g, 30 mmol	**irritant**
• Diethylzinc (FW 123.5), 4.5 mL, 40 mmol	**flammable, pyrophoric**
• CuI (FW 190.4), 60 mg, 0.3 mmol	**toxic**
• Dry cobalt(II) bromide (FW 218.8), 218 mg, 1 mmol	**harmful, irritant**
• Octanoyl chloride (FW 162.7), 1.62 g, 10 mmol	**corrosive**
• Dry ether	**flammable**
• Dry NMP	**irritant**

1. Charge the flame dried and argon flushed Schlenk flask with CuI, 4-iodobutyl pivalate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 55 °C with an oil-bath, close the argon inlet, and stir the reaction mixture at 55 °C for 12 h (e.g. overnight).
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50 °C, 4 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(4-pivaloxybutyl)zinc in ether (10 mL) at rt.
7. Charge the three-necked flask with dry cobalt(II) bromide, NMP (4 mL), and ether (2 mL). Cool to −10 °C.
8. Add octanoyl chloride and then the *bis*(4-pivaloxybutyl)zinc solution (4 mL of the above prepared solution).
9. Stir the resulting blue solution for 30 min at −10 °C.
10. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 19:1) to afford the desired product (2.2 g, 78%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 11.
Cobalt catalysed allylation of a primary dialkylzinc: preparation of 6-heptenyl pivalate[25]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Protocol 11. *Continued*

Equipment

- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles

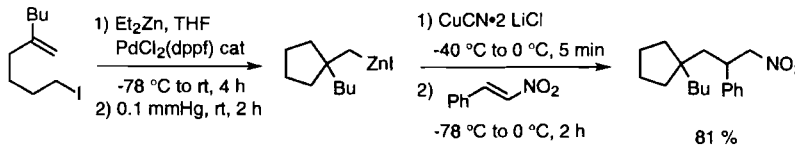
Materials

- *Bis*(4-pivaloxybutyl zinc), 1.5 molar in THF, 6.66 mL, 10 mmol (see Protocol 10, prepare the solution in THF) — **flammable, pyrophoric**
- Dry cobalt(II) bromide (FW 218.8), 218 mg, 1 mmol — **harmful, irritant**
- Allyl bromide (FW 121), 2.42 g, 20 mmol — **toxic, flammable**
- Dry THF — **flammable**

1. Charge the three-necked flask with dry cobalt(II) bromide and THF (5 mL). Cool to –10 °C.
2. Add allyl bromide and the *bis*(4-pivaloxybutyl)zinc solution (see Protocol 10).
3. Stir the resulting solution for 5 h at –10 °C.
4. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 19:1) to afford the desired product (3.32 g, 84%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 12.
Palladium-mediated intramolecular carbozincation: preparation of 1-butyl-1-(3-nitro-2-phenylpropyl)cyclopentane[28]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

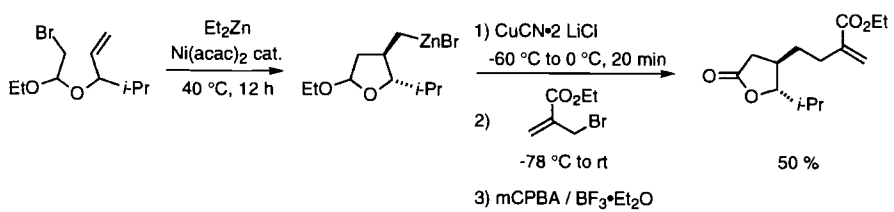
Materials

• $PdCl_2$(dppf) (FW 731.7), 73 mg, 0.1 mmol	**toxic**
• 2-Butyl-6-iodo-1-hexene (FW 266.2), 1.33 mg, 5 mmol	**irritant**
• Diethylzinc (FW 123.5), 1 mL, 10 mmol	**flammable, pyrophoric**
• CuCN (FW 89.6), 0.45 g, 5 mmol	**highly toxic**
• LiCl (FW 42.4), 0.42 g, 10 mmol	**irritant, hygroscopic**
• 2-Nitrostyrene (FW 149.2), 1.12 g, 7.5 mmol	**irritant**
• Dry THF	**irritant, flammable, hygroscopic**

1. Charge the flame dried and argon flushed three-necked flask with $PdCl_2$(dppf) and THF (5 mL), and cool to –78°C.
2. Add 2-butyl-6-iodo-1-hexene and diethylzinc (Caution !). Allow to warm to rt and stir for 4 h.
3. Confirm the alkylzinc iodide formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
4. Remove the solvent and the excess diethylzinc in vacuum (rt, 2 h, *ca.* 0.1 mmHg).
5. Meanwhile, weigh the CuCN and the LiCl into the two-necked flask. Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150°C for 2 h.
6. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl in dry THF (5 mL) at rt. A slight exothermic reaction is observed and a light yellow/green solution is formed.
7. Dissolve the organozinc iodide in THF (5 mL) and cool to –40°C. Add the CuCN•2LiCl solution. Warm to 0°C and stir for 5 min, recool to –78°C.
8. Add a solution of nitrostyrene in THF (3 mL), then slowly warm the reaction mixture to 0°C, and stir for a further 2 h.
9. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 9:1) to afford the desired product (1.16 g, 81%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 13.
Nickel catalysed intramolecular carbozincation: preparation of *trans*-4-(3-carbethoxy-3-butenyl)-4,5-dihydro-(3H)-5-isopropyl-2-furanone[31]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Protocol 13. *Continued*

Equipment

- Three two-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

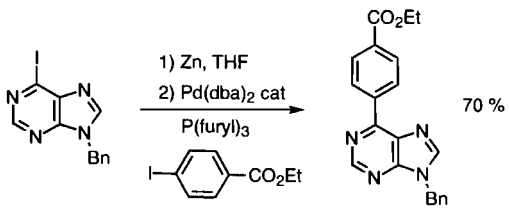
- 1-Bromo-2-ethyoxy-4-isopropyl-3-oxa-5-hexene (FW 251.2), 1.26 g, 5 mmol
- LiI (FW 133.9), 160 mg, 1.25 mmol
- $Ni(acac)_2$ (FW 256.9), 60 mg, 0.25 mmol — **harmful**
- Diethylzinc (FW 123.5), 1 mL, 10 mmol — **flammable, pyrophoric**
- CuCN (FW 89.6), 1.33 g, 15 mmol — **highly toxic**
- LiCl (FW 42.4), 1.26 g, 30 mmol — **irritant, hygroscopic**
- Ethyl (2-bromomethyl)acrylate (FW 193), 2.95 g, 15 mmol — **toxic**
- *m*-Chloroperbenzoic acid (FW 172.6, *ca.* 50%), 1.64 g, 9.6 mmol — **corrosive**
- Boron trifluoride etherate (FW 141.9), 0.2 mL, 1.6 mmol — **flammable, corrosive**
- Magnesium sulfate (FW 120), 2 g, 16.6 mmol
- Dry THF — **irritant, flammable, hygroscopic**
- Dry CH_2Cl_2 — **harmful**

1. Charge the first flame dried and argon flushed two-necked flask with 1-bromo-2-ethyloxy-4-isopropyl-3-oxa-5-hexene, lithium iodide, $Ni(acac)_2$, and THF (5 mL). Cool the suspension to –78 °C.
2. Add diethylzinc (Caution!). Replace the septum cap with a glass stopper.
3. Allow the reaction mixture warm to rt, then heat to 40 °C, and stir for 12 h.
4. Confirm the formation of the cyclized zinc species by performing an iodolysis and a hydrolysis as described in Protocol 1.
5. Meanwhile, weigh the CuCN and the LiCl into the second two-necked flask (equipped with a glass stopper, a magnetic stirring bar, and an argon inlet). Dry the salts by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 150 °C for 2 h.
6. Cool to rt, flush with argon, and dissolve the CuCN•2LiCl at rt in dry THF (15 mL). A slight exothermic reaction is observed and a light yellow/green solution is formed.
7. Transfer the solution of the organozinc into the three-necked flask and cool to –60 °C. Add the CuCN•2LiCl solution and warm to 0 °C. Stir for 20 min at 0 °C.
8. Cool to –78 °C and add ethyl (2-bromomethyl)acrylate. Allow to warm to rt and stir for a further 5 min. Work-up as described in Protocol 1. Evaporate the solvents and dissolve the resulting tetrahydrofuran intermediate in CH_2Cl_2 (3 mL).
9. Weigh the *m*-chloroperbenzoic acid into the third two-necked flask. Add CH_2Cl_2 (10 mL), $MgSO_4$ (2 g), and stir for 15 min.

10. After filtration, add slowly boron trifluoride etherate, and then the solution of the tetrahydrofuran intermediate in CH_2Cl_2 (3 mL). Stir for 1 h.
11. Dilute with ether (30 mL), wash successively with saturated aqueous sodium thiosulfate solution (2 × 20 mL), saturated aqueous potassium carbonate solution (10 mL), and brine (2 × 20 mL). Dry over $MgSO_4$, filter, and concentrate under reduced pressure. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 4:1) to afford the desired product (0.63 g, 50% overall). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 14.
Palladium catalysed coupling reaction of a heteroaromatic zinc compound with a functionalized aryl iodide: preparation of *N*-benzyl-6-(4-ethylcarboxyphenyl)-purine[33]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, internal thermometer, and a magnetic stirring bar
- Argon gas supply and inlet
- One two-necked, round-bottomed flask (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Dry, gas-tight syringes and steel needles

Materials

- Zinc dust (FW 65.4), 0.85 g, 13 mmol
- 1,2-Dibromoethane (FW 187.9), 0.15 g, 0.8 mmol — **toxic**
- Me_3SiCl (FW 108.6), 0.1 g, 0.92 mmol — **flammable, corrosive**
- *N*-Benzyl-6-iodopurine (FW 336.1), 0.75 g, 2.2 mmol — **irritant, toxic**
- $Pd(dba)_2$ (FW 574.2), 15 mg, 0.026 mmol — **toxic**
- Tri(2-furyl)phosphine (FW 232.2), 28 mg, 0.12 mmol — **irritant**
- Ethyl 4-iodobenzoate (FW 276.1), 0.95 g, 3.4 mmol — **irritant**
- Dry THF — **irritant, flammable, hygroscopic**
- CH_2Cl_2 — **harmful**

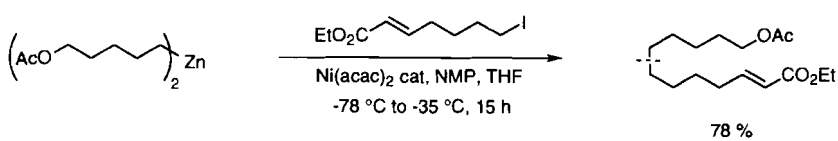
1. Weigh zinc dust into the flame dried and argon flushed three-necked flask (50 mL) and add THF (3 mL).

Protocol 13. *Continued*

2. Add 1,2-dibromoethane, warm with a heat gun to gently boil the THF. Cool to rt and repeat this heating–cooling process two more times.
3. Add Me_3SiCl dropwise and then stir for 15 min. The zinc dust is now activated and ready for use.
4. Add a solution of *N*-benzyl-6-iodopurine in THF (3 mL).
5. Stir for 4 h at rt. The progress of the zinc insertion may be monitored by taking a small aliquot of the reaction mixture and quenching of this aliquot with saturated aqueous ammonium chloride. TLC (ether) shows the protonated product at R_f = 0.1. Upon complete formation of the zinc species, stop stirring and allow the excess zinc dust to settle.
6. Meanwhile charge the flame dried and argon flushed two-necked flask (25 mL) with $Pd(dba)_2$ and tri(2-furyl)phosphine. Add THF (2 mL) and stir until the red colour is discharged (10 min) indicating the formation of the catalyst.
7. Add slowly a solution of ethyl 4-iodobenzoate in THF (2 mL) to the catalyst and then the red coloured solution of the zinc compound. Wash the excess of zinc dust with THF (2 mL) and add the resulting solution to the reaction mixture.
8. Heat the reaction mixture to 65–70°C and stir for 5 h at this temperature.
9. Cool to rt and quench with saturated aqueous NH_4Cl. Extract the aqueous phase with CH_2Cl_2 (2 × 50 mL), combine the organic extracts, dry, and evaporate the solvents at reduced pressure to give a solid.
10. Purify the crude residue by chromatography (hexanes:ether, 5:1 to 1:1) to afford the desired product (0.54 g, 70%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 15.
Nickel catalysed cross-coupling of a dialkylzinc with an alkyl iodide: preparation of (*E*)-ethyl 12-acetoxy-2-dodecenoate[34]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



78 %

Equipment

- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

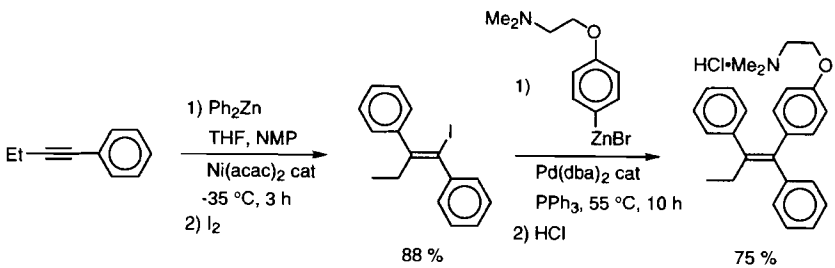
Materials

- 5-Iodopentyl acetate (FW 256.1), 6.14 g, 24 mmol — **irritant**
- Diethylzinc (FW 123.5), 3.5 mL, 35 mmol — **flammable, pyrophoric**
- CuI (FW 190.4), 4 mg, 0.02 mmol — **toxic**
- $Ni(acac)_2$ (FW 256.9), 116 mg, 0.45 mmol — **harmful**
- (*E*)-Ethyl 7-iodo-2-heptenoate (FW 282.1), 1.69 g, 6 mmol — **irritant**
- Dry THF — **irritant, flammable, hygroscopic**
- Dry NMP — **irritant**

1. Charge the flame dried and argon flushed Schlenk flask with CuI, 5-iodopentyl acetate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper.
3. Slowly heat the Schlenk flask to 50 °C with an oil-bath, close the argon inlet, and stir the reaction mixture at 50 °C for 8 h (e.g. overnight).
4. Remove the ethyl iodide formed and the excess diethylzinc in vacuum (50 °C, 2 h, *ca.* 0.1 mmHg).
5. Confirm the dialkylzinc formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
6. Dissolve the resulting oil of *bis*(5-acetoxypentyl)zinc in THF (2 mL) at rt.
7. Charge the three-necked flask with $Ni(acac)_2$, NMP (1.5 mL), and THF (2.5 mL), and cool to −40 °C.
8. Add (*E*)-ethyl 7-iodo-2-heptenoate. Cool to −78 °C.
9. Slowly add the solution of *bis*(5-acetoxypentyl)zinc. Allow the reaction mixture to warm to −35 °C and stir for 15 h at this temperature.
10. Carefully add dropwise a saturated aqueous NH_4Cl solution (10 mL) to quench the reaction.
11. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 19:1 to 5:1) to afford the desired product (1.33 g, 78%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 16.
Nickel catalysed carbozincation and palladium catalysed cross-coupling: preparation of (*Z*)-Tamoxifen[35]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- Three two-necked, round-bottomed flasks (25 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- One dropping funnel (25 mL)
- Argon gas supply and inlet
- Two three-necked, round-bottomed flasks (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar
- Dry, gas-tight syringes and steel needles

Materials

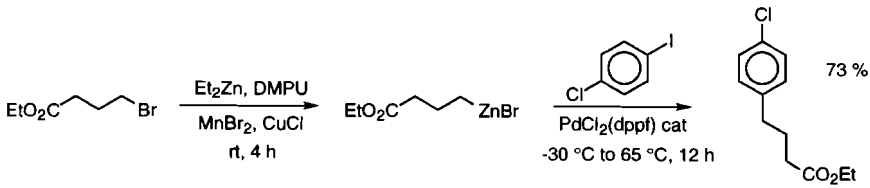
- $Ni(acac)_2$ (FW 256.9), 0.32 g, 1.25 mmol — **harmful**
- 1-Phenyl-1-butyne (FW 130.2), 0.65 g, 5 mmol — **harmful**
- Diphenylzinc (FW 219.4), 2.19 g, 10 mmol — **flammable**
- Iodine (FW 253.8), 15.2 g, 60 mmol — **corrosive, harmful**
- Dry zinc(II) bromide (FW 225.2), 1.08 g, 4.8 mmol — **corrosive**
- 1-Iodo-4-(dimethylamino)ethoxybenzene (FW 290.9), 4.39 g, 4.8 mmol — **irritant**
- $Pd(dba)_2$ (FW 574.2), 92 mg, 0.16 mmol — **toxic**
- Triphenylphosphine (FW 261.9), 0.17 g, 0.64 mmol — **irritant**
- *n*-BuLi solution, 1.38 M in hexane, 3.6 mL, 4.96 mmol — **flammable**
- HCl solution, saturated in ether, 20 mL — **corrosive, flammable, hygroscopic**
- $Na_2S_2O_3$ solution, saturated in water, 100 mL
- Dry THF — **irritant, flammable, hygroscopic**
- Dry ether — **flammable**
- Dry NMP — **irritant**

1. Weigh the $Ni(acac)_2$ into a flame dried and argon flushed three-necked flask and dissolve it in THF (3.75 mL) and NMP (1.25 mL).
2. Cool to –40 °C and add 1-phenyl-1-butyne.
3. Cool to –78 °C and add diphenylzinc in ether (5 mL). Allow to warm to –35 °C and stir for 3 h.

4. Meanwhile, weigh the iodine into a flame dried and argon flushed two-necked flask and dissolve in THF (10 mL).
5. Cool the zinc compound to –78 °C and slowly add the solution of iodine using a dropping funnel.
6. Allow the reaction mixture to warm to –10 °C and pour into an Erlenmeyer containing an aqueous $Na_2S_2O_3$ solution (100 mL).
7. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes) to afford the desired product (1.47 g, 88%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.
8. Weigh the zinc(II) bromide into the two-necked flask. Dry the salt by connecting to the vacuum (*ca.* 0.1 mmHg) and heating with an oil-bath to 140 °C for 2 h. Cool to rt, flush with argon, and dissolve in ether (4 mL).
9. Charge a flame dried and argon flushed three-necked flask with 1-iodo-4-(dimethylamino)ethoxybenzene and THF (5 mL), and cool to –78 °C.
10. Add dropwise *n*-BuLi solution to the aryl iodide solution and stir for 15 min at –78 °C.
11. Warm to –40 °C and add the zinc(II) bromide solution. Warm to 0 °C, stir for 1 min, and then cool to –25 °C.
12. Meanwhile, charge a two-necked flask with (*Z*)-1-iodo-1,2-diphenyl-1-butene, $Pd(dba)_2$, and triphenylphosphine, and dissolve in THF (5 mL).
13. Add the catalyst solution to the arylzinc bromide solution at –25 °C. Allow to warm to rt, then heat the reaction mixture at 55 °C for 10 h.
14. Work-up as described in Protocol 1. Evaporate the solvents and dissolve the residue in ether. Add HCl solution (20 mL) and stir for 5 min at rt.
15. Evaporate the solvents and purify the crude residue obtained after evaporation of the solvent by recrystallization from hexanes:EtOAc (1:1) to afford the desired product (1.22 g, 75%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

Protocol 17.
Palladium catalysed cross-coupling of an alkylzinc bromide with an aryl iodide: preparation of ethyl 4-(*p*-chlorophenyl)butanoate[43]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. For handling diethylzinc wear a long laboratory coat, leather gloves, and a helmet with a face protection shield.



Equipment

- One two-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a septum cap, and a magnetic stirring bar
- Argon gas supply and inlet
- Dry, gas-tight syringes and steel needles
- One three-necked, round-bottomed flask (50 mL) equipped with an argon inlet, a low temperature thermometer, a septum cap, and a magnetic stirring bar

Materials

- $MnBr_2$ (FW 214.7), 64 mg, 0.3 mmol
- CuCl (FW 99), 17 mg, 0.2 mmol — **harmful**
- Ethyl 4-bromobutyrate (FW 195.1), 1.17 g, 6 mmol — **harmful**
- Diethylzinc (FW 123.5), 0.54 mL, 5.4 mmol — **flammable, pyrophoric**
- $PdCl_2$(dppf) (FW 731.7), 185 mg, 0.2 mmol — **toxic**
- 4-Chloroiodobenzene (FW 238.5), 1.19 g, 5 mmol — **irritant**
- HCl solution, 2 M in water — **corrosive**
- Dry THF — **irritant, flammable, hygroscopic**
- Dry DMPU — **harmful, irritant**

1. Charge the flame dried and argon flushed three-necked flask with $MnBr_2$, CuCl, DMPU (5 mL), ethyl 4-bromobutyrate, and diethylzinc (Caution!).
2. Replace the septum cap with a glass stopper. Stir for 4 h at rt.
3. Confirm the alkylzinc bromide formation by performing an iodolysis and a hydrolysis as described in Protocol 1.
4. Meanwhile, weigh the $PdCl_2$(dppf) into the two-necked flask and flush with argon. Add 4-chloroiodobenzene and dissolve in THF (5 mL).
5. Cool the alkylzinc bromide solution to –30 °C and then slowly add the above prepared $PdCl_2$(dppf) solution.
6. Allow the reaction mixture to warm to rt and stir for 30 min. Then warm to 65 °C and stir at this temperature overnight.

7. Cool to rt and carefully add dropwise an aqueous 2 N HCl solution (20 mL).
8. Work-up as described in Protocol 1. Purify the crude residue obtained after evaporation of the solvent by flash chromatography (hexanes:ether, 10:1) to afford the desired product (0.82 g, 73%). Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

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11

Palladium and nickel catalysed reactions of organozinc compounds

EI-ICHI NEGISHI

1. Introduction

Although organozinc compounds represent some of the earliest examples of organometallic reagents,[1] their use in organic synthesis had been rather limited until recently. This largely stemmed from the fact that their reactivity as nucleophiles towards various common electrophiles, including carbon electrophiles, such as organic halides, carbonyl compounds, and epoxides, is generally much lower than that of the corresponding Grignard and organolithium reagents.[2] However, over the last few decades the use of transition metal catalysts, especially those containing Pd and Ni, has converted otherwise unreactive or sluggishly reactive organozincs into highly reactive reagents for the formation of carbon–carbon bonds. It is equally significant to note that the low nucleophilicity of organozincs used in conjunction with Pd and Ni catalysts, which are generally even more tolerant of various carbon electrophiles, makes Pd or Ni catalysed organozinc reactions chemoselective in the conventional sense.

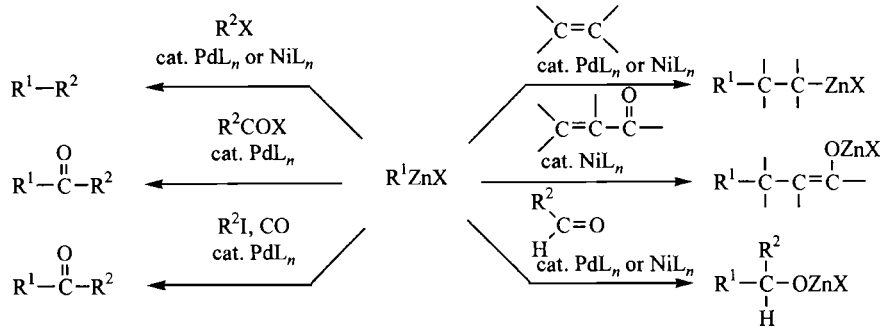
This chapter discusses:

(a) Cross-coupling reactions, including acylation to give ketones.

(b) Conjugate addition and other addition reactions with alkenes and alkynes.

(c) Carbonyl addition reactions of organozincs which are catalysed by Pd or Ni complexes.

These are summarized in Scheme 11.1. Due to space limitations, this is not intended to be a comprehensive review of the topic, and the readers are referred to some recent extensive reviews[3–5] for additional information.



Scheme 11.1

2. Palladium and nickel catalysed cross-coupling reactions of organozincs

2.1 Overview

The Ni catalysed cross-coupling reaction of Grignard reagents was discovered in 1972.[6] Several years later, the Pd catalysed cross-coupling reactions of Grignard reagent,[7] organoalanes,[8] and organozincs[9] were discovered independently by a few groups. It was also found in early studies[7,10] that organolithiums and other organoalkali metals were generally unsatisfactory, while metals of intermediate electronegativity, such as Al, Zr, and Zn in particular, were satisfactory. Although intrinsically less reactive, B and Sn were also shown to be effective in the Pd catalysed alkynyl–aryl cross-coupling.[10] The effectiveness of B[11] and Sn[12] have since been significantly elevated through the development of various improved procedures. More recently, even Si[13] has been shown to participate in the Pd catalysed cross-coupling. Today, synthetic organic chemists should consider at least seven metals, i.e. Mg, Zn, B, Al, Sn, Zr, and Cu, to be used in the Pd or Ni catalysed cross-coupling. It is also reasonable to state that Zn, B, and Sn are currently the three most widely used metals in the Pd catalysed cross-coupling, even though toxicity, general difficulty in completely removing organostannane by-products, and comparatively low intrinsic reactivity associated with the organostannane cross-coupling present some serious problems to be solved. In general, the intrinsic reactivity of organozincs is considerably higher than that of the corresponding organoboron derivatives, and the overall scope of the Pd catalysed organozinc cross-coupling appears to be broader. On the other hand, the greater stability of organoboron derivatives towards air and moisture and their lower nucleophilicity towards common organic electrophiles represent some of the advantages that the B-based cross-coupling offers.

In comparison with the Ni catalysed cross-coupling[14] as well as the Cu promoted or Cu catalysed cross-coupling,[15] the Pd catalysed cross-coupling[16] has exhibited a broader scope with respect to the two carbon groups to be coupled,

and it is more generally applicable within a given type of cross-coupling. Thus, Ni catalysts are generally not well suited for cross-coupling involving alkynes and conjugated dienes, because they tend to induce oligomerization and polymerization of these classes of organic compounds. One of the major difficulties associated with the Cu-based cross-coupling methodology is the thermal instability of organocoppers. Indeed, the applicability of the Cu promoted or Cu catalysed cross-coupling is strongly substrate-dependent. It is striking that many cross-coupling reactions of organocoppers can be catalysed by Pd complexes, as in the Sonogashira alkyne synthesis[17] and alkene syntheses involving alkenylcoppers.[18] There are some disadvantages associated with Pd. Its relatively high cost is one, and its generally lower reactivity towards organic bromides and chlorides as compared with that of Cu and even Ni is another.

2.2 Palladium or nickel catalysed cross-coupling between unsaturated organozincs and unsaturated organic electrophiles

Catalysis by palladium has been shown to be effective for all nine classes of cross-coupling reactions shown in Table 11.1, although cross-homo scrambling leading to the formation of alkyne homodimers is often problematical in the alkynyl–alkynyl coupling. On the other hand, the Ni catalysed version is satisfactory mainly in the aryl–aryl, aryl–alkenyl, and alkenyl–aryl coupling. Aryl–alkenyl coupling refers to the coupling reaction between arylmetals and alkenyl electrophiles, while alkenyl–aryl coupling refers to that between alkenylmetals and aryl electrophiles.

Table 11.1 Satisfactory metals in cross-coupling between two unsaturated carbon groups

$$R^1ZnY + R^2X \xrightarrow{\text{cat. } PdL_n \text{ or } NiL_n} R^1R^2 + ZnXY$$

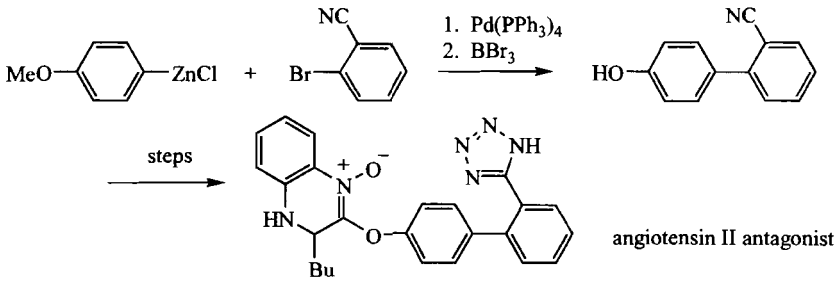
X = I, Br, OTf, etc. Y = C or halogen group.

R^2 of R^2X / R^1 of R^1ZnY	Aryl	Alkenyl	Alkynyl
Aryl	Ni or Pd	Ni or Pd	Pd
Alkenyl	Ni or Pd	Pd	Pd
Alkynyl	Pd	Pd	Pd

2.2.1 Aryl–aryl coupling

Various Pd or Ni catalysed procedures for aryl–aryl coupling have been developed,[10–12,14,16] but those involving organozincs[19] appear to be among the

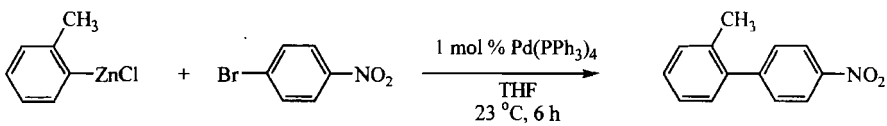
most favourable and operationally simple (Protocol 1) and have been applied to the synthesis of a number of drugs, such as angiotensin II antagonist[20] (Scheme 11.2), and polymeric materials.



Scheme 11.2

Protocol 1.
Palladium catalysed aryl–aryl coupling: preparation of 2-methyl-4'-nitrobiphenyl[19]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Magnetic stirrer
- Two- or three-necked round-bottomed flask (500 mL)
- Rubber septum
- Tubing adapter
- Magnetic stirring bar
- Dropping funnel (200 mL)
- Mercury bubbler (or an equivalent outlet)
- Glass syringes of appropriate sizes
- Wide-stemmed funnel
- Nitrogen or argon line
- Water aspirator
- Six inch medium gauge needles
- Bath for cooling with dry ice:isopropanol or water
- Other usual equipment for work-up and isolation, such as rotary evaporator and separatory funnel

Materials

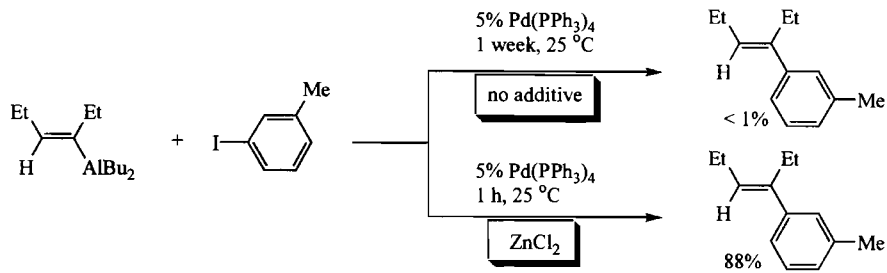
- Dry ice
- Isopropanol
- *o*-Iodotolutene (FW 218.04), 98%, 26.2 g, 120 mmol
- Dry diethyl ether, 360 mL — **flammable**
- *t*-Butyllithium, 1.56 M in hexane, 154 mL, 240 mmol — **highly pyrophoric! air- and moisture-sensitive**
- Dry tetrahydrofuran, 240 mL — **flammable, moisture-sensitive**
- Dry zinc chloride (FW 136.28), 16.3 g, 120 mmol — **hygroscopic**
- $Pd(PPh_3)_4$ (FW 1155.58), 99%, 1.16 g, 1 mmol

- 1-Bromo-4-nitrobenzene (FW 202.01), 20.2 g, 100 mmol
- 3 N hydrochloric acid, 300 mL
- Saturated, aqueous sodium bicarbonate
- Anhydrous magnesium sulfate
- Hexane, 350 mL
- Ethanol, 125 mL

1. Dry glassware, syringe needles, and a stirring bar in a drying oven (≥ 120°C) for several hours before use.
2. Assemble the reaction system while the glassware is still hot, and flush the system with nitrogen or argon.
3. Place the system under a static pressure (back pressure) of nitrogen or argon and immerse it in a dry ice-bath.
4. Introduce *o*-iodotoluene (26.2 g, 120 mmol) and ether (60 mL) using syringes.
5. Add slowly and carefully *t*-butyllithium (highly pyrophoric!) from a dropping funnel, and stir the mixture for 1 h at –78°C.
6. Warm the mixture to room temperature, and concentrate it using a water aspirator until most of the volatile solvents are evaporated.
7. Dissolve dry zinc chloride (16.3 g, 120 mmol) in dry tetrahydrofuran (200 mL), add slowly the resultant solution while cooling the reaction flask with an ice-bath, and stir the mixture for 1 h at room temperature.
8. Add 1-bromo-4-nitrobenzene (20.2 g, 100 mmol) and tetrahydrofuran (40 mL).
9. Replace momentarily the septum inlet with a wide-stemmed funnel under a slightly positive pressure of nitrogen or argon and introduce $Pd(PPh_3)_4$ (1.16 g, 1 mmol).
10. Stir the mixture for 6 h at room temperature and monitor the progress of the reaction by TLC or GC. The reaction time should be accordingly adjusted.
11. Pour the reaction mixture into a mixture of ether (100 mL) and ice-cold 3 N HCl (300 mL).
12. Separate the organic layer and extract the aqueous layer with ether (2 × 100 mL).
13. Wash the combined organic layer with saturated aqueous sodium bicarbonate and dry over magnesium sulfate.
14. Filter off the drying agent, and evaporate the solvents to obtain a light brown solid.
15. Recrystallize from hexane to obtain 16 and 2.4 g of yellow crystals in two crops, which were further recrystallized from ethanol (two crops) to obtain 16.5 g (78% yield) of 2-methyl-4'-nitrobiphenyl (m.p. 99–101°C) which displayed appropriate spectral and analytical data.

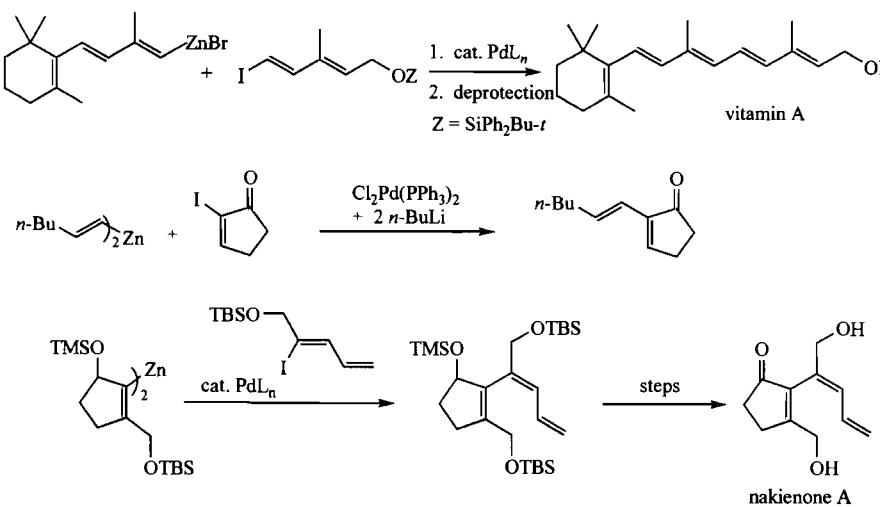
2.2.2 Alkenyl–aryl, aryl–alkenyl, and alkenyl–alkenyl coupling

The Pd or Ni catalysed cross-coupling with alkenylmetals can be most conveniently achieved using alkenylalanes obtainable via hydroalumination[8,20] and carboalumination,[21] alkenylzirconiums obtainable via hydrozirconation,[22] and alkenylboranes obtainable via hydroboration[11] of appropriate alkynes. However, the highest rates of cross-coupling are usually observed with alkenylzincs.[23] It is noteworthy that zinc chloride or bromide can serve as the second catalyst in the reactions of organometals containing other metals, such as Al, Cu, and Zr[21] (Scheme 11.3).



Scheme 11.3

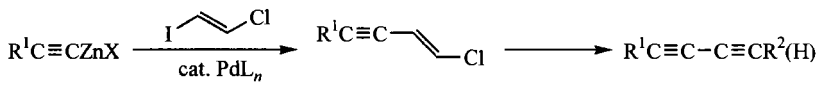
The superior reactivity of alkenylzincs has been exploited in more difficult cases of alkenyl–alkenyl coupling, such as the syntheses of vitamin A[24] and nakienone A,[25] as well as α-alkenylation of enones[26] (Scheme 11.4).



Scheme 11.4

2.2.3 Cross-coupling involving alkynes

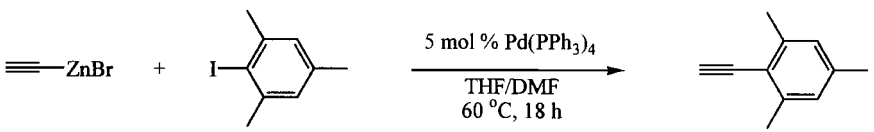
As already mentioned earlier, Pd catalysts are generally far superior to Ni counterparts in cross-coupling reactions involving alkynes. Although the Sonogashira protocol[17] involving the use of CuI and a base, such as Et_2NH, appears to be currently most widely used, its scope is more limited in some respects than that of the alkynylzinc reaction. Specifically, the latter is readily applicable to the direct synthesis of terminal alkynes without protection–deprotection (Protocol 2),[27] while the former is not. Furthermore, the Sonogashira coupling[17] tends to fail in cases where the alkynyl group is conjugated with electron withdrawing groups, while the Zn–Pd procedure can readily overcome such a difficulty.[28] Due to the relatively high acidity or electronegativity of alkynyl groups, a mixture of an organometal and an alkynyl halide has a high propensity for undergoing metal–halogen exchange leading to cross-homo scrambling. It is therefore advisable to use alkynylmetals rather than alkynyl halides. This option, however, is not available in the alkynyl–alkynyl coupling. Despite a limited number of selective alkynyl–alkynyl coupling reactions,[29] the development of generally satisfactory Pd catalysed procedures largely remains to be developed. In cases where a high selectivity is critically important, an indirect route involving Pd catalysed reaction of alkynylzincs with 1,2-dihaloethenes, e.g. (*E*)-ICH=CHCl,[30] should be considered. (Scheme 11.5).



Scheme 11.5

Protocol 2.
Palladium catalysed alkynyl–aryl coupling: preparation of mesitylacetylene[27]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Magnetic stirrer
- Two- or three-necked round-bottomed flask (50–100 mL)
- Rubber septum
- Tubing adapter
- Magnetic stirring bar
- Mercury bubbler (or an equivalent outlet)
- Other usual equipment for work-up and isolation, such as rotary evaporator and separatory funnel

Protocol 2. *Continued*

- Glass syringes of appropriate sizes
- Nitrogen or argon line
- Six inch medium gauge needles
- Bath for cooling with ice-water

Materials

- Ice
- Ethynylmagnesium bromide, 0.5 M in THF, 6 mL, 3 mmol — **air- and moisture-sensitive**
- Dry zinc bromide (FW 225.19), 657 mg, 3 mmol — **hygroscopic**
- Iodomesitylene[a] (FW 246.08), 492 mg, 2 mmol
- $Pd(PPh_3)_4$ (FW 1155.58), 115 mg, 0.1 mmol
- Dry *N,N*-dimethylformamide (FW 73.1), 439 mg, 6 mmol — **hygroscopic**
- Brine
- Anhydrous magnesium sulfate
- Ether, 40 mL — **flammable**
- Dry tetrahydrofuran, 14 mL — **flammable, moisture-sensitive**
- Hexane, 200 mL — **flammable**
- Ethyl acetate, 10 mL — **flammable**

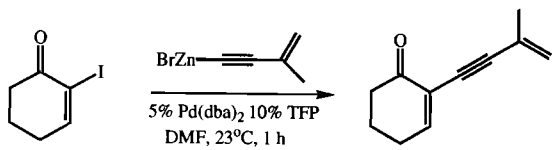
1. Dry glassware, syringe needles, and a stirring bar in a drying oven (≥ 120°C) for several hours before use.
2. Assemble the reaction system while the glassware is still hot, and flush the system with nitrogen or argon.
3. Place the system under a static pressure (back pressure) of nitrogen or argon.
4. Introduce ethynylmagnesium bromide (6 mL of 0.5 M solution in THF, 3 mmol) using a syringe.
5. Dissolve dry zinc bromide (675 mg, 3 mmol) in dry tetrahydrofuran (9 mL), add slowly the resultant solution while cooling the reaction flask with an ice-bath, and stir the mixture for 0.5 h at room temperature.
6. Add iodomesitylene (492 mg, 2 mmol), tetrahydrofuran (5 mL), and *N,N*-dimethylformamide (439 mg, 6 mmol).
7. Remove momentarily the septum under a slightly positive pressure of nitrogen or argon and introduce $Pd(PPh_3)_4$ (115 mg, 0.1 mmol).
8. Stir the mixture for 18 h at 60°C and monitor the progress of the reaction by TLC or GC. The reaction time should be accordingly adjusted.
9. Pour the reaction mixture into a mixture of ether (20 mL) and brine (20 mL).
10. Separate the organic layer and extract the aqueous layer with two 10 mL portions of ether.
11. Dry the combined organic layer over magnesium sulfate.
12. Filter off the drying agent, and evaporate the solvents.
13. Purify by column chromatography (silica gel 230–400, 5% ethyl acetate: hexane) to obtain 195 mg (68% yield) of mesitylacetylene which displayed appropriate spectral and analytical data.

[a] Iodomesitylene was prepared from bromomesitylene by lithiation followed by iodinolysis.

More recently, previously difficult α-alkynylation of α-iodoenones has been achieved through modification of the Sonagashira coupling[31] and the Zn–Pd procedure.[32] While both procedures have provided satisfactory results, comparison of the results indicate the significantly higher reactivity of alkynylzincs.

Protocol 3.
Palladium catalysed α-substitution of α-iodoenone via alkynyl–alkenyl coupling: preparation of 2-(3-methyl-3-buten-1-ynyl)-2-cyclohexen-1-one[32]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



TFP = tris(2-furyl)phosphine

Equipment

- Two magnetic stirrers
- Two two- or three-necked round-bottomed flasks (25–50 mL)
- Rubber septa
- Two tubing adapters
- Two magnetic stirring bars
- Two mercury bubblers (or an equivalent outlet)
- Glass syringes of appropriate sizes
- Nitrogen or argon line
- Water aspirator
- Six inch medium gauge needles
- Long wide gauge double-ended needle
- Bath for cooling with dry ice:isopropanol
- Other usual equipment for work-up and isolation, such as rotary evaporator and separatory funnel

Materials

- Dry ice
- Isopropanol
- 2-iodo-2-cyclohexen-1-one[33] (FW 222.02), 0.666 g, 3 mmol
- *n*-butyllithium, 2.5 M in hexanes, 1.56 mL, 3.9 mmol — **highly pyrophoric! air- and moisture-sensitive**
- Dry tetrahydrofuran, 5 mL — **flammable, moisture-sensitive**
- Dry dimethylformamide, 10 mL — **moisture-sensitive**
- Anhydrous zinc bromide (FW 225.19), 0.88 g, 0.39 mmol — **hygroscopic**
- $Pd(dba)_2$ (FW 574), 86 mg, 0.15 mmol
- Tris(2-furyl)phosphine (FW 232.18), 70 mg, 0.3 mmol
- 2-methyl-1-buten-3-yne (FW 66.1), 0.27 g, 0.38 mL, 4 mmol — **flammable**
- Saturated aqueous ammonium chloride
- Anhydrous magnesium sulfate
- Ether — **flammable**

For setting-up the reactor system, follow Protocol 1, steps 1–3.

1. Introduce 2-methyl-1-buten-yne (0.27 g, 0.38 mL, 4 mmol) and tetrahydrofuran (5 mL) with syringes.

Protocol 3. *Continued*

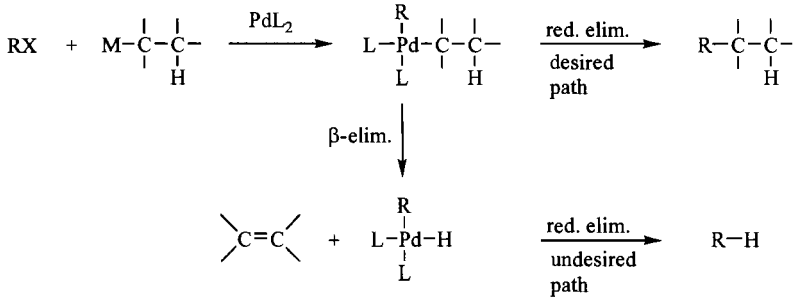
2. Place the system in a dry ice:isopropanol bath, add *n*-butyllithium (3.9 mmol, 1.56 mL) dropwise using a syringe, and stir the mixture for 10 min at –78°C.
3. Dissolve zinc bromide (0.88 g, 3.9 mmol) in dry tetrahydrofuran (5 mL) and transfer it to the organolithium solution prepared above.
4. Warm the mixture to 23°C and stir it for 30 min.
5. Attach the system to water aspirator and concentrate the mixture until most of the volatile solvents are evaporated.
6. Add dry dimethylformamide (5 mL) using a syringe to dissolve the mixture.
7. Place in another flask $Pd(dba)_2$ (86 mg, 0.15 mmol), tris(2-furyl)phosphine (70 mg, 0.3 mol), and dry dimethylformamide (5 mL). Stir the mixture until the dark solution turns clear.
8. Add 2-iodocyclohexen-1-one (0.666 g, 3 mmol) and then the organozinc solution prepared above via cannula.
9. Stir the reaction mixture at 23°C for 1 h, dilute with ether, and quench with saturated aqueous ammonium chloride.
10. Extract the aqueous layer with ether (three times), wash the combined organic layer with water and brine, dry it over anhydrous magnesium sulfate, and concentrate using a rotary evaporator.
11. Purify crude product by flash column chromatography (silica gel 230–400 mesh, 1:20, ethyl acetate:hexane) to obtain 0.42 g (87%) of the desired product which displayed appropriate spectral data.

2.3 Palladium or nickel catalysed cross-coupling involving alkyl, allyl, propargyl, and benzyl groups

2.3.1 Palladium or nickel catalysed alkylation

Alkyl halides other than aryl and vinyl halides do not readily undergo oxidative addition with Pd and must, in general, first be converted to alkylmetals. In this connection, however, a recent report on the Ni catalysed selective alkyl–alkyl cross-coupling with $Ni(acac)_2$ and LiI in THF represents a significant breakthrough.[34] In cases where the alkyl group contains a β-H atom, reduction of the organic halide via β-dehydropalladation reductive elimination can be a serious side-reaction (Scheme 11.6).

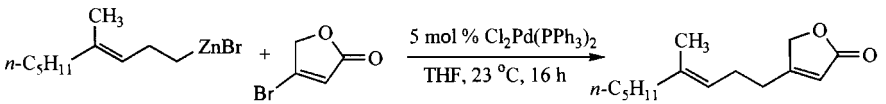
Primary alkylzinc derivatives including homoallyl- and homopropargylzincs can undergo cross-coupling in preference to reductive dehalogenation.[35] Although secondary alkylzincs can also undergo cross-coupling, secondary-to-primary isomerization of the alkyl group, which undoubtedly occurs via dehydropalladation–hydropalladation, is another serious side-reaction.[35b] This difficulty, however, has been overcome for the cross-coupling reaction of *sec*-BuMgCl through the use of chelating ligands, such as dppp and dppf,[36a] even though its applicability remains to be further delineated.



Scheme 11.6

Protocol 4.
Palladium catalysed conjugate substitution via alkyl–alkenyl coupling: preparation of 4-[(*E*)-4-methyl-3-nonenyl]-2(5H)-furanone[35a]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Two magnetic stirrers
- Two two- or three-necked round-bottomed flasks (50–100 mL)
- Rubber septa
- Two tubing adapters
- Two magnetic stirring bars
- Two mercury bubblers (or an equivalent outlet)
- Glass syringes of appropriate sizes
- Nitrogen or argon line
- Six inch medium gauge needles
- Long double-ended wide gauge needle
- Bath for cooling with ice-water
- Other usual equipment for work-up and isolation, such as rotary evaporator and separatory funnel

Materials

- Magnesium turnings (FW 24.31), 0.24 g, 10 mmol
- Iodine, a small piece — **skin irritant**
- Dry tetrahydrofuran, 17 mL — **flammable**
- Methyl iodide, a few small drops
- (*E*)-1-bromo-4-methyl-3-nonene (FW 219.16),[a] 1.1 g, 5 mmol
- Anhydrous zinc bromide (FW 225.19), 1.13 g, 5 mmol — **moisture-sensitive**
- Dichloro*bis*(triphenylphosphine)palladium (FW 701.89), 105 mg, 0.15 mmol
- 4-bromo-2(5*H*)-furanone (FW 162.96), 0.49 g, 3 mmol
- Saturated aqueous ammonium chloride
- Hexanes — **flammable**
- Saturated aqueous sodium bicarbonate
- Anhydrous magnesium sulfate
- Alumina, neutral
- Hexane:ethyl acetate, 9:1 mixture — **flammable**

Protocol 4. *Continued*

For setting-up the reactor system, follow Protocol 1, steps 1–3.

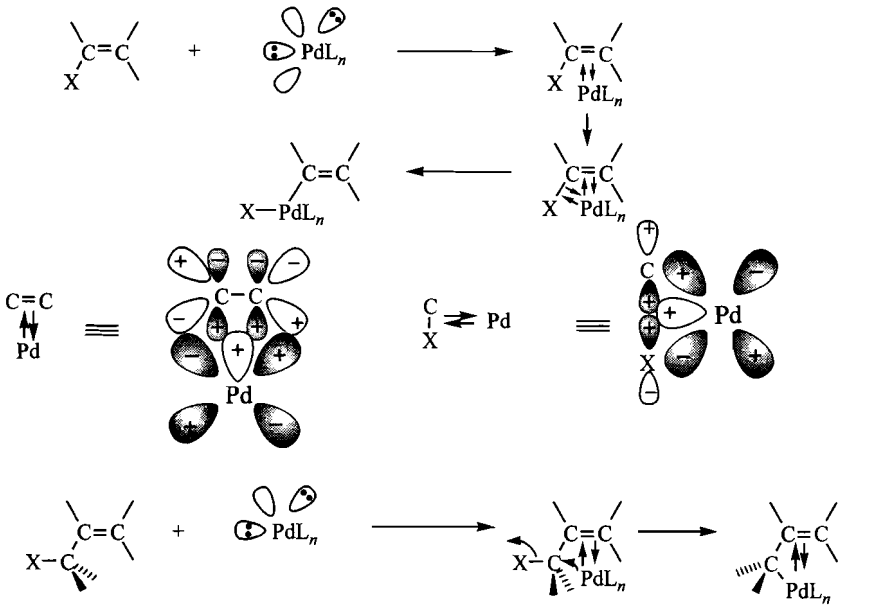
1. Place magnesium turnings (0.24 g, 10 mmol) and a small piece of iodine in the flask and add tetrahydrofuran (3 mL).
2. Add at 23°C a few drops of methyl iodide and about 10% of (*E*)-1-bromo-4-methyl-3-nonene (1.1 g, 5 mmol) in 7 mL of tetrahydrofuran to initiate generation of the desired Grignard reagent.
3. Add dropwise the remainder of the homoallyl bromide so as to maintain a moderate rate of reaction, and stir the resultant mixture at room temperature for 1–2 h.[b]
4. In another flask similarly set-up, add dry zinc bromide (1.13 g, 5 mmol) dissolved in tetrahydrofuran (5 mL).
5. Add via cannula the supernatant solution of the Grignard reagent to zinc bromide at 0°C. Use tetrahydrofuran (2 × 1 mL) to insure complete transfer of the Grignard reagent.
6. Stir the mixture at 0°C for 30 min and then warm to 23°C.
7. Add $Cl_2Pd(PPh_3)_2$ (105 mg, 0.15 mmol)[c] and 4-bromo-2(5*H*)-furanone (0.49 g, 3 mmol)[d] in 3 mL of tetrahydrofuran.
8. Stir the resultant mixture for 16 h at 23°C and then quench with saturated aqueous ammonium chloride.
9. Extract with hexanes, wash the organic layer with saturated aqueous sodium bicarbonate, and dry over magnesium sulfate. Filter off inorganic salts.
10. Evaporate the volatiles to obtain about 95% pure product in about 70% yield and purify it by passing it through a short-path neutral alumina column using 9:1 hexane and ethyl acetate. The product displayed appropriate spectral (≥ 98% *E*) and analytical data.

[a] 1-heptyne is first converted to (*E*)-4-methyl-3-nonen-1-ol in 78% yield via Zr catalysed carboalumination, ate complexation, and hydroxymethylation. Tosylation in pyridine at 0°C followed by treatment with LiBr and acetone at 23°C gives (*E*)-1-bromo-4-methyl-3-nonene in 73% yield based on the alcohol.
[b] It is advisable to check the yield of the Grignard reagent, which should be typically 80%, by analysis of the iodinolysis product.
[c] Earlier, $Cl_2Pd(PPh_3)_2$ was reduced with two molar equivalent of DIBAL-H in hexane. It has since been shown that the use of a reducing agent is unnecessary.
[d] This compound was prepared from propargyl alcohol via carbonation and addition of aqueous HBr.[35a]

2.3.2 Palladium catalysed allylation, benzylation, and propargylation

The presence of an alkenyl, phenyl, or alkynyl group one carbon away from a halogen, oxygen, or another electronegative atom, such as sulfur, makes allylic, benzyllic, and propargyllic electrophiles very reactive in oxidative addition

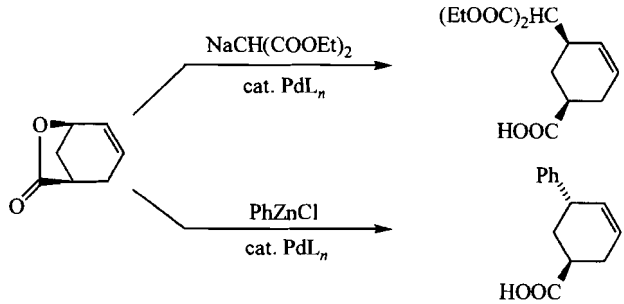
with palladium or nickel complexes. These facts strongly suggest that complexation of Pd and Ni with π-bonds plays a crucial role in their oxidative addition. It is important to note that, whereas oxidative addition with alkenyl, aryl, and alkynyl halides, triflates, and related electrophiles proceeds with retention of configuration, that with allyl, benzyl, and propargyl electrophiles the process involves inversion. The orbital interaction schemes shown in Scheme 11.7 are consistent with the observed facts.



Scheme 11.7

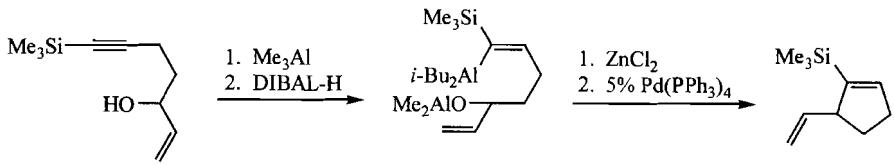
Despite their high reactivity towards Pd, it was earlier thought that the Pd catalysed allylation was limited to that of enolates and related soft nucleophiles, i.e. the Tsuji–Trost reaction.[37] However, various types of organometals, such as those containing Al and Zn, have been shown to react readily with allyl and propargyl electrophiles[38] as well as benzyl electrophiles[19a,39] in the presence of Pd catalysts. Somewhat puzzlingly, the use of allylic and propargylic nucleophiles has been much less satisfactory even though the same diorganylpalladiums are thought to be generated as intermediates. It is also important to note that the overall stereochemistry of the organometallic allylation proceeding with an overall inversion is the opposite to the corresponding reaction of enolates[40] (Scheme 11.8).

In general, allylic and propargyllic electrophiles are much more reactive than alkenyl and alkynyl electrophiles. Thus, a wide variety of electrophiles containing halogens, e.g. I, Br, and Cl, and oxygen groups, e.g. sulfonates, phosphates, carboxylates, carbonates, alkyl and aryl ethers, and even silyl



Scheme 11.8

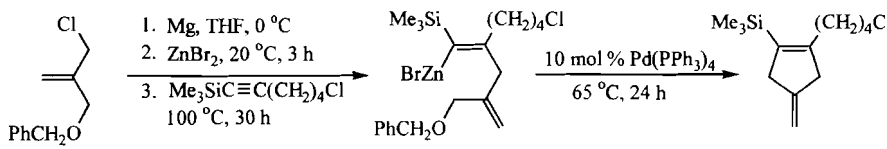
ethers, have been shown to participate in the Pd catalysed cross-coupling.[38] The wide scope with respect to the leaving group makes easy the preparation of acyclic precursors containing both nucleophilic and electrophilic moieties for cyclic cross-coupling as exemplified by a Zn promoted alkenylalane cyclization[41] (Scheme 11.9) and a related alkenylzinc cyclization[42] (Protocol 5).



Scheme 11.9

Protocol 5.
Palladium catalysed alkenyl–allyl coupling: preparation of 1-(trimethylsilyl)-2-(4′-chlorobutyl)-4-methylene-1-cyclopentene[42]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Two round-bottomed flasks with a side-arm (25–50 mL)
- Two tubing adapters
- Two magnetic stirring bars
- Rubber septa
- Two mercury bubblers (or equivalent outlet)
- Magnetic stirrer
- Water-bath
- Nitrogen or argon line
- Glass syringes of appropriate sizes

- Other usual equipment for work-up and isolation, such as rotary evaporator, separatory funnel, and chromatographic column
- Six inch medium gauge needles
- Carius tube[43]

Materials

• Magnesium (FW 24.31), **twice sublimed**, 0.36 g, 15 mmol	**flammable, air- and moisture-sensitive**
• Dry tetrahydrofuran, 12 mL	**flammable, moisture-sensitive**
• 2-chloromethyl-2-propenyl benzyl ether[a,42] (FW 196.66), 0.49 g, 2.5 mmol	**irritant**
• 1,2-dibromoethane (FW 187.87), 94 mg, 0.5 mmol	**cancer suspect, toxic**
• Anhydrous zinc bromide (FW 225.19), 0.9 g, 4 mmol	**irritant, hygroscopic**
• 1-(trimethylsilyl)-6-chloro-1-hexyne (FW 188.77)[b,44] 0.378 g, 2 mmol	
• $Pd(PPh_3)_4$ (FW 1155.58), 231 mg, 0.2 mmol	**light-sensitive**
• Saturated aqueous sodium bicarbonate	
• Ether	
• Anhydrous sodium sulfate	

For setting-up the reactor system, follow Protocol 1, steps 1–3.

1. Suspend magnesium (twice sublimed, 0.36 g, 15 mmol) in tetrahydrofuran (4 mL).
2. Add 2-chloromethyl-2-propenyl benzyl ether[a,42] (0.49 g, 2.5 mmol) and 1,2-dibromoethane (0.094 g, 0.5 mmol), and regulate the reaction temperature so as to induce and maintain a smooth reaction of the chloride with magnesium producing the desired Grignard reagent (about 90% yield).
3. Place dry zinc bromide (0.9 g, 4 mmol) in tetrahydrofuran (8 mL) in another flask.
4. Add slowly via cannula the above prepared Grignard reagent to the zinc bromide and stir the mixture at 20°C for 3 h.
5. Add 1-(trimethylsilyl)-6-chloro-1-hexyne[b,44] (0.378 g, 2 mmol), transfer the resultant mixture in a Carius tube[43] via cannula, and heat at 100°C for 30 h.
6. Cool the mixture, add $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol), and heat again at 65°C for 24 h.
7. Quench the mixture with saturated aqueous sodium bicarbonate and extract with ether.
8. Dry the organic layer with anhydrous sodium sulfate.
9. Concentrate using a rotary evaporator and purify by chromatography the title compound (75% by GLC) which displayed appropriate spectral data.

[a] This compound may be prepared from 2-chloromethyl-3-chloropropene by treatment with sodium benzyloxide in 59% yield.[42]

[b] It can be prepared from 5-hexyn-1-ol by silylation and chlorination.[44]

2.4 Palladium catalysed acylation

In addition to various unsaturated carbon electrophiles discussed earlier, acyl chlorides and other halides readily undergo oxidative addition to Pd. Indeed,

Table 11.2 Pd catalysed reaction of organozincs with acyl chlorides[a]

R^1ZnX	R^2COCl	Yield (%)[b] of R^1COR^2
n-BuZnCl	MeCOCl	– (80)
(*E*)-*n*-PentCH=CHZnCl	MeCOCl	76 (98)
n-PentC≡CZnCl	MeCOCl	81 (97)
p-ClC_6H_4ZnCl	PhCOCl	– (95)
$PhCH_2ZnBr$	CH_2=CHCOCl	77
PhZnCl	(*E*)-MeCH=CHCOCl	89
n-OctZnCl	MeOCOCl	78

[a] The catalyst was 1–5 mol% of $Pd(PPh_3)_4$ except in the case of (*E*)-*n*-PentCH=CHZnCl where 1 mol% of $Cl_2Pd(PPh_3)_2$ plus 2 *i*-Bu_2AlH was used.
[b] The numbers in parentheses are NMR or GLC yields.

the Pd catalysed reaction of various types of organozincs with acyl chlorides has proved to be one of the most general and selective methods for the synthesis of ketones,[45,46] as indicated by the results summarized in Table 11.2.[45] Some other related acylation reactions[2] of organometals containing Mg, Cd, Mn, and Cu have been widely used in the past. Although their relative merits and demerits have not yet been delineated, the Mg-based method is less tolerant of other functional groups, and the organocopper reaction may not produce satisfactorily α,β-unsaturated ketones, as they are known to undergo conjugate addition with organocoppers. The Pd catalysed acylation can also be achieved with organostannanes[47] and organomercuries.[48]

Protocol 6.
Palladium catalysed acylation of organozincs: preparation of 3-nonyn-2-one[45]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.

$$n\text{-}C_5H_{11}C{\equiv}CZnCl + ClCOCH_3 \xrightarrow[THF,\ 23\ ^\circ C,\ 2\ h]{5\ mol\ \%\ Pd(PPh_3)_4} n\text{-}C_5H_{11}C{\equiv}CCOCH_3$$

Equipment

- Magnetic stirrer
- Two- or three-necked round-bottomed flask (100 mL)
- Rubber septum
- Tubing adapter
- Magnetic stirring bar
- Mercury bubbler (or an equivalent outlet)
- Glass syringes of appropriate sizes
- Nitrogen or argon line
- Six inch medium gauge needles
- Bath for cooling with ice-water
- Other usual equipment for work-up and isolation, such as rotary evaporator and separatory funnel

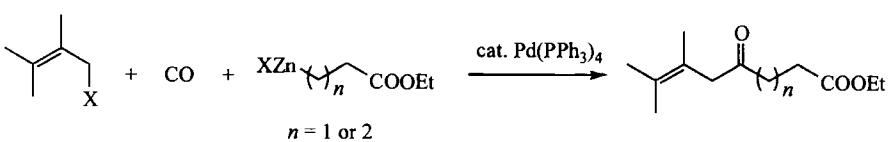
Materials

- 1-heptyne (FW 96.17), 0.96 g, 10 mmol — **flammable**
- Dry tetrahydrofuran, 15 mL — **flammable, harmful**
- *n*-butyllithium, 2.3 M in hexane, 4.8 mL, 11 mmol — **flammable**
- Zinc chloride, 0.5 M in tetrahydrofuran, 22 mL, 11 mmol — **moisture-sensitive**
- Acetyl chloride (FW 78.5), 0.71 mL, 10 mmol — **skin and eye irritant**
- $Pd(PPh_3)_4$ (FW 1155.58), 0.58 g, 0.5 mmol
- 3 N hydrochloric acid, 50 mL
- Pentane
- Anhydrous magnesium sulfate

For the initial set-up of the reaction system, follow Protocol 1, steps 1–3.

1. Place 1-heptyne (0.96 g, 10 mmol) and tetrahydrofuran (10 mL) in the reaction flask cooled at 0°C using syringes.
2. Introduce *n*-butyllithium (11 mmol) in hexane (2.3 M, 4.8 mL) and stir the reaction mixture for 10 min at 0°C.
3. Add zinc chloride (11 mmol) in tetrahydrofuran (0.5 M, 22 mL).
4. After stirring the mixture for 15 min, add acetyl chloride (0.71 mL, 10 mmol) and $Pd(PPh_3)_4$ (0.58 g, 0.5 mmol) in tetrahydrofuran (5 mL).
5. Warm the reaction mixture to 23°C.
6. After stirring for 2 h, treat the mixture with 3 N HCl (50 mL) and extract with pentane.
7. Dry the combined extract over magnesium sulfate, concentrate, and distill to obtain 1.11 g (81%) of 3-nonyn-2-one (b.p. 85°C at 12 mmHg) which displayed appropriate spectral data.

Closely related to the acylation reaction discussed above is the Pd catalysed carbonylative cross-coupling originally developed for organostannanes.[49] The high reactivity of organozincs generally makes it difficult to achieve the carbonylative cross-coupling, since direct cross-coupling tends to compete favourably with the desired carbonylative process. In some favourable cases, however, the carbonylative cross-coupling can take place preferentially, as shown in Scheme 11.10.[50]



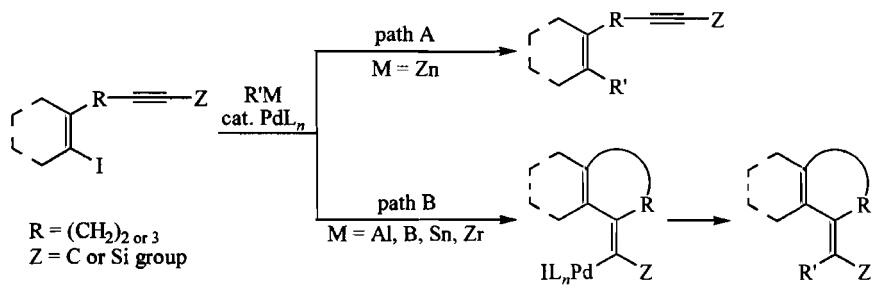
$n = 1$ or 2

Scheme 11.10

2.5 Other notable aspects of palladium or nickel catalysed organozinc cross-coupling

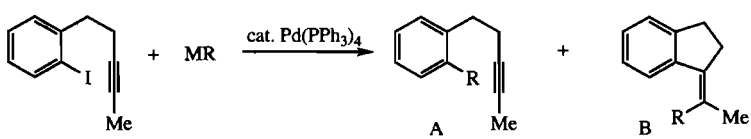
2.5.1 Tandem cyclic carbopalladation cross-coupling process

The high reactivity of organozincs is also detrimental in the tandem cyclic carbopalladation cross-coupling reaction[51] (Scheme 11.11). In these cases, the lower intrinsic reactivity of organometals containing Al, B, Sn, and Zr has proved to be effective in avoiding the unwanted direct cross-coupling[51] (Table 11.3).



Scheme 11.11

Table 11.3. Reaction of *o*-iodo-3-phenylbenzene with organometallics catalysed by $Pd(PPh_3)_4$

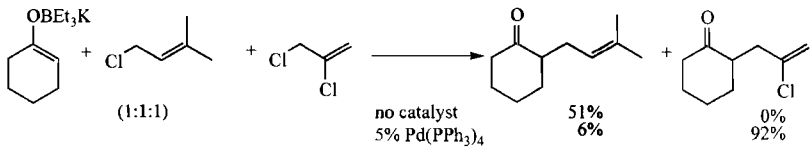


R	M	A (%)	B (%)
(*E*)-1-Hexenyl	ZnCl	68	19
	$ZrCp_2Cl$	≤ 3	84
	$SnMe_3$	≤ 2	69
	$AlBu_2$	32	57
	$BO_2C_6H_4$	≤ 4	41
Phenyl	ZnCl	57	34
	$AlPh_2$	≤ 2	93

2.5.2 Palladium catalysed allylation of ordinary ketone and aldehyde enolates

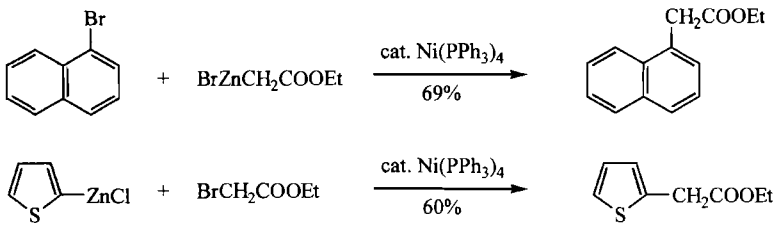
Alkali metal enolates of ordinary ketones and aldehydes tend to fail to undergo the Tsuji–Trost allylation.[37] However, it has been found that their enoxyborates and zinc enolates[52] readily undergo the Pd catalysed allylation which proceeds with net retention just like the other examples of the

Tsuji–Trost reaction (Scheme 11.12). γ,γ′-Disubstituted allyl derivatives can react with retention of the alkene geometry although γ-monosubstituted allyl derivatives undergo geometrical scrambling typically to the extent of 10–15%.



Scheme 11.12

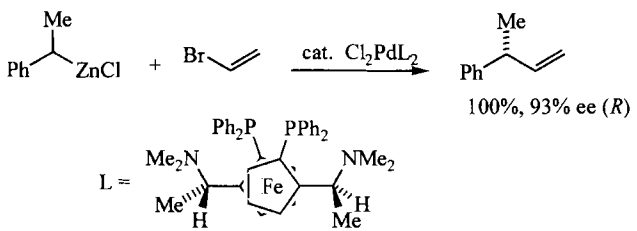
The Reformatsky reagents, i.e. zinc enolates of esters, undergo Ni catalysed cross-coupling with aryl halides.[53] The Ni catalysed reaction of arylzincs with α-bromoacetates also permits α-arylation of esters[54] (Scheme 11.13). However, α-alkenylation of enolates of ketones, aldehydes, and esters has been less satisfactory. Its further development is clearly desirable. Alternatively, α-alkenylation of α-iodoenones in conjunction with conjugate reduction discussed earlier should be considered.



Scheme 11.13

2.5.3 Pd catalysed asymmetric benzylation of vinyl bromide

The Pd catalysed reaction of 1-phenylethylzinc chloride with vinyl bromide proceeds to give 3-phenyl-1-butene in 100% yield in 93% *ee* using a chiral *bis*(diphenylphosphino)ferrocene derivative[55] (Scheme 11.14). While the results are very attractive, the scope of Pd catalysed asymmetric alkylation remains to be further delineated.



Scheme 11.14

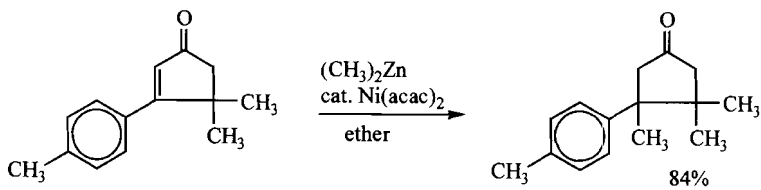
3. Nickel or palladium catalysed conjugate addition and other carbozincation reactions

3.1 Background

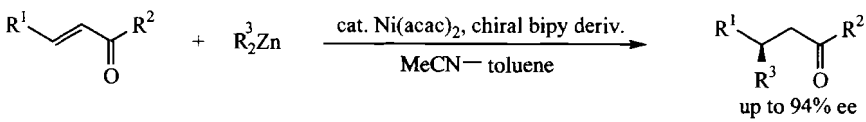
Until recently, the scope of the organozinc addition to alkynes and alkenes, i.e. carbozincation, had been essentially limited to those involving allyl and related derivatives, which can participate in concerted six-centred carbometallation processes.[3–5] The Zr catalysed carbozincation of alkynes with dialkylzincs reported in 1983[56] appears to represent one of the earliest examples of the transition metal catalysed carbozincation. More recently, Ni and Pd complexes have been shown to serve as catalysts for conjugate addition and various types of other carbozincation reactions of alkenes and alkynes including intramolecular versions producing five-membered rings. Collectively, these transition metal catalysed carbozincation reactions represent the second most important breakthrough along the line of expansion of organozinc chemistry through transition metal catalysis.

3.2 Nickel catalysed conjugate addition

It has been known that various types of organozincs undergo conjugate addition reactions.[3–5] By and large, however, these uncatalysed reactions have not shown noteworthy advantages over other conjugate addition reactions, such as those with organocopper reagents,[57] and their scope is rather limited. The development of the Ni catalysed conjugate addition[58] has significantly expanded the scope of conjugate addition of organozincs to α,β-unsaturated ketones and aldehydes. Its merits and demerits relative to the organocopper reaction are not very clear at this time. However, some results reported in these studies, such as those shown in Scheme 11.15, are allegedly far superior to the previously reported results. Also noteworthy is the asymmetric version of the Ni catalysed conjugate addition of dialkylzincs,[59] proceeding in up to 96% yield and 94% *ee* (Scheme 11.16).



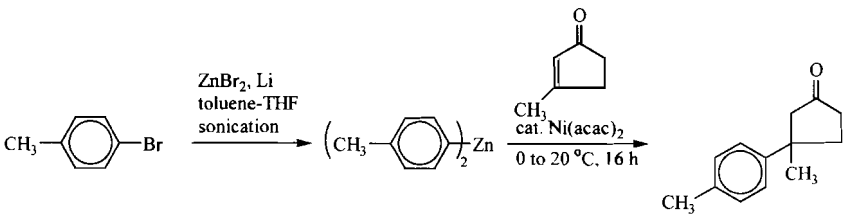
Scheme 11.15



Scheme 11.16

Protocol 7.
Nickel catalysed conjugate addition of *bis*(*p*-tolyl)zinc to 3-methyl-2-cyclopent-1-one to give 3-methyl-3-(*p*-tolyl)cyclopentanone[58]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Three-necked round-bottomed flask (100 mL) with a septum inlet, a tubing adapter, and an adapter for an ultrasonic probe
- Ultrasonic system with a probe and a holder[a]
- Round-bottomed flask with a side-arm (100 mL)
- Two tubing adapters
- Two magnetic stirring bars
- Rubber septa
- Two mercury bubblers (or equivalent outlet)
- Magnetic stirrer
- Nitrogen or argon line
- Bath for temperature control
- Glass syringes of appropriate sizes
- Six inch medium gauge needles
- Long wide gauge double-ended needle
- Other usual equipment for work-up and isolation, such as rotary evaporator, separatory funnel, and chromatographic column

Materials

- *p*-bromotoluene (FW 171.04), 1.71 g, 10 mmol — **irritant**
- Anhydrous zinc bromide (FW 225.19), 1.13 g, 5 mmol — **hygroscopic, irritant**
- Dry toluene, 22 mL — **flammable**
- Dry tetrahydrofuran, 4.3 mL
- Lithium wire (FW 6.94), 99.9% in mineral oil, 150 mg, 21 mmol — **flammable solid**
- 3-methyl-2-cyclopenten-1-one (FW 96.13), 0.384 g, 4 mmol — **flammable**
- Nickel acetylacetonate (FW 256.91), 21 mg, 0.08 mmol — **cancer suspect agent, hygroscopic**
- Saturated aqueous ammonium chloride
- Anhydrous magnesium sulfate

For setting-up the reactor system, follow Protocol 1, steps 1–3.

1. Place *p*-bromotoluene (1.71 g, 10 mmol) and zinc bromide (1.13 g, 5 mmol) in 5:1 toluene:tetrahydrofuran (24 mL) in a flask with an ultrasonic probe,[a] a magnetic stirrer, a side-arm, and a tubing adapter connected to a mercury bubbler.
2. Place lithium wire (150 mg, 21 mmol) in the holder under the ultrasonic probe.[a]
3. Cool the flask to 0°C and start sonication, while adjusting the sonication energy level to the minimum giving the cavitation noise.[b]

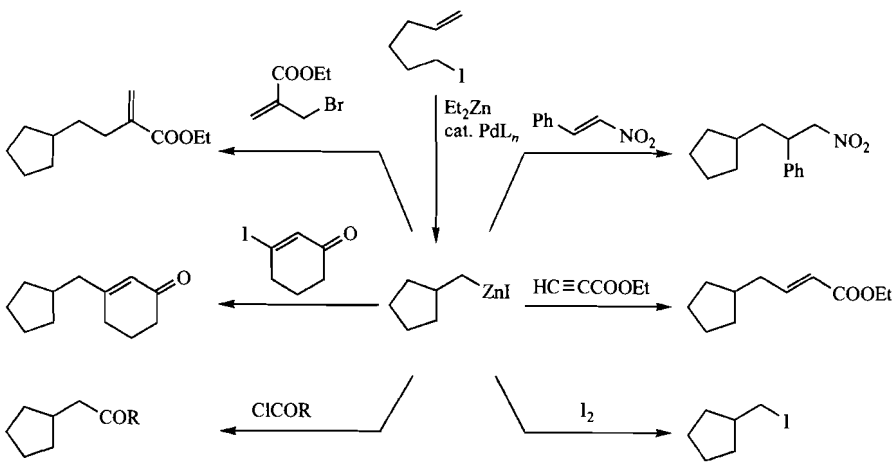
Protocol 7. *Continued*

4. Stop sonication after 30 min and transfer via cannula the resultant black solution into a round-bottom flask with a magnetic stirring bar, and then cool to 0°C.
5. Prepare a solution of 3-methyl-2-cyclopenten-1-one (0.384 g, 4 mmol) and $Ni(acac)_2$ (21 mg, 0.08 mmol) in 5:1, toluene:tetrahydrofuran (2 mL), and slowly add this solution to the organozinc reagent prepared above at 0°C.
6. Warm the mixture to 20°C and stir it for 16 h with periodical monitoring by TLC.
7. Pour the mixture into saturated aqueous ammonium chloride and separate.
8. Wash the organic layer with water, dry it over magnesium sulfate, and evaporate the volatiles using a rotary evaporator.
9. Purify by column chromatography (silica gel) to obtain the title compound in 87% yield.

[a]An Ultrason-Annemasse system (Sonimasse) emitting a 30 KHz wave may be used.[58]
[b]A black colour is immediately developed.

3.3 Nickel or palladium catalysed carbozincation

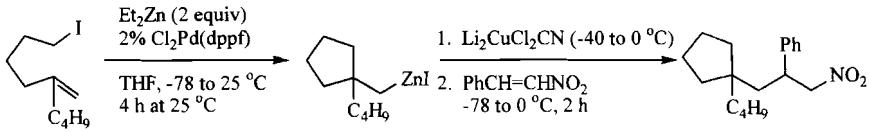
Palladium complexes, e.g. $Cl_2Pd(dppf)$, have been shown to catalyse not only Zn–I exchange between alkyl iodides and dialkylzincs but also intramolecular carbozincation to produce cyclopentylmethylzincs.[60] Once cyclopentylmethylzincs are formed, they may be utilized in cross-coupling, conjugate addition, and other synthetically useful transformation reactions (Scheme 11.17).



Scheme 11.17

Protocol 8.
Palladium catalysed cyclic carbozincation of ω-iodoalkenes and copper promoted conjugate addition of alkylzincs to nitroalkenes: preparation of 1-butyl-1-(3-nitro-2-phenylpropyl)cyclopentane[60]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Two-necked round-bottomed flask (50–100 mL)
- Magnetic stirring bar
- Tubing adapter
- Rubber septa
- Magnetic stirrer
- Mercury bubbler (or an equivalent outlet)
- Bath for temperature control
- Nitrogen or argon line
- Glass syringes of appropriate sizes
- Six inch medium gauge needles
- Other usual equipment for work-up and isolation, such as rotary evaporator, vacuum pump, and column chromatographic apparatus

Materials

- $Cl_2Pd(dppf)$ (FW 731.7), 0.73 g, 0.1 mmol — **irritant**
- Dry tetrahydrofuran, 18 mL — **flammable, harmful**
- 2-butyl-6-iodo-1-hexene,[a] 1.33 g, 5 mmol
- Diethylzinc, 1.23 g, 1 mL, 10 mmol — **pyrophoric, air- and moisture-sensitive**
- Li_2CuCl_2CN (FW 174.35), 0.87 g, 5 mmol
- *trans*-β-nitrosytrene (FW 149.15), 1.12 g, 7.5 mmol — **irritant**
- 3 N hydrochloric acid — **irritant**
- Ether — **flammable**
- Hexanes — **flammable**
- Dry ice
- Isopropanol — **flammable**
- Anhydrous magnesium sulfate

For the initial set-up of the reaction system, follow Protocol 1, steps 1–3.

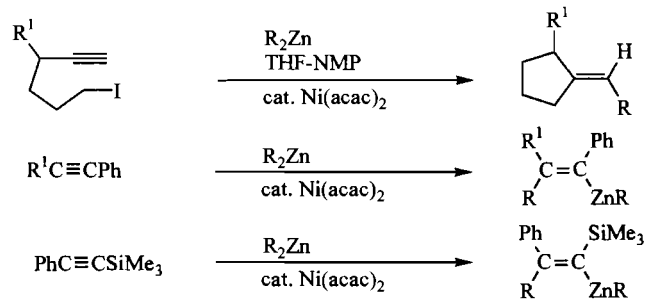
1. Add $Cl_2Pd(dppf)$ (0.073 g, 0.1 mmol) and tetrahydrofuran (5 mL), cool to –78°C, and add 2-butyl-6-iodo-1-hexene[a] (1.33 g, 5 mmol) and diethylzinc (1.23 g, 1 mL, 1 mmol) (Caution!).
2. Warm the mixture to 25°C and stir it for 4 h.
3. Evaporate off the solvent and excess diethylzinc at 25°C and 0.1 mmHg over 1 h.
4. Add tetrahydrofuran (5 mL) and Li_2CuCl_2CN (0.87 g, 5 mmol) in tetrahydrofuran (5 mL) at –40°C, and warm the mixture to 0°C.
5. Cool the mixture to –78°C and add nitrosytrene (1.12 g, 7.5 mmol) in tetrahydrofuran (3 mL).

Protocol 8. *Continued*

6. Warm the mixture to 0°C and stir it for 2 h.
7. Add 3 N HCl and extract with ether.
8. Dry over magnesium sulfate and evaporate the volatiles using a rotary evaporator.
9. Purify the residue by flash column chromatography (1:9, ether:hexanes) to obtain the title compound as a clear oil (1.16 g, 81%).

[a] This compound can be prepared via iodination of 5-butyl-5-hexen-1-ol, which, in turn can be obtained by the reaction of 5-hexyn-1-ol with *n*-BuCu·$MgBr_2$.[61]

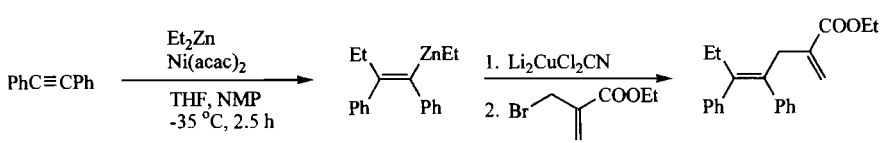
Recent development of a Ni catalysed alkylzincation of alkynes[62] has further expanded the scope of both intramolecular and intermolecular carbozincation. It should be noted, however, that carbozincation may be followed by cross-coupling under the reaction conditions. The current scope of the intramolecular process appears to be limited to five-membered ring formation, and that of the intermolecular version has been limited to phenylethyne derivatives (Scheme 11.18). Further exploration of the scope of this reaction is highly desirable.



Scheme 11.18

Protocol 9.
Nickel catalysed ethylzincation of diphenylethyne to give (*E*)-(1,2-diphenyl-1-butenyl)ethylzinc and its conversion to ethyl (*E*)-2-methylene-4,5-diphenyl-4-heptenoate by copper promoted coupling with ethyl α-(bromomethyl)acrylate[62]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Two round-bottomed flasks (50 mL)
- Two tubing adapters
- Two magnetic stirring bars
- Rubber septa
- Two mercury bubblers (or equivalent outlet)
- Magnetic stirrer
- Cooling bath
- Argon line
- Heating bath with silicon oil
- Vacuum pump system
- Glass syringes of appropriate sizes
- Six inch medium gauge needles
- Wide gauge double-ended needle
- Other usual equipment for work-up and isolation, such as rotary evaporator, separatory funnel, and chromatographic column

Materials

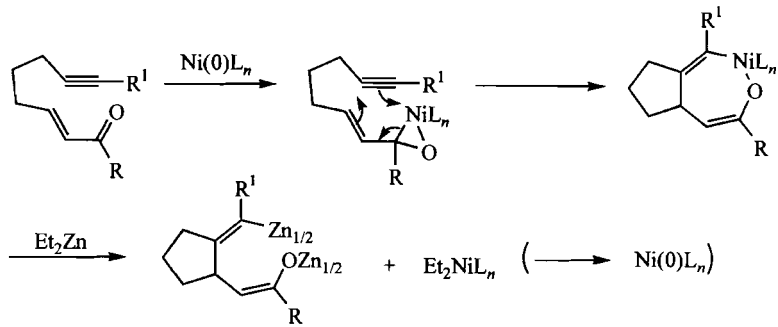
- Diphenylethyne (FW 178.23), 0.89 g, 5 mmol
- Nickel acetylacetonate (FW 256.91), 320 mg, 1.25 mmol — **cancer suspect agent, hygroscopic**
- Dry tetrahydrofuran, 14 mL — **flammable, harmful**
- Dry *N*-methylpyrrolidinone, 1.25 mL — **irritant, hygroscopic**
- Diethylzinc (FW 123.49), 1.23 g, 1.02 mL, 10 mmol — **pyrophoric, air- and moisture-sensitive**
- Copper cyanide (FW 89.56), 1.79 g, 20 mmol — **toxic, irritant**
- Lithium chloride (FW 42.39), 1.69 g, 40 mmol
- Ethyl α-(bromomethyl)acrylate,[63] 4.82 g, 25 mmol
- Hexanes — **flammable**
- Ether — **flammable**
- Silica gel
- Dry ice
- Isopropanol

For setting-up the reaction system, follow Protocol 1, steps 1–3.

1. Dissolve diphenylethyne (0.89 g, 5 mmol) and $Ni(acac)_2$ (320 mg, 1.25 mmol) in tetrahydrofuran (3.75 mL) and *N*-methylpyrrolidinone (1.25 mL).
2. Add carefully at –78°C diethylzinc (1 mL, 10 mmol) using a syringe (Caution!).
3. Warm the reaction mixture to –35°C and stir for 2.5 h.
4. Dry a mixture of copper cyanide (1.79 g, 20 mmol) and lithium chloride (1.69 g, 40 mmol) placed in another flask *in vacuo* at 130°C for 2 h, and then cool to room temperature and dissolve in tetrahydrofuran (10 mL).
5. Cool the copper solution to –60°C and add by cannula to the reaction mixture at –78°C. Warm the resulting mixture to 0°C for a few minutes and then cool back to –78°C again.
6. Add ethyl α-(bromomethyl)acrylate[63] (4.82 g, 25 mmol) and warm the reaction mixture to 25°C.
7. Work-up in the usual manner.
8. Purify the crude product by flash chromatography (20:1, hexanes:ether) to obtain the title ester (1.13 g, 3.53 mmol, 71% yield, *E*/*Z* > 99/1) as a white powder.

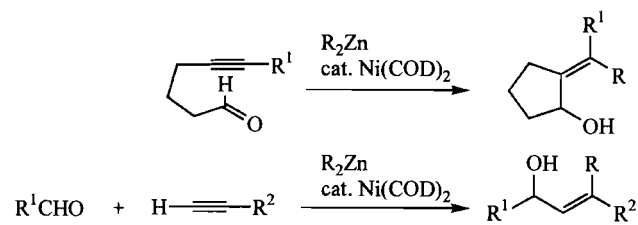
ω-Alkyne substituted α,β-unsaturated ketones and esters undergo a Ni catalysed cyclic carbozincation with dialkylzincs to produce five-membered rings.[64] These reactions most probably involve generation of Ni(0) species which may then interact with conjugated carbonyl derivatives to produce

allylnickel species capable of undergoing allylnickelation with the alkynyl group. The role of organozincs is primarily to reduce Ni(II) species to Ni(0) species, although alkylation by organozincs may occur as a side-reaction. The following mechanism appears to be plausible (Scheme 11.19).



Scheme 11.19

More recently, the scope of the Ni catalysed alkyne carbozincation has been extended to the cases of ω-alkynyl aldehydes and even mixtures of aldehydes and alkynes.[65] These reactions are generally accompanied by alkylation with organozincs (Scheme 11.20).

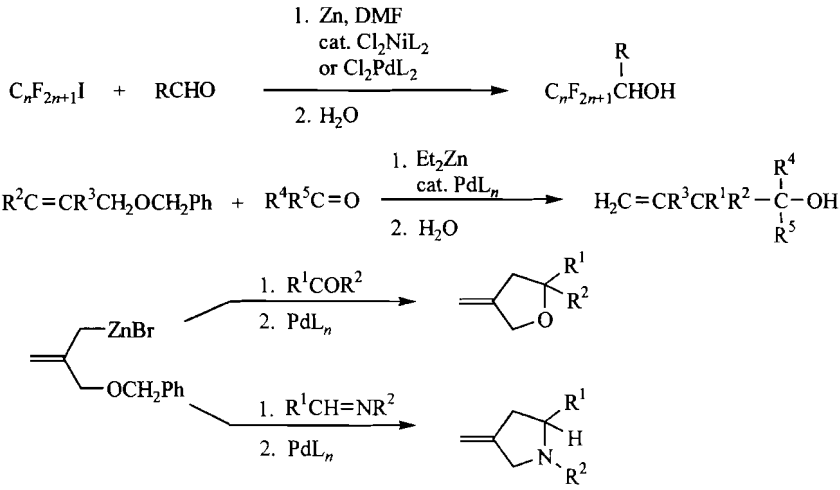


Scheme 11.20

4. Nickel or palladium catalysed carbonyl addition and related reactions

Various addition reactions of organozincs with aldehydes, ketones, and related carbon electrophiles have been catalysed by Ni and Pd complexes. In general, however, catalysis by these transition metals pertains to oxidative addition[66] and some processes other than carbonyl addition, such as cross-coupling.[42] Since organozincs are known to add to aldehydes and some ketones, it is not clear if Ni or Pd is at all involved in the carbonyl addition step itself (Scheme 11.21). It should be noted that allylzinc derivatives tend to

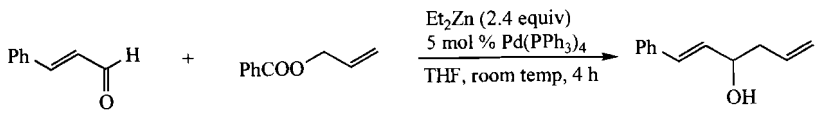
preferentially undergo 1,2-addition with enones[66] rather than the conjugate addition discussed earlier[58] (Protocol 10).



Scheme 11.21

Protocol 10.
Palladium catalysed reaction of cinnamaldehyde with allyl benzoate and diethylzinc to produce (*E*)-1-phenyl-1,5-hexadien-3-ol[66]

Caution! All procedures in this chapter should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and safety goggles should be worn.



Equipment

- Round-bottomed flask with a side-arm (25 mL)
- Tubing adapter
- Magnetic stirring bar
- Rubber septum
- Mercury bubbler (or an equivalent outlet)
- Magnetic stirrer
- Nitrogen line
- Glass syringes of appropriate sizes
- Six inch medium gauge needles
- Water-bath
- Other usual equipment for work-up and isolation, such as rotary evaporator and separatory funnel

Materials

- $Pd(PPh_3)_4$ (FW 1155.58), 58 mg, 0.05 mmol — **light-sensitive**
- Dry tetrahydrofuran, 3 mL — **flammable, harmful**
- Allyl benzoate (FW 162.19), 0.195 g, 1.2 mmol
- Cinnamaldehyde (FW 132.16), 0.132 g, 1 mmol — **irritant**

Protocol 10. *Continued*

- Diethylzinc, 2 M in hexanes, 1.2 mL, 2.4 mmol — **pyrophoric, air- and moisture-sensitive**
- Ethyl acetate
- Benzene
- 2 N hydrochloric acid — **irritant**
- Saturated aqueous sodium bicarbonate
- Anhydrous magnesium sulfate
- Silica gel 60

For setting-up the reactor system, follow Protocol 1, steps 1–3.

1. Place $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and dry tetrahydrofuran (3 mL) in the flask.
2. Add successively under nitrogen allyl benzoate (0.195 g, 1.2 mmol), cinnamaldehyde (0.132 g, 1.0 mmol), and diethylzinc (1.2 mL, 2.4 mmol), and stir the mixture at room temperature for 4 h.
3. Dilute the pale yellow mixture with ethyl acetate and wash successively with 2 N hydrochloric acid and aqueous sodium bicarbonate.
4. Dry over magnesium sulfate and concentrate using a rotary evaporator.
5. Purify by chromatography (20 × 1.5 cm, silica gel 60) with benzene:ethyl acetate to obtain 0.169 g (97%) of the title compound as a colourless oil which displayed appropriate spectral data.

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5. Conclusions

The Pd or Ni catalysed cross-coupling reaction of organozincs was discovered about 20 years ago. Today, it is one of the most widely used methods, along with its B and Sn analogues, for the formation of carbon–carbon bonds. From a different perspective, this reaction has significantly elevated the synthetic usefulness of organozinc compounds. More recently, various transition metal catalysed carbozincation reactions involving either early or late transition metals have further elevated the significance of organozinc chemistry. None the less, the scope and synthetic utility of these carbozincation reactions need to be further explored and expanded. It is reasonable to anticipate that other transition metal catalysed organozinc reactions will emerge in the near future.

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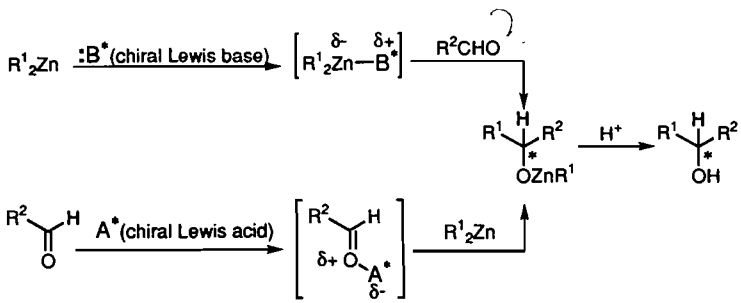
12

Asymmetric additions using diorganozincs

KENSO SOAI and TAKANORI SHIBATA

1. Introduction

Enantioselective additions of organometallic reagents to carbonyl compounds (1,2-addition to aldehydes and 1,4-addition to enones) and imines are important methods for the preparation of optically active *sec*-alcohols, β-substituted ketones, and amines, respectively. The reactivities of diorganozincs toward the additions to carbonyl compounds and imines are usually much lower than those of the corresponding organolithium and organomagnesium reagents. Without any catalyst, diorganozincs do not usually add to aldehydes and imines in synthetically useful yields. However, owing to the low reactivities of diorganozincs, the catalytic enantioselective additions of diorganozincs to aldehydes, enones, and imines have become possible by using either chiral Lewis acids or Lewis bases as chiral catalysts.[1] Chiral Lewis bases activate diorganozincs by coordinating to the zinc atom and by forming chiral zincate (Scheme 12.1), because of the enhanced nucleophilicity of organo moiety of chiral zincate, this activated organo moiety adds to, for example, aldehydes in the enantioselective manner. On the other hand, chiral Lewis acids activate aldehydes by coordinating to the oxygen atom of aldehydes. Thus the electrophilicity of aldehyde is enhanced enough to be attacked by diorganozinc from one enantioface of the aldehydes.



Scheme 12.1

Herein, we describe highly enantioselective and diastereoselective additions of diorganozincs to aldehydes, imines, and enones. Enantioselective cyclopropanation of allylic alcohols will also be mentioned.

2. Enantioselective additions of diorganozincs to aldehydes using chiral catalysts

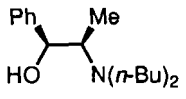
As the nucleophilicity of dialkylzinc is accelerated by the presence of β amino-alcohol, diethylzinc adds to benzaldehyde to afford 1-phenylpropanol.[2] Several chiral β-aminoalcohols **1–7** have been proven to be highly enantioselective catalysts for the addition of primary dialkylzincs mostly to aromatic aldehydes. For example, 1-phenylpropanol is prepared with high *ee* from the enantioselective addition of diethylzinc to benzaldehyde using **1–7** (Fig. 12.1, the *ee* and configuration of prepared 1-phenylpropanol are shown in parentheses).[3a-g]

Among chiral β-aminoalcohols, (1*S*, 2*R*)-*N*,*N*-dibutylnorephedrine (DBNE) **1** is a highly enantioselective catalyst even for the addition to aliphatic aldehydes affording various aliphatic *sec*-alcohols with up to 93% *ee*.[3a] The enantioselectivities of the chiral aliphatic alcohols obtained are higher than those obtained by the enantioselective reduction of aliphatic ketones. Most of the chiral β-aminoalcohols contain one asymmetric carbon atom bound to the oxygen atom, whereas diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) **2a**[3b] contains only one asymmetric carbon atom bound to the nitrogen atom. Enals such as (*E*)-cinnamaldehyde are alkylated to afford optically active allylic alcohols. Highly enantioselective chiral catalysts other than aminoalcohols are chiral bipyridylalkanol **8**,[3h] piperazine **9**,[3i] oxazaborolidine **10**,[3j] aminothiolate **11**,[3k] aminothiols **12**,[3l,m] and aminothioester **13**[3n] (Fig. 12.1).

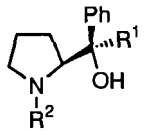
Asymmetric amplification, i.e. *ee* of the product is higher than that of the chiral catalyst, is observed with some chiral β-aminoalcohols **7**[3g] and **3**.[3o] Formation of the less reactive dimeric complex from (+) and (–) catalysts increases the *ee* of the higher reactive monomeric catalyst. The remaining monomeric chiral catalyst with higher *ee* than that of the total chiral catalyst affords *sec*-alcohols with higher *ee*.[3o]

With regard to diorganozincs other than primary dialkylzincs, various diorganozincs such as divinylzinc (> 96% *ee*, addition to benzaldehyde),[4a] difurylzinc (72% *ee*, addition to benzaldehyde),[5] diphenylzinc (78–82% *ee*, addition to various aldehydes),[6a] and diisopropylzinc (93% *ee*, addition to benzaldehyde)[7] have been utilized in the chiral β-aminoalcohol catalysed reactions. Alkenyl(alkyl)zincs[4b,c] and alkynyl(alkyl)zincs[8] afford the corresponding chiral allylic and propargyl alcohols.

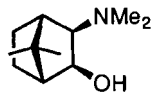
The enantioselective addition of dialkylzinc to aldehydes catalysed by chiral β-aminoalcohol has also excellent chemoselectivities which are not usually achieved with Grignard reagents and alkyllithiums both of which have excess reactivities. Thus enantio- and chemoselective addition of dialkylzincs



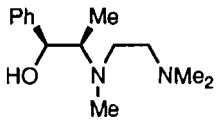
1 (90% *ee*, *S*)



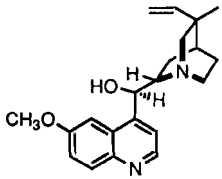
2a; R^1=Ph, R^2=Me (97% *ee*, *S*)
2b; R^1=H, R^2=CH_2-*t*-Bu (100% *ee*, *R*)



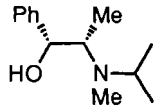
3 (99% *ee*, *S*)



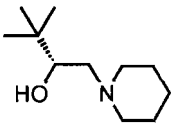
4 (91% *ee*, *S*)



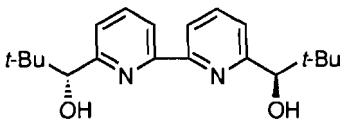
5 (68% *ee*, *R*)



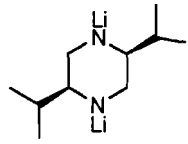
6 (80% *ee*, *R*)



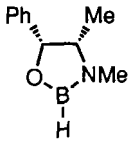
7 (98% *ee*, *R*)



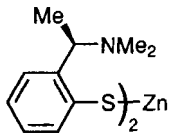
8 (97% *ee*, *R*)



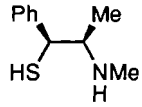
9 (92% *ee*, *R*)



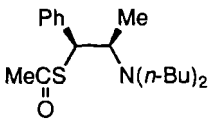
10 (95% *ee*, *R*)



11 (94% *ee*, *S*)



12 (80% *ee*, *R*)



13 (99% *ee*, *S*)

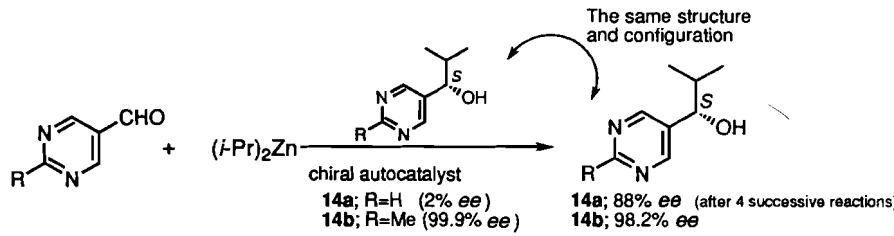
Fig. 12.1

to formylesters and ketoaldehydes using chiral catalysts **1** and **2a** afford the corresponding optically active γ- and δ-hydroxyesters (thus γ-butyro-, δ-valerolactones)[9] and γ-hydroxyketones[10] with high *ee*.

Unlike conventional asymmetric synthesis, asymmetric autocatalytic reaction does not require the use of any chiral catalyst of different structure

from the product and the separation process of the catalyst from the product.

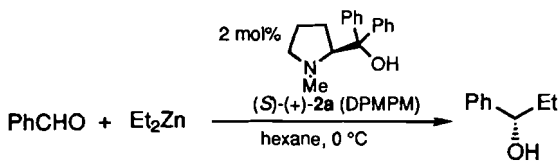
Highly enantioselective asymmetric autocatalytic reactions have been reported using chiral pyrimidyl-[11a,b] and quinolylalkanols (Scheme 12.2).[11c] (*S*)-2-methyl-1-(2-methyl-5-pyrimidyl)-1-propanol (**14b**, 99.9% *ee*) autocatalyses the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde to afford **14b** itself of the same configuration with 98.2% *ee*.[11a] Moreover **14a** shows asymmetric autocatalytic reaction with amplification of *ee*. Thus, starting from (*S*)-**14a** with only 2% *ee*, four successive autocatalytic reactions afford (*S*)-**14a** with 88% *ee*.[11b]



Scheme 12.2

Protocol 1.
Enantioselective addition of diethylzinc to benzaldehyde using (*S*)-DPMPM (Structure 2a) as a chiral catalyst[3b]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Equipment

- Two-necked, round-bottomed flask (30 mL) fitted with a reflux condenser, and a magnetic stirring bar—a three-way stopcock is fitted to the top of the condenser and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- Oil-bath for heating

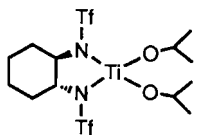
Materials

- (*S*)-(+)-**2a** (DPMPM)[e] (FW 267.37), 5.3 mg, 0.02 mmol
- Distilled benzaldehyde (FW 106.12), 106.1 mg, 1 mmol — **toxic**
- 1 M hexane solution of diethylzinc 2.2 mL, 2.2 mmol — **flammable liquid, moisture-sensitive**
- Dry, distilled hexane — **flammable liquid, irritant**

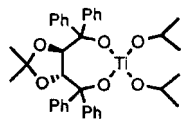
1. Flame dry the reaction vessel and syringe fitted with injection needle *in vacuo*. Fill the reaction vessel with argon after it cools to room temperature.
2. Add a solution of DPMPM and benzaldehyde in hexane (2.5 mL). Reflux the mixture for 20 min using oil-bath, then cool it to 0°C.
3. Add a solution of diethylzinc in hexane over 5 min, then stir the reaction mixture for 4 h at 0°C.
4. Add 1 M HCl (5 mL) for quenching the reaction and extract the aqueous layer with dichloromethane (3 × 15 mL). Dry the combined extracts with anhydrous sodium sulfate and concentrate under reduced pressure.
5. Purify the crude product by silica gel TLC (Merck Kieselgel 60 $_{GF254}$) using chloroform, pure 1-phenylpropanol is obtained in quantitative yield. Identify it by ^{1}H NMR, IR, comparing with an authentic sample.
6. Determine the enantiomeric excess by optical rotation or by HPLC using a chiral column to be 97% *ee*. (HPLC analysis: chiral column, Daicel Chiralcel OB, 4.6 × 250 mm; detection, 254 nm UV light; eluent, 3% 2-propanol in hexane; flow rate, 0.5 mL/min; retention time, 19 min for *S* isomer, 26 min for *R* isomer.)

[a]Both of (*S*)-(+)- and (*R*)-(−)-DPMPM are commercially available from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan).

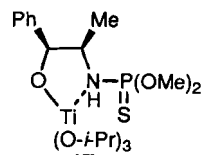
Chiral Lewis acids for the highly enantioselective addition of diorganozincs to aldehydes include chiral disulfonamide-Ti(O*i*-Pr)$_2$ **15**,[12] chiral TADDOL-Ti(O*i*-Pr)$_2$ **16**,[13] and chiral thiophosphoramidate-Ti(O*i*-Pr)$_3$ **17**[14] (Fig. 12.2). The reactions using these Lewis acid catalysts proceed faster than those of the Lewis base catalysed reaction. Aldehydes are activated by coordination to titanium. The presence of a stoichiometric amount of Ti(O*i*-Pr)$_4$ is needed in the reactions using **15–17**. The role of a stoichiometric amount of Ti(O*i*-Pr)$_4$ is believed to convert the formed zinc alkoxide into titanium alkoxide which facilitates the dissociation of the chiral catalyst from the chiral product, thereby accelerating the catalytic cycle.[13,14] Both aromatic and aliphatic aldehydes are alkylated with high enantioselectivities. Enals are alkylated to afford chiral allylic alcohols.[15] Various dialkylzincs prepared *in situ* from Grignard reagents can be used with **16**.[13] Several functionalized diorganozincs possess-



15 (Tf = SO_2CF_3)



16



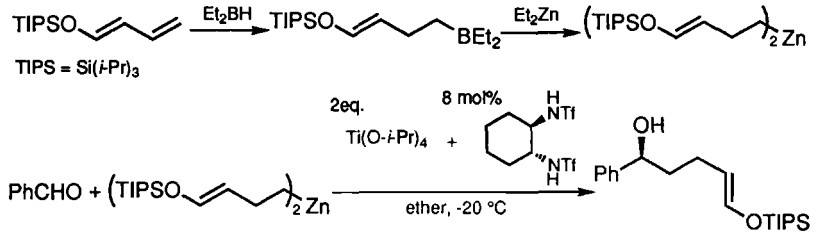
17

Fig. 12.2

ing moieties such as silyl enol ether[16a] and ester groups,[16b] prepared from the corresponding halides or by the transmetallation reaction, have been successfully utilized in the catalytic enantioselective addition to aldehydes using **15**.

Protocol 2.
Enantioselective addition of functionalized diorganozinc to benzaldehyde catalysed by chiral disulfonamide-Ti(O*i*-Pr)$_2$ (Structure 15)[16a]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times. Keep flammable substances, especially organic solvents, from reaction vessels when handling neat diethylzinc because it ignites immediately in the air.



A. *Preparation of functionalized diorganozinc by hydroboration and boron–zinc exchange*

Equipment

Materials

- Two-necked flask (50 mL), and a magnetic stirring bar—a three-way stopcock is fitted to one of the tops and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- Ice-bath for cooling to 0°C and water-bath for warming to 35°C

- (*E*)-1-(triisopropylsiloxy)-1,3-butadiene (FW 226.4), 1.13 g, 5 mmol
- Triethylborane (FW 98), 0.549 g, 5.6 mmol — **moisture-sensitive, flammable liquid pyrophoric, toxic**
- Borane–methyl sulfide complex (FW 76.97), 0.431 g, 5.6 mmol
- Diethylzinc (FW 123.49, d 1.205), 1 mL, 10 mmol — **moisture-sensitive, flammable liquid pyrophoric, moisture-sensitive**

1. Flame dry the reaction vessel and syringe fitted with injection needle *in vacuo*. Fill the reaction vessel with argon after it gets cool.
2. Charge (*E*)-1-(triisopropylsiloxy)-1,3-butadiene into the reaction vessel, then add diethylborane, prepared from triethylborane and borane–methyl sulfide complex, at 0°C over 10 min.
3. Warm the reaction mixture to 35°C and stir it for 6 h at the temperature, then

evaporate the volatiles *in vacuo* (0.7 mmHg) to afford the hydroborated product.

4. Add neat diethylzinc to the organoborane at 0°C and stir the reaction mixture for 20 min, then evaporate it *in vacuo* (0.7 mmHg) for 10 h at room temperature to eliminate the excess diethylzinc and formed triethylborane.
5. Dilute the resulting dialkylzinc with diethyl ether (20 mL) which is directly used in the enantioselective alkylation.

B. *Enantioselective alkylation of benzaldehyde*

Equipment

- Two-necked flask (50 mL), and a magnetic stirring bar—a three-way stopcock is fitted to one of the tops and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- Ethanol:dry ice bath for cooling

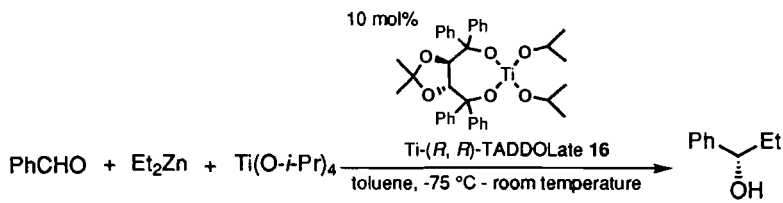
Materials

- (1*R*,2*R*)-1,2-*N*,*N*'-*bis*(trifluoromethanesulfonylamino)cyclohexane[12] (FW 394.51), 30 mg, 0.08 mmol
- Titanium(IV) isopropoxide (FW 284.26), 0.57 g, 2 mmol — **flammable liquid, irritant**
- 0.98 M hexane solution of diethylzinc, 12.4 mL, 12.2 mmol — **flammable liquid, moisture-sensitive**
- Distilled benzaldehyde (FW 106.12), 120 mg, 1.13 mmol — **toxic**
- Dry, distilled diethyl ether — **flammable liquid, toxic**

1. Flame dry the reaction vessel and syringe fitted with injection needle *in vacuo*. Fill the reaction vessel with argon after it cools to room temperature.
2. Add a solution of titanium(IV) isopropoxide in diethyl ether (1 mL), then add (1*R*,2*R*)-1,2-*N*,*N*'-*bis*(trifluoromethanesulfonylamino)cyclohexane, and cool the reaction mixture to –60°C.
3. Add the functionalized diorganozinc via syringe within 10 min, stir the green reaction mixture at –60°C for 20 min, then warm it to –20°C and stir it for additional 10 min. Finally add benzaldehyde and stir the reaction mixture for 10 h at the temperature.
4. Add brine (30 mL) for quenching the reaction and extract the aqueous layer with diethyl ether. Dry the extracts over anhydrous sodium sulfate and concentrate under reduced pressure.
5. Purify the crude product by chromatography (diethyl ether:hexane, 1:8) and the pure alcohol is obtained with 77% yield. Identify it by ^{1}H and ^{13}C NMR, IR, elemental analysis, and mass spectrum.
6. Determine the enantiomeric excess by NMR spectrum of the corresponding *O*-acetylmandelate, which is prepared from the obtained alcohol and (*S*)-(+)-*O*-acetylmandelic acid (> 96% *ee* (*S*): ratio of the integration of the doublet peak at 6.28 and 6.03 p.p.m.).

Protocol 3.
Enantioselective addition of diethylzinc to benzaldehyde catalysed by titanium-TADDOLate (Structure 16)[13]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times. Keep flammable substances, especially organic solvents, from reaction vessels when handling neat diethylzinc because it ignites immediately in the air.



Equipment

- Two-necked, round-bottomed flask (100 mL), and a magnetic stirring bar—a three-way stopcock is fitted to one of the tops and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- Dry ice bath for cooling

Materials

- (*R*,*R*)-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) (FW 466.58), 233.3 mg, 0.5 mmol
- Dry, distilled titanium(IV) isopropoxide (FW 284.26), 142.1 mg, 0.5 mmol for Ti-TADDOL and 1.71 g, 6 mmol — **flammable liquid, irritant**
- Distilled benzaldehyde (FW 106.12), 530.6 mg, 5 mmol — **toxic**
- 2 M toluene solution of diethylzinc, 9 mL, 18 mmol — **flammable liquid, moisture-sensitive**
- Dry, distilled toluene — **flammable liquid, toxic**

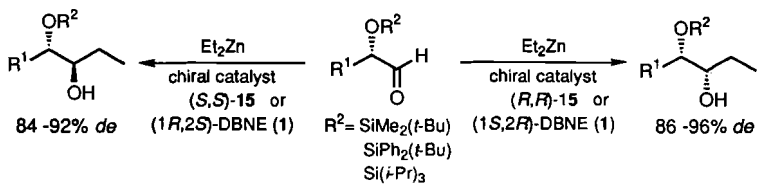
1. Flame dry the reaction vessel and syringe fitted with injection needle *in vacuo*. Fill the reaction vessel with argon after it cools to room temperature.
2. Add TADDOL, then a solution of titanium(IV) isopropoxide in toluene (15 mL), and stir the resulting yellow solution for 3 h at room temperature. Remove solvent and 2-propanol liberated by ligand exchange under high vacuum at room temperature and dry the obtained residue under the same conditions for 1–2 h.
3. Add a solution of titanium(IV) isopropoxide in toluene (15 mL) and benzaldehyde and cool the resulting yellow solution to –25°C, then add diethylzinc at such a rate that the reaction temperature can be kept below –20°C.
4. Stir the reaction mixture for 15 h at *ca.* –25°C, then add saturated aqueous ammonium chloride solution (15 mL) for quenching the reaction, and warm the mixture slowly to room temperature. Filter the mixture through celite to remove the insoluble products resulting from hydrolysis.

5. Separate the organic phase and extract the aqueous layer with diethyl ether (3 × 30 mL). Wash the combined organic phase with brine, dry over magnesium sulfate, and concentrate under reduced pressure.
6. Purify the crude product by bulb-to-bulb distillation or flash chromatography (SiO_2: 0.040–0.063 mm, Fluka, Switzerland) to give pure 1-phenylpropanol with 99% yield. Identify it by ^1H NMR, comparing with an authentic sample.
7. Determine the enantiomeric excess by capillary gas chromatography (HRGC or MEGA HRGC 5160, Carlo Erba); column: WCOT fused silica, CP-Cyclodextrin-β-2,3,6-M-19, 50 m × 0.25 mm (chrompack); injector temperature, 230°C; detector temperature, 250°C; initial temperature, 80°C; heating rate, 1°C/min; pressure, 1.3 kPa (H_2).

Heterogeneous chiral catalysts are useful because of the easier separation of catalyst from the product and recovery process than homogeneous chiral catalysts. Heterogeneous chiral catalysts supported on polystyrene-type resin catalyse the highly enantioselective addition of dialkylzincs to aldehydes.[17]

3. Chiral catalyst controlled diastereoselective addition of diorganozincs to chiral aldehydes

Diastereoselective addition of organometallic reagents to α-chiral aldehydes usually follows the Cram's rule or Felkin–Ahn model. However, the sense of the diastereoselectivity in the catalysed addition of dialkylzinc to α-chiral aldehydes is determined not by the chirality of aldehyde but by the configuration of the chiral catalysts. By choosing the appropriate enantiomer of the chiral catalyst, one can obtain the desired diastereomer from the diastereoselective addition of dialkylzincs to α-chiral aldehydes.[18] Either of the diastereomers of protected chiral 1,2-diols and 1,3-diols is synthesized using the appropriate enantiomer of the chiral catalysts [(1*S*,2*R*)-**1**, (*R*,*R*)-**15**, and their enantiomers] from the addition of diorganozincs to protected α-hydroxy-[19] and β-hydroxyaldehydes (Scheme 12.3).[20]



Scheme 12.3

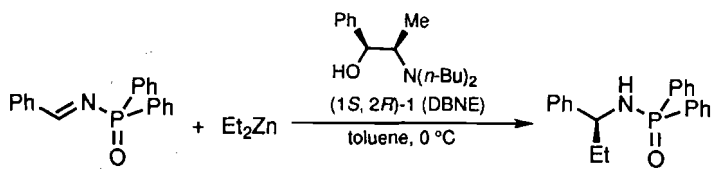
4. Enantioselective addition of dialkylzincs to imines using chiral ligands; asymmetric synthesis of optically active amines

Enantioselective addition of organometallic reagents to prochiral imines is a less developed reaction compared with the enantioselective addition to prochiral aldehydes. As the nucleophilicity of diethylzinc is not strong enough, diethylzinc does not add to *N*-phenyl- and *N*-alkylimines even in the presence of an aminoalcohol. However, highly enantioselective additions of dialkylzincs to imines has been reported using activated imines with an electron withdrawing group on the nitrogen atom. *N*-diphenylphosphinyl-arylimine[21a,b] and -ferrocenylimine[21c] are alkylated enantioselectively in the presence of chiral *N*,*N*-dialkylnorephedrines such as DBNE **1** or 2-morpholino-1-phenylpropan-1-ol with dialkylzincs in up to 95% *ee*.[21b] Heterogeneous chiral ligands, i.e. ephedrine supported on polystyrene[22] and the co-polymer[21b] of *N*-alkyl-*N*-vinylbenzylnorephedrine and styrene, also accelerate the enantioselective addition of diethylzinc to *N*-diphenylphosphinylimine.

Most of the product, i.e. *N*-diphenylphosphoramides, are crystalline and their *ee*s can often be improved to > 98% *ee* by the recrystallization.[21a] *N*-diphenylphosphinyl group can be easily removed by acid hydrolysis (3 M HCl-THF,[23] *p*-TsOH-MeOH-H_2O[21c]) and the corresponding chiral amines are obtained without racemization. In addition, *N*-acylimines are utilized in the enantioselective addition of diethylzinc promoted by DBNE **1** affording chiral amides with up to 76% *ee*.[24]

Protocol 4.
Enantioselective ethylation of *N*-diphenylphosphinylimine using DBNE as a chiral ligand[21a]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Equipment

- Two-necked, round-bottomed flask (30 mL), and a magnetic stirring bar—a three-way stopcock is fitted to one of the tops and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- Ice-bath for cooling to 0°C

Materials

- (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE **1**)[a] (FW 263.42), 65.9 mg, 0.25 mmol
- Recrystallized *N*-diphenylphosphinylimine (FW 305.32), 76.3 mg, 0.25 mmol — **white solid**
- 1 M hexane solution of diethylzinc, 0.75 mL, 0.75 mmol — **flammable liquid, moisture-sensitive**
- Dry, distilled toluene — **flammable liquid, toxic**

1. Flame dry the reaction vessel and syringe fitted with injection needle *in vacuo*. Fill the reaction vessel with argon after it cools to room temperature.
2. Add a solution of DBNE **1** and phosphinylimine in toluene (1.5 mL) at room temperature and stir the mixture for 10 min.
3. Cool the reaction vessel to 0°C, add diethylzinc slowly, and stir the reaction mixture for 22 h at the temperature.
4. Add saturated aqueous ammonium chloride (5 mL) for quenching the reaction and extract the aqueous layer with dichloromethane (4 × 10 mL). Dry the combined extracts over anhydrous sodium sulfate and concentrate under reduced pressure.
5. Purify the crude product by silica gel TLC (Merck Kieselgel 60 $_{GF254}$) (developing solvent, acetone:hexane, 1:2) and the pure phosphoramide is obtained with 61% yield. Identify it by ^{1}H NMR and IR.
6. Determine the enantiomeric excess to be 84% *ee* by HPLC using a chiral column (HPLC analysis: chiral column, Daicel Chiralcel OD, 4.6 × 250 mm; detection, 254 nm UV light; eluent, 3% 2-propanol in hexane; flow rate, 1 mL/min; retention time, 14 min for *R* isomer, 20 min for *S* isomer).
7. Improve the enantiomeric excess of the phosphoramide to 98% *ee* by recrystallization.

[a] Both of (1*S*,2*R*)- and (1*R*,2*S*)-DBNE 1 are commercially available from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan).

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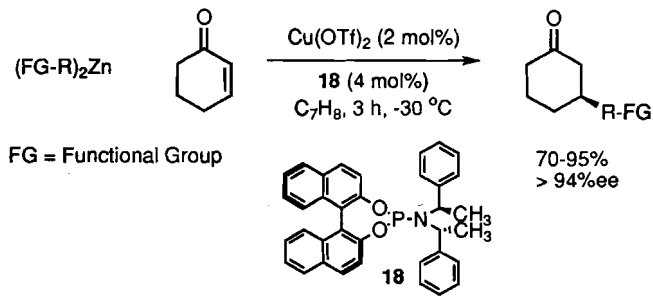
5. Enantioselective conjugate addition of dialkylzincs to enones using chiral catalysts; asymmetric synthesis of β-substituted ketones

Enantioselective conjugate addition of organometallic reagents to enones afford optically active β-substituted ketones.[25] The conjugate addition of dialkylzinc to enones is accelerated by the presence of Ni(acac)$_2$ (acac = acetylacetonate).[26] The first highly enantioselective catalytic conjugate addition of diethylzinc to chalcone is reported by the use of Ni(acac)$_2$, (1*S*,2*R*)-**1** (DBNE), bipyridine in mixed solvent containing acetonitrile (up to 90% *ee*).[27] Chiral bipyridylalkanol **8**[28] and aminoalcohols[29] other than DBNE have been utilized for the same reaction. In these reactions, acetonitrile is the solvent

of choice. A chiral nickel catalyst supported on zeolite also catalyses the conjugate addition of diethylzinc to chalcone.[30]

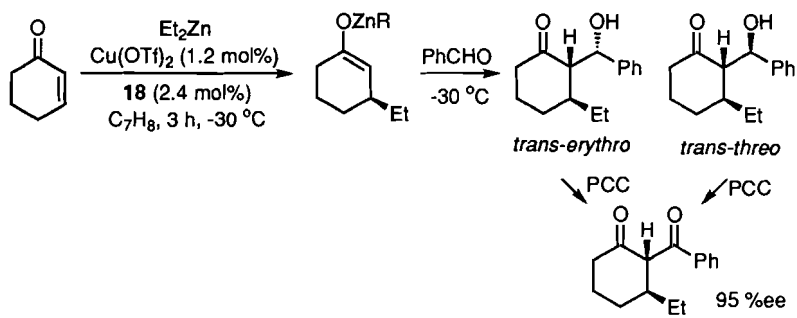
A substoichiometric or stoichiometric amount of chiral aminoalcohol accelerates the enantioselective addition of diethylzinc to enones even without $Ni(acac)_2$ in up to 94% *ee*.[31]

Recently, Feringa has documented highly enantioselective conjugate addition reactions of functionalized dialkylzinc reagents to cyclic and acyclic enones catalysed by a chiral copper complex of phosphorus amidites.[32] The phosphorous amidate **18** contains two chiral structural units, the (*R,R*)-*bis*(1-phenylethyl)amine and the (*S*)-2,2′-binaphthol, and the catalyst is prepared from the $Cu(OTf)_2$ (2 mol%) and the phosphorous amidate (4 mol%). Excellent yields and enantiomeric excesses are realized in the addition of functionalized dialkylzinc reagents to cyclohexenone and substituted cyclohexenones, yields typically 70–95% with enantiomeric excesses ranging from 94% to greater than 98%.



Scheme 12.4

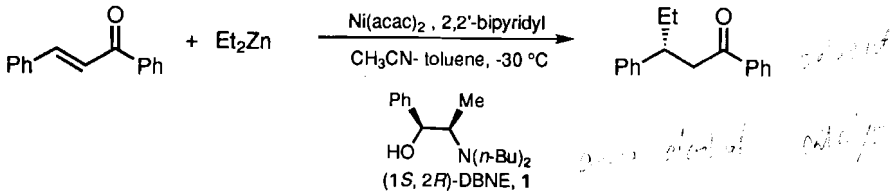
The reaction has been further extended into a tandem conjugate addition/enolate trapping sequence, whereby the *in situ* generated zinc enolate was trapped with benzaldehyde. This resulted in an approximately 3:7 mixture of *trans-erythro*:*trans-threo* aldol adducts, isolated in 88% yield. Subsequent oxidation of these products gave a single isomer of the corresponding diketone with 95% *ee*.



Scheme 12.5

Protocol 5.
Enantioselective catalytic conjugate addition of diethylzinc to chalcone using DBNE (Structure 1) as a chiral ligand[27]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



(1*S*, 2*R*)-DBNE, **1**

Equipment

- Two-necked, round-bottomed flask (30 mL), and a magnetic stirring bar—a three-way stopcock is fitted to one of the tops and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- Oil-bath for warming to 80°C and bath for cooling to 0°C

Materials

- $Ni(acac)_2$ (FW 256.91), 36 mg, 0.14 mmol — **hygroscopic**
- 1 M toluene solution of diethylzinc, 2.4 mL, 2.4 mmol — **flammable liquid, moisture-sensitive**
- Chalcone (FW 208.26), 416.5 mg, 2 mmol
- (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE **1**) (FW 263.42), 89.6 mg, 0.34 mmol
- 2,2'-bipyridyl (FW 156.19), 21.9 mg, 0.14 mmol — **toxic, irritant**
- Dry, distilled acetonitrile — **flammable liquid, toxic**

1. Flame dry the reaction vessel and syringe fitted with injection *in vacuo*. Fill the reaction vessel with argon after it cools to room temperature.
2. Add $Ni(acac)_2$ and DBNE **1** in CH_3CN (2 mL), stir the mixture at 80°C for 1 h, then remove the solvent *in vacuo*.
3. Add 2,2'-bipyridyl and CH_3CN (2 mL), stir the mixture at 80°C for 1 h, then cool the resulting green solution to room temperature.
4. Add a solution of chalcone in CH_3CN (4 mL) and stir the mixture at room temperature for 20 min, then cool it to –30°C, then add dropwise diethylzinc, and stir the reaction mixture for 12 h at –30°C.
5. Add 1 M hydrochloric acid (6 mL) for quenching the reaction and extract aqueous layer with dichloromethane (4 × 7 mL). Dry the combined organic extracts over anhydrous sodium sulfate and concentrate under reduced pressure.
6. Purify the crude product by silica gel TLC (Merck Kieselgel 60 $_{GF254}$) (developing solvent, chloroform:hexane, 1:1) and the product is obtained in 47% yield. Identify it by ^1H NMR and IR.

Protocol 5. *Continued*

7. Determine the enantiomeric excess by HPLC using a chiral column to be 90% *ee* (HPLC analysis: chiral column, Daicel Chiralcel OD, 4.6 × 250 mm; detection, 254 nm UV light; eluent, 0.25% 2-propanol in hexane; flow rate, 0.5 mL/min; retention time, 40 min for *S* isomer, 45 min for *R* isomer).

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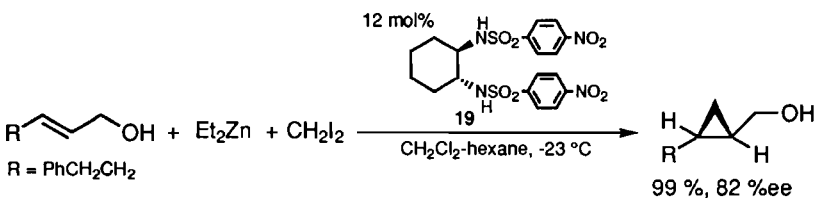
6. Enantioselective cyclopropanation of allylic alcohols using chiral catalysts

Cyclopropanation of olefins (Simmons–Smith reaction) smoothly proceeds using diethylzinc in combination with diiodomethane. The reaction is much faster with allylic alcohols or its ether derivatives than that with simple olefins.

There is only one example of a catalytic enantioselective cyclopropanation of allylic alcohols using an electron withdrawing chiral disulfonamide **19** as a chiral ligand (Protocol 6).[33] Stoichiometric highly enantioselective cyclopropanations of allylic alcohols are reported using a chiral diethyl tartrate[34] and a chiral tartamide.[35]

Protocol 6.
Enantioselective cyclopropanation of an allylic alcohol using chiral disulfonamide (Structure 19) as a chiral catalyst[33b]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl and/or latex gloves and chemical-resistant goggles at all times.



Equipment

- Two-necked, round-bottomed flask (500 mL), and a magnetic stirring bar—a three-way stopcock is fitted to one of the tops and connected to a vacuum/argon source; another top is sealed with a rubber septum
- Syringe fitted with injection needle
- Vacuum/inert gas source (argon source is an argon balloon)
- CCl_4:dry ice bath for cooling at –23 °C

Materials

- (1*R*,2*R*)-1,2-*N*,*N*'-*bis*(4-nitrobenzenesulfonylamino)-cyclohexane **19**[12a] (FW 484.51), 354 mg, 0.73 mmol
- (*E*)-5-phenyl-2-penten-1-ol[a] (FW 162.23), 988 mg, 6.1 mmol — **highly toxic, flammable liquid**
- 0.98 M hexane solution of diethylzinc, 12.4 mL, 12.2 mmol — **flammable liquid, moisture-sensitive**
- Dry, distilled diiodomethane (FW 267.84), 4.89 g, 18.3 mmol — **corrosive, light-sensitive**
- Dry, distilled dichloromethane — **irritant, toxic**

1. Flame dry the reaction vessel and syringe fitted with injection needle *in vacuo*. Fill the reaction vessel with argon after it cools to room temperature.
2. Add a solution of the chiral sulfonamide and (*E*)-5-phenyl-2-penten-1-ol in dichloromethane (200 mL) at room temperature.
3. Cool the reaction vessel to –23°C, add diethylzinc and then a solution of diiodomethane in dichloromethane (20 mL), and stir the reaction mixture for 5 h at the temperature.
4. Add 2 M NaOH (40 mL) for quenching the reaction and extract the aqueous layer with diethyl ether. Wash the combined extracts with saturated NaCl solution, dry it over anhydrous sodium sulfate, and concentrate under reduced pressure.
5. Purify the crude product by silica gel TLC (Merck Kieselgel 60 $_{GF254}$) (developing solvent, ethyl acetate:hexane, 1:4) and pure (2*R*,3*R*)-5-phenyl-2,3-methano-1-pentanol is obtained in quantitative yield. Identify it by ^{1}H NMR, IR, and mass spectrum.
6. Determine the enantiomeric excess to be 82% *ee* by HPLC using a chiral column (HPLC analysis: chiral column, Daicel Chiralpak AD, 4.6 × 250 mm; detection, 254 nm UV light; eluent, 2% 2-propanol in hexane; flow rate, 0.5 mL/min; retention time, 30 min for (2*R*,3*R*)-isomer, 33 min for (2*S*,3*S*)-isomer).

[a] (*E*)-5-phenyl-2-penten-1-ol was prepared by *E*-selective Horner–Emmons reaction of 3-propionaldehyde and triethylphosphonoacetate, followed by a usual reduction of ethyl ester to allyl alcohol.

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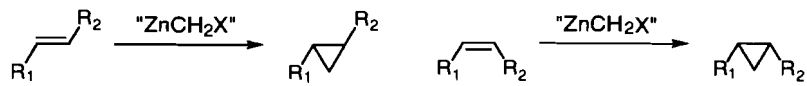
13

Cyclopropanation mediated by zinc organometallics

ANDRÉ B. CHARETTE

1. Introduction

Haloalkylzinc-derived organometallics are among the reagents of choice for the stereoselective conversion of olefins to cyclopropanes. These reagents were shown to be very effective cyclopropanating reagents with unique properties and reactivities. They allow the stereospecific conversion of (*E*)- or (*Z*)-alkenes to (*E*)- or (*Z*)-cyclopropanes (Scheme 13.1). Although a variety of olefins containing various functional groups have been successfully converted into cyclopropanes under these conditions, these reactions are best performed on electron-rich olefins or those containing basic groups that can pre-coordinate to the reagent.[1] More specifically, the highest yields and reaction rates are usually observed in the cyclopropanation of allylic alcohols and ethers in non-etheral solvents. Table 13.1 summarizes the methods available to generate these reagents. The synthetic potential of the oldest member in this class of reagents, $IZnCH_2I$, was disclosed by Simmons and Smith in 1958.[2] This reagent was recently characterized by NMR[3] and X-ray crystallography.[4]



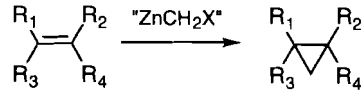
R_1 and/or R_2 = alkyl, aryl, alkenyl, CH_2OR, OR, NHBoc, $B(OR_2)$, AlR_2, I, SiR_3, SnR_3, etc.

Scheme 13.1

$IZnCH_2I$ was traditionally prepared by mixing an activated form of zinc (such as zinc–copper couple) with CH_2I_2 in etheral solvents (Table 13.1, entry 1).

Numerous methods or procedures have been reported for the activation of zinc[5] and the cyclopropanation of the steroid derivatives **1** and of 2-cyclohexen-1-one serve as examples to illustrate two commonly used methods to activate the zinc dust (Equations 13.1 and 13.2, Protocols 1 and 2).[6,7] The first reaction is a nice example of the directing ability and acceleration effect of an alcohol or of the zinc alkoxides under the Simmons–Smith conditions.

Table 13.1 Important methods for the preparation of cyclopropanating reagents 'MCH_2X' (X = Cl, I)

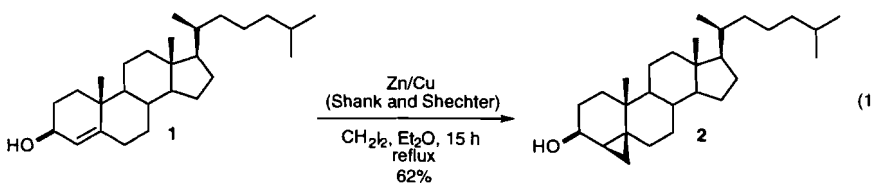


Entry	Method	Reactants	Reagent
1	Oxidative addition	Zn/activator, CH_2I_2	$IZnCH_2I$
2a	Metal–halogen exchange	$EtZnI:CH_2I_2$ (1:1)	$IZnCH_2I$
2b		$Et_2Zn:CH_2I_2$ (1:1)	$EtZnCH_2I$
2c		$Et_2Zn:XCH_2I$ (1:2)	$Zn(CH_2X)_2$
3a	Nucleophilic displacement	$ZnX_2:CH_2N_2$ (1:1)	$XZnCH_2X$
3b		$ZnX_2:CH_2N_2$ (1:2)	$Zn(CH_2X)_2$

Pure zinc dust (99.998%, activated with 5% HCl)[8] and CH_2I_2 are also suitable precursors to $IZnCH_2I$, but ether must necessarily be used as solvent.[9] If zinc dust of lower purity is used, then pre-activation with TMSCl is necessary. It should be emphasized that this transformation cannot be accomplished in THF since $IZnCH_2I$ further reacts with zinc dust in this solvent.

Protocol 1.
Preparation of $IZnCH_2I$ from Zn–Cu couple (Shank and Shechter) and CH_2I_2:[10] the Simmons–Smith cyclopropanation of 3β-hydroxy-Δ^4-cholestene[6]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



(1)

Equipment

- One Erlenmeyer (500 mL) and a magnetic stirrer
- One three-necked flask (50 mL) equipped with gas inlet, a septa, a condenser, and magnetic stirring bar
- One Büchner funnel
- Dry gas-tight syringes with stainless steel needles
- Argon gas supply and inlet

Materials

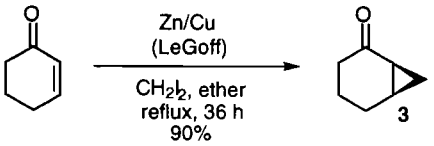
• Zn dust (FW 65.37), 49.2 g, 0.75 mol	**flammable solid, moisture-sensitive**
• 3% aqueous HCl	**corrosive, toxic**
• 2% aqueous $CuSO_4$	**toxic, irritant**
• Anhydrous ether	**flammable liquid, toxic**
• Distilled diiodomethane[a] (FW 267.84), 704 μL, 8.74 mmol	**corrosive, light-sensitive**
• Iodine, one crystal	**highly toxic, corrosive**
• 3β-hydroxy-Δ^4-cholestene (FW 386.65), 967 mg, 2.5 mmol	**harmful**

1. Weigh the zinc dust in an Erlenmeyer flask and add 3% aqueous HCl (40 mL). Stir rapidly for 1 min and decant the supernatant liquid.
2. Wash the zinc dust (as above) successively with three portions of 3% aqueous HCl (3 × 40 mL), five portions of distilled H_2O (5 × 100 mL), two portions of 2% aqueous $CuSO_4$ (2 × 75 mL), five portions of distilled H_2O (5 × 100 mL), four portions of absolute EtOH (4 × 100 mL), and five portions of anhydrous ether (4 × 100 mL).
3. Transfer the zinc dust into a Büchner funnel and wash with additional anhydrous ether. After removal of the solvent by filtration, place the zinc dust in a vacuum desiccator over P_2O_5 for 24 h.
4. Flame dry a round-bottomed flask and accessories under dry argon. After cooling the apparatus to room temperature, add the zinc–copper couple (687 mg) and anhydrous ether (12 mL). Add a crystal of iodine and CH_2I_2 and stir at 35°C for 30 min.
5. Add a solution of 3β-hydroxy-Δ^4-cholestene in anhydrous ether (7 mL) over 20 min.
6. Maintain the reaction mixture under reflux for 1 h.
7. Cool to room temperature and add saturated aqueous NH_4Cl. Decant the solution from the precipitate and wash it with two portions of ether. Wash the organic layer with brine. Dry over Na_2SO_4, and evaporate the solvent.
8. Purify the crude residue by flash chromatography using hexanes:EtOAc (90:10). Pure 3β-hydroxy-4β,5-methanocholestane (622 mg, 62%) is obtained as white solid that can be crystallized from acetone. Characterize the product by ^1H NMR, IR spectroscopy, m.p., and elementary analysis.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.

Protocol 2.
Preparation of $IZnCH_2I$ from Zn–Cu couple (LeGoff) and CH_2I_2:[11] diastereoselective cyclopropanation of 2-cyclohexen-1-one[7]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



(2)

Equipment

- One Erlenmeyer (25 mL) and a magnetic stirrer
- One two-necked round-bottomed flask (100 mL) equipped with a refluxing condenser, a gas inlet, a septa, a magnetic stirring bar, a glass stopper
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

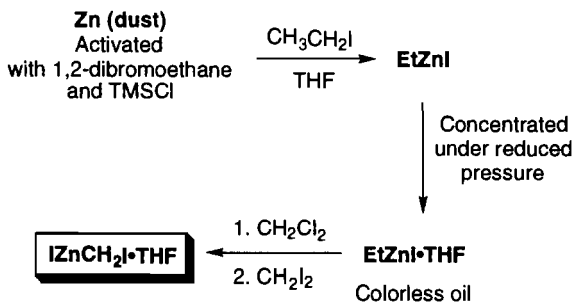
• Zn dust (FW 65.37), 2.8 g, 42.8 mmol	**flammable solid, moisture-sensitive**
• $Cu(OAc)_2 \cdot H_2O$ (FW 199.65), 0.16 g, 0.8 mmol	**irritant**
• Glacial acetic acid	**corrosive, hygroscopic**
• Ether	**flammable liquid, toxic**
• Distilled diiodomethane[a] (FW 267.84), 2.3 mL, 29 mmol	**corrosive, light-sensitive**
• 2-cyclohexen-1-one (FW 96.13), 0.96 g, 10 mmol	**highly toxic**
• Distilled, dry ether[b]	**toxic, irritant**

1. Weigh the cupric acetate monohydrate in an Erlenmeyer flask. Dissolve cupric acetate monohydrate in glacial acetic acid (5 mL).
2. Add zinc dust. After 90 sec, decant as much as the supernatant acetic acid as possible.
3. Wash the dark reddish grey couple with acetic acid (1 × 5 mL) and then with ether (3 × 10 mL). The moist couple is ready to use.
4. Flame dry the reaction flask and accessories under dry argon. After cooling the apparatus to room temperature, add the moist couple and anhydrous ether (20 mL).
5. Heat the mixture to reflux and add a few drops of CH_2I_2. After the mild exothermic reaction has been initiated, add a mixture of 2-cyclohexen-1-one and CH_2I_2 over 30 min via a syringe.
6. After the addition, replace the septum on the neck used for the addition with a glass stopper, heat the mixture under reflux for 36 h (under argon), and then cool to room temperature.
7. Add H_2O (2 mL) slowly and stir for 1 h. Add 10% aqueous HCl solution (10 mL) and dilute with ether (50 mL). Stir until both layers are clear.

8. Separate the organic and aqueous layers. Wash the organic layer with H_2O (10 mL) and with brine (10 mL). Dry over $MgSO_4$, and concentrate under reduced pressure. Distill the residual liquid and collect the colourless liquid boiling at 91 °C at 15 mmHg (1 g, 90%). Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, and high-resolution mass spectrometry.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] Ether was distilled over sodium benzophenone.

Another very good, but underused method for preparing $IZnCH_2I$ involves treatment of EtZnI•THF with CH_2I_2 (Table 13.1, entry 2a, Scheme 13.2).[12,13] This two-step sequence is particularly suitable for the large scale preparation of $IZnCH_2I$ for several reasons. The new convenient way to activate zinc metal *in situ* ($BrCH_2CH_2Br$, TMSCl)[14] in the first oxidative addition step precludes the tedious pre-activation of zinc powder. The Et–CH_2I exchange is clean and quantitative when EtZnI•THF is mixed with CH_2I_2. Most of the THF can easily be replaced by a more suitable solvent for the cyclopropanation reaction (one to two equivalents of THF must remains after the concentration under reduced pressure. This is necessary otherwise the Schlenk equilibrium is displaced toward the formation of Et_2Zn!). Once EtZnI is formed, the appropriate solvent can be added followed by CH_2I_2 to produce the reagent. Complications arising from the potential decomposition of $IZnCH_2I$ in the presence of excess zinc metal are, therefore, avoided with this method. As mentioned above, this side-reaction is often a problem when $IZnCH_2I$ is prepared from zinc dust and CH_2I_2 in THF. An application of this procedure is shown below (Protocol 6).



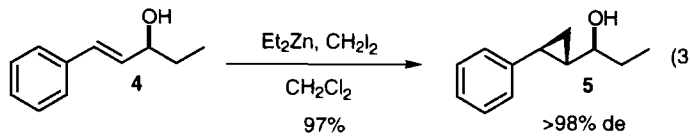
Scheme 13.2

More sophisticated methods to prepare various halomethylzinc reagents that avoid pre-activation of one of the precursors are also available. One of the most practical method to prepare these electrophilic halomethylzinc reagents has been disclosed by Furukawa and co-workers.[15] They found that

the substitution of the Zn–Cu couple by Et_2Zn to presumably form $EtZnCH_2I$ greatly facilitated the synthesis of the zinc carbenoid species (Table 13.1, entry 2b). Furthermore, since neat Et_2Zn is available, this method allowed the use of various non-basic solvents. The Furukawa reagent produced the highest diastereoselectivities in the cyclopropanation of chiral allylic alcohols (Equation 13.3, Protocol 3).[16]

Protocol 3.
Preparation of the Furukawa's reagent ($EtZnCH_2I$): *syn*-diastereoselective cyclopropanation of chiral acyclic allylic alcohols[16]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- One one-necked round-bottomed flask (50 mL) equipped with a gas inlet, a septa, a magnetic stirring bar.
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

- Et_2Zn neat (FW 123.49), 1 mL, 10 mmol — **pyrophoric, moisture-sensitive**
- Distilled diiodomethane[a] (FW 267.84), 0.8 mL, 10 mmol — **corrosive, light-sensitive**
- Distilled, dry CH_2Cl_2[b] — **toxic, irritant**
- (*E*)-1-phenyl-1-penten-3-ol (FW 162.23), 325 mg, 2 mmol — **harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add allylic alcohol **4** and CH_2Cl_2 (20 mL).
2. Cool the resulting solution to –10°C (acetone:ice), add Et_2Zn, and stir 5 min. Add diiodomethane and allow to warm to 25°C over 3 h.
3. Stir for an additional 1 h and check for the completion of the reaction by TLC analysis of the crude reaction mixture.
4. Add a saturated aqueous NH_4Cl solution (10 mL) to the reaction mixture, followed by ether (80 mL) and 10% aqueous HCl solution (10 mL). Stir the mixture until both layers are clear.
5. Separate the organic and aqueous layers. Wash the organic layer successively with a saturated aqueous Na_2SO_3 solution (20 mL), with a saturated aqueous $NaHCO_3$ solution (20 mL), and with brine (20 mL). Dry over $MgSO_4$, and evaporate the solvent.

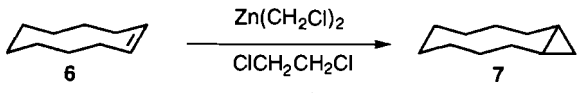
6. Purify the crude residue by flash chromatography using hexanes:EtOAc (85:15). Pure *syn*(1*S**,1′*S**,2′*S**)-1-(2-phenylcyclopropyl)-1-propanol (341 mg, 97%) is obtained as a colourless oil. Characterize the product by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and high-resolution mass spectrometry.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] CH_2Cl_2 was distilled over calcium hydride.

Denmark has recently demonstrated that $Zn(CH_2X)_2$ (X = I, Cl) could also be prepared by changing the stoichiometry of the reactants (Table 13.1, entry 2c).[17] These reagents were formed by mixing one equivalent of Et_2Zn with two equivalents of diiodomethane (X = I) or chloroiodomethane (X = Cl). The *bis*(iodomethyl)zinc was the first zinc carbenoid to be characterized by X-ray crystallography.[18] *Bis*(chloromethyl)zinc is slightly more reactive than the analogous iodo reagent and is especially useful in the cyclopropanation of non-activated olefins (Equation 13.4, Protocol 4)[17] or less reactive iodo-substituted allylic alcohols (Equation 13.5, Protocol 5).[19]

Protocol 4.
Preparation of $Zn(CH_2Cl)_2$ from Et_2Zn and $ClCH_2I$: cyclopropanation of *cis*-cyclodecene[17]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



(4)

Equipment

- One one-necked round-bottomed flask (50 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

- Et_2Zn neat (FW 123.49), 520 μL, 5.07 mmol — **pyrophoric, moisture-sensitive**
- Distilled chloroiodomethane (FW 176.38), 730 μL, 10 mmol — **corrosive, light-sensitive**
- Distilled, dry $ClCH_2CH_2Cl$[a] — **toxic, irritant**
- Distilled *cis*-cyclodecene (FW 166.31), 400 μL, 2.52 mmol — **harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add *cis*-cyclodecene and $ClCH_2CH_2Cl$ (12.5 mL).

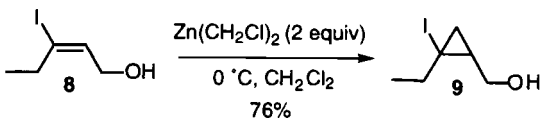
Protocol 4. *Continued*

2. Cool the resulting solution to 0°C, add Et_2Zn. Add $ClCH_2I$ dropwise and stir for 20 min at 0°C.
3. Carefully add a saturated aqueous NH_4Cl solution (20 mL) and warm to room temperature. Stir vigorously for 10 min and extract with *t*-butyl methyl ether (3 × 20 mL).
4. Separate the organic and aqueous layers. Wash the organic layer successively with H_2O (20 mL) and brine (20 mL). Dry over K_2CO_3, and evaporate the solvent.
5. Purify the crude residue by bulb-to-bulb distillation (110–115°C, 30 mmHg). Pure bicyclo[8.1.0]undecane (335 mg, 87%) is obtained as a colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry, and elementary analysis.

[a] $ClCH_2CH_2Cl$ was distilled over calcium hydride.

Protocol 5.
Cyclopropanation using preformed $Zn(CH_2Cl)_2$: cyclopropanation of (*E*)-3-iodopent-2-en-1-ol[19]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



(5)

Equipment

- One one-necked round-bottomed flask (25 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Dry gas-tight syringes with stainless steel needles
- One one-necked round-bottomed flask (5 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Temperature controlled bath

Materials

- Et_2Zn neat (FW 123.49), 0.2 mL, 2 mmol — **pyrophoric, moisture-sensitive**
- Chloroiodomethane[a] (FW 176.38), 705 mg, 4 mmol — **corrosive, light-sensitive**
- Distilled, dry, degassed $ClCH_2CH_2Cl$[b] — **toxic, irritant**
- (*E*)-3-iodopent-2-en-1-ol (FW 212.03), 140 mg, 0.66 mmol — **harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add dry, degassed $ClCH_2CH_2Cl$ (5 mL) and Et_2Zn to 25 mL flask.

2. Cool the resulting solution to 0°C and add chloroiodomethane. Stir at 0°C for 5 min.
3. Add a solution of the iodoalkene **8** in dry, degassed $ClCH_2CH_2Cl$ (1.5 mL) (5 mL flask), via cannulation. Stir at 0°C for 12 min.
4. Add a 1:1 mixture of a saturated aqueous NH_4Cl solution and a saturated aqueous $Na_2S_2O_3$ solution (2 mL). Warm to 25°C, dilute with CH_2Cl_2 (15 mL) and a saturated aqueous solution of NH_4Cl (20 mL).
5. Separate the organic and aqueous layers. Wash the organic layer successively with H_2O (20 mL) and with brine (20 mL). Dry over Na_2SO_4, and evaporate the solvent.
6. Purify the crude residue by flash chromatography using hexanes:ether (60:40). *trans*-1-ethyl-2-(hydroxymethyl)-1-iodocyclopropane (113 mg, 76%) is obtained as a colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectrometry, and elementary analysis.

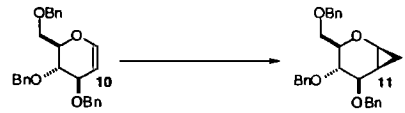
[a] Commercial chloroiodomethane was passed through a short column of oven dried basic alumina (activity 1) into a flame dried Schlenk flask containing copper wire, and then was degassed via the freeze-pump-thaw method. The reagent was stored under an atmosphere of Ar in the Schlenk flask, which was covered with aluminium foil.
[b] $ClCH_2CH_2Cl$ was distilled over calcium hydride and then was degassed via the freeze-pump-thaw method.

Finally, Wittig[20] reported that treatment of zinc iodide with either one or two equivalents of diazomethane was an alternative method to prepare $IZnCH_2I$ (Table 13.1, entry 3a) or the analogous *bis*(iodomethyl)zinc reagent $[(Zn(CH_2I)_2]$ (Table 13.1, entry 3b). This method, however, has not attracted much attention from synthetic organic chemists due to the hazards involved when diazomethane is used on multigram scale.[21]

It should be emphasized that the nature of the solvent used in these reactions is extremely important to maximize the electrophilic character of the reagent. For example, most cyclopropanation reactions carried out in basic solvents (ether, THF, DME) usually require higher temperatures and reaction times than those carried in non-basic solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, benzene, toluene, hexanes). This is especially true if an unactivated olefin is submitted to these iodomethylzinc reagents. However, it is often beneficial to stabilize the reagent by adding one or two equivalents of THF or DME when the cyclopropanation of unfunctionalized alkenes is carried out in non-etheral solvents to avoid its premature decomposition. The importance of the solvent is obvious in the rate of the cyclopropanation of tri-*O*-benzyl-D-glucal (**10**) (Table 13.2).

The cyclopropanated material **11** is formed quantitatively after 6 h when the reaction is carried out with five equivalents of the reagent and in the presence of ether (Table 13.2, entry 1, 2). Conversely, the reaction takes about 5 h if the

Table 13.2 Diastereoselective cyclopropanation of tri-*O*-benzyl-D-glucal (**10**)

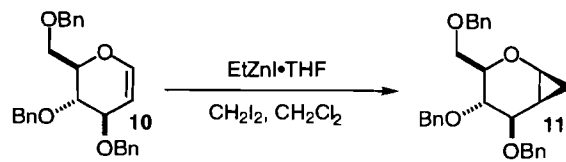


Entry	Conditions	Reaction time	Yield	Reference
1	Et_2Zn (5), CH_2I_2 (5), 25°C, ether:hexanes	6 h	92	22
2	Zn, CuCl, AcCl, CH_2I_2, ether:hexanes	Not reported	89	23
3	EtZnI•THF (3), CH_2I_2 (3), CH_2Cl_2	5 h	93	Protocol 6
4	Et_2Zn (3), CH_2I_2 (3), CH_2Cl_2, –10°C	20 min	95	Protocol 7

$IZnCH_2I$•THF complex is used in CH_2Cl_2 (Table 13.2, entry 3, Protocol 6). In the absence of a basic solvent (Table 13.2, entry 4), the cyclopropanation takes less than 20 min at –10°C if three equivalents of Et_2Zn and CH_2I_2 in CH_2Cl_2 are used (Protocol 7)! In all the cases, only the *syn*-isomer could be detected.

Protocol 6.
Preparation of $IZnCH_2I$ from EtZnI by an alkyl exchange reaction: cyclopropanation of tri-*O*-benzyl-D-glucal

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Equipment

- Two one-necked round-bottomed flasks (25 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

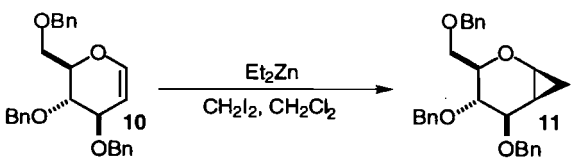
- Zinc dust (FW 65.4), –325 mesh 0.3 g, 4.6 mmol — **flammable solid**
- 1,2-dibromoethane (FW 187.8), 28 mg, 0.15 mmol — **toxic, cancer suspect agent**
- Distilled Me_3SiCl (FW 108.64), 0.01 mL, 0.08 mmol — **flammable, corrosive**
- Distilled, dry THF[a] — **flammable, irritant**
- Iodoethane (FW 155.97), 0.37 mL, 4.6 mmol — **corrosive, moisture-sensitive**
- Distilled, dry CH_2Cl_2[b] — **toxic, irritant**
- Distilled diiodomethane[c] (FW 267.84), 0.37 mL, 4.6 mmol — **corrosive, light-sensitive**
- Tri-*O*-benzyl-D-glucal (FW 416.52), 638 mg, 1.5 mmol — **moisture-sensitive**

1. Weigh the zinc dust into the one-necked, round-bottomed flask, flush with argon, and add the 1,2-dibromoethane in dry THF (1 mL). Heat gently with a heat gun to boil the THF. After *ca.* 1 min, the reaction mixture foams and the heating is interrupted. After *ca.* 1 min repeat this heating–cooling process two more times. The foaming is indicative of a good activation of the zinc surface.
2. Add Me_3SiCl and stir the reaction mixture for *ca.* 5 min at 25°C.
3. Add a solution of iodoethane in THF (1 mL) and stir at 30°C for 1 h.
4. Evaporate the solvent under vacuum. Dissolve the residue with CH_2Cl_2 (8 mL).
5. Cool to 0°C and add diiodomethane. Stir for 10 min at 0°C.
6. Add a solution of tri-*O*-benzyl-D-glucal in CH_2Cl_2 (8 mL) and allow the mixture to warm to room temperature. Stir for 6 h and check for completion of the reaction by TLC (*ca.* 6 h).
7. Carefully add a saturated aqueous NH_4Cl solution (5 mL) to the reaction mixture followed by ether (40 mL) and 10% aqueous HCl solution (5 mL). Stir the mixture until both layers are clear.
8. Separate the organic and aqueous layers. Wash the organic layer successively with a saturated aqueous Na_2SO_3 solution (15 mL), with a saturated aqueous $NaHCO_3$ solution (15 mL), and with brine (15 mL). Dry over $MgSO_4$, and evaporate the solvent.
9. Purify the crude residue by flash chromatography using hexanes:EtOAc (80:20). Cyclopropane **11** (595 mg, 92%) is obtained as a colourless oil which slowly solidified over several days. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, $[\alpha]_D$, m.p., and elementary analysis.

[a] THF was distilled over sodium benzophenone.
[b] CH_2Cl_2 was distilled over calcium hydride.
[c] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.

Protocol 7.
Cyclopropanation of tri-*O*-benzyl-D-glucal with Furukawa's reagent ($EtZnCH_2I$)

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Protocol 7. *Continued*

Equipment

- One one-necked round-bottomed flask (25 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

- Et_2Zn neat (FW 123.49), 0.47 mL, 4.6 mmol — **pyrophoric, moisture-sensitive**
- Distilled diiodomethane[a] (FW 267.84), 0.37 mL, 4.6 mmol — **corrosive, light-sensitive**
- Distilled, dry CH_2Cl_2[b] — **toxic, irritant**
- Tri-*O*-benzyl-D-glucal (FW 416.52), 638 mg, 1.5 mmol — **moisture-sensitive**

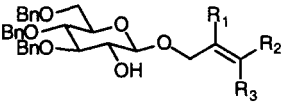
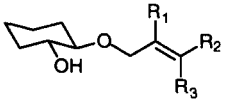
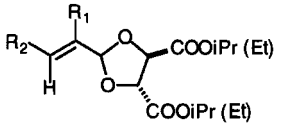
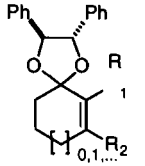
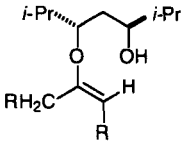
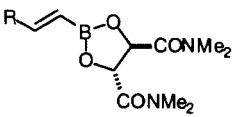
1. Weigh tri-*O*-benzyl-D-glucal into the dry one-neck, round-bottomed flask, flush with argon, and add dichloromethane (10 mL).
2. Cool to −10°C (acetone:ice bath) and add Et_2Zn followed by CH_2I_2. Stir at −10°C and check the reaction for completion (*ca.* 20 min).
3. Carefully add a saturated aqueous NH_4Cl solution (5 mL) to the reaction mixture, followed by ether (40 mL), and 10% aqueous HCl (5 mL). Stir the mixture until both layers are clear.
4. Separate the organic and aqueous layers. Wash the organic layer successively with a saturated aqueous Na_2SO_3 solution (15 mL), with a saturated aqueous $NaHCO_3$ solution (15 mL), and with brine (15 mL). Dry over $MgSO_4$, and evaporate the solvent.
5. Purify the crude residue by flash chromatography using hexanes:EtOAc (80:20). Cyclopropane **11** (620 mg, 96%) is obtained as a colourless oil which slowly solidified over several days. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, $[\alpha]_D$, m.p., and elementary analysis.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] CH_2Cl_2 was distilled over calcium hydride.

2. Synthesis of chiral, non-racemic cyclopropanes

In recent years, most of the attention has focused on the stereocontrolled synthesis of cyclopropanes. The isolation of several structurally intriguing natural product has revived the interest of the scientific community for the development of new methods. Several efficient and practical chiral auxiliaries have been developed for the enantioselective cyclopropanation of olefins. The most efficient chiral auxiliaries have been specifically designed for the cyclopropanation of acyclic allylic alcohols (Table 13.3, entry 1, 2, Protocol 8),[24] alkenones,[25] cycloalkenones[26] (Table 13.3, entry 3, 4, Protocol 9), vinyl ethers[27] (Table 13.3, entry 5, Protocol 10), and vinylboronate esters[28] (Table 13.3,

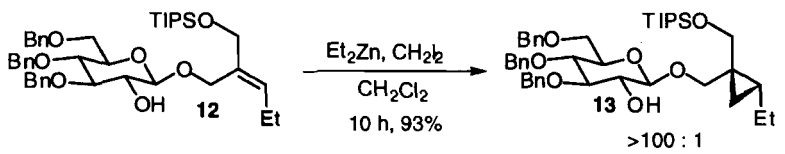
Table 13.3 Chiral auxiliaries for halomethylzinc-derived cyclopropanations

Entry	Substrates	Conditions	Yield (de)
1		Et_2Zn (10 equiv) CH_2I_2 (10 equiv) Toluene	≥95% (≥98%)
2		Et_2Zn (3 equiv) $ClCH_2I$ (3 equiv) Toluene	90-98% (≥93%)
3		Et_2Zn (5 equiv) CH_2I_2 (10 equiv) Hexane	50-95% (93-97%)
4		Zn/Cu (≥6 equiv) CH_2I_2 (3 equiv) Ether	62-90% (92-95%)
5		Et_2Zn (7.5 equiv) CH_2I_2 (10 equiv) Ether	57-80% (99%)
6		Zn/Cu (excess) CH_2I_2 (3 equiv) Ether	46-67% (94-97%)

entry 6). Cyclopropylboronate esters have been found to be useful coupling partners in the palladium catalysed Suzuki reactions and as useful precursors to cyclopropanol derivatives.[29]

Protocol 8.
Stereoselective cyclopropanation of acyclic allylic alcohols: glucose-derived chiral auxiliary[24d]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Protocol 8. *Continued*

Equipment

- One one-necked round-bottomed flask (250 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

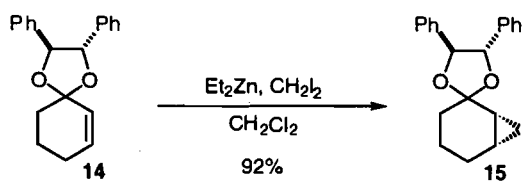
- Et_2Zn neat (FW 123.49), 8.4 mL, 81.9 mmol — **pyrophoric, moisture-sensitive**
- Distilled diiodomethane[a] (FW 267.84), 4.7 mL, 58.5 mmol — **corrosive, light-sensitive**
- Distilled, dry CH_2Cl_2[b] — **toxic, irritant**
- Glucopyranoside **12** (FW 705.01), 8.25 g, 11.7 mmol — **harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add allylic ether **12** and CH_2Cl_2 (120 mL).
2. Cool the resulting solution to –30°C, add Et_2Zn, and stir 10 min. Add diiodomethane over 1 min.
3. Stir for an additional 10 h at –30°C and check for the completion of the reaction by TLC.
4. Pour into a mixture of ether (200 mL) and saturated aqueous NH_4Cl solution (50 mL) at 0°C. Add just enough 10% aqueous HCl solution to dissolve the white precipitate.
5. Separate the organic and aqueous layers. Wash the aqueous layer with two portions of ether (2 × 25 mL). Wash the combined organic layers successively with a 0.05 M aqueous Na_2SO_3 solution (50 mL), with a saturated aqueous $NaHCO_3$ solution (50 mL), and with brine (50 mL). Dry over $MgSO_4$, and concentrate under reduced pressure.
6. Purify the crude residue by flash chromatography using hexanes:EtOAc (94:6). Pure cyclopropane **13** (7.8 g, 93%) is obtained as a viscous colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, and $[\alpha]_D$.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] CH_2Cl_2 was distilled over calcium hydride.

Protocol 9.
Stereoselective cyclopropanation of cyclic enones: dihydrobenzoin-derived chiral auxiliary

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



14 **15**

Equipment

- One one-necked round-bottomed flask (25 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

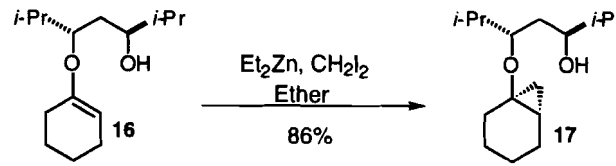
- Et_2Zn neat (FW 123.49), 0.15 mL, 1.47 mmol — **pyrophoric, moisture-sensitive**
- Distilled diiodomethane[a] (FW 267.84), 0.23 mL, 2.94 mmol — **corrosive, light-sensitive**
- Distilled, dry CH_2Cl_2[b] — **toxic, irritant**
- Acetal **14** (FW 292.38), 215 mg, 0.73 mmol — **harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add acetal **14** and CH_2Cl_2 (5 mL).
2. Cool the resulting solution to −10°C and add Et_2Zn, then stir 10 min. Add diiodomethane over 1 min.
3. Stir for an additional 30 min at −10°C and check for the completion of the reaction by TLC (hexanes:EtOAc, 95:5).
4. Pour into a mixture of ether (20 mL) and saturated aqueous NH_4Cl solution (10 mL) at 0°C. Add just enough 10% aqueous HCl solution to dissolve the white precipitate.
5. Separate the organic and aqueous layers. Wash the aqueous layer with two portions of ether (2 × 10 mL). Wash the combined organic layers successively with a saturated aqueous Na_2SO_3 solution (20 mL), with a saturated aqueous $NaHCO_3$ solution (20 mL), and with brine (20 mL). Dry over $MgSO_4$, and concentrate under reduced pressure.
6. Purify the crude residue by flash chromatography using hexanes:EtOAc (97:3). Pure cyclopropane **15** (208 mg, 92%) is obtained as a white solid. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, m.p., $[\alpha]_D$, and high-resolution mass spectrometry.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] CH_2Cl_2 was distilled over calcium hydride.

Protocol 10.
Diastereoselective cyclopropanation of enol ethers: preparation of cyclopropanol derivatives[27c]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



>99.5% de

Equipment

- One one-necked round-bottomed flask (50 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles

Materials

- Et_2Zn, 1 M in hexanes (FW 123.49), 10.3 mL, 10.3 mmol — **pyrophoric, moisture-sensitive**
- Distilled diiodomethane[a] (FW 267.84), 1.2 mL, 14.9 mmol — **corrosive, light-sensitive**
- Distilled, dry ether[b] — **toxic, flammable liquid**
- Alcohol **25** (FW 240.38), 333 mg, 1.39 mmol — **harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add alcohol **16** and dry ether (10.3 mL).
2. Add Et_2Zn and stir for a minute at room temperature, then add diiodomethane over 10 min.
3. After addition, stir for an additional 2 h at room temperature.
4. Pour into saturated aqueous NH_4Cl solution (10 mL) and separate the organic and aqueous layers. Wash the aqueous layer with two portions of ether (2 × 10 mL). Dry the combined organic layers over $MgSO_4$, and concentrate under reduced pressure.
5. Purify the crude residue by MPLC on silica gel using hexanes:EtOAc (94:6). Pure cyclopropane **17** (304 mg, 86%) is obtained as a colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, and elementary analysis.

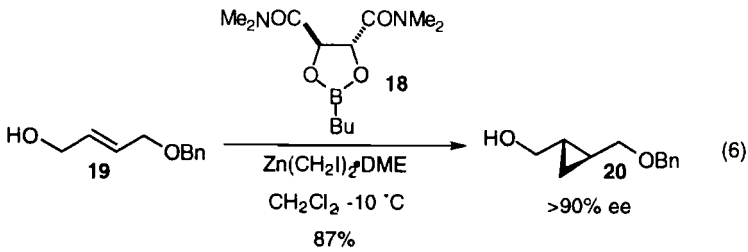
[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] Ether was distilled over sodium benzophenone.

A number of good reagent-based approaches have appeared in the last few years,[30] but the chiral dioxaborolane ligand **18** has turned out to be superior.[31]

The enantioselective cyclopropanation of acyclic allylic alcohols can be achieved with excellent enantioselectivities when the reaction is carried out in the presence of the chiral dioxaborolane ligand **18** (Equation 13.6, Protocol 11). This reaction also features the preparation of $Zn(CH_2I)_2$•DME complex which is soluble in dichloromethane.[32] This chiral additive is also very effective for the synthesis of 1,2,3-substituted cyclopropanes, when 1,1-substituted diiodoalkanes are used as precursors.[33] Finally, this method has been used extensively in natural product synthesis.[34]

Protocol 11.
Preparation of the $Zn(CH_2I)_2$•DME complex: enantioselective cyclopropanation of allylic alcohols with chiral ligand

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



(6)

Equipment

- One one-necked round-bottomed flask (200 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Two one-necked round-bottomed flasks (25 mL) equipped with a gas inlet and a septa
- Argon gas supply and inlet
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

• Et_2Zn neat (FW 123.49), 1.44 mL, 14 mmol	**pyrophoric, moisture-sensitive**
• Distilled diiodomethane[a] (FW 267.84), 2.3 mL, 28.1 mmol	**corrosive, light-sensitive**
• Distilled, dry DME[b]	**flammable**
• Distilled, dry CH_2Cl_2[c]	**toxic, irritant**
• Dioxaborolane **18** (FW 270.13), 2.3 g, 8.4 mmol	**harmful**
• Allylic alcohol **19** (FW 178.23), 1.25 g, 7 mmol	**harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add CH_2Cl_2 (40 mL) and DME (1.6 mL) to 200 mL flask.
2. Cool the resulting solution to –10°C and add Et_2Zn. Add diiodomethane at a rate to maintain the internal temperature below –5°C (*ca.* 5 min).
3. Stir for an additional 10 min at –10°C and add, by cannula, a solution of the dioxaborolane **12** in CH_2Cl_2 (15 mL) (25 mL flask), followed by a solution of the

Protocol 11. *Continued*

allylic alcohol **13** in CH_2Cl_2 (15 mL) (25 mL flask). Warm to room temperature and stir the reaction mixture for 8 h.

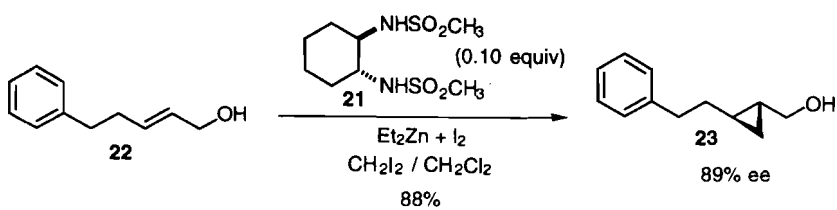
4. Add saturated aqueous NH_4Cl (30 mL) solution, followed by 10% aqueous HCl (70 mL) solution. Dilute with ether (120 mL) and separate the organic and aqueous layers.
5. Wash the organic layers successively with a 10% aqueous HCl solution (70 mL), with a 2 M aqueous NaOH solution (90 mL) containing 30% aqueous H_2O_2 (10 mL), with a 10% aqueous HCl solution (100 mL), with a saturated aqueous $NaHCO_3$ solution (100 mL), and with brine (100 mL). Dry over $MgSO_4$, and concentrate under reduced pressure.
6. Purify the crude residue by flash chromatography using hexanes:EtOAc (60:40). Pure cyclopropane **14** (1.18 g, 87%) is obtained as a colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, and high-resolution mass spectrometry.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] DME was distilled over sodium benzophenone.
[c] CH_2Cl_2 was distilled over calcium hydride.

Finally, two substoichiometric chiral systems are available, but limited success has been achieved thus far. The cyclohexyldisulfonamide system **21** converts allylic alcohols to cyclopropanes in *ee*'s up to 89% (Equation 13.7, Protocol 12)[35,36] whereas the Ti-TADDOLATE **25** converts 3-aryl substituted allylic alcohols in *ee*'s up to 91% (Scheme 13.3, Protocol 13).[37] Both of these reactions are very capricious and the level of enantiomeric purity is highly substrate-dependent. However, it is anticipated that even more effective and general catalysts will emerge in the next few years.

Protocol 12.
Asymmetric cyclopropanation of (*E*)-5-phenyl-2-pentenol using cyclohexyldisulfonamide system[36b]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



(7)

Equipment

- One two-necked round-bottomed flask (15 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- One two-necked round-bottomed flask (25 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- One two-necked round-bottomed flask (100 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

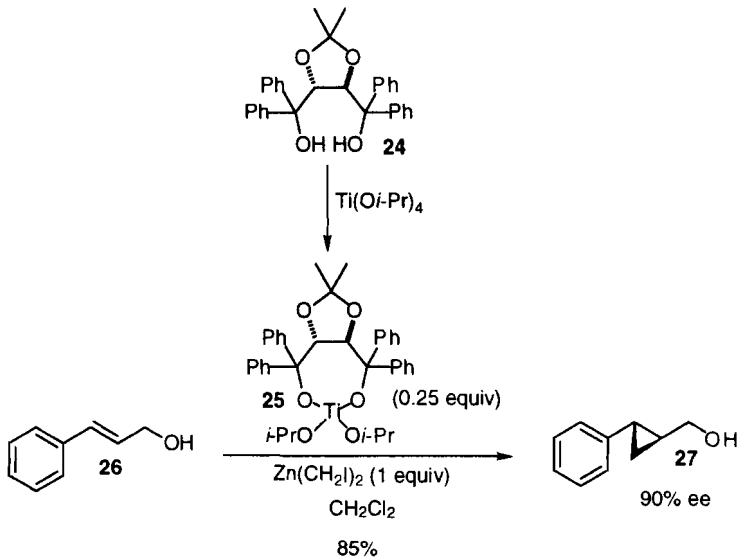
• Et_2Zn neat (FW 123.49), 319 μL, 3.1 mmol	**pyrophoric, moisture-sensitive**
• Distilled diiodomethane[a] (FW 267.84), 161 μL, 2 mmol	**corrosive, light-sensitive**
• Iodine (FW 253.81), 508 mg, 2 mmol	**highly toxic, corrosive**
• Distilled, dry CH_2Cl_2[b]	**toxic, irritant**
• Cyclohexyldisulfonamide **21** (FW 270.37), 27 mg, 0.1 mmol	**harmful**
• (*E*)-5-phenyl-2-pentenol (FW 162.23), 162 mg, 1 mmol	**harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add (*E*)-5-phenyl-2-pentenol and cyclohexyldisulfonamide **21** to the 15 mL flask (flask A). Add CH_2Cl_2 (3 mL) and cool the resulting solution to 0°C. Add diethylzinc (113 μL, 1.1 mmol) and stir at 0°C for 10 min.
2. Add iodine and CH_2Cl_2 (10 mL) to the 25 mL flask (flask B) and cool the resulting solution to 0°C. Add diethylzinc (103 μL, 1 mmol) and stir at 0°C for 10 min.
3. Add diiodomethane and CH_2Cl_2 (24 mL) to the 100 mL flask (flask C) and cool the resulting solution to 0°C. Add diethylzinc (103 μL, 1 mmol) and stir at 0°C for 5 min.
4. Add, by cannula, the contents of flask A to flask B over ~ 30 sec. Stir the resulting slurry for 2 min at 0°C and add it to flask C.
5. After 30 min at 0°C, add a 2 M aqueous NaOH solution (13 mL). Separate the organic and aqueous layers. Wash the aqueous layer with two portions of CH_2Cl_2 (2 × 20 mL). Dry the combined organic layers over $MgSO_4$, and concentrate under reduced pressure.
6. Purify the crude residue by flash chromatography using hexanes:EtOAc (75:25), followed by bulb-to-bulb distillation (80°C, 0.02 mmHg). Pure (1*R*,2*R*)-2-(2-phenylethyl)cyclopropanemethanol (155 mg, 88%) is obtained as a clear, colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, $[\alpha]_D$, high-resolution mass spectrometry, and elementary analysis.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled over CaH_2 and under reduced pressure, stored over copper, and protected from light.
[b] CH_2Cl_2 was distilled over calcium hydride.

Protocol 13.
Titanium-TADDOL derived catalyst: enantioselective cyclopropanation of cinnamyl alcohol[37]

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 13.3

Equipment

- Two one-necked round-bottomed flasks (10 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- One one-necked round-bottomed flask (25 mL) equipped with a gas inlet, a septa, a magnetic stirring bar
- Argon gas supply and inlet
- Vacuum source
- Dry gas-tight syringes with stainless steel needles
- Temperature controlled bath

Materials

• Et_2Zn neat (FW 123.49), 100 μL, 0.98 mmol	**pyrophoric, moisture-sensitive**
• Distilled diiodomethane[a] (FW 267.84), 160 μL, 2 mmol	**corrosive, light-sensitive**
• Distilled $Ti(Oi\text{-}Pr)_4$ (FW 284.26), 74 μL, 0.25 mmol	**flammable, irritant**
• Dry molecular sieves 4 Å activated powder	**irritant**
• Distilled, dry toluene[b]	**flammable, toxic**
• Distilled, dry CH_2Cl_2[c]	**toxic, irritant**
• TADDOL **24** (FW 466.57), 117 mg, 0.25 mmol	**harmful**
• Distilled cinnamyl alcohol (FW 134.18), 134 mg, 1 mmol	**harmful**

1. Flame dry the reaction vessel and accessories under dry argon. After cooling the apparatus to room temperature, add TADDOL **24** and toluene (5 mL)

to a 10 mL flask (flask A). Add $Ti(O\textit{i}\text{-}Pr)_4$ and stir the resulting mixture at room temperature for 3 h. Remove solvent under argon circulation, then dry under vacuum for 2 h.

2. Add molecular sieves 4 Å (1 g) and CH_2Cl_2 (5 mL).
3. Add diiodomethane and CH_2Cl_2 (5 mL) to the 25 mL flask (flask B) and cool the resulting solution to 0 °C. Add diethylzinc and stir at 0 °C for 10 min, then cool at –78 °C.
4. Add, by cannula, the contents of flask A to flask B, then add a solution of cinnamyl alcohol in CH_2Cl_2 (3 mL) at –78 °C. Warm the resulting mixture at 0 °C and stir for 1–5 h at this temperature.
5. Add saturated aqueous NH_4Cl solution (15 mL) and separate the organic and aqueous layers. Wash the aqueous layer with three portions of CH_2Cl_2 (3 × 10 mL). Wash the combined organic layers successively with a saturated aqueous $NaHCO_3$ solution (10 mL) and with brine (10 mL). Dry over $MgSO_4$, and concentrate under reduced pressure.
6. Purify the crude residue by flash chromatography using hexanes:EtOAc (80:20). Pure (1*S*,2*S*)-2-phenylcyclopropanemethanol (125 mg, 85%, 90% *ee*) is obtained as a clear, colourless oil. Characterize the product by ^1H NMR, ^{13}C NMR, IR spectroscopy, and $[\alpha]_D$.

[a] Diiodomethane was washed with an aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and distilled under reduced pressure.
[b] Toluene was distilled over sodium.
[c] CH_2Cl_2 was distilled over calcium hydride.

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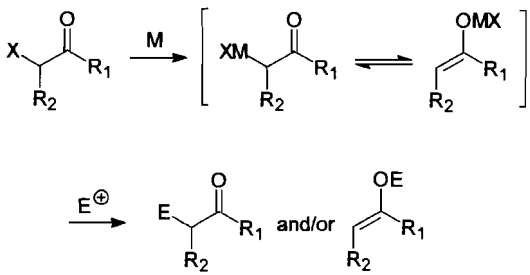
14

The Reformatsky reaction

ALOIS FÜRSTNER

1. Introduction

In a general sense, the Reformatsky reaction can be taken as subsuming all enolate formations by oxidative addition of a metal or a low-valent metal salt into a carbon–halogen bond activated by a vicinal carbonyl group, followed by reaction of the enolates thus formed with an appropriate electrophile (Scheme 14.1).[1–3] The insertion of metallic zinc into α-haloesters is the historically first and still most widely used form of this process,[4] to which this chapter is confined. It is the mode of enolate formation that distinguishes the Reformatsky reaction from other fields of metal enolate chemistry.



Scheme 14.1 The Reformatsky reaction: X = halogen, $E^{\oplus}$ =+ electrophile, M = Zn (this chapter) or another metal or low-valent metal salt.

2. Scope and limitations

The oxidative insertion of zinc into α-halo carbonyl compounds and the subsequent reaction of the zinc enolates formed with various electrophiles can either be carried out in a one-pot 'Barbier-type' fashion or in two consecutive steps.[1–3] Zinc enolates exhibit a reasonably high stability over a wide temperature range (from –78 °C to above 80 °C for short periods of time) compared to other metal enolates. Although it has been reported that solutions of $BrZnCH_2COOtBu$ can be stored for several days without loss in activity,[5] it is generally advisable to use freshly prepared reagents in order to avoid

problems of reproducibility. The major path of decomposition of zinc ester enolates is the loss of ROZnX with formation of ketene which immediately acylates an intact enolate and hence leads to β-ketoesters as by-products.[6]

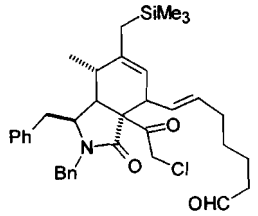
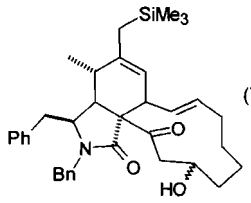
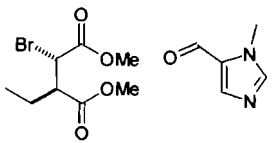
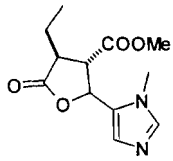
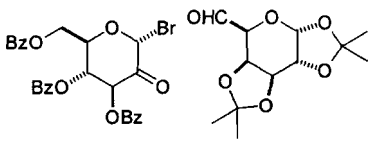
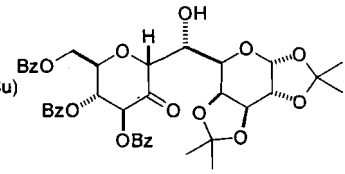
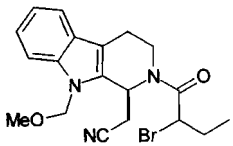
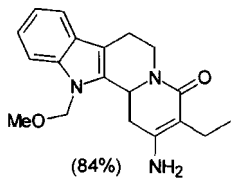
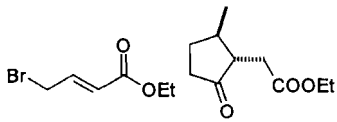
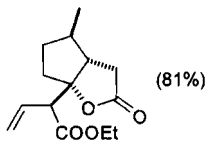
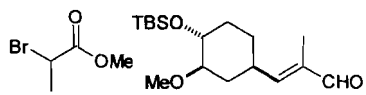
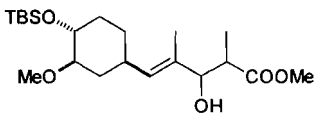
Zinc enolates can be prepared in solvents of greatly different polarity, including THF, DME, Et_2O, 1,4-dioxane, benzene, toluene, dimethoxymethane, DMF, $B(OMe)_3$, DMSO, and mixtures thereof, just to mention the most frequently used ones.[1–3] Reformatsky reactions in the absence of a solvent have also been described.[7] The reagent is dimeric in the crystal state and in solution except for the most polar media.[5,8]

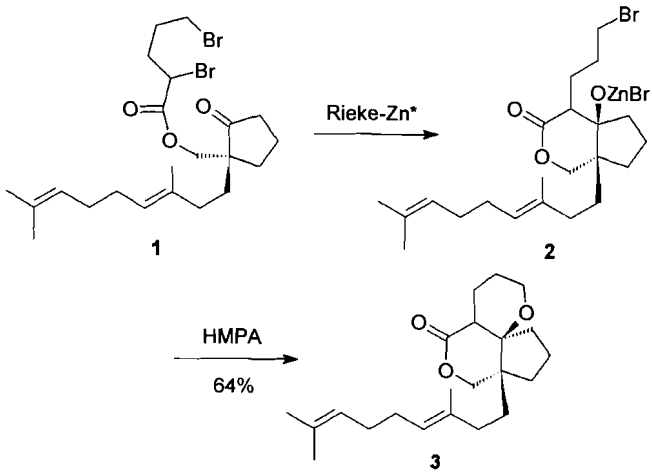
A particular advantage stems from the fact that the site of reaction is strictly determined by the halogen moiety. This may be advantageously used for regioselective enolate formations in polycarbonyl compounds which are difficult to achieve by proton abstraction methods. As a consequence, the Reformatsky reaction is well suited for applications to the synthesis of complex target molecules and turned out to be applicable to intramolecular aldol processes, even if medium sized rings are formed.[1–3] The few selected examples compiled in Table 14.1 are meant to illustrate the performance and selectivity that might be gained by a Reformatsky process. This includes the key steps of a total syntheses of cytochalasan (entry 1)[9] as well as of pilocarpine (entry 2),[10] the formation of a C-disaccharide (entry 3),[11] an application to the indole alkaloid series in which the zinc enolate is intramolecularly trapped by a nitrile group (entry 4),[12] and the α-selective addition of methyl 4-bromocrotonate as a vinylogous Reformatsky donor, which constitutes a pivotal step on a way to retigeranic acid (entry 5).[13]

Aldehydes and ketones are by far the most widely used electrophiles to intercept zinc enolates.[1–3] Since the latter are only weakly basic, the Reformatsky reaction can also be applied to highly enolizable carbonyl compounds. Sterically hindered ketones do not pose particular problems, α,β-unsaturated carbonyl compounds react regioselectively in a 1,2-addition mode (Table 14.1, entry 6),[14] and acylsilanes may be used as aldehyde surrogates.[15,16] The moderate reactivity of zinc enolates as compared to their alkali metal counterparts is responsible for the high degree of chemoselectivity (cf. Table 14.1),[1–3] which also allows to incorporate this reaction into sequential transformations. A notable example is Heathcock's elegant approach to the core segment of daphnilactone and related natural products, which is triggered by the regioselective insertion of activated zinc into the dibromo derivative **1** at its α-haloester site. The corresponding zinc ester enolate formed then reacts exclusively with the proximate cyclopentanone moiety giving rise to the zinc alkoxide **2**, which is subsequently alkylated by the terminal bromine atom upon addition of HMPA. This sequence leads to the intricate tricyclic skeleton **3** of the target in a one-pot transformation (Scheme 14.2).[17]

A problem encountered in many conventional Reformatsky reactions is the unselective dehydration of the aldols initially formed. This inconvenience has been overcome either by substantially lowering the reaction temperature or

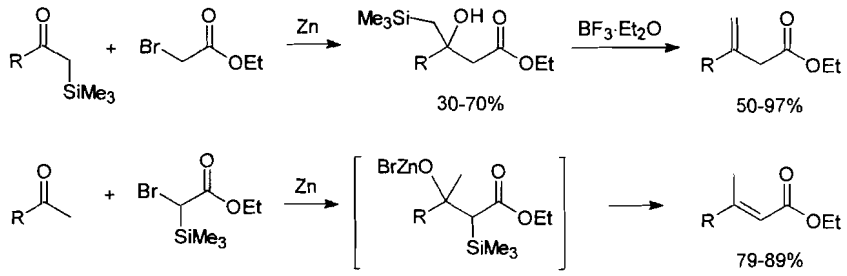
Table 14.1 Some applications of the Reformatsky reaction in natural product synthesis

Entry	Substrates	Reagent	Product (yield %)
1		Rieke-Zn*	 (75%)
2		Zn(Ag) Me_2AlCl	 (94%) major isomer (91 : 9)
3		Zn(Cu)	 (quant.) major isomer (8 : 1)
4		Zn(Ag) ultrasound	 (84%)
5		Zn(Cu)	 (81%)
6		Zn	 (92%) *syn* : *anti* = 3 : 7



Scheme 14.2 An intramolecular Reformatsky reaction/alkylation sequence.[17]

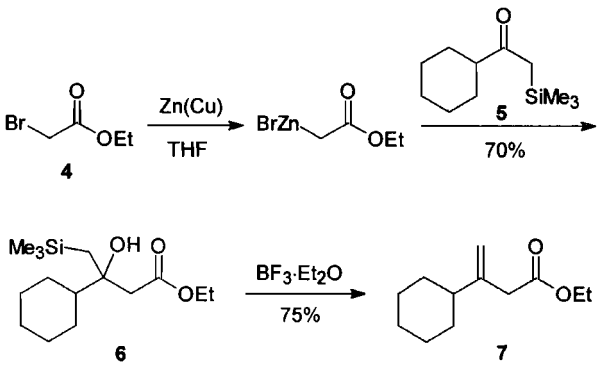
by using silylated starting materials, which account for highly efficient Reformatsky reaction/Peterson elimination sequences.[15,18,19] Scheme 14.3 illustrates how to control the regioselectivity of the elimination step by using either α-silylated zinc enolates or α-silylated carbonyl compounds as the substrates (Protocols 1 and 4). It is noteworthy that even the fairly labile α-trimethylsilyl ketones which are prone to proto-desilylation react without incident.



Scheme 14.3 Reformatsky reaction/Peterson elimination sequences.[15,18]

Protocol 1.
Ethyl 3-cyclohexyl-3-hydroxy-4-trimethylsilylbutanoate (Structure 6) and ethyl 3-cyclohexyl-3-butenoate (Structure 7)

Caution! Ethyl bromoacetate is a lacrymator that strongly irritates the eyes and the skin. Wear gloves and safety goggles and carry out all manipulations in an efficiently ventilated hood.



Equipment

- Round-bottomed flasks, three-necked (100 mL), two-necked (50 mL)
- Pressure-equalizing dropping funnel (20 mL)
- Reflux condenser
- Nitrogen (argon) bubbler
- Dry nitrogen (argon)
- Thermostatted hot plate stirrer
- Magnetic stirring bar
- Oil-bath
- Separatory funnel (250 mL)
- Rotary evaporator
- Column for flash chromatography (30 cm × 2 cm)

Materials

- Ethyl bromoacetate, 4.18 g, 25 mmol — **irritant, lacrymator, toxic**
- Zinc powder, 6.54 g, 100 mmol
- CuCl, 990 mg, 10 mmol — **irritant**
- 1-(cyclohexyl)-2-(trimethylsilyl)ethanone,[a] 1.98 g, 10 mmol — **moisture-sensitive**
- Diethyl ether, 100 mL — **highly flammable, may form peroxides**
- Anhydrous THF,[b] 50 mL — **irritating, flammable, may form peroxides**
- Anhydrous CH_2Cl_2,[c] 60 mL — **irritant**
- Hexane:ethyl acetate (3:1), 1 L — **flammable, irritant**
- $BF_3.Et_2O$ in CH_2Cl_2 (1%, w/w), 1 mL — **toxic, corrosive**
- Silica (Merck 60, 230–400 mesh) — **irritant**

1. Equip the three-necked flask with the reflux condenser bearing the nitrogen bubbler, the pressure-equalizing dropping funnel, and the magnetic stirring bar, evacuate the flask, and flame dry all glassware. Allow it to cool to ambient temperature *in vacuo* and flush with dry nitrogen (argon). Keep a positive pressure of nitrogen throughout the reaction.

Protocol 1. *Continued*

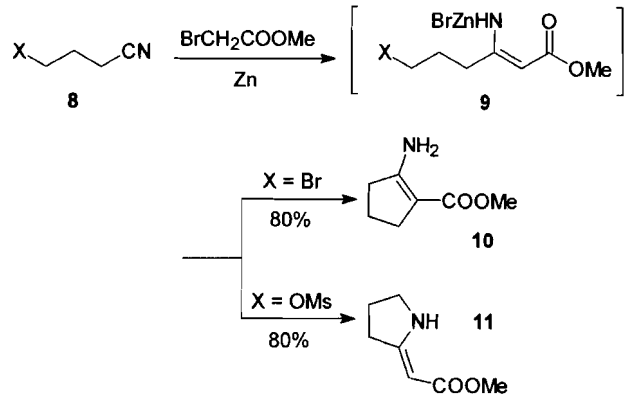
2. Charge the flask with zinc dust (6.54 g, 100 mmol) and CuCl (990 mg, 10 mmol), add anhydrous THF (20 mL), and reflux the suspension for 30 min. During this activation period, charge the dropping funnel with ethyl bromoacetate (4.18 g, 25 mmol) and THF (10 mL).
3. Discontinue the heating. Add *ca.* 1/10 of the bromoacetate solution at once to the stirred Zn(Cu) couple while still hot. When the Reformatsky reaction gets started, the suspension becomes turbid and the solvent begins to boil. Add the rest of the content of the dropping funnel to the suspension in such a rate as to maintain a gentle reflux (*ca.* 15 min).
4. Cool the solution of $BrZnCH_2COOEt$ thus formed to ambient temperature. Charge the dropping funnel with the α-trimethylsilylated ketone **5** (1.98 g, 10 mmol)[a] dissolved in THF (10 mL), add this solution to the zinc enolate over a period of 10 min, and stir the resulting mixture for 2 h at ambient temperature.
5. Filter off the unreacted Zn(Cu) couple, rinse it with Et_2O (100 mL) in several portions, extract the combined filtrates with water (30 mL), filter off the precipitate formed through a sintered glass funnel, and rinse with Et_2O (50 mL). Wash the organic phase with brine (20 mL), dry the separated layer over Na_2SO_4, and evaporate the solvent on the rotary evaporator.
6. Purify the residue by flash chromatography on silica using hexane:ethyl acetate (3:1) as the eluent. This affords compound **6** as a colourless syrup, 2.01 g, 70%. ^1H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 9H), 0.88–1.82 (m, 13H), 1.31 (t, 3H), 2.69 and 2.83 (AB, 2H, J = 16), 3.50 (br. s, 1H), 4.23 (q, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.9, 14.3, 26.7, 26.8, 26.9, 27.0, 27.7, 28.0, 28.2, 48.3, 61.7, 77.1, 167.1.
7. Charge a flame dried two-necked flask with compound **6** (0.573 g, 2 mmol) and anhydrous CH_2Cl_2 (20 mL), add a solution of $BF_3.Et_2O$ in CH_2Cl_2 (1%, w/w, 1 mL), and stir the mixture for 2 h at room temperature under nitrogen. For work-up, quench the reaction mixture with water (30 mL), extract the organic layer twice with CH_2Cl_2 (20 mL each), dry the combined organic layers over Na_2SO_4, evaporate the solvent on a rotary evaporator, and purify the residue by rapidly passing it through a short pad of silica using hexane:ethyl acetate (3:1) as the eluent. This affords alkene **7** as a colourless syrup, 294 mg, 75%. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10–1.86 (m, 11H), 1.27 (t, 3H), 3.48 (s, 2H), 4.18 (q, 2H), 4.85 (s, 1H), 5.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 26.4, 26.5, 29.7, 32.2, 32.5, 44.4, 61.4, 113.5, 147.8, 167.4.

[a] Prepared in 70% yield by adding a solution of cyclohexylcarboxylic acid chloride (71.1 mmol) in THF to a solution of trimethylsilylmethylmagnesium chloride (72 mmol) and CuI (35.6 mmol) in THF at –40°C, followed by a standard extractive work-up, and distillation under reduced pressure. Colourless liquid, b.p. = 82–86°C (1.5 torr).

[b] Anhydrous THF is obtained by distillation over potassium/benzophenone or Mg-anthracene.

[c] Anhydrous CH_2Cl_2 is obtained by distillation over CaH_2.

In addition to aldehydes and ketones, a variety of other functional groups can be used as electrophiles in Reformatsky-type reactions.[1–3] Among them, nitriles play a prominent role since they lead to β-oxoesters after hydrolytic work-up (the primary enamines initially formed can only be isolated when stabilized by extended conjugation or by conformational means, cf. Table 14.1, entry 4).

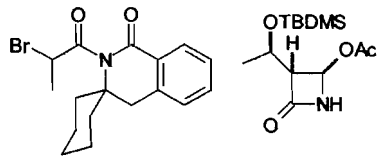
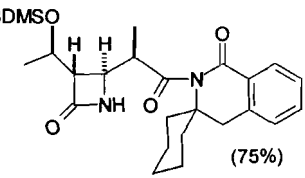
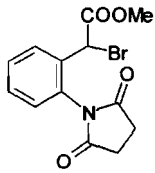
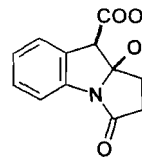
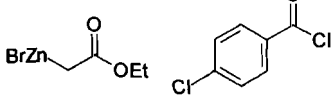
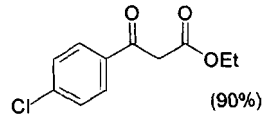
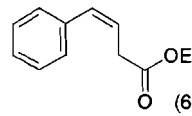
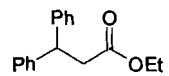
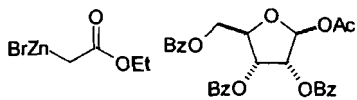
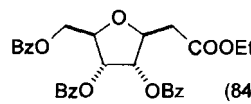
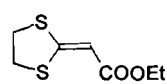
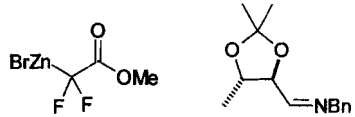
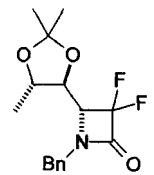


Scheme 14.4 A Blaise reaction/alkylation sequence.[22]

Based on this process, which is sometimes referred to as the 'Blaise reaction',[20,21] a straightforward entry into the saxitoxin and gonyautoxin series has been devised (Scheme 14.4) which relies upon the selective alkylation of the ambident zinc enamide **9** initially formed at its 'soft' or 'hard' site according to the HSAB principle.[22] Specifically, a terminal halide group in substrate **8** (X = Br) affords the carbocyclic product **10** via C-alkylation, whereas a terminal sulfonate entity (X = OSO_2Me) leads to the pyrrolidine derivative **11** via the N-alkylation pathway.

The insight that zinc ester enolates can be prepared prior to the addition of the electrophile has largely expanded the scope of the Reformatsky reaction.[1–3] Substrates such as azomethines that quaternize in the presence of α-haloesters do react without incident under these 'two-step' conditions.[23] The same holds true for acyl halides which readily decompose on exposure to zinc dust, but react properly with preformed zinc ester enolates in the presence of catalytic amounts of Pd(0) complexes.[24] Alkylations of Reformatsky reagents are usually difficult to achieve and proceed only with the most reactive agents such as methyl iodide or benzyl halides.[25] However, zinc ester enolates can be cross-coupled with aryl- and alkenyl halides or -triflates, respectively, in the presence of transition metal catalysts in a Negishi-type reaction.[26] Table 14.2 compiles a few selected examples of Reformatsky reactions with electrophiles other than aldehydes or ketones.[27]

Table 14.2 Reformatsky reactions with less conventional electrophiles: selected examples

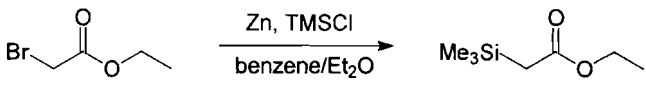
Entry	Substrates	Conditions	Product (yield %)
1		Zn	 (75%)
2		Zn, ultrasound	 (70%)
3		Pd(0) cat.	 (90%)
4		Pd(0) cat.	 (68%)
5			 (96%)
6		$TiCl_4$ (50 mol%)	 (84%)
7			 (71%)
8			 (71%) (*syn*:*anti* = 4.3:1)

The selective C-silylation of some zinc enolates on treatment with chlorotrimethylsilane deserves mentioning because it is in clear contrast to the preponderant O-alkylation of other metal enolate reagents. Although this transformation is essentially confined to alkyl bromozincacetate and halozinc-

acetonitrile,[28] it provides ready access to highly valuable synthons (Protocol 2). Specifically, ethyl trimethylsilylacetate **12** can be conveniently prepared on a large scale by this method. This material has found widespread use as substrate for Peterson olefination reactions,[29a] for the preparation of enol ethers under very mild conditions,[28b] and for the synthesis of 2-trimethylsilylethanol and valuable protecting groups derived thereof (e.g. SEMCl).[29b,c] Upon bromination it affords ester **13** (Protocol 3) which itself can be used for selective Reformatsky reactions followed by a spontaneous Peterson elimination as outlined in Scheme 14.3 (Protocol 4).[18]

Protocol 2.
Synthesis of ethyl trimethylsilylacetate (Structure 12)

Caution! Ethyl bromoacetate is a lacrymator that strongly irritates the eyes and the skin. Benzene is a cancer suspect agent. Wear gloves and safety goggles and carry out all manipulations in an efficiently ventilated hood.



4 **12**

Equipment

- Three-necked, round-bottomed flask (1 L)
- Pressure-equalizing dropping funnel (500 mL)
- Reflux condenser
- Nitrogen (argon) bubbler
- Dry nitrogen (argon)
- Thermostatted hot plate stirrer
- Magnetic stirring bar
- Oil-bath
- Separatory funnel (1 L)
- Erlenmeyer flask (1 L)
- Rotary evaporator
- Vigreux column, 15 cm

Materials

- Ethyl bromoacetate, 110.2 g, 660 mmol — **irritant, lacrymator, toxic**
- Zinc powder, 59 g, 903 mmol
- Iodine — **irritant**
- Chlorotrimethylsilane, 65 g, 598 mmol — **moisture-sensitive, flammable, toxic**
- Anhydrous diethyl ether[a] — **highly flammable, may form peroxides**
- Anhydrous benzene[b,c] — **cancer suspect agent, flammable**
- Aqueous HCl — **corrosive, toxic**
- Aqueous $NaHCO_3$, saturated

1. Dry all glassware and the stirring bar in an electric oven (105°C) for 1 h prior to use. Equip the flask with the reflux condenser bearing the nitrogen bubbler, with the dropping funnel, and the magnetic stirring bar while hot, purge the apparatus with dry N_2 (or Ar), and keep a positive N_2 (Ar) pressure throughout the reaction.
2. Charge the pressure-equalizing dropping funnel with ethyl bromoacetate

Protocol 2. *Continued*

(110.2 g, 73.2 mL, 660 mmol), chlorotrimethylsilane (65 g, 76 mL, 598 mmol), benzene (50 mL), and ether (50 mL).

3. Charge the three-necked flask with zinc dust (59 g, 903 mmol), benzene (200 mL), and ether (100 mL). Add a few crystals of iodine (*ca.* 50 mg) and reflux the stirred suspension for 30 min in order to etch the zinc surface.
4. Remove the heating bath. Add *ca.* 1/10 of the content of the dropping funnel at once to the stirred suspension of the activated zinc while still hot. The mixture becomes turbid and the strongly exothermic Reformatsky reaction causes the solvent to boil.
5. Add the remaining content of the dropping funnel to the flask at such a rate as to maintain the reaction at gentle reflux (*ca.* 30 min). Once the addition is complete, the mixture is refluxed for another 2 h.
6. Allow the reaction mixture to cool to ambient temperature. Decant the solvent into a separatory funnel, rinse the unreacted zinc with ether (2 × 20 mL), and extract the combined organic layers with aqueous HCl (5%, 150 mL).
7. Extract the aqueous phase with diethyl ether (2 × 50 mL), wash the combined organic layers successively with saturated aqueous $NaHCO_3$ (50 mL) and brine (100 mL), dry the organic phase over Na_2SO_4, and evaporate the solvent on the rotary evaporator.
8. Distil the remaining liquid through a 15 cm Vigreux column at reduced pressure. This affords ethyl trimethylsilylacetate **12** as a colourless liquid which exhibits a pleasant and characteristic odour, 58.5–65 g, 61–68%, b.p. = 82–84°C (47 mm), 93–94°C (105 mm). The product is stable to standard manipulations and can be stored for extended periods of time.

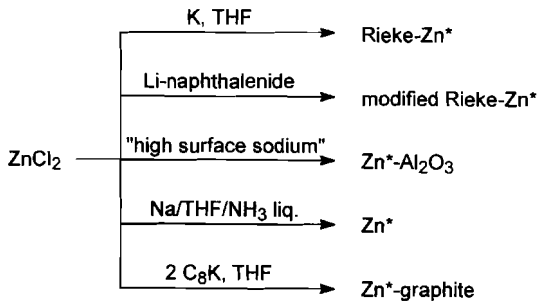
[a] Anhydrous diethyl ether is obtained by distillation over $LiAlH_4$.
[b] Anhydrous benzene is obtained by distillation over sodium wire.
[c] In this procedure it is not recommended to replace the benzene by toluene since the higher boiling point of the latter renders the isolation of the product by distillation difficult.

3. The role of zinc activation

Reformatsky reactions have a bad reputation as being difficult to entrain. To the authors experience, however, the reactive donors such as alkyl bromoacetates do not pose particular problems even under rather conventional conditions. Commercial zinc dust activated by pre-treatment with either iodine or preferentially with cuprous chloride (i.e. Zn(Cu)) readily inserts into these halocarbonyl compound with formation of the corresponding zinc enolates. Protocols 1 and 2 describe prototype examples for Reformatsky reaction in the conventional 'two-step' or 'Barbier-type' set-up, respectively.

However, zinc activation becomes exceedingly important as soon as less

reactive halides are employed.[30] This includes α-bromoalkanoates of long chain carboxylic acids and α-chloroalkanoates independent of their length. Activated zinc samples (Zn*) are usually prepared by reduction of $ZnCl_2$ in an inert solvent with rigorous exclusion of oxygen and moisture. This provides slurries of highly dispersed and non-passivated zinc particles which exhibit a considerably enhanced reactivity as compared to commercial zinc dust. By the proper choice of the reducing agent, the performance of the Zn* can be tuned to some extent (Scheme 14.5).[31–35]



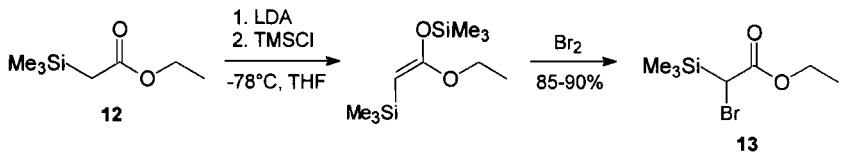
Scheme 14.5 Preparation of activated zinc (Zn*).

Particularly effective is the use of the potassium–graphite intercalation compound C_8K which combines the high reducing ability of potassium with the efficient electron transfer capacity of the extended π-electron system of its graphite host.[30] Reduction of $ZnCl_2$ with 2 moles of C_8K provides nano sized Zn particles uniformely covering the surface of the graphite flakes.[32–34] Since this simple physisorption prevents premature aggregation of the highly sensitive particles, the exceptional metalating ability of Zn–graphite is retained even under quite forcing conditions. Co-reduction of $ZnCl_2$ and AgOAc leads to Zn(Ag)*–graphite, which is even more reactive (Protocol 4).[34] These and related Zn* samples promote Reformatsky reactions at very low temperatures even if less reactive haloesters are employed, they suppress undesirable side-reactions, and can lead to a significant increase in the selectivity observed in reactions with diastereotopic carbonyl compounds.[30–35] Obviously, the improved reliablity makes metal activation techniques attractive in the context of multistep syntheses of, e.g. natural products or analogues thereof (cf. Table 14.1). Protocol 4 reports a prototype experiment and outlines the preparation and handling of Zn(Ag)*–graphite as one of the most active forms of this metal described to date. Although the potential user may be intimitated by the pyrophoric nature of active metal systems, many of these reagents are reasonably easy to handle via routine Schlenk techniques.[35] It is obvious that highly activated Zn* is not only useful in the context of the Reformatsky reaction but may also serve as superior metalating agent in other transformations which are difficult to achieve by conventional methods.[30,36]

Finally, the use of ultrasound to entrain Reformatsky reactions deserves mentioning.[37] Since a conventional laboratory cleaning bath is usually sufficiently effective, this easily adaptable method should find wider use in particular for large scale preparations. The same may hold true for the use of sacrificial anodes and/or for Reformatsky-type reactions triggered by electrochemical means.[38]

Protocol 3.
Synthesis of ethyl (bromo) (trimethylsilyl)acetate (Structure 13)

Caution! Bromine is highly irritating and corrosive. Wear gloves and safety goggles and carry out all manipulations in a well-ventilated hood.



Equipment

- Three-necked, round-bottomed flask (1 L)
- Pressure-equalizing dropping funnels (150 mL, 150 mL, 25 mL)
- Nitrogen (argon) bubbler
- Dry nitrogen (argon)
- Vacuum pump
- Magnetic stirrer
- Magnetic stirring bar
- Ice-bath
- Dry ice:acetone bath
- Separatory funnel (1 L)
- Erlenmeyer flask (1 L)
- Rotary evaporator
- Vigreux column, 15 cm

Materials

- Diisopropylamine,[a] 20.2 g, 200 mmol — **irritates the eyes**
- Anhydrous THF,[b] 280 mL — **irritating, flammable, may form peroxides**
- *n*-BuLi, 1.6 M in hexane, 124 mL, 198 mmol — **corrosive, moisture-sensitive, flammable**
- Ethyl trimethylsilylacetate, 21.6 g, 135 mmol — **flammable**
- Chlorotrimethylsilane, 30.4 g, 280 mmol — **moisture-sensitive, flammable, toxic**
- Bromine, 32.4 g, 202.5 mmol — **toxic, corrosive**
- Diethyl ether, 300 mL — **highly flammable, may form peroxides**

1. Equip the three-necked flask with the magnetic stirring bar, the nitrogen (argon) bubbler, and a pressure-equalizing dropping funnel. Evacuate and flame dry the glassware, allow to cool to ambient temperature under vacuum, and purge with dry nitrogen (argon). Keep a positive pressure of nitrogen (argon) throughout the reaction.
2. Charge the flask with diisopropylamine (20.2 g, 28 mL, 200 mmol) and anhydrous THF (120 mL), and immerse it in an ice-bath. Slowly add *n*-BuLi (124 mL, 1.6 M in hexane, 198 mmol) via the dropping funnel to the stirred solution (*ca.* 20 min), and continue stirring for another 10 min after the addition is complete. During that time, rapidly replace the dropping funnel by a

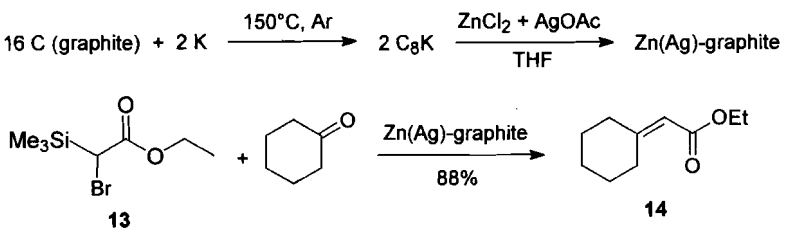
new one which is charged with THF (100 mL) and ethyl trimethylsilylacetate (21.6 g, 135 mmol).

3. Immerse the flask in a dry ice:acetone bath. After stirring for 5 min, add the content of the dropping funnel to the cooled LDA solution over a period of 40 min, and continue stirring for 1 h at –78 °C.
4. Charge the dropping funnel with chlorotrimethylsilane (30.4 g, 35.5 mL, 280 mmol) and anhydrous THF (60 mL), and add this solution to the flask at –78 °C over a period of 15 min. After complete addition, continue stirring at that temperature for another 60 min before allowing the mixture to warm to ambient temperature.
5. Replace the dropping funnel by a new one which is charged with bromine (32.4 g, 10.4 mL, 202.5 mmol). Add the Br_2 to the silylketene acetal over a period of 30 min and continue stirring for 2 h at room temperature.
6. Carefully add water (150 mL) to the flask, transfer the mixture to the separatory funnel, extract the aqueous layer with diethyl ether (3 × 100 mL), wash the combined organic layers with brine (100 mL), dry them over Na_2SO_4, evaporate the solvent on a rotary evaporator, and distil the residue under reduced pressure through a Vigreux column (15 cm). This affords the product as a colourless liquid, 27.4–29 g, 85–90%, b.p. = 82–85 °C (13 mm).

[a] Diisopropylamine is purified by distillation over NaOH.
[b] Anhydrous THF is obtained by distillation over potassium/benzophenone or Mg anthracene.

Protocol 4.
Reformatsky reaction/Peterson elimination sequence using highly activated Zn(Ag)*–graphite: preparation of ethyl cyclohexylideneacetate (Structure 14)

Caution! Potassium and potassium–graphite laminate (C_8K) are pyrophoric and react violently with water, low molecular weight alcohols, and chlorinated solvents. They must be handled with care and used in strictly anhydrous solvents. Excess K or C_8K can be safely destroyed by suspending them in anhydrous THF and slowly adding an excess of isopropanol (technical grade).



13 14

Protocol 4. *Continued*

Equipment

- Three-necked round-bottomed flask (50 mL)
- Reflux condenser
- Argon bubbler
- Dry argon
- Vacuum pump
- Thermostatted hot plate stirrer
- Magnetic stirring bar
- Oil-bath
- Dry ice:acetone bath
- Syringe (5 mL)
- Sintered glass funnel
- Column for chromatography (30 cm × 2 cm)

Materials

• Graphite powder,[a] 3 g, 250 mmol	**do not inhalate**
• Potassium, 1.2 g, 30.7 mmol	**reacts violently with water, flammable solid**
• Anhydrous THF,[b] 60 mL	**irritating, flammable, may form peroxides**
• Anhydrous $ZnCl_2$,[c] 2 g, 14.7 mmol	**corrosive**
• AgOAc, 0.2 g, 1.2 mmol	**irritant, sensitive to light**
• Ethyl (bromo) (trimethylsilyl)acetate, 1.91 g, 8 mmol	**irritant**
• Cyclohexanone, 690 mg, 7 mmol	**flammable**
• Silica (Merck 60, 230–400 mesh)	**irritant**
• Distilled hexane, 250 mL	**flammable, irritant**
• Ethyl acetate, 70 mL	**flammable**
• Isopropanol (technical grade), 20 mL	**flammable**

1. Equip the three-necked flask with the magnetic stirring bar and the reflux condenser bearing the argon bubbler and charge it with graphite powder (3 g, 250 mmol). Evacuate the flask and heat the slowly stirred graphite to 150°C (oil-bath temperature) under vacuum for 10 min in order to remove any moisture and oxygen.
2. Flush the flask with argon and rapidly add potassium (1.2 g, 30.7 mmol) in small pieces to the vigorously stirred graphite powder while keeping the temperature at 150°C. This leads to the formation of the beautifully bronze coloured potassium–graphite laminate (C_8K) within 5–10 min.
3. Cool the C_8K powder to ambient temperature, suspend it in anhydrous THF (30 mL), and add a mixture of finely ground anhydrous $ZnCl_2$ (2 g, 14.7 mmol) and AgOAc (0.2 g, 1.2 mmol) under a stream of Ar in one portion to the rapidly stirred suspension. The ensuing exothermic reduction causes the solvent to boil. Once the reaction has ceased, reflux the black mixture for 30 min in order to ensure quantitative reduction of the zinc and silver salts.
4. Cool the suspension of Zn(Ag)–graphite thus formed to –78°C by immersing the flask in a dry ice:acetone bath. Add a solution of ethyl (bromo) (trimethylsilyl)acetate **13** (1.91 g, 8 mmol) and cyclohexanone (690 mg, 7 mmol) in anhydrous THF (3 mL) via a syringe and stir the mixture for 30 min at that temperature.
5. Filter off the insoluble residues through a short pad (*ca.* 2 cm) of silica in a sintered glass funnel, rinse the graphite with THF (20 mL) in three portions, and evaporate the combined filtrates to dryness on a rotary evaporator.

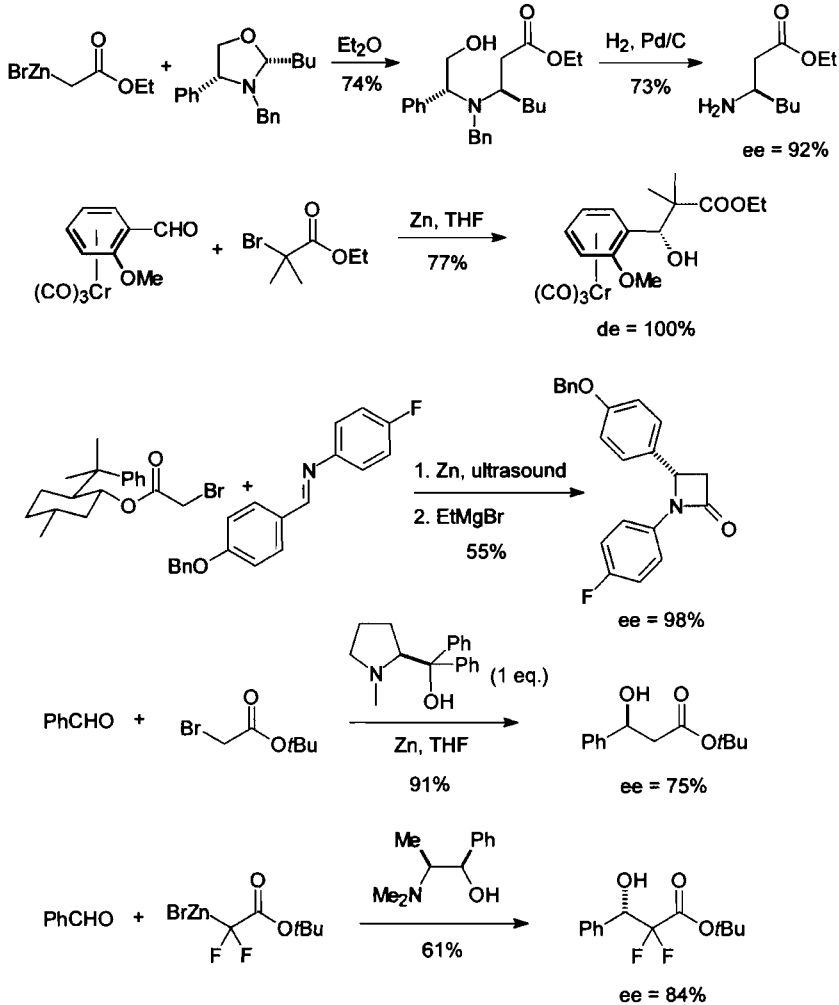
6. Destroy the Zn(Ag)–graphite residues by slowly passing THT/isopropanol (1:1) (technical grade) (20 mL) through the funnel.
7. Purify the crude product by flash chromatography on silica using hexane: ethyl acetate (4:1) as the eluent. This affords compound **14** as a colourless syrup, 1.04 g, 88%, b.p. = 48–50 °C (0.02 torr).

[a] Both natural graphite and synthetic graphite powder may be used.
[b] Anhydrous THF is obtained by distillation over potassium/benzophenone or Mg anthracene.
[c] $ZnCl_2$ is rather hygroscopic and should be handled under Ar. Anhydrous $ZnCl_2$ may be purchased or can be obtained by heating $ZnCl_2$ overnight at 80 °C under vacuum (10^{-3} torr).

4. Stereoselective Reformatsky reactions

Despite considerable efforts, a general method for performing highly stereoselective Reformatsky reactions is still missing. Many attempts make use of the known affinity of Zn(2+) towards nitrogen donors which may be present either in one of the substrates or in an appropriate external ligand. For example, the addition of zinc enolates to aminocarbonyl compounds was found to be highly diastereoselective, with the diastereomeric excess being a function of the complexing ability of the amino group.[39] However, some impressive diastereoselectivities have also been obtained in reactions with enantiomerically pure oxazolidines[40] as well as with π-complexed aromatic aldehydes or imines, in which the attack of the zinc enolates is biased solely by the attached $Cr(CO)_3$ template for steric and stereoelectronic reasons.[41] Some success has also been reported by using bromocarbonyl compounds attached to appropriate chiral auxiliaries.[42]

Particularly challenging is the use of chiral ligands in order to impose enantiocontrol on a Reformatsky reaction. Although preparatively useful levels of asymmetric induction have been described in the recent literature by using enantiomerically pure amino alcohol ligands,[43] this reaction has not yet reached a similar level of perfection as the enantioselective addition of other organozinc reagents to aldehydes in the presence of the same type of additives. Some selected examples of stereoselective Reformatsky type reactions which delineate the present state of the art are summarized in Scheme 14.6.



Scheme 14.6 Selected examples of stereoselective Reformatsky reactions.

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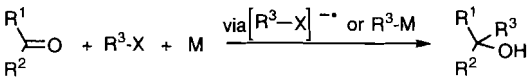
15

Zinc-mediated Barbier reactions

JEAN-LOUIS LUCHE and LUIS A. SARANDESES

1. Introduction

Among the synthetic accesses to alcohols, the nucleophilic addition of organometallics to carbonyl groups is certainly one of the more versatile and frequently used, and can be achieved by using a Grignard reaction. The paramount importance of the latter has left somewhat in the shade the Barbier reaction, frequently considered as its 'ancestor' in all respects. Barbier's student V. Grignard discovered the two-step procedure to which his name remained attached, as a development of the original one-step condensation between an organic halide, a carbonyl compound, and a metal (Scheme 15.1).[1,2] The latter, direct and easy to perform, has a number of advantages. The preliminary preparation of the organometallic is avoided, an interesting point when this preparation is long, tedious, or difficult (benzylic organometallics ...), or the reagent is unstable and undergoes elimination, cyclization, polymerization, etc.



R_1 can be H ; M = Li, Na, Mg, Zn, ...

Scheme 15.1

Historically, Frankland then Saytzeff were the first to study this system, using zinc as the metal.[3] Due to a relatively low reactivity and a limited scope of the process, zinc was replaced first by magnesium (by Barbier himself)[4] then lithium.[5] The much broader domain of applicability thus obtained, accompanied by good yields under reasonable conditions of temperature and time, was further extended by ultrasonic activation.[6,7] Mechanistically, it was considered for a long time that the Barbier reaction is a one-step Grignard condensation. This statement seems to be only partially true,[8] and a more complex pathway should be considered: the actual reactive entity adding to the carbonyl group is a radical anion or the *in situ* generated organometallic, according to the nature of the halogen and the reaction conditions.[9,10]

In modern synthetic chemistry, the advantages of zinc were rediscovered. New selective reactions illustrated below were found, together with an unexpected possibility of performing some condensations in aqueous media.

2. Activation of the metal

Commercial ordinary zinc is generally poorly reactive due to the inertness of the oxide passivation layer, its compactness, and adherence to the underlying metal.[11] The Barbier reaction (and others) requires activation which can be accomplished by several methods.

Cementation consists in the formation of a surface alloy with a less reactive metal. For zinc, alloying can be effected with mercury (amalgamation), copper, silver, nickel.[12] The reactivity of a cemented metal can be explained considering that the supporting metal plays only the role of an electron reservoir, the 'true' chemistry is effected by the superficial additional metal. Zinc can also be activated by washing with aqueous ammonium chloride,[13] or by reacting the powder with trimethyl-chlorosilane.[14] In this latter case, Barbier reactions were effected even at 0°C in short times. The activation mechanism was not determined.

A highly reactive form of zinc is obtained by dispersion of the metal in graphite and the lamellar structure of the solid matrix protects the large surface area reagent from oxidation.[15]

Ultrasound constitutes an easily performed activation method, which does not require any expensive or specialized equipment.[7,16] In most cases, it is not necessary to pre-activate the metal before addition of the organic co-reagents. The changes in morphology and surface composition brought about by sonication were studied by electron microscopy and Auger effect analysis.[17]

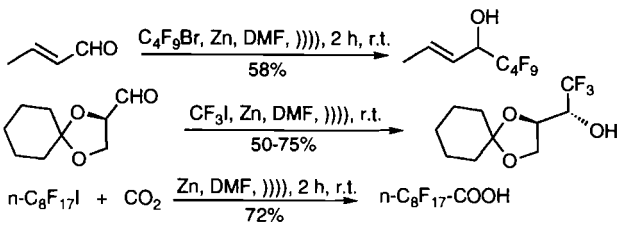
Rieke obtained activation of metals by an indirect method, the reduction of salts, most of the time the chlorides, with potassium or lithium.[18] The method was further improved by effecting the reduction with lithium under sonication,[19] which avoids the use of potassium, prolonged heating at relatively high temperatures, and a possible deactivation of the metal slurry by annealing.

3. Reactions

In general, the zinc promoted condensation of alkyl halides with aliphatic aldehydes and ketones gives only poor results.[2] In contrast good results are obtained when one of the reactants is unsaturated. Thus the addition of an allylic group to a carbonyl compound, or the conjugate addition of an alkyl moiety to an activated olefin, occur in excellent yields. Some corrections to this schematic view will be given in the following discussion.

3.1 Addition of alkyl groups to carbonyl functionalities

The most important case in this class of reactions is the addition of perfluoroalkyl chains (Scheme 15.2).[20]

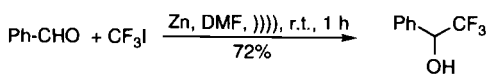


Scheme 15.2

The precursor is generally a perfluoroalkyl iodide, and the preferred solvent dimethylformamide (DMF).[21,22] Since a two-step Grignard process would give rise to difficulties, the one-step reaction was preferred giving good yields, which are still improved by sonochemical activation, minimizing β-elimination.[23,24] Perfluoroalkyl carboxylic acids can be prepared by running the reaction in the presence of carbon dioxide.

Protocol 1.
Preparation of 2,2,2-trifluoro-1-phenylethanol[24]

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.3

Equipment

- Ultrasonic cleaning bath
- Round-bottom flask (100 mL)
- Dry ice:acetone reflux condenser
- Erlenmeyer flask (250 mL)
- Magnetic bar (2.5 cm)
- Separation funnel
- Bulb-to-bulb distillation set-up

Materials

- Zinc powder, 1.3 g, 20 mmol — **pyrophoric**
- Trifluoromethyl iodide, 3 g, 30 mmol — **toxic**
- Benzaldehyde, 1.06 g, 10 mmol
- *N,N*-dimethylformamide, dry, 30 mL — **harmful by inhalation**
- Aqueous hydrochloric acid, 2%, 100 mL — **corrosive**
- Diethyl ether, 60 mL — **flammable**
- Magnesium sulfate

Protocol 1. *Continued*

1. Pour cold water in the ultrasonic bath (30–50 kHz) half of its depth and switch it on. Observe the places of maximum agitation on the water surface to determine the horizontal X and Y coordinates of the energy maxima. Place a stainless steel coil connected to a cold water tap in the bath and circulate water. Adjust the vertical Z coordinate of the energy maximum by adding water slowly so as to obtain a geyser at the surface (ultrasonic fountain).
2. Place zinc powder (1.3 g, 20 mmol), trifluoromethyl iodide (3 g, 30 mmol), benzaldehyde (1.06 g, 10 mmol), and *N,N*-dimethylformamide (dry, 30 mL) in a flame dried round-bottom flask, which is equipped with a dry ice:acetone condenser.
3. Clamp the flask firmly in the ultrasonic bath at the maximum energy position, bringing to coincidence the liquid levels inside and outside the flask. Start the irradiation.
4. After 1 h, discontinue sonication, pour the reaction mixture into a 2% HCl solution, then extract the mixture with diethyl ether (3 × 20 mL).
5. Dry the combined ethereal phases ($MgSO_4$), filter the solution, and evaporate the solvent on a rotary evaporator. Distil the residue to obtain the title compound (b.p. 105–108°C/16 mmHg, 1.27 g, 72%).

3.2 Allylic and propargylic halides

Unsaturated halides participate successfully to Barbier condensations in the presence of zinc. One of these is 1,1,1-trifluoro-2-bromo-2-propene, which was added to an aldehyde carbonyl group in the presence of zinc and copper chloride.[25] However, this case is unusual and most of the time, the unsaturated halides are allylic or propargylic derivatives. Allylation of carbonyl groups with a variety of organometallics was reviewed recently.[26] Here the advantages of the Barbier procedure appear clearly, since the preparation of allylic organometallics from the corresponding halides is frequently impaired by Wurtz couplings. An important distinction should be made between the procedures which make use of classical (i.e. dry) conditions in aprotic media, and the a priori unexpected procedures conducted in aqueous solvents.

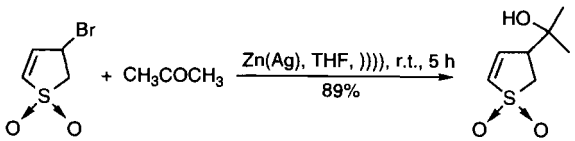
3.2.1 Reactions in classical solvents

In diethyl ether, the yields of the zinc-mediated Barbier condensation are medium or poor,[1] and THF should be preferred for most of the synthetic uses. Sonication is frequently used, e.g. in the reaction of methallyl bromide and salicylaldehyde which provide the expected alcohol.[27] The condensation of 4-bromo-2-sulfolene with a series of aldehydes and ketones was effected with the zinc–silver couple and ultrasound.[28] The reaction occurs without transposition, which is not the case in the presence of magnesium. In refluxing

THF, the zinc–copper couple was used to prepare a precursor of taxol.[29] *E*-5-bromo-1,3-pentadiene reacts with aldehydes in the presence of zinc to give dienols with transposition. Sonication helps the reaction on the metal, which also requires activation by catalytic amounts of aluminium chloride.[30]

Protocol 2.
Preparation of 4-(1-hydroxy-1-methylethyl)-2-sulfolene[28]

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.4

Equipment

- Ultrasonic bath
- Round-bottom flask (20 mL)
- Sintered glass funnel

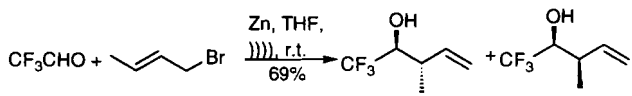
Materials

• 4-bromo-2-sulfolene, 98.5 mg, 0.5 mmol	**irritant**
• Acetone, 41 mg, 0.7 mmol	**flammable**
• Zinc–silver couple, 38 mg, 0.6 mmol	**pyrophoric**
• Tetrahydrofuran, 3.5 mL	**flammable**
• Ethyl acetate, 10 mL	**flammable**
• Celite	
• Silica gel	

1. Optimize the acoustic energy emission as in Protocol 1.
2. In a flame dried round-bottom flask, place 4-bromo-2-sulfolene (98.5 mg, 0.5 mmol), acetone (41 mg, 0.7 mmol), and THF (3.5 mL), then add the zinc–silver couple (38 mg, 0.6 mmol). Flush with dry nitrogen then stopper the flask with a rubber septum.
3. Clamp the flask in the ultrasonic bath and sonicate at room temperature for 5 h.
4. Add ethyl acetate (10 mL), then filter the mixture through a Celite pad on a sintered glass funnel, concentrate the filtrate on a rotary evaporator, and purify the residue by column chromatography (SiO_2, eluent *n*-hexane:ethyl acetate) to obtain the pure product (78 mg, 89%)

An advantage of the zinc-mediated reaction involving allylic substrates is the possibility to use allylic mesylates or phosphates instead of a halide,[31] in the presence of lithium iodide and a polar solvent.

A number of examples involving fluorinated substrates have been published, and a review discusses these results.[32] The advantage of using zinc instead of lithium or magnesium in the present case is the decreased occurrence of side-reactions. The sonochemical reaction between crotyl bromide and trifluoroacetaldehyde (Scheme 15.5) is easier and cleaner than the silent equivalent but the stereoselectivity remains essentially the same.[33] Propargyl bromides give acetylenic products in most cases,[34] but some authors did observe the formation of allenic compounds.[35] This transposition does not occur with 1,1-difluoropropargylic bromides, which condense with aldehydes in good yields.[36]



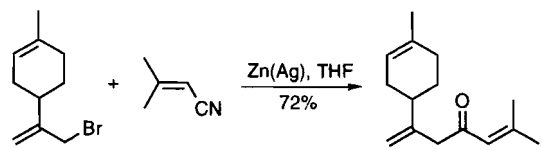
(*threo* / *erythro* : 3/ 2)

Scheme 15.5

Compounds with carbon–nitrogen multiple bonds were also successfully used in the Barbier procedure. Allylic groups add to imines in high yields (> 77% in the examples published), even enolizable substrates, possibly due to the low basicity of the medium.[37] Additions to nitriles occur in THF in the presence of the zinc–silver couple.[38] Terpenic ketones were prepared by this method.

Protocol 3.
Preparation of β-atlantone[38]

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.6

Equipment

- Round-bottom flask (25 mL)
- Magnetic bar (1 cm)
- Dropping funnel (15 mL)
- Magnetic stirrer
- Erlenmeyer flask (200 mL)
- Separating funnel

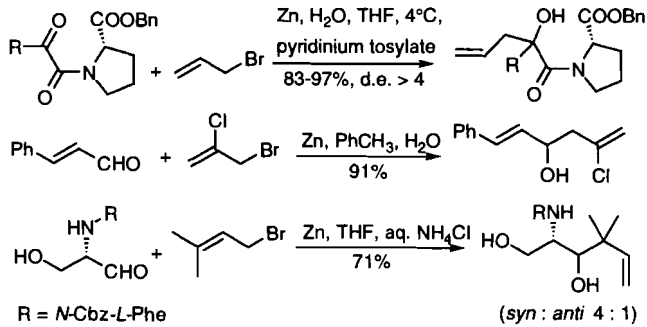
Materials

- Zinc–silver couple, 3.27 g, 52 mmol[12] **pyrophoric**
- 2,2-dimethylacrylonitrile, 3.3 g, 37.5 mmol **toxic**
- Anhydrous tetrahydrofuran, 10 mL **flammable**
- 2-(4-methyl-3-cyclohexenyl)-3-bromo-1-propene, 8.06 g, 37.5 mmol[39] **irritant**
- Saturated aqueous ammonium chloride
- Diethyl ether, 200 mL **flammable**
- Sodium sulfate

1. In a flame dried round-bottom flask fitted with magnetic bar and dropping funnel, place zinc–silver couple (3.27 g, 52 mmol) and dimethylacrylonitrile (3.30 g, 37.5 mmol) in anhydrous THF (10 mL).
2. Add 2-(4-methyl-3-cyclohexenyl)-3-bromo-1-propene (8.06 g, 37.5 mmol) over a 4 h period via the dropping funnel.
3. After 14 h at 20 °C, pour the mixture onto cold water (20 mL), saturated aqueous ammonium chloride (50 mL), and diethyl ether (50 mL) in an Erlenmeyer flask (200 mL), and stir vigorously for 10 min.
4. The ethereal layer is separated and the aqueous phase extracted with ether (3 × 50 mL). The combined organic phases are dried (Na_2SO_4) and the solvent evaporated. The residue is distilled to give β-atlantone in 72% yield.

3.2.2 In aqueous media

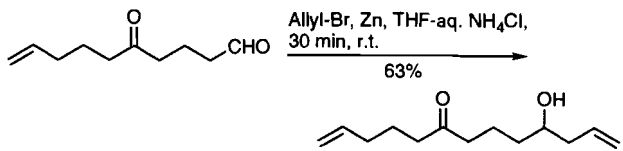
An organometallic-like reaction occurs between a carbonyl compound, an allylic halide, most of the time a bromide, and zinc in a mixture of THF and water under sonication (Scheme 15.7). When water is replaced by saturated aqueous ammonium chloride, sonication is unnecessary and high yields can be obtained in a few minutes at room temperature. Among the recent synthetic applications, allylation, crotylation, and propargylation of protected glyceraldehyde were described.[40] In some examples the presence of the organic co-solvent was found unnecessary.[41] A reverse-phase chromatography support such as C-18 silica was also used as a 'solid organic phase'.[42] Iodides and bromides react faster than chlorides,[43] allowing selective reactions.[44] As expected, the reaction can be effected with substrates containing a free hydroxyl group. The allylic group reacts with electrophiles through the more substituted carbon.[40,45] Selectivity is high in favour of aldehydes, with respect to ketones,[46] and to esters.[47,48] The reaction seems to take place via a radical mechanism on the metal surface, where the stereoselectivity is determined.[49] This stereochemical aspect was further examined in the allylation of chiral α-aminoaldehydes.[50] The high reactivity of allylic halides over their saturated and vinylic counterparts allows selective transformations, such as with 2,3-dichloropropene and 1-chloro-3-iodopropene, which reacts only at their allylic carbon–halogen bond.[44,51] Lower selectivity is observed with cinnamyl bromides which give α and γ adducts together with various coupling products, suggesting the role of radicals as reaction intermediates.[52]



Scheme 15.7

Protocol 4.
Preparation of 10-hydroxy-1,12-tridecadiene-6-one[53]

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.8

Equipment

- Round-bottom flask (20 mL)
- Ovoidal magnetic bar (1 cm)
- Magnetic stirrer
- Separation funnel
- Erlenmeyer flask (50 mL)

Materials

- Zinc powder, 0.07 g, 1.1 mmol — **pyrophoric**
- Allyl bromide, 130 mg, 1.1 mmol — **lachrymator**
- 6-keto-1-decene-10-al, 200 mg, 1 mmol[54]
- Saturated aqueous ammonium chloride
- Tetrahydrofuran, 1 mL — **flammable**
- Anhydrous magnesium sulfate
- Diethyl ether, 30 mL — **flammable**

1. Place allyl bromide (130 mg, 1.1 mmol), 6-keto-1-decene-10-al (200 mg, 1 mmol), saturated aqueous ammonium chloride (5 mL), and tetrahydrofuran (1 mL) in the round-bottom flask.
2. Under medium rate stirring, add slowly the zinc powder (0.07 g, 1.1 mmol) over a 10 min period, then continue stirring for an additional 20 min.

3. Pour the mixture into saturated aqueous ammonium chloride (20 mL) and extract with ether (3 × 10 mL). The ethereal phase is washed with water (3 × 20 mL), dried ($MgSO_4$). The solvent is evaporated to give an oil (200 mg, 63%).

The reaction can be applied to imines. Recently, the preparation of chiral allylglycines was effected by addition of allyl groups to the C=N bond in glyoxylic acid oximes modified as chiral sultams (Oppolzer chiral induction methodology).[55] The yields (> 88%) and the diastereoselectivity (d.e. > 80:20) are excellent.

3.3 Conjugate additions

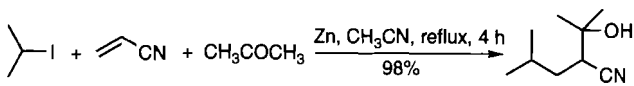
The Michael and related conjugate additions[56] can be effected conventionally without the need of the preparation of the organometallic, by a Barbier procedure using zinc. Many of the present developments of this procedure make use of the sonochemical method in aqueous alcohols.

3.3.1 Conventional conditions

Various examples of conjugate addition of an alkyl group to an activated olefin in the presence of zinc were described.[57,58] The reaction applies to aldehydes, ketones, and nitriles. A cyclization process yielding a spiroketone was described.[59] Addition of perfluoroalkyl groups to itaconic acid gives perfluoroalkyl succinic acids.[60] Mechanistically, an enolate intermediate is formed, which can be trapped by an electrophile. Interestingly this addition–trapping sequence can be effected 'one-pot', and is applicable to annellation.[61] A recent version of this reaction has been published, in which manganese (activated by lead dichloride) replaces zinc.[62]

Protocol 5.
Preparation of 2,5-dimethyl-3-cyano-2-hexanol[61]

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.9

Equipment

- Two-necked round-bottom flask (50 mL)
- Magnetic bar (0.8 cm)
- Reflux condenser
- Dropping funnel
- Erlenmeyer flask (150 mL)
- Separating funnel

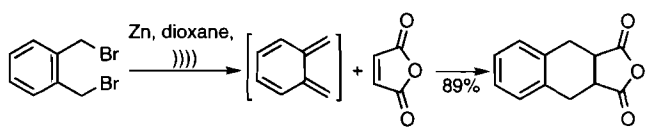
Protocol 5. *Continued*

Materials

• Zinc powder, 2.4 g, 37 mmol	**pyrophoric**
• Freshly distilled acrylonitrile, 0.4 g, 7.6 mmol	**toxic, flammable**
• Acetone, 0.133 g, 23 mmol	**flammable**
• Isopropyl iodide, 2.62 g, 22 mmol	**irritant, suspected carcinogen**
• Acetonitrile, 14 mL	**poisonous**
• Saturated aqueous ammonium chloride	
• Diethyl ether, 30 mL	**flammable**
• Anhydrous sodium sulfate	

1. Place a mixture of zinc powder (2.4 g, 37 mmol), freshly distilled acrylonitrile (0.4 g, 7.6 mmol), acetone (0.133 g, 23 mmol), and acetonitrile (14 mL) in a round-bottom flask under a nitrogen atmosphere. Heat to reflux under stirring.
2. Add some of the isopropyl iodide (0.655 g, 5.5 mmol) dropwise via the dropping funnel. Caution: an exothermic reaction takes place.
3. After the vigorous reaction has subsided, add a second portion of isopropyl iodide (1.96 g, 16.5 mmol) over 10 min and reflux the mixture for 4 h.
4. After cooling, pour the mixture into an Erlenmeyer flask (150 mL) containing saturated aqueous ammonium chloride (30 mL) and 15 mL diethyl ether. Separate the ethereal solution in a separating funnel, wash it with saturated aqueous ammonium chloride (3 × 20 mL), then dry it over magnesium sulfate. Evaporate the solvents. Distillation of the residue gives the title compound in 98% yield.

Another annellation reaction starts from α,α′-dibromo-*o*-xylene, an activated olefin and zinc.[63] This reaction, according to the authors proceeds by a Diels–Alder cycloaddition via the *o*-xylylene (Scheme 15.10), and was employed in carbohydrate chemistry to prepare anthracyclinones analogues.[64] No reaction occurs without sonication. Instead of a cycloaddition, another explanation can be postulated, consisting first of addition of a mono-organozinc reagent to the activated olefin, followed by alkylation of the resulting enolate by the second benzylic bromide.

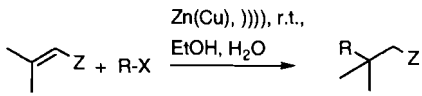


Scheme 15.10

3.3.2 In aqueous solvents

Alkyl groups add to electron deficient alkenes in the presence of a zinc–copper couple (Scheme 15.11). Sonication is necessary in practically all the

examples published. The medium consists of a mixture of water with lower alcohols, acetone, or even pyridine. In some cases, the composition corresponds to a maximum structuredness of the liquid, which parallels an optimal absorption of acoustic energy.[65] These additions most probably occur on the metal surface via successive electron transfers. Olefins activated by aldehyde, ketone, ester, amide, and cyano groups undergo the addition successfully. Bromides and iodides can be used with secondary and tertiary alkyl substrates, but iodides are required for primary ones. Chlorides are inert, and a hydroxyl group does not inhibit the reaction, offering possibilities to introduce functional moieties.[66]

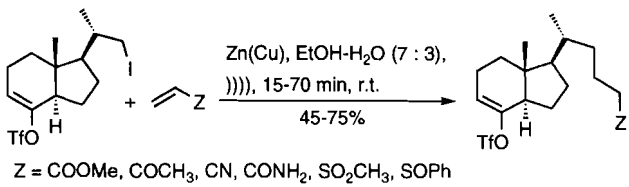


Z = aldehyde, ketone, ester, amide, nitrile

Scheme 15.11

The addition of an allylic group was reported in the synthesis of heneicos-6-en-11-one, the sex pheromone of the Douglas fir tussock moth.[67] This method was compared advantageously to the classical processes employing the toxic tin hydrides, with respect to the rates, yields, and chemoselectivity.[68,69] Concerning the stereoselectivity however, no major difference exists between the conventional and sonochemical methods.[70,71]

Construction of vitamin D_3 analogues was accomplished by sonicating iodides containing the preformed C and D rings, and a series of activated olefins (Scheme 15.12).[72,73] Even vinyl sulfoxides and sulfones can be reacted successfully. The yields are generally excellent, even in the presence of a free hydroxyl or a vinylic triflate on carbon 8 (steroid numbering). The elaboration of the vitamin was completed using the vinylic triflate functionality. A more direct approach was followed by grafting the side chain directly on the desired final trienic structure. The way that such a fragile system can survive in the reaction conditions illustrates the mildness of this method.[74]

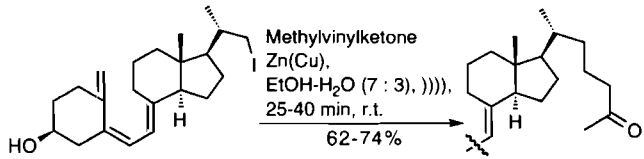


Z = COOMe, $COCH_3$, CN, $CONH_2$, SO_2CH_3, SOPh

Scheme 15.12

Protocol 6.
Preparation of 25-keto-27-norvitamin D_3[72]

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.13

Equipment

- Thermostatted ultrasonic cleaning bath
- Round-bottomed flasks (2 × 10 mL)
- Syringe (5 mL)
- Separating funnel (25 mL)
- Erlenmeyer flasks (2 × 25 mL)

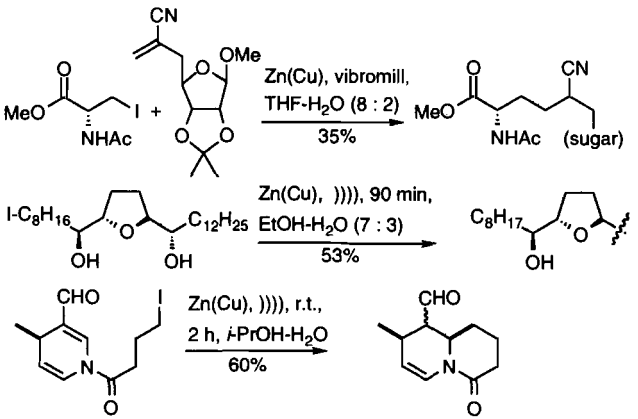
Materials

- Zinc powder, 100 mg, 1.54 mmol — **pyrophoric**
- Copper(I) iodide, 125 mg, 0.66 mmol
- Ethanol, 2.8 mL — **flammable**
- Water, 1.2 mL
- (5*E*,7*Z*)-22-iodo-23,24-dinor-9,10-seco-5,7,10(19)-cholantrien-3β-ol, 100 mg, 0.23 mmol
- Methylvinylketone, 140 mg, 0.17 mL, 2 mmol — **toxic, flammable**
- Saturated aqueous sodium chloride, 15 mL
- Dichloromethane, 30 mL — **harmful by inhalation**
- Anhydrous magnesium sulfate

1. Optimize the energy of the bath as in Protocol 1.
2. In an argon flushed round-bottomed flask (10 mL), stopped with a septum, place zinc powder (100 mg, 1.54 mmol), copper(I) iodide (125 mg, 0.66 mmol), ethanol (0.7 mL), and water (0.3 mL).
3. Place the reaction flask in a ultrasonic bath and switch the generator on. The initial grey mixture turns rapidly to a deep black, heavy suspension.
4. In a second round-bottomed flask, dissolve the iodide (100 mg, 0.23 mmol) and methylvinylketone (0.17 mL, 2 mmol) in ethanol (2.1 mL) and water (0.9 mL). Add this solution to the zinc–copper couple via a syringe, under sonication, and continue ultrasonic irradiation for 35 min.
5. Stop sonication, and pour the content of the reaction flask into brine (15 mL), with vigorous stirring.
6. Extract the mixture with dichloromethane (3 × 10 mL). Dry the combined organic phase with magnesium sulfate, filter the solution, and evaporate the solvent on a rotary evaporator.

7. Purify the residue by preparative HPLC (Zorbax silica 250 × 10 mm), eluting with 5% 2-propanol in hexane. Evaporate the solvent on a rotary evaporator, to obtain the product as a viscous oil, which solidifies on standing; 65 mg, 74%.

Functionalized halides also give good results (Scheme 15.14); β-iodo-*N*-acetylalanine methyl ester was used to introduce the amino acid residue onto an olefinic sugar.[75] The authors estimate that sonication is not necessary, but since they used a vibromill stirrer, cavitation produced by this method is certainly at the origin of the activation. With a iodoalkyl tetrahydrofuranic diol, only C–I bond reduction was observed.[76] An intramolecular reaction was effected using this procedure,[77] the unsaturated aldehyde cyclizing regioselectively, contrasting with the non-selectivity of conventional methods. During this reaction the monocyclic reduction product was also formed in 30% yield however. Other more unusual applications have been found, such as the addition of alkyl groups to vinylphosphine oxides.[78]

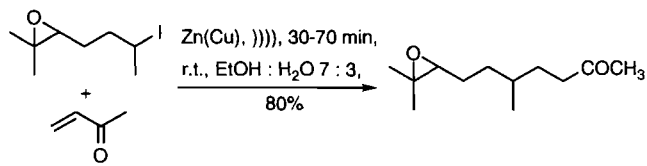


Scheme 15.14

The protocol was also applied to alkyl halides containing sensitive epoxide groups, which would give rise to severe difficulties using conventional organometallic methods. The additions proceeded in good yields with preservation of the epoxide ring,[79] provided at least three carbons separate the functionalities. This result provides further evidence for a radical mechanism, a carbanionic species would probably open the three-membered ring of the epoxide intra- or intermolecularly.

Protocol 7.
Synthesis of 5,9-dimethyl-8,9-epoxy-2-decanone

Caution! Carry out all procedures in a well-ventilated hood, and wearing disposable vinyl or latex gloves and chemical-resistant safety goggles.



Scheme 15.15

Equipment

- Thermostatted ultrasonic cleaning bath
- Round-bottom flask (25 mL)
- Syringe (10 mL)
- Separating funnel (50 mL)
- Erlenmeyer flask (50 mL)

Materials

- Zinc powder, 294 mg, 4.5 mmol — **pyrophoric**
- Copper(I) iodide, 285 mg, 1.5 mmol
- Ethanol, 7 mL — **flammable**
- Water, 3 mL
- 2-methyl-2,3-epoxy-6-iodoheptane, 254 mg, 1 mmol — **irritant**
- Methylvinylketone, 280 mg, 0.33 mL, 4 mmol — **toxic, flammable**
- Saturated aqueous ammonium chloride, 15 mL
- Dichloromethane, 30 mL — **harmful by inhalation**
- Anhydrous magnesium sulfate

1. Optimize the energy emission as in Protocol 1.
2. In the round-bottomed flask (25 mL), place zinc powder (196 mg, 3 mmol), copper(I) iodide (190 mg, 1 mmol), ethanol (5 mL), and water (3 mL), then flush the flask with argon and stopper with a septum.
3. Clamp the flask in the ultrasonic bath, at a position of maximum energy. Switch the generator on. The original grey suspension turns to a deep black, heavy mixture.
4. Dissolve the epoxyiodide and methylvinylketone in 2 mL of ethanol.
5. Add this solution to the zinc–copper couple via a syringe, dropwise over a period of 30 min.
6. Add a second portion of zinc powder (98 mg, 1.5 mmol) and copper(I) iodide (95 mg, 0.5 mmol) into the reaction flask and continue the irradiation for 30 min.
7. Discontinue sonication and pour the content of the flask into saturated ammonium chloride (15 mL) under vigorous stirring.

8. Extract the mixture with dichloromethane (3 × 10 mL), dry the combined organic extracts on $MgSO_4$, filter the solution, and evaporate the solvent on a rotary evaporator.
9. Purify the residue on a silica gel column (20 g), eluting with 10% EtOAc in hexane. Evaporate the solvent on a rotary evaporator to obtain the product (oil); 145 mg, 73%.

In conclusion, it can be stated that the Barbier reaction was an important discovery for organic synthesis. Besides the historical and theoretical interests, we can see that the applications in various domains of synthesis are numerous, due to the experimental simplicity and the good to excellent results, frequently equal or better than more complicated conventional techniques. These qualities appear in the examples discussed above and zinc is the metal of choice for many applications. The discovery of the aqueous reactions should lead to more and more applications, especially as a result of the care being paid to environmental questions by chemists.

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A1

Compilation of organozinc reagents

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The following compilation is not intended to be comprehensive, but rather to provide a convenient source of references to full procedures for the preparation of a representative sample of organozinc reagents. It must be emphasized that with the exception of Organic synthesis procedures, the experimental procedures have not been checked independently. Reagents are grouped by the number of carbons in the main transferable organic group bound directly to the metal (excluding those in protecting groups) and, within these groups, they are organized by the molecular formula of the complete organic group. Abbreviated references, as used in Comprehensive Heterocyclic Chemistry, are given alongside the reagents with full reference details listed at the end of the compilation. In generation the abbreviated references are self-evident (82JOM117 = *J. Organomet. Chem.* **1982**, *117*).

AC: *Angewandte Chemie*
CB: *Chemische Berichte*
CC: *Chem. Commun.*
CCCC: *Collect. Czech. Chem. Commun.*
CEJ: *Chem. Eur. J.*
CL: *Chem. Lett.*
CR: *Chem. Rev.*
HCA: *Helv. Chim. Acta*
JACS: *J. Am. Chem. Soc.*
JOC: *J. Org. Chem.*
JOM: *J. Organomet. Chem.*
OM: *Organometallics*
S: *Synthesis*
SC: *Synth. Commun.*
SL: *Synlett*
TH: *Tetrahedron*
TL: *Tetrahedron Lett.*

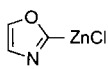
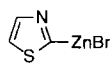
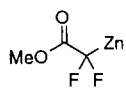
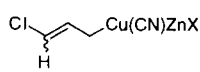
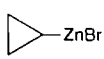
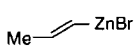
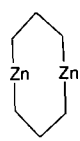
C1

CF_3	CF_3ZnI•bipyr	80JOM117

C2

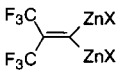
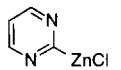
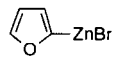
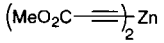
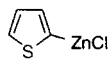
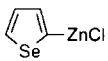
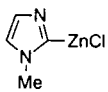
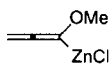
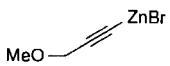
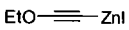
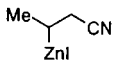
C_2F_3		94TH2993, 92TH9577
C_2F_5	C_2F_5ZnI	84TL4117
C_2HF_2		96TL7237
C_2HF_2		96TL8799
C_2H_2N	$BrZnCH_2CN$	91JOC2018

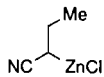
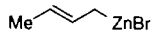
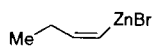
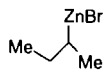
C3

C_3F_7	$(CF_3)_2C(F)ZnI$	92TH189
C_3F_7	*i*-C_3F_7ZnI	84TL4117
$C_3H_2F_3$		92TL511
C_3H_2NO		96S583
C_3H_2NS		97TH7237
$C_3H_3F_2O_2$		89S571
C_3H_4Cl		93TL3145
C_3H_4N	$NC(CH_2)_2ZnI$	95JOC1365
C_3H_4N	$NC(CH_2)_2Cu(CN)ZnI$	94CC703
C_3H_4N	NC(Me)CHZnCl	91JOC2018
C_3H_5		92TH9577
C_3H_5		92TH9577
C_3H_5		92TH9577
C_3H_6		96AC229

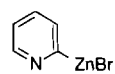
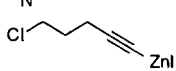
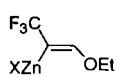
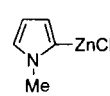
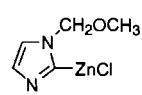
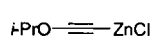
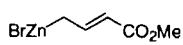
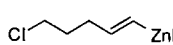
C_3H_9Sn	$(CH_3)_3SnZnCl$	92TH9577

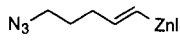
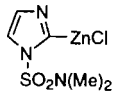
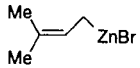
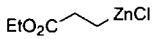
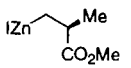
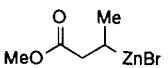
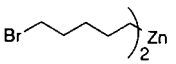
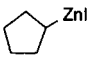
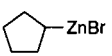
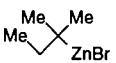
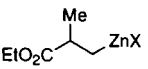
C4

C_4F_6		93JACS5430
$C_4H_3N_2$		97CCCC137
C_4H_3O		96AC1812, 92TH9577
$C_4H_3O_2$		93JOC814
C_4H_3S		97TL1941
C_4H_3S		94CC1923, 92TH9577
C_4H_3Se		92TH9577
C_4H_4N		97CCCC137
$C_4H_5N_2$		97CCCC137, 97TH7237, 92TH9577
C_4H_5O		92TH9577
C_4H_5O		96S82
C_4H_5O		92S495
$C_4H_5O_2$		83JOC4108
$C_4H_5O_2S$		95TL7105
C_4H_6	t-BuZnBr	95JACS10775
C_4H_6		87JACS8056
C_4H_6		87JACS8056

C_4H_6N	$NC(CH_2)_3ZnI$	94TL1177, 95JOC1365
C_4H_6N	$NC(CH_2)_3Cu(CN)ZnX$	94CC703, 93JACS5941, 94SL849
C_4H_6N		91JOC2018
C_4H_7		92TH9577
C_4H_7		92TH9577
C_4H_7O		92TH9577
$C_4H_7O_2$	EtO_2CCH_2ZnBr	85TL1027, 83JOC4108, 87JOC4796, 91JOC2018
C_4H_8Cl	$(Cl(CH_2)_4)_2Zn$	94JOC4143, 94TL5849, 94JOC3760
C_4H_8Cl	$Cl(CH_2)_4ZnX$	94TL1177, 88S485, 97SL477
C_4H_9		95JACS10775

C5

C_5H_4N		92TL5373, 97TH7237
C_5H_4N		92TL5373
C_5H_6Cl		93TL4623
$C_5H_6F_3O$		96JOC3200
C_5H_6N		97CCCC137
$C_5H_7N_2O$		97CCCC137
C_5H_7O		92S495
$C_5H_7O_2$		83JOC4108
C_5H_8Cl		93TL4623
C_5H_8N		92TH9577

C_5H_8N	$NC(CH_2)_4Cu(CN)ZnX$	94CC703
C_5H_8N	$NC(CH_2)_4ZnCl$	95SC101
C_5H_8N	$NC(CH_2)_4ZnI$	95JOC1365
$C_5H_8N_3$		92JACS3983
$C_5H_8N_3O_2S$		92TH9577
C_5H_9		92TH9577
$C_5H_9O_2$	$EtO_2C(CH_2)_2Cu(CN)ZnX$	93JACS5941, 93JOC1038, 93JACS3146, 88S485
$C_5H_9O_2$		95TL4439, 88S485, 86TL83
$C_5H_9O_2$		93TL5939, 87JACS8056
$C_5H_9O_2$		94TL7205
$C_5H_9O_2$	$MeO_2C(CH_2)_3Cu(CN)ZnX$	91TH1861, 93JOC5121
C_5H_9Si	$(Me)_3SiC{\equiv}CZnCl$	92TH9577
$C_5H_{10}Br$		96TL7201, 97TL715, 94TL4539
C_5H_{11}		96CEJ1204
C_5H_{11}		95JACS10775
C_5H_{11}		95JACS10775
$C_5H_{11}O_2$		83JOC4108, 92JOC4013, 87JOC4418, 88CC610

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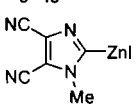
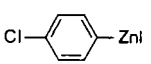
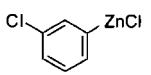
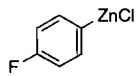
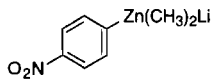
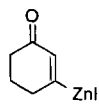
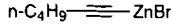
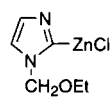
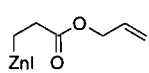
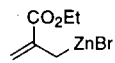
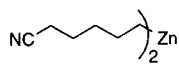
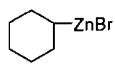
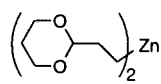
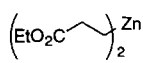
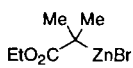
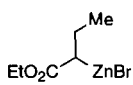
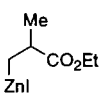
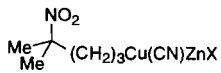
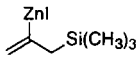
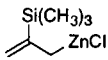
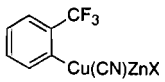
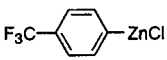
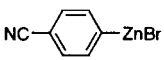
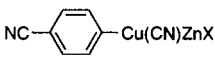
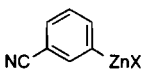
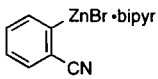
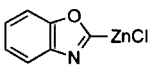
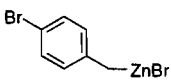
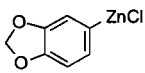
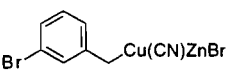
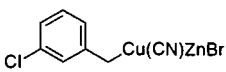
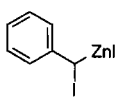
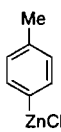
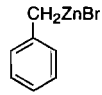
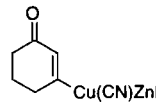
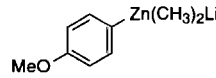
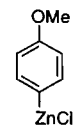
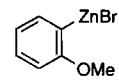
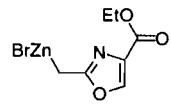
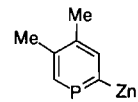
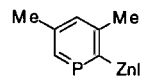
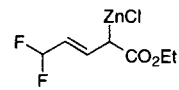
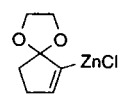
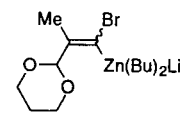
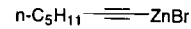
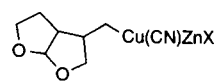
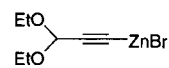
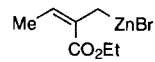
C_6F_5	$C_6F_5Cu(CN)ZnX$	94TL1047
C_6F_5	$(C_6F_5)_2Zn$	64JOM377
C_6F_{13}	$C_6F_{13}ZnI$	84TL4117
$C_6H_3N_4$		94TL1047, 97TH7237
C_6H_4Cl		93TL4623, 83TL5181, 91JOC1445
C_6H_4Cl		91JOC4052

C_6H_4F		91JOC4052
$C_6H_4NO_2$		94JOC4717
C_6H_7O		96TL7201, 97TL715
C_6H_9		96S82
$C_6H_9N_2O$		92TH9577
$C_6H_9O_2$		87JACS8056
$C_6H_9O_2$		87TL59, 88JOM1
$C_6H_{10}N$		96TL7201, 97TL715
$C_6H_{10}N$	$NC(CH_2)_5ZnI$	95JOC1365
C_6H_{11}		95JACS10775
$C_6H_{11}O_2$	$i\text{-}PrO_2C(CH_2)_2Cu(CN)ZnX$	93JOC5121
$C_6H_{11}O_2$		92TL5719
$C_6H_{11}O_2$	$BrZnCH_2CO_2t\text{-}Bu$	82TL3945
$C_6H_{11}O_2$	$(CH_3CO_2(CH_2)_4)_2Zn$	94TL5849, 94JOC3760
$C_6H_{11}O_2$	$EtO_2C(CH_2)_3ZnI$	88S485, 94TL1177, 94CC703
$C_6H_{11}O_2$		95TL7061
$C_6H_{11}O_2$		92JOC4013
$C_6H_{11}O_2$		92JOC4013
$C_6H_{11}O_2$		87JACS8056
$C_6H_{12}Br$	$(Br(CH_2)_6)_2Zn$	94TL4539
$C_6H_{12}Br$	$Br(CH_2)_6Cu(CN)ZnX$	93SL499
$C_6H_{12}Cl$	$Cl(CH_2)_6ZnBr$	91TL2865

$C_6H_{12}NO_2$		93OM3340
$C_6H_{12}NO_2$	$NO_2(CH_2)_6Cu(CN)ZnX$	94S410
$C_6H_{13}Si$		84TL4583
$C_6H_{13}Si$		93SL277

C7

$C_7H_4F_3$		94TL1047
$C_7H_4F_3$		93SL425, 92TH9577
C_7H_4N		96TL7201, 97TL715
C_7H_4N		94SL849, 94TL1047, 94TL5637, 92CC283
C_7H_4N		94TL5637
C_7H_4N		82JOM121
C_7H_4NO		96S583
C_7H_5Br		97TL1749
$C_7H_5O_2$		94SL349
C_7H_6Br		91TL2033
C_7H_6Cl		91TL2033
C_7H_6I		83S924
C_7H_7		92TH9577

C_7H_7		96SL185, 88JOC5789
C_7H_7O		97TL7201
C_7H_7O		94JOC4717, 93SL425
C_7H_7O		92TH9577
C_7H_7O		93SL425
$C_7H_8NO_3$		92JOC4797
C_7H_8P		96OM794
C_7H_8P		92TL3537
$C_7H_9F_2O_2$		92SL977
$C_7H_9O_2$		87CL1007
$C_7H_{10}BrO_2$		94TL7987
C_7H_{11}		95S82
$C_7H_{11}O_2$		94TL8349
$C_7H_{11}O_2$		96S82
$C_7H_{11}O_2$		89S571

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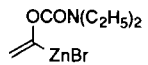
$C_7H_{12}NO_2$		96TL6057
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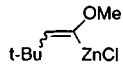
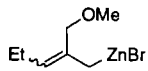
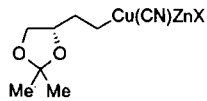
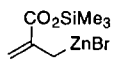
$C_7H_{13}O$		92TH9577
$C_7H_{13}O$		92TH9577
$C_7H_{13}O_2$		94CB1447
$C_7H_{13}O_2$	$(AcO(CH_2)_5)_2Zn$	94JOC4143, 93TL4623
$C_7H_{13}O_2$	$EtO_2C(CH_2)_4Cu(CN)ZnX$	94CC703, 94TL1177, 93JOC3850
$C_7H_{13}O_2Si$		83JOC4108
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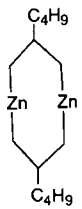
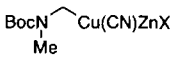
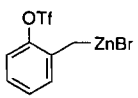
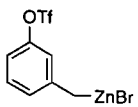
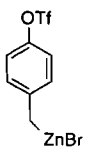
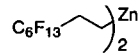
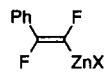
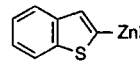
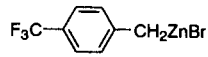
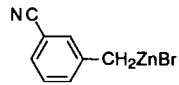
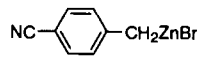
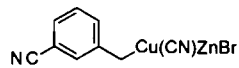
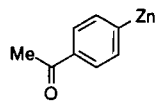
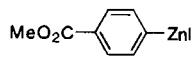
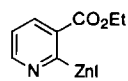
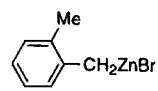
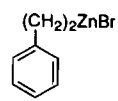
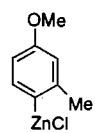
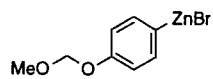
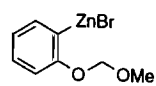
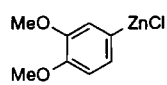
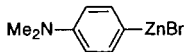
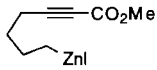
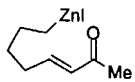
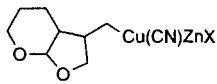
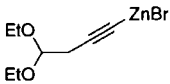
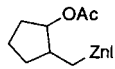
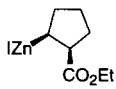
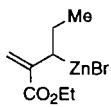
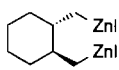
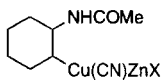
C_7H_{14}		96AC229
$C_7H_{14}NO_2$		95TL225

C8

$C_8H_4F_3O_3S$		97TL1749
$C_8H_4F_3O_3S$		97TL1749
$C_8H_4F_3O_3S$		97TL1749

$C_8H_4F_{13}$		96TL7201, 97TL715
$C_8H_5F_2$		94TH2993
C_8H_5S		93TL4623
$C_8H_6F_3$		94TL5637
C_8H_6N		93TL4623, 94TL5637
C_8H_6N		94TL5637
C_8H_6N		91TL2033
C_8H_7O		93SL425
$C_8H_7O_2$		93SL425, 92CC283
$C_8H_8NO_2$		92TL5373
C_8H_9		94TL5637
C_8H_9		96SL185, 92TH9577
C_8H_9O		92TH9577
$C_8H_9O_2$		94SL349
$C_8H_9O_2$		94SL349
$C_8H_9O_2$		94CC845

$C_8H_{10}N$		93SL425
$C_8H_{11}O_2$		93OM3340
$C_8H_{13}O$		93OM3340
$C_8H_{13}O_2$		94TL8349
$C_8H_{13}O_2$		96S82
$C_8H_{13}O_2$		93S266
$C_8H_{13}O_2$		93TL5939
$C_8H_{13}O_2$		94TH1111
C_8H_{14}		97TH987
$C_8H_{14}NO$		94TH2415
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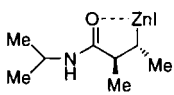
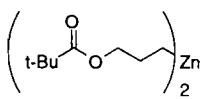
$C_8H_{15}NO$		96TL1045
$C_8H_{15}O_2$		97TL1749
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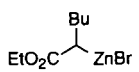
$C_8H_{15}O_2$		92JOC4013
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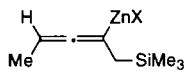
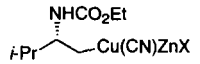
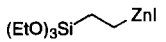
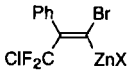
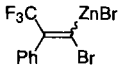
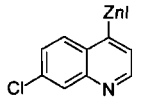
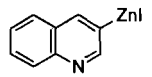
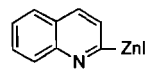
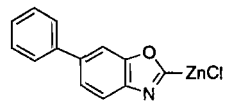
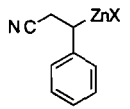
$C_8H_{15}Si$		95TL723

$C_8H_{16}NO_2$		94TH2415
$C_8H_{19}SiO_3$		93TL4623

C9

$C_9H_5BrClF_2$		93JACS5430
$C_9H_5BrF_3$		94S969
C_9H_5ClN		97TH7237
C_9H_6N		97TH7237
C_9H_6N		97TH7237
C_9H_6NO		96S583
C_9H_8N		90OM3053
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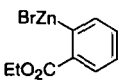
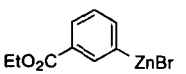
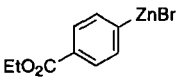
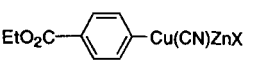
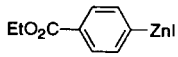
$C_9H_9O_2$		91JOC1445
$C_9H_9O_2$		91JOC1445
$C_9H_9O_2$		91JOC1445
$C_9H_9O_2$		94TL1047

$C_9H_9O_2$		94TL1047
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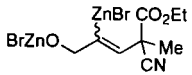
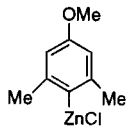
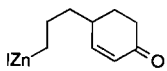
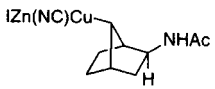
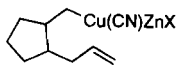
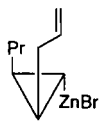
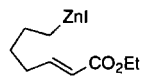
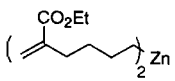
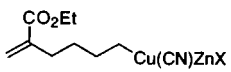
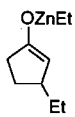
$C_9H_{11}NO_3$		75TL3147
$C_9H_{11}O$		92TH9577
$C_9H_{13}O$		93OM3340
$C_9H_{14}NO_2$		94TH2415
C_9H_{15}		93TL7911
C_9H_{15}		95SL723
$C_9H_{15}O_2$		93OM3340
$C_9H_{15}O_2$		94TL4539
$C_9H_{15}O_2$		94S410
$C_9H_{16}O$		96TL5141
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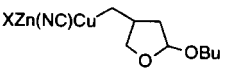
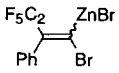
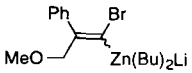
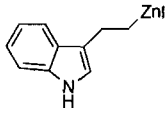
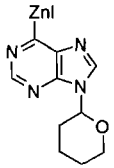
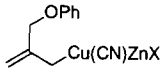
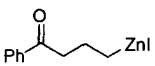
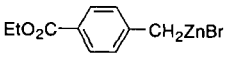
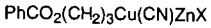
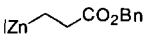
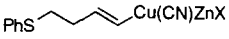
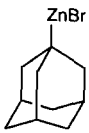
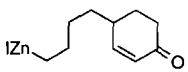
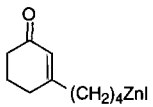
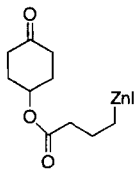
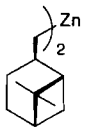
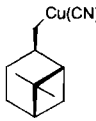
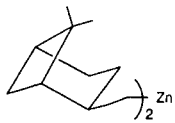
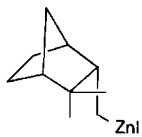
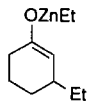
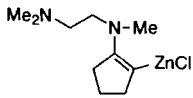
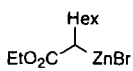
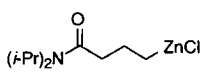
$C_9H_{17}O_2$	$PivO(CH_2)_4Cu(CN)ZnX$	94SL849
$C_9H_{17}O_2$		94TL8349

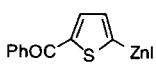
C10

$C_{10}H_4F_{17}$	$C_8F_{17}(CH_2)_2ZnI$	97TL1749

$C_{10}H_5BrF_5$		94S969
$C_{10}H_{10}BrO$		94TH7987, 92JOC5805
$C_{10}H_{10}N$		91JOC5974
$C_{10}H_{11}N_4O$		96TL1045
$C_{10}H_{11}O$		92TL475, 88TL3579
$C_{10}H_{11}O$		95JA6126
$C_{10}H_{11}O_2$		93TL4623, 93OM3340
$C_{10}H_{11}O_2$		94SL410
$C_{10}H_{11}O_2$		92CC1587
$C_{10}H_{11}S$		93JACS12625
$C_{10}H_{15}$		95JACS10775
$C_{10}H_{15}O$		93OM3340
$C_{10}H_{15}O$		93OM3340
$C_{10}H_{15}O_3$		88JOC2390

$C_{10}H_{16}$		96TL7201, 97TL715
$C_{10}H_{17}$		94SL410
$C_{10}H_{17}$		96TL7201, 97TL715
$C_{10}H_{17}$		96TL7201, 97TL715
$C_{10}H_{17}BrO_2$	$THPO(CH_2)_4(Br)C(H)ZnBu_2Li$	91TL1573
$C_{10}H_{17}O_4$	$(EtO_2)CH(CH_2)_3Cu(CN)ZnX$	94S410
$C_{10}H_{18}O$		96TL5141
$C_{10}H_{19}N_2$		87CL1007
$C_{10}H_{19}O_2$	$(PivO(CH_2)_5)_2Zn$	94JOC3760, 94TL5849, 94JOC4143
$C_{10}H_{19}O_2$	$PivO(CH_2)_5Cu(CN)ZnX$	94S410
$C_{10}H_{19}O_2$	$IZn(CN)Cu(CH_2)_7CO_2Et$	91TL4909
$C_{10}H_{19}O_2$		92JOC4013
$C_{10}H_{20}NO$		95SC101

C11

$C_{11}H_7OS$		94TL1047
$C_{11}H_{12}BrO$		93JOC2958

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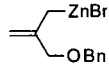
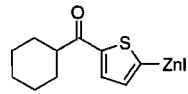
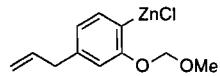
$C_{11}H_{13}O$		88TL3579
$C_{11}H_{13}OS$		94TL1047
$C_{11}H_{13}O_2$		95JOC1856
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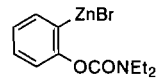
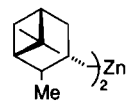
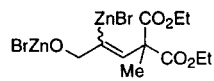
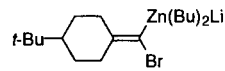
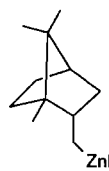
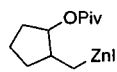
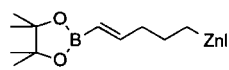
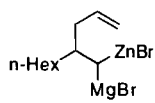
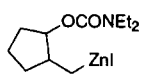
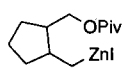
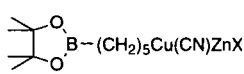
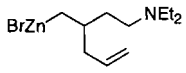
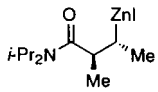
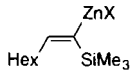
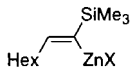
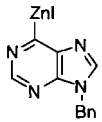
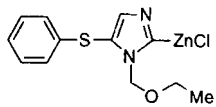
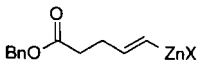
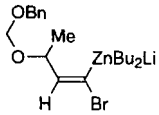
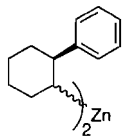
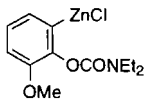
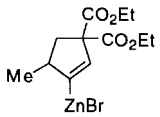
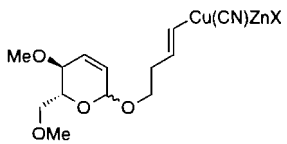
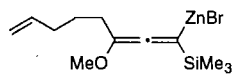
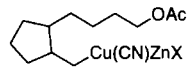
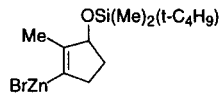
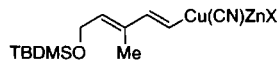
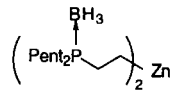
$C_{11}H_{14}NO_2$		94S349
$C_{11}H_{15}$		96TL7201, 97TL715
$C_{11}H_{16}O_5$		75TL3147
$C_{11}H_{18}Br$		93JOC4897
$C_{11}H_{19}$		96TL7201, 97TL715
$C_{11}H_{19}O_2$		93S266
$C_{11}H_{20}BO_2$		93TL4623
$C_{11}H_{20}BrMg$		93TL4623
$C_{11}H_{20}NO_2$		93S266
$C_{11}H_{21}O_2$		93TL7911
$C_{11}H_{22}BO_2$		94S410

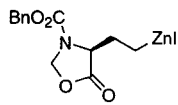
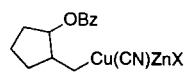
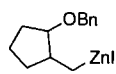
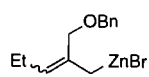
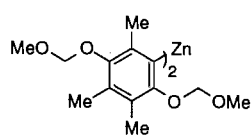
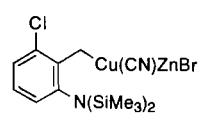
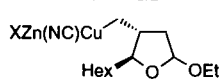
$C_{11}H_{22}N$		73JOM241
$C_{11}H_{22}NO$		96TL1045
$C_{11}H_{23}Si$		95JOC290
$C_{11}H_{23}Si$		95JOC290

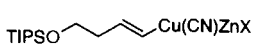
C12

$C_{12}H_9N_4$		96TL1045
$C_{12}H_{13}N_2OS$		92TH9577
$C_{12}H_{13}O_2$		94TL5197
$C_{12}H_{14}BrO_2$		93JOC4897
$C_{12}H_{15}$		96JOC8229
$C_{12}H_{16}NO_3$		94SL349
$C_{12}H_{17}O_4$		78S150
$C_{12}H_{19}O_4$		93JACS12625

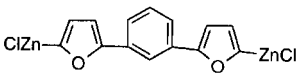
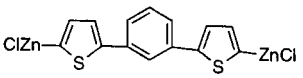
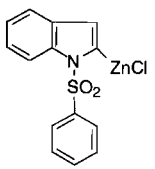
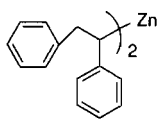
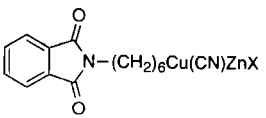
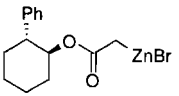
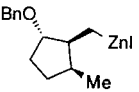
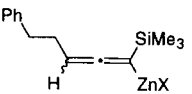
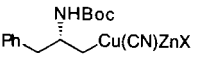
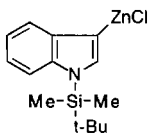
$C_{12}H_{21}OSi$		95JOC863
$C_{12}H_{21}O_2$		93TL7911
$C_{12}H_{23}OSi$		92TH9577
$C_{12}H_{23}OSi$		93JACS12625
$C_{12}H_{27}OSi$		94JOC4143
$C_{12}H_{29}BP$		96TL2209

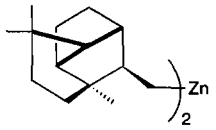
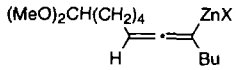
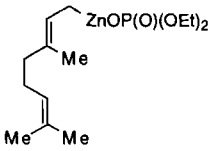
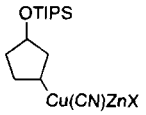
C13

$C_{13}H_{14}NO_4$		94SL379
$C_{13}H_{15}O_2$		93TL7911
$C_{13}H_{17}ClNO$		94SL347
$C_{13}H_{17}O$		93TL7911
$C_{13}H_{17}O$		92TH9877
$C_{13}H_{18}NO$		94SL347
$C_{13}H_{19}O_4$		90HCA1068
$C_{13}H_{23}ClNSi$		91JOC1445
$C_{13}H_{25}O_2$		94TL8349

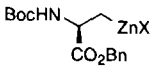
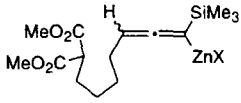
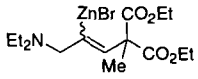
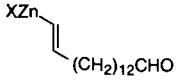
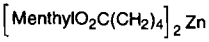
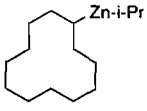
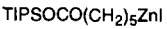
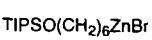
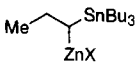
$C_{13}H_{27}OSi$		93JACS12625

C14

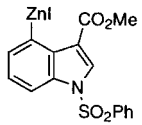
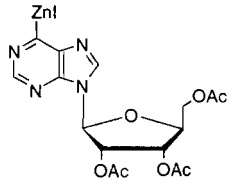
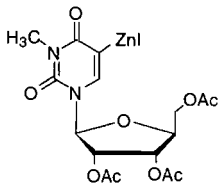
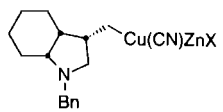
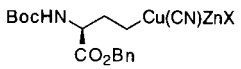
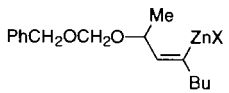
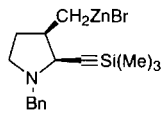
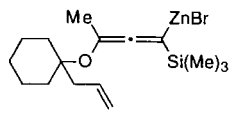
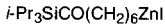
$C_{14}H_8O_2$		92TH9577
$C_{14}H_8S_2$		92TH9577
$C_{14}H_{10}NO_2S$		97JOC3160
$C_{14}H_{13}$		96TL7201, 97TL715
$C_{14}H_{16}NO_2$		94SL410
$C_{14}H_{17}O_2$		91TL3417
$C_{14}H_{19}O$		93TL7911
$C_{14}H_{19}Si$		95TL723
$C_{14}H_{20}NO_2$		94TH2415
$C_{14}H_{20}NO_2$		94SL347
$C_{14}H_{20}NSi$		97JOC3160

$C_{14}H_{23}$		96TL7201, 97TL715
$C_{14}H_{25}O_2$		93JOC6166
$C_{14}H_{27}O_4P$		92JOC5425
$C_{14}H_{29}OSi$		94S410

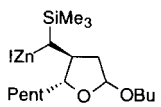
C15

$C_{15}H_{20}NO_4$		93SL499, 94SL293, 94TL4417, 95SL819
$C_{15}H_{25}O_4Si$		95TL723
$C_{15}H_{26}NO_4$		75TL3147
$C_{15}H_{27}O$		93JACS1593
$C_{15}H_{27}O_2$		94TL5849
$C_{15}H_{30}$		97AC245
$C_{15}H_{31}O_2Si$		97SL477
$C_{15}H_{33}OSi$		95SL1113
$C_{15}H_{33}Sn$		92SL891

C16

$C_{16}H_{12}NSO_4$		93TL5955
$C_{16}H_{16}N_4O_7$		96TL8375
$C_{16}H_{18}N_2O_9$		96TL8375
$C_{16}H_{22}N$		94TL8349
$C_{16}H_{22}NO_2$		92SL219, 93SL499
$C_{16}H_{23}O_2$		93JOC4897
$C_{16}H_{24}NSi$		97TL89
$C_{16}H_{27}OSi$		95TL1263
$C_{16}H_{33}OSi$		95JACS6126

C17

$C_{17}H_{35}O_2Si$		95TL231

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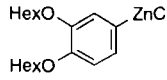
$C_{18}H_{29}O_2$		94CC845

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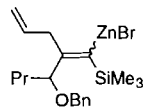
$C_{19}H_{29}OSi$		83JOC5409

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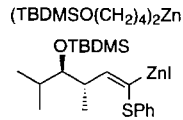
$C_{20}H_{27}OSi$		94TL4539
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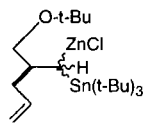
$C_{21}H_{44}OSn$		95SL723

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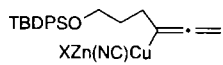
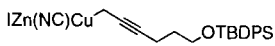
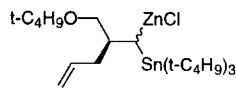
$C_{22}H_{27}OSi$		93JOC528
$C_{22}H_{27}OSi$		93JOC528
$C_{22}H_{45}OSn$		95SL723

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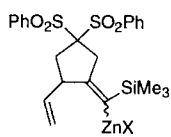
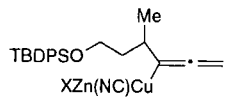
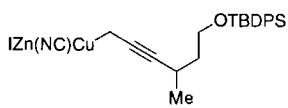
$C_{23}H_{27}O_4S_2Si$		94TL7939
$C_{23}H_{29}OSi$		93JOC528
$C_{23}H_{29}OSi$		93JOC528

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List of suppliers

Acros Chimica
See Janssen Chimica

Aldrich Chemical Co. Ltd.
France: 80 Rue de Lozais, BP 701, 38070, St. Quentin, Fallavier Cedex, Lyon. Tel. 74822800
Germany: Sigma–Aldrich Chemie GmbH, Geschäftsbereich Aldrich, Riedstraße 2, D-89555 Steinheim. Tel. 0130-7272
Japan: Aldrich Chemical Co. Inc. (Japan), Kyodo-building Shinkanada, 10 Kandamikura-chou, Chiyoda-ku, Tokyo 101. Tel. 03-54344712
UK: The Old Brickyard, New Road, Gillingham, Dorset SP8 4JL. Tel. 0800-717181
USA: PO Box 355, Milwaukee, WI 53201. Tel. 0414-2733850

Alfa
France: Johnson Matthey SA, BP 50240, Rue de la Perdix, Z1 Paris Nord LL, 95956 Roissy, Charles De Gaulle Cedex. Tel. 1-48632299
Germany: Johnson–Matthey GmbH, Zeppelinstraße 7, D-76185 Karlsruhe. Tel. 0721-840070
UK: Catalogue Sales, Materials Technology Division, Orchard Road, Royston, Hertfordshire SG8 5HE. Tel. 01763-253715
USA: Alfa/Johnson Matthey, PO Box 8247, Ward Hill, MA 01835-0747. Tel. 0508-5216300

Avocado
Germany: ABCR GmbH & Co., PO Box 21 01 35, D-76151 Karlsruhe. Tel. 0721-950610
UK: Avocado Research Chemicals Ltd., Shore Road, Port of Heyshan, Industrial Park, Heyshan LA3 2XY. Tel. 01524-850506

BDH
UK: Head Office and International Sales, Merck Ltd., Merck House, Poole, Dorset BH15 1TD. Tel. 0202-665599

Boulder Scientific Co.
USA: 598 3rd Street, PO Box 548, Mead, CO 80542. Tel. 03035354494

Fluka Chemika-BioChemika
France: Fluka S.a.r.l., F-38297 St Quentin, Fallvier Cedex, Lyon. Tel. 74822800
Germany: Sigma Aldrich Chemie GmbH, Geschäftsbereich Fluka, Grünwalder Weg 30, D-82041 Deisenhofen. Tel. 0130-2341
Japan: Fluka Fine Chemical, Ciyoda-Ku, Tokyo. Tel. 03-32554787
UK: Fluka Chemicals Ltd., Gillingham, Dorset SP8 4JL. Tel. 01747-823097
USA: Fluka Chemical Corp., Ronkonkoma, NY 11779-7238. Tel. 0516-4670980

FMC Corporation, Lithium Division
Japan: Asia Lithium Corporation (ALCO), Shin-Osaka Daiichi-Seimei Building 11F, 5–24, Miyahara 3-Chome, Yodogawa-Ku, Osaka. Tel. 06-3992331
UK and Mainland Europe: Commercial Road, Bromborough, Merseyside L62 3NL. Tel. 0151–3348085
USA: 449 North Cox Road, Gastonia, NC 28054. Tel. 0704-8685300

Heraeus
Germany: Alter Weinberg, D-76228 Karlsruhe 41-Ho. Tel. 0721-4716769

ICN Biomedicals/K and K Rare and Fine Chemicals
France: ICN Biomedicals France, Parc Club Orsay, 4 rue Jean Rostand, 91893 Orsay Cedex. Tel. 01-60193460
Germany: ICN Biomedicals, GmbH, Thüringer Straße 15, D-37269 Eschwege. Tel. 0180-230-6160
Japan: ICN Pharmaceuticals, c/o Kyowa Bldg. 1–3, 2 Chrome, Kyobashi Chuo-ku, Tokyo 104. Tel. 081-332758020
UK: ICN Biomedicals Ltd., Unit 18, Thame Park Business, Centre Wenman Road, Thame OX9 3XA. Tel. 0800-282474
USA: ICN Pharmaceuticals, Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626. Tel. 0800-8540530

Janssen Chimica (Acros Chimica)
Mainland Europe, Central Offices Belgium: Janssen Pharmaceuticalaan 3, 2440 Geel. Tel. 014-604200
UK: Hyde Park House, Cartwright Street, Newton, Hyde, Cheshire SK14 4EH. Tel. 01613-244161
USA: Spectrum Chemical Mgf. Corp., 14422 South San Pedro Street, Gardena, CA 90248. Tel. 0800-7728786

Johnson Matthey Chemical Products
France: Johnson Matthey SA, BP 50240, Rue de la Perdix, Z1 Paris Nord LL, 95956 Roissy, Charles De Gaulle Cedex. Tel. 48632299

Germany: Johnson–Matthey GmbH, Zeppelinstraße 7, D-67185 Karlsruhe. Tel. 0721-840070
UK: Catalogue Sales, Materials Technology Division, Orchard Road, Royston, Hertfordshire SG8 5HE. Tel. 01763-253715
USA: Alfa/Johnson Matthey, PO Box 8247, Ward Hill MA 01835-0747. Tel. 0508-5216300

Kanto Chemical Co. Inc.
Japan: 2–8, Nihonbashi-honcho-3-chome, Chuo-ku, Tokyo 103. Tel. 03-2791751

Kerry Ultrasonics Ltd.
Hunting Gate Wilbury Way, Hitchin SG4 0TQ. Tel. 01462-450761

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France: Lancester Synthesis Ltd., 15 Rue de l'Atome, Zone Industrielle, 67800 Bischheim, Strasbourg. Tel. 05035147
Germany: Lancaster Synthesis GmbH, Postfach 15 18, D-63155 Mülheim am Main. Tel. 0130-6562
Japan: Hydrus Chemical Inc., Kurihara Building, 2–12, Uchikanda 3-chome Chiyoda-ku, Tokyo 101. Tel. 03-32585031
UK: Lancaster Synthesis, Eastgate, White Lund, Morecambe, Lancashire LA3 3DY. Tel. 0800-262336
USA: Lancaster Synthesis Inc., PO Box 1000, Windham, NH 03087-99777. Tel. 0800-2382324

Merck
Germany: Merck KGaA, Frankfurter Str. 250, D-64271 Darmstadt. Tel. 06151720
Japan: Merck Japan Ltd., ARCO Tower, SF, 8–1, Shimomeguro-1-chome, Merguro-ku, Tokyo 153. Tel. 03-54355712
UK: Merck Ltd., Merck House, Poole, Dorset BH15 1TD. Tel. 01202-669700
USA: EM Science, 480 Gibbsotwn NJ 08027. Tel. 609-4236300

Mitsuwa Scientific Corp.
Japan: 11–1, Tenma-1-Chome, Kita-ku, Osaka 530. Tel. 06-3519631

Nacalai Tesque, Inc.
Japan: Karasuma-nishi-iru, Nijo-dori, Nakagyo-Ku, Kyoto 604. Tel. 075-2315301

Organometallics, Inc.
USA: PO Box 287, East Hampstead, NH. Tel. 0603-3296021

Parish Chemical Company
USA: 145 North Geneva Road, Orem, UT 84057. Tel. 0801-2262018

Prolabo
UK etc.: see Rhône–Poulenc
France: 12, Rue Pelee, BP 369, 75526, Paris Cedex 11. Tel. 1-49231500

Rhône–Poulenc
France: Rhône–Poulenc SA, 25 Quai Paul Donmer, F-92408 Courbezoie Cedex. Tel. 1-47681234
Germany: Rhône–Poulenc GmbH, Staedelstraße 10, Postfach 70 08 62, Frankfurt am Main. Tel. 069-60930
Japan: Rhône–Poulenc Japan Ltd., 15 Kowa Building Annexe, Central PO Box 1649, Tokyo 107. Tel. 03-3584691
UK: Rhône–Poulenc Chemicals Ltd., Laboratory Products, Liverpool Road, Barton Moss, Eccles, Manchester M30 7RT. Tel. 0161-7895878
USA: Rhône–Poulenc Basic Chemicals Co., 1 Corporate Drive, Shelton, CT 06484. Tel. 0203-9253300; or Rhône-Poulenc Inc., Fine Organics, CN 7500 Cranbury, NJ 08512-7500. Tel. 0609-860400

Riedel de Haen
Germany: Wun storfer Straße 40, Postfach, D-30926 Seelze. Tel. 05137-9990

Strem
France: Strem Chemicals, Inc., 15 Rue de l'Atome, Zone Industrielle, 67800 Bischheim. Tel. 88625260
Germany: Strem Chemicals GmbH, Postfach 1215, D-77672 Kehl. Tel. 07851-75879
Japan: Hydrus Chemical Co., Tomikata Building, 8–1, Uchkanada, 2-Chome, Chiyoda-ku, Tokyo 101. Tel. 03-2585031
UK: Strem Chemicals UK, 48 High Street, Orwell Royston, SG8 5QN. Tel. 01223-207430
USA: Strem Chemicals, Inc., Dexter Industrial Park, 7 Mulliken Way, Newburyport, MA 01950-4098. Tel. 0508-4623191

Tokyo Kasei Kogyo Co. Ltd.
Japan: 3–1–13, Nihonbashi-Honcho, Chuo-ku, Tokyo 103. Tel. 03-38082821
UK: Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire SK13 9RY. Tel. 01457-868921
USA: PCI America, 9211 North Harbourgate Street, Portland, OR 97203. Tel. 503-2831681

Ventron
See Alfa

Wako
Japan: 3–10 Dosho-Machi, Higashi-Ku, Osaka 541. Tel. 06-2033741

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