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TRANSITION METAL CATALYZED REACTIONS OF ORGANOZINC REAGENTS

ENDER ERDIK
Ankara University, Science Faculty, Department of Chemistry, Ankara 06100, Turkey

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CONTENTS

1. INTRODUCTION

Organozinc reagents are now extensively used in synthesis.[1,2] The use of activation methods for preparation of organozinc reagents has considerably increased their versatility.[3,4] Cross-coupling reactions of organozinc reagents with a variety of organic electrophiles using transition metal catalysts provide novel methods for C–C bond formation chemo-, regio- and stereoselectively. In many cases organometallics containing Zn exhibit high reactivity. Transition metal catalyzed reactions of Reformatsky reagents [2-(bromozincio)acetates] and so-called remote Reformatsky reagents, [alkyl 3-, 4-, 5- or higher(halozincio)alkanoates and halozincio derivatives of other carbonyl compounds] with various electrophiles, have also been investigated.

There are excellent reviews describing transition metal catalyzed cross-coupling reactions of organometallics. Pd- and Ni-catalyzed coupling of organometallics containing Li, Mg, Zn, Cd, Hg, B, Al, Zr, and Sn with organic halides and related electrophiles have been described by Negishi.[5–7] The mechanisms of these catalyzed reactions have been discussed in detail.[8] Pd- and Ni-catalyzed cross-coupling of Grignard reagents were surveyed by Felkin[9] and Kumada.[10] Pd-Catalyzed cross-coupling of organotin reagents was surveyed by Stille.[11] Hegedus published a series of reviews surveying the use of transition metals in organic synthesis including their catalytic role in organometallic reactions.[12–14] Furstner has briefly mentioned the transition metal catalyzed reactions of Reformatsky and remote Reformatsky reagents in his comprehensive review on the Reformatsky reaction.[15]

The transition metal catalyzed reactions of organozinc reagents have not yet been the subject of review. It is clear that transition metal catalyzed organozinc reagents have advantages over the conventional ones because they are synthetically useful, particularly for control of the chemo-, regio- and stereo-selectivity. In continuation of our interest in transition metal catalyzed reactions of organolithium, Grignard[16] and organozinc reagents, we now survey transition metal catalyzed reactions of organozinc reagents with the particular emphasis being placed on their scope and limitations without mechanistic discussion (literature coverage through 1991).

In this Report, no details are given about the conditions of the transition metal catalyzed reactions of organozinc reagents, except for their preparation. The catalyzed reaction sequence comprises addition of catalyst or its solution to the organozinc reagent in an appropriate solvent followed by addition of the substrate in given molar ratios. (The organozinc reagent and the substrate may also be added to the catalyst.) Organozinc reagents can be prepared either by direct reaction of organic halide with zinc or activated zinc[3,4] or by transmetallation of the corresponding organolithium or Grignard reagents with a zinc halide. In most cases, the reactions of organozinc reagents did not take place in the absence of transition metal catalysts or gave quite low yields.

A wide variety of Ni^0, Pd^0, Ni^{II}, Pd^{II} and Cu^I catalysts (**1–9**) have been used for promoting the reactions of organozinc reagents. The most generally used ligands (L) are phosphines. Triphenylphosphine is inexpensive and is a most satisfactory ligand for the desired catalysis. Ni^0 and Pd^0 catalysts are considerably less stable than Ni^{II} and Pd^{II} catalysts. However, in some cases Ni^0 and Pd^0 catalysts are prepared *in situ* by reducing Ni^{II} and Pd^{II} catalysts.

$Pd(PPh_3)_4$ and a '$Pd(PPh_3)_2$' complex,[17] generated *in situ* by treating $Pd(PPh_3)_2Cl_2$ with two equivalents of diisobutylaluminium hydride or *n*-butyllithium, work satisfactorily: the latter has exhibited a greater reactivity in some instances. Pd Complexes appear to be more compatible with various functional groups than the corresponding Ni complexes. A list of chiral and achiral phosphines which have been used are given (Table 1).

The intention has not been to provide an exhaustive tabulation of all transition metal catalyzed

NiL_4	PdL_4	NiL_2X_2	PdL_2X_2	NiX_2 or $NiX_2.L$	PdX_2 or $PdX_2.L$
1	**2**	**3**	**4**	**5**	**6**
(L: See TABLE 1)		(X:Cl, Br)		(X: acac[a], dba[b], $OCOCH_3$)	

CuX or CuX.L	CuX_2 (X: acac)	AgX_2 (X:$OCOCH_3$)
7	**8**	**9**
(X: CN, Br, I, L : $(CH_3)_2S$)		

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[a] acac: acetylacetonate

[b] dba: dibenzylideneacetone

Fig. 1.

TABLE 1

Achiral and chiral phosphine ligands used in Ni and Pd complexes (1-6) and their abbreviations

L : PPh_3
(a)

L : $P(2\text{-}CH_3C_6H_4)_3$
(b)

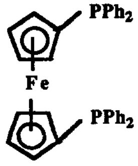
L : $PPh_nR_{3\text{-}n}$ (R: CH_3, C_2H_5, n-C_4H_9, c-C_6H_{11}, n: 0-2)
(c)

L_2 : $Ph_2P(CH_2)_2PPh_2$ (dppe)
(d)

L_2 : $Ph_2P(CH_2)_3PPh_2$ (dppp)
(e)

L_2 : $Ph_2P(CH_2)_4PPh_2$ (dppb)
(f)

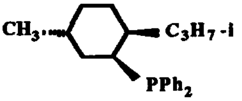
L_2:



(dppf)

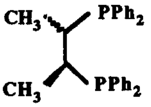
(g)

L :



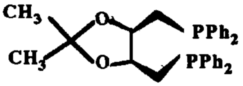
nmdpp
(h)

L_2:



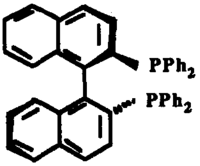
(S, S) – chiraphos
(i)

L_2:



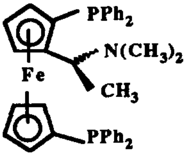
(R, R) – diop
(j)

L_2:



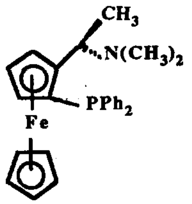
(S) – binap
(k)

L_2:



(S, R) –bffa
(l)

L_2:



(S, R) – ppfa
(m)

reactions of various organozinc reagents, but to illustrate the reported methods. A list of electrophiles that have been reacted with organozinc reagents, is given at the end of each section.

2. TRANSITION METAL CATALYZED COUPLING OF ORGANOZINC REAGENTS

Group 10 transition metals, Pd and Ni, are particularly effective in catalyzing the cross-coupling of organozincs with organic halides and related electrophiles (eqn 1). Organozinc compounds can tolerate

$$RZnX + R^1Y \xrightarrow{\text{"Pd" or "Ni"}} RR^1 + ZnXY$$

X : Cl, Br, I

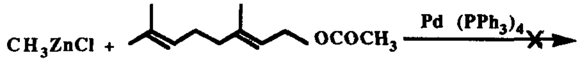
Y : Cl, Br, I, $OCOCH_3$, OSO_2CF_3, etc (1) a wide range of functional groups in either or both of the coupling partners. Organic halides, especially iodides and bromides, are the most reactive class of electrophiles. However, the use of other leaving groups such as acetates and triflates has also been investigated. In transition metal catalyzed cross-coupling reactions, the reactivity of organometals with respect to metals including Zn has been discussed in detail.[5,6,8] In this Report, cross-coupling of organozinc reagents has not been examined by comparing with the reactions of other organometallics. However, recent papers investigating the scope of the transition metal catalyzed reactions of organometallics with respect to the metal are included. Despite its short history, the Pd- and Ni-catalyzed cross-coupling of organozinc reagents rivals the Cu-catalyzed cross-coupling of organolithiums and Grignard reagents[16] in scope and synthetic utility. The two methods are often complementary.

The most satisfactory cross-coupling of organozinc derivatives under Pd- or Ni-catalysis, involves the coupling of two unsaturated partners. Coupling of organozincs containing simple alkyl groups has been shown to be feasible, but this reaction is subject to isomerization of the alkyl group. They show a strong tendency to undergo dehydrometallation involving the β-hydrogens. Simple alkyl halides as electrophiles are generally unreactive in coupling with organozincs in contrast to the highly reactive unsaturated and allylic, benzylic and propargylic halides.*

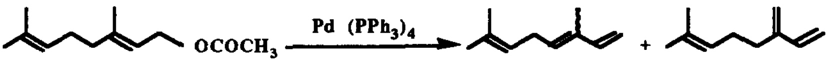
2.1. *Coupling of alkyl, homoallylic, homobenzylic and homopropargylic zinc reagents*

2.1.1. *Alkyl substrates.* No work has been published to date.

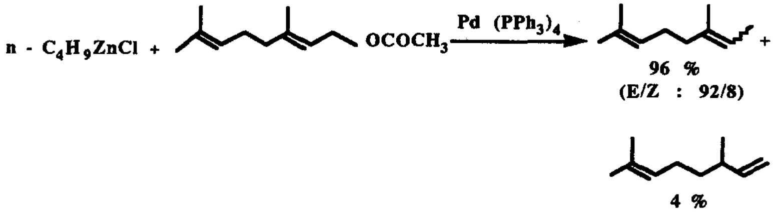
2.1.2. *Allylic, benzylic and propargylic substrates.* The reaction of methylzinc chloride with geranyl acetate in the presence of $Pd(PPh_3)_4$ (eqn 2) was found[18] not to produce at 25°C any product containing the geranyl moiety. There is essentially complete recovery of starting material. Since the reaction of geranyl acetate with $Pd(PPh_3)_4$ in the absence of any organometallic reagent induces a slow 1,4-elimination (eqn 3), methylzinc chloride must be acting as an inhibitor. The use of alkylmetals containing β-hydrogens such as *n*-butylzinc chloride, leads to the reductive C–O cleavage of geranyl acetate (eqn 4).



(2)



(3)



(4)

Alkylzinc reagents have been found by Nakamura and Sekiya[19] to undergo highly regioselective and chemoselective high yielding allylation reactions under very mild conditions. Allylation of alkylzinc reagents under Cu-catalysis takes place in an S_N2' substitution manner involving γ-attack

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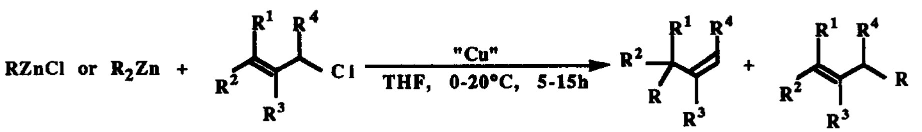
* The term, A–B coupling, in this Report refers to the coupling of an organozinc reagent containing the A group with an organic halide containing the B group.

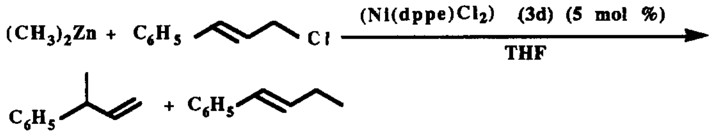


62-85 % (combined yield)
(S_N2'/S_N2 : 100/0-91/9)

Cu catalyst : $CuBr.(CH_3)_2S$ (5 mol %)
R: CH_3, C_2H_5, n - C_4H_9
R^1, R^2, R^3, R^4 : H, C_6H_5, H, H; CH_3, $(CH_3)_2C = CH\ CH_2CH_2$, H, H;
H, H, CH_3, (E) - $CH_3COOCH_2CH = (CH_3)CH_2CH_2$ (geranyl)

Scheme 1.

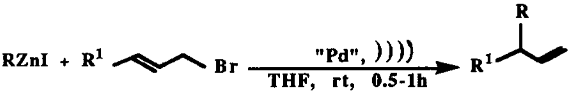
(Scheme 1). However the Ni-catalyzed allylation of methylzinc chloride with cinnamyl chloride took an entirely different course to giving the S_N2 substitution product involving α-attack (eqn 5).



65 % (combined yield)
(S_N2'/S_N2 : 8/92)

(5)

The reaction of perfluoroalkylzinc iodides with allyl halides using a Pd-catalyst proceeded smoothly giving γ-substitution products (Scheme 2).[20] Organozinc reagents were prepared *in situ* from perfluoroalkyl iodides and ultrasonically dispersed zinc. Without the aid of ultrasonic irradiation, the reaction did not occur.

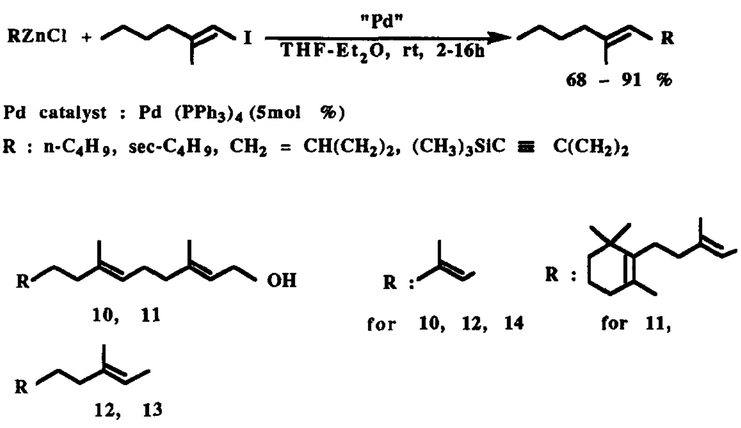


63-78 %

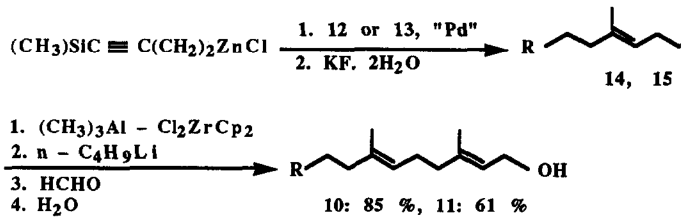
Pd catalyst: $Pd(OCOCH_3)_2$ (5 mol %)
R : CF_3, i-C_3F_7, n- C_4F_9
R^1 : CH_3, C_6H_5

Scheme 2.

2.1.3. *Alkenyl, aryl and alkynyl substrates.* The Pd-catalyzed cross-coupling of homoallylic or homopropargylic organozincs with (*E*)-1-iodo-2-methyl-1-hexene has provided a new selective route to 1,5-dienes and 1,5-enynes (Scheme 3).[21] Organozincs were prepared by treating the Grignard reagents with $ZnCl_2$. The cross-coupling procedure provides an expeditious route to 1,5-dienes of the terpenoid type. To demonstrate its synthetic utility, the synthesis of (*E*,*E*)-farnesol **10** and a tetraenol **11** has been chosen (Scheme 4). The trimethylsilyl derivative of homopropargylic zinc chloride was mixed with the alkenyl halide **12** or **13** and $Pd(PPh_3)_4$ (5 mol%) giving the desired cross-coupled product. Treatment with $KF \cdot 2\ H_2O$ dissolved in DMF gave the 1,5-enyne **14**, **15**. Without further purification the 1,5-enyne was subjected to carbometallation with $Me_3Al–Cl_2ZrCp_2$ in CH_2Cl_2 at room temperature followed by ate complexation with *n*-BuLi and treatment with paraformaldehyde yielding **10** or **11** as stereochemically and regiochemically pure isomers.

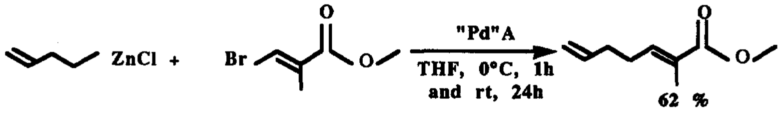


Scheme 3.

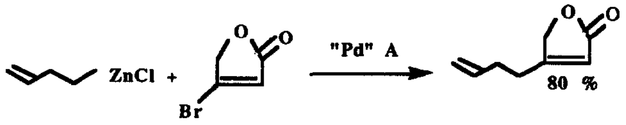


Scheme 4.

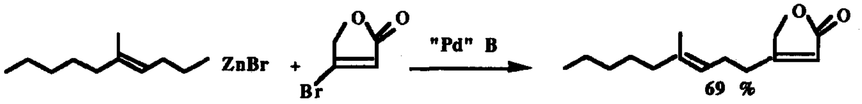
Negishi adapted[22] the Pd-catalyzed reaction of alkylzincs with alkenyl halides to effect the conjugate substitution reaction of stereodefined homoallylzincs with β-halo-α,β-unsaturated carbonyl compounds (eqns 6–8).



(6)



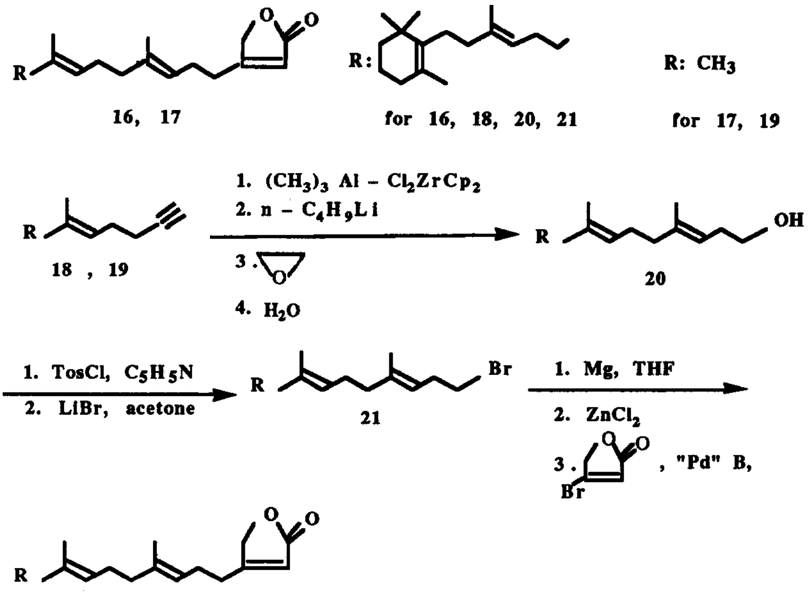
(7)



(8)

Pd catalysts : A : $Pd(PPh_3)_4$, B : $Pd(PPh_3)_2Cl_2$ + $(i-C_4H_9)_2AlH(1:2)$ (5 mol %)

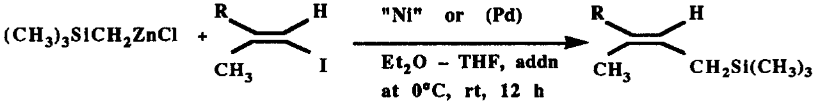
This reaction provides a highly stereoselective and efficient route to butenolides and furans of terpenoid origin such as mokupalide **16** and the butenolide **17** (Scheme 5). For the synthesis of **16**, the 1,5-enyne **18** was converted into the tetraenol **20**, which was tosylated and treated with LiBr yielding the bromotetraene **21**. The homoallylic Grignard reagent prepared from **21** was transmetallated to the zinc derivative and reacted with 4-bromo-2(5*H*)-furanone giving **16** with stereoisomeric and regioisomeric purities >95% : **17** was synthesized using **19** with a 98% stereoselectivity.



Scheme 5.

The use of stereodefined homoallylzincs requires careful control of reaction conditions. Homoallyl bromides can be stereospecifically (>98%) converted into the corresponding zinc derivatives by treating them first with magnesium and then with zinc chloride or bromide. The formation of homocoupled dimers of the homoallylic halides in this procedure can be suppressed by treating the homoallylic halides with a mixture of magnesium and zinc chloride or bromide in THF: the maximum stereospecificity observed under these conditions is 94%.

The Ni- or Pd-catalyzed reaction of alkenyl iodides with trimethylsilylmethylzinc chloride provides allyltrimethylsilanes in good yields in a highly stereo- and regio-selective manner (eqn 9).[23]

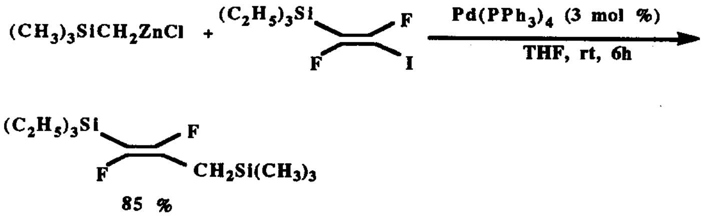


(9)

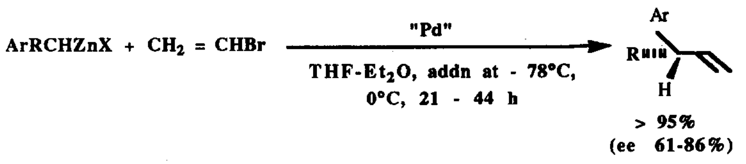
Ni or Pd catalyst : Ni $(PPh_3)_4$, Pd $(PPh_3)_4$ (5 mol %)

R	yield, %
n-C_4H_9	74 (with "Pd")
n-C_6H_{13}	47 (with "Ni"), 83 (with "Pd")

Trimethylsilylmethylzinc chloride was prepared by transmetallation of trimethylsilylmethyllithium in Et_2O with zinc bromide in THF. It was then reacted with 1,2-difluoro-1-triethylsilyl-1-iodoethene to afford the coupled product (eqn 10).[24]

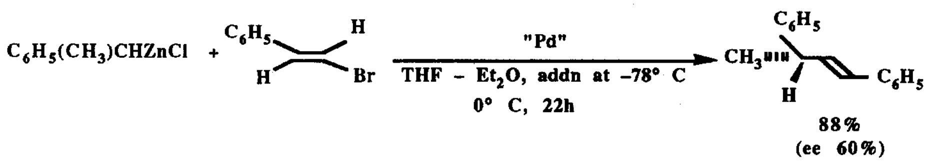


(10)

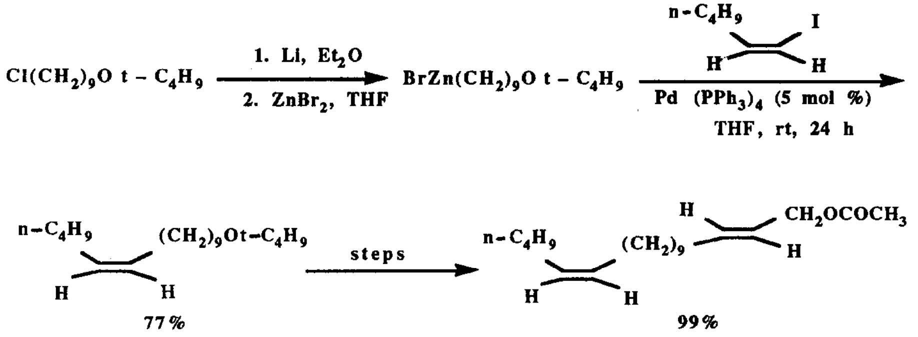


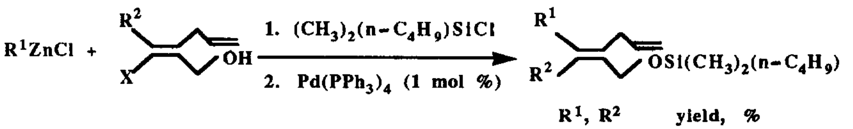
Pd catalyst : Pd[(R,S)-ppfa]Cl_2 (4m) (0.5 mol %)
Ar,R,X : C_6H_5, CH_3, Cl ; C_6H_5, CH_3, I; 4-CH_3 C_6H_4, CH_3,I; C_6H_5, C_2H_5,I

Scheme 6.

 (11)

Kumada and coworkers reported that secondary alkylzinc reagents react with vinyl bromide and (*E*)-β-bromostyrene in the presence of a Pd-catalyst to give the cross-coupled products of up to 86% *ee* (Scheme 6 and eqn 11).[25] Alkylzinc reagents were prepared *in situ* from Grignard reagents in Et_2O and zinc halide in THF in the presence of the catalyst and vinyl bromide. Preparation from alkyl halide and zinc gave lower yields.

 (12)

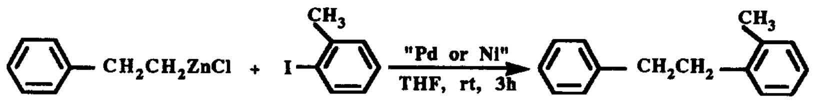
 (13)

R^1, R^2	yield, %
n-C_4H_9, CH_3	86
CH_3, n-C_4H_9	97

Pd-Catalyzed alkyl–alkenyl coupling provided the starting compound in the preparation of the *Z*-moiety of (*E*,*Z*)-2,13-octadienyl acetate, a sex pheromone (eqn 12).[26]

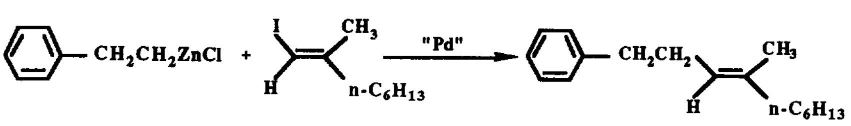
Pd-Catalyzed reaction of alkylzinc reagents with substituted 1-halo-1,4-dienes produced the coupled products in high yields (eqn 13).[27]

Negishi and coworkers extended the methodology of Pd-catalyzed cross-coupling of homoallylic and homopropargylic zincs with alkenyl halides to the homobenzyl–aryl, homobenzyl–alkenyl, homoallyl–aryl and homopropargyl–aryl cases. The first entry in each case represents the corresponding organozinc reagent (eqns 14–17).[28]



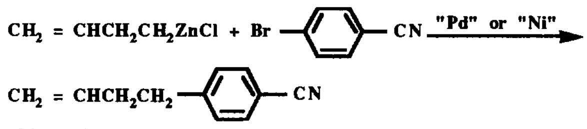
(14)

73% (with "Pd"), 70% (with "Ni")



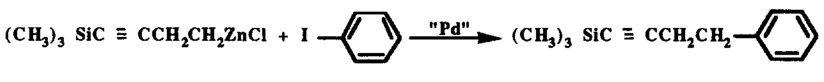
(15)

92 %



(16)

78% (with "Pd"), 82% (with "Ni")



(17)

Pd or Ni catalysts : $Pd(PPh_3)_4$ or $Ni(PPh_3)_4$ (5 mol %)

The use of Pd- or Ni-catalysts gave comparable results. Minor formation (<5–10%) of the dimers of aryl or alkenyl halides was observed. The reaction of 2-phenylethylzinc chloride with 1-octynyl bromide or iodide in the presence of 5 mol% of $Pd(PPh_3)_4$ produced the desired coupling product in 30–40% yields. The product was contaminated with significant amounts of 2-phenylethyl halide and 1-octyne, which were presumably formed by metal–halogen exchange.

Several Pd- and Ni-complexes containing bidentate phosphine ligands were examined by Kumada and coworkers for their catalytic activity in the reactions of *n*- and *s*-butylzinc chloride with bromobenzene (Scheme 7).[29,30] *n*-Butyl and *s*-butylzinc chloride were prepared *in situ* by mixing

$$\mathrm{RZnCl} + \mathrm{C_6H_5Br} \xrightarrow[\text{THF, addition at -78°C, rt, 20h}]{\text{"Pd" or "Ni"}} \mathrm{R\,C_6H_5} \quad \text{1-100 \%}$$

R : $n\text{-}C_4H_9$, sec- C_4H_9

Pd or Ni catalyst : PdL_2Cl_2 or NiL_2Cl_2 (1mol %)

catalyst	yield, % $n\text{-}C_4H_9C_6H_5$	yield, % sec-$C_4H_9C_6H_5$
Pd (dppf)Cl_2 (4g)	100	100
Pd (dppp)Cl_2 (4e)	66	13
Pd (dppb)Cl_2 (4f)	90	—
Ni (dppp)Cl_2 (3e)	3	45
Pd $(PPh_3)_2Cl_2$ (4a)	34	3
Ni $(PPh_3)_2Cl_2$ (3a)	42	1

Scheme 7.

zinc chloride and catalyst in THF with *n*-butyllithium in hexane and *s*-butylmagnesium chloride in Et_2O. $Pd(dppf)Cl_2$ **4g** was the most active and selective catalyst, giving *n*-butyl and *s*-butylbenzene. In addition, the coupling reaction with $Pd(dppf)Cl_2$ is much faster than that with other Pd- or Ni-catalysts, which induced as side reactions the isomerization of the butyl group and its reduction to some extent. The use of $Pd(PPh_3)_4$ resulted in very low yields of the coupling product, *s*-butylbenzene.

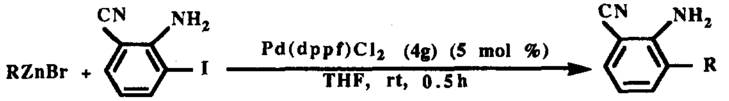
The reaction of *n*-butylzinc halides with *m*- and *p*-bromoacetophenones and with *p*-bromobenzaldehyde in the presence of a Pd-catalyst was reported by Okamoto and coworkers to take place chemoselectively giving the *m*- and *p*-(*n*-butyl)-substituted acetophenones and *p*-(*n*-butyl)-substituted benzaldehyde in good yields (Scheme 8).[31] Organozinc reagents were prepared from the corresponding Grignard reagents and zinc halide in THF. $Pd(PPh_3)_2Cl_2$ **4a** exhibited the highest catalytic activity among the Pd- or Ni-complexes which were examined including $Pd(dppf)Cl_2$ **4g**, $Pd(dppp)Cl_2$ **4e**, $Pd(dppb)Cl_2$ **4f**, $PdCl_2$, $Ni(PPh_3)_2Cl_2$ **3a** and $Ni(dppp)Cl_2$ **3e**. The yield of *p*-*n*-butylacetophenone was 90% by the use of $Pd(PPh_3)_2Cl_2$ as a catalyst and 45–50% by the use of other catalysts given above. The highest yield of cross-coupled product was obtained in a mixed solvent of THF–HMPA (1 : 2) boiled under reflux.

Pd catalyst : Pd $(PPh_3)_2Cl_2$ (2mol %)

X	yield, %
3 - CH_3CO	69
4 - CH_3CO	90
4 - CH_3CO	87

Scheme 8.

$Pd(dppf)Cl_2$ **4g** was also used in the cross-coupling of isobutyl and cyclopropylzinc reagents with 3-iodo-2-aminobenzonitrile (eqn 18).[32]

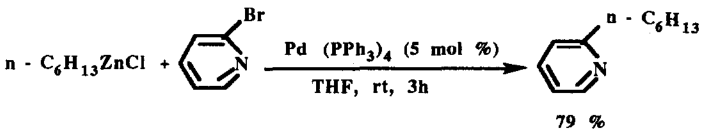


(18)

R	yield, %
i-C_4H_9	35
▽	98

Organozinc reagents were prepared by transmetallation of Grignard reagents with zinc bromide in THF.

Negishi and coworkers have reported that *n*-hexylzinc chloride, prepared by treating the Grignard reagent with zinc chloride, reacts with 2-bromopyridine in the presence of $Pd(PPh_3)_4$ (eqn 19).[33] While the reaction is complete, producing the cross-coupled product in a high yield, that of the Grignard reagent alone merely consumed the 2-bromopyridine without producing the desired product in any more than a trace amount (<2%).



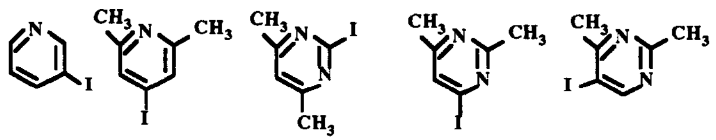
(19)

4-Chlorobutylzinc iodide, prepared from the corresponding alkyl iodide with Zn–Cu couple in benzene–DMA reacted with N-heteroaryl iodides in the presence of $Pd(PPh_3)_2Cl_2$ **4a** yielding 4-chlorobutyl substituted N-heteroarenes (Scheme 9).[34]

$$Cl(CH_2)_4ZnI + \text{Het-ArI} \xrightarrow[\text{Benzene-DMA, rt–80°C, 0.5–3h}]{\text{"Pd"}} \text{Het-Ar}(CH_2)_4Cl \quad 22\text{–}95\%$$

Pd catalyst: Pd $(PPh_3)_2$ Cl_2 (4mol %)

Het-ArI :



Scheme 9.

Perfluoroalkylzinc iodides prepared *in situ* from perfluoroalkyl iodides and ultrasonically dispersed zinc also coupled with vinyl and aryl halides as well as allyl halides under Pd-catalysis (Scheme 10).[20]

$$\text{R ZnI} + \text{Ar CH= CHBr} \xrightarrow[\text{TRF, rt, 0.5-1h}]{\text{"Pd"}} \text{Ar CH= CHR} \quad 62\text{-}72\ \%$$

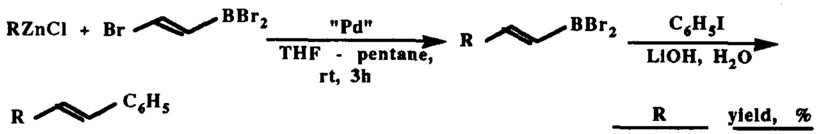
Pd catalyst: $Pd(PPh_3)_4$ (20mol %)
R: CF_3, $i\text{-}C_3F_7$, $n\text{-}C_4F_9$
Ar: C_6H_5, $4\text{-}CH_3C_6H_4$

$$\text{R ZnI} + \text{Ar I} \xrightarrow[\text{THF, rf, 0.5 h}]{\text{"Pd"}} \text{ArR} \quad 59\text{-}82\%$$

Pd catalyst: $Pd(PPh_3)_2$ Cl_2 (10 mol %)
R: CF_3, $n\text{-}C_3F_7$, $i\text{-}C_3F_7$
Ar: C_6H_5, $2\text{-}CH_3C_6H_4$, $3\text{-}CH_3C_6H_4$

Scheme 10.

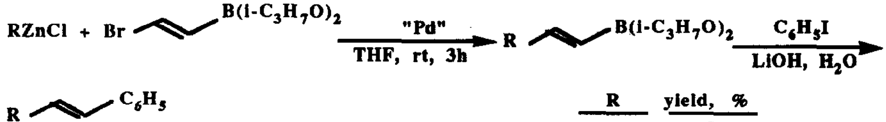
Suzuki and coworkers have reported that (*E*)-(2-bromoethenyl)dibromoborane and (*E*)-(2-bromoethenyl)diisopropoxyborane are useful precursors for the synthesis of (*E*)-1,2-disubstituted ethenes by the stepwise cross-coupling reaction with organozinc chlorides catalyzed by a Pd-catalyst and then reaction with organic halides in the presence of a base (eqns 20[35] and 21[36]).



Pd catalyst : $Pd(PPh_3)_2Cl_2$ (for R : $n\text{-}C_4H_9$), $Pd(dppf)Cl_2$ (for R : $sec\text{-}C_4H_9$) (5mol %)

R	yield, %
$n\text{-}C_4H_9$	88
$sec\text{-}C_4H_9$	75
 $(CH_2)_3$	61

(20)



Pd catalyst: $Pd(PPh_3)_2Cl_2$ (5 mol %)

R	yield, %
$n\text{-}C_4H_9$	79
$sec\text{-}C_4H_9$	77

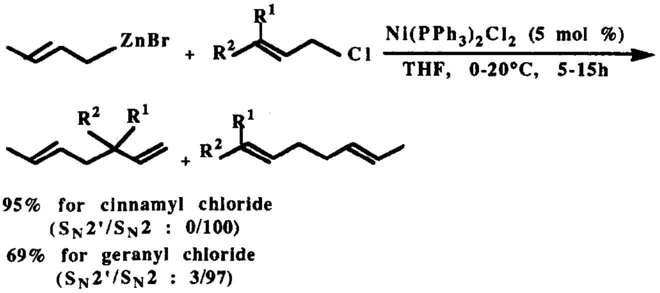
(21)

Butylzinc chlorides were prepared by the transmetallation of butyllithium with zinc chloride in THF which was then added to a mixture of 2-bromoethenylborane and Pd-catalyst. The cross-coupled product was not isolated and the second substitution was achieved stereospecifically (>96%) by the addition of a base and iodobenzene.

2.2. *Coupling of allylic, benzylic and propargylic zinc reagents*

2.2.1. *Alkyl substrates.* No work has been published to date.

2.2.2. *Allylic, benzylic and propargylic substrates.* (*E*)-Crotylzinc bromide was found to react with (*E*)-cinnamyl chloride and with geranyl chloride through exclusive S_N2 substitution stereospecifically under Ni-catalysis (eqn 22).[19]

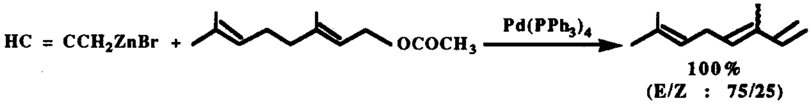


(22)

R^1,R^2 : H, C_6H_5 ; CH_3, $(CH_3)_2C=CHCH_2CH_2$

Although formation of a C–C bond between the two methylene groups was achieved by coupling homoallylic, homobenzylic and homopropargylic zincs with aryl or alkenyl halides under Pd- or Ni-catalysis, the coupling of benzylzinc bromide with α-bromo-*p*-xylene, allyl bromide or propargyl bromide failed and led to mixtures of cross- and homo-coupled products.[28]

The reaction of propargylzinc bromide with geranyl acetate in the presence of a Pd-catalyst gives 1,4-elimination regioselectively producing a mixture of (*E*)- and (*Z*)-ocimene (eqn 23). Neryl acetate gives pure myrcene by exclusive *anti* 1,4-elimination (eqn 24).[18]



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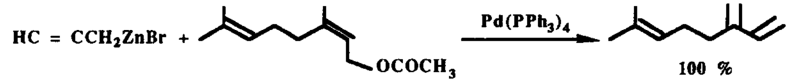


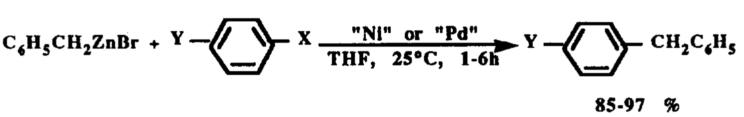
(24)

Such regiospecificity has not been matched by any other class of organometallic reagents or bases so far examined.

2.2.3. *Alkenyl, aryl and alkynyl substrates.* Negishi and coworkers have reported that the reaction of benzylzinc bromide with aryl bromides or iodides in the presence of a catalytic amount of a Ni- or Pd-catalyst provides a general and high chemoselective and regioselective route to unsymmetrical diarylmethanes (Scheme 11).[37] Benzylzinc bromide was prepared by the direct metallation of benzyl bromide with zinc powder.

Benzyl–aryl coupling was also accomplished by reacting benzylzinc bromide with aryl fluoroalkanesulfonates under Pd-catalysis (Scheme 12).[38]

Pd-Catalyzed benzyl–aryl and benzyl–heteroaryl coupling was reported by Kumada and coworkers.[39,40] 1,2-Dibromobenzene, 3,4-dibromothiophene, 2,6-dichloropyridine and 2,6-dibromopyridine are highly selectively monobenzylated by reacting with benzylzinc bromide in the



Ni or Pd catalyst : $Ni(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ + (i- $C_4H_9)_2AlH$ (1:2) (5 mol %)
X,Y : Br, $COOCH_3$; Br, CN; I, NO_2

Scheme 11.

$$C_6H_5CH_2ZnBr + ArOSO_2R \xrightarrow[\text{DMF- benzene, 75-80°C, 18-30h}]{\text{"Pd"}} ArCH_2C_6H_5 \quad 60\text{-}66\%$$

Pd catalyst : $Pd(PPh_3)_4$ (7.5 or 10mol %)
Ar : 2-ClC_6H_4, 4-ClC_6H_4, 3-$CH_3OC_6H_4$
R : $CHF_2CF_2OCF_2CF_3$

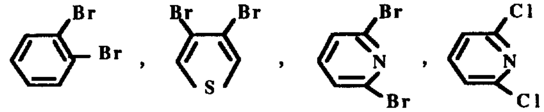
Scheme 12.

presence of a Pd-catalyst (Scheme 13).[39] The use of benzylmagnesium chloride in reaction with 1,2-dibromobenzene gave 20% coupling. This shows the effect of the counterion of the organometallic reagent upon the coupling.

$$C_6H_5CH_2ZnBr + ArX \xrightarrow[\text{THF, 50°C, 16-20 h}]{\text{"Pd"}} ArCH_2C_6H_5 \quad 52\text{-}68\%$$

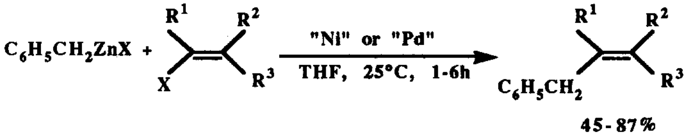
Pd catalyst: $Pd(PPh_3)_4$ (1mol %)

ArX :



Scheme 13.

Negishi and coworkers have reported[41] that the Ni- or Pd-catalyzed cross-coupling of benzylzinc halides with alkenyl halides provides a highly selective and expeditious route to allylated arenes (Scheme 14). Although both Pd- and Ni-catalysts are effective, Ni-catalysts tend to isomerize the allylated arene products to the conjugated isomers. Ni-Catalysts are therefore inferior to Pd-catalysts. In the absence of a Pd- or Ni-catalyst, no coupling occurs. Attempts to synthesize benzylated alkynes by the Pd-catalyzed reactions of benzylzincs with 1-halo-1-alkynes was less successful (eqn 25), the yield of desired products being quite low.

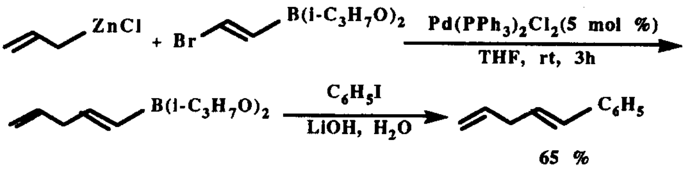


Ni or Pd catalyst : Ni $(PPh_3)_4$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ + (2-$C_4H_9)_2$ AlH (1:2) (5mol %)
X : Cl, Br
R^1,R^2,R^3,X : H, n-C_4H_9,H,X; C_2H_5,C_2H_5,H,I ; C_2H_5, C_2H_5,H,Br;
H, $COOCH_3$, CH_3,Br ; CH_3, n-C_6H_{13}, H, I

Scheme 14.

$$C_6H_5CH_2ZnX + HC{\equiv}CX \xrightarrow{\text{"Ni" or "Pd"}} HC{\equiv}CCH_2C_6H_5 \quad <10\text{-}20\ \% \qquad (25)$$

Suzuki and coworkers also used allylzinc chloride in the cross-coupling reactions of organozinc chlorides with (*E*)-(2-bromoethenyl)diisopropoxyborane. Subsequent reaction with an organic halide provided 1,4-dienes (eqn 26).[36]

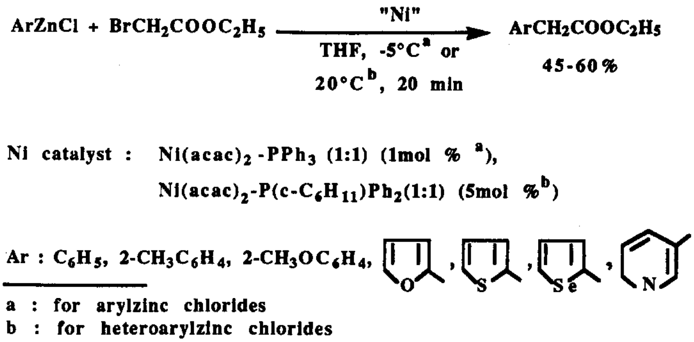


(26)

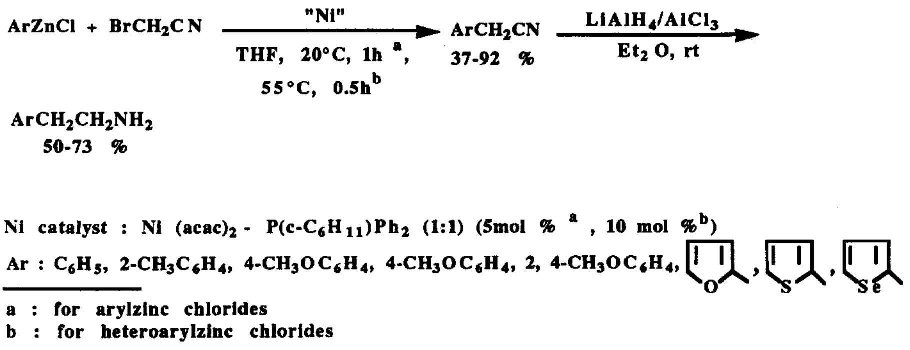
2.3. *Coupling of alkenyl, aryl and alkynyl zinc reagents*

2.3.1. *Alkyl substrates.* Frejd and Klingstedt obtained arylacetic ethyl esters and arylacetonitriles by Ni-catalyzed reactions of arylzinc chlorides with ethyl bromoacetate or bromoacetonitrile respectively (Schemes 15[42] and 16[43]). Arylzinc chlorides were prepared by zinc chloride treatment of aryllithium derivatives. No coupling occurred without the presence of catalyst. Coupling did occur if only $Ni(acac)_2$ was used with ligands. The best yields were obtained with a ligand to metal ratio of (1 : 1). The use of $Pd(acac)_2$ gave no coupling. Ethyl bromoacetate was found to be more reactive than bromoacetonitrile. In both cases, the heteroarylzinc chlorides are less reactive requiring more catalyst and higher temperatures.

2.3.2. *Allylic, benzylic and propargylic substrates.* The reaction of phenylzinc chloride with

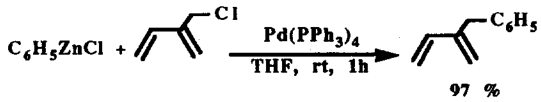


Scheme 15.



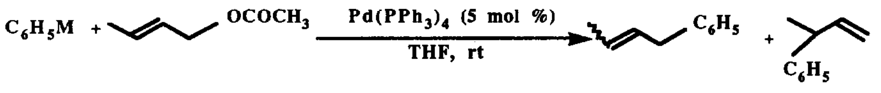
Scheme 16.

isoprenyl chloride gives isoprenylbenzene in the presence of $Pd(PPh_3)_4$ (eqn 27).[44] In the absence of the catalyst, the yield of the coupled product is 57% after 24 h and 36% after 1 h.



(27)

The effects of metal counterions in the Pd-catalyzed reaction of (*E*)-crotyl acetate with phenylmetals containing Mg, Zn, Cd, Al and Zr were examined (eqn 28) by Negishi and coworkers.[45]



(28)

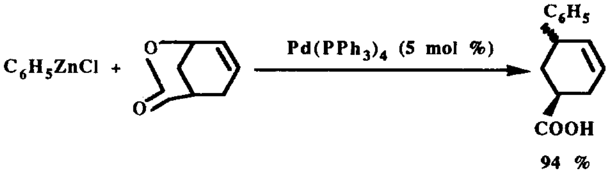
The metal counterions influenced the regioselectivity and the product yield. The maximum yield and regioselectivity and minimum reaction time were observed in the coupling reaction of phenylzinc chloride (Table 2).

TABLE 2

Reaction of phenylmetals with (E)-crotyl acetate catalyzed by $Pd(PPh_3)_4$

	reaction time, h	combined yield, %	product composition	
			S_N2	S_N2'
MgBr	3	15	48	52
ZnCl	3	100	77	23
CdCl	12	96	77	23
$Al(C_6H_5)_2$	3	55	62	38
$Zr(C_6H_5)_3$	24	25	46	54

The reaction of phenylzinc chloride with 7-oxabicyclo[3.2.1]oct-2-en-6-one in the presence of $Pd(PPh_3)_4$ produced the cross-coupled product (eqn 29).[46]



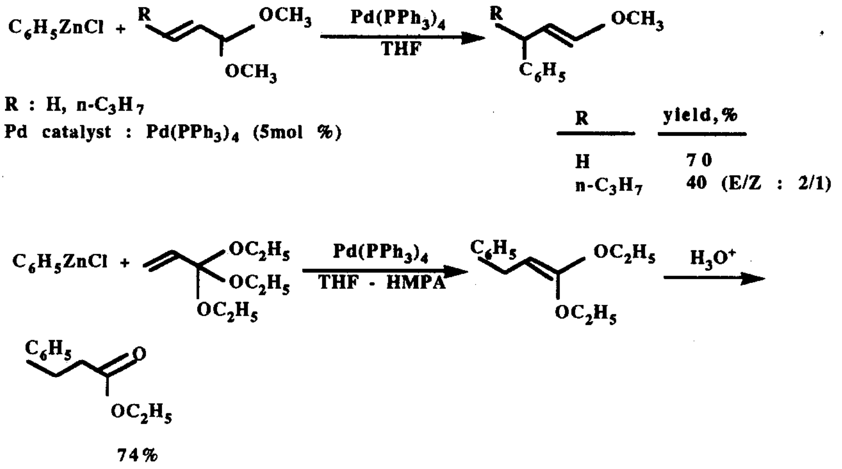
(29)

Phenylzinc chloride reacts with benzyl bromide under Pd-catalysis giving the cross-coupled product in a high yield (eqn 30). However, the corresponding reaction with propargyl bromide yielded phenylallene (eqn 31).[41]

$$C_6H_5ZnCl + C_6H_5CH_2Br \xrightarrow[THF]{Pd(PPh_3)_4} (C_6H_5)_2CH_2 \quad 92\% \tag{30}$$

$$C_6H_5ZnCl + HC \equiv CCH_2Br \xrightarrow[THF]{Pd(PPh_3)_4} C_6H_5CH = C = CH_2 \quad 92\% \tag{31}$$

Negishi and coworkers also investigated Pd-catalyzed reaction of phenylzinc chloride with α,β-unsaturated acetals and orthoesters. They found that the reaction proceeds via γ-attack to provide the S_N2' substitution product (Scheme 17).[47]



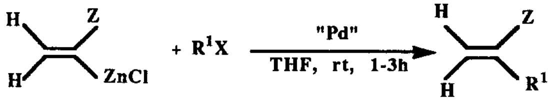
R : H, n-C_3H_7
Pd catalyst : $Pd(PPh_3)_4$ (5mol %)

R	yield,%
H	70
n-C_3H_7	40 (E/Z : 2/1)

74%

Scheme 17.

2.3.3. *Alkenyl, aryl and alkynyl substrates.* It was observed by Negishi and coworkers that alkenylzincs containing α-alkoxy or α-alkylthio substituents react readily and stereospecifically with aryl or alkenyl halides in the presence of a Pd-catalyst producing arylated alkenes or conjugated dienes, respectively. The stereospecificity of these reactions is >98% (Scheme 18).[48] Zinc derivatives were prepared by lithium–zinc exchange. The method provides a convenient and selective entry into stereodefined and heterofunctional conjugated dienes. No coupling occurs in the absence of the catalyst.

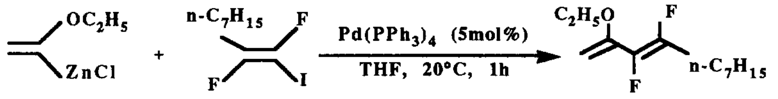


67-80 %

Z : OC_2H_5, SC_2H_5
Pd catalyst : $Pd(PPh_3)_4$ (5mol %)
R^1X : $CH_2 = CHBr$, (E) – n-C_5H_{11} $CH = CHI$, C_6H_5I, 4-ClC_6H_4I

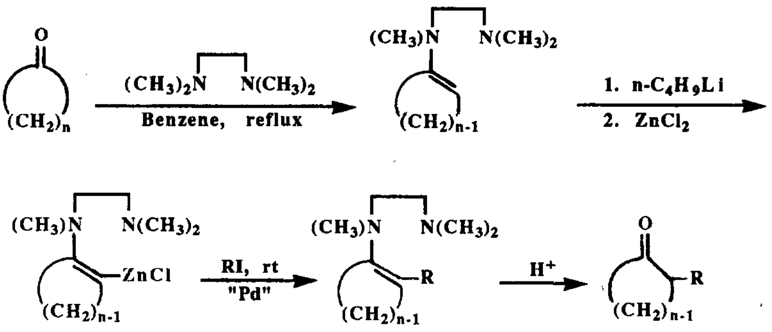
Scheme 18.

α-Ethoxyvinylzinc chloride (the zinc salt of the enol ether of acetaldehyde) couples with 1,2-difluoro-1-iodononene under Pd-catalysis (eqn 32).[49] The yield of coupled product with vinylzinc chloride was also found to be low (35%).[50]

 (32)

37 %

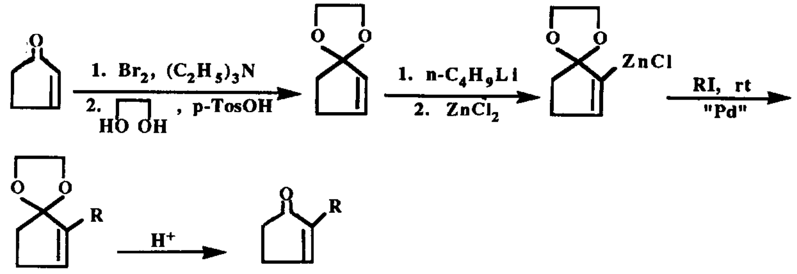
Two procedures for α-alkenylation and α-arylation of ketones that permit the introduction of an aryl or a stereodefined alkenyl group at the α-position of cyclic ketones in high yields were reported



Pd catalyst : $Pd(PPh_3)_4$ (1mol %) or $Ni(PPh_3)_2Cl_2$ + $n\text{-}C_4H_9Li$(1:2)

R	yield, % n=4	yield, % n=5
(Z)- $n\text{-}C_4H_9CH = CH$	80	
(Z)- $n\text{-}C_6H_{13}CH = CH$	78	67
4- $CH_3C_6H_4$	76	74

Scheme 19.



80 - 92 %

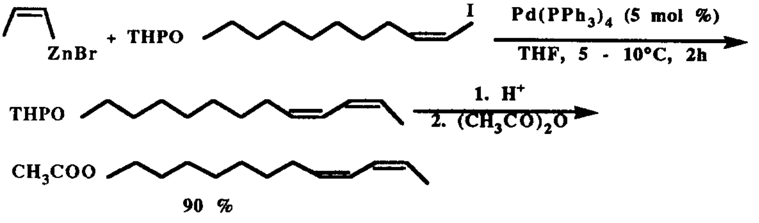
Pd catalyst : $Pd(PPh_3)_4$ (1mol %)

R : (Z)- $n\text{-}C_4H_9CH{=}CH$, (Z)-$n\text{-}C_6H_{13}$ CH=CH, 4-$CH_3C_6H_4$

Scheme 20.

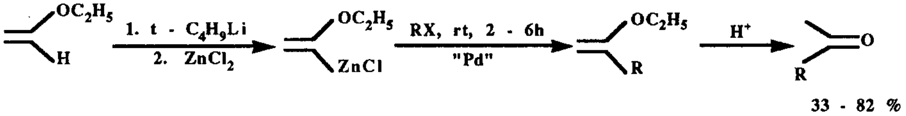
by Negishi and coworkers.[51] The zinc derivative of the enamine prepared from cyclopentanone or cyclohexanone was generated by treatment of the lithio derivative with zinc chloride, and reacted with alkenyl or aryl iodide under Pd-catalysis. This produced 2-alkenyl or 2-aryl derivatives with complete retention of the alkenyl stereochemistry, which gave alkenyl or aryl ketones upon hydrolysis (Scheme 19). The use of alkenyllithium instead of the zinc derivative did not give more than 5% yield. The zinc derivative of the cyclic ketal prepared from 2-cyclopentenone was generated by treatment of the lithio derivative with zinc chloride and reacted with alkenyl or aryl halide in the presence of a Pd-catalyst to give 2-alkenyl- or 2-aryl-2-cyclopentenone with essentially complete regio- and stereo-control (Scheme 20).

Pd-Catalyzed coupling of an alkenylzinc reagent with an alkenyl halide was used for the synthesis of the sex pheromone, 8-(*Z*),10-(*Z*)-dodecadienyl acetate (eqn 33).[52] The product was found to be 97% isomerically pure.



(33)

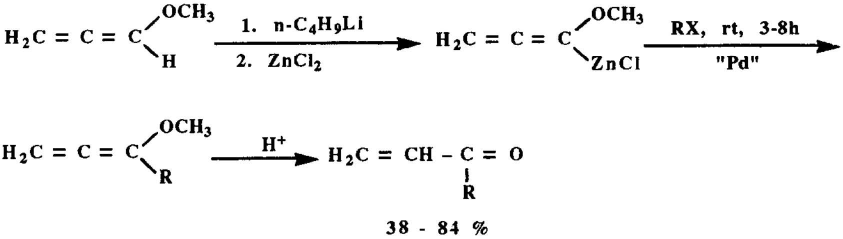
Hegedus and Russel investigated[53] the Pd-catalyzed reactions of aryl and alkenyl halides with zinc salts of enol ethers and allenic ethers. They reported that these type of reactions can be used to introduce acyl and α,β-unsaturated acyl groups into aryl and alkenyl halides. For acylation of aryl and alkenyl halides with enol ether anions, the enol ether of acetaldehyde was lithiated and then transmetallated with zinc chloride. Addition of a Pd-catalyst, followed by halide substrate resulted in acetylation (Scheme 21). The reaction was relatively insensitive to the nature of the Pd-catalyst. The catalysts given in Scheme 21 all resulted in similar yields of acylation product. Most of the work was done with the catalyst prepared from $Pd(PPh_3)_2Cl_2 + (i\text{-}C_4H_9)_2AlH$ (1 : 2) but the investigators reported that $Pd(dba)_2 + PPh_3$ (1 : 2) and $Pd(dba)_2$+dppe (1 : 1) are the reagents of choice. By transmetallating allenic ether anions, which are available by lithiation, with zinc chloride and then reacting with halide substrate under Pd-catalysis, the nucleophilic introduction of an α,β-unsaturated carbonyl(acryloyl) group in these substrates is possible (Scheme 22).



RX : C_6H_5I, $2\text{-}CH_3C_6H_4I$, $3\text{-}CH_3C_6H_4I$, $4\text{-}CH_3C_6H_4I$, $3\text{-}CH_3OC_6H_4I$, $2\text{-}NO_2C_6H_4I$, $2\text{-}CH_3OC_6H_4Br$, $2\text{-}CH_3OC_6H_4I$, (E)- $C_6H_5CH{=}CHBr$, (Z)-$C_6H_5CH{=}CHBr$, (E)-n-$C_4H_9CH{=}CHI$, (E)-n-$C_4H_9(CH_3)$ $C{=}CHI$, (E)-n-$C_4H_9CH{=}CI(Si(CH_3)_3)$

Pd catalyst: $Pd(PPh_3)_2Cl_2$ + $(iC_4H_9)_2AlH$(1:2); $Pd(dba)_2$ + PPh_3(1:2); $Pd(dba)_2$+PPh_3(1:4); $Pd(dba)_2$+dppe(1:1)(dba:dibenzylideneacetone)(5mol %)

Scheme 21.

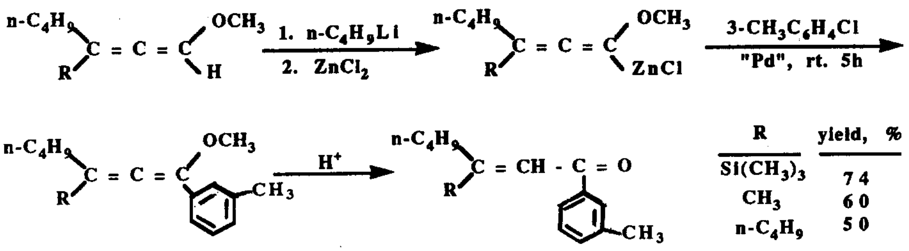


RX : $2\text{-}CH_3C_6H_4I$, $3\text{-}CH_3C_6H_4I$, $4\text{-}CH_3C_6H_4I$, $C_6H_5CH_2Br$, (E)-$C_6H_5CH{=}CHBr$, (E)-$nC_4H_9CH{=}CHI$, (E)-n-$C_4H_9(CH_3)C{=}CHI$, (E)-n-$C_4H_9CH{=}CI(Si(CH_3)_3)$

Pd catalyst : $Pd(PPh_3)_2Cl_2$ + $(i\text{-}C_4H_9)_2AlH$(1:2) (5mol %)

Scheme 22.

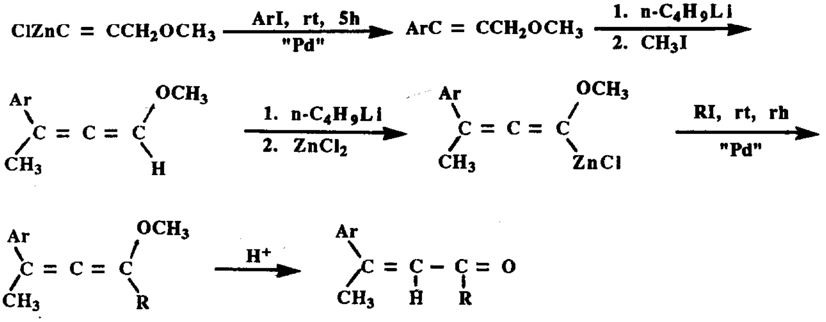
Mixtures of α- and γ-anions were obtained upon lithiation of γ-monosubstituted allenic ethers. Attempts to generate exclusively the α-anion has not been successful. γ,γ-Dialkyl-substituted allenic ethers were lithiated, transmetallated and then coupled to aryl halides with the Pd-catalyzed reaction. This led to fair yields of β,β-dialkyl-α,β-unsaturated aryl ketones (Scheme 23). γ-Arylallenic ethers were prepared by the Pd-catalyzed coupling of aryl halides with alkynylzinc reagents giving the γ-arylpropargylic ethers, followed by lithiation and alkylation at the γ-position with methyl iodide. This allenic ether was lithiated, transmetallated to zinc and coupled to aryl and alkenyl halides with Pd-catalyst. This produced β-aryl-β-methyl-α,β-unsaturated ketones (Scheme 24). When the γ-aryl group was a 2- or 4-tolyl group, the coupling proceeded as expected. However with a 3-tolyl or phenyl group at the γ-position, coupling did not occur. An alternative approach to unreactive allenic



R	yield, %
$Si(CH_3)_3$	74
CH_3	60
$n\text{-}C_4H_9$	50

Pd catalyst : $Pd(PPh_3)_2Cl_2{}^{+}(i\text{-}C_4H_9)_2AlH$ (1:2) (5mol %)

Scheme 23.

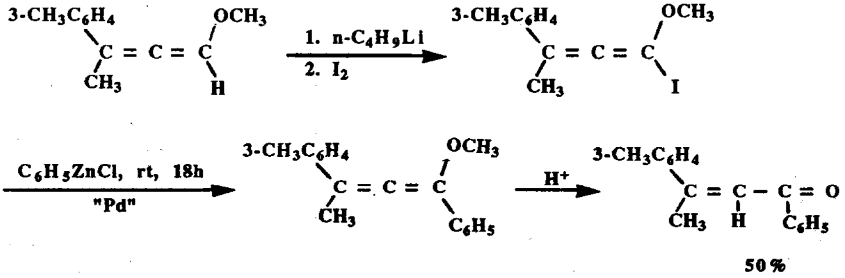


Pd catalyst : $Pd(PPph_3)_2Cl_2 + (i\text{-}C_4H_9)_2AlH$ (1:2) (5mol %)

Ar	yield of allenic ether, %	Ar, R	yield of ketone, %
C_6H_5	75	$4\text{-}CH_3C_6H_4$, $2\text{-}CH_3C_6H_4$	59
$2\text{-}CH_3C_6H_4$	87	$4\text{-}CH_3C_6H_4$, (E)-$n\text{-}C_4H_9CH = CH$	44
$3\text{-}CH_3C_6H_7$	84	$2\text{-}CH_3C_6H_4$, $2\text{-}CH_3C_6H_4$	43
$4\text{-}CH_3C_6H_4$	80		
$3\text{-}CH_3OC_6H_4$	64		

Scheme 24.

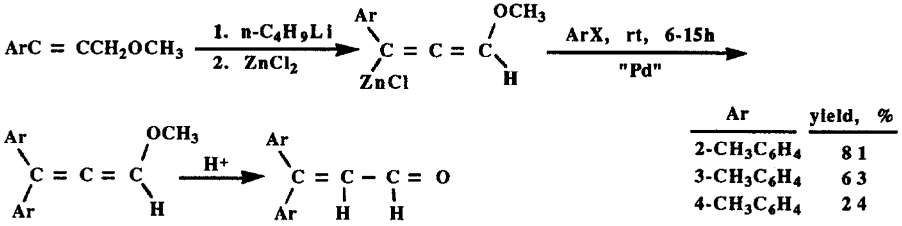
ether anion precursors consisted of using the allenic ether as the halide member of the coupling reaction. The allenic ether was lithiated and iodinated with iodine. Reaction with an organozinc reagent and a Pd-catalyst led to coupling in modest yields (eqn 34).


(34)

Pd catalyst : $Pd(PPh_3)_2Cl_2 + (i\text{-}C_4H_9)_2AlH$ (1:2) (5mol %)

Attempts to couple the γ-anions of allenic ethers with aryl iodides also succeeded (Scheme 25).

As seen, the Pd-catalyzed cross coupling reactions of organozinc reagents allows the efficient direct introduction of the carbonyl functional groups, CH_3CO, $CH_2{=}CHCO$, $R_2C{=}CHCO$ (R = alkyl, aryl) into aryl and alkenyl halides. The reaction proceeds under mild conditions in fair to good yields with alkenyl halides and the stereochemistry of the alkenyl group is maintained.

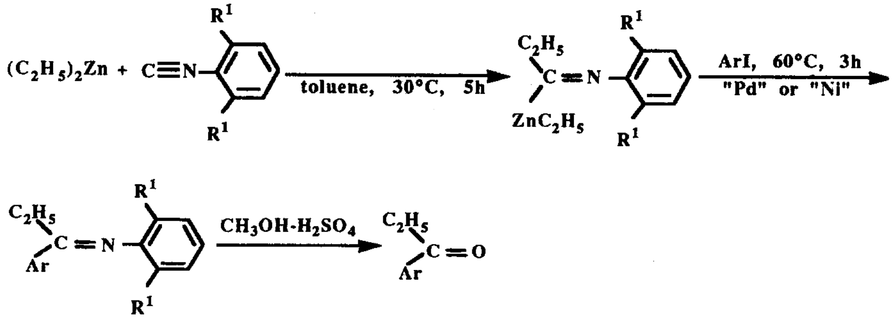


Ar	yield, %
$2\text{-}CH_3C_6H_4$	81
$3\text{-}CH_3C_6H_4$	63
$4\text{-}CH_3C_6H_4$	24

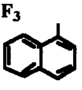
Pd catalyst : $Pd(PPh_3)_2Cl_2$ + $(i\text{-}C_4H_9)_2AlH$ (1:2)

Scheme 25.

[1-(Arylimino)alkyl]zinc, prepared by α-addition of organozinc to aryl isocyanide, was coupled with aryl iodides in the presence of a Pd- or Ni-catalyst giving the corresponding *N*-aryl arylimine chemoselectively (Scheme 26).[54] Alkenyl iodide, aryl chloride or aryl bromide did not react under these conditions. Synthetic transformation of the *N*-aryl imines was achieved by hydrolysis of imino functionality to ketone. This demonstrated the utility of [1-(arylimino)alkyl]zinc as an acyl anion equivalent.

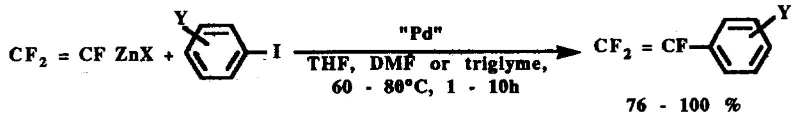


Pd or Ni catalyst : $Pd(PPh)_3Cl_2$ (1-2 mol %) for $R^1 = CH_3$,
$Ni(dppp)Cl_2$ (3e) (1-2 mol %) for $R^1 = CF_3$

Ar : C_6H_5, 4-Br, $4\text{-}CH_3OC_6H_4$, $4\text{-}CH_3COC_6H_4$, $4\text{-}C_2H_5OOC\,C_6H_4$, 

Scheme 26.

Pd-Catalyzed coupling of perfluoroalkenylzinc reagents was investigated by Burton and Heinze[55,56] and by Sauvetre and coworkers.[24,49,50,57–59] Burton and Heinze reported that trifluoroethenylzinc reagent and (*E*)- and (*Z*)-2-trifluoromethyldifluoroethenylzinc reagents couple with aryl iodides under Pd-catalysis giving the corresponding arylalkenes. α,β,β-Trifluorostyrenes (Scheme 27)[55] and (*E*)- and (*Z*)-1-arylperfluoropropenes (Scheme 28)[56] were prepared in good yields. Perfluoroalkenylzinc reagents were generated from corresponding perfluoroalkenylbromides or iodides and activated zinc powder using THF, DMF or triglyme as solvent. (*E*)- and (*Z*)-1-arylperfluoropropenes were prepared stereoselectively. Aryl iodides gave the most consistent results



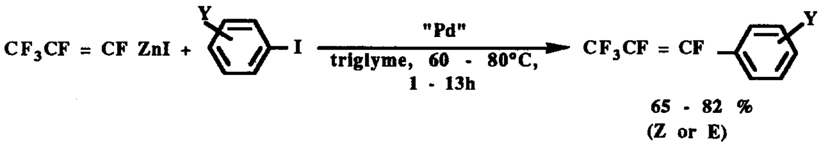
X : Br,I

Pd catalyst: $Pd(PPh_3)_4$ (0.5-2.5 mol %)

Y : H, 2-Br, 2-I, 4-Cl, 3-CH_3, 2-$CH(CH_3)_2$, 4-CH_3O, 2-CF_3, 2-C_6H_5, 2-NO_2, 3-NO_2, 4-CF_2 = CF [a], 2,5-Cl_2[b]

[a] rt, [b] 2days

Scheme 27.



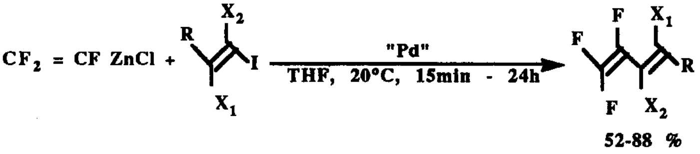
Pd catalyst: $Pd(PPh_3)_4$ (0.5-2.5 mol %)

Y : H, 4-Cl, 4-CH_3, 3-NO_2

Scheme 28.

and aryl bromides often did not give any reaction. $Pd(PPh_3)_4$ was the only catalyst found to give good results.

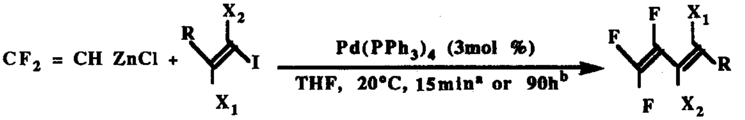
Sauvetre and coworkers reported alkenylation[24,49,50,57,58] and arylation[57–59] reactions of various fluorovinylzinc reagents which were prepared by transmetallation of the corresponding lithium reagents with zinc chloride at low temperatures. Stereoselectively perfluorinated conjugated dienes (Scheme 29,[49,50] eqn 35,[49] Scheme 30,[49,50] eqn 36[57] and eqn 37[24]) and styrenes (Scheme 31[58,59] and eqn 38[59]) were obtained in high yields by coupling under Pd-catalysis.



Pd catalyst : $Pd(PPh_3)_4$ (3-5 mol %)

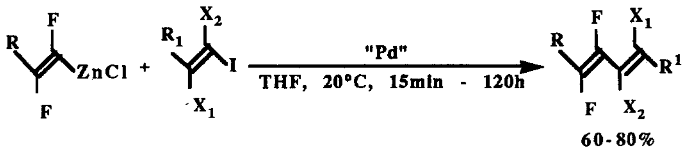
R,X_1,X_2 : n-C_6H_{13},H,H; H,n-C_6H_{13}, H; n-C_7H_{15},F,F; F,n-C_7H_{15},F; n-C_5H_{11},F,Cl; C_6H_5,F,Cl

Scheme 29.



(35)

R,X_1,X_2	yield, %
n-C_6H_{13},H,H[a]	83
n-C_7H_{15},F,F[b]	86

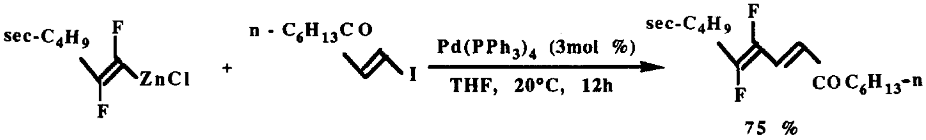


Pd catalyst : $Pd(PPh_3)_4$ (3-5mol %)

R : $n\text{-}C_4H_9$, $sec\text{-}C_4H_9$, $n\text{-}C_7H_{15}$, C_6H_5

R^1, X^1,X^2: $n\text{-}C_6H_{13}$,H,H; H, n,C_6H_{13}, H; CH_3,CH_3,H; $n\text{-}C_4H_9$, F,I; $n\text{-}C_5H_{11}$,F,Cl; $sec\text{-}C_4H_9$, F,F; $t\text{-}C_4H_9$, F,F; H,H,H, Br instead of I

Scheme 30.



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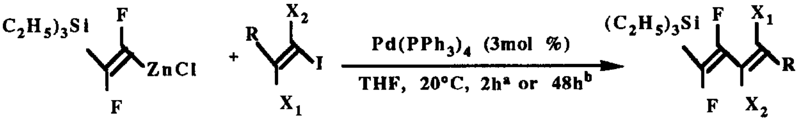


(37)

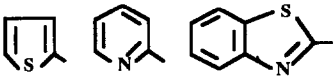
R,X_1,X_2	yield, %
C_2H_5,H,H^a	76
$n\text{-}C_5H_{11}$,F,F^b	80

$$CF_2 = CF\,ZnCl + ArI \xrightarrow[\text{THF, 20° C, 12-24h}]{\text{"Pd"}} CF_2 = CFAr$$

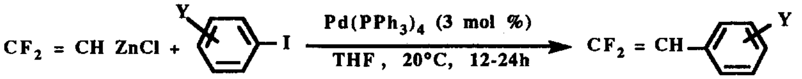
40-80%

Pd catalyst : $Pd(PPh_3)_4$ (3mol %)

Ar : $4\text{-}CH_3C_6H_4$, $4\text{-}CH_3OC_6H_4$, $4\text{-}IC_6H_4$,



Scheme 31.



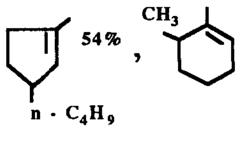
(38)

Y	yield, %
H	70
$4\text{-}CH_3$	80
$4\text{-}CH_3O$	87

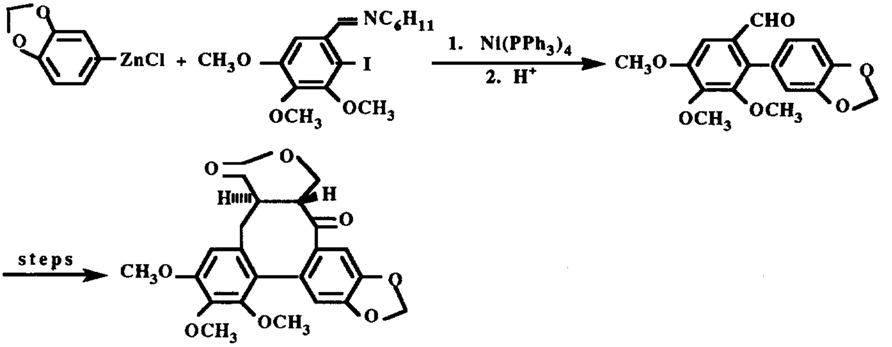
Some regiodefined dienes were prepared by the Pd-catalyzed reaction of vinylzinc chloride with the corresponding cycloalkenyl triflates (eqn 39).[60]

$$CH_2=CHZnCl + ROSO_2CF_3 \xrightarrow[\text{THF, rt, 13h}]{Pd(PPh_3)_4\text{ (3mol \%)}} CH_2=CHR \qquad (39)$$

R :

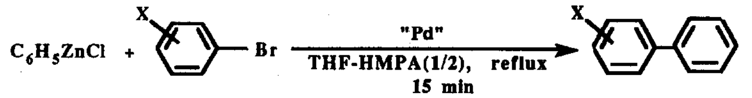


The synthesis of steganone by Raphael and Larson demonstrates the synthetic potential of Ni-catalyzed aryl–aryl coupling (eqn 40).[61]



(40)

Okamoto and coworkers investigated the Pd-catalyzed coupling between phenylzinc chloride and *m*- and *p*-bromoacetophenones and *p*-bromobenzaldehyde (Scheme 32).[31] The yield of 4-acetylbiphenyl was given in parentheses obtained by using different Ni- and Pd-catalysts: Pd(PPh$_3$)$_2$Cl$_2$ (98%), Ni(PPh$_3$)$_2$Cl$_2$ (84%), Pd(dppf)Cl$_2$ **4g** (75%), Ni(dppp)Cl$_2$ **3e** (75%), Pd(dppb)Cl$_2$ **4f** (70%), PdCl$_2$ (61%), Pd(dppp)Cl$_2$ **4e** (60%). The reactivity toward phenylzinc chloride in the presence of Pd(PPh$_3$)$_2$Cl$_2$ falls in the order: *p*-CHOC$_6$H$_4$Br > C$_6$H$_5$Br > C$_6$H$_5$CHO.

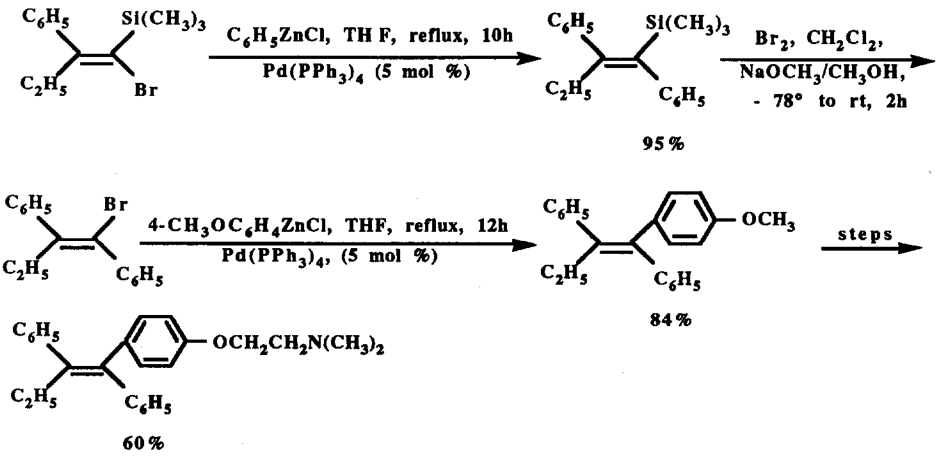


Pd catalyst : Pd(PPh$_3$)$_2$ Cl$_2$ (2mol %)

X	yield, %
3-CH$_3$CO	98
4-CH$_3$CO	79
4-CHO	82

Scheme 32.

Miller and Al-Hassan used Pd-catalyzed cross-coupling of arylzinc chlorides with alkenyl halides in the stereospecific synthesis of *trans*-tamoxifen (eqn 41),[62,63] *cis*-tamoxifen (eqn 42)[63] and clomid (eqn 43).[64]



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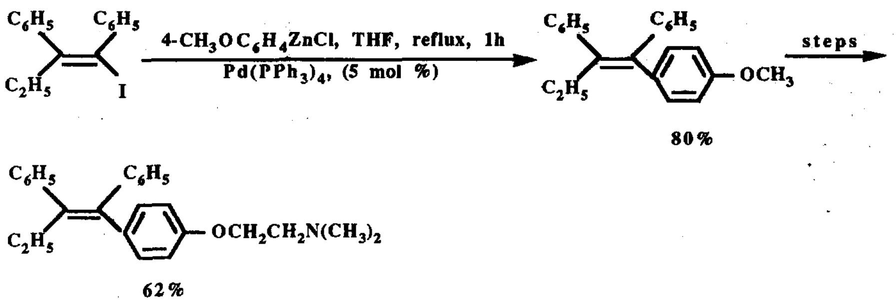

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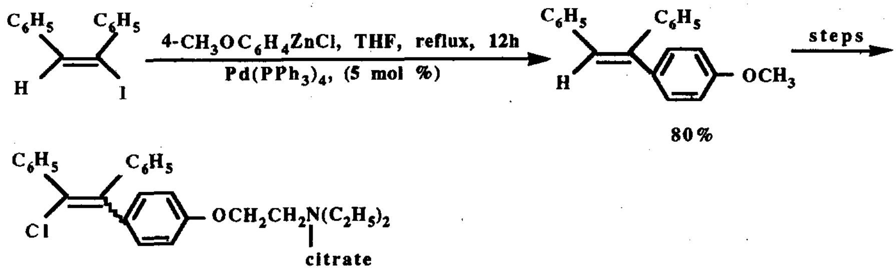
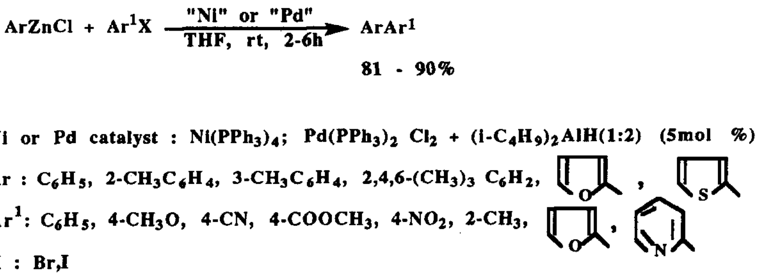


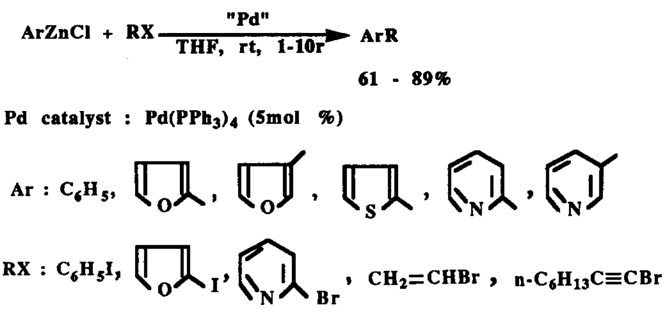
(43)

Ni- or Pd-catalyzed coupling of arylzinc reagents with aryl bromides or iodides was investigated in detail by Negishi and coworkers.[37,65] The reaction represents one of the most general and satisfactory routes to unsymmetrical biaryls (Scheme 33).[37] Ni- and Pd-complexes may be used interchangeably. In cases where sterically hindered aryl reagents, such as mesitylzinc chloride, are used, Ni-catalysts tend to lead to higher product yields than the corresponding Pd-catalysts. As a general rule, Ni-catalyzed aryl–aryl cross-coupling proceeds smoothly with both aryl iodides and bromides, whereas aryl bromides must be activated by an electron-withdrawing group in Pd-catalyzed cross-coupling. However, Pd-catalyzed cross-coupling is more chemoselective than Ni-catalyzed cross-coupling. Arylzinc reagents were obtained by the reaction of the corresponding aryllithium reagents with zinc chloride. In aryl–aryl cross-coupling, zinc appears to be among the most satisfactory metals from the standpoint of (a) product yield; (b) cross/homo ratio; (c) chemoselectivity; and (d) ease of preparation. The synthesis of 2-methyl-4′-nitrobiphenyl by coupling of *o*-tolylzinc chloride with *p*-nitrobromobenzene has been published in detail.[65]



Scheme 33.

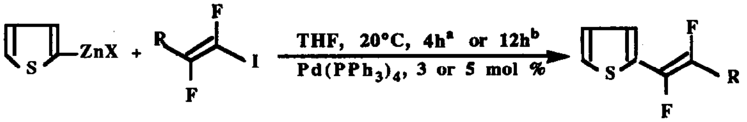
Negishi and coworkers also investigated the Pd-catalyzed coupling of phenyl- and heteroarylzinc reagents with phenyl, heteroaryl, vinyl and alkynyl halides (Scheme 34).[33] The reaction produces substituted heteroaromatic compounds cleanly and regiospecifically in high yields. In some cases, proper selection of the reagents in the Pd-catalyzed cross-coupling is of critical importance.



Scheme 34.

Thus, while both 2-iodofuran and 2-furylzinc chloride can be readily converted into 2-phenylfuran, only 3-furylzinc chloride, but not 3-bromofuran, can be converted into 3-phenylfuran. Likewise, while 3-pyridylzinc chloride can be successfully employed, the use of 3-bromopyridine was not successful.

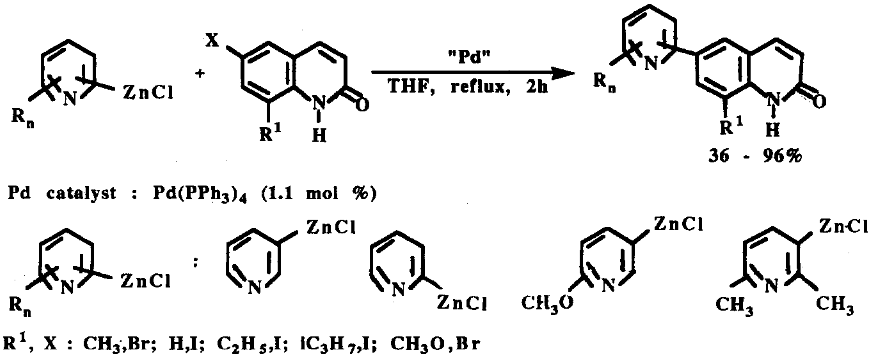
2-Thienylzinc chloride[57] and bromide[24] react with 1,2-difluoro-3-methyl-1-iodohexene and 1,2-difluoro-2-triethylsilyl-1-iodoethene, respectively, under Pd-catalysis providing coupled products (eqn 44).



(44)

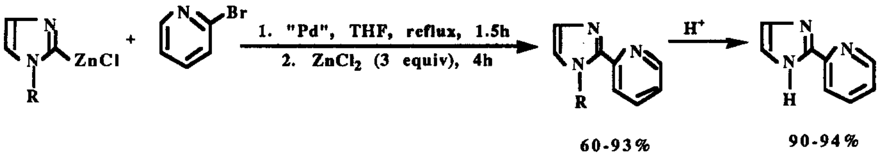
X	R	yield, %
Br ^{a}	$Si(C_2H_5)_3$	41
Cl ^{b}	sec-C_4H_9	57

Direct regioselective synthesis of 6-pyridinyl-2(1*H*)-quinolines by the Pd-catalyzed coupling of pyridinylzinc reagents with haloquinolines was achieved by Roberts and coworkers (Scheme 35).[66] Organozinc reagents were prepared by transmetallation of corresponding lithium and Grignard reagents.



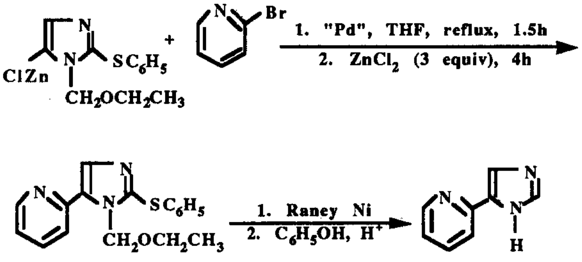
Scheme 35.

The same methodology was extended to the synthesis of 2- and 4(5)-(2-pyridinyl)imidazoles (Scheme 36 and eqn 45).[67]



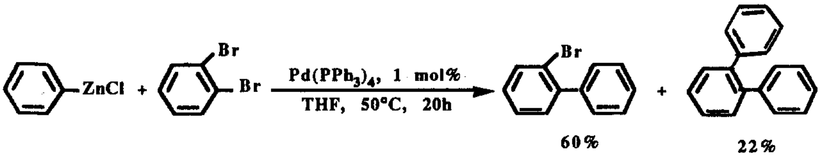
Pd catalyst : Pd$(PPh_3)_4$ (0.8mol %)
R : CH_3, $CH_2OCH_2CH_3$, $SO_2N(CH_3)_2$

Scheme 36.

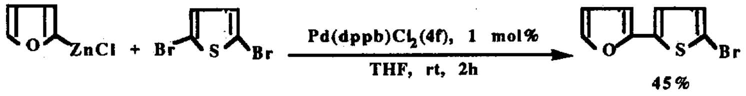


(45)

Kumada and coworkers reported Pd-catalyzed aryl–aryl coupling (eqn 46)[39] and heteroaryl–heteroaryl coupling (eqn 47)[68] using organozinc reagents.

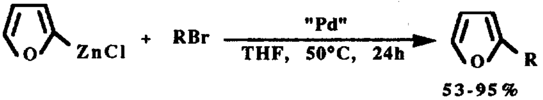


(46)



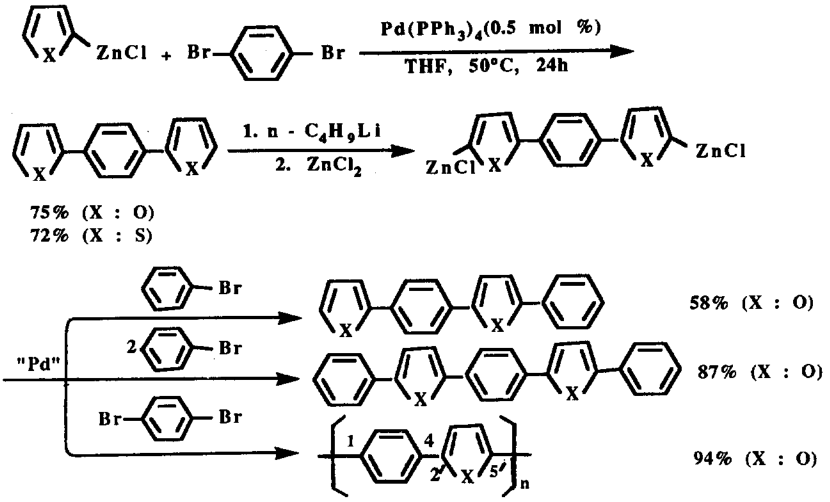
(47)

Pelter and coworkers prepared 2-substituted furans by Pd-catalyzed coupling of 2-furylzinc chlorides with allyl, benzyl and aryl bromides (Scheme 37).[69] Organozinc reagents were prepared by reacting corresponding organolithium derivatives with zinc chloride. The coupling yield was quite low in the presence of $Ni(PPh_3)_2Cl_2$ as a catalyst. 1,4-Dibromobenzene gave the doubly coupled product in its reaction with 2-furylzinc chloride or 2-thienylzinc chloride (eqn 48).



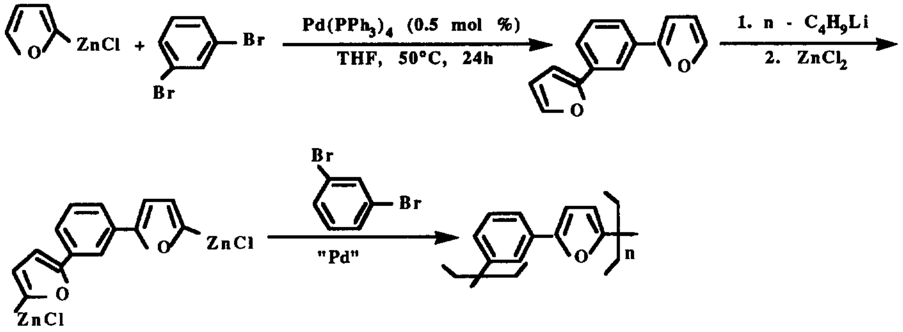
Pd catalyst : Pd$(PPh_3)_4$ (0.5mol %)
R : C_6H_5, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 3-$CH_3OC_6H_4$, 3,4$(CH_3O)_2C_6H_3$, 4-$NO_2C_6H_4$,
$C_6H_5CH_2$, $C_6H_5CH = CHCH_2$

Scheme 37.



(48)

It was observed[70] that their bis(chlorozincio) derivatives reacted with 1 or 2 equiv. of bromobenzene under Pd-catalysis and also with 1,4-dibromobenzene giving a polymer. The polymers exist in an extended, approximately planar form and are unique for the following reasons: (i) the units of which they are composed are unequivocally and solely linked 1,4- and 2′,5′-throughout; (ii) the order of the units is defined; (iii) the stoichiometry is defined; and (iv) there is neither branching nor cross-linking. They have extended the process by reacting 2-furylzinc chloride with 1,3-dibromobenzene under Pd-catalysis (eqn 49) and obtained a spiral polymer. These Pd-catalyzed polymerisation processes yield polyaromatics including heteroaromatics with highly desirable characteristics.



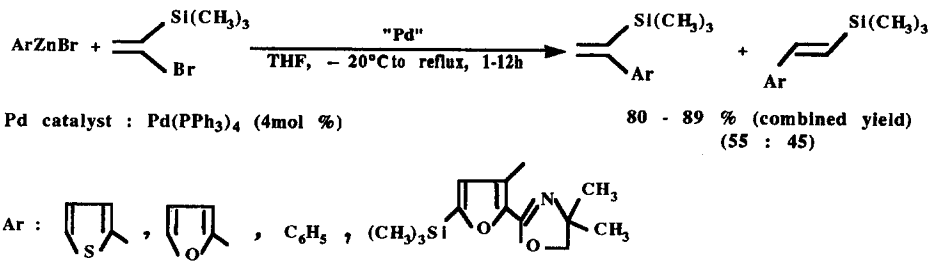
(49)

Pd-Catalyzed coupling reactions of arylzinc bromides with 1-bromovinyltrimethylsilane gave not only the expected 1-substituted vinylsilanes, but also the isomeric 2-substituted vinylsilanes (Scheme 38).[71] No reactions occurred in the absence of Pd-catalyst.

Pd-Catalyzed coupling reactions of arylzinc chlorides with benzocycloheptenyl triflate provide an efficient synthesis of conformationally restricted antiestrogens (Scheme 39).[72]

A convenient synthesis of 2-methoxy-5-aryltropones by coupling of arylzinc chlorides with 2-methoxy-5-[[(trifluoromethyl)sulfonyl]oxy]tropone in the presence of a Pd-catalyst has been reported (Scheme 40).[73] Arylzinc reagents were obtained by transmetallation of corresponding aryllithium reagents.

Rieke and coworkers recently reported[4] a high yield Pd-catalyzed aryl–aryl (eqn 50) and alkenyl–

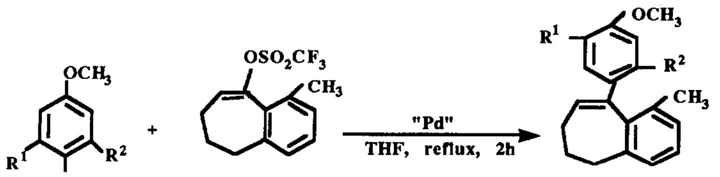


Pd catalyst : $Pd(PPh_3)_4$ (4mol %)

80 - 89 % (combined yield)
(55 : 45)

Ar : , , C_6H_5 , $(CH_3)_3Si$

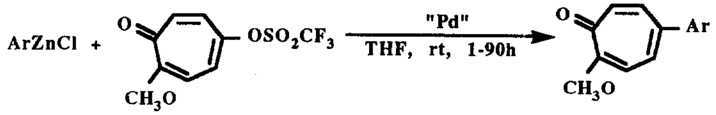
Scheme 38.



Pd catalyst : $Pd(PPh_3)_4$ (3mol %)

R^1,R^2	yield,%
H,H	92
CH_3,H	89
CH_3,CH_3	67

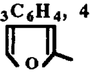
Scheme 39.



42-97%

Pd catalyst : $Pd(PPh_3)_4$ (5mol %)

Ar : 3-C_6H_5 , 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$CF_3C_6H_4$, 2,6-$(CH_3)OC_6H_3$
2,3,4-$(CH_3)_3C_6H_2$,



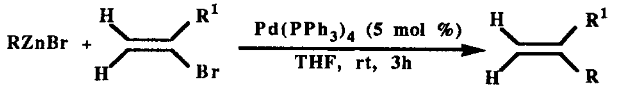
Scheme 40.

alkenyl coupling (eqn 51) using functionalized organozinc reagents. These reagents were prepared from highly reactive zinc obtained by the lithium naphthalenide reduction of zinc chloride.

$$\mathrm{ArZnBr + Ar^1X \xrightarrow[\text{THF, rt, 3h}]{\text{Pd(PPh}_3)_4\text{ (5 mol \%)}} ArR^1} \tag{50}$$

82-95%

Ar : 3-$C_2H_5OOCC_6H_4$, 2-CNC_6H_4, 4-CNC_6H_4
Ar^1 X : 4-BrC_6H_4CN, 4-$IC_6H_4COOC_2H_5$, 4-BrC_6H_4 $COOC_2H_5$

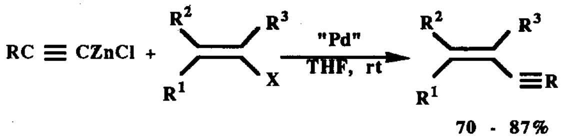


(51)

85-95%

R : $CH_2=CC_6H_5$, (E)-2-$C_2H_5OOCC_6H_5CH=CH$
R^1 : H,CH_3

Negishi and coworkers have investigated the coupling of alkynylzinc reagents with alkenyl halides in the presence of a Pd-catalyst.[74] The reaction provides terminal or internal conjugated enynes in high yields. The stereospecificity of the reaction is ⩾97% (Scheme 41). Alkynylzinc reagents were obtained from the corresponding alkynyllithium reagents and zinc chloride.



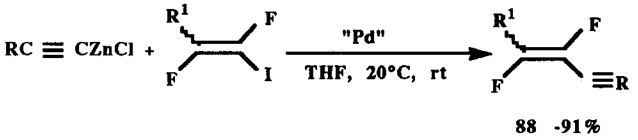
Pd catalyst : $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ + $(i\text{-}C_4H_9)_2AlH$ (1:2) (5mol %)

R : H, $n\text{-}C_4H_9$, $n\text{-}C_5H_{11}$

R^1,R^2,R^3,X : $n\text{-}C_4H_9$, H,H,I; H,$n\text{-}C_4H_9$,H,I;C_2H_5,$n\text{-}C_4H_9$,H,I; CH_3,$COOCH_3$,H,Br

Scheme 41.

Sauvetre and coworkers have reported the synthesis of fluorinated enynes by Pd-catalyzed cross-coupling of alkynylzinc reagents with fluorinated alkenes (Scheme 42 and eqn 52).[75] Alkynyl zinc reagents were prepared by the transmetallation of the corresponding alkynyllithium reagents with zinc chloride. 1-Heptynylzinc bromide also coupled with 1,2-difluoro-2-triethylsilyl-1-iodoethene under Pd-catalysis (eqn 53).[24]



Pd catalyst : $Pd(PPh_3)_4$ (3mol %)

R : $n\text{-}C_4H_9$, $n\text{-}C_3H_7$, $n\text{-}C_6H_{13}$

R^1 : (Z)-$n\text{-}C_4H_9$, (Z)-sec-C_4H_9, (Z)-C_6H_5, (E)-$n\text{-}C_7H_{15}$

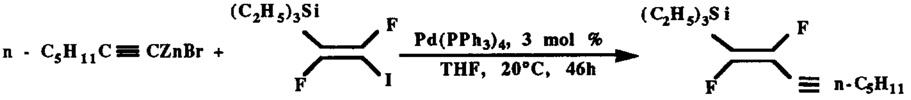
Scheme 42.

$$n\text{-}C_6H_{13}C\equiv CZnCl + CF_2=CFI\ (\text{or } CF_2=CHI) \xrightarrow[\text{THF,20°C, 24h}]{\text{"Pd"}} CF_2=CFC\equiv Cn\text{-}C_6H_{13} \tag{52}$$

62%

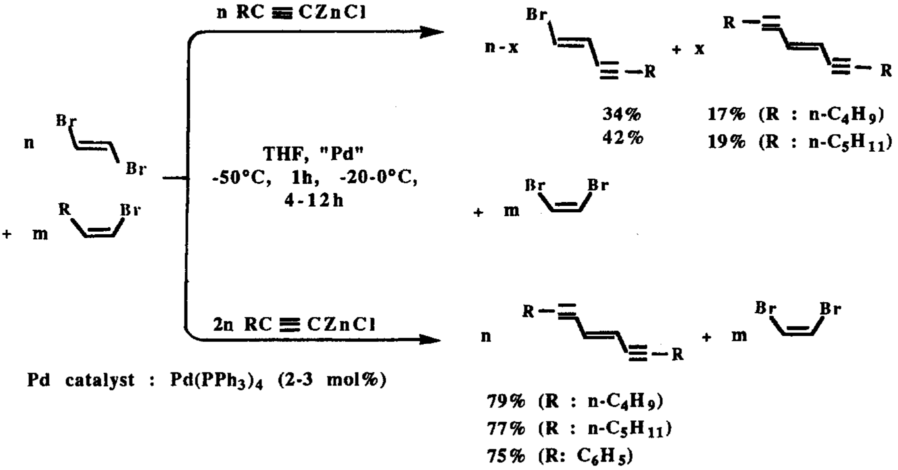
(or $CF_2=CHC\equiv Cn\text{-}C_6H_{13}$)

66%



(53)

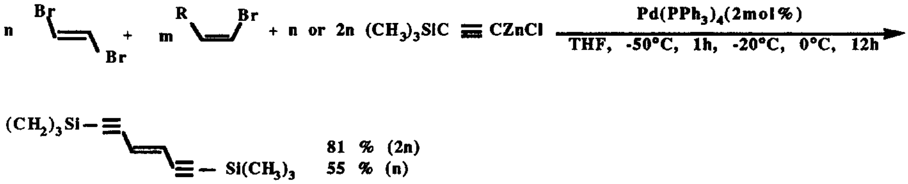
Rossi and coworkers found that[76,77] 1-alkynylzinc chlorides react with a mixture of 1,2-dibromoethene diastereoisomers [(*E*)/(*Z*) = 33 : 67] under Pd-catalysis. Since (*E*)-1,2-dibromoethene reacts preferentially in the presence of (*Z*)-1,2-dibromoethene, (*E*)-1-bromo-1-en-3-ynes and 1,6-disubstituted (*E*)-3-en-1,5-diynes are obtained diastereoselectively according to the ratio of reagents (Scheme 43). The reaction of *n* equiv. of alkynylzinc chloride with a diastereoisomeric mixture of 1,2-dibromoethene containing *n* equiv. of (*E*)-stereoisomer produced a modest yield of (*E*)-monoalkynylated product with high stereoisomeric purity together with a significant amount of (*E*)-dialkynylated product. The use of 2*n* equiv. of alkynylzinc chloride provided the (*E*)-dialkynylated product with high stereoisomeric purity in good yield. An improved diastereoselective monoalkynylation was obtained by using 0.5 equiv. of alkynylzinc chloride: the yields of monoalkylated products increased to 56% in the case of R = $n\text{-}C_4H_9$ and R = $n\text{-}C_5H_{11}$. However, when a similar



Scheme 43.

procedure was used in the case of R = 2-thienyl, mono- and di-alkynylated products were obtained in 15% and 56% yields, respectively.

It was observed that[78] trimethylsilylethynylzinc chloride affords dialkynylated product diastereoselectively in the Pd-catalyzed reaction with a diastereomeric mixture of 1,2-dibromoethene in spite of the molar ratio of the reagents used (eqn 54). It was also reported that[78] trimethylsilylethynylzinc chloride reacts with (*E*)-1-alkenyl bromides under Pd-catalysis preferentially in the presence of corresponding (*Z*)-stereoisomers to provide (*E*)-1-trimethylsilyl-3-en-1-ynes with high stereoisomeric purity (Scheme 44). 1,2-Dibromo-1,2-diphenylethene reacted with 1-heptynylzinc chloride in the presence of Pd-catalyst giving diphenylacetylene selectively instead of cross-coupling products (eqn 55).[77]



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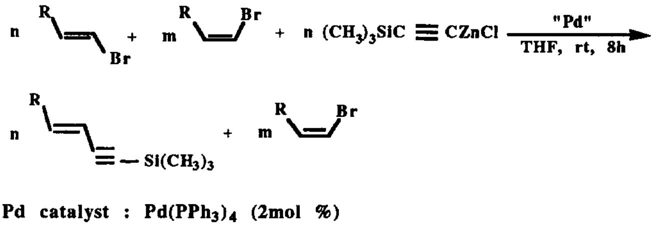
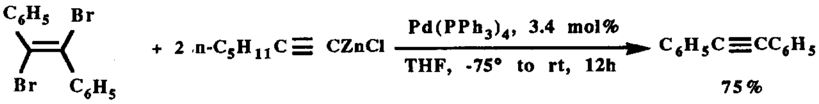


R	yield, %
n-C_3H_7	75
n-C_4H_9	77
n-C_5H_{11}	81

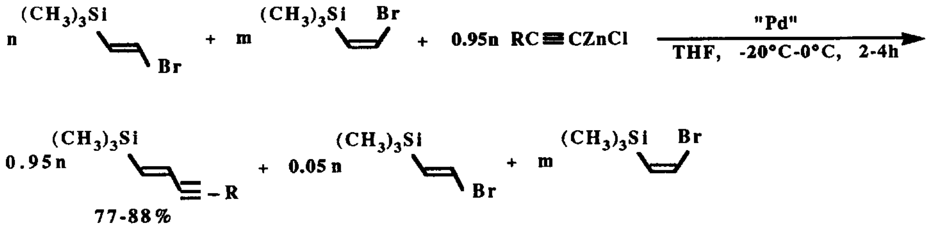
Scheme 44.



(55)

An explanation was offered for the stereoselectivity of these Pd-catalyzed alkynyl–alkenyl coupling reactions.[77] Organozinc chlorides were prepared by treatment of 1-alkynes with ethylmagnesium bromide and then transmetallation of Grignard reagents with zinc chloride.

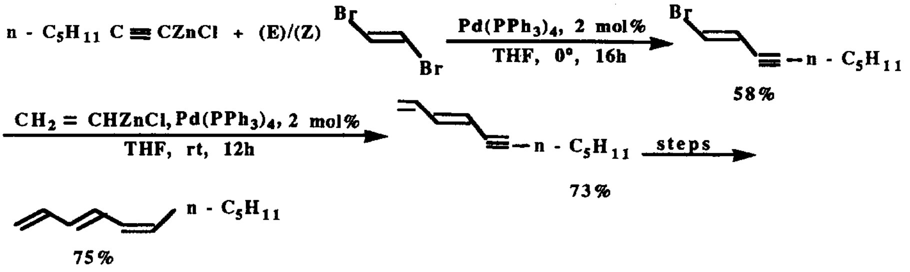
1-Alkynylzinc chlorides react with (*E*)-2-bromovinyltrimethylsilane in the presence of the corresponding (*Z*)-stereoisomer under Pd-catalysis affording (*E*)-1-trimethylsilyl-1-en-3-ynes in good yield with high stereoisomeric purity (Scheme 45).[79]



Pd catalyst : $Pd(PPh_3)_4$ (3mol %)
R : $(CH_3)_3Si$, $n\text{-}C_5H_{11}$, C_6H_5

Scheme 45.

The synthetic potential of the diastereoselective alkynyl–alkenyl coupling was indicated by using these reactions in highly stereo- and regio-selective syntheses of natural products. (3*E*,5*Z*)-1,3,5-Undecatriene with 98% stereoisomeric purity has been prepared by using Pd-catalyzed coupling of 1-heptynylzinc chloride with a molar excess of (*E*)/(*Z*)-1,2-dibromoethene as the key step (eqn 56).[80] Pd-Catalyzed coupling of trimethylsilylethynylzinc chloride with molar excesses of (*E*)/(*Z*)-1-alkenyl bromides has been used as a step for the synthesis of (3*E*,5*E*)- and (3*Z*,5*E*)-1,3,5-undecatriene (eqn 57).[80] These compounds occur together in the male attracting oils of seaweeds. They are used in perfumery.



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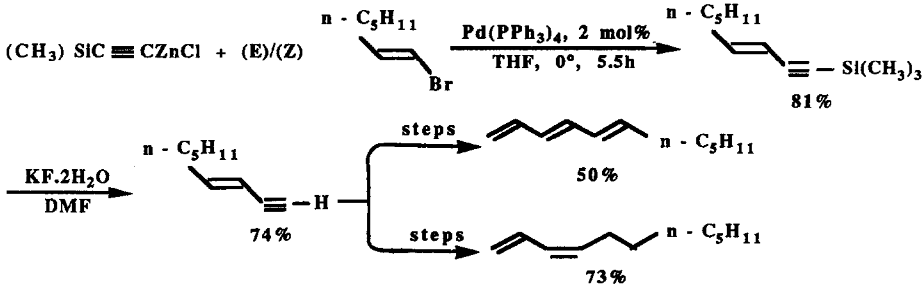
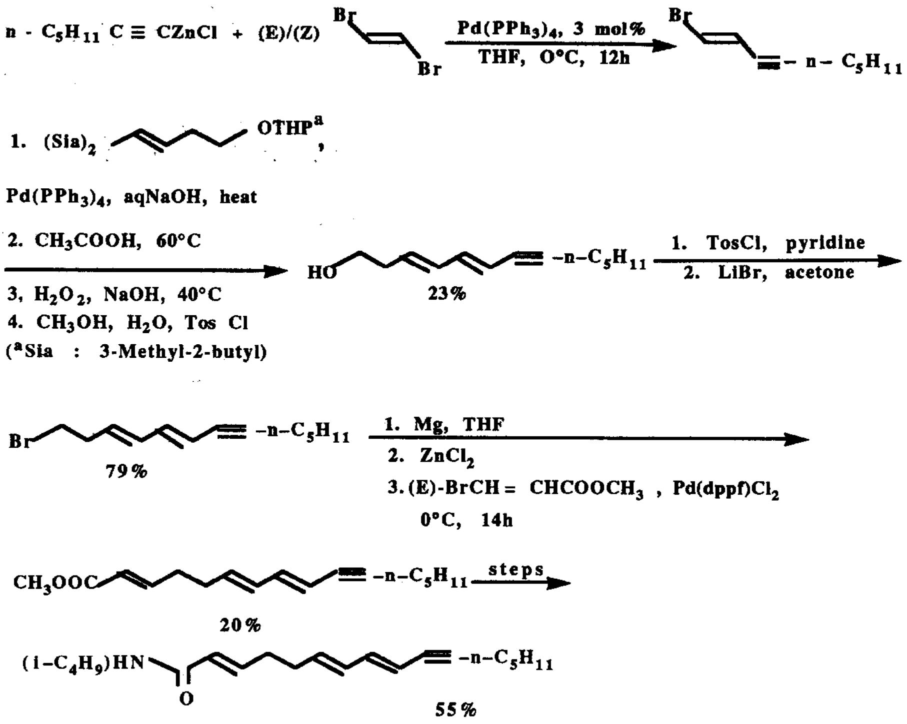


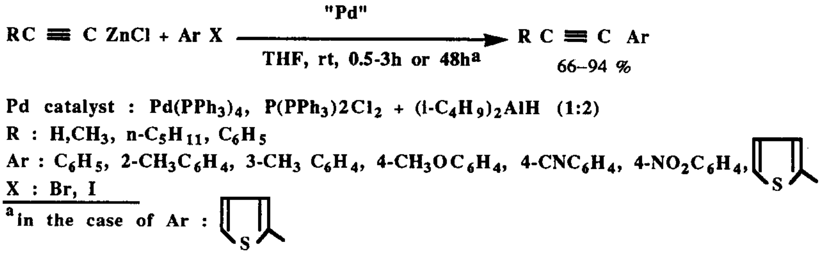
(57)

A naturally occurring acetylenic substance, (2*E*,6*E*,8*E*)-*N*-(2-methylpropyl)-2,6,8-hexadecatriene-10-ynamide has been synthesized by using alkynyl–alkenyl and homoallyl–alkenyl coupling reactions involving organozinc reagents in the presence of a Pd-catalyst (Scheme 46).[81]

Negishi and coworkers reported that alkynylzinc reagents also react with aryl halides producing



Scheme 46.



$$RC \equiv C\,ZnCl + Ar\,X \xrightarrow[\text{THF, rt, 0.5-3h or 48h}^{a}]{\text{"Pd"}} R\,C \equiv C\,Ar \quad 66\text{–}94\ \%$$

Pd catalyst : $Pd(PPh_3)_4$, $P(PPh_3)2Cl_2 + (i\text{-}C_4H_9)_2AlH$ (1:2)

R : H,CH_3, n-C_5H_{11}, C_6H_5

Ar : C_6H_5, 2-$CH_3C_6H_4$, 3-CH_3 C_6H_4, 4-$CH_3OC_6H_4$, 4-CNC_6H_4, 4-$NO_2C_6H_4$,

X : Br, I

[a] in the case of Ar :

Scheme 47.

cross-coupled products in the presence of a Ni- or Pd-catalyst (Scheme 47).[82] The procedure appears to be generally applicable to the direct synthesis of arylated ethenes. The use of $Ni(PPh_3)_4$ as a catalyst induced the desired cross-coupling reaction. However, the product yields were low and no complete consumption of aryl halides was observed. They also reported[83] that Pd-catalyzed coupling of 3,3-dimethyl-1-butynylzinc bromide with iodobenzene providing the coupled product in high yield (eqn 58). The use of organolithium reagent resulted in quite a low yield showing the marked dependence of the yield on the countercation of organometallic reagent partner.

$$t\text{-}C_4H_9C{\equiv}CM + C_6H_5M \xrightarrow[\text{THF, 22°C,3h or 24h}^{a}]{Pd(PPh_3)_4\ \text{(5mol \%)}} t\text{-}C_4H_9C{\equiv}C\ C_6H_5 \qquad (58)$$

---

[a] in the case of M : Li

M	yield, %
ZnCl	90
Li	10

$$RC\equiv C\,ZnCl + ArOSO_2R^1 \xrightarrow[\text{DMF - benzene, } 70-80^\circ C,\ 12-30h]{\text{"Pd"}} RC\equiv C\,Ar \quad 67-87\%$$

Pd catalyst : $Pd(PPh_3)_4$ (7.5-10 mol %)

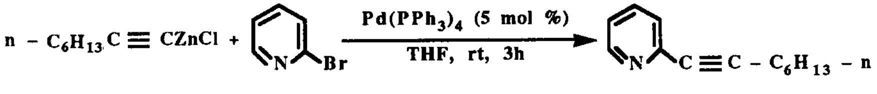
R : CH_3OCH_2, n-C_4H_9, C_6H_5

Ar : 2-ClC_6H_4, 4-ClC_6H_4, 3-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$ (R^1: $CHF_2OCF_2CF_2$); C_6H_5(R^1:CF_3)

Scheme 48.

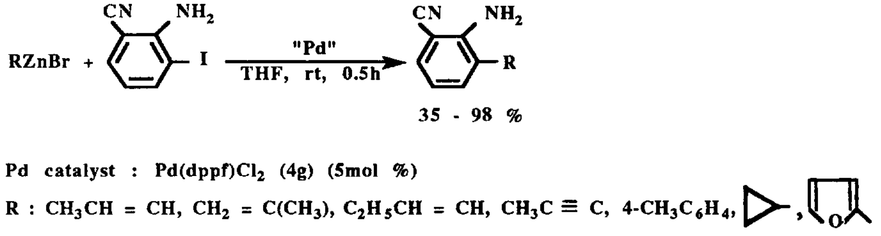
Alkynyl–aryl coupling was also accomplished by reacting alkynylzinc chlorides with aryl fluoroalkanesulfonates under Pd-catalysis (Scheme 48).[38]

Alkynyl–heteroaryl coupling was reported by Negishi and coworkers (eqn 59).[33]



(59)

Coupling of alkenyl, aryl and alkynyl zinc reagents with 3-iodo-2-aminobenzonitrile in the presence of a Pd-catalyst (Scheme 49) has been reported.[32]



Pd catalyst : $Pd(dppf)Cl_2$ (4g) (5mol %)

R : $CH_3CH = CH$, $CH_2 = C(CH_3)$, $C_2H_5CH = CH$, $CH_3C\equiv C$, 4-$CH_3C_6H_4$,

Scheme 49.

Coupling of alkenyl, aryl and alkynylzinc reagents with aryl or alkenyl iodides under Pd-catalysis was studied in detail by Negishi and coworkers (Scheme 50).[84] Pd-Catalysts were prepared by treating $Pd(PR_3)_2Cl_2$ with *n*-butyllithium in a 1 : 2 mole ratio. '$Pd(PR_3)_2$' Catalysis[17] gave the desired cross-coupled products in good to high yields. Regardless of R and R^1, the cross/homo ratios were uniformly high ($\geqslant 17$) in those cases where '$Pd(PPh_3)_2$' was used as a catalyst. On the other hand, when $Pd[P(C_2H_5)_3]_2$, $Pd[PPh(CH_3)_2]_2$ and $Pd[PPh_2(CH_3)]_2$ were used as catalysts, the cross/homo ratios were low (<5) in the alkenyl–alkenyl, alkenyl–aryl and aryl–aryl couplings, although it was high (46) in the alkynyl–aryl coupling. Organozinc reagents were prepared by reacting organolithium reagents with zinc chloride.

$$RZnCl + R^1I \xrightarrow[\text{THF, } 22^\circ C,\ 6min-12h]{\text{"Pd"}} RR^1 \quad 60-95\ \%$$

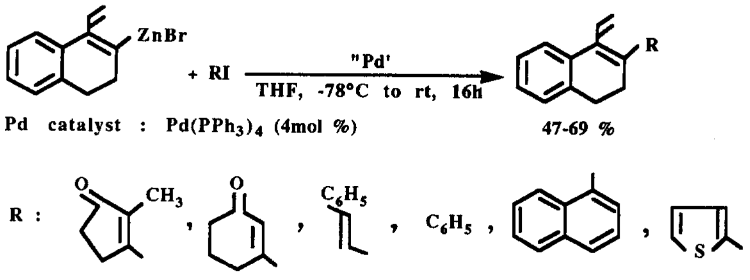
Pd catalyst : $Pd(PR_3)_2Cl_2$ + n-C_4H_9Li (1:2) (PR_3 : PPh_3, PPh_2CH_3, $PPh(CH_3)_2$, $P(C_2H_5)_3$)

R : (E)-n-$C_6H_{13}CH{=}CH$, C_6H_5, 4-$CH_3C_6H_4$, t-$C_4H_9C\equiv C$

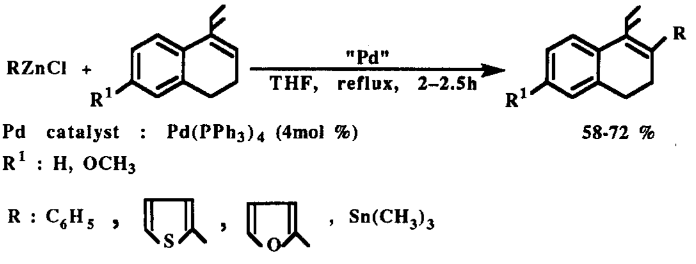
R^1 : (E)-n-$C_4H_9CH{=}CH$, (E)-n-$C_6H_{13}CH = CH$, C_6H_5

Scheme 50.

The synthesis of conjugated trienes was achieved by a simple and direct method which is based on Pd-catalyzed coupling of 1-ethenyl-3,4-dihydro-2-naphthylzinc bromide with aryl and alkenyl

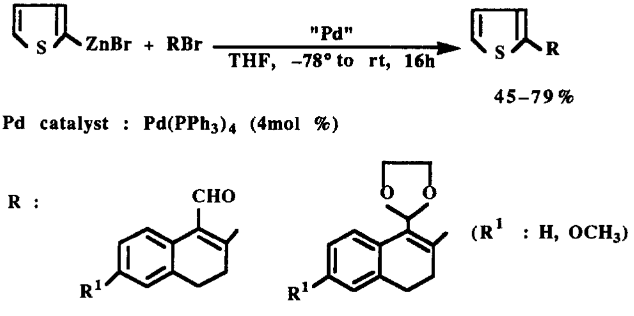


Scheme 51.



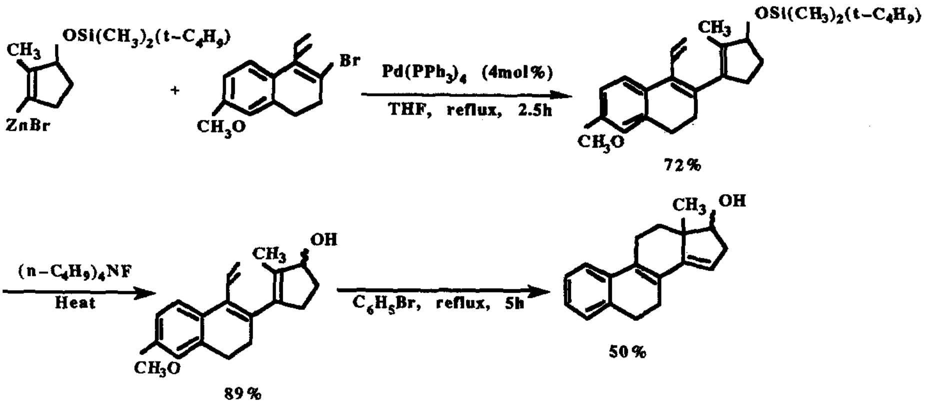
Scheme 52.

iodides (Scheme 51)[85] as reported by Gilchrist and coworkers. 1-Ethenyl-2-bromo-3,4-dihydronaphthalene was also coupled as the electrophilic component with several alkenyl- and aryl-zinc halides (Scheme 52).[85,86] The organozinc reagents were prepared by transmetallation of the corresponding organolithium reagents. The coupling reaction was also carried out with 2-bromo-3,4-dihydro-naphthalene-1-carbaldehyde, with its 6-methoxy derivative, and with their acetals (Scheme 53)[85,86] with 2-thienylzinc bromide. This inverse coupling procedure proved useful, because none of these compounds could be successfully coupled by way of their bromozincio derivatives.



Scheme 53.

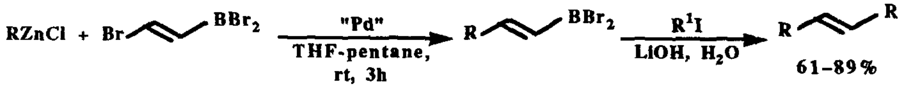
Electrocyclic ring closure of the products of the Pd-catalyzed coupling reactions was achieved by heating them in solution under nitrogen.[85–87] In the synthesis of aromatic steroids by Pd-catalyzed coupling and electrocyclic ring closure, the steroid nucleus was assembled using Pd-catalyzed alkenyl–alkenyl coupling (eqn 60).[87]



(60)

Suzuki and coworkers have investigated the coupling of various alkenyl, aryl and alkynylzinc reagents with (*E*)-(2-bromoethenyl)dibromoborane and with (*E*)-(2-bromoethenyl)diisopropoxyborane under Pd-catalysis followed by reaction with an organic halide (Scheme 54[35] and Scheme 55[36]). The reaction provides (*E*)-1,2-disubstituted ethenes. The use of an α-methoxyvinylzinc chlorides led to stereoselective synthesis of α,β-unsaturated ketones (Scheme 56).[88] Organozinc reagents were prepared by transmetallation of the corresponding Grignard reagents with zinc chloride. α-Methoxyvinylzinc chlorides were obtained by treatment of vinyl methyl ether with *t*-butyllithium and zinc chloride.

Pd-Catalyzed reactions of organozinc reagents with propargylic halides and esters[89–91] and with allenic halides[89,90,92,93] were investigated by Versmeer and coworkers. Coupling of organozincs with propargylic halides in the presence of a Pd-catalyst gives pure allenes (Scheme 57).[89,90] The stereochemistry of this synthetically useful reaction was investigated in both the steroid and non-steroid series.[91] $Pd(PPh_3)_4$ Catalyzed reaction of some esters derived from (*R*)-(−)-1-phenyl-2-

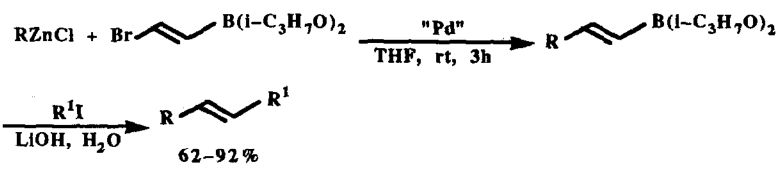


Pd catalyst : $Pd(PPh_3)_2Cl_2$ (5mol %)

R : $CH_2 = C(Si(CH_3)_3)$, C_6H_5, 2-$CH_3C_6H_4$, 2,3-(OCH_2O)-C_6H_3, n-C_6H_{13} $C \equiv C$

R1 : $C_6H_5CH_2$, (E)-n-$C_6H_{13}CH{=}CH$, (Z)-n-C_6H_{13} $CH{=}CH$, C_6H_5, 2-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$, 3,5-$(CH_3O)_2C_6H_3$,4-BrC_6H_4

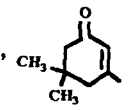
Scheme 54.



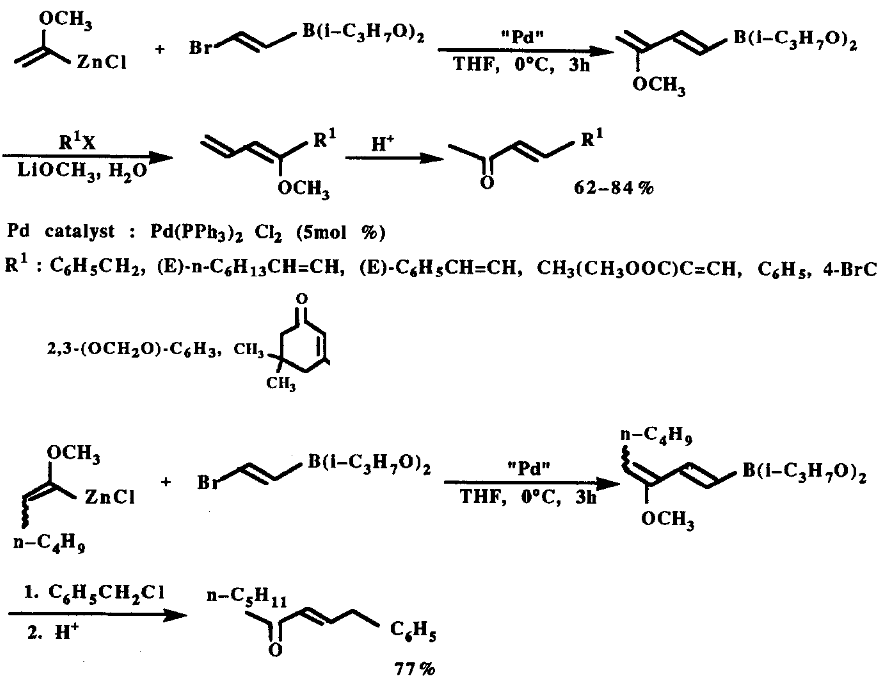
Pd catalyst : $Pd(PPh_3)_2Cl_2$ (5mol %)

R : CH_2 = $C(Si(CH_3)_3)$, CH_2 = CCH_3, CH_2 = C C_6H_5, (E)-n-$C_4H_9CH{=}CH$, $(CH_3)_2$ $C{=}CH$, C_6H_5, n-C_6H_{13} $C \equiv C$

R^1: $C_6H_5CH_2$, (E)-n-C_6H_{13} $CH{=}CH$, (Z)-n-$C_6H_{13}CH{=}CH$, C_6H_5,



Scheme 55.

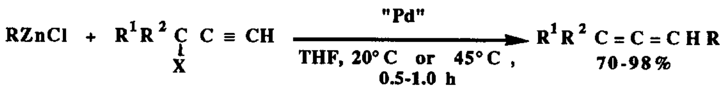


Pd catalyst : $Pd(PPh_3)_2Cl_2$ (5mol %)

R^1 : $C_6H_5CH_2$, (E)-n-$C_6H_{13}CH=CH$, (E)-$C_6H_5CH=CH$, $CH_3(CH_3OOC)C=CH$, C_6H_5, 4-BrC_6H_4,

2,3-(OCH_2O)-C_6H_3,

Scheme 56.



$$RZnCl + R^1R^2\underset{X}{C}\,C\equiv CH \xrightarrow[\text{THF, 20° C or 45° C, 0.5-1.0 h}]{\text{"Pd"}} R^1R^2C=C=CHR \quad 70\text{-}98\%$$

Pd catalyst : $Pd(PPh_3)_4$ (0.4-40 mol %)

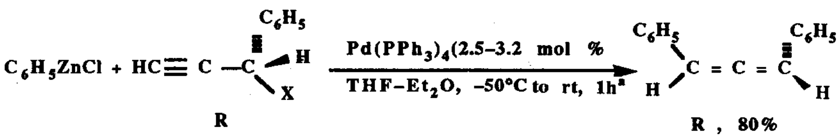
X : Br, $OCOCH_3$, $OSOCH_3$, OSO_2CH_3, $OPO(OC_2H_5)_2$

R : $CH_2=CH$, t-C_4H_9 $CH=C=CH$, $CH_2=C(CH_3)$-$C\equiv C$, $(CH_3)_2C=C=CH$, $HC\equiv C$, $C_6H_5C\equiv C$, $(CH_3)_3SiC\equiv C$, $HC\equiv CC\equiv C$, C_6H_5

R^1,R^2 : H,H; H;CH_3; H,t-C_4H_9; H,n-C_5H_{11}; CH_3,CH_3; CH_3, i-C_3H_7

Scheme 57.

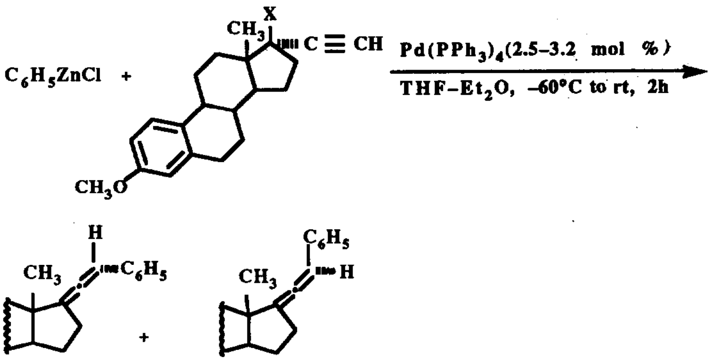
propyn-1-ol with phenylzinc chloride proceeded with antistereoselectivity to give the (*R*)-(−)-allene (eqn 61). In the steroid case, epimeric *anti-* and *syn*-products were obtained from $Pd(PPh_3)_4$ catalyzed reaction of some esters derived from mestranol with phenylzinc chloride (eqn 62).



(61)

X : $OCOCH_3$, $OCOCF_3$, $OSOCH_3$

a : With X : $OCOCH_3$



(62)

anti + syn

50-80% (combined yield)
(anti/syn : 98/2 - 84/16)

Coupling of organozincs with allenic halides in the presence of a Pd-catalyst also provides allenes (Scheme 58).[89,90] The use of an allenic acetate (R^1,R^2 = CH_3, X = $OCOCH_3$) in the reaction with trimethylsilylethynylzinc chloride resulted in a very low yield. Trimethylsilylethynylmetal compounds, $(CH_3)_3SiC{\equiv}CM$ (M = Li, MgCl, Zn, $Zn_{1/2}$, Cu, $Cu_{1/2}Li_{1/2}$, Ag, $Ag_{1/2}Li_{1/2}$) were reacted with propargylic halides, propargylic esters and allenic bromides[90] (Table 3). Organozinc compounds are very suitable for the preparation of allenes. Grignard reagents and copper and silver compounds also form allenes in high yields while lithio-derivatives give low yields.

The stereochemistry of the conversion of allenic halides into phenyl-substituted allenes with phenylzinc reagents in the presence of $Pd(PPh_3)_4$ as a catalyst has been established. The products are obtained with a moderate to high degree of inversion of configuration around the allenyl moiety when allenic chlorides and bromides are used (eqn 63).[92,93] The origin and type of phenylzinc reagent (diphenylzinc or phenylzinc chloride) and the amount of catalyst appeared to influence the stereochemistry. With allenic iodides, retention of configuration was observed.

$$RZnCl + R^1R^2C{=}C{=}CHX \xrightarrow[\text{THF, 20°C or 45°C, 0.5-2.0h}]{\text{"Pd"}} R^1R^2C{=}C{=}CHR$$

90-100 %

Pd catalyst : $Pd(PPh_3)_4$ (1.0-4.0 mol %)

X : Br, I,

R : $CH_2{=}CH$, $t\text{-}C_4H_9CH{=}C{=}CH$, $CH_2{=}C(CH_3)C\equiv C$, $(CH_3)_2C{=}C{=}CH$, $C_6H_5C\equiv C$, $(CH_3)_3SiC\equiv C$, $HC\equiv CC\equiv C$

R^1,R^2 : H,H;H,CH_3;H,C_6H_5; CH_3,CH_3

Scheme 58.

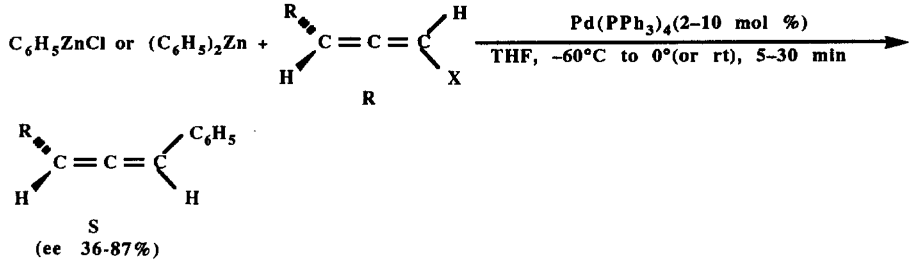
Coupling of allenic zinc reagents with aryl and vinylic iodides in the presence of a Pd-catalyst can be used to obtain cross-coupled products in almost quantitative yields (Scheme 59).[94] No coupling took place in the absence of a Pd-catalyst. The formation of substituted allenes was observed in the case of allenic Grignard reagents and cuprates but not with allenic lithiums. The reaction of the vinylic iodides proceeds with retention of configuration.

TABLE 3

Reaction of trimethylsilylethynylmetals ($(CH_3)_3SiC{\equiv}CM$) with various propargylic halides, esters and with an allenic bromide catalyzed by $Pd(PPh_3)_4$

M	yield, % with $(CH_3)_2C(X)=C=CH^a$					yield, % with
	X					
	Br	$OCOCH_3$	$OSOCH_3$	OSO_2CH_3	$OPO(OC_2H)_2$	$(CH_3)_2C=C=CHBr^b$
Li	0	0	—	—	20	3
MgCl	70	75	90	—	98	80
ZnCl	98	—	—	—	—	100
$Zn_{1/2}$	—	98	—	—	98	—
Cu	—	98^c	98^d	—	—	33
$Cu_{1/2}\ Li_{1/2}$	—	98	98	—	—	$100^{e,f}$
Ag	98	86	<5	30	80	23
$Ag_{1/2}\ Li_{1/2}$	98	90	—	98	—	—

[a] Reaction conditions are given in Scheme 57.
[b] Reaction conditions are given in Scheme 58.
[c] Without the Pd-catalyst, 72%.
[d] Without the Pd-catalyst.
[e] Without the Pd-catalyst, 0%.
[f] Both $(CH_3)_3SiC{\equiv}C$ groups are transferred.



(63)

X : Cl, Br
R : C_6H_5, t-C_4H_9

[a] : With R : t-C_4H_9

Chiral induction in the synthesis of 1-phenyl-3-*t*-butylallene by a Pd-catalyzed cross-coupling reaction between either allenic zinc chloride and iodobenzene (Route A) or phenylzinc chloride and allenic bromide (Route B) has also been investigated by Boersma and coworkers using chiral phosphine complexes of Pd (Scheme 60).[95] High enantiomeric excess (25%) was obtained by Route A with catalysis by Pd[(*R*,*R*)-diop]Cl_2 **4j**. The enantiomeric excess (19%) when Pd[(*R*,*R*)-diop]$_2$ **2j** was used appeared to be independent of the temperature, the amount of the catalyst and the ratio of the reagents.

$$R^1R^2C{=}C{=}CHZnCl + RI \xrightarrow[\text{THF or THF-HMPA, 25-50°C, 1-4h}]{\text{"Pd"}} \underset{>98\ \%}{R^1R^2C=C=CHR}$$

Pd catalyst : $Pd(PPh_3)_4$ (2mol %)
R^1R^2 : H,H; CH_3,CH_3; t-C_4H_9,H
R: C_6H_5, 4-ClC_6H_4, 4-$NO_2C_6H_4$, (Z)-n-C_4H_9 CH=CH, (E)-n-C_4H_9 CH=CH, (Z)-t-C_4H_9CH=CH

Scheme 59.

Route A

$$t\text{-}C_4H_9CH{=}CHZnCl + C_6H_5I \xrightarrow[\text{THF, 20°C, 1-42h, } 50°C^{a}\text{, } 24h^{a}]{\text{"Pd"}} t\text{-}C_4H_9CH{=}C{=}CHC_6H_5$$

S (R^{b})33-100 %
(ee 5-25 %)

---

[a] in the case of Pd[S,S -chiraphos] (2i)
[b] in the case of Pd[S,R)bppfa]Cl_2 (4m)

catalyst, 0.4-2.0mol%	ee, %	catalyst, 0.4-2.0mol%	ee, %
$Pd(PPh_3)_4$ 2(a)	—	$Pd(nmdpp)_2Cl_2$ (4h)	19
Pd[(R,R)-diop]$_2$ (2j)	21	Pd[S,R)-bppfa]Cl_2 (4m)	21
Pd[R,R)-diop]Cl_2 (4j)	25	Pd[(R,S)-ppfa]Cl_2 (4l)	5
Pd(PhI)[(R,R)-diop]	25	Pd[(S)-binap]Cl_2(4k)	6
		Pd[(S,S)-chiraphos] (2i)	5

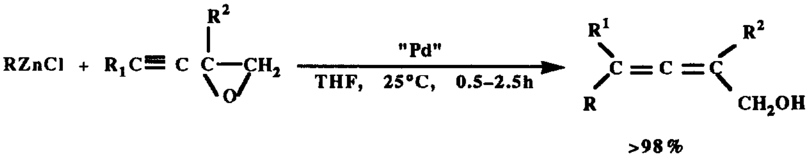
Route B

$$C_6H_5ZnCl + t\text{-}C_4H_9CH{=}C{=}CHBr \xrightarrow[\text{THF, 20°C}]{\text{Pd[(R,R)-diop]}_2\text{(1.0 mol \%)}} t\text{-}C_4H_9CH{=}C{=}CHC_6H_5$$

S, 100 %
(ee 3-9 %)

Scheme 60.

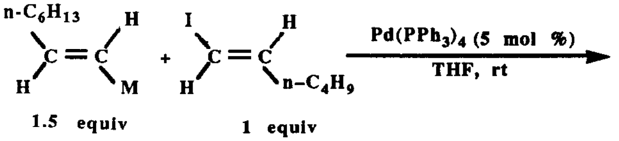
Vermeer and coworkers also converted α-acetylenic epoxides into α-allenic alcohols by means of a Pd-catalyzed reaction with organozinc compounds (Scheme 61).[96] Coupling took place with organocuprates, but not with Grignard reagents and organolithiums. No reaction was observed in the absence of a Pd-catalyst.



Pd catalyst : $Pd(PPh_3)_4$ (2mol %)
R : $(CH_3)_3SiC≡C$, $(CH_3)_3SiC≡CC≡C$, $H_2C{=}CH$, $t\text{-}C_4H_9CH{=}C{=}CH$
R^1 : H,CH_3 R^2 : H,CH_3

Scheme 61.

Negishi and coworkers explored the scope of the Pd- or Ni-catalyzed cross-coupling with respect to metals in the organometallic reagents.[97] They chose the Pd-catalyzed reaction of (*E*)-1-octenylmetals containing various metals with (*E*)-1-hexenyl iodide by using $Pd(PPh_3)_4$ as catalyst (eqn 64). (*E*)-1-Alkenylmetals containing Zn, Cd, Al and Zr give the desired cross-coupled products in ⩾70% yield within 1–6 h at room temperature while Li, Mg, Hg, B, Si, Sn, Ti and Ce do not (Table 4). Although the yield of the desired cross-coupled product observed with Cd is satisfactory, significant amounts of homocoupled products were formed.



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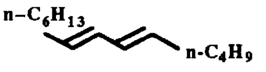
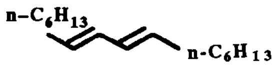
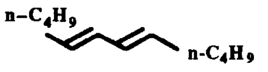


A



B



C

TABLE 4

Reaction of (E) -1- octenylmetals with (E) -1- hexenyl iodide catalyzed by $Pd(PPh_3)_4$

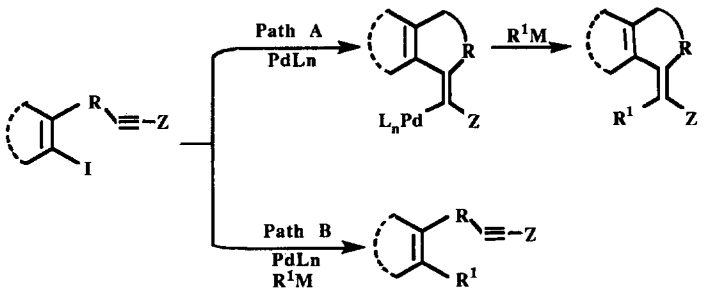
M	reaction time, h	unreacted iodide, %	yield of dienes, % A	B	C
Li	1	0	40	25	16
MgCl	1	46	32	7	8
ZnCl	1	trace	95	3	3
CdCl	1	trace	86	17	8
Hg	1	57	40	80	3
$B(Sia)_2$	1	69	65	5	1
$Al(i\text{-}C_4H_9)_2$	6	3	75	7	6
$Si(CH_3)_3$	3	100	0	0	0
$Sn(i\text{-}C_4H_9)_2$	3	66	2	trace	4
$TiCp_2$	1	73	trace	21	0
$ZrCp_2Cl$	1	7	93	trace	trace
$CeCl_2$	1	0	42	33	26

[a] Sia : 3- Methyl - 2- butyl

[b] Cp : cyclopentadienyl

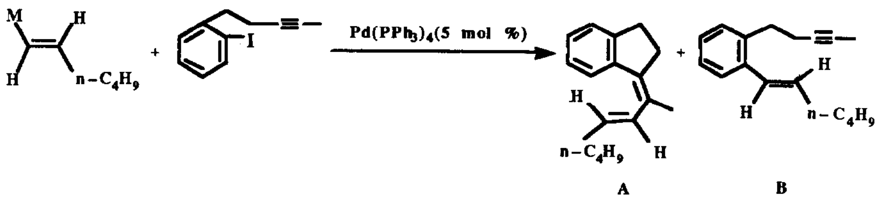
On the basis of the above survey of metals in alkenylmetals, Zn, Zr and Al were selected as three highly satisfactory metals for the Pd-catalyzed cross-coupling reactions of alkenylmetals. To compare their relative reactivity and efficiency, the catalytic turnover number was determined for these three metals in the reactions of (*E*)-1-octenylmetals with phenyl iodide in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF at room temperature. The turnover numbers [mmol iodobenzene consumed or (*E*)-1-octenylbenzene formed per mmol $Pd(PPh_3)_4$ per hour] were 2(Al), 3(Zr) and at least 2000(Zn). Specifically, the reaction of (*E*)-1-octenylzinc chloride (1.5 equiv.) with iodobenzene in THF with 0.05 mol% $Pd(PPh_3)_4$ was complete in 1 h at room temperature and produced (*E*)-1-octenylbenzene in quantitative yield. The turnover numbers for Al and Zr at 50°C were 25 and 30, respectively. These results clearly indicate that the alkenylzinc reagent is far more efficient than those containing Al or Zr.

In their recent work, they reported that organozincs under Pd-catalysis might actually be unsuitable reagents for achieving cross-coupling via carbopalladiation (Path A) due to direct cross-coupling (Path B) (eqn 65).[98]



(65)

They have chosen Pd-catalyzed reactions of alkenyl, aryl and alkynylmetals containing Li, Mg, Zn, B, Al, Sn, Zr and Cu with *o*-iodo-(3-alkynyl)benzenes (eqns 66 and 67), with *o*-iodo-(4-alkynyl)benzenes (eqn 68) and with ω-(*Z*-β-iodoalkenyl)alkynes (eqn 69) as test systems to investigate the effectiveness of these metals in cyclic carbopalladiation–cross-coupling. Zr seems to be the most effective metal for introducing an alkenyl group but not for introducing aryl or alkynyl groups. Sn is effective for incorporating alkenyl or alkynyl groups but not aryl groups. Al seems the most effective for the cyclization–arylation reaction. Stereoselectivity in each case was 98%. In Table 5–8, A and B refer to coupling products formed via carbopalladiation and direct coupling, respectively.



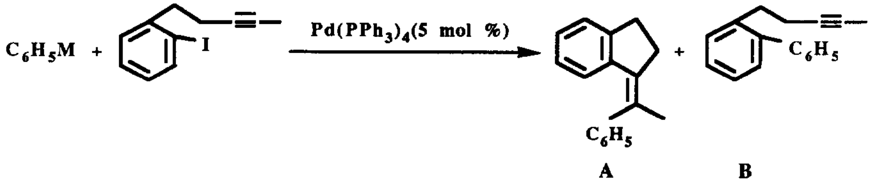
(66)

TABLE 5

Reaction of (E) -1- hexenylmetals with o- iodo- (3-pentynyl) benzene catalyzed by $Pd(PPh_3)_4$

M	reaction conditions	yield, %	
		A	B
ZnCl	THF, rt	19	68
$ZrCp_2Cl$[a]	THF, reflux	84	≤3
$Sn(CH_3)_3$	THF-HMPA, reflux	69	≤2
$Al(i\text{-}C_4H_9)_2$	THF, reflux	57	32
$BO_2C_6H_4$	benzene reflux	41	≤4
Li	THF, rt	trace	trace
MgI	THF, reflux	trace	trace

[a] Cp: cyclopentadienyl

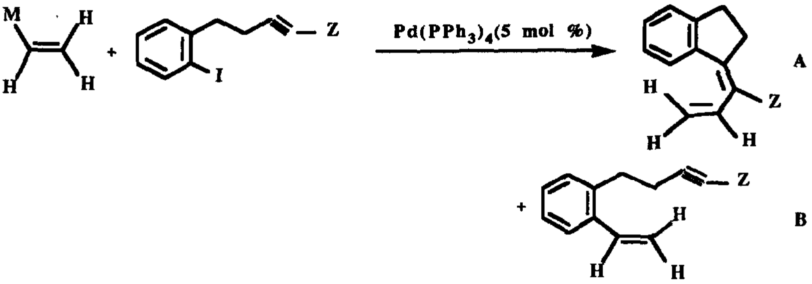


(67)

TABLE 6

Reaction of phenylmetals with o- iodo- (3-pentynyl)-benzene catalyzed by $Pd(PPh_3)_4$

M	reaction conditions	yield, %	
		A	B
ZnCl	THF, rt	34	57
$Al(C_6H_5)_2$	benzene, reflux	93	<2
$Al(CH_3)_2$	THF, reflux	40	5
$Sn(n\text{-}C_4H_9)_3$	THF-HMPA, reflux	trace	trace

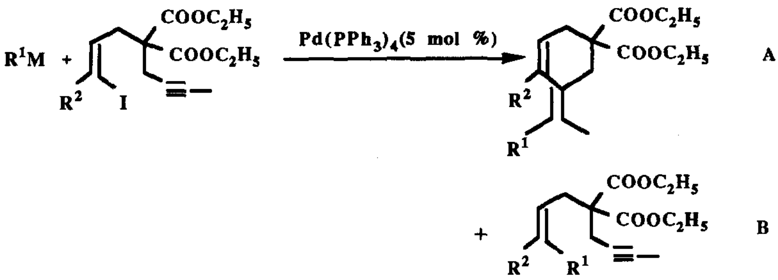


(68)

TABLE 7

Reaction of vinymetals with o- iodo- (3-alkynyl) benzene catalyzed by Pd(PPh$_3$)$_4$

Z	M	reaction conditions	yield, % A	B
CH_3	ZnCl	THF, rt	trace	63
n-C_4H_9	Sn(n-C_4H_9)$_3$	THF-HMPA, reflux	89	<5



(69)

TABLE 8

Reaction of alkynyl and alkenylmetals with w- iodo- (Z-β-iodo-alkenyl) alkynes catalyzed by Pd(PPh$_3$)$_4$

R^2	R^1M	reaction conditions	yield, % A	B
n-C_4H_9	(n-$C_4H_9C{\equiv}C)_2Zn$	THF, rt	8	75
"	n-$C_4H_9C{\equiv}CSn(CH_3)_3$	THF-HMPA, reflux	73	5
"	n-$C_4H_9C{\equiv}C(n\text{-}C_4H_9)_3Li$	THF, rt	45	a
"	n-$C_4H_9C{\equiv}CH$ + CuI(5%) n-$C_4H_9NH_2$ (5 equiv)	benzene, rt	16	49
"	[(E)-n-$C_4H_9CH{\equiv}CH]_2Zn$	THF, rt[a]	trace	50
n-C_3H_7	[(E)-n-$C_4H_9CH{\equiv}CH]ZrCp_2Cl$[b]	THF,reflux	85	a

[a] not determined

[b] Cp: cyclopentadienyl

A list of organozinc reagents cross-coupled with various organic halides under Pd- or Ni-catalysis will be given after discussing their related reactions with acyl halides in Section 2.4.

2.4. *Coupling with acyl halides*

Organozinc reagents react with acyl chlorides to provide ketones. The Pd-catalyzed reactions give higher yields and selectivities than uncatalyzed reactions. Acylation of organozinc reagents under Pd-catalysis appears to be a highly general cross-coupling reaction. Related investigations are summarized below.

The reactions of organozinc reagents with acyl chlorides catalyzed by Pd-complexes, provides a highly general route to ketones as reported by Negishi and coworkers,[99] by Grey,[100] by Fujisawa and coworkers[101] and by Yoshida and coworkers.[102] Negishi and coworkers[99] prepared the organozinc reagents by treating the corresponding organolithium reagents with zinc chloride (Scheme 62). The uncatalyzed reaction of organozinc chlorides with acyl chlorides did not give the desired ketones satisfactorily (yields <10%). For the acylation reactions of alkenylzinc reagents, a Pd-catalyst generated *in situ* from $Pd(PPh_3)_2Cl_2$ and $(i\text{-}C_4H_9)_2AlH$ (1 : 2) was found to be superior to $Pd(PPh_3)_4$ in relation to product yield. In the preparation of alkenyl ketones via alkenylzinc reagents or α,β-unsaturated acyl chlorides, the stereospecificity was found >98%. The Pd-catalyzed acylation of organozincs proceeds rapidly in solvents containing THF. The corresponding reaction in Et_2O was much more sluggish.

$$\mathrm{RZnCl} + \mathrm{R^1COCl} \xrightarrow[\mathrm{THF,rt,6h}]{\text{"Pd"}} \underset{52\text{-}92\%}{\mathrm{RCOR^1}}$$

Pd catalyst : Pd $(PPh_3)_4$ (1,2.5 or 5 mol %), $Pd(PPh_3)_2Cl_2$ + $(i\text{-}C_4H_9)_2AlH$ (1:2) (1 or 5mol %)

R : $n\text{-}C_4H_9$, $n\text{-}C_8H_7$, (E)-$n\text{-}C_4H_9CH{=}CH$, (E)-$n\text{-}C_5H_{11}CH{=}CH$, (E)-$n\text{-}C_6H_{13}CH{=}CH$, (E)-n- $C_6H_{13}(CH_3)C{\equiv}CH$, $n\text{-}C_5H_{11}C \equiv CH$, $n\text{-}C_6H_{13}C \equiv CH$, $C_6H_5CH_2$, C_6H_5, $2\text{-}CH_3C_6H_4$, $4\text{-}ClC_6H_4$

R^1 : CH_3, $CH_2{=}CH$, (E)-$CH_3CH{=}CH$, CH_3O, C_6H_5

Scheme 62.

Grey[100] prepared the organozinc reagents by treating Grignard reagents with zinc chloride. The reaction with acyl chlorides (Scheme 63) led to a high yield synthesis of ketones. However, reactions involving aromatic acyl chlorides formed the corresponding aryl halide as a significant by-product. By either using Et_2O as the sole solvent or by $Pd(dppf)Cl_2$ as the catalyst, the by-product was minimized. $Pd(PPh_3)_4$, although less active than $Pd(PhCH_2)(PPh_3)_2Cl$ was also an effective catalyst for this ketone synthesis.

$$\mathrm{R_2Zn} + \mathrm{R^1COCl} \xrightarrow[\substack{\mathrm{THF\text{-}Et_2O\ or\ Et_2O,} \\ 0^\circ,\ \mathrm{0.5h\ and\ rt,1h}}]{\text{"Pd"}} \underset{75\text{-}98\%}{\mathrm{RCOR^1}}$$

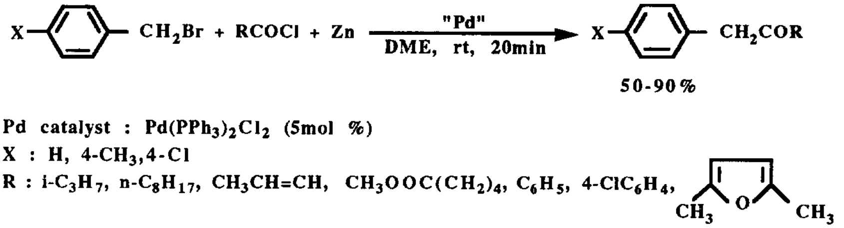
Pd catalyst : $Pd(PhCH_2)(PPh_3)_2Cl$ (0.5mol %)

R : $n\text{-}C_3H_7$, $i\text{-}C_3H_7$, $n\text{-}C_4H_9$, C_6H_5

R^1: CH_3, $n\text{-}C_3H_7$, C_6H_5, $4\text{-}ClCOC_6H_4$

Scheme 63.

Fujisawa and coworkers[101] succeeded in the similar coupling reaction preparing benzyl ketones in good yields directly from benzyl bromide and acyl chlorides by the combined use of Zn and a Pd-



Pd catalyst : $Pd(PPh_3)_2Cl_2$ (5mol %)
X : H, 4-CH_3,4-Cl
R : i-C_3H_7, n-C_8H_{17}, $CH_3CH{=}CH$, $CH_3OOC(CH_2)_4$, C_6H_5, 4-ClC_6H_4,

Scheme 64.

catalyst under mild conditions (Scheme 64). In this reaction, the molar ratio of benzyl bromide/acyl chloride/Zn was 1 : 1 : 2. Replacement of benzyl bromide with benzyl chloride or methyl iodide resulted in lower yields. The presence of a Pd-catalyst was essential for the reaction. $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ were superior to $Pd(PhCN)_2Cl_2$, $Pd(CH_3COO)_2$, $PdCl_2$ and $Ni(PPh_3)_2Cl_2$. The use of these catalysts produced considerable amounts of bibenzyl, the homocoupling product of benzyl bromide. The reaction was influenced markedly by the solvents and DME was found to be the best solvent. Aromatic, heteroaromatic and linear aliphatic acyl chlorides gave the corresponding ketones in >80% yields. However, a branched aliphatic acyl chloride (R = *t*-C_4H_9) did not give the ketone. Functional groups such as α,β-unsaturated double bond, ester and aryl halogen were tolerated, but the reaction of oxalyl chloride gave the ketone (34% yield). *p*-Chloro and *p*-methyl substituents in benzyl bromide did not affect the yield but the presence of *p*-methoxy and *p*-nitro substituents led to poor yields (10%). The reaction of phenethyl bromide with nonanoyl chloride gave the ketone (55% yield).

Yoshida and coworkers[102] reported that alkylzinc iodides with a wide structural variety can be prepared in good yields by the direct reaction with alkyl iodides and Zn–Cu couple in benzene containing a small amount of DMF. They give ketones in high yield by the Pd-catalyzed coupling with acyl chlorides (Scheme 65). Organozinc iodides were unreactive toward acyl chlorides without Pd-catalyst. With respect to organozincs, both primary and secondary alkylzincs and organozincs functionalized with double or triple bonds were prepared quantitatively and coupled with acyl chlorides to offer the ketones in high yields. With respect to acyl chlorides, saturated, unsaturated and aromatic acyl chlorides gave satisfactory results. Ketones prepared from acyl chlorides with electron withdrawing substituents at the α-position did not react further with organozincs. No condensations or other side reactions for ketones with highly enolizable protons, or Michael additions with α,β-unsaturated ketones took place.

Fluorovinylzinc reagents used by Sauvetre and coworkers[24,49,50,57–59] in the Pd-catalyzed coupling with alkenyl and aryl halides were reported to couple with acyl halides and ethyl chloroformate (Scheme 66[57,58] and eqn 70[57,58]).

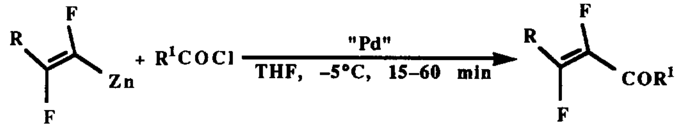
$$RZnI + R^1COCl \xrightarrow[\text{Benzene-DMF, rt,0.5h}]{\text{"Pd"}} \underset{66\text{-}100\ \%}{RCOR^1}$$

Pd catalyst : $Pd(PPh_3)_4$ (4mol %)

R : CH_3, n-C_3H_7, i-C_3H_7, n-C_8H_{17}, n-$C_{12}H_{25}$,c-C_6H_{11},$Cl(CH_2)_4$, $C_2H_5C{\equiv}C(CH_2)_2$,
$CH_2{=}CHCH_2CH(CH_3)$

R^1 : C_2H_5,$CH(CH_3)Cl$, n-C_2H_{15},$C_6H_5CH_2$,$CH_2{=}CH$,$CH_3CH{=}CH$,$CH_2{=}C(CH_3)$,
C_6H_5 $CH{=}CH$,C_6H_5, 2-$CH_3C_6H_4$,4-$CH_3OC_6H_4$,4-ClC_4H_4,4-$NO_2C_6H_4$

Scheme 65.



30–86%

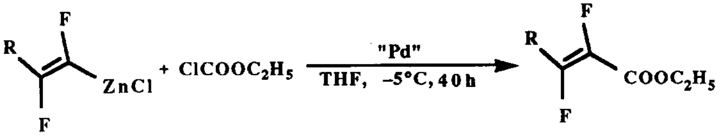
Pd catalyst : $Pd(PPh_3)_4$ (3mol %)

R : $n\text{-}C_4H_9$, $sec\text{-}C_4H_9$,$n\text{-}C_7H_{15}$,C_6H_5

R^1 : CH_3, $i\text{-}C_3H_7$, $CH_3CH{=}CH$, $(CH_3)_2C{=}CH$, $C_2H_5CF{=}CH$, $(CH_3)_2C{=}CF$,

$s\text{-}C_4H_9CF{=}CF$, C_6H_5, 

Scheme 66.



(70)

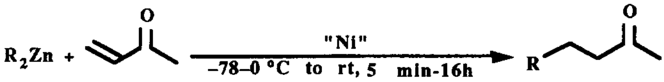
R	yield, %
$s\text{-}C_4H_9$	73
C_6H_5	57

The information given in Section 2 is summarized in Table 9.

3. TRANSITION METAL CATALYZED ADDITION OF ORGANOZINC REAGENTS

Ni-Catalyzed conjugate additions of organozinc reagents to α,β-unsaturated carbonyl compounds have been investigated in detail.[103–113] Additions of organozinc reagents to double bonds[114] and triple bonds[115] under Ni- and Cu-catalysis, respectively, have also been reported.

Luche and coworkers reported[103–107] efficient and rapid preparation of organozinc reagents by sonication from organic halides, lithium and zinc halide and their clean and selective conjugate addition to α,β-unsaturated ketones and aldehydes in the presence of catalytic amounts of nickel acetylacetonate [$Ni(acac)_2$]. Sonication of alkyl, benzyl, alkenyl or aryl halides, metallic lithium and zinc bromide (molar ratio 1 : 2.1 : 0.5) in Et_2O, THF or toluene–THF mixtures produced the organozinc compounds almost quantitatively within 20–40 min.[3,107] The reagents prepared by this method are diorganozincs which transfer only one organic group. Their addition to α,β-unsaturated ketones (Scheme 67)[103,105,107] and aldehydes (Scheme 68)[103,106,107] in the presence of $Ni(acac)_2$

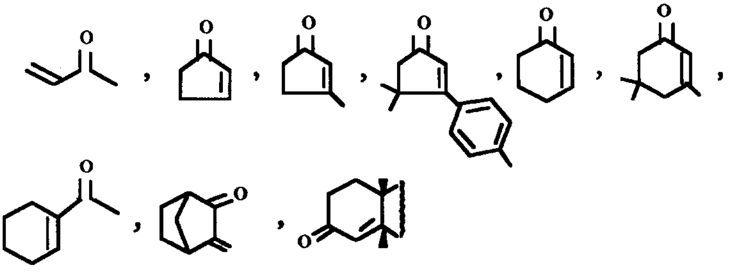


42–90%

Ni catalyst : $Ni(acac)_2$ (1mol %)

R : CH_3,$t\text{-}C_4H_9$,$n\text{-}C_7H_{15}$, $C_6H_5CH_2$,(E)-$CH_3CH{=}CH$,$(CH_3)_2C{=}CH$, $2\text{-}CH_3C_6H_4$, $4\text{-}CH_3C_6H_4$

α, β-enone :



Scheme 67.

TABLE 9

Transition metal catalyzed coupling reactions of organozinc reagent with organic halides and acyl halides

R of RZnX	alkyl	homoallylic	homobenzylic	homo-propargylic	allyic	benzylic
alkyl					scheme 1[19], scheme 2[20]	
homo-allylic						
homo-benzylic						
homo-propargylic						
allyic					eq 22[19]	
benzylic						
propargylic						
alkenyl						scheme 22[53]
aryl	scheme 15[42], scheme 16[43]				scheme 17[47], scheme 37[69], eq 27[44],eq 28[45]	scheme 37[69], eq 30[41]
alkenyl						

[a] X : Cl, Br, I

[b] Y : Cl, Br, I, $OCOCH_3$, OSO_2CF_3

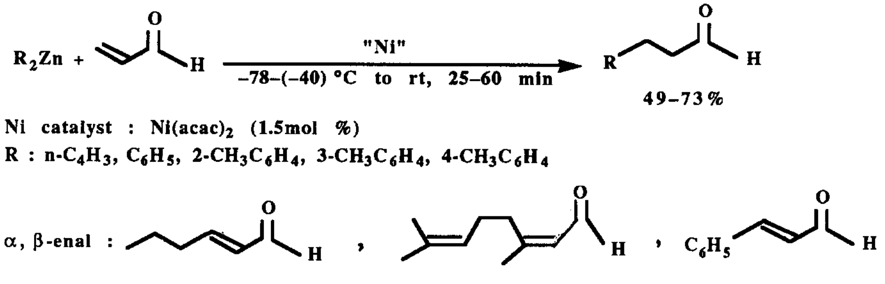
[c] Transition metal catalysts 1-7 with ligands, L, a-m (TABLE 1) were used.

Table 9—*continued*

$$\mathrm{RZnX}^{a} + \mathrm{R}^1\mathrm{Y}^{b} \xrightarrow{\text{catalyst}^{c}} \mathrm{RR}^1 + \mathrm{ZnXY}$$

R^1 of $\mathrm{R}^1\mathrm{Y}$

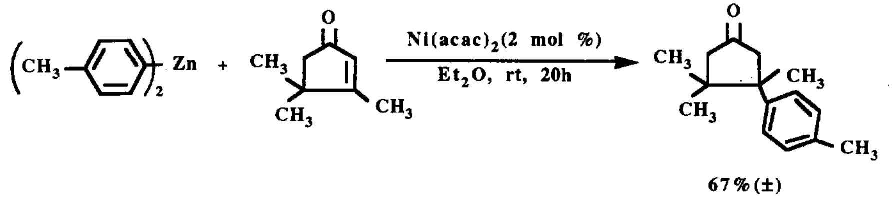
propargylic	alkenyl	aryl	alkynyl	acyl
	scheme 3[21], scheme 10[20], eq9[23], eq10[24],eq20[35],eq21[36]	scheme 7[29,30], scheme 8[31], scheme 9[34], scheme 10[20], eq18[32], eq19[33]		scheme 62[99], scheme 63[100], scheme 65[102]
	scheme 3[21], scheme 46[81], eq6[22], eq7[22],eq8[22],eq11[25], eq13[27]	eq16[28]		scheme 65[102]
	eq15[28]	eq14[28]		
	scheme 3[21]	eq17[28]		scheme 65[102]
	eq26[36]			
	scheme 6[25],eq11[25]	scheme 13[39,40], scheme14[41]	scheme 11[37], scheme 12[38], eq25[41]	scheme 62[99], scheme 64[101]
scheme 57[89,90] scheme 61[96]	scheme 18[48],scheme 19[51], scheme 20[51],scheme 21[53], scheme 22[53],scheme 29[49,56], scheme 30[49,50],scheme 50[84], scheme 51[85],scheme 52[85,86], scheme 53[85,86],scheme 54[35], scheme 55[36],scheme 56[88], scheme 57[89,90],scheme 58[89,90], scheme 59[94],scheme 60[95], eq39[60],eq51[4],eq64[97],eq69[98]	scheme 18[48],scheme 19[51], scheme 20[51],scheme 21[53], scheme 22[53],scheme 23[53], scheme 24[53],scheme 25[53], scheme 26[54],scheme 27[55], scheme 28[56],scheme 31[58,59], scheme 50[84],scheme 51[85], scheme 52[85,86], scheme 59[94] scheme 60[95], eq41[62,63], eq42[63],eq43[64],eq66[98],eq68[98]		scheme 66[57,58] scheme 62[99]
scheme 57[89,90], scheme 61[96], eq34[42]	scheme 34[33],scheme 38[71] scheme 39[72],scheme 40[73] scheme 53[85,86],scheme 54[35] scheme 56[88],scheme 57[89,90] scheme 58[89,90],scheme 60[95] eq34[52]	scheme 32[31],scheme33[37,65], scheme 34[33],scheme 35[66], scheme 36[67],scheme 37[69], scheme 49[32],scheme 50[84], scheme 52[85,86],eq48[69,70], eq49[70], eq50[4], eq67[98]		scheme 62[99], scheme 63[100]
scheme 57[89,90] scheme 61[96]	scheme 41[74],scheme 42[75], scheme 43[76,77],scheme 44[78], scheme 45[79],scheme 46[81], scheme 54[35],scheme 55[36], scheme 58[89,90],eq52[75], eq53[24], eq54[78], eq56[80], eq57[80], eq69[98]	scheme 24[52],scheme 47[82], scheme 48[33],scheme 49[32], scheme 50[84], eq58[83], eq59[33],		scheme 62[99]



Scheme 68.

occurs under mild conditions in preparative yields. In the absence of Ni(acac)$_2$, the conjugate addition proceeds at a much reduced rate or sometimes does not occur. Conjugate addition of di(cyclohexyl)zinc to 2-cyclopentenone gave a lower yield (29%). Side reactions can occur in some cases. Coupling of the reagent can be observed for diarylzincs. Reduction of the double bond with organozincs possessing *β*-hydrogens to the metal can take place. Ni(acac)$_2$ Catalyzed conjugate addition gave racemic products.

Luche and coworkers also illustrated the largely unrecognized potency of organozinc reagents in conjugate addition by describing two straightforward and efficient syntheses of *β*-cuparenone (eqns 71 and 72).[104] The starting enones were resistant to several Cu-catalyzed conjugate addition



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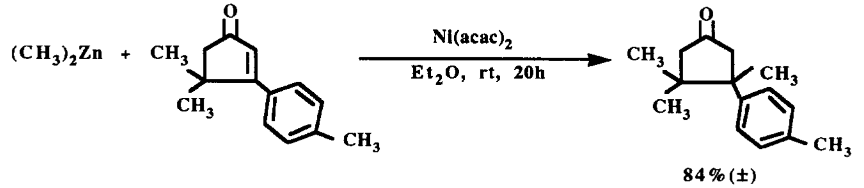
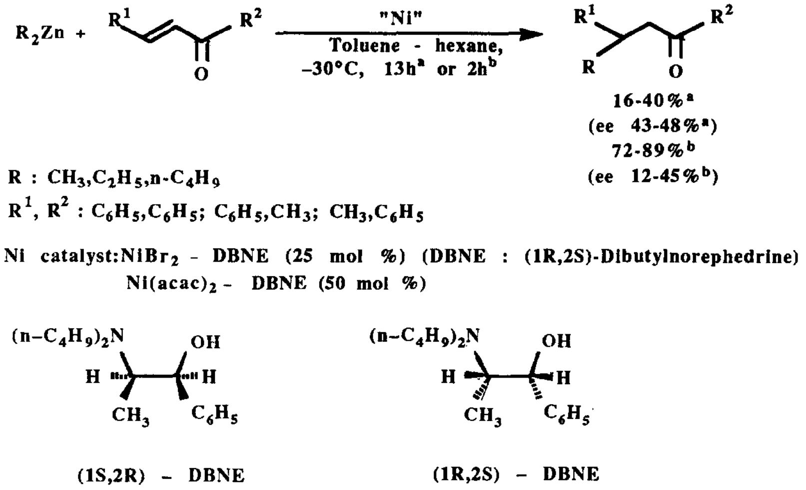


(72)

processes. However Ni(acac)$_2$ catalyzed conjugate addition was found to proceed smoothly. No appreciable amount of the 1,2-addition product was formed.

Enantioselective conjugate addition of dialkylzinc reagents to aryl-substituted *α*,*β*-unsaturated ketones yielding optically active *β*-substituted ketones in moderate enantiomeric excess was achieved by Soai and coworkers using a chiral catalyst prepared from NiBr$_2$[108] or Ni(acac)$_2$[109] and either (1*S*,2*R*)- or (1*R*,2*S*)-dibutylnorephedrine (DBNE) (Scheme 69). Without the catalyst, no reaction took place. Both enantiomers of the chiral ligand were employed and *ee*'s were found to increase with increase of the molar ratio.

A Ni-catalyst possessing both chiral and achiral ligands was also examined. Using the chiral ligand Ni(acac)$_2$-2,2′-bipyridyl, in acetonitrile–toluene as the catalyst system afforded *β*-substituted ketones in up to 90% *ee* (Scheme 70).[110] Apart from the chiral ligand and Ni(acac)$_2$, both the chiral ligand and acetonitrile were essential to obtain the product in high *ee*. Without the achiral ligand, the *ee* was very low. A variety of achiral ligands were effective in improving the enantioselectivities. 2,2′-Bipyridyl and piperazine provided the highest *ee*. Acetonitrile was found to be an essential solvent because in its absence low *ee*'s were obtained.



R : $CH_3, C_2H_5, n\text{-}C_4H_9$

R^1, R^2 : C_6H_5, C_6H_5; C_6H_5, CH_3; CH_3, C_6H_5

Ni catalyst: $NiBr_2$ - DBNE (25 mol %) (DBNE : (1R,2S)-Dibutylnorephedrine)
$Ni(acac)_2$ - DBNE (50 mol %)

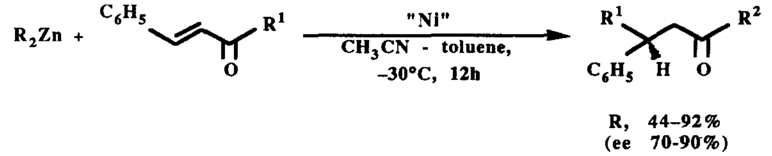
(1S,2R) - DBNE (1R,2S) - DBNE

---

[a] : with Ni catalyst containing $NiBr_2$

[b] : with Ni catalyst containing $Ni(acac)_2$

Scheme 69.



R : $C_2H_5, n\text{-}C_4H_9$

R^1 : $C_6H_5, 4\text{-}CH_3OC_6H_4$

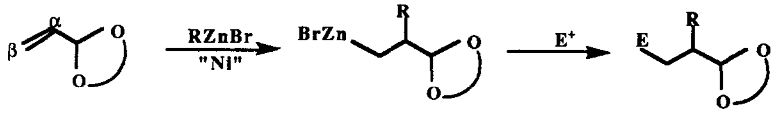
Ni catalyst: $Ni(acac)_2$-chiral ligand-achiral ligand (0.06 equiv-0,14 equiv-0,06 equiv for 1 equiv of R_2Zn)

chiral ligand : (1S,2R)-DBNE

achiral ligand: 2,2'- bipyridyl, piperazine, 1,10-phenanthroline, 2,2'-bipyridyl ketone, 2,2'-biquinoline, 1,2-bis(diphenylphosphino)ethane, morpholine, quinuclidine, pyridine

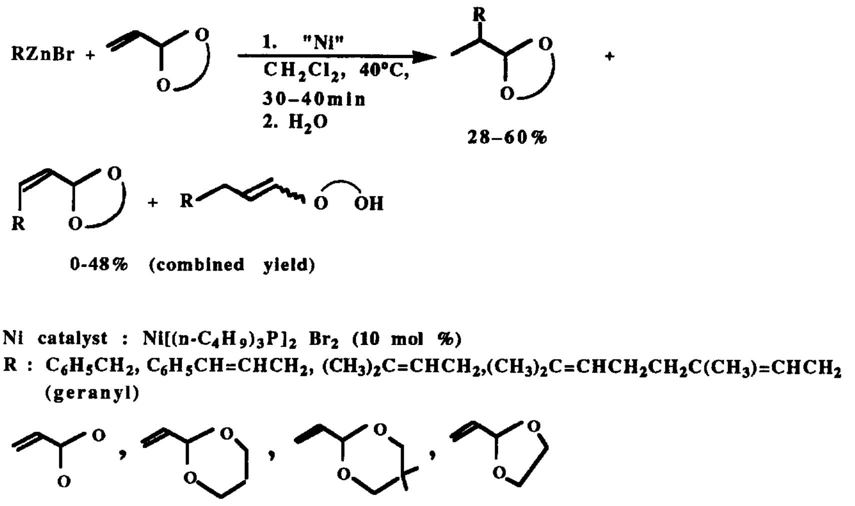
Scheme 70.

Yamamoto and coworkers found[111] that α,β-unsaturated acetals undergo rapid metallation upon treatment with allylzinc reagents in the presence of a Ni-catalyst. The allylzinc reagent acts as a nucleophile, attacking at an α-carbon of the acetal, and then the resulting carbanion at β-position reacts with a variety of electrophiles (eqn 73).



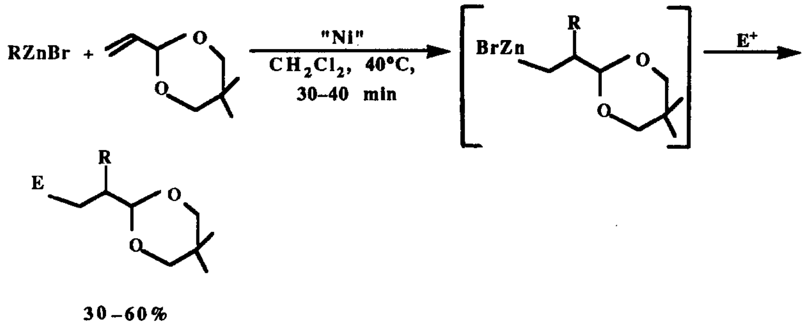
(73)

Treatment of an α,β-unsaturated acetal with an allylzinc bromide prepared by treatment of an allylic bromide with activated zinc powder in THF, and dissolved in CH_2Cl_2 after removal of THF, gave α- and β-adducts under Ni-catalysis in fair to good yields (Scheme 71). The choice of acetal is crucial



Ni catalyst : $Ni[(n\text{-}C_4H_9)_3P]_2Br_2$ (10 mol %)
R : $C_6H_5CH_2$, $C_6H_5CH{=}CHCH_2$, $(CH_3)_2C{=}CHCH_2$,$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2$ (geranyl)

Scheme 71.

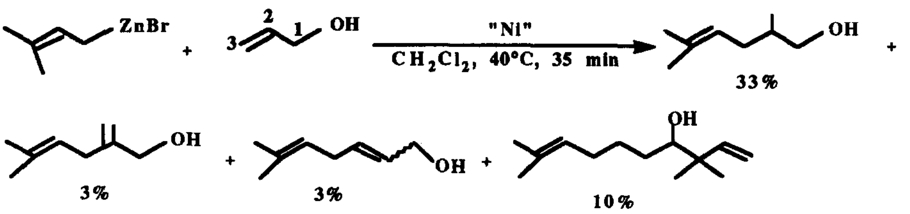


Ni catalyst : $Ni[(n\text{-}C_4H_9)_3P]_2Br_2$ (10 mol %)
R : $(CH_3)_2C{=}CHCH_2$,$C_6H_5CH_2$, $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2$ (geranyl)
E$^+$: D_2O,I_2,CH_3I/HMPA, $H_2C{=}CHCH_2I/CuCN.2LiCl$, $HC{\equiv}CCH_2Br/CuCN.2LiCl$

Scheme 72.

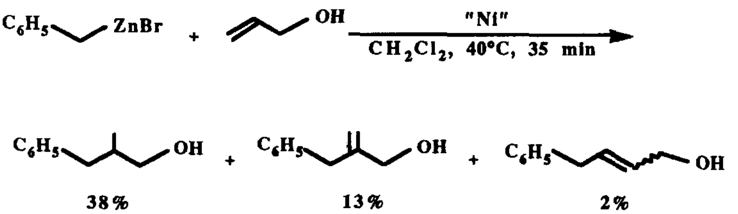
in order to obtain the α-alkylated acetal selectively. The acetal derived from 2,2-dimethyl-1,3-propandiol was effective for this purpose. Allylzinc bromide did not give an alkylation product. β-Zincioacetal was also generated *in situ* and reacted with various electrophiles (Scheme 72). Reaction with allyl or propargyl iodide could be accomplished after transmetallation with CuCN·2LiCl according to the procedure of Normant.[112,113]

Yamamoto and coworkers also accomplished allylmetallation of allylic alcohols by treatment with allylzinc reagents under Ni-catalysis.[114] Allyl alcohol was found to be less reactive towards allylzinc reagents than α,β-unsaturated acetal. Allyl alcohol gave a mixture of the C-2 and C-3 adducts (eqn 74). Benzylzinc gave similar results (eqn 75).



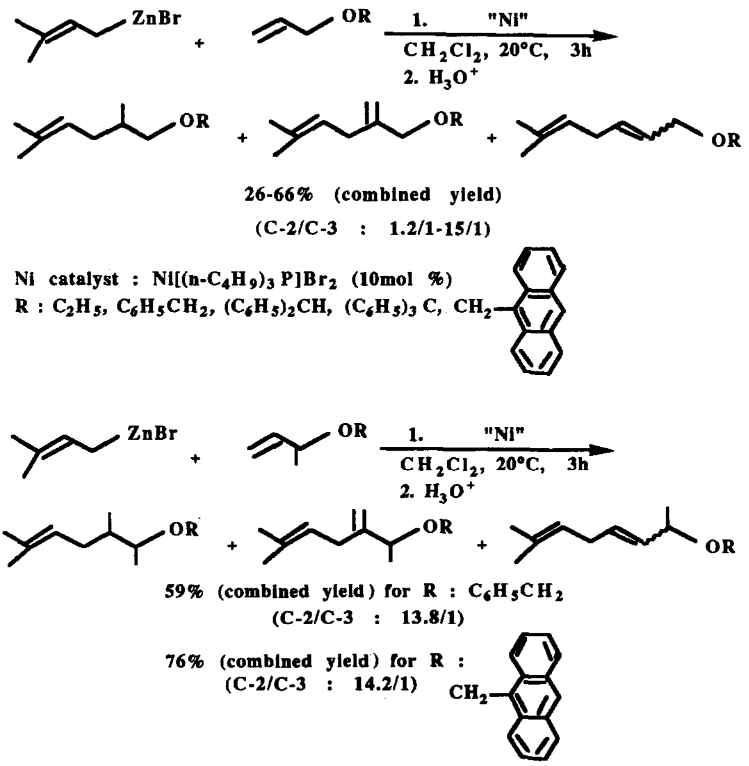
Ni catalyst : $Ni[(n\text{-}C_4H_9)_3P]Br_2$

(74)



(75)

However, an allyl ether reacted rapidly with an allylzinc reagent (Scheme 73) giving exclusively C-2 adduct(s). Higher C-2/C-3 regioselectivity was achieved by increasing the number of phenyl substituents in the $-OCR_3$ group and high regioselectivity was observed in the case of triphenylmethyl ether. Use of allyl 9-anthrylmethyl ether, proved satisfactory in relation to regioselectivity and chemical yields. The presence of an alkyl substituent at the C-1 position of the allyl alcohol resulted in higher regioselectivity.



26-66% (combined yield)
(C-2/C-3 : 1.2/1-15/1)

Ni catalyst : $Ni[(n\text{-}C_4H_9)_3P]Br_2$ (10mol %)
R : C_2H_5, $C_6H_5CH_2$, $(C_6H_5)_2CH$, $(C_6H_5)_3C$, CH_2–

59% (combined yield) for R : $C_6H_5CH_2$
(C-2/C-3 : 13.8/1)

76% (combined yield) for R :
(C-2/C-3 : 14.2/1) CH_2–

Scheme 73.

The reaction of perfluoroalkyl iodides with 1-alkynes and ultrasonically dispersed zinc in the presence of CuI as a catalyst gave the corresponding perfluoroalkylalkenes (Scheme 74).[115] Cu Metal produced from the reduction of CuI with ultrasonically dispersed Zn seemed to enhance the perfluoroalkylation.

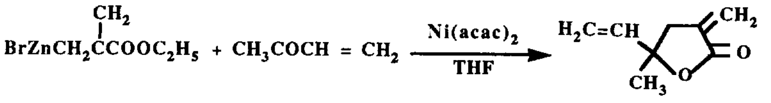
$$\mathrm{R\,ZnI} + \mathrm{R^1C\equiv CH} \xrightarrow[\text{THF,rt,2h}]{\text{"Cu",)))}} \mathrm{R^1CH{=}CHR}$$

52-74%
(Z/E : 24/76-32/68)

Cu catalyst : CuI
R : CF_3,n-C_3F_7,i-C_3F_7,n-C_4F_9, n-C_6F_{13}
R^1 : n-C_4H_9, $HOCH_2$, C_6H_5

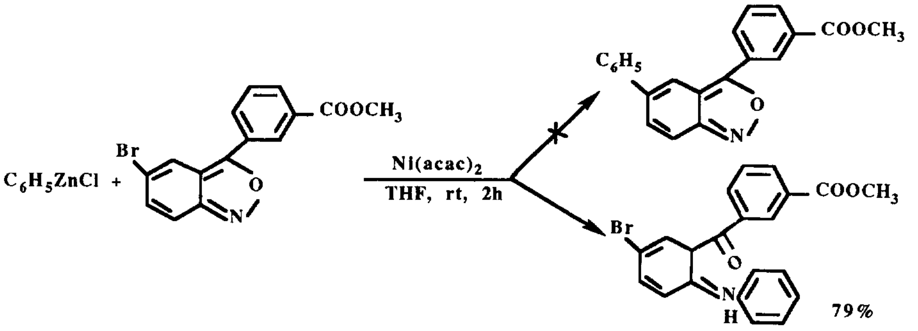
Scheme 74.

The organozinc derivative of α-bromomethyl acrylate gave 1,2-addition with methyl vinyl ketone providing the α-methylene-γ-butyrolactone (eqn 76).[116]



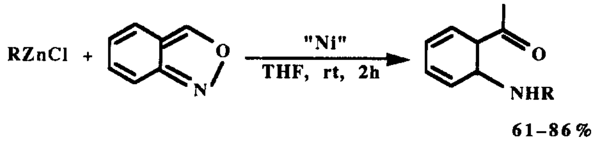
(76)

A transformation of 2,1-benzisoxazoles involving nitrogen–oxygen bond rupture with concomitant nitrogen–carbon bond formation by reaction with organozinc reagents in the presence of a Ni-catalyst was reported. 5-Bromo-3-(*o*-carboxyphenyl)-2,1-benzisoxazole methyl ester did not give carbon–carbon coupling by displacing the 5-bromo substituent under Ni-catalysis, but nitrogen–carbon coupling took place (eqn 77).[117]



(77)

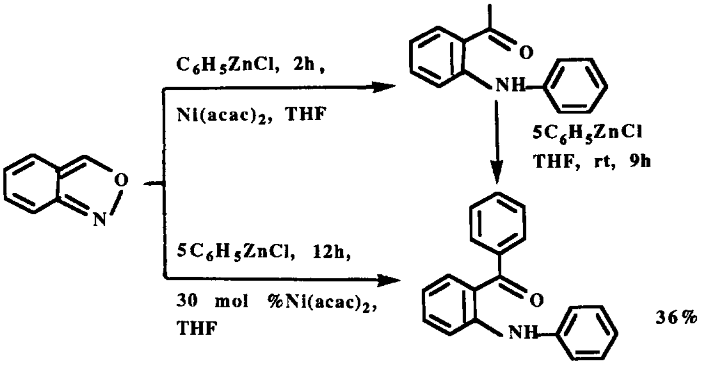
The reaction of anthranil with various organozinc reagents provided *o*-(*N*-substituted amino)-benzaldehydes in good yields (Scheme 75). No reaction occurs in the absence of catalyst. The use



Ni (catalyst) : $Ni(acac)_2$ or $Ni(acac)_2$-H_2O
R: $CH3^a$,C_6H_5,2-$CH_3OC_6H_4$, 3-$CH_3OC_6H_4$,4-$CH_3OC_6H_4$,  (15% yield)
^{a}: 70% yield dropped to 53% by using CuI as a catalyst

Scheme 75.

of a large excess or organozinc reagent and extended reaction time led to the formation of benzyl alcohol (eqn 78).



(78)

Organozinc reagents were prepared by reacting the corresponding organolithium reagents with zinc chloride.

A list of transition metal catalyzed addition reactions of organozinc reagents is given in Table 10.

TABLE 10

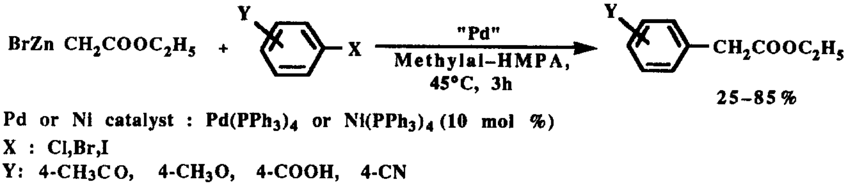
Transition metal catalyzed addition reactions of organozinc reagents

Y	catalyst	scheme and ref
COR	$Ni(acac)_2$	scheme 67[103, 105,107]
COR	$NiBr_2$-chiral ligand or $Ni(acac)_2$-chiral ligand	scheme 69[108,109], scheme 70[110]
CHO	$Ni(acac)_2$	scheme 68[103,106,107]
acetal	Ni $P(n\text{-}C_4H_9)_3Br_2$	scheme 71[111], scheme 72[111]
CH_2OH	Ni $P(n\text{-}C_4H_9)_3Br_2$	eq 74[114], eq 75[114]
CH_2OR	Ni $P(n\text{-}C_4H_9)_3Br_2$	scheme 73[114]

4. TRANSITION METAL CATALYZED REFORMATSKY REACTIONS

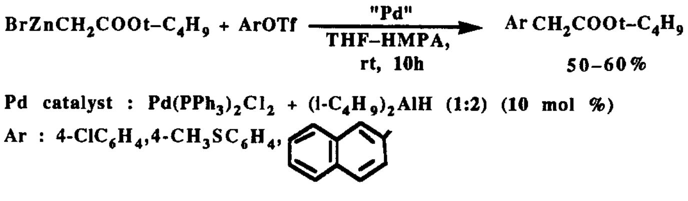
The Reformatsky reaction, in its classical form, yields 3-hydroxyalkanoates from ethyl 2-(halozincio)acetates and aldehydes or ketones. These conditions are also applicable to various other alkyl 2-(halozincio)alkanoates and other 2-(halozincio)-substituted carbonyl compounds using electrophiles other than aldehydes and ketones.[12] Reactions of Reformatsky reagents with various electrophiles under transition metal catalysis, e.g. arylation, vinylation, allylation and acylation as well as transition metal catalyzed Reformatsky-type aldol reactions have been identified.

Fauvarque and Jutand[118-120] and Orsini and Pelizzoni[121] reported Pd- and Ni-catalyzed arylation and vinylation reactions of Reformatsky reagents. Arylation of Reformatsky reagents providing arylacetic esters were carried out either in HMPA–methylal by using aryl halides (Scheme 76)[118,119] or in THF–HMPA by using aryl triflates (Scheme 77).[120] In the first case, the Reformatsky reagent was prepared in methylal. The use of HMPA or other dipolar aprotic solvents (DMF, DMSO) was found to be necessary to achieve the catalytic coupling under homogeneous conditions by solubilizing the Ni-complexes. $Pd(PPh_3)_4$ and $Ni(PPh_3)_4$ appeared to be the best catalysts. $Pd(PPh_3)_2Cl_2$ and $Ni(PPh_3)_2Cl_2$ were inactive. In the other case, the Reformatsky reagent was prepared in THF and



Pd or Ni catalyst : $Pd(PPh_3)_4$ or $Ni(PPh_3)_4$ (10 mol %)
X : Cl,Br,I
Y: 4-CH_3CO, 4-CH_3O, 4-COOH, 4-CN

Scheme 76.



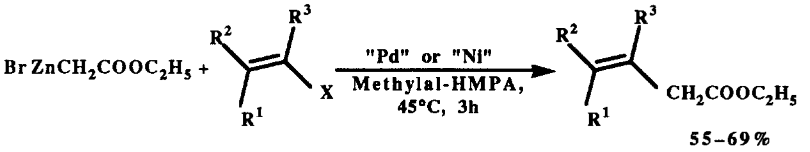
Pd catalyst : $Pd(PPh_3)_2Cl_2$ + $(i\text{-}C_4H_9)_2AlH$ (1:2) (10 mol %)
Ar : 4-ClC_6H_4,4-$CH_3SC_6H_4$,

Scheme 77.

after removal of the solvent, the reagent was dissolved in HMPA. The use of $Pd(PPh_3)_4$ required higher reaction temperatures and led to a mixture of isomeric products.

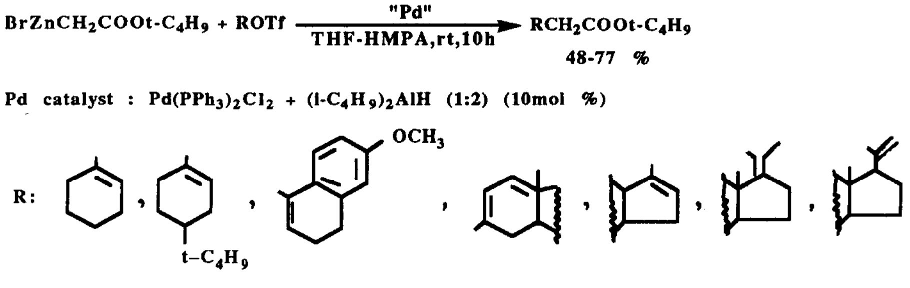
Vinylation of the Reformatsky reagent giving β,γ-unsaturated esters was also achieved using vinyl halides (Scheme 78)[120] or triflates (Scheme 79)[121] in the presence of Pd- or Ni-catalysts. The reaction of vinyl halides proceeded stereospecifically. The use of $Pd(dppf)Cl_2$ **4g** as a catalyst resulted in the recovery of the starting vinylic triflate and formation of the reduction product.

Pd-Catalyzed coupling of Reformatsky reagent with aryl halides was found to be applicable to *N*-heteroaryl halides (Scheme 80).[122] The Reformatsky reagent was prepared by the metallation of ethyl bromoacetate with fresh zinc formed by reduction of zinc chloride with potassium in THF.[3]



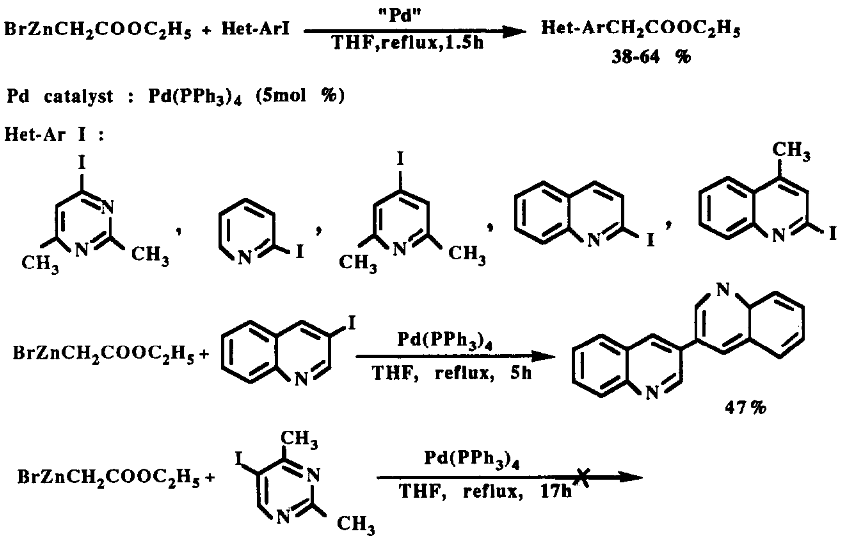
Pd catalyst : $Pd(PPh_3)_4$ or $Ni(PPh_3)_4$ (10mol %)
R^1,R^2,R^3 : H,H,H; H,H,CH_3; H,CH_3,H and CH_3,H,H; H,C_6H_5,H and C_6H_5,H,H; C_6H_5,H,H

Scheme 78.



Pd catalyst : $Pd(PPh_3)_2Cl_2$ + $(i\text{-}C_4H_9)_2AlH$ (1:2) (10mol %)

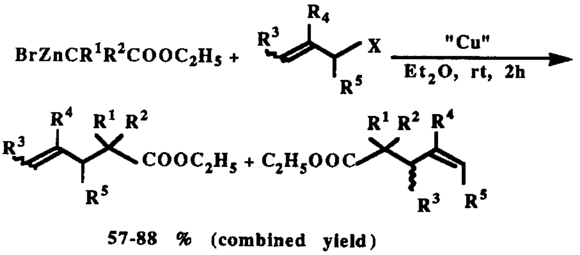
Scheme 79.



Scheme 80.

The yield of the coupled product was found to be highest when $Pd(PPh_3)_4$ was used as a catalyst. *N*-Heteroaryl iodides were concluded to be the best substrates for coupling among chlorides, bromides and iodides. However, the position of iodine with respect to ring nitrogen seemed to have an effect on the cross/homo-coupling ratio of the products. If iodine is located at the *o*- or *p*-position, ethyl *N*-heteroarylacetates were the sole products with concomitant formation of the bis-*N*-heteroaryl compound in some cases. If iodine is located at the *m*-position, the reaction resulted in the exclusive formation of the bis-*N*-heteroaryl compound or the recovery of starting material.

Reformatsky reagents also react with allylic halides under Cu-catalysis[123] or with allylic acetates under Pd-catalysis.[124] Allylation of Reformatsky reagents provide γ,δ-unsaturated esters in good yields. Reformatsky reagents, prepared in Et_2O by using activated Zn at reflux temperature, reacted with allylic halides in the presence of Cu salts in a highly S_N2 substitution manner via α-attack (Scheme 81).[123] The reaction is stereospecific and the use of DMSO as a cosolvent was found to increase the S_N2/S_N2' ratio.



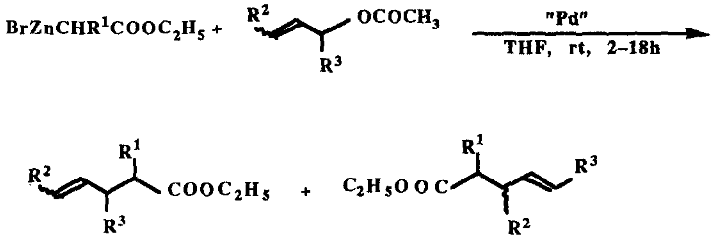
Cu catalyst : Cu $(acac)_2$ (5mol %)

R^1,R^2 : H,H; H,C_2H_5; CH_3,CH_3
X : Cl,Br
R^3,R^4,R^5 : H,H,H; H,CH_3,H; E-and Z- CH_3,H,H; H,H,CH_3

R^3,R^4,R^5	S_N2/S_N2'
H,H,H	100/0
H,CH_3,H	100/0
E-orZ-CH_3,H,H	90/10-60/40
H,H,CH_3	95/5-75/25

Scheme 81.

Reformatsky reagents, prepared in THF by using Zn–graphite or Zn–Cu couple at 0°C, reacted with allylic acetates regioselectively in the presence of Pd-catalysts (Scheme 82).[124] The regiochemical course of the reaction is under steric control and the main product always arises from the attack at the less substituted carbon. The organozinc compound derived from α-bromo-γ-butyrolactone similarly reacts with allylic acetates (eqns 79 and 80).

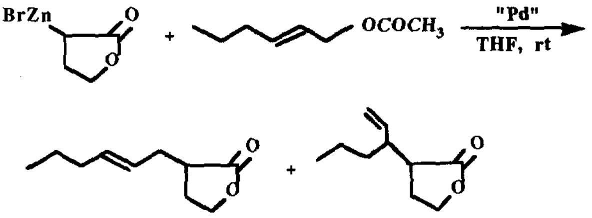


67-79% (combined yield)

Pd catalyst : $Pd(PPh_3)_4$ (8mol %)
R^1 : H,CH_3
R^2,R^3 : $H,n\text{-}C_5H_{11}$; $E\text{-}n\text{-}C_3H_7,H$; $E\text{-}n\text{-}C_8H_{17},H$; $Z\text{-}Ph,H$

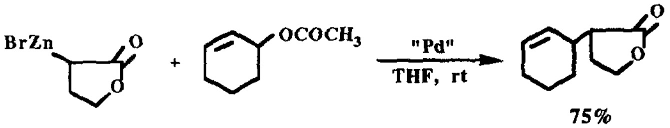
R^2,R^3	S_N2/S_N2'
$H,n\text{-}C_5H_{11}$	8/59-3/71
$n\text{-}C_5H_{11},H$	57/8-42/6
Ph,H	59/6

Scheme 82.



78% (combined yield)
(S_N2/S_N2' : 76/3)

(79)



75%
(diastereomer ratio : 65/35)

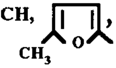
(80)

Fujisawa and coworkers reported that 3-ketoesters were obtained in good yields by the reaction of the Reformatsky reagents with acyl chlorides under Pd-catalysis (Scheme 83).[125] Aromatic, *N*-heteroaromatic and α,β-unsaturated acyl chlorides gave good yields. Reformatsky reagents were prepared in methylal, and after removal of solvent, the reagent was dissolved in DME. The reaction of Reformatsky reagent with aliphatic acyl chlorides resulted in low yields.

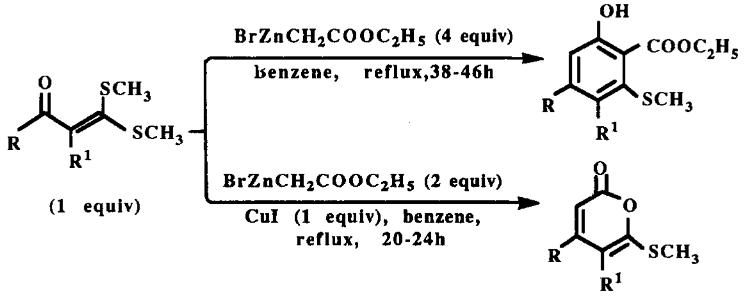
The reaction of α-oxoketene dithioacetals with an excess of Reformatsky reagent has been reported to provide a novel route for regiospecifically substituted 2-hydroxy-6-(methylthio)-benzoates (eqn 81a).[126] However, in the presence of CuI, the reaction follows a different course, yielding the corresponding pyrones (eqn 81b). A possible mechanism to account for this deviation has been proposed.

$$BrZnCH_2COOC_2H_5 + RCOCl \xrightarrow[DME,0°C,2h]{"Pd"} \underset{24\text{-}89\%}{RCOCH_2COOC_2H_5}$$

Pd catalyst : $Pd(PPh_3)_2Cl_2 + (i\text{-}C_4H_9)_2AlH$ (1:2) (1mol %)

R: C_6H_5, $4\text{-}ClC_6H_4$, $4\text{-}CH_3C_6H_4$, $4\text{-}NO_2C_6H_4$, $4\text{-}CH_3OC_6H_4$, (E)-$CH_3CH{=}CH$, (E)-$C_6H_5CH{=}CH$,  , $n\text{-}C_8H_{17}$, $i\text{-}C_3H_7$, $t\text{-}C_4H_9$

Scheme 83.



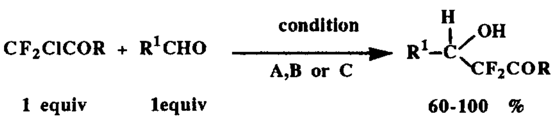
(81 a)

(81 b)

R,R^1 : $4\text{-}ClC_6H_4$,H; C_6H_5,H; $4\text{-}CH_3OC_6H_4$,H; CH_3,H; CH_3,CH_3 ;

Ishihara and Kuroboshi reported[127,128] an efficient and general method for the Reformatsky-type reaction of chlorodifluoromethyl ketones with a wide variety of aldehydes and ketones in the presence of Zn dust and CuCl or $AgOCOCH_3$ providing α,α-difluoro-β-hydroxy ketones (Schemes 84 and 85). When chlorodifluoromethyl ketone was treated with an aldehyde or ketone in the presence of Zn dust (activated by acid washing[3]) in refluxing THF, α,α-difluoro-β-hydroxy ketone was produced only in low or variable yields. In some cases unexpectedly long reaction times were required for completion of the reaction. However, in the presence of CuCl as an activator or promoter, the reaction time decreased and the yield increased. Difluoromethyl ketone zinc enolates were detected in these reactions.

A list of transition metal catalyzed Reformatsky reactions is given in Table 11.

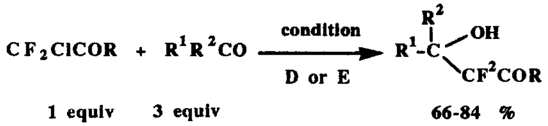


condition A (for R : alkyl) : Zn(3 equiv), CuCl(0.3 equiv) THF, reflux, 4h
condition B (for R : aryl) : Zn (3 equiv), CuCl(0.3 equiv), THF-Et_2O(1:4), reflux, 1h
condition C (for R : aryl, 1-alkynyl) : Zn(3 equiv),CuCl(0.3 equiv)-$BF_3.Et_2O$ (1.1 equiv); THF-Et_2O(1:4), -20°C,1h

R : $CH_3(CH_2)_5$, $c\text{-}C_6H_{11}$, $C_6H_5CH_2$, C_6H_5, $CH_3(CH_2)_5C \equiv C$, $C_6H_5C \equiv C$

R^1 : C_2H_5,$n\text{-}C_3H_7$,$CH_3(CH_2)_5$ $i\text{-}C_3H_7$, $t\text{-}C_4H_9$, (E)-$CH_3CH = CH$, (E)-$CH_3CH{=}C(CH_3)$,C_6H_5

Scheme 84.



condition D(for R : alkyl) : Zn(3 equiv), $AgOCOCH_3$ (0.1 equiv) $(C_2H_5)_2AlCl$(1 equiv), THF,reflux, 9h
condition E (for R : aryl) : Zn(3 equiv), $AgOCOCH_3$ (0.1 equiv), THF-Et_2O(1:4), reflux,4h

R : $CH_3(CH_2)_5$, $C_6H_5CH_2$, C_6H_5
R^1,R^2 : n-C_3H_7,n-C_3H_7; $CH_2=C(CH_2)_2$, CH_3;C_6H_5,CH_3

Scheme 85.

TABLE 11

Transition metal catalyzed coupling reactions of Reformatsky reagents

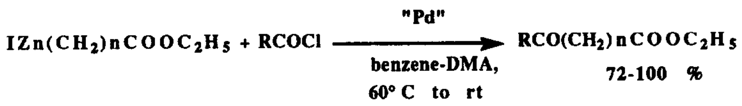
$$BrZnCH_2COY + \text{Electrophile, EX} \xrightarrow{\text{Catalyst}} ECH_2COY$$

Y	electrophile, EX	catalyst	scheme and ref
OC_2H_5	allylic halide	Cu (acac)$_2$	scheme 81[123]
OC_2H_5	allylic halide	$Pd(PPh_3)_4$	scheme 82[124]
OC_2H_5	vinylic halide	$Pd(PPh_3)_4$, $Ni(PPh_3)_4$	scheme 78[120]
Ot-C_4H_9	vinylic triflate	"$Pd(PPh_3)_2$"	scheme 79[121]
OC_2H_5	aryl halide	$Ni(PPh_3)_4$, $Ni(PPh_3)_4$	scheme 76[119], scheme 80[120]
Ot-C_4H_9	aryl triflate	"$Pd(PPh_3)_2$"	scheme 77[121]
OC_2H_5	acyl halide	"$Pd(PPh_3)_2$"	scheme 83[125]

5. TRANSITION METAL CATALYZED REMOTE REFORMATSKY REACTIONS

Zinc derivatives of 3-, 4- or higher halocarbonyl compounds, esters, ketones and nitriles can act as carbon nucleophiles to form C–C bonds at the 3-, 4- or higher positions with respect to the carbonyl group. While the common Reformatsky conditions were reported to be unsuitable to prepare these reagents, Zn–Cu and Zn–Ag couples and solvent mixtures containing DMF, DMA, DMSO and HMPA were found to be suitable for metallation of iodoesters, ketones and nitriles bearing the halogen atom in various positions. Using various additives and/or catalysts, these reagents can be reacted with various electrophiles by so-called 'remote Reformatsky reactions'.[12] Two research groups have investigated transition metal catalyzed remote Reformatsky reactions. Yoshida and coworkers reported[129–134] the reactions of zinc homoenolate and bishomoenolate, that is 3- and 4-halozincioesters with acyl halides,[129,133] aryl and vinyl halides,[130] allyl halides[131] and with α,β-unsaturated carbonyl compounds.[134] They also described the reactions of 3-iodozinc ketones or higher homologues with various carbon nucleophiles. Nakamura and coworkers described a variety of similar C–C bond forming reactions of zinc homoenolates,[135–141] involving conjugate addition,[135,139,141] allylation,[139] arylation,[138,139] vinylation[138,139] and acylation[135,138,139] and the synthetic utility of a chiral homoenolate.[140]

Ethyl 3-(iodozincio)propionate and ethyl 4-(iodozincio)butyrate were utilized for the Pd-catalyzed coupling reaction with acyl halides to provide 4- and 5-ketoesters quantitatively (Scheme 86).[129] Zinc homoenolate and bishomoenolate were prepared by the reaction of ethyl 3-iodopropionate and ethyl 4-iodobutyrate with a Zn–Cu couple in benzene containing 7% DMA or



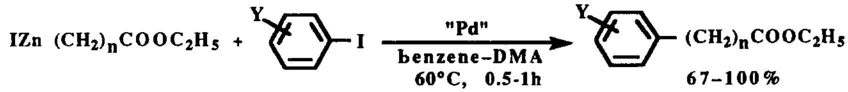
$$IZn(CH_2)nCOOC_2H_5 + RCOCl \xrightarrow[\text{benzene-DMA, } 60° \text{C to rt}]{\text{"Pd"}} RCO(CH_2)nCOOC_2H_5 \quad 72\text{-}100\ \%$$

Pd catalyst : $Pd(PPh_3)_4$ (4mol %)
n = 2, R: C_2H_5, n-C_7H_{15}, C_6H_5, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$,
4-$ClC_6H_4CH{=}CH$, $CH_2{=}C(CH_3)$
n = 3, R : n-C_7H_{15}, $CH_3OOC(CH_2)_n$ (n= 4,7,8)

Scheme 86.

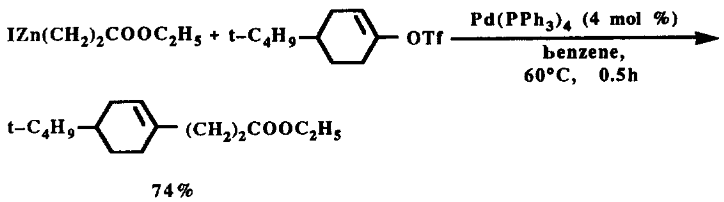
DMF. In the absence of DMA or DMF, no formation of enolates were discernible, DMA showed better and more satisfactory results than DMF. Synthesis of ethyl 5-oxo-6-methyl-6-heptenoate from ethyl 4-iodobutyrate and methacryloyl chloride was reported.[133]

Ethyl 3-(iodozincio)propionate and ethyl 4-(iodozincio)butyrate also react with aryl iodides and vinyl iodides or triflates in the presence of catalytic amounts of Pd- or Ni-complexes giving 3- and 4-aryl substituted esters in high yields (Scheme 87).[130] The coupling reaction might be catalyzed by other Pd- or Ni-catalysts, such as $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ or $Ni(PPh_3)_2Br_2$. However, all of these catalysts were found to be inferior to $Pd[P(2\text{-}CH_3C_6H_4)_3]_2Cl_2$ mainly due to the formation of homocoupled products, biaryls. The coupling reaction tolerates the presence of both electron-donating and electron-withdrawing groups. The Pd-catalyzed coupling reaction of zinc homoenolate with 1-cyclohexenyl triflate (eqn 82) and reaction of zinc bishomoenolate with vinyl iodides and triflates provide 5-hexenoates in good yields (Scheme 88). The reaction is stereospecific.



Pd catalyst : Pd $(P(2\text{-}CH_3C_6H_4)_3)_2$ Cl_2 (1mol %)
n=2, Y : H, 2-CH_3, 2-CH_3OOC, 4-CH_3O, 4-Br, 4-NO_2
n=3, Y : H, 2-CH_3, 2-CH_3OOC, 4-CH_3O, 4-Br

Scheme 87.



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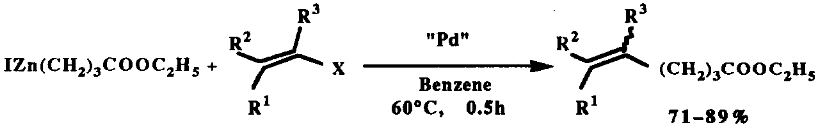


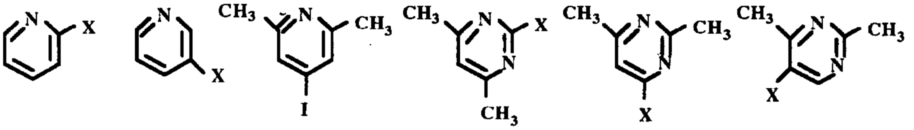
Pd catalyst : $Pd(PPh_3)_4$ (4mol %)
R^1,R^2,R^3,X : H,H,n-C_4H_9,OTf; CH_3,CH_3,CH_3,OTf; H,H,i-C_3H_7,OTf,
H,C_6H_5,H,I; n-C_4H_9,H,H,I; H,n-C_4H_9,H,I

Scheme 88.

Yoshida's method of coupling of zinc homoenolate and zinc bishomoenolate with aryl iodides was also applied to their coupling with *N*-heteroaryl halides. The reaction provides a good synthesis of 2-ethoxycarbonylethyl- and 3-ethoxycarbonylpropyl substituted *N*-heteroarenes (Scheme 89).[34]

$$IZn(CH_2)nCOOC_2H_5 + \text{Het-Ar X} \xrightarrow[\text{rt-60°C, 0.5-12h}]{\text{"Pd"} \atop \text{benzeane-DMA,}} \text{Het-Ar}(CH_2)_nCOOC_2H_5$$

n= 2,3
Pd catalyst : $Pd(PPh_3)_2Cl_2$ (4mol %)
Het-ArX :



X : Cl, Br, I

Scheme 89.

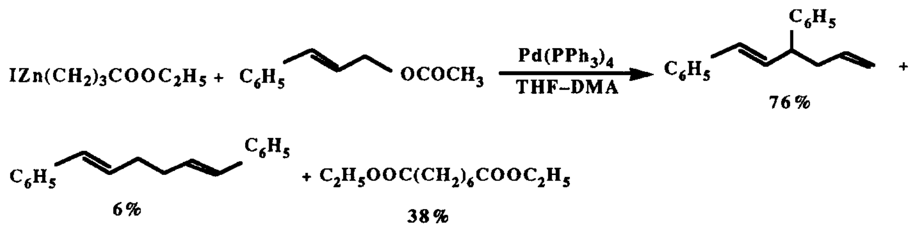
In the Pd-catalyzed arylation of zinc homoenolates, aryl fluoroalkanesulfonates may also be used (Scheme 90).[38]

$$IZn(CH_2)_2COOC_2H_5 + Ar\ OSO_2R \xrightarrow[\text{80-90°C, 12-32h}]{\text{"Pd"} \atop \text{DMF-benzene,}} \underset{60\text{-}67\ \%}{Ar(CH_2)_2COOC_2H_5}$$

Pd catalyst : $Pd(PPh_3)_4$ (7.5 or 10 mol %)
Ar : C_6H_5, $3\text{-}CH_3OC_6H_4$, $4\text{-}CH_3OC_6H_4$, $4\text{-}ClC_6H_4$
R : CF_3, $CHF_2CF_2OCF_2CF_2$, $H(CF_2CF_2)_2OCF_2CF_2$

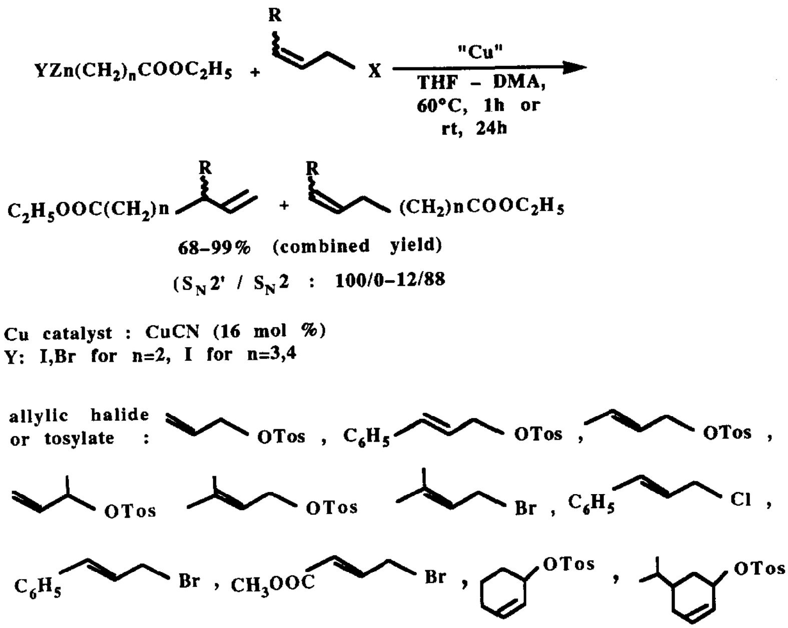
Scheme 90.

Allylation of ethyl 3-(iodozincio)propionate, ethyl 3-(bromozincio)propionate, ethyl 4-(iodozincio)butyrate and 5-(iodozincio)pentanoate with allylic halides and tosylates under Cu-catalysis provide ethyl 5-hexenoates, ethyl 6-heptenoates and ethyl 7-octenoates in high yields (Scheme 91).[131] Reactive allylic bromides give S_N2' products. Less reactive halides and tosylates provide a mixture of S_N2 and S_N2' products. In the absence of CuCN, the yield was low. Pd-Catalyzed allylation resulted in a self-coupling and the expected product was not detected (eqn 83).



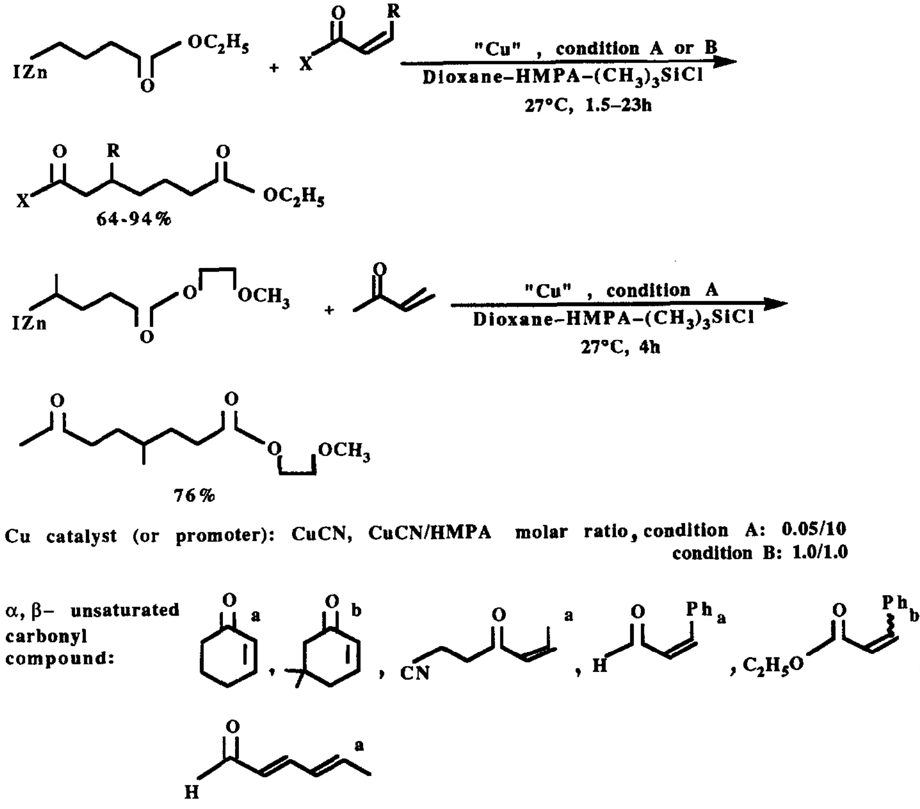
(83)

Cu-Catalyzed conjugate addition reactions of a zinc bishomoenolate were carried out by reacting ethyl 4-(iodozincio)butyrate, (prepared *in situ* by the reaction of the corresponding iodide with Zn–Cu couple in dioxane–HMPA) with an α,β-unsaturated carbonyl compound in the presence of CuCN and Me_3SiCl (Scheme 92).[134] Cu-Promoted conjugate addition reactions of 3-(iodozincio)esters (zinc homoenolates), 3- and 4-iodozincionitriles and 4-iodozincio-2-aminoesters with α,β-unsaturated carbonyl compounds were also explored (eqns 84–87).



Cu catalyst : CuCN (16 mol %)
Y: I,Br for n=2, I for n=3,4

Scheme 91.



Cu catalyst (or promoter): CuCN, CuCN/HMPA molar ratio, condition A: 0.05/10
condition B: 1.0/1.0

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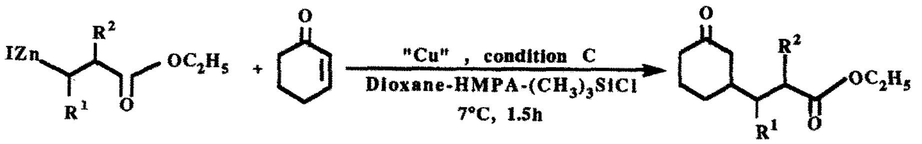
[a] condition A , [b] condition B

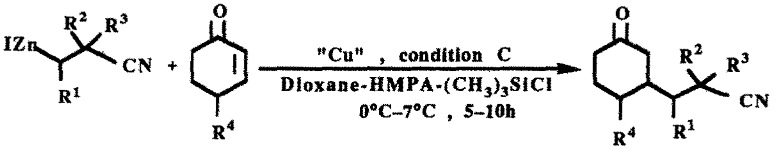
Scheme 92.



(84)

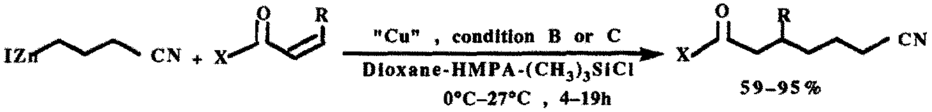
condition C : CuCN/HMPA molar ratio : 0.35/1.0

R	yield, %
H,CH₃	70
CH₃,H	78



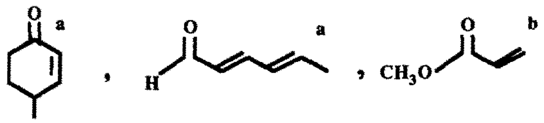
(85)

R^1,R^2,R^3,R^4	yield, %
H,H,CH₃,H	70%
H,CH₃,CH₃,i-C₃H₇	54%
CH₃,H,H,H	62%



(86)

α, β unsaturated carbonyl campound:



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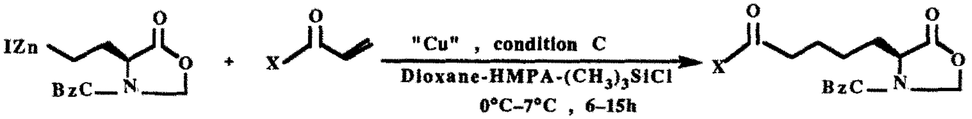
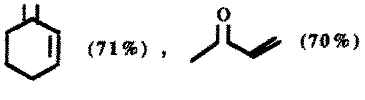
[a] condition C, [b] condition B



(87)

α, β - enone:



$$RCO(CH_2)_nZnI + R^1COCl \xrightarrow[\text{benzene-HMPA, 25-50°C, 1h or 2h}]{\text{"Pd"}} RCO(CH_2)nCOR^1$$

34-82%

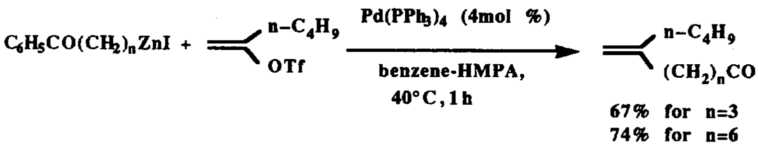
Pd catalyst : $Pd(PPh_3)_4$ (4mol %)
n=2–6
R : CH_3, C_2H_5, C_6H_5
R^1 : C_2H_5, n-C_7H_{15}, C_6H_5, 4-$CH_3OC_6H_4$, $H_2C{=}CH$

Scheme 93.

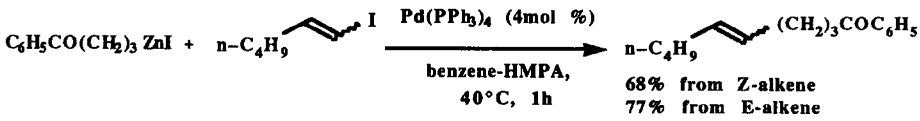
3-, 4-, 5-, 6- and 7-Iodozincio ketones react with various carbon electrophiles by Pd- or Cu-catalysis. Iodozincio ketones were prepared by the reaction of iodoketones with Zn–Cu couple in benzene containing HMPA (HMPA/iodoketone ratio = 1.7 : 1). This is essential for the generation of the organozinc derivative. DMF or DMA may serve as a cosolvent, but HMPA is by far the most satisfactory because it reduces the reaction temperature and stabilizes the organozinc compound. The Pd-catalyzed reaction of iodozincio ketones with acyl halides provides diketones (Scheme 93).[132] Arylation (eqn 88), vinylation (eqns 89 and 90) and allylation (eqn 91) reactions of iodozincio ketones under Pd- or Cu-catalysis give coupling products in good yields. These reactions proceed stereospecifically.

$$C_6H_5CO(CH_2)_3ZnI + C_6H_5I \xrightarrow[\text{benzene-HMPA, 40° C , 1 h}]{Pd[P(2\text{-}CH_3C_6H_4)_3]_2Cl_2 \text{ (2mol \%)}} C_6H_5CO(CH_2)_3C_6H_5 \quad (88)$$

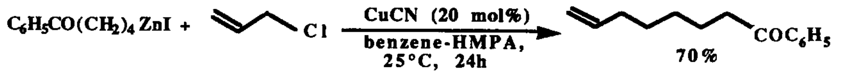
99%



(89)

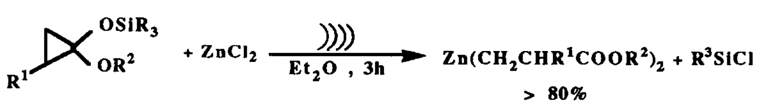


(90)



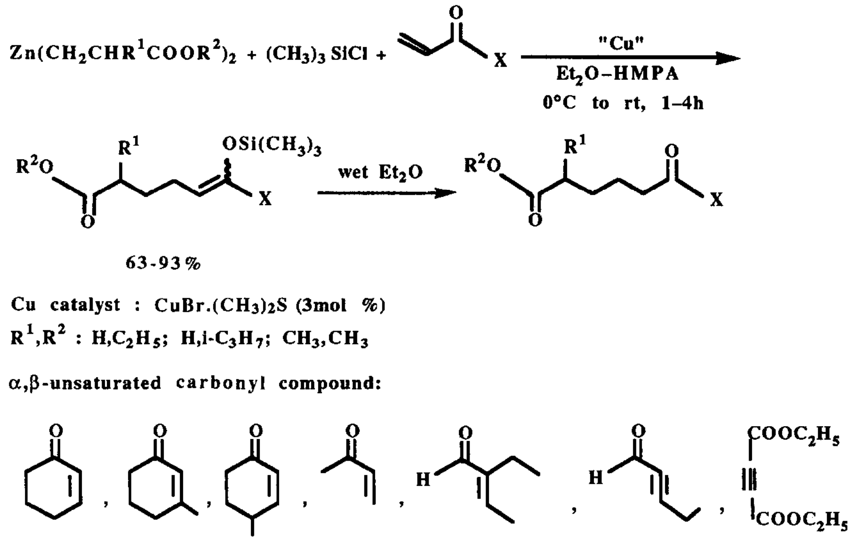
(91)

Nakamura and Kuwajima prepared zinc homoenolate of alkyl propionate and its congeners by the reaction of siloxycyclopropane and zinc chloride in ether under sonication (eqn 92).[135,136,139] The simple and efficient method for the conjugate addition of the zinc homoenolate consists of the *in situ* preparation of a mixture of the zinc homoenolate and chlorotrimethylsilane followed by successive addition of a catalytic amount of CuBr · Me_2S complex, HMPA, and the α,β-unsaturated



(92)

R^1,R^2,SiR_3: H,C_2H_5,$Si(CH_3)_3$; H,i-C_3H_7,$Si(CH_3)_3$; CH_3,CH_3,$Si(CH_3)_3$
C_6H_5,C_2H_5,$Si(CH_3)_3$; CH_3,CH_3,$Si(CH_3)_2$t-C_4H_9



63-93%

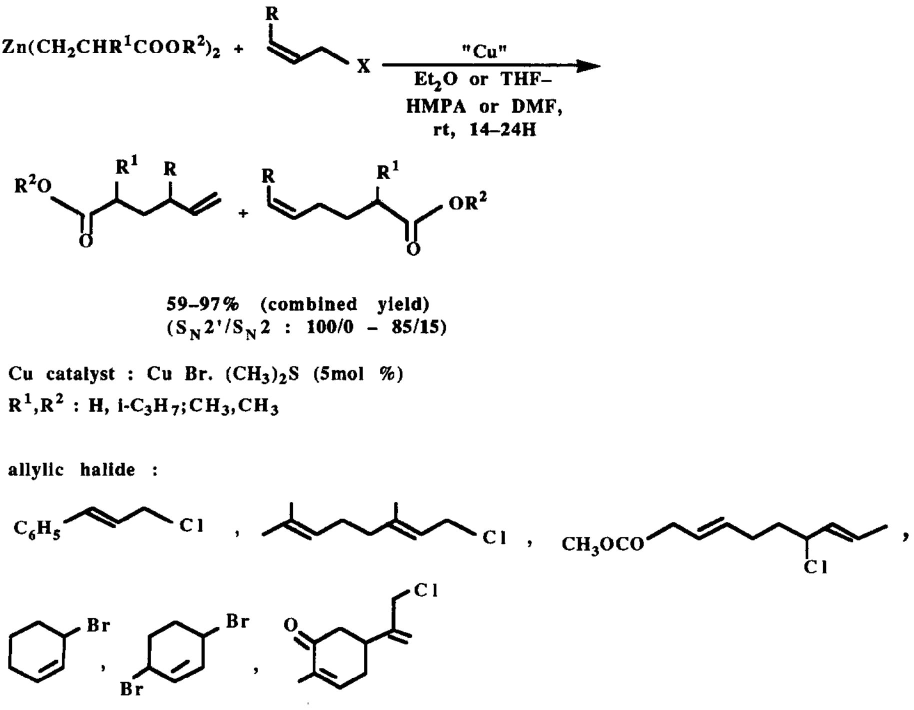
Cu catalyst : $CuBr.(CH_3)_2S$ (3mol %)

R^1,R^2 : H,C_2H_5; $H,i\text{-}C_3H_7$; CH_3,CH_3

α,β-unsaturated carbonyl compound:

Scheme 94.

carbonyl compound (Scheme 94).[135,139] Nonaqueous work-up gives the desired 6-ketoester as its silyl enol ether with the double bond specifically located at the expected position. The reaction proceeds exclusively via the 1,4-addition pathway and applies well to α,β-enones, α,β-enals and some acetylenic compounds. The silyl group can be removed readily by wet ether or may be exploited for a number of subsequent synthetic operations. Findings pertaining to the reaction mechanism



59–97% (combined yield)
(S_N2'/S_N2 : 100/0 – 85/15)

Cu catalyst : Cu Br. $(CH_3)_2S$ (5mol %)

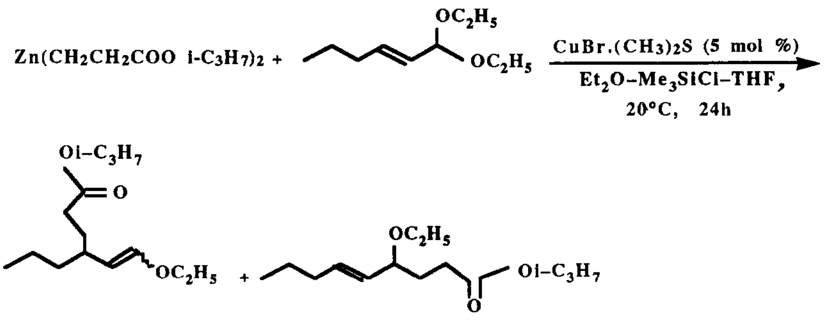
R^1,R^2 : H, $i\text{-}C_3H_7$;CH_3,CH_3

allylic halide :

Scheme 95.

demonstrate that all of the reagents present in the reaction mixture, including HMPA and Me_3SiCl are necessary for the smooth conjugate addition. Without Me_3SiCl, which is generated during the preparation of zinc homoenolate, almost no reaction occurred in the presence of HMPA. Application of the conjugate addition reaction to the synthesis of cortisone and andrenosterone has been reported.[137] Synthesis of ethyl 3-[3-(trimethylsilyloxy)cyclohex-2-enyl] propionate from 1-trimethylsilyloxy-1-ethoxycyclopropane and cyclohexen-1-one was published.[141]

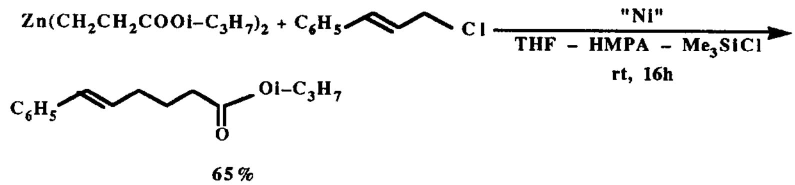
Zinc homoenolates were found to undergo highly selective S_N2' reaction with allylic halides under Cu-catalysis (Scheme 95)[139] as also reported by Yoshida.[131] Polar additives such as HMPA or DMF greatly improved the S_N2' selectivity of the reaction and increased the yield. The allylation and the conjugate addition proceed under essentially the same conditions but conjugative addition also needs Me_3SiCl. Due to this important difference, the allylation could be selectively performed in the presence of an α,β-enone function in the same molecule. Two examples of S_N2 reactions of the homoenolate were described. The zinc homoenolate was found to react in an S_N2 fashion in the presence of Cu catalyst, Me_3SiCl or $BF_3 \cdot Et_2O$ and THF. In the absence of Me_3SiCl or $BF_3 \cdot Et_2O$ no reaction was observed: the amount of Me_3SiCl had a controlling effect on the regioselectivity (eqn 93).



65% (combined yield)
(S_N2'/S_N2: 6/94)

(93)

Ni-Catalyzed allylation proceeded in an S_N2 manner (eqn 94). The high degree of S_N2' selectivity in Cu-catalyzed allylation and change of selectivity to S_N2 by using Ni-catalysis was also reported in the allylation of alkylzinc reagents[19] as well as the allylation of a zinc homoenolate.

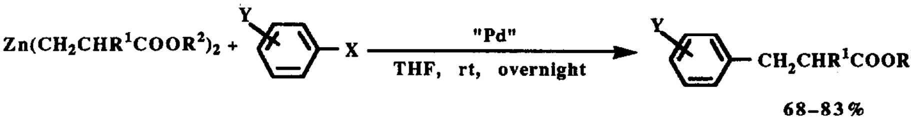


65%

(94)

Ni catalyst : Ni $(dppe)_2Cl_2$(3d) or $Ni(dppf)_2Cl_2$ (3g) (5mol %)

Arylation and vinylation reactions of zinc homoenolates[138,139] did not require either HMPA or Me_2SiCl. Iodides reacted much faster than bromides. In Pd-catalyzed reactions, $P(2\text{-}CH_3C_6H_4)_3$ and dppf g was found to be superior as ligands (Schemes 96 and 97). Phenyl triflate did not react even in refluxing THF–HMPA mixture but quantitative conversion of vinyl triflate occurred rapidly at room temperature in THF–DMA mixture. The reaction slows down when an aryl halide has an *o*-substituent. High chemoselectivity is illustrated where *p*-bromoacetophenone reacted only at the halide position and did not show any complication due to the ketone function. The reaction of vinylic halides is stereospecific.

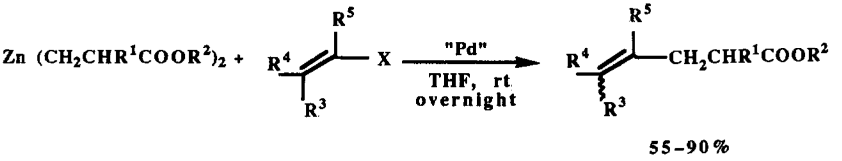


Pd catalyst : $Pd[P(2\text{-}CH_3C_6H_4)_3]_2Cl_2$ (5 mol %)

R^1,R^2 : H,C_2H_5; C_6H_5,C_2H_5

Y,X : H,Br; H,I; 2-CH_3,Br; 4-CH_3CO,Br; 2-CH_3OCH_2O and 5-CH_3,I; 2-$(CH_3)_2N$,I

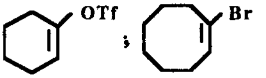
Scheme 96.



Pd catalyst : $Pd[P(2\text{-}CH_3C_6H_4)_3]_2Cl_2$ (5mol %)

R^1,R^2 : H, i-C_3H_7; H,C_2H_5; CH_3,CH_3

R^3,R^4,R^5,X : H,H,C_6H_5,Br; H,H,2-$CH_3C_6H_4$,Br; H,C_6H_5,H,Br; H,n-C_4H_9,H,Br;

n-C_4H_9,H,H,Br; H,CH_3, $Si(CH_3)_3$, Br; 

Scheme 97.

Zinc homoenolates react with acyl chlorides giving 4-ketoesters either in the presence of HMPA as a reaction promoter or under Pd-catalysis or Cu/HMPA-catalysis (Scheme 98).[135,138,139]

$$Zn(CH_2CHR^1COOR^2)_2 + R^3COCl \xrightarrow[Et_2O,\ rt,\ 2h]{\text{"Pd" or "Cu"}} R^3COCH_2CHR^1COOR^2 \quad 50\text{-}93\ \%$$

Pd catalyst : $Pd(PPh_3)_2Cl_2$ (5mol %) or Cu catalyst : $CuBr.(CH_3)_2S$ (5mol %) HMPA

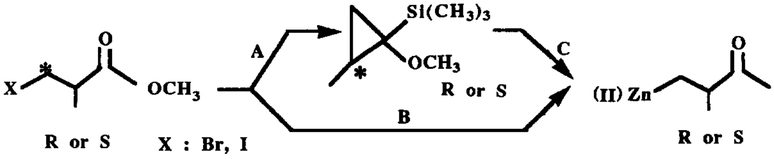
R^1,R^2 : H, i-C_3H_7; H,C_2H_5;CH_3,CH_3

R^3 : t-C_4H_9, $C_6H_5CH_2CH_2$, $(CH_3)_2C{=}CH$, C_6H_5

Scheme 98.

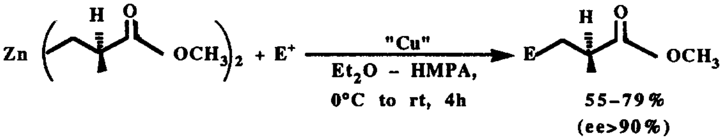
Despite their lower reactivities than Grignard reagents or even simple zinc alkyls, zinc homoenolates, zinc bishomoenolates and even 3- and higher halozincio ketones react with a variety of electrophiles to undergo synthetically important C–C bond forming reactions. These reactions take place in the presence of transition metal catalysts without interference by the internal carbonyl group.

The chiral homoenolate of methyl isobutyrate prepared from optically active methyl 3-haloisobutyrate either by Nakamura's method (A)[139] or by Yoshida's method (B) (eqn 95)[129] was



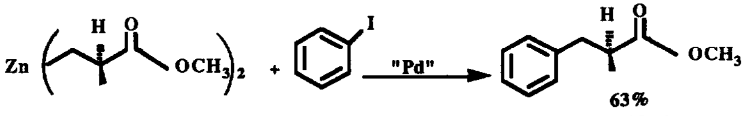
(95)

A: $Na/(CH_3)_3SiCl$, B: $ZnCl_2/Et_2O$, C: Zn-Ag, benzene - DMA reported to react with various carbon electrophiles giving chiral α-methyl-β-substituted esters in good to high yields with high enantioselectivity (Scheme 99).[140] The ring opening reaction of the (*R*)-siloxycyclopropane with zinc chloride cleanly gave (*S*)-homoenolate (60–70% yield). The optical purity was found to be at least 95% *ee*. The configuration was fully retained even after two days. (*R*)- or (*S*)-3-Haloester was prepared from optically active 3-hydroxyester and transformed to the desired chiral zinc homoenolate of isobutyrate through formation of *dl*-siloxypropane (route A). The homoenolate generated by route B also retains the configuration as shown by Pd-catalyzed arylation reaction (eqn 96).



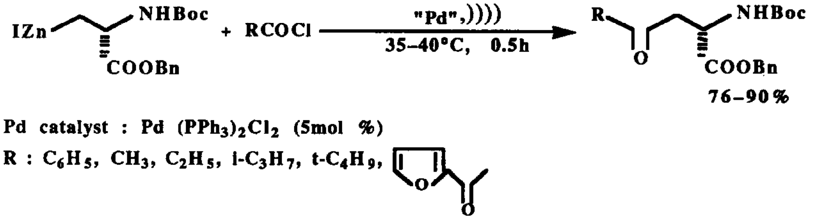
Cu catalyst : $CuBr.(CH_3)_2S$ (2,5 mol %)

Scheme 99.

 (96)

Pd catalyst : $Pd(PPh_3)_4$ (4 mol %%)

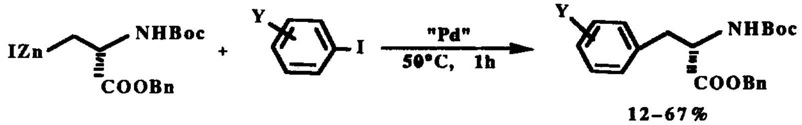
The organozinc reagent prepared from the 3-iodoalanine derivative reacts with acyl chlorides[142] and aryl iodides[143] under Pd-catalysis giving high yields of enantiomerically pure 3-acylalanine and 3-arylalanine derivatives, respectively, as reported by Jackson and coworkers (Schemes 100 and 101).[142,143] Protected 3-iodoalanine derivative was transformed to 3-(iodozincio)alanine derivative by treating with Zn–Cu couple in benzene–DMA followed by sonication. (*S*)-3-(Iodozincio)alanine



Pd catalyst : Pd $(PPh_3)_2Cl_2$ (5mol %)

R : C_6H_5, CH_3, C_2H_5, i-C_3H_7, t-C_4H_9,

Scheme 100.



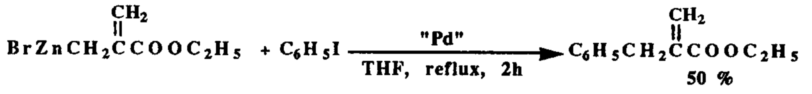
Pd catalyst : $Pd[P(2\text{-}CH_3C_6H_4)_3]_2Cl_2$ (5mol %)

Y : H, 2-CH_3CO, 2-F, 2-CH_3O, 4-CH_3CO, 4-Br, 4-CH_3, 4-NO_2

Scheme 101.

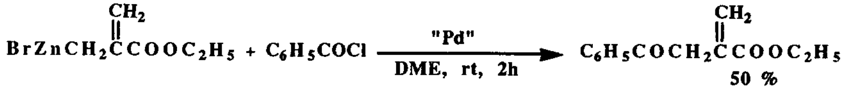
was acylated and arylated to provide (*S*)-alanine derivatives. (*R*)-3-(Iodozincio)alanine was also acylated with benzoyl chloride to give (*R*)-3-benzoylalanine derivative (62% yield). The use of 2-iodothiophene and 2-bromopyridine as heteroaryl halides in the reaction with (*S*)-3-iodozincioalanine resulted in 10% and 59% of arylation yields, respectively. (*S*)-3-(Iodozincio)alanine reacted with cyclohexenyl triflate (36%).

Villieras and coworkers investigated the reactions of the organozinc derivative of ethyl 2-bromomethyl acrylate with various electrophiles.[116] It was unreactive in alkylation and in conjugate addition reactions, but its arylation and acylation can be carried out in the presence of a Pd-catalyst (eqns 97 and 98).



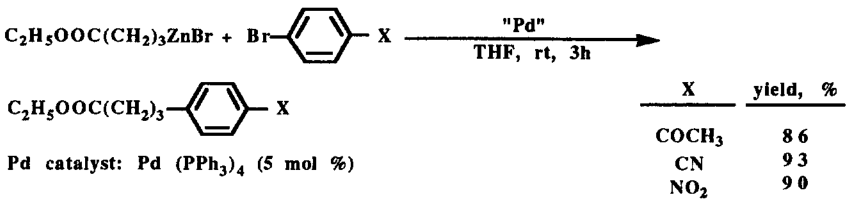
$$BrZnCH_2\overset{\overset{CH_2}{\|}}{C}COOC_2H_5 + C_6H_5I \xrightarrow[\text{THF, reflux, 2h}]{\text{"Pd"}} \underset{50\ \%}{C_6H_5CH_2\overset{\overset{CH_2}{\|}}{C}COOC_2H_5} \qquad (97)$$

Pd catalyst : $Pd(PPh_3)_4$ (3mol %)



$$BrZnCH_2\overset{\overset{CH_2}{\|}}{C}COOC_2H_5 + C_6H_5COCl \xrightarrow[\text{DME, rt, 2h}]{\text{"Pd"}} \underset{50\ \%}{C_6H_5COCH_2\overset{\overset{CH_2}{\|}}{C}COOC_2H_5} \qquad (98)$$

Rieke and coworkers recently reported[4] that highly reactive zinc prepared by the lithium naphthalenide reduction of zinc chloride also readily undergoes oxidative addition to ethyl 4-bromobutyrate as well as alkyl, aryl and alkenyl halides. Ethyl 4-(bromozincio)butyrate couples with *p*-substituted bromobenzenes (eqn 99).



Pd catalyst: Pd $(PPh_3)_4$ (5 mol %)

X	yield, %
$COCH_3$	86
CN	93
NO_2	90

(99)

A list of transition metal catalyzed remote Reformatsky reactions is given in Table 12.

6. CONCLUDING REMARKS

The increasing accessibility of transition metal catalysis in reactions of various organozinc reagents coupled with the use of activation methods for their preparation renders the organozinc reagents an important class of organometallic compounds.

The present review has tried to classify the transition metal catalyzed reactions of organozinc reagents and to show their synthetic advantages. However, reaction parameters as well as the factors which determine the outcome of the reactions have not been determined in many cases. Furthermore, a different chemo-, regio- and stereo-selectivity can be observed by the use of different catalysts. However, no generalisations have been made so far.

Many possibilities for the use of transition metal catalysis in the reactions of organozinc reagents remain to be investigated. It is hoped that this Report reflects the current rapid increase of the interest in this area.

TABLE 12

Transition metal catalyzed reactions of remote Reformatsky reagents

$$\mathrm{IZn(CH_2)_nCOY} + \text{Electrophile, EX} \xrightarrow{\text{Catalyst}} \mathrm{E(CH_2)_nCOY}$$

Y	n	electrophile, EX	catalyst	scheme and ref
OR	2	allylic halide	CuCN	scheme 91[131]
"	"	" "	CuBr. Me_2S	scheme 95[139],scheme 99[140]
"	"	" "	$Ni(dppf)Cl_2$	eq 94[139]
"	"	allylic tosylate	CuCN	scheme 91[131]
"	"	vinylic halide	$Pd[P(2\text{-}CH_3C_6H_4)_3]Cl_2$	scheme 97[139]
"	"	" "	CuBr. Me_2S	scheme 99[140]
"	"	vinylic triflate	$Pd(PPh_3)_4$	eq 82[130]
"	"	" "	$Pd[P(2\text{-}CH_3C_6H_4)_3]Cl_2$	scheme 97[139]
"	"	aryl halide	$Pd(PPh_3)_4$	eq 96[140], eq 97[116]
"	"	" "	$Pd[P(2\text{-}CH_3C_6H_4)_3]Cl_2$	scheme 87[130],scheme 96[139] scheme 101[143]
"	"	" "	CuBr. Me_2S	scheme 99[140]
"	"	aryl triflate	$Pd(PPh_3)_4$	scheme 90[38]
"	"	acyl halide	$Pd(PPh_3)_4$	scheme 86[129],eq 98[116]
"	"	" "	$Pd(PPh_3)_2Cl_2$	scheme 98[135, 139], scheme100[142],
"	"	α, β-unsaturated carbonyl compd.	CuCN	eq 84 and 85[134]
"	"	" "	CuBr. Me_2S	scheme 94[135, 139]
OR	3	allylic halide	CuCN	scheme 91[131]
"	"	allylic acetate	$Pd(PPh_3)_4$	eq 83[131]
"	"	allylic tosylate	CuCN	scheme 91[131]
"	"	vinylic iodide	$Pd(PPh_3)_4$	scheme 88[130]
"	"	vinylic triflate	$Pd(PPh_3)_4$	scheme 88[130]
"	"	aryl halide	$Pd[P(2\text{-}CH_3C_6H_4)_3]Cl_2$	scheme 87[130]
"	"	" "	$Pd(PPh_3)_2Cl_2$	scheme 89[34]
"	"	" "	$Pd(PPh_3)_4$	eq 99[4]
"	"	acyl halide	$Pd(PPh_3)_4$	scheme 86[129, 133]
"	"	α, β-unsaturated carbonyl compd.	CuCN	scheme 92[134],eq 87[134]
OR	4	allylic tosylate	CuCN	scheme 91[131]
R	2	acyl halide	$Pd(PPh_3)_4$	scheme 93[132]
R	3	vinyl iodide	$Pd(PPh_3)_4$	eq 90[132]
"	"	vinyl triflate	$Pd(PPh_3)_4$	eq 89[132]
"	"	aryl halide	$Pd[P(2\text{-}CH_3C_6H_4)_3]Cl_2$	eq 88[132]
"	"	acyl halide	$Pd(PPh_3)_4$	scheme 93[132]
R	4	allylic halide	CuCN	eq 91[132]
"	"	acyl halide	$Pd(PPh_3)_4$	scheme 93[132]
CN	2	α, β-unsaturated carbonyl compd.	CuCN	eq 85[134]
"	3	α, β-unsaturated carbonyl compd.	CuCN	eq 86[134]

Note added in proof—Since this Report has been written, I have become aware of Seebach's relevant publication, which describes enantioselective addition of dialkylzinc compounds to aldehydes catalyzed by a spirotitanate synthesized from (*R*,*R*)-tartaric acid.[144]

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