



III.2.12 Palladium-Catalyzed Cross-Coupling Involving α -Hetero-Substituted Organic Electrophiles

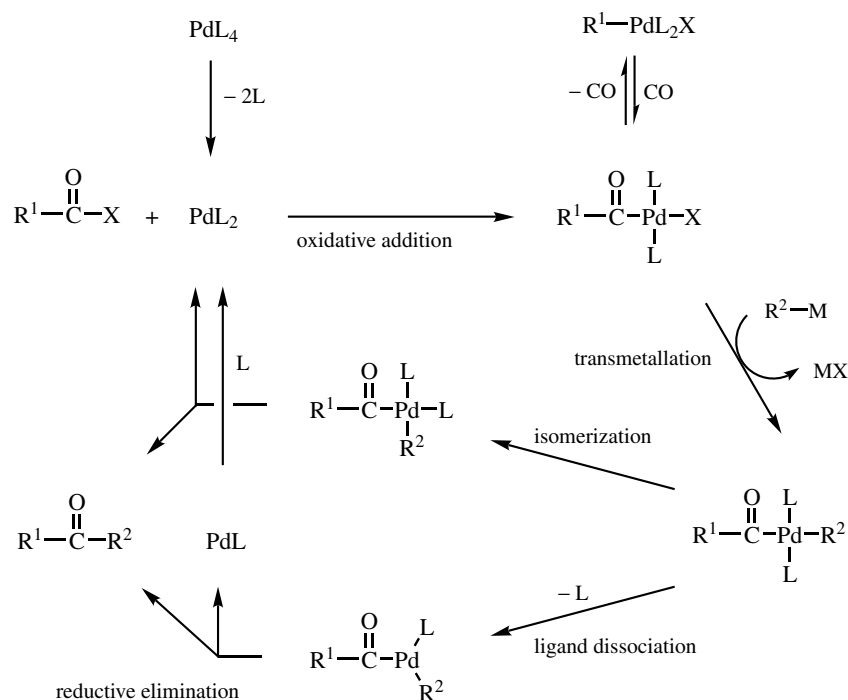
III.2.12.1 Palladium-Catalyzed Cross-Coupling with Acyl Halides and Related Electrophiles

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A. INTRODUCTION

Although the Pd-catalyzed cross-coupling reactions of organometallic compounds with alkenyl and aryl halides to produce the substituted alkenes and arenes have been extensively investigated (see previous sections), the reaction with acyl halides giving ketones has attracted little attention. The major reason may be the existence of various known methods. A variety of organometallic compounds, such as organomagnesium,^[1] zinc,^[1] cadmium,^[1] aluminum,^[2] copper,^[3] iron,^[4] boron,^[5] rhodium,^[6] silicon,^[7] mercury,^[8] manganese,^[9] zirconium,^[10] and tin compounds,^[11] have frequently been used for reactions with acyl halides. Even when the reactions are carried out under strictly controlled conditions, the side reaction upon the further addition of the organometallic compounds to the produced ketones cannot be suppressed completely. To overcome this problem, mild conditions using organotransition metal complexes, especially palladium-derived ones, as catalysts have been developed. The plausible mechanism of the Pd-catalyzed cross-coupling reaction of organometallic compounds with acyl halides is shown in **Scheme 1**.

First, coordinatively unsaturated active palladium catalyst, PdL_2 , is produced via dissociation of the ligands, which then reacts with acyl halide to give the acylpalladium intermediate. Since deinsertion of CO of the acylpalladium derivatives may occur simultaneously,^[12] the next step, transmetalation (so-called metathesis), is the most crucial for the efficiency of the overall reaction. A variety of organometallic compounds, such as boron, aluminum, copper, zinc, mercury, silicon, tin, lead, zirconium, and bismuth, are used as the partner in this coupling reaction without loss of CO. In this section, the important features of the cross-coupling reactions of a variety of organometallic compounds with acyl halides and related electrophiles are discussed.

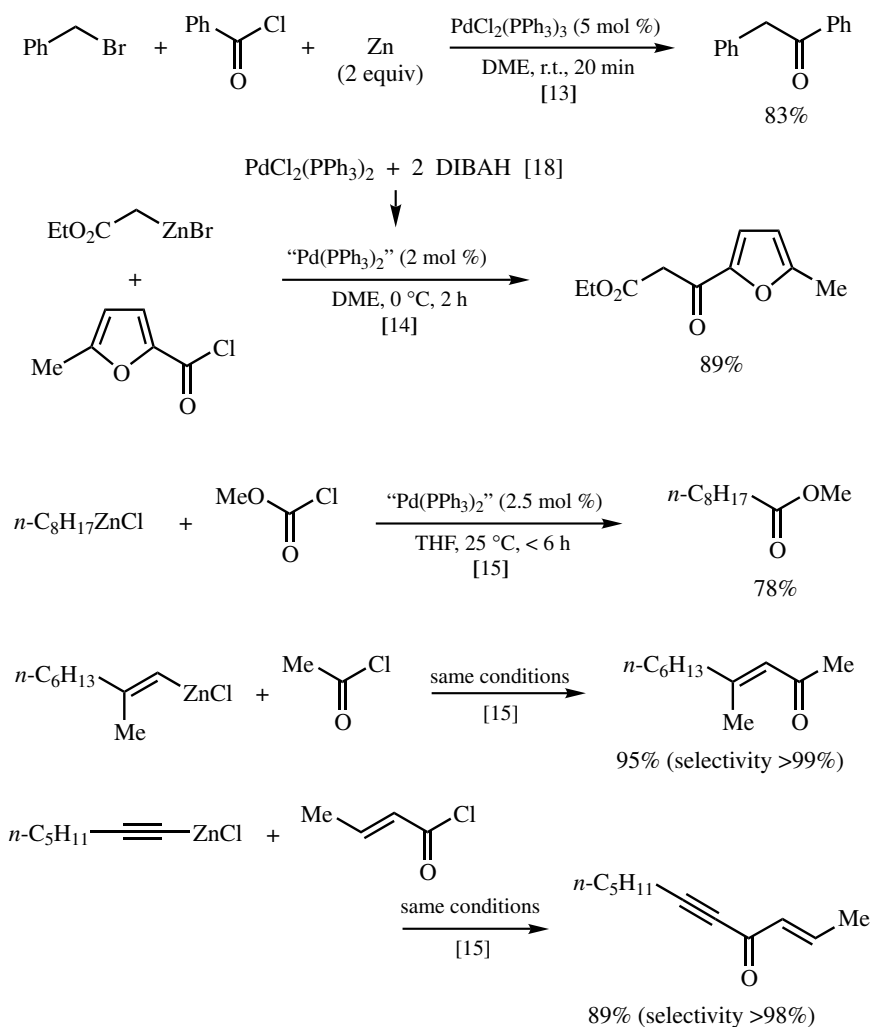


B. COUPLING REACTIONS WITH ORGANOZINC COMPOUNDS

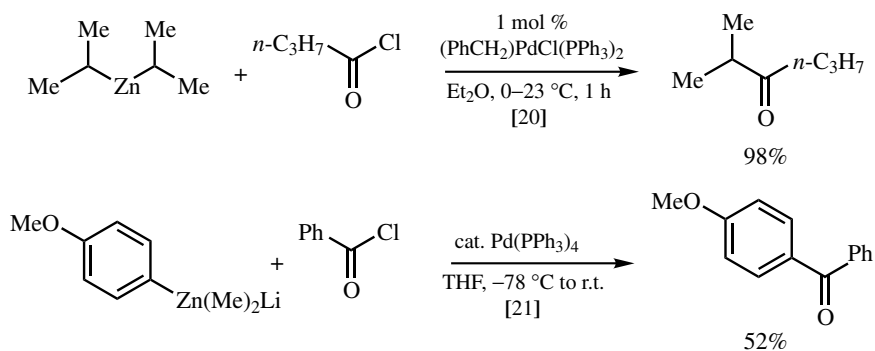
As discussed before (**Sect. III.2.1**), Pd-catalyzed cross-coupling reactions of organozinc compounds with alkenyl and aryl halides can be carried out under mild conditions and are the fastest among all reactions using various organometallics. The reaction with acyl halides is not an exception. Usually, the reaction is completed at lower than room temperature within a couple of hours.^{[13]–[16]} Since organozinc compounds are coordinatively unsaturated and sterically less bulky, the transmetallation step is facilitated,^[17] therefore the overall reaction proceeds under mild conditions. Another interesting feature using organozinc compounds is that not only alkenyl and alkenyl groups but also an alkyl group can couple with acyl chlorides with great success (**Scheme 2**).^[15]

It is known that alkylpalladium intermediates having β -hydrogens tend to undergo dehydropalladation to give the alkenes.^[19] This process can be suppressed completely by the use of organozinc compounds to give the desired alkyl ketones in excellent yields even when the alkylzinc compounds have β -hydrogens.^[15] Not only alkenyl and aryl chlorides but also alkyl chloride and chloroformates can be used as the partner in this coupling reaction.^[15] While monoalkylzinc halides^{[13]–[15]} and dialkylzincs^[20] can be used for the cross-coupling reaction with acyl chlorides, the reaction of lithium trialkylzincate does not proceed efficiently (**Scheme 3**).^[21]

When organozinc halides are synthesized *in situ* by the reaction of organic halides with zinc metal or the zinc–copper couple, DME or benzene–DMA can be used as the solvent.^{[13],[14],[16]} In the case of organozinc halides prepared by transmetallation of



Scheme 2



Scheme 3

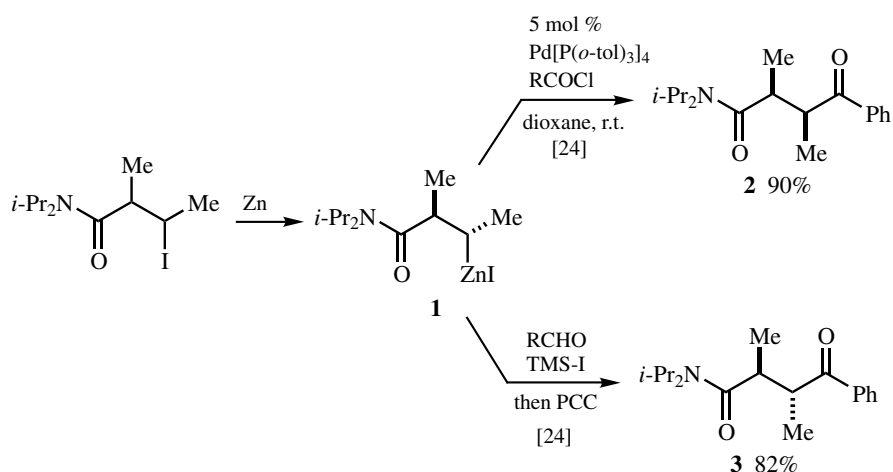
the corresponding lithium or magnesium compounds with zinc halides, use of THF as the solvent is necessary to bring about satisfactory results, whereas the reaction in Et₂O or THF-Et₂O becomes sluggish.^[15] In contrast, Et₂O can also be used as the solvent in the coupling reaction of dialkylzincs prepared by the transmetallation method.^[20]

A variety of palladium–phosphine complexes are used as catalyst in the cross-coupling reactions. Since the coordinatively unsaturated palladium complexes are considered as the active catalyst, Pd(PPh₃)₂, which is prepared by treatment of PdCl₂(PPh₃)₂ with 2 equiv of DIBAH^[18] or *n*-BuLi,^[22] is reliable to carry out the reaction successfully. The use of Pd[P(*o*-tol)₃]₄, which easily produces the coordinatively unsaturated complex due to the steric repulsion between the ligands, also brings about good results.^{[16],[23],[24]}

Organozinc compounds can be prepared by direct metallation of organic halides with zinc metal. The procedure makes the coupling reaction more convenient. A mixture of alkyl halide, acyl chloride, and zinc metal upon stirring in the presence of palladium catalyst at room temperature gives the desired ketone.^{[13],[14]} While direct metallation can be carried out efficiently when the zinc–copper couple is used in some cases,^{[16],[25]} the presence of copper ion sometimes prevents the coupling reaction with acyl chloride.^[26]

An interesting feature of the reaction of organozinc compounds is shown in **Scheme 4**.^[24] Reaction of β -iodozinc derivative **1** with benzoyl chloride in the presence of Pd[P(*o*-tol)₃]₄ catalyst gave the *syn*-isomer **2**, while the *anti*-isomer **3** was produced by reaction of **1** with benzaldehyde followed by oxidation. The nucleophilic addition to the aldehyde occurs via inversion of the configurations in contrast to the Pd-catalyzed cross-coupling reaction, which proceeds via retention of the configurations.

The Pd-catalyzed cross-coupling reaction of organozinc compounds is fast and can be carried out under mild conditions. Simple extracting work-up gives the desired products, since the by-product of the reaction is water-soluble ZnX₂. When the functional groups present do not easily react with organozinc compounds, this method is the most convenient.



Scheme 4

C. COUPLING REACTIONS OF ORGANOTIN COMPOUNDS

Since Heck suggested the potential utility of organotin compounds for his reaction,^[27] the cross-coupling reaction of organotin compounds with acyl halides has been studied extensively due to their ease of handling.^{[28],[29]} Not only alkyl, alkenyl, aryl, and alkynyl groups but also hydride^[30] is coupled with acyl halides to give the corresponding ketones and aldehydes. The ease of transfer of alkyl group (R^1) from the tin center to acyl carbon follows the order $R^2 = \text{PhC}\equiv\text{C}- > n\text{-PrC}\equiv\text{C}- > \text{PCH}=\text{CH}- \approx \text{CH}_2=\text{CH}- > \text{Ph} > \text{PhCH}_2 > \text{CH}_3\text{OCH}_2 > \text{CH}_3 > n\text{-Bu} \approx \text{Et} > i\text{-Pr}$ (**Table 1**).^[31]

The rate of alkyl transfer of Me_4Sn is five times faster than that of Me_3SnCl , which is presumably produced in the coupling reaction of Me_4Sn with acyl chlorides, and Me_2SnCl_2 and MeSnCl_3 are inert for the coupling reaction.^[29] Moreover, disproportionation of organotin halides does not happen easily. This is the reason why more than 1 equiv of organotin compounds is required to bring about fruitful results in the coupling reaction.

Originally, benzene and HMPA were used as the solvent in the reaction,^{[28],[29]} but later 1,2-dichloroethane and CHCl_3 were found to be as good as HMPA.^{[32],[33]} Oxygen has an accelerating effect on the reaction, and thus, the reaction is reported to be carried out under air atmosphere. In some cases, deinsertion of CO of the acylpalladium intermediate may occur, and this results in lowered yields of the desired ketones. To suppress the deinsertion, the reaction is sometimes carried out under an atmospheric pressure of CO.^[33] Typical examples of the coupling reactions are shown in **Scheme 5**.

Another way to suppress the possible decarbonylation of the acylpalladium intermediate is promotion of transmetalation by addition of a catalytic amount of ZnCl_2 ^[34] or CuI ^[35]. Since a single transmetalation process of high activation energy could be replaced by multiple transmetalation processes of low kinetic barriers, coordinatively unsaturated metal salts having low steric requirement, such as Zn and Cu salts, can be utilized to promote the transmetalation.^[17]

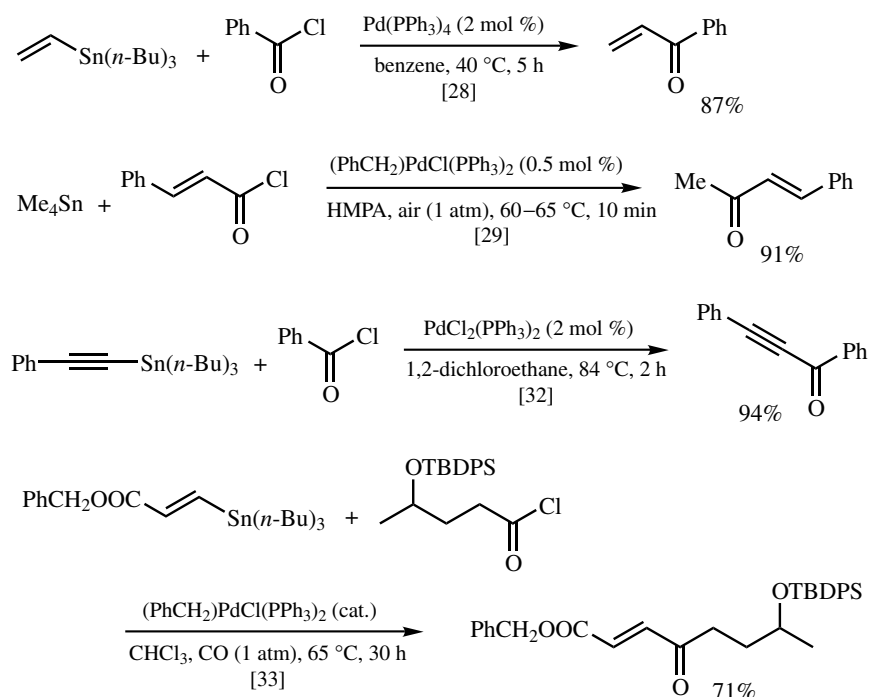
Not only acyl chloride but also sulfonyl chloride^[36] and isocyanide dichloride^[37] can be used in the coupling reaction (**Scheme 6**).

TABLE 1. Relative Reaction Rates of Benzoyl Chloride with Organotins Catalyzed by $(\text{PhCH}_2)_2\text{PdCl}(\text{PPh}_3)_2$ ^[31]

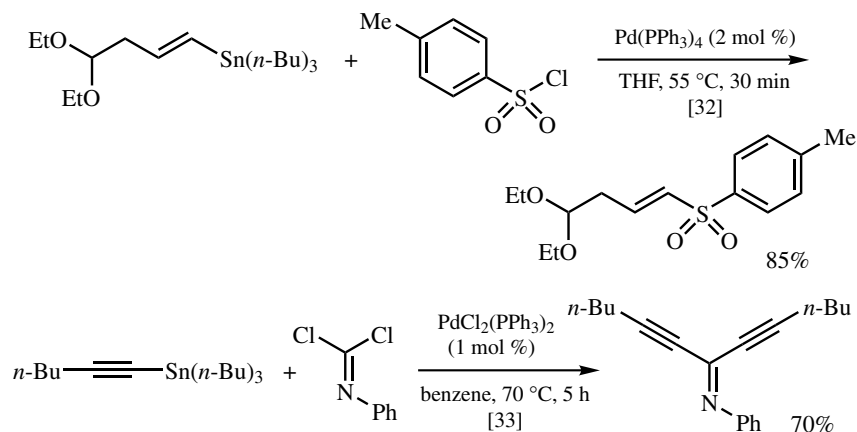
$$\begin{array}{c}
 5 \text{ R}^1_3\text{SnR}^2 \\
 + \\
 \text{Ph}-\text{C}(=\text{O})-\text{Cl} \\
 \text{O}
 \end{array}
 \xrightarrow[\text{solvent, 65 } ^\circ\text{C}]{(\text{PhCH}_2)_2\text{PdCl}(\text{PPh}_3)_2 \text{ (2.5-3.0 mol \%)}}
 \begin{array}{c}
 \text{R}^2-\text{C}(=\text{O})-\text{Ph} \\
 \text{O}
 \end{array}$$

$$\begin{array}{c}
 5 \text{ R}^1_3\text{SnPh}
 \end{array}
 \xrightarrow[\text{solvent, 65 } ^\circ\text{C}]{(\text{PhCH}_2)_2\text{PdCl}(\text{PPh}_3)_2 \text{ (2.5-3.0 mol \%)}}
 \begin{array}{c}
 \text{Ph}-\text{C}(=\text{O})-\text{Ph} \\
 \text{O}
 \end{array}$$

R ¹	Solvent	R ₂							
		PhCC-	<i>n</i> -PrCC-	PhC=C-	CH ₂ =CH-	Ph-	PhCH ₂ -	CH ₃ -	<i>n</i> -Bu-
Me	CHCl ₃	46	21	10	8	1	—	0.1	—
<i>n</i> -Bu	CHCl ₃	100	48	10	17	1	—	—	0.01
<i>n</i> -Bu	HMPA	—	>100	—	70	1	0.5	—	0.14



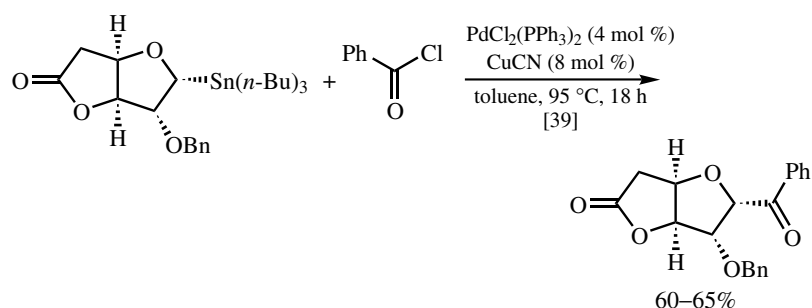
Scheme 5



Scheme 6

For the palladium catalysts, the order of catalytic activity is as follows: $\text{PdCl}_2(\text{PPh}_3)_2 > \text{BnPdCl}(\text{PPh}_3)_2 \approx \text{Pd}(\text{PPh}_3)_4 > \text{PhPdCl}(\text{PPh}_3)_2$.^[32] The combination of $\text{Pd}_2(\text{dba})_3/\text{CHCl}_3$ and AsPh_3 or $\text{P}(2\text{-furyl})_3$ has been reported as the best catalyst so far.^[38]

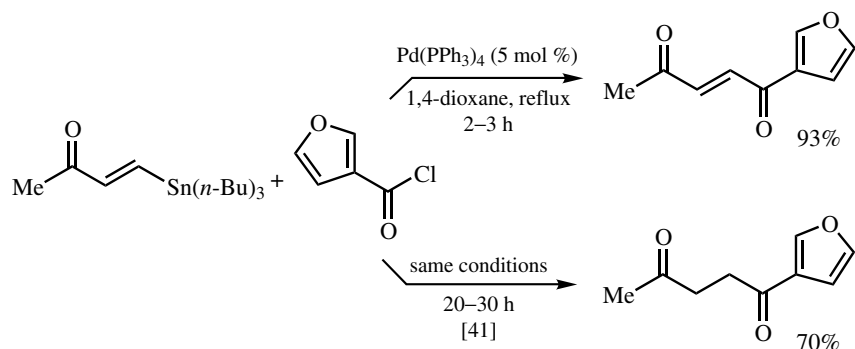
Tetraalkyltin compounds having the chiral alkoxy group at the α -position undergo the Pd-catalyzed cross-coupling reaction of acyl chlorides with complete retention of the configuration (Scheme 7).^{[39],[40]}



Scheme 7

During the reaction, trialkyltin chloride is produced as the by-product. Tributyltin chloride is known to react with the palladium complex to produce the hydropalladium species via β -hydrogen elimination. If the reaction takes a long time, 2-buten-1,4-dione moiety is reduced (Scheme 8).^[41]

The coupling reactions of organotin compounds have been widely used, since these compounds are quite stable in water. The by-products, such as R_3SnX , are considered possible nervous system disturbing agents and/or endocrine disrupting chemicals. Researchers should be very careful when carrying out these reactions.



Scheme 8

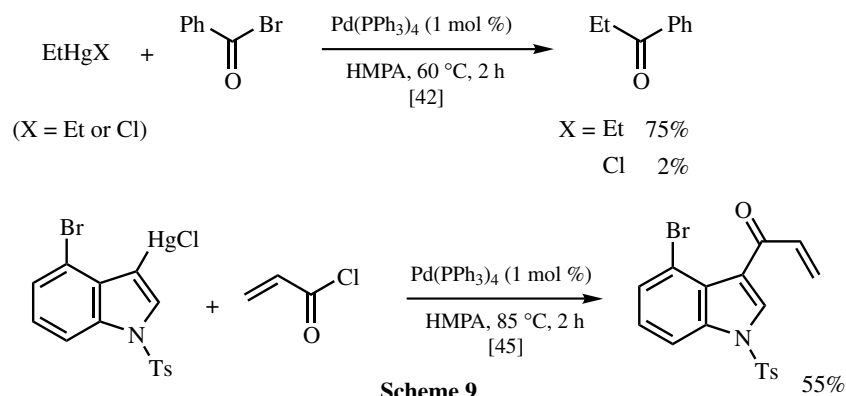
D. COUPLING REACTIONS OF ORGANOMERCURY COMPOUNDS

Historically, the first report of the Pd-catalyzed cross-coupling reaction with acyl halide used organomercury compounds.^[42] Although alkyl- and arylmercury chlorides did not work, the use of dialkyl- and diarylmercury compounds gave the desired ketones in good yields. Acyl bromides are necessary to bring about fruitful results. The use of HMPA as the solvent is also unavoidable (Scheme 9).

Arylmercury chlorides can also be coupled with acyl chloride in the presence of iodine and a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$.^{[43],[44]} In this case, not only HMPA but also acetone and THF can be used as the solvent. More recently, the Pd-catalyzed coupling reaction of

3-(chloromercurio)indol and acryloyl chloride has been carried out without additives (**Scheme 9**).^[45] The reactivity of organomercury compounds in the coupling reaction depends on the type of functionality present.

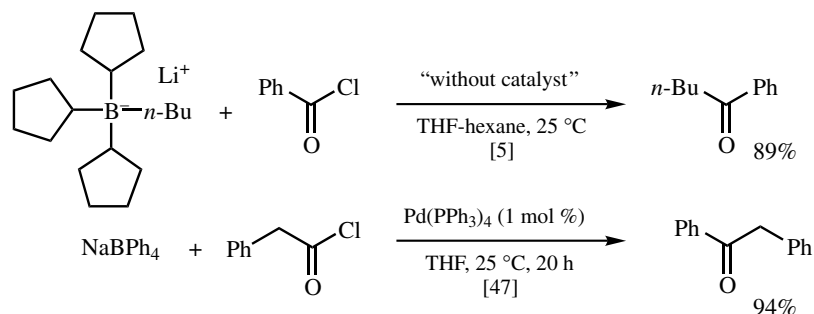
Some organomercury compounds are known to be highly toxic. This may be the reason why the reactions using organomercury compounds have not been studied extensively.



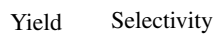
E. COUPLING REACTIONS OF ORGANOBORON, ALUMINUM, COPPER, SILICON, LEAD, BISMUTH, AND ZIRCONIUM COMPOUNDS

Other organometallic compounds have also been utilized for the coupling reaction with acyl halides.

The Suzuki protocol (see **Sect. III.2.2**) for organoboron compounds [R_3B and RB(OR')_2] cannot be applied for the cross-coupling reaction, since acyl halides react readily with NaOH to give the less reactive carboxylic acids. Instead of these organoboranes, organoborates (R_4B^-) were used for the reaction. Actually, organoborates themselves are known to react with acyl chlorides smoothly in THF-hexane mixed solvent system to give the desired ketones in good yields (**Scheme 10**).^{[5],[46]} Neither alkenylboranes nor alkenylborates undergo clean acylation even in the presence of palladium catalyst.^[15] In contrast, when sodium tetraphenylborate was used, the coupling reaction with acyl chlorides did not proceed, but the desired ketones were produced in the presence of palladium catalyst (**Scheme 10**).^[47]



by palladium (**Scheme 11**).^[15]



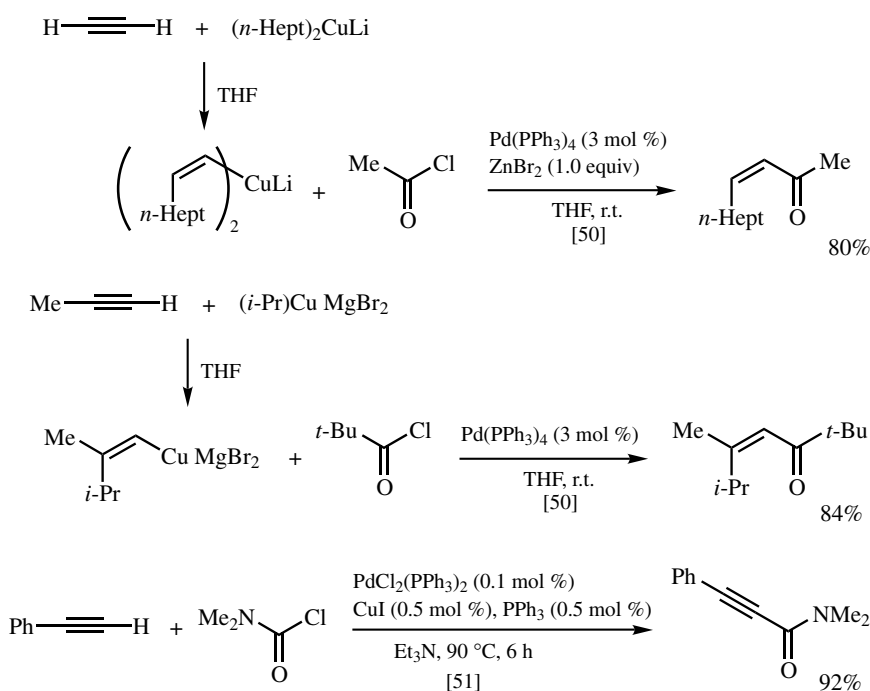
Scheme 11

chlorides to give α -diketones (**Scheme 12**).^[49]



Scheme 12

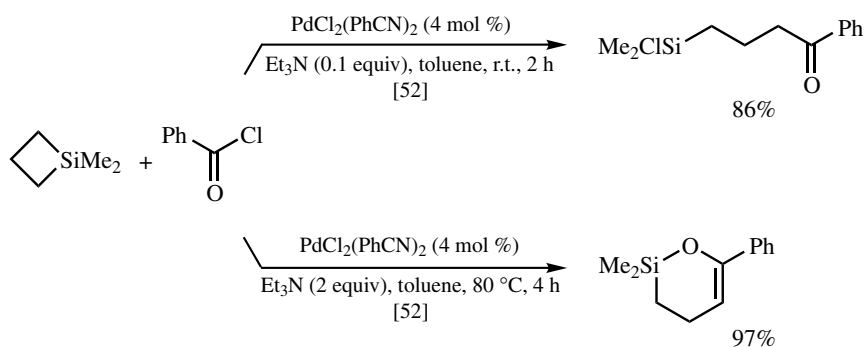
Organocopper compounds are known to react with acyl halides to produce ketones.^[3] In the case of alkenyl- and alkynylcopper compounds, however, the conjugated addition of the organocopper compounds to the resultant ketones has been observed. To carry out the reaction successfully, palladium–phosphine complexes are used as catalysts. Alkenylcopper compounds in association with magnesium salts couple with acyl halides in the presence of $\text{Pd}(\text{PPh}_3)_4$ to give the desired ketones in good yields (**Scheme 13**).^[50] In the case of lithium dialkenylcuprate, MgCl_2 or ZnCl_2 is required to perform the coupling reaction successfully. The coupling reaction of alkynes with acyl halides can be carried out in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI catalysts (**Scheme 13**).^[51]



Scheme 13

Tetraalkylsilanes are stable compounds. Therefore, it is necessary to activate the compounds for the coupling reaction. Since dialkylsilacyclobutanes have high strain energy, palladium complexes can easily insert into the carbon–silicon bond oxidatively, and the resultant complexes couple with acyl chlorides to give 1-sila-2-oxa-3-cyclohexene derivatives (**Scheme 14**).^[52]

As mentioned before, the Pd-catalyzed coupling reaction of tetraalkyltins with acyl halides is troublesome: the reaction is slow and requires high temperature. In particular, when tetraalkyltin compounds bearing longer alkyl chains are used, the reaction becomes sluggish. In such cases, tetraalkylleads can be used instead of tetraalkyltins (**Scheme 15**).^[53] It is noteworthy that two alkyl groups on the lead can be used for the coupling reaction, whereas only one alkyl group can couple with acyl chlorides when organotin compounds are used. The reason for the different reactivity is presumably

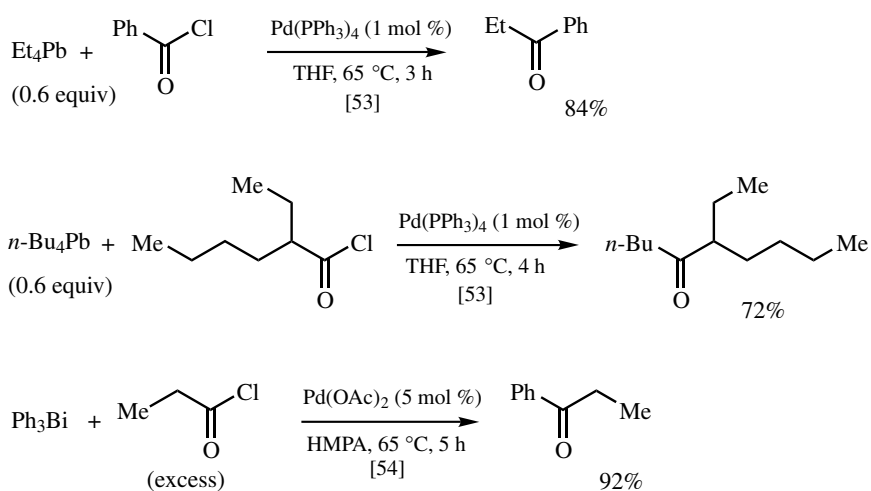


Scheme 14

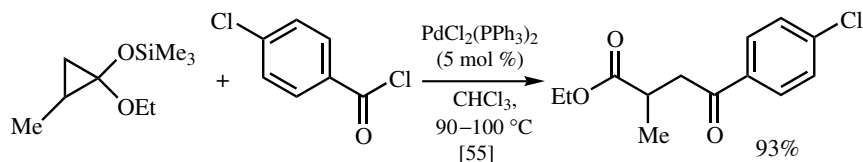
due to the ease of disproportionation of trialkylchloroleads to tetraalkylleads and dialkyldichloroleads.

Triphenylbismuth can also be utilized for the coupling reaction (**Scheme 15**).^[54] All three phenyl groups on bismuth can be used, since disproportionation of the intermediary dialkylchloro- and alkyldichlorobismuth is fast.

Siloxycyclopropanes are considered as homoenolate equivalents and also undergo the coupling reaction with acyl halides to produce 1,4-dicarbonyl compounds (**Scheme 16**).^[55]



Scheme 15



Scheme 16

F. SUMMARY

1. Palladium-catalyzed coupling reactions of organozinc compounds with acyl halides are the fastest and mildest among the known methods using a variety of organometallic compounds.

2. Since organotin compounds are stable to water and oxygen, the method has widely been utilized for the synthesis of various compounds although the reaction requires a long time and high temperature.

3. Organometallic compounds, such as organomercury, boron, aluminum, zirconium, copper, silane, lead, and bismuth, can also be utilized for the coupling reactions, although these methods have not been studied extensively.

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