Reviews

Reactions of organic halides with organometallic compounds and terminal acetylenes catalyzed by palladium complexes

N. A. Bumagin

Department of Chemistry, M. V. Lomonosov Moscow State University,
Vorob'evy Gory, 119899 Moscow, Russian Federation.
Fax: 007 (095) 939 0126. E-mail: bna@bumagin.chem.msu.su

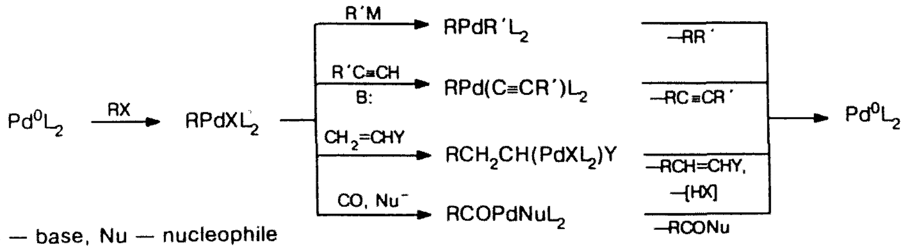
The results of the investigation of the cross-coupling of organometallic compounds and terminal acetylenes with organic halides catalyzed by transition metal complexes are generalized and analyzed. The influence of different factors on the rate and selectivity of catalytic cross-coupling is discussed. A detailed mechanism of the cross-coupling of Grignard reagents with organic halides is suggested. The cross-coupling reaction involving organotin compounds proceeds under very mild conditions in the presence of a ligand-free Pd catalyst. Examples of using catalytic cross-coupling of organic halides with organomagnesium, organozinc, and organotin compounds are presented.

Key words: organometallic compounds, organic halides, cross-coupling reaction; palladium, catalysis.

Introduction

Of the numerous reactions of organic and organometallic substrates involving transition metals, the reactions of organic electrophiles with nucleophilic reagents catalyzed by Pd complexes play a special role. Processes of this type proceed *via* the common palladium intermediate $RPdXL_2$ formed due to the oxidative addition of the organic electrophile RX to the Pd^0 complex. The $RPdXL_2$ complexes are highly reactive and react readily with organometallic compounds (OMC), terminal alkynes, olefins, and carbon oxide (Scheme 1). The subsequent transformations of the palladium complexes formed result in the regeneration of

Scheme 1



B — base, Nu — nucleophile

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 2148—2167, September, 1996.

the Pd^0 complex and the formation of the corresponding products containing the substituent R.

Unlike "classical" reactions, the reactions presented in Scheme 1 occur selectively, under mild conditions, and in high yields, which makes them useful for synthesis. However, wide adoption of similar catalytic processes in the everyday practice of organic synthesis is prevented by the use of rather difficult to obtain and expensive phosphine Pd complexes as catalysts in these processes. Easily accessible Pd^{II} salts could be used as catalysts to avoid the application of these reagents and, in addition, to provide chemists with a new powerful method for the synthesis of drugs, natural compounds, liquid crystals, herbicides, and dyes. In addition, "classical" and catalytic organic reactions usually occur in such toxic and flammable solvents such as THF, ether, benzene, HMPA, DMF, and others. It seemed very attractive to eliminate if possible the use of organic solvents and to perform the catalytic reactions in an aqueous medium.

The present review opens a series of publications that will generalize and analyze the results of studies of catalytic reactions involving Pd complexes (see Scheme 1) performed by the author and co-workers in the M. V. Lomonosov Moscow State University from 1979 to 1996. It has been shown that Pd compounds containing no phosphine ligands are considerably more efficient catalysts than phosphine palladium complexes. We conventionally call these catalysts "ligand-free" palladium complexes, although they can contain molecules of the solvent and the reagents, and various anions as weakly coordinated ligands. Since bulky "ballast" phosphine ligands are absent in the coordination sphere of Pd, particular stages of the catalytic cycles occur very easily and rapidly, which makes it possible for the catalytic processes presented in Scheme 1 to occur under considerably milder conditions at high rates.

Palladium-catalyzed reactions of organic halides with organometallic compounds

Cross-coupling of organometallic compounds with organic halides catalyzed by Pd or Ni complexes[1–3] is widely used in modern organic synthesis for the formation of new carbon—carbon bonds.

$$RM + R'X \longrightarrow R{-}R' + MX \qquad (1)$$

The cross-coupling reaction was discovered in 1972 in two independent research groups,[4,5] which showed that the reactions of organolithium compounds and Grignard reagents with alkenyl and aryl halides occur readily in the presence of Ni complexes. In 1975, the $Pd(PPh_3)_4$ complex was established to be an efficient catalyst of the reaction.[6] The use of less reactive organic derivatives of Zn,[7] Al,[8] Zr,[9] B,[10] Sn,[11] and Hg [12] in cross-coupling reactions widened considerably the synthetic possibilities of the cross-coupling method and made it possible to develop ways for synthesizing various classes of organic compounds containing almost any functional groups.

However, the catalytic reactions of organic halides with OMC often result in the formation of the products of homocoupling — R_2 and R'_2. The ratio between the cross- and homocoupling products in the reactions of R'X with RM catalyzed by transition metal complexes is determined by the nature of the R and R' groups, the type of the nontransition metal M in the organometallic reagent, and the nature of the transition metal whose complex is used as the catalyst. The nature of the ligands in the transition metal complex (mono- or bidentate, alkyl- or arylphosphine, *etc.*) often plays a crucial role. Despite a seeming abundance of published data, the effects of these factors on the duration and selectivity of reaction (1) has been poorly studied. The mechanism of the formation of by-products has also not been studied well. The question of what groups of OMC or organic halides are preferable for insertion into the cross-coupling product has almost not been considered at all. Therefore, we have studied the effects of the factors listed above on the regularities of catalytic cross-coupling reactions.

Effects of the type of nontransition metal, the organic groups, the structure of the reagent, and the composition of the catalyst on the regularities of cross-coupling. The reactions of phenyl and ethynyl metal derivatives with 4-iodoanisole[13] were chosen as model reactions to study the effect of the nature of the nontransition metal in OMC on the duration and selectivity of reaction (1).

$$PhM + 4\text{-}MeOC_6H_4I \xrightarrow{[Pd]} 4\text{-}MeOC_6H_4Ph + Ph_2 + (4\text{-}MeOC_6H_4)_2 \qquad (2)$$

$M = Li, MgCl, ZnCl, CdCl, Cu, B(OMe)_2, AlPh_2, TiCl_3$

Reagents and conditions: 1 mol.% $PdCl_2(PPh_3)_2$ or $PdCl_2(MeCN)_2$, THF—ether (2 : 1), PhM : ArI = 1.5 : 1.0, 20 °C, $C_0 = 0.25$ mol L^{-1}.

In all cases (except the reactions with Zn and Al derivatives), the homocoupling products, Ph_2 and $(4\text{-}MeOC_6H_4)_2$, are formed in considerable amounts along with the cross-coupling product, $4\text{-}MeOC_6H_4Ph$. The maximum rate and selectivity are observed for the reaction of 4-iodoanisole with PhZnCl, which gives 4-methoxydiphenyl in quantitative yield in 5 min for any type of Pd catalyst used. Unlike magnesium and zinc derivatives, triphenylaluminum in the presence of $PdCl_2(PPh_3)_2$ does not react with 4-iodoanisole at room temperature. However, $4\text{-}MeOC_6H_4Ph$ in 90% yield is obtained at 50 °C in 6 h. Unfortunately, only one phenyl group of Ph_3Al is involved in the cross-coupling.

Unlike reaction (2), no homocoupling product is formed from organic halide in the reactions of phenylethynyl metal derivatives with 4-iodoanisole.

$$\mathrm{PhC{\equiv}CM + 4\text{-}MeOC_6H_4I \xrightarrow{[Pd]} 4\text{-}MeOC_6H_4C{\equiv}CPh + (PhC{\equiv}C)_2} \qquad (3)$$

M = Li, MgBr, ZnCl, Bu^i_2Al, Cu

Reagents and conditions: 1 mol.% $PdCl_2(PPh_3)_2$, $PdCl_2(MeCN)_2$, or $PdCl_2(dppf)$; THF, PhC≡CM : ArI = 1.5 : 1.0, 20 °C, C_0 = 0.25 mol L^{-1}.

When phosphine Pd complexes are used as the catalysts, magnesium and zinc phenylacetylenides react readily to give the cross-coupling products in quantitative yields. The maximum rate is observed for the reaction of PhC≡CZnCl catalyzed by $PdCl_2(dppf)$ (dppf is 1,1′-bis(diphenylphosphino)ferrocene). Pd complexes containing no phosphine ligands exhibit, unlike phenyl metal derivatives, low catalytic activity. The complex $PdCl_2(MeCN)_2$ turned out to be the most efficient catalyst in the case of $PhC{\equiv}CAlBu^i_2$. In the presence of this complex, the reaction occurs at a low rate, but relatively selectively. Copper phenylacetylenides react smoothly with 4-iodoanisole in HMPA in the presence of Bu_4NI.

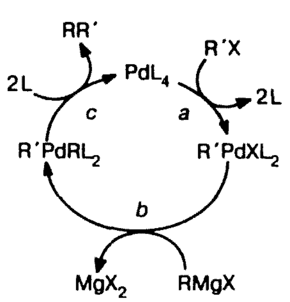
The cross- and homocoupling products and anisole are formed in the reactions of Mg and Zn vinyl derivatives with 4-iodoanisole catalyzed by $PdCl_2(PPh_3)_2$.[14]

$$\mathrm{CH_2{=}CHM + 4\text{-}MeOC_6H_4I \xrightarrow[2.\ MeOH]{1.\ [Pd]} \underset{(69\text{—}70\%)}{4\text{-}MeOC_6H_4CH{=}CH_2} + \underset{(15\text{—}19\%)}{(4\text{-}MeOC_6H_4)_2} + \underset{(\sim 10\%)}{MeOPh}} \qquad (4)$$

The zinc derivative $CH_2{=}CHZnCl$ reacts with 4-iodoanisole at a higher rate than vinylmagnesium bromide, but the selectivity of the reaction remains low. The formation of the homocoupling products can be suppressed completely using $PdCl_2(dppf)$ as the catalyst, in the presence of which reaction (4) results in the formation of 4-methoxystyrene in quantitative yield.

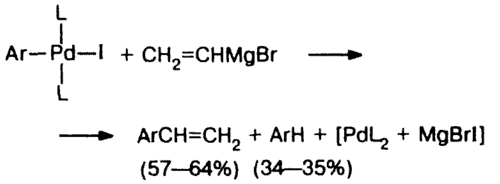
Thus, homocoupling products R_2 and R'_2 as well as hydrocarbons R′H are formed along with cross-coupling products RR′ in many reactions of organometallic compounds RM with organic halides R′X catalyzed by Pd complexes. It is noteworthy that the catalytic cycle (Scheme 2)[15] usually discussed in the literature, which includes the stages of oxidative addition (*a*), transmetallation (*b*), and reductive elimination (*c*), reflects only the most general features of cross-coupling. It does not take into account, for example, configurations of Pd complexes with one and two σ-linked organic groups, the mechanisms of isomerization of the complexes, ligand exchange, and the formation of by-products.

Scheme 2



The study of the stoichiometric reactions of the $RPdR'L_2$ complexes with organic halides[16] and Grignard reagents[17] allowed one to establish that reductive elimination occurs only from $RPdR'L_2$ complexes in the *cis*-configuration; *trans*—*cis*-isomerization is promoted by organomagnesium compounds; and the reductive elimination of R—R′ from *cis*-$RPdR'L_2$ proceeds *via* the dissociative mechanism through the T-like intermediate *cis*-[RPdR′L]. The acceleration of reductive elimination from the *trans*-Ar_2PdL_2 complexes in the presence of organic halide mentioned previously[18,19] is caused by the fast isomerization of *trans*-Ar_2PdL_2 to *cis*-Ar_2PdL_2 under the action of *trans*-$Ar'PdIL_2$, which is formed due to the oxidative addition of Ar′I to Pd^0L_2, rather than by the intermediate formation of Pd^{IV} complexes (see Ref. 18). The isomerization catalyzed by $Ar'PdIL_2$ is accompanied by the exchange of organic groups, which results in the formation of diaryl compounds of three types:[16] Ar_2, ArAr′, and Ar'_2.

However, if there is a constant excess of RMgX in the reaction under the catalytic conditions (RMgX : R′X : Pd ≈ 1.50 : 1.00 : 0.01), the *trans*-$RPdR'L_2$ → *cis*-$RPdR'L_2$ isomerization under the action of $RPdXL_2$ seems highly improbable, because the $RPdXL_2$ complex undergoes rapid *trans*-transmetallation with RMgX. We assumed that the *trans*—*cis*-isomerization of $RPdR'L_2$ in catalytic cross-coupling reactions occurs under the action of an organomagnesium compound (*cf.* Ref. 17). This was proved by a study of the stoichiometric reactions of $ArPdIL_2$ (Ar = 4-PhC_6H_5) with vinylmagnesium bromide ($ArPdIL_2$: $CH_2{=}CHMgBr$ = 1 : 100, THF, 20 °C, then MeOH). Under these conditions, 4-phenylstyrene and diphenyl are formed in 30 min, and the order at which the reagents are mixed makes no difference.[20]


(5)

$$\mathrm{Ar{-}\overset{L}{\underset{L}{Pd}}{-}I + CH_2{=}CHMgBr \longrightarrow \underset{(57\text{—}64\%)}{ArCH{=}CH_2} + \underset{(34\text{—}35\%)}{ArH} + [PdL_2 + MgBrI]} \qquad (5)$$

Ar = 4-PhC_6H_4; L = PPh_3

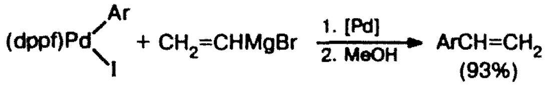
It is important that the $PdCl_2(PPh_3)_2$-catalyzed reaction of 4-iododiphenyl with $CH_2{=}CHMgBr$ (THF, 20 °C) results in the similar products.

$$\mathrm{ArI + CH_2{=}CHMgBr \xrightarrow[2.\ MeOH]{1.\ [Pd]} \underset{(59\%)}{ArCH{=}CH_2} + \underset{(31\%)}{ArH}} \quad (6)$$

Ar = 4-PhC_6H_4

The similar ratios of the yields of $ArCH{=}CH_2$ and ArH in the stoichiometric and catalytic reactions testify that the stoichiometric reaction in fact models the catalytic process.

The formation of by-products in the catalytic reaction, as mentioned above, can be suppressed completely using a Pd catalyst with bidentate ligands. A similar regularity is observed in the stoichiometric reaction. On going from *trans*-$ArPdI(PPh_3)_2$ to *cis*-ArPdI(dppf), the yield of the cross-coupling product (THF, 20 °C) becomes almost quantitative.



$$\mathrm{(dppf)Pd(Ar)I + CH_2{=}CHMgBr \xrightarrow[2.\ MeOH]{1.\ [Pd]} \underset{(93\%)}{ArCH{=}CH_2}} \quad (7)$$

Ar = 4-PhC_6H_4

The results obtained made it possible to refine the general mechanism of cross-coupling (see Scheme 2).[20] The reaction of *trans*-$R'PdXL_2$ with RMgX results in the formation of *trans*-$RPdR'L_2$ (transmetallation reaction). Then, under the action of an organomagnesium compound, this product is isomerized to a complex with the *cis*-configuration, which undergoes reductive elimination. It is likely that the key stage of this isomerization is the exchange of organic groups between the T-like coordinationally unsaturated complex *trans*-[RPdR'L] and RMgX. The exchange of the same groups (R) results in *trans—cis*-isomerization (Scheme 3, route *a*), while the exchange of different groups (R and R') leads to the formation of a new organomagnesium compound R'MgX and a Pd complex with the two same organic groups *cis*-[RPdRL] (route *b*). Reductive elimination from this complex results in the formation of the homocoupling product R_2 (from RMgX). The newly formed organomagnesium compound R'MgX can enter the transmetallation reaction with $R'PdXL_2$, which finally gives the homocoupling product R'_2 (from the organic halide R'X). The portion of compound R'MgX that does not react with the Pd complex transforms to the hydrocarbon R'H (see Scheme 3) after the decomposition of the reaction mixture.

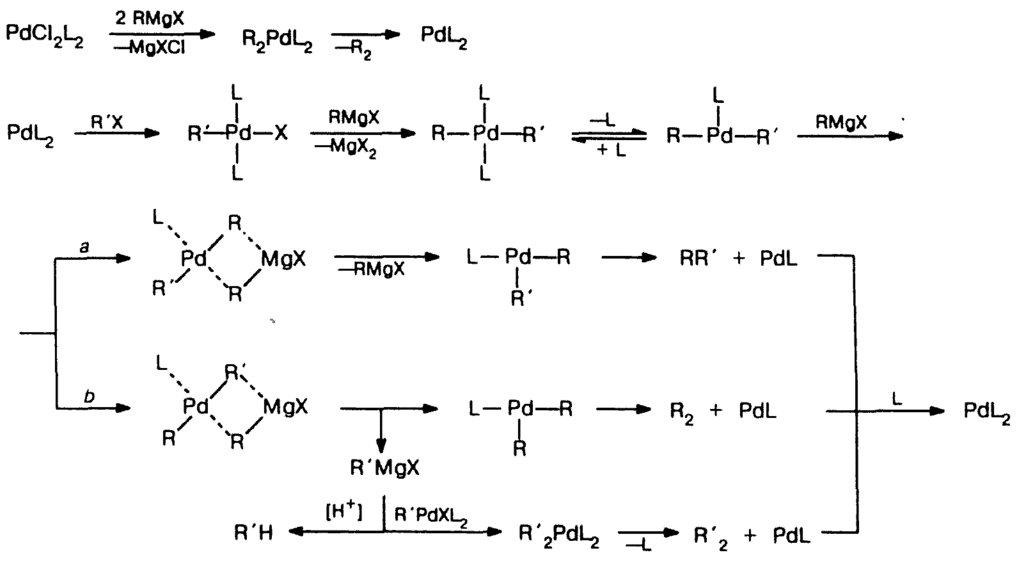
The ratio between the cross- and homocoupling products depends not only on the type of nontransition metal in RM, but also on the nature of the groups R and R' and on which of these groups the organic halide contains and which of them is present in the organomagnesium compound.

The reactions of phenyl, phenylethynyl, *n*-propyl, and allyl metal derivatives with 4-iodoanisole in the presence of $PdCl_2L_2$ complexes (L = PPh_3, MeCN) were chosen as model reactions for the study of the effect of the organic group in OMC on catalytic aryldemetallation. The effect of the organic group in organic halide was studied using as an example the reactions of PhM and 4-$MeOC_6H_4M$ (M = MgBr and ZnCl) with PhI, PhC≡CBr, Pr^nI, and AllBr in the presence of $PdCl_2L_2$. These reactions lead *via* different routes to the formation of the same cross-coupling products, therefore, the study of the effect of the nature of R and R' on transformations (8) is equivalent to the solution of the problem of a reasonable method for the preparation of the cross-coupling products.[21]

$$\mathrm{RM + R'X \xrightarrow{[Pd]} R{-}R' \xleftarrow{[Pd]} R'M + RX} \quad (8)$$

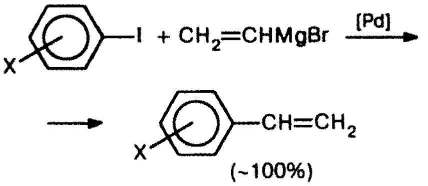
R, R' = Ph, 4-$MeOC_6H_4$, PhC≡C, Pr^n, All

Scheme 3



We have studied reactions resulting in the formation of substituted benzenes. In the majority of the cases, the use of organozinc compounds makes it possible to perform selective cross-coupling in the presence of Pd complexes. Both combinations of reagents (PhZnCl + 4-$MeOC_6H_4I$ and 4-$MeOC_6H_4ZnCl$ + PhI) are almost equivalent for the preparation of 4-methoxydiphenyl. Substantial differences are often observed for the reactions resulting in the formation of alkyl- and allylbenzenes and tolans. For example, 4-methoxytolan is obtained from phenylethynylzinc chloride and 4-iodoanisole rather than from PhC≡CBr and 4-$MeOC_6H_4ZnCl$, 4-allylanisole, by contrast, can be obtained from 4-$MeOC_6H_4ZnCl$ and allyl bromide, and 4-*n*-propylanisole can be preferably obtained from *n*-propylzinc chloride and 4-iodoanisole. The yield of a target product can be forced to become quantitative by varying the nature of the metal in RM or by the selection of the components RM and R'X (or RX and R'M) and the ligand surrounding the Pd complex. In the case of bidentate ligands, which lead to the *cis*-configuration of mono- and diorganic Pd complexes, transmetallation reactions followed by reductive elimination are considerably faster than exchange processes, therefore, the use of complexes with bidentate ligands often solves the problem of selectivity, especially when the organic groups in RM and R'X are similar in nature. These regularities were used for the development of methods for the synthesis of various compounds from organic halides and OMC.

Organomagnesium compounds. As shown above, reactions of organomagnesium compounds with organic halides can involve exclusively cross-coupling when Pd complexes with bidentate ligands are used as the catalysts. The $PdCl_2(dppf)$ complex turned out to be the most efficient one. This catalyst was used for the preparation of styrenes containing both electron-donating and electron-withdrawing substituents by the reactions of vinylmagnesium bromide with aryl iodides (THF, 20 °C).[22–24]



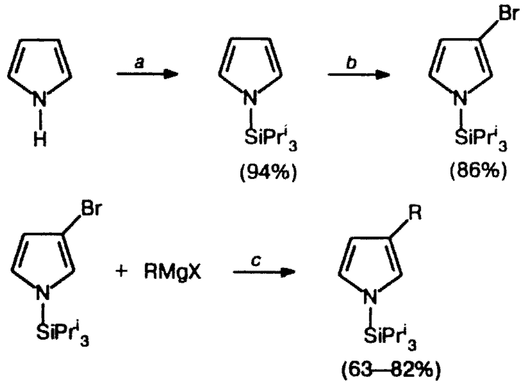
(9)

X = 4-HO, 4-MeO, H, 4-Ph, 4-Br, 4-Cl, 3-COOH

The catalytic activity of this complex is so high that the reaction can result in a quantitative yield even in the presence of 0.001 mol.% catalyst. This means that each molecule of $PdCl_2(dppf)$ participates in at least 100,000 catalytic cycles.

Based on complex uses of Pd-catalyzed cross-coupling reactions and protection of the N atom of the pyrrole ring by the bulky triisopropylsilyl group, we have developed new methods for the synthesis of 3-substituted and 3,4-disubstituted pyrroles from pyrrole with a wide range of substituents[25–28] (Scheme 4).

Scheme 4

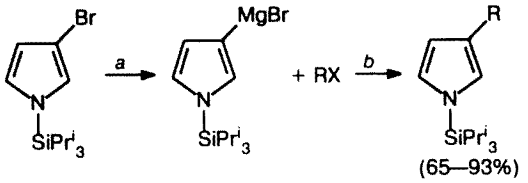


R = n-C_5H_{11}, n-C_8H_{17}, 4-$MeOC_6H_4$, 2,4,6-$Me_3C_6H_2$, Ph, 4-ClC_6H_4

Reagents and conditions: *a.* 1) BuLi, THF, −78 °C; 2) $ClSiPr^i_3$, −78 → +20 °C; *b.* *N*-bromosuccinimide, THF, −78 °C; *c.* 1 mol.% $PdCl_2(dppf)$, THF, Δ.

In the presence of 1 mol.% $PdCl_2(dppf)$ in boiling THF, the reaction of 3-bromo-1-(triisopropylsilyl)pyrrole with organomagnesium compounds (see Scheme 4) is completed after 1—10 h and results in 3-substituted pyrroles in preparative yields.[25] The range of 3-substituted pyrroles thus synthesized is fairly wide, but is restricted to organic halides from which Grignard reagents can be obtained. In particular, these halides cannot contain unprotected hydroxyl, carboxyl, or amino groups.

We have suggested one more method for the synthesis of 3-substituted pyrroles, which allows one to synthesize derivatives with a wider range of functional groups.[27,28] This method is the transformation of 3-bromo-1-(triisopropylsilyl)pyrrole to an organomagnesium compound under the action of magnesium followed by the $PdCl_2(dppf)$-catalyzed cross-coupling of the Grignard reagent obtained with organic halides.



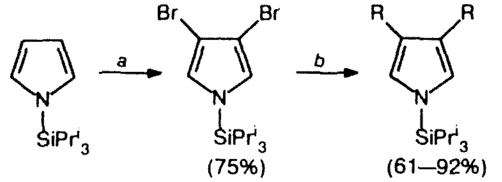
(10)

RX = PhBr, 4-FC_6H_4Br, 4-$HOOCC_6H_4Br$, 4-HOC_6H_4Br, 3-HOOC-4-HOC_6H_3Br, 3-HOOC-4-$NH_2C_6H_3Br$, 3,4-$(MeO)_2C_6H_3I$, n-$C_7H_{15}I$

Reagents and conditions: *a.* Mg, THF, Δ; *b.* [Pd], THF, Δ.

It is noteworthy that when $PdCl_2(dppf)$ is used as the catalyst even alkyl iodides react readily with the organomagnesium compound (see also Ref. 29).

The $PdCl_2(dppf)$-catalyzed cross-coupling of alkyl and aryl Grignard reagents with 3,4-dibromo-1-(triisopropylsilyl)pyrrole turned out to be a convenient method for the preparation of 3,4-disubstituted pyrroles, which are of great interest as the initial compounds for the synthesis of porphyrins.[28]



(11)

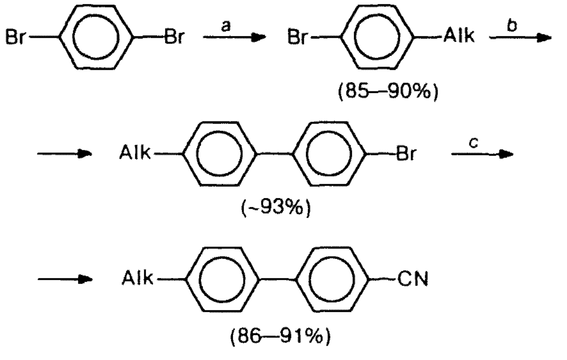
Reagents and conditions: *a.* *N*-bromosuccinimide, THF, −78 °C; *b.* 2 RMgX, [Pd], THF, Δ.

The 1-(triisopropylsilyl)pyrroles obtained (see Scheme 4 and reactions (10) and (11)) are liberated quantitatively from the protective group under the action of Bu_4NF in THF at 20 °C.

The unique catalytic properties of $PdCl_2(dppf)$ made it possible to suggest a completely new approach to the synthesis of liquid-crystalline 4,4′-disubstituted diphenyls based on Pd-catalyzed reactions of 1,4-dibromobenzene with Grignard reagents.[30—33]

We have found that in the presence of 1 mol.% $PdCl_2(dppf)$ 1,4-dibromobenzene reacts with *n*-alkyl Grignard reagents at room temperature to give *n*-alkyl-4-bromobenzenes in preparative yields in 1 h. Then the bromoarenes obtained are transformed into Grignard reagents under the action of Mg in THF, and the Grignard reagents undergo $PdCl_2(dppf)$-catalyzed cross-coupling with 1,4-dibromobenzene. The reaction is completed at room temperature after 10—15 min and results in the formation of 4-*n*-alkyl-4′-bromodiphenyls in high yields. As is known, the replacement of the Br atom by a cyano group in bromoarenes is performed by treatment with CuCN in boiling DMF. The duration of this stage can be shortened from 10—12 h to 2 h in the presence of 1 mol.% $PhPdI(PPh_3)_2$ (Scheme 5).[32]

Scheme 5

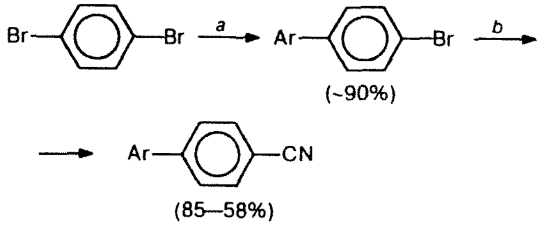


Alk = Me, Pr^n, Bu^n, *n*-C_6H_{13}, *n*-C_8H_{17}

Reagents and conditions: *a.* AlkMgBr, [Pd], THF—ether, 20 °C; *b.* 1) Mg, THF; 2) 1,4-$Br_2C_6H_4$, [Pd], THF, 20 °C; *c.* CuCN, [Pd], DMF, Δ.

Thus, a new three-stage method for the synthesis of *n*-alkyl-4′-cyanodiphenyls from easily accessible reagents in a total yield of ~70% based on highly selective palladium-catalyzed reactions of monoalkylation and monoarylation of 1,4-dibromobenzene has been developed.

A similar approach was used for the synthesis of 4-*n*-alkoxy-4′-cyanodiphenyls.[31]



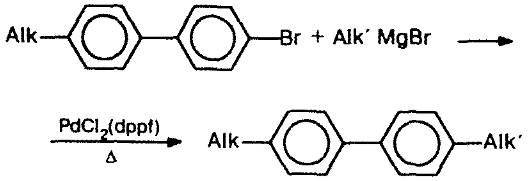
(12)

Ar = 4-*n*-$AlkOC_6H_4$

Reagents and conditions: *a.* ArMgBr, [Pd]; *b.* CuCN, [Pd], DMF, Δ.

The initial 4-*n*-alkoxybenzenes were obtained by the alkylation of 4-bromophenol by *n*-alkyl bromides in the presence of alkali and in the absence of a solvent.[34]

The strategy for the synthesis of 4-*n*-alkyl(alkoxy)-4′-cyanodiphenyls was expanded to the preparation of 4,4′-dialkyldiphenyls.[33] For this purpose, after the end of the penultimate stage of the synthesis (see Scheme 5), an alkyl Grignard reagent was added to the reaction mixture containing 4-*n*-alkyl-4′-bromodiphenyl, and 4,4′-dialkyldiphenyls were obtained in ~95% yields after 2 h at the boiling point of THF.

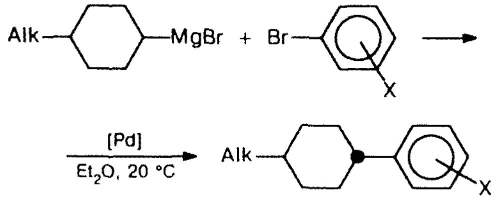


(13)

Alk, Alk′ = Me, Pr^n, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}

It is noteworthy that reaction (13) occurs with the Pd catalyst that remains in the reaction mixture after the end of the preceding stage.

Very interesting results were obtained in the study of the cross-coupling of 4-*n*-alkylcyclohexyl Grignard reagents with aryl bromides.[33] It turned out that in the presence of $PdCl_2(dppf)$ these organomagnesium compounds, which are likely a mixture of *cis*- and *trans*-isomers, react rapidly with aryl bromides in ether at 20 °C to give (4-*n*-alkylcyclohexyl)arenes in only *trans*-configurations in quantitative yields.



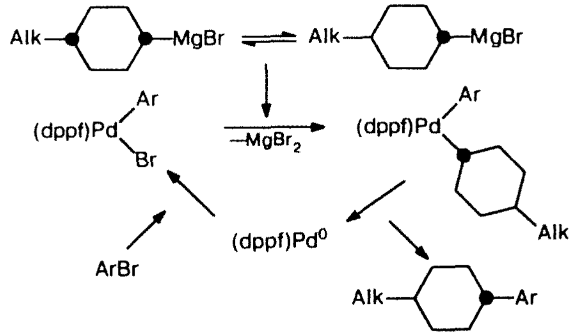
(14)

Alk = Pr^n, Bu^n; X = H, 3-F, 4-F

It should be mentioned that (4-*n*-alkylcyclohexyl)benzenes obtained by the Nenitzescu reaction[35] are a mixture of *cis*- and *trans*-isomers.

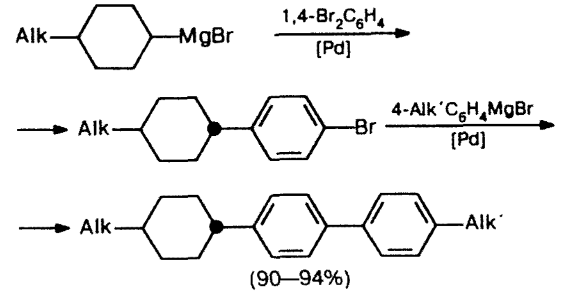
The fact that the products of reaction (14) are in the *trans*-configuration may be caused by higher reactivity of one of the isomers of (4-*n*-alkylcyclohexyl)magnesium bromide at the stage of transmetallation with the ArPdBr(dppf) complex (Scheme 6).

Scheme 6



The use of (4-*n*-alkylcyclohexyl)magnesium bromides instead of alkyl Grignard reagents (see Scheme 5 and reaction (13)) made it possible to develop an efficient method for the synthesis of 4,4′-disubstituted diphenyls containing the *trans*-4-*n*-alkylcyclohexane fragment (Scheme 7).

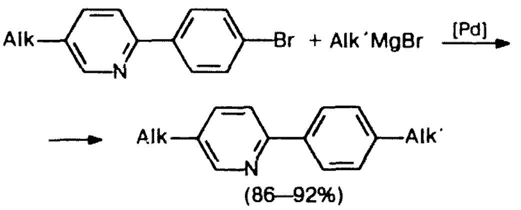
An alternative and simplier scheme of the synthesis is based on the reaction of the 4-(*trans*-4-*n*-alkylcyclohexyl)bromobenzenes obtained without isolation with the Grignard reagents formed from 4-*n*-alkyl- or *trans*-4-*n*-alkylcyclohexylbromobenzenes (Eq. (15)).



(15)

Alk = Pr^n, n-C_5H_{11}; Alk′ = Et, 4-$Pr^nC_6H_{11}$, 4-n-$C_5H_{11}C_6H_{11}$

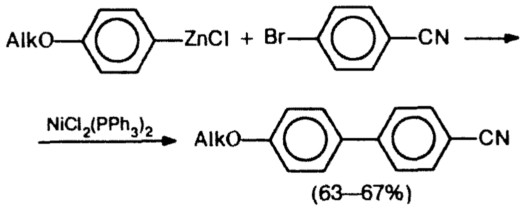
The $PdCl_2$(dppf) complex was used as the catalyst of the cross-coupling of 5-*n*-alkyl-2-(4-bromophenyl)pyridine with *n*-alkylmagnesium bromides. The reaction proceeds with heating in THF and results in the formation of 5-*n*-alkyl-2-(4-*n*-alkylphenyl)pyridines in high yields, which are of interest as components of liquid-crystalline materials.[36]



(16)

Alk = Pr^n, n-C_5H_{11}; Alk′ = Pr^n, n-C_5H_{11}, n-C_7H_{15}, n-C_9H_{19}

Organozinc compounds. As is known,[1] the main advantage of organozinc compounds is they make it possible to obtain cross-coupling products with many types of functional groups sensitive to the action of Grignard reagents. In addition, cross-coupling involving organozinc compounds often proceeds with higher selectivity than the similar reactions of organomagnesium compounds. This allowed us to develop a convenient method for the synthesis of liquid-crystalline 4-*n*-alkoxy-4′-cyanodiphenyls (Eq. (17)), which have been previously obtained by a multistage synthesis with a total yield not higher than 20%. Not only Pd complexes but also more accessible Ni complexes[37] can be used successfully as catalysts of the reactions of 4-*n*-alkoxyphenylzinc chlorides obtained *in situ* from Grignard reagents and $ZnCl_2$ with 4-bromobenzonitrile (THF, 20 °C).

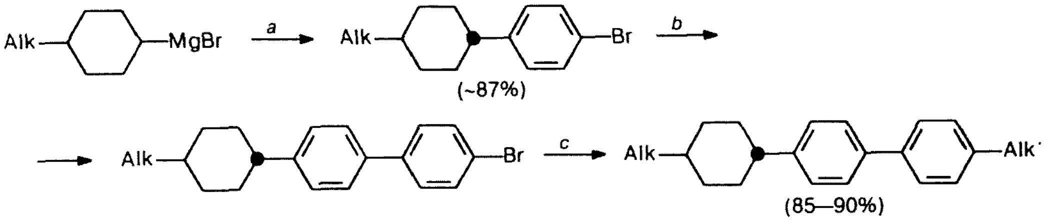


(17)

Alk = n-C_nH_{2n+1}; n = 1, 3, 5, 7, 9

4-*n*-Alkyl-4′-cyanodiphenyls, representatives of another class of liquid crystals, were also obtained by the

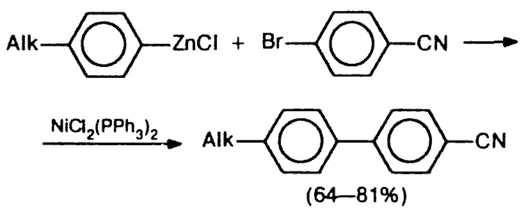
Scheme 7



Alk = Pr^n, n-C_5H_{11}; Alk′ = Et, 4-$Pr^nC_6H_{11}$, 4-n-$C_5H_{11}C_6H_{11}$

Reagents and conditions: *a.* 1,4-$Br_2C_6H_4$, [Pd]; *b.* 1) Mg, THF; 2) 1,4-$Br_2C_6H_4$, [Pd]; *c.* Alk′MgBr, [Pd].

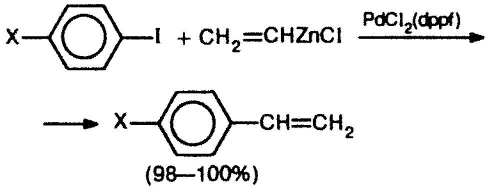
cross-coupling of 4-bromobenzonitrile with 4-*n*-alkylphenylzinc chlorides.[14] Although the $PdCl_2(dppf)$ complex, as in many other reactions listed above, turned out to be the most selective catalyst, $NiCl_2(PPh_3)_2$, which is considerably less selective but is easily accessible, was chosen for the synthesis of 4-*n*-alkyl-4′-cyanodiphenyls.



(18)

Alk = n-C_nH_{2n+1}; n = 1, 3, 4, 6, 8, 11

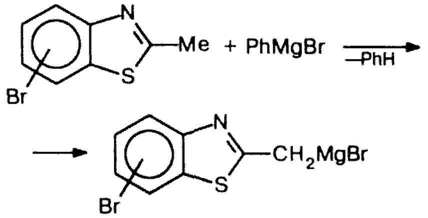
The zinc derivative obtained *in situ* from CH_2=CHMgBr and $ZnCl_2$ (see Ref. 38) was used instead of vinylmagnesium bromide to enlarge the range of substituted styrenes in the reaction of aryl iodides. The inertness of organozinc compounds to cyano and keto groups at room temperature makes it possible to synthesize 4-cyano- and 4-acetylstyrenes in quantitative yields (THF, 20 °C).



(19)

The yield of the corresponding styrenes turned out to be insignificant in the reactions with 4-iodobenzaldehyde and 4-iodonitrobenzene.

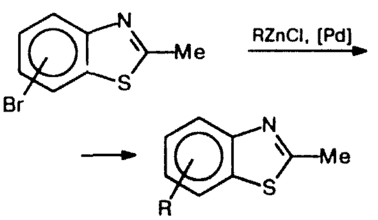
Organozinc compounds were also used for the preparation of 5- and 6-substituted 2-methylbenzothiazoles,[26,39] which are the initial reagents for the synthesis of thiacarbocyanine dyes. The reactions of 5- and 6-bromo-2-methylbenzothiazoles with Grignard reagents occur nonselectively, and the yields of the target products are not higher than 17—43%. The low yields may be caused by the replacement of a reactive proton of the methyl group in 2-methylbenzothiazole by the organomagnesium compound.



(20)

Upon going to less reactive (and less basic) organozinc compounds, the metallation of the methyl group is completely suppressed. In the presence of $PdCl_2(dppf)$, the cross-coupling reaction occurs very selectively in THF at 20 °C and is complete after 0.5—2.0 h, giving 5- and 6-alkyl(aryl)-2-methylbenzothiazoles in yields close to quantitative.

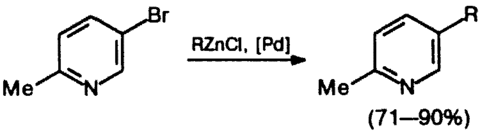
$$RMgBr \xrightarrow{ZnCl_2} RZnCl \qquad (21)$$



(22)

R = 4-C_7H_{15}, XC_6H_4; X = 4-MeO, 2-Me, 4-Me, H, 4-Cl, 3,4-$(MeO)_2C_6H_3$

A similar approach made it possible to synthesize 5-alkyl(aryl)-2-picolines (THF, 20 °C).[26]



(23)

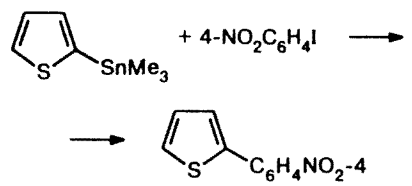
R = Pr^i, Ph, 4-$MeOC_6H_4$

Thus, methods for the synthesis of compounds of various classes containing a wide set of substituents (see Ref. 40) can be developed on the basis of cross-coupling reactions involving organozinc compounds. The use of organotin derivatives, which are inert to almost all functional groups, made it possible to enlarge considerably the synthetic possibilities of the cross-coupling.

Organotin compounds. Organotin compounds occupy a special position among OMC used in cross-coupling reactions.[41] Tin derivatives attract attention of researchers because they allow one to retain the functions of organic halides and they themselves can contain various substituents as well. The methods for the synthesis of organotin compounds are well known and, in the predominant majority of cases, they are stable toward air oxygen and moisture. However, their reactivity in cross-coupling processes catalyzed by phosphine Pd complexes is considerably lower than that of Mg and Zn derivatives. Therefore, these reactions often require fairly rigid conditions.[42,43] Evidently, this is associated with the fact that, on going to organotin compounds, the stage of the transmetallation between $RSnR''_3$ and $R'PdXL_2$ becomes the slowest step in the catalytic cycle.

We have shown[44—47] that Pd complexes containing no phosphine ligands are considerably more reactive catalysts of the cross-coupling of $RSnMe_3$ with ArI. These complexes can be easily obtained directly in the

Scheme 8

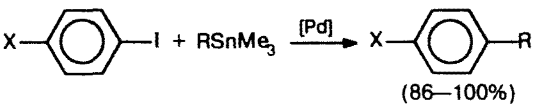


Reagents and conditions: 2.5 mol.% [Pd], HMPA, 20 °C

[Pd]	t/min	Yield (%)
$PdCl_2$	60 [24 h]	Traces [100]
$LiPdCl_3$	30	100
$Pd(OAc)_2$	30	100
$Pd(acac)_2$	60 [24 h]	Traces [100]
$(\pi\text{-}C_3H_5PdCl)_2$	60 [24 h]	36 [100]
$PdCl_2(MeCN)_2$	15	100
$Pd(dba)_2$	15	100

reaction medium from various Pd compounds and even from $PdCl_2$, however, the maximum reaction rate (see Scheme 8) is observed in the case of $PdCl_2(MeCN)_2$ and $Pd(dba)_2$ (dba is dibenzylideneacetone).

In the presence of $PdCl_2(MeCN)_2$, the reactions of organotin compounds with aryl iodides proceed at almost the same rates as in the case of the Grignard reagents, and considerably exceed the latter in synthetic possibilities. In addition, the reactions of organotin compounds can be performed in air, and HMPA, DMF, or acetone can be used as solvents. High yields of the cross-coupling products were obtained in all solvents studied, and the reaction rates turned out to be maximum in HMPA and minimum in acetone. The reactivity of organotin compounds decreases in the following order: vinyl- > 2-thienyl- ≈ phenylethynyl- ≫ aryltrimethyltin. For example, styrenes, diaryls, tolans, and 2-arylthiophenes containing reactive functional groups in the aromatic ring were synthesized in high yields by the reactions of $RSnMe_3$ with aryl iodides (DMF, 20 °C).[46]



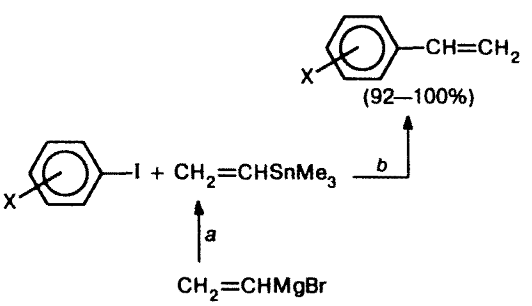
(24)

X = 2,4-$(NO_2)_2$, NO_2, CN, MeCO, MeOOC, Cl, H
R = $CH_2{=}CH$, $PhC{\equiv}C$, 2-C_4H_3S, 4-YC_6H_4; Y = MeO, Me, H, Cl

We later showed that organotin compounds can be obtained *in situ* from the corresponding organomagnesium derivatives and Me_3SnCl and then introduced into the cross-coupling reaction (Scheme 9). Styrenes with various functional groups were synthesized by this method.[38]

It is noteworthy that when the phosphine Pd complex is used as the catalyst the reaction occurs considerably more slowly than in the presence of $PdCl_2(MeCN)_2$ (Scheme 10).

Scheme 9



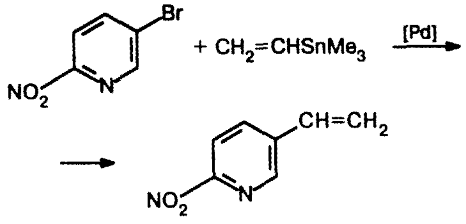
X = 2-NO_2, 3-NO_2, 4-NO_2, 4-CN, 4-MeCO, 4-CHO, 3-COOH
Reagents and conditions: *a*. Me_3SnCl; *b*. $PdCl_2(MeCN)_2$, THF—DMF, 20 °C.

Scheme 10

$$4\text{-}NO_2C_6H_4I + CH_2{=}CHSnMe_3 \xrightarrow{[Pd]} 4\text{-}NO_2C_6H_4CH{=}CH_2$$

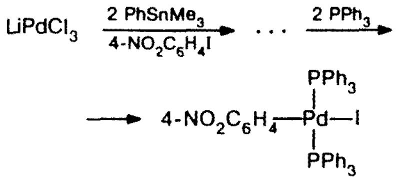
[Pd]	t/min	Yield (%)
$PdCl_2(MeCN)_2$	<3	100
$PdCl_2(PPh_3)_2$	~180	100

More accessible aryl bromides can be used instead of aryl iodides. Since aryl bromides are less reactive in oxidative addition to Pd^0 complexes than aryl iodides, the cross-coupling should be performed at high temperatures. For example, 5-bromo-2-nitropyridine reacts with trimethylvinyltin in the presence of 1 mol.% $PdCl_2(MeCN)_2$ at 70 °C for 10 min to form 2-nitro-5-vinylpyridine in 89% yield.[38]



(25)

For the four reactions listed above (see Eqs. (24) and (25) and Schemes 9 and 10), it has been suggested that the standard mechanism of the cross-coupling includes the stages of oxidative addition, transmetallation, and reductive elimination. Pd^0 and Pd^{II} complexes, in which solvent molecules play the role of stabilizing weakly coordinated ligands L, are the intermediates in the catalytic cycle proposed. This is confirmed by the following experimental facts.[47] In aprotic solvents (HMPA, DMF, and acetone), the complexes $LiPdCl_3$, $PdCl_2(MeCN)_2$, $(\pi\text{-}C_3H_5PdCl)_2$, and PdOAc react rapidly with organotin compounds to yield palladium black. However, when the reaction is performed in the presence of 4-iodonitrobenzene, no Pd is formed, and the reaction mixture remains homogeneous for a long time. When PPh_3 is added to the reaction mixture, the known Pd complex, *trans*-4-$NO_2C_6H_4PdI(PPh_3)_2$, is formed in 84% yield.



$$LiPdCl_3 \xrightarrow[4\text{-}NO_2C_6H_4I]{2\ PhSnMe_3} \ldots \xrightarrow{2\ PPh_3} 4\text{-}NO_2C_6H_4{-}Pd(PPh_3)_2{-}I$$

(26)

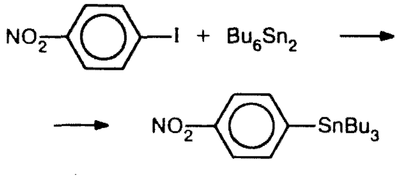
In addition, if PPh_3 (3 equiv. calculated per Pd) is added to the reaction mixture after the cessation of the catalytic reaction of $PhSnMe_3$ with 4-$NO_2C_6H_4I$ ($PhSnMe_3$: ArI = 1.0 : 1.5, 5 mol.% $LiPdCl_3$), *trans*-4-$NO_2C_6H_4PdI(PPh_3)_2$ is formed in 91% yield (calculated per $LiPdCl_3$).

The methodology developed for catalysis by "ligand-free" palladium[44—46] has been widely used by other authors[48—50] in various reactions involving organotin compounds.

Hexaalkyldistannanes. The reactions of hexaalkyldistannanes with organic halides RX can serve as a convenient method for the synthesis of organotin compounds of the $RSnAlk_3$ type used in cross-coupling reactions.

$$RX + Alk_6Sn_2 \longrightarrow RSnAlk_3 + Alk_3SnX \qquad (27)$$

The possibility of obtaining difficultly accessible tin derivatives, containing substituents that are sensitive to the action of reactive OMC, by this method is of great interest. We have found that aryl iodides activated by electron-withdrawing substituents react with hexabutyldistannane at 135—150 °C in HMPA to form aryltributylstannanes.[51,52] The reaction usually proceeds with low selectivity, but in some cases it can be of interest as a preparative method. For example, 4-$NO_2C_6H_4SnBu_3$ was obtained by this method in 72% yield.

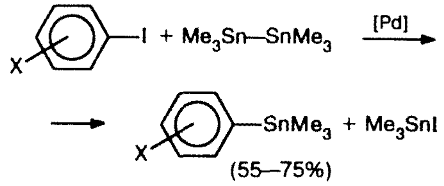


(28)

Further studies have shown that in the presence of salts whose anions possess a high affinity for the Sn atom, for example, Bu_4NF or Bu_4NCl, hexaalkyldistannanes react with activated iodoarenes in benzene even at 20 °C. Considerable amounts of the reduction product of the initial iodides, ArH, are formed along with $ArSnAlk_3$. A study of the Bu_6Sn_2—Bu_4NF system by ^{19}F NMR spectroscopy made it possible to establish that the increase in the reactivity of distannanes under the action of Bu_4NF is caused by the coordination of the fluorine atom to the Sn atom in Alk_6Sn_2 followed by the heterolytic cleavage of the Sn—Sn bond.[53]

$$Alk_6Sn_2 + Bu_4NF \rightleftharpoons [Alk_3Sn{-}SnAlk_3F]^-Bu_4N^+ \rightleftharpoons Alk_3Sn^-Bu_4N^+ + Alk_3SnF \qquad (29)$$

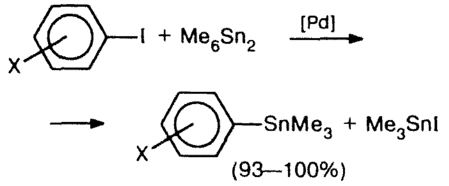
The use of transition metal complexes as the catalysts in reaction (27) turned out to be the most general and promising from the viewpoint of synthesis. In the presence of the $(\pi\text{-}C_3H_5PdCl)_2$ complex, we succeeded in performing the reaction of Me_6Sn_2 with aryl iodides containing electron-withdrawing functional groups under mild conditions (CH_2Cl_2, 20 °C, 1—24 h) and in high yields.[54]



(30)

X = 2,4-$(NO_2)_2$, 2-NO_2, 3-NO_2, 4-NO_2, 4-MeOOC, H

Under these conditions, hexamethyldistannane not only reacts with organic halide, but also undergoes the disproportionation under the action of Me_3SnI to form Me_4Sn and $(Me_2Sn)_n$. The yield of the organotin compound is likely determined by the ratio between the reaction rates of the transmetallation and the disproportionation of Me_6Sn_2. The optimum ratio, as has been shown using the model reaction of 2,4-dinitroiodobenzene with Me_6Sn_2 in different solvents as an example, is achieved in DMF and acetone.[55] When reaction (30) occurs in DMF (2 mol.% $PdCl_2(MeCN)_2$, ArI : Me_6Sn_2 = 1.0 : 1.2, 20 °C), the yield of $ArSnMe_3$ increases to become quantitative and the duration of the process shortens to 5—15 min. A convenient method for the preparation of previously difficultly accessible aryltrimethylstannanes containing electron-withdrawing substituents in the aromatic ring has been thus developed.



(31)

X = 2,4-$(NO_2)_2$, 2-NO_2, 3-NO_2, 4-$(NO_2)_2$, 4-CN, 4-MeCO, 4-MeOOC

Reaction (31) has been expanded to other hexaalkyldistannanes and organic halides. It turned out that hexaethyl- and hexabutyldistannanes react readily with alkyl, aryl, and heteroaryl iodides in HMPA at room temperature for 5 to 140 min. The use of HMPA is due to the low solubility of these distannanes in DMF.[56]

$$\mathrm{RI + Alk_6Sn_2 \xrightarrow{[Pd]} RSnAlk_3 + Alk_3SnI} \qquad (32)$$

R = Me, Et, 2,4-$(NO_2)_2C_6H_3$, 2-C_4H_3S, 4-XC_6H_4; X = H, Cl, MeOOC, NO_2
Alk = Et, Bu

Catalytic reactions of distannanes with simple halides, MeI and EtI, were successful for the first time. The reaction of ethyl iodide with Bu_6Sn_2 (6 h, 68% $EtSnBu_3$) should be specially emphasized. This is one of few examples of the successful use of alkyl halides with a β-H atom in Pd-catalyzed reactions in the absence of special bidentate ligands. It should be noted that in the case of aryl iodides containing electron-withdrawing substituents the Pd complexes can be replaced by a more accessible catalyst, nickel bromide.[52]

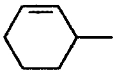
In the presence of the palladium catalyst, hexamethyldistannane also reacts with allyl acetates. The $PdCl_2(PPh_3)_2$-catalyzed reaction occurs in HMPA at room temperature and after 0.7—22 h results in the corresponding allyltrimethylstannanes in high yields.[57]

$$\mathrm{AllOAc + Me_6Sn_2 \xrightarrow{[Pd]} AllSnMe_3 + Me_3SnOAc} \qquad (33)$$

All = CH_2=$CHCH_2$, *E*-PhCH=$CHCH_2$

The attempts to use the $(\pi\text{-}C_3H_5PdCl)_2$ complex as a more reactive catalyst failed. At the same time, the reactions of allyl halides with Me_6Sn_2 in the presence of $(\pi\text{-}C_3H_5PdCl)_2$ occur in 10—15 min (HMPA, 20 °C) to give allyltrimethylstannanes in high yields.[57]

$$\mathrm{AllX + Me_6Sn_2 \xrightarrow{(\pi\text{-}C_3H_5PdCl)_2} \underset{(41\text{—}85\%)}{AllSnMe_3} + Me_6SnX} \qquad (34)$$

All = CH_2=$CHCH_2$, *E*-PhCH=$CHCH_2$,  ,
MeCH=$CHCH_2$, MeCHCH=CH_2,

In the reactions with crotyl bromide and 3-chloro-1-butene, the main product of the cross-coupling is an organotin compound in which the Me_3Sn group is linked with the least substituted C atom.

A convenient method for the synthesis of distannanes R_6Sn_2 is the Pd-catalyzed dehydrogenation of organotin hydrides R_3SnH.[56,58] These hydrides were obtained by the reduction of the corresponding chlorides by $LiAlH_4$ and were used in the subsequent transformations without isolation from the reaction mixture after decomposition of the excess $LiAlH_4$ by a minimum amount of water.

$$\mathrm{R_3SnCl \xrightarrow{a,\ b,\ c} \underset{(71\text{—}89\%)}{R_6Sn_2}} \qquad (35)$$

R = Me, Et, Bu, Ph

Reagents and conditions: *a*. $LiAlH_4$, Et_2O, 20 °C, 4 h; *b*. H_2O; *c*. $PdCl_2(MeCN)_2$ or $PhPdI(PPh_3)_2$, 20 °C, 0.25—100 h.

Attention should be given to the fact that the use of the "raw" (nonpurified) hexaalkyldistannanes obtained in reaction (35) as the initial substrates in cross-coupling with organic halides does not result in a decrease in the yield of $RSnAlk_3$. Thus, the whole cycle of transformations of Alk_3SnCl into $RSnAlk_3$ can be carried out without isolation of tin hydrides or purification of the intermediate distannanes.[56]

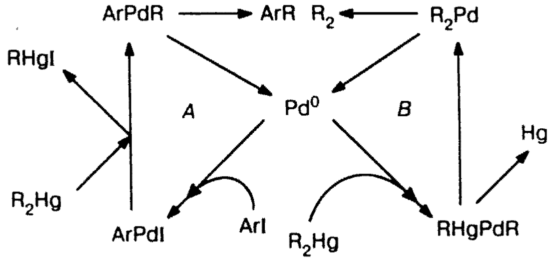
$$\mathrm{Alk_3SnCl \xrightarrow{[H]} Alk_3SnH \xrightarrow[-H_2]{[Pd]} Alk_6Sn_2 \xrightarrow[-Alk_3SnX]{RX,\ [Pd]} RSnAlk_3} \qquad (36)$$

Organomercury compounds. Organomercury derivatives are one more class of OMC that can be used in cross-coupling reactions with organic halides containing reactive substituents. In addition, unlike other metal derivatives, organomercury compounds can contain amino, acetamino, and hydroxy groups in the aromatic ring. However, the reaction of R_2Hg with ArI in the presence of $PhPdI(PPh_3)_2$ (HMPA, 80 °C, 3 h) results in the formation of the product of the oxidative demercuration of R_2 along with the cross-coupling product ArR (see Refs. 12, 59, and 60).

$$\mathrm{Ph_2Hg + 4\text{-}NO_2C_6H_4I \xrightarrow{[Pd]} \underset{(35\%)}{4\text{-}NO_2C_6H_4Ph} + \underset{(10\%)}{Ph_2}} \qquad (37)$$

Therefore, oxidative demercuration, which is also catalyzed by the Pd^0 complex (Scheme 11, cycle *B*, ligands are omitted), occurs in parallel with the cross-coupling (cycle *A*).

Scheme 11



We have found that oxidative demercuration can be completely suppressed if the reactions of R_2Hg with ArI are performed in the presence of the iodide ion (Bu_4NI). In addition, the fact that I^- is a nucleophilic catalyst facilitates the transmetallation stage. The effect of the nucleophilic assistance of the iodide ion is so great that the reactivity of organomercury compounds in cross-coupling reactions approach that of organic derivatives of Mg and Zn. The reaction occurs in various solvents including acetone, and NaI can serve as a source of the iodide ion. The advantage of the reaction is that it involves both organic groups from R_2Hg. Therefore, not only symmetric R_2Hg compounds, but also organomercury salts can be used as the reagents (HMPA, 20—70 °C). It is noteworthy that the cross-coupling reactions involving organomercury compounds proceed better in an inert atmosphere.

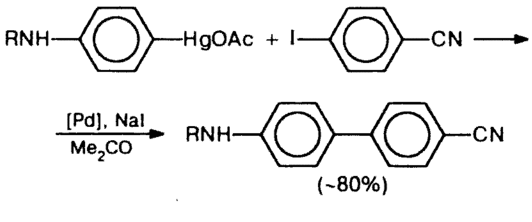
$$R_2Hg\ (2\ RHgX) + 2\ YC_6H_4I \xrightarrow{[Pd],\ I^-} \underset{(63-99\%)}{2\ RC_6H_4Y} + \underset{(0-37\%)}{R_2} \qquad (38)$$

R = Me, 2,4,6-$Me_3C_6H_2$, ZC_6H_4; Z = 4-NH_2, 4-AcNH, 2-HO, 2-MeO, 4-MeO, 4-Me, H, 4-Cl
Y = 2-NO_2, 3-NO_2, 4-NO_2, 2,4-$(NO_2)_2$, 2,4,6-$(NO_2)_3$, 4-CN, 4-MeCO, 4-MeOOC

The practical aspect of the use of reaction (38) to synthesize 4-*n*-alkylamino-4′-cyanodiphenyls, which have good liquid-crystalline parameters, is of interest. These compounds are not easily accessible, since by the usual method of preparation their yields are not greater than 6—7%. We have developed an efficient method for the synthesis of 4-*n*-alkylamino-4′-cyanodiphenyls (reaction (39)).[61]

$$PhNH_2 \xrightarrow{RCOCl} RCONHPh \xrightarrow{LiAlH_4} RCH_2NHPh \xrightarrow{Hg(OAc)_2} RCH_2NHC_6H_4HgOAc \xrightarrow[I^-]{4\text{-}CNC_6H_4I,\ [Pd]} RCH_2NHC_6H_4C_6H_4CN \qquad (39)$$

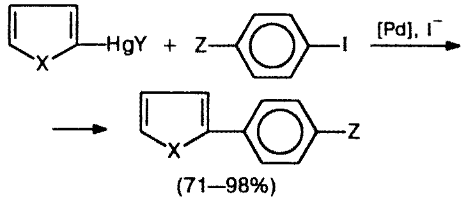
The key stage of the scheme suggested is the cross-coupling of an organomercury compound with 4-iodobenzonitrile. The reaction occurs at room temperature in acetone in the presence of the $PhPdI(PPh_3)_2$ complex and NaI.



(40)

Due to the high selectivity of the particular stages of the method suggested, the total yield of 4-*n*-alkylamino-4′-cyanodiphenyls is 40% per initial carboxyl chloride.

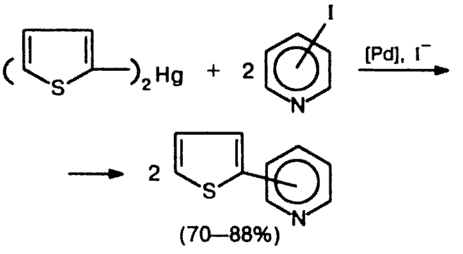
The cross-coupling reactions of organomercury compounds with organic halides turned out to be a convenient method for the preparation of arylated heterocycles.[62] Thiophene and furan organomercury derivatives react with aryl iodides under mild conditions (20 °C) in the presence of 2—3 equiv. Bu_4NX (X = Br, I) in HMPA or NaI in acetone and 1 mol.% Pd complex to give aryl derivatives of heterocycles in high yields.



(41)

X = O, S
Y = Br, Cl, 2-C_4H_3S
Z = NO_2, CN, MeCO, MeOOC

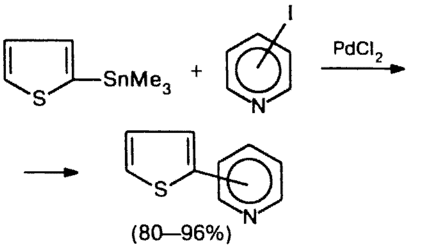
Heterocyclic fragments can be introduced into the target product not only from an organomercury compound, but from an organic halide as well. For example, the reactions of bis-2-thienylmercury with 2-, 3-, and 4-iodopyridines (20 °C) result in the formation of (2-thienyl)pyridines.



(42)

The by-product in these reactions is bis(2-thienyl), whose yield reaches 30% in some cases.

Tin derivatives can be used along with organomercury compounds for the preparation of (2-thienyl)pyridines.



(43)

Organotin compounds possess several advantages over organomercury compounds: first, reactions involving organotin compounds proceed without the formation of by-products; second, no nucleophilic catalysts are required; third, no inert atmosphere is required; and finally, $PdCl_2$ can be used as the catalyst. At the same time, Hg derivatives are more accessible: they can be obtained not only from the corresponding organolithium and organomagnesium compounds, but also by the direct mercuration of thiophene and furan. In addition, in the case of organotin compounds, only one organic group (Ar in $ArSnMe_3$) reacts, while both organic radicals are involved in the transformations of mercury derivatives.

We have found that, although in the presence of the iodide ion cross-coupling of organomercury compounds with aryl iodides proceeds and oxidative demercuration is suppressed, the halide ion facilitates the latter process as well. In the presence of iodide ion additives (2 equiv.), the oxidative demercuration of arylmercury derivatives catalyzed by Pd complexes occurs readily at room temperature. The most efficient catalyst of the demercuration of Ar_2Hg is the $PhPdI(PPh_3)_2$ complex, while in the case of ArHgX it is $[Rh(CO)_2Cl]_2$. Both polar (HMPA, DMF, MeCN, acetone, and THF) and nonpolar solvents (benzene and methylene dichloride) can be used in these reactions. The halide ion is introduced into the reaction in the form of Bu_4NX (X = Br, I) or NaI in acetone. The oxidative demercuration of Ar_2Hg and ArHgX (X = Cl, OAc) catalyzed by Pd or Rh complexes can be used for the synthesis of symmetric diaryls containing both electron-withdrawing and electron-donating substituents and for the preparation of the corresponding dimers of aromatic heterocycles.[63,64]

$$\mathrm{Ar_2Hg} \xrightarrow[\mathrm{I^-}]{[\mathrm{Pd}]} \mathrm{Ar_2 + Hg}$$

(74—83%)

$$2\,\mathrm{Ar'HgX} \xrightarrow[\mathrm{I^-}]{[\mathrm{Pd}]/[\mathrm{Rh}]} \mathrm{Ar'_2 + Hg + HgX_2} \qquad (44)$$

(63—99%)

Ar = $4\text{-}MeOC_6H_4$, Ph, $4\text{-}ClC_6H_4$, $2\text{-}C_4H_3S$

Ar′ = $4\text{-}XC_6H_4$; X = Me_2N, NH_2, MeO, Me, H

Organocopper compounds. As is known, the reactions of Cu acetylenides with aryl iodides occur under fairly drastic conditions (refluxing for 8—16 h in DMF[65] or for 6 h in pyridine[66]). We have found[67,68] that in the presence of catalytic amounts of Pd complexes, Cu phenylacetylenide reacts with aryl iodides under milder conditions (20—70 °C). It turned out that the addition of a nucleophilic catalyst, tetraalkylammonium halide or alkali metals, makes it possible for the cross-coupling of PhC≡CCu with various aryl iodides to occur under very mild conditions at a high rate. In the presence of Bu_4NI, more accessible aryl bromides can be used in the reaction. The cross-coupling of PhC≡CCu with heteroaryl iodides allows one to synthesize substituted acetylenes containing a heterocyclic fragment. β-Bromostyrene and allyl bromide react very readily (HMPA, 20 °C, 0.3—4.0 h) to form *E*-1,4-diphenyl-1,3-butenine and allyl(phenyl)acetylene, respectively, in high yields.

$$\mathrm{PhC{\equiv}CCu + RX \xrightarrow{PhPdI(PPh_3)_2,\ Bu_4NI} PhC{\equiv}CCu + CuX} \qquad (45)$$

(89—96%)

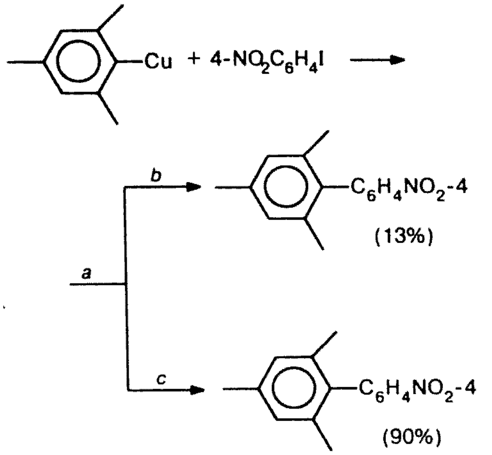
R = $2\text{-}C_4H_3S$, 2-py, $4\text{-}YC_6H_4$; Y = NO_2, CN, MeCO, MeOOC, H; X = I

R = $4\text{-}MeCOC_6H_4$, $2,4\text{-}(NO_2)C_6H_3$, *E*-PhCH=CH, CH_2=$CHCH_2$; X = Br

The effect of the halide ion additives is so great that the duration of the reaction and the yield of the cross-coupling product depend weakly on the nature of the solvent (HMPA, DMSO, DMF, THF, acetone, MeCN, ethanol, or methylene dichloride). The reaction can occur even in such nonpolar solvents as benzene and hexane. When it is performed in acetone, more accessible NaI, LiBr, and LiCl can be used instead of Bu_4NI.

In the presence of the iodide ion, the reaction involving various palladium complexes ($PhPdI(PPh_3)_2$, $PdCl_2(AsPh_3)_2$, $PdCl_2(SbPh_3)_2$, $PdCl_2(dppf)$, $Pd(acac)_2$, $PdCl_2(MeCN)_2$, and $LiPdCl_3$) occurs at a fairly high rate. It is very significant that the accessible and cheap salt $PdCl_2$ can be used as an efficient catalyst of the reaction. The catalytic activity of the Ni complexes is considerably lower than that of the Pd complexes.

4-Nitrotolan is formed in 91% yield in the stoichiometric reaction of PhC≡CCu with the $4\text{-}NO_2C_6H_4PdI(PPh_3)_2$ complex (1 equiv. Bu_4NI, THF, 20 °C, 1 h). The initial Pd complex is regenerated in 72% yield after the addition of 4-iodonitrobenzene to the reaction mixture. The halide ion additives not only favor the removal of solid copper phenylacetylenide (insoluble CuX in the form of the CuX · MX complex) from the surface, but also exert a nucleophilic coaction at the stage of transmetallation with $RPdXL_2$ due to the formation of the ate-complex $[PhC{\equiv}CCuX]^-M^+$. However, it is impossible to distinguish these effects due to the insolubility of PhC≡CCu. Nucleophilic catalysis was



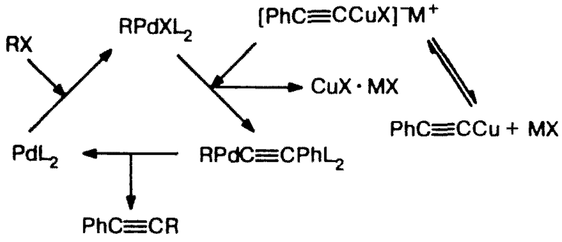
(46)

Reagents and conditions: *a*. [Pd], THF, 20 °C, *b*. 42 h; *c*. Bu_4NBr, 10 min.

observed in the explicit form for the reaction of soluble mesitylcopper with 4-iodonitrobenzene in the presence of a palladium catalyst.[69] After 42 h, this reaction results in the formation of 2,4,6-trimethyl-4′-nitrodiphenyl in 13% yield. In the presence of 1 equiv. Bu_4NBr, the yield of the cross-coupling product after only 10 min reaches 90% (Eq. (46)).

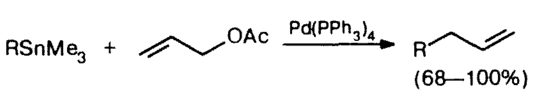
Thus, the catalytic reaction can be presented as the reaction of $RPdXL_2$ with the ate-complex $[PhC{\equiv}CCuX]^-M^+$ (transmetallation stage); the $RPdC{\equiv}CPhL_2$ complex obtained undergoes reductive elimination to form $PhC{\equiv}CR$ and PdL_2. Then the oxidative addition of RX to PdL_2 results in the regeneration of the initial complex $RPdXL_2$, and the cycle is repeated (Scheme 12).

Scheme 12



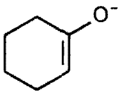
Palladium-catalyzed allyldemetallation of organometallic compounds

Organotin compounds. Allylation of various nucleophiles occupies a special position in the series of Pd-catalyzed reactions.[70] These reactions have found a wide application in organic synthesis.[71] They involve π-allyl Pd intermediates and usually include a nucleophilic attack on the π-allyl ligand by "soft" carbanions similar to the malonic ester anion.[72] It turned out that the use of organotin compounds in Pd-catalyzed allyldemetallation reactions makes it possible to perform the allylation of quite various CH-acids.[73—77] The advantage of the use of stannylated ketones, esters, and hydrocarbons with high CH-acidity over the corresponding Li or Na derivatives is that it is possible to obtain only the monoarylation product (HMPA, 20 °C).



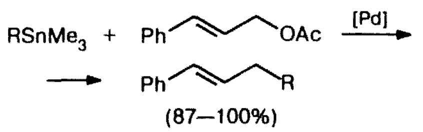
(47)

R = $CH_2{=}CHCH_2$, E-PhCH=CH, $MeCOCH_2$, PhCH(COOEt),



, $9\text{-}C_9H_{13}$; indenyl, Cp, $4\text{-}XC_6H_4$; X = Me, H, Cl

The *trans*-configuration of the cinnamyl fragment is observed in the reactions of $RSnMe_3$ with cinnamyl acetate (HMPA, 20 °C)



(48)

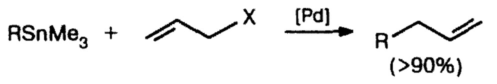
R = Ph, $CH_2{=}CHCH_2$

The reaction of trimethylphenyltin with cyclohexen-2-yl acetate results in the formation of 1,3-cyclohexadiene in 68% yield instead of the 3-phenylcyclohexene expected.

Allyl halides can also be introduced into reaction (47), but they are considerably less reactive than allyl acetates. Allyl iodide exhibits higher activity than allyl chloride and bromide: 56% 4-allyltoluene (60% conversion) is formed in 6 h in the reaction of trimethyl(4-tolyl)tin.

Phenylethynyl- and trimethyl(2-thienyl)tin do not react with allyl acetates, but they react with allyl halides to give the allyldemetallation products in 3—18% yields (5 mol.% $Pd(PPh_3)_4$, HMPA, 20 °C). In addition, the reactions of trimethyl(2-thienyl)tin with allyl chloride and bromide result in the formation of bis(2-thienyl) in 56 and 33% yields, respectively. No dimeric products are formed in the reaction with allyl iodide. When the reaction of trimethyl(2-thienyl)tin with allyl iodide is performed at 70 °C, it is 45% complete after 6 h, giving allylthiophene in 40% yield.

In the presence of 1 mol.% Pd^{II} compounds containing no phosphine ligands, the reactions of $RSnMe_3$ with allyl halides occur in HMPA or DMSO at room temperature in 15—20 min to give the allyldemetallation products in quantitative yields.[44,76]

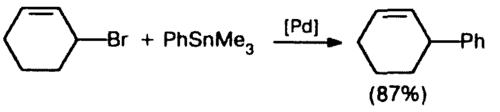


(49)

R = $CH_2{=}CHCH_2$, $9\text{-}C_9H_{13}$, $4\text{-}YC_6H_4$; Y = MeO, Me, H, Cl;
X = Cl, Br, I
[Pd] = $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, $(\pi\text{-}C_3H_5PdCl)_2$, $Pd(OAc)_2$, $LiPdCl_3$, $PdCl_2$

In the reaction of $4\text{-}ClC_6H_4SnMe_3$ with allyl bromide, the maximum yield of the cross-coupling product is achieved in DMF. When the reaction is performed in HMPA, the yield of 4-allylchlorobenzene is not greater than 30%, and the dimer $(4\text{-}ClC_6H_4)_2$ (68%) is the main product.

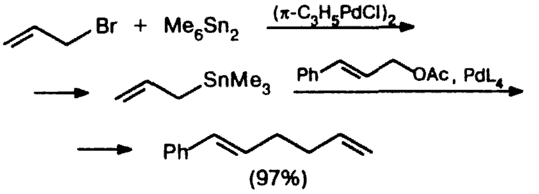
The reaction of trimethylphenyltin with cyclohexen-2-yl bromide (HMPA, 20 °C, 1 h), unlike the reaction with the corresponding acetate, results in the formation of the 3-phenylcyclohexene expected.[47]



(50)

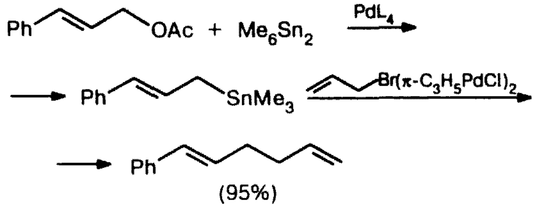
In the case of other substituted allyl halides (cinnamyl bromide, crotyl bromide, and 3-chlorobutene), homocoupling products are formed along with the allyldemetallation products. The selectivity of the reactions increases considerably on going from HMPA and DMF to the less polar solvents, chloroform, acetone, and THF.[73]

As is shown above, the reactions of allyl halides and acetates with hexamethyldistannane catalyzed by Pd complexes result in the formation of the corresponding allyltrimethylstannanes in high yields, and the whole chain of the transformations of Alk_3SnCl into $RSnAlk_3$ can be performed in high yields without isolation of tin hydrides, which are sensitive to air, and without any purification of the intermediate hexaalkyldistannanes. In turn, the allylstannanes obtained by this method can be introduced into various reactions also without isolation from the reaction mixture. The synthesis of nonsymmetric 1,5-dienes (HMPA, 20 °C) can be presented as an example.[57]



(51)

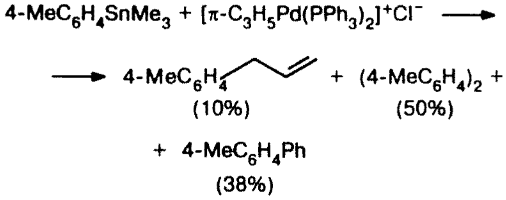
An alternative scheme of the synthesis (HMPA, 20 °C) gives the target product almost in the same yield.



(52)

Stoichiometric reactions of π-allyl palladium complexes with organotin compounds. According to contemporary views, π-allyl palladium complexes, which are ambidentate electrophiles, are intermediates in the palladium-catalyzed reactions of allyl substrates with nucleophiles.[72] Therefore, a nucleophile, depending on its nature, attacks either the π-allyl ligand or the Pd atom and then reductive elimination occurs.

The stoichiometric reactions of the complex $[\pi\text{-}C_3H_5Pd(PPh_3)_2]^+Cl^-$ (**1**) obtained from bis(π-allylpalladium chloride) and 4 equiv. PPh_3 with organotin compounds $RSnMe_3$ were studied to check the possibility of the participation of π-allyl intermediates in the catalytic allyldemetallation of organotin compounds.[77] However, when 4-allyltoluene is formed quantitatively (measured per reacted $RSnMe_3$) in the catalytic reaction of trimethyl(4-tolyl)tin with allyl chloride, its yield in the stoichiometric reaction (HMPA, 20 °C) is low and the main products are bis(4-tolyl) and 4-methyldiphenyl.

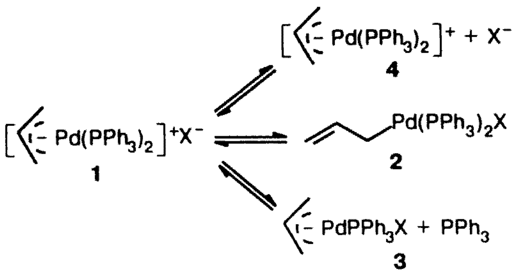


(53)

The differences observed in the compositions of the products are likely caused by the fact that the stoichiometric reaction results in the formation of the coordinationally unsaturated complex $Pd(PPh_3)_2$, which involves the initial organotin compound in side transformations (see also Ref. 78). In order to exclude the formation of $Pd(PPh_3)_2$ and to suppress thus the side processes, reaction (53) was performed in the presence of 1 equiv. allyl chloride, which is reactive in oxidative addition to Pd^0 complexes. In this case, 4-allyltoluene is formed in 85% yield (87% conversion).

As follows from the published data,[79] several equilibria, whose positions depend strongly on the nature of the solvent and the leaving group X, can exist in a solution of π-allyl complex **1** (Scheme 13).

Scheme 13

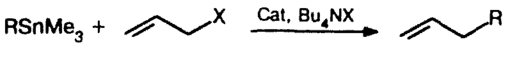


In this connection, the question arose about the participation of the other palladium compounds (**2**, **3**, and **4**) along with complex **1** in the reaction with $RSnMe_3$. To answer this question, we have studied the effect of additives of the same ion on the course of the reaction of trimethyl(4-tolyl)tin with $CH_2{=}CHCH_2X$ (X = OAc, I) catalyzed by $Pd(PPh_3)_4$. It turned out that the effect of the common ion in this reaction is very significant. By contrast, the effect of the same ion additives turned out to be rather weak for the catalysis of complex **3** obtained independently (Table 1).

Table 1. Effect of additives of the same ion in reaction (54)

R	X	Cat	*t*/h	Yield (%)*
4-MeC_6H_4	OAc	$Pd(PPh_3)_4$	6	27 (100)
4-MeC_6H_4	I	$Pd(PPh_3)_4$	6	0 (56)
Ph	OAc	3	25	81 (88)
Ph	I	3	30	40 (55)
2-Thienyl	I	$Pd(PPh_3)_4$	6	46 (18)

* The yields in the absence of 1 equiv. Bu_4NX are given in parentheses.



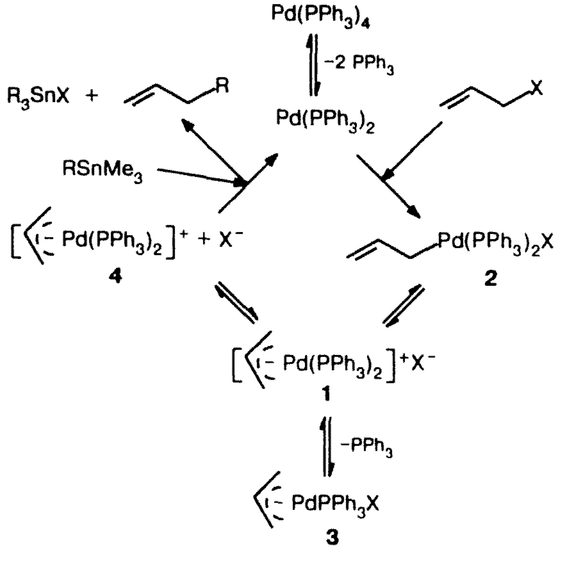
(54)

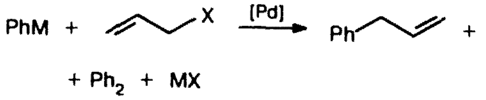
The results obtained allowed us to assume that cationic complex **4** is the most reactive intermediate in the reactions of $ArSnMe_3$ with allyl substrates. A possible mechanism of the reactions of organotin compounds with $CH_2=CHCH_2X$ catalyzed by $Pd(PPh_3)_4$ is presented in Scheme 14.

Since the positive effect of the common ion is observed for the reaction of trimethyl(2-thienyl)tin with allyl iodide, it is not excluded that complex **2** is the reactive intermediate in this case, *i.e.*, the reaction proceeds as normal cross-coupling with the attack of the nucleophile on the Pd atom in the σ-allyl complex.

Organomagnesium, -zinc, -cadmium, and -aluminum compounds. Like for other catalytic reactions involving OMC, we studied the effect of the nature of the metal and the organic radical for organomagnesium, -zinc, -cadmium, and -aluminum compounds as well as the effect of the nature of the leaving group in the allyl substrate on Pd-catalyzed allyldemetallation reactions (THF, 20 °C).[80]

Scheme 14





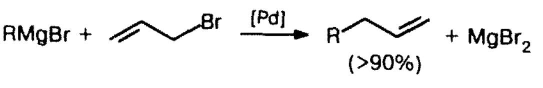
(55)

M = MgBr, ZnCl, CdBr, $AlCl_2$
X = Br, OAc, OPh, Et_3N^+

The reactivity of PhM decreases in the following series: PhMgBr > PhZnCl > PhCdBr ≫ $PhAlCl_2$. For example, the $Pd(PPh_3)_4$-catalyzed reaction of a Grignard reagent with allyl bromide is completed for 15 min, the reaction of PhZnCl requires in 3.5 h, and that of PhCdBr takes 12 h, while in the case of the organoaluminum compound, only traces of allylbenzene are formed in 20 h. The ratio between the cross-coupling and homocoupling products depends on the nature of the leaving group. On going from allyl bromide to allyl acetate, allyl phenyl ether, and allyltrimethylammonium chloride, the amount of diphenyl formed increases. The yield of diphenyl also increases when allyl bromide is replaced by cinnamyl bromide in the reaction with PhMgBr: Ph_2 (22%) is formed along with 1,3-diphenylpropene (77%). It is assumed that the formation of the homocoupling products is the result of the exchange processes of M—X involving Pd-containing intermediates (see also Ref. 20).

The ratio between the cross-coupling and homocoupling products also depends on the type of Pd complex used as a precursor of the active form of the catalyst. The highest selectivity is observed when $Pd(PPh_3)_4$ is used as the catalyst, and on going to $PdCl_2(PPh_3)_2$ and $(\pi\text{-}C_3H_5PdCl)_2$ the reaction becomes considerably less selective. At the same time, by varying the nature of the metal in OMC, the contributions of side processes can be decreased. For example, $PhAlCl_2$ does not enter reaction (55) in the presence of $Pd(PPh_3)_4$, but reacts readily with allyl bromide when the $(\pi\text{-}C_3H_5PdCl)_2$ complex, containing no phosphine ligands, is used as the catalyst.

To find out how the nature of the R radical in RM affects the rate of the process and the ratio between $RCH_2CH=CH_2$ and R_2, we studied the Pd-catalyzed reactions of RMgBr, RZnCl, and $RAlCl_2$ (R = Ar, $PhCH_2$, *E*-PhCH=CH, PhC≡C, 9-fluorenyl, and 2-thienyl) with allyl bromide in THF at room temperature. It turned out that the reactions of Grignard reagents with allyl bromide are considerably faster and more selective in the presence of $Pd(PPh_3)_4$ than in its absence. This makes it possible to obtain the corresponding allylation products under mild conditions and in high yields.



(56)

R = Ph, 4-MeC_6H_4, 4-BrC_6H_4, $PhCH_2$, 9-C_9H_{13}, 2-C_4H_3S

In the series of organomagnesium and organozinc aryl compounds, the insertion of electron-donating substituents (MeO, Me_2N) into the aromatic ring results in a decrease in the yield of the allyldemetallation product and an increase in the yield of diaryls, and the selectivity of the reactions increases on going from RMgBr to ArZnCl. The use of bis(π-allylpalladium chloride) as the catalyst instead of $Pd(PPh_3)_4$ in the reactions of RZnCl (R is 9-fluorenyl, 2-thienyl) with allyl bromide results in an increase in the allyldemetallation rate, however, a considerable amount of the homocoupling products R_2 is formed. By contrast, no R_2 dimers are formed in the reactions of $RAlCl_2$ catalyzed by "ligand-free" palladium.

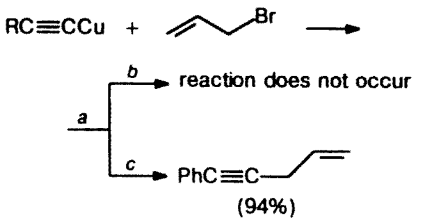
The appearance of homocoupling products is most typical of β-styryl magnesium, zinc, and aluminum derivatives. For example, the reaction of PhCH=CHMgBr with allyl bromide results after 30 min in the formation of 1,4-diphenylbutadiene in quantitative yield. In the reactions of PhCH=CHZnCl and $PhCH=AlCl_2$ with allyl bromide, the yields of $(PhCH=CH)_2$ are 47 and 31%, respectively, at 100% conversion with respect to the organometallic compound. In this case, an organotin compound should be preferred (see above) because of the low yield of the allyldemetallation product.

Thus, the reactions of OMC with allyl substrates can be directed almost exclusively to the allyldemetallation route, by varying the nature of the metal in RM and the ligand surrounding of the palladium catalyst.

Reactions of organic halides with terminal acetylenes

Allyl halides. As has been shown previously, in the Pd-catalyzed reactions of PhC≡CM with aryl iodides, the highest yields of the cross-coupling products are observed in the case of organomagnesium and organozinc compounds. However, the synthetic possibilities of these reactions are limited to the range of acetylenides and organic halides containing no substituents sensitive to the action of reactive OMC. From this viewpoint, copper acetylenides are more attractive, because they can be easily obtained from terminal acetylenes under the action of copper(I) halide in the presence of a base. It has been noted above that the Pd-catalyzed cross-coupling of PhC≡CCu with aryl halides occurs smoothly only in the presence of a nucleophilic catalyst, Bu_4NI or NaI.

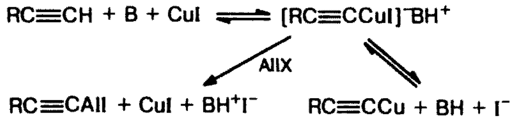
The analysis of the published data[81] and the results obtained allowed us to assume that the active intermediates in the reactions of copper acetylenides with organic halides are ate-complexes $[RC{\equiv}CCuX]^-M^+$ (M = Bu_4N, Na, *etc.*). The reactivity of these complexes is so high that some of their transformations occur in the absence of a metal complex catalyst. For example, in the presence of NaI, PhC≡CCu reacts readily with allyl bromide at room temperature to give 5-phenyl-1,4-pentenine.[82]



(57)

Reagents and conditions: *a.* DMF, 20 °C; *b.* 1 h; *c.* NaI, 15 min.

The reaction occurs without iodide ion additives if the initial acetylenide is obtained from terminal acetylene and CuI in the presence of a base. In this case, the ate-complex is generated *in situ.*



(58)

Compounds Et_3N, K_2CO_3, and Na_2CO_3 were used as the base B in reaction (58). Potash turned out to be the most efficient: in the presence of K_2CO_3 and 1 equiv. CuI, terminal acetylenes react only with allyl halides in DMF or acetone at 20—45 °C to form 1,4-enines in 0.5—4 h in almost quantitative yields.

$$RC{\equiv}CH + AllX \xrightarrow{K_2CO_3,\ CuI} \underset{(92\text{—}100\%)}{RC{\equiv}CAll} \qquad (59)$$

R = Ph, CH_2OH, n-C_5H_{11}

It has been shown, using the reactions of phenylacetylene with prenyl chloride and 1,3-dichloro-2-butene as an example, that under the experimental conditions cross-coupling is not accompanied by allyl rearrangement.

$$PhC{\equiv}CH + Me_2C{=}CHCH_2Cl \longrightarrow$$
$$\longrightarrow \underset{(99\%)}{Me_2C{=}CHCH_2C{\equiv}CPh} \qquad (60)$$

$$PhC{\equiv}CH + MeCCl{=}CHCH_2Cl \longrightarrow$$
$$\longrightarrow \underset{(100\%)}{MeCCl{=}CHCH_2C{\equiv}CPh} \qquad (61)$$

Reaction (59) was performed in the presence of catalytic amounts of CuI (10 mol.%). Despite the fact that the rate of the catalytic reaction is much lower than that of the stoichiometric reaction, its completion required heating of the mixture to 40—50 °C for 2—7 h.

Aryl halides. It is known that terminal acetylenes react with aryl halides under fairly drastic conditions.[83] Nevertheless, the reaction can be performed under very mild conditions if combined catalysis by copper(I) halide and a Pd complex[84] in diethylamine is used. It is noteworthy that this reaction occurs at a substantially lower rate in the absence of CuX.

In order to find the optimum conditions for the cross-coupling, using the reactions of PhC≡CH with $4\text{-}NO_2C_6H_4I$ and $4\text{-}ClC_6H_4I$ as well as that of $HC{\equiv}CCH_2OH$ with $4\text{-}NO_2C_6H_4I$, we studied the effects of the solvent, catalyst, and base on the duration of the process and the yield of the cross-coupling product.[85] It turned out that 1.5—2.0 equiv. amine is enough to enable the reactions of terminal acetylenes with organic halides catalyzed by the Pd complexes and copper(I) halides to occur. The reaction occurs readily even in such nonpolar solvents as benzene and chloroform (20—70 °C, 0.4—4.0 h). The maximum catalytic activity is manifested by the Pd complexes containing ligands that are less basic than Ph_3P (MeCN, dba, *etc.*). A change in the basicity of the amine within a small range has a slight effect on the reaction rate and the yield of the cross-coupling product.

$$RC{\equiv}CH + R'X \xrightarrow[Et_3N,\ PhH]{PhPdI(PPh_3)_2,\ CuI} \underset{(\sim100\%)}{RC{\equiv}CR'} \qquad (62)$$

R = Ph, CH_2OH, $n\text{-}C_5H_{11}$
R' = *E*-PhCH=CH, $2\text{-}C_4H_3S$, 4-py, $4\text{-}YC_6H_4$; Y = NO_2, CN, Cl, COOMe, COOH, H, MeO
X = I, Br

Alkali or potash can be used instead of triethylamine in reaction (62).[86] However, the cross-coupling product is not formed in the $PhPdI(PPh_3)_2$-catalyzed reaction of PhC≡CH with $4\text{-}NO_2C_6H_4I$ in THF. The addition of 18-crown-6 ether (10 mol.%), which has the function of a phase-transfer catalyst, to the reaction mixture results in the quantitative formation of 4-nitrotolan already in 3 h at room temperature. Additions of CuI (1 mol.%) accelerate the reaction considerably.

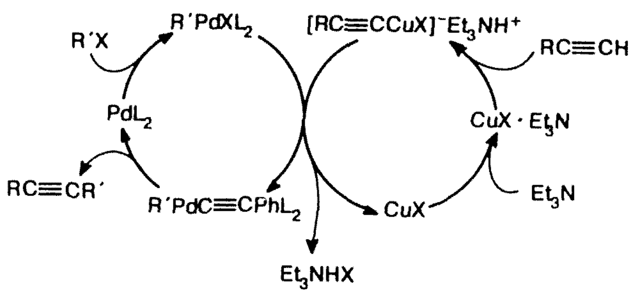
$$RC{\equiv}CH + 4\text{-}NO_2C_6H_4I \longrightarrow \xrightarrow{a} \begin{cases} \xrightarrow{b} \underset{(100\%)}{4\text{-}NO_2C_6H_4C{-}CPh} \\ \xrightarrow{c} \underset{(95\%)}{4\text{-}NO_2C_6H_4C{-}CPh} \end{cases} \qquad (63)$$

Reagents and conditions: *a*. THF, 18-crown-6, [Pd], 20 °C; *b*. 3 h; *c*. CuI, 1.5 h.

Potash can be used along with alkali as the base, if the coupling process is performed with slight heating.

A mechanism for reaction (62), consisting of two coupled catalytic cycles, has been suggested. Unlike the standard cross-coupling of RM with R'X catalyzed by the palladium complexes, in the given case, OMC (in the form of the soluble ate-complex $[RC{\equiv}CCuX]^-Et_3NH^+$) is generated in catalytic amounts directly during the reaction (Scheme 15).[47]

Scheme 15



Synthesis of aryl-, heteroaryl-, and vinylacetylenes. As is known, terminal acetylenes are key intermediates in the synthesis of unsaturated alcohols, ketones, amines, and other acetylenic compounds. We have developed a convenient method for the preparation of aryl-, heteroaryl-, and vinylacetylenes from easily accessible propargyl alcohol and the corresponding organic halides.[87,88] These compounds under the conditions of reaction (64) give 3-substituted propargyl alcohols in high yields.

$$HC{\equiv}CCH_2OH + RX \xrightarrow[PhH]{Et_3N,\ CuI,\ [Pd]} \underset{(81-98\%)}{RC{\equiv}CCH_2OH} \qquad (64)$$

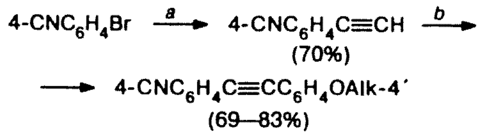
R = YC_6H_4; Y = $2\text{-}NO_2$, $3\text{-}NO_2$, $4\text{-}NO_2$, 4-CN, 4-Ac, 2-MeOOC, 4-MeOOC, 4-Cl, 4-Br, $4\text{-}Pr^n$
X = Cl, Br

The simultaneous oxidation—decarbonylation of substituted propargyl alcohols occurs under the action of technical MnO_2 (10—15 equiv.) and KOH (2—5 equiv.) to give terminal acetylenes in high yields.

$$RC{\equiv}CCH_2OH \xrightarrow[PhH]{MnO_2,\ KOH} \underset{(77-99\%)}{RC{\equiv}CH} \qquad (65)$$

Terminal acetylenes can be synthesized without isolation of intermediate propargyl alcohols. For this purpose, after the cross-coupling ceases, the reaction mixture is diluted with benzene and treated with KOH and MnO_2. When organic halides, which are less reactive than aryl iodides, are used, it is reasonable to use 10—30 mol.% CuI and the equivalent (calculated per CuI) amount of Bu_4NBr (to facilitate the formation of the ate-complex) and to perform the oxidation—decarbonylation after $RC{\equiv}CH_2OH$ is isolated.

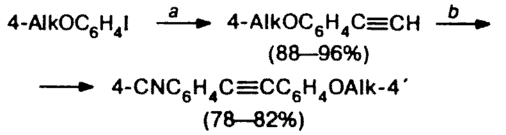
The method developed for the synthesis of arylacetylenes has been used for the preparation of liquid-crystalline 4-*n*-alkoxy-4'-cyanotolans.[37] These compounds have been synthesized by two methods (reactions (66) and (67)).



$$4\text{-}CNC_6H_4Br \xrightarrow{a} \underset{(70\%)}{4\text{-}CNC_6H_4C{\equiv}CH} \xrightarrow{b} \underset{(69\text{—}83\%)}{4\text{-}CNC_6H_4C{\equiv}CC_6H_4OAlk\text{-}4'} \qquad (66)$$

Alk = $n\text{-}C_nH_{2n+1}$; n = 3, 4, 5, 8, 10

Reagents and conditions: *a.* 1) $HC{\equiv}CCH_2OH$, Et_3N, CuI, [Pd], PhH; 2) MnO_2, KOH, PhH; *b.* $4\text{-}AlkOC_6H_4I$, Et_3N, CuI, [Pd], PhH.



$$4\text{-}AlkOC_6H_4I \xrightarrow{a} \underset{(88\text{—}96\%)}{4\text{-}AlkOC_6H_4C{\equiv}CH} \xrightarrow{b} \underset{(78\text{—}82\%)}{4\text{-}CNC_6H_4C{\equiv}CC_6H_4OAlk\text{-}4'} \qquad (67)$$

Alk = Pr^n, Bu^n

Reagents and conditions: *a.* 1) $HC{\equiv}CCH_2OH$, Et_3N, CuI, [Pd], PhH; 2) MnO_2, KOH, PhH; *b.* $4\text{-}CNC_6H_4I$, Et_3N, CuI, [Pd], PhH.

The methods suggested are characterized by high yields and simple isolation of target products as well as by high reaction rates and selectivity.

* * *

Thus, the palladium-catalyzed reactions of organic halides with organometallic compounds and terminal acetylenes occur under mild conditions with high rates and the formation of target products in high yields, which makes it possible to use them as efficient methods for the synthesis of organic compounds of various classes.

References

1. E. I. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340.
2. B. M. Trost and T. R. Verchoeven, in *Comprehensive Organometallic Chemistry*, Pergamon Press, Oxford, 1982, **8**, 799.
3. E. I. Negishi, T. Takahashi, and K. Akiyoshi, in *Catalysis of Organic Reactions*, Eds. P. N. Rylander, H. Greenfield, and R. L. Augustine, Marcel Dekker, New York, 1988, 381.
4. R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 1972, 144.
5. K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 4374.
6. M. Yamamura, I. Moritani, and S. Murahashi, *J. Organomet. Chem.*, 1975, **91**, C39.
7. E. Negishi and A. O. King, *J. Org. Chem.*, 1977, **42**, 1821.
8. E. Negishi and S. Baba, *J. Chem. Soc., Chem. Commun.*, 1976, 596.
9. E. Negishi and D. E. van Horn, *J. Am. Chem. Soc.*, 1977, **99**, 3168.
10. N. Miyaura and A. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1979, 866.
11. M. Kosugi, K. Sasazawa, I. Shimizu, and T. Migita, *Chem. Lett.*, 1977, 301.
12. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 2413 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1981, **30** (Engl. Transl.)].
13. N. A. Bumagin, A. B. Ponomarev, and I. P. Beletskaya, *Zh. Org. Khim.*, 1987, **23**, 1345 [*J. Org. Chem. USSR*, 1987, **23** (Engl. Transl.)].
14. N. P. Andryukhova, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1989 (in Russian).
15. N. A. Bumagin and I. P. Beletskaya, *Usp. Khim.*, 1990, **59**, 2005 [*Russ. Chem. Rev.*, 1990, **59** (Engl. Transl.)].
16. F. Ozawa, T. Hidaka, T. Yamamoto, and A. Yamamoto, *J. Organomet. Chem.*, 1987, **330**, 253.
17. F. Ozawa, K. Kurihara, T. Yamamoto, and A. Yamamoto, *J. Organomet. Chem.*, 1985, **279**, 233.
18. A. Moravskiy and J. K. Stille, *J. Am. Chem. Soc.*, 1981, **103**, 4182.
19. F. Ozawa, M. Mujimori, T. Yamamoto, and A. Yamamoto, *Organometallics*, 1986, **5**, 2144.
20. N. A. Bumagin, N. P. Andryukhova, and I. P. Beletskaya, *Metalloorg. Khim.*, 1989, **2**, 893 [*Organomet. Chem. USSR*, 1989, **2**, 467 (Engl. Transl.)].
21. N. A. Bumagin, A. B. Ponomarev, and I. P. Beletskaya, *Zh. Org. Khim.*, 1987, **23**, 1354 [*J. Org. Chem. USSR*, 1987, **23** (Engl. Transl.)].
22. N. A. Bumagin, N. P. Andryukhova, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1681 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 1561 (Engl. Transl.)].
23. N. A. Bumagin, N. P. Andryukhova, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1987, **297**, 1126 [*Dokl. Chem.*, 1987, **297** (Engl. Transl.)].
24. N. A. Bumagin, N. P. Andryukhova, and I. P. Beletskaya, *Metalloorg. Khim.*, 1989, **2**, 605 [*Organomet. Chem. USSR*, 1989, **2**, 308 (Engl. Transl.)].
25. N. A. Bumagin, A. F. Sokolova, and I. P. Beletskaya, *Zh. Org. Khim.*, 1993, **29**, 162 [*Russ. J. Org. Chem.*, 1993, **29** (Engl. Transl.)].
26. A. F. Nikitina, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1994 (in Russian).
27. N. A. Bumagin, A. F. Sokolova, and I. P. Beletskaya, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 2009 [*Russ. Chem. Bull.*, 1993, **42**, 1926 (Engl. Transl.)].
28. N. A. Bumagin, A. F. Sokolova, and I. P. Beletskaya, *Zh. Org. Khim.*, 1994, **30**, 1047 [*Russ. J. Org. Chem.*, 1994, **30** (Engl. Transl.)].
29. P. L. Castle and D. A. Widdowson, *Tetrahedron Lett.*, 1986, **27**, 6013.
30. F. S. Safarov, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1993 (in Russian).
31. N. A. Bumagin, F. S. Safarov, and I. P. Beletskaya, *Dokl. Akad. Nauk*, 1993, **332**, 48 [*Dokl. Chem.*, 1993, **332** (Engl. Transl.)].
32. N. A. Bumagin, E. V. Luzikova, and I. P. Beletskaya, *Zh. Org. Khim.*, 1995, **31**, 1650 [*Russ. J. Org. Chem.*, 1995, **31** (Engl. Transl.)].
33. N. A. Bumagin, E. V. Luzikova, and I. P. Beletskaya, *Zh. Org. Khim.*, 1995, **31**, 1657 [*Russ. J. Org. Chem.*, 1995, **31** (Engl. Transl.)].
34. N. A. Bumagin, F. S. Safarov, and I. P. Beletskaya, *Vestn. Mosk. Univ., Ser. 2. Khim.*, 1990, **31**, 382 (in Russian).
35. C. D. Nenitzescu and J. G. Gavat, *Liebigs Ann.*, 1935, **519**, 260.
36. N. A. Bumagin, E. V. Luzikova, and I. P. Beletskaya, *Zh. Org. Khim.*, 1996, **31**, 1662 [*Russ. J. Org. Chem.*, 1996, **31** (Engl. Transl.)].
37. A. B. Ponomarev, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1986 (in Russian).

38. N. A. Bumagin, N. P. Andryukhova, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1989, **307**, 375 [*Dokl. Chem.*, 1989, **307** (Engl. Transl.)].
39. N. A. Bumagin, A. F. Nikitina, and I. P. Beletskaya, *Zh. Org. Khim.*, 1996, **31** [*Russ. J. Org. Chem.*, 1996, **31** (Engl. Transl.)].
40. E. Erdic, *Tetrahedron*, 1992, **48**, 9577.
41. J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508.
42. A. N. Kashin, I. G. Bumagina, N. A. Bumagin, I. P. Beletskaya, and O. A. Reutov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 479 (in Russian).
43. A. N. Kashin, I. G. Bumagina, N. A. Bumagin, and I. P. Beletskaya, *Zh. Org. Khim.*, 1987, **23**, 21 [*J. Org. Chem. USSR*, 1987, **23** (Engl. Transl.)].
44. I. G. Bumagina, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1981 (in Russian).
45. N. A. Bumagin, I. G. Bumagina, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1983, **272**, 1384 [*Dokl. Chem.*, 1983, **272** (Engl. Transl.)].
46. N. A. Bumagin, I. G. Bumagina, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1984, **274**, 818 [*Dokl. Chem.*, 1984, **274** (Engl. Transl.)].
47. N. A. Bumagin, D. Sc. (Chem.) Thesis, Moscow State Univ., Moscow, 1986 (in Russian).
48. J. K. Stille and B. L. Croh, *J. Am. Chem. Soc.*, 1987, **109**, 813.
49. C. Sterro and J. K. Stille, *Organometallics*, 1990, **9**, 687.
50. A. Degl'Innocenti, A. Caperucci, L. Bartoletti, A. Mordini, and G. Reginato, *Tetrahedron Lett.*, **1994**, **35**, 2081.
51. Yu. V. Gulevich, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1985 (in Russian).
52. N. A. Bumagin, Yu. V. Gulevich, G. A. Artamkina, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 1195 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 1098 (Engl. Transl.)].
53. N. A. Bumagin, Yu. V. Gulevich, G. A. Artamkina, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1985, **280**, 633 [*Dokl. Chem.*, 1985, **280** (Engl. Transl.)].
54. A. N. Kashin, I. G. Bumagina, N. A. Bumagin, V. N. Bakunin, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 2185 (in Russian).
55. N. A. Bumagin, I. G. Bumagina, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1984, **274**, 1103 [*Dokl. Chem.*, 1984, **274** (Engl. Transl.)].
56. N. A. Bumagin, Yu. V. Gulevich, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 1137 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 1044 (Engl. Transl.)].
57. N. A. Bumagin, A. N. Kasatkin, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 636 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 588 (Engl. Transl.)].
58. N. A. Bumagin, Yu. V. Gulevich, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 2639 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
59. I. O. Kalinovskii, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1984 (in Russian).
60. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 1619 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 1469 (Engl. Transl.)].
61. N. A. Bumagin, K. V. Nikitin, and I. P. Beletskaya, *Vestn. Mosk. Univ., Ser. 2. Khim.*, 1989, **30**, 374 (in Russian).
62. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *Khim. Geterotsikl. Soedin.*, 1983, 1467 [*Chem. Heterocycl. Compd.*, 1983 (Engl. Transl.)].
63. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *Zh. Org. Khim.*, 1982, **18**, 1324 [*J. Org. Chem. USSR*, 1982, **18** (Engl. Transl.)].
64. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 2580 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 2364 (Engl. Transl.)].
65. A. [illegible] Sladkov, A. Yu. Ukhin, and V. V. Korshak, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1963, 2213 (in Russian).
66. C. E. Castro and R. D. Stephenes, *J. Org. Chem.*, 1963, **28**, 3313.
67. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 2836 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1981, **30** (Engl. Transl.)].
68. N. A. Bumagin, I. O. Kalinovskii, A. B. Ponomarev, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1983, **265**, 1138 [*Dokl. Chem.*, 1983, **265** (Engl. Transl.)].
69. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, *J. Organomet. Chem.*, 1984, **267**, C1.
70. J. Tsuji, H. Takahashi, and M. Morikawa, *Tetrahedron Lett.*, 1965, 4387.
71. J. Tsuji, *Pure Appl. Chem.*, 1982, **54**, 197.
72. B. M. Trost and N. R. Schmuff, *Tetrahedron Lett.*, 1981, **22**, 2999.
73. A. N. Kasatkin, Ph. D. (Chem.) Thesis, Moscow State Univ., Moscow, 1983 (in Russian).
74. I. P. Beletskaya, A. N. Kasatkin, S. A. Lebedev, and N. A. Bumagin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 2414 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1981, **30** (Engl. Transl.)].
75. N. A. Bumagin, A. N. Kasatkin, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1982, **286**, 862 [*Dokl. Chem.*, 1982, **286** (Engl. Transl.)].
76. N. A. Bumagin, I. G. Bumagina, A. N. Kashin, and I. P. Beletskaya, *Zh. Obshch. Khim.*, 1982, **52**, 714 [*J. Gen. Chem. USSR*, 1982, **52** (Engl. Transl.)].
77. N. A. Bumagin, A. N. Kasatkin, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 912 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 828 (Engl. Transl.)].
78. N. A. Bumagin, I. G. Bumagina, and I. P. Beletskaya, *Zh. Org. Khim.*, 1984, **20**, 457 [*J. Org. Chem. USSR*, 1984, **20** (Engl. Transl.)].
79. B. Akermark, G. Akermark, L. S. Hegedus, and K. Zetterberg, *J. Am. Chem. Soc.*, 1981, **103**, 3037.
80. N. A. Bumagin, A. N. Kasatkin, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 1858 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 1696 (Engl. Transl.)].
81. J. F. Norman, M. Bougain, and A. M. Rone, *Compt. Rend. Acad. Sci. Paris, Ser. C*, 1970, **270**, 354.
82. N. A. Bumagin, A. B. Ponomarev, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1565 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 1445 (Engl. Transl.)].
83. M. S. Shvartsberg, A. A. Moroz, and I. L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1972, 981 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1972, **21** (Engl. Transl.)].
84. K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.
85. N. A. Bumagin, A. B. Ponomarev, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 1561 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 1433 (Engl. Transl.)].
86. N. A. Bumagin, A. B. Ponomarev, A. N. Ryabtsev, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 604 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 507 (Engl. Transl.)].
87. N. A. Bumagin, A. B. Ponomaryov, and I. P. Beletskaya, *Synthesis*, 1984, 728.
88. N. A. Bumagin, A. B. Ponomarev, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, 1985, **283**, 630 [*Dokl. Chem.*, 1985, **283** (Engl. Transl.)].

Received June 17, 1996;
in revised form July 30, 1996