

Transition metal-catalyzed reactions in heterocyclic chemistry*

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Abstract: The palladium-catalyzed substitution reactions forming carbon–carbon and carbon–element bonds, as well as nickel-catalyzed addition of E–H and E–E' bonds across multiple bonds, are considered in their application to the chemistry of heterocyclic compounds.

INTRODUCTION

There are two different aspects in the application of transition metal-catalyzed reactions to the chemistry of heterocyclic compounds. One of them concerns the building of the heterocyclic backbone itself, while in the other, the heterocyclic fragment is used in one of the reaction components. Both groups of reactions are equally important for the chemistry of heterocyclic compounds, though the second one (and our works belong to this group) usually has no individual features of its own, replicating the regularities observed in the chemistry of aromatic compounds.

It is a well-known fact that the use of reactions catalyzed by transition-metal complexes, and especially palladium, has changed the face of modern organic synthesis and led to the development of radically new methods of building carbon–carbon and carbon–element bonds.

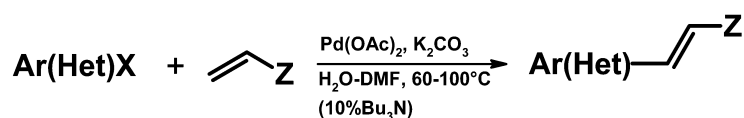
In this paper, we will cover the cross-coupling reactions involving various organometallic compounds, the reactions of Heck, Sonogashira, carbonylation, performed in neat water, aqueous media or microemulsions, and wherever possible in a phosphine-free manner. We will focus on the reactions forming C–P(O)(OR)₂, C–PR₂, C–NR₂, C–SeAr bonds, in which the carbon atom is part of a heterocyclic system or HNR¹R² belongs to a heterocyclic compound. Recently, particular attention has been paid to the catalytic addition reactions to multiple bonds, which being chemo-, regio- and stereoselective, are fully compliant with the “atom efficiency” principle. We will consider the new addition reactions of P–H and P–P bonds to triple and double bonds catalyzed by Pd and Ni complexes. All these reactions were carried out in the Laboratory of Organoelement Compounds of the Chemistry Department of Moscow State University.

FORMATION OF CARBON–CARBON BONDS

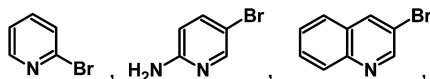
We were the first to carry out the cross-coupling reactions of organomercury compounds with Ar(Het)X [1,2]. These reactions required the presence not only of the Pd-catalyst, but also a nucleophilic catalyst—the iodide anion. Under protective argon atmosphere they gave high yields of the cross-coupling products. Many of the organomercury compounds were obtained by direct mercuriation of aromatic substrate in situ. The organomercury compounds can themselves belong to heterocyclic series. It is important that all the organic moieties of the organomercury compound are utilized in the reaction.

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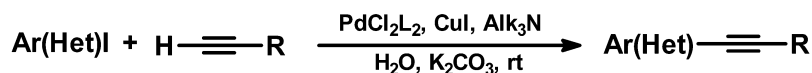


Ar = YC₆H₄ (Y = H, o-, p-Me, p-MeO, p-OH, p-Cl, m-CF₃, o-, m-CO₂H, p-CHO, p-NO₂)



Scheme 7

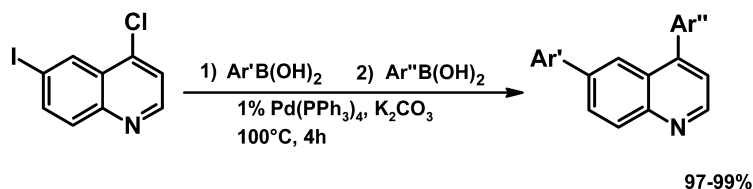
The Sonogashira reaction was also carried out in aqueous solutions in the presence of a small amount of R₃N or organic solvent [7,10].



R also can be Het

Scheme 8

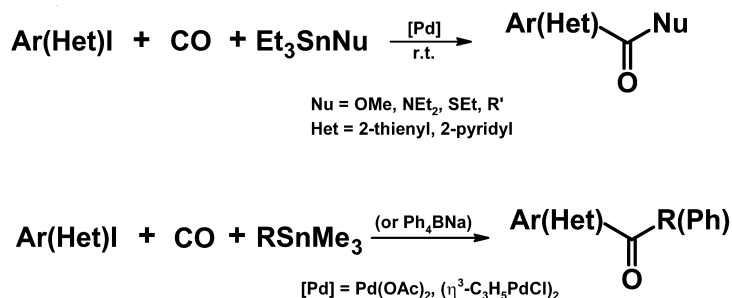
The 4-chloro-6-iodoquinoline was used as a model compound to compare the reactivity of C_{sp}²-I and an activated C_{sp}²-Cl bond in arylation and acetylenation reactions. It turned out that in all cases, the substitution of iodine is a much faster process than the substitution of chloride. In aqueous THF, the first stage may be accomplished with a ligandless catalyst, Pd(OAc)₂, while increasing the number of phosphine ligands in going from PdCl₂(PPh₃)₂ to Pd(PPh₃)₄ results in a sharp activity drop. However, for the second stage, the best results are achieved with Pd(PPh₃)₄, therefore it was used in a one-pot procedure. The reaction time can be greatly reduced by using aqueous dioxane instead of neat organic solvent. In that case, the first stage is completed in 0.5 h, and the second in 4 h instead of 48 h. Acceleration in the presence of water is evident from the comparison of the product yields in aqueous dioxane and in neat dioxane in the presence of phase transfer agent (97 and 37 %, respectively). The nature of the base also affects the reaction rate.



Scheme 9

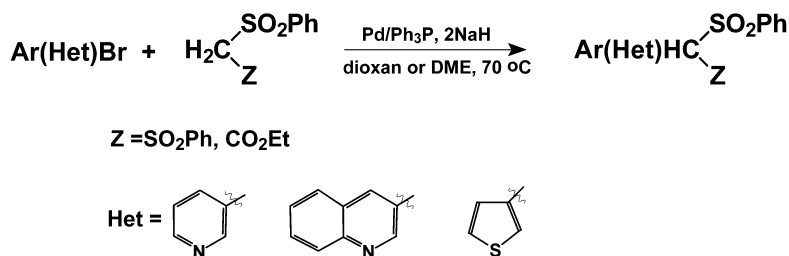
The Sonogashira reaction of the same substrate with phenylacetylene confirmed that the first stage involves the substitution of iodide. The results show that although the reaction can be carried out under palladium complexes catalysis or under catalysis with copper complex alone, the best results are achieved with the combination of both. The most prominent effect is produced by the addition of water. In aqueous acetonitrile or dioxane the first stage is completed in several minutes.

Carbonylation of organic halides under the action of Pd-complexes is a tricomponent process. The carbonylation of water-soluble aryl iodides, even if they have strongly donating groups, goes smoothly in neat water with “ligandless” palladium, while those insoluble in water, and heteroaromatic compounds belong to this group, are carbonylated in aqueous organic media [7,12]. We have shown that “ligandless” palladium catalysis allows one to carry out the carbonylation of Ar(Het)I using organotin compounds as the donor of an organic group (synthesis of ketones) or nucleophile (synthesis of ethers, anides, tioethers). In the case of ketones, Ph₄BNa was also used.



Scheme 10

The reactions with stabilized carbanions form a very special group of cross-coupling reactions. The typical problems involve the proper choice of the base for the deprotonation of CH-acid and the low reactivity of such carbanions. We have found that sulfonyl group-stabilized carbanions (also containing some other electron-withdrawing group) can be arylated with Ar(Het)X with catalysis by a common Pd(PPh₄)₄ complex, if NaH is used in excess [13]. The interesting fact is that the transmetalation product was not observed in the stoichiometric reaction, and the formation of the product in the reaction with the preformed carbanion takes place only in the presence of base.

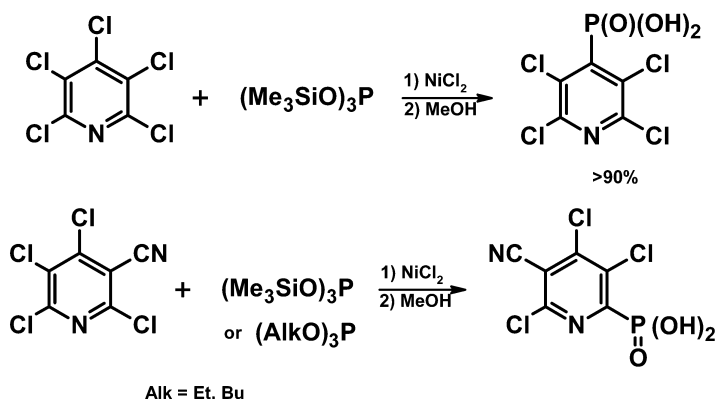


Scheme 11

FORMATION OF CARBON–ELEMENT BONDS

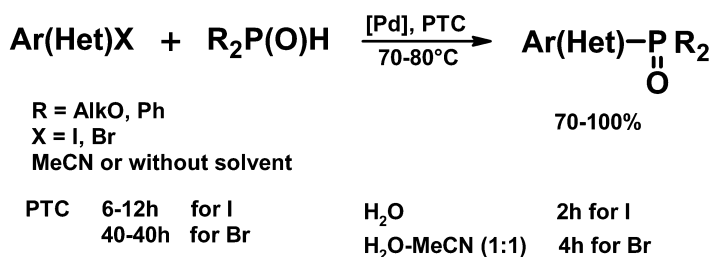
Formation of C–P bonds

Arylphosphonates can be easily obtained from pentafluoropyridine by a common S_N2–Ar aromatic nucleophilic substitution reaction. The substitution proceeds selectively in position 4. However, the reaction with perchloropyridine already needs catalysis. In the case of cyanotetrachloropyridine, the substitution follows a different regioselectivity [14].



Scheme 12

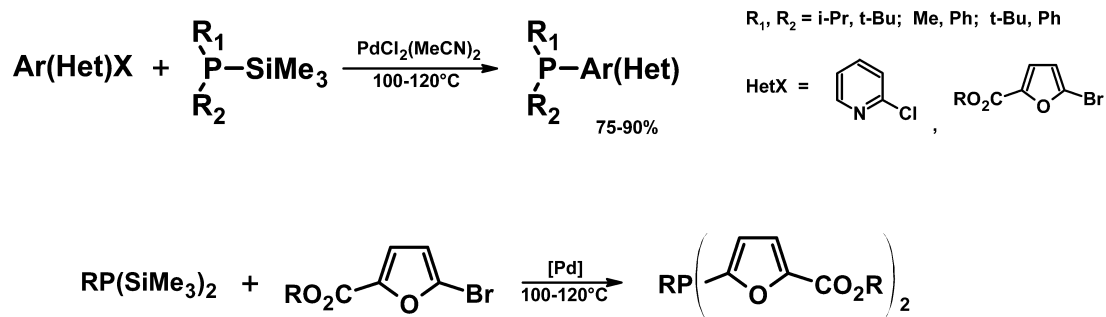
The aryl(hetaryl) phosphonates can be synthesized from unactivated Ar(Het)X by a Pd-catalyzed reaction with diethylphosphites. In the case of aryl (hetaryl) iodides, the use of “ligandless” palladium salts is sufficient, while bromides require the use of phosphine complexes. The reaction can be carried out under phase-transfer catalysis (PTC) conditions in a solid–liquid system, and even without solvent, but takes a long time to complete. In aqueous solvents, the reaction finishes much sooner (for instance, 2 h instead of 20 h for aryl bromides) [7,14].



Scheme 13

Perfluoropyridilphosphines can be obtained by a regioselective (in γ -position) S_N2Ar reaction. However, for the ordinary Ar(Het)Hal Pd-catalysis is required.

The reactions of aryl (hetaryl) iodides with $R_1R_2PSiMe_3$ ($R_1=R_2=Alk$; $R_1=H$, $R_2=Alk$) under the catalysis with Pd-complexes allows one to obtain tertiary and secondary phosphines, and the excellent ligand, trifurylphosphine with a hydrophilic group, among them.

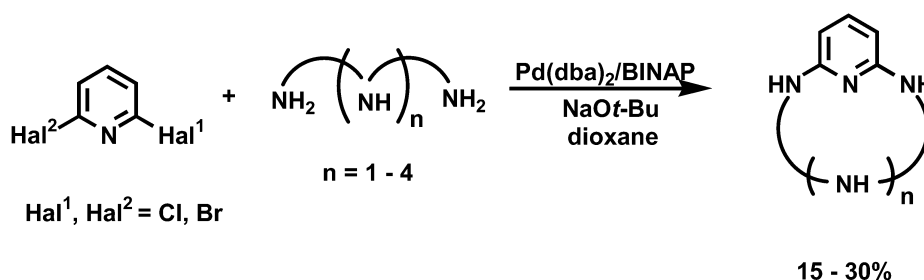


Scheme 14

Formation of C–N bonds

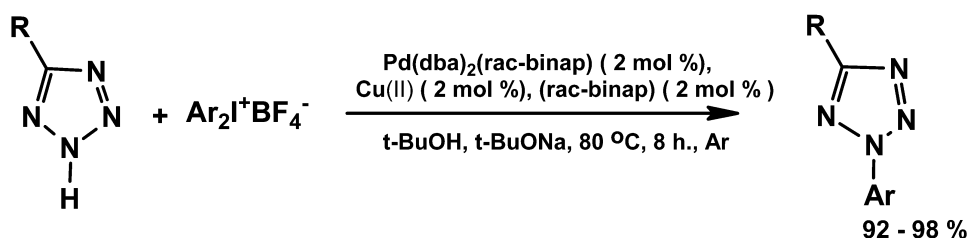
As in the case of phosphonates and phosphines, perfluoropyridine readily reacts with all types of amines, including polyamines and cyclam, for which the fully substituted derivatives were obtained.

The amination of unactivated aryl(hetaryl) halides takes place under Hartwig–Buchwald conditions. A large number of new macroheterocycles were obtained in the reaction of 1,8-dichloroanthracene and 1,8-dichloroantraquinone with polyamines and cyclams and in the reaction with dihalobenzenes and pyridines with polyamines [15].



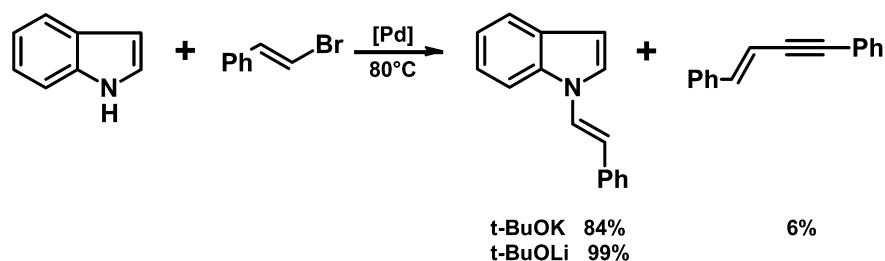
Scheme 15

With benzotriazole, which forms stable *N*-anions, the C–N bond-forming reaction does not need strong donor ligands, but requires the presence of Cu-complexes, in addition to Pd-complexes, to improve the selectivity. The reaction can be carried out in water using Ar_2IX in the presence of Pd-complex with water-soluble ligand [16]. Less reactive 5-aryltetrazoles [including 5-(4-Py) tetrazole] were arylated under the action of Ar_2IBF_4 in the $\text{Pd}(\text{dba})_2$ -BINAP system, with high product yields. However, in all these cases, the presence of copper salt as a co-catalyst was necessary for the reaction to proceed regioselectively [17].



Scheme 16

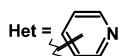
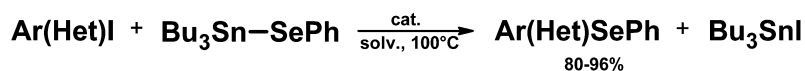
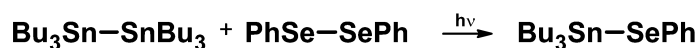
Recently, we described the first example of Pd-catalyzed vinylation of azoles and phenotiazine. The use of a strong base, which is necessary for the amination reaction, results in a side reaction producing alkynes by a base-induced elimination of HBr. This was avoided by the use of *t*-BuOLi in place of *t*-BuOK(Na). The styrylindole was obtained in 99 % yield [18].



Scheme 17

Formation of C–Se bonds

While preference in the formation of C–P and C–N bonds is clearly given to the reactions with the free amines and phosphines, in the case of C–Se bond-forming reactions, it is more convenient to use ArSeSnBu_3 , which is easily obtained from Bu_3Sn_2 and the corresponding diaryldiselenide [19].



solv. = xylene
solv. = DMF

cat. = $\text{Pd}(\text{PPh}_3)_4$
cat. = $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$

Scheme 18

ADDITION REACTIONS

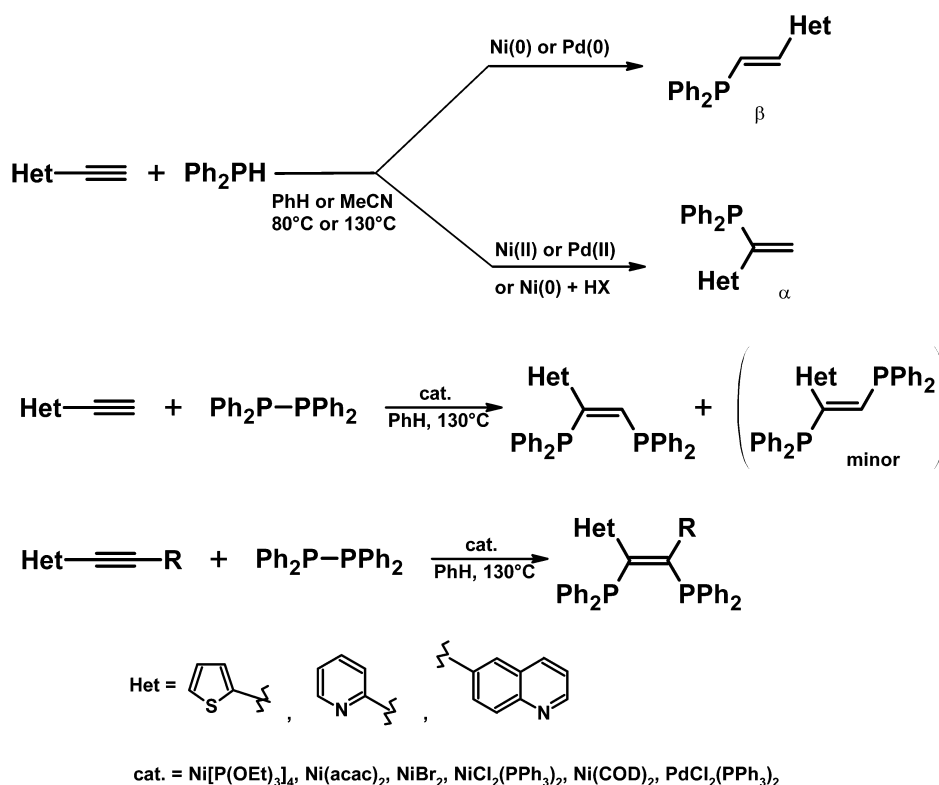
From the viewpoint of “green chemistry”, addition reactions have always been preferred over substitution reactions. Ideally, they give no waste material, and best agree with “atom economy” and “atom efficiency” principles.

The addition reactions of H–E and E–E’ bonds are of a special interest, since they open new routes to the regio- and stereoselective synthesis of C–E bonds [20].

We have carried out addition reactions of alkynes with diphenylphosphine and tetraphenyldiphosphine and reaction of styrenes with Ph_2PH . These reactions allow one to obtain various types of mono- and bidentate phosphines, simply and efficiently [21,22].

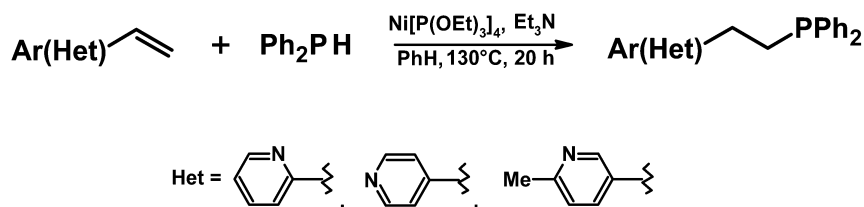
In all the cases, the nickel complexes were shown to be more efficient than the palladium complexes [23].

The addition reactions of Ph_2PH to alkynes result in different regioselectivity under different reaction conditions. α -Isomers are formed as the major or the only products in the presence of Ni(II) complexes, which upon reduction produce a catalytic amount of acid. The preferential or exclusive formation of the β -isomer takes place in the presence of Ni(0) and Pd(0) complexes.



Scheme 19

The reaction of Ph_2PH with styrenes Ar(Py)CH=CH_2 is highly selective, proceeding in the β -position and resulting in almost quantitative yields. The reaction is feasible not only for terminal, but also for internal alkynes and proceeds as a stereoselective *syn*-addition.

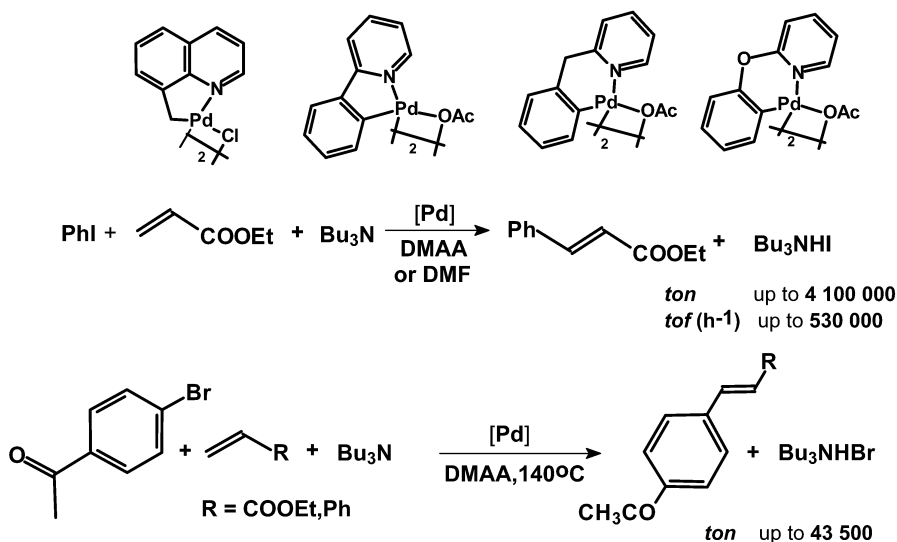


Scheme 20

PALLADOCYCLES WITH Pd←N COORDINATION AS CATALYSTS

Along with the studies which see their aim in the recycling of the catalyst, there is an intense search going on for more efficient catalytic systems, which allow one to carry out transformations with maximum possible TON and TOF numbers. Among such extraordinarily active catalytic systems are the palladocycles with intramolecular coordination, usually with phosphorus atom [24]. We have synthesized and tested in the Heck reaction a new series of palladocycles, where Pd is coordinated to the nitrogen atom of pyridine or quinoline ring. All these catalysts proved to be thermally stable and showed high

catalytic activity. They allowed us to achieve extremely high TON and TOF values and carry out the reactions not only with iodobenzene but also with bromobenzene.



Scheme 21

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