

To the memory of A.A.Petrov

Reaction of 4-(*N,N*-Dimethylaminophenyl)magnesium Bromide with Palladium Tetrakis(triphenylphosphine)

V. S. Zavgorodnii,¹ S. A. Klyuchinskii,¹ J.-F. Fauvarque,² G. Lalleve,² and I. Bispo²

¹St. Petersburg State Technological Institute, St. Petersburg, 190013 Russia

²Conservatoire national des arts et metiers, Paris, France

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Abstract—The influence of reaction conditions on catalyzed by Pd(PPh₃)₄ cross-coupling of 4-*N,N*-dimethylaminophenylmagnesium bromide with 4-bromobenzonitrile in tetrahydrofuran was investigated. The yield of the product of the catalytic process, 4-*N,N*-dimethylamino-4'-cyanobiphenyl, and of the main product of noncatalytic process, 4-*N,N*-dimethylaminophenyl 4'-bromophenyl ketone, is mainly governed by the order of introduction of reagents and catalyst into the reaction zone. Experimental observations and analysis of side products suggested conclusions on the processes resulting in deactivation of the catalyst.

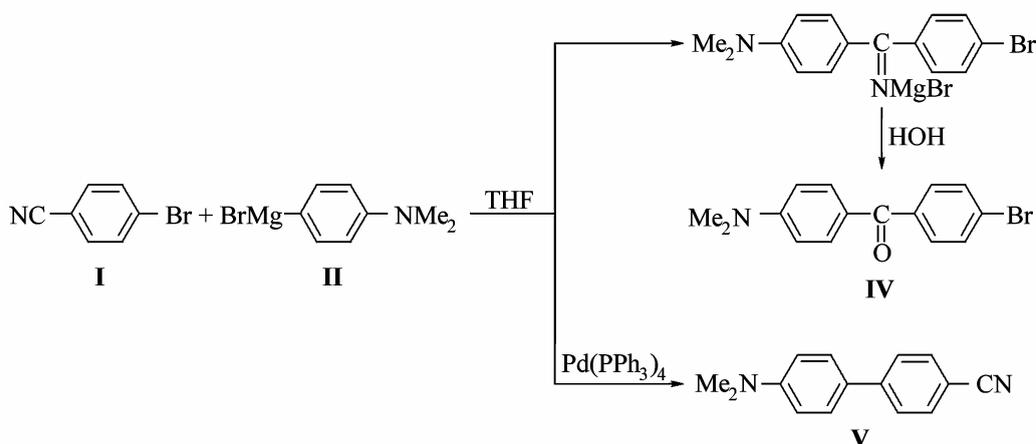
Since in 1972 was discovered a fast and efficient method of building up carbon-carbon bonds by cross-coupling catalyzed with transition metals [1, 2] organomagnesium compounds were extensively used for preparation of versatile compounds by this procedure [3, 4]. However the application of Grignard reagents is significantly limited by their high reactivity toward such groups as C≡N, C=O, NO₂, and therefore frequently this method cannot be used for preparation of compounds with these substituents. Further development of the method consisted in the search for ligands which increased the regioselectivity of palladium catalyst in the cross-coupling processes.

The application of palladium complexes with bidentate ligands, e.g. PdCl₂(*dppe*), PdCl₂(*dppp*), PdCl₂(*dppb*) [5], extended the range of functional groups in haloaryl compounds fit for selective cross-coupling with Grignard reagents. However even at the use of the most efficient PdCl₂(*dppf*) that provided a possibility to obtain quantitative yield of cross-coupling products from vinylmagnesium bromide with aryl iodides [6–8], in reaction with 4-iodobenzonitrile the yield was considerably lower. A little later the Grignard compounds were shown to be applicable in cross-coupling with aryl iodides containing active group in the presence of a large amount of Pd(PPh₃)₄ (10%) [9]. These studies significantly altered the con-

cept on application limits for organomagnesium compounds in cross-coupling with functionalized organyl halides. The important factor in selection of the latter was the maximum high reactivity of the C-Hal bond as compared to that of the functional group. This is just the reason why in the reactions with Grignard reagents are used iodine derivatives.

Taking into account that bromides are more available than iodides we studied in this work reaction of 4-bromobenzonitrile (**I**) with *N,N*-dimethylaminophenylmagnesium bromide (**II**) in THF in the presence of Pd(PPh₃)₄ (**III**). The latter was chosen because it relatively readily transformed into the catalytic form Pd(PPh₃)₂ under the reaction conditions. Additional goal of the study was the need of convenient preparation method for 4-*N,N*-dimethylamino-4'-cyanobiphenyl that possessed specific electrooptical characteristics [10].

Without catalyst Grignard reagent **II** added at heating to the cyano group. Initially the reaction occurs with heat evolution, but 4-*N,N*-dimethylaminophenyl 4'-bromophenyl ketone (**IV**) forms in a moderate yield (see table, run no. 1). No product of cross-coupling, 4-*N,N*-dimethylamino-4'-cyanobiphenyl (**V**) was obtained under these conditions. In the presence of Pd(PPh₃)₄ the cross-coupling reaction proceeds alongside the noncatalytic one.



The ratio and yield of the products arising in these reactions depend on the conditions. The transformation of Pd(PPh₃)₄ into Pd(PPh₃)₂ is known to occur with an induction period, and its further participation in the catalytic cycle depends both on the reaction temperature and on the character of the aryl halide [11]. The catalyst activation can be attained both by preliminary heating of Pd(PPh₃)₄ with an aryl halide to produce a complex Hlg Pd(PPh₃)₂Ar [12] that lies on the coordinate of the catalytic cross-coupling process. To this end a solution of the catalytic amount of Pd(PPh₃)₄ (6.7 mol%) and 4-bromobenzonitrile in THF were heated for 1 h. The gradual darkening of the solution evidenced the reaction between its components. The addition thereto at room temperature of Grignard reagent II prepared from equimolar to bromide I amount of 4-bromo-*N,N*-dimethylaniline (VI) no visible changes in the reaction mixture were observed. The reaction mixture was maintained for 120 h at 25°C, and a sample thereof after hydrolysis was analyzed by GLC using mesitylene as internal reference. The chromatogram contained peaks of the initial 4-bromobenzonitrile (prevailing), *N,N*-dimethylaniline (VII), and reaction products: biphenyl V and ketone IV in amounts not exceeding some percent (see table, run no. 2). After subsequent heating and hydrolysis of the reaction mixture a complex mixture of products was isolated. In the ¹H NMR spectrum of the mixture in the region 3 ppm appeared a series of signals belonging to dimethylamino groups of identified products: dimethylaniline (VII), bromodimethylaniline (VI), biphenyl V, ketone IV tetramethylbenzidine (VIII), and also unidentified compounds. The overall yield of reaction products was no more than 10%. Relatively fast (within several minutes) addition of Grignard reagent to the freshly prepared solution of catalyst with 4-bromobenzonitrile in THF (see table, run no. 3) or addition of the catalyst preliminary

mixed with the Grignard reagent to 4-bromobenzonitrile (see table, run no. 4) at 25°C resulted only in slightly higher yield of ketone IV. Thus at room temperature both catalyzed and noncatalyzed processes proceed slowly and ambiguously affording very low yields of the reaction products.

On addition to Grignard reagent (II) of catalyst III solution in THF heat evolution was observed. The subsequent fast addition of this solution to a solution of bromide I in THF at room temperature did not result in any changes in the reaction mixture. However at heating the solution quickly turned cherry-red; the same color acquired at heating the mixture of organomagnesium compound II with a catalytic amount of Pd(PPh₃)₄ also without bromide I. After heating of the reaction mixture for 3 h till 70% conversion of the Grignard reagent the system was cooled, and crystals precipitated whose ¹H NMR spectrum was identical to that of (PPh₃)₂PdCl₂. The absence of chlorides in the reaction mixture suggested assignment to the compound obtained the structure of (PPh₃)₂PdBr₂ (30% with respect to the initial catalyst). On hydrolysis of the reaction mixture were isolated initial bromide I, dimethylaniline (VII), and tetramethylbenzidine (VIII). Neither ketone IV or biphenyl V were detected among the products (see table, run no. 5). The overall amount of compounds VII and VIII according to ¹H NMR spectrum was close to the quantity of the initial bromide I. Probably under the given conditions the concentration of bromide I which is less reactive than the Grignard reagent is insufficient for involvement into both catalytic and noncatalytic reactions. At the same time the heat evolution at adding the catalyst to the Grignard reagent reveals their interaction, most probably consisting in insertion of palladium into the C-Mg bond. The latter reaction, as shown in [13], leads to formation of homocoupling product. As follows from

Conditions of reaction between 4-bromobenzonitrile (**I**) and 4-(*N,N*-dimethylaminophenyl)magnesium bromide (**II**), and yields of the main reaction products

Run no.	Reagents, mmol ^a		Pd (PPh ₃) ₄ mol%	<i>t</i> , °C	Reaction time, ^b min	Order of components mixing ^c	Yield of reaction products, %	
	(I)	(II)					(IV)	(V)
1	5 (1.5)	5 (1)	–	66	(10) 60	A	55	–
2	5 (0.2)	5 (1)	6.7	25	20	B	^d	^d
				66	20 h		^d	^d
3	2 (0.6)	(1)	1	25	(5) 55	C	5	^d
4	2 (0.6)	2 (1)	1	25	(5) 55	D	5	^d
5	3 (0.1)	3 (0.3)	6.7	25	(5 c)	D		
				66	3 h		–	–
6	4 (1)	4 (1.2)	1	60	(20)	C	5	35
				66	60		15	35
7	4 (1)	4 (1)	1	60–66	(20)	D	5	45
					60		10	45
8	4 (1)	4 (1)	1	66	(20)	E	15	^d
					60		25	^d
9	4 (1)	4 (1.2)	1	66	(20) 60	F	–	–
10	4 (1)	3 (1)	1.7	66	(10)	E	5	^d
					60		25	^d
11	4 (1)	3 (1)	1.7	66	(10) 60	D	5	55
12	4 (1)	3 (1)	1+0.7	66	(10) 60	G	^d	70
13	6 (1)	5 (1)	1	66	(15) 60	H	5	65
14	4 (1)	4 (1)	1	66	(10 c)	D	^d	^d
					30		15	^d
15	15 (1)	15 (1)	1	66	4 h	D	35	10
					4 h		25	15
16	4 (1) ^e	3 (1)	1	35–45	(20) 60	D	5	25
17	4 (1) ^f	3 (1)	1	70	(20) 60	D	30	5
18	4 (1)	3 (1)	0.5	66	(10) 60	D	15	40
19	4 (1)	3 (1)	1.25	66	(10) 60	D	15	50
20	4 (1)	3 (1)	2	66	(10) 60	D	10	60
21	4 (1)	3 (0.2)	10	66	(15) 60	D	30	10

^a Initial concentrations of reagents, mol/l, is given in parentheses.

^b In parentheses is given the time of reagents addition, outside the parenthesis the overall time of reaction.

^c Order of reagents introduction into the reaction zone as follows: A – **II** to **I**; B – **II** to preliminary heated solution of **I** with **III**; C – **II** to freshly prepared solution of **I** with **III**; D **II** with **III** to **I**; E – **I** with **III** to **II**; F – **I** with **II** to **III**; G – **II** with **III** to **I** with **III**; H – **II** in parallel with **III** to **I** with **III**.

^d Several percent.

^e In ether.

^f In benzene.

the above, the concentration of bromide **I** in the reaction zone should be significantly higher than that of the Grignard reagent. This can be achieved alongside the increasing of bromide concentration also by gradual addition of the Grignard reagent into the reaction mixture. In its turn the the concentration of the catalyst should be decreased due to its limited solubility. Actu-

ally, the tenfold increase in the initial concentration of bromide **I** and relatively slow addition thereto of the Grignard reagent at 66°C irrespective to which reagent was primarily added the catalyst resulted in higher yield of the cross-coupling product, biphenyl **V** (see table, runs nos. 6,7) although the introduction of the catalyst together with the Grignard reagent furnished

somewhat better yield of the target product (see table, run no. 7). It should be noted that in this case the reaction started at 60°C with heat evolution, and the reaction mixture turned gray-green. Then within several seconds the color of the reaction mixture became yellow, and nearly at once throughout the bulk of the solution started formation of crystalline product V. In both cases the cross-coupling reaction finished virtually immediately after the end of the Grignard reagent addition. On the contrary, addition of bromide I together with the catalyst to Grignard reagent II (see table, run no. 8) or of bromide I to a mixture of Grignard reagent II with the catalyst (see table, run no. 9) resulted in suppression of the cross-coupling. In the latter case the ketone formation is also suppressed, and occurs formation of the product of homocoupling, tetramethylbenzidine. These results show that the preparation of a definite product is governed by the way of all reagents introduction into the reaction zone.

It is especially clear from comparison of runs nos. 10–12 (see table) where was used the same solution of Grignard reagent divided in three portions; bromide I was taken in 30% excess, and the amount of catalyst was somewhat increased. At addition of a freshly prepared mixture of bromide I solution with 1.7% of Pd(PPh₃)₄ to the Grignard reagent at 66°C only ketone IV was found in the reaction products (see table, run no. 10). Addition of new portions of catalyst (up to 5%) an longer reaction time did not favor in this case the cross-coupling product formation, although unreacted initial compounds I and II remained in the reaction mixture. The addition of Grignard reagent II with the same catalyst amount under the same conditions to bromide I resulted in the predominant formation of biphenyl V (see table, run no. 11). However the best result in cross-coupling was attained at dividing the catalyst between the Grignard reagent (1%) and bromide (0.7%) (see table, run no. 12). Apparently the catalyst and bromide concentration at the start of the reaction should be at the level ensuring fast formation of the catalytic complex involved in the cross-coupling process. But at adding 1–2 mol% of the catalyst with the Grignard reagent its fraction in the reaction mixture at the initial moment may be less than 0.01%. It was observed in [14] at arylation of aryl halides with Grignard reagents in the presence of Pd(PPh₃)₄ in THF that the decrease in the catalyst concentration to 0.0001 molar equivalent (i.e. to 0.01%) did not notably reduce the yield of the biphenyl compound, but in

this case at the use of bromides the reaction time should be increased. Under these conditions it is difficult to avoid the concurrent noncatalytic processes. These difficulties can be overcome by adding of a small (< 1%) amount of catalyst into the solution of bromide I, and constant uniform addition of the catalyst together or parallel (see table, run no. 13) with the Grignard reagent favors higher conversion of the bromide.

Reduction of mixing time of reagents to some seconds decreases the ratio of bromide to Grignard reagent, and this prevents development of the cross-coupling process (see table, run no. 14). The considerably increased time of Grignard reagent addition (up to several hours) reduces the yield of the cross-coupling product V and increases the yield of ketone IV (see table, run no. 15) due to passivation of the catalyst and growing role of the side processes. Further heating of the reaction mixture led only to decreased yields of products IV and V apparently because of their further transformations. The data obtained are presented in the table.

In order to reveal the reasons of palladium catalyst deactivation the formation of some side products was analyzed. After prolonged heating of the reaction mixture in the reaction products was detected a significant amount (up to 10% from the content of compound V) of compounds with fragments of tetrahydrofuran ring opening. By column chromatography on silica gel (eluent dichloromethane) a fraction of these compounds was isolated from the products of run no. 15 as oily yellow fluid.

In the ¹H NMR spectrum of this fraction appeared signals of aliphatic protons at δ, ppm: 0.95 t, 1.45 m, 4.37 t, [³J(¹H–¹H) 7 Hz], corresponding to a butoxy group. In the region of aliphatic protons were observed signals at 7.53 d and 7.70 d ppm, [³J(¹H–¹H) 7.7 Hz], characteristic of *para*-substituted aromatic rings. This signals both in aliphatic and aromatic regions are overlapped with the resonances of the other groups thus indicating that the fraction is not an individual compound. The analysis of the strongest signals suggests that the main compound in this fraction is 4-butoxybenzotrile. No signals of dimethylamino group in the 3 ppm region and of hydroxy group around 10 ppm show that the formation of a butoxy group was not caused by direct reaction between THF and the Grignard compound. I. Pri-Bar & J.K. Stille [15] demonstrated that palladium triphenylphosphine complexes

reaction products. The comparative analysis of the effect of the catalyst quantity on the yield of the main reaction products (see table runs nos. 11, 18-20) shows that at increase of catalyst amount from 0.5 to 2% the yield of the cross-coupling product simultaneously grows from 40 to 60%. However further increase in the amount of catalyst (up to 10%) results in a sharp decrease in the yield of biphenyl **V** (see table, run no. 21). Although additional volume of solvent was required for dissolving the catalyst we presume that the main cause of the cross-coupling suppression was increased role of the parallel processes and fast formation of products deactivating the catalytic properties of Pd(PPh₃)₄.

Our results demonstrated that in reactions of organomagnesium compounds with the functionalized aryl halides a significant role belongs not only to the nature of reagents but also to the reaction conditions, among them the ratio of all components of the process, reagents concentrations, amount of catalyst, reaction temperature, duration of the process, and especially the order of introducing reagents and catalyst into the reaction zone.

In the system we studied the most favorable for cross-coupling to occur are the following conditions: excess aryl bromide with respect to Grignard reagent, reagents concentration close to that of saturated solution, catalyst amount of 1.5-2 mol%, reaction temperature maintained by slight boiling of the THF solution, slow addition of the Grignard reagent together with 75% of the catalyst to the solution of bromide in THF containing 25% of the catalyst. It should be noted however that overall increase in the amount of the reaction mixture may result in lower yield of the cross-coupling product due to growing importance of processes of catalyst passivation at prolonged reaction time.

EXPERIMENTAL

¹H and ¹³C NMR spectra were registered on spectrometer Bruker AM-200 (at operating frequencies 200.132 and 50.323 MHz respectively) from solutions in CDCl₃. GLC analyses were performed on a Hewlett Packard 5890 (II) instrument equipped with a capillary quartz column 25000 × 0.22 mm, stationary phase methylsilicone HP-1, flame-ionization detector, automatic temperature control in 250°C mode. As reference compounds were used mesitylene and dodecylbenzene.

For quantitative evaluation were averaged 3-5 determinations, accuracy within 5%. GC-MS measurements were carried out on a Hewlett Packard HP-5995 instrument at electron impact, ionizing electrons energy 70 eV. Temperature of separator and ion source 250°C, capillary quartz column 250006 × 0.32 mm, stationary phase ultra-2 (0.53 μ, 95% silicone, 5% phenylmethylsilicone). Preparative isolation was carried out on a glass column 800×25 mm on silica gel 40-63 μ (Merck) with quartz protection of the upper sorbent layer, eluents dichloromethane or toluene.

Pd(PPh₃)₄ (99%), 4-bromobenzonitrile (99%), 4-bromo-*N,N*-dimethylaniline (99%), magnesium prepared as thin plates for Grignard synthesis, and anhydrous THF sealed in ampules under argon were purchased from Aldrich and used without further purification.

All operations were performed in usual laboratory equipment for air-sensitive compounds, dried in a vacuum with heating by an open flame and cooled in an atmosphere of dry argon free of oxygen. The stirring was performed on magnetic stirrers. The exact dosing of solutions and sampling for analysis was carried out with syringes.

***N,N*-dimethylaminophenylmagnesium bromide (II)**. Into a flask was placed 3 mmol (with 5% excess) of magnesium, 0.5 ml of THF, and several drops of dibromoethane. At slight heating gas bubbles appeared on the magnesium surface. The flask was cooled, and from the dropping funnel containing a solution of 3 mmol of 4-bromo-*N,N*-dimethylaniline in 3 ml of THF was added several drops of the solution. If the reaction did not start within 30 min, the reaction mixture was heated to boiling without stirring. The heating was stopped after the reaction began as seen from the darkening of the solution. The remaining bromide solution was added with the rate maintaining self-sustaining boiling, and after the end of addition the heating was carried on for another 30 min. The analysis for Grignard reagent usually showed 95% yield.

Our attempts of preparation of this Grignard reagent in ethyl ether were unsuccessful.

4-Bromophenyl 4'-*N,N*-dimethylaminophenyl ketone (IV). To a solution of 4-bromobenzonitrile in THF was added dropwise at stirring the solution of Grignard reagent (II). The reaction mixture therewith turned light orange and self-heated. After heating on a water bath the reaction mixture was hydrolyzed with

water, the volatile products were removed by steam distillation. On cooling in the reaction flask below the water layer on the bottom collected a viscous substance that solidified on cooling. The water was decanted, the residue was dried under slight heating in a vacuum of a water-jet pump. The organic substance was dissolved in dichloromethane, and the ketone was isolated by column chromatography. On removing the solvent light-yellow crystals were obtained, mp 129–130°C [19]. ¹³C NMR spectrum (CDCl₃), δ, ppm: 110.49, 124.2, 125.7, 130.02, 131.15, 132.52, 137.97, 153.32 (arom), 193.72 (C=O).

4-*N,N*-Dimethylamino-4'-cyanobiphenyl (V).

The reaction conditions for biphenyl V preparation are presented in table and described in the text of the paper. Biphenyl V was isolated by the same procedure as ketone IV, mp 222–223°C, long needle-like crystals, opalescent solutions.

¹³C NMR spectrum (CDCl₃), δ, ppm: 108.89, 112.45, 126.20, 127.76, 132.39, 145.45, 150.63 (arom), 40.22 (C–N), 119.31 (C≡N).

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