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Successive Replacement of Halogen Atoms in 4,6-Dihaloquinolines in Cross-coupling Reactions with Arylboronic Acids Catalyzed by Palladium and Nickel Complexes

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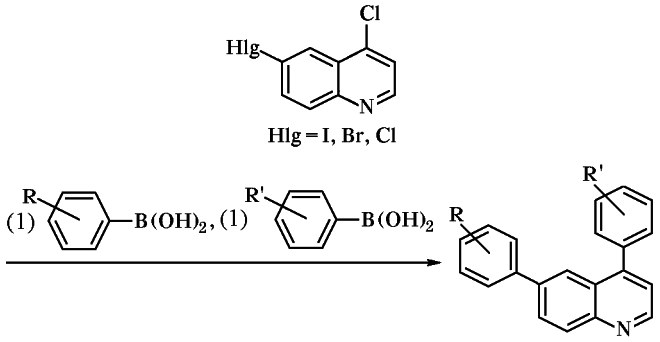
Abstract—Conditions were found where in 6-halo-4-quinolines (halogen = iodine, bromine, or chlorine) the halogen atoms were replaced in succession by similar or different aryl groups in cross-coupling reactions with arylboric acids catalyzed by palladium and nickel complexes. Basing on successive Suzuki reaction a convenient procedure was developed for preparation of diarylquinolines that did not require isolation of the intermediate monoarylation product and afforded almost quantitative yields of diarylquinolines.

Cross-coupling reactions catalyzed by transition metal complexes are nowadays a widely applied instrument of building up a carbon-carbon bond in versatile organic compounds. High yields of products, the tolerance to a wide range of functional groups, the opportunity to carry out the reaction under mild conditions permits the use of the reactions in the synthesis of pharmaceuticals, analogs of naturally occurring molecules, and organic materials.

The possibility to perform successive introduction of several substituents into a substrate by means of the cross-coupling reaction considerably extends the prospects of the method and opens a simple synthetic way to versatile classes of aromatic compounds. Such approach was successfully applied to the synthesis of polyaryl-substituted benzenes [1, 2], and also pyridines [3, 4], quinolines [5], isoquinolines [6], indoles [7], furans [8]. However the chemoselectivity attained is essentially affected by the substrate structure, ligand surrounding of the catalyst, and external conditions. Therefore the choice of conditions for a selective succession of functionalization for each definite substrate is a separate problem which not always has a standard solution.

To study the possibility of successive halogens replacement in cross-coupling reactions we chose as model Suzuki reaction with 6-halo-4-chloroquinolines as substrate (where halogen was iodine, bromine, or chlorine).

It is difficult to forecast the relative reactivity of carbon–halogen bonds in the cross-coupling for these



compounds, taking into account that the chlorine in the *4* position of the quinoline system is fairly active in reactions of aromatic nucleophilic substitution, whereas the C(sp^2)–I(Br) bond is more active in the cross-coupling reactions. These substrates attract additional interest because some functionally-substituted quinolines are known to possess a biological activity [9–13]. In the organic synthesis the opportunity to replace in succession halogenes in the 4,6-dihaloquinolines by cross-coupling reactions opens a simple way to diaryl-substituted quinolines with various functional groups in the aryl rings.

Preliminary experiments revealed that iodine in the 6-iodo-4-chloroquinoline was selectively and quantitatively substituted within 4 h at the use of a stoichiometric amount of 4-anisylboric acid in the presence of $Pd(PPh_3)_4$ and potassium carbonate in dioxane. Regardless of the high yield of the monoarylation product the replacement of chlorine under these conditions occurred very slowly, and the diarylated product was obtained in 48 h with an yield

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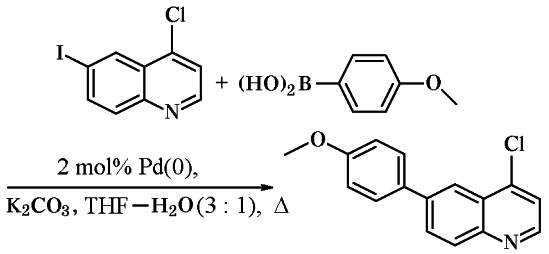
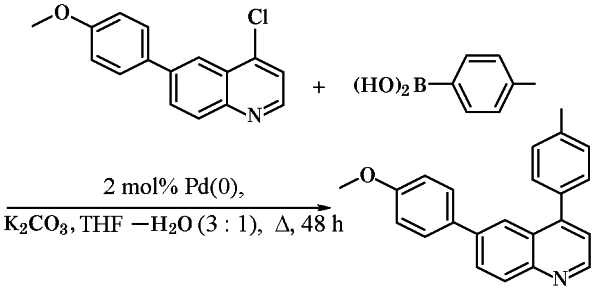
of only 7%. This result demanded to carry out a systematic search for optimum conditions for substitution of both halogens in the 6-halo-4-chloroquinolines (halogen was I, Br, Cl).

The effect of the catalyst nature on the rate of substitution was studied in the mixture THF–H_2O in the presence of K_2CO_3 (Table 1).



The best results were obtained at the use of "ligandless" palladium $Pd(OAc)_2$ and of the complex $Pd(dppf)Cl_2$. The reaction catalyzed by $Pd(PPh_3)_4$ was relatively slow but in all cases the yield was quantitative. The position of the introduced aryl group in these and also in all following experiments was confirmed by ^1H NMR spectra and elemental analyses.

On the contrary, the highest yield of product originating from chlorine substitution (82% in 48 h) was obtained with $Pd(PPh_3)_4$ as catalyst. The other palladium catalysts gave poor results (Table 2).



We found that the successive replacement of two halogen atoms may be performed without isolation of the intermediate product by adding the second aryl-

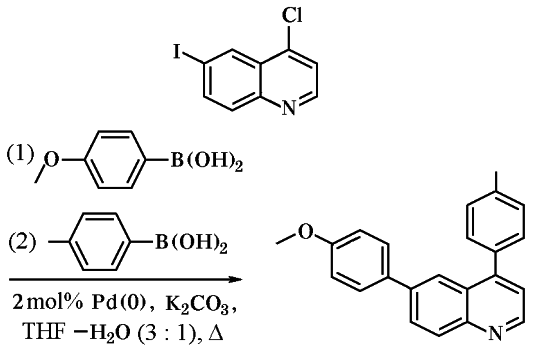


Table 1. Effect of the nature of palladium catalyst on the rate of selective monoarylation of 6-iodo-4-chloroquinoline

Run no.	Catalyst	Time, h	Yield, %
1	$Pd(PPh_3)_4$	15	100
2	$Pd(PPh_3)_2Cl_2$	5	100
3	$Pd(dppf)Cl_2$	4	100
4	$Pd(OAc)_2$	4	100

Table 2. Effect of the nature of palladium catalyst on the yield of arylation product of 6-(4-methoxyphenyl)-4-chloroquinoline

Run no.	Catalyst	Yield, %
1	$Pd(PPh_3)_4$	82
2	$Pd(PPh_3)_2Cl_2$	21
3	$Pd(dppf)Cl_2$	11
4	$Pd(OAc)_2$	4

Table 3. Effect of the catalyst nature on the yield of successive diarylation product of 6-iodo-4-chloroquinoline

Run no.	Catalyst	Time of 1st stage, h (yield 100%)	Time of 2nd stage, h	Yield, %
1	$Pd(PPh_3)_4$	15	48	82
2	$Pd(PPh_3)_2Cl_2$	5	48	19
3	$Pd(dppf)Cl_2$	4	48	3
4	$Pd(OAc)_2$	4	48	< 1

boric acid into the reaction mixture after completion of the first reaction (TLC monitoring) (Table 3). This procedure rules out the use of additional amount of palladium catalyst and the isolation and purification of the intermediate product.

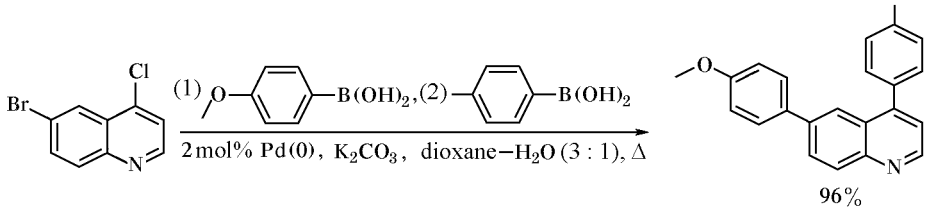
We studied the effect of the solvent nature on the yield of diarylation product using as catalyst $Pd(PPh_3)_4$. It turned out that the process in benzene–water mixture and in aqueous THF required long boiling of the reaction mixture at both stages. The use of aqueous acetonitrile and especially of aqueous dioxane resulted in considerable acceleration of the reaction (Table 4).

The observed acceleration is caused not only by increased boiling point of the solvent but also by the change in the solvent nature. The first stage in aqueous dioxane at 64°C occurred faster than in

THF–water mixture at the same temperature (Table 4, runs nos. *1*, *5*); the second stage failed to proceed in aqueous dioxane at 64°C (Table 4, run no. *5*). It should be noted that at room temperature even the iodine substitution (first stage) is very slow (Table 4, run no. *6*).

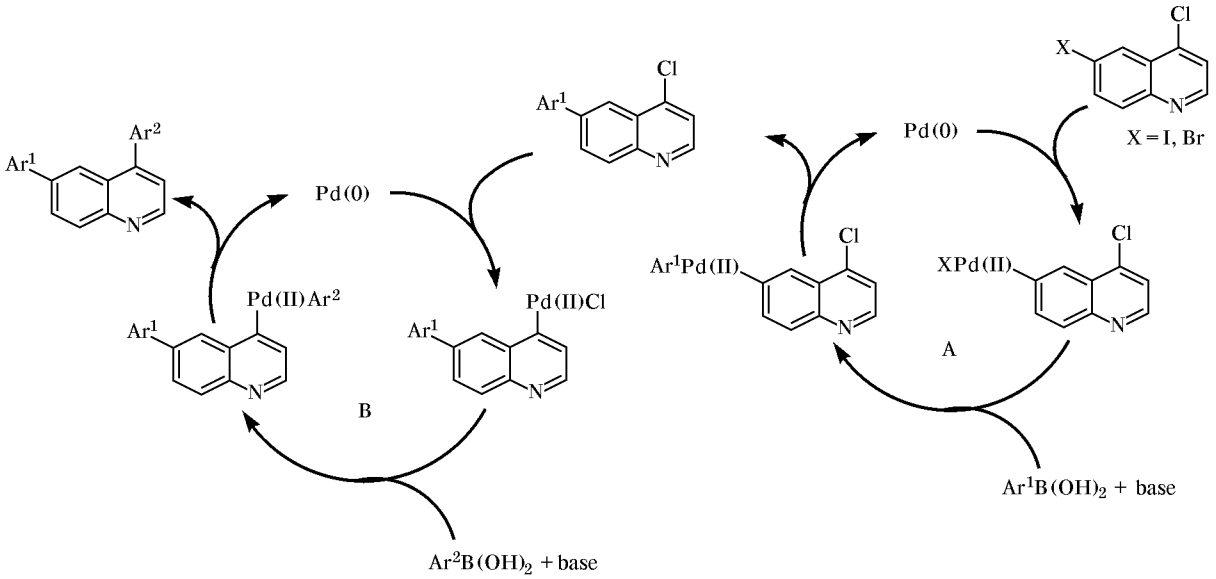
The base nature is also a significant factor (Table 5). The best results produced the application as base of K_3PO_4. The activity of bases diminished in the series $K_3PO_4 \sim K_2CO_3 > Ba(OH)_2 > CsF$ but the yield of diarylation products was high in all cases. It should be noted that the insignificant difference in the reaction rate at the use of K_3PO_4 and K_2CO_3 permits the application of the more accessible potassium carbonate without a loss in the yield of the target product.

It turned out that the reaction selectivity under the chosen optimum conditions [boiling in the dioxane–water mixture in the presence of $Pd(PPh_3)_4$ and K_2CO_3] was not reduced at the use as substrate



of 6-bromo-4-chloroquinoline, and the yield of the products was the same.

There is no reason to believe that the reaction mechanism of the cross-coupling between 4,6-dihaloquinolines and arylboric acids is different from the general mechanism of Suzuki reaction [14]. This mechanism applied to the successive halogen substitution in the 4,6-dihaloquinolines is as follows.



The oxidative addition of Pd(0) occurs initially exclusively to iodine or bromine in position *6* of the quinoline ring. At the use of a stoichiometric amount of arylboric acid the chlorine in position *4* remains intact, and the reaction completed affording 6-aryl-4-chloroquinoline (catalytic cycle A). On addition of the second arylboric acid into the reaction mixture occurred the chlorine substitution (catalytic cycle B).

To demonstrate the prospects of the method we synthesized several diarylquinolines with identical or different aryl groups in high preparative yields (Table 6).

Table 4. Effect of solvent on the yield of successive diarylation product of 6-iodo-4-chloroquinoline[a]

Run no.	Solvent	Time of 1st stage, h (yield, %)	Time of 2nd stage, h	Yield, %
1	THF–H_2O	15 (100)	48	82
2	Benzene–H_2O	15 (100)	48	50
3	MeCN–H_2O	2 (100)	14	83
4	Dioxane–H_2O	0.5 (100)	4	97
5	Dioxane–H_2O (64°C)	5 (100)	48	0
6	Dioxane–H_2O (20°C)	48 (44)		

[a] 2 mol% of $Pd(PPh_3)_4$, 6 equiv of K_2CO_3, heating at reflux. 1st stage: 1.0 equiv of 4-$MeOC_6H_4B(OH)_2$; 2nd stage: 1.3 equiv of 4-$MeC_6H_4B(OH)_2$.

Table 5. Effect of base on the yield of successive diarylation product of 6-iodo-4-chloroquinoline[a]

Run no.	Base	Time of 1st stage completion, h	Time of 2nd stage completion, h	Yield %
1	K_2CO_3	0.5	4	97
2	K_3PO_4	0.25	4	97
3	CsF	7	12	97
4	$Ba(OH)_2$	0.25	4	88

[a] 2 mol% of $Pd(PPh_3)_4$, 6 equiv of base, dioxane–H_2O (3 : 1), heating at reflux. 1st stage: 1.0 equiv of 4-$MeOC_6H_4B(OH)_2$; 2nd stage: 1.3 equiv of 4-$MeC_6H_4B(OH)_2$.

The character of substituent arising in the *6* position of the quinoline ring in the first stage of reaction affected the rate of the subsequent chlorine replacement. For instance, the substitution of chlorine in 4-chloro-6-(4-chlorophenyl)quinoline proceeded faster than in 4-chloro-6-(4-tolyl)quinoline or in 4-chloro-6-(4-anisyl)quinoline. This results in some decrease in selectivity, and with 6-(4-chlorophenyl)-4-chloroquinoline caused diminishing in the yield of the successive diarylation product. It should be noted that under the applied conditions the chlorine in the 4-chlorophenyl moiety did not undergo substitution.

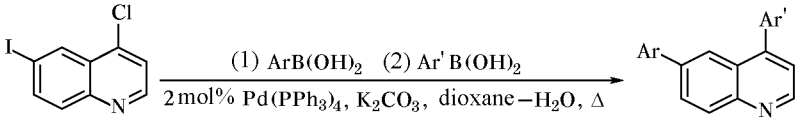
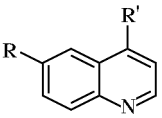


Table 6. Yield of successive diarylation products of 6-iodo-4-chloroquinoline[a]

Run no.	Reaction product	Time of completion, h		Yield, %[b]	mp, °C
		of 1st stage	of 2nd stage		
1	R = 4-$MeOC_6H_4$, R' = 4-MeC_6H_4	0.5	4	97 (96)[c]	127
2	R = R' = 4-MeC_6H_4	0.5	4	97 (96)	124
3	R = 4-ClC_6H_4, R' = 4-MeC_6H_4	0.5	2.5	89 (87)	124
4	R = R' = 4-ClC_6H_4	3[d]		100 (99)	116

[a] 2 mol% of $Pd(PPh_3)_4$, 6 equiv of K_2CO_3, dioxane–H_2O (3 : 1), heating at reflux. 1st stage: 1.0 equiv of $ArB(OH)_2$; 2nd stage: 1.3 equiv $Ar'B(OH)_2$.

[b] Preparative yield given in parentheses.

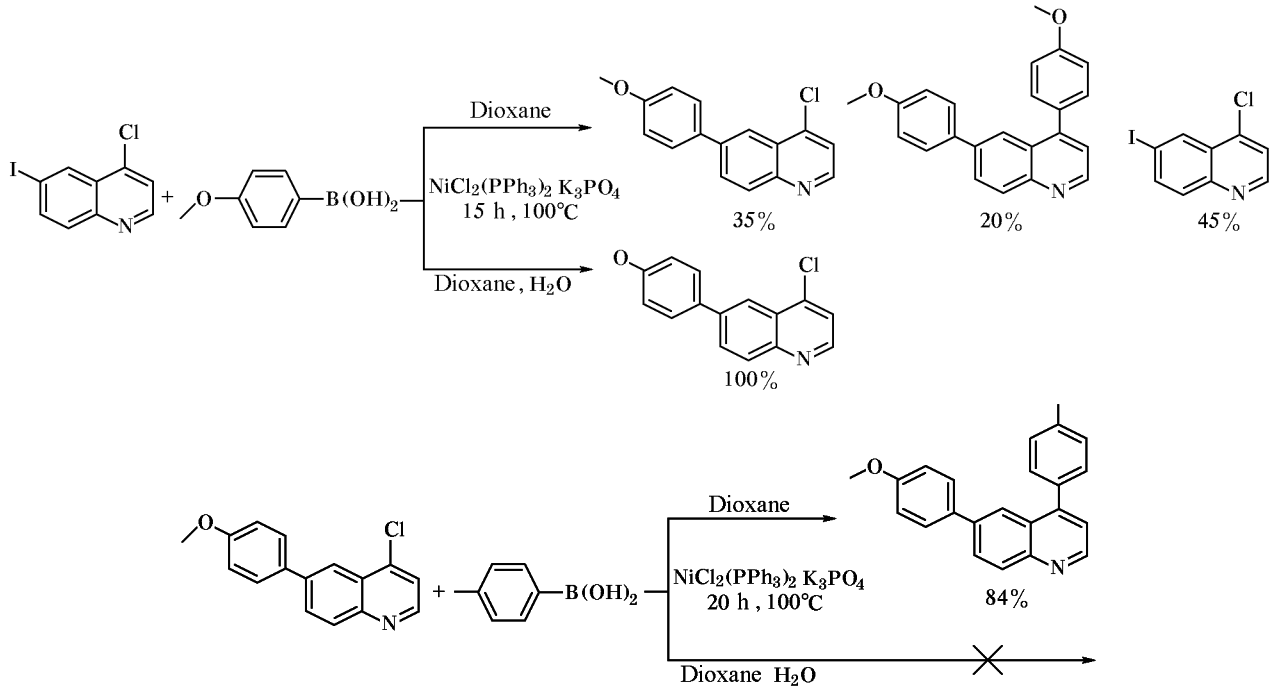
[c] The product was obtained in this yield both from 6-iodo-4-chloroquinoline and from 6-bromo-4-chloroquinoline.

[d] 2.3 equiv of 4-$ClC_6H_4B(OH)_2$.

The coupling of 6-iodo-4-chloroquinoline with arylboric acids on nickel catalysts in anhydrous dioxane occurred with considerably lower selectivity at the stage of iodine substitution. At the same time the reaction carried out in a dioxane–water mixture resulted in exclusive replacement of iodine, and the corresponding 6-aryl-4-chloroquinoline was obtained in quantitative yield.

However further substitution of chlorine in the 6-aryl-4-chloroquinoline by Suzuki reaction in aqueous dioxane in the presence of $NiCl_2(PPh_3)_2$ did not occur even at prolonged boiling, and the reaction was likely to proceed only under anhydrous conditions.

Thus the best way to carry out the successive diarylation of 6-iodo-4-chloroquinoline with the use of $NiCl_2(PPh_3)_2$ as catalyst is performing reaction in two stages: the first stage should occur in aqueous dioxane and provide the product of iodine substitution, the second stage of chlorine replacement should be carried out in anhydrous dioxane.



The nickel complexes used as catalysts provide a possibility to carry out the cross-coupling of 4,6-dichloroquinoline with arylboric acids. However the outcome of the reaction depended essentially on the nature of phosphine ligands in the nickel complex. For instance, $NiCl_2(PPh_3)_2$, $Ni(acac)_2$, and $NiCl_2$–$6H_2O$ are inadequately efficient and selective and afford mixtures of mono- and disubstituted products (Table 7, runs nos. *1*, *2*, *3*, *7*, *9*). Complexes $NiCl_2$(dppe), $NiCl_2$(dppb), and $NiCl_2$(dppf) turned out to be more efficient, but also afforded mixtures of products. Note however that in case both chlorine atoms should be replaced by the same aryl the applications of these catalysts is favorable.

We succeeded in selective replacement of chlorine in the more active *4* position at the use as catalyst a complex $NiCl_2$(dppm). However this complex was inefficient in the second stage of reaction (the substitution of chlorine in *6* position). We managed to carry out the second stage by adding into the reaction

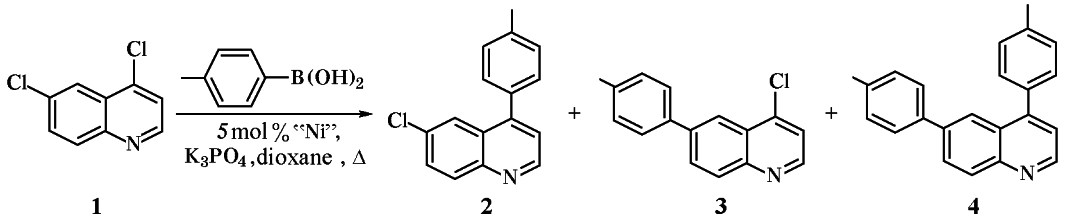
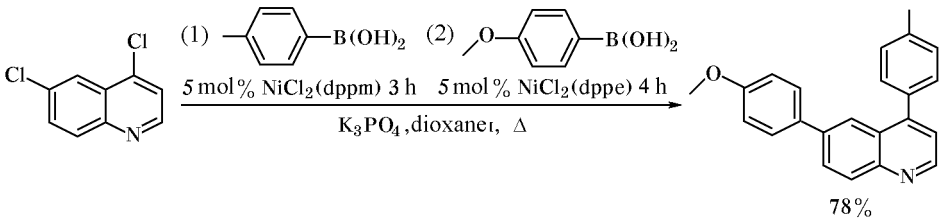


Table 7. Yield of diarylation products of 4,6-dichloroquinoline

Run no.	Catalyst	Time (h)	Base	Solvent	Composition of reaction mixture (%)			
					1	2	3	4
1	$NiCl_2(PPh_3)_2$	1	K_3PO_4	Dioxane	67	22	-	11
2	$NiCl_2(PPh_3)_2$	1	K_3PO_4	Dioxane/water	100	-	-	-
3	$NiCl_2(PPh_3)_2$/ butyllithium	1	K_3PO_4	Dioxane	57	29	-	14
4	$NiCl_2$(dppb)	1	K_3PO_4	Dioxane	34	33	-	33
5	$NiCl_2$(dppe)	1	K_3PO_4	Dioxane	29	34	Traces	37
6	$NiCl_2$(dppm)	1	K_3PO_4	Dioxane	23	69	2	6
7	$Ni(acac)_2$	1	K_3PO_4	Dioxane	98	2	-	-
8	$NiCl_2$(dppf)	1	K_3PO_4	Dioxane	48	11	-	41
9	$NiCl_2$–$6H_2O$	20	K_3PO_4	Dioxane	38	45	7	10

mixture simultaneously with the second arylboric acid also a more active catalyst, $NiCl_2$(dppe).

Thus at the use of nickel-catalyzed coupling with 4,6-dichloroquinoline the assembling of the diarylquinoline structure can be performed in a reverse order as compared to reactions with 4-chloro-6-iodoquinoline or 4-chloro-6-bromoquinoline.



The yield of arylation products obtained from 4,6-dihaloquinolines was measured by means of ^1H NMR spectroscopy (save the experiments with preparative isolation of the products).

EXPERIMENTAL

The progress of reactions was monitored by TLC on Silufol UV-254 plates and by ^1H NMR spectroscopy. ^1H NMR spectra were registered on spectrometer Varian VXR 400 at operating frequency 400 MHz. Chemical shifts are given inδ-scale with respect to HMDS.

6-iodo-4-chloroquinoline [15], 6-bromo-4-chloroquinoline [16], and 4,6-dichloroquinoline [17] were prepared by known procedures starting with the corresponding 4-haloaniline and diethyl (2-ethoxymethylene)malonate.

Cross-coupling of 6-iodo-4-chloroquinoline with 4-anisylboric acid catalyzed with palladium complexes. In a flask equipped with a reflux condenser was mixed in an argon atmosphere 50.0 mg (0.173 mmol) of 6-iodo-4-chloroquinoline, 26.2 mg (0.173 mmol) of 4-methoxyphenylboric acid, 71.6 mg (0.519 mmol) of K_2CO_3, 4 mg (3.5 μmol) of $Pd(PPh_3)_4$, 1.5 ml of THF, and 0.5 ml of water. The reaction mixture was heated at reflux for an appropriate time (TLC monitoring), then it was cooled, diluted with dichloromethane, filtered through a 3 cm bed of silica gel, the solvents were evaporated at reduced pressure. The product was purified by column chromatography on silica gel, eluent petroleum ether–ethyl ether (1 : 1).

6-(4-Anisyl)-4-chloroquinoline. Yield 46.5 mg (100 %). mp 113°C. ^1H NMR spectrum, δ, ppm: 8.73 d (1H, *J* 4.7 Hz), 8.33 d (1H, *J* 2.1 Hz), 8.15 d (1H, *J* 8.8 Hz), 7.98 d.d (1H, *J* 8.8, 2.1 Hz), 7.66 m (2 H), 7.47 d (1H, *J* 4.7 Hz), 7.02 m (2H), 3.86 s (3H). Found, %: C 71.44; H 4.39; N 4.98. $C_{16}H_{12}ClNO$. Calculated, %: C 71.25; H 4.48; Cl 13.14; N 5.19.

Cross-coupling of 6-(4-anisyl)-4-chloroquinoline with 4-tolylboric acid catalyzed by palladium

complexes. In a flask equipped with a reflux condenser was mixed in an argon atmosphere 50.0 mg (0.186 mmol) of 6-(4-anisyl)-4-chloroquinoline, 30.5 mg (0.223 mmol) of 4-methylphenylboric acid, 77.0 mg (0.558 mmol) of K_2CO_3, 4.3 mg (3.7 μmol) of $Pd(PPh_3)_4$, 1.5 ml of THF, and 0.5 ml of water. The reaction mixture was heated at reflux for an appropriate time (TLC monitoring), then it was cooled, diluted with dichloromethane, filtered through a 3 cm bed of silica gel, the solvents were evaporated at reduced pressure. The product was purified by column chromatography on silica gel, eluent petroleum ether–ethyl ether (1 : 1).

6-(4-Anisyl)-4-(4-tolyl)quinoline. Yield 49.6 mg (82%). mp 127°C. ^{1}H NMR spectrum, δ, ppm: 8.87 d (1H, *J* 4.7 Hz), 8.20 d (1H, *J* 8.8 Hz), 8.06 d (1H, *J* 2.1 Hz), 7.92 d.d (1H, *J* 8.8, 2.1 Hz), 7.52 m (2H), 7.42 m (2H), 7.31 (3H), 6.95 m (2H), 3.81 s (3H), 2.44 s (3H).

Successive cross-coupling of 6-iodo-4-chloroquinoline and 6-bromo-4-chloroquinoline with arylboric acids catalyzed by palladium complexes. In a flask equipped with a reflux condenser was mixed in an argon atmosphere 0.173 mmol of 6-halo-4-chloroquinoline, 0.173 mmol of the first arylboric acid, 143.2 mg (1.04 mmol) of K_2CO_3, 3.5 μmol of palladium catalyst, 1.5 ml of dioxane, and 0.5 ml of water. The reaction mixture was heated at reflux till complete consumption of 6-halo-4-chloroquinoline (TLC monitoring), then 0.225 mmol of the second arylboric acid was added, and the heating was continued till the full completion of the reaction (TLC monitoring). Then the reaction mixture was cooled, diluted with dichloromethane, filtered through a 3 cm bed of silica gel, the solvents were evaporated at reduced pressure. The product was purified by column chromatography on silica gel, eluent petroleum ether–ethyl ether (1 : 1).

4-(4-Tolyl)-6-(4-anisyl)quinoline was prepared from 50 mg of 6-iodo-4-chloroquinoline in 54.0 mg (96%) yield, or from 41.7 mg of 6-bromo-4-chloroquinoline in 54.0 mg (96%) yield. mp 127°C. ^{1}H NMR spectrum, δ, ppm: 8.87 d (1H, *J* 4.7 Hz), 8.20 d (1H, *J* 8.8 Hz), 8.06 d (1H, *J* 2.1 Hz), 7.92 d.d (1H, *J* 8.8, 2.1 Hz), 7.52 m (2H), 7.42 m (2H), 7.31 (3H), 6.95 m (2H), 3.81 s (3H), 2.44 s (3H). Found, %: C 84.56; H 9.67; N 4.19. $C_{23}H_{19}N$. Calculated, %: C 84.89; H 9.89; N 4.30.

4,6-Bis(4-tolyl)quinoline was prepared from 50.0 mg of 6-iodo-4-chloroquinoline in 51.1 mg (98%) yield. mp 124°C. ^{1}H NMR spectrum, δ, ppm: 8.86 d (1H, *J* 4.7 Hz), 8.19 d (1H, *J* 8.8 Hz), 8.09 d (1H, *J* 2.1 Hz), 7.93 d.d (1H, *J* 8.8, 2.1 Hz), 7.47 m (2H), 7.42 m (2H), 7.29 (3H), 7.21 m (2H), 3.81 s (3H), 2.44 s (3H). Found, %: C 89.18; H 6.49; N 4.22. $C_{23}H_{19}N$. Calculated, %: C 89.28; H 6.19; N 4.53.

4-(4-Tolyl)-6-(4-chlorophenyl)quinoline was prepared from 50 mg of 6-iodo-4-chloroquinoline in 49.7 mg (87%) yield. mp 124°C. ^{1}H NMR spectrum, δ, ppm: 8.91 d (1H, *J* 4.4 Hz), 8.21 d (1H, *J* 8.8 Hz), 8.07 d (1H, *J* 2.1 Hz), 7.90 d.d (1H, *J* 8.8, 2.1 Hz), 7.50 m (2H), 7.36 (7H), 2.46 s (3H). Found, %: C 79.94; H 4.95; N 4.13; $C_{22}H_{16}ClN$. Calculated, %: C 80.11; H 4.89; N 4.25.

4,6-Bis(4-chlorophenyl)quinoline was prepared from 50 mg of 6-iodo-4-chloroquinoline and 62.1 mg of 4-chlorophenylboric acid in 60.0 mg (99%) yield. (99%). mp 116°C. ^{1}H NMR spectrum, δ, ppm: 8.92 d (1H, *J* 4.4 Hz), 8.24 d (1H, *J* 8.8 Hz), 7.96 d (1H, *J* 2.1 Hz), 7.91 d.d (1H, *J* 8.8, 2.1 Hz), 7.48 (4H), 7.43 m (2H), 7.36 m (2H), 7.29 d (1H, *J* 4.4 Hz). Found, %: C 72.26; H 3.90; N 3.86. $C_{21}H_{13}Cl_2N$. Calculated, %: C 72.01; H 3.74; N 4.00.

Cross-coupling of 4,6-dichloroquinoline with 4-tolylboric acid catalyzed with nickel complexes. In a flask equipped with a reflux condenser was mixed in an argon atmosphere 50 mg (0.254 mmol) of 4,6-dichloroquinoline, 34.5 mg (0.254) mmol of the 4-tolylboric acid, 164 mg (0.762 mmol) of K_3PO_4, 12.7 μmol (6.5 mg, 5 mol%) of $NiCl_2$(dppm), and 2 ml of dioxane. The reaction mixture was heated at reflux for 1 h, then cooled, diluted with dichloromethane, filtered through a 3 cm bed of silica gel, the solvents were evaporated at reduced pressure. The product was purified by column chromatography on silica gel, eluent petroleum ether–ethyl ether (1 : 1).

4-(4-Tolyl)-6-chloroquinoline. Yield 38.4 mg (60%). Yield 69% according to ^{1}H NMR spectrum. mp 125°C. ^{1}H NMR spectrum, δ, ppm: 8.89 d (1H, *J* 4.4 Hz), 8.09 d (1H, *J* 9.1 Hz), 7.89 d (1H, *J* 2.4 Hz), 7.63 d.d (1H, *J* 9.1, 2.4 Hz), 7.35 m (4H), 7.33 d (1H, *J* 4.4 Hz), 2.46 s (3H). Found, %: C 75.24; H 4.23; N 5.49. $C_{16}H_{12}ClN$. Calculated, %: C 75.74; H 4.77; N 5.52.

Successive cross-coupling of 4,6-dichloroquinoline with arylboric acids catalyzed by nickel complexes. The reaction was carried out in keeping with the general procedure of palladium-catalyzed cross-coupling of 6-iodo-4-chloroquinoline in anhydrous dioxane using K_3PO_4 instead of K_2CO_3 and $NiCl_2$(dppm) (5 mol%) as catalyst. After completion of the first reaction stage (TLC monitoring) into the

reaction mixture together with the second arylboric acid was added $NiCl_2$(dppe).

4-(4-Tolyl)-6-(4-anisyl)quinoline was prepared from 50 mg of 4,6-dichloroquinoline in 84 mg (78%) yield. mp 127°C. ^{1}H NMR spectrum, δ, ppm: 8.87 d (1H, *J* 4.7 Hz), 8.20 d (1H, *J* 8.8 Hz), 8.06 d (1H, *J* 2.1 Hz), 7.92 d.d (1H, *J* 8.8, 2.1 Hz), 7.52 m (2H), 7.42 m (2H), 7.31 (3H), 6.95 m (2H), 3.81 s (3H), 2.44 s (3H).

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