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CHEMISTRY

Palladium-Catalyzed Reactions of Halogen Derivatives of *N*,*N*-Dimethyl-1-Phenylethanamine with Arylboronic Acids as a Novel Approach to the Synthesis of Biaryls with Central and Axial Chirality

I. N. Shishkina, I. A. Dotsenko, V. M. Demyanovich, N. A. Bumagin, and Academician N. S. Zefirov

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Biaryls with axial chirality (atropoisomerism), which appears due to hindered rotation around the Ar–Ar bonds in the presence of at least one bulky substituent in the *ortho*-position, occur as structural units in some natural molecules [1]. Examples of these compounds are the antibiotic vancomycin [2], the antitumor lignan steganacin [3], and the anti-HIV agent Michelamine B [4]. Furthermore, biaryl derivatives with axial chirality are widely used in the catalytic asymmetric synthesis as efficient ligands [5].

Currently, substituted biaryls are synthesized most often by the palladium-catalyzed reaction of aryl halides with arylboronic acids (Suzuki reaction) [6]. This reaction is also used for the synthesis of axially chiral biaryls [7, 8]. The most significant results were obtained by using a central chirality unit present in the aryl halide for stereoinduction or by using complexes with chiral ligands as catalysts.

An important problem is practical accessibility of the initial chiral compounds and the possibility of obtaining them as both enantiomers. One of such compounds is 1-phenylethanamine (**1**), which has already been used to prepare chiral compounds, as described in a review [9]. However, there are still no publications on the use of this amine in the synthesis of atropoisomeric biaryls.

We studied catalytic cross-coupling reactions of 1-(2', 3', 4'-bromo- and 2'-iodo-phenyl)-*N*,*N*-dimethylethanamines (**2–5**) as electrophilic synthons with arylboronic acids $R-C_6H_4B(OH)_2$ as nucleophilic synthons. All halogen derivatives were prepared by known procedures: **2** and **5** were obtained from *N*,*N*-dimethyl-1-phenylethanamine via the *ortho*-lithiation step [10], and **3** and **4** were obtained from the corresponding acetophenones [11].

For studying the reactivities of these synthons, the model reaction of 1-(2'-bromophenyl)-*N*,*N*-dimethylethanamine (**2**) with arylboronic acids **6a**, **6d–6f** was chosen. In view of the low reactivity of aryl bromide **2** caused by steric hindrance created by the *ortho*-dimethylaminoethyl group, we modified the classical Suzuki procedure, in particular, rejected the use of organic solvents. The reaction was carried out in water at the boiling point of the solution in the presence of 1 mol % of the palladium complex $PdCl_2$(dppf) (dppf = 1,1-bis(diphenylphosphino)ferrocene) and 1 mol % of a phase transfer agent, *n*-Bu_4NBr. This gave the product of cross-coupling of aryl bromide **2** with arylboronic acid **6e**, amino-biaryl **7e**, in a 30% yield, while symmetric biaryl **8e** was formed as the major reaction product in a 60% yield (Scheme 1).

Unlike *ortho*-isomer **2**, the corresponding *meta*- and *para*-substituted aryl bromides (**3** and **4**) react quantitatively with arylboronic acids **6b–6d** to give unsymmetrical aminobiaryls **9b–9d** and **10b–10d** (Scheme 2). The structures of the obtained compounds were confirmed by ^1H NMR spectroscopy. For identification, compounds **9b–9d** and **10b–10d** were converted to their iodomethylates.

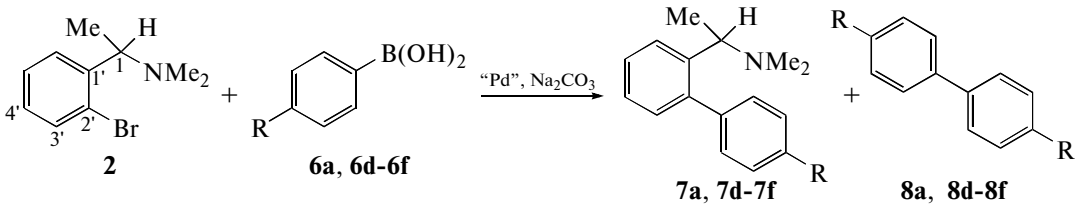
When the reaction of aryl bromide **2** with arylboronic acids **6a, 6d–6f** was carried out by the classical procedure in dioxane (60°C, 10 h) in the presence of palladium(0) triphenylphosphine complex, $Pd(PPh_3)_4$, only traces of cross-coupling products **7a**, **7d–7f** were detected in the reaction mixtures, the initial aryl bromide **2** remained unreacted, and arylboronic acids were converted to symmetric biaryls **8a, 8d–8f** (see Scheme 1). Dimers **8** are apparently formed via oxidative coupling of arylboronic acids. The possible mech-

Moscow State University, Moscow, 119992 Russia

Characteristics of the reaction products of halo-substituted *N*,*N*-dimethyl-1-phenylethanamines (**2**–**5**, **5a**, (***S***)-**5**, (***S***)-**5a**) with arylboronic acids (**6b**–**6e**)

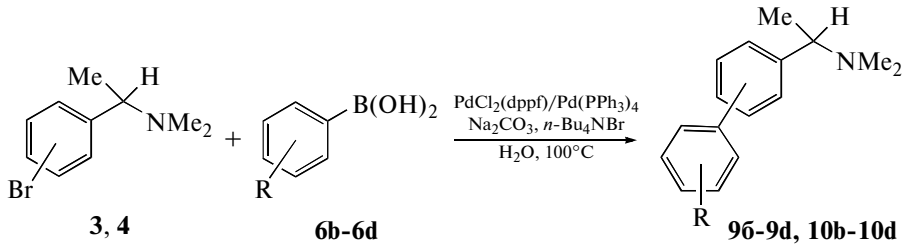
Reactants; reaction products (yield, %)	Biaryl mp, °C	^{1}H NMR, δ, ppm Elemental analysis data
2 + **6e**; **7e** (30) + **8e** (60)	–	ABA: 1.32 d (*J* 6.8 Hz, 3H, C$\underline{H}_3$CH), 2,10 s (6H, (C$\underline{H}_3$)$_2$N), 3.33 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 3.86 s (3H, *p*-C$\underline{H}_3$O), 6.92–7.59 m (8H, arom).
3 + **6b**; **9b** (~100)	IM: 215 (dec.)	ABA: 1.53 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.32 s (6H, (C$\underline{H}_3$)$_2$N), 2.37 s (3H, *o*-C$\underline{H}_3$), 3.46 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.30–7.46 m (8H, arom). IM: 1.78 d (*J* 6.8 Hz, 3H C$\underline{H}_3$CH), 2.26 s (3H, *o*-C$\underline{H}_3$), 3.03 s (9H, (C$\underline{H}_3$)$_3$NI), 4.87 q (*J* 6.8 Hz, 1H, CH$_3$C$\underline{H}$), 7.25–7.58 m (8H, arom).
3 + **6c**; **9c** (~100)	IM: 229 (dec.)	ABA: 1.52 d (*J* 6.8 Hz, 3H, C$\underline{H}_3$CH), 2.31 s (6H, (C$\underline{H}_3$)$_2$N), 2.43 s (3H, *m*-C$\underline{H}_3$), 3.56 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$); 7.18–7.52 m (8H, arom). IM: 1.79 d (*J* 6.8 Hz, 3H, C$\underline{H}_3$CH,), 2.41 s (3H, *m*-C$\underline{H}_3$), 3.04 s (9H, (C$\underline{H}_3$)$_3$NI), 4.88 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 7.21–7.84 m (8H, arom). Found, %: O 56.62, H 6.44, N 3.79. $C_{18}H_{24}IN$. Calculated, %: O 56.70, H 6.34, N 3.67.
3 + **6d**; **10d** (~100)	IM: 239 (dec.)	ABA: 1.57 d (*J* 6.9 Hz, 3H, C$\underline{H}_3$CH), 2.37 s (6H, (C$\underline{H}_3$)$_2$N), 2.53 s (3H, *p*-C$\underline{H}_3$), 3.49 q (*J* 6.9 Hz, 1H, OH$_3$C$\underline{H}$), 7.24–7.67 m (8H, arom). IM: 1.79 d (*J* 6.9 Hz, 3H, C$\underline{H}_3$CH), 2.37 s (3H, *p*-C$\underline{H}_3$), 3.04 s (9H, (C$\underline{H}_3$)$_3$NI), 4.87 q (*J* 6.9 Hz, 1H, OH$_3$C$\underline{H}$), 7.29–7.83 m (8H, arom).
4 + **6b**; **10b** (~100)	ABA: 231 (dec.)	ABA: 1.52 d (*J* 6.8 Hz, 3H C$\underline{H}_3$CH), 2.25 s (6H, (C$\underline{H}_3$)$_2$N), 2.34 s (3H, *o*-C$\underline{H}_3$), 3.54 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 7.20–7.34 m (8H, arom). IM: 1.78 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.26 s (3H, *o*-C$\underline{H}_3$), 3.04 s (9H, (C$\underline{H}_3$)$_3$NI), 4.89 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.22–7.68 m (8H, arom).
4 + **6c**; **10c** (~100)	IM: 243 (dec.)	ABA: 1.53 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.33 s (6H, (C$\underline{H}_3$)$_2$N), 2.51 s (3H, *m*-C$\underline{H}_3$), 3.49 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.21–7.63 m (8H, arom). IM: 1.76 d (*J* 6.9 Hz, 3H, C$\underline{H}_3$CH), 2.39 s (3H, *m*-C$\underline{H}_3$), 3.05 s (9H, (C$\underline{H}_3$)$_3$NI), 4.92 q (*J* 6.9 Hz, 1H, OH$_3$C$\underline{H}$), 7.18–7.77 m (8H, arom).
4 + **6d**; **10d** (~100)	IM: 247 (dec.)	ABA: 1.52 d (*J* 6.8 Hz, 3H, C$\underline{H}_3$CH), 2.35 s (6H, (C$\underline{H}_3$)$_2$N), 2.49 s (3H, *p*-C$\underline{H}_3$), 3.43 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 7.29–7.64 m (8H, arom). IM: 1.76 d (*J* 6.8 Hz, 3H C$\underline{H}_3$CH), 2.36 s (3H, *p*-C$\underline{H}_3$), 3.03 s (9H, (C$\underline{H}_3$)$_3$NI), 4.87 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 7.28–7.77 m (8H, arom). Found, %: O 56.95, H 6.61, N 3.82. $C_{18}H_{24}IN$. Calculated, %: O 56.70, H 6.34, N 3.67.
5 + **6c**; **7c** (70)	IM: 208 (dec.)	ABA: 1.40 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.19 s (6H, (C$\underline{H}_3$)$_2$N), 2.47 s (3H, *m*-C$\underline{H}_3$), 3.60 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.11–7.71 m (8H, arom). IM: 1.82 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.37 s (3H, *m*-C$\underline{H}_3$), 2.75 s (9H, (C$\underline{H}_3$)$_3$NI), 4.77 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.25–8.06 m (8H, arom).
5 + **6d**; **7d** (87)	–	ABA: 1.33 d (*J* 6.8 Hz, 3H, C$\underline{H}_3$CH), 2.17 s (6H, (C$\underline{H}_3$)$_2$N), 2.43 s (3H, *p*-C$\underline{H}_3$), 3.44 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 7.01–7.62 m (8H, arom).
5 + **6e**; **7e** (80)	–	ABA: 1.32 d (*J* 6.8 Hz, 3H, C$\underline{H}_3$CH), 2.10 s (6H, (C$\underline{H}_3$)$_2$N), 3.33 q (*J* 6.8 Hz, 1H, OH$_3$C$\underline{H}$), 3.86 s (3H, *p*-C$\underline{H}_3$O), 6.92–7.59 m (8H, arom).
5a + **6d**; **11** (~100)	IM: 238 (dec.)	IM: 1.82 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.39 s (3H, *p*-C$\underline{H}_3$), 2.76 s (9H, (C$\underline{H}_3$)$_3$NI), 4.80 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.19–7.81 m (8H, arom).
(***S***)-**5** + **6b**; **12** (~100, 1 : 1 diastereomer mixture)	–	ABA: 1.25 d (*J* 6.6 Hz, 3H, C$\underline{H}_3$CH), 2.04 and 2.08 s (3H, *o*-C$\underline{H}_3$), 2.11 and 2.13 s (6H, (C$\underline{H}_3$)$_2$N), 2.90 and 3.05 q (*J* 6.6 Hz, 1H, OH$_3$C$\underline{H}$), 7.05–7.67 m (8H, arom).
(***S***)-**5a** + **6b**; **13** (~100, 2 : 1 diastereomer mixture)	–	IM: 1.96 d (3H, C$\underline{H}_3$CH), 2.20 and 1.97 s (3H, *o*-C$\underline{H}_3$), 3.20 s (9H, (C$\underline{H}_3$)$_3$NI), 4.71 and 4.21 q (1H, OH$_3$C$\underline{H}$), 6.91–7.66 m (8H, arom).

Note: ABA is amino biaryl, and IM is iodomethylate.

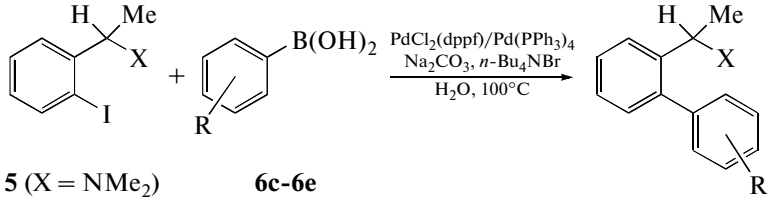


[R = H(**a**), 2'-Me(**b**), 3'-Me(**c**), 4'-Me(**d**), 4'-OMe(**e**), 4'-Cl(**f**)]

Scheme 1.



Scheme 2.



Scheme 3.

anism may include the oxidative addition of arylboronic acid to the Pd(0) complex, symmetrization of the Ar–Pd–$B(OH)_2$ complexes (the ligands are omitted) to give Ar–Pd–Ar and $(HO)_2B$–Pd–$B(OH)_2$ complexes, which then undergo reductive elimination to give biaryls and diboronic acids and to recover the Pd(0) complex.

Since iodides are most reactive among aryl halides, we used 1-(2'-iodophenyl)-*N*,*N*-dimethylethanamine (**5**), instead of aryl bromide **2**, in the cross-coupling reactions. As a result, irrespective of the type of the catalyst used, $PdCl_2$(dppf) or $Pd(PPh_3)_4$, the reactions were completed over a period of 5–10 min and gave high yields of the expected cross-coupling products, aminobiaryls **7c–7e** (Scheme 3), which were characterized as iodomethylates.

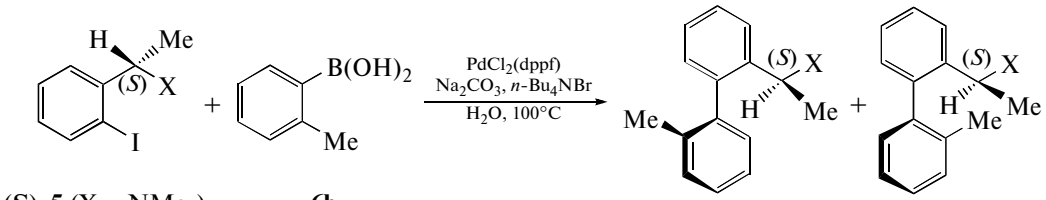
Furthermore, we demonstrated that not only free amine but also its iodomethylate can be introduced into the cross-coupling reaction: iodomethylate of iodoamine **5** (**5a**) quantitatively reacts with arylboronic acid **6d** to give the iodomethylate of the corresponding biaryl **11** (Scheme 3). The iodomethylate of aryl bromide **2** does not react under these conditions.

Of most interest are biaryls for which the axial chirality is possible. We carried out the reaction of the optically active aryl iodide (*S*)-**5** with 2-methylphenylboronic acid **6b**, which afforded a 1 : 1 mixture of diastereomeric aminobiaryls **12** in a quantitative yield, i.e., the reaction lacks stereoselectivity (Scheme 4).

The diastereomer ratio was determined by ^{1}H NMR spectroscopy from the integrated intensity ratio of the corresponding proton signals: C<u>H</u>CH_3, N<u>Me</u>$_2$, ArC<u>H</u>$_3$. We failed to separate the diastereomers by either crystallization or chromatography on silica gel.

The increase in the substituent bulk on going from (*S*)-**5** to its iodomethylate (*S*)-**5a** resulted in stereoselective reaction with quantitative formation of iodomethylates of diastereomeric aminobiaryls **13** (Scheme 4) in a 2 : 1 ratio.

Thus, we carried out and optimized the first cross-coupling reactions of *ortho*-, *meta*-, and *para*-halogen-substituted *N*,*N*-dimethyl-1-phenylethanamines and their iodomethylates with arylboronic acids. In the case of *ortho*-substituted aryl halides, high yields of aminobiaryls were observed only when aryl iodide **5** or its iodomethylate **5a** was used.



(**S**)-**5** (X = NMe_2) **6b**
(**S**)-**5a** (X = NMe_3I)

12 (X = NMe_2)
13 (X = NMe_3I)

Scheme 4.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer (400 MHz) in $CDCl_3$ (for iodomethylates, in DMSO-d_6) with internal TMS. The elemental analysis was performed in the microanalysis laboratory of the Department of Chemistry, Moscow State University.

Synthesis of Biaryls

Procedure A. Aryl halide or iodomethylate (1 mmol), arylboronic acid (1.3 mmol), *n*-Bu_4NBr (0.01 mmol), Na_2CO_3 (2.5 mmol), and water (5 mL) were charged into a reactor equipped with a magnetic stirrer and an argon supply system. $PdCl_2$(dppf) (0.01 mmol) or $Pd(PPh_3)_4$ (0.01 mmol) was added with stirring under argon. The mixture was heated to 100°C with stirring. The reaction was continued until the organic layer floated-up (5 to 10 min). The reaction mixture was extracted with diethyl ether and the combined ethereal extracts were passed through a silica gel layer. Evaporation of the solvent gave the corresponding biaryls as colorless oils, which were characterized as iodomethylates.

Procedure B [12]**.** Aryl bromide **2** (1.1 mmol), arylboronic acid (1.2 mmol), $Pd(PPh_3)_4$ (0.08 mmol), Na_2CO_3 (2.4 mmol), and freshly distilled dioxane (10 mL) were charged into a reactor equipped with a magnetic stirrer and an argon supply system. The reaction mixture was stirred at 60°C under argon for 10 h. Then, CH_2Cl_2 (30 mL) and a 2 M solution of Na_2CO_3 (25 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel (elution with hexane–ethyl acetate, 10 : 1).

The physicochemical characteristics of the obtained biaryls **8a**, **8d–8f** (yields 67–87%) correspond to published data.

The structure of amino biaryls **7c–7e, 9c**, **9d, 10c, 10d**, **12**, and **13** and their iodomethylates were confirmed by ^{1}H NMR spectroscopy (table).

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