# Catalytic Sandmeyer Bromination

Irina P. Beletskaya,*[a] Alexander S. Sigeev,[a] Alexander S. Peregudov,[b] Pavel V. Petrovskii[b]

[a] Department of Chemistry, M. V. Lomonosov Moscow State University, 119992 Moscow, Russian Federation
[b] A. N. Nesmeyanov Institute of Organo-Element compounds, Russian Academy of Science, Vavilova str. 28, 119991 Moscow, Russian Federation
Fax +7(495)9381844; E-mail: Beletska@org.chem.msu.ru

**Abstract:** An efficient catalyst system for Sandmeyer bromination is proposed. Aryl bromides and dibromides can be obtained with excellent yield by this synthetic protocol.

**Key words:** catalysis, copper, diazo compounds, Sandmeyer reaction, halogenation

Aryl bromides are a class of compounds widely used in the organic synthesis. In recent years, interest in these compounds as substrates for the synthesis has been heightened by the development of carbon–carbon bond-formation reactions such as the cross-coupling[1,2a] or Heck reactions[1,3] and carbon–heteroatom bond-formation reactions[1,2b] catalyzed by transition metal complexes. The C(sp$^2$)–Hal units are also important structural motifs in many natural products and synthetic drugs.[4] Recently, a tendency to replace palladium complexes usually used in these reactions by copper complexes was revealed.[5]

The most general synthetic pathways to aryl bromides are the direct electrophilic bromination of arenes[6] and the Sandmeyer reaction.[7] The latter is the reaction between arenediazonium salt and HBr which proceeds at high temperatures (up to 100–120 °C) in the presence of CuBr and requires an excess of CuBr and the concentrated acid.

Earlier, we showed that the Sandmeyer reaction with potassium cyanide[8] and thiocyanate[9] can be performed in the presence of catalytic quantities of copper salts under mild conditions to give the corresponding aryl nitrile or aryl thiocyanate in high yields. In the present work, we have applied this synthetic protocol to the Sandmeyer bromination reaction.

Screening of catalytic system activities was carried out for the reaction of 4-fluorophenyldiazonium tetrafluoroborate with potassium bromide in the presence of a phase transfer catalyst (PTC: crown-ether or tetraalkylammonium salt) in acetonitrile at room temperature (Equation 1). The presence of fluorine substituent allowed us to use $^{19}$F NMR spectroscopy for the fast determination of the yields and ratios of the products. As catalysts we used copper(I) and copper(II) salts with different counter-ions in the presence of bidentate nitrogen ligands [1,10-phenanthroline (phen), and α,α′-bipyridine (bpy)] (Equation 1).
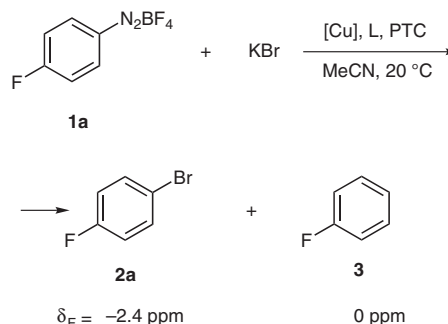


**Equation 1**

The application of 'homovalent' catalyst containing only copper(I) salts (Table 1, entries 1 and 3) or copper(II) salts (Table 1, entries 2 and 4) was rather ineffective, also in the case of cyanation.[8] It should be noted that in the presence of the Cu(I) salts, the reaction gave aryl bromide **2a** in moderate yield whereas the use of the Cu(II)-based catalyst led to the predominant formation of fluorobenzene (**3**). In contrast, when the 'heterovalent' Cu(I)/Cu(II) catalytic systems were used, the reaction furnished **2a** in a yield from high to excellent (Table 1, entries 5–8). We earlier described a similar effect for the analogous reaction with potassium cyanide.[8] Under the foregoing conditions, we have found that the nature of phase-transfer catalyst has little effect on the yield of product **2a** (Table 1, entries 8–11). Thus, replacing crown-ether by the tetraalkylammonium salt led only to a negligible change of the yield. Similarly, the change of N,N-ligand, 1,10-phenanthroline, for α,α′-bipyridine produced almost no effect on the yield of aryl bromide **2a** (Table 1, entries 8,12). However, without ligand the yield of **2a** dramatically decreased (Table 1, entry 13). In contrast to weak influence of the nature of phase-transfer agent and N,N-ligand we have found significant dependence of the yield of bromination product **2a** on the counter-ion in copper salts used as precursors of the catalyst. This effect can be observed on both the 'homovalent' Cu(I) or Cu(II) catalytic systems (Table 1, entries 1–4) and the 'heterovalent' Cu(I)/Cu(II) pairs (Table 1, entries 5–8).

Since the copper bromides are not easily available, we attempted to develop a method that would allow us to use commonly available copper salts such as chlorides or acetates. We envisaged that the first stage of complex formation was anion exchange with the formation of copper bromides.

**Table 1** Reaction of 4-Fluorophenyldiazonium Fluoroborate with KBr[a]

| Entry | [Cu] | PTC | L | Yield (%)[b] 2a | 3 |
|-------|------|-----|---|----------------|---|
| 1 | CuBr | Dibenzo-18-crown-6 | phen | 47 | 43 |
| 2 | CuBr$_2$ | Dibenzo-18-crown-6 | phen | 21 | 68 |
| 3 | (MeCN)$_4$CuBF$_4$ | Dibenzo-18-crown-6 | phen | 41 | 55 |
| 4 | Cu(BF$_4$)$_2$ | Dibenzo-18-crown-6 | phen | 11 | 77 |
| 5 | (MeCN)$_4$CuBF$_4$ + Cu(BF$_4$)$_2$ | Dibenzo-18-crown-6 | phen | 78 | 15 |
| 6 | CuBr + Cu(BF$_4$)$_2$ | Dibenzo-18-crown-6 | phen | 83 | 14 |
| 7 | (MeCN)$_4$CuBF$_4$ + CuBr$_2$ | Dibenzo-18-crown-6 | phen | 84 | 10 |
| 8 | CuBr + CuBr$_2$ | Dibenzo-18-crown-6 | phen | 99 | <1 |
| 9 | CuBr + CuBr$_2$ | Dicyclohexyl-18-crown-6 | phen | 98 | – |
| 10 | CuBr + CuBr$_2$ | 18-Crown-6 | phen | 100 | – |
| 11 | CuBr + CuBr$_2$ | Et$_3$BnNCl | phen | 97 | 2 |
| 12 | CuBr + CuBr$_2$ | Dibenzo-18-crown-6 | bpy | 97 | 2 |
| 13 | CuBr + CuBr$_2$ | Dibenzo-18-crown-6 | – | 31 | 65 |

[a] The reactions were carried out with ArN$_2$BF$_4$ (1 mmol), KBr (2 mmol), PTC (0.1 mmol, 10 mol%), L (0.1 mmol, 10 mol%), and copper salt (0.1 mmol, 10 mol%) in MeCN (4 mL).
[b] Yields according to $^{19}$F NMR spectroscopy.

We tested three versions of catalyst preparation, each including this exchange (Figure 1). In procedure **A**, KBr and PTC were added to a mixture of copper salts and a ligand, 1,10-phenanthroline. We used this method in the catalyst screening. In procedure **B**, KBr and PTC were added to a mixture of Cu(I)/Cu(II) fluoroborates that was followed by addition of the ligand after several minutes. In procedure **C**, the anion exchange was carried out separately for Cu(I) and Cu(II) salts. The solutions obtained were mixed and then the ligand was added.

For procedure **A** we had good yields of aryl bromide but also the reduction product **3** was formed (Table 2, entries 1 and 2). Better results were obtained when procedure **B** was employed but **3** still formed in noticeable amounts.

(Table 2, entries 3 and 4). In both cases the time of mixing did not influence the yield of products (Table 2, entries 1–4). Procedure **C** turned out to be the best providing aryl bromide **2a** with almost quantitative yield (Table 2, entry 5). It means that the catalyst structure is slightly different depending on the way of its formation.

Procedure **C** allows application of a number of easily available copper salts such as CuCl, CuCl$_2$, Cu(OAc)$_2$ (Table 2, entries 6–9) and the yields of the target product are correspondingly excellent. Even the use of copper chlorides as catalyst precursors does not lead to the formation of the corresponding aryl chloride in amounts detectable by $^{19}$F NMR spectroscopy.
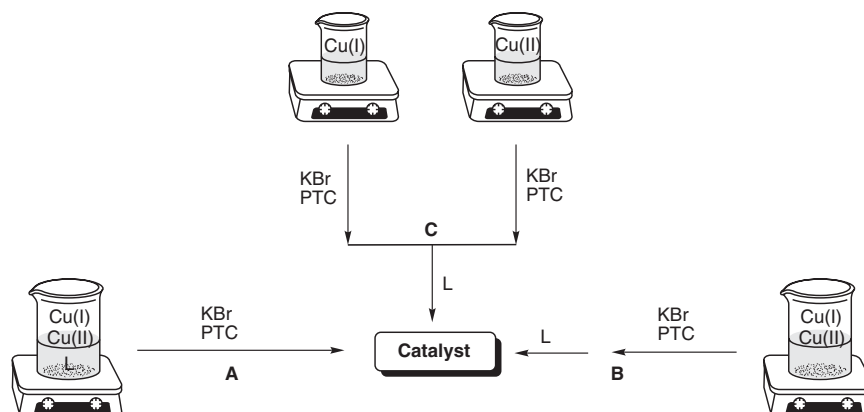


**Figure 1**   Methods of catalyst preparation

**Table 2** Effect of the Catalyst Preparation Method on the Yields of Products **2a** and **3**[a]

| Entry | Cu(I) | Cu(II) | Procedure[b] | Yield (%)[c] | |
|---|---|---|---|---|---|
| | | | | **2a** | **3** |
| 1 | (MeCN)$_4$CuBF$_4$ | Cu(BF$_4$)$_2$ | A | 78 | 15 |
| 2 | (MeCN)$_4$CuBF$_4$ | Cu(BF$_4$)$_2$ | A[d] | 79 | 14 |
| 3 | (MeCN)$_4$CuBF$_4$ | Cu(BF$_4$)$_2$ | B | 87 | 9 |
| 4 | (MeCN)$_4$CuBF$_4$ | Cu(BF$_4$)$_2$ | B[d] | 88 | 8 |
| 5 | (MeCN)$_4$CuBF$_4$ | Cu(BF$_4$)$_2$ | C | 97 | 1 |
| 6 | (MeCN)$_4$CuBF$_4$ | CuCl$_2$ | C | 96 | 2 |
| 7 | (MeCN)$_4$CuBF$_4$ | Cu(OAc)$_2$ | C | 98 | 1 |
| 8 | CuCl | Cu(BF$_4$)$_2$ | C | 96 | 2 |
| 9 | CuCl | CuCl$_2$ | C | 97 | 1 |

[a] The reactions were carried out with ArN$_2$BF$_4$ (1 mmol), KBr (2 mmol), PTC (0.1 mmol, 10 mol%), L (0.1 mmol, 10 mol%), and copper salt (0.1 mmol, 10 mol%) in MeCN (4 mL).
[b] See Figure 1.
[c] Yields according to $^{19}$F NMR spectroscopy.
[d] Stirred 30 min instead of 2 min before addition of the diazonium salt.

Under the optimized conditions, a variety of arenediazonium salts with electron-donating and electron-withdrawing substituents can be involved in the reaction with KBr (Table 3, Equation 2). In contrast to catalytic cyanation,[8] electron effects of substituents have little influence on the reaction. In most cases the yields of ArBr were close to quantitative (Table 3, entries 1–7, 9–14, and 16). In contrast, the steric effect is significant. For instance, the presence of the methyl group in the *ortho*-position decreased the yield to 82% from 98% for *para*-substituted **1f** (cf. Table 3, entries 6 and 8). At the same time, two halogen atoms in the 2- and 6-positions led to a drastic decrease in the yield (56%) with formation of substantial amounts (32%) of reduction product – 3-bromo-5-chlorotoluene (Table 3, entry 15).
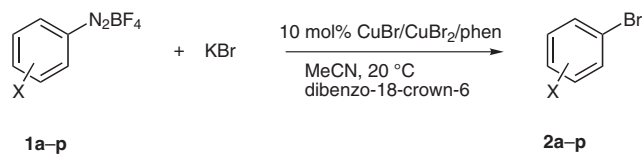


**Equation 2**
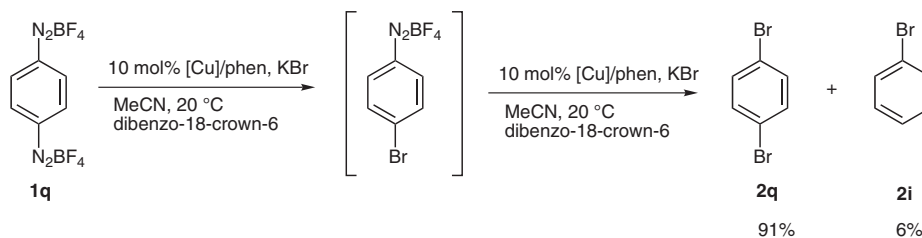
**Table 3** Synthesis of Aryl Bromides[a]

| Entry | ArN$_2$BF$_4$ | X | ArBr | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | 4-F | **2a** | 98 |
| 2 | **1b** | 4-Cl | **2b** | 99 |
| 3 | **1c** | 3-Cl | **2c** | 99 |
| 4 | **1d** | 4-NO$_2$ | **2d** | 99 |
| 5 | **1e** | 4-MeO | **2e** | 97 |
| 6 | **1f** | 4-Me | **2f** | 98 |
| 7 | **1g** | 3-Me | **2g** | 96 |
| 8 | **1h** | 2-Me | **2h** | 82 |
| 9 | **1i** | H | **2i** | 98 |
| 10 | **1j** | 4-CO$_2$Et | **2j** | 99 |
| 11 | **1k** | 3,5-Cl$_2$ | **2k** | 99 |
| 12 | **1l** | 3,4,5-Cl$_3$ | **2l** | 99 |
| 13 | **1m** | 4-NEt$_2$ | **2m** | 95 |
| 14 | **1n** | 4-Ac | **2n** | 99 |
| 15 | **1o** | 2-Br,4-Me,6-Cl | **2o** | 56 |
| 16 | **1p** | 3-Br,4-Me | **2p** | 97 |

[a] The reactions were carried out with ArN$_2$BF$_4$ (3 mmol), KBr (6 mmol), PTC (0.3 mmol, 10 mol%), L (0.3 mmol, 10 mol%), copper salt (0.3 mmol, 10 mol%) in MeCN (12–18 mL).
[b] Isolated yield.

Bisdiazonium salts can also be involved in this reaction. In general, the results were similar to ones obtained for monodiazonium salts. However the yields of target products were slightly lower due to formation of the corresponding monobromide by the side reaction of dediazotization. For example, in the reaction of benzene-1,4-bisdiazonium fluoroborate (**1q**), 1,4-dibromobenzene (**2q**) was obtained in 91% yield with 6% of bromobenzene as a product of partial dediazotization (Scheme 1).

Sterically hindered naphthalene-1,8-bisdiazonium fluoroborate (**1r**) gave 1,8-dibromonaphthalene (**2r**) in 81% yield together with 13% of 1-bromonaphthalene (Scheme 2).

In conclusion, we have offered a catalytic version of the Sandmeyer bromination reaction employing a Cu(I)/
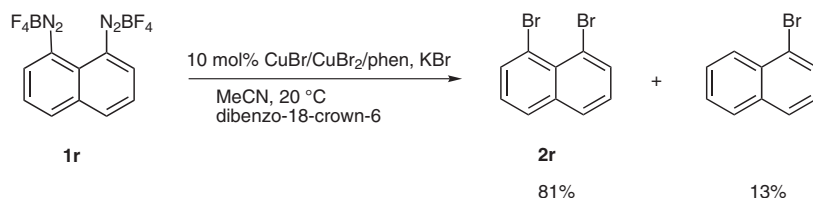


**Scheme 1**

**Scheme 2**

Cu(II)/phen catalytic system. This synthetic protocol seems to be highly useful for the preparation of various aryl bromides and dibromides in excellent yields.

The reactions were carried out by using standard Schlenk technique under $N_2$ with magnetic stirring. MeCN was distilled over $CaH_2$. PE refers to the petroleum ether fraction with boiling point range of 40–70 °C. Column chromatography was performed on silica gel 0.035–0.070 mm. TLC was performed on Fluka silica gel plates and visualized by UV (254 nm). $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ on a Bruker AMX400 spectrometer (400.13 and 100.61 MHz, respectively). $^{19}$F NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 300 spectrometer (282.38 MHz). Chemical shifts are given in ppm relative to the resonance of the residual protons of the solvent ($^1$H: $CHCl_3$ = 7.25 ppm). $^{19}$F chemical shifts are given relative to PhF. $(MeCN)_4CuBF_4$ was prepared by dissolving $Cu_2O$ in a boiling mixture of MeCN and 40% $HBF_4$ (50:1 by volume) and recrystallized from MeCN.

**Arenediazonium Tetrafluoroborates 1a–r; General Procedure**
To a solution of the corresponding amine (0.1 mol) in concd HCl (30 mL) and $H_2O$ (30 mL) cooled to 0–5 °C, was slowly added a cold solution of $NaNO_2$ (6.9 g, 0.1 mol) in $H_2O$ (15 mL). The resulting solution was filtered, cooled, and a solution of $NH_4BF_4$ (13.7 g, 0.13 mol) in $H_2O$ (50 mL) was added. After stirring for 30 min at 0 °C, the precipitate formed was filtered, washed with cold 5% solution of $NH_4BF_4$, cold MeOH, and $Et_2O$. Diazonium salt was air-dried and stored at 0 °C before use. Bisdiazonium salts were prepared analogously from 0.05 mol of the corresponding diamine. The yields of arenediazonium tetrafluoroborates were 61–97%.

**Catalyst Screening**
To a stirred suspension of KBr (2 mmol) in a solution of a phase-transfer catalyst (0.1 mmol, 10 mol%) in anhyd MeCN (2 mL), was added the appropriate quantities of copper salts (see Table 1) and 0.1 mmol (10 mol%) of a ligand. After stirring for 2 min at r.t., a solution of **1a** (0.210 g, 1 mmol) in anhyd MeCN (2 mL) was slowly syringed into the mixture. When the gas evolution had ceased, 0.4 mL of the solution was mixed with 0.2 mL of DMSO-$d_6$ and $^{19}$F NMR spectrum was recorded.

**Variations of Catalyst Preparation**
*Procedure A*: To a stirred suspension of KBr (0.238 g, 2 mmol) in a solution of dibenzo-18-crown-6 (0.036 g, 0.1 mmol, 10 mol%) in anyhd MeCN (2 mL), were added $(MeCN)_4CuBF_4$ (0.031 g, 0.1 mmol, 10 mol%), $Cu(BF_4)_2$ (0.024 g, 0.1 mmol, 10 mol%), and 1,10-phenanthroline (0.018 g, 0.1 mmol, 10 mol%). After stirring for 2 min at r.t., a solution of **1a** (0.210 g, 1 mmol) in anhyd MeCN (2 mL) was slowly syringed into the mixture.

*Procedure B*: To a stirred suspension of KBr (0.238 g, 2 mmol) in a solution of dibenzo-18-crown-6 (0.036 g, 0.1 mmol, 10 mol%) in anyhd MeCN (2 mL), were added $(MeCN)_4CuBF_4$ (0.031 g, 0.1 mmol, 10 mol%), and $Cu(BF_4)_2$ (0.024 g, 0.1 mmol, 10 mol%). After stirring for 2 min at r.t., 1,10-phenanthroline (0.018g, 0.1 mmol, 10 mol%) was added to the mixture. The mixture was stirred anoth-

er 2 min and a solution of **1a** (0.210 g, 1 mmol) in anhyd MeCN (2 mL) was slowly syringed into the mixture.

*Procedure C*: To a stirred suspension of KBr (0.119 g, 1 mmol) in a solution of dibenzo-18-crown-6 (0.018 g, 0.05 mmol) in anhyd MeCN (2 mL), was added Cu(I) salt (0.1 mmol, 10 mol%), and the resulting mixture was stirred at r.t. for 5 min. Copper(II) salt (0.1 mmol, 10 mol%) was pretreated similarly. To the combined solutions, was added 1,10-phenanthroline (0.018g, 0.1 mmol, 10 mol%) and then, after stirring for 2 min, a solution of **1a** (0.210 g, 1 mmol) in anhyd MeCN (2 mL) was slowly syringed into the mixture.

**Aryl Bromides 2a–p; General Procedure**
To a stirred suspension of KBr (0.714 g, 6 mmol) in anhyd MeCN (6 mL) were added dibenzo-18-crown-6 (0.108 g, 0.3 mmol, 10% mol), CuBr (0.043 g, 0.3 mmol, 10% mol), and $CuBr_2$ (0.067 g, 0.3 mmol, 10% mol). After stirring for 2 min, 1,10-phenanthroline (0.054 g, 0.3 mmol, 10% mol) was added. A solution of diazonium salt **1** (3 mmol) in anhyd MeCN (6–12 mL) was added dropwise to the resulting mixture. The mixture was stirred for 20 min at r.t., diluted with $Et_2O$ (50 mL) and passed through a layer of Celite to remove inorganic salts. The organic solvents were removed in vacuum, and the residue, if necessary, was subjected to column chromatography to give the corresponding aryl bromide. $^1$H NMR spectra of **2a–n,p–q** were identical with those of the authentic compounds.

**1-Bromo-4-chlorobenzene (2b)**
Purified by column chromatography (PE); yield: 0.568 g (99%); colorless solid; mp 64–65 °C (Lit.[10] mp 64–66 °C).

**1-Bromo-3-chlorobenzene (2c)**
Purified by the column chromatography (PE); yield: 0.568 g (99%); colorless liquid.

**4-Bromoanisole (2e)**
Purified by the column chromatography (PE–EtOAc, 99:1); yield: 0.544 g (97%); colorless liquid.

**1-Bromo-3,5-dichlorobenzene (2k)**
Yield: 0.677 g (99%); white crystals; mp 76–77 °C (EtOH) (Lit.[10] mp 76–76.5 °C).

**1-Bromo-3,4,5-trichlorobenzene (2l)**
Yield: 0.781 g (99%); colorless needles; mp 55–56 °C (EtOH) (Lit.[11] mp 56 °C).

**4-Bromo-*N,N*-diethylaniline (2m)**
Purified by column chromatography (PE–EtOAc, 97:3); yield: 0.650 g (95%); colorless solid; mp 33–34 °C (Lit.[12] mp 33 °C).

**4′-Bromoacetophenone (2n)**
Yield: 0.591 g (99%); colorless crystals; mp 51–52 °C (PE) (Lit.[13] mp 51–52 °C).

**1,2-Dibromo-3-chloro-5-methylbenzene (2o)**

The synthesis and work-up were carried out as described in the general procedure. After column chromatography (PE), 3-bromo-5-

chlorotoluene (first band) (32%) and pure **2o** (second band) were obtained.

### 3-Bromo-5-chlorotoluene
Yield: 0.197 g (32%); colorless oil.

### 2o
Yield: 0.478 g (56%); colorless solid; mp 51–53 °C (EtOH) (Lit.[12] mp 51–52 °C).

$^1$H NMR (CDCl$_3$): δ = 2.45 (s, 3 H), 7.14 (s, 1 H), 7.30 (s, 1 H).

$^{13}$C NMR (CDCl$_3$): δ = 26.4 (CH$_3$), 125.2, 129.1 (C), 131.2, 133.6 (CH), 136.4, 144.2 (C).

### 2,4-Dibromotoluene (2p)
Purified by column chromatography (PE); yield: 0.727 g (97%); colorless oil.

### Catalytic Sandmeyer Bromination; General Procedure for Bis-diazonium Salts
To a stirred suspension of KBr (1.428 g, 12 mmol) in anhyd MeCN (12 mL), were added dibenzo-18-crown-6 (0.216 g, 0.6 mmol, 10% mol), CuBr (0.086 g, 0.6 mmol, 10% mol), and CuBr$_2$ (0.134 g, 0.6 mmol, 10% mol). After stirring for 2 min, 1,10-phenanthroline (0.108 g, 0.6 mmol, 10% mol) was added. A solution of diazonium salt **1q** or **1r** (3 mmol) in anhyd MeCN (20 mL) was added dropwise to the resulting mixture. The mixture was stirred for 20 min at r.t., diluted with Et$_2$O (50 mL) and passed through a layer of Celite to remove inorganic salts. The organic solvents were removed under vacuum, and the residue was subjected to column chromatography (eluent: PE) to give the corresponding aryl bromide.

### 1,4-Dibromobenzene (2q)
Column chromatography provided PhBr (**2i**) (first band) and pure **2r** (second band).

### 2i
Yield: 0.028 g (6%).

### 2q
Yield: 0.644 g (91%); colorless leaflets; mp 89 °C (EtOH) (Lit.[14] mp 89 °C).

### 1,8-Dibromonaphthalene (2r)
Column chromatography gave 1-bromonaphthalene (first band) and pure **2r** (second band).

### 1-Bromonaphthalene
Yield: 0.081 g (13%).

### 2r
Yield: 0.695 g (81%); colorless crystals; mp 105–106 °C (EtOH) (Lit.[15] mp 106 °C).

## References

(1) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, **2002**.

(2) (a) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**. (b) Hartwig, J. F. In *Comprehensive Coordination Chemistry II*, Vol. 9; McCleverty, J. A.; Meyer, T., Eds.; Elsevier: Amsterdam, **2004**, 369.

(3) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, **1985**.

(4) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411.

(5) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

(6) (a) de la Mare, P. D. B. *Electrophilic Halogenation*; Cambridge University Press: New York, **1976**. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(7) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251.

(8) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2004**, *689*, 3810.

(9) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *Mendeleev Commun.* **2006**, 250.

(10) Raznikiewicz, T. *Ark. Kemi* **1963/1964**, 301; *Chem. Abstr.* **1965**, *59*, 11317c.

(11) Kravtsov, D. N.; Kvasov, B. A.; Khazanova, T. S.; Fedin, E. I. *J. Organomet. Chem.* **1973**, *61*, 207.

(12) Gorelik, M. V.; Lomzakova, V. I.; Khamidova, E. V.; Shteiman, V. Y.; Kuznetsova, M. G.; Andrievski, A. M. *Russ. J. Org. Chem.* **1995**, *31*, 508.

(13) Mirarchi, D.; Ritchie, G. L. D. *Aust. J. Chem.* **1981**, *34*, 1443.

(14) Buncel, E.; Manderviller, R. A.; Dust, J. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1019.

(15) Klusmer, P. A. A.; Hanekamp, J. C.; Brandsma, L.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1311.