DOI: 10.1002/ejoc.200701126

Regioselective Generation of Aryllithiums from Substituted Bromobenzenes XC_6H_4Br (X = 4-Br, 4-I, 4-CN, 2-CN)

Sergiusz Luliński,*[a] Janusz Serwatowski,[a] and Magdalena Szczerbińska[a]

Keywords: Lithiation / Arenes / Lithium / Halides / Cyanides

Selected activated bromobenzenes XC_6H_4Br (X = 4-Br, 4-I, 4-CN, 2-CN) were successfully deprotonated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at –80 °C. Thus, 2,5-dibromo-, 2-bromo-5-iodo-, 5-bromo-2-cyano-, and 3-bromo-2-cyanophenyllithium were obtained as stable intermediates and could be converted by subsequent reactions into various functionalized derivatives with good yields. A competition of directing effects of bromine versus iodine and cyano groups is discussed.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

The metalation of bromoarenes is potentially a useful method for the diverse functionalization of these important reagents.[1] However, there are severe limitations for this protocol. Firstly, only lithium dialkylamides can be used to effect deprotonation, as alkyllithiums cause Br–Li exchange. Bromine is a relatively weak *ortho*-directing group and another acidifying substituent is required to allow proton abstraction.[2–4] Once formed, *ortho*-bromoaryllithiums are thermally labile and may release benzynes already at low temperatures (below –70 °C)[5] unless they are stabilized by another strongly electron-withdrawing *ortho* substituent, for example, halogen, CF_3, or OCF_3.[6] Alternatively, bromine migration is driven by the formation of a thermodynamically more-stable isomer, for example, 2,3-dibromophenyllithium initially generated from 1,2-dibromobenzene rearranges into the 2,6-dibromo isomer at –75 °C,[7] which is stable in THF up to ca –40 °C.[8] In this context, it should be noted that the treatment of selected aryl bromides and bromopyridines with the bulky TMP-zincate (tBu$_2$ZnTMP)Li provides *ortho*-metalated derivatives that do not collapse into arynes.[9]

It was reported previously that 1,4-dibromobenzene (**1**) is deprotonated with LTMP at –75 °C, but no further details were given.[7] It is known that 2,5-dibromophenyllithium (**1**-Li) decomposes rapidly under metalation conditions to form a highly reactive aryne, that is, 4-bromo-1,2-dehydrobenzene, which forms substituted biphenyls[10] or anilines[8] depending on the composition of the reaction mixture. However, **1**-Li proved sufficiently stable to be trapped by using an in situ quench technique with the use of LDA/TMSCl in THF at ca –70 °C.[8] Unfortunately, a mixture composed of the starting material, monosilylated and 2,5-disilylated derivatives was obtained, whereas 1,4-bis(trimethylsilyl)-2,5-dibromobenzene forms selectively with a high yield by using an excess amount of base and electrophile. Importantly, the internal quench implies that only selected electrophiles can be employed, which limits the synthetic value of this method.

[a] Warsaw University of Technology, Faculty of Chemistry, Noakowskiego 3, 00-664 Warsaw, Poland

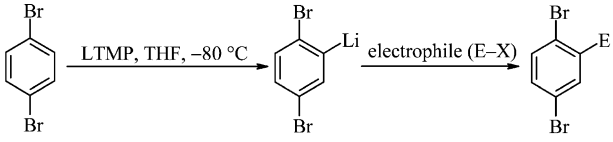
Results and Discussion

We were interested in optimizing the reaction conditions as to allow the selective synthesis of 2,5-dibromophenyllithium (**1**-Li) as an intermediate stable on a macroscopic timescale,[11] that is, for at least several minutes. This time is necessary to perform a subsequent reaction with an external electrophile. It can be prepared readily from 1,2,4-tribromobenzene by using Br–Li exchange in THF at –105 °C, but the reaction suffers from poor selectivity and possible side reactions, which reduce the yields of the desired 2,5-dibromo-substituted benzenes to ca 50%.[12] The attempted deprotonation of **1** with the use of LTMP activated with PMDTA in THF at ca –100 °C failed, but the reaction proceeds effectively over a few minutes at –80 °C. Under these conditions, **1**-Li is stable for at least 1 to 2 h. Typically, slow decomposition manifested by gradual darkening of the reaction mixture starts above –70 °C, and the rapid degradation accompanied with a substantial temperature jump is observed at ca –60 °C. However, in a few experiments we observed this rapid decomposition even at ca –75 °C, so it is advisable not to exceed –80 °C during the lithiation step, as well as during the subsequent addition of the electrophile. Further optimization was performed concerning the choice of metalating agent. In fact, LTMP alone (i.e., without the addition of PMDTA) works equally well, as evidenced by the yields of 2,5-dibromobenzoic acid **1a** obtained from trapping with CO_2 (Table 1). In contrast,

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

LTMP proved better than LDA, as carboxylation followed by acidic hydrolysis afforded 2,5-dibromobenzoic acid in 84 and 68% yields, respectively. The synthetic value of **1**-Li was confirmed, as we synthesized several functionalized 1,4-dibromobenzenes in good yields. The results are summarized in Table 1.

Table 1. Lithiation of 1-bromo-4-iodobenzene: Synthesis of substituted 1,4-dibromobenzenes **1a**–**h**.



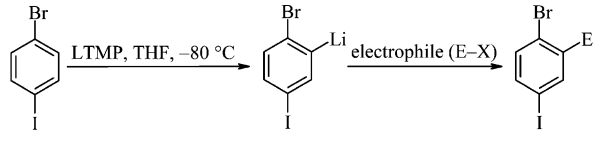
1 **1**-Li **1a–h**

Compound	Electrophile	E	Yield [%]
1a	CO_2	CO_2H	84[a]
1a			82[b]
1a			68[c]
1b	*t*BuNCO	CONH-*t*Bu	68[a]
1c	$(CO_2Me)_2$	$COCO_2Me$	61[a]
1d	2-$MeOC_6H_4CHO$	2-$MeOC_6H_4CH(OH)$	50[a]
1e	Me_3SiCl	Me_3Si	74[a]
1f	Bu_3SnCl	Bu_3Sn	84[a]
1g	$(MeS)_2$	SMe	75[a]
1h	I_2	I	70[a]

[a] Lithiation with LTMP. [b] LTMP–PMDTA. [c] LDA.

We employed the above protocol for the functionalization of 1-bromo-4-iodobenzene (**2**). We showed previously that the in situ metalation/disilylation of **2** with LDA/TMSCl gives a mixture of 2,5- and 2,6-disilylated derivatives in a ratio of 3:1.[13] Such a result suggests that the *ortho*-directing ability of bromine is only slightly stronger than that of iodine. However, when we subjected **2** to the metalation with LTMP/THF at ca –80 °C, followed by electrophilic quench with CO_2 and DMF, we isolated 2-bromo-5-iodobenzoic acid (**2a**) and corresponding benzaldehyde **2b**, respectively, with good yields and free of its regioisomers resulting from lithiation *ortho* to iodine (Table 2). It seems that LTMP as a bulkier base is able to discriminate better between two lithiation sites than LDA does. A similar behavior was reported previously for the lithiation of 1-bromo-4-chlorobenzene, where LTMP deprotonated preferentially at the sterically less-hindered position *ortho* to the chlorine atom, whereas LDA generated a comparable proportion of regioisomeric 2-bromo-5-chlorophenyllithium.[14] The formation of the 2-iodo-5-bromophenyllithium byproduct was proved only in the synthesis of **2c**, as the major product was contaminated with a small amount (ca. 3%) of the regioisomeric 1-bromo-4-iodo-3-(methylthio)-benzene (**2d**). This indicates that the lithiation of **2** is not perfectly regioselective, but the higher instability of *ortho*-iodoaryllithium species with respect to its *ortho*-bromo analogue results in the effective fate of the former intermediate during aging of the reaction mixture. In fact, the attempted lithiation of 1,4-diiodobenzene with LTMP in THF at –80 °C, followed by carboxylation, failed to yield the desired 2,5-diiodobenzoic acid and simultaneously only a small amount of the starting material was recovered. This indicates that the lithiation of 1,4-diiodobenzene occurs quite effectively, but the resultant 2,5-diiodophenyllithium is too labile at –80 °C and decomposes rapidly via the aryne pathway (with elimination of LiI), although it can be trapped even at slightly higher temperature by using an internal TMSCl quench as demonstrated previously.[13]

Table 2. Lithiation of 1-bromo-4-iodobenzene: Synthesis of 2-substituted 1-bromo-4-iodobenzenes **2a**–**c**.



2 **2**-Li **2a–c**

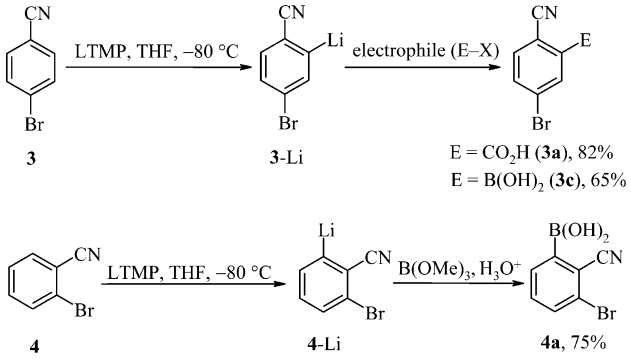
Compound	Electrophile	E	Yield [%]
2a	CO_2	CO_2H	63
2b	Me_2NCHO	CHO	65
2c	$(MeS)_2$	MeS	55[a]

[a] Contaminated with 3% 1-bromo-4-iodo-3-(methylthio)benzene (**2d**).

Despite a significant synthetic potential, the lithiation of bromobenzonitriles has not been extensively investigated. As expected, 3-bromobenzonitrile lithiates at C-2 with LTMP owing to a cooperating acidifying effect of two adjacent substituents to give an intermediate stable at –75 °C.[15] We found previously that the in situ metalation/disilylation of 4-bromobenzonitrile (**3**) with LDA/TMSCl gives 2,5-bis-(trimethylsilyl)-4-bromobenzonitrile, which might reflect comparable *ortho*-directing ability of bromine with respect to the CN group.[13] Similarly, the in situ lithiation/disilylation of 2-bromobenzonitrile (**4**) is also very effective and provides 3,6-bis(trimethylsilyl)-2-bromobenzonitrile with a high yield.[13] Indeed, lithiation of **3** with LDA/THF at –80 °C, followed by carboxylation, afforded a mixture of 5-bromo-2-cyano- (**3a**) and 2-bromo-5-cyanobenzoic acid (**3b**) in a ratio of ca. 2:1 and a total yield of ca. 50%. However, we found that treatment of **3** with LTMP/THF at –80 °C gives selectively 5-bromo-2-cyanophenyllithium (**3**-Li), which was carboxylated to give **3a** in high yield (Scheme 1).[16] This means that the nitrile wins over bromine in its *ortho*-directing ability with LTMP used as a deprotonating agent. In this case, bromine contributes only with a potent long-range *meta*-acidifying effect, which obviously strongly facilitates proton abstraction from the position adjacent to the CN group and increases the stability of resultant **3**-Li.

In addition, we observed that the metalation of **4** with LTMP/THF at –80 °C occurs selectively *ortho* to the CN group to give 3-bromo-2-cyanophenyllithium (**4**-Li). Derivatization of **3**-Li and **4**-Li with $B(OMe)_3$ followed by hydrolysis afforded corresponding boronic acids **3c** and **4a**, respectively, with reasonable yields (Scheme 1). Similar results were obtained recently by using in situ lithiation/boronation of **3** and **4** with LTMP/$B(OiPr)_3$.[17] However, it was reported that the obtained neopentylglycol ester of **3c**

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Regioselective *ortho*-CN lithiation of 4- and 2-bromobenzonitrile.

was contaminated with 10% of the regioisomeric product arising from the lithiation/boronation *ortho* to the bromine atom. Our interpretation of this difference involves a plausible extensive degradation of the lithiation byproduct 2-bromo-5-cyanophenyllithium, which is therefore trapped less effectively with external electrophiles than with major product **3**-Li. Indeed, the yield of **3c** prepared by using our stepwise protocol is lower (65%) than that reported for the in situ quench,[17] where the 90:10 mixture of two boronated 4-bromobenzonitriles was isolated in 98% yield. The synthesis of **3c** is a useful alternative to the Ir-catalyzed borylation of **3**, which produces the synthetically equivalent pinacol ester of **3c**.[18]

Conclusion

The lithiation of four substituted bromobenzenes can be performed with LTMP at –80 °C to provide regioselectively the corresponding bromoaryllithiums as stable intermediates in good yields. Subsequent derivatization provides convenient access to various functionalized bromoarenes, including synthetically valuable arylcarboxylic and arylboronic acids.

Experimental Section

General Comments: All reactions involving air- and moisture-sensitive reagents were carried out under an argon atmosphere. Et_2O and THF were stored over sodium wire before use. Starting bromobenzenes and other important reagents, including *tert*-butylisocyanate, dimethyl oxalate, 2-methoxybenzaldehyde, chlorotrimethylsilane, chlorotributyltin, *N*,*N*-dimethylformamide, dimethyl disulfide, iodine, *n*BuLi (10 M solution in hexanes), 2,2,6,6-tetramethylpiperidine, and trimethyl borate were received from Aldrich. The NMR chemical shifts are given relative to TMS by using known chemical shifts of residual proton (^{1}H) or carbon (^{13}C) solvent resonances. In the ^{1}H and ^{13}C NMR spectra of tin derivative **1f** satellite peaks were observed due to ^{1}H–Sn (^{119}Sn and ^{117}Sn) and ^{13}C–Sn couplings, respectively. In the ^{13}C NMR spectra of arylboronic acids **3b** and **4a**, the resonances of boron-bound carbon atoms were not observed due to their broadening by a quadrupolar boron nucleus. New compounds gave satisfactory elemental analyses except for **4a**, which formed an air-stable hydrate.

2,5-Dibromobenzoic Acid (1a): A solution of **1** (11.8 g, 50 mmol) in THF (50 mL) was added to a stirred solution of LTMP freshly prepared from TMP (7.8 g, 55 mmol) and *n*BuLi (10 M, 5.5 mL, 55 mmol) in THF (70 mL) at –80 °C. After ca. 40 min stirring at ca. –80 °C (internal temperature), a mixture containing lithiate **1**-Li was cooled to ca. –100 °C and saturated with a stream of gaseous CO_2. The mixture was stirred for 30 min at –75 °C and then left to warm to ca. –20 °C, followed by careful hydrolysis with aqueous sulfuric acid (1.5 M, 50 mL). The water phase was separated and extracted with diethyl ether (2 × 50 mL). The combined organic layer was concentrated under reduced pressure. A solid residue was filtered and washed consecutively with water (3 × 50 mL), toluene (2 × 25 mL), and hexane (50 mL). Drying in vacuo afforded the title compound as a white powder. M.p. 157–159 °C (ref.[19] 155–156 °C). Yield: 11.7 g (84%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.93 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.52 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.45 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 165.5, 136.0, 135.5, 134.2, 134.1, 120.9, 120.4 ppm.

2-(*tert*-Butylaminocarbonyl)-1,4-dibromobenzene (1b): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with a solution of *t*BuNCO (5.5 g, 55 mmol) in Et_2O (10 mL) at ca. –80 °C, and the resultant mixture was stirred for ca. 30 min at ca. –75 °C. Further workup was performed as described for **1a**. A crude product was filtered and washed consecutively with water (3 × 50 mL) and hexane (2 × 25 mL). Drying in vacuo afforded the title compound as a white powder. M.p. 120–122 °C. Yield: 11.4 g (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H, Ph), 7.39 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.33 (dd, $J_{H,H}$ = 8.5, 2.0 Hz, 1 H, Ph), 5.81 (br., 1 H, NH), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.3, 140.5, 134.5, 133.6, 132.0, 121.4, 117.7, 52.4, 28.6 ppm. $C_{11}H_{13}Br_2NO$ (335.04): calcd. C 39.43, H 3.91, N 4.18; found C 39.76, H 3.78, N 4.53.

Methyl 2-(2′,5′-Dibromophenyl)-2-oxoacetate (1c): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with a solution of $(CO_2Me)_2$ (6.1 g, 52 mmol) in THF (30 mL) at ca. –85 °C, and the resultant mixture was stirred for ca. 30 min at ca. –75 °C. Further workup was performed as described for **1a**. A crude product was filtered and washed consecutively with water (3 × 50 mL) and hexane (2 × 20 mL) and dried. Recrystallization from CH_2Cl_2/hexane (1:1, 50 mL) at –50 °C afforded the title compound as a pale yellow powder. M.p. 65–66 °C. Yield: 9.8 g (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H, Ph), 7.55 (dd, $J_{H,H}$ = 8.5, 2.0 Hz, 1 H, Ph), 7.49 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 3.96 (s, 3 H, OMe) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 185.5, 162.0, 137.1, 136.8, 135.0, 134.1, 121.8, 120.0, 53.5 ppm. $C_9H_6Br_2O_3$ (321.95): calcd. C 33.58, H 1.88; found C 33.90, H 1.69.

α-(2′-Methoxyphenyl)-2,5-dibromobenzyl Alcohol (1d): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with a solution of 2-methoxybenzaldehyde (7.1 g, 50 mmol) in THF (30 mL) at ca. –80 °C, and the resultant mixture was stirred for ca. 30 min at ca. –75 °C. Further workup was performed as described for **1a**. A crude product was filtered and washed consecutively with water (3 × 50 mL) and hexane (2 × 20 mL) and dried. Recrystallization from toluene/hexane (1:2, 50 mL) afforded the title compound as colorless crystals. M.p. 130–132 °C. Yield: 9.3 g (50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.40 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.32–7.28 (m, 2 H, Ph, Ph′), 6.94–6.89 (m, 3 H, Ph′), 6.33 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, C*H*OH), 3.90 (s, 3 H, OMe), 3.12 (d, $^3J_{H,H}$ = 3.0 Hz,

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

1 H, CHO*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 157.0, 143.5, 133.9, 133.1, 131.9, 131.8, 129.6, 129.3, 127.7, 121.6, 120.7, 110.6, 70.4, 55.5 ppm. $C_{14}H_{12}Br_2O_2$ (372.05): calcd. C 45.20, H 3.25; found C 45.45, H 3.41.

1,4-Dibromo-2-(trimethylsilyl)benzene (1e): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with TMSCl (5.6 g, 52 mmol) at ca. –80 °C, and the resultant mixture was stirred for ca. 30 min at ca. –75 °C. Further workup was performed as described for **1a**. A crude oily product was dissolved in hexane (50 mL), and the resultant solution was washed with water (50 mL), dried with $MgSO_4$, and concentrated. Fractional distillation in vacuo afforded the title compound as a colorless oil. B.p. 73–76 °C (0.5 Torr). Yield: 11.4 g (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.39 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.31 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph), 0.41 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.0, 138.6, 134.3, 133.5, 128.7, 121.4, –0.8 ppm. $C_9H_{12}Br_2Si$ (308.09): calcd. C 35.09, H 3.93; found C 35.18, H 3.99.

1,4-Dibromo-2-(tributylstannyl)benzene (1f): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with Bu_3SnCl (16.3 g, 50 mmol) at ca. –80 °C, and the resultant mixture was stirred for ca. 30 min at ca. –75 °C. Further workup was performed as described for **1e**. Fractional distillation in vacuo afforded the title compound as a colorless oil. B.p. 139–143 °C (0.5 Torr). Yield: 22.0 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.35 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ph), 7.26 (dd, $J_{H,H}$ = 8.0, 2.0 Hz, 1 H, Ph), 1.59–1.53 (m, 6 H, $CH_2CH_2CH_2CH_3$), 1.40–1.31 (m, 6 H, $CH_2CH_2CH_2CH_3$), 1.18 (t, 6 H, $CH_2CH_2CH_2CH_3$), 0.91 (t, $^3J_{H,H}$ = 7.0 Hz, 9 H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 149.8, 140.2, 133.2, 132.7, 131.4, 121.6, 28.9, 27.3, 13.7, 10.9 ppm. $C_{18}H_{30}Br_2Sn$ (524.95): calcd. C 41.18, H 5.76; found C 41.35, H 5.70.

1,4-Dibromo-2-(methylthio)benzene (1g): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with $(MeS)_2$ (4.9 g, 52 mmol at ca. –80 °C, and the resultant mixture was stirred for ca. 30 min at ca. –75 °C. Further workup was performed as described for **1a**. A crude oily product was dissolved in diethyl ether (80 mL), and the resultant solution was washed with water (50 mL), dried with $MgSO_4$, and concentrated. Fractional distillation in vacuo afforded a crude product as a low-melting solid. B.p. 90–95 °C (0.5 Torr). Recrystallization from cold hexane (30 mL, –20 °C) furnished the title compound as colorless crystals. M.p. 62–63 °C (ref.[12] 59–60 °C). Yield: 10.7 g (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.17 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H, Ph), 7.10 (dd, $J_{H,H}$ = 8.5, 2.0 Hz, 1 H, Ph), 2.47 (s, 3 H, SMe) ppm.

1,4-Dibromo-2-iodobenzene (1h): Compound **1**-Li was prepared as described above in the synthesis of **1a**. It was then treated with I_2 (14.0 g, 55 mmol) at ca. –90 °C, and the resultant mixture was stirred for ca. 30 min at ca. –80 °C. Further workup was performed as described for **1a**. A crude oily product was diluted with diethyl ether (80 mL), and the resultant solution was washed with aqueous $Na_2S_2O_3$ (1 M, 30 mL) and water (50 mL), dried with $MgSO_4$, and concentrated. Fractional distillation in vacuo afforded a crude product as yellow oil. B.p. 95–105 °C (0.5 Torr). Recrystallization from cold hexane (30 mL, –50 °C) furnished the title compound as almost colorless crystals. M.p. 38–39 °C (ref.[20] 38–39 °C). Yield: 12.7 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.46 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.32 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph) ppm.

2-Bromo-5-iodobenzoic Acid (2a): This compound was prepared as described for **1a** from 1-bromo-4-iodobenzene **2** (5.7 g, 20 mmol). A crude product was dissolved in aqueous NaOH (1 M, 30 mL), and the resultant solution was filtered and washed with toluene (20 mL) and hexane (20 mL). The product was precipitated with aqueous HCl (1 M, 30 mL), filtered, and washed with water (2 × 20 mL). Drying in vacuo afforded the title compound as a white powder. M.p. 172–174 °C. Yield: 4.1 g (63%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 11.8 (br., 1 H, COOH), 8.15 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.79 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph), 7.51 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 165.7, 142.3, 140.4, 136.8, 135.6, 121.5, 92.4 ppm. $C_7H_4BrIO_2$ (326.91): calcd. C 25.72, H 1.23; found C 26.00, H 1.52.

2-Bromo-5-iodobenzaldehyde (2b): This compound was prepared as described for **2a** by using DMF (2.2 g, 30 mmol) as the electrophile. A crude product was recrystallized from hexane (15 mL) to give the title compound as pale yellow crystals. M.p. 105–107 °C. Yield: 4.05 g (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.22 (s, 1 H, CHO), 8.17 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 7.72 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph), 7.36 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 190.3, 143.8, 138.5, 135.3, 134.6, 126.6, 92.9 ppm. C_7H_4BrIO (310.91): calcd. C 27.04, H 1.30; found C 27.28, H 1.70.

1-Bromo-4-iodo-2-(methylthio)benzene (2c): This compound was prepared from **2** as described for **1g**. A crude product was recrystallized from hexane (15 mL) to give the title compound as colorless crystals. M.p. 47–48 °C. Yield: 3.6 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, ^4J = 2.0 Hz, 1 H, Ph), 7.28 (dd, J = 8.5, 2.0 Hz, 1 H, Ph), 7.20 (d, ^3J = 8.5 Hz, 1 H, Ph), 2.45 (s, 3 H, SMe) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.2, 134.4, 133.9, 133.2, 121.1, 92.9, 15.7 ppm. C_7H_6BrIS (329.00): calcd. C 25.55, H 1.84; found C 25.93, H 1.56. The product was contaminated with 3% of 1-bromo-4-iodo-3-(methylthio)benzene **2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph), 7.13 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 6.96 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph), 2.46 (s, 3 H, SMe) ppm.

5-Bromo-2-cyanobenzoic Acid (3a): This compound was prepared as described for **1a** from 4-bromobenzonitrile **3** (9.1 g, 50 mmol). A crude product was washed with water (2 × 20 mL), toluene (2 × 20 mL) and hexane (20 mL). Drying in vacuo afforded the title compound as a white powder. M.p. 169–171 °C (dec.). Yield: 9.3 g (82%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.30 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ph), 8.02 (dd, $J_{H,H}$ = 8.5, 2.5 Hz, 1 H, Ph), 7.88 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 164.1, 137.3, 136.9, 135.2, 134.9, 127.6, 117.4, 112.7 ppm. $C_8H_4BrNO_2$ (226.03): calcd. C 42.51, H 1.78, N 6.20; found C 42.71, H 2.11, N 6.18.

5-Bromo-2-cyanophenylboronic Acid (3c): This compound was prepared as described for **3a** by using $B(OMe)_3$ (6.3 g, 60 mmol) as the electrophile. A crude product was washed with water (2 × 20 mL), toluene (3 × 20 mL), and hexane (20 mL). Drying in vacuo afforded the title compound as a white powder. M.p. 280–285 °C (dec.). Yield: 7.3 g (65%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.63 [br., $B(OH)_2$], 8.02 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H, Ph), 7.78 (dd, $J_{H,H}$ = 8.5, 2.0 Hz, 1 H, Ph), 7.70 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, Ph) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 138.4, 135.8, 134.1, 127.3, 119.3, 116.1 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 28.0 ppm. $C_7H_5BBrNO_2$ (225.84): calcd. C 37.23, H 2.23, N 6.20; found C 37.42, H 2.49, N 6.16.

3-Bromo-2-cyanophenylboronic Acid Monohydrate (4a·H$_2$O): This compound was prepared as described for **3b** from 2-bromobenzonitrile **4** (3.65 g, 20 mmol). A crude product was washed with water

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(2 × 10 mL), toluene (2 × 10 mL), and hexane (10 mL). Drying in vacuo afforded **4a**·H_2O as colorless crystals. M.p. 264–267 °C (dec.). Yield: 3.7 g (75%). ^{1}H NMR (400 MHz, [D_6]acetone): δ = 7.85–7.81 (m, 2 H, Ph), 7.57 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ph), 3.18 (br., 2 H, H_2O) ppm. ^{13}C NMR (100.6 MHz, [D_6]acetone): δ = 134.7, 133.94, 133.93, 126.6, 119.3, 118.1 ppm. ^{11}B NMR (64.2 MHz, [D_6]acetone): δ = 28.0 ppm. $C_7H_5BBrNO_2$·H_2O (243.85): calcd. C 34.48, H 2.89, N 5.74; found C 35.04, H 3.08, N 5.86.

Acknowledgments

This work was supported by the Warsaw University of Technology and by the Polish Ministry of Science and Higher Education (Grant No. N N205 055633). The support by Aldrich Chemical Co., Milwaukee, WI, U.S.A., through continuous donation of chemicals and equipment is gratefully acknowledged.

[1] M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393, and references therein.
[2] a) A. J. Bridges, A. Lee, E. C. Maduakor, C. E. Schwartz, *Tetrahedron Lett.* **1992**, *33*, 7495–7498; b) A. J. Bridges, A. Lee, E. C. Maduakor, C. E. Schwartz, *Tetrahedron Lett.* **1992**, *33*, 7499–7502.
[3] J. Moyroud, J.-L. Guesnet, B. Bennetau, J. Mortier, *Tetrahedron Lett.* **1994**, *36*, 881–884.
[4] a) C. Heiss, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 447–451; b) M. Marull, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 2771–2777.
[5] a) H. Gilman, R. D. Gorsich, *J. Am. Chem. Soc.* **1956**, *78*, 2217–2222; b) L. S. Chen, G. J. Chen, C. Tamborski, *J. Organomet. Chem.* **1980**, *193*, 283–292; c) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046–3047; d) see also: H. F. Bettinger, M. Filthaus, *J. Org. Chem.* **2007**, *72*, 9750–9752.
[6] a) F. Mongin, O. Desponds, M. Schlosser, *Tetrahedron Lett.* **1996**, *37*, 2767–2770; b) F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1996**, *38*, 6551–6554; c) M. Schlosser, E. Castagnetti, *Eur. J. Org. Chem.* **2001**, 3991–3997.
[7] F. Mongin, E. Marzi, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 2771–2777.
[8] S. Luliński, J. Serwatowski, *J. Org. Chem.* **2003**, *68*, 5384–5387.
[9] a) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515; b) T. Imahori, M. Uchiyama, T. Sakamoto, Y. Kondo, *Chem. Commun.* **2001**, 2450–2451.
[10] F. Leroux, M. Schlosser, *Angew. Chem. Int. Ed.* **2002**, *41*, 4272–4274.
[11] J. P. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, **2002**, p. 174.
[12] S. Luliński, J. Serwatowski, A. Zaczek, *Eur. J. Org. Chem.* **2006**, 5167–5173.
[13] S. Luliński, J. Serwatowski, *J. Org. Chem.* **2003**, *68*, 9384–9388.
[14] F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1997**, *38*, 1559–1562.
[15] K. Mendel, E. L. Fisher, L. DiMichele, D. E. Frantz, T. D. Nelson, M. H. Kress, *J. Org. Chem.* **2006**, *71*, 2188–2191.
[16] A similar regioselective zincation of **3** was mentioned, but no details were provided. See: T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082–8083.
[17] M. Lysén, H. M. Hansen, M. Begtrup, J. L. Kristensen, *J. Org. Chem.* **2006**, *71*, 2518–2520.
[18] G. A. Chotana, M. A. Rak, M. R. Smith, *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544.
[19] W. E. Parham, R. M. Piccirilli, *J. Org. Chem.* **1977**, *42*, 257–260.
[20] P. Karastatiris, J. A. Mikroyannidis, I. K. Spiliopoulos, A. P. Kulkarni, S. A. Jenekhe, *Macromolecules* **2004**, *37*, 7867–7878.

Received: November 28, 2007
Published Online: February 13, 2008

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim