Regioselective Halogen–Metal Exchange Reaction of 3-Substituted 1,2-Dibromo Arenes: The Synthesis of 2-Substituted 5-Bromobenzoic Acids

Karsten Menzel,*[a] Lisa Dimichele,[b] Paul Mills,[a] Doug E. Frantz,[a,1] Todd D. Nelson,[a] Michael H. Kress[a]

[a] Merck Research Laboratories, Department of Process Research, 466 Devon Park Drive, Wayne, Pennsylvania 19087, USA

[b] Merck Research Laboratories, Department of Process Research, 126 Lincoln Avenue, Rahway, New Jersey 07065, USA
Fax +1(215)9932100; E-mail: karsten_menzel@merck.com

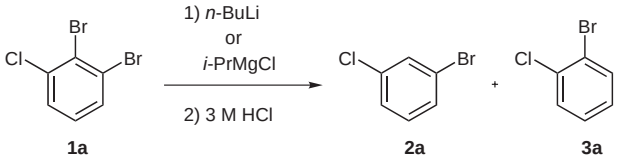
Received 23 March 2006

Abstract: Regioselective halogen–metal exchange reactions using isopropylmagnesium chloride were carried out on 3-substituted 1,2-dibromo arenes. Eleven examples are given.

Key words: 1,2-dibromobenzene, Grignard reactions, substitutent effect, regioselectivity, carboxylic acids

A common strategy in organic synthesis is the functionalization of polyhalogenated arenes. Primarily, iodo-bromo arenes are used in the regioselective functionalization. In recent years, increasing efforts have been made to investigate the regioselective functionalization of diiodo- or dibromo arenes.[2–5] In 1,4- and 1,3-dibromo arenes, a regioselective halogen–metal exchange reaction using butyllithium is well documented.[6,7] Interestingly, there are only a few examples of the regioselective halogen–metal exchange on 1,2-dibromo arenes.[8,9] This lack of precedence may be attributed to the accessibility and availability of 1,2-dibromo arenes.[10] Additionally, vicinal bromo-lithio arenes in general tend to decompose via a well known benzyne pathway even at low temperatures.[11] In contrast, using isopropylmagnesium chloride for the halogen–metal exchange of 1,2-dibromo arenes has several advantages: (a) higher thermodynamic stability of the resulting arylmagnesium intermediate; (b) prevention of benzyne pathways at low temperatures and (c) generation of highly functionalized arylmagnesium compounds.[12]

In general, the regioselective functionalization of the 2-position in 3- or 3,5-substituted bromobenzene derivatives afforded mixtures of 1,3,4- and 1,2,3- or 1,2,3,4- and 1,3,4,5-bromobenzene derivatives, respectively. We envisioned that 3-substituted 1,2-dibromobenzene derivatives could be regioselective functionalized in a halogen–metal exchange reaction. In order to test our hypothesis 1,2-dibromo-3-chlorobenzene (**1a**) was treated with butyllithium at –78 °C in tetrahydrofuran or diethyl ether (Scheme 1).[6] The halogen–metal exchange occurred exclusively at the 2-position (entries 1 and 2, Table 1).[13] However, 3-bromo-1-chlorobenzene (**2a**) was formed only in 75% and 67%, respectively,[14] as determined by HPLC versus a standard prepared from commercially available authenic material. When reacting isopropylmagnesium chloride with 1,2-dibromo-3-chlorobenzene (**1a**) at –40 °C, 1-bromo-3-chlorobenzene (**2a**) and 1-bromo-2-chlorobenzene (**3a**) were afforded in 93% and 5% yields, respectively (entry 3). The high regioselectivity in the halogen–metal exchange, the high yield of **2a** and the thermodynamic stability of the arylmagnesium intermediate encouraged us to study the reaction conditions using isopropylmagnesium chloride in more detail.



Scheme 1 Study of reaction conditions for the regioselective halogen–metal exchange on 1,2-dibromo-3-chlorobenzene (**1a**)

A similar regioselectivity between **2a** and **3a** and a lower yield of **2a** were observed if the reaction was carried out at –78 °C (entry 4). Both yield of **2a** (71%) and regioselectivity (90:10) decreased when the halogen–metal exchange was performed at room temperature (entry 5). When the reaction mixture was kept at room temperature for 24 hours, the ratio worsened to 81:19 and a significant decrease in the yield of **2a** was observed (18%, entry 6).[15] It has been reported that the halogen–metal exchange of aryl bromide using isopropylmagnesium chloride is faster in the presence of lithium chloride, which was attributed to the formation of a reactive complex between isopropylmagnesium chloride and lithium chloride.[9] When this complex was applied on **1a** a slight decrease in regioselectivity to 88:12 and yield (79%) for **2a** was observed (entry 7).[16]

The selectivity and reactivity in reactions using Grignard reagents are being affected by the solvent or additives.[17] In order to evaluate the solvent effect on the regioselectivity the halogen–metal exchange on 1,2-dibromo-3-chlorobenzene (**1a**) was performed in toluene (entry 8) and *tert*-butyl methyl ether (entry 9).[18] In both experiments the regioselectivity of **2a** versus **3a** increased slightly to 97:3 and 98:2, respectively, while the yields decreased. Other additives [TMEDA, potassium methoxide, lithium *tert*-butoxide, 1,4-dioxane, 18-crown-6, (1*S*,2*R*)-(–)-2-(dibutylamino)-1-phenyl-1-propanol], which are known in the literature for coordinating Grignard reagents and accelerating the halogen–metal exchange, showed almost

SYNLETT 2006, No. 12, pp 1948–1952
Advanced online publication: 24.07.2006
DOI: 10.1055/s-2006-947362; Art ID: S04006ST

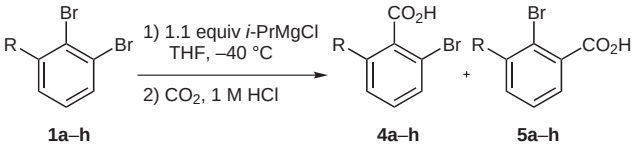
Table 1 Conditions for the Regioselective Halogen–Metal Exchange of 1,2-Dibromo-3-chlorobenzene (**1a**)

Entry	Conditions	Yield of **1a** (%)[d]	Yield of **2a** (%)[a]	Ratio **2a**:**3a**
1	BuLi, –78 °C, THF–hexane	0	75	>99:1[c]
2	BuLi, –78 °C, Et_2O–hexane	<1	67	>99:1[c]
3	*i*-PrMgCl, –40 °C THF	0	93	95:5
4	*i*-PrMgCl, –78 °C, THF	23	73	96:4
5	*i*-PrMgCl, 22 °C, THF	0	71[b]	90:10
6	*i*-PrMgCl, age for 19 h at 22 °C, THF	0	18[b]	81:19
7	*i*-PrMgCl·LiCl, –40 °C, THF	0	79	88:12
8	*i*-PrMgCl, –40 °C, toluene	2	90	97:3
9	*i*-PrMgCl, –40 °C, *tert*-butyl methyl ether	16	82	98:2

[a] Yields were determined by HPLC analysis vs. a standard prepared from commercially available authentic material.
[b] Chlorobenzene and polyhalogenated biphenyl compounds were identified by GC-MS as major side products.
[c] Minor regioisomer **3a** was not observable.
[d] Recovered starting material.

no effect on the regioselectivity (between 92:8 and 95:5). High product yield, good regioisomeric ratio, wide functional group tolerance and the commercial availability of isopropylmagnesium chloride in tetrahydrofuran encouraged us to apply the reaction conditions reported under entry 3 (Table 1) to different substrates.

A variety of 3-substituted 1,2-dibromobenzene derivatives were prepared following literature procedures.[10,24,25] Generally, all substrates (Table 2) underwent a highly regioselective halogen–metal exchange reaction. The halogen–metal exchange on 3-halo-1,2-dibromobenzenes (**1a**–**c**) occurred predominantly in the 2-position and gave benzoic acids (**4a**–**c**) after CO_2 addition to the arylmagnesium species in good isolated yields (62–84%). The decrease in regioselectivity from fluoride (**1b**) to bromide (**1c**) as shown in Table 2, could be explained with an increase in van der Waals radius and a decrease in electronegativity of the substituent in the 3-position.[19,20]



Scheme 2 Regioselectivity in the halogen–metal exchange reaction of 3-substituted 1,2-dibromo arenes

Similar regioselectivities of 94:6 and 92:8 were observed when 3-trifluoromethyl- (**1d**), 3-cyano- (**1e**)[22] and 3-methylcarboxyl-1,2-dibromobenzene (**1f**) were reacted with isopropylmagnesium chloride. When the magnesiated 2-bromo-5-cyanobenzene was quenched with CO_2, 4-bromo-2-benzofuran-1,3-dione[23] was isolated in 75% yield. Additionally, the halogen–metal exchange with isopropylmagnesium chloride can be carried out on the comparable more electron-rich 1,2-dibromo-3-methoxybenzene (**1g**),[24] affording the corresponding benzoic acid **4g** in 75% yield. The high regioselectivity for the halogen–metal exchange on the electron-rich 1,2-dibromoarene (**1g**) may be consistent with a coordination between the oxygen lone pair electrons and the Grignard reagent, directing the isopropylmagnesium chloride to the 2-position and affording **4g** after CO_2 addition. Interestingly, if 1,2-dibromo-3-methylbenzene (**1h**)[25] was subjected to reaction with isopropylmagnesium chloride, the bromide in the 1-position was exclusively exchanged (entry 8, Table 2). This result led to the assumption that a sterically hindered electron-donating group, like methyl, without coordinating abilities, hinders the attack of the reagent at the 2-position.[26]

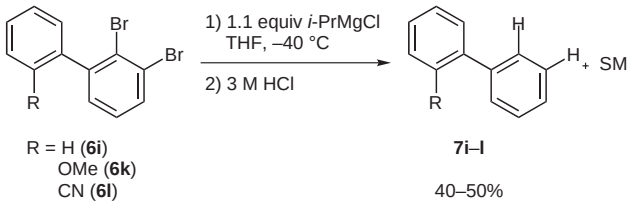
Table 2 Regioselective Halogen–Metal Exchange on a Variety of Substrates

Entry	Compound	R	Ratio **4**:**5**	Yield (%)[a]
1	**1a**	Cl	95:5	62[b]
2	**1b**	F	99:1	84
3	**1c**	Br	90:10	73
4	**1d**	CF_3	94:6	89
5	**1e**	CN	94:6	75[b,c]
6	**1f**	CO_2Me	92:8	54[d]
7	**1g**	OMe	90:10	75
8	**1h**	Me	1:99	85[e,f]

[a] Isolated yield of **4**.
[b] 1.4 Equiv of *i*-PrMgCl were used in order to drive the reaction to completion.
[c] Isolated yield of 4-bromo-2-benzofuran-1,3-dione.
[d] 15% Recovered starting material.
[e] Isolated yield of 2-bromotoluene.
[f] 7 Equiv of *i*-PrMgCl were used in order to drive the reaction to completion.[21]

The unambiguous assignments of the major regioisomers formed in the halogen–metal exchange was achieved by converting the arylmagnesium intermediates generated from **1a**–**h** into the benzoic acids **4a**–**h** and **5a**–**h**,[27] respectively, by the addition of CO_2 as depicted in Scheme 2. The advantage of the benzoic acid was the simple purification and the opportunity to analyze the products by a variety of NMR experiments.[28]

The halogen–metal exchange carried out on 2,3-dibromobiphenyl (**6i**),[29] 2,3-dibromo-2′-methoxy-biphenyl (**6k**)[30] and 2′,3′-dibromo-biphenyl-2-carbonitrile (**6l**)[31] led to a mixture of debrominated products (**7i**–**l**) and starting materials (**6k**–**l**, Scheme 3). This is most likely due to an intramolecular proton abstraction from the neighboring phenyl ring.



Scheme 3 Halogen–metal exchange on biphenyl derivatives resulted primarily in overall reduction

In summary, we have shown that 3-substituted 1,2-dibromo arenes undergo an isopropylmagnesium chloride-mediated regioselective halogen–metal exchange. When the 3-substituent was either electron-withdrawing and/or possessed lone pair electrons that enabled chelation of isopropylmagnesium chloride, a high bias (between 90:10 and 99:1) for the halogen–metal exchange adjacent to the 3-substituents resulted. This method was used to prepare 1-substituted-5-bromobenzoic acids in 62–89% isolated yields.

General Procedure for the Halogen–Metal Exchange Reaction: 2-Bromo-6-fluorobenzoic Acid (4b)

In a Schlenk flask, 0.60 g (2.35 mmol) of 1,2-dibromo-3-fluorobenzene were dissolved in 5 mL of THF under nitrogen. The reaction mixture was cooled to –40 °C and charged slowly with 1.30 mL (2.58 mmol, 1.98 M) of *i*-PrMgCl in THF. The reaction mixture was aged for 2 h at –40 °C before a slow stream of CO_2 was passed through the reaction mixture for 1 h at –40 °C. The organic stream was added to 10 mL of 1 M NaOH and the organic layer was extracted two times with a total of 20 mL of 1 M NaOH. The combined aqueous layer was acidified using 3 M HCl and extracted three times with a total amount of 30 mL EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The white residue was purified by flash column chromatography (EtOAc–hexane, 10:1) affording 0.43 g (84%) of a white solid. ^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.19–7.23 (m, 1 H), 7.37 (td, *J* = 8.2, 6.0 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, MeOH-d_4): δ = 116.1 (d, *J* = 22.5 Hz, 1 C), 120.5 (d, *J* = 7.5 Hz, 1 C), 127.2 (d, *J* = 22.5 Hz, 1 C), 129.9, 133,2 (d, *J* = 7.5 Hz, 1 C), 160.5 (d, *J* = 247 Hz, 1 C), 167.0. ^{19}F NMR (282 MHz, MeOH-d_4): δ = –115.

2-Bromo-6-chlorobenzoic Acid (4a)

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.30 (t, *J* = 8.1 Hz, 1 H), 7.47 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, MeOH-d_4): δ = 120.1, 129.6, 132.1, 132.4 (2 C), 138,2, 168.6.

2,6-Dibromobenzoic Acid (4c)

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.22 (t, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (75 MHz, MeOH-d_4): δ = 119.9, 132.6 (2 C), 132.9 (2 C), 140.1, 169.2.

2-Bromo-6-trifluoromethylbenzoic Acid (4d)

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.51 (td, *J* = 8.0, 0.6 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 1 H), 7.92 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR (75 MHZ, MeOH-d_4): δ = 121.1, 122.5, 125.9-126.9 (m, 1 C), 129.6 (q, *J* = 30 Hz, 1 C), 132.0, 136.5, 137.8, 168.9. ^{19}F NMR (282 MHz, MeOH-d_4): δ = –61.9.

2-Bromo-6-methoxybenzoic acid (4f)

^{1}H NMR (300 MHz, MeOH-d_4): δ = 3.85 (s, 3 H), 7.05 (t, *J* = 8.1 Hz, 1 H), 7.18 (dd, *J* = 8.0, 0.5 Hz, 1 H), 7.28 (t, *J* = 8.2 Hz, 1 H). ^{13}C NMR (75 MHz, MeOH-d_4): δ = 56.8, 111.5, 119.8, 125.5, 128.4, 132.4, 158,4, 169.8.

2-Bromo-6-methylbenzoic Acid (5g)

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.40–7.48 (m, 2 H), 7.27–7.32 (m, 1 H), 2.45 (s, 3 H). ^{13}C NMR (75 MHz, MeOH-d_4): δ = 23.9, 123.3, 128.2, 128.7, 134.0, 136.6, 140.8, 170.8.

References and Notes

(1) New address: Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9038, USA.
(2) Cross-coupling reactions of 1,4-dibromobenzene derivatives: Dirk, S. M.; Proce, D. W.; Chanteau, S.; Kosynki, D. V.; Tour, J. M. *Tetrahedron* **2001**, *57*, 5109.
(3) Cross-coupling reactions of 1,3-dibromobenzene derivatives: Allen, D. W.; Nowell, I. W.; March, L. A.; Taylor, B. F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2523.
(4) Cross-coupling reactions of 1,2-dibromobenzene derivatives: (a) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453. (b) Staab, H. A.; Hone, M.; Krieger, C. *Tetrahedron Lett.* **1988**, *29*, 1905. (c) Cheng, X.; Hou, G.-H.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2004**, *6*, 2381. (d) 1,2-Dibromofuran derivative: Stock, C.; Hofer, F.; Bach, T. *Synlett* **2005**, 511.
(5) For a general review on site selective transition-metal-catalyzed reactions of polyhalogenated heteroaromatic ring systems, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
(6) Halogen–metal exchange of 1,4-dibromobenzene derivatives using alkyllithium: (a) Dabrowski, M.; Kubicka, J.; Lulinski, S.; Serwatowski, J. *Tetrahedron* **2005**, *61*, 6590. (b) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257. (c) Voss, G.; Gerlach, H. *Chem. Ber.* **1989**, *122*, 1199. (d) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *49*, 2327.
(7) Halogen–metal exchange of 1,3-dibromobenzene derivatives using alkyllithium: (a) Sunthankar, S. V.; Gilman, H. *J. Org. Chem.* **1951**, *16*, 8. (b) Barluenga, J.; Montserrat, J. M.; Florez, J. *J. Org. Chem.* **1993**, *58*, 5976. (c) Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703. (d) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097.

(8) Halogen–metal exchange of 1,2-dibromobenzene derivatives using alkyllithium: (a) Piette, J. L.; Renson, L. *Bull. Soc. Chim. Belg.* **1970**, *79*, 353. (b) Hardcastle, I. R.; Hunter, R. F.; Quayle, P. *Tetrahedron Lett.* **1994**, *35*, 3805. (c) Schlosser, M.; Heiss, C. *Eur. J. Org. Chem.* **2003**, 447. (d) Halogen–metal exchange of 1,2,3-trichlorobenzene using alkyllithium: Haiduc, I.; Gilman, H. *J. Organomet. Chem.* **1968**, *13*, P4.

(9) Halogen–metal exchange of 1,2-dibromo-benzene derivatives using isopropylmagnesium chloride: (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (b) Cottet, F.; Castagnetti, E.; Schlosser, M. *Synthesis* **2005**, 798. (c) Van der Winkel, Y.; Akkerman, O. S.; Bickelhaupt, F. *Main Group Met. Chem.* **1988**, *11*, 91.

(10) For the preparation of 3-substituted 1,2-dibromo arene derivatives, see: Menzel, K.; Fisher, E. L.; DiMichele, L.; Frantz, D. E.; Nelson, T. D.; Kress, M. H. *J. Org. Chem.* **2006**, *71*, 2188.

(11) (a) Dabrowski, M.; Kubicka, J.; Lulinski, S.; Serwatowski, J. *Tetrahedron* **2005**, *61*, 4175. (b) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, **1967**. (c) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 2045. (d) Wenwei, L.; Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4258.

(12) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

(13) Authentic samples of 3-bromo-1-chlorobenzene (**2a**) and 2-bromo-1-chlorobenzene (**3a**) are commercially available from Aldrich. Both **2a** and **3a** can be followed by HPLC and are baseline-separated signals with different retention times. Therefore the regioisomeric distribution of **2a** and **3a** could be analyzed by integration of the corresponding signal areas.

(14) Major by-products of the halogen–metal exchange reaction were debrominated chlorobenzene derivatives and polyhalogenated biphenyls. The debrominated chloro arene may be indicative of a benzyne side reaction.

(15) The decomposition was accompanied by copious amounts of chlorobenzene and biphenyl derivatives, which can be generated by a dehydrobenzene pathway.

(16) Significant amounts of debrominated arenes and biphenyl derivatives had been identified by GC-MS. The impurity profiles of theses reaction conditions and using *n*-BuLi were similar.

(17) Reetz, M. T.; Harmat, N.; Mahrwald, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 342.

(18) It is well known that in THF the Grignard reagents tend to form solvent-separated aggregates. In less-coordinating solvents, like methyl-*tert*-butyl ether or toluene, the Grignard reagents favor the formation of halogen-bridged dimers. For reference, see: Parris, G. E.; Ashby, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 106.

(19) Van der Waals radius: fluoride (135 pm), chloride (175 pm), bromide (185 pm): Iikubo, T.; Itoh, T.; Hirai, K.; Takahashi, Y.; Kawano, M.; Ohashi, Y.; Tomioka, H. *Eur. J. Org. Chem.* **2004**, 3004.

(20) Similar conclusions were drawn for the regioselective deprotonation reaction of haloarenes using LDA or LiTMP: (a) Gorecka, J.; Heiss, C.; Scopelliti, R.; Schlosser, M. *Org. Lett.* **2004**, *6*, 4591. (b) Pozharskii, A. F.; Ryabtsova, O. V.; Ozeryanskii, V. A.; Degtyarev, A. V.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. *J. Org. Chem.* **2003**, *68*, 10109. (c) Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1576. (d) Mongin, F.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2771.

(21) An acceleration of exchange reaction using excess of Grignard reagents: Hoffmann, R. W.; Holzer, B.; Knopff, O.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3072.

(22) The ratio of 94:6 corresponds to the protonated products of A and B. The regioselectivity was confirmed by commercially available samples of 2- and 3-bromo-benzonitrile.

(23) Chou, T.; Chen, S.; Chen, Y. *Tetrahedron* **2003**, *59*, 9939.

(24) (a) 1,2-dibromo-3-methoxybenzene (**1g**) was prepared following a modified procedure of: Shnur, R. C.; Morvilee, M. *J. Med. Chem.* **1986**, *29*, 770. (b) **Preparation of 1,2-Dibromo-3-methoxybenzene (1g).**
In a round-bottom flask, 1.12 mL (4.09 mmol) of a 25% w/w solution of MeONa in MeOH was added to a solution of 2,3-dibromo-1-fluorobenzene (500 mg, 1.97 mmol) in MeOH (6 mL) and DMSO (10.5 mL) under nitrogen. The solution was heated to reflux for 2 h and then allowed to cool to 25 °C before being transferred into H_2O (20 mL). The stream was extracted three times with a total volume of 60 mL *tert*-butyl methyl ether. The combined organic layers were washed with H_2O (2 × 15 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The remaining residue was purified by flash column chromatography (3% EtOAc in hexane) affording 430 mg (60%) of a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.14 (t, *J* = 8.1 Hz, 1 H), 6.83 (dd, *J* = 8.2, 1.3 Hz, 1 H), 3.90 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 128.8, 126.3, 125.6, 114.9, 110.3, 56.6.

(25) **Preparation of 1,2-Dibromo-3-methylbenzene (1h).**
In a Schlenk flask, a BuLi solution in hexane (1.44 M, 14.7 mL, 21.2 mmol) was diluted with THF (22 mL) under nitrogen. The solution was cooled to –50 °C before 2,2,6,6-tetramethylpiperidine (3.0 g, 21.2 mmol) of was added dropwise. After 15 min the reaction mixture was cooled to –100 °C and then charged with 1,2-dibromobenzene (2.5 g, 10.6 mmol). The reaction mixture was aged for 2 h at –100 °C before 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (4.90 g, 26.3 mmol) was added. After 30 min at –100 °C the reaction mixture was allowed to warm to 15 °C before brine (20 mL) was added to the reaction mixture. The organic layer was separated and the aqueous phase was extracted two times with a total amount of 20 mL of *tert*-butyl methyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The remaining solid (3.0 g) was diluted in 5% *tert*-butyl methyl ether in hexane and purified by flash column chromatography affording 1.3 g (34%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 12 H), 7.14 (t, *J* = 7.62 Hz, 1 H), 7.48 (dd, *J* = 7. 30, 1.52 Hz, 1 H), 7.66 (dd, *J* = 7.97, 1.60 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 84.6, 126.0, 127.8, 129.3, 134.4, 135.5 (C–B not seen).
In a Schlenk flask, 2-(2,3-dibromophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (3.0 g, 8.3 mmol) was dissolved in toluene (80 mL), EtOH (8 mL) and 2 M aq K_2CO_3 solution (8 mL) under nitrogen. The biphasic reaction mixture was charged with MeI (1.42 g, 10.0 mmol) followed by tetrakis (triphenylphosphine)palladium (350 mg, 0.30 mmol). The reaction mixture was heated to 80 °C for 18 h and then cooled down to 0 °C in an ice bath The reaction mixture was charged carefully with a 1 M aq HCl solution (20 mL). The organic layer was separated and the aqueous phase was extracted two times with a total amount of 30 mL of *tert*-butyl methyl ether. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuum. The liquid residue was purified by flash column chromatography (1% *tert*-butyl methyl ether in hexane) affording 1.7 g (82%) of a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s,

3 H), 7.06–7.11 (m, 1 H), 7.18–7.20 (m, 1 H), 7.45–7.48 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 125.6, 127.1, 128.0, 129.3, 131.2, 140.8.

(26) 1,2-Dibromo-3-methylbenzene underwent the halogen–metal exchange with complete consumption in the presence of 7 equiv of isopropylmagnesium chloride. If 1.1 equiv are used, only a 50% conversion is observed at –25 °C after 24 h.

(27) The ratio between benzoic acid **4** and **5** in general was determined by a combination of LC-MS and ^{1}H NMR.

(28) The regioselective assignments were done by proton–carbon coupling constants along the aromatic ring structure which are different for the regioisomeric structure of **4** and **5**, see: Dimichele, L.; Menzel, K.; Mills, P.; Frantz, D. E.; Nelson, T. D. *Magn. Reson. Chem.* **2006**, *44*, submitted.

(29) Biphenyl **6i** was prepared following the experimental procedure described in ref. 25 by using iodobenzene in the cross coupling reaction: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.25 (m, 2 H), 7.34–7.37 (m, 2 H), 7.39–7.44 (m, 3 H), 7.65 (dd, *J* = 6.29, 3.29 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.4, 126.3, 128.0, 128.1 (2 C), 128.2, 129.2 (2 C), 129.8, 132.8, 141.8, 145.5.

(30) Biphenyl **6k** was prepared following the experimental procedure described in ref. 25 by using 2-iodoanisole in the cross coupling reaction: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.64 (m, 1 H), 7.40 (ddd, *J* = 8.00, 6.39, 5.11 Hz, 1 H), 7.18–7.23 (m, 2 H), 7.14 (dd, *J* = 7.42, 1.78 Hz, 1 H), 7.03 (td, *J* = 7.40, 1.04 Hz, 1 H), 6.99 (d, *J* = 10.11 Hz, 1 H), 3.79 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 142.5, 132.5, 130.8, 130.4, 130.0, 129.6, 127.9, 126.7, 125.6, 120.3, 110.9, 55.5. GC-MS: *m*/*z* = 342, 261, 246, 182, 152, 139.

(31) Biphenyl **6l** was prepared following the experimental procedure described in ref. 25 by using 2-iodo-1-cyano-benzene in the cross coupling reaction: ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.27–7.35 (m, 2 H), 7.40 (dd, *J* = 7.73, 0.80 Hz, 1 H), 7.53 (dt, *J* = 1,20, 7.63 Hz, 1 H), 7.68 (dt, *J* = 1.28, 7.67 Hz, 1 H), 7.74–7.79 (m, 2 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 125.4, 126.3, 128.0, 128.1 (2 C), 128.2, 129.2 (2 C), 129.8, 132.8, 141.8, 145.5.