Palladium-Catalyzed Multiple Aryl Aminations of Polybromobenzenes

Bernhard Witulski,* Stefan Senft, Andreas Thum
Fachbereich Chemie, Universität Kaiserslautern, Erwin Schrödinger Straße, D-67663 Kaiserslautern, Germany
Fax: +49 (0)631 205 3921; Bernhard@chemie.uni-kl.de

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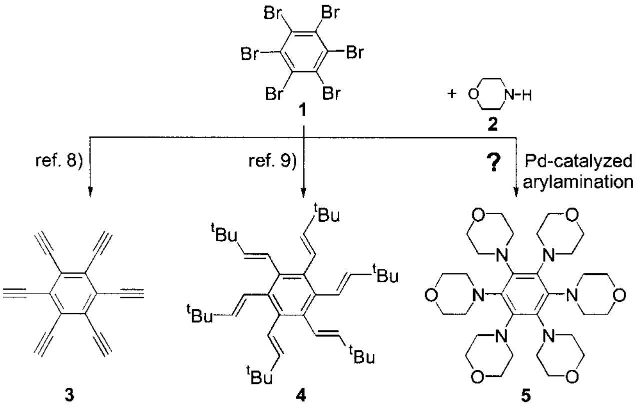
Abstract: Morpholinobenzenes with up to four *N*-morpholino groups have been synthesized efficiently from the corresponding bromobenzenes *via* palladium catalyzed multiple aryl amination reactions. Surprisingly, hexabromobenzene (**1**) yielded selectively 1,2,4,5-(*N*,*N*,*N*,*N*)-tetra-(**23**) and 1,3,5-(*N*,*N*,*N*)-trimorpholinobenzene (**14**).

Benzenes having two and more amino substituents have received considerable interest due to their strong electron donor character, their easy oxidation to the mono-, di-, or even higher cations,[1] and their capability to form crystalline charge transfer complexes and radical salts with suitable electron acceptor molecules.[2] Whereas 1,3,5-*N*,*N*,*N*-(dialkyl)-substituted aminobenzenes have served as model systems for the understanding of the electrophilic aromatic substitution,[3] aminobenzenes with C_3 or higher symmetry have gained interest in the quest for the benzene dication and for organic ferromagnetic compounds.[4] However, the access to oligoaminobenzenes is often limited by multistep syntheses, forcing reaction conditions, and/or the scope of the available methods.[1-5]

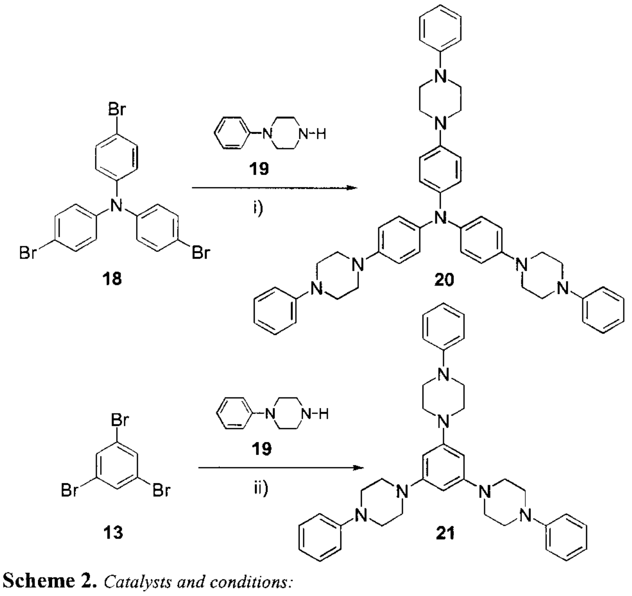
A direct approach to this class of electron-rich aminobenzenes can be imagined in the palladium mediated multiple coupling of primary or secondary amines to readily available polybromobenzenes. Inter- and intramolecular palladium catalyzed aryl aminations of numerous bromobenzenes with primary and secondary amines have been studied by the groups of Buchwald and Hartwig in detail.[6] However, the efficiency of multiple aryl aminations,[7] which would transform more or less electron-poor benzenes into extremely electron-rich ones, and the compatibility of the palladium mediated catalytic cycle with such easily oxidizable aminobenzenes have not been investigated yet.

From the background of already achieved palladium catalyzed sixfold alkynylations[8] and alkenylations[9] of hexabromobenzene (**1**) yielding **3** and the sterically encumbered benzene **4**, respectively, we investigated the palladium catalyzed multiple amination reactions of morpholine (**2**) with various polybromobenzenes, asking whether the sixfold coupling of **2** with **1** could lead to the hexaaminated product **5** (Scheme 1).



Scheme 1

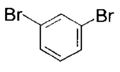
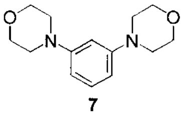
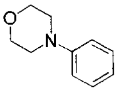
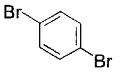
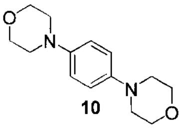
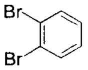
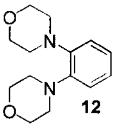
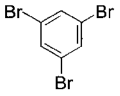
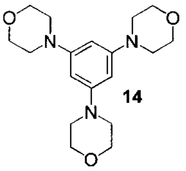
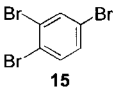
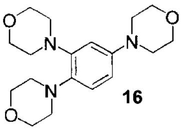
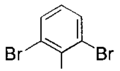
Products, yields, and reaction conditions of the two- and threefold coupling reactions of **2** with 1,3-di- (**6**), 1,4-di- (**9**) and 1,2-dibromobenzene (**11**), as well as with 1,3,5-tri- (**13**), 1,2,4-tri- (**15**) and 1,2,3-tribromobenzene (**17**) are summarized in Table 1: With the exception of the 1,4-dibromobenzene-(**9**) case - where significant higher yields of the double aminated product **10** were obtained with P(*o*-tolyl)$_3$ as ligand - catalysts based on the bidentate ligands BINAP, or DPPF turned out to be consistently more efficient. Particularly, the bidentate ligands BINAP and DPPF were essential for aryl aminations at two adjacent positions (see entries 3 and 5, Table 1).[11] Major by-products, that were formed *via* a β-hydride elimination from reactive palladium-amido intermediates yielding the hydrogenolysis of the aryl bromide, were either *N*-morpholinobenzene (**8**) in the case of twofold aryl aminations, or 1,3-(*N*,*N*)-bismorpholinobenzene (**7**) in the case of **13** and **15**, respectively. The coupling of **2** with three adjacent positions could not be achieved under the conditions employed. Interestingly, 1,2,3-tribromobenzene (**17**) yielded selectively 1,3-(*N*,*N*)-bismorpholinobenzene (**7**). Its isomer **12** could not be found in the reaction mixture.



Scheme 2. *Catalysts and conditions:*
i) Pd(dba)$_2$ (2 mol%), P(*o*-tolyl)$_3$ (4 mol%), 3.6 eq. **19**, 4.2 eq. NaO^{t}Bu, toluene, 100 °C, 2 d, (60%); ii) Pd$_2$(dba)$_3$ (1 mol%), BINAP (3 mol%), 3.6 eq. **19**, 4.2 eq. NaO^{t}Bu, toluene, 100 °C, 1 d, (98%)

The difference in reactivity between multifold couplings in 1,4- and 1,3-position seemed to be due to the enhanced electron donating effect of a para amino substituent causing an increase in the rates of β-hydride eliminations, and such electronic effects appear to be less favorable for catalyst systems based on bidentate ligands. This result was underlined by the reactions of *N*-phenylpiperazidine (**19**) with *tris*(4-bromophenyl)amine (**18**)[12] and **13** (Scheme 2).[11] Once more P(*o*-tolyl)$_3$ was the more efficient ligand for coupling reactions resulting in products having a 1,4-bis-aminobenzene moiety. Whereas product **20** was isolated in 60% yield with P(*o*-tolyl)$_3$ as ligand, complex mixtures of aryl amination and reduction products were obtained with BINAP as ligand. In contrast the latter gave best results for the threefold coupling of **19** with **13**. The efficiency of this protocol leading to **21** (98% yield)[13] might have potential for the synthesis of higher generation

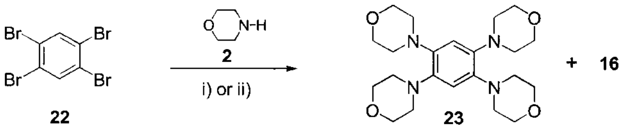
Table 1. Palladium catalyzed multifold aminations of di- and tribromobenzenes with morpholine (**2**) [a, 10]

Entry	Arylbromide	Time [d]	Product(s)	Ligand	Yield [%][b)]
1	 **6**	1	 **7** +  **8**	P(*o*-tolyl)$_3$[c)] BINAP[d)]	**7** [83], **8** [<5] **7** [98]
2	 **9**	1	 **10** + **8**	P(*o*-tolyl)$_3$[c)] BINAP[d)]	**10** [75]; **8** [21] **10** [52]; **8** [46]
3	 **11**	2	 **12** + **8**	P(*o*-tolyl)$_3$[c)] BINAP[d)] DPPF[e)]	**12** [0]; **8** [<10] **12** [56]; **8** [22] **12** [70]; **8** [18]
4	 **13**	1	 **14** + **7**	P(*o*-tolyl)$_3$[c)] BINAP[d)]	**14** [50]; **7** [24] **14** [98]
5	 **15**	3	 **16** + **7**	P(*o*-tolyl)$_3$[c)] BINAP[d)]	**16** [0]; **7** [traces] **16** [66]; **7** [16]
6	 **17**	2	**7** + **8**	P(*o*-tolyl)$_3$[c)] BINAP[d)]	**7** [traces] **7** [70]; **8** [traces]

a) conditions: toluene, 100 °C, 1.2 eq. **2** and 1.3 eq. NaO^{t}Bu per bromine functionality, catalyst and time as indicated; b) yield of isolated products; c) Pd(dba)$_2$ (1 mol%) and P(*o*-tolyl)$_3$ (2 mol%) per bromine functionality; d) Pd$_2$(dba)$_3$ (0.5 mol%) and BINAP (1 mol%) per bromine functionality; e) Pd(DPPF)Cl$_2$•CHCl$_3$ (2 mol%) and DPPF (6 mol%) per bromine functionality, reaction carried out in THF at 100 °C

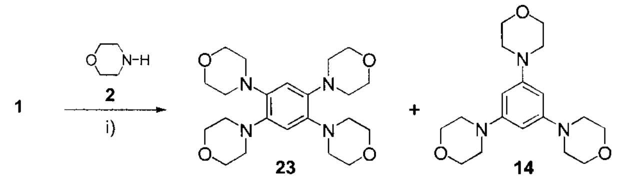
dendrimers; dendrimers that should have very interesting redox and electron transfer properties.[4, 12]

A fourfold coupling reaction could be achieved with 1,2,4,5-tetrabromobenzene (**22**) and **2** and with either Pd$_2$(dba)$_3$/BINAP, or Pd(DPPF)Cl$_2$/DPPF as catalyst providing 1,2,4,5-(*N,N,N,N*)-tetramorpholinobenzene (**23**) in 72% and 43% yield, respectively.[14] The 1,2,4-tris-isomer **16** was the major by-product (Scheme 3).



Scheme 3. *Catalysts and conditions:* i) Pd$_2$(dba)$_3$ (3 mol%), BINAP (9 mol%), 4.8 eq. **2**, 5.5 eq. NaO ^{t}Bu, toluene, 100 °C, 2 d, **23** (72%), **16** (21%); ii) as above but Pd(DPPF)Cl$_2$ (6 mol%), DPPF (15 mol%), THF, 100 °C, 4 d, **23** (43%), **16** (19%)

The palladium catalyzed aryl amination of hexabromobenzene (**1**) with **2** did not give the exhaustively aminated product **5**. Surprisingly, 1,2,4,5-(*N,N,N,N*)-tetra-(**23**) and 1,3,5-(*N,N,N*)-trimorpholinobenzene (**14**) were isolated instead in 37% and 36% yield, respectively (Scheme 4). The pronounced selectivity observed in this case and in aryl aminations with 1,2,3-tribromobenzene (**13**) indicates that three adjacent amino groups cannot be introduced into an aromatic ring *via* the palladium catalyzed multiple arylamination reaction, at least under the conditions employed here. In addition the β-hydride elimination 'side-reaction' yielding a hydrogenolysis of the aryl bromide seems to be more facile between two amino substituents, and that should be mainly attributed to steric effects. This result is illustrated by the observed selectivity in the palladium catalyzed aryl amination reactions with **13**, **15**, **17**, and **1** (see Table 1 and Scheme 4).



Scheme 4. *Catalyst and conditions:* i) Pd$_2$(dba)$_3$ (4 mol%), BINAP (12 mol%), 7.2 eq. **2**, 8.4 eq. NaO^{t}Bu, toluene, 100 °C, 3 d, **23** (37%), **14** (36%)

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(11) All new compounds were characterized by IR, MS, ^{1}H- and ^{13}C NMR, elemental analysis and/or HRMS.

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(13) Spectroscopic data of **21**: colorless solid; m.p. 169-171 °C; R_f = 0.24 (Alox/N-TLC, hexanes/ethyl acetate = 9 : 1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (dd, J = 7.3 Hz, J = 8.1 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 6.20 (s, 1H), 3.30 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1 (s), 151.2 (s), 129.1 (d), 116.2 (d), 119.9 (d), 98.5 (d), 49.9 (t), 49.4 (t); IR (KBr) ν = 3058 cm^{-1}; 3035, 2956, 2820, 1590, 1499, 1448, 1382, 1335, 1310, 1271, 1234, 1205, 1152, MS (EI, 70 eV) m/z (%): 558 (28, M^+), 426 (81), 266 (14), 120 (25), 44 (100); $C_{36}H_{42}N_6$: calc.: C 77.38, H 7.58, N 15.04; found C 76.91, H 7.44; N 14.69. EI-HRMS: calc. for $C_{36}H_{42}N_6$ 558.3471; found 558.3486.

(14) ***Typical procedure:*** In a Schlenk tube with screw cap were introduced under argon 1,2,4,5-tetrabromobenzene (**22**) (276 mg, 0.70 mmol), morpholine (**2**) (292 mg, 3.36 mmol), sodium *tert*-butoxide (376 mg, 3.92 mmol), $Pd_2(dba)_3$ (19 mg, 0.02 mmol), BINAP (39 mg, 0.06 mmol), and toluene (5 ml). The sealed tube was kept at 100 °C for 2 d. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. After evaporation of the solvents the organic residues were extracted with diethyl ether dissolving compound **16** only. Column chromatography of the residue (SiO_2; CH_2Cl_2/hexanes/ethyl ether = 8 : 2 : 2 (v/v/v)) gave analytically pure **23** (210 mg, 0.50 mmol, 72%). Compound **16** was obtained after chromatography of the ether extracts (SiO_2, hexanes/diethyl ether = 3 : 7 (v/v) yielding analytically pure **16** (50 mg, 0.15 mmol, 21%).

23: colorless plates ($CHCl_3$/pentane); m.p. >300 °C; R_f = 0.3 (SiO_2-TLC, CH_2Cl_2/hexanes/diethylether = 8 : 2 : 2 (v/v/v)); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.53 (s, 2H), 3.80 (‘t’, J ~ 4.5 Hz, 16 H), 3.15 (‘t’, J ~ 4.5 Hz, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.6 (s), 109.3 (d), 67.6 (t), 50.3 (t); IR (KBr) ν = 2965 cm^{-1}; 2794, 1514, 1438, 1258, 1209, 1113, 972, 934, 915; MS (EI, 70 eV) m/z (%): 419 (25); 418 (100, M^+), 360 (2), 302 (2), 243 (4); $C_{22}H_{34}N_4O_4$: calc.: C 63.13, H 8.19, N 13.39; found: C 62.73, H 7.99, N 13.19.

16: colorless plates (CH_2Cl_2/hexanes), m.p. 125-126 °C;[10] R_f: 0.3 (SiO_2-TLC, hexanes/ethyl acetate = 3 : 7 (v/v)); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.83-6.9 (m, 1 H), 6.52-6.57 (m, 2 H), 3.79-3.87 (m, 12 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 147.7 (s), 145.4 (s), 138.1 (s), 119.0 (d), 109.8 (d), 107.7 (d), 67.6 (t), 66.9 (t), 50.5 (t), 50.2 (t), 50.1 (t); IR (KBr) ν = 2957 cm^{-1}, 2850, 1602, 1506, 1448, 1253, 1117; MS (70 eV) m/z (%): 333 (85, M^+), 249 (13), 248 (100), 190 (30), 132 (37); $C_{18}H_{27}N_3O_3$ calc.: C 64.84, H 8.16, N 12.60; found: C 64.79, H 8.11, N 12.77.