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SYNTHETIC CONNECTIONS TO THE AROMATIC DIRECTED METALATION REACTION. FUNCTIONALIZED ARYL BORONIC ACIDS BY IPSO BORODESILYLATION. GENERAL SYNTHESES OF UNSYMMETRICAL BIPHENYLS AND m-TERPHENYLS

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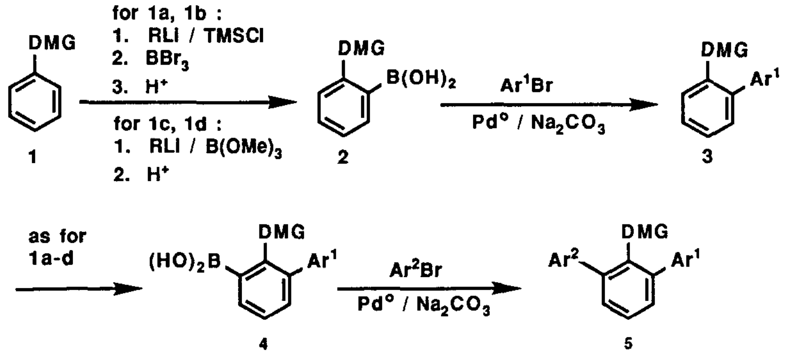
Abstract: Aryl boronic acids **2a-d** and **4a-d** obtained by metalation-$B(OMe)_3$ or metalation silylation-ipso borodesilylation sequences, participate in efficient Pd°-catalyzed cross coupling reactions with aryl bromides to give unsymmetrical biphenyls **3a-d** and m-terphenyls **5a-d** respectively.

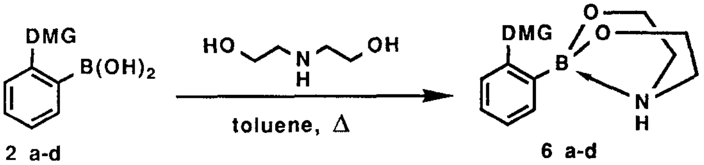
We have recently described[1] a general Pd-catalyzed cross coupling protocol[2] for the synthesis of unsymmetrical biaryls which takes advantage of the regiospecific construction of substituted benzamide 2-boronic acids by directed ortho metalation chemistry (**1a** → **2a**). The efficacy of this method and the increasing interest in the preparation and properties of polyphenyls[3] provided the impetus for the extension of the cross coupling tactic for the construction of m-terphenyls and higher order polyphenyls. Herein we report on a) the expansion of the cross coupling reaction to encompass the $OCONR_2$, OMOM, and $NHCO_2$t-Bu directed metalation groups **2a-d**; b) a new ipso borodesilylation method to obtain the starting o-boronic acids (**1a,b** → **2a,b**); and c) a sequential metalation-cross coupling procedure (**3** → **4** → **5**) for the synthesis of substituted m-terphenyls. As demonstrated in the accompanying letter,[4] this work opens new methodological doors for rational entries into highy functionalized polyphenyl systems.



DMG = Directed Metalation Group : a : CON(i-Pr)$_2$; b: $OCONEt_2$; c : OMOM ; d : $NHCO_2$t-Bu

Scheme

The earlier metalation-$B(OMe)_3$ procedure for the preparation of the benzamide 2-boronic acid **2a** [1] from **1a** has been superseded by a more efficient metalation-silylation-ipso borodesilylation method which is also applicable for the conversion of the corresponding carbamate **1b** into **2b**. Thus the o-silylated intermediates obtained from **1a** [5] and **1b** [6] were treated with BBr_3 (1.5 equiv/CH_2Cl_2/-78°C → RT)[7] followed by acidic workup (5% aq HCl) to give **2a** and **2b** respectively in excellent yields. On the other hand, the corresponding methoxymethoxy and $NHCO_2t$-Bu arylboronic acids **2c** and **2d** bearing Lewis acid sensitive groups were prepared from **1c** and **1d** in modest yields using the metalation-$B(OMe)_3$ procedure.[1] For purification and characterization,[8] compounds **2a-d** were converted into their more stable diethanolamine adducts **6a-d**.

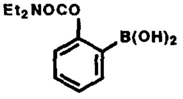
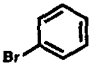
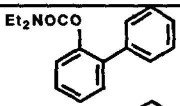
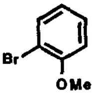
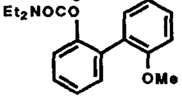
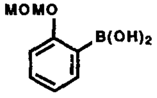
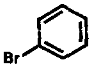
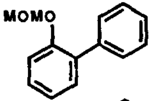
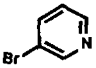
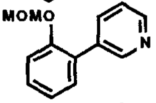
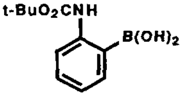
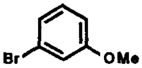
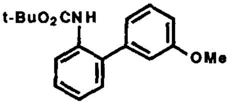
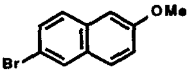
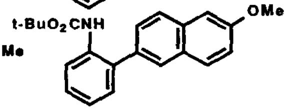
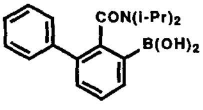
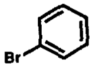
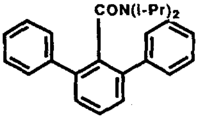
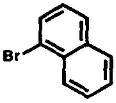
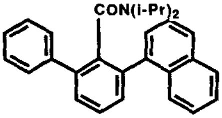
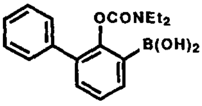
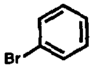
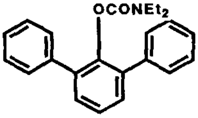
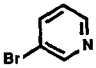
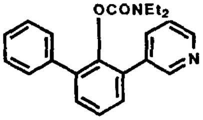
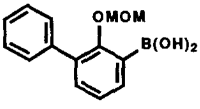
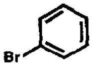
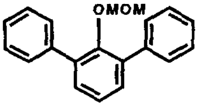
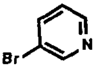
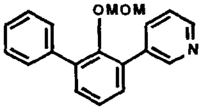
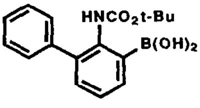
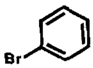
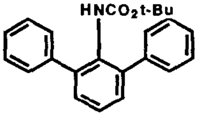


When **2b** was subjected to the cross coupling conditions of Suzuki (ArBr as limiting reagent/3 mmol % of $Pd(PPh_3)_4$/2 M aq Na_2CO_3/toluene/reflux/6-12 h),[2a] biphenyl carbamates **(Table, entries 1, 2)** were obtained in modest yields. Similarly, the methoxymethoxy **(2c)** and $NHCO_2t$-Bu **(2d)** derivatives led to analogous biphenyl products in good yields (entries 3, 4).

The synthesis of unsymmetrical m-terphenyls **5 (Scheme)** was initiated by metalation-$B(OMe)_3$ or metalation-silylation-ipso borodesilylation sequences on **3a-d** according to the conditions, identical and corresponding, to those used for the preparation of the phenylboronic acids **2a-d**. Thus **3a** afforded the biphenyl boronic acid **4a** [9] which was coupled under conditions used for the preparation of **2a-b** to give functionalized m-terphenyls **5a (Table, entries 7, 8)**. However, adaption of the Suzuki conditions to the carbamate and methyoxymethoxy biphenyls **(4b and 4c)** led to significant amounts (10-20%) of phenolic substances in addition to the desired coupling products. This could be avoided by using a modified Gronowitz procedure (3 equiv $NaHCO_3$/glyme/reflux/4-6 h)[2b] which furnished the coupled m-terphenyls in good yields **(Table, entries 9-13)**.

Thus we have demonstrated that the combination of aromatic directed metalation and transition metal-catalyzed cross coupling reactions offers a powerful and general synthetic strategy for the preparation of unsymmetrical, highly functionalized m-terphenyls which supersedes in scope and mild conditions the classical Ullmann and related reactions.[3a] These results coupled with the further demonstration of iterative metalation-cross coupling tactics[4]

Table. Synthesis of Unsymmetrical Biphenyls 3 and m-Terphenyls 5.

Entry	Boronic Acid	Aryl Halide	Product[a]	Yield, %[b]	mp (bp)
1	 2 b			52	120 (0.1 mm)
2				55	105-115 (0.2 mm)
3	 2 c			90	124-125 (0.7 mm)
4				83	138-140 (0.45 mm)
5	 2 d			80	120-121 (hexane)
6				59	127-128 (hexane)
7	 4 a			91	142-143 (Et_2O-hexane)
8				84	176-178 (Et_2O-hexane)
9	 4 b			87	72.5-73.5 (Et_2O-hexane)
10				75	215-220 (0.3 mm)
11	 4 c			88	82.5-84.5 (hexane)
12				73	61-62 (Et_2O-hexane)
13	 4 d			44[c]	177-178.5 (Et_2O-hexane)

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[a] All compounds show analytical and spectral (IR,NMR,MS) data in accord with the assigned structures.
[b] Yields are of chromatographically pure materials. [c] Based on recovered biphenyl (3d).

constitute models for rational approaches to a variety of polyaryl systems of potential interest in macrocyclic chemistry.[10,11,12]

Typical Experimental Procedures: Ipso Borodesilylation: A solution of BBr$_3$ (1.2 - 1.5 equiv) in CH$_2$Cl$_2$ was added by syringe to a stirred solution of the aryl silane derived from **1**, DMG = CON(*i*-Pr)$_2$, OCONEt$_2$ (5 mmol) in anhydrous CH$_2$Cl$_2$ (25 mL) at - 78°C under an argon atmosphere. The mixture was allowed to warm to room temp over 8 h, cooled to -78°C, and quenched with dry MeOH (4.5 equiv). 5% aq HCl was added at room temp and the resulting mixture was concentrated **in vacuo**. The aq slurry was extracted (CH$_2$Cl$_2$), dried (Na$_2$SO$_4$), and evaporated to dryness **in vacuo** to afford the boronic acid **2** (> 85% yield) as a foam which was used without purification. **Cross Coupling:** A stirred mixture of the aryl bromide (1 mmol), Ph(PPh$_3$)$_4$ (0.03 mmol) in toluene or glyme (25 mL) under nitrogen was successively treated with the aryl boronic acid (1.1 mmol), dissolved in a minimum volume of EtOH, and aq Na$_2$CO$_3$ solution (1.1 mL, 2M). The resulting mixture was heated at reflux for 8 h, cooled, subjected to filtration. The filtrate was evaporated to dryness **in vacuo** and the residue was treated with satd NaCl solution. The resulting mixture was extracted (CH$_2$Cl$_2$), dried (Na$_2$SO$_4$), and evaporated to dryness to give material which was purified by flash chromatography (silica gel) and recrystallization or distillation.[11]

References and Footnotes

1. Sharp, M.J.; Snieckus, V. *Tetrahedron Lett.* **1985**, 5997.
2. To the best of our knowledge, this method is due to Suzuki: a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Syn. Commun.* **1981**, *11*, 513. It has been extensively used by Gronowitz for unsymmetrical heterobiaryl synthesis; b) Gronowitz, S.; Lawitz, K. *Chem. Scripta*, **1984**, *24*, 5 and references therein; c) See also Thomson, W.J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237; Miller, R.B.; Dugar, S. *Organometallics*, **1984**, *3*, 1261.
3. Reviews: a) Ried, W.; Freitag, D. *Angew. Chem. Internat. Ed. Engl.* **1968**, *7*, 835; Ames, G.R. *Chem. Rev.* **1958**, *58*, 895. Recent work: b) Tius, M.A.; Savariar, S. *Synthesis*, **1983**, 467; Stahly, G.P. *J. Org. Chem.* **1985**, *50*, 3091; Harada, K.; Hart, H.; Du, F.C.-J. *ibid.* **1985**, *50*, 5524 and references cited therein.
4. Cheng, W.; Snieckus, V. *Tetrahedron Lett.* accompanying Letter.
5. Mills, R.J.; Snieckus, V. *J. Org. Chem.*, **1983**, *48*, 1565.
6. Sibi, M.P.; Snieckus, V. *J. Org. Chem.*, **1983**, *48*, 1935.
7. Arylhaloboranes hae been recently prepared by ipso desilylation. Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W.; *J. Organomet. Chem.*, **1986**, *315*, 1.
8. These derivatives show interesting ^{1}H NMR spectroscopic properties, see Lauer, M.; Wulff, G. *J. Organometal. Chem.* **1983**, *256*, 1; Contreras, R.; Garcia, C.; Mancilla, T. *ibid.* **1983**, *246*, 213.
9. That metalation had not occurred on the non-functionalized ring of **3** was proved by treatment of lithiated **3a**, Ar^1 = Ph with benzaldehyde followed by reaction with HOAc (reflux/6 h) which gave 2,6-diphenylphthalide, mp 92-94°C (hexane); ν_{max} (CHCl$_3$) 1765 cm^{-1}. Metalation of 2-aminobiphenyl has been reported to occur on the bare aromatic ring as evidenced by subsequent reaction with DMF and cyclization to phenanthridine, see Narasimhan, N.S.; Chandrachood, P.S. *Synthesis*, **1979**, 589.
10. Cram, D.J.; Kaneda, T.; Helgeson, R.C.; Brown, S.B.; Knobler, C.B.; Maverick, E.; Trueblood, K.N. *J. Am. Chem. Soc.* **1985**, *107*, 3645.
11. All new compounds show analytical and spectral (NMR, IR, MS) data consistent with the proposed structures.
12. We are grateful to NSERC Canada, Imperial Oil, and Merck Frosst Canada for financial support.

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