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Directed ortho Metalation - Suzuki Cross Coupling Connections. Convenient Regiospecific Routes to Functionalized *m*- and *p*-Teraryls and *m*-Quinquearyls

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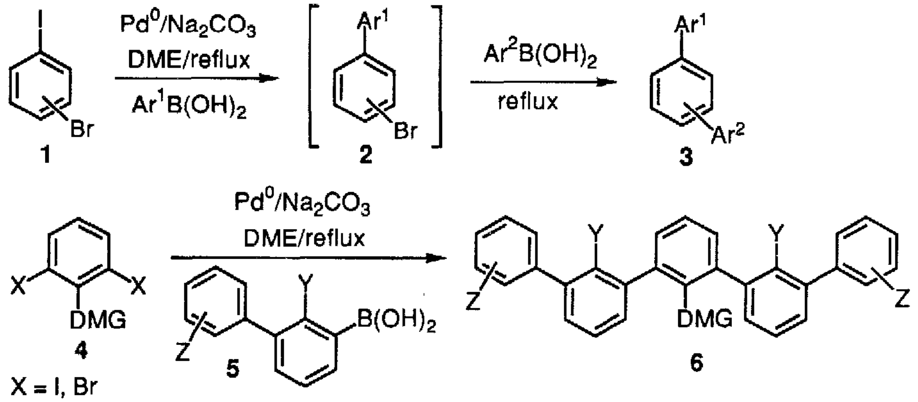
Abstract: *Rapid access to a variety of substituted m- and p- teraryls and m- quinquearyls (**Table**) via Pd-catalyzed, one-pot, sequential and 1:2 cross coupling of aryl halides with aryl boronic acids, both available by metal-halogen exchange or directed ortho metalation tactics, is described.*

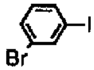
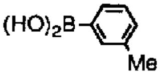
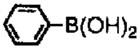
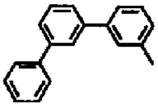
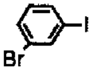
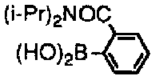
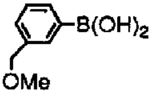
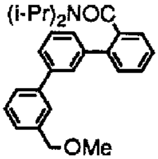
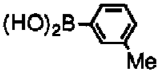
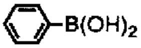
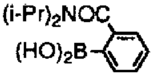
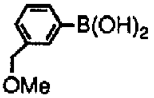
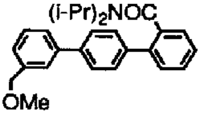
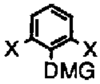
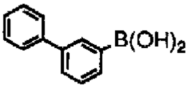
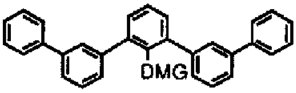
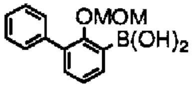
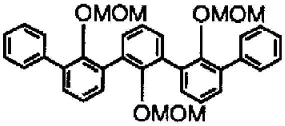
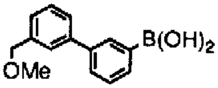
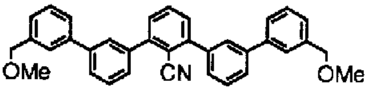
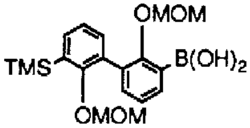
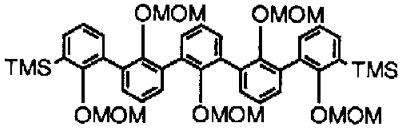
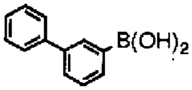
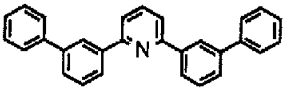
The regioselective construction of teraryls,[1,2] quateraryls,[3] quinquearyls,[4] and higher order polyaryls[4] is a subject of intensifying interest due to the prominence of these substances as intermediates or sub-units in materials related to molecular recognition,[2c,f,g,3a,b] liquid crystal,[2a,d,e] and polymer[4b,5] fields of study. As a sequel to previous work involving iterative aryl-aryl bond formation based on the Pd(0) - catalyzed aryl boronic acid-aryl halide cross coupling regimen,[1] we have developed and report herein efficient one-pot procedures which allow regiospecific access to diversely functionalized *m*- and *p*- teraryls (**1**→**2**→**3**) and *m*-quinquearyls (**4** + **5**→**6**) (**Scheme**). Since this method is linked to the directed ortho metalation strategy,[6] it presents synthetic advantages for predetermined regiospecificity and greater scope in substitution patterns compared to competitive methods.[4]

Scheme



X = I, Br
DMG = Directed Metalation Group

Table. Synthesis of *m*- and *p*-Teraryls and *m*-Quinquearyls

Entry	Method[a]	ArX	$Ar^1B(OH)_2$	$Ar^2B(OH)_2$	Product	Yield, %[b]
1	A					77
2	A					61
3	A					74
4	A					55
						
		DMG X			DMG	
5	B	CONEt$_2$ I			CONEt$_2$	69
6	B	CN I			CN	89
7	C	OMOM Br[c]			OMOM	90
8	C	NH$_2$ Br			NH$_2$	67
9	C	OMOM Br				86
10	B	CN I				84
11	C	OMOM Br				48
12	C					87

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[a] See ref. 7. [b] Refers to chromatographed and recrysyallized or distilled material. [c] Prepared from commercial 2,6-dibromophenol.

Selected cross coupling results are collected in the **Table**. In the sequential route to teraryls **1**→**3**, advantage is taken of the I > Br rate of cross coupling in **1** to obtain intermediates **2** which, without isolation, are subjected to a second coupling process. In the convergent route to quinquearyls **6**, dihalobenzenes **4**, are cross coupled with an excess of biaryl boronic acids **5**.[7] Thus cross coupling of commercial bromoiodobenzenes with readily available aryl boronic acids[8] according to the sequential regimen furnished functionalized unsymmetrical *m*- and *p*- teraryls as single isomers in good yields (entries 1-4). 1:2 Cross coupling of 2,6-dihalobenzenes[9] with aryl boronic acids proceeded smoothly under modified conditions[7] to afford a variety of *m*-quinquearyls. Thus symmetrical products with central amide, nitrile, oxygen, and (unprotected) amino group are available (entries 5-8), as are further functionalized derivatives (entries 9 and 10). Highly oxygenated systems with silicon groups for potential further ipso substitution chemistry[10] may be prepared (entry 11). A quinquearyl with a central pyridine ring is obtained in high yield (entry 12).[11]

In summary, we have devised sequential and 1:2 Suzuki cross coupling protocols for the preparation of teraryls and quinquearyls. The quick assemblage based on readily available starting materials, the link to the versatile directed ortho metalation chemistry, and the good yields posits this method in favorable competition with others for application in timely areas of supramolecular chemistry. Further studies on the structure, physical properties, and elaboration of the quinquearyls are in progress.[12,13]

References and Notes

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4. By Ulmann and Ni-catalyzed ArMgX + ArI cross coupling: a) Ozasa, S.; Fujioka, Y.; Hashino, H.; Kimura, N.; Ibuki, E. *Chem. Pharm. Bull. Jpn.* **1983**, *31*, 2313 and earlier papers in this series. b) By cyclization of 3-dimethyl-aminohex-5-en-1-ynes: Unroe, M.R.; Reinhardt, B.A. *Synthesis*, **1987**, 981.

5. Work mainly dealing with poly(phenylenes) exhibiting various properties: Tour, J.M.; Sthephens, E.B. *J. Am. Chem. Soc.*, **1991**, *113*, 2309; Kim, Y.H.; Webster, O.W. *J. Am. Chem. Soc.*, **1990**, *112*, 4592; Pelter, A.; Maud, J.M.; Jenkins, I.; Sadeka, C.; Coles, G. *Tetrahedron Letters*, **1989**, *30*, 3461 and references cited therein.

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7. Representative procedures: **Method A:** To a stirred solution of *m*-iodobromobenzene (1 mmol) in DME (100 mL) under nitrogen was added $Pd(PPh_3)_4$ (0.06 mmol). After 15 min, aq Na_2CO_3 (6 mmol, 2M solution) and $Ar^1B(OH)_2$ (1 mmol) in a minimum volume of EtOH were sequentially added and the mixture was refluxed for 24 h. The mixture was cooled to rt and treated with $Ar^2B(OH)_2$ (1 mmol) in EtOH. Following reflux for 24 h, the solution was filtered through a celite filter pad, the filtrate was concentrated, and the residue extracted with Et_2O. The Et_2O extract was washed succesively with H_2O, 5% aq NaOH, 10% aq HCl, satd $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a residue which was purified by flash column chromatography. **Method B:** A DME solution of diiodide (1 mmol) was treated with catalyst (0.1 mmol) and the boronic acid (4 equiv). The mixture was stirred at rt for 2 d and then refluxed for 8-12 h. Workup followed Method A. **Method C:** Method B was followed except that the dibromide and aq $NaHCO_3$ (4 equiv, 1M solution) were used and the mixture was refluxed for 24 h.

8. Prepared by metal-halogen exchange from the corresponding aryl bromide or by directed ortho metalation-boronation of the corresponding amide, see Alo, B.I.; Kandil, A.; Patil, P.A.; Sharp, M.J.; Siddiqui, M.A.; Josephy, P.D.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.

9. The preparation of N,N-diethyl 2,6-dibromo and diiodobenzamides was carried out according to Mills, R.J.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093. 2,6-dibromo and 2,6-diiodobenzonitrile were obtained in 58-62% yields from PhCN as follows: 1. LiTMP (2 equiv)/TMSCl (5 equiv)/THF/-78°C → RT (see Krizan, T.D.; Martin, J.C. *J. Am. Chem. Soc.* **1983**, *105*, 6155); 2. Br_2 or ICl (4 equiv)/CCl_4 reflux/72 h. Products were recrystallized from PhMe.

10. Mills, R.J.; Taylor, N.J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.

11. *For coupling of 2,6-dibromopyridine with pyridyl boranes, see ref 2h.*

12. All new compounds show spectral (^1H and ^{13}C NMR, MS) and analytical data fully consistent with their represented structures.

13. We thank NSERC Canada for financial support of our synthetic programs and Dr. P.J. Cox for astute preliminary experiments.

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