

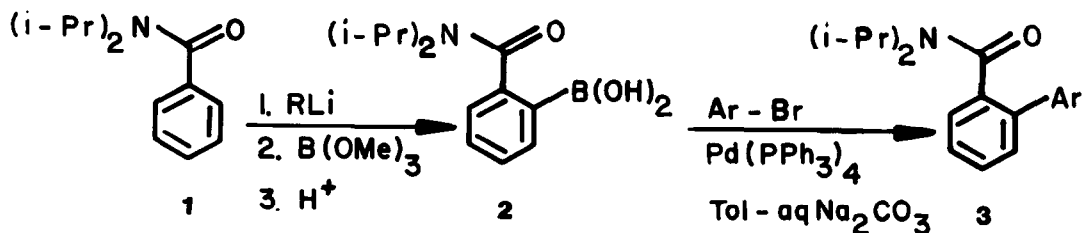
SYNTHETIC CONNECTIONS TO THE AROMATIC DIRECTED METALATION REACTION.  
UNSYMMETRICAL BIARYLS BY PALLADIUM-CATALYZED CROSS COUPLING OF DIRECTED  
METALATION-DERIVED ARYLBORONIC ACIDS WITH ARYL HALIDES

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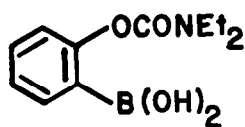
**Abstract:** The arylboronic acids **2** and **4** derived by directed ortho metalation of benzamides and carbamates, undergo an efficient palladium-catalyzed cross coupling reaction with a variety of aryl halides to yield unsymmetrical biaryls and heterobiaryls (**Table**).

The Ni- and Pd-catalyzed cross coupling reaction of organometallic reagents with organic halides is rapidly becoming an important synthetic methodology for regio- and stereo-selective carbon-carbon formation.<sup>1</sup> Its versatility is underscored by a) the potential of using electronegative metal-based organometallics, (e.g. Zn, Al, Zr) b) coupling with a broad range of alkyl, alkenyl, alkynyl, benzyl, and aryl halides<sup>2</sup> and c) compatibility of organic halides with reactive functional groups (CO<sub>2</sub>R, CONR<sub>2</sub>, CN, NO<sub>2</sub>) with the electronegative metal-derived organometallics. For the synthesis of unsymmetrical biaryls and hetero biaryls, the cross coupling tactic has involved the use of ArMgX,<sup>3</sup> HetArMgX,<sup>4</sup> ArZnX,<sup>5</sup> HetArZnX,<sup>4</sup> and ArB(OH)<sub>2</sub><sup>6</sup> intermediates. Herein we report on the efficient cross coupling reaction of arylboronic acids **2**, derived from **1** by directed ortho metalation, with aryl, heteroaryl, and benzyl bromides to yield unsymmetrical biaryls **3**. In view of the broad scope and diverse synthetic utility of the directed metalation reaction,<sup>7</sup> its connection to the transition metal-catalyzed cross coupling reaction will significantly broaden the horizons for unsymmetrical biaryl construction.<sup>8</sup>

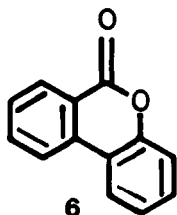


The crystalline carboxamido phenylboronic acid **2** was prepared in 80% overall yield by sequential standard metalation ( $\underline{s}$ -BuLi/TMEDA/THF/-78°C) and treatment with  $B(OMe)_3$ ,<sup>9</sup> followed by acidic workup (5% aq HCl).<sup>6b</sup> When **2** was subjected to the excellent cross coupling procedure of Suzuki (3 mmol % of  $Pd(PPh_3)_4$ /2M aq  $Na_2CO_3$ /Toluene/reflux/6 - 12 h)<sup>6a</sup> in the presence of bromobenzene (limiting reagent), the biphenyl carboxamide (entry 1, **Table**) was obtained in high yield.<sup>10</sup> No evidence for homo coupling was observed (< 2%).

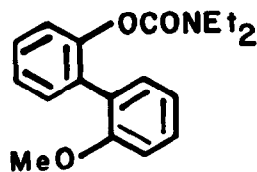
Results of representative cross coupling reactions are depicted in the **Table**. Steric hindrance appears not to be a major impediment to high yields (entry 2) unless the *o*-functionality is an exceedingly bulky and electron-withdrawing group in the bromo aromatic component (entry 4). In these cases, longer reflux times (12-20 h) were used. Hetero cross coupling occurs smoothly with bromo-thiophene, -pyridine, and -thiazole systems (entries 5, 6, 9). Although benzyl bromide provided the expected product in excellent yield (entry 8), attempts to couple **2** with allyl, crotyl, and vinyl bromides have been unsuccessful to date.



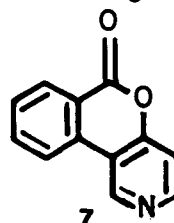
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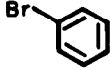
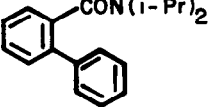
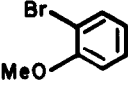
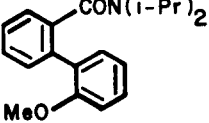
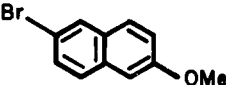
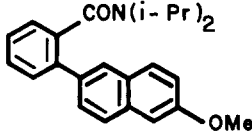
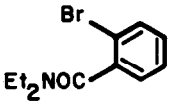
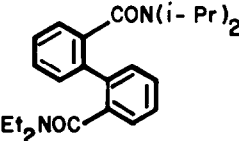
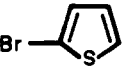
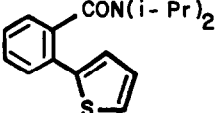
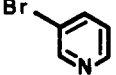
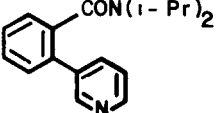
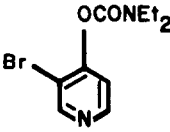
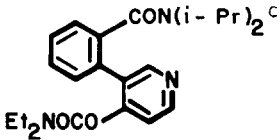
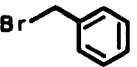
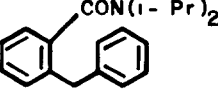
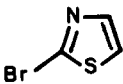
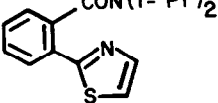


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The cross coupling methodology may be extended to other directed metalation-derived aryl boronic acids. The *o*-carbamoyloxy phenyl boronic acid **4**, obtained as described for **2** by directed metalation<sup>11</sup> and  $B(OMe)_3$  treatment of *N,N*-diethyl *O*-phenyl carbamate, was coupled with *o*-bromo anisole to afford the unsymmetrical biphenyl carbamate **5** in 40% yield.

As an indication of further scope of the cross coupling procedure for heterocyclic

Table Synthesis of Unsymmetrical Biaryls from *o*-Carboxamido Phenyl Boronic Acid 2.

| Entry | Aryl Bromide  | Product <sup>a</sup>  | Yield, % <sup>b</sup> | Mp(bp) °C                          |
|-------|---|---|-----------------------|------------------------------------|
| 1     |    |    | 82                    | 106-108<br>(hexane)                |
| 2     |    |    | 85                    | 95-98<br>(hexane)                  |
| 3     |    |    | 95                    | 188-189<br>(hex-Et <sub>2</sub> O) |
| 4     |    |    | 44                    | 175-178<br>(hex-Et <sub>2</sub> O) |
| 5     |   |   | 92                    | 102-103<br>(hex-Et <sub>2</sub> O) |
| 6     |  |  | 90                    | 86-87<br>(hex-Et <sub>2</sub> O)   |
| 7     |  |  | 80                    | oil                                |
| 8     |  |  | 83                    | 120-125/<br>0.2 mm)                |
| 9     |  |  | 87                    | 111-113<br>(hexane)                |

<sup>a</sup> All products showed analytical and spectral (IR, NMR, MS) data consistent with the proposed structures. <sup>b</sup> Yields correspond to chromatographically pure materials. <sup>c</sup> Obtained by metalation (*s*-Buli/TMEDA/THF/-78°C) and treatment with BrCH<sub>2</sub>CH<sub>2</sub>Br of N,N-diethyl 4-pyridyl *O*-carbamate, Miah, M.A.J.; Snieckus, V. submitted for publication.

synthesis, the product of entry 2 was converted (1.  $\text{BBr}_3/\text{CH}_2\text{Cl}_2/-78^\circ\text{C}\rightarrow\text{RT}$ ; 2.  $\text{HOAc}/\text{reflux}/12\text{h}$ ) into 3,4-benzocoumarin (**6**)<sup>12</sup> in 89% yield. Similarly the product of entry 7 was transformed (2M  $\text{HCl}/\text{reflux}/6\text{ h}$ ) into the analogous pyridocoumarin **7** in 92% yield.

These preliminary studies demonstrate that connecting the directed metalation strategy<sup>7</sup> to the transition metal-catalyzed cross coupling reaction of arylboronic acids<sup>6a</sup> leads to the production of unsymmetrical biaryls and heterobiaryls which are difficult to obtain by classical procedures.<sup>8</sup> The increasing interest in biaryls, especially as chiral catalysts,<sup>13</sup> provides the impetus for the generalization and expansion of this strategy in our laboratories.<sup>14</sup>

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