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# THE DIRECTED ORTHO METALATION CONNECTION TO ARYL-ARYL CROSS COUPLING. A GENERAL REGIOSPECIFIC SYNTHESIS OF PHENANTHROLS

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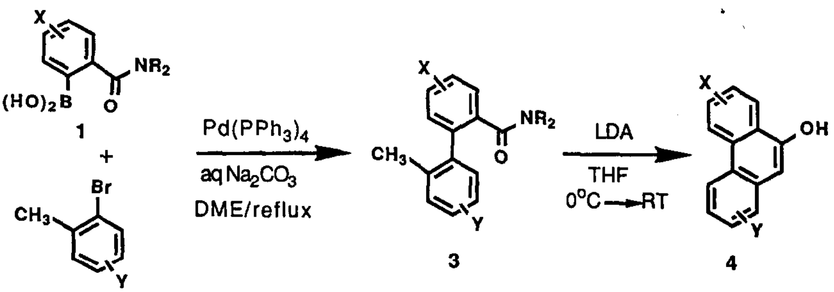
**Summary:** A general directed metalation-based cross coupling synthesis of phenanthrols **4** has been developed (**Scheme 1**); reactions of derived triflates and carbamates **10** lead to a variety of substituted phenanthrenes **7** → **12** (**Scheme 2**).

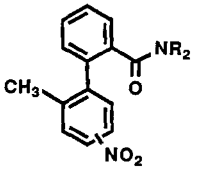
The phenanthrenes constitute a significant class of fossil fuel-derived aromatic hydrocarbons,[1] an expanding group of natural products,[2] and synthons for several major classes of alkaloids.[3] Synthetic approaches to polysubstitued phenanthrenes are based on classical Pschorr,[4] Ullmann[5] and, more recently, Mallory photocyclization[6] methodologies. Most methods are compromised in efficacy and brevity by their dependence on non-regioselective synthetic protocols for substituted benzene derivatives.

We report a new general and efficient methodology for phenanthrenes based on the vinylogous acidity of the 2′-methyl group in the conversion **3** → **4** (**Scheme 1**) and on the ready availability of the precursors **3** by the recently developed cross coupling regimen of arylboronic acids with aryl bromides.[7] Since benzamide o-boronic acids **1** are conveniently and rapidly obtained by the regiospecific directed ortho metalation strategy,[7a,8] the new phenanthrene synthesis promises overall advantage compared to classical methods.[4,5,6]

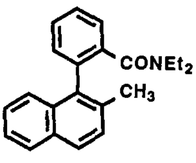


**Scheme 1**

Treatment of the biphenyl diethyl amide **3** (X = Y = H, R = Et)[9] with LDA (2.5 equiv/THF/ 0°C → rt, 3 h) gave 9-phenanthrol (**Table**, entry 1) in high yield. The corresponding diisopropyl amide **3** (X = Y = H, R = i-Pr) afforded 9-phenanthrol in even higher yield thus suggesting either a lack of a steric effect in the carbinolamine-forming step or a driving force for expulsion of the bulky $N(i\text{-}Pr)_2$ leading to a stable phenolate. A number of substituted biphenyls[9] likewise led in good to excellent yields to phenanthrols bearing Cl, OMe, and $CONEt_2$ substituents (entries 3 → 7). The facile synthesis of the known[10] 5-hydroxybenz[a]anthracene (entry 8) suggests applicability of this method to more highly condensed polycyclic aromatics. Although nitrobiphenyls **5** were readily prepared by the cross coupling regimen,[9] their cyclization under LDA (up to 4 equiv LDA/THF/reflux) or other basic (e.g. NaH) conditions was unsuccessful.[11] The naphthylphenyl coupled product **6** also failed to undergo cyclization presumably due to a developing peri hydrogen-phenyl interaction.

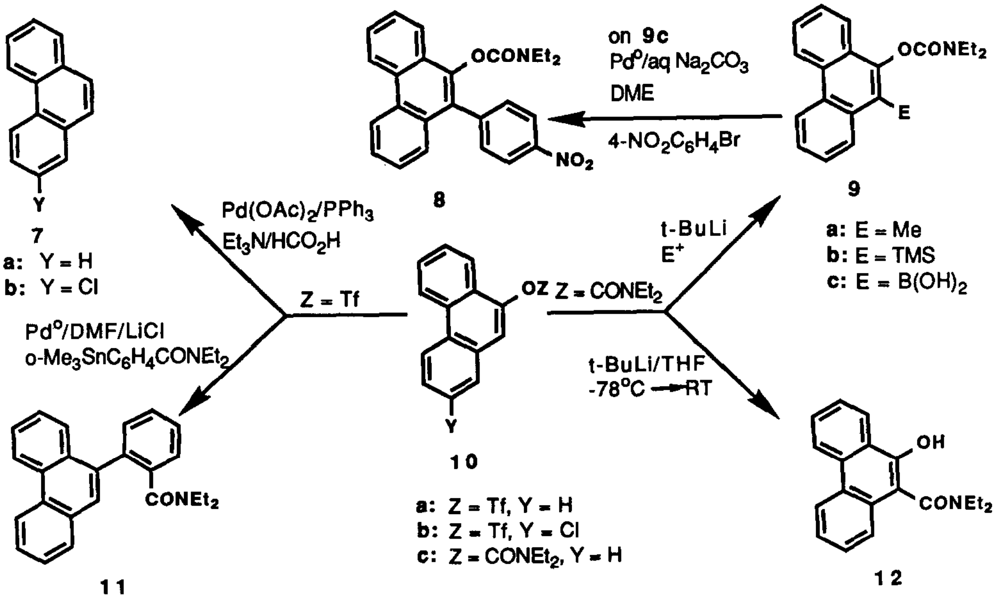


**5**



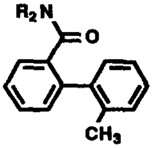
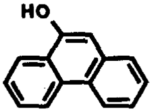
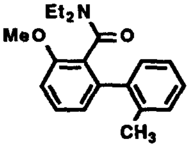
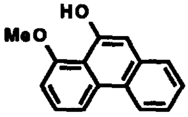
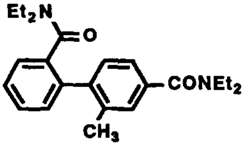
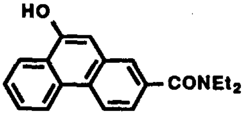
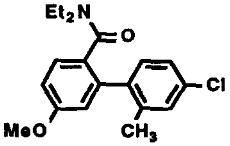
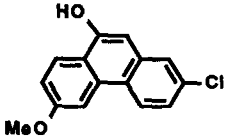
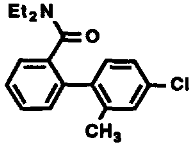
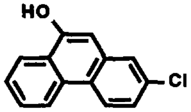
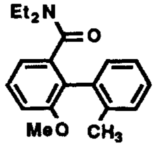
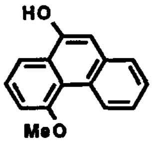
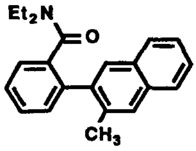
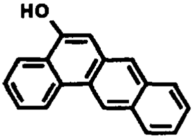
**6**

To demonstrate accessibility of the parent hydrocarbons, two phenanthrols were transformed into triflates **10a** and **10b** (**Scheme 2**) and thence into the corresponding phenanthrenes **7a** and **7b** using emerging methodology.[12] Significantly, this overall route is favorably competitive with previous published procedures, e.g. for the synthesis of methoxy phenanthrenes corresponding to phenanthrols of entries 3 and 7[13]. To provide additional scope to the new phenanthrene synthesis, the prototype 9-O-carbamate **10c** was metalated (t-BuLi/THF/-78°C) and converted into either substituted (**9a**, 92%; **9b**, 88%) or anionic Fries rearranged (**12**, 81%) products.[14] Furthermore, the boronic acid **9c**, obtained from **9b**,[7b] was cross coupled with 1-bromo-4-nitrobenzene to give **8** (80%) and the parent triflate **10a** led, upon treatment with o-stannylated benzamide[15] under Stille's conditions,[16] to biaryl **11** (76%).



**Scheme 2**

**Table.** Synthesis of Phenanthrols

| Entry | Biphenyl | Phenanthrol | Yield, %[a] | mp °C |
|---|---|---|---|---|
| 1 |  <br>R = Et |  | 92 | 151-152[b] |
| 2 | R = i-Pr | | 98 | (PhH) |
| 3 |  |  | 92 | 133-134<br>(cyclohexane) |
| 4 |  |  | 78 | 217-219<br>(EtOAc) |
| 5 |  |  | 93 | 164-167<br>(hexane<br>$-CH_2Cl_2$) |
| 6 |  |  | 96 | 119.5-120.5[c]<br>(hexane) |
| 7 |  |  | 92 | 75-77[d]<br>(hexane-<br>$CH_2Cl_2$) |
| 8 |  |  | 90 | 124-127[d,e]<br>(hexane-<br>$CH_2Cl_2$) |

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[a] Represent yields of products purified by column chromatography. Most phenanthrols were somewhat unstable under ambient conditions; [b] Lit. mp 149-152°C (Hunsberger, I. M.; Ketcham, R.; Gutowsky, H. S. J. Am. Chem. Soc. **1952**, 74, 4839); [c] Mp of triflate; [d] Mp of acetate; [e] Lit.[10] mp 127-128°C.

In summary, a general and efficient methodology for the regiospecific construction of polysubstituted phenanthrenes from biphenyls has been devised. Its dependence on the powerful directed ortho metalation and cross coupling strategies[7,8] provide it broad scope and versatility while further transformations of resulting phenanthrols offer new opportunities in aromatic chemistry.[17,18]

**References and Footnotes**

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9. Prepared according to the procedure[7a,7b] in 67-98% yields with the exception of biphenyl of entry 7 (23%).

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11. In all cases, starting material was recovered. SET reactions may be operating, see Houge-Frydrych, C.S.V.; Motherwell, W.B.; O'Shea, D.M. J.C.S., Chem. Commun. **1987**, 1819 and refs. therein.

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17. All new compounds show analytical and spectral (IR, NMR, MS) data fully consistent with the given structures.

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