

New Efficient Protocol for Aryne Generation. Selective Synthesis of Differentially Protected 1,4,5-Naphthalenetriols

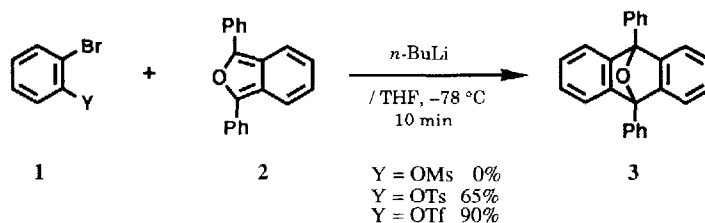
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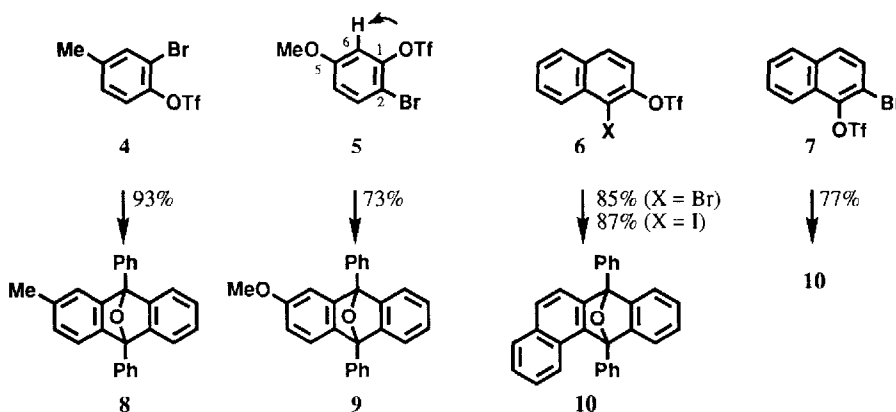
Summary: Arynes are generated cleanly and rapidly by halogen-lithium exchange of *ortho*-haloaryl triflates with *n*-BuLi at -78 °C. [2+4]-Cycloaddition of α -alkoxyaryne with 2-methoxyfuran proceeded regioselectively (*head-to-head*) to afford 1,4,5 naphthalenetriols.

We report herein a new efficient protocol for aryne generation by halogen-lithium exchange of *ortho*-haloaryl triflates.^{1,2)} Regioselective [2+4]-cycloaddition of the α -alkoxyarynes, generated by this method, with 2-methoxyfuran is also described as a facile approach to differentially protected 1,4,5-naphthalenetriols.

For comparing the reactivities as aryne precursor, three *ortho*-bromophenyl sulfonates **1** were treated with *n*-BuLi (1.2 equiv.) in THF at -78 °C in the presence of 1,3-diphenylisobenzofuran (**2**; 2.0 equiv.) as a trapping agent. Even though the starting materials were rapidly consumed, mesylate and tosylate were unsatisfactory. In sharp contrast, the triflate gave an excellent result to afford **3** in 90% yield.

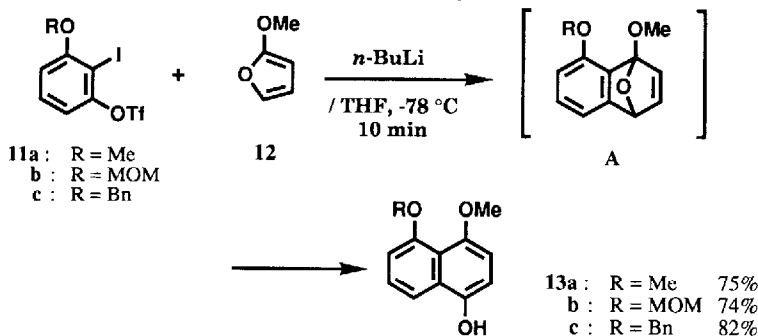


Halotriflates **4–7** also underwent smooth [2+4]-cycloaddition.³⁾ Adducts **8–10** were obtained in good to excellent yields by employing two equivalents of diene **2**, while conventional methods generally require large excess of "aryophile" for achieving reasonable yield. Particularly notable is that the reaction of triflate **5** with a methoxy substituent proceeded regioselectively to give **9** as the sole product. In spite of the



doubly increased acidity of C(6)-H (arrowed), aryne was cleanly generated by halogen-lithium exchange and trapped. Other salient features of the present method are as follows: (1) bromide and iodide were equally employable (6→10); (2) switching of the position of the halide (-X) and the leaving group (-OTf) posed essentially no effect on the yields (6,7→10). These trapping experiments clearly show that the present protocol for aryne generation is quite effective in terms of rapidity and high yield.

α -Alkoxyarynes, generated from **11a–c**, were found to undergo regioselective [2+4]-cycloadditions in reactions with 2-methoxyfuran (**12**).⁴⁾ Triflates **11a–c** were treated with *n*-BuLi in THF at -78 °C in the presence of 2.0 equivalents of **12**. During the stirring at -78 °C for 10 min, aryne generation, cycloaddition to give **A** and its aromatization occurred sequentially to afford naphthols **13a–c** in good yields.³⁾ Notably, all these [2+4]-cycloadditions proceeded regioselectively in the *head-to-head* manner (as shown) to give **13a–c**, and no *head-to-tail* adducts were detected. This regiochemical mode of cycloaddition can be attributed to the polar effect of the alkoxy substituent in the aryne intermediate.¹⁾



This single operation offers a direct access to the naphthols **13** in which all three hydroxyls are suitably differentiated, which are promising synthetic intermediates toward gilvocarcin-class antibiotics.⁵⁾ Indeed, naphthol **13c** is a key synthetic intermediate in the Martin's approach to defucogilvocarcins.^{5b)} Work is now under way directed toward the total synthesis of gilvocarcin antibiotics via the present approach.

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References and Notes:

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- All new compounds were fully characterized by ¹H NMR, IR, and elemental analysis.
- Regiochemistry was confirmed by NOE study (for **13b**, **13c**) or by comparison with the literature data (for **13a**). K. A. Parker, T. Iqbal, *J. Org. Chem.*, **45**, 1149 (1980); H. Laatsch, *Liebigs Ann. Chem.*, **1980**, 1321; N. F. Hayes, R. H. Thomson, *J. Chem. Soc.*, **1955**, 904.
- For synthetic approaches, see a) K. A. Parker, C. A. Coburn, *J. Org. Chem.*, **56**, 1666 (1991); b) P. P. Deshpande, O. R. Martin, *Tetrahedron Lett.*, **31**, 6313 (1990) and references cited therein.

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