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Synthesis of Unsymmetrical 2,8- and 2,9-Dihalo-1,10-phenanthrolines and Derivatives‡

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Abstract: A general method for the preparation of the unsymmetrical 2,8- and 2,9-dihalophenanthrolines is presented. The use of these halophenanthrolines as synthetic substrates in the Suzuki and Sonogashira/Castro-Stevens palladium catalyzed chemistry is exemplifed. These derivatized phenanthrolines are seen as key building blocks for the design and construction of topologically complex polynuclear metal coordination complexes.

Control of the regiochemistry of halogenation (substitution) around the phenanthroline nucleus is a suprisingly difficult synthetic problem. [1,2] Although the 2,9 (flanking positions) and 3,8 (axial positions) have been identified as key attachment points for the design and stabilization of self-assembled polynuclear metal-coordination complexes of specific geometry and topology, [3-5] the obvious 2,8 subtitution pattern is essentially unexplored. In addition, although Sauvage has shown the utility of a Tschitschibaban-like reaction for the synthesis of 2,9-diaryl-1,10-phenanthrolines, general intermediates for 2-X,9-Y disubstitution are much rarer. [6] Classical heterocyclic ring syntheses, such as the Skraup or Friedlander reactions, [7-10] can yield many phenanthroline derivatives, but access to general methods for the preparation of dihalo-1,10-phenanthrolines would provide a convenient design intermediate from which modern organometallic chemistry could be implemented. We provide here another very useful step toward the general preparation of halophenanthrolines and exemplify their use in palladium catalyzed cross coupling reactions. [11-14]

Recently, we prepared 3-bromo and 3,8-dibromo-1,10-phenanthroline by a direct one-pot bromination of phenanthroline hydrochloride. [15] Attempts to extend this to the bromination of 2-aryl-1,10-phenanthroline led to aryl bromination with halophenanthroline side products, but overall an unuseful procedure. Halogenation (Cl or Br) of one flanking phenanthroline position can be effected by a three-step procedure to give 2-halo-1,10-phenanthroline. [16,17] Although this procedure also works well starting from 2-halo-1,10-phenanthroline to yield the 2,9 dihaloderivatives, we were surprised at our inability as of yet, to carry out this procedure starting from 3-bromophenanthroline to prepare 3,9 (i.e. 2,8) dihaloderivatives. Fortunately, simply reversing the order of halogenation solves this problem. Reaction of 2-chloro-1,10-phenanthroline hydrochloride with bromine in nitrobenzene leads to the 8-bromo-2-chloro-1,10-phenanthroline (**1**) in 50% yield after chromatography; some starting material is recovered and can be recycled. The chloride of **1** can be displaced by iodide to give 8-bromo-

‡ Dedicated to Michinori Oki on occasion of his 70th birthday.

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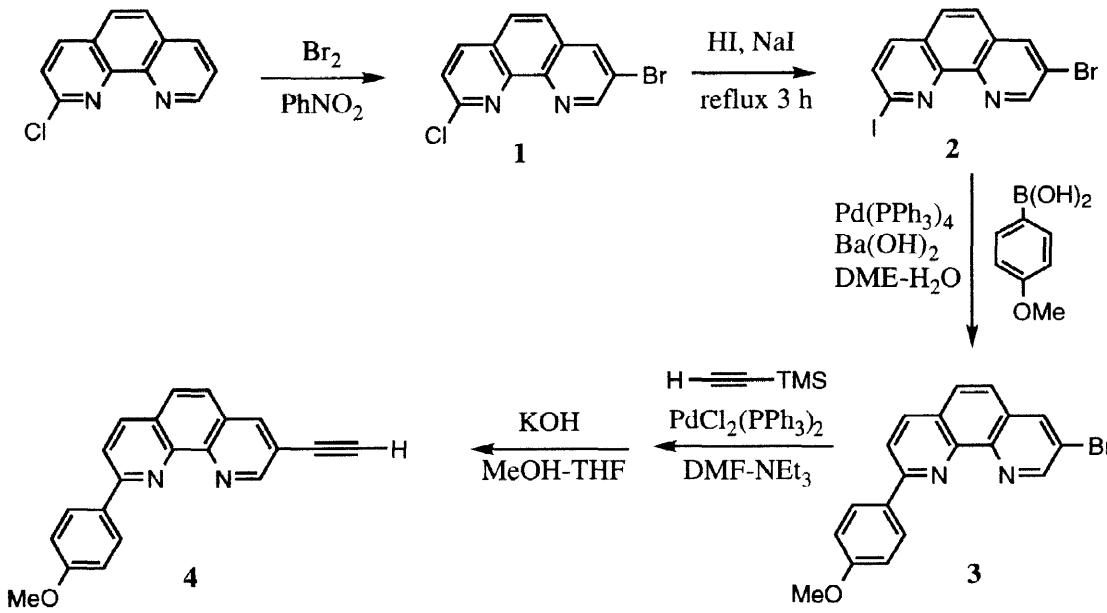
2-iodo-1,10-phenanthroline (**2**) (74% yield). Regioselective palladium catalyzed coupling reactions of **2** occur at the 2-iodo position. For example, 8-bromo-2-(4-methoxyphenyl)- 1,10-phenanthroline (**3**) is prepared in 51% yield by reacting 1 equivalent of the 4-boronic ester of anisole with **2** under Suzuki conditions (6% $Pd(PPh_3)_4$, $Ba(OH)_2$, DME-H_2O, 80°, 3 h). [18] The remaining bromine in position 8 is then available for other couplings. A useful example of this is the reaction of TMS acetylene with **3** under Sonogashira conditions (6% $PdCl_2(PPh_3)_2$; DMF, 80°, 3 h) [19] followed by deprotection to prepare 2-(4-methoxyphenyl)-8-ethynyl-1,10-phenanthroline (**4**) in ca 75% yield for two steps.

Scheme 1

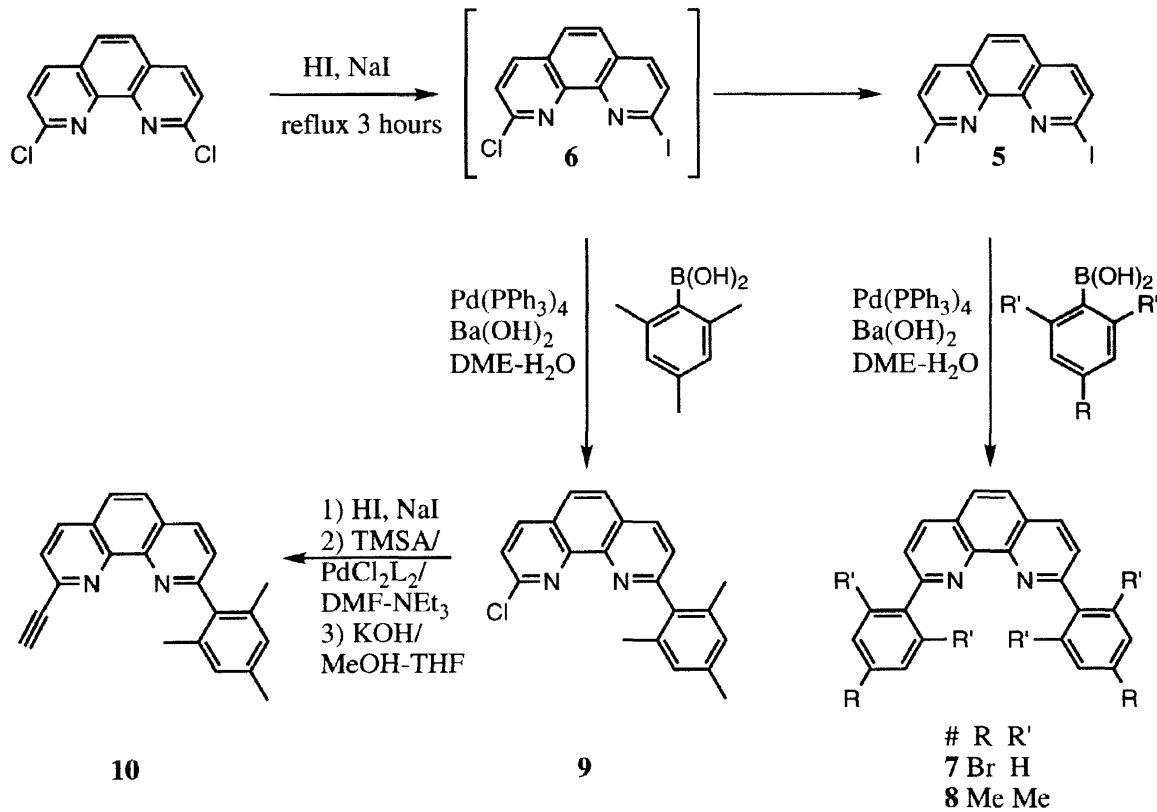


In the course of our investigation, we realized that 2,9-diiodo-1,10-phenanthroline (**5**) has not been reported, although it should be readily prepared from 2,9-dichloro-1,10-phenanthroline by nucleophilic substitution. Indeed, this reaction occurs in moderate yield (74%), and careful observation of the reaction with time shows the growing in and then disapperance of the 2-chloro,9-iodo-1,10-phenanthroline (**6**). Thus, taking advantage of this discrete reactivity, one can isolate either the symmetrical **5** or the unsymmetrical **6** by controlling the exposure time.

Clean reactions occur between **5** and the 4-boronic esters of anisole under Suzuki conditions, but this product can be obtained much more easily by direct Sauvage arylation of 1,10-phenanthroline. [6] More important examples are the reaction of the 4-boronic acid of bromobenzene and mesitylboronic acid with **5** under Suzuki conditions (6% $Pd(PPh_3)_4$; $Ba(OH)_2$; DME, 80°, 3 h) [18] to produce bis-2,9-(4-bromophenyl)-1,10-phenanthroline (**7**), a useful building block, and the sterically congested 2,9-dimesityl-1,10-phenanthroline (**8**) in yields of 50 % and 68 %, respecitvely.

The differential reactivity of the halogens in **6** makes possible the synthesis of some unsymmetrical 2,9-diaryl or 2-aryl-9-ethynyl derivatives that would be unattainable by Sauvage chemistry. Coupling of **6** with mesitylboronic acid (6% $Pd(PPh_3)_4$; $Ba(OH)_2$; DME, 80°, 3 h) produces 2-chloro-9-mesityl-1,10-phenanthroline (**9**) in 71 % yield. Conversion of the 2-chloride to the iodide followed by coupling with trimethylsilylactylene under Sonogashira conditions (6% $PdCl_2(PPh_3)_2$; DMF-NEt_3, 80°, 3 h) [19] and hydroxide induced desilation (MeOH-THF, KOH) produced **10** in 65 % yield.

Scheme 2



It has been long realized that flanking substitution on 1,10-phenanthroline helps to induce and kinetically stabilize ML_2 coordination complexes of tetrahedral ligand field. [6] Phenanthroline and bipyridine oligomers linked through the flanking positions are the basis for tetrahedral-based helicate design. [20-22] Axial substitution is important for construction of grids and weaves as well as for octahedral-based triple helicates. [23-26] The methods presented in this paper provide the bricks necessary to build these molecular architechtures and should motivate even more creative topological constructions using phenanthroline metal templating strategies.

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References.

1. Katritzky, A. R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects*; Academic Press: San Diego, 1990; Vol. (47 of Adv. Heterocyclic Chem).
2. Kress, T. J.; Costantino, S. M. *Heterocyclic Chem.* **1973**, *10*, 409-10.
3. Chambron, J.-C.; Dietrich-Buchecker, C. O.; Heitz, H.; Nierengarten, F.; Sauvage, J.-P.; Pascard, C.; Guilhem, J. *Pure & Appl. Chem.* **1995**, *67*, 233-240.
4. Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
5. Sauvage, J.-P. *Acc. Chem. Res.* **1990**, *23*, 319-327.
6. Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1982**, *23*, 5291-5294.
7. Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37-201.
8. Manske, R. H. F.; Kulka, M. *Org. React.* **1953**, *7*, 59-98.
9. Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, *61*, 3017-3022.
10. Case, F. H. *J. Org. Chem.* **1951**, *16*, 941-45.
11. Farina, V. *Transition Metal Alkyl Complexes: Oxidative Addition and Transmetallation*; ; Abel, E. W. S., F.G.A.; Wilkinson, G., Ed., 1995; Vol. 12, pp 161-240.
12. Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons, Ltd.: Chichester, 1995.
13. Heck, R. F. *Palladium Assisted Couplings of Aryl, Alkenyl, Allyl, and Alkyl Derivatives*; Academic Press: Orlando, 1985.
14. All new compounds are characterized by ^{1}H and ^{13}C NMR, mp, and HRMS.
15. Tzalis, D.; Tor, Y.; Failla, S.; Siegel, J. S. *Tetrahedron Lett.* **1995**, *36*, 3489-3490.
16. Lewis, J.; O'Donoghue, T. D. *J. Chem. Soc., Dalton Trans.* **1980**, 736-742.
17. Yamada, M.; Nakamura, Y.; Kuroda, S.; Shimao, I. *Bull. Chem.Soc. Jpn.* **1990**, *63*, 2710-2712.
18. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
19. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synth.* **1980**, 627-630.
20. Lehn, J.-M.; Rigault, A.; Siegel, J.; Harrowfield, J.; Chevrier, B.; Moras, D. *Proc. Natl. Acad. Sci. USA* **1987**, *8*, 2565-2569.
21. Dietrich-Buchecker, C. O.; Sauvage, J.-P.; De Cian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2231-2232.
22. Piguet, P.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005-62.
23. Youinou, M.-T.; Rahmouni, N.; Fischer, J.; Osborn, J. A. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 733-735.
24. Krämer, R.; Lehn, J.-M.; De Cian, A.; Fischer, J. *Angew. Chem. Int. Ed. Engl.* **1993**, *31*, 703-706.
25. Baxter, P. N. W.; Hanan, G. S.; Lehn, J.-M. *Chem. Comm.* **1996**, 2019-2020.
26. Hasenknopf, B.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1838-1840.