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A Highly Regioselective Sonogashira Coupling as a Key Step in the Preparation of the First Phenanthroline with Two Diverse Reactive Groups in 3,8-Positions

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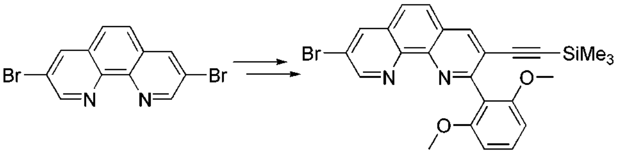
ABSTRACT

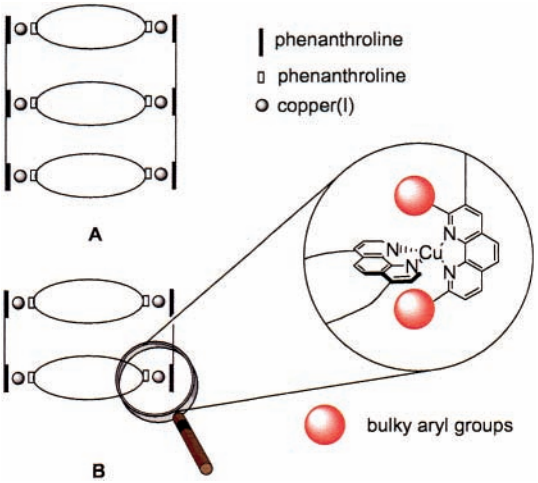


The preparation of 3,8-unsymmetric phenanthrolines is described. Desymmetrization of 3,8-dibromophenanthroline was achieved after monoarylation followed by regioselective Pd-catalyzed monoalkynylation that was controlled by the methoxy group of the dimethoxyphenyl substituent.

Metal phenanthroline complexes currently enjoy a renaissance because they find frequent use in exciting molecular structures,[1] such as molecular knots,[2] rotaxanes,[3] dendrimers,[4] and catenanes,[5] as well as in enantioselective and supramolecular catalysts[6] or so-called molecular machines.[7] We are currently utilizing our selective approach to heteroleptic copper(I) bisphenanthroline complexes, which is based on the use of bulky 2,9-aryl groups[8] as steric blocking units (either mesityl or 2,6-dimethoxyphenyl groups), for the defined construction of nanocubes and nanotubes through a highly convergent and quantitative self-assembly process.[9]

Having structures **A** and **B** available now (Scheme 1),[10] it would be highly desirable to connect two or more of the analogous units **C** either by covalent or noncovalent linkages in order to build artificial nanotubes **D**.

Scheme 1



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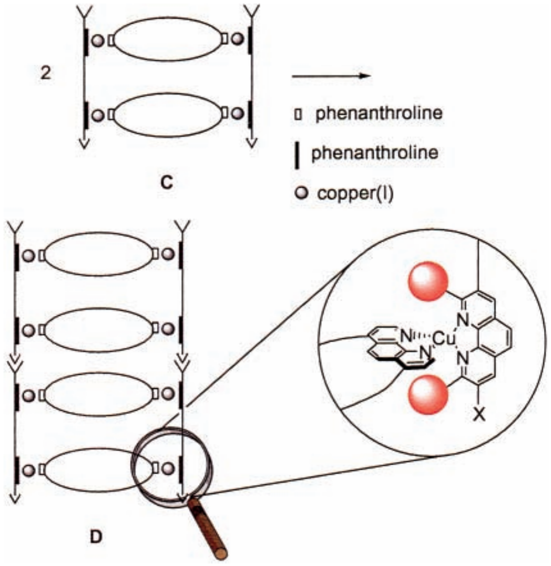
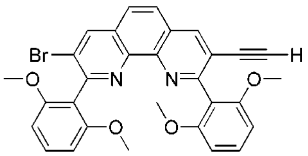
10.1021/ol006514k CCC: $19.00

Scheme 2



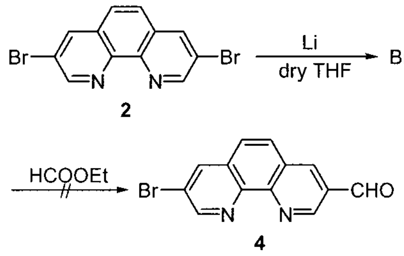
As a prerequisite for the preparation of **D** (Scheme 2), we need linear bis- or oligophenanthrolines containing both the steric blocking units (see Scheme 1) and two different reactive functionalities at the 3,8-positions of the phenanthroline core. A search in the Beilstein database reveals that basically all 3,8-unsymmetric phenanthrolines follow the pattern 3-R (R = Hal, alkyl, aryl, C(=O)R′) and 8-H. An exception is 3-*tert*-butyl-8-methylphenanthroline,[11] but that is not a suitable candidate for linear extension. Herein, we want to describe the difficulties we encountered in preparing 3,8-unsymmetric phenanthroline ligands and finally detail a convenient and brief synthetic access to the unsymmetric phenanthroline **1**. Our approach constitutes the first preparation of an unsymmetric phenanthroline with two diverse reactive groups in the 3,8-positions allowing for extending linearly the phenanthroline to open up a multitude of potential applications, e.g., in material chemistry for tunable fluorophores.[12]



1

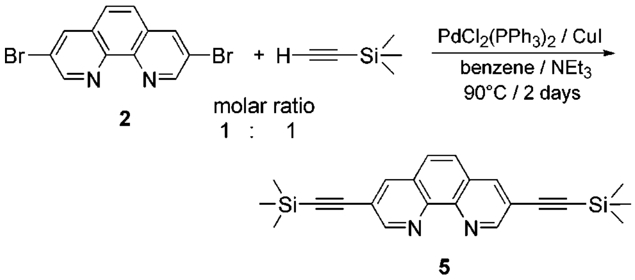
In principle, several ways to prepare unsymmetric 3,8-disubstituted 1,10-phenanthrolines should be feasible. However, since regioselective aromatic halogenation at the phenanthroline core using two different halogens is still an unsolved problem, a synthetic procedure was searched allowing for the preparation of unsymmetric 3,8-disubstituted 1,10-phenanthrolines starting from 3,8-dibromo-1,10-phenanthroline (**2**). In a first attempt, we sought to effect monolithiation of **2** (Scheme 3). However, when **2** was reacted with lithium (2 equiv) only a small amount of 3-bromo-8-lithiophenanthroline (**3**) was obtained (18%). Moreover, reactivity of **3** vs ethyl formate to furnish **4** was too low for an efficient trapping of the lithiated species.

Scheme 3



Another attempt was to react **2** with trimethylsilylacetylene (1 equiv) in the presence of $PdCl_2(PPh_3)_2$, but to our surprise only the symmetric ligand **5** (26%) was formed in addition to some unreacted starting material (Scheme 4). This finding can be explained because of the low solubility of **2**. As the first alkynylation increases drastically the solubility, the subsequent alkynylation to furnish **5** is an efficient homogeneous phase reaction. To avoid this problem, we reacted **2** with equal amounts of trimethylsilylacetylene and propargyl alcohol again under Sonogashira coupling conditions.

Scheme 4



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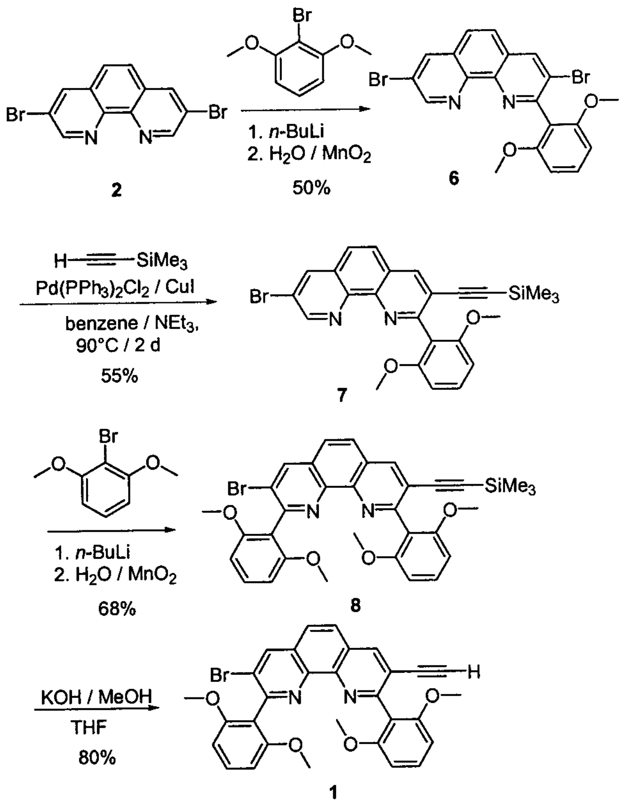
Scheme 5



However, only phenanthrolines **5** and **2** and no 3,8-unsymmetric phenanthroline were detected.

With the difficulties encountered in the above reaction, we realized that despite the ample use of Pd(0)-catalyzed reactions[13] there is a remarkable shortage of reports addressing regioselective bond formation.[14] For example, the role of adjacent groups in controling regioselectivity, e.g., in polybrominated arenes,[15] has not been studied sufficiently to provide a conceptual framework for reliable predictions.

As we searched specifically for a 3,8-unsymmetric phenanthroline with bulky aryl groups in the 2,9-position, we finally reasoned that one should first desymmetrize **2** through monoarylation. The aryl substituent should then be used to guide the regioselective functionalization at the 3-position through the intermediacy of oxapalladacycles or azapalladacycles.[16]

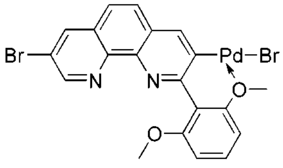
Indeed, the successful preparation of **1** (Scheme 5) is based on (a) the selective monoarylation of **2** with 2,6-dimethoxyphenyllithium followed by (b) a regioselective Sonogashira coupling with trimethylsilylacetylene making use of the coordinating properties of the methoxy groups at the aryl group. Accordingly, the commercially available 2-bromo-1,3-dimethoxybenzene was first treated with n-BuLi to generate the corresponding aryllithium which then underwent nucleophilic aromatic substitution at **2**[17] followed by oxidative workup with MnO_2 to afford the target phenanthroline **6** in a satisfying yield. Subsequent palladium-catalyzed coupling reaction of phenanthroline **6** and trimethylsilylacetylene occurred regioselectively at the 3-position.

Purification of **7** was readily achieved, allowing us to assign rigorously the substitution pattern on the basis of characteristic chemical shifts in the DEPT NMR spectrum. It should be noted that variations of the molar ratio of trimethylsilylacetylene/**6** and of reaction time exerted a notable effect on the outcome of this transformation (Table 1). The highest yield (55%) was received in an experiment with a 1.5:1 ratio and 2 d reaction time. It is important to note that no bisfunctionalization was observed. We assume that after oxidative addition complexation of the Pd metal center by the methoxy group, as depicted in **9**, is a key stabilization motif for achieving the high regioselectivity, in line with models in the literature of oxa- and azapalladacycles.[16]

Table 1. Sonogashira Coupling of Phenanthroline **6** and Trimethylsilylacetylene

entry	reaction time (day)	molar ratio[a]	**7**, % yield
1	2	1.2:1	15
2	2	1.5:1	55
3	2	2:1	38
4	2	2.5:1	19
5	4	1.5:1	28
6	1	1.5:1	45

[a] Molar ratio of trimethylsilylacetylene and phenanthroline **6**.



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A second aromatic substitution at **7** with 2,6-dimethoxyphenyllithium provides phenanthroline **8** in 68% yield, and subsequent hydroxide-induced desilylation finally leads to the target phenanthroline **1** in 80% yield.

All phenanthrolines **7**, **8**, and **1** are 3,8-unsymmetrically substituted phenanthrolines, whose functionalities along the axis of the ligand in the 3- and 8-position can independently be manipulated for further linear extensions using Sonogashira coupling protocols. For example, after desilylation of **7** with KOH in methanol/THF and subsequent reaction

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with 1,4-diiodobenzene in a Sonogashira coupling, the corresponding linear bisphenanthroline was afforded.[18]

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Supporting Information Available: Full experimental details and characterization data for **1** and **6**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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