Template-Directed Synthesis of Helical Phenanthroline Cyclophanes**

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Recently the synthesis and study of assorted carbocyclic cyclophanes and cage compounds[1] has been augmented by novel heterocyclic arrays. Representative examples include bis-2,2'-bipyridine units in twisted diyne dehydroannulenes for spectroscopic detection of metal ions,[2] butadiyne-bridged [4,4]pyridinophanes,[3] rigid cross-conjugated acetylenic macrocycles as a cyclic alternative for 4,4'-bipyridine functionalities for metal complexation,[4] and related thioephene-bridged macrocycles.[5]

Phenanthroline-based investigations involve studies of copper complex induced DNA cleavage,[6] the mechanism of strand scission,[7] enhancement of Diels–Alder reactions,[8] and applications of a cationic platinum–phenanthroline complex.[9] Substituted 1,10-phenanthrolines are highly fluorescent and the spectra are modulated by protonation or metal-ion complexation,[10] and related thiophene-bridged macrocycles.[11]

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We report here the synthesis of the helical 1,10-phenanthroline-capped cyclophanes 1 (Figure 1) and 11 (Scheme 2), which possess the potential for complexation with various metals, as illustrated by the insertion of copper(II) ions in 2 and 12. Bromosilylacetylene 3 was converted into its organozincate[12-14] by in situ halogen metal exchange with nBuLi, followed by transmetalation with ZnBr2 (Scheme 1). Addition of [Pd(PPh3)4] and 3,8-dibromophenanthroline (4)[14] afforded 5 in 87% yield when DMF was used as a co-solvent.[15] Suzuki couplings also provide 3,8-diaryl-1,10-phenanthrolines.[16, 17] Deprotection of 5 with K2CO3 in MeOH/THF provided 6 in 85% yield.

We anticipated that controlled addition of copper(I) acetate to 6 (diethyl ether/pyridine) would initially generate the intermediate complex 7. This “copper template” would then facilitate the desired coupling reaction and circumvent the competing formation of acetate 8 from direct coordination with Cu(OAc)2.[17] The geometric environment of intermediate 8 will inhibit the desired reaction relative to that of 7 in which the terminal acetylene groups are suitably disposed for intermolecular coupling. In addition, polymerization pathways often observed in similar dimerizations should be diminished.[18]

Experimentally, addition of copper(I) acetate (initially 0.5 equiv) in a mixture of pyridine/diethyl ether initiated the reaction and allowed for the formation of 7. Subsequent addition of excess reagent (5.5 equiv) completed the coupling and afforded the copper(II)-complexed cyclophane 2 in 84% yield (Scheme 1). Supporting evidence for this mechanism was provided by the observed color changes from yellow (6) to red (7) to green after an excess of Cu(OAc)2 was added. Further confirmation of the importance of the copper...
template in these oxidative couplings was revealed by the diminished yield of 2 (15\%) when the reaction was conducted with direct exposure of 6 to \(\text{Cu(OAc)}_{2}\) (6 equiv, pyridine/diethyl ether).[19]

The parent cyclophane 1, was liberated from the copper(i)-coordinated phenanthroline cyclophane 2 upon treatment with aqueous potassium cyanide. Unfortunately, cyclophane 1 was only sparingly soluble in a range of organic solvents. The synthesis of the \(N,N\)-dibutylamine-substituted analogue 11 was investigated in an attempt to circumvent this difficulty and provide a substituted member of this series for comparison of the electronic properties. In addition, the butyl groups are diastereotopic in helical (chiral) cyclophane conformations and this should be reflected in the \(^{13}\text{C}\) NMR spectrum, thus allowing the conformational behavior of the cyclophane to be probed.[20]

A very direct synthesis of 11 has been developed to improve the preparation of these compounds. Dibromide 4 was treated with known iodide 9 through a parallel palladium coupling sequence to generate diacetylene 10 (Scheme 2). Compound 10 was transformed into the metal-free cyclophane 11 in a single reaction vessel by a sequential in situ desilylation/dimerization/decomplexation protocol related to the experiments we have developed recently.[21] These steps culminated in an aqueous potassium cyanide work-up to give 11 in 39\% yield. Cyclophane 11 was soluble in a variety of chlorinated solvents.

Copper(i) complexes 2 and 12 were prepared independently as above, but crystals suitable for X-ray analysis were not obtained. However, molecular modeling studies (Figure 2) revealed the twisted nature and key features of the phenanthroline copper complex 2 (Figure 1).[22] The heterocyclic rings displayed an orthogonal disposition with respect to each other and created a pseudotetrahedral coordination site for copper(i) or other electronically related metal ions. The helical nature of cyclophane 12 resulted from our synthetic protocol and the bridges selected.[14-4]

Variable temperature \(^{13}\text{C}\) NMR analysis of 12 indicated the helical isomerization barrier was 13.6 kcal mol\(^{-1}\), an increase of approximately 4 kcal mol\(^{-1}\) relative to the uncomplexed cyclophane 11 (Figure 3). Different metals and substituent combinations may increase this barrier sufficiently to inhibit isomerization and facilitate resolution of the individual enanomers.

Electronic absorption (Figure 4) were obtained for cyclophanes 1, 2, 11, and 12 and compared to related compounds (Table 1). Copper template 7 absorbed in the 600 to 700 nm range, which is indicative of copper(i) complexes. Emission spectra (Figure 5) of 1 and 11 were recorded but the metal-cyclophanes (2 and 12) did not fluoresce.

In summary, we have developed a short, efficient syntheses of a series of functionalized acetylenic phenanthroline cyclophanes by Pd- and Cu-mediated coupling reactions. Molecular modeling studies have established the nature of the

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**Scheme 2. Synthesis of phenanthroline cyclophanes 11 and 12.**

- a) 1. 9, nBuLi, THF, –78°C; 2. ZnBr\(_2\), 0°C, 15 min; 3. 4, [Pd(PPh\(_3\))\(_4\)], THF/DMF (1/1), Δ, 72 h, 70%; b) 1. TBAF, diethyl ether/py, 15 min; 2. Cu(OAc\(_2\)); (0.5 equiv), diethyl ether/py, 2 h; 3. Cu(OAc\(_2\)); (5.5 equiv), diethyl ether/py, 2 h; 4. KCN (aq), 39%; c) [Cu(MeCN)\(_4\)PF\(_6\)], CH\(_2\)Cl\(_2\), 15 min, 97%; d) KCN (aq), CH\(_2\)Cl\(_2\), 5 min, 97%. py = pyridine.

**Figure 2. Molecular models of cyclophanes 1 and 2.**

**Figure 3. Potential energy diagram for the enantioseparation of cyclophanes 2 and 12.** \(\Delta G_i^\circ < 9.4\) kcal mol\(^{-1}\), \(\Delta G_{i,\text{H}}^\circ = 13.6\) kcal mol\(^{-1}\), \(\Delta \Delta G^\circ > 4.2\) kcal mol\(^{-1}\).

**Figure 4. UV/Vis absorption spectra of 1, 11, and 12.**
copper-complexed core. In addition, resolution of the helical isomers may be feasible with additional ring substituents and copper-complexed core. In addition, resolution of the helical

Table 1. UV/Vis absorption maxima of phenanthroline compounds and copper-phenanthroline complexes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{\text{max}} ) (abs) [nm]</th>
<th>( \lambda_{\text{max}} ) (em) [nm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (R = H)[20]</td>
<td>440</td>
<td>584</td>
</tr>
<tr>
<td>[Cu(13)]²⁺ (R = H)[20]</td>
<td>458</td>
<td>523</td>
</tr>
<tr>
<td>13 (R = CuCl-Ph)[19]</td>
<td>346</td>
<td>376, 395</td>
</tr>
<tr>
<td>13 (R = CuCl-(p-PhNMe₂))²⁺[11]</td>
<td>410</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>307 (sh)</td>
<td>416</td>
</tr>
<tr>
<td>2 [Cu(1)]²⁺</td>
<td>473, 553 (sh)</td>
<td></td>
</tr>
<tr>
<td>7 [Cu(6)]²⁺</td>
<td>462</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>383</td>
<td></td>
</tr>
<tr>
<td>12 [Cu(11)]²⁺</td>
<td>407</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Normalized fluorescence spectra of 1 and 11 (n: counts).[24]

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Density functional theory (DFT) calculations were obtained using a DN basis set with the Cerius2-Dmol3 molecular modeling suite from Molecular Simulations Inc. San Diego, 1999 (counterion in 2 not shown for clarity).

Electronic absorption spectra [23] were measured in CH2Cl2, and the data are given in Table 1. Aromatic absorption maxima were found at 285 ± 288 nm; [24] for the 1,3,5-functionalized ketone 1, the aromatic absorption maxima were found at 232 ± 233 nm. [25] The 1,3,5-functionalization of 1 was confirmed by the presence of a single aromatic absorption maximum at 232 ± 233 nm. The aromatic absorption maxima were found at 232 ± 233 nm. For the 1,3,5-functionalized ketone 1, the aromatic absorption maxima were found at 232 ± 233 nm. The aromatic absorption maxima were found at 232 ± 233 nm.

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In particular, there is still a great need to find efficient syntheses for the construction of C-15 macrocyclic ketones possessing specific unsaturation. We herein report the first application of a new synthetic strategy in which the target compounds are obtained from an appropriately functionalized tricyclic system by two consecutive fragmentations. This approach is complementary to the metathesis-based annulation approach is complementary to the metathesis-based annulation.

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The 1,3,5-functionalization of 1, in which one oxygen atom is adjacent to a bridgehead and the two other oxygen atoms are situated at bridgehead positions, is ideally suited for cascade Grob fragmentations [6] and should allow, via inter-

Access to C-15 Macrocyclic Ketones by Iterative Fragmentations of a Tricyclic System

Charles Fehr,* José Galindo, Olivier Etter, and Walter Thommen

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