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Chiral auxiliary-mediated synthesis of planar chiral [2.2]metacyclophanes

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\textbf{ABSTRACT}

The synthesis of planar chiral [2.2]metacyclophanes has been readily accomplished in a single synthetic step by the directed ortho metation of a pro-chiral meta-substituted metacyclophane. The use of (-)-menthyl chloroformate as chiral auxiliary allows the introduction of the useful carbonyl functional group into the aryl ring, giving access to carboxy-substituted racemic mixtures of planar chiral [2.2]metacyclophanes. The optical resolution has been easily accomplished by semipreparative HPLC, allowing the structural analysis of a single diastereoisomer by X-ray crystallography and NMR spectroscopy. The structural features of the planar chiral metacyclophanes and their high inversion barriers, determined at 473 K, encourage future investigations as chiral catalysts and ligands. This synthetic route complements our previously reported enantioselective synthesis avoiding the restrictive use of (-)-sparteine as chiral ligand.

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\textbf{Introduction}

The chemistry of constrained [2.2]cyclophanes has received a remarkable attention from the synthetic community since their discovery in the late 1899.\textsuperscript{1} Short bridged cyclophanes share some unique and attractive structural features, such as through-space interactions between aromatic systems, distortion of aryl rings from planarity and chirality.\textsuperscript{2} Specific substitutions of the aryl rings induces planar chirality as a consequence of the high conformational strain of the cyclophane ring.\textsuperscript{3} This has led to planar chiral [2.2]paracyclophanes recently finding application as promising chiral ligands in asymmetric catalysis,\textsuperscript{4} but in contrast their related chiral meta isomers have not progressed to a comparable extent. The original racemic synthesis of [2.2]metacyclophanes and their late-stage functionalization entails tedious and non-selective synthetic routes.\textsuperscript{5} Therefore, the development of synthetic methodologies giving access to planar chiral [2.2]metacyclophanes represents an important target in organic synthesis. As part of our ongoing interest in selective metatalation,\textsuperscript{6} we recently employed benzylic C-H selective LiNK metatation conditions (BuLi, KOTBu, TMP(H)) for the synthesis of planar chiral [2.2]metacyclophanes (Scheme 1A).\textsuperscript{7} The racemic synthesis can be efficiently accomplished by submitting the appropriately substituted m-xylene derivatives through an iterative regioselective benzylic metatation-oxidative coupling sequence. Racemic resolution affords access to the planar chiral metacyclophanes following a short two-step procedure from inexpensive starting materials.\textsuperscript{8} An enantioselective synthesis of planar chiral [2.2]metacyclophanes has also been described, where the key desymmetrization step relies on a (-)-sparteine mediated directed ortho-lithiation of a pro-chiral [2.2]metacyclophane, followed by electrophilic quench (Scheme 1B).\textsuperscript{9} The enantioselectivity of the process is governed by the chiral amine ligand, disclosing the lithiation reaction as the enantiodiscriminating step. Although enantiomerically pure (-)-sparteine is extremely powerful in controlling the stereochemical outcome of the lithiation process,\textsuperscript{10} some related drawbacks are associated with its use. In particular, there is a cyclic shortage of (-)-sparteine from the main commercial sources which limit its availability, a stoichiometric quantity is required, resulting in the associated cost being high. Moreover, since the stereochemical outcome of the reaction is dictated by (-)-sparteine, the lack of (+)-sparteine enantiomer restricts access to the opposite stereoisomer.\textsuperscript{11} In this work it was envisaged that the use of chiral auxiliaries\textsuperscript{12} might represent a practical alternative to the use of (-)-sparteine allowing access to both enantiomers. In the this preliminary report the use of (-)-menthyl chloroformate as chiral electrophile is explored for the synthesis of planar chiral [2.2]metacyclophanes by the directed ortho metation method and as a new method for the optical resolution of the planar chiral metacyclophane products (Scheme 1C). The synthesis, chromatographic resolution, configurational stability and structural characterization of (+)-menthyl substituted 5-methoxy[2.2]metacyclophane are described. A comparative study using an achiral ethyl chloroformate to assess the chiral...
induction of (-)-menthyl chloroformate versus (+)-sparteine is also discussed.

**A: LINK Chemistry: short racemic synthesis**

**B: LINK Chemistry: three-steps enantioselective synthesis**

**C: This work: chiral auxiliary mediated synthesis**

Scheme 1. Synthetic approaches to planar chiral [2.2]metacyclophanes. LiNK conditions utilize butyllithium (BuLi), potassium tert-butoxide (KoBu) and 2,2,6,6-tetramethylpiperidine (TMP(H)) in THF.

**Results and discussion**

Following the previously reported procedure, the synthesis of 5-methoxy[2.2]metacyclophane (1) was accomplished in two steps starting from commercially available m-xylene and 1-methoxy-3,5-dimethylbenzene. As the 5-methoxy substituent is known to be capable of directing kinetic ortho-metalations, the prochiral 1 was successfully ortho-metalated by treatment with BuLi/KO-Bu in THF at -78 °C for 15 min. Subsequent in situ electrophilic quench with either (-)-menthyl chloroformate or ethyl chloroformate allowed an easy desymmetrization of the cyclophane scaffold producing the [2.2]metacyclophane esters 2 and 3 in good yields after column chromatography (Scheme 2a).

Investigation of 2 and 3 by analytical chiral HPLC showed both products to be racemic mixtures indicating that the chiral (-)-menthyl chloroformate imparted no enantio-discrimination in the reaction sequence. This approach allows the introduction of useful carbonyl functional groups into the C-4 aryl ring position, giving access to carboxy-substituted racemic mixtures of planar chiral [2.2]metacyclophanes in a single synthetic operation.

The racemic mixture of methyl ester 2 was analyzed by analytical HPLC, showing good separation on chiral stationary phases while unfortunately no acceptable resolution of the diastereoisomers was observed on reversed-phase C18 columns. Compared to racemic ethyl ester 3, optical resolution of 2 was easier to accomplish by semi-preparative chiral HPLC using a Chiralcel OD column with enantiomer retention times separated by 1.7 min (see ESI for details). This highlights an advantage of using a chiral auxiliary electrophile over the (-)-sparteine approach as this methodology give access to both planar chiral cyclophane forms.

The absolute configuration of the separated diastereoisomers was assessed by X-ray crystallography. The shorter-retention time isomer crystallized by slow evaporation of an acetone solution at room temperature into the orthorhombic P2₁2₁2₁ space group, with absolute cyclophane configuration assigned as (S)ₖ. Analysis of the X-ray crystal structure of (S)ₖ-2, which incorporates the chiral auxiliary, are summarized in Table 1 and compared with the racemic ethyl ester 3, which crystallized after from an acetone solution into the orthorhombic space group Pca₂₁ (Table 1). Characteristic ¹H NMR data collected at 500 MHz are included for both compounds.

Table 1. Crystal structures and selected ¹H NMR data for [2.2]metacyclophanes (S)ₖ-2 and 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Measurement</th>
<th>(S)ₖ-2</th>
<th>rac-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intra-annular distance (C8 to C16)</td>
<td>2.64(6) Å</td>
<td>2.64(6) Å</td>
</tr>
<tr>
<td>2</td>
<td>A ring distortion from planarity</td>
<td>9.20(5)°</td>
<td>9.38(4)°</td>
</tr>
<tr>
<td>3</td>
<td>B ring distortion from planarity</td>
<td>6.68(6)°</td>
<td>7.49(1)°</td>
</tr>
<tr>
<td>4</td>
<td>Bond length C1-C2</td>
<td>1.57(14) Å</td>
<td>1.57(18) Å</td>
</tr>
<tr>
<td>5</td>
<td>Angle C1-C2-C3</td>
<td>111.34(8)°</td>
<td>110.46(10)°</td>
</tr>
<tr>
<td>6</td>
<td>Torsion angle C3-C4-C18-O1</td>
<td>94.77(1)°</td>
<td>104.47(2)°</td>
</tr>
<tr>
<td>7</td>
<td>Hc chemical shift (δ)</td>
<td>3.15</td>
<td>3.15</td>
</tr>
<tr>
<td>8</td>
<td>Hc chemical shift (δ)</td>
<td>1.94</td>
<td>1.95</td>
</tr>
<tr>
<td>9</td>
<td>Hc chemical shift (δ)</td>
<td>4.51</td>
<td>4.53</td>
</tr>
<tr>
<td>10</td>
<td>Hc chemical shift (δ)</td>
<td>3.93</td>
<td>3.94</td>
</tr>
</tbody>
</table>

¹H NMR chemical shifts (δ) are reported in ppm in CDCl₃.

Review of the X-ray structural data for (S)ₖ-2 and rac-3 confirmed the expected stepwise anti conformation of the [2.2]metacyclophane system (Table 1). This positioned the two aryl rings close together with a short intra-annular distance of 2.64
For the reaction using achiral ethyl chloroformate, electrophilic reaction occurs at 473 K.

Further investigations on planar chiral [2.2]metacyclophanes are currently ongoing and the results will be reported in due course.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary Material

Experimental procedures and detailed characterization data of all new compounds. All \(^1\)H and \(^13\)C NMR spectra for compounds 2, 3 and (R)\(_9\)-2. X-Ray crystallographic data for (S)\(_9\)-2 and rac-3. Chiral semi-preparative HPLC plots of 2 and 3 and racemization plots data. This material is available free of charge via the Internet at http://...
13. Crystal structure data deposited at the Cambridge Crystallographic Data Centre with deposit number CCDC 2016230.
14. Crystal structure data deposited at the Cambridge Crystallographic Data Centre with deposit number CCDC 2016231.