Organic helicenes, which are helical derivatives made of ortho-fused aromatic rings,[1] usually feature a minimum of six consecutive rings to ensure a large enough helical pitch and configurational stability at room temperature. Higher order helicenes, including axially[2] or laterally extended derivatives,[3] present greater racemization barriers and, importantly, modified properties brought by the extension of the helical framework. Strategies have thus been developed to extend helicene scaffolds by, for instance, additions of ortho-fused rings at terminal ends of preexisting skeletons (Scheme 1a).[4] However, due to the inherent difficulty to post-functionalize helicenes regioselectively, and at terminal ends in particular, such efforts have been limited so far.[5] Diaza [4]helicenes of type 1, [6] cationic derivatives related to triangulenium salts,[7] are prepared in two steps from 1,3-dimethoxybenzene (R=alkyl, 60–77% overall yield). These helicenes can be isolated as single enantiomers on gram scale using established resolution procedures.[8] Thanks to a high configurational stability (ΔG°_racem=42 kcal mol⁻¹),[9] compounds 1 can be handled at high temperature conveniently. They display fluorescence within the transparency window of biological media[10] and have proven their ability to selectively bind DNA[11] or behave as chiroptical switch.[12] Of most relevance to this study, helicenes 1 react under nitration or Vilsmeier–Haack conditions to afford products of electrophilic substitution at position 6 exclusively (Scheme 1b).[13] While useful for the tuning of physico-chemical properties, these reactions did not open a synthetic access to elongated helicenes. Alternative protocols that would allow electrophilic substitutions at terminal rings exclusively were thus looked for.

Herein, using strongly acidic conditions for thermodynamic control, late stage electrophilic functionalizations of cationic 1,13-dimethoxy [4]helicenes 1 are reported at terminal rings. Reactions performed in polyphosphoric acid (PPA) or with Eaton’s reagent (7.5 %P₂O₅ in CH₃SO₃H)[14] lead over time to derivatives 2 or 3 carrying functional groups at position 2 or at positions 2 and 12 exclusively (Scheme 1c). Extension of this
reactivity to cationic [6]helicenes affords compounds 4. With substitutions happening next to the terminal MeO groups in 2 or 3, elongation strategies could be developed to yield extended [5] and [6]helicenes, precursors providing a general access to a variety of enantiopure elongated helicenes. Recently, it was shown that cationic diaza [6]helicenes react with electrophiles and, like [4]helicenes 1, with preferred substitutions on the central (top) benzene ring (See Equation S1 in the Supporting Information). It was then conceivable that a different regioselectivity would also occur in PPA or Eaton’s reagent. To our satisfaction, products 4a, 4b, 4c of functionalization at terminal rings were isolated in low to good yields (17–89%, Table 1, Entries 5 to 7).

With these results showing a distinct regioselectivity in strong acid conditions, control experiments were carried out (Table 2). First, acylation of 1 with benzoic acid was performed at 30 °C for 1 h (Entry 1). Interestingly, in addition to starting material 1 and adduct 2a, regioisomer 7 was observed in relatively equal proportion. Longer reaction time (3 h) or higher temperature (60 °C) led to the predominant formation of 2a (Entries 2 and 3). Then, submission of isomer 7 to Eaton’s reagent for 1 h at 60 °C yielded 1 and regioisomer 2a quasi exclusively (Entry 4). Finally, 2a was treated under the same conditions (Entry 5). After 1 h, 2a remained the major component (59%) of the crude along with 1 (33%) and 7 (8%). All together, these experiments indicate that the formation of 2a and 7 occurs under thermodynamic and kinetic control, respectively. Under strongly acidic conditions, terminal ring functionalization is thus favored by higher temperatures and longer reaction times.

Care was then taken to tackle the goal of the project, that is, the elongation of 1 to [5] and possibly [6]helicene derivatives (Scheme 2). To that effect, substrate 1 was treated in Eaton’s reagent with salicylic acid at 50 °C for 24 h to afford synthetic intermediate 8 (X = OH), which was engaged immediately under basic conditions to provoke an intramolecular S$_2$Ar cyclization. In fact, treatment of 8 with an excess of Et$_3$N in acetonitrile at 65 °C afforded [5]helicene 5a in 56% combined yield (two steps). The procedure is general as sulfur-containing 5b was isolated in 58% combined yield starting from 1 and thiosalicylic acid. Using sterically hindered 1-hydroxy-2-naphthoic acid as reagent, it was necessary to adopt more forcing conditions for the cyclization step (aq. NaOH, 0.1 M in acetonitrile)

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**Table 1. Terminal ring(s) functionalization of [4] and [6]helicenes.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Additive</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>1 [%]</th>
<th>2a [%]</th>
<th>7 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>PhCO$_2$H</td>
<td>30</td>
<td>1</td>
<td>38</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>PhCO$_2$H</td>
<td>30</td>
<td>3</td>
<td>13</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>PhCO$_2$H</td>
<td>60</td>
<td>1</td>
<td>7</td>
<td>89</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>PhCO$_2$H</td>
<td>60</td>
<td>1</td>
<td>75</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>–</td>
<td>60</td>
<td>3</td>
<td>33</td>
<td>59</td>
<td>8</td>
</tr>
</tbody>
</table>

[a] Proportions determined by $^1$H NMR spectroscopy on crude reaction mixtures. Average of two reactions. [b] Compounds 2a or 7 were heated without PhCO$_2$H. [c] 3 Equiv.

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**Table 2. Thermodynamic versus kinetic control in the formation of 2a in Eaton’s reagent.**

Entry | Substrate | Product | T [°C] | t [h] | 1 [%] | 2a [%] | 7 [%]
---|-----------|---------|--------|-------|-------|--------|------
1 | 2a | 2a | 80 | 91 | 1 | 60 | 81 |
2 | 2b | 2b | 24 | 90 | 77 | 19 | 60 | 75 |
3 | 3c | 3c | 2 | 60 | 93 | 5 | 60 | 70 |
4 | 3d | 3d | 2 | 90 | 89 | 1 | 60 | 89 |
5 | 4a | 4a | 2 | 80 | 89 | 5 | 60 | 70 |
6 | 4b | 4b | 2 | 80 | 83 | 22 | 50 | 58 |
7 | 4c | 4c | 2 | 80 | 83 | 22 | 50 | 58 |

[a] Stick view of the crystal structure of rac-2a (H-atoms, BF$_4^-$ counterion, and part of n-propyl chains omitted). [b] Reactions performed with 3 equiv of electrophiles in PPA under vigorous mechanical stirring. [c] Reactions performed with 3 equiv of electrophiles in 7.5% P$_2$O$_5$ in CH$_3$SO$_2$H under magnetic stirring. [d] Isolated yields.

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trile) and compound 5c was isolated in 23% due to the steric encumbrance. Finally, with 5b in hand, the (inside) sulfur atom was oxidized with m-CPBA. The corresponding sulfoxide 5d was isolated in excellent yield (95%) as a single diastereomer (d.r. > 49:1).\(^{[21]}\)

For the homologation to \([6]\) helicene scaffolds, the use of more reactive (electron-poor) o-fluorobenzoic acid 9 was necessary, as compounds 5a or 5b did not react with salicylic or thiosalicylic acids under above-described conditions. Even with 9, acylation of 5a was slow in Eaton’s reagent (15% conv. after 3 d at 50°C). The use of even more acidic conditions was required.\(^{[22]}\) In fact, treatment of 5a with 9 for 15 min at 80°C in trifluoromethanesulfonic acid (TFOH) containing P,O\(_2\) (18 wt%) resulted in acylated intermediate 10a (Scheme 3). This compound was engaged immediately in demethylating conditions with lithium iodide in DMF at 140°C to form dioxoa 6aa (36%, X-ray: Table 3, left). In this case, the in situ generated phenoxide of type 11 reacts ipso to the fluorine atom by intramolecular S\(_2\)Ar to ensure the final ring closure after fluoride anion elimination (Scheme 3, path 1). With 5b as substrate, the same conditions afforded intermediate 10b and then mixed oxathia 6ab in 53% yield. Finally, to prepare dithia 6bb (54%), intermediate 10b was treated with sodium sulfide (3.6 equiv) in presence of Cul (40 mol%) in DMF (80°C, 16 h). An intermolecular substitution of the fluorine by a sulfur atom occurs to generate intermediate 12 prior to an intramolecular S\(_2\)Ar of the MeO group (Scheme 3, path 2). This second type of approach will be beneficial for the enantiospecificity (see below).

At that stage, all reactions had been performed in racemic series. Care was thus taken to perform the elongations using enantiopure M-1 or P-1 as substrates. Satisfactorily, as analyzed by chiral stationary phase (CSP)-HPLC (Figures S2–S8 in the Supporting Information), extended \([5]\) helicenes 5a and 5b were obtained in excellent enantiomeric purity (ee > 98%) while 5c was isolated with a 90% ee.\(^{[23]}\) VCD (vibrational circular dichroism) analysis of (−) and (+)-5a (optical rotations measured at 365 nm at 20°C) establishes unambiguously P and M configuration\(^{[24]}\) for the helicenes made from P-1 and M-1, respectively (Figure 1).\(^{[25]}\) As it could be expected, retention of helical configuration happens upon terminal ends elongation. However, and significantly, the second ring elongation led to either full racemization or complete enantioméricity depending on the synthetic route (Scheme 3, path 1 or path 2). This dual behavior can be explained mechanistically. In path 1, after formation of 11, the loss of enantiomeric purity is due to the transient formation of an achiral (planar) diazaoxatriangulenium intermediate 13 by an intramolecular attack of the phenoxide anion onto the extended ring [Eq. (1)]. Such a racemization process cannot occur following path 2. This was demonstrated

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**Scheme 2.** Reaction conditions: (a) Eaton’s reagent, 50°C, 3–24 h, 3 equiv ArCHO, HCl. (b) 2.5:1 mixture of MeCN/RT, 65°C, 2–6 h. (c) 1:1 mixture of MeCN/aq. NaOH (0.1 M), reflux, 8 h. (d) m-CPBA, CH\(_2\)Cl\(_2\), 20°C, 4 h. Isolated yields [%] for the combined steps.

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**Scheme 3.** Reaction conditions: [a] P,O\(_2\) (18 wt%) in TFOH, 90°C, 15–30 min. [b] DMF, LiI (10 equiv), 140°C, 1–6 h. [c] DMF, Na,S (3.6 equiv), Cul (40 mol%), 80°C, 16 h. Isolated yields [%] for the combined steps.

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**Table 3.** Stick views of 6aa, 5b, and 6bb and relevant data for X-ray structures of 5b, 5c, 6a, 6aa, and 6bb.\(^{[26]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Helicene</th>
<th>X, Y</th>
<th>d(X, Y) [Å]</th>
<th>Helical pitch [Å]</th>
<th>Helical angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5c</td>
<td>O, O</td>
<td>2.80</td>
<td>2.82</td>
<td>49.0</td>
</tr>
<tr>
<td>2</td>
<td>6aa</td>
<td>O, O</td>
<td>2.68</td>
<td>2.68</td>
<td>35.0</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td>O, S</td>
<td>3.12</td>
<td>3.01</td>
<td>61.7</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>O, S</td>
<td>3.03</td>
<td>2.97</td>
<td>55.6</td>
</tr>
<tr>
<td>5</td>
<td>6bb</td>
<td>S, S</td>
<td>3.47</td>
<td>3.47</td>
<td>56.6</td>
</tr>
</tbody>
</table>

[a] Compounds classified as a function of the inward heteroatoms, O or S. M configurations displayed arbitrarily. H atoms and anionic counterions are removed for clarity. [b] Helical pitch determined by the distance between the first and the last atom in ortho position of the helicene framework. [c] Helical angle calculated for two planes generated from the first and the last rings, counting as part of the helicene framework.
in the enantiospecific synthesis of 6ab that occurs, through the second route, in excellent enantiomeric purity (ee 99%, 47% yield for two steps).

In terms of structural properties, compounds 5 and 6 display very high configurational stability ($\Delta G^+ > 36 \text{ kcal mol}^{-1}$), as shown by the lack of racemization of 5a at 180 °C in DMSO (VT-ECD variable temperature electronic circular dichroism monitoring, 21–180 °C, Figures S9–S11 in the Supporting Information).\cite{15c} Single crystals of 5b, 5c, 5d, 6aa, and 6bb were furthermore obtained and analyzed by X-ray diffraction. Clearly, the nature of the inwards heteroatoms (O or S) influences the geometry of the helicene frameworks (Table 3). Dioxa derivatives (5c, 6aa) present the shortest distances between the inside heteroatoms. Helical angle and pitch values are also lower for 5c and 6aa than for oxathia (5b, 5d) and dithia (6bb) analogues. This is probably due to the larger atomic radius of the sulfur over the oxygen atom, 1.83 versus 1.37 Å, respectively.\cite{26}

(Chir)optical properties, UV and ECD, of extended [5] and [6]helicenes were recorded in CH$_3$CN (Figures S12–S18 in the Supporting Information). The effect of the inwards heteroatoms can be again clearly noticed. In the dioxa series (5a, 5c, 6aa), the extension of the helical scaffold produced little effect in absorption (Figure 2, bottom). ECD spectra were however affected in the UV region (Figure 2, top). In fact, a progressive enhancement of the ECD band intensities in the 350–400 nm domain is observed from [4] to [6]helicenes. On the other hand, the insertion of sulfur atom(s) led to noticeable i) red shifts of the lowest energy transitions in absorption spectra and ii) strong Cotton effects in ECD in the visible region (Figure 3).

In summary, in PPA or Eaton’s reagent, direct late-stage functionalizations at terminal ends of cationic diaza helicenes have been achieved. Thanks to the strongly acidic conditions that permit reversible electrophilic substitutions, acylations, sulfonylations, or alkylations occur at the extremity(ies) of the helical core. This exclusive regioselectivity was used to generate extended [5] or [6]helicenes from [4]helicenes in successive one-pot processes. Retention of configuration and excellent enantiospecificity (up to 99%) can be further obtained for the helicene elongation in the enantiopure series.
Experimental Section

Synthetic procedures and spectral characterization of new compounds 2–6 are reported in the Supporting Information. CCDC 1550987 (2a), 1550988 (5b), 1550989 (5c), 1550990 (5d), 1550991 (6aa), and 1550992 (6bb) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenium ions · helicenes · regioselectivity · $S_1 Ar$ · $S_2 Ar$ · thermodynamic control
The presence of the benzoyl group forces a change in conformation for the neighboring MeO that is not coplanar anymore with the aromatic ring (torsion angle: 62.1°). In solution (1H NMR), it leads to a shielding of the MeO signal (3.05 vs. 3.79 ppm). The acyl group is also twisted out of conjugation.


Regioisomer 7 was prepared via an unrelated route using reported conditions, see ref. [13b].

This interconversion of the acyl group through acid catalysis probably occurs with the intermediacy of ipso arenium ions, see ref. [17] and W. M. Schubert, H. K. Latourette, J. Am. Chem. Soc. 1952, 74, 1829–1834.

MeO groups of quinacridiniums 1 are readily substituted by nucleophiles thanks to the electron-withdrawing ability of the central cationic core. See ref. [7].

The relative configuration was established by X-ray diffraction analysis (see the Supporting Information). Clearly, the peracid approaches the less hindered side of the sulfur atom, reacting with the pro-R lone pair of M-5b (or pro-S of P-5b). In fact, functionalizations of stereogenic heteroatoms embedded in helical frameworks are often highly stereoselective, see: P. Allard, D. Dova, V. Magne, P. Retallacke, S. Cauteruccio, E. Licandro, A. Voituriez, A. Marinetti, Chem. Commun. 2016, 52, 10984–10987.

Compounds 1–6 are effective dyesthat absorb light from the UV to roughly 650 nm; the sign of the optical rotation depends sometimes upon the incident wavelength of light.

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