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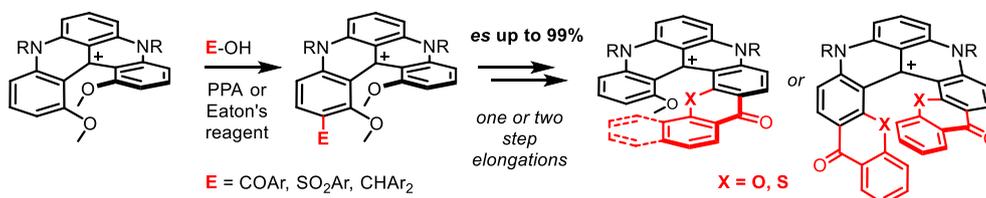
Enantiospecific Elongation of Cationic Helicenes by Electrophilic Functionalization at Terminal Ends

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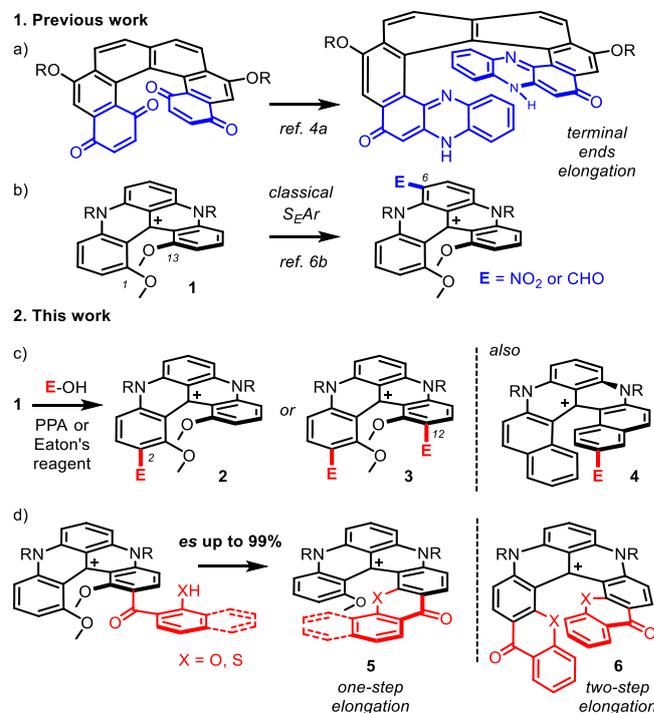


Abstract: A strategy for late-stage electrophilic functionalizations of cationic helicenes is exposed. Thanks to strongly acidic conditions that permit reversible electrophilic substitutions, regioselective acylations, sulfonations or alkylations occur at the extremity(ies) of the helical cores. Extended [5] or [6]helicenes can then be generated from cationic [4]helicenes in successive one-pot elongation processes. Retention of configuration and excellent enantiospecificity (up to 99%) are observed for the helicene growth in the enantiopure series.

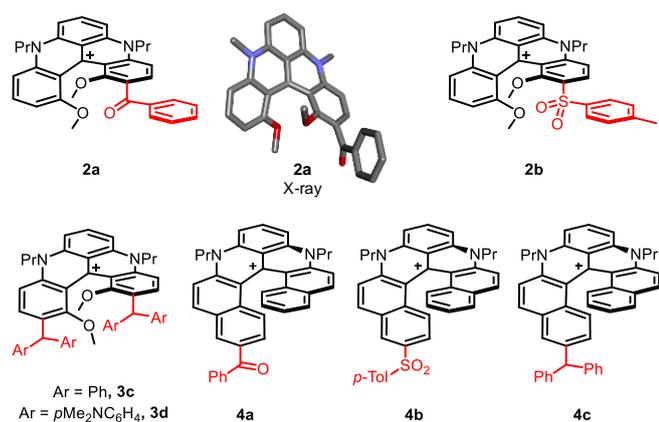
Organic helicenes, which are helical derivatives made of *ortho*-fused aromatic rings,^[1] usually feature a minimum of five consecutive rings to ensure large enough helical pitch and configurational stability at room temperature. Higher order helicenes, including axially^[2] or laterally extended derivatives,^[3] 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] Herein, using the intrinsic reactivity of cationic 1,13-dimethoxy[4]helicenes **1** towards electrophiles and strongly acidic conditions for thermodynamic control, an orthogonal mode of late stage functionalization at terminal rings is reported. In fact, contrary to classical electrophilic aromatic substitutions that occur at position 6 of compounds **1** (Scheme 1b),^[6] reactions performed in polyphosphoric acid (PPA) or with Eaton's reagent (7.5% P₂O₅ in CH₃SO₃H)^[7] 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, products **5** and **6** respectively (Scheme 1d). Importantly, these configurationally stable cationic derivatives ($\Delta G^\ddagger > 36$ kcal/mol, 180 °C)^[8] can be generated with high enantiospecificity (es up to 99%) from *M*-**1** or *P*-**1** precursors providing a general access to a variety of enantiopure elongated helicenes.

Diaza[4]helicenes of type **1**, cationic derivatives related to triangulenium salts,^[9] 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.^[10] Thanks to a high

configurational stability ($\Delta G^\ddagger_{\text{racem}} \sim 42$ kcal.mol⁻¹),^[11] compounds **1** can be handled at high temperature conveniently. They display fluorescence within the transparency window of biological media^[12] and have proven their ability to selectively bind DNA^[13] or behave as chiroptical switch.^[14] 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). 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 of the terminal rings exclusively were thus looked for.



Scheme 1. a) Helicene growth by terminal ends elongation. b) Reported regioselective electrophilic aromatic substitutions of [4]helicenes **1**. c) Orthogonal regioselectivity by thermodynamically-driven functionalizations in PPA or Eaton's reagent. d) Enantiospecific syntheses of extended helicenes **5** and **6**. Numbers in italic indicate substituent positions.

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

Entry	Product	PPA ^[b]			Eaton's reagent ^[c]		
		Time	Temp	Yield	Time	Temp	Yield
1	2a	2 h	80 °C	91%	1 h	60 °C	81%
2	2b	24 h	90 °C	77%	19 h	60 °C	75%
3	3c	2 h	60 °C	93%	5 h	60 °C	70%
4	3d	2 h	90 °C	89%	1 h	60 °C	89%
5	4a	2 h	80 °C	89%	6 h	50 °C	66%
6	4b	2 h	80 °C	83%	22 h	50 °C	58%
7	4c	2 h	80 °C	-	3 h	50 °C	17%

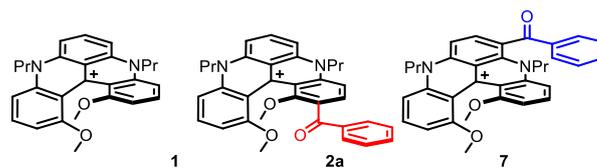
[a] Isolated yields [%]. Stick view of the crystal structure of *rac*-**2a** (H-atoms, BF₄⁻ counterion and part of *n*-propyl chains omitted). [b] Reactions performed with 3 equiv of electrophiles in PPA under vigorous mechanical stirring. [c] Reactions performed with 3 equiv of electrophiles in 7.5% P₂O₅ in CH₃SO₃H under magnetic stirring.

In this context, combinations of strong Brønsted acids and dehydrating agents, such as PPA or Eaton's reagent (7.5% P₂O₅ in CH₃SO₃H), had been reported to promote Friedel-Craft alkylations and acylations.^[7] It was also established that strong acids can provoke the general isomerization of substituted arenes; molecular rearrangements leading to interconversions of constitutional isomers.^[15] It was then conceivable that such conditions could lead to efficient electrophilic functionalizations of [4]helicene **1** but with a markedly different regioselectivity. Salt [**1**][BF₄] (R = *n*-Pr) was thus treated with benzoic acid in PPA at 80 °C for 2h (Table 1). To our satisfaction, salt [**2a**][BF₄] was obtained in excellent yield as a single isomer (91%, entry 1); the regioselectivity of which was ascertained by NMR spectroscopy and X-ray diffraction analysis.^[16] Using *p*-toluenesulfonic acid as reagent, sulfone **2b** was isolated in 75% yield. With bisarylcarbinol reagents (3 equiv), double alkylations at the terminal rings occurred leading to products **3c** and **3d** in excellent yields (89–93%, Ar = Ph, *p*Me₂NC₆H₄, entries 3 and 4). These results were encouraging but scale-up was difficult in viscous PPA. Eaton's reagent was selected as substitute. Satisfactorily, products **2a**, **2b**, **3c** and **3d** were isolated in good to excellent yields (70–89%).

Recently, it was shown that cationic diaza[6]helicenes react with electrophiles, like [4]helicenes **1**, spontaneously on the central (top) benzene ring (eq S1, supporting information).^[6] It was then conceivable that a different regioselectivity would 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 separate regioselectivity in strong acid conditions, a series of control experiments was performed to rationalize the reactivity. The results are detailed in Table 2. First, acylation of **1** with benzoic acid was performed at 30 °C instead of 60 °C for 1h (entry 1). Three components were detected in the crude mixture: starting material **1**, adduct **2a** and, interestingly, regioisomer **7** in relatively equal proportions; longer reaction time or higher temperatures leading to a larger amount of **2** over **7** (entries 2 & 3). Isomer **7** was submitted to Eaton's reagent for 1h at 60 °C in the absence of benzoic acid.^[17] Significantly, an essentially complete transformation of **7** into [4]helicene **1** and regioisomer **2a** was observed (entry 4). Finally, product **2a** was submitted to the same conditions (Eaton's, 60 °C). After 1h, **2a** remained the major component of the crude along with **1**; adduct **7** being only a minor component (entry 5). All together, these experiments indicate that the formation of **2a** occurs under thermodynamic control while the formation of "classical" isomer **7** is kinetically preferred. Terminal ring functionalization is thus clearly favored by higher temperatures and longer reaction times under strongly acidic conditions.^[18]

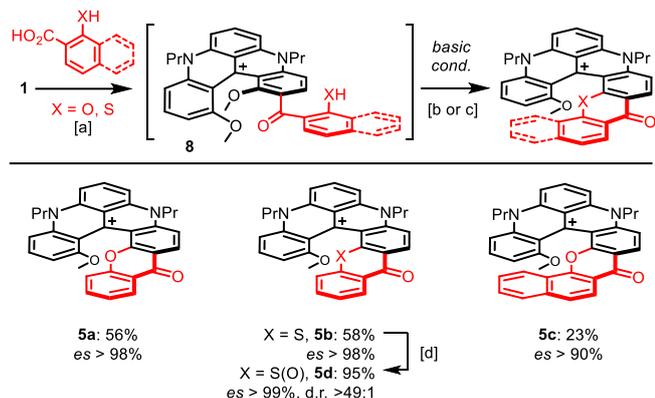
Table 2. Thermodynamic vs. kinetic control in the formation of **2a** in Eaton's reagent.^[a]

Entry	Substrate	Additive	Temp	Time	1	2a	7
1	1	PhCO ₂ H (3 equiv)	30 °C	1h	38%	33%	29%
2	1	PhCO ₂ H (3 equiv)	30 °C	3h	13%	57%	30%
3	1	PhCO ₂ H (3 equiv)	60 °C	1h	7%	89%	4%
4 ^[b]	7	-	60 °C	1h	75%	21%	4%
5 ^[b]	2a	-	60 °C	3h	33%	59%	8%

[a] Proportions determined by ¹H-NMR spectroscopy on crude reaction mixtures. Average of two reactions. [b] Compounds **2a** or **7** were heated without PhCO₂H.

Care was then taken to tackle the goal of the project, *ie* 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 24h to afford synthetic intermediate **8** (X = OH) which was engaged immediately under basic conditions to provoke an intramolecular S_NAr cyclization.^[19] In fact, treatment of **8** with an excess of Et₃N 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) and compound **5c** was isolated in 23% only 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). The relative configuration was established by X-ray diffraction analysis (Figure 1, left). Clearly, the peracid approaches the less hindered side of the sulfur atom, *ie* the *pro*-R lone pair for an *M* configuration of **5b**.^[20]



Scheme 2. Reaction conditions: [a] Eaton's reagent, 50 °C, 3-24h, 3 equiv ArCO₂H. [b] 2.5:1 mixture of MeCN:Et₃N, 65 °C, 2-6h. [c] 2:1 mixture of MeCN:aq. NaOH (0.1M), reflux, 8h. Isolated yields [%] for the combined steps.

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 days at 50 °C). The use of even more acidic conditions was required.^[21] In fact, treatment of **5a** with **9** for 15 min at 80 °C in trifluoromethanesulfonic acid (TfOH) containing P₂O₅ (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 dioxo **6aa** (36%, Figure 1, right). In this case, the in-situ generated phenoxide of type **11** reacts *ipso* to the fluorine atom by intramolecular S_NAr 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 CuI (40 mol%) in DMF (80 °C, 16h). An intermolecular substitution of the fluorine by a sulfur atom occurs to generate intermediate **12** prior to an intramolecular S_NAr of the MeO group (Scheme 3, *path 2*). This second type of approach will be beneficial for the enantiospecificity (see below).

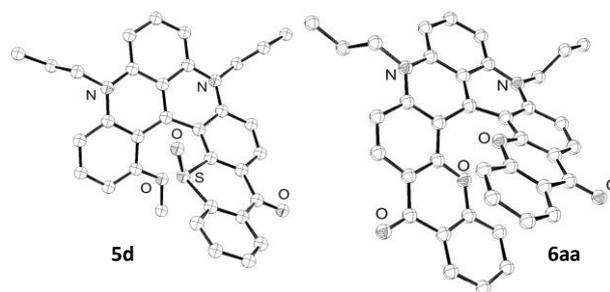
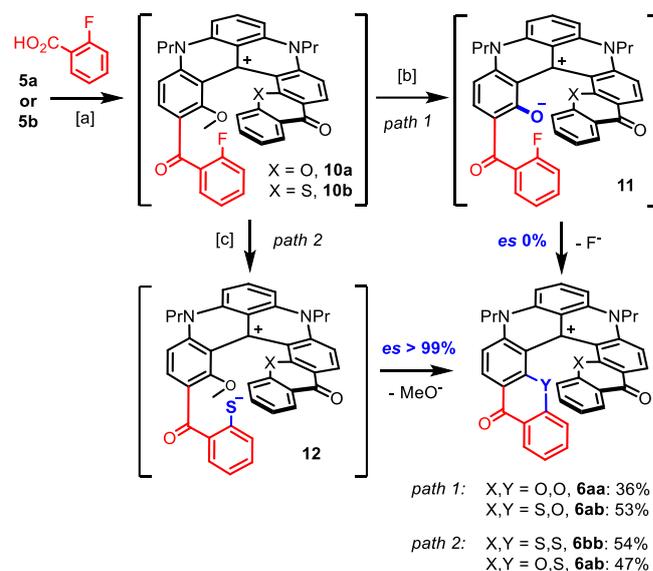


Figure 1. ORTEP views of sulfoxide [5]helicene **5d** (left) and dioxo [6]helicene **6aa** (right). *M*-configurations displayed arbitrarily. H-atoms and anionic counterions are removed for clarity.



Scheme 3. Reaction conditions: [a] P₂O₅ (18% wt) in TfOH, 90 °C, 15-30 min. [b] DMF, LiI (10 equiv), 140 °C, 1-6h. [c] DMF, N₂, Na₂S (3.6 equiv), CuI (40 mol%), 80 °C, 16h. Isolated yields [%] for the combined steps.

At that stage, all reactions had been performed in racemic series and it was questionable whether the helicene growth would be enantiospecific. In fact, ring expansions **1** → **5** or **5** → **6** occur by reactions at terminal methoxy groups. These moieties are essential for the helical pitch and the configurational stability of the helicene framework. It was then conceivable that their replacement by other groups could lead to a racemization. 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), extended [5]helicenes **5a** and **5b** were obtained in excellent enantiomeric purity (*ee* > 98%) while **5c** was isolated with a 90% *ee*. Clearly, in this later case, the harsher ring closure conditions are responsible for the moderate loss of enantiospecificity. The compounds display a very high configurational stability ($\Delta G^\ddagger > 36$ kcal/mol) as shown by the lack of racemization of **5a** at 180 °C in DMSO (VT-ECD monitoring, 21-180 °C, Figure S9-S11).^[8c] Electronic circular dichroism (ECD) spectra present symmetrical curves in the 240 to 700 nm region (Figures S12-S18). VCD analysis of (–) and (+)-**5a** (optical rotations measured at 365 nm at 20 °C) establishes unambiguously *P* and *M* configurations^[22] for the helicenes made

from *P*-1 and *M*-1 respectively (Figure 2).^[23] As it could be expected, retention of helical configuration happens upon terminal ends elongation.

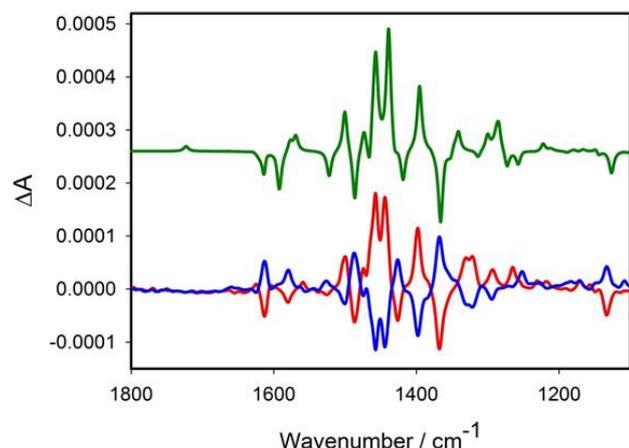
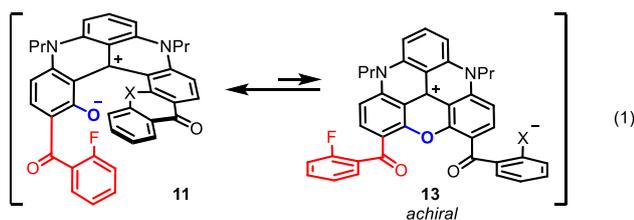


Figure 2. Experimental VCD spectra (CD_2Cl_2 , 298K) of (+) (blue) and (-) (red) enantiomers of **5a** (optical rotations measured at 365 nm). The calculation (green spectrum) was done on the *P*-enantiomer.

Finally and significantly, depending on the synthetic route, the second ring elongation leads to either full racemization or complete enantiospecificity (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 in the enantiospecific synthesis of **6ab** that occurs, though this second route, in excellent enantiomeric purity (*ee* 99%, yield 47 % for two steps).



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

4

Synthetic procedures and spectral characterization of new compounds **2-6** are reported in the electronic supporting information. CCDC XXXXX-XXXXXX, products **2a**, **5b**, **5c**, **5d**, **6aa** and **6bb**, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: Carbenium ions • Helicenes • Regioselectivity • $S_{\text{E}}\text{Ar}$ • $S_{\text{N}}\text{Ar}$ • Thermodynamic control

• $S_{\text{N}}\text{Ar}$ • Thermodynamic control

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