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COMMUNICATION

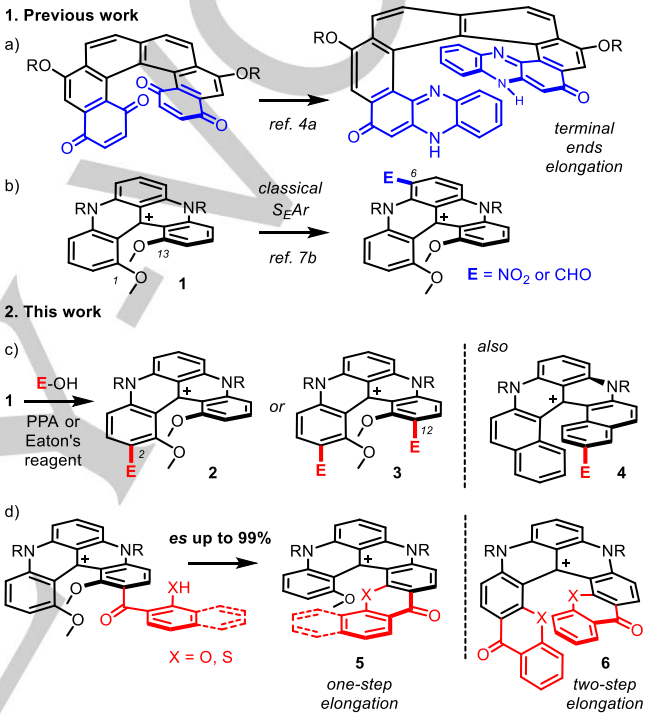
Enantiospecific Elongation of Cationic Helicenes by Electrophilic Functionalization at Terminal Ends

Romain Duwald,[a] Simon Pascal,[a] Johann Bosson,[a] Stéphane Grass,[a] Céline Besnard,[b] Thomas Bürgi,[c] and Jérôme Lacour*[a]

Dedication ((optional))

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, sulfonylations 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 six 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] 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 ($\Delta G^{\ddagger}_{racem}$ ~ 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.



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.

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% P_2O_5 in CH_3SO_3H)[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, products **5** and **6** respectively (Scheme 1d). Importantly, these configurationally stable cationic derivatives ($\Delta G^{\ddagger}_{racem}$ > 36 kcal/mol, 180 °C)[15] can be generated with high enantiospecificity (*es* up to 99%, retention) from *M*-**1** or *P*-**1** precursors providing a general access to a variety of enantiopure elongated helicenes.

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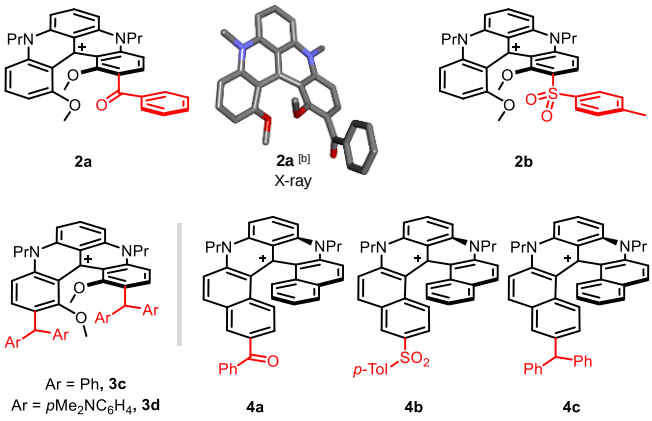
Table 1. Terminal ring(s) functionalization of [4] and [6]helicenes.[a]



Entry	Product	PPA[c]			Eaton's reagent[d]		
		Time	T [°C]	Yield	Time	T [°C]	Yield
1	**2a**	2 h	80	91%	1 h	60	81%
2	**2b**	24 h	90	77%	19 h	60	75%
3	**3c**	2 h	60	93%	5 h	60	70%
4	**3d**	2 h	90	89%	1 h	60	89%
5	**4a**	2 h	80	89%	6 h	50	66%
6	**4b**	2 h	80	83%	22 h	50	58%
7	**4c**	2 h	80	-	3 h	50	17%

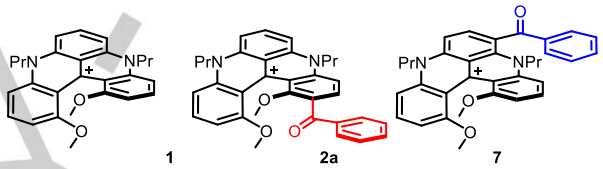
[a] Isolated yields. [b] Stick view of the crystal structure of *rac*-**2a** (H-atoms, BF_4^- counterion and part of *n*-propyl chains omitted). [c] Reactions performed with 3 equiv of electrophiles in PPA under vigorous mechanical stirring. [d] Reactions performed with 3 equiv of electrophiles in 7.5% P_2O_5 in CH_3SO_3H under magnetic stirring.

Previously, combinations of strong Brønsted acids and dehydrating agents, such as PPA or Eatons' reagent (7.5% P_2O_5 in CH_3SO_3H), had been reported to promote Friedel-Craft alkylations and acylations.[14] Salt [**1**][BF_4] (R = *n*-Pr) was thus treated with benzoic acid in PPA at 80 °C for 2 h (Table 1). To our satisfaction, salt [**2a**][BF_4] 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*$Me_2NC_6H_4$, 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 and, like [4]helicenes **1**, with preferred substitutions on the central (top) benzene ring (eq S1, supporting information).[13] 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,[17] 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 & 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).[18] 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.[19]

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

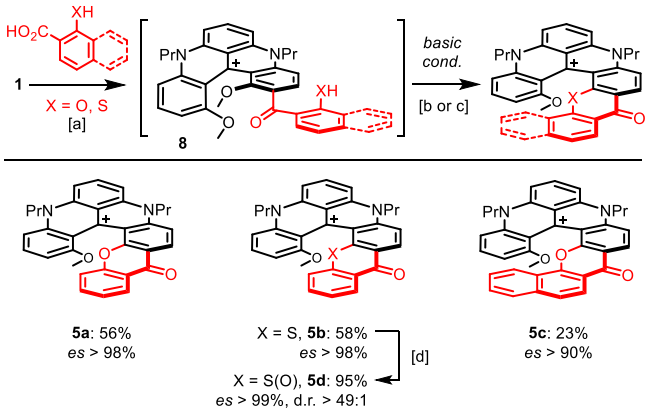


Entry	Substrate	Additive	T [°C]	Time	**1**	**2a**	**7**
1	**1**	$PhCO_2H$ (3 equiv)	30	1 h	38%	33%	29%
2	**1**	$PhCO_2H$ (3 equiv)	30	3 h	13%	57%	30%
3	**1**	$PhCO_2H$ (3 equiv)	60	1 h	7%	89%	4%
4[b]	**7**	-	60	1 h	75%	21%	4%
5[b]	**2a**	-	60	3 h	33%	59%	8%

[a] Proportions determined by ^{1}H-NMR spectroscopy on crude reaction mixtures. Average of two reactions. [b] Compounds **2a** or **7** were heated without $PhCO_2H$.

Care was then taken to tackle the goal of the project, *i.e.* 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_NAr cyclization.[20] In fact, treatment of **8** with an excess of Et_3N 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% 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]



Scheme 2. Reaction conditions: [a] Eaton's reagent, 50 °C, 3-24 h, 3 equiv $ArCO_2H$. [b] 2.5:1 mixture of MeCN:Et_3N, 65 °C, 2-6 h. [c] 2:1 mixture of MeCN:aq. NaOH (0.1 M), reflux, 8 h. 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.[22] In fact, treatment of **5a** with **9** for 15 min at 80 °C in trifluoromethanesulfonic acid (TfOH) containing P_2O_5 (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 dioxa **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_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, 16 h). 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).

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), extended [5]helicenes **5a** and **5b** were obtained in excellent enantiomeric purity (*ee* > 98%) while **5c** was isolated with a 90% *ee*.[23] VCD analysis of (–) and (+)-**5a** (optical rotations measured at 365 nm at 20 °C) establishes unambiguously *P* and *M* configurations[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.

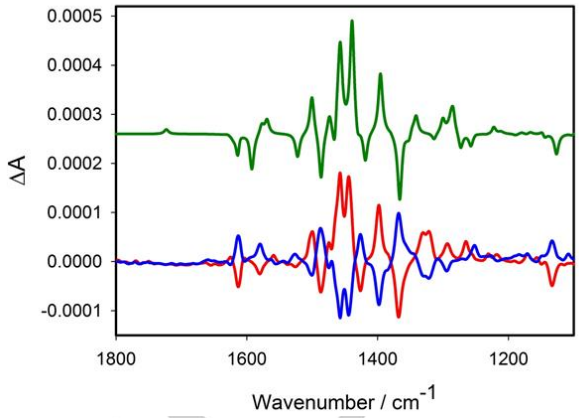
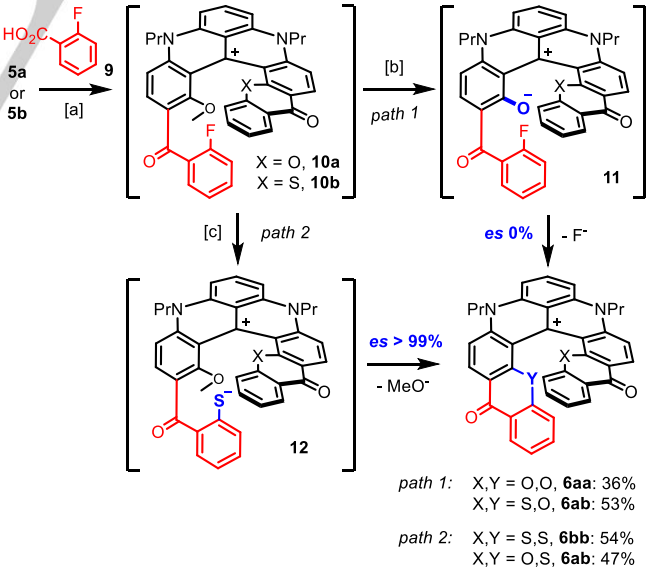
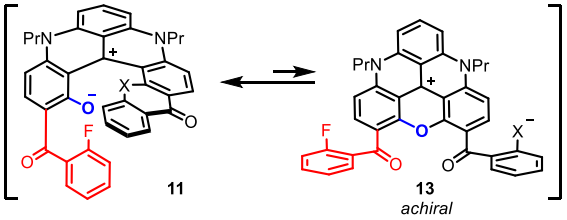


Figure 1. Experimental VCD spectra (CD_2Cl_2, 298 K) of (+) (blue) and (–) (red) enantiomers of **5a** (optical rotations measured at 365 nm). The calculation (green spectrum) was done on the *P*-enantiomer.

However and significantly, the second ring elongation led to either full racemization or complete enantiospecificity 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 in the enantiospecific synthesis of **6ab** that occurs, through the second route, in excellent enantiomeric purity (*ee* 99%, 47% yield for two steps).



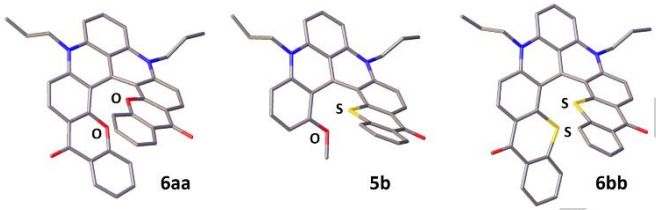
Scheme 3. Reaction conditions: [a] P_2O_5 (18% wt.) in TfOH, 90 °C, 15-30 min. [b] DMF, LiI (10 equiv), 140 °C, 1-6 h. [c] DMF, N_2, Na_2S (3.6 equiv), CuI (40 mol%), 80 °C, 16 h. Isolated yields [%] for the combined steps.



(1)

In terms of structural properties, compounds **5** and **6** display 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).[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) influence 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 *vs.* 1.37 Å respectively.[26]

Table 3. Stick views of **6aa**, **5b** and **6bb** and relevant data for X-ray structures of **5b**, **5c**, **5d**, **6aa** and **6bb**.[a]



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

[a] Compounds classified as a function of the inwards heteroatoms, O or S. *M*-configurations displayed arbitrarily. H-atoms and anionic counterions are removed for clarity. [b] Helical angle calculated for two planes generated from the first and the last rings counting as part of the helicene framework. [c] Helical pitch determined by the distance between the first and the last atom in *ortho*-position of the helicene framework.

(Chir)optical properties, UV and ECD, of extended [5] and [6]helicenes were recorded in CH_3CN (Figures S12-S18). 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).

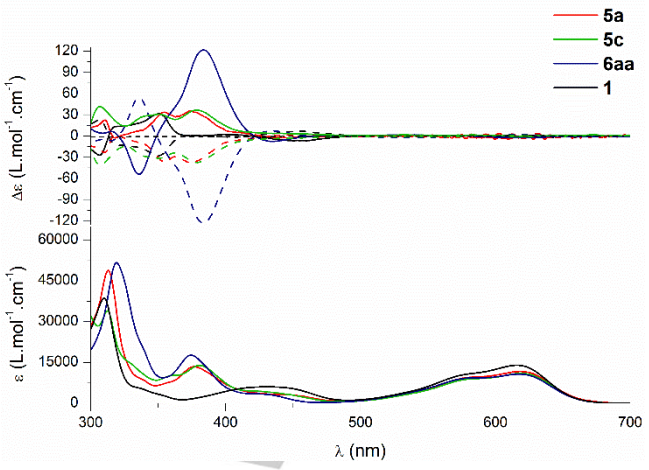


Figure 2. ECD (top) and UV (bottom) spectra of dioxa **5a**, **5c**, **6aa** (CH_3CN, 10^{-5} M) and comparison with that of **1**. Plain line and dashed line correspond to *P* and *M* enantiomers respectively.

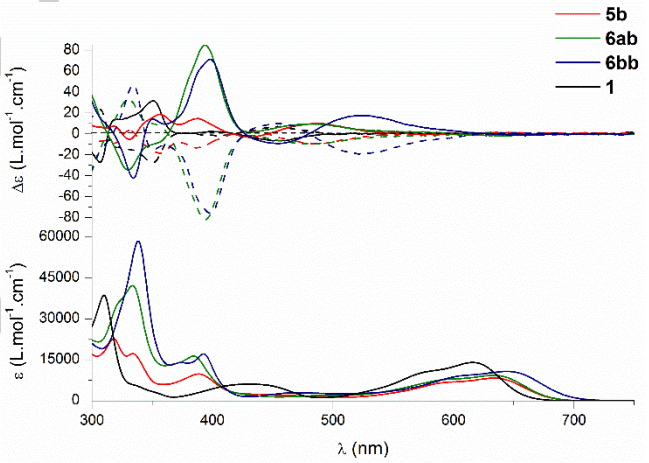


Figure 3. ECD (top) and UV (bottom) spectra of S-containing **5b**, **6ab** and **6bb** (CH_3CN, 10^{-5} M) and comparison with that of **1**. Plain line and dashed line correspond to *P* and *M* enantiomers respectively.

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 electronic supporting information. CCDC 1550987-1550992, 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_EAr • S_NAr • Thermodynamic control

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

[21] The relative configuration was established by X-ray diffraction analysis (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. Aillard, D. Dova, V. Magne, P. Retailleau, S. Cauteruccio, E. Licandro, A. Voituriez, A. Marinetti, *Chem. Commun.* **2016**, *52*, 10984-10987.

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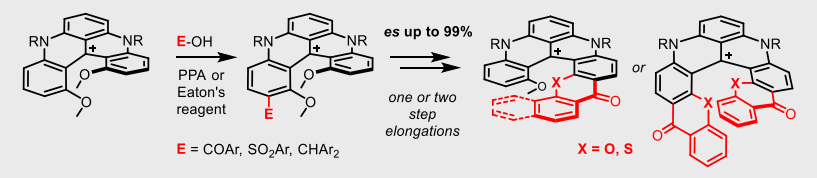
Entry for the Table of Contents

COMMUNICATION



*R. Duwald, S. Pascal, J. Bosson, S. Grass, C. Besnard, T. Bürgi, and J. Lacour**

Page No. – Page No.

Enantiospecific Elongation of Cationic Helicenes by Electrophilic Functionalization at Terminal Ends

[6]-appeal: Direct late-stage functionalization at the terminal ends of cationic diaza helicenes is readily achieved under thermodynamic control, in PPA or Eaton's reagent as solvent. This orthogonal regioselectivity can be used to generate extended [5] or [6]helicenes in successive one-pot elongation processes. Retention of configuration and excellent enantiospecificity (up to 99%) are furthermore obtained in the enantiopure series.