Helicenes

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Modular Synthesis, Orthogonal Post-Functionalization, Absorption, and Chiroptical Properties of Cationic [6]Helicenes**

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Helicenes,[1] which are *ortho*-condensed polyaromatic compounds, are omnipresent in chemistry, biochemistry, and physics as a result of their many different properties and applications.[2] Of importance, these properties can be addressed by introducing substituents at the periphery of the helical cores or by changing the nature of the atoms within. From a synthetic standpoint, such modifications are not always trivial. Introduction of heteroatoms or post-functionalization of helicenes with exocyclic substituents can be difficult to achieve selectively.[3] For this reason, changes are usually made on building blocks prior to the completion of the helical skeletons. Herein, in an effort to overcome this limitation, we report a new class of cationic diaza-, azaoxo-, and dioxo[6]helicenes. The compounds **1**–**3** (Figure 1) are prepared in one step from a single common advanced synthetic intermediate. Selective functionalization of **1** is readily achieved by series of orthogonal regioselective aromatic electrophilic and vicarious nucleophilic substitutions. Reduction, cross-coupling, or condensation reactions also introduce diversity. As a consequence, UV/Vis absorption properties are easily tuneable up to the near-infrared region thanks to these late-stage transformations.

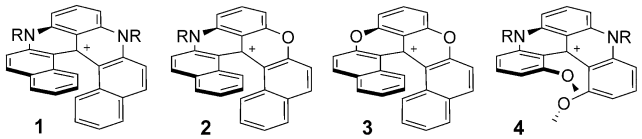
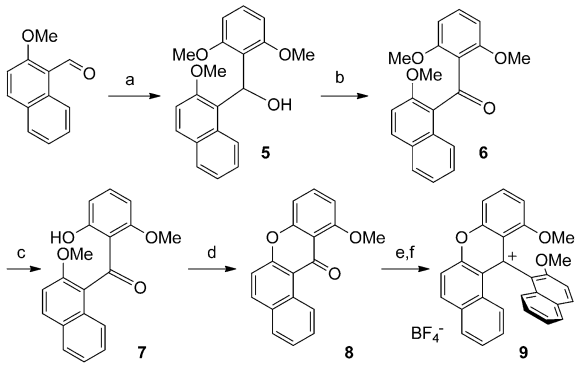


Figure 1. The cationic diaza **1**, azaoxo **2**, and dioxo **3** [6]helicenes, and the [4]helicene quinacridinium derivatives of type **4**. Only the *P* enantiomers are shown. R = alkyl chains.

Previously, quinacridinium derivatives of type **4** have been reported (Figure 1). They are configurationally stable [4]helicenes ($\Delta G^{\neq}$ of racemization is ca. 42 kcal mol^{-1}) and very stable carbocations ($pK_{R+} \approx 19$).[4] Quite a few applications of these compounds have been developed.[5] None of them mention, however, a peripheral functionalization of the aromatic core. In fact, attempts to introduce substituents to **4** lead to mixtures of products because of the lack of chemical differentiation among the three benzo rings.[6] It was thus decided to prepare other cationic heterohelicenes, which could be highly tuneable after their formation, such as the [6]helicenes **1**–**3**.

Access to these compounds was achieved using a modular route made of stepwise additions of the aromatic subunits and controlled sequential ring closures, as summarized in Scheme 1. The first step was the addition of (2,6-dimethoxyphen-1-yl)lithium to 2-methoxy-1-naphthaldehyde. The resulting alcohol **5** (68%) was oxidized to the ketone **6** (98%, DDQ, CH_2Cl_2). Then, treatment with BBr_3 (1 equiv) regioselectively generated the phenol **7**, which underwent a clean O-ring closure upon heating at 225 °C (neat, combined yield 93% for the two steps). Reaction of the resulting tetracyclic ketone **8** with (2-methoxynaphthalen-1-yl)lithium in the presence of $CeCl_3$[7,8] then afforded, after work-up with HBF_4, [**9**][BF_4] in excellent yield (97%). The whole sequence is readily performed on multigram scale.



Scheme 1. Reagents and reaction conditions: a) (2,6-dimethoxyphen-1-yl)lithium, Et_2O, 16 h, −78→25 °C, 68%; b) DDQ, CH_2Cl_2, 20 h, 25 °C, 98%; c) BBr_3, CH_2Cl_2, 4 h, −78→25 °C, 94%; d) neat, 2 h, 225 °C, 99%; e) (2-methoxynaphthalen-1-yl)lithium, $CeCl_3$, Et_2O,14 h, −78→25 °C; f) HBF_4, 97% over 2 steps. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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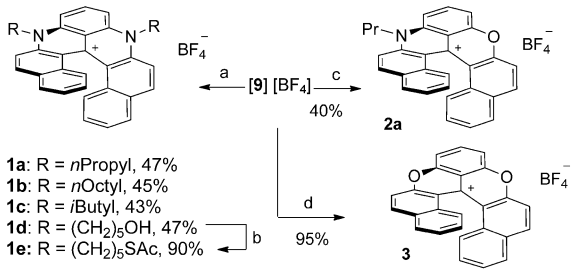
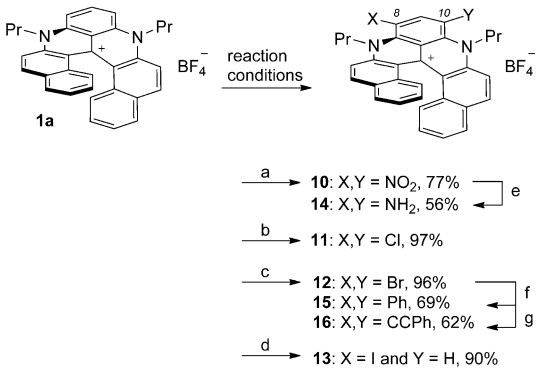
Helicenes of type **1**, **2**, and **3** were then prepared using [**9**][BF_4] as single common precursor. The diaza derivatives **1a–d** (Scheme 2) were synthesized by treatment of [**9**][BF_4] with the corresponding anhydrous aliphatic amines (25 equiv, NMP) and rapid heating under microwave irradiation (170 °C, 10 min).[9] The resulting blue salts, **1a–d**, were isolated in moderate yields (43–47 %). In the case of **1d**, facile transformation of the diol side chains into thioacetyl groups using Mitsunobu-type conditions was achieved to give **1e** (90 %). To obtain the purple azaoxa salt **2a**, **9** was heated in neat anhydrous *n*-propylamine at reflux (49 °C, 30 min). Then, after complete evaporation of the amine in vacuo at 20 °C, application of a burst of heat (200 °C, 5 min) afforded the mixed azaoxo derivative [**2a**][BF_4] in 40 % yield. Finally, rapid treatment of [**9**][BF_4] in molten Pyr·HCl (224 °C, 2 min) and ion-exchange metathesis (HBF_4, 25 °C) afforded the red dioxo helicene **3** as its BF_4 salt in excellent yield (95 %).



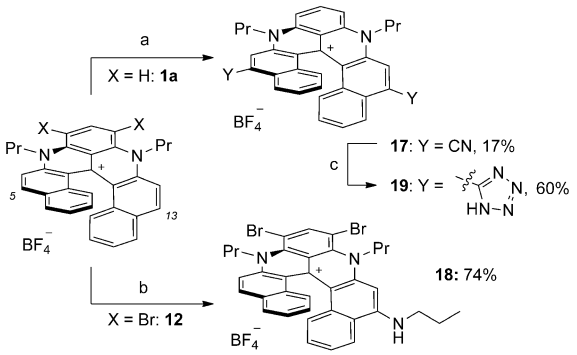
Scheme 2. Reagents and reaction conditions: a) Anhydrous RNH_2 (25 equiv), NMP, MW 170 °C, 10 min; b) PPh_3, DIAD, CH_3COSH, THF, 25 °C; c) *n*-$PrNH_2$, 49 °C, 30 min, then heated neat at 200 °C, 5 min; d) Pyr·HCl, 224 °C, 2 min then ion exchange metathesis with HBF_4. DIAD = diisopropyl azodicarboxylate, MW = microwave, NMP = *N*-methyl-2-pyrrolidone, THF = tetrahydrofuran.



Scheme 3. Reagents and reaction conditions: a) HNO_3, 15 min, 25 °C; b) NCS (3 equiv), $CHCl_3$, AcOH, 15 h, 25 °C; c) NBS (3 equiv), $CHCl_3$, AcOH, 15 h, 25 °C; d) NIS (3 equiv), $CHCl_3$, AcOH, 15 h, 25 °C; e) H_2, PtO_2 (10 wt %), EtOH, 1 h, 25 °C; f) [$Pd(PPh_3)_4$] (10 %), $PhB(OH)_2$ (5 equiv), K_2CO_3 (5 equiv), 1,4-dioxane, 15 h, 80 °C; g) [$Pd(PPh_3)_4$] (20 %), CuI (30 %), PhC≡CH (10 equiv), Et_3N, 3 h, 90 °C. NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, NIS = *N*-iodosuccinimide.

With these derivatives in hand, in particular salt [**1a**][BF_4], orthogonal routes to the selective functionalization of the helical core were developed. Electrophilic aromatic substitution reactions were first studied. A higher reactivity of the median phenyl ring over the flanking naphthyl subunits was predicted on account of the two donor nitrogen atoms attached to this ring (instead of one for the naphthyl groups). This assumption was rapidly confirmed. Treatment of [**1a**][BF_4] under nitration or halogenation reaction conditions (Scheme 3) afforded the corresponding dinitro **10**, dichloro **11**, and dibromo **12** derivatives in good to excellent yields (77, 97, and 96 % respectively). A perfect regioselectivity was observed, wherein only positions 8 and 10 of the helical core, *ortho*/*para* to the two N atoms, reacted under these reaction conditions. Interestingly, with NIS, a milder monoiodination was obtained (**13**, 90 %). Moreover, additional derivatizations were feasible with **10** and **12**. For example, [**10**][BF_4] was readily reduced (H_2, cat. PtO_2) to the corresponding diamino derivative **14** (56 %), and [**12**][BF_4] was reacted under Suzuki–Miyaura and Sonogashira conditions to yield the corresponding diphenyl **15** (69 %) and diphenylethynyl **16** (62 %) derivatives.[10]

Alternatively, taking into consideration the cationic character of the compounds **1** and the propensity of naphthyl rings to react with nucleophiles,[11] [**1a**][BF_4] was treated with an excess of NaCN (3 equiv) in an open flask (Scheme 4).[12] Full conversion was achieved but the resulting salt, [**17**][BF_4], bearing two nitrile groups at positions 5 and 13, was found to be sensitive to purification conditions (SiO_2, 17 %). A similar reactivity was obtained in the treatment of [**12**][BF_4] with *n*-$PrNH_2$ (neat, 25 °C) to afford the trisubstituted [**18**][BF_4] in good yield (74 %). These vicarious nucleophilic substitutions afford, therefore, another means by which to modify the helical core under orthogonal (nucleophilic oxidative rather than electrophilic) conditions.[13] Salt [**17**][BF_4] can be further transformed by reaction with trimethylsilyl azide to obtain the bis(tetrazole) analogue [**19**][BF_4] (60 %).



Scheme 4. a) NaCN (3 equiv), DMF, 60 h, 25 °C; b) *n*-$PrNH_2$, 16 h, 25 °C; c) $TMSN_3$ (3 equiv), Bu_2SnO (20 %), PhCl, 16 h, 60 °C. DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl.

Crystals of [**12**][BF_4] were grown by slow diffusion of Et_2O into a CH_2Cl_2 solution. Structural analysis by X-ray diffraction revealed, as expected, a helical conformation of the *ortho*-condensed framework (Figure 2).[14] The compound **12** presents a larger helical pitch (3.31 Å) and angle (64.5°) between the two mean planes defined by the edge rings in

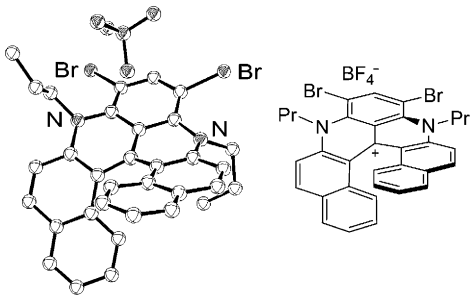


Figure 2. ORTEP view of the crystal structure of [**12**][BF_4]·CH_2Cl_2; *M* enantiomer shown. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms and solvent molecule are omitted for clarity.[27]

Table 1: Electronic properties: maximum absorption band (λ_{max}) and extinction coefficients (ε). CH_2Cl_2 solutions (2×10^{-5} mol L^{-1}).

Entry	Substituents	Compound	λ_{max} [nm]	ε [$M^{-1}cm^{-1}$]
1	8,10-NO_2	**10**	567	18300
2	8,10-Cl_2	**11**	620	13000
3	8,10-Br_2	**12**	620	13000
4	8-I	**13**	620	13000
5	8,10-C≡CPh	**16**	637	15400
6	8,10-Ph	**15**	643	14600
7	8,10-NH_2	**14**	700	5100
8	5,13-tetrazole	**19**	620	17350
9	5,13-CN	**17**	690	17700
10	5-HN-*n*Pr 8,10-Br_2	**18**	600	30400

comparison to those of the classical carbo[6]helicene[2b,15] (3.22 Å and 58.5° respectively).[16]

As briefly mentioned, the novel salts [**1a**][BF_4], [**2a**][BF_4], and [**3**][BF_4] are colorful dyes and their electronic absorption spectra were recorded and are presented in Figure 3 (CH_2Cl_2, 2×10^{-5} mol L^{-1}).[17] All derivatives are characterized by moderately strong absorptions in the visible region ($13050 < \varepsilon < 16800\ M^{-1}cm^{-1}$). The dioxo [**3**][$BF_4$] displays a maximum absorption band (λ_{max}) at 574 nm. No shift of this band is observed when one oxygen atom is replaced by a nitrogen atom.[18] The presence of two nitrogen atoms causes, however, a moderate red shift of 45 nm (λ_{max} = 619 nm).

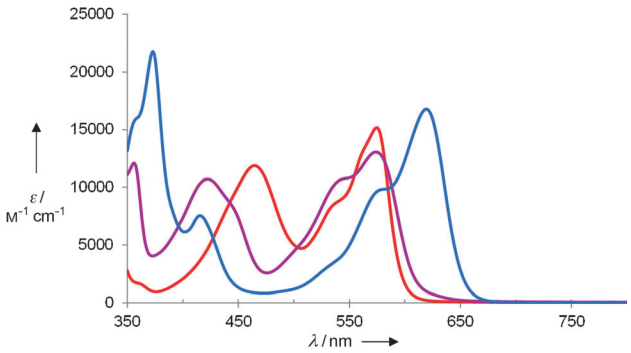


Figure 3. UV/Vis spectra of a) [**1a**][BF_4] (blue), b) [**2a**][BF_4] (purple), and c) [**3**][BF_4] (red) recorded in CH_2Cl_2 (CH_2Cl_2, 2×10^{-5} mol L^{-1}).

Of importance to the current study is a rather strong modulation of the visible absorption properties offered by the substituents introduced at the periphery of cation **1a**. Results are summarized in Table 1 and the corresponding spectra are displayed in the Supporting Information. When substituents are introduced on the upper phenyl ring (entries 1–7), the maximum absorption band varies from λ_{max} = 567 to 700 nm. Electron-withdrawing (EWG) and electron-donating (EDG) groups afford blue and red shifts, respectively. Interestingly, the opposite trend is observed when substitution occurs on the naphthyl rings (entries 8–10, $600 < \lambda_{max} < 690$ nm), with the lowest energy transition being that made by **17**, bearing two cyano EWGs, and is in sharp contrast to the EDG-substituted **18** (λ_{max} = 600 nm).[19]

The enantiomeric resolution of **1a** was also performed using the hexacoordinated phosphorus bis(tetrachlorobenzenediolato)-mono([1,1′]binaphthalenyl-2,2′-diolato)phosphate(V) anion (BINPHAT; **20**, Δ or Λ enantiomer; see the Supporting Information) as a resolving agent.[20] The racemic salt [**1a**][BF_4] and [Me_2NH_2][Λ-**20**] (1.2 equiv) were mixed in a 1:1 mixture of CH_2Cl_2 and acetone. After concentration, NMR spectroscopic analysis ($CDCl_3$, 400 MHz) was performed and revealed an efficient enantiodifferentiation of **1a** by anion **20**.[21,22] The crude mixture was dissolved in pure acetone and, upon cooling to 0 °C, the formation of a precipitate was noticed. The blue solid was collected by filtration. The mother liquor was concentrated and ^1H NMR analysis ($CDCl_3$) indicated the presence of essentially one diastereomeric salt this time. Both fractions of the BINPHAT salts were converted into hexafluorophosphate salts by treatment with an excess of HPF_6 and KPF_6 in a mixture of CH_2Cl_2 and water. The salts (+)-[**1a**][PF_6] (e.r. 98:2) and (−)-[**1a**][PF_6] (e.r. 96:4) resulted from the mother liquor and solid fractions in 45% and 35% yields, respectively.[23] Electronic circular dichroism (ECD) spectra (see the Supporting Information) displayed symmetrical curves in the λ = 240 to 700 nm region.

The absolute configuration of the helicene **1a** was then established by vibrational circular dichroism (VCD).[24] IR absorption and VCD spectra were measured for solutions (CD_2Cl_2) of both (+)- and (−)-[**1a**][PF_6] and compared to the Boltzmann averaged spectrum calculated for (*P*)-**1a** (Figure 4) taking into account the most stable conformers found. Overall, a good agreement between the experimental and theoretical spectra is observed, thus allowing the assignment of *P* and *M* configurations for the carbenium ion in salts (+)- and (−)-[**1a**][PF_6], respectively.

Finally, the determination of the racemization barrier was attempted. DMSO solutions of (−)-[**1a**][PF_6] were heated at 180 °C and monitored in ECD at a single wavelength (λ = 620 nm).[25] No evidence could be found for a racemization after 5 hours of continuous heating. Performing the experiment at higher temperature (≥ 190 °C) in dibutyl sulfoxide failed as **1a** degraded in situ. As no racemization was observed after 5 hours at 180 °C, it is fair to say that **1a** presents a barrier of racemization of at least 37 kcal.mol^{-1}, which is within the range for that of [6]helicene.[1,26]

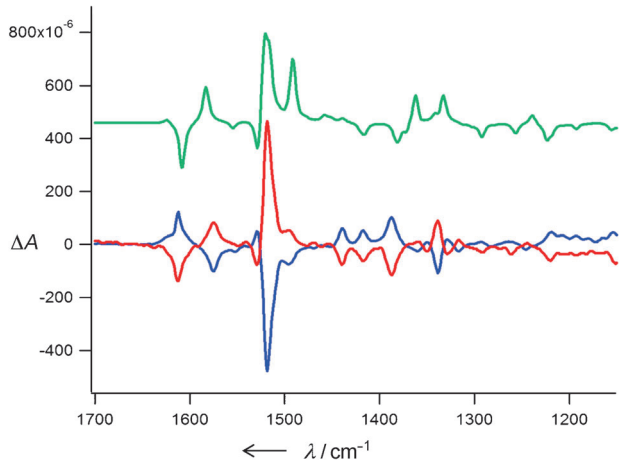


Figure 4. Experimental VCD spectra (CD_2Cl_2, 298 K) of (−)-[**1a**][PF_6] (blue) and (+)-[**1a**][PF_6] (red). Calculated spectrum of (*P*)-**1a** (green).

Herein, we have thus presented novel cationic diaza-, azaoxo-, and dioxo[6]helicenes. These three classes of derivatives were prepared in one step from a common advanced intermediate. Straightforward, yet orthogonal, aromatic electrophilic and vicarious nucleophilic substitution reactions afforded a series of mono-, di-, and trisubstituted diazahelicenes which were additionally derivatized through cross-coupling, reduction, or condensation processes. The importance of this regioselective late-stage functionalization of the helical core was further evidenced in the strong modulation of the visible absorption properties of the cationic dyes. The diazahelicene can be resolved into single enantiomers, which demonstrates a high barrier to racemization.

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Keywords: arenes · helical structures · synthetic methods · UV/Vis spectroscopy · vicarious nucleophilic substitution

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[6] For instance, treatments of **4** with electrophilic reagents like *N*-chloro- and *N*-bromosuccinimide (1 equiv, AcOH/$CHCl_3$) afford unreacted starting material along with complex mixtures of regioisomeric mono- and polyhalogenated derivatives.

[7] Without a stoichiometric amount of $CeCl_3$, the yield drops to 64%.

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[9] The reactions can be performed using regular heating (oil bath) at 140 °C for 4 h with similar yields.

[10] In fact, the reaction conditions for the cross-coupling experiments are somewhat forcing (high mol% of Pd, 5 equiv of $PhB(OH)_2$ or 10 equiv PhC≡CH). The major by-product is the derivative of monofunctionalization with one bromine being replaced by a hydrogen atom.
[11] A. I. Meyers, K. A. Lutomski, *Synthesis* **1983**, 105 – 107.
[12] Most probably, **1a** undergoes successive nucleophilic attacks of cyanide anions at the activated positions 5 and 13 followed each time by hydride abstraction reactions under the oxidative conditions in air.
[13] For a recent review on vicarious nucleophilic substitutions, see: M. Mąkosza, *Chem. Soc. Rev.* **2010**, *39*, 2855 – 2868; for a selected example of VNS functionalization on a dye, see: V. Leen, M. Van der Auweraer, N. Boens, W. Dehaen, *Org. Lett.* **2011**, *13*, 1470 – 1473.
[14] Both monoclinic (racemate) and orthorhombic (conglomerate enantiopure) structures were found in the crystallization batch; the first kind being of higher quality and the only one reported. One side chain possesses an *anti* conformation while the other presents a gauche orientation. In the orthorhombic packing, both side chains were gauche, that is with the terminal methyl groups pointing back to the aromatic core. The pitch measured was 3.31 and 3.17 Å for the monoclinic and orthorhombic structures, respectively.
[15] a) I. R. Mackay, J. M. Robertson, J. G. Sime, *J. Chem. Soc. D* **1969**, 1470 – 1471; b) C. De Rango, G. Tsoucaris, J. P. Declerq, G. Germain, J. P. Putzeys, *Cryst. Struct. Commun.* **1973**, *2*, 189 – 192.
[16] The angle between the two mean planes defined by the inner naphthyl rings of **12** is of 52.6°, which is significantly larger than that of the related [4]helicene **4** (39.2°, CCDC 205385).
[17] Compounds **1** present essentially identical UV-Vis properties in CH_2Cl_2.
[18] Differences between [**2a**][BF_4] and [**3**][BF_4] can however be observed at higher energies in the spectra.
[19] Comparison of the spectra of **18** and **12** indicates that the donor aminopropyl group is responsible for a blue shift with the bromine having little influence on the absorption properties (comparison of **12** and **1a**).
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[21] J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073 – 7089.
[22] Because of the presence of the anion **20**, which acts as a NMR chiral solvating agent, two sets of signals are observed in the ^{1}H NMR spectrum: one for each the *P* and *M* enantiomers of **1a**. Integration of the respective signals indicates a 1:1 diastereomeric ratio. See the Supporting Information.
[23] The enantiomeric purity was determined by CSP-HPLC (CHIRALPAK AD-H) on the neutral hydride adduct obtained by simple treatment of [**1a**][PF_6] with $NaBH_4$ in EtOH. See the Supporting Information.
[24] a) L. A. Nafie, T. A. Keiderling, P. J. Stephens, *J. Am. Chem. Soc.* **1976**, *98*, 2715 – 2723; b) G. Holzwarth, E. C. Hsu, H. S. Mosher, T. R. Faulkner, A. Moscowit, *J. Am. Chem. Soc.* **1974**, *96*, 251 – 252; c) T. B. Freedman, X. L. Cao, R. K. Dukor, L. A. Nafie, *Chirality* **2003**, *15*, 743 – 758.
[25] This experiment was performed on an ECD apparatus having a low to high temperature attachment which allows ECD experiments from −80 to +230 °C.
[26] Considering first-order kinetics for the racemization, a barrier of 37 kcal mol^{-1} corresponds to a half-life of 15 h at 180 °C.
[27] CCDC 904858 ([**12**][BF_4]·CH_2Cl_2) contains 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.

