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Fluoroaromatics

Aromatic Fluorine as a Versatile Control Element for the Construction of Molecules with Helical Chirality**

*Tim Rasmusson, L. James P. Martyn, Gang Chen, Alan Lough, Megan Oh, and Andrei K. Yudin**

The π–π stacking and edge–face contacts between aromatic groups occupy prominent positions among noncovalent interactions,[1] with helicity being one the most significant kinds of supramolecular organization driven by these interactions. Apart from stabilizing the structure of large molecules such as DNA, helicity has also been explored in the realm of synthetic small molecules. The so-called helicenes were originally developed merely as aesthetically pleasing molecules, however their unusual optical and electronic[2] properties have attracted a great deal of attention of late.[3] The chiral backbones of these molecules have given them roles in a variety of applications ranging from asymmetric catalysis[4] to molecular motors[5] and remote chirality sensors.[6] Furthermore, the original helicene synthesis involving stilbene photocyclizations has evolved into more modern approaches, including various ring-closing methods such as domino Diels–Alder reactions,[7] palladium-catalyzed arylations,[8] cobalt-catalyzed cycloisomerizations of aromatic triynes,[9] and ruthenium-catalyzed olefin metathesis.[10] Despite these important advances, the synthesis of chiral helicenes is still tedious and requires considerable synthetic prowess.

Due to their ability to undergo directional aggregation, helical molecules that are easy to prepare and modify are of considerable significance. Our group has been interested in versatile precursors to helically chiral molecules that would be amenable to regio- and stereoselective structural alterations at a late stage of synthesis; molecules meeting these criteria are practically unknown.[11] Herein we describe a methodology that allows us to generate several families of helically chiral compounds by straightforward intramolecular fluorine substitution.

We have long been interested in molecules that contain aromatic fluorine. To the best of our knowledge, there are no reports on fluorine-containing helically chiral compounds apart from a few intriguing supramolecular perfluoroalkane helicates.[12a] Fluorine substitution is known to modulate aromatic/aromatic interactions by affecting the HOMO–LUMO gap, which leads to a strong propensity for the molecules to aggregate.[12b–d] Extended wave function delocalization in the resulting materials leads to high electron mobility, as observed upon going from pentacene to perfluoropentacene.[12e] The versatile 1,1′-binaphthalene-2,2′-diol (binol, **1**) skeleton was taken as a starting point for our purposes. The synthesis and applications of several fluorine-substituted binol analogues with various fluorination patterns have been developed by us and others previously.[13] The act of fluorination causes significant perturbation in the electronic character of binol (Figure 1) with no substantial steric consequences.

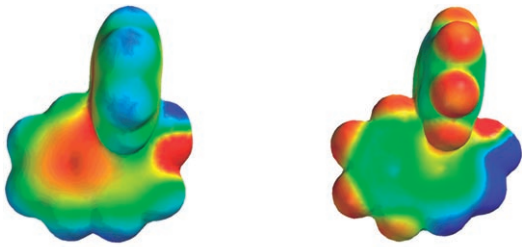

Figure 1. Electrostatic potential surfaces (AM1) of **1** and **2** obtained with Spartan Pro.

Our interest was piqued when F_8-binol (**2**) was found to undergo quantitative cyclization in the presence of potassium hydroxide to give the planar molecule **3** (Scheme 1). This fascinating compound is highly fluorescent but is only sparingly soluble in common organic solvents. Furthermore, it has a melting point well above 250 °C and can be grown into a needle-like crystalline material, thus hinting at the directionality of the intermolecular contacts formed during the course of packing. It was our hope that the remaining fluorines in **3** would be susceptible to nucleophilic aromatic substitution, although we soon found that the S_NAr transformations were unselective. Thus, we managed to obtain several soluble products upon treating **3** with sodium methoxide in methanol but their NMR spectra were undecipherable. Nonetheless, the isolation of **3** was significant as it inspired us to pursue cyclization reactions that induce helical chirality from polyfluorinated derivatives of **1** with lower symmetry.

We were pleased to find that the helically chiral compound **6** can be synthesized from monomethoxy-F_8-binol (**5**),

[*] T. Rasmusson, Dr. L. J. P. Martyn, G. Chen, Dr. A. Lough, M. Oh, Dr. A. K. Yudin
Davenport Research Laboratories, Department of Chemistry
University of Toronto, 80 St. George St.
Toronto, ON, M5S3H6 (Canada)
Fax: (+1) 416-946-7676
E-mail: ayudin@chem.utoronto.ca

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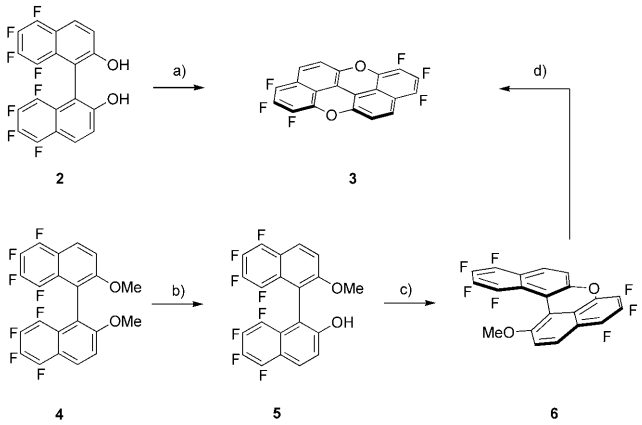
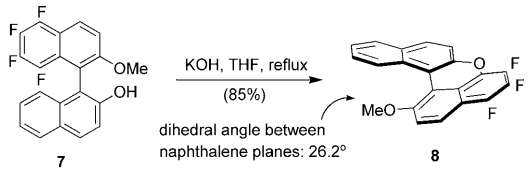


Scheme 1. Intramolecular aromatic substitutions of F_8-binol derivatives. a) KOH, THF, reflux, quantitative; b) BBr_3 (1 equiv), CH_2Cl_2, RT, 72%; c) KOH, THF, reflux, quantitative; d) BBr_3, CH_2Cl_2, RT, quantitative.

which is in turn available in a surprisingly high yield upon mono-demethylation of **4**. Compound **6** is a bright yellow-green solid characterized by similar quadrupole moments on both aromatic substituents.[14] The treatment of **6** with BBr_3 in an attempt to form a free hydroxyl group resulted in **3**.

Encouraged by these findings, we pursued cyclization precursors with "mixed" electronic characteristics as we supposed that such donor/acceptor systems could exhibit modulated interactions in the solid state.[15] Importantly, there was also the possibility of being able to compare such species with **6** directly due to the very similar steric requirements of H and F. Indeed, we were able to synthesize the helically chiral compound **8** by refluxing the F_4-binol[13b] precursor **7** as a template with KOH in THF (Scheme 2). Attempts to isolate enantiopure **8** proved unsuccessful as the compound readily racemizes at room temperature.



Scheme 2. Cyclization of **7** under basic conditions.

Stabilizing intermolecular interactions between aromatic rings are known to affect the charge-transfer properties of a solid, thereby playing a pivotal role in the design of molecules for photovoltaic applications.[16a] The charge transfer that takes place between molecularly ordered aromatic rings is due to the high degree of electronic coupling between these molecules, therefore flexible synthetic systems that help us to understand how structural alterations can affect aggregation are of great interest.[16b] We have found that the difference in electronic character between isosteric molecules **6** and **8** leads to different packing arrangements. The crystal packing motifs of **6** and **8** with the helical enantiomers presented in different colors are shown in Figure 2. Compound **6**, which has fluorine substituents on both naphthalene rings, displays a relatively balanced charge distribution between the two halves of the molecule. The aromatic rings of each naphthalene substituent interact with each other, thereby maximizing the offset face–

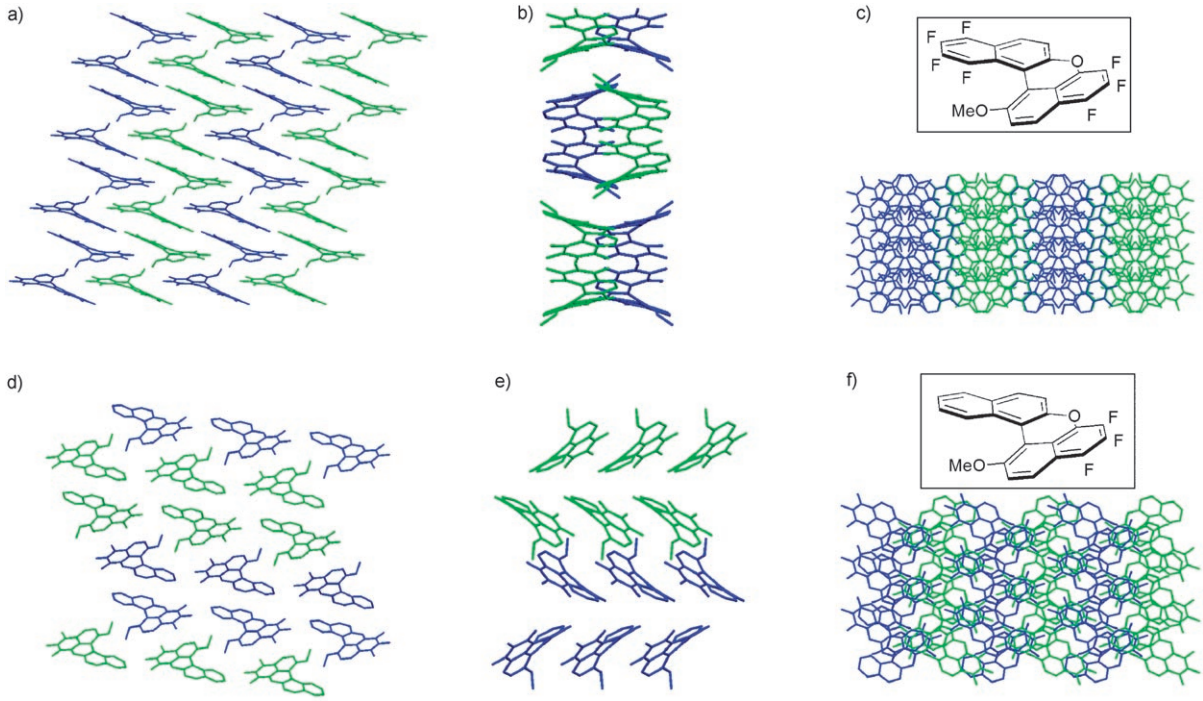
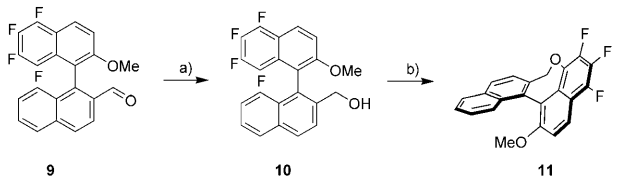


Figure 2. X-ray crystal packing of **6** (top) and **8** (bottom) with hydrogen atoms omitted for clarity. a) **6** looking along the *b* axis; b) **6** from the side, looking along the *c* axis; c) **6** from above, looking along the *a* axis; d) **8** along the *b* axis; f) **8** from the side, looking along the *a* axis; f) **8** from above, looking along the *c* axis. Blue and green represent opposite enantiomers.

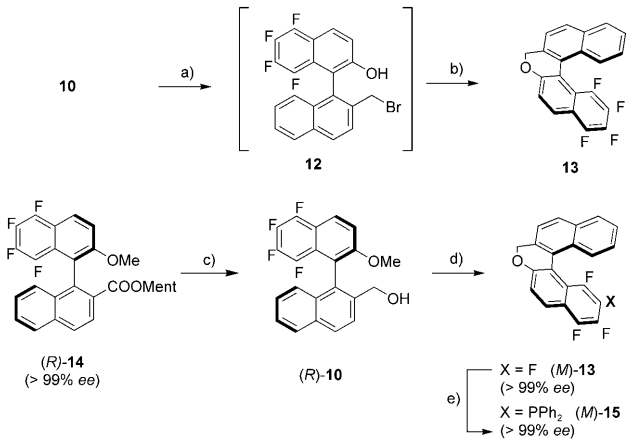
face (OFF) stacking. Each enantiomer forms a homochiral coiled column interlocked with adjacent helical columns of the opposite twist to create alternating stacks of *M* and *P* enantiomers. Compound **8**, on the other hand, has only one fluorinated naphthyl ring, therefore the resulting uneven electronic distribution causes molecules of this compound to line up in a mixture of OFF stacking and edge–face interactions. The OFF stacking takes place between the fluorinated naphthalene rings, while the edge–face interactions occur between the non-fluorinated components. As opposed to its isosteric version **6**, compound **8** shows no helical coiling or any chiral aggregation.

To prevent racemization in this novel series of helical molecules, the aldehyde **9**,[13b] a precursor to **7** and the product of an Ullmann hetercoupling between 1-bromo-2-methoxy-5,6,7,8-tetrafluoronaphthalene and 1-bromo-2-naphthaldehyde, was successfully reduced and cyclized to give **11** (Scheme 3). To our delight, this extension of the bridge by one atom rendered the molecule configurationally stable—its naphthalene rings stagger in the solid state in order to minimize unfavorable steric interactions, which precludes the possibility for OFF stacking, and edge–face interactions now dominate the crystal lattice.[17]



Scheme 3. Reduction and cyclization to give compound **11**. a) $NaBH_4$, *i*PrOH/Et_2O (1:1), quantitative; b) potassium hexamethyldisilazide, THF, reflux, 82%.

Our next design called for an electronically unsymmetrical molecule equipped with aromatic donor and acceptor regions separated by a 2–2′ bridge. We surmised that such species can be coaxed into undergoing "self-recognition" in the solid state, thereby increasing their potential for effective charge transfer.[18] Fortuitously, the bromomethyl compound **12** was isolated upon treatment of compound **10** with BBr_3, and subsequent basic hydrolysis furnished the tetrafluorobinaphthylpyran **13**. The enantiomers of **13** were easily resolved by chiral HPLC, and we were happy to note that **13** was stable to racemization. We also investigated the photochemical racemization of **13** and found it to be stable during the course of irradiation, unlike its hydrido analogue, which has received considerable attention in the past.[19] A straightforward synthetic route to enantiomerically pure **13** (Scheme 4) was also developed. Thus, after synthesis of the (−)-menthyl ester by Ullmann heterocoupling, fractional crystallization from hexanes gave enantiopure (*R*)-**14**, reduction of which followed by deprotection and cyclization led to (*M*)-**13** with no observed loss of chiral purity. In contrast to our repeated failure to modify the flat molecule **3**, we were now able to perform highly selective S_NAr reactions. Lithiated diphenyl phosphide was chosen as the nucleophile and was found to provide selective substitution at the 7-position. These S_NAr transformations were also found to proceed with preservation of chirality.



Scheme 4. Racemic and enantioselective syntheses, and selective substitution of **13**. a) BBr_3, CH_2Cl_2, RT; b) NaOH, THF/H_2O, reflux, 90% over two steps; c) $LiAlH_4$, Et_2O, 84%; d) BBr_3, CH_2Cl_2, RT; then NaOH, THF/H_2O, reflux, 75%; (e) Ph_2PH, *n*BuLi, THF, −78 °C, 16% (unoptimized, one regioisomer).

Evidence to support our proposal for solid-state organization driven by the interspersed donor and acceptor regions came from an analysis of the packing preferences of enantiopure (*M*)-**13**. When looking along the crystallographic *b* axis, the molecules can be seen to line up in a columnar arrangement; these columns are easily distinguished when looking along the *a* axis (Figure 3). The fluorinated rings π stack with each other, whereas the non-fluorinated naphthalene rings do not. The column, as viewed along the *c* axis, regularly alternates between coiled and stacked molecules in the vertical direction. There are no observed edge–face interactions in the entire crystal lattice.

Compounds **6, 8, 11**, and **13** absorb strongly in the UV region (300–400 nm) upon dissolution in ethyl acetate due to π–π* transitions; they emit in the indigo to aqua range. The emission peaks of this series of molecules appear at 501, 474, 420, and 427 nm, respectively. Due to the propensity of these molecules to readily form crystals, their fluorescence intensities can be expected to increase in the solid state with fluorophore density. Furthermore, in light of their stability, these novel helically chiral molecules have potential for use as blue-emitting photoluminescent dopant materials and will be intriguing candidates for energy-transfer studies.[20a]

In summary, we have developed a methodology that can be employed to create families of helically chiral molecules from a common precursor. This chemistry should help in the design of novel materials with space-separated donor–acceptor regions. The simultaneous presence of intrinsic donor–acceptor characteristics in some of these molecules should also allow the investigation of heterojunctions formed in the resulting materials.[20b] Along with the possibility for S_NAr fluorine displacement, our method paves the way to the formation of a huge number of helically chiral molecules from a common precursor. We stress that the foundation of this chemistry lies in aromatic fluorine, a fascinating "nugget" that can play an important role as a control element in designing helically chiral molecules.

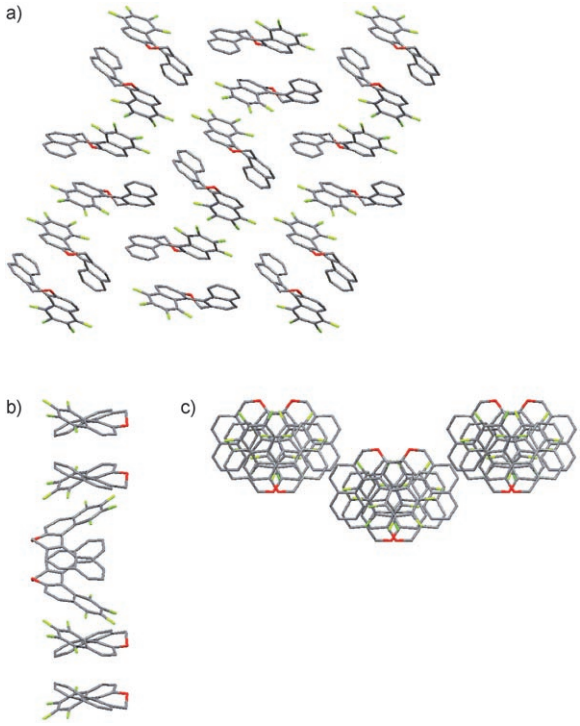


Figure 3. X-ray crystal structure of (*M*)-**13** with hydrogen atoms omitted for clarity. a) Packing of (*M*)-**13** along the crystallographic *b* axis; b) side view along the *c* axis of the column; c) top view of columns looking along the *a* axis. C gray, O red, F yellow.

Experimental Section

Crystal data: **6**: $C_{21}H_7F_7O_2$; $a = 20.0993(14)$, $b = 7.9970(4)$, $c = 20.3834(15)$ Å, $\beta = 105.992(3)°$, space group *C*2/*c*. **8**: $C_{21}H_{11}F_3O_2$; $a = 11.7868(2)$, $b = 5.8709(10)$, $c = 22.1895(6)$ Å, $\beta = 97.843(8)°$, space group $P2_1/n$. **11**: $C_{22}H_{13}F_3O_2$. $a = 19.7889(3)$ $b = 7.9275(4)$ $c = 20.9980(6)$ Å, space group *Pbca*. **13**: $C_{21}H_{10}F_4O$; $a = 18.8931(8)$ $b = 8.1212(4)$ $c = 21.0551(10)$ Å, $\beta = 111.653(2)°$, space group *I*2.CCDC-691491 (**6**),CCDC-691492 (**13**), CCDC-691493 (**8**), and CCDC-691494 (**11**) 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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