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The Synthesis of Rigid Polycyclic Structures for the Study of Diatropic or Steric Effects of a Phenyl Ring on CF Bond

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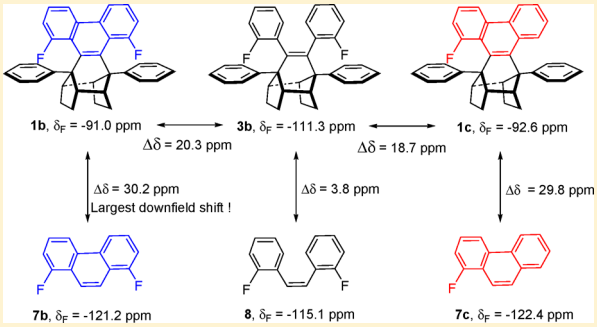
Supporting Information

ABSTRACT: Polycyclic compounds **1a–c** were synthesized to study the diatropic effects of a flanking phenyl ring on nearby CH and CF bonds. ^{19}F NMR spectra of **1b** and **1c** were strongly deshielded compared with those of the ring-opened compounds **3b**, **7b**, and **7c**. DMol3 calculations on **1a–c** provided quantitative bond lengths and torsional angles to support the conclusion that the downfield shifts in the ^{19}F NMR spectra are mainly due to steric interactions between the CF bonds and the π clouds of the phenyl ring(s).



Inter- and intramolecular CH–π and CF–π interactions play important roles in host–guest chemistry, molecular assembly, and the folding of proteins and polynucleotides.[1] The CH–π interaction is a weak force (0.5–2.5 kcal/mol)[2a] that is usually difficult to measure directly using molecules with flexible conformations. Therefore, the measurement of this weak interaction in molecules with intramolecular folding and unfolding has intrigued chemists for decades.[2] Recently, Tsuzuki[3a] reported an excellent review that summarizes recently reported gas-phase measurements and high-level ab initio calculations of the CH–π interactions. Ab initio calculations show that the major source of attraction in the CH–π interactions is the dispersion interaction, while the contribution from electrostatic interactions is small. On the other hand, Nishio et al.[3b] surveyed and analyzed literature results relevant to the CH–π interactions in crystal packing and conformations based on data reported in crystallographic databases (CSD and PDB). Moreover, as the organofluoride compounds are getting more popular in medicinal chemistry, the need to study CF–π interactions in organic and biological molecules has markedly increased. In order to study such CF–π interactions efficiently, one needs to have a special molecular design in which the CF bond is pointing toward conformationally rigid π bonds or aromatic rings.[4]

In previous literature, the typical CF–π interactions between fluoromethane and benzene/hexafluorobenzene were only theoretically studied. For example, the very weak attractive interaction between the fluorine of HF and hexafluorobenzene was measured on the basis of theoretical calculations.[5a] Kawahara also indicated that a weak interaction between fluoromethane and hexafluorobenzene was observed; furthermore, it is worth noting that this was an attractive force.[5b] Nowak, however, studied CF–π interactions by measuring the effect of fluorine on the reactivity of a proximal double bond using a polyfluorinated indacene system.[6] The through-space interactions between the CF bond and the π electrons of alkenes were explained by Lectka[7] to be due to steric hindrance, anchimeric assistance, and the repulsive interactions from overlap of lone-pair electrons on fluorine with the π electrons on the olefin. Furthermore, they reported that the fluorine was little perturbed by anisotropic effects from the π electrons of the alkene, and only a slight upfield shift relative to theoretical values of fluorine chemical shifts was observed.[7] We report here the synthesis of the rigid polycyclic compounds **1a–c** and subsequent NMR spectral studies and theoretical calculations to measure the diatropic effect of a phenyl ring on sterically close aryl CH (**1a**) and CF bonds (**1b** and **1c**).

Tandem Diels–Alder reactions followed by sequential photocyclization reactions were the two key steps in our synthesis of the rigid polycyclic structures **1a–c**. One of us[8a] and Winkler[8b] have provided excellent reviews of tandem Diels–Alder reactions demonstrating that they are exceptionally powerful methods in the synthesis of intricate polycarbocycles.[8,9] Iodine-induced photocyclization of stilbene to phenanthrene has also been well-studied.[10] The CH and CF bonds in the series of polycyclic frameworks **1a–c** can be arranged in a very close proximity to the aromatic ring, and hence, ^{1}H and/or ^{19}F NMR spectroscopy can be used to estimate the strength of the interactions between them and the π-cloud of the phenyl ring. Moreover, theoretical calculations were carried out on the polycyclic frameworks **1a–c** to obtain optimized geometries, bond distances, and torsional angles.

Synthesis of ***1a***. Compound **1a** was obtained through a two-step sequence that started by refluxing tetraphenylcyclopentadienone (**2a**) with 1,5-cyclooctadiene to afford compound **3a**[9] in 71% yield (Scheme 1). Iodine-catalyzed photocyclization[10]

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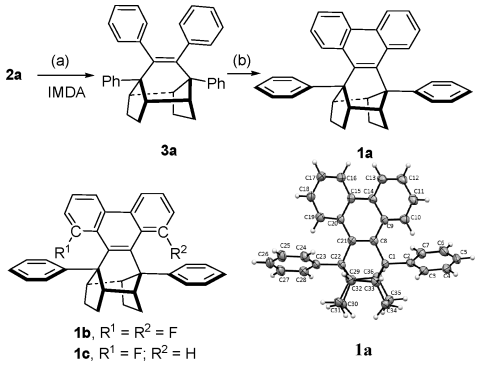
Scheme 1. Synthesis[a] and X-ray Crystal Structure of 1a

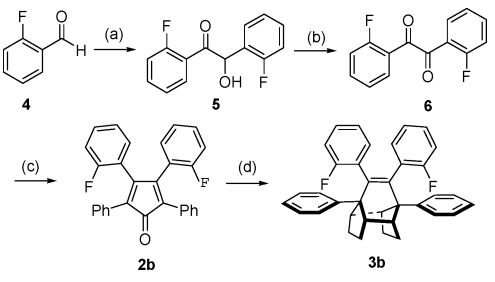


[a]Reagents and conditions: (a) 1,5-cyclooctadiene, reflux, 4 days, 71%; (b) I_2, toluene, Rayonet, 300 nm, 58%.

of **3a** in toluene afforded the target polycyclic compound **1a** in 58% yield. Because the target compounds **1a** and **3a** have similar polarities (R_f = 0.5 in hexane eluent), it was difficult for us to obtain pure **1a** even after repeated column chromatography. The ^{1}H NMR spectrum of the purified sample of **1a** still showed about 10% of the starting material **3a**; however, their signals can be easily discerned through chemical shift analysis. In particular, a new doublet signal around 8.5 ppm appeared, which is regarded as one of the characteristic protons of the phenanthrene ring in **1a**. Moreover, the signals of the aromatic protons of **1a** showed a significant downfield shift compared with those of **3a** (Figure S18 in the Supporting Information). Furthermore, the formation of **1a** could be easily recognized by GC–MS analysis, which showed a new peak with retention time (r_t) of 50.9 min (with m/z 462.5) as opposed to the peak for the starting material **3a** at r_t = 33.6 min (with m/z 464.6) (see Figure S20 in the SI). Finally, we were lucky to obtain a single crystal of **1a** by crystallization from a mixed solvent of dichloromethane and ethanol (2:8 v/v). The single-crystal X-ray structure of **1a** (shown in Scheme 1) proved that it has a rigid polycyclic structure.

Synthesis of ***1b***. Encouraged by the successful synthesis of the polycyclic compound **1a**, we then applied this methodology to construct the fluoride analogue **1b**. The synthesis of fluorinated substrates **2b** and **3b** is shown in Scheme 2. The fluorinated substrate **2b** was obtained through a three-step synthesis. First, the benzoin condensation of 2-fluorobenzene was conducted using catalytic amount of sodium cyanide in ethanol to give the desired product, 2,2′-difluorobenzoin (**5**),[11] in 72% yield. Benzoin **5** was then oxidized by copper(II) acetate in 80%

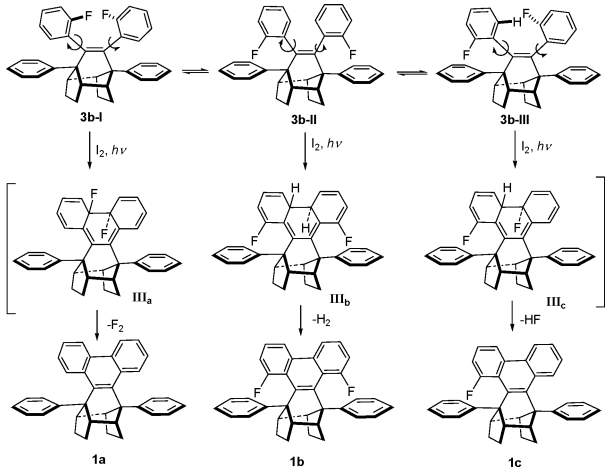
Scheme 2. Synthesis of 2b and 3b[a]



[a]Reagents and conditions: (a) cat. NaCN, EtOH, reflux, 3 h, 72%; (b) $Cu(OAc)_2$, 80% AcOH, reflux, 2 h, 72%; (c) KOH, dibenzyl ketone, EtOH, reflux, 1 h, 35%; (d) 1,5-cyclooctadiene, reflux, 24 h, 68%.

acetic acid to afford 2,2′-difluorobenzil (**6**)[11] in 72% yield. Subsequent aldol condensation of **6** with dibenzyl ketone under alkaline conditions gave the difluorinated substrate **2b** in 35% yield. After tandem Diels–Alder reactions of **2b** with 1,5-cyclooctadiene, we obtained precursor **3b** in 68% yield. The photocyclization of **3b** with a catalytic amount of iodine was conducted by irradiation in a Rayonet photoreactor (λ_{max} = 250 nm) at room temperature (Scheme 3). The photocyclization

Scheme 3. Products of the Photocyclization of 3b



reaction of **3b** was monitored by ^{1}H NMR spectroscopy (Figure S17 in the Supporting Information). After irradiation at 250 nm for 10 min, new signals around δ_H = 8–9 ppm emerged, while signals of the aromatic protons of the starting compound **3b** gradually decreased. The photocyclization reaction of compound **3b** was completed within 6 h of irradiation at 254 nm.

Similar to the trouble we met in purifying the products of the photocyclization of **3a**, we also had difficulty in purifying the products of the photocyclization of **3b** because products **1a–c** have similar polarities. Even after separation by column chromatography and recrystallization, the reaction mixture analyzed by HPLC still showed three major peaks at r_t = 23.9, 24.8, and 25.9 min with an area ratio of 8:85:5 (Figure S21 in the Supporting Information). The three products were recognized by mass spectrometry as **1b** (r_t = 23.9 min, m/z 498), **1c** (r_t = 24.8 min, m/z 481), and **1a** (r_t = 25.9 min, m/z 463) (see Scheme 3). Notably, photolysis of **3b** afforded not only the prospective fluorine product **1b** but also the defluorinated and dehydrofluorinated side products **1a** and **1c** (Figures S20 and S21 in the Supporting Information). The structure of **1a** was fully characterized by ^{1}H and ^{13}C NMR, DEPT-135, HRMS, and single-crystal X-ray analysis (vide supra and the Experimental Section). Photolysis of compound **3b** in the presence of a catalytic amount of iodine may extrude F_2(g), H_2(g), and HF(g) from the difluorodihydrophenanthrene intermediates **IIIa–c**, leading to the formation of the aromatized products[10a] **1b**, **1c**, and **1a** in 8%, 85%, and 5% yield, respectively, based on HPLC area ratios (Scheme 3).

Three factors must have played important roles in the conformational distributions of **3b** in its ground state (Scheme 3): (1) intramolecular electronic repulsion between the two CF bonds in **3b-I**, (2) intramolecular steric hindrance between the two CF bonds and the flanking phenyl rings in **3b-II**, and (3) intramolecular hydrogen-bonding interactions between CF and

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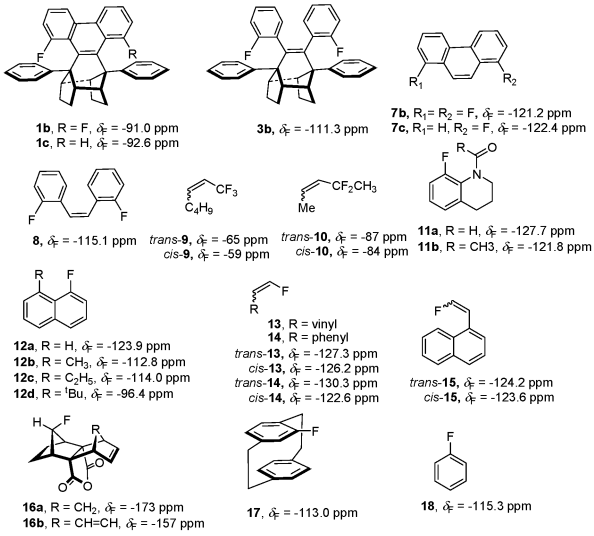
CH bonds in **3b-III**. Among the three major conformations of **3b**, the conformer **3b-III** became the most stable one and therefore led to the formation of compound **1c** as the major product (85% in HPLC ratio).

All attempts to separate the product mixtures failed, and we could only collect a small amount of **1c** by analytical HPLC separation. After obtaining the fluorinated polycyclic compound **1c** and the mixture of **1b** and **1c**, we then took the intended measurement on CF−π interaction using ^{19}F NMR spectroscopy. The ^{19}F NMR spectra of **1b**, **1c**, and **3b** showed the fluorine peaks at −91.0, −92.6, and −111.3 ppm, respectively, using hexafluorobenzene (δ_F = −162.2 ppm)[12] as an external standard. To our big surprise, the ^{19}F NMR peaks of **1b** and **1c** were downfield-shifted by 20.3 and 18.7 ppm, respectively, compared with that of **3b** (Figure S15 in the Supporting Information); however, they were downfield-shifted by 30.2 and 29.8 ppm compared with those of 1,8-difluorophenanthrene **7b** (δ_F = −121.2 ppm)[13c] and 1-fluorophenanthrene **7c** (δ_F = −122.4 ppm),[13a] respectively. Furthermore, compound **3b** is downfield-shifted by 3.8 ppm compared with **8** (δ_F = −115.1 ppm).[13b] Since the C−F bonds of **1b** and **1c** are located very close to their phenyl rings, one would have expected to see a significant upfield shift in their ^{19}F NMR resonances due to the diatropic shielding effect of the phenyl rings. To our surprise, the fluorine chemical shifts of **1b** and **1c** did not show any shielding effect of the phenyl ring but instead showed strong deshielding (vide supra)!! Thus, the diatropic shielding effect of phenyl rings did not seem to play any role in determining the fluorine chemical shift of the C−F bond, and other factors must have played more important roles leading to the significant downfield shift of the ^{19}F NMR peaks of **1b** and **1c**.

It has been reported that the ring-current effect is relatively less important in ^{19}F NMR than in ^{1}H NMR,[14a,b] whereas steric effects have a stronger influence on the chemical shift in ^{19}F NMR. Even though the strong deshielding of the ^{19}F NMR peaks of **1b** and **1c** were opposite to what we originally expected, the results are fully explainable by steric effects in fluorine NMR.[14a,b] The fluorine chemical shifts of *para*- and *meta*-substituted fluorobenzenes showed a reasonable correlation with the resonance and inductive effects of the substituents;[14i−k] however, because of the intramolecular steric effect between these substituents and the adjacent fluorine atom, the fluorine chemical shifts of *ortho*-substituted fluorobenzenes exhibit a poor correlation.[14i−k] Dolbier and others[13,14] reported that all sterically congested or hindered organofluoride compounds are downfield-shifted in ^{19}F NMR compared with those that are sterically unhindered (see Table 1). For example, the ^{19}F NMR peaks of *cis*-**9**−**11** were downfield-shifted by 3−6 ppm compared to those of *trans*-**9**−**11**;[14a−c] furthermore, the peaks of *cis*-**13**−**15** were downfield-shifted by 1−8 ppm compared with those of *trans*-**13**−**15**.[14d−f] The deshielding effect of a bulkier substituent on the ^{19}F NMR spectrum is even more obvious in compounds **12a**−**d**, where the ^{19}F NMR peak of **12d** shows the largest downfield-shift effect when its 8-substituent changed from H to *t*-Bu ($\Delta\delta$ = 27.5 ppm).[14a,b]

In addition, Lectka and co-workers[7] synthesized compounds **16a** and **16b** to investigate the intramolecular CF−π interactions. The C−F bond of **16b** is very close to a double bond, causing a 16.0 ppm downfield shift of its ^{19}F NMR resonance compared with that of **16a**.[7] The ^{19}F NMR peak of 4-fluoro[2.2]paracyclophane (**17**),[14g] which has its CF bond parallel to a nearby phenylcyclophane, was downfield-shifted by only 2.3 ppm compared with that of fluorobenzene (**18**).[14h] It is important to note that our molecules **1b** and **1c** exhibited downfield shifts of 30.2 and 29.8 ppm in their ^{19}F NMR spectra compared with those of **7b** and **7c**, respectively, which are by far the largest downfield shift effects ever reported. Thus, a nearby π cloud mainly exerts a steric effect on the ^{19}F NMR peak of a CF bond instead of the traditional diatropic effect and therefore leads to strong downfield shifts of molecules **1b** and **1c**.

Table 1. ^{19}F NMR Data for Organofluoride Compounds 1b, 1c, 3b, and 7−18[13,14]



The fluorine chemical shifts of compounds **1b** and **1c** were also calculated by means of a published method,[17] namely, gauge including atomic orbitals (GIAO) combined with B3LYP DFT using the cc-pVTZ basis set. The calculated fluorine chemical shifts of compounds **1b** (δ_F = −101.9 ppm) and **1c** (δ_F = −101.0 ppm) are upfield-shifted by 10.9 and 8.4 ppm compared with the observed values (Table S10 in the Supporting Information).

DMol3 Calculations of the Conformations of 1a−c. In order to rationalize the conformations of **1a−c**, we also calculated their geometry-optimized structures by the DMol3 molecular modeling method[15a,b] and simulated in a $CHCl_3$ environment, in which the B3LYP functional with the double-numeric-quality with polarization functions (DNP) basis set was used. The size of the DNP basis set is comparable to that of the Gaussian 6-31G** basis set, but DNP is more accurate than a Gaussian basis set of the same size.[15c] The optimized geometries of **1a−c** are displayed and related data of these calculations are summarized in Tables S1−S6 in the Supporting Information). In the optimized geometries of **1a−c**, the distances between the tips of the C−H and C−F bonds to the center of a phenyl ring were measured to be 2.737, 3.367, and 3.393 Å, respectively. For most literature reports on CH−π interactions, the distances between the tip of the C−H/C-F bond to the center of a phenyl ring range from 2.9 to 3.5 Å (typically 3.05 Å).[2c,3b,16] Even though the C−H bonds of phenanthrene on **1a** are not pointing toward its flanking phenyl rings, they still fit conventional CH−π interaction characteristics. The C10−C9−C8−C1 torsional angles, Φ, of **1a−c** were calculated to be 20.5°, 28.8°, and 35.0°, respectively, suggesting the increase in repulsive interaction between CH/CF bonds and a phenyl ring,

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as one would expect from the overlap of the π system with the fluorine or hydrogen atoms. As a result of the steric hindrance between phenanthrene and the flanking phenyl rings in the crystal structure of **1a**, the conformations of phenanthrene and the cyclic skeleton (C1−C33−C32−C22−C29−C36) in **1a** are nonplanar and a twisted boat, respectively. The distance between the tip of the CH bond and the center of a phenyl ring was determined to be 2.567 Å, and the torsional angle Φ of **1a** was shown to be 18.0°, so the Dmol3-calculated results for **1a** were very close to those of the crystal structure of **1a**. We infer that steric hindrance plays a pivotal role in the interactions between the CF bond(s) and the phenyl ring(s) in **1b** and **1c**, leading to their strong deshielding in the ^{19}F NMR spectra compared with those without such a sterically hindered environment.

In conclusion, we have designed and synthesized a series of rigid polycyclic structures **1a−c** where the key steps of the synthesis involves (1) tandem Diels−Alder reactions and (2) the photocyclization followed by extrusion of F_2, H_2, and HF from the difluorodihydro- phenanthrene intermediates **IIIa−c**, respectively. According to the observed ^{19}F NMR of **1b** and **1c**, their chemical shift were downfield shifted by 30.2 and 29.8 ppm when compared to those of the **7b** and **7c**, respectively. Even though the strong deshielding of the ^{19}F NMR of **1c** was opposite to what we originally expected, the results are fully explainable by *"steric effect"* on fluorine NMR. The torsional angles of **1a−c** increased from 20.5° in **1a**, to 28.8° in **1b**, and 35.0° in **1c**, suggesting the increase in repulsive interaction between C−H/C-F bonds and a phenyl ring. We conclude that steric hindrance must have played a pivotal role in the interaction between the CF bond and the phenyl ring in **1c**, leading to its strong deshield in ^{19}F NMR compared to those without such a steric hindered environment.

EXPERIMENTAL SECTION

General Methods. Column chromatography was performed on 70−230 or 230−400 mesh silica gel; thin-layer chromatography (TLC) was performed on aluminum plates coated with silica gel 60 F_{254}. Melting points were determined with a melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a 300 MHz spectrometer with the residual solvent peak (usually $CHCl_3$ or DMSO-d_6) as the internal standard. Natural-abundance ^{13}C NMR spectra were recorded using pulse Fourier transform techniques with a 300 MHz spectrometer operating at 75.4 MHz. ^{19}F NMR spectra were measured on a 470 MHz spectrometer with the solvent peak (C_6F_6) as an external standard (δ_F = −162.2 ppm).[12] High-resolution mass spectrometry (HRMS) was performed with a magnetic-sector-type analyzer using the EI method. UV/vis spectra were recorded with a spectrophotometer, and solvents were of HPLC grade. HPLC experiments were recorded with a Nucleosil-5 C18 column (4.5 mm × 250 mm), and solvents were of HPLC grade; the mobile phase was 90−100% (v/v) MeOH/H_2O. Compounds **5** and **6** were prepared according to literature procedures.[11]

Photocyclization of 3a to 1a. A mixture of compound **3a** (0.10 g, 0.215 mmol) and a catalytic amount of iodine (0.547 mg, 0.0022 mmol) in THF (250 mL) was stirred at room temperature and irradiated in a Rayonet photoreactor at 300 nm for 8 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with a 10% aqueous solution of $Na_2S_2O_3$ followed by a saturated aqueous solution of Na_2CO_3, and dried over anhydrous $MgSO_4$, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (hexane, R_f = 0.5) to afford a mixture of **3a** and **1a** in which **1a** was obtained in 58% yield based on ^{1}H NMR peak ratios. Single crystals of **1a** were obtained from crystallization of the mixture of **3a** and **1a** using a mixed solvent of dichloromethane and ethanol (2:8 v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.49 (d, J = 8.1 Hz, 2H), 7.38 (m, 3.0 Hz, 4H), 7.34−7.19 (m, 8H), 7.05 (d, J = 8.1 Hz, 2H), 7.00−6.88 (m, 2H), 2.79 (s, 4H), 2.04 (d, J = 9.3 Hz, 4H), 1.72 (d, J = 9.7 Hz, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 147.3 (Cq), 138.5 (Cq), 130.3 (Cq), 130.3 (Cq), 128.8 (CH), 128.0 (CH), 126.0 (CH), 125.9 (CH), 124.5 (CH), 124.0 (CH), 122.9 (CH), 56.7 (Cq), 48.2 (CH), 29.7 (CH_2), 25.4 (CH_2). EI-MS: m/z 463 ($[M + H]^+$). HRMS (EI): m/z calcd for $C_{36}H_{30}$ 462.2348, found 462.2351.

X-ray Crystal Data for (1a)$_3$·CH$_2$Cl$_2$. $C_{109}H_{92}Cl_2$, M = 1472.73, monoclinic, a = 16.037(3) Å, b = 11.554(2) Å, c = 21.481(4) Å, α = 90°, β = 109.402(4)°, γ = 90°, V = 3754.0(13) Å^3, space group $P\bar{1}$, Z = 2, calculated density 1.303 Mg/m^{-3}, crystal dimensions: 0.52 mm × 0.50 mm × 0.08 mm, T = 200(2) K, λ(Mo Kα) = 0.71073 Å, μ = 0.142 mm^{-1}, 24974 reflections collected, 6543 independent reflections (R_{int} = 0.0981), 501 parameters refined on F^2, R_1 = 0.0673, $wR_2(F^2)$ = 0.1621 (all data), goodness of fit on F^2 = 1.018, $\Delta\rho_{max}$ = 0.342 e Å^{-3}. CCDC 963498 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.

Synthesis of 2b. To a solution of **6** (0.49 g, 1.99 mmol) and KOH (0.06 g, 1.07 mmol) in EtOH (15 mL) was added 1,3-diphenylacetone (0.42 g, 1.99 mmol), and the mixture was refluxed for 30 min and then cooled to room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (50 × 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated. The residue was recrystallized from EtOH to afford the product **2b** as a dark-red solid in 35% yield. Mp 160−161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 7.35−7.29 (m, 5H), 6.98−6.86 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C 199.4 (Cq), 159.3 (d, J = 248 Hz, Cq), 149.3 (Cq), 130.6 (d, J = 8.4 Hz, CH), 130.4 (Cq), 130.2 (CH), 129.4 (CH), 128.1 (CH), 127.8 (CH), 126.6 (CH), 123.9 (CH), 121.4 (d, J = 17 Hz, Cq), 115.7 (d, J = 22 Hz, CH). EI-MS: m/z 420.1 (M^+). HRMS (EI): m/z calcd for $C_{29}H_{18}F_2O$ 420.1326, found 420.1333.

Synthesis of 3a.[9] Compound **2a** (2.50 g, 6.51 mmol) in 1,5-cyclooctadiene (10 mL) was heated at reflux for 4 days. After cooling to room temperature, the suspension was filtered to afford the product **3a** as a white solid (2.14 g, 71%). Mp 305−306 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.23 (d, J = 7.4 Hz, 4H), 7.00 (t, J = 7.5 Hz, 4H), 6.89 (t, J = 7.2 Hz, 2H), 6.72−6.56 (m, 6H), 6.51 (dd, J = 7.6, 1.7 Hz, 4H), 2.88 (s, 4H), 1.95 (d, J = 9.1 Hz, 4H), 1.54 (s, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 144.8 (Cq), 142.2 (Cq), 141.4 (Cq), 130.6 (CH), 128.4 (CH), 127.0 (CH), 126.0 (CH), 124.9 (CH), 124.2 (CH), 56.6 (Cq), 45.8 (CH), 25.01 (CH_2). EI-MS: m/z 464.4 (M^+). HRMS (EI): m/z calcd for $C_{36}H_{32}$ 464.2504, found 464.2496.

Synthesis of 3b. A solution of compound **2b** (0.10 g, 0.238 mmol) in 1,5-cyclooctadiene (0.37 mL) was heated at reflux for 24 h. After cooling to room temperature, the suspension was filtered to afford the product **3b** as a white solid (8.30 mg, 68%). Mp 275−276 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.44 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 7.08−6.88 (m, 6H), 6.67−6.58 (m, 4H), 6.50 (t, J = 7.2 Hz, 2H), 6.40 (t, J = 8.9 Hz, 2H), 6.52−6.47 (m, 1H), 3.0 (d, J = 12.1 Hz, 2H), 2.86 (m, 2H), 2.04−1.88 (m, 4H), 1.68−1.45 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 190.2 (Cq), 162.9 (d, J = 254 Hz, Cq), 136.7 (dd, J_1 = 6 Hz, J_2 = 4 Hz, CH), 130.7 (CH), 124.9 (CH), 121.2 (dd, J_1 = 10 Hz, J_2 = 3 Hz, Cq), 116.4 (d, J = 22 Hz, CH). EI-MS: m/z 500.2 (M^+). HRMS (EI): m/z calcd for $C_{36}H_{30}F_2$ 500.2316, found 500.2305.

Photocyclization of 3b to 1a−c. A mixture of compound **3b** (0.1g, 0.199 mmol) and a catalytic amount of iodine (5.0 mg, 0.0197 mmol) in THF (100 mL) was stirred at room temperature and irradiated at 250 nm in a Rayonet photoreactor for 8 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with a 10% aqueous solution of $Na_2S_2O_3$ followed by a saturated aqueous solution of Na_2CO_3, and dried over anhydrous $MgSO_4$, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (hexane, R_f = 0.5) and recrystallization. However, the reaction mixture analyzed by HPLC still showed three major peaks at r_t = 23.9, 24.8,

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and 25.9 min with an area ratio of 8:85:5. The mixture of compounds **1a**–**c** was also confirmed by EI-MS and HRMS. For **1a**: *m*/*z* 463 ([M + H]$^+$); HRMS (EI) calcd for $C_{36}H_{30}$ 462.2348, found 462.2354. For **1c**: *m*/*z* 481 ([M + H]$^+$); HRMS (EI) calcd for $C_{36}H_{29}F$ 480.2253, found 480.2250. For **1b**: *m*/*z* 498 (M$^+$); HRMS (EI) calcd for $C_{36}H_{29}F_2$ 498.2159, found 498.2163. The **1b**:**1c**:**1a** peak-area ratio was determined to be 8:85:5 by HPLC analysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data for **1a** (CIF); ^{1}H and ^{13}C NMR spectra and MS data for compounds **1a**–**c**, **2b**, **3a**, **3b**, **5**, and **6**; and DMol3 calculation data for compounds **1a**–**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4808–4842. (b) Jose, D.; Datta, A. *J. Phys. Chem. Lett.* **2010**, *1*, 1363–1366. (c) Raghavender, U. S.; Aravinda, S.; Shamala, N.; Kantharaju; Rai, R.; Balaram, P. *J. Am. Chem. Soc.* **2009**, *131*, 15130–15132. (d) Zhao, R.; Matsumoto, S.; Akazome, M.; Ogura, K. *Tetrahedron* **2002**, *58*, 10233–10241. (e) Brandl, M.; Weiss, M. S.; Jabs, A.; Sühnel, J.; Hilgenfeld, R. *J. Mol. Biol.* **2001**, *307*, 357–377. (f) Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185–6191.

(2) (a) Zhao, C.; Parrish, R. M.; Smith, M. D.; Pellechia, P. J.; Sherrill, C. D.; Shimizu, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 14306–14309. (b) Nijamudheen, A.; Jose, D.; Shine, A.; Datta, A. *J. Phys. Chem. Lett.* **2012**, *3*, 1493–1496. (c) Carroll, W. R.; Zhao, C.; Smith, M. D.; Pellechia, P. J.; Shimizu, K. D. *Org. Lett.* **2011**, *13*, 4320–4323.

(3) (a) Tsuzuki, S. *Annu. Rep. Prog. Chem., Sect. C: Phys. Chem.* **2012**, *108*, 69–95. (b) Nishio, M.; Umezawa, Y.; Honda, K.; Tsuboyama, S.; Suezawa, H. *CrystEngComm* **2009**, *11*, 1757–1788.

(4) (a) Sun, H.; Tottempudi, U. K.; Mottishaw, J. D.; Basa, P. N.; Putta, A.; Sykes, A. G. *Cryst. Growth Des.* **2012**, *12*, 5655–5662. (b) Chopra, D.; Guru Row, T. N. *CrystEngComm* **2011**, *13*, 2175–2186. (c) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 1–14. (d) Bissantz, G.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 5061–5084.

(5) (a) Alkorta, I.; Rozas, I.; Elguero, J. *J. Fluorine Chem.* **2000**, *100*, 233–238. (b) Kawahara, S.-I.; Tsuzuki, S.; Uchimaru, T. *J. Phys. Chem. A* **2004**, *108*, 6744–6749.

(6) Nowak, I. *J. Fluorine Chem.* **1999**, *99*, 59–66.

(7) Scerba, M. T.; Bloom, S.; Haselton, N.; Siegler, M.; Jaffe, J.; Lectka, T. *J. Org. Chem.* **2012**, *77*, 1605–1609.

(8) (a) Ho, T.-L. *Tandem Reactions in Organic Synthesis*; Wiley: New York, 1992. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176.

(9) Akhtar, I. A.; Fray, G. I.; Yarrow, J. M. *J. Chem. Soc. C* **1968**, 812–815.

(10) (a) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1–456. (b) Mallory, F. B.; Wood, C. S.; Gordon, J. T. *J. Am. Chem. Soc.* **1962**, *84*, 4361–4362. (c) Mallory, F. B.; Gordon, J. T.; Wood, C. S. *J. Am. Chem. Soc.* **1963**, *85*, 828–829. (d) Mallory, F. B.; Wood, C. S.; Gordon, J. T. *J. Am. Chem. Soc.* **1964**, *86*, 3094–3102. (e) Wood, C. S.; Mallory, F. B. *J. Org. Chem.* **1964**, *29*, 3373–3377. (f) Mallory, F. B.; Mallory, C. W. *J. Am. Chem. Soc.* **1972**, *94*, 6041–6048. (g) Lewis, F. D.; Kurth, T. L.; Kalgutkar, R. S. *Chem. Commun.* **2001**, 1372–1373.

(11) Romanov-Michailidis, F.; Besnard, C.; Alexakis, A. *Org. Lett.* **2012**, *14*, 4906–4909.

(12) Stadlbauer, S.; Ohmori, K.; Hattori, F.; Suzuki, K. *Chem. Commun.* **2012**, *48*, 8425–8427.

(13) (a) Dewar, M. J. S.; Kelemen, J. *J. Chem. Phys.* **1968**, *49*, 499–508. (b) Byrne, P. A.; Rajendran, K. V.; Muldoon, J.; Gilheany, D. G. *Org. Biomol. Chem.* **2012**, *10*, 3531–3537. (c) Luthe, G.; Ariese, F.; Brinkman, U. A. Th. *Chromatographia* **2004**, *59*, 37–41.

(14) This unexpected deshielding was explained as due to the direct overlap of the van der Waals radii of the adjacent substituents and fluorine, causing the restricted motion of electrons on the fluorine and thus making the fluorine nucleus respond to the magnetic field as if the electron density were lowered. See: (a) Dolbier, W. R. *Guide to Fluorine NMR for Organic Chemists*; Wiley: New York, 2009. (b) Gribble, G. W.; Keavy, D. J.; Olson, E. R.; Rae, I. D.; Staffa, A.; Herr, T. E.; Ferraro, M. B.; Contreras, R. H. *Magn. Reson. Chem.* **1991**, *29*, 422–432. Also see: (c) Rae, I. D.; Staffa, A.; Diz, A. C.; Giribet, C. G.; Ruiz de Azúa, M. C.; Contreras, R. H. *Aust. J. Chem.* **1987**, *40*, 1923–1940. (d) Dolbier, W. R.; Gray, T. A.; Keaffaber, J. J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* **1990**, *112*, 363–367. (e) Landelle, G.; Turcotte-Savard, M.-O.; Angers, L.; Paquin, J.-F. *Org. Lett.* **2011**, *13*, 1568–1571. (f) Uno, H.; Sakamoto, K.; Semba, F.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 210–217. (g) Ernst, L.; Ibrom, K. *Magn. Reson. Chem.* **1997**, *35*, 868–876. (h) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem.* **2008**, *120*, 6082–6085. (i) Fifolt, M. J.; Sojka, S. A.; Wolfe, R. A.; Hojnicki, D. S. *J. Org. Chem.* **1989**, *54*, 3019–3023. (j) Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Anderson, K. K.; Davis, G. T. *J. Am. Chem. Soc.* **1963**, *85*, 3146–3156. (k) Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Anderson, K. K.; Davis, G. T. *J. Am. Chem. Soc.* **1963**, *85*, 709–724.

(15) (a) Delley, B. *J. Chem. Phys.* **1990**, *92*, 508–517. (b) Delley, B. *J. Chem. Phys.* **2000**, *113*, 7756–7764. (c) Benedek, N. A.; Snook, I. K.; Latham, K.; Yarovsky, I. *J. Chem. Phys.* **2005**, *122*, No. 144102.

(16) Mooibroek, T. J.; Gamez, P. *CrystEngComm* **2012**, *14*, 8462–8467.

(17) Saielli, G.; Bini, R.; Bagno, A. *Theor. Chem. Acc.* **2012**, *131*, 1140.