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Stepwise Preparation of All-*cis* 1,3,4-Trifluoro-2-phenylcyclohexane, Avoiding a Phenonium Intermediate

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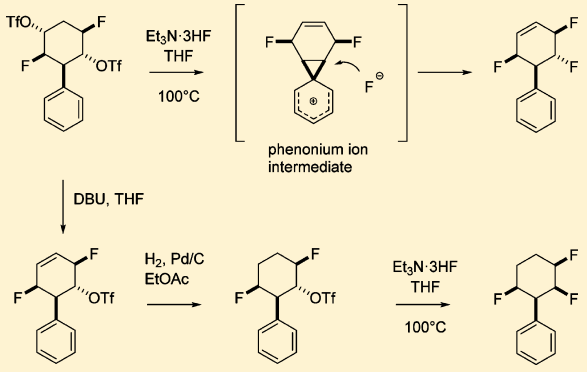
Supporting Information

ABSTRACT: The original synthesis of all-*cis* 1,2,4,5,-tetrafluoro-2-phenylcyclohexane resulted in a trifluorocyclohexene as a significant co-product of the final fluorination step. This product was notable in that an elimination reaction was accompanied by C−F bond formation that had occurred with a retention of configuration. In order to deconvolute this reaction, the two isomers of the ditriflate diol precursor were separated, and they were each treated independently with $Et_3N{\cdot}3HF$. One gave the original all-*cis* 1,2,4,5,-tetrafluoro-2-phenylcyclohexane and the other the trifluorocyclohexene. A deuterium labeling experiment was carried out, resulting in a distribution of the isotope in the trifluorocyclohexene consistent with an intermediate (symmetrical) phenonium intermediate. Cognisant of this, a controlled elimination reaction of one of the diastereoisomers with DBU, followed by hydrogenation, gave a cyclohexane triflate, which, on fluorination, gave the all-*cis* 1,2,3-trifluoro-2-phenylcyclohexane now with an inversion of configuration.



INTRODUCTION

Selectively fluorinated organic motifs continue to attract wide attention in the development of performance organic compounds.[1−5] We have recently executed the syntheses of cyclohexanes carrying arrays of vicinally distributed C−F bonds (Figure 1).[6−8] These include isomers of tetrafluorocyclohexanes with an all-*cis* stereochemistry such that the fluorines are orientated on one face of the cyclohexane ring.[6,7] This imparts polarity to the rings and generates polar structural motifs. For example all-*cis* 1,2,4,5-**1**[7] and 1,2,3,4-**2**[6] tetrafluorocyclohexanes are perhaps unexpectedly crystalline despite their aliphatic nature without significant hydrogen bonding donor or acceptor capacities and their relatively low molecular weight. They are, however, polarized due to the molecular dipole moment associated with the diaxial C−F bonds arrangement, which is satisfied in each case, even with cyclohexane ring inversion.[9] This confers facial polarity to these cyclohexanes with a −ve electrostatic fluorine face and a +ve electrostatic hydrogen face.

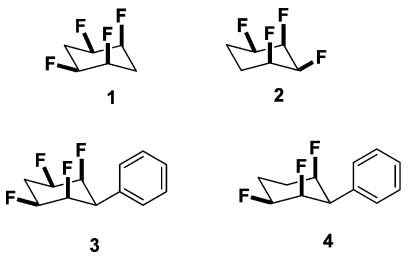


Figure 1. Previously synthesized all-*cis* tetrafluorocyclohexane based compounds **1**, **2**, and **3**.[6−8] Also, the target all-*cis* 1,2,4-trifluoro-3-phenylcyclohexane **4**.

Most recently, we have reported[10] the synthesis of all-*cis* 1,2,4,5-tetrafluoro-3-phenylcyclohexane **3** (Scheme 1). Compound **3** has potential as a polar building block for use in discovery chemistry programs. Phenylcyclohexane **3** was readily converted to a range of derivatives using standard electrophilic aromatic substitution reactions. In developing a preparation of **3**, different strategies were explored from *syn*-diepoxide **5**. It proved most efficient to mediate epoxide ring opening with $Et_3N{\cdot}3HF$ to generate a mixture of fluorohydrins **6** and **7**. The fluorohydrins were converted, as a mixture to triflates **8** and **9**, which, in turn, were treated, also as a mixture, with $Et_3N{\cdot}3HF$. This gave rise to the desired product **3**, but the reaction generated olefin **10** as the major product. It was noteworthy that the fluorination had occurred with a retention of configuration in the generation of **10**. There was no trifluoroolefin with an inverted stereochemistry, suggesting that elimination to the olefin and the fluorination with a retention of configuration, were linked. In this paper, we present evidence that the retention of configuration in

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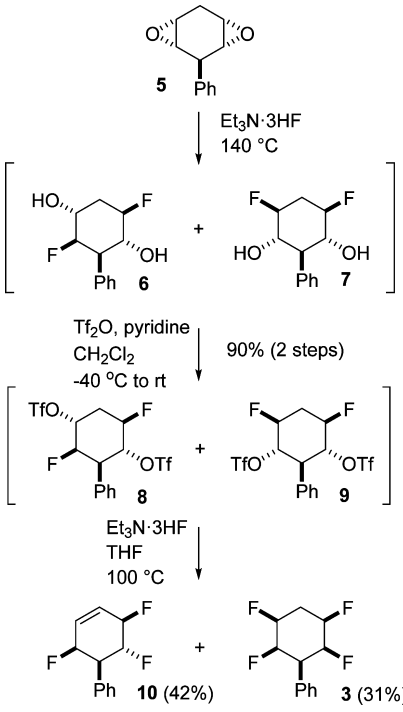
Scheme 1. Previous Synthesis of Tetrafluorocyclohexane 3 and Trifluorocyclohexene 10[10]

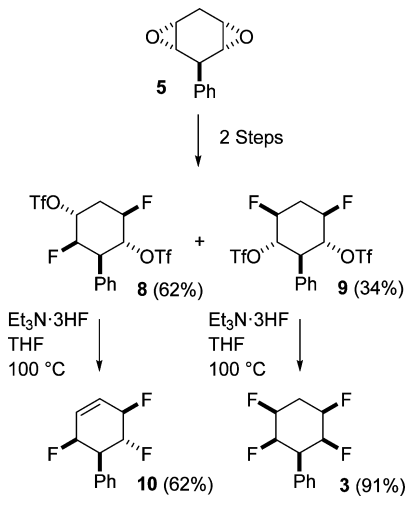


generating **10** arises solely from **8** via a phenonium ion[11−18] and that an obligate elimination precedes fluorination. By controlling the elimination reaction, and separating it from the fluorination event, then an efficient preparation of all-*cis* 1,3,4-trifluoro-2-phenylcyclohexane **4** is achieved and provides access to another attractive polar cyclohexane building block.

RESULTS AND DISCUSSION

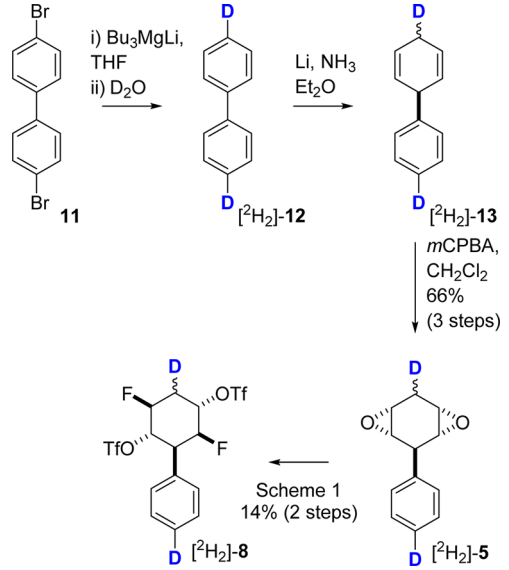
It was an objective to deconstruct the fluorination reaction of the mixture of triflate isomers **8** and **9** and understand how they contribute to products **10** and **3**, respectively. In order to establish if each isomer generates a unique product, the isomers were separated by careful chromatography (Scheme 2). Treatment of **8** with $Et_3N·3HF$ gave the trifluoroolefin **10**.

Scheme 2. Separate Fluorinations of Ditriflates 8 and 9 Generate Unique Products 10 and 3, Respectively



Elimination clearly occurs due to the ability of the triflate C−O bond to adopt an antiperiplanar arrangement to a methylene C−H bond in **8**. On the other hand, treatment of **9** with $Et_3N·3HF$ gave a smooth conversion to **3**. Only substitution occurs, presumably because there is no C−H bond lying antiperiplanar to the triflate groups in **9**. There was no crossover in product formation from the individual isomers, illustrating that the product outcome was isomer-dependent. Thus, isomer **9** was processed as anticipated, but isomer **8** behaved in an unexpected manner. In order to explore the reaction of ditriflate isomer **8** to olefin **10** more closely, a deuterium labeling experiment was designed, using ditriflate $[^2H_2]$-**8** as a substrate. The required isotopically labeled precursor was prepared as illustrated in Scheme 3 from [4,4′-$^2H_2$]-biphenyl,

Scheme 3. Isotope Incorporation and Synthesis of Ditriflate $[^2H_2]$-8 from Biphenyl



itself prepared by treatment of dibromide **11** with $LiBu_3Mg$, followed by a D_2O quench.[19] Birch reduction[20] gave $[^2H_2]$-**13**, followed by mCPBA-mediated diepoxidation to generate $[^2H_2]$-**5**. Diepoxide $[^2H_2]$-**5** was then converted to ditriflate $[^2H_2]$-**8** following the three-step protocol illustrated in Scheme 1. This material was a 1:1 mixture of diastereoisomers due to the lack of any stereochemical bias of the deuterium situated at the 4-position of the cyclohexane ring in **8**.

Treatment of $[^2H_2]$-**8** with $Et_3N·3HF$ led to an efficient conversion to three observable (by ^{19}F and ^{13}C NMR) populations of $[^2H]$-**10**. The introduction of the double bond requires elimination of the triflate group and the antiperiplanar hydrogen/deuterium at C-4.[12] Only 50% of the stereospecific elimination will result in a deuterium retention. For the molecules that retained deuterium in the cyclohexene ring, an equal scrambling of the isotope was apparent between the double bond carbons, C3 and C4, as deduced from the ^1H, ^{13}C, and ^{19}F NMR spectra. For ^{19}F NMR, integrations were consistent with 50% deuterium retention distributed over both olefinic carbons. In the ^{13}C NMR, 25% of each olefin carbon signal was coupled to deuterium, and in the $^{19}F\{^1H\}$ NMR spectrum (Figure 2), isotope induced shifts were consistent with an equal distribution of deuterium across these carbons. This isotope labeling pattern is illustrated in Scheme 4.

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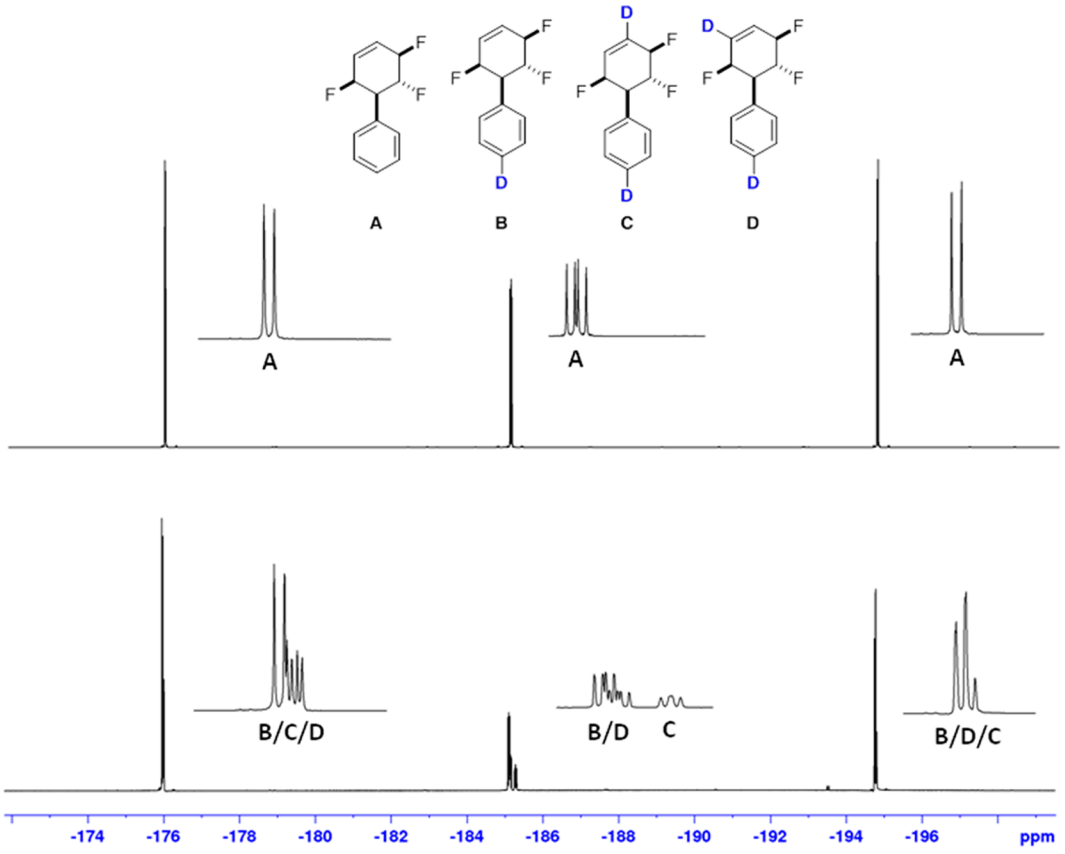
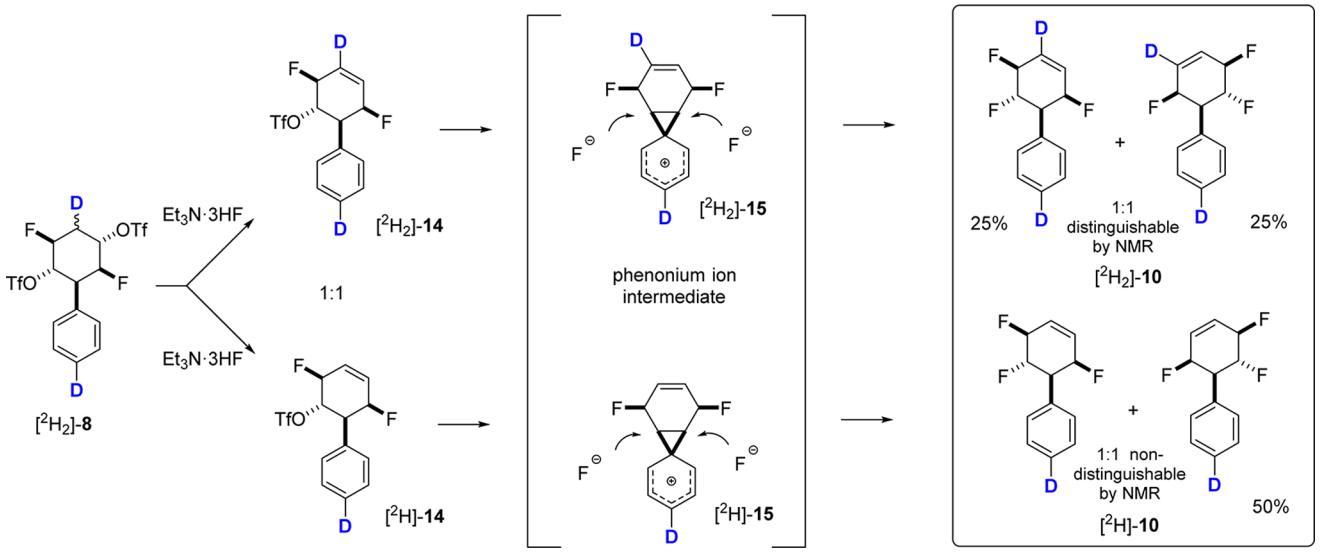


Figure 2. $^{19}F\{^{1}H\}$ NMR of three isotope populations of **10** after the fluorination of $[^{2}H_2]$-**8**.

Scheme 4. Fluorination of Ditriflate $[^{2}H_2]$-8 Results in an Isotope Distribution Consistent with a Phenonium Intermediate 15



The equal distribution of the isotope across the double bond of **10** is consistent with fluoride ion attack onto the symmetrical phenonium ion intermediate **15**. This intermediate appears to form only after elimination has occurred to introduce the double bond. There is no evidence for a fluorine substituted product without elimination, or a tetrafluoro product arising from double fluorination of ditriflate **8**. We reasoned, however, that, if a controlled elimination was carried out, under nonfluorination conditions, then the product of elimination might be isolated. To this end, when **8** is treated with DBU, then cyclohexene **16** is generated in good yield, as shown in Scheme 5.

Hydrogenation of cyclohexene **16** proved to be straightforward and gave cyclohexane triflate **17**, which, on treatment with $Et_3N{\cdot}3HF$, resulted in a smooth conversion to all-*cis* trifluorocyclohexane **4**, in a reaction proceeding with an inversion of configuration. No elimination occurs, as there are no antiperiplanar C−H/triflate arrangements. There was no evidence of diastereoisomer **18**, with retained stereochemistry, a reference sample of which could be generated separately by

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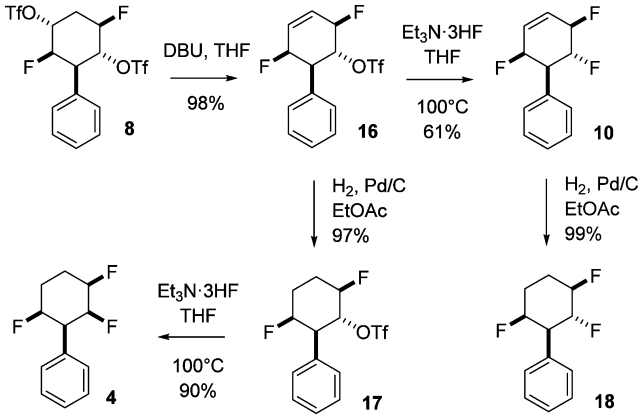
Scheme 5. Subsequent Transformations of 16 after the Controlled Elimination Reaction of Ditriflate 8.



hydrogenation of **10**. Thus, it appears that the phenonium intermediate **15** and the observed retention of configuration only occur after the elimination to generate the cyclohexene. Presumably, the presence of the double bond in **15** flattens the six-membered ring and this accommodates phenonium ion formation.

The ability to circumvent the phenonium ion participation by a controlled elimination, followed by hydrogenation, allows access to all-*cis* trifluorocyclohexane **4**. The X-ray structure of **4** is shown in Figure 3, and it can be seen that the phenyl ring lies

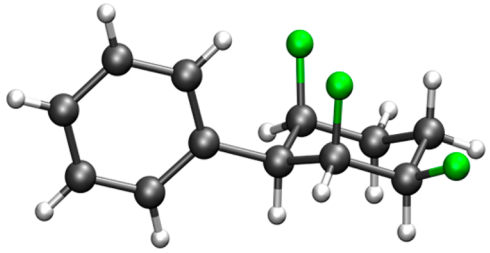


Figure 3. X-ray structure of **4** showing the 1,3-diaxial C−F bonds and the perpendicular orientation of the aryl ring.

equatorial with two of the C−F bonds orientating 1,3-diaxial to each other and rendering this also a polar organic motif. The plane of the phenyl ring lies perpendicular to the plane of the cyclohexane ring, in a manner explored in detail with **3**.[10,21]

CONCLUSION

In this study, we have deconvoluted the relationship between the ditriflate isomers **8** and **9** and their products of fluorination **10** and **3**. Both are efficiently converted to their respective products, and there is no product crossover in reaction of the individual isomers. For the reaction of isomer **8**, the unexpected product outcome was shown to arise by a sequential elimination and then a substitution reaction proceeding via a phenonium intermediate. This was deduced by carrying out a controlled elimination, and also a deuterium isotope experiment with [$^2H_2$]-**8**. An understanding of this process has enabled a synthetic protocol that decouples the elimination from the fluorination reaction. Hydrogenation of the elimination product then allows efficient access to the all-*cis* trifluorocyclohexane **4**. We present **4** in addition to **3** as polar hydrophobic building blocks with unusual facially polarized cyclohexane rings for inclusion in discovery chemistry programs.

EXPERIMENTAL SECTION

2,5-Difluoro-3-phenylcyclohexane-1,4-diyl Bis(trifluoromethanesulfonate) (8) and 4,6-Difluoro-2-phenylcyclohexane-1,3-diyl Bis(trifluoromethanesulfonate) (9). To a solution of diepoxide **5** (565 mg, 3 mmol) in anhydrous THF (0.75 mL) at room temperature was added $Et_3N·3HF$ (3.91 mL, 24 mmol, 8 equiv). After 45 h stirring at 130 °C under an argon atmosphere, the mixture was poured into sat. aq. sodium bicarbonate (150 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (2:5:5 petroleum ether/CH_2Cl_2/EtOAc) to afford a mixture of difluorohydrins **6** and **7** (557 mg, 81%, **6**:**7** = 1.8:1) as a colorless solid.

The aforementioned mixture was dissolved in anhydrous CH_2Cl_2 (19 mL), and trifluoromethanesulfonic anhydride (1.23 mL, 7.32 mmol, 3 equiv) and pyridine (0.79 mL, 9.76 mmol, 4 equiv) were added subsequently under an argon atmosphere at −40 °C. The mixture was allowed to warm to room temperature. After 24 h stirring, the mixture was filtered through a small pad of silica gel (2:3:2 petroleum ether/CH_2Cl_2/EtOAc) and the filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (10:5:1 petroleum ether/CH_2Cl_2/Et_2O) to afford the asymmetric ditriflate **8** (746 mg, 62%) as a colorless crystalline solid; mp 99.0−102.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.36 (5H, m, C$\underline{H}$), 5.40 (1H, td, J = 11.2, 8.8 Hz, C$\underline{H}$), 5.30 (1H, m, C$\underline{H}$), 5.03 (1H, dddd, J = 49.1, 11.8, 8.8, 5.3 Hz, C$\underline{H}$F), 4.94 (1H, m, C$\underline{H}$F), 3.31 (1H, dd, J = 37.6, 11.7 Hz, C$\underline{H}$), 2.79 (1H, m, C$\underline{H_AH_B}$), 2.50 (1H, m, CH$_A\underline{H_B}$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 131.9 (s, $\underline{C}$), 129.4 (d, J = 2.4 Hz, $\underline{C}$H), 129.3 (s, $\underline{C}$H), 129.2 (s, $\underline{C}$H), 118.4 (q, J = 319.6 Hz, $\underline{C}F_3$), 118.0 (q, J = 320.6 Hz, $\underline{C}F_3$), 89.8 (d, J = 181.6 Hz, $\underline{C}$HF), 87.0 (d, J = 185.8 Hz, $\underline{C}$HF), 85.1 (dd, J = 18.4, 2.6 Hz, $\underline{C}$H), 79.8 (dd, J = 34.3, 13.2 Hz, $\underline{C}$H), 46.1 (dd, J = 17.4, 5.1 Hz, $\underline{C}$H), 30.9 (d, J = 22.8 Hz, $\underline{C}H_AH_B$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −74.9 (3F, s, C$\underline{F}_3$), −75.1 (3F, d, J = 9.0 Hz, C$\underline{F}_3$), −188.1 (1F, q, J = 9.0 Hz, CH$\underline{F}$), −194.0 (1F, s, CH$\underline{F}$); HRMS (EI-TOF) calcd for $C_{14}H_{12}F_8O_6S_2$ (M^+): 491.9948; found 491.9950.; MS (EI) m/z 492 ([M]$^+$, 32%), 192 (100%), 173 (18%), 133 (20%), 115 (20%), 91 (28%); and the symmetric ditriflate **9** (405 mg, 34%) as a colorless crystalline solid; mp 110.0 °C (dec., CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.40 (3H, m, C$\underline{H}$), 7.31−7.27 (2H, m, C$\underline{H}$), 5.14−5.04 (2H, m, C$\underline{H}$), 4.93−4.68 (2H, m, C$\underline{H}$F), 3.13 (1H, t, J = 11.4 Hz, C$\underline{H}$), 2.96 (1H, dquint, J = 12.8, 5.2 Hz, C$\underline{H_AH_B}$), 2.19 (1H, m, CH$_A\underline{H_B}$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 130.5 (s, $\underline{C}$), 129.8 (s, $\underline{C}$H), 129.6 (s, $\underline{C}$H), 128.8 (s, $\underline{C}$H), 117.9 (q, J = 319.6 Hz, $\underline{C}F_3$), 86.7 (dd, J = 189.0, 15.1 Hz, $\underline{C}$HF), 86.2 (d, J = 19.1 Hz, $\underline{C}$H), 47.9 (t, J = 6.1 Hz, $\underline{C}$H), 31.7 (t, J = 21.5 Hz, $\underline{C}H_AH_B$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −75.1 (6F, d, J = 9.0 Hz, C$\underline{F}_3$), −185.9 (2F, br d, J = 8.7 Hz, CH$\underline{F}$); HRMS (EI-TOF) calcd for $C_{14}H_{12}F_8O_6S_2$ (M^+): 491.9948; found 491.9945; MS (EI) m/z 492 ([M]$^+$, 22%), 192 (100%), 172 (16%), 147 (15%), 133 (18), 115 (22%), 91 (31%).

3,4,6-Trifluoro-5-phenylcyclohexene (10). To a solution of the asymmetric ditriflate **8** (148 mg, 0.30 mmol) in anhydrous THF (0.5 mL) was added $Et_3N·3HF$ (1.20 mL, 7.50 mmol, 25 equiv) at room temperature. After 69 h stirring at 100 °C under an argon atmosphere, the mixture was poured into sat. aq. sodium bicarbonate (50 mL) at room temperature. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel column chromatography to give trifluorocyclohexenes **10** (39 mg, 62%).[10]

All-*cis* 1,2,4,5-Tetrafluoro-3-phenylcyclohexane (3). Fluorination of symmetric ditriflate **5** (690 mg, 1.40 mmol) with $Et_3N·3HF$ (4.60 mL, 28.0 mmol, 20 equiv) in anhydrous THF (1 mL) according to the procedure described for **4** gave tetrafluorocyclohexane **8** (297 mg, 91%).[10]

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6,4′-[$^2H_2$]-2-Phenyl-4,8-dioxatricyclo[5.1.0.03,5]octane ([$^2H_2$]-5). *n*-Butyllithium (10 mL, 2.3 M in THF, 23 mmol, 2.4 equiv) was added to a solution of butylmagnesium bromide (5.7 mL, 2.0 M in THF, 11.4 mmol, 1.2 equiv) in THF (20 mL) at 0 °C. After 15 min stirring at 0 °C, a solution of 4,4′-dibromobiphenyl **11** (2.96 g, 9.5 mmol, 1 equiv) in THF (20 mL) was dropwise added to the reaction mixture over 10 min, and the reaction mixture was stirred for an additional 1 h before D_2O (1 mL, 50 mmol, 5.3 equiv) was added. The mixture was stirred for 1 h at 0 °C and then treated with sat. aq. ammonium chloride (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give 4,4′-[$^2H_2$]-biphenyl [$^2H_2$]-**12**.

The crude 4,4′-[$^2H_2$]-biphenyl [$^2H_2$]-**12** was dissolved in anhydrous diethyl ether (50 mL) and added to liquid ammonia (100 mL) at −78 °C. Lithium (150 mg, 21.3 mmol, 2.2 equiv) was added portionwise to the reaction mixture over 10 min, resulting in the formation of a deep blue-brown color. The reaction mixture was warmed to −25 °C, stirred for 30 min, and then quenched by addition of solid ammonium chloride (8 g), resulting in a colorless suspension. After warming to room temperature, water (50 mL) and diethyl ether (50 mL) were added subsequently. The aqueous phase was washed with diethyl ether (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to offer 6,4′-[$^2H_2$]-3-phenyl-1,4-cyclohexadiene [$^2H_2$]-**13** as a colorless oil.

The aforementioned crude product was dissolved in CH_2Cl_2 (50 mL) at 0 °C, and *m*CPBA (3.44 g, 70%, 19.9 mmol, 2.1 equiv) was then added. After 14 h stirring at room temperature, the mixture was quenched with 10% KOH (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a colorless crystalline solid. This was purified via silica gel chromatography (4:1 hexane/ethyl acetate) to afford [$^2H_2$]-**5** (1.2 g, 66%) as a colorless crystalline solid containing a 1:1 mixture of diastereoisomers with respect to the deuterium: mp 129.5−130.5 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.39 (2H × 2, m, C<u>H</u>), 7.33−7.30 (2H × 2, m, C<u>H</u>), 3.97 (1H × 2, s, C<u>H</u>), 3.22−3.19 (2H × 2, m, C<u>H</u>O), 3.13−3.10 (2H × 2, m, C<u>H</u>O), 2.91 (1H, s, C<u>H</u>$_x$D$_y$), 2.44−2.41 (1H, m, CD$_x$<u>H</u>$_y$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 138.3 (s, <u>C</u>), 129.2 (s, <u>C</u>H), 128.6 (s, <u>C</u>H), 127.7 (t, *J* = 24.3 Hz, <u>C</u>D), 53.6 (s, <u>C</u>HO), 53.6 (s, <u>C</u>HO), 49.4 (s, <u>C</u>HO), 49.3 (s, <u>C</u>HO), 23.5 (t, *J* = 19.2 Hz, <u>C</u>HD); HRMS (APCI − ion trap mass analysis) calcd for $C_{12}H_{11}O_2D_2$ ([M + H]$^+$): 191.1036; found 191.1032.; MS (APCI) *m*/*z* 381 ([2M + H]$^+$, 60%), 191 ([M + H]$^+$, 100%), 173 ([M + H − H_2O]$^+$, 55%), 155 (20%), 146 (80%).

6,4′-[$^2H_2$]-2,5-Difluoro-3-(phenyl)cyclohexane-1,4-diyl Bis-(trifluoromethanesulfonate) ([$^2H_2$]-8). A solution of [$^2H_2$]-**5** (200 mg, 1.1 mmol, 1 equiv) in Et_3N·3HF (2.5 mL, 2.5 g, 15 mmol, 14 equiv) was stirred at 150 °C in a Teflon flask for 14 h. The reaction mixture was cooled down to room temperature, quenched with sat. aq. (50 mL), and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product as a brown crystalline solid.

Triflic anhydride (0.53 mL, 0.89 g, 3.2 mmol, 3 equiv) and pyridine (0.34 mL, 0.33 g, 4.2 mmol, 4 equiv) were added subsequently to a solution of the aforementioned crude product in CH_2Cl_2 (20 mL) at 0 °C. After 20 h stirring at room temperature, the reaction mixture was treated with sat. aq. $CuSO_4$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The brown solid was purified via silica gel chromatography, (2:1 petroleum ether/CH_2Cl_2) to afford [$^2H_2$]-**8** (72 mg, 14%) as a colorless crystalline solid containing a 1:1 mixture of diastereoisomers with respect to the deuterium: mp 98.0−99.5 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.36 (4H × 2, m, C<u>H</u>), 5.46−5.36 (1H × 2, m, C<u>H</u>), 5.33−5.28 (1H × 2, m, C<u>H</u>), 5.10−4.89 (2H × 2, m, C<u>H</u>F), 3.32 (1H × 2, dd, *J* = 37.7, 11.8 Hz, C<u>H</u>), 2.77 (1H, s, C<u>H</u>$_A$D$_B$), 2.53−2.44 (1H, m, CD$_A$<u>H</u>$_B$); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 132.1 (s, <u>C</u>), 129.5 (d, *J* = 2.4 Hz, <u>C</u>H), 129.4−128.8 (m, <u>C</u>H, <u>C</u>D), 118.5 (q, *J* = 319.7 Hz, <u>C</u>F$_3$), 118.1 (q, *J* = 319.5 Hz, <u>C</u>F$_3$), 90.0 (d, *J* = 181.8 Hz, <u>C</u>HF), 87.2 (d, *J* = 185.7 Hz, <u>C</u>HF), 85.3 (d, *J* = 18.4 Hz, <u>C</u>H), 79.9 (dd, *J* = 34.7, 13.2 Hz, <u>C</u>H), 46.2 (dd, *J* = 17.4, 5.1 Hz, <u>C</u>H), 30.3 (q, *J* = 20.8 Hz, <u>C</u>HD); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ −74.5 (3F × 2, s, C<u>F</u>$_3$), −74.7 (3F × 2, d, *J* = 9.0 Hz, C<u>F</u>$_3$), −187.7 (1F, q, *J* = 9.0 Hz, CH<u>F</u>), −187.8 (1F, q, *J* = 9.0 Hz, CH<u>F</u>), −193.6 (1F, s, CH<u>F</u>), −193.6 (1F, s, CH<u>F</u>); HRMS (APCI-ion trap mass analysis) calcd for $C_{14}H_{10}F_8O_6S_2D_2$ (M$^+$): 494.0068; found 494.0064; MS (APCI) *m*/*z* 524(100%), 494 ([M]$^+$, 5%), 437 (25%), 427 (25%), 195 ([M − 2OTf + H]$^+$, 20%), 175 ([M − 2OTf − HF + H]$^+$, 20%).

1/2,4′-[$^2H_2$]-3,4,6-Trifluoro-5-phenylcyclohexene ([$^2H_2$]-10) and 4′-[^{2}H]-3,4,6-Trifluoro-5-phenylcyclohexene ([^{2}H]-10). A solution of [$^2H_2$]-**8** (30 mg, 0.061 mmol, 1 equiv) in Et_3N·3HF (1.0 mL, 6.1 mmol, 100 equiv) was stirred at 100 °C in a Teflon flask for 60 h. The reaction mixture was cooled down to room temperature, quenched with sat. aq. sodium bicarbonate (50 mL), and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The brown solid was then purified via silica gel chromatography, (4:1 petroleum ether/Et_2O) to afford [$^2H_2$]-**10** (11 mg, 85%), an isotopic mixture, as a colorless crystalline solid: mp 122.0−124.0 °C ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.39 (2H, m, C<u>H</u>), 7.38−7.35 (2H, m, C<u>H</u>), 6.16−6.07 (2H, m, C<u>H</u>), 5.44−5.21 (2H, m, C<u>H</u>F), 5.07−4.94 (1H, m, C<u>H</u>F), 3.23−3.11 (1H, m, C<u>H</u>); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 134.9 (s, <u>C</u>), 131.1−130.6 (m, <u>C</u>H/D), 129.3 (s, <u>C</u>H), 128.7 (s, <u>C</u>H), 127.8 (t, *J* 24.4 Hz, <u>C</u>D), 127.4−127.0 (m, <u>C</u>H/D), 92.0−90.3 (m, <u>C</u>HF), 89.3 (dd, *J* = 182.1, 19.0 Hz, <u>C</u>HF), 88.2−86.6 (m, <u>C</u>HF), 48.5 (td, *J* = 19.6, 7.3 Hz); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ −176.0 (1F, d, *J* = 10.5 Hz, CH<u>F</u>), −176.0 (1F, d, *J* = 10.5 Hz, CH<u>F</u>), −176.0 (1F, d, *J* = 10.5 Hz, CH<u>F</u>), −185.1 (1F, dd, *J* = 14.5, 10.5 Hz, CH<u>F</u>), −185.1 (1F, dd, *J* = 14.4, 10.5 Hz, CH<u>F</u>), −185.3 (1F, dd, *J* = 13.5, 11.2 Hz, CH<u>F</u>), −194.7− (−194.8) (1F × 3, m, CH<u>F</u>); HRMS *m*/*z* (APCI-ion trap mass analysis) calcd for $C_{12}H_9F_3D_2$ ([M]$^+$): 214.0933; found 214.0928; MS (APCI) *m*/*z* 287 (50%), 286 (45%), 214 ([M($^2H_2$)]$^+$, 5%), 213 ([M($^2H_1$)]$^+$, 5%), 195 ([M($^2H_2$) + H − HF]$^+$, 70%), 194 ([M($^2H_1$) + H − HF]$^+$, 55%), 175 ([M($^2H_2$) + H − 2HF]$^+$, 75%), 174 ([M($^2H_1$) + H − 2HF]$^+$, 100%).

3,6-Difluoro-5-phenylcyclohexen-4-yl Trifluoromethanesulfonate (16). To a solution of the asymmetric ditriflate **8** (492 mg, 1.00 mmol) in anhydrous THF (4 mL) at 0 °C under an argon atmosphere was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.160 mL, 1.05 mmol, 1.05 equiv). The resulting solution was allowed to warm up to room temperature, stirred for 1 h, and then concentrated under reduced pressure. The residue was purified via silica gel chromatography (8:2:1 petroleum ether/CH_2Cl_2/Et_2O) to afford cyclohexenyl monotriflate **16** (334 mg, 98%) as a colorless crystalline solid; mp 83.0−84.0 °C (dec., CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.35 (5H, m, C<u>H</u>), 6.24−6.11 (2H, m, C<u>H</u>), 5.64 (1H, m, C<u>H</u>), 5.34 (1H, m, C<u>H</u>F), 5.08 (1H, m, C<u>H</u>F), 3.22 (1H, dddd, *J* = 30.1, 12.5, 3.0, 1.1 Hz, C<u>H</u>); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 133.1 (s, <u>C</u>), 130.1 (dd, *J* = 23.0, 10.0 Hz, <u>C</u>H), 129.8 (d, *J* = 3.1 Hz, <u>C</u>H), 128.8 (s, <u>C</u>H), 128.7 (s, <u>C</u>H), 127.4 (dd, *J* = 17.0, 8.9 Hz, <u>C</u>H), 118.1 (q, *J* = 319.6 Hz, <u>C</u>F$_3$), 89.9 (dd, *J* = 178.6, 3.6 Hz, <u>C</u>HF), 86.6 (dd, *J* = 175.0, 1.4 Hz, <u>C</u>HF), 84.5 (d, *J* = 18.8 Hz, <u>C</u>H), 48.6 (dd, *J* = 19.3, 5.8 Hz, <u>C</u>H); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −75.1 (3F, d, *J* = 9.8 Hz, C<u>F</u>$_3$), −175.3 (1F, d, *J* = 10.0 Hz, CH<u>F</u>), −183.4 (1F, dq, *J* = 10.0, 9.8 Hz, CH<u>F</u>); HRMS *m*/*z* (EI-TOF) Found: [M]$^+$ 342.0348. $C_{13}H_{11}F_5O_3S^+$ requires *m*/*z* 342.0349; MS (EI) *m*/*z* 342 ([M]$^+$, 45%), 252 (75%), 192 (31%), 172 (21%), 154 (19%), 133 (17%), 119 (100%), 115 (14%), 91 (88%).

3,4,6-Trifluoro-5-phenylcyclohexene (10). Fluorination of cyclohexenyl monotriflate **16** (51 mg, 0.150 mmol) with Et_3N·3HF (0.490 mL, 3.00 mmol, 20 equiv) in anhydrous THF (0.49 mL) according to the procedure described for **8** gave trifluorocyclohexene **10** (20 mg, 61%).[10]

3,6-Difluoro-5-phenylcyclohexan-4-yl Trifluoromethanesulfonate (17). 10% palladium on activated carbon (14 mg) was added to a solution of cyclohexenyl monotriflate **16** (0.20 g, 0.584 mmol) in EtOAc (7 mL). After 2.5 h stirring under a hydrogen atmosphere, the mixture was filtered through a pad of Celite and

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concentrated under reduced pressure. The residue was purified via silica gel column chromatography (10:2:1 petroleum ether/CH_2Cl_2/Et_2O) to give **17** (195 mg, 97%) as a colorless crystalline solid; mp 95.0−96.0 °C (dec., $CHCl_3$/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.32 (5H, m, C$\underline{H}$), 5.42 (1H, td, J = 11.1, 8.7 Hz, C$\underline{H}$), 4.90 (1H, m, C$\underline{H}$F), 4.75 (1H, m, C$\underline{H}$F), 2.95 (1H, dd, J = 34.7, 11.6 Hz, C$\underline{H}$), 2.35−2.11 (3H, m, C$\underline{H}_2$), 1.72 (1H, m, C$\underline{H}_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 134.4 (s, $\underline{C}$), 129.2 (d, J = 3.0 Hz, $\underline{C}$H), 128.8 (s, $\underline{C}$H), 128.5 (s, $\underline{C}$H), 118.0 (q, J = 319.5 Hz, $\underline{C}F_3$), 91.4 (dd, J = 178.0, 1.8 Hz, $\underline{C}$HF), 91.2 (d, J = 185.1 Hz, $\underline{C}$HF), 87.7 (dd, J = 18.2, 1.9 Hz, $\underline{C}$H), 51.4 (dd, J = 17.8, 4.9 Hz, $\underline{C}$H), 27.8 (dd, J = 21.7, 11.3 Hz, $\underline{C}H_2$), 24.8 (dd, J = 19.3, 1.9 Hz, $\underline{C}H_2$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −75.3 (3F, d, J = 8.8 Hz, $C\underline{F}_3$), −179.6 (1F, q, J = 8.8 Hz, CH$\underline{F}$), −194.4 (1F, s, CH$\underline{F}$); HRMS m/z (EI-TOF) Found: $[M]^+$ 344.0503. $C_{13}H_{13}F_5O_3S^+$ requires m/z 344.0506; MS (EI) m/z 344 ($[M]^+$, 32%), 194 (57%), 174 (15%), 148 (100%), 135 (16%), 129 (25%), 115 (25%), 91 (43%).

All-*cis* 3,4,6-Trifluoro-5-phenylcyclohexene (4). Fluorination of **17** (173 mg, 0.502 mmol) with $Et_3N{\cdot}3HF$ (1.65 mL, 10.0 mmol, 20 equiv) in anhydrous THF (0.75 mL) according to the procedure described for **8** gave trifluorocyclohexane **4** (96 mg, 90%) as a colorless crystalline solid; mp 122.0−123.0 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, br d, J = 6.9 Hz, C$\underline{H}$), 7.40−7.30 (3H, m, C$\underline{H}$), 5.10 (1H, dd, J = 51.7, 8.7 Hz, C$\underline{H}$F), 4.89 (1H, m, C$\underline{H}$F), 4.64 (1H, ddddd, J = 45.6, 25.7, 12.1, 4.8, 2.2 Hz, C$\underline{H}$F), 2.70 (1H, t, J = 38.1 Hz, C$\underline{H}$), 2.52−2.29 (2H, m, C$\underline{H}_A\underline{H}_B$), 1.98 (1H, m, C$H_A\underline{H}_B$), 1.70 (1H, m, C$H_A\underline{H}_B$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 137.5 (s, $\underline{C}$), 129.2 (t, J 2.4 Hz, $\underline{C}$H), 128.6 (s, $\underline{C}$H), 127.6 (s, $\underline{C}$H), 90.6 (dd, J = 187.6, 17.2 Hz, $\underline{C}$HF), 90.2 (dd, J = 184.5, 19.3 Hz, $\underline{C}$HF), 89.0 (d, J = 181.3 Hz, $\underline{C}$HF), 48.3 (td, J = 18.1, 5.4 Hz, $\underline{C}$H), 28.5 (dd, J = 22.6, 12.0 Hz, $\underline{C}H_A\underline{H}_B$), 20.4 (dd, J = 20.2, 3.3 Hz, $\underline{C}H_A\underline{H}_B$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −183.3 (1F, d, J = 14.2 Hz, CH$\underline{F}$), −191.6 (1F, d, J = 26.1 Hz, CH$\underline{F}$), −210.1 (1F, dd, J = 26.1, 14.2 Hz, CH$\underline{F}$); HRMS (EI-TOF) calcd for $C_{12}H_{13}F_3$ (M^+): 214.0969; found 214.0970; MS (EI) m/z 214 ($[M]^+$, 100%), 194 (10%), 153 (28%), 135 (37%), 122 (30%), 115 (23%), 109 (22%), 91 (55%).

3,4,6-Trifluoro-5-phenylcyclohexane (18). Catalytic hydrogenation of trifluorocyclohexene **10** (42 mg, 0.200 mmol) with 10% palladium on activated carbon (3 mg) in EtOAc (2.5 mL) according to the procedure described for **9** gave **18** (40 mg, 93%) as a colorless crystalline solid; mp 108.0−109.0 °C (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.30 (5H, m, C$\underline{H}$), 5.12 (1H, dddd, J = 51.3, 12.8, 11.4, 8.3 Hz, C$\underline{H}$F), 4.84 (1H, m, C$\underline{H}$F), 4.75 (1H, m, C$\underline{H}$F), 2.90 (1H, dt, J = 35.7, 10.1 Hz, C$\underline{H}$), 2.29−2.01 (3H, m, C$\underline{H}_2$), 1.70 (1H, m, CH_2); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 136.2 (s, $\underline{C}$), 128.7 (d, J = 1.7 Hz, $\underline{C}$H), 128.6 (s, $\underline{C}$H), 127.7 (s, $\underline{C}$H), 93.7−90.6 (m, $\underline{C}$HF), 51.3 (td, J = 18.6, 6.4 Hz, $\underline{C}$H), 28.0 (ddd, J = 21.6, 11.4, 1.2 Hz, $\underline{C}H_2$), 24.5 (ddd, J = 19.5, 6.9, 2.0 Hz, $\underline{C}H_2$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −183.0 (1F, d, J = 15.8 Hz, CH$\underline{F}$), −194.4 (1F, d, J = 15.8 Hz, CH$\underline{F}$), −195.0 (1F, s, CH$\underline{F}$); HRMS m/z (EI-TOF) Found: $[M]^+$ 214.0965. $C_{12}H_{13}F_3^+$ requires m/z 214.0969; MS (EI) m/z 214 ($[M]^+$, 100%), 194 (10%), 153 (20%), 135 (32%), 122 (19%), 115 (21%), 109 (23%), 91 (58%), 78 (10%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic files and NMR spectra. 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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