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Photoredox Catalyzed Intramolecular Fluoroalkylarylation of Unactivated Alkenes

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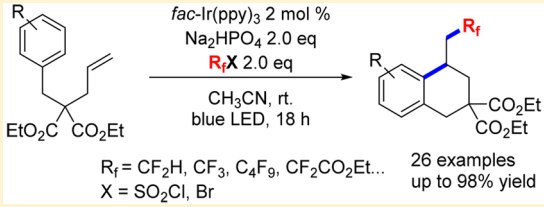
Supporting Information

ABSTRACT: The first example of photoredox catalyzed difluoromethylation of unactivated alkenes coupled with C−C bond formation to an aryl ring is reported. The reactions are conducted under mild conditions and afford tetralin derivatives bearing difluoromethyl as well as other fluoroalkyl groups in good to high yields. In addition, the study indicates that 6-exo radical cyclization of an alkyl radical to a phenyl ring is faster than the respective 5-exo radical cyclization. A computational study provides insights to the experimental results.



INTRODUCTION

Fluorine substituents and fluoroalkyl groups have been widely recognized as playing a strategic role in pharmaceutical research and drug development due to their demonstrated ability to enhance properties related to biological activity, such as improved lipophilicity, metabolic stability, and bioavailability.[1] Therefore, substantial effort has been devoted to the development of synthetic methods for introduction of the fluorine substituent and fluoroalkyl groups into various organic building block molecules. Foremost among them has been the development of methods for incorporation of the trifluoromethyl group, work extending over the past few decades.[2] In contrast, methods for introduction of partially fluorinated alkyl groups has been much more limited.[3] In particular, the difluoromethyl group, which can offer a more lipophilic H-bond donor than either an OH or NH, is of great current interest,[4] and recently much elegant work related to difluoromethylation of aromatics or heteroaromatics has been reported.[5] Also, alkene difluoromethylation reactions that simultaneously incorporate H, halogen and N or O functionalities have been shown to constitute an efficient strategy for construction of Csp^3−CF_2H.[6] A worthy extension of such chemistry is the making of a C−C bond as part of the chain process. Recent chemistry of that type includes our 2014 report of the photoredox catalyzed difluoromethylation of *N*-arylacrylamides, which was accompanied by a tandem 5-*exo*-trig cyclization onto the aryl ring to construct oxindoles.[7] In the same year Tan's group developed a silver catalyzed difluoromethylation that produced the same result.[7,8] In 2015, Hu and co-workers reported a novel fluoroalkylative aryl migration of conjugated *N*-arylsulfonylated amides,[9] and earlier this year our group reported a photoredox catalyzed intramolecular difluoromethylation of *N*-benzylacrylamides that led to a dearomatizing spirocyclization reaction.[10] All of these previous arylative difluoromethylation reactions used α,β-unsaturated amide derivatives as substrates. In this article we will present a further extension of this methodology that allows the formation of carbocycle rings.

Carbocycles such as tetralin are found in many natural products and bioactive compounds (Figure 1), and it is reasonable to consider that their fluoroalkylated analogues might exhibit altered potency[11] However, the approaches for their preparation are extremely limited. So far only one example involving a copper catalyzed carbo trifluoromethylation of alkenes to introduce CF_3 has been reported by the Sodeoka group.[12] Introducing other fluoroalkyl groups such as CF_2H, CF_2CH_3, or CF_2COOEt using this kind of chemistry has until now been unreported, and it was considered that a synthesis of fluoroalkylated tetralin derivatives using a photoredox catalyzed intramolecular fluoroalkylarylation initiated by the addition of fluoroalkyl radicals to arylalkenes would be worthwhile. Our previous experience indicated that the treatment of an alkene not conjugated to an electron withdrawing group under photoredox difluoromethylative conditions leads primarily to the chloro or bromo products by radical or cation pathways.

RESULTS AND DISCUSSION—EXPERIMENTAL WORK

Inspired by Sodeoka's work,[12] we envisioned that cyclization could be induced to compete satisfactorily with simple addition by taking advantage of the Thorpe-Ingold effect. Indeed, we report here the effective use of bis-carboalkoxy groups to facilitate a photoredox catalyzed six-membered-ring cyclization to form fluoroalkyltetralin derivatives.

Exploration of Reaction Conditions for Difluoromethylation. In our initial experiments designed to determine the feasibility of the proposed process, compound **1a** was chosen as the model substrate. It was encouraging to find that, using *fac*-$Ir(ppy)_3$ as catalyst in DCM at room temperature and difluoromethanesulfonyl chloride as the source of difluoro-

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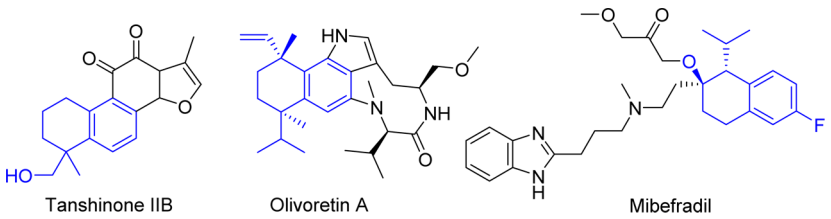
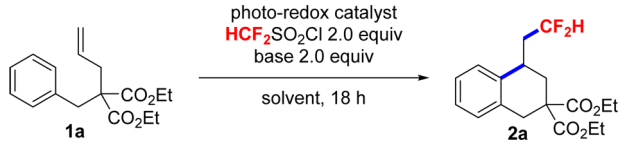


Figure 1. Representative drugs and bioactive molecules.

methyl radicals, 28% of the desired cyclization product was formed, along with 61% of remaining starting material (Table 1, entry 1). Surprisingly, only trace amounts of the undesired chlorination product were found. Other solvents were then screened, with CH_3CN turning out to be the best solvent, affording 46% of product with 33% starting material recovered (entry 4). In order to increase the conversion, the amount of catalyst was increased to 2 mol%, with the result that the yield increased to 64% (entry 5).

Table 1. Screening of Reaction Conditions[a]



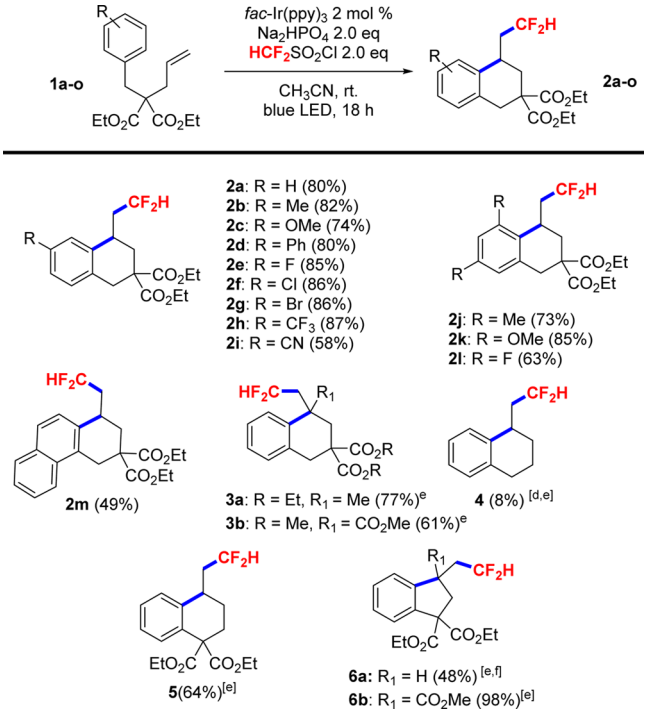
entry	catalyst	solvent	base	yield[b]/%
1	*fac*-Ir(ppy)$_3$ 1 mol%	DCM	K_2HPO_4	28
2	*fac*-Ir(ppy)$_3$ 1 mol%	DCE	K_2HPO_4	27
3	*fac*-Ir(ppy)$_3$ 1 mol%	dioxane	K_2HPO_4	16
4	*fac*-Ir(ppy)$_3$ 1 mol%	CH_3CN	K_2HPO_4	46
5	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	K_2HPO_4	64
6	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	Na_2HPO_4	66
7	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	Na_2CO_3	37
8	*fac*-Ir(ppy)$_3$ 3 mol%	CH_3CN	Na_2HPO_4	47
9[c,d]	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	Na_2HPO_4	78
10[d]	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	Na_2HPO_4	73
11[e]	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	Na_2HPO_4	66
12[f]	*fac*-Ir(ppy)$_3$ 2 mol%	CH_3CN	Na_2HPO_4	80

[a]Reactions were run using 0.1 mmol of **1a**, 0.2 mmol of HCF_2SO_2Cl, 0.2 mmol of base, and 0.001 mmol of catalyst in 1 mL of solvent under visible light. [b]All yields were based on **1a** using *N*,*N*-dimethyltrifluoroacetamide as the internal standard. [c]Reaction run 36 h. [d]Reaction carried out at 50 °C. [e]Reaction carried out at 75 °C. [f]Using blue led.

A change of base to Na_2HPO_4, led to a slight increase in yield (entry 6). Further increases in amounts of catalyst did not prove beneficial (entry 8). When the reaction was run for a longer time (36 h) a higher yield was obtained (entry 9), and higher temperatures were also beneficial (entries 9−11). Finally, switching the light source to a blue LED provided the best results, with 80% being obtained after only 18 h at room temperature (entry 12).

Scope of the Reaction for Difluoromethylation. Having established optimal reaction conditions, the scope of the reaction with respect to substrates was examined (Scheme 1). First, the electronic effect of substituents on the phenyl ring was tested, with modest effect being observed for either electron-donating or electron-withdrawing substituents, affording the six membered ring products in good yield (**2a**−**2i**). Two meta substituents on the phenyl ring, such as methyl, fluoro and methoxy groups, also led to cyclization products **2j**−**2l** in good yield. In contrast, when a naphthalene ring was used, only product **2m** was isolated in a moderate yield. For these 6-exo cyclizations, substituents at the *β*-position of the alkene such as methyl and carbomethoxy did not have a significant effect on the desired reaction, with products **3a** and **3b** being observed in 77% and 61% yields, respectively.

Scheme 1. Difluoromethylation Coupled with Construction of Carbocycles[a,b,c]



[a]Reactions were carried out using 0.2 mmol of **1a**, 0.4 mmol of HCF_2SO_2CI, 0.4 mmol of base, and 0.004 mmol of catalyst in 2 mL of CH_3CN under blue LED light, 18 h. [b]Yields are isolated yields. [c]Blue, bold lines indicate new bonds that have formed in the reaction. [d]Not isolated; yield was determined by ^{19}F NMR using *N*,*N*-dimethyltrifluoroacetamide as internal standard. [e]Substrates for these products are obvious based upon the product structures and the indicated bonds that have been formed. [f]Reaction carried out under visible light at 70 °C for 48 h.

When no ester groups were present in the substrate, only 8% yield of product **4** could be observed by ^{19}F NMR, with the major product being that derived from chlorine addition. (Product **4** was not isolated or fully characterized.) Moving the gem-diester groups one carbon farther from the alkene reaction site led to a diminished, but still moderate yield of product **5**. Comparing the relative yields of products **2a** (under conditions of Table 1, entry 9, 78%) and **6a** (48%) indicated that the 6-exo cyclization process was more competitive than the analogous 5-

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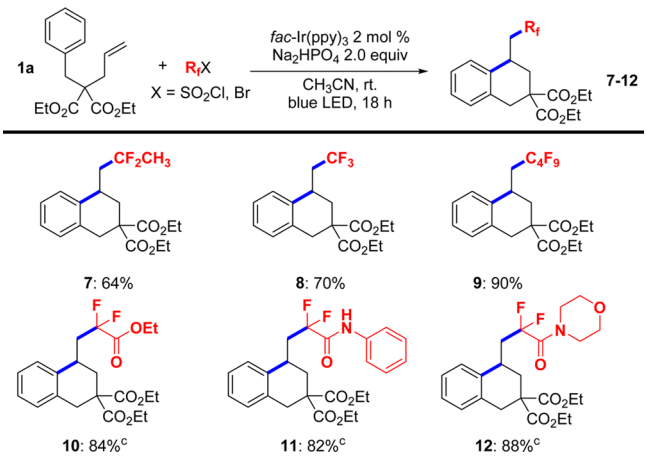
exo cyclization process. The high yield of **6b** indicated that an ester group at the radical site enhances the competitiveness of the 5-exo cyclization with respect to chlorine atom transfer.

Incorporation of Other Fluoroalkyl Groups. To develop a more general strategy for introduction of various fluoroalkyl groups into the tetralin system, other fluoroalkylsulfonyl chlorides were examined as possible fluoroalkyl radical sources (Scheme 2). Thus, it was found that the CH_3CF_2 group could

Scheme 2. Construction of 6-Membered Ring Carbocycles Bearing Other Fluoroalkyl Groups[a,b]



[a]Reactions were run with 0.2 mmol of **1a**, 0.4 mmol of R_fSO_2Cl, 0.4 mmol of base, and 0.004 mmol of catalyst in 2 mL of CH_3CN under blue led light. [b]Isolated yield. [c]Using 1.2 equiv R_fBr instead of R_fSO_2Cl.

be introduced into the carbocyclic product **7** smoothly in moderate yield, while perfluoroalkyl groups, such as CF_3 and C_4F_9, could also be transferred to form desired products **8** and **9** in 70 and 90% yield, respectively. Considering the broad existence of the difluoroester and difluoroamide functionality in drugs and bioactive compounds, and because the respective bromo compounds have been shown to be good radical sources under photoredox catalysis,[13] a bromodifluoroacetic ester and respective amides were examined as radical sources under the usual conditions (Scheme 2). Due to the relative stability of the bromo compounds under the reaction conditions, only 1.2 equiv of bromo compounds were needed to give good yields of desired products **10**–**12**.

Mechanistic Considerations. A reasonable mechanism for these reactions, is proposed in Scheme 3. In earlier publications related to photoredox chemistry of CF_2HSO_2Cl, it was demonstrated that both photocatalyst and light were required for the reaction to occur, and that thermal free radical initiators were ineffective to initiate formation of the observed products.[6e] First the sulfonyl chloride is reduced by the excited Ir catalyst, inducing formation of the difluoromethyl radical. Then the CF_2H radical attacks the double bond to form intermediate radical **A**, which quickly undergoes cyclization to form the intermediate radical **B**. Intermediate **B** then is oxidized by the high valence Ir catalyst to form intermediate carbocation **C**, thus regenerating the catalyst. Finally, the carbocation is deprotonated to form the product. Consistent with our earlier reports on the use of CF_2HSO_2Cl as a source of the difluoromethyl radical, a cyclic catalytic process involving efficient reductive and oxidative steps is required for such an effective photoredox process as is observed in this study.

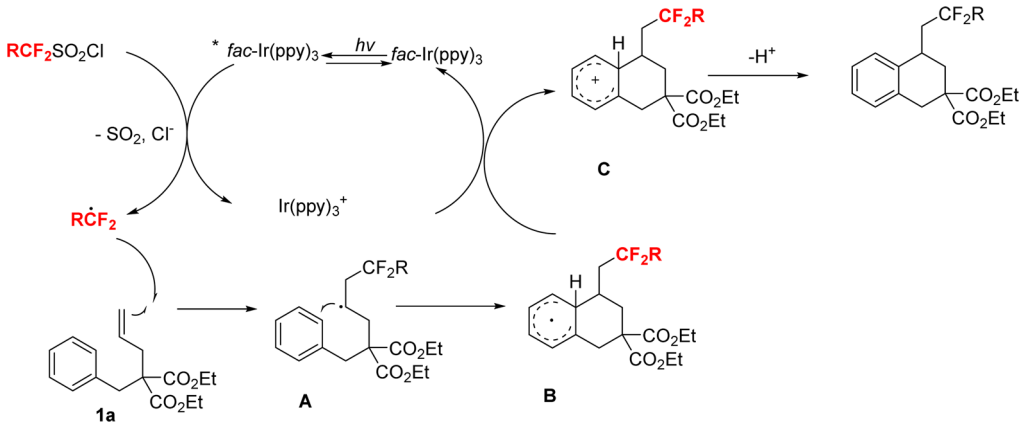
RESULTS AND DISCUSSION—COMPUTATIONAL

As was proposed by Sodeoka,[12] and regarding the relative ease of formation of product **2a** versus **6a** in our study, 6-*exo*-cyclization to the ortho position of the aryl ring must be faster than the analogous 5-*exo* cyclization. There are few experimental or computational studies of radical cyclization rates that involve cyclization to a benzene ring. In order to have a better understanding of the relative reactivities of the radicals generated in this work, ground and transition states including acetonitrile as a solvent (SMD model), were calculated at the M06-2X/6-311+G(2df,p) // M06-L/6-31G(d) level of theory.[14−17] Details related to the computational methodology may be found in the Experimental Section.

Methodology Validation. In order to validate the computational method, four radical cyclization systems were evaluated (**13**−**16**, Figure 2): the 5-exo cyclizations of the 5-hexenyl and 3-phenylpropyl radicals (**13** and **15**), and the 6-exo cyclizations of the 6-heptenyl and 4-phenylbutyl radicals (**14** and **16**). While **13** and **14** are well studied systems both experimentally and computationally,[18−25] there are, to our knowledge, no experimental data for cyclizations of **15** and **16**, with only a few related computational papers having appeared recently.[26−29]

Table 2 shows that although the calculated transition state free energies for cyclization of radicals **13** and **14** are slightly different from those reported in the literature,[18−25] they all

Scheme 3. Proposed Mechanism



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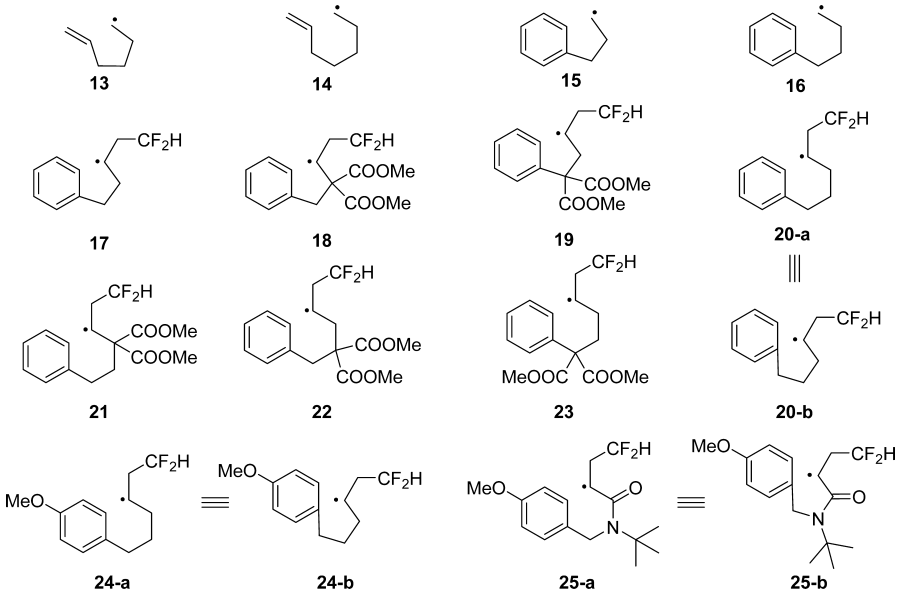

Figure 2. Radicals examined in the computational study.

Table 2. Relative 298 K Free Energies (kcal/mol) in CH_3CN for Transition States (TS) and Products (PD) for Structures 13−16[a]

	13	14	15	16
TS	9.2	10.5	18.8	11
PD	−14.6	−18.5	−1.3	−8.7

[a]Computational method validation.

follow the same expected trends; that is a lower transition state free energy for the 5-exo cyclization of **13** than for the 6-exo cyclization of **14**. Both have chairlike transition states and the free energy of the reaction (product) is significantly exergonic in both cases.

The calculated C−C bond distances for the new bonds at the transition states for **13** and **14** are 2.243 and 2.295 Å, respectively. In both cyclizations the radical approaches the double bond at a nearly tetrahedral angle. These results are similar to those previously reported.[18−25]

The calculations for cyclization of radicals **15** and **16** confirmed that the transition state free energy for the 5-exo cyclization of the 3-phenylpropyl radical (**15**) is much higher than that for the 6-exo cyclization of the 4-phenylbutyl radical (**16**) (Table 2). In order for radical **15** to follow the Burgi-Dunitz trajectory[23] and approach the double bond at as close to a tetrahedral angle as possible, the CH_2 at the ipso carbon has to be out of the benzene plane by 9.9°, which increases strain and thus the transition state energy. The additional carbon in radical **16** allows for a less strained cyclization transition state, with the CH_2 at the ipso carbon only being 5.40° out of the benzene plane. These factors are also reflected in the free energy of the product radicals. The reaction free energy for cyclization of **16** is significantly more exergonic than that for **15** (Table 2). The calculated distances for the new C−C bonds for the cyclization transition states are 2.126 and 2.171 Å for **15** and **16**, respectively. These results are similar to those previously reported.[26−29]

Computational Results for New Systems. Thus, the results for the systems used for validation of the computational method follow the expected energy and structure trends and this allowed us to use this same level of theory to examine more specifically the experimental systems that were studied in this work. One of the questions that we wanted to answer is how the gem-diester groups and their location affect the rates of cyclization. The transition state structures (and products) for the 5-exo cyclization of **17−19** and **20−23** (Figure 2) were therefore calculated.

The unsubstituted system (**17**) has a significantly higher free energy at the transition state compared to the gem-diester substituted systems (**18** and **19**, Table 3). This has been

Table 3. Relative 298 K Free Energies (kcal/mol) in CH_3CN for Transition States (TS) and Products (PD) for Structures 17−23[a]

	17	18	19	20-a	21	22	23
TS	18.9	16.8	16.4	12.6	13	12.4	10.2
PD	4.5	2.2	−0.2	−0.5	−1.6	−3.1	−6

[a]Gem-diester substituent effect.

previously described in the literature as a kinetic effect.[21] Since the substituents increase the number of gauche interactions in the open chain system, both ΔH and $-T\Delta S$ decrease for the transition state and product. This can also be observed in the less endergonic cyclization reactions of **18** and **19** compared to **17** (Table 3). The transition state energy is lower for **19** than **18** due to higher steric interactions in the latter; however, structure **19** could also benefit from the Thorpe−Ingold effect which may lower the energy of the transition state.[19] The calculated distances for the new C−C bonds at the transition state are similar for all structures (**17−19**), 2.101 Å.

The 6-exo cyclizations of radicals **20-a−23**, follow a similar trend to those of the **17−19** radicals (Table 3). With the exception of **21**, the free energy at the transition state is lower when the gem-diester is present. In structure **21** there seems to be an unfavorable interaction between the CF_2H group and the syn ester group, which could increase the energy at the transition state. Nevertheless, in all cases the exergonicities of the cyclizations of the gem-diester substituted systems are greater than that for the cyclization of **20-a**. The farther away

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the substituents are from the radical, the lower the free energy of the transition state and product. The calculated distances for the new C−C bonds in the transition states range between 2.11 and 2.16 Å. The shorter the distance, the higher the free energy at the transition state. These results help us to understand why product **2a** (Scheme 1) was formed in 80% yield, whereas **3** was only formed in 8% yield. Not only is the free energy lower at the transition state for the cyclization of radical **1a**, but the reaction is also significantly more exergonic, which drives the reaction equilibrium more in favor of the product in a radical system such as **1a**.

It is important to highlight that none of the experimental systems in this work yielded an ipso-5-exo cyclization product such as that which was observed in one of our previous studies.[10] This is the case even with the MeO- substituent in the *para*-position (**1c**, Scheme 1). We previously hypothesized that the methoxy group might favor the ipso-5-exo cyclization due to stabilization of the cyclic radical intermediates. In order to provide insight into these contrasting results, we included calculations of the transition states (and product) structures for the 6-exo and ipso-5-exo cyclizations of **20**, **24**, and **25** within the current computational study.

For **20** and **24**, the transition state free energies are significantly lower for the 6-exo cyclizations (**a**) than for the alternative ipso-5-exo cyclizations (**b**) (Table 4). However, for the amide system (**25**) used in our earlier spirocyclization report,[10] the ipso-5-exo cyclization (**25-b**) has a significantly lower transition state energy and the cyclization process is significantly exergonic. A careful look at both the transition state and product structures of **25-a** and **25-b** indicates that the amide system is more planar in **25-b** than in **25-a** (Figure 3, Experimental Section).

Table 4. Relative 298 K Free Energies (kcal/mol) in CH_3CN for Transition States (TS) and Products (PD) for Structures 17, 21, and 22[a]

	20-a	20-b	24-a	24-b	25-a	25-b
TS	12.6	16	11.7	16.6	14.8	8.7
PD	−0.5	0.2	0.5	−0.9	0.1	−8.2

[a]6-exo vs ipso-5-exo cyclization.

That is, there is greater conjugation within the N-CO function (shorter distance) in **25-b** than in **25-a**. This seems to be due to the intrinsically favored planar structure of a 5-membered ring, compared to a 6-membered ring.

These results lead us to conclude that the ipso-5-exo cyclization of radical **25** is most likely kinetically favored because of its amide function and not because of its *p*-methoxy substituent, which then explains why we observed only the 6-exo cyclization products in the present work.

The computational calculations show that the presence of the gem-diester groups favors the cyclization both kinetically (lower transition state free energy) and thermodynamically (more exergonic reactions), relative to the unsubstituted systems. The farther the gem-diester groups are from the reactive CH radical site of the intermediate (i.e., A), the more favorable is its cyclization. Finally, the ipso-5-exo cyclizations are preferred only for the rigid systems, such as radical **25** with its amide group, which facilitate the intrinsically planar structure of the 5-membered ring that is being formed.

CONCLUSIONS

In conclusion, photoredox catalyzed radical difluoromethylations and fluoroalkylations of unactivated alkenes coupled with cyclization of the resultant radical with an aryl ring to form fluoroalkyl tetralins is reported. In order for the cyclization reactions to be efficient, gem-diester substituents are crucial, likely as a result of the resultant Thorpe−Ingold effect, which allows cyclization to compete favorably with the chlorination side reaction. This work comprises the first example of introduction of difluoromethyl groups into the tetralin skeleton system. Furthermore, the study provides a unified strategy for introduction of other valuable perfluoroalkyl and partially fluorinated alkyl groups into the tetralin system under mild conditions in moderate to good yield. A computational study provided mechanistic insights, including that 6-exo cyclizations to a phenyl ring are faster than 5-exo cyclizations. Further investigations of this reaction system, including kinetic studies are under way in our laboratory.

EXPERIMENTAL SECTION

All reactions were carried out under N_2 atmosphere. All anhydrous solvents were purchased from Aldrich and stored over 4A molecular

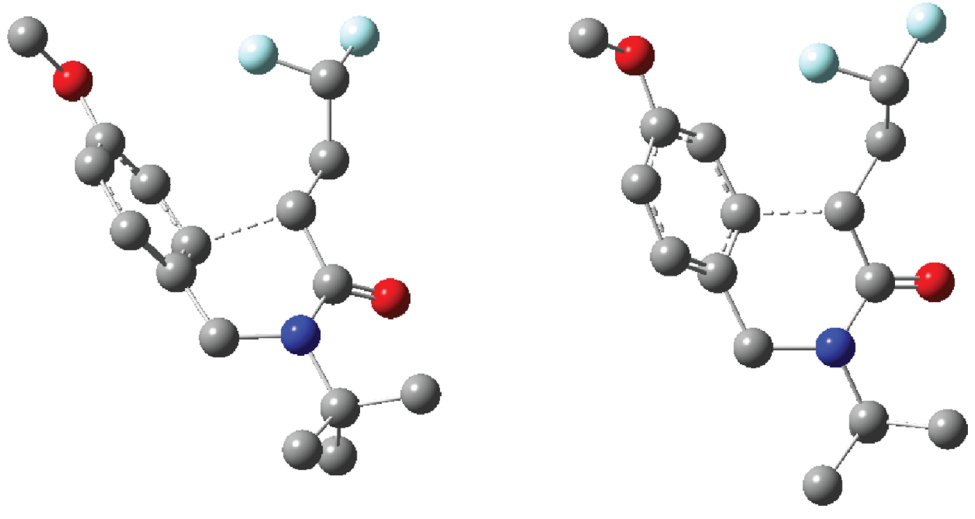

Figure 3. Transition state structures for the ipso-5-exo (left) and 6-exo cyclization of **22** (amide system). Hydrogen atoms are omitted for clarity.

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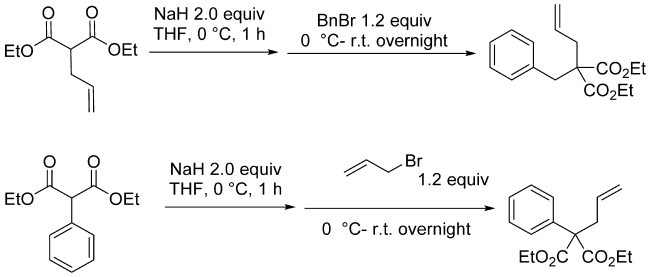
sieves. Reagents were purchased at commercial quality and were used without further purification. All NMR spectra were run using $CDCl_3$ as solvent, unless otherwise specified. ^1H NMR spectra were recorded at 500 MHz unless otherwise specified, and chemical shifts are reported in ppm relative to TMS. ^{19}F NMR spectra were recorded at 282 MHz, and chemical shifts are reported in ppm relative to $CFCl_3$ as the external standard. ^{13}C NMR spectra were recorded at 126 MHz unless otherwise specified, with proton decoupling, and chemical shifts are reported in ppm relative to $CDCl_3$ (−77.0 ppm) as the reference. The visible light was generated from a fluorescent light bulb (daylight GE Energy Smart, 26 W, 1600 lm). Blue led was bought from FEIT Electric (16 W, 120 VAC, 60 Hz, 130 mA). All the sulfonyl chlorides and difluoroacetic esters and amides were prepared by literature procedures.[7,12]

Synthesis of Substrates. All starting materials were prepared according to previously reported procedures, which are exemplified by the equations in Scheme 4.[13b]

Scheme 4. Synthesis of Starting Materials



***fac*-Ir(ppy)$_3$ Catalyzed Intramolecular Fluoroalkylarylation of Unactived Alkenes.** To an oven-dried 17 × 60 mm (8 mL) borosilicate vial equipped with a magnetic stirrer, were added diethyl 2-allyl-2-benzylmalonate (**1a**) (58.0 mg, 0.2 mmol), *fac*-Ir(ppy)$_3$ (2.4 mg, 0.004 mmol, 0.002 equiv), and Na_2HPO_4 (57 mg, 0.4 mmol, 2.0 equiv). To this mixture were added 2 mL CH_3CN and CF_2HSO_2Cl (60 mg, 0.4 mmol, 2 equiv) under a blanket of nitrogen. The vial was sealed, and stirred under blue led at room temperature for 18 h. The temperature would gradually increase to 55 °C heated by the light. After this time, the CH_3CN was removed in vacuo, and the residue purified by column chromatography on silica gel eluting with hexanes/ethyl acetate (15:1) to (5:1). This gave product **2a** as colorless oil (54 mg, 80% yield).

*Diethyl 4-(2,2-Difluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2a**).* ^1H NMR δ 7.16 (d, J = 14.7 Hz, 4H), 5.98 (tdd, J = 56.7, 6.0, 3.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.10 (tq, J = 7.1, 3.3, 2.5 Hz, 2H), 3.34 (dd, J = 15.8, 2.3 Hz, 1H), 3.26−3.16 (m, 2H), 2.73 (dd, J = 13.2, 5.7 Hz, 1H), 2.57−2.37 (m, 1H), 2.17−2.01 (m, 1H), 1.97 (dd, J = 13.6, 10.1 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.67, 170.49, 136.87, 134.09, 129.27, 126.84, 126.70, 126.60, 119.37−112.50 (m), 61.81, 61.49, 53.73, 40.60 (t, J = 20.6 Hz), 35.19, 34.53, 30.71 (t, J = 5.7 Hz), 14.06, 13.94. ^{19}F NMR δ −110.54 − −120.33 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{18}H_{23}F_2O_4$ 341.1559; Found 341.1562.

*Diethyl 4-(2,2-Difluoroethyl)-6-methyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2b**).* Prepared according to general method and isolated in 82% yield after chromatography as a colorless oil (58.0 mg). ^1H NMR δ 7.03 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 10.3 Hz, 2H), 5.98 (tdd, J = 56.6, 5.9, 3.5 Hz, 1H), 4.21 (qd, J = 7.1, 1.4 Hz, 2H), 4.11 (qd, J = 7.1, 5.5 Hz, 2H), 3.30 (dd, J = 16.2, 2.1 Hz, 1H), 3.20 (d, J = 7.2 Hz, 1H), 3.14 (d, J = 16.0 Hz, 1H), 2.71 (ddd, J = 13.8, 7.0, 2.1 Hz, 1H), 2.46 (qt, J = 15.7, 5.2 Hz, 1H), 2.30 (s, 3H), 2.14−1.99 (m, 1H), 1.95 (dd, J = 13.6, 10.1 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 171.8, 170.6, 136.6, 136.4, 131.0, 129.2, 127.6, 127.4, 116.6 (t, J = 239.4 Hz), 61.8, 61.5, 53.8, 40.8 (t, J = 20.6 Hz), 34.9, 34.6, 31.1, 30.4 (m), 21.3, 14.2, 14.0. ^{19}F NMR δ −114.70 − −115.26 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{19}H_{25}F_2O_4$ 355.1715; Found 355.1708.

*Diethyl 4-(2,2-Difluoroethyl)-6-methoxy-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2c**).* Prepared according to general method and isolated in 74% yield after chromatography as a colorless oil (55 mg). ^1H NMR δ 7.05 (d, J = 8.3 Hz, 1H), 6.75−6.69 (m, 1H), 6.69 (d, J = 2.6 Hz, 1H), 5.98 (tdd, J = 56.5, 5.9, 3.6 Hz, 1H), 4.20 (qd, J = 7.1, 1.7 Hz, 2H), 4.10 (qd, J = 7.1, 3.4 Hz, 2H), 3.77 (s, 3H), 3.30−3.23 (m, 1H), 3.20 (t, J = 5.2 Hz, 1H), 3.14−3.08 (m, 1H), 2.70 (ddd, J = 13.6, 6.7, 2.0 Hz, 1H), 2.52−2.32 (m, 1H), 2.14−1.97 (m, 1H), 1.93 (dd, J = 13.6, 10.0 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.8, 170.6, 158.5, 138.1, 130.2, 126.2, 116.5 (t, J = 239.4 Hz), 112.5, 112.2, 61.8, 61.5, 55.4, 53.9, 40.8 (t, J = 20.7 Hz), 34.6, 34.5, 31.4, 30.5 (m), 14.1, 14.0. ^{19}F NMR δ −114.93 (AB, ddd, J = 56.7, 27.5, 15.9 Hz, 1F), −115.00 (AB, ddd, J = 56.6, 32.4, 15.9 Hz, 1F). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{19}H_{25}F_2O5$ 371.1665; Found 371.1674.

*Diethyl 4-(2,2-Difluoroethyl)-6-phenyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2d**).* Prepared according to general method and isolated in 80% yield after chromatography as a colorless oil (67 mg). ^1H NMR δ 7.58−7.53 (m, 2H), 7.44 (dd, J = 8.5, 6.8 Hz, 2H), 7.41−7.37 (m, 2H), 7.37−7.31 (m, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.03 (tdd, J = 56.5, 5.9, 3.5 Hz, 1H), 4.25 (qd, J = 7.1, 1.5 Hz, 2H), 4.15 (qd, J = 7.1, 5.0 Hz, 2H), 3.43−3.37 (m, 1H), 3.35−3.28 (m, 1H), 3.24 (d, J = 16.0 Hz, 1H), 2.78 (ddd, J = 13.9, 6.6, 2.1 Hz, 1H), 2.63−2.44 (m, 1H), 2.21−2.07 (m, 1H), 2.03 (dd, J = 13.6, 10.1 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.7, 170.6, 141.0, 140.0, 137.3, 133.2, 129.8, 128.9, 127.4, 127.1, 125.6, 116.5 (t, J = 239.4 Hz), 61.9, 61.6, 53.8, 40.8 (t, J = 20.7 Hz), 35.0, 34.6, 31.2, 30.6 (m), 14.1, 14.0. ^{19}F NMR δ −114.87 (AB, ddd, J = 56.7, 21.4, 16.0 Hz, 1F), −114.93 (AB, ddd, J = 54.0, 24.3, 16.2 Hz, 1F). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{24}H_{26}F_2O_4$ 417.1872; Found 417.1865.

*Diethyl 4-(2,2-Difluoroethyl)-6-fluoro-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2e**).* Prepared according to general method and isolated in 85% yield after chromatography as a colorless oil (61 mg). ^1H NMR δ 7.13−7.06 (m, 1H), 6.87 (ddd, J = 13.5, 7.3, 4.2 Hz, 2H), 5.98 (tdd, J = 56.4, 5.7, 3.4 Hz, 1H), 4.21 (qd, J = 7.1, 1.3 Hz, 2H), 4.11 (qd, J = 7.1, 2.2 Hz, 2H), 3.30 (dd, J = 15.7, 2.0 Hz, 1H), 3.20 (dq, J = 10.2, 5.1 Hz, 1H), 3.12 (d, J = 15.9 Hz, 1H), 2.72 (ddd, J = 13.7, 6.8, 2.0 Hz, 1H), 2.48−2.30 (m, 1H), 2.15−1.98 (m, 1H), 1.93 (dd, J = 13.6, 10.2 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.5, 170.4, 161.8 (d, J = 244.5 Hz), 139.1 (d, J = 6.8 Hz), 130.7 (d, J = 8.1 Hz), 129.8 (d, J = 3.0 Hz), 116.3 (t, J = 240.0 Hz), 113.9(d, J = 21.4 Hz), 113.4 (d, J = 21.7 Hz), 62.0, 61.7, 53.8, 40.5 (t, J = 20.8 Hz), 34.6, 34.3, 30.9 (t, J = 5.3 Hz), 14.1, 14.0. ^{19}F NMR δ −115.02 (AB, ddd, J = 56.5, 19.6, 16.1 Hz, 1F), −115.09 (AB, ddd, J = 54.0, 21.6, 16.1 Hz, 1F), −115.62 − −115.87 (m, 1F). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{18}H_{22}F_3O_4$ 359.1465; Found 359.1433.

*Diethyl 6-Chloro-4-(2,2-difluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2f**).* Prepared according to general method and isolated in 86% yield after chromatography as a colorless oil (64 mg). ^1H NMR δ 7.16 (d, J = 2.1 Hz, 1H), 7.14−7.10 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.98 (tdd, J = 56.3, 5.9, 3.5 Hz, 1H), 4.21 (qd, J = 7.1, 1.2 Hz, 2H), 4.15−4.06 (m, 2H), 3.33−3.25 (m, 1H), 3.19 (dq, J = 10.2, 5.4, 4.9 Hz, 1H), 3.12 (d, J = 16.1 Hz, 1H), 2.77−2.66 (m, 1H), 2.51−2.32 (m, 1H), 2.04 (dddd, J = 24.4, 18.7, 12.2, 3.6 Hz, 1H), 1.93 (dd, J = 13.7, 10.2 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 171.4, 170.3, 138.9, 132.7, 132.6, 130.6, 126.9, 126.9, 116.2 (t, J = 239.7 Hz), 62.0, 61.7, 53.6, 40.5 (t, J = 20.8 Hz), 34.7, 34.3, 31.1, 30.3 (m), 14.1, 14.0. ^{19}F NMR δ −114.76 − −115.57 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{18}H_{22}ClF_2O_4$ 375.1169; Found 375.1155.

*Diethyl 6-Bromo-4-(2,2-difluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2g**).* Prepared according to general method and isolated in 86% yield after chromatography as a colorless oil (72 mg). ^1H NMR δ 7.33 (s, 1H), 7.28 (dt, J = 8.6, 1.5 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 5.99 (tdd, J = 56.4, 5.7, 3.3 Hz, 1H), 4.27−4.19 (m, 2H), 4.13 (qd, J = 7.2, 5.4 Hz, 2H), 3.30 (dd, J = 15.9, 2.0 Hz, 1H), 3.26−3.16 (m, 1H), 3.12 (d, J = 16.1 Hz, 1H), 2.73 (dd, J = 13.6, 6.1 Hz, 1H), 2.44 (qt, J = 15.7, 4.8 Hz, 1H), 2.06 (ddt, J = 14.3, 10.2, 4.6

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Hz, 1H), 1.95 (dd, J = 13.7, 10.2 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.4, 170.3, 139.3, 133.2, 130.9, 129.8, 129.8, 120.6, 118.5, 113.64 (m), 62.0, 61.7, 53.5, 40.4 (t, J = 20.8 Hz), 34.7, 34.2, 30.7 (t, J = 5.7 Hz), 14.1, 14.0. ^{19}F NMR δ −114.87 − −115.34 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{18}H_{22}BrF_2O_4$ 419.0664; Found 419.0683.

*Diethyl 4-(2,2-Difluoroethyl)-6-(trifluoromethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2h**).* Prepared according to general method and isolated in 87% yield after chromatography as a colorless oil (75 mg). ^{1}H NMR δ 7.43 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.00 (tdd, J = 56.3, 5.7, 3.4 Hz, 1H), 4.25−4.18 (m, 2H), 4.16−4.08 (m, 2H), 3.39 (d, J = 16.3 Hz, 1H), 3.30−3.15 (m, 2H), 2.83−2.71 (m, 1H), 2.55−2.39 (m, 1H), 2.15−2.02 (m, 1H), 1.99 (dd, J = 13.7, 10.2 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.3, 170.3, 138.4, 137.9, 129.8, 129.3 (q, J = 32.3 Hz), 124.2 (q, J = 271.9 Hz), 123.7 (q, J = 3.9 Hz), 123.5 (q, J = 3.8 Hz), 116.2 (t, J = 239.8 Hz), 62.1, 61.8, 53.5, 40.4 (t, J = 20.8 Hz), 35.2, 34.3, 31.8, 29.80 (m), 14.1, 14.0. ^{19}F NMR δ −62.50 (s, 3F), −114.97 − −115.52 (m, 2F). HRMS (ESI/TOF) m/z: [M+Na]+ Calcd for $C_{19}H_{21}F_5O_4Na$ 431.1252; Found 431.1254.

*Diethyl 6-Cyano-4-(2,2-difluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2i**).* Prepared according to general method and isolated in 58% yield after chromatography as a colorless oil (42 mg). ^{1}H NMR δ 7.50 (s, 1H), 7.48−7.41 (m, 1H), 7.27 (d, J = 8.1 Hz, 1H), 6.01 (tdd, J = 56.1, 5.6, 3.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.18−4.10 (m, 2H), 3.40 (d, J = 16.9 Hz, 1H), 3.22 (d, J = 16.5 Hz, 2H), 2.76 (dd, J = 13.6, 5.7 Hz, 1H), 2.46 (tdd, J = 16.2, 11.2, 5.1 Hz, 1H), 2.09 (ddt, J = 18.2, 8.4, 4.0 Hz, 1H), 1.99 (dd, J = 13.7, 10.3 Hz, 1H), 1.31−1.24 (m, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.1, 170.1, 140.1, 138.6, 130.7, 130.2, 130.1, 118.8, 116.0 (td, J = 240.5, 239.9, 3.0 Hz), 110.9, 62.2, 61.9, 53.3, 40.1 (t, J = 21.1 Hz), 35.3, 34.1, 30.5, 14.1, 14.0. ^{19}F NMR δ −115.01 − −115.48 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{19}H_{22}F_2NO_4$ 366.1511; Found 366.1522.

*Diethyl 4-(2,2-Difluoroethyl)-5,7-dimethyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2j**).* Prepared according to general method and isolated in 73% yield after chromatography as a colorless oil (54 mg), ^{1}H NMR δ 6.85 (d, J = 1.9 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 5.91 (tdd, J = 56.5, 5.7, 3.5 Hz, 1H), 4.30−4.16 (m, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.45 (ddt, J = 11.2, 8.1, 4.2 Hz, 1H), 3.19 (s, 2H), 2.61 (dd, J = 14.3, 7.5 Hz, 1H), 2.28−2.26 (m, 1H), 2.25 (d, J = 3.8 Hz, 6H), 2.10−1.82 (m, 2H), 1.28 (td, J = 7.1, 0.9 Hz, 3H), 1.07 (td, J = 7.1, 0.9 Hz, 3H). ^{13}C NMR δ 172.5, 171.1, 136.1, 135.12, 134.0, 133.7, 130.4, 127.8, 116.8 (t, J = 239.4 Hz), 61.9, 61.5, 54.0, 39.9 (t, J = 20.2 Hz), 35.3, 34.1, 28.8 (dd, J = 7.0, 4.1 Hz), 20.9, 19.1, 14.1, 14.0. ^{19}F NMR δ −115.17 (AB, dddd, J = 296.1, 56.4, 16.3, 13.6 Hz), −116.88 (AB, dddd, J = 284.8, 57.1, 22.6, 16.0 Hz). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{20}H_{27}F_2O_4$ 369.1872; Found 369.1889.

*Diethyl 4-(2,2-Difluoroethyl)-5,7-dimethoxy-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2k**).* Prepared according to general method and isolated in 85% yield after chromatography as a colorless oil (68 mg), ^{1}H NMR δ 6.29 (d, J = 2.4 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 5.87 (tt, J = 57.0, 5.1 Hz, 1H), 4.21 (dddd, J = 17.9, 10.8, 7.1, 3.7 Hz, 2H), 4.07 (dt, J = 7.5, 6.5 Hz, 2H), 3.77 (s, 6H), 3.40 (qd, J = 7.5, 3.4 Hz, 1H), 3.24−3.04 (m, 2H), 2.68 (ddd, J = 13.9, 7.9, 2.0 Hz, 1H), 2.41−2.25 (m, 1H), 2.08 (dd, J = 14.0, 7.0 Hz, 1H), 1.99−1.74 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 172.0, 170.6, 159.2, 158.1, 136.2, 118.2, 117.6 (t, J = 239.0 Hz), 104.8, 97.2, 61.9, 61.4, 55.4 (d, J = 7.8 Hz), 53.8, 39.9 (t, J = 19.9 Hz), 36.0, 34.7, 26.7 (t, J = 5.9 Hz), 14.1, 14.0. ^{19}F NMR δ −113.92 (AB, dddd, J = 282.0, 57.1, 21.2, 14.5 Hz), −115.34 (AB, dddd, J = 282.0, 56.8, 20.2, 13.7 Hz). HRMS (ESI/TOF) m/z: [M+Na]+ Calcd for $C_{20}H_{26}F_2O_6Na$ 423.1590; Found 423.1591.

*Diethyl 4-(2,2-Difluoroethyl)-5,7-difluoro-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**2l**).* Prepared according to general method and isolated in 63% yield after chromatography as a colorless oil (47 mg), ^{1}H NMR δ 6.81−6.50 (m, 2H), 5.91 (tt, J = 56.5, 4.8 Hz, 1H), 4.29−4.16 (m, 2H), 4.11−4.05 (m, 2H), 3.48 (d, J = 8.8 Hz, 1H), 3.26−3.14 (m, 2H), 2.74 (dd, J = 14.6, 8.1 Hz, 1H), 2.44−2.23 (m, 1H), 2.10−2.02 (m, 1H), 2.04−1.91 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.2, 169.9, 162.1 (dd, J = 53.6, 12.9 Hz), 160.1 (dd, J = 53.8, 13.4 Hz), 138.1 (dd, J = 9.3, 5.9 Hz), 120.4 (m), 116.4 (t, J = 239.8 Hz), 111.6 (dd, J = 21.0, 3.4 Hz), 102.5 (dd, J = 26.7, 25.3 Hz), 62.0, 61.6, 53.5, 40.6, 38.7 (m), 35.3, 34.0, 26.37 (d, J = 5.6 Hz), 14.0, 13.9. ^{19}F NMR δ −110.91 (t, J = 9.3 Hz, 1F), −112.77 (q, J = 8.4 Hz), −114.70 − −115.39 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{18}H_{21}F_4O_4$ 377.1370; Found 377.1376.

*Diethyl 1-(2,2-Difluoroethyl)-1,4-dihydrophenanthrene-3,3(2H)-dicarboxylate (**2m**).* Prepared according to general method and isolated in 49% yield after chromatography as a colorless oil (38 mg), ^{1}H NMR δ 8.08−8.02 (m, 1H), 7.85−7.78 (m, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.56−7.53 (m, 1H), 7.50−7.45 (m, 1H), 7.30 (d, J = 8.6 Hz, 1H), 6.15−5.82 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.14−3.95 (m, 3H), 3.92 (d, J = 16.5 Hz, 1H), 3.51−3.29 (m, 2H), 2.83 (dd, J = 13.8, 6.8 Hz, 1H), 2.61−2.29 (m, 1H), 2.07 (dd, J = 13.6, 9.7 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 172.0, 170.5, 133.8, 132.3, 132.1, 129.3, 128.5, 127.3, 126.6, 125.7, 125.2, 123.2, 116.6 (t, J = 241.5 Hz), 62.1, 61.6, 53.7, 42.4, 39.99 (m), 34.1, 31.5, 31.2, 14.2, 14.0. ^{19}F NMR δ −114.82 (AB, ddd, J = 56.7, 48.1, 15.8 Hz), δ −114.82 (AB, ddd, J = 56.7, 15.8, 11.1 Hz). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{22}H_{25}F_2O_4$ 391.1715; Found 371.1698.

*Diethyl 4-(2,2-Difluoroethyl)-4-methyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**3a**).* Prepared according to general method and isolated in 77% yield after chromatography as a colorless oil (50 mg), ^{1}H NMR δ 7.31−7.21 (m, 2H), 7.21−7.17 (m, 2H), 5.76 (tdd, J = 56.1, 5.8, 3.5 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.36 (d, J = 16.1 Hz, 1H), 3.18 (d, J = 16.0 Hz, 1H), 2.59 (d, J = 14.6 Hz, 1H), 2.38 (d, J = 14.6 Hz, 1H), 2.24 (qd, J = 15.2, 5.9 Hz, 1H), 2.12 (tdd, J = 18.6, 15.0, 3.5 Hz, 1H), 1.37 (s, 3H). ^{13}C NMR δ 172.1, 171.8, 140.8, 133.2, 129.3, 127.2, 126.8, 126.0, 116.6 (t, J = 239.0 Hz), 53.0, 52.7, 52.5, 47.0 (t, J = 19.8 Hz), 39.8, 35.3, 34.9 (t, J = 5.1 Hz), 30.5. ^{19}F NMR δ −111.06 (ddd, J = 56.2, 18.5, 15.3 Hz). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{19}H_{25}F_2O_4$ 327.1402; Found 327.1409.

*Trimethyl 1-(2,2-Difluoroethyl)-1,4-dihydronaphthalene-1,3,3(2H)-tricarboxylate (**3b**).* Prepared according to general method and isolated in 61% yield after chromatography as a colorless oil (45 mg), ^{1}H NMR δ 7.33−7.22 (m, 3H), 7.22−7.17 (m, 1H), 5.89 (tdd, J = 56.1, 5.5, 3.7 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.35 (d, J = 15.9 Hz, 1H), 3.16 (d, J = 15.8 Hz, 1H), 3.13 (d, J = 15.1 Hz, 1H), 2.84 (qd, J = 14.6, 14.0, 5.4 Hz, 1H), 2.61 (d, J = 14.8 Hz, 1H), 2.42 (dtd, J = 20.8, 14.4, 3.7 Hz, 1H). ^{13}C NMR δ 174.4, 171.8, 171.2, 134.5, 134.4, 129.4, 127.9, 127.3, 127.2, 35.0, 34.6 (m), 116.0 (t, J = 239.5 Hz), 53.1, 53.0, 52.8, 46.5−46.2 (m), 43.4 (t, J = 21.9 Hz), 41.3, 35.3, 34.9. ^{19}F NMR δ −112.01 − −112.50 (m). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{18}H_{21}F_2O_6$ 371.1301; Found 371.1305.

*Diethyl 4-(2,2-Difluoroethyl)-3,4-dihydronaphthalene-1,1(2H)-dicarboxylate (**5**).* Prepared according to general method and isolated in 64% yield after chromatography as a colorless oil (44 mg), ^{1}H NMR δ 7.43 (dd, J = 7.9, 1.5 Hz, 1H), 7.28 (dd, J = 7.5, 1.5 Hz, 1H), 7.23−7.15 (m, 2H), 5.93 (tt, J = 56.5, 4.6 Hz, 1H), 4.35−4.09 (m, 4H), 3.15 (dd, J = 9.6, 4.9 Hz, 1H), 2.45 (qd, J = 5.5, 4.7, 3.3 Hz, 2H), 2.33−1.94 (m, 3H), 1.87−1.71 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.7, 171.3, 139.2, 132.3, 130.8, 128.8, 128.3, 126.4, 116.7 (t, J = 239.3 Hz), 62.0, 62.0, 58.9, 40.9 (t, J = 20.4 Hz), 32.4 (t, J = 5.3 Hz), 27.4, 24.8, 14.2, 14.1. ^{19}F NMR δ −115.48 (dddd, J = 56.5, 31.6, 18.5, 16.3 Hz). HRMS (ESI/TOF) m/z: [M+Na]+ Calcd for $C_{18}H_{22}F_2O_4Na$ 363.1384; Found 363.1385.

*Diethyl 3-(2,2-Difluoroethyl)-2,3-dihydro-1H-indene-1,1-dicarboxylate (**6a**).* Prepared according to general method and isolated in 25% yield after chromatography as a colorless oil (16.3 mg), ^{1}H NMR δ 7.59 (dd, J = 7.5, 1.6 Hz, 1H), 7.36−7.28 (m, 2H), 7.22−7.18 (m, 1H), 6.00 (tt, J = 56.4, 4.6 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.23−4.14 (m, 2H), 3.52 (dt, J = 11.8, 5.9 Hz, 1H), 3.05 (dd, J = 13.6, 7.9 Hz, 1H), 2.56−2.34 (m, 2H), 2.13−1.93 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 170.7, 170.4, 145.8, 139.0, 129.1, 127.6, 127.1, 123.6, 119.9, 112.7 (m), 65.0, 61.98, 61.95, 40.6, 39.6 (t, J = 21.0 Hz), 37.3, 14.2, 14.1. ^{19}F NMR δ −115.15 (dtd, J

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Table 5. Relative 298 K Free Energies (kcal/mol) in the Gas Phase and in CH_3CN for Transition States (TS) and Products (PD) of All Structures Calculated

	13		14		15		16	
	TS1	PD	TS1	PD	TS1	PD	TS1	PD
ΔH(gas)	8.4	−14.6	8.8	−21.0	18.2	−2.0	9.6	−10.6
ΔG(gas)	11.0	−13.3	12.3	−17.4	20.9	0.7	12.9	−7.0
ΔH(slv)	8.5	−14.0	8.9	−20.3	18.1	−2.1	9.6	−10.4
ΔG(slv)	9.2	−14.6	10.5	−18.5	18.8	−1.3	11.0	−8.7
	17		18		19			
	TS1	PD	TS1	PD	TS1	PD		
ΔH(gas)	17.1	2.0	19.2	4.8	16.7	0.5		
ΔG(gas)	20.1	5.5	18.8	4.6	17.9	1.0		
ΔH(slv)	17.8	2.9	19.0	4.4	17.1	1.2		
ΔG(slv)	18.9	4.5	16.8	2.2	16.4	−0.2		
	20a		21		22		23	
	TS1	PD	TS1	PD	TS1	PD	TS1	PD
ΔH(gas)	10.4	−4.1	12.5	−3.1	13.2	−4.0	8.7	−7.7
ΔG(gas)	14.6	0.5	15.0	0.1	15.7	−0.3	12.0	−4.0
ΔH(slv)	10.4	−3.2	12.3	−3.0	11.9	−4.9	8.7	−7.9
ΔG(slv)	12.6	−0.5	13.0	−1.6	12.4	−3.1	10.2	−6.0
	20a		24a		25a			
	TS1	PD	TS1	PD	TS1	PD		
ΔH(gas)	10.4	−4.1	10.2	−2.8	15.7	1.1		
ΔG(gas)	14.6	0.5	13.7	1.8	17.0	2.4		
ΔH(slv)	10.4	−3.2	10.1	−2.2	15.5	0.7		
ΔG(slv)	12.6	−0.5	11.7	0.5	14.8	0.1		
	20b		24b		25b			
	TS1	PD	TS1	PD	TS1	PD		
ΔH(gas)	13.5	−3.1	12.9	−4.0	11.8	−6.6		
ΔG(gas)	17.4	0.6	17.2	−0.6	11.9	−6.0		
ΔH(slv)	14.0	−1.6	14.2	−2.4	10.5	−6.9		
ΔG(slv)	16.0	0.2	16.6	−0.9	8.7	−8.2		

= 56.4, 17.4, 9.2 Hz). HRMS (ESI/TOF) *m/z*: [M+Na]+ Calcd for $C_{17}H_{20}F_2O_4Na$ 349.1222; Found 349.1215.

*1,1-Diethyl 3-Methyl 3-(2,2-difluoroethyl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (**6b**).* Prepared according to general method and isolated in 98% yield after chromatography as a colorless oil (75 mg), ^{1}H NMR δ 7.59−7.53 (m, 1H), 7.36 (d, J = 2.7 Hz, 3H), 5.97 (tt, J = 56.1, 4.8 Hz, 1H), 4.29−4.18 (m, 4H), 3.64 (s, 3H), 3.41 (d, J = 14.4 Hz, 1H), 3.07 (d, J = 14.5 Hz, 1H), 2.88 (dddd, J = 19.5, 14.6, 13.0, 4.6 Hz, 1H), 2.27 (dddd, J = 19.4, 14.6, 12.7, 4.9 Hz, 1H), 1.29 (td, J = 7.1, 3.5 Hz, 6H). ^{13}C NMR δ 173.5, 170.1, 170.0, 143.7, 138.9, 129.5, 129.0, 127.0, 124.3, 115.9 (t, J = 239.9 Hz), 65.0, 62.4, 62.0, 53.9 (t, J = 5.2 Hz), 52.8, 42.6 (t, J = 21.5 Hz), 41.1, 14.1. ^{19}F NMR δ −113.16 (AB, dddd, J = 290.5, 56.0, 18.4, 13.8 Hz), δ −114.50 (AB, dddd, J = 290.5, 56.2, 19.5, 13.5 Hz). HRMS (ESI/TOF) *m/z*: [M+Na]+ Calcd for $C_{19}H_{22}F_2O_6Na$ 407.1277; Found 407.1278.

*Diethyl 4-(2,2-Difluoropropyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**7**).* Prepared according to general method and isolated in 64% yield after chromatography as a colorless oil (45 mg), ^{1}H NMR δ 7.21−7.08 (m, 4H), 4.21 (qd, J = 7.0, 1.4 Hz, 2H), 4.15−4.06 (m, 2H), 3.33 (dd, J = 15.9, 2.2 Hz, 1H), 3.28 (d, J = 9.2 Hz, 1H), 3.22−3.17 (m, 1H), 2.90−2.79 (m, 1H), 2.51 (dtd, J = 22.0, 15.2, 3.0 Hz, 1H), 2.07 (ddt, J = 20.1, 14.6, 9.8 Hz, 1H), 1.93 (dd, J = 13.8, 10.3 Hz, 1H), 1.70 (t, J = 18.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.9, 170.7, 138.0, 134.2, 129.2, 127.1, 126.9, 126.4, 126.3, 122.1 (m), 61.8, 61.5, 54.0, 45.2 (t, J = 24.5 Hz), 35.8, 35.4, 31.1 (t, J = 3.7 Hz), 24.1 (t, J = 27.8 Hz), 14.2, 14.0. ^{19}F NMR δ −87.02 (AB, ddqd, J = 229.5, 21.4, 18.6, 10.2 Hz, 1F), −89.63 (AB, dpd, J = 229.5, 18.5, 15.1 Hz, 1F). HRMS (ESI/TOF) *m/z*: [M+H]+ Calcd for $C_{19}H_{25}F_2O_4$ 355.1715; Found 355.1714.

*Diethyl 4-(2,2,2-Trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**8**).* Prepared according to general method and isolated in 70% yield after chromatography as a colorless oil (50 mg), ^{1}H NMR δ 7.23−7.10 (m, 4H), 4.22 (qd, J = 7.1, 0.9 Hz, 2H), 4.15−4.07 (m, 2H), 3.34 (dd, J = 16.0, 2.1 Hz, 1H), 3.24−3.15 (m, 1H), 2.84 (dd, J = 13.7, 6.6 Hz, 1H), 2.77 (ddd, J = 15.1, 11.7, 3.3 Hz, 1H), 2.28 (dt, J = 15.3, 10.4 Hz, 1H), 1.97 (dd, J = 13.8, 10.1 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.7, 170.5, 136.3, 134.2, 129.4, 127.1, 127.0 (q, J = 278.4 Hz), 126.89, 126.88, 61.9, 61.6, 53.8, 41.0 (q, J = 27.5 Hz), 35.3, 35.0, 30.7 (d, J = 2.8 Hz), 14.2, 14.0. ^{19}F NMR δ −63.53 (t, J = 11.2 Hz). Its ^{1}H NMR, ^{13}C and ^{19}F NMR were consistent with data reported in the literature.[30]

*Diethyl 4-(2,2,3,3,4,4,5,5,5-Nonafluoropentyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**9**).* Prepared according to general method and isolated in 90% yield after chromatography as a colorless oil (91 mg), ^{1}H NMR δ 7.32−7.11 (m, 4H), 4.24 (m, 2H), 4.19−4.05 (m, 2H), 3.51 (dd, J = 10.3, 7.3 Hz, 1H), 3.37 (dd, J = 16.4, 2.0 Hz, 1H), 3.27−3.20 (m, 1H), 2.91 (ddt, J = 13.9, 6.7, 2.1 Hz, 1H), 2.75 (ddd, J = 34.5, 15.9, 7.5 Hz, 1H), 2.30 (ddt, J = 31.6, 16.2, 8.9 Hz, 1H), 2.07−1.99 (m, 1H), 1.30 (t, J = 7.1 Hz, 4H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.6, 170.4, 136.6, 134.3, 129.5, 127.2, 127.1, 126.9, 121.5, 106.1 (m), 62.0, 61.6, 53.9, 38.2 (t, J = 20.9 Hz), 35.8 (d, J = 3.1 Hz), 35.3, 29.6 (d, J = 3.1 Hz), 14.1, 14.0. ^{19}F NMR δ −81.04 (tt, J = 9.7, 3.3 Hz), −109.84 − −115.91 (m), −124.37 (ddd, J = 10.3, 5.1, 2.8 Hz), −125.64 − −126.12 (m). HRMS (ESI/TOF) *m/z*: [M+H]+ Calcd for $C_{21}H_{22}F_9O_4$ 509.1369; Found 509.1379.

*Diethyl 4-(3-Ethoxy-2,2-difluoro-3-oxopropyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**10**).* Prepared according to general method and isolated in 84% yield after chromatography as a colorless oil (69.2 mg), ^{1}H NMR (300 MHz) δ 7.20−7.16 (m, 2H), 7.14−7.10

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(m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.09 (qd, J = 7.1, 1.9 Hz, 2H), 3.39−3.27 (m, 2H), 3.18 (dd, J = 15.9, 1.2 Hz, 1H), 2.90−2.62 (m, 2H), 2.28 (dddd, J = 20.1, 15.2, 12.2, 9.4 Hz, 1H), 2.07−1.89 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 171.8, 170.5, 164.7−163.8 (m), 137.0, 134.3, 129.3, 127.2, 127.0, 126.7, 63.2, 61.9, 61.5, 53.9, 41.9 (t, J = 22.4 Hz), 35.5, 35.4, 31.7, 14.2, 14.1, 14.0. ^{19}F NMR δ −102.22 (AB, ddd, J = 260.9, 21.6, 12.2 Hz), −105.17 (AB, ddd, J = 260.9, 20.1, 16.4 Hz). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{21}H_{27}F_2O_6$ 413.1770; Found 413.1773.

*Diethyl 4-(2,2-Difluoro-3-oxo-3-(phenylamino)propyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**11**).* Prepared according to general method and isolated in 82% yield after chromatography as a colorless oil (75 mg), ^{1}H NMR δ 8.22 (s, 1H), 7.61 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.27 (d, J = 8.2 Hz, 1H), 7.20 (q, J = 8.7, 7.9 Hz, 2H), 7.15 (d, J = 5.9 Hz, 2H), 4.22 (qd, J = 7.0, 2.0 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.41−3.30 (m, 2H), 3.23 (d, J = 16.0 Hz, 1H), 2.94 (dddd, J = 28.5, 15.2, 7.0, 4.3 Hz, 2H), 2.46−2.30 (m, 1H), 2.08−1.94 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 171.7, 170.6, 162.1 (t, J = 28.5 Hz), 137.1, 136.1, 134.1, 129.3, 129.2, 127.2, 127.0, 126.6, 125.7, 120.5, 118.5 (t, J = 254.9 Hz), 61.8, 61.5, 53.9, 40.9 (t, J = 22.2 Hz), 35.7, 35.3, 30.4 (t, J = 3.1 Hz), 14.1, 13.9. ^{19}F NMR δ −101.37 (AB, dddd, J = 256.6, 21.9, 12.0, 2.7 Hz, 1F), −105.04 (AB, dddd, J = 256.6, 20.7, 18.0, 3.2 Hz, 1F). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{25}H_{28}F_2NO_5$ 460.1930; Found 460.1952.

*Diethyl 4-(2,2-Difluoro-3-morpholino-3-oxopropyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**12**).* Prepared according to general method and isolated in 88% yield after chromatography as a colorless oil (80 mg), ^{1}H NMR δ 7.29 (d, J = 7.7 Hz, 1H), 7.17 (td, J = 7.3, 2.2 Hz, 1H), 7.14−7.08 (m, 2H), 4.20 (tdd, J = 8.7, 6.5, 1.4 Hz, 2H), 4.09 (dddd, J = 14.1, 12.0, 7.1, 3.6 Hz, 2H), 3.78 (t, J = 4.6 Hz, 2H), 3.76−3.69 (m, 4H), 3.67 (dd, J = 10.5, 5.0 Hz, 2H), 3.38 (q, J = 8.8 Hz, 1H), 3.35−3.30 (m, 1H), 3.19 (d, J = 15.9 Hz, 1H), 2.99−2.81 (m, 2H), 2.32 (ddt, J = 25.2, 15.7, 10.4 Hz, 1H), 1.98 (dd, J = 13.7, 10.1 Hz, 1H), 1.26 (td, J = 7.1, 1.1 Hz, 3H), 1.11 (td, J = 7.2, 1.2 Hz, 3H). ^{13}C NMR δ 171.8, 170.6, 162.1 (t, J = 29.3 Hz), 137.8, 134.1, 129.1, 127.4, 126.9, 126.5, 119.8 (t, J = 255.5 Hz), 66.9, 66.8, 61.8, 61.4, 54.0, 46.7 (t, J = 6.4 Hz), 43.6, 42.0 (t, J = 21.7 Hz), 36.1, 35.4, 30.3, 14.1, 14.0. ^{19}F NMR δ −95.51 (AB, ddd, J = 282.0, 26.4, 11.5 Hz, 1F), −99.74 (AB, ddd, J = 282.0, 24.4, 15.6 Hz, 1F). HRMS (ESI/TOF) m/z: [M+H]+ Calcd for $C_{23}H_{30}F_2NO_6$ 454.2036; Found 454.2050.

Computational Details and Results. Molecular optimizations were done at the M06-2X/6-311+G(2df,p) // M06-L/6-31G(d) level of theory.[14,16,30] Frequency calculations were used to characterize the optimized structures as either minima or transition state, and also to compute thermal contributions to enthalpy and free energy.[31,32] The influence of acetonitrile as a solvent was evaluated using the SMD continuum solvation model.[17] Composite free energies in acetonitrile were computed by summing gas-phase M06-L thermal contributions with SMD/M06-2X single-point energies. Since the Gibbs free energies in the gas phase are calculated at 0.0446 M (1 atm), and in acetonitrile are reported in a standard state of 1 M, the correction was made by adding −1.9 kcal/mol (RT ln ([Sln]/[Gas])) to the free energy of each molecule. All density functional calculations were accomplished with Gaussian 09 revision D.01.[33] The discussion presented in the next section is all based on the free energies obtained for both transition states (Figure 3) and products including the solvent effect, and which are contained in Table 5.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03012.

NMR spectra of all new compounds and table of atom coordinates (PDF)

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Recent reviews: (a) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, *14*, 941−951. (b) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Fluorine Chem.* **2013**, *152*, 119−128. (c) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529−2591. (d) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, UK, 2009. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (f) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (g) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886.

(2) Recent reviews on trifluoromethylations: (a) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683−730. (b) Charpentier, J.; Fruh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650−682. (c) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513−1522. (d) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (e) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617−626. (f) Macé, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, *2012*, 2479−2494.

(3) For reviews, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475−4521. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470−477. (c) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, *2012*, 6679−6687. (d) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, *48*, 7465−7478.

(4) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626−1631. (b) Xu, Y.; Qian, L.; Pontsler, A. V.; McIntyre, T. M.; Prestwich, G. D. *Tetrahedron* **2004**, *60*, 43−49. (c) Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. *J. Med. Chem.* **2009**, *52*, 1525−1529. (d) Rewcastle, G. W.; Gamage, S. A.; Flanagan, J. U.; Frederick, R.; Denny, W. A.; Baguley, B. C.; Kestell, P.; Singh, R.; Kendall, J. D.; Marshall, E. S.; Lill, C. L.; Lee, W.-J.; Kolekar, S.; Buchanan, C. M.; Jamieson, S. M. F.; Shepherd, P. R. *J. Med. Chem.* **2011**, *54*, 7105−7126.

(5) (a) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524−5527. (b) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090−12094. (c) Matheis, C.; Jouvin, K.; Goossen, L. *Org. Lett.* **2014**, *16*, 5984−5987. (d) Gu, Y.; Leng, X.-B.; Shen, Q. *Nat. Commun.* **2014**, *5*, 5405. (e) Xu, L.; Vicic, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 2536−2539.

(6) (a) Lin, Q.-Y.; Xu, X.-H.; Zhang, K.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2016**, *55*, 1479−1483. (b) Zhang, Z.; Tang, X.; Thomoson, C. S.; Dolbier, W. R., Jr. *Org. Lett.* **2015**, *17*, 3528−3531. (c) Arai, Y.; Tomita, R.; Ando, G.; Koike, T.; Akita, M. *Chem. - Eur. J.* **2016**, *22*, 1262−1265. (d) Tang, X.-J.; Dolbier, W. R., Jr. *Angew. Chem., Int. Ed.* **2015**, *54*, 4246−4249. (e) Cao, P.; Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, 737−738.

(7) Tang, X.-J.; Thomoson, C. S.; Dolbier, W. R., Jr. *Org. Lett.* **2014**, *16*, 4594−4597.

(8) Liu, J.; Zhuang, S.; Gui, Q.; Chen, X.; Yang, Z.; Tan, Z. *Eur. J. Org. Chem.* **2014**, *2014*, 3196−3202.

(9) He, Z.; Tan, P.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 1838−1841.

(10) Zhang, Z.; Tang, X. J.; Dolbier, W. R., Jr. *Org. Lett.* **2016**, *18*, 1048−1051.

(11) (a) Park, J.; Kim, J. H.; Kim, Y. M.; Jeong, H. J.; Kim, D. W.; Park, K. H.; Kwon, H.-J.; Park, S.-J.; Lee, W. S.; Ryu, Y. B. *Bioorg. Med. Chem.* **2012**, *20*, 5928−5935. (b) Irie, K.; Kajiyama, S.; Funaki, A.; Koshimizu, K.; Hayashi, H.; Arai, M. *Tetrahedron* **1990**, *46*, 2773−

DOI: 10.1021/acs.joc.6b03012
J. Org. Chem. 2017, 82, 2589−2598

2788. (c) Lee, H. K.; Lee, Y. S.; Roh, E. J.; Rhim, H.; Lee, J. Y.; Shin, K. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4424−4427.
(12) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000−4003.
(13) (a) Gao, F.; Yang, C.; Ma, N.; Gao, G.-L.; Li, D.; Xia, W. *Org. Lett.* **2016**, *18*, 600−603. (b) Wang, L.; Wei, X.-J.; Jia, W.-L.; Zhong, J.-J.; Wu, L.-Z.; Liu, Q. *Org. Lett.* **2014**, *16*, 5842−5845.
(14) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101.
(15) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(16) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157−167.
(17) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(18) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1776.
(19) Newcomb, M. Kinetics of Radical Reactions: Radical Clocks. In *Radicals in Organic Synthesis*; Wiley-VCH, 2008; pp 316−336.
(20) Gansäuer, A.; Seddiqzai, M.; Dahmen, T.; Sure, R.; Grimme, S. *Beilstein J. Org. Chem.* **2013**, *9*, 1620−1629.
(21) Matlin, A. R.; Leyden, M. C. *Int. J. Org. Chem.* **2013**, *03*, 169−175.
(22) Jager, C. M.; Hennemann, M.; Mieszała, A.; Clark, T. *J. Org. Chem.* **2008**, *73*, 1536−1545.
(23) Pinter, B.; De Proft, F.; Van Speybroeck, V.; Hemelsoet, K.; Waroquier, M.; Chamorro, E.; Veszpremi, T.; Geerlings, P. *J. Org. Chem.* **2007**, *72*, 348−356.
(24) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472−473.
(25) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742.
(26) Modglin, J. D.; Dunham, J. C.; Gibson, C. W.; Lin, C. Y.; Coote, M. L.; Poole, J. S. *J. Phys. Chem. A* **2011**, *115*, 2431−2441.
(27) Modglin, J. D.; Erdely, V. K.; Lin, C. Y.; Coote, M. L.; Poole, J. S. *J. Phys. Chem. A* **2011**, *115*, 14687−14696.
(28) Van Speybroeck, V.; Borremans, Y.; Van Neck, D.; Waroquier, M.; Wauters, S.; Saeys, M.; Marin, G. B. *J. Phys. Chem. A* **2001**, *105*, 7713−7723.
(29) Van Speybroeck, V.; Van Neck, D.; Waroquier, M. *J. Phys. Chem. A* **2002**, *106*, 8945−8950.
(30) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(31) Cramer, C. J. *Essentials of Computational Chemistry: Theories and Models*, 2nd ed.; John Wiley & Sons: Chichester, 2004.
(32) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556−14562.
(33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.

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J. Org. Chem. 2017, 82, 2589−2598