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A Chelating Nucleophile Plays a Starring Role: 1,8-Naphthyridine-Catalyzed Polycomponent α,α-Difluorination of Acid Chlorides

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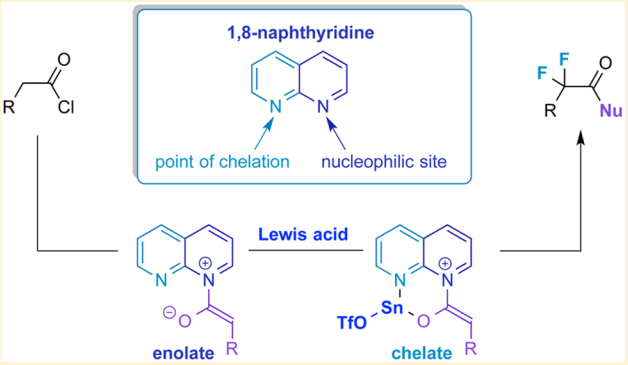
Supporting Information

ABSTRACT: A dually activated ketene enolate, generated from an acid chloride, the unusual chelating nucleophile (1,8-naphthyridine), and a Lewis acid, reacts to afford a host of α,α-difluorinated products in the presence of a benchtop-stable fluorinating agent (Selectfluor). The use of this method to synthesize otherwise difficult to make products is highlighted along with computational and spectroscopic support for the proposed chelate.



Imagine a nucleophile that can attack an electrophilic partner and simultaneously coordinate a metal or Lewis acid complex. If the bound Lewis acid complex and electrophile interact, a chelate is formed—one that could potentially give rise to interesting patterns of reactivity (Figure 1). Such a special

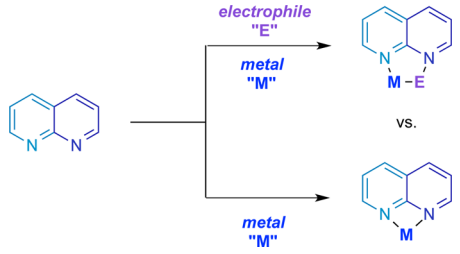


Figure 1. Chelating modes of 1,8-naphthyridine.

nucleophile need not be structurally complex; in this note, we report the use of the simple, commercially available molecule 1,8-naphthyridine as a putatively chelating nucleophile to effect otherwise difficult to achieve α,α-difluorination reactions. Importantly, these results point to the possibility that 1,8-naphthyridine can play a more general salutary role in other α-functionalization reactions of carboxylic acid derivatives.

It is known that organic nucleophiles can be combined with Lewis acids to generate dually activated enolates that enhance thermal stability and help introduce stereochemical control.[1,2] Lewis acid assisted chelate organization has proven to be a particularly useful tool in asymmetric halogenation reactions.[3] To this end, fluorination strategies have attracted significant interest because of fluorine's auspicious role in the pharmaceutical industry.[4] Stereoselective α-fluorination of β-ketoesters has been explored with titanium,[5] palladium,[6] and copper[7] catalysts. While monofluorination through Lewis acid chelated intermediates has been extensively studied, use of chelated nucleophiles for fluorination remains uncharted. Some time ago, we published a tricomponent catalytic system utilizing a Lewis acid, $Sn(OTf)_2$, a nucleophilic base (pyridine), and an anionic phase transfer catalyst, $KB(C_6H_6)_4$, to effect the selective α,α-difluorination of a series of acid chlorides in the presence of Selectfluor.[8] Although notable, our methodology was very limited to extensively acidified, electron deficient aromatics and β-dicarbonyl compounds. We reasoned this system could provide a suitable foundation for the application of a chelating nucleophile.

In our original findings, we noted that sulfur containing compound **1** (Figure 2) underwent difluorination more readily

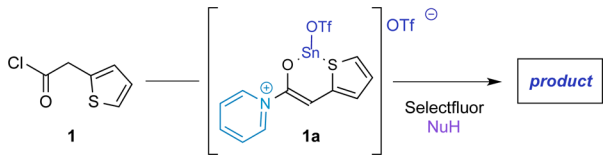


Figure 2. Proposal of a chelated intermediate.

than its oxygen and nitrogen counterpart. This effect could not solely be attributed to the increased acidity at the α-position; instead, it was reasoned that sulfur may coordinate to the tin catalyst to form an internal chelate along with the carbonyl (**1a**). Accordingly, a nucleophile that combines both a point of chelation and a nucleophilic site could prove advantageous, simultaneously generating the ketene enolate and binding the

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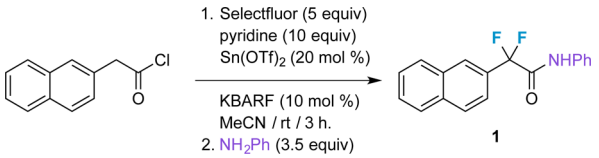
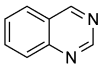
tin. We began the study by examining cyclic amidine derivatives, as they have been shown to operate as efficient *N*-acylation catalysts.[9] Several amidine catalysts were screened employing 2-naphthylacetyl chloride, a compound that had previously failed to difluorinate under our original conditions, and aniline as a quenching agent (Table 1).

Table 1. Amidine Co-catalyst Screen[a]



entry	catalyst	yield %	entry	catalyst	yield %
1	none	0	5		15
2		4	6		52[a]
3		5	7		6
4		11	8		28

[a]Reactions performed with 10 mol % catalyst loading; (a) 10 mol % $Sn(OTf)_2$, 5 mol % KBARF.

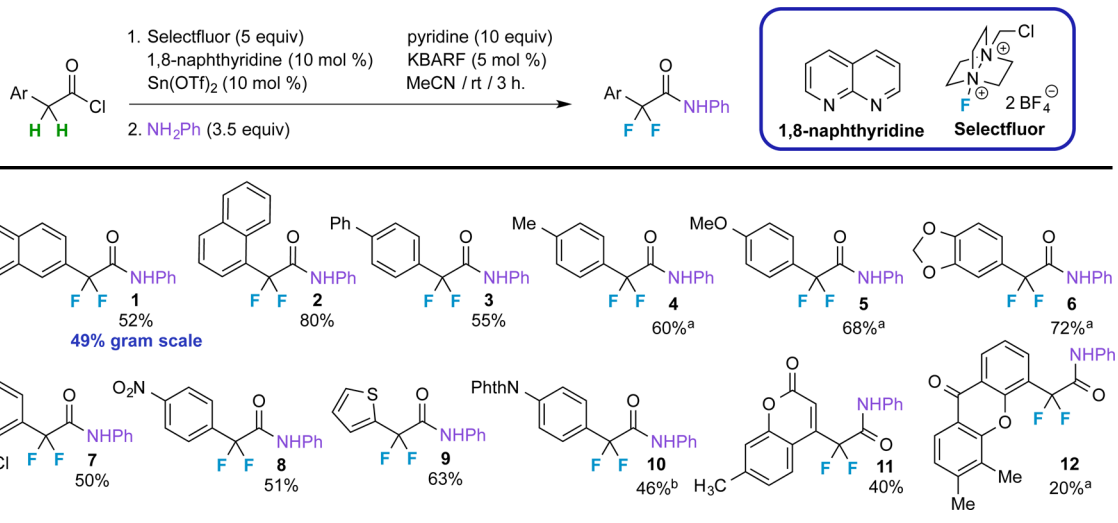
As bicyclic isothioureas (entries 2−5, Table 1) showed relatively low conversion rates, we considered other amidine catalysts possessing a fused bicyclic core. Naphthyridines, a class of compounds consisting of two fused pyridine rings, are emblematic of such a system. 1,8-Naphthyridines are present in the antimicrobials nalidixic acid and gemifloxacin and have been employed in drug candidates for the treatment of Alzheimer's disease.[10,11] Chemically, 1,8-naphthyridine is a versatile ligand with monodentate and bidentate bridging capacities and is known for the formation of weak chelates with single metal centers that possess small bite angles.[12] When we employed a catalytic amount of 1,8-naphthyridine in the test reaction (entry 5), we found it was compatible with Selectfluor, unlike other nucleophilic sources (such as DMAP) and were rewarded with a considerable increase in both yield and selectivity. Other heterocyclic isomers, on the other hand (entries 7 and 8), fared less well.

Given our success with 2-naphthylacetyl chloride, we turned to other highly conjugated systems (**1**−**3**) in the hope of observing the corresponding difluorinated products. We found these compounds underwent modest to excellent difluorination (Table 2). What is more, the reaction was shown (using **1**) to be scalable up to a gram or more without loss in yield. Previously, aromatic compounds with electron-rich substituents had afforded little to no difluorinated product; however, upon the addition of catalytic 1,8-naphthyridine, moderate yields were reported for this class of molecules. For electron-rich compounds exemplified by **6**, it was found that increasing the tin loading from 10 mol % to 50 mol % greatly improved the yield. Paradoxically, highly electron-withdrawing substrates had also proven challenging to difluorinate. In the naphthyridine based system, 4-nitrophenylacetyl chloride reacted to afford a fair amount of product, **8**. Unfortunately the system was not conducive to aliphatic compounds; an investigation of butyryl chloride revealed minor (<10% by NMR) difluorination yields.

The applicability of this system to medicinally relevant molecules was also investigated. Phthalimide derivatives (**10**) have been used as anesthetics,[13] tumoricidals, and DNA-cleaving agents.[14] In particular, *N*-phthaloyl aminocarboxylic acids have been shown to have antimicrobial properties.[15] Entry **11** is an example of a coumarin, a class of bioactive molecules with reported anti-HIV, antitumor, and antiseptic properties.[16] Coumarins have also been used to treat asthma and lymphedema.[17] Vadimezan, the carboxylic acid derivative of **12**, is a tumor-vascular disrupting agent with promising phase II clinical trial results regarding the treatment of advanced nonsmall cell lung cancer when combined with other mitotic inhibitors.[18]

Combining difluorination with natural product derivatization can yield a new class of intriguing medicinally relevant compounds (Figure 3). As this reaction is thought to proceed through a highly reactive ketene enolate, it is possible to quench it with a range of nucleophiles to produce various highly functionalized products.[19] The investigation of natural

Table 2. Isolated Yields of Difluorinated Products[a]



[a]Key: (a) 50 mol % $Sn(OTf)_2$; (b) yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard due to product instability.

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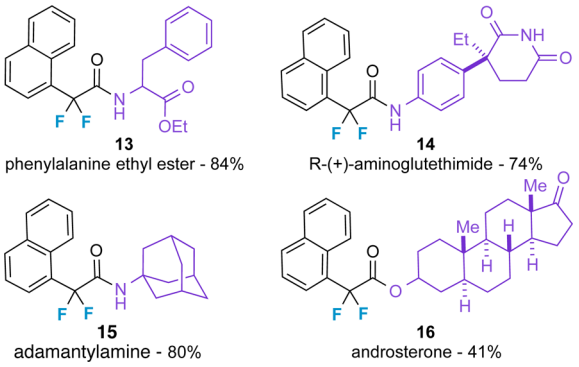

Figure 3. Natural product and pharmaceutical derivatization.

product derivatization began with a protected amino acid, phenylalanine ethyl ester, because of its commercial availability, high solubility in acetonitrile, and single nucleophilic site. (*R*)-(+)-Aminoglutethimide was an attractive candidate because of its role in blocking the production of cholesterol-derived steroids through potent inhibition of P450*scc* and aromatase.[20] Adamantylamine was another promising nucleophile as it makes up the core of memantine, a NMDA antagonist used to treat Alzheimer's disease.[21] We then turned our attention from amines to alcohols; when the endogenous steroid hormone, androsterone, was used as the nucleophilic quenching agent, a lower isolated yield compared to amine-based nucleophiles was observed; a simple argument in relative nucleophilicity supports this finding.

In order to gain insight into the reaction mechanism and the role of the proposed chelate, IR and ^{19}F NMR studies were undertaken as no ^{119}Sn NMR signal was obtainable in the solution phase. By comparing IR shifts, it was possible to probe for a coordinated intermediate. In acetonitrile, 1-naphthylacetyl chloride absorbed strongly at 1797 cm^{-1}, characteristic of acid chlorides.[22] When 1,8-naphthyridine was combined with the acid chloride, bands were observed at 1628 and 1606 cm^{-1}, indicative of an acylpyridinium salt.[23] Upon the addition of $Sn(OTf)_2$ to the naphthyridine–acid chloride mixture, a band emerged at 1736 cm^{-1}, suggesting coordination between tin and the carbonyl group.[24] Moreover, bands at 1272 and 1375 cm^{-1} imply ionic $CF_3SO_3^-$ and monodentate-bound trifluoromethanesulfonate, respectively.[25] Additionally, a peak at 482 cm^{-1} is characteristic of bonds between imino nitrogen atoms and tin.[26] Although these data are suggestive of a chelate, they do not provide definitive proof; we therefore turned to ^{19}F NMR for further validation. We carefully observed the ^{19}F signal of the enolizable substrate, 2-fluoro-2-phenylacetyl chloride, in CD_3CN (Figure 4). When stoichiometric 1,8-naphthyridine was added a precipitate formed (putatively the acyl naphthyridinium salt). Following the addition of stoichiometric $Sn(OTf)_2$, a slight shift (+0.05 ppm) was also detected. To generate the enolate complex, 1 equiv of pyridine was then added and the solution became homogeneous again. This caused the sharp doublet at −161.45 to disappear and a singlet at −123.25 ppm to emerge, which is consistent with that of analogous fluorinated silyl enolates.[27] On the basis of the IR data, a chelated enolate with a single monodentate-bound trifluoromethanesulfonate was further examined computationally; we deemed the nonfluorinated enolate most relevant as ^{19}F NMR studies indicated that the first fluorination is rate-determining. The distance between nitrogen and tin was calculated at B3LYP/LanL2DZ to be 2.36 Å, which is

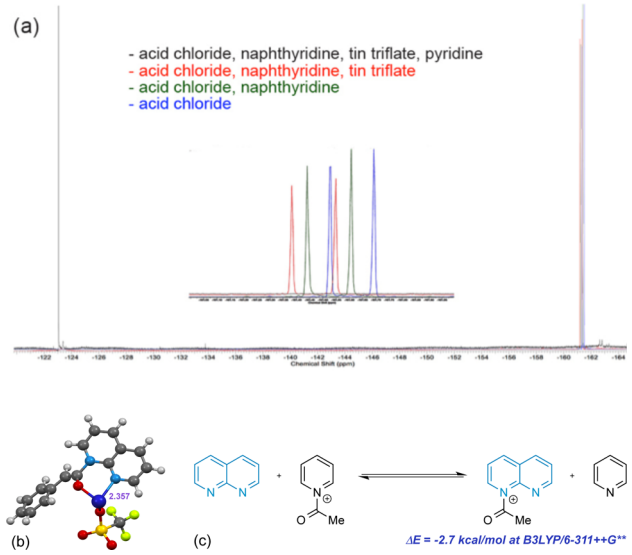

Figure 4. (a) ^{19}F NMR spectra overlay; (b) B3LYP/LanL2DZ calculations for chelated tin–nitrogen bond length; and (c) B3LYP/6-311++G** naphthyridine–pyridine acetylation isodesmic reaction.

comparable with average tin(II)–nitrogen bonds reported to be ∼2.39 Å.[28] Computations at the B3LYP/6-311++G** level of theory also revealed that naphthyridine acylation is thermodynamically favorable over that of pyridine (Figure 4). From this calculation, it can be reasoned that even in the presence of excess pyridine a naphthyridine–tin chelate can form in situ.

In conclusion, we have demonstrated that the chelating nucleophile 1,8-naphthyridine successfully augments difluorination methodology to increase substrate scope and selectivity. Quenching the reaction with natural products proved an effective strategy for the generation of late-stage difluorinated molecules; future efforts will focus on the application of chelating nucleophiles for difluorination of aliphatic compounds.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and acid chloride compounds were dried and distilled by standard methods. All reactions were performed on a 0.24 mmol scale with respect to the acid chloride except for *β*-naphthylacetyl chloride (1 g scale). ^{1}H spectra were acquired on a 400 MHz NMR spectrometer in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR spectrometer in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and or trichlorofluoromethane ($CFCl_3$, δ 0.00 ppm). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants [Hz], integration). IR data was obtained using FT-IR with a NaCl cell. High-resolution mass spectra (HRMS) were recorded using ESI-TOF (electrospray ionization–time-of-flight) mass spectrometry. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 2,2-difluoro-*N*-phenyl-2-(thiophene-2-yl)acetamide (**9**) was consistent with literature precedent.[8] Compound **10** was reported as crude spectra due to product decomposition. Spectral data was processed with ACD/NMR Processor Academic Edition.[29]

General Procedure for Synthesis of *α*,*α*-Difluorinated Products. An oven-dried, 100 mL, round-bottom flask equipped with a stir bar was placed under an atmosphere of N_2. Selectfluor (8.66, 24.4 mmol, 5.00 equiv), 1,8-naphthyridine (0.064 g, 0.49 mmol,

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0.10 equiv), potassium tetrakis(pentafluorophenyl)borate (0.175 g, 0.244 mmol, 0.0500 equiv), tin(II) trifluoromethanesulfonate (0.248 g, 0.488 mmol, 0.100 equiv), and β-naphthylacetyl chloride (1.00 g, 4.88 mmol, 1.00 equiv) were added. Pyridine (3.9 mL, 48 mmol, 10. equiv) was then added dropwise. The mixture stirred for 3 h, at which time the reaction was quenched with aniline (4.0 mL, 44 mmol, 9.0 equiv). The product was extracted into CH_2Cl_2 and washed with 1 M HCl followed by saturated $NaHCO_3$ solution. The organics were dried with $MgSO_4$ and filtered through Celite. The solvents were removed by rotary evaporation, and the residue was subjected to column chromatography on silica with a mixture of ethyl acetate/hexanes as eluent to afford 2,2-difluoro-2-(naphthalen-2-yl)-*N*-phenylacetamide as a white solid (0.72 g, 49%).

Computational Methods. The Gaussian 09[30] package and Spartan '10[31] were used for all calculations. Geometry optimizations of 1,8-naphthyridine, pyridine, acylpyridine, and acylnaphthyridine were determined at the B3LYP/6-311++G** level. Geometry optimization of the chelated enolate was determined at the B3LYP/6-31G* (LANL2DZ on Sn) level.

Compound Characterization. *2,2-Difluoro-2-(naphthalen-2-yl)-N-phenylacetamide (**1**):* brown solid; mp 128−129 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 8.13 (br s, 1H), 7.96−7.87 (m, 3H), 7.73 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.58 (m, 4H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 162.2 (t, *J* = 30.7 Hz), 136.1 (s), 134.3 (s), 132.4 (s), 131.0 (s), 129.8 (t, *J* = 24.8 Hz), 129.2 (s), 129.1 (s), 128.9 (s), 128.8 (s), 127.8 (s), 127.7 (s), 127.0 (s), 126.0 (t, *J* = 7 Hz), 122.8 (s), 122.1 (t, *J* = 5.1), 120.2 (s), 115.1 (t, *J* = 253 Hz); ^{19}F NMR ($CDCl_3$) δ −102.3 (s, 2F); IR (C═O) 1714 cm^{-1}; HRMS (ESI^+) calcd for $C_{18}H_{13}F_2NONa^+$ 320.0863, found 320.0865; yield 0.72 g (49%) and 37.8 mg (52%).

*2,2-Difluoro-2-(naphthalen-1-yl)-N-phenylacetamide (**2**):* amorphous solid; ^{1}H NMR ($CDCl_3$) δ 8.26 (dt, *J* = 7.2, 1.0 Hz, 1H), 8.24 (br s, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.91 (t, *J* = 8 Hz, 2H), 7.61−7.50 (m, 5H), 7.35 (t, *J* = 8 Hz, 2H), 7.19 (tt, *J* = 7.4, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.8 (t, *J* = 30.7 Hz), 136.1 (s), 134.1 (s), 132.3 (s), 129.6 (s), 129.2 (s), 128.9 (s), 128.1 (t, *J* = 23.4 Hz), 127.4 (s), 126.4 (s), 125.6 (s), 125.4 (t, *J* = 9.1 Hz), 124.5 (t, *J* = 3.3 Hz), 124.4 (s), 120.2 (s), 116.2 (t, *J* = 254 Hz); ^{19}F NMR ($CDCl_3$) δ −98.4 (s, 2F); IR (C═O) 1717 cm^{-1}; HRMS (ESI^+) calcd for $C_{18}H_{13}F_2NONa^+$ 320.0863, found 320.0861; yield 57.8 mg (80%).

*2-([1,1′-Biphenyl]-4-yl)-2,2-difluoro-N-phenylacetamide (**3**):* white solid; mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (br s, 1H), 7.77−7.67 (m, 4H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.41−7.35 (m, 2H), 7.96−7.87 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.8 (t, *J* = 31.5 Hz), 148.3 (s), 144.1 (s), 140.0 (s), 136.1 (s), 131.4 (t, *J* = 25.6 Hz), 129.3 (s), 128.9 (s), 128.0 (s), 127.4 (d, *J* = 17.6 Hz), 126.1 (t, *J* = 6.2 Hz), 125.6 (s), 120.2 (s), 112.4 (t, *J* = 255 Hz); ^{19}F NMR ($CDCl_3$) δ −102.6 (s, 2F); IR (C═O) 1715 cm^{-1}; HRMS (ESI^+) calcd for $C_{20}H_{15}F_2NONa^+$ 346.1019, found 346.1021; yield 43.2 mg (55%).

*2,2-Difluoro-N-phenyl-2-(p-tolyl)acetamide (**4**):* tan solid; mp 103−105 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (br s, 1H), 7.57−7.54 (m, 4H), 7.33 (t, *J* = 8 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.0 (t, *J* = 31.5 Hz), 140.3 (s), 129.0 (s), 128.7 (s), 128.3 (s), 128.1 (s), 125.5 (t, *J* = 2.9 Hz), 125.4 (s), 120.2 (s), 114.0 (t, *J* = 254 Hz), 20.3 (s); ^{19}F NMR ($CDCl_3$) δ −102.4 (s, 2F); IR (C═O) 1715 cm^{-1}; HRMS (ESI^+) calcd for $C_{15}H_{13}F_2NONa^+$ 284.0863, found 284.0867; yield 38.5 mg (60%).

*2,2-Difluoro-2-(4-methoxyphenyl)-N-phenylacetamide (**5**):* yellow solid; mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (br s, 1H), 7.60−7.54 (m, 4H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6 (s), 136.1 (s), 131.6 (s), 129.1 (s), 127.2 (t, *J* = 6.2 Hz), 125.5 (s), 124.6 (t, *J* = 25.6 Hz), 120.1 (s), 114.9 (t, *J* = 254 Hz), 114.0 (s), 55.4 (s); ^{19}F NMR ($CDCl_3$) δ −100.2 (s, 2F). IR (C═O) 1715 cm^{-1}; HRMS (ESI^+) calcd for $C_{15}H_{13}F_2NO_2Na^+$ 300.0812, found 300.0815; yield 46.1 mg (68%).

*2-(Benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-N-phenylacetamide (**6**):* tan solid; mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (br s, 1H), 7.59−7.56 (m, 2H), 7.35 (t, *J* = 8 Hz, 2H), 7.21−7.13 (m, 3H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 161.8 (t, *J* = 31.5 Hz), 149.9 (s), 148.0 (s), 136.1 (s), 129.2 (s), 126.5 (s), 126.3 (s), 125.6 (s), 120.2 (s), 120.1 (t, *J* = 6.6 Hz), 114.7 (t, *J* = 255 Hz), 108.3 (s), 106.3 (t, *J* = 6.2); ^{19}F NMR ($CDCl_3$) δ −101.1 (s, 2F); IR (C═O) 1716 cm^{-1}; HRMS (ESI^+) calcd for $C_{15}H_{11}F_2NO_3Na^+$ 314.0605, found 314.0601; yield 51.5 mg (72%).

*2-(2-Chlorophenyl)-2,2-difluoro-N-phenylacetamide (**7**):* blue solid; mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (br s, 1H), 7.79−7.86 (m, 1H), 7.57−7.55 (m, 2H), 7.34−7.49 (m, 5H), 7.16−7.24 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 161.0 (t, *J* = 29.2 Hz), 136.1 (s), 132.3 (t, *J* = 1.4 Hz), 131.8 (s), 130.8 (s), 130.6 (s), 129.2 (s), 128.3 (t, *J* = 8.7 Hz), 126.9 (s), 125.6 (s), 120.2 (s), 114.1 (t, *J* = 255 Hz); ^{19}F NMR ($CDCl_3$) δ −102.3 (s, 2F); IR (C═O) 1716 cm^{-1}; HRMS (ESI^+) calcd for $C_{14}H_{10}ClF_2NONa^+$ 304.0317, found 304.0320; yield 34.2 mg (50%).

*2,2-Difluoro-2-(4-nitrophenyl)-N-phenylacetamide (**8**):* brown solid; mp 101−102 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, *J* = 9 Hz, 2H), 8.21 (br s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.59−7.55 (m, 2H), 7.41−7.34 (m, 2H), 7.22 (tt, *J* = 7.5, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 160.6 (s), 149.6 (s), 138.4 (t, *J* = 25.8 Hz), 135.6 (s), 129.3 (s), 127.2 (t, *J* = 6 Hz), 126.0 (s), 123.7 (s), 120.2 (s), 113.8 (t, *J* = 256 Hz); ^{19}F NMR ($CDCl_3$) δ −103.4 (s, 2F); IR (C═O) 1717 cm^{-1}; HRMS (ESI^+) calcd for $C_{14}H_{10}F_2N_2O_3Na^+$ 315.0557, found 315.0552; yield 36.4 mg (51%).

*2,2-Difluoro-N-phenyl-2-(thiophene-2-yl)acetamide (**9**).* Spectral and analytical data were in agreement with previous reports.[8] Yield: 38.9 mg (63%).

*2-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-2,2-difluoro-N-phenylacetamide (**10**):* ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H) 7.80 (m, 2H) 7.55−7.32 (m, 6H) 7.06 (br. s. 1H); ^{13}C NMR ($CDCl_3$) δ 165.9 (s), 165.2 (s), 161.6 (s), 133.6 (s), 130.5 (s), 130.0 (s), 128.1 (t, *J* = 6.2 Hz), 126.3 (s), 126.2 (s), 125.6 (s), 122.8 (t, *J* = 8.7 Hz), 121.8 (s), 120.0 (s), 119.3 (s), 115.5 (t, *J* = 255 Hz); ^{19}F NMR ($CDCl_3$) δ −105.96 (s, 2F). IR (C═O) 1716, 1727 cm^{-1}; HRMS (ESI^+) calcd for $C_{22}H_{14}F_2N_2O_3Na^+$ 415.0870, found 415.0877; ield 43.8 mg (46%).

*2,2-Difluoro-2-(7-methyl-2-oxo-2H-chromen-4-yl)-N-phenylacetamide (**11**):* . brown solid; mp 172−173 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (br s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 9.2 Hz, 2H), 7.39 (m, 2H), 7.25−7.11 (m, 3H), 6.78 (s, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6 (s), 159.4 (s), 154.2 (s), 144.8 (t, *J* = 24 Hz), 144.2 (s), 135.5 (s), 129.3 (s), 126.1 (s), 126.1 (s), 125.6 (s), 120.3 (s), 117.6 (s), 115.1 (t, *J* = 10.3 Hz), 113.1 (t, *J* = 257 Hz), 112.3 (s), 21.6 (s); ^{19}F NMR ($CDCl_3$) δ −103.55 (s, 2F); IR (C═O) 1718, 1731 cm^{-1}; HRMS (ESI^+) calcd for $C_{18}H_{13}F_2NO_3Na^+$ 352.0761, found 352.0758; yield 32.1 mg (40%).

*2-(5,6-Dimethyl-9-oxo-9H-xanthen-4-yl)-2,2-difluoro-N-phenylacetamide (**12**):* tan solid; mp 217−219 °C; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, *J* = 7.9 Hz, 1H), 8.43 (br s, 1H), 8.10 (d, *J* = 6.6 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.24−7.16 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.4 (s), 160.8 (s), 154.0 (s), 153.1 (s), 144.9 (s), 136.1 (s), 132.6 (t, *J* = 8.1 Hz), 130.2 (s), 129.3 (s), 126.5 (s), 125.7 (s), 125.0 (s), 123.5 (s), 123.2 (s), 122.1 (s), 121.2 (t, *J* = 24.9 Hz), 119.9 (s), 119.7 (s), 114.4 (t, *J* = 256 Hz), 20.7 (s), 11.6 (s); ^{19}F NMR ($CDCl_3$) δ −101.68 (s, 2F); IR (C═O) 1660, 1720 cm^{-1}; HRMS (ESI^+) calcd for $C_{23}H_{17}F_2NO_3Na^+$ 416.1074, found 416.1070; yield 19.2 mg (20%).

*Ethyl (2,2-difluoro-2-(naphthalen-1-yl)acetyl)phenylalaninate (**13**):* amorphous solid; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, *J* = 7.4 Hz, 1H), 7.98 (d, *J* = 8.2, 1H), 7.89 (m, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.55 (m, 2H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.18 (m, 3H), 6.93 (d, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 7.4 Hz, 1H), 4.91 (dd, *J* = 12.9, 5.87 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.15 (qd, *J* = 12.1, 5.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 163.4 (t, *J* = 30.7 Hz), 134.9 (s), 133.9 (s), 132.0 (s), 129.4 (s), 129.1 (s), 128.7 (s), 128.5 (s), 128.4 (s), 128.2 (s), 127.9 (s), 127.3 (s), 127.2 (s), 126.3 (s), 125.3 (t, *J* = 8.8 Hz), 124.6 (t, *J* = 3.3 Hz), 124.4 (s), 115.9 (t, *J* = 253 Hz), 61.8 (s), 53.2 (s), 37.4 (s), 14.0 (s); ^{19}F NMR ($CDCl_3$) δ −101.68 (s, 2F);

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IR (C═O) 1720, 1740 cm^{-1}; HRMS (ESI^+) calcd for $C_{23}H_{21}F_2NO_3Na^+$ 420.1387, found 420.1381; yield 81.3 mg (84%).

*(S)-N-(4-(3-Ethyl-2,6-dioxopiperidin-3-yl)phenyl)-2,2-difluoro-2-(naphthalen-1-yl)acetamide (**14**):* white solid; mp 210−212 °C; ^1H NMR (C_2D_6OS) δ 11.05 (s, 1H), 10.94 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.70 (m, 3H), 7.35 (d, J = 8.8 Hz, 2H), 2.38 (d, J = 3.1 Hz, 2H), 2.19 (m, 2H), 1.88 (sxt, J = 7.2 Hz, 2H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (C_2D_6OS) δ 175.6 (s), 172.7 (s), 161.8 (t, J = 31.5 Hz), 136.3 (s), 136.1 (s), 133.5 (s), 132.1 (s), 129.1 (s), 128.8 (s), 128.1 (s), 127.9 (s), 127.6 (s), 126.8 (s), 126.5 (s), 125.7 (t, J = 8.4 Hz), 124.8 (s), 123.9 (s), 121.1 (s), 116.1 (t, J = 252 Hz), 54.9 (s), 49.9 (s), 32.1 (s), 29.1 (s), 25.9 (s), 8.9 (s); ^{19}F NMR (C_2D_6OS) δ −96.22 (2F); IR (C═O) broad 1710 cm^{-1}; HRMS (ESI^+) calcd for $C_{25}H_{22}F_2N_2O_3Na^+$ 459.1496, found 459.1491; yield 78.9 mg (74%)

*N-((3s,5s,7s)-Adamantan-1-yl)-2,2-difluoro-2-(naphthalen-1-yl)-acetamide (**15**):* white solid; mp 136−138 °C; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.55 (m, 3H), 6.19 (br s, 1H), 2.06 (s, 9H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 161.7 (t, J = 29.3 Hz), 133.0 (s), 130.9 (s), 128.7 (s), 128.1 (s), 127.8 (s), 126.1 (s), 125.2 (s), 124.3 (t, J = 9.1 Hz), 123.6 (s), 123.4 (s), 114.9 (t, J = 253 Hz), 51.9 (s), 46.7 (s), 40.1 (s), 35.1 (s), 28.3 (s); ^{19}F NMR ($CDCl_3$) δ −99.29 (dd, J = 451.6, 267.0 Hz, 2F); IR (C═O) 1705 cm^{-1}; HRMS (ESI^+) calcd for $C_{22}H_{23}F_2NONa^+$ 378.1645, found 378.1649; yield 67.8 mg (80%).

*(5S,8R,9S,10S,13S,14S)-10,13-Dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2,2-Difluoro-2-(naphthalen-1-yl)acetate (**16**):* white solid; mp 179−180 °C; ^1H NMR ($CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.9 (m, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.59−7.49 (m, 3H), 4.82 (spt, J = 5.3 Hz, 1H), 2.42 (dd, J = 19.2, 8.3 Hz, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.79−1.72 (m, 4H), 1.68−1.42 (m, 4H), 1.30−1.14 (m, 6H), 0.86 (m, 2H), 0.83 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8 (s), 162.9 (t, J = 34.4 Hz), 132.8 (s), 128.8 (s), 128.5 (s), 128.2 (s), 128.0 (s), 127.7 (s), 126.1 (s), 125.2 (s), 123.8 (t, J = 9.5 Hz), 123.4 (s), 123.2 (s), 113.3 (t, J = 251 Hz), 53.1 (s), 50.2 (s), 46.6 (s), 43.5 (s), 35.4 (s), 34.8 (s), 34.5 (s), 33.9 (s), 32.3 (s), 30.4 (s), 29.6 (s), 27.0 (s), 25.9 (s), 20.7 (s), 19.4 (s), 12.7 (s), 11.2 (s); ^{19}F NMR ($CDCl_3$) δ −100.47 (s, 2F); IR (C═O) 1735, 1756 cm^{-1}; HRMS (ESI^+) calcd for $C_{31}H_{36}F_2O_3Na^+$ 517.2530, found 517.2537; yield 50.3 mg (42%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization for new compounds and computational, kinetic, and spectroscopic data. 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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