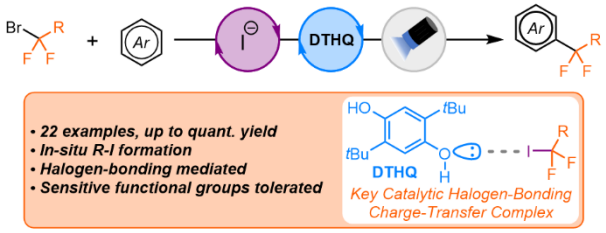
A Dual Catalytic Approach for the Halogen-Bonding-Mediated Reductive Cleavage of α-Bromodifluoroesters and Amides

Tarannum Tasnim, Negin Shafiei, Katelyn J. Laminack, Bailey S. Robertson, Nash E. Nevels, Christopher J. Fennell and Spencer P. Pitre*

Department of Chemistry, Oklahoma State University, 107 Physical Sciences, Stillwater, Oklahoma 74078, United States

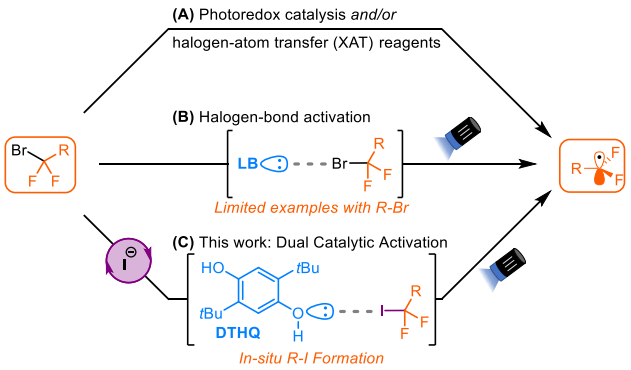
Supporting Information Placeholder



ABSTRACT: While charge-transfer complexes involving halogen-bonding interactions have emerged as an alternative strategy for the photogeneration of carbon radicals, examples using (fluoro)alkyl bromides are limited. This report describes a dual catalytic approach for radical generation from α-bromodifluoroesters and amides under visible light irradiation. Mechanistic studies suggest that the reaction proceeds through *in-situ* bromide displacement using a catalytic iodide salt, generating a C–I bond that can be engaged by our halogen-bonding photocatalysis platform.

The development of many mild, catalytic methods for the generation of carbon-centered radicals makes them an invaluable tool in chemical synthesis, particularly for the construction of C–C bonds.[1] However, the requirement for prior synthetic steps to activate substrates as radical precursors detracts from the potential utility of the elegant radical reactions that have been developed.[2] In this regard, alkyl halides are an ideal solution, as structurally diverse alkyl halides are readily available from commercial suppliers, and these substrates do not require prior synthetic steps to participate in radical reactions. The traditional method of generating carbon radicals from alkyl halides was the use of tributyltin hydride;[3] however, the chemical community has moved on from these reactions owing to the toxicity of tin. The more contemporary approaches involve the reductive cleavage of the C–X bond of the alkyl halide using a sufficiently reducing source of electrochemical potential, like an excited state photocatalyst (Scheme 1A).[4] However, as these approaches rely on generating sufficient electrochemical potential to render the SET to the alkyl halide exergonic, groups that could otherwise be reduced at these redox potentials cannot be included in the reaction substrates, thereby diminishing the functional group tolerance of these reactions. Another more recent strategy involves halogen atom abstraction via a photocatalytically generated silyl, α-aminoalkyl, or aryl radical species.[5] While these reactions enable carbon radical generation from a broad scope of alkyl halides, these methods generally require stoichiometric amounts of the halogen atom transfer agent.

Scheme 1. Modern approaches to carbon radical formation from alkyl bromides.



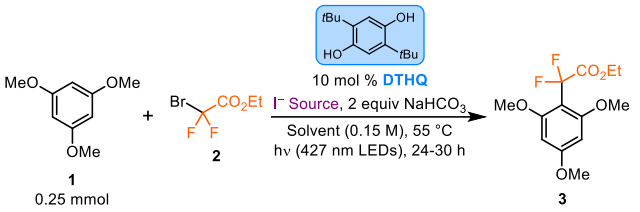
Charge-transfer complexes involving halogen-bonding interactions between a Lewis base and a C–X bond have emerged as an alternative strategy for the photogeneration of carbon radicals from alkyl halides.[6] A halogen-bonding interaction can be described as consisting of a partial n → σ* charge-transfer from the non-bonding orbital of the Lewis base (halogen-bond acceptor) and the σ* orbital of the C–X bond (halogen-bond donor).[7] Previous reports have demonstrated that stoichiometric Lewis bases, especially aliphatic

amines, can efficiently form charge-transfer complexes (CTCs) with alkyl iodides through halogen-bonding interactions, enabling a range of visible-light mediated radical transformations.[6c,8] More recently, efforts towards employing catalytic Lewis bases, such as amines,[9] pyridines,[10] phosphines,[11] and phenols,[12] have been reported. However, methods for the activation of alkyl bromides using a halogen-bonding strategy are limited,[10,13] owing to the less accessible σ* orbital of C–Br bonds, making them weaker halogen-bond donors than alkyl iodides (Scheme 1B).[14] Therefore, a general strategy for expanding this reactivity to C–Br bonds would be highly beneficial, as alkyl bromides are inherently more bench-stable and more widely available commercially compared to their alkyl iodide counterparts.

Herein, we report a dual catalytic approach for the generation of carbon radicals from α-bromodifluoroesters and amides under visible light irradiation. Leveraging our prior experience in developing halogen-bonding photocatalyzed reactions,[12a] our strategy involves *in-situ* bromide displacement using a catalytic Finkelstein-type reaction with an iodide salt to generate a stronger C–I halogen-bond donor, facilitating formation of the key visible-light absorbing CTC with our halogen-bond acceptor catalyst, 2,5-di-*tert*-butylhydroquinone (DTHQ, Scheme 1C). Our approach has enabled the radical coupling of a series of α-bromodifluoroesters and amides with a variety of electron-rich (hetero)aromatics. Insights into the underlying mechanism of the reaction are also presented.

We chose to begin our investigation of the dual catalytic approach for carbon radical generation from C–Br bonds with the *gem*-difluoroalkylation of 1,3,5-trimethoxybenzene (**1**) using ethyl bromodifluoroacetate (**2**) photocatalyzed by DTHQ under 427 nm irradiation as the model system (Table 1, see SI for full optimization). In a preliminary set of experiments, it was identified that tetra-*N*-butylammonium iodide (Bu_4NI) was the optimal iodide salt (entries 1 and 2), and DMSO was the best solvent for the reaction (entries 3-7). The loading of Bu_4NI could be reduced to 20 mol% (entries 8 and 9) and the equivalents of **2** could be decreased to 2.5 without negatively impacting the yield (entry 10). The absence of Bu_4NI resulted in a significant decrease in the yield of **3** (entry 11), consistent with our prior results which indicated that fluoroalkyl bromides do not react efficiently with our DTHQ halogen-bonding photocatalyst.[12a] A small amount of conversion was observed in the absence of the DTHQ (entry 12), likely owing to background reactivity from an observed CTC between I^- and **2** (see SI for further details).[15] Further control experiments also indicated that the base, degassed conditions, and LED irradiation were all necessary for optimal reactivity (entries 13-15). Finally, addition of TEMPO to the reaction mixture resulted in complete suppression of the formation of **3**, and the TEMPO–CF_2CO_2Et adduct was observed in 39% yield, providing support for a radical mechanism (see SI).

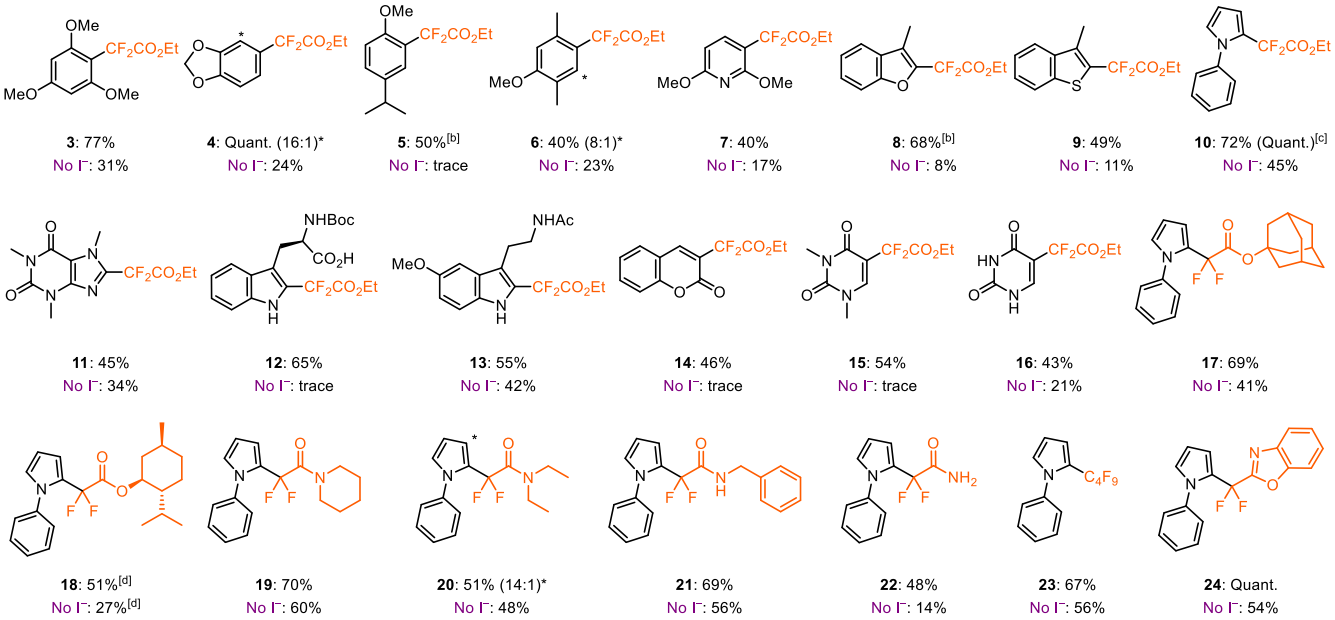
Table 1. Optimization of reaction conditions.



entry	I^- source (mol %)	equiv **2**	solvent	yield of **3**[a]
1	NaI (100)	3	11:1 Acetone:H_2O	24%
2	Bu_4NI (100)	3	11:1 Acetone:H_2O	48%
3	Bu_4NI (100)	3	Acetone	91%
4	Bu_4NI (100)	3	MeCN	18%
5	Bu_4NI (100)	3	THF	65%
6	Bu_4NI (100)	3	DMF	73%
7	Bu_4NI (100)	3	DMSO	Quant.
8	Bu_4NI (40)	3	DMSO	90%
9	Bu_4NI (20)	3	DMSO	79%
10	Bu_4NI (20)	2.5	DMSO	87%
11	None	2.5	DMSO	31%
12	Bu_4NI (20)	2.5	DMSO	11%[b]
13	Bu_4NI (20)	2.5	DMSO	26%[c]
14	Bu_4NI (20)	2.5	DMSO	22%[d]
15	Bu_4NI (20)	2.5	DMSO	Trace[e]

[a] Yields determined by ^{19}F NMR using C_6F_6 as an external standard. [b] No DTHQ. [c] No $NaHCO_3$. [d] Under air. [e] No light.

Scheme 2. Reaction scope.[a]

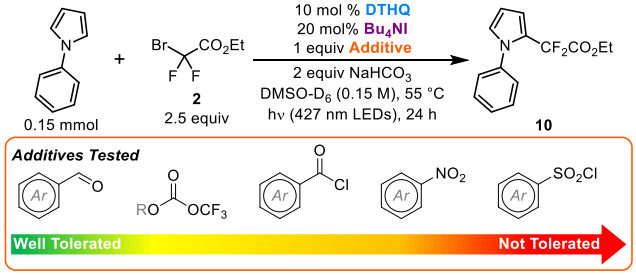


[a] Standard conditions: (Hetero)arene (0.5 mmol), R–Br (2.5 equiv), DTHQ (10 mol%), Bu_4NI (20 mol%) and $NaHCO_3$ (2 equiv) in DMSO (0.15 M) were irradiated under argon with two Kessil PR-160L 427 nm LEDs for 24 h at 55 °C. Yields are reported as isolated yields of the purified products. The control reactions in the absence of Bu_4NI (No I^-) were performed at 0.15 mmol scale, and the yields were determined by ^{19}F NMR using C_6F_6 as an external standard. [b] 40 mol% Bu_4NI was used. [c] Reaction performed at 1 mmol scale. [d] (Hetero)arene (2.5 equiv), R–Br (0.5 mmol).

With the optimized conditions identified, we examined the scope of the dual-catalyzed *gem*-difluoroalkylation of electron-rich (hetero)arenes (Scheme 2). Using **2** as the radical precursor, several electron rich aromatics were *gem*-difluoroalkylated in moderate to good yields (**3**-**6**). Electron-rich heteroarenes, such as 2,6-dimethoxypyridine (**7**), benzofurans (**8**), benzothiaphenes (**9**), and pyrroles (**10**) were also well tolerated. Notably, the reaction with *N*-phenylpyrrole (**10**) could be performed at 1 mmol scale with no loss in reactivity (see SI). Medicinally relevant heteroarenes such caffeine (**11**), Boc-Trp-OH (**12**), melatonin (**13**), coumarin (**14**), and uracil (**15**, **16**) were all compatible substrates for our *gem*-difluoroalkylation reaction. Next, the scope of α-bromodifluoroesters and amides was evaluated using *N*-phenylpyrrole as the coupling partner. α-Bromodifluoroesters derived from adamantanol and L-menthol provided *gem*-difluoroalkylated products **17** and **18**, respectively, in good yields. A series of α-bromodifluoroamides also reacted smoothly under our reaction conditions (**19**-**22**). Aryl difluoroamides are often found in biologically active compounds, such as FKBP12 inhibitors,[16] highlighting potential utility of this method to provide facile access to these scaffolds. Finally, perfluorobutyl bromide (**23**) and a α-bromodifluorobenzoxazole derivative (**24**) were also competent radical precursors using this approach. In every case, removing the Bu_4NI resulted in decreased yields for the *gem*-difluoroalkylated products (see Scheme 2).

As our approach for radical generation from these α-halodifluoroesters and amides proceeds through direct activation of the C–X bond through a halogen-bonding interaction,[12a] we hypothesized that our method may tolerate sensitive functional groups that would otherwise not be amenable to a highly reducing environment. To this end, we performed a small robustness screen by adding substrates with functional groups prone to single-electron reduction (see SI for details).[17] Our observations using the *gem*-difluoroalkylation of *N*-phenylpyrrole as the model reaction are summarized in Scheme 3. In general, aldehydes, trifluoroacetic anhydrides, and acid chlorides were all well tolerated under our reaction conditions, providing either a negligible or a modest impact to the overall yield of **10**. Of note, trifluoroacetic anhydride, the additive tested with the lowest reduction potential ($E_{p/2}$ = −0.20 V vs. SCE),[18] was completely recovered after the reaction, indicating no competitive reduction of the additive had occurred. In all cases, greater than 70% of the additive was recovered after the reaction. These results highlight the benefit of our halogen-bonding approach, providing support for the direct activation and reduction of C–X bonds even in the presence of other easily reducible functional groups. Finally, nitro groups and sulfonyl chlorides were found to be incompatible under our reaction conditions, significantly impacting the yield of **10**.

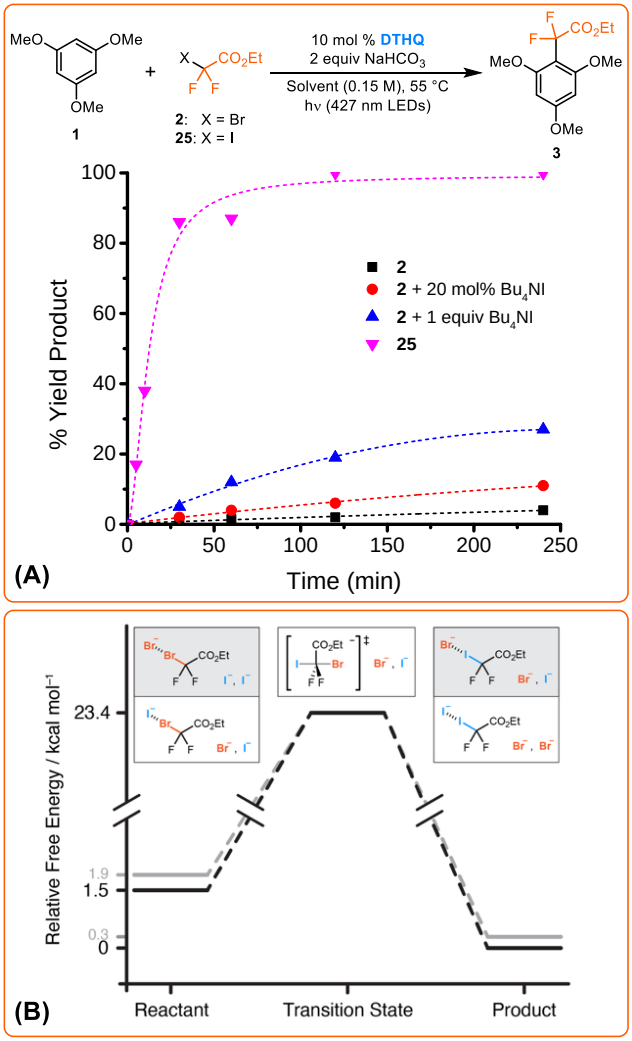
Scheme 3. Sensitive functional group screen.



Next, we performed a series of mechanistic studies to understand the role of Bu_4NI in our reaction. Using our initial model system, we sought to determine the effect of Bu_4NI

on the initial rate of the reaction (Scheme 4A). As anticipated, the rate of the reaction is significantly enhanced when starting with ethyl iododifluoroacetate (**25**) versus **2**, as **25** is expected to be a significantly stronger halogen-bond donor compared to **2**.[14] Furthermore, while the halogen-bonding CTC between DTHQ and **25** absorbs in the visible region (> 400 nm), the visible absorption CTC between DTHQ and **2** is negligible (see SI), highlighting that formation of **25** is likely required for reactivity under 427 nm LED irradiation. In this vein, the initial rate was observed to increase almost proportionally for the reaction with **2** upon adding increasing concentrations of Bu_4NI (see Scheme 4). These data support the involvement of Bu_4NI in the rate-determining step of the reaction.

Scheme 4. (A) Effect of Bu_4NI on the initial reaction rate. (B) Free energy diagram for the proposed Finkelstein displacement step.

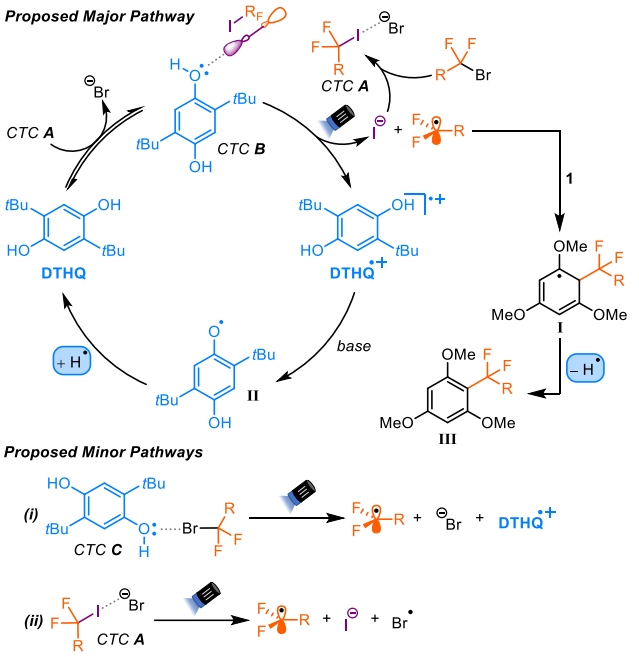


To provide support for our hypothesis that our reaction is proceeding via the *in-situ* formation of *gem*-difluoroalkyl iodides, we performed a series of computational studies. Optimization and frequency density functional theory calculations of all possible combinations of reactants, products, and transition state halogen-bonded complex systems were performed using Gaussian16.[19] The calculations were performed using the B3LYP functional with dispersion corrections and the Weigand and Ahlrichs basis set projected to the continuous basis set limit.[20] Comparisons of free energy estimations (Scheme 4B) show that the *gem*-difluoroalkyl iodide halogen-bonded to either a free iodide or bromide is thermodynamically preferable relative to *gem*-difluoroalkyl bromide by 1.5 and 1.6 kcal/mol, respectively, in DMSO polarized continuum implicit solvent. The activation energy for the Finkelstein reaction between the *gem*-difluoroalkyl bromide with free I^- is 23.4 kcal/mol. This is an increase over the gas phase activation energy of 18.1 kcal/mol. This approximately 5 kcal/mol difference is attributed to the ion desolvation penalty in formation of the activated complex. The thermodynamic favorability of the *gem*-difluoroalkyl iodide complex and the calculate activation energy, along with the experimentally observed dependence of the rate of reactivity on the concentration of I^-, supports the involvement of Finkelstein displacement of bromide in the presence of free iodide in solution.

The proposed mechanism for this transformation is outlined in Scheme 5. Initially, the α-bromodifluoroester or amide undergoes *in-situ* bromide displacement by I^-, generating CTC ***A***. CTC ***A*** can be intercepted by DTHQ to generate the photoactive CTC ***B***, which upon excitation produces the difluoroalkyl radical, $DTHQ^{\bullet+}$, and regenerates I^-. The difluoroalkyl radical subsequently adds to the electron-rich (hetero)arene to give intermediate **I**, which undergoes a HAT reaction with the DTHQ phenoxy radical (**II**) to yield the *gem*-difluoroalkylated (hetero)arene (**III**) and DTHQ, completing the catalyst turnover step. Given our mechanistic data, we have also identified two minor pathways which lead to product formation. The first involves the inefficient formation of the weak halogen-bonding complex between DTHQ and the α-bromodifluoroester or amide (CTC ***C***), which upon excitation also leads to product formation (see Table 1, entry 11). A second potential minor pathway involves the direct excitation of CTC ***A***, resulting in intra-complex single-electron transfer to eventually furnish difluoroalkyl radicals. This is supported by the observed inefficient product formation in the absence of the DTHQ catalyst (see Table 1, entry 12).

In summary, we have developed a dual catalytic approach for the generation of carbon radicals from α-bromodifluoroesters and amides under visible light irradiation. The reaction is proposed to proceed via an *in-situ* bromide displacement mediated by catalytic I^-, generating a *gem*-difluoroalkyl iodide that can be engaged by our DTHQ halogen-bonding photocatalyst. Given the greater abundance and increased stability of alkyl bromides compared to their iodide counterparts, we anticipate that this strategy can serve as a general solution for expanding halogen-bonding-mediated photochemical radical generation to less reactive alkyl bromide substrates, greatly increasing the scope of these transformations.

Scheme 5. Proposed mechanism for the dual-catalyzed radical *gem*-difluoroalkylation reactions.



EXPERIMENTAL SECTION

General. All reactions were conducted in oven-dried glassware under an atmosphere of argon, unless otherwise stated. All solvents and reagents were purchased from commercial suppliers (Fisher Scientific, TCI America, Sigma Aldrich, Oakwood Chemicals, Ambeed, Combi-Blocks Inc.) and were used as received unless otherwise noted. All photochemistry experiments were performed using two Kessil PR-160L 427nm LEDs (40 W output at 100% intensity) placed 2.5 cm from the reaction vessels equipped with an overhead fan to maintain the temperature at approximately 55 °C. Thin-layer chromatography (TLC) was conducted with silica gel 60 F254 pre-coated plates (0.25 μm) and visualized by exposure to UV-light (254 nm) or potassium permanganate ($KMnO_4$) staining. Flash column chromatography was performed using a Biotage Isolera Four equipped with Sorbtech Purity flash column cartridges (60 Å porosity, 40-75 μm). ^{1}H NMR spectra were recorded at 400 MHz and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 101 or 201 MHz. Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR spectra were recorded at 376 MHz. Data for ^{19}F NMR spectra are reported as follows: chemical shift, multiplicity, coupling constant (Hz), and integration. IR spectra were recorded on a Shimadzu IRAffinity-1S FT-IR spectrophotometer equipped with a QATR 10 single reflectance ATR accessory and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained with a quadrupole-Orbitrap hybrid mass spectrometer at Oklahoma State University. Absorption spectra were recorded on a Shimadzu UV-2600 UV-vis spectrophotometer.

Synthesis of α-Bromodifluoroesters. To a stirred solution of 2-bromo-2,2-difluoroacetic acid (1.75 g, 10 mmol, 1 equiv) and oxalyl chloride (1.7 mL, 20 mmol, 2 equiv) in 20 mL of dry CH_2Cl_2 was added 8 drops of DMF at room temperature under an argon atmosphere. After 2 hours, the reaction mixture was cooled to 0 °C, and a solution of the corresponding alcohol (10.5 mmol, 1.05 equiv) and NEt_3 (1.53 mL, 11 mmol, 1.1 equiv) in 20 mL of dry CH_2Cl_2 was added dropwise over 20 minutes. The reaction mixture was allowed to warm to room temperature and was stirred for 24 hours or until TLC analysis indicated the reaction had reached completion. The reaction mixture was then transferred to a separatory funnel and washed with 25 mL of H_2O. The aqueous phase was then extracted with 25 mL or CH_2Cl_2, and the combined organic phases were washed with 25 mL of sat. $NaHCO_{3(aq)}$, dried with $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography to afford the corresponding α-bromodifluoroesters. Alternatively, the same procedure can be employed starting directly from bromodifluoroacetyl chloride (940 μL, 10 mmol). All α-bromodifluoroesters synthesized were known compounds, and the spectra data agreed with those previously reported.[21]

Synthesis of α-Bromodifluoroamides. A neat mixture of bromodifluoroacetate (1.28 mL, 10 mmol, 1 equiv) and the corresponding amine (10 mmol, 1 equiv) was stirred at room temperature for 24 hours or until TLC analysis indicated the reaction had reached completion. The neat reaction mixture was directly purified by flash column chromatography to afford the corresponding α-bromodifluoroamides. All α-bromodifluoroamides synthesized were known compounds, and the spectra data agreed with those previously reported.[22]

General Procedure for Radical Fluoroalkylation Reactions. An oven-dried two-dram vial equipped with a magnetic stir bar was charged with a (hetero)arene (0.5 mmol, 1 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84.0 mg, 1.0 mmol, 2 equiv). DMSO was added (3.3 mL, 0.15 M), and the reaction mixture was degassed by sparging with argon for 5-6 minutes. To this, fluoroalkyl bromide (1.25 mmol, 2.5 equiv) was added under argon. The reaction mixture was then sonicated and irradiated with two Kessil PR-160L 427nm LED lamps for 24 h at approximately 55 °C. The reaction mixture was transferred into a separatory funnel and diluted with 20 mL of DCM and washed with 20 mL of 10 mM $Na_2S_2O_{3(aq)}$. The aqueous phase was extracted with 20 mL of DCM. The combined organic phases were dried with $MgSO_4$ and concentrated. The crude reaction mixture was purified by flash column chromatography using a Biotage Isolera Four. Yields are reported as isolated yields of the purified products.

Characterization Data.

Ethyl 2,2-difluoro-2-(2,4,6-trimethoxyphenyl)acetate (3)[23]: Prepared according to the general procedure from **1** (84 mg, 0.5 mmol, 1 equiv), **2** (162 μL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 60% EtOAc in Hex) to give the title compound as a white solid in 77% yield (113 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H).^{13}C NMR

(201 MHz, $CDCl_3$): δ 164.8 (t, *J* = 33.3 Hz), 163.3, 160.2 – 160.1 (m), 113.4 (t, *J* = 247.7 Hz), 102.8 (t, *J* = 24.2 Hz), 91.4, 62.3, 56.2, 55.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -96.23 (s, 2F). R_f: 0.45 (2:1 Hex:EtOAc).

Ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoroacetate (4)[24]: Prepared according to the general procedure from 1,2-methylene dioxybenzene (58 µL, 0.5 mmol, 1 equiv), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 10% EtOAc in Hex) to give the regioisomeric mixture of 16:1 of the title compound as a colorless oil in quantitative yield (124 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 – 7.09 (m, 1H), 7.07 – 7.04 (m, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.02 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 164.2 (t, *J* = 35.9 Hz), 149.8, 147.9, 126.5 (t, *J* = 26.0 Hz), 121.8, 119.9 (t, *J* = 6.8 Hz), 114.5, 111.9, 108.3, 106.1 (t, *J* = 6.3 Hz), 101.7, 63.1, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -101.83 (s, 2F). R_f : 0.51 (4:1 Hex:EtOAc).

Ethyl 2-(5-(*tert*-butyl)-2-methoxyphenyl)-2,2 difluoroacetate (5): Prepared according to the general procedure from 1-(*tert*-butyl)-4-methoxybenzene (88 µL, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (74 mg, 0.20 mmol, 40 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 20% EtOAc in Hex) to give the title compound as a colorless oil in 50% yield (71 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.46 (d, *J* = 8.8, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.35 – 1.28 (m, 12H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 164.3 (t, *J* = 33.8 Hz), 154.4 (t, *J* = 5.0 Hz), 143.5, 129.1, 123.1 (t, *J* = 7.2 Hz), 121.1 (t, *J* = 23.4 Hz), 112.5 (t, *J* = 248.1 Hz), 111.0, 62.6, 55.7, 34.3, 31.4, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -102.02 (s, 2F). R_f: 0.57 4:1 (Hex:EtOAc) HRMS (ESI) *m/z*: $[M+H]^+$ calcd. 287.1459, observed 287.1456. IR (neat, cm^{-1}): 2964, 2907, 2872, 1774, 1616, 1505, 1464, 1444, 1365, 1303, 1273, 1256, 1229, 1181, 1158, 1100, 1072, 1032, 901, 819, 766, 693.

Ethyl 2,2-difluoro-2-(4-methoxy-2,5-dimethylphenyl)acetate (6): Prepared according to the general procedure from 2-methoxy-1,4-dimethylbenzene (71 µL, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 10% EtOAc in Hex) to give a 8:1 regioisomeric mixture of the title compound as a colorless oil in 40% yield (51 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 1H), 6.64 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.39 (s, 2H), 2.20 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 164.6 (t, *J* = 36.0 Hz), 159.1, 158.0, 136.4, 135.5, 128.4 (t, *J* = 8.5 Hz), 124.0, 122.5 (t, *J* = 23.9 Hz), 118.3 (t, *J* = 9.1 Hz), 115.8 – 113.4 (m), 113.1, 62.9, 55.3, 19.7, 15.7, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -99.71 (s, 2F). R_f: 0.66 (4:1 Hex:EtOAc) HRMS (ESI) *m/z*: $[M+H]^+$ calcd. 259.1146, observed 259.1139. IR (neat, cm^{-1}): 2939, 2855, 1761, 1617, 1579, 1512, 1465, 1322, 1285, 1262, 1134, 1084, 1040, 948, 894, 850, 761.

Ethyl 2-(2,6-dimethoxypyridin-3-yl)-2,2-difluoroacetate (7)[11a]: Prepared according to the general procedure from 2,6-dimethyloxypyridine (66 µL, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 20 % EtOAc in Hex) to give the title compound as colorless oil in 40% yield (52 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 8.2 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 165.2, 164.2 (t, *J* = 34.5 Hz), 160.1 (t, *J* = 5.2 Hz), 138.7 (t, *J* = 6.2 Hz), 112.6 (t, *J* = 247.9 Hz), 107.6 (t, *J* = 26.3 Hz), 101.7, 63.2, 54.2, 54.0, 14.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ -101.68 (s, 2F). R_f: 0.6 (4:1 Hex:EtOAc).

Ethyl 2,2-difluoro-2-(3-methylbenzofuran-2-yl)acetate (8)[25]: Prepared according to the general procedure from 3-methylbenzofuran (64 µL, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (74 mg, 0.20 mmol, 40 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 10% EtOAc in Hex) to give the title compound as a colorless oil in 68% yield (85 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 162.5 (t, *J* = 34.1 Hz), 154.2, 1401.0 (t, *J* = 32.3 Hz), 128.9, 126.3, 123.1, 120.4, 118.1, 111.6, 110.4 (t, *J* = 249.6 Hz), 63.6, 13.9, 7.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ -103.42 (s, 2F). R_f: 0.65 (4:1 Hex:EtOAc).

Ethyl 2,2-difluoro-2-(3-methylbenzo[*b*]thiophen-2-yl)acetate (9)[26]: Prepared according to the general procedure from 3-methyl-benzothiophene (66 µL, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 10% EtOAc in Hex) to give the title compound as colorless oil in 49% yield (62 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.81 (m, 1H), 7.80 – 7.73 (m, 1H), 7.47 – 7.40 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.53 (t, *J* = 2.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 163.2 (t, *J* = 35.6 Hz), 140.1, 138.9, 128.2 (t, *J* = 28.4 Hz), 126.0, 124.6, 122.7, 122.5, 112.6 (t, *J* = 252.2 Hz), 63.5, 13.9, 12.1. ^{19}F NMR (376 MHz, CDCl3): δ -94.38 (s, 2F). R_f : 0.7 (4:1 Hex:EtOAc).

Ethyl 2,2-difluoro-2-(1-phenyl-1*H*-pyrrol-2-yl)acetate (10)[27]: Prepared according to the general procedure from 1-phenylpyrrole (72 mg, 0.5 mmol, 1 equiv), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 8% EtOAc in Hex) to give the title compound as a colorless oil in 72% yield (95 mg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.41 (m,

3H), 7.39-7.37 (m, 2H), 6.88-6.87 (m, 1H), 6.65-6.64 (m, 1H), 6.29 (t, *J* = 3.25 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 163.1 (t, *J* = 34.1 Hz), 139.3, 128.8, 128.4, 127.3, 126.9, 124.3 (t, *J* = 29.9 Hz), 113.0 (t, *J* = 5.0 Hz), 110.7 (t, *J* = 246.0 Hz), 108.4, 63.1, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -92.22 (s, 2F). R_f: 0.55 (4:1 Hex:EtOAc).

Ethyl 2,2-difluoro-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)acetate (11)[24]: Prepared according to the general procedure from caffeine (97 mg, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 35% EtOAc in Hex) to give the title compound as white solid in 72% yield (71 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 (q, *J* = 7.2 Hz, 2H), 4.18 (t, *J* = 1.5 Hz, 3H), 3.54 (s, 3H), 3.41 (s, 3H), 1.41 (t, *J*= 7.1 Hz, 1H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 161.0 (t, *J* = 31.1 Hz), 155.5, 151.4, 146.7, 141.4 (t, *J* = 30.4 Hz), 109.6, 109.2 (t, *J* = 251.1 Hz), 64.1, 33.4 – 33.3 (m), 29.8, 28.1, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -103.27 (s, 2F). R_f: 0.68 (1:1 Hex:EtOAc).

(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1*H*-indol-3-yl)propanoic acid (12): Prepared according to the general procedure from Boc-Trp-OH (152 mg, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 10% EtOAc in Hex) to give the title compound as white solid in 65% yield (138 mg). ^{1}H NMR (800 MHz, DMSO-D_6): δ 11.45 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.60 (bs, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.21 – 4.17 (m, 1H), 3.47 (q, *J* = 7.0 Hz, 1H), 3.31 (dd, *J* = 14.6, 6.1 Hz, 1H), 3.14 – 3.06 (m, 1H), 1.30 – 1.13 (m, 12H). ^{13}C NMR (201 MHz, DMSO-D_6): δ 173.6, 163.1 (t, *J* = 35.6 Hz), 155.5, 136.5, 128.3, 124.7 (t, *J* = 29.3 Hz), 123.8, 120.5, 119.9, 113.2, 112.5, 112.2, 78.5, 64.1, 56.5, 55.4, 28.5, 26.6, 14.1. ^{19}F NMR (753 MHz, DMSO-D_6): δ -97.20 – -99.26 (m, 2F). R_f: 0.9 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: calcd. 427.1680, observed 427.1680. IR (neat, cm^{-1}): 3355, 2982, 2930, 1750, 1695, 1506, 1456, 1394, 1368, 1301, 1244, 1155, 1094, 1059, 1022, 909, 853, 741.

Ethyl 2-(3-(2-acetamidoethyl)-5-methoxy-1*H*-indol-2-yl)-2,2-difluoroacetate (13)[28]**:** Prepared according to the general procedure from melatonin (116 mg, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 20% EtOAc in Hex) to give the title compound as colorless oil in 55% yield (89 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (bs, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.69 (bs, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.55 (q, *J* = 6.5 Hz, 2H), 3.08 (t, *J* = 6.7 Hz, 2H), 1.94 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 170.3, 163.5 (t, *J* = 35.9 Hz), 154.8, 130.8, 128.4, 124.5, 115.8, 114.9 – 114.8 (m), 112.6, 111.3, 100.6, 63.8, 55.9, 40.2, 29.7, 23.9, 23.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -100.42. R_f: 0.4 (4:1 Hex:EtOAc).

Ethyl 2,2-difluoro-2-(2-oxo-2*H*-chromen-3-yl)acetate (14)[29]**:** Prepared according to the general procedure from coumarin (73 mg, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 15 % EtOAc in Hex) to give the title compound as colorless oil in 46% yield (62 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.68 – 7.60 (m, 2H), 7.42 – 7.43 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 162.3 (t, *J* = 32.7 Hz), 158.0 (t, *J* = 4.4 Hz), 154.2, 142.0 (t, *J* = 6.8 Hz), 133.7, 129.3, 125.2, 121.1 (t, *J* = 25.6 Hz), 117.5, 117.0, 110.5 (t, *J* = 250.9 Hz), 63.6, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.14. R_f = 0.39 (7:1 Hex:EtOAc).

Ethyl 2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (15)[24]: Prepared according to the general procedure from 1,3-dimethyluracil (70 mg, 0.5 mmol, 1 equiv), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 50% EtOAc in Hex) to give the title compound as a colorless oil in 54% yield (70 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 3H), 3.31 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 162.7 (t, *J* = 33.0 Hz), 160.3 (t, *J* = 4.1 Hz), 151.1, 142.6 (t, *J* = 8.1 Hz), 111.1 (t, *J* = 249.7 Hz), 107.1 (t, *J* = 25.2 Hz), 63.4, 37.7, 27.8, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -103.67 (s, 2F). R_f: 0.39 (2:1 Hex:EtOAc).

Ethyl 2-(2, 4-dioxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl)-2, 2-difluoroacetate (16)[29]: Prepared according to the general procedure from uracil (56 mg, 0.5 mmol), **2** (162 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 60% EtOAc in Hex) to give the title compound as white solid in 43% yield (50 mg). ^{1}H NMR (400 MHz, Acetone-D_6) δ 10.36 (bs, 2H), 7.98 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (201 MHz, Acetone-D_6) δ 162.3 (t, *J* = 33.6 Hz), 161.1 (t, *J* = 4.4 Hz), 150.1, 141.6 (t, *J* = 8.0 Hz), 111.6 (t, *J* = 246.5 Hz), 106.8 (t, *J* = 25.0 Hz), 62.7, 13.2. ^{19}F NMR (376 MHz, Acetone-D_6) δ -104.67(s, 2F). R_f: 0.23 (1:1 Hex: EtOAc)

Adamantan-1-yl 2,2-difluoro-2-(1-phenyl-1H-pyrrol-2-yl)acetate (17): Prepared according to the general procedure from 1-phenylpyrrole (72 mg, 0.5 mmol), adamantan-1-yl 2-bromo-2,2-difluoroacetate[21] (387 mg, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 7% EtOAc in Hex) to

give the title compound as a colorless oil in 72% yield (94 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.30 (m, 5H), 6.86-6.85 (m, 1H), 6.63- 6.61 (m, 1H), 6.26 (t, *J* = 3.3 Hz, 1H), 2.25 – 2.14 (m, 3H), 2.04 (d, *J* = 3.0 Hz, 6H), 1.64 (t, *J* = 3.0 Hz, 6H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 161.5 (t, *J* = 33.0 Hz), 139.7, 128.8, 128.1, 127.1, 126.8, 124.5 (t, *J* = 29.3 Hz), 113.1 (t, *J* = 5.4 Hz), 110.5 (t, *J* = 246.5 Hz), 108.3, 84.7, 40.7, 35.8, 30.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -91.92 (s, 2F), -96.78. R_f: 0.81 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: calcd. 372.1775, observed 372.1776. IR (neat, cm^{-1}): 2908, 2853, 1755, 1595, 1542, 1497, 1456, 1425, 1355, 1319, 1281, 1256, 1197, 1112, 1095, 1069, 1034, 962, 934, 875, 837, 804, 769, 730, 696, 602, 550, 509.

(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2,2-difluoro-2-(1-phenyl-1*H*-pyrrol-2-yl)acetate (18): Prepared according to the general procedure from 1-phenylpyrrole (179 mg, 1.25 mmol, 2.5 equiv), (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2,2-difluoroacetate[21] (111 µL, 0.5 mmol), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 4% EtOAc in Hex) to give the title compound as colorless oil in 51% yield (97 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.31 (m, 5H), 6.88 – 6.86 (m, 1H), 6.60 – 6.57 (m, 1H), 6.27 (t, *J* = 3.3 Hz, 1H), 4.73 (td, *J* = 10.9, 4.4 Hz, 1H), 1.89 – 1.84 (m, 1H), 1.78 – 1.74 (m, 1H), 1.72 – 1.61 (m, 2H), 1.48 – 1.38 (m, 2H), 1.11 – 0.91 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 – 0.81 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 162.8 (t, *J* = 33.7 Hz), 139.6 129.7, 128.8, 128.2, 127.4, 126.9, 124.1 (t, *J* = 29.0 Hz), 120.9, 120.5, 113.2 (t, *J* = 5.2 Hz), 110.9 (t, *J* = 246.5), 108.4, 77.8, 46.6, 40.0, 34.0, 31.3, 25.9, 23.2, 21.9, 20.6, 16.1.^{19}F NMR (376 MHz, $CDCl_3$) δ -91.74 (s, 2F). R_f: 0.81 (4:1 Hex:EtOAc). HRMS (ESI) *m/z*: [M+H]$^+$ calc. 376.2088, observed 376.2083. IR (neat, cm^{-1}): 2955, 2927, 2872, 1753, 1598, 1499, 1456, 1295, 1258, 1199, 1112, 1091, 1069, 1035, 1022, 950, 910, 765, 727, 693.

2,2-Difluoro-2-(1-phenyl-1*H*-pyrrol-2-yl)-1-(piperidin-1-yl)ethan-1-one (19): Prepared according to the general procedure from 1-phenylpyrrole (72 mg, 0.5 mmol), 2-bromo-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one[22a] (195 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 20% EtOAc in Hex) to give the title compound as white solid in 70% yield (107 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.37 (m, 5H), 6.88 – 6.85 (m, 1H), 6.56 – 6.52 (m, 1H), 6.25 (t, *J* = 3.30 Hz, 1H), 3.49 (t, *J* = 5.4 Hz, 2H), 3.33 (t, *J* = 5.6 Hz, 2H), 1.69 – 1.45 (m, 4H), 1.46 – 1.36 (m, 2H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 160.9 (t, *J* = 28.8 Hz), 139.5, 128.8, 128.3, 127.2, 126.8, 125.1 (t, *J* = 28.1 Hz), 112.9 (t, *J* = 5.4 Hz), 112.2 (t, *J* = 243.1 Hz), 108.4, 47.4 – 47.4 (m), 44.3, 25.9, 25.4, 24.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ -85.56 (s, 2F). R_f: 0.40 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: [M+H]$^+$ calcd. 305.1465, observed 305.1461. IR (neat, cm^{-1}): 2938, 2858, 1659, 1597, 1542, 1498, 1459, 1450, 1442, 1419, 1350, 1322, 1308, 1262, 1202, 1149, 1105, 1093, 1059, 1025, 1002, 938, 856, 765, 697, 607.

***N,N*-diethyl-2,2-difluoro-2-(1-phenyl-1*H*-pyrrol-2-yl)acetamide (20)**: Prepared according to the general procedure from 1-phenylpyrrole (72 mg, 0.5 mmol), 2-bromo-*N,N*-diethyl-2,2-acetamide[22b] (184 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 20% EtOAc in Hex) to give a 14:1 regioisomeric mixture of the title compound as a colorless oil in 51% yield (75 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 5H), 6.87-6.85 (m, 1H), 6.51-6.49 (m, 1H), 6.25 (t, *J*= 3.30 Hz 1H), 3.37 – 3.21 (m, 1H), 1.09 (t, *J* = 7.1 Hz, 1H), 1.02 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 161.8 (t, *J* = 29.0 Hz), 139.5, 128.7, 128.2, 127.2, 126.9, 125.2 (t, *J* = 28.4 Hz), 112.7 (t, *J* = 5.4 Hz), 112.3 (t, *J* = 244.0 Hz), 108.4, 42.6 (t, *J* = 3.3 Hz), 41.4, 30.2, 29.3, 13.7, 12.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -86.57 (s, 2F). R_f: 0.40 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: calcd. 293.1465, observed 293.1461. IR (neat, cm^{-1}): 2975, 2933, 1668, 1598, 1541, 1499, 1464, 1425, 1382, 1321, 1283, 1257, 1203, 1170, 1103, 1087, 1059, 1037, 928, 850, 767, 732, 680.

***N*-benzyl-2,2-difluoro-2-(1-phenyl-1*H*-pyrrol-2-yl)acetamide (21)**: Prepared according to the general procedure from 1-phenyl pyrrole (72 mg, 0.5 mmol), *N*-benzyl-2,bromo-2,2-difluoroacetamide[22c] (330 mg, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 25% EtOAc in Hex) to give the title compound as white solid in 67% yield (124 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.34 (m, 5H), 7.36 – 7.28 (m, 3H), 7.24 – 7.15 (m, 2H), 6.86 – 6.84 (m, 1H), 6.69 – 6.67 (m, 1H), 6.35 (s, 1H), 6.27 (t, *J* = 3.25 Hz, 1H), 4.35 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 162.9 (t, *J* = 30.0 Hz), 139.5, 136.5, 128.82, 128.75, 127.9, 127.5, 127.2, 126.1, 124.2 (t, *J* = 29.3 Hz), 113.7 (t, *J* = 5.2 Hz), 112.4 (t, *J* = 247.4 Hz), 108.4, 43.7. ^{19}F NMR (376 MHz, $CDCl_3$): -92.50 (s, 2F). R_f : 0.37 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: [M+H]$^+$ calcd. 327.1309, observed 327.1306. IR (neat, cm^{-1}): 3224, 3090, 2933, 1706, 1683, 1564, 1538, 1497, 1456, 1424, 1351, 1303, 1263, 1226, 1200, 1127, 1062, 1045, 967, 926, 912, 811, 756, 696, 602, 543.

2,2-Difluoro-2-(1-phenyl-1*H*-pyrrol-2-yl)acetamide (22): Prepared according to the general procedure from 1-phenylpyrrole (72 mg, 0.5 mmol), 2,bromo-2,2-difluoroacetamide (217 mg, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 60% EtOAc in Hex) to give the title compound as a colorless oil in 48% yield (56 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 5H), 6.88 – 6.87 (m, 1H), 6.71 – 6.69 (m, 1H), 6.27 (t, *J* = 3.3 Hz, 1H), 6.08 – 5.92 (m, 2H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 165.3 (t, *J* = 30.8 Hz), 139.4, 128.8, 128.5, 127.7, 127.2, 123.9 (t, *J* = 28.9 Hz), 121.0, 113.7 (t, *J* = 5.3 Hz), 112.1 (t, *J* = 247.3 Hz), 108.4. ^{19}F NMR (376 MHz, $CDCl_3$)

δ -92.48 (s, 2F). R_f: 0.25 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: calcd. 237.0839, observed 237.0839. IR (neat, cm^{-1}): 3450, 3310, 3192, 1688, 1613, 1596, 1540, 1500, 1459, 1412, 1356, 1319, 1309, 1261, 1204, 1174, 1108, 1090, 1071.

2-(Perfluorobutyl)-1-phenyl-1*H*-pyrrole (23)[30]: Prepared according to the general procedure from 1-phenylpyrrole (72 mg, 0.5 mmol), perfluorobutyl bromide (194 µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 5% EtOAc in Hex) to give the title compound as a colorless oil in 67% yield (124 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.36 (m, 3H), 7.31 – 7.21 (m, 1H), 7.10 (t, *J* = 2.2 Hz, 2H), 6.36 (t, *J* = 2.2 Hz, 2H). ^{13}C NMR (201 MHz, $CDCl_3$): 140.9, 129.6, 125.6, 120.6, 119.4, 118.2 – 112.9 (m), 110.4, 110.1 – 106.6 (m). ^{19}F NMR (376 MHz, $CDCl_3$): δ -81.07 (t, *J* = 10.1 Hz, 3F), -101.12 (t, *J* = 13.5 Hz, 2F), -121.25 – -121.62 (m, 2F), -125.85 (m, 2F). R_f: 0.89 (4:1 Hex: EtOAc).

2-(Difluoro(1-phenyl-1*H*-pyrrol-2-yl)methyl)benzo[*d*]oxazole (24): Prepared according to the general procedure from 1-phenyl pyrrole (72 mg, 0.5 mmol), 2-(bromodifluoromethyl)-1,3-benzoxazole (253µL, 1.25 mmol, 2.5 equiv), DTHQ (11.5 mg, 0.05 mmol, 10 mol%), Bu_4NI (37 mg, 0.10 mmol, 20 mol%) and $NaHCO_3$ (84 mg, 1.0 mmol, 2 equiv) in 3.3 mL of dry DMSO. The reaction was irradiated with two Kessil 427 nm LEDs for 24 h at 55 °C. Purified by flash column chromatography (0 → 15% EtOAc in Hex) to give the title compound as white solid in quantitative yield (170 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.72 (m, 1H), 7.53 – 7.51 (m, 1H), 7.45 – 7.36 (m, 2H), 7.30 – 7.23 (m, 5H), 6.92 – 6.91 (m, 1H), 6.70 – 6.68 (m, 1H), 6.33 (t, *J* = 3.25 Hz, 1H). ^{13}C NMR (201 MHz, $CDCl_3$): δ 157.7 (t, *J* = 35.6 Hz), 150.4, 140.0, 139.1, 128.6, 128.3, 127.6, 127.0, 126.7, 125.1, 121.3, 113.3 (t, *J* = 4.6 Hz), 111.4 (t, *J* = 238.1 Hz), 111.2, 108.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ -85.32 (s, 2F). R_f: 0.40 (4:1 Hex: EtOAc). HRMS (ESI) *m/z*: calcd. 311.0999, observed 311.0996. IR (neat, cm^{-1}): 3106, 3068, 1618, 1595, 1541, 1499, 1450, 1427, 1362, 1347, 1320, 1297, 1260, 1240, 1204, 1174, 1101, 1056, 1029, 1017, 948, 906, 876, 774, 734, 698, 545.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, reaction optimization, control reactions, UV-vis studies, computational studies, and NMR spectra.

AUTHOR INFORMATION

Corresponding Author

*Email: spencer.p.pitre@okstate.edu

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

Any additional relevant notes should be placed here.

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