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Dual Catalytic Switchable Divergent Synthesis: An Asymmetric Visible-light Photocatalytic Approach to Fluorine-containing γ-Keto Acid Frameworks

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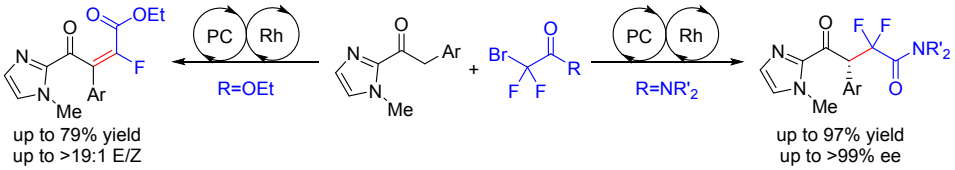


ABSTRACT

Herein, we describe a novel and efficient method for constructing a series of fluorine-containing γ-keto acid derivatives through combining visible-light photoredox catalysis and chiral Lewis acid catalysis. With this dual catalytic strategy, a variety of chiral γ-keto amides containing a *gem*-difluoroalkyl group and a series of fluorine-containing α,β-unsaturated-γ-keto esters were successfully constructed with high stereoselectivities, respectively. A series of experiments showed that the chemoselectivity of this process was highly dependent on the fluorine reagents besides the Lewis acid catalysts. This approach facilitates rapid access to γ-keto acid derivatives, an important class of precursors for pharmaceuticals, plasticizers, and various other additives.

KEYWORDS

visible-light photocatalysis, chiral Lewis acid catalysis, asymmetric difluoroalkylation, γ-keto acid derivatives

INTRODUCTION

Fluorine-containing organic substances have been widely used as pharmaceuticals,[1] agrochemicals,[2] materials[3] and tracers for positron emission tomography[4] due to their unique physical, chemical and biological properties[5]. The great demand of fluoro-organic compounds[1-4] continues to attract researchers' interests to develop new catalytic transformations for the incorporation of various fluorine bearing groups. Recently, a number of methodologies,[6] including the asymmetric ones,[7] have been established and successfully applied into building a variety of bioactive molecules[2,8]. Nevertheless, the methods for enantioselective incorporation of a difluoroalkyl group into organic molecules[9] and the stereoselective construction of fluorine-bearing olefin skeletons,[10] which also play important roles in medicinal and pesticide chemistry (Figure 1), still remain quite limited.

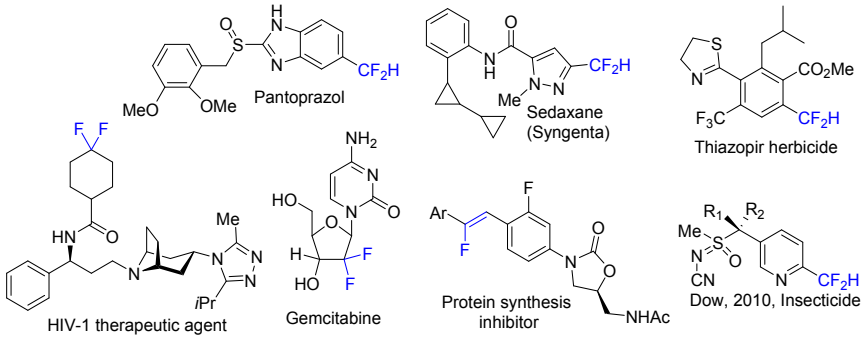
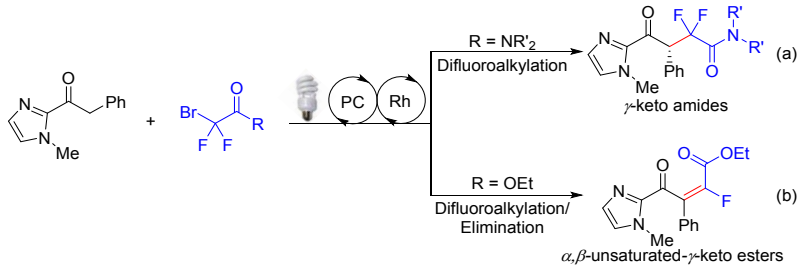


Figure 1.Some fluorine-containing bioactive molecules.

Over the past decade, visible-light-induced photoredox catalysis has become a powerful method to generate reactive open-shell species from abundant native functional groups under mild conditions.[11] When coupled with another catalytic cycle in a dual catalytic system, this catalytic protocol could provide a novel and efficient access to asymmetric transformations associated with highly reactive radical intermediates,[12] which would bring new opportunity for the catalytic asymmetric incorporation of fluorine-containing groups. In 2009, MacMillan and co-workers first elegantly established the mild catalytic asymmetric α-trifluoromethylation of aldehydes via combining visible-light photoredox catalysis and chiral enamine catalysis.[13a] Very recently, Xiao and co-workers reported the enantioselective di-/perfluoroalkylation of *β*-ketoesters enabled by cooperative photoredox/nickel catalysis.[13d] Different from this dual catalysis strategy, Melchiorre's group utilized visible-light-induced phase transfer catalysis to realize the enantioselective perfluoroalkylation of β-ketoesters,[13b] and Meggers' group realized the catalytic asymmetric perfluoroalkylation of ketones with a chiral iridium photoredox catalyst[13c]. Several key advances have recently been made in this area,[13-15] however, reports on the catalytic asymmetric difluoroalkylation reaction under mild visible-light irradiation conditions remain rare.[7]

Scheme 1.The stereoselective construction of fluorine-containing γ-keto acid derivatives by dual catalytic strategy.



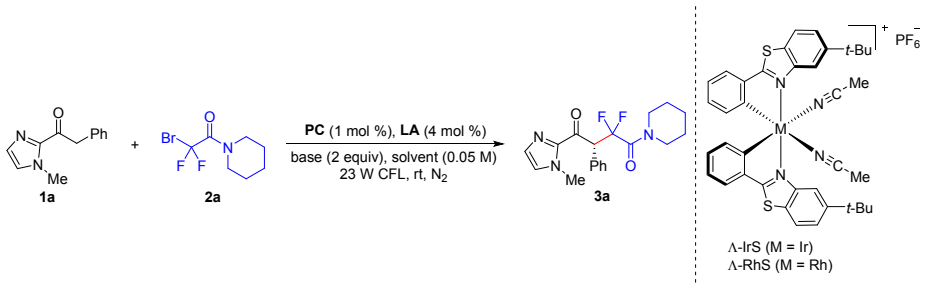
Our earlier work on the catalytic enantioselective α-fluorination via the chiral iridium complex catalysis prompted us to explore novel and efficient catalytic methods for the asymmetric difluoroalkylation reaction.[16] Based on our continuous interest in visible-light photoredox catalysis,[17] we successfully developed a visible-light photoredox catalytic enantioselective difluoroalkylation of ketones with commercially available bromodifluoroacetamides to construct a series of *γ*-keto amides bearing a *gem*-difluoromethylene group via coupling with chiral Lewis acid catalysis. (**Scheme 1a**)

This mild dual catalytic strategy provides a novel and straightforward method for the synthesis of fluorine-containing *gamma*-keto acid derivatives that are widely used as precursors for pharmaceuticals and plasticizers,[18] and building blocks or starting materials for a wide number of compounds. Furthermore, another kind of valuable fluorine-containing α,β-unsaturated-γ-keto ester was obtained under the similar dual catalytic conditions by only replacing bromodifluoroacetamide with ethyl bromodifluoroacetate as the fluorine resource (**Scheme 1b**). A series of experiments demonstrated that the chemoselectivity of this reaction was highly dependent on the reactivity of fluorinated reagent.

RESULTS AND DISCUSSION

Initially, we tested the feasibility of the reaction of 2-acyl imidazole **1a** and bromodifluoroacetamide **2a** in the presence of stoichiometric amounts of diisopropylethylamine (DIPEA) in acetone at room temperature under visible-light irradiation with a 23 W compact fluorescent lamp (CFL). Disappointingly, no desired difluoroalkylation product **3a** was observed when the chiral-at-metal catalyst Λ-IrS was employed as both the photoredox and Lewis acid catalyst (Table 1, entry 1). An extra photocatalyst added to the reaction mixture did not change the result， either (Table 1, entry 2). Fortunately, when the chiral Lewis acid catalyst Λ-IrS was replaced by a rhodium complex Λ-RhS, the expected product **3a** was obtained in 42% yield with excellent enantioselectivity (Table 1, entry 3), which can be mainly attributed to the increased ligand exchange kinetics of the rhodium complexes involved in the catalytic cycle.[19] Encouraged by the results, a series of photocatalysts were tested and $Ir(ppy)_2(dtbbpy)(PF_6)$ gave satisfactory yield and enantioselectivity (88% yield and 97% ee) (Table 1, entries 4-6). Further screening of bases and solvents showed that DIPEA was the optimal base while the inorganic bases did not catalyze this transformation, and CH_2Cl_2 was the optimal solvent for this reaction to give the product **3a** in 94% yield with 98% ee (Table 1, entries 7-13). Control experiments showed that photocatalyst, Λ-RhS, an organic amine base and visible-light were all essential to this reaction (Table 1, entries 14-17).

Table 1. Optimization of the reaction conditions[a]



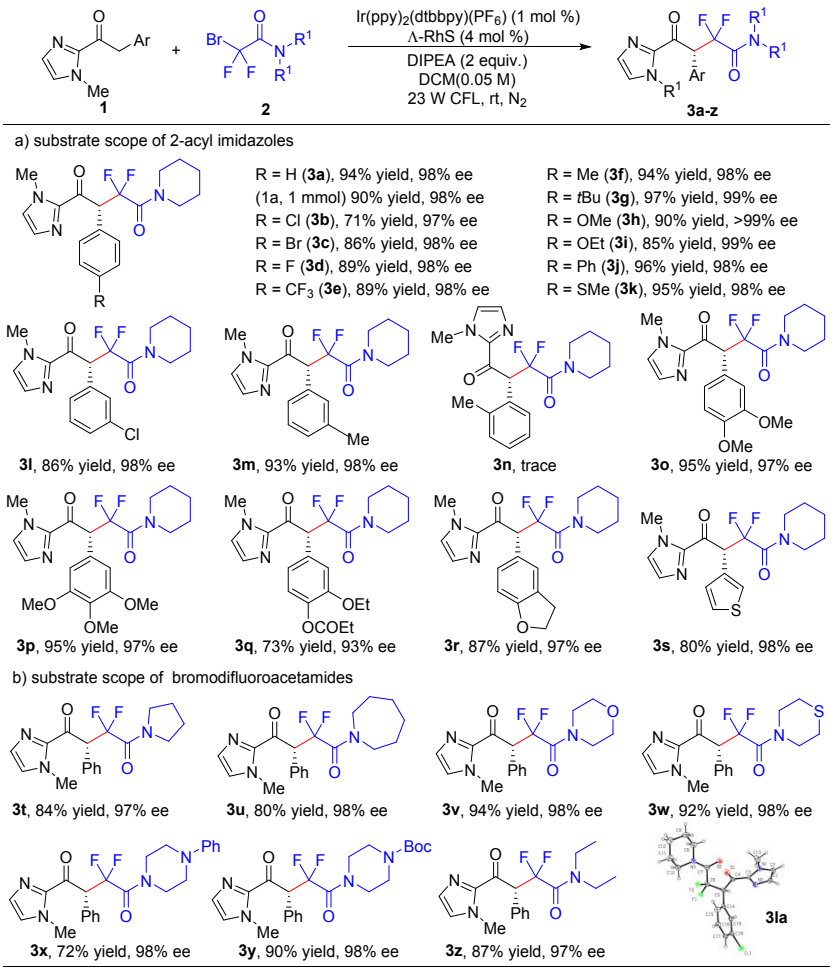
Entry	LA	PC	base	solvent	yield[b] (%)	ee[c] (%)
1	Λ-IrS		DIPEA	acetone	0	n.a.
2	Λ-IrS	$Ru(bpy)_3(PF_6)_2$	DIPEA	acetone	0	n.a.
3	Λ-RhS	$Ru(bpy)_3(PF_6)_2$	DIPEA	acetone	42	97
4	Λ-RhS	*fac*-$Ir(ppy)_3$	DIPEA	acetone	78	97

5	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	acetone	88	97
6	Λ-RhS	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	DIPEA	acetone	87	97
7	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	CH_2Cl_2	94	98
8	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	DCE	78	98
9	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	THF	36	97
10	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	DMF	42	96
11	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	Et_3N	CH_2Cl_2	92	98
12	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	K_2HPO_4	CH_2Cl_2	trace	n.a.
13	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	K_3PO_4	CH_2Cl_2	trace	n.a.
14	Λ-RhS	/	DIPEA	CH_2Cl_2	0	n.a.
15	/	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	CH_2Cl_2	0	n.a.
16	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	/	CH_2Cl_2	0	n.a.
17[d]	Λ-RhS	$Ir(ppy)_2(dtbbpy)PF_6$	DIPEA	CH_2Cl_2	0	n.a.

[a]Reaction conditions: **1a**(0.1 mmol), **2a** (0.2 mmol), a chiral Lewis acid (4 mol %), a photocatalyst (1 mol %) and a base (2.0 equiv) in a solvent (2.0 mL) at rt under irradiation with a 23 W CFL. [b]Isolated yield after chromatography. [c]Determined by HPLC on a chiral stationary phase. [d]Under dark. DIPEA = diisopropylethylamine; bpy = 2,2′-bipyridine; ppy = 2-phenylpyridine; dtbbpy = 4,4′-di-tert-butyl-2,2′-bipyridine; n.a. = not applicable.

We then evaluated the generality of this visible-light photocatalytic difluoroalkylation process under the optimized reaction conditions described in Table 1, entry 7. We first studied the substrate scope of a variety of 2-acyl imidazole **1**. As shown in Scheme 2a, various substrates with either electron-withdrawing groups or electron-donating groups at the *para*-position of the benzene ring were smoothly converted to the corresponding difluoroalkylation products in good to excellent yields (71-97%) with excellent enantioselectivities (97-99%) (**3b**-**3k**). In addition, different substituents at the *meta*-position of the benzene ring such as a methyl group and a chloride atom were also well tolerated under the standard conditions to furnish the desirable products with 86-93% yields and 98-99% ee (**3l**, **3m**). However, when a substrate with a methyl group at the *ortho*-position of the benzene ring was applied to this *α*-difluoroalkylation process, only a trace amount of the difluoroalkylation product (**3na**) was detected. Multifunctional substrates were also suitable for this reaction to furnish the corresponding products in good yields with excellent enantioselectivities (**3o**-**3r**). A product bearing a heteroaryl framework was also successfully synthesized, as shown for the thiophenyl-substituted adduct **3s**. Finally, this reaction could be scaled up to 1.0 mmol, and the large scale reaction proceeded well to furnish **3a** in 90% yield with excellent enantioselectivity (98% ee).The absolute configuration was unequivocally confirmed by single crystal X-ray crystallographic analysis of the compound **3l**. (see the Supporting Information, CCDC: 1574697).

Scheme 2. Substrate scope of difluoroalkylation reaction[a,b,c]

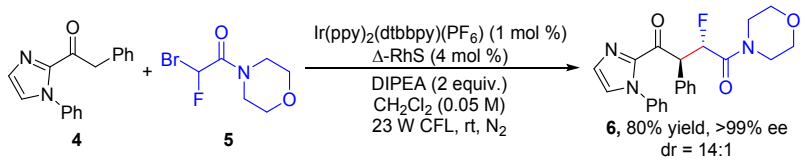


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Ir(ppy)_2(dtbbpy)(PF_6)$ (1 mol %), Λ-RhS (4 mol %), and DIPEA (2.0 equiv) in CH_2Cl_2 (2.0 mL) at r.t. under irradiation with a 23 W CFL. [b]Isolated yield after chromatography. [c]Enatioselectivity was determined by HPLC on a chiral stationary phase.

We then probed the substrate scope of bromodifluoroacetamides **2**, which could introduce different *gem*-difluoroalkyl groups into the final products. As shown in Scheme 2b, it was found that bromodifluoroacetamides **2** bearing a five-membered or seven-membered ring worked well with **1**, affording **3t** and **3u** in good yields (80-84%) with excellent enantioselectivities (97-98% ee), respectively. Some other cyclic amides containing multiple heteroatoms were also suitable substrates for this reaction, furnishing the corresponding difluoroalkylation products in good yields with high enantioselectivities (**3v**-**3y**). Furthermore, *N*,*N*-diethylaectamide provided the product **3z** in 87% yield and 97% ee.

Very interestingly, besides constructing a series of γ-keto amides bearing *gem*-difluoroalkyl groups, this mild protocol could also be applied to synthesize monofluorinated adducts. As shown in scheme 3, when bromofluoroacetamide **5** was used as the fluorinated reagent, a fluorine-containing γ-keto amide derivative **6** was successfully obtained in 80% yield and excellent enantioselectivity (>99% ee) with good diastereoselectivity (dr = 14:1) through this dual catalytic system.

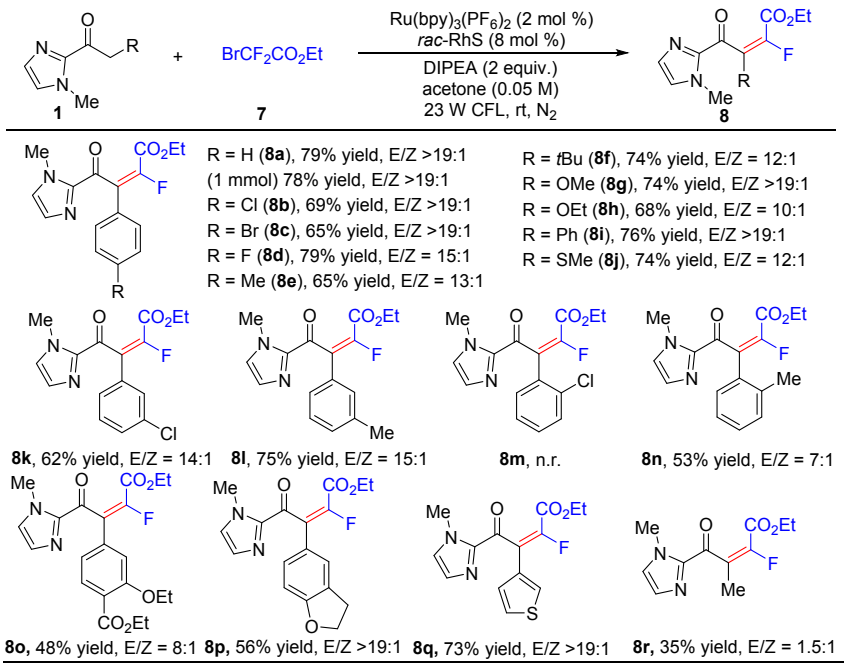
Scheme 3. Monofluoroalkeylation of 2-acyl imidazole



Having synthesized a variety of valuable fluorine-containing *γ*-keto amide derivatives, we then questioned whether or not this protocol could be used to prepare more useful fluorine-containing *γ*-keto esters. To our surprising, when commercially available ethyl bromodifluoroacetate **7** was used as the fluorine resource under the optimized conditions, a fluorine-containing *α,β*-unsaturated keto ester derivative **8** was smoothly obtained while the expected *γ*-keto esters bearing a *gem*-difluoromethene group was not detected. Although the monofluoroalkene skeleton is widely found in various bioactive molecules, which can also be applied to various organic transformations, reports for the stereoselective synthesis of this valuable skeleton are very rare.

Therefore, we decided to optimize this method for the efficient synthesis of these versatile monofluoroalkene synthons using this dual catalytic strategy(see Table S1 in Supporting Information for details).Under the optimized reaction conditions, we examined the scope of 2-acyl imidazoles 1 (**Scheme 4**). It was found that substrates with various halo-substituents (F, Cl, Br) or electron-donating groups such as alkyls, alkoxys, phenyl and methylthio at the *para*- or *meta*-positions of the benzene ring were smoothly converted to the desired monofluoroalkenes in good yields (60-79%) with good to excellent E/Z ratios (10:1->19:1) (**8a-8l**). However, *ortho*-substituents had a significant effect on this reaction, for instance, product **8m** was not formed and **8n** was generated in 53% yield with low E/Z ratio (7:1). Bifunctional and thiophenyl-substituted substrates were also suitable for this reaction to give the corresponding products (**8o-8q**). Furthermore, this reaction also worked for the substrate containing an aliphatic substituent to afford product **8r** with a reduced yield (35%) as mixtures of E and Z isomers (E/Z=1.5:1). Finally, this reaction could be scaled up from 0.1 mmol to 1.0 mmol, and the large scale reaction proceeded well to furnish **8a** in 78% yield (E/Z >19:1).

Scheme 4. Substrate scope of monofluoroalkenylation reaction[a,b,c]

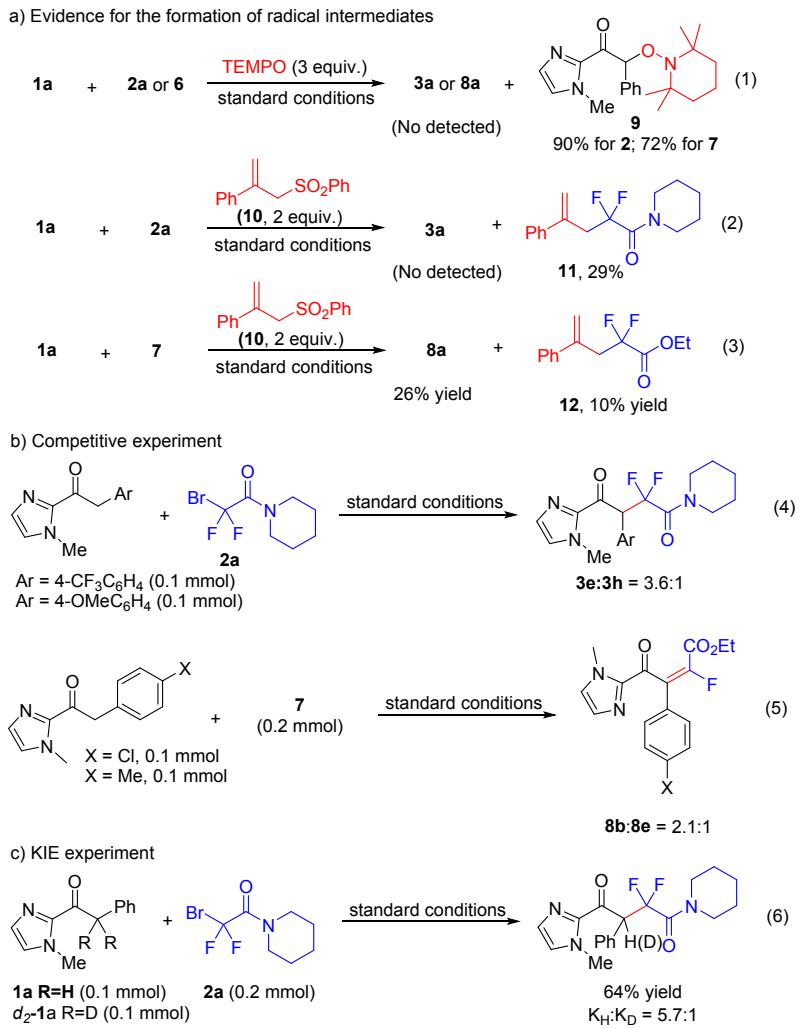


[a]Reaction conditions: **1** (0.1 mmol), **7** (0.2 mmol), $Ru(bpy)_3(PF_6)_2$ (2 mol %), *rac*-RhS (8 mol %), and DIPEA (2.0 equiv) in acetone (2.0 mL) at r.t. under irradiation with a 23 W CFL. [b]Ratio of E/Z was determined by ^1H NMR. [c]Isolated yield after chromatography.

To understand the reaction mechanism, several control experiments were performed (**Scheme 5**). When 2, 2, 6, 6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction mixture of **1a** and **2a**or**7**, no product was generated. However, TEMPO-trapped product **9** was obtained in 90% yield and 72% yield, which indicated that the reaction involved a radical process and *α*-carbonyl carbon radical was formed from the imidazole substrate (Scheme 5a, eq 1). When l-(phenylsulfonyl)-2-phenyl-2-propene **10** was added into the reaction mixture under the standard conditions, the difluoroalkylation reaction was also completely inhibited, and product **11** was isolated in 29% yield, indicating that the difluoroacetyl radical was generated in this dual catalytic process (Scheme 5a, eq 2). The similar result was found when radical trapping reagent **10** was added into the mixture of **1a** and **7** (Scheme 5a, eq 3). In addition, a competition reaction using electronically different substrates **1** with **2a** afforded **3e**/**3h** in a ratio of 3.6:1, which suggested that the difluoroalkyl radical species attacked the more stable electron-rich enolate intermediate more favorably in the catalytic system (Scheme 5b, eq 4). This competition reaction was also applied to the monofluoroalkenylation reaction and gave us the same result (Scheme 5b, eq 5). Furthermore, the light-dark interval experiments were performed according the general catalysis procedure, which showed that this dual catalytic process was highly dependent on the visible-light (see the Supporting Information). To understand the rate-determining step for the photoreaction, the reaction of a 1:1 mixture of **1a** and d_2-**1a** with **2a** was carried out under the conditions described for Scheme 5c. The intermolecular KIE was found to be 5.7, indicating that the deprotonation of **1** was a turnover limiting step of the difluoroalkylation reaction (Scheme 5c). The quantum yield of the difuoroalkylation reaction was determined as 2.00 which indicated that the reaction might be involved in a chain process. (see the

Supporting Information)

Scheme 5.Mechanistic investigations.



In addition, we performed a series of Stern-Volmer quenching experiments to verify the initial electron transfer (SET) step of the photoredox process (Figure 2 and Supporting Information). These results showed that only the intermediate Rh-enolate but no other component is capable of quenching the excited state of the photosensitizer $Ir(ppy)_2(dtbbpy)PF_6$, and this is most likely through a reductive quenching cycle. Also we tested the redox potentials of the substrates and the Rh-enolate intermediate, and confirmed that Rh-enolate (E_p^{ox} = 0.49 V vs SCE in CH_2Cl_2) has a significantly lower oxidation peak potential than **1a** (E_p^{ox} = 2.25 V vs SCE in CH_2Cl_2) (see the Supporting Information).

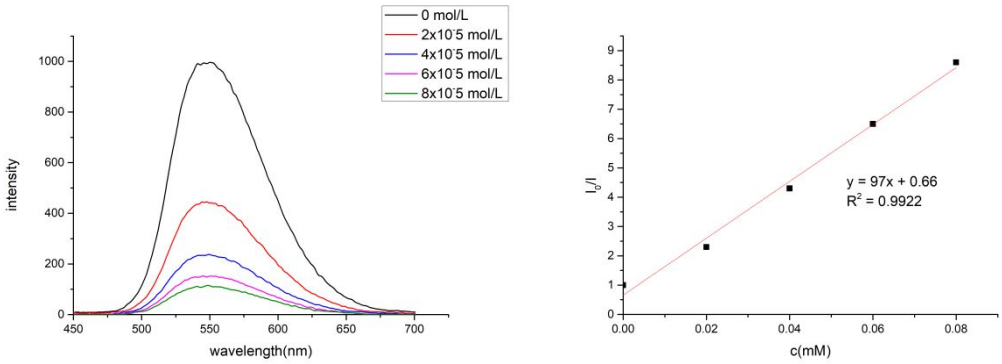


Figure 2. Stern−Volmer quenching experiments of RhS-**1a** with photoexcited $Ir(ppy)_2(dtbbpy)PF_6$ (0.1 mM, λ_{ex} = 345 nm, λ_{em} = 552 nm). I_0 and I are respective luminescence intensities in the absence and presence of the indicated concentrations of the corresponding quencher.

The elimination step of the reaction is the E1cB process. According to the literature reports[21], when the carbanion is more stable which means the acidity of the α-position of the leaving group is stronger, making deprotonation irreversible, elimination process in the reaction is easier to undergo.To explore the chemoselectivity of this transformation, we calculated the pKa of the substrate **1a** and two kinds of difluoroalkylated products by utilizing Gaussian 09W. The calculation showed that the amide containing the *gem*-difluoromethene group (pKa = 30.4) was less acidic than the corresponding ester (pKa = 28.2), which was in accord with experiment results that *γ*-keto amides bearing a *gem*-difluoromethylene group could be smoothly obtained, but the corresponding *γ*-keto esters were not detected (Figure 3). And we also found that the pKa reduced siginificantly and the ΔpKa was increased from 2.2 to 3.1 when catalyst RhS was coordinated with these two kinds of difluoroalkylated compounds, which means *γ*-keto ester bearing a *gem*-difluoromethylene group was much easier to deprotonation and enolization.

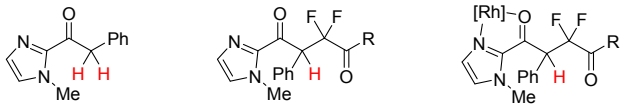


Figure 3.DFT calculations.

Based on the obtained results, a reaction mechanism for this dual catalytic process was proposed, as descripted in Figure 4. Substrate **1** first binds with rhodium complex RhS in a bidentate fashion to provide intermediate **I**, which is deprotonated to generate a rhodium enolate complex **II**. A single electron transfer (SET) process between the excited photocatalyst ($[PC^*]^{n+}$) and the electron-rich intermediate **II** which serves as the reducing agent[20] generates the highly reducing $[PC]^{(n-1)+}$, which in turn transfers a single electron to the fluorine reagent **2** or **7**. Generated difluoroacetyl radical **III** is subsequently added to the electron-rich double bond of the rhodium enolate complex **II** to give the radical intermediate **IV** accompanied by the stereoselective control.[22]The radical intermediate **IV** is a strong oxidizing agent and eitherdirectly reduces the fluorine reagents*via* chain propagation or

quenches photoexcited catalyst to produce the reduced photoredox sensitizer, which is simultaneously converted to an Rh-coordinated difluoroalkylated product **V**. For the difluoroalkylation reaction, the desired product **3** is directly released through the ligand exchange of coordinated product **V** by another substrate **1** molecule (Path A). For the other pathway, a deprotonation step occurs to generate the second rhodium enolate complex **VI** when $BrCF_2CO_2Et$ is used as the reaction partner, and an $E_{1C}B$ elimination process occurs to intermediate **VI** to give **VII**. Finally, the monofluoroalkene product **8** is released through the ligand exchange of coordinated product **VII** by another substrate **1** molecule (Path B).

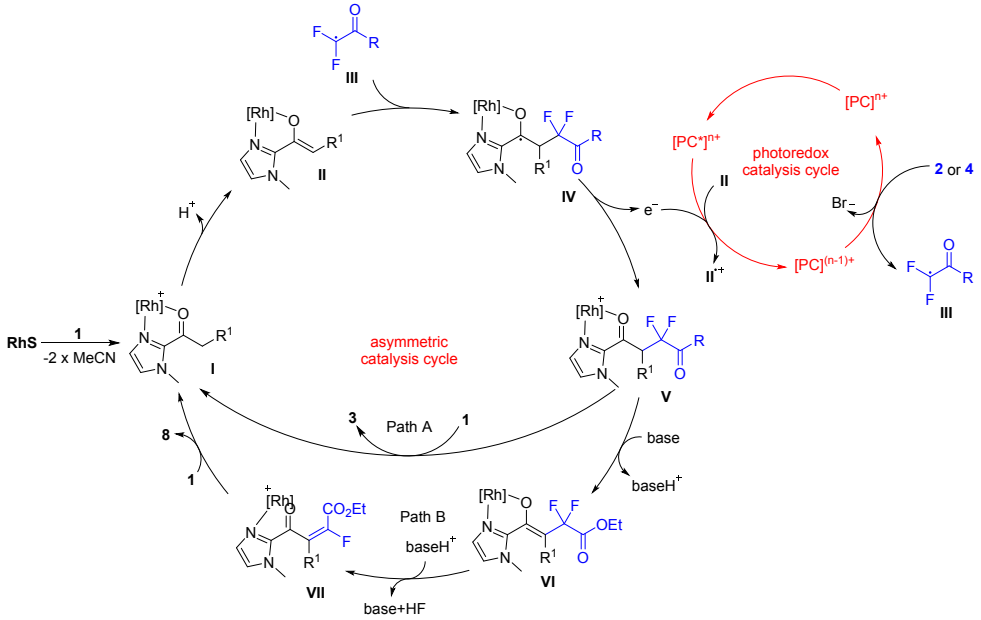


Figure 4. Proposed Reaction Mechanism

CONCLUSION

In summary, we have developed a novel and mild method for the chemo, stereo-selective synthesis of fluorine-containing *γ*-keto acid derivatives via merging visible-light photocatalysis and Lewis acid catalysis. Corresponding difluoroalkylated products were prepared in high yields with excellent enantioselectivites, and the monofluoroalkenes were obtained in good yields with good to excellent E/Z ratios. The calculations demonstrated the reason for the high chemoselectivity of the reaction between 2-acyl imidazoles and fluorine reagents.

EXPERIMENTAL SECTION

General information. All glassware was thoroughly oven-dried. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Thin-layer chromatography (TLC) plates were visualized by exposure to ultraviolet light and/or staining with phosphomolybdic acid followed by heating on a hot plate. Flash chromatography was carried out using silica gel (200-300 mesh). ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz). The spectra were recorded in CDCl3 as solvent at room temperature, ^{1}H, ^{1}Fand ^{13}C NMR chemical shifts are reported in ppm relative to the residual solvent peak. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale (CDCl3: δH = 7.26

ppm, δC = 77.00 ppm). Data for ^{1}H NMR and ^{19}F NMR are reported as follows: chemical shift (δ ppm), mul-tiplicity (s = singlet, d = doublet, t = triplet, q=quartet, m = mul-tiplet, dd = doublet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported as chemical shift and mul-tiplicity (d = doublet, t = triplet, dd = doublet). HRMS were performed on a Bruker Apex II mass instrument (ESI).

2-acyl imidazoles[16] and bromodifluoroacetamides[23] were prepared according to reported procedures.

Synthesis of 2-phenylacetic-2,2-d_2 acid: A mixture of phenylacetic acid (3.0 g; 20.0 mmol), anhydrous potassium carbonate (11.06 g; 80.0 mmol) and deuterium oxide (15 mL) was refluxed overnight. After cooling to room temperature, the reaction mixture was acidified to pH 2 with 6 N hydrochloric acid. The solution was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. This procedure was repeated to give 2-phenylacetic-2,2-d_2 acid as a white solid in 90% yield. All spectroscopic data were in agreement with the literature report.[24]

General catalysis procedure for the synthesis of product 3: A dried 10 mL reaction tube was charged with the catalyst Λ-RhS (4 mol %, 3.5 mg), $Ir(ppy)_2(dtbbpy)(PF_6)_2$ (1 mol %, 0.9 mg) and the corresponding 2-acyl imidazole **1** (0.1 mmol, 1.0 equiv.). The tube was purged with nitrogen and then CH_2Cl_2 (2.0 mL), bromodifluoroacetamides **2** (0.2 mmol, 2.0 equiv.) and DIPEA (0.2 mmol, 25.9 mg, 2.0 equiv.) were added via a syringe. The reaction mixture was degassed by three cycles of freeze-pump-thaw. After the mixture was thoroughly degassed, the reaction was then irradiated under a 23W CFL. After completion of the reaction, the crude mixture was purified by flash chromatography (silica gel, mixtures of petroleum ether/ethyl acetate) to afford the pure product **3**.

General catalysis procedure for the synthesis of product 3a at a 1 mmol scale: A dried reaction tube was charged with the catalyst Λ-RhS (4 mol %, 35 mg), $Ir(ppy)_2(dtbbpy)(PF_6)_2$ (1 mol %, 9 mg) and the corresponding 2-acyl imidazole **1** (1 mmol, 200 mg). The tube was purged with nitrogen and then CH_2Cl_2 (20 mL), bromodifluoroacetamides **2** (2 mmol, 2.0 equiv.) and DIPEA (2 mmol, 259 mg, 2.0 equiv.) were added via a syringe. The reaction mixture was degassed by three cycles of freeze-pump-thaw. After the mixture was thoroughly degassed, the reaction was then irradiated under a 23W CFL. After completion of the reaction, the crude mixture was purified by flash chromatography (silica gel, petroleum ether:ethyl acetate = 1.5:1) to afford the pure product **3a** (324 mg, 90% yield, 98% ee).

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-3-phenyl-1-(piperidin-1-yl)butane-1,4-dione (**3a**) white solid, 94% yield, 34.1 mg (PE:EA = 1.5:1), mp = 160-162 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20 °C, tr (major) = 17.0 min, tr (minor) = 8.5 min.) $[\alpha]_D^{20}$ = -150.00 (c 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (m, 2H), 7.36-7.30 (m, 3H), 7.10 (s, 1H), 6.92 (s, 1H), 6.16 (dd, J = 27.6 Hz, 7.6 Hz, 1H), 3.93 (s, 3H), 3.74-3.54 (m, 3H), 3.40-3.37 (m, 1H), 1.63-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.0 (dd, J = 289.52 Hz, 7.52 Hz, 1F), -103.3 (dd, J = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.7 (d, J = 9 Hz), 161.0 (t, J = 28 Hz), 142.3

(d, *J* = 6 Hz), 130.8, 129.3, 128.4, 128.2, 127.2, 118.1 (dd, *J* = 268 Hz, 254 Hz), 55.3 (dd, *J* = 25 Hz, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 36.0, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{19}H_{22}F_2N_3O_2$ $[M+H]^+$ calcd. 362.1675, found 362.1674.

(R)-3-(4-chlorophenyl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione (**3b**)white solid, 71% yield, 28.0 mg (PE:EA = 1.5:1), mp = 122-124 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 97% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 11.8 min, t_r (minor) = 7.7 min.) $[\alpha]_D^{20}$ = -150.00 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.12 (s, 1H), 6.96 (s, 1H), 6.14 (dd, *J* = 26.8 Hz, 7.6 Hz, 1H), 3.95 (s, 3H), 3.78-3.54 (m, 3H), 3.42-3.37 (m, 1H), 1.66-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.0 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.4 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.3 (d, *J* = 9 Hz), 160.8 (t, *J* = 28 Hz), 142.1 (d, *J* = 6 Hz), 134.4, 132.2, 129.5, 129.4, 128.6, 127.4, 118.0 (dd, *J* = 268 Hz, 254 Hz), 54.6 (dd, *J* = 25 Hz, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.6, 36.1, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{19}H_{21}ClF_2N_3O_2$ $[M+H]^+$ calcd. 396.1285, found 396.1277;

(R)-3-(4-bromophenyl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione (**3c**) white solid, 80% yield, 35.0 mg (PE:EA = 1.5:1), mp = 120-122°C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 10.6 min, t_r (minor) = 7.0 min.) $[\alpha]_D^{20}$ = -120.90 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.47-7.45 (m, 4H), 7.12 (s, 1H), 6.96 (s, 1H), 6.13 (dd, *J* = 26.8 Hz, 8.0 Hz, 1H), 3.96 (s, 3H), 3.74-3.54 (m, 3H), 3.42-3.37 (m, 1H), 1.66-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.0 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.4 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.2 (d, *J* = 10 Hz), 160.8 (t, *J* =28 Hz), 142.1 (d, *J* = 6 Hz), 132.5, 131.6, 129.9, 129.5, 127.4, 122.7, 118.0 (dd, *J* = 269 Hz, 255 Hz), 54.7 (dd, *J* = 24 Hz, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.6, 36.1, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{19}H_{21}BrF_2N_3O_2$ $[M+H]^+$ calcd. 440.0780, found 440.0776.

(R)-2,2-difluoro-3-(4-fluorophenyl)-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione(**3d**)white solid, 89% yield (PE:EA = 1.5:1), 33.8 mg, mp = 74-76 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 10.9 min, t_r (minor) = 6.7 min.) $[\alpha]_D^{20}$ = -155.00 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 5.6 Hz, 8.4 Hz, 2H), 7.12 (s, 1H), 7.03 (t, *J* = 8.4 Hz, 2H), 6.96 (s, 1H), 6.15 (dd, *J* = 26.8 Hz, 7.6 Hz, 1H), 3.96 (s, 3H), 3.76-3.54 (m, 3H), 3.42-3.37 (m, 1H), 1.66-1.56 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.2 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.5 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F), -114.0--114.1 (m, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.6 (d, *J* = 9 Hz), 162.8 (d, *J* = 246 Hz), 160.9 (t, *J* = 28 Hz), 142.2 (d, *J* = 5 Hz), 132.5 (d, *J* = 8 Hz), 129.4, 127.3, 126.6, 118.0 (dd, *J* = 269 Hz, 255 Hz), 115.2, 54.4 (dd, *J* = 24 Hz, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.6, 36.1, 26.3, 25.5, 24.3; HRMS (ESI) for $C_{19}H_{21}F_3N_3O_2$ $[M+H]^+$ calcd. 380.1580, found 380.1588.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)butane-

1,4-dione(**3e**)white solid, 89% yield (PE:EA = 1.5:1), 38.3 mg, mp = 135-137 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 90:10, flow rate 1.0 mL/min, 20°C, t_r (major) = 6.4 min, t_r (minor) = 4.9 min.) $[\alpha]_D^{20}$ = -123.00 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.13 (s, 1H), 6.98 (s, 1H), 6.25 (dd, *J* = 26.8 Hz, 7.6 Hz, 1H), 3.97 (s, 3H), 3.74-3.54 (m, 3H), 3.41-3.38 (m, 1H), 1.65-1.60 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.7 (s, 3F), -93.8 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.0 (dd, *J* = 289.52 Hz, 30.08 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 184.9 (d, *J* = 9 Hz), 160.7 (t, *J* = 28 Hz), 142.1 (d, *J* = 6 Hz), 135.1, 131.2, 130.3 (q, *J* = 32 Hz), 129.6, 128.0, 127.5, 125.2 (t, *J* = 4 Hz), 122.6, 118.1 (dd, *J* = 269 Hz, 255 Hz), 55.0 (dd, *J* = 24 Hz, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.6, 36.1, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{20}H_{21}F_5N_3O_2$ $[M+H]^+$ calcd. 430.1548, found 430.1539.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)-3-(p-tolyl)butane-1,4-dione (**3f**) white solid, 94% yield, 35.1 mg (PE:EA = 1.5:1), mp = 139-141 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 290 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 21.8 min, t_r (minor) = 11.0 min.) $[\alpha]_D^{20}$ = -151.46 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.09 (s, 1H), 6.90 (s, 1H), 6.11 (dd, *J* = 27.2 Hz, 8.0 Hz, 1H), 3.92 (s, 3H), 3.74-3.53 (m, 3H), 3.41-3.36 (m, 1H), 2.30 (s, 3H), 1.64-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.2 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.4 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.7 (d, *J* = 9 Hz), 161.0 (t, *J* = 28 Hz), 142.2 (d, *J* = 6 Hz), 138.0, 130.6, 129.3, 129.1, 127.6, 127.1, 118.1 (dd, *J* = 268 Hz, 254 Hz), 54.9 (dd, *J* = 24 Hz, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 35.9, 26.3, 25.5, 24.2, 21.0; HRMS (ESI) for $C_{20}H_{24}F_2N_3O_2$ $[M+H]^+$ calcd. 376.1831, found 376.1823.

(R)-3-(4-(tert-butyl)phenyl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-di one (**3g**) white solid, 97% yield (PE:EA = 1.5:1), 40.3 mg, mp = 196-198 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 99% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 13.7 min, t_r (minor) = 7.7 min.) $[\alpha]_D^{20}$ = -120.34 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 6.91 (s, 1H), 6.13 (dd, *J* = 27.6 Hz, 8.0 Hz, 1H), 3.94 (s, 3H), 3.75-3.54 (m, 3H), 3.40-3.36 (m, 1H), 1.64-1.58 (m, 6H), 1.28 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -93.9 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.2 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.8 (d, *J* = 10 Hz), 161.1 (t, *J* = 28 Hz), 150.9, 142.3 (d, *J* = 5 Hz), 130.4, 129.3, 127.6, 127.1, 125.4, 118.2 (dd, *J* = 268 Hz, 254 Hz), 54.8 (dd, *J* = 24 Hz, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.5, 36.1, 34.4, 31.2, 26.3, 25.5, 24.3; HRMS (ESI) for $C_{23}H_{30}F_2N_3O_2$ $[M+H]^+$ calcd. 418.2301, found 418.2305.

(R)-2,2-difluoro-3-(4-methoxyphenyl)-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dion e (**3h**) white solid, 90% yield (PE:EA = 1.5:1), 35.3 mg, mp = 126-128 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = >99% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 18.2 min, t_r (minor) = 11.5 min.) $[\alpha]_D^{20}$ = -168.55 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.10 (s, 1H),

6.92 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.09 (dd, *J* = 27.2, 8.0 Hz, 1H), 3.94 (s, 3H), 3.76-3.71 (m, 4H), 3.67-3.54 (m, 2H), 3.42-3.36 (m, 1H), 1.65-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.3 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.5 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 185.8 (d, *J* = 9 Hz), 161.1 (t, *J* = 28 Hz), 159.5, 142.2 (d, *J* = 6 Hz), 131.9, 129.3, 127.1, 122.6, 118.1 (dd, *J* = 268 Hz, 253 Hz), 113.8, 55.0, 54.4 (dd, *J* = 24, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 36.0, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{20}H_{23}F_2N_3O_3Na$ $[M+Na]^+$ calcd. 414.1600, found 414.1599.

(R)-3-(4-ethoxyphenyl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione(**3i**) white solid, 85% yield, 34.3 mg (PE:EA = 1.5:1), mp = 150-152 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 99% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 19.1 min, t_r (minor) = 12.4 min.) $[\alpha]_D^{20}$ = -146.60 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.11 (s, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.08 (dd, *J* = 27.2, 8.0 Hz, 1H), 3.98 (q, *J* = 7.6 Hz, 2H), 3.94 (s, 3H), 3.76-3.54 (m, 3H), 3.42-3.36 (m, 1H), 1.65-1.58 (m, 6H), 1.38 (t, *J* = 7.6 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.4 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.6 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 185.9 (d, *J* = 9 Hz), 161.1 (t, *J* = 29 Hz), 158.9, 142.2 (d, *J* = 5 Hz), 131.9, 129.3, 127.1, 122.4, 118.1 (dd, *J* = 268 Hz, 253 Hz), 114.3, 63.2, 54.4 (dd, *J* = 24, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.5, 36.1, 26.3, 25.5, 24.3, 14.7; HRMS (ESI) for $C_{21}H_{26}F_2N_3O_3$ $[M+H]^+$ calcd. 406.1937, found 406.1930.

(R)-3-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-di one (**3j**) white solid, 96% yield, 41.8 mg (PE:EA = 1.5:1), mp = 164-166 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 260 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 16.2 min, t_r (minor) = 11.1 min.) $[\alpha]_D^{20}$ = -130.79 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 8.8 Hz, 4H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 6.92 (s, 1H), 6.21 (dd, *J* = 27.2, 7.6 Hz, 1H), 3.95 (s, 3H), 3.77-3.55 (m, 3H), 3.42-3.37 (m, 1H), 1.63-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -93.9 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.1 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 185.6 (d, *J* = 10 Hz), 161.0 (t, *J* = 28 Hz), 142.3 (d, *J* = 5 Hz), 141.0, 140.4, 131.2, 129.8, 128.6, 127.3, 127.2, 127.1, 127.0, 118.2 (dd, *J* = 268 Hz, 254 Hz), 54.9 (dd, *J* = 24, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.5, 36.1, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{25}H_{26}F_2N_3O_2$ $[M+H]^+$ calcd. 438.1988, found 438.1982.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-3-(4-(methylthio)phenyl)-1-(piperidin-1-yl)butane-1,4-dione (**3k**) white solid, 95% yield, 39.8 mg (PE:EA = 1.5:1), mp = 147-149 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 19.3 min, t_r (minor) = 11.6 min.) $[\alpha]_D^{20}$ = -121.38 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 4H), 7.10 (s, 1H), 6.93 (s, 1H), 6.11 (dd, *J* = 27.2, 7.6 Hz, 1H), 3.94 (s, 3H), 3.74-3.54 (m, 3H), 3.42-3.37 (m, 1H), 2.43 (s, 3H), 1.65-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.2 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.4 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$):

δ 185.5 (d, *J* = 10 Hz), 160.9 (t, *J* = 28 Hz), 142.1 (d, *J* = 5 Hz), 138.8, 131.2, 129.4, 127.3, 127.2, 126.1, 118.1 (dd, *J* = 268 Hz, 254 Hz), 54.7 (dd, *J* = 24, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 36.0, 26.3, 25.4, 24.2, 15.3; HRMS (ESI) for $C_{20}H_{24}F_2N_3O_2S$ $[M+H]^+$ calcd. 408.1552, found 408.1545.

(R)-3-(3-chlorophenyl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione (**3l**) white solid, 86% yield, 34.2 mg (PE:EA = 1.5:1), mp = 160-162 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 11.2 min, t_r (minor) = 8.2 min.) $[\alpha]_D^{20}$ = -142.30 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.48-7.47 (m, 1H), 7.30-7.25 (m, 2H), 7.12 (s, 1H), 6.96 (s, 1H), 6.14 (dd, *J* = 26.8 Hz, 7.6 Hz, 1H), 3.95 (s, 3H), 3.74-3.54 (m, 3H), 3.42-3.37 (m, 1H), 1.66-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -93.8 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.1 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.0 (d, *J* = 10 Hz), 160.8 (t, *J* = 28 Hz), 142.1 (d, *J* = 6 Hz), 134.1, 132.8, 130.6, 129.5(3), 129.4(6), 129.2, 128.4, 127.4, 118.0 (dd, *J* = 269 Hz, 255 Hz), 54.6 (dd, *J* = 24 Hz, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.6, 36.0, 26.3, 25.4, 24.2; HRMS (ESI) for $C_{19}H_{21}ClF_2N_3O_2$ $[M+H]^+$ calcd. 396.1285, found 396.1277.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)-3-(m-tolyl)butane-1,4-dione (**3m**) white solid, 94% yield, 35.1 mg (PE:EA = 1.5:1), mp = 158-160 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 17.9 min, t_r (minor) = 10.9 min.) $[\alpha]_D^{20}$ = -174.25 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.38 (m, 2H), 7.25-7.21 (m, 1H), 7.13-7.10 (m, 2H), 6.91 (s, 1H), 6.11 (dd, *J* = 27.2 Hz, 7.6 Hz, 1H), 3.93 (s, 3H), 3.75-3.53 (m, 3H), 3.42-3.36 (m, 1H), 2.34 (s, 3H), 1.64-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.0 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.2 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.7 (d, *J* = 10 Hz), 161.0 (t, *J* = 28 Hz), 142.2 (d, *J* = 5 Hz), 138.0, 131.3, 130.5, 129.3, 129.0, 128.2, 127.9, 127.1, 118.1 (dd, *J* = 268 Hz, 254 Hz), 55.1 (dd, *J* = 24 Hz, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 36.0, 26.3, 25.5, 24.2, 21.3; HRMS (ESI) for $C_{20}H_{24}F_2N_3O_2$ $[M+H]^+$ calcd. 376.1831, found 376.1828.

(R)-3-(3,4-dimethoxyphenyl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione (**3o**) white solid, 95% yield, 39.8 mg (PE:EA = 1:1), mp = 69-71 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 97% (HPLC: IC-3, 280 nm, hexane/isopropanol = 50:50, flow rate 1.0 mL/min, 20°C, t_r (major) = 24.3 min, t_r (minor) = 17.6 min.) $[\alpha]_D^{20}$ = -161.91 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.11 (m, 3H), 6.95 (s, 1H), 6.84 (d, *J* = 8.0 Hz,1H), 6.08 (dd, *J* = 27.2, 7.6 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H), 3.74-3.56 (m, 3H), 3.42-3.39 (m, 1H), 1.64-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.4 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.4 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.6 (d, *J* = 10 Hz), 160.9 (t, *J* = 29 Hz), 148.8, 148.4, 142.1 (d, *J* = 5 Hz), 129.2, 127.1, 123.3, 122.7, 118.0 (dd, *J* = 268 Hz, 254 Hz), 113.3, 110.6, 55.6, 55.5, 54.5 (dd, *J* = 24, 17 Hz), 46.4 (t, *J* = 6 Hz), 44.4, 35.9, 26.2, 25.4, 24.1; HRMS (ESI) for $C_{21}H_{26}F_2N_3O_4$ $[M+H]^+$ calcd. 422.1886, found 422.1880.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)-3-(3,4,5-trimethoxyphenyl)butane-1,4-dione (**3p**) white solid, 95% yield (PE:EA = 1:2), 42.7 mg, mp = 160-162 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 97% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 0.7 mL/min, 20°C, t_r (major) = 51.8 min, t_r (minor) = 60.8 min.) $[\alpha]_D^{20}$ = -125.77 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (s, 1H), 6.99 (s, 1H), 6.81 (s, 2H), 6.07 (dd, *J* = 27.2, 7.6 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 6H), 3.82 (s, 3H), 3.75-3.61 (m, 3H), 3.44-3.41 (m, 1H), 1.65-1.59 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.1 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.3 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.5 (d, *J* = 9 Hz), 160.9 (t, *J* = 28 Hz), 152.8, 142.2 (d, *J* = 5 Hz), 137.7, 129.3, 127.2, 126.0, 118.1 (dd, *J* = 269 Hz, 254 Hz), 107.7, 60.6, 56.0, 54.5 (dd, *J* = 24, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 36.0, 26.3, 25.5, 24.2; HRMS (ESI) for $C_{22}H_{28}F_2N_3O_5$ $[M+H]^+$ calcd. 452.1992, found 452.1978.

Ethyl (R)-4-(3,3-difluoro-1-(1-methyl-1H-imidazol-2-yl)-1,4-dioxo-4-(piperidin-1-yl)butan-2-yl)-2-ethoxybenzoate (**3q**) white solid, 73% yield, 34.6 mg (PE:EA = 2:1), mp = 115-117 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 93% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 17.2 min, t_r (minor) = 13.8 min.) $[\alpha]_D^{20}$ = -84.000 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.21-7.18 (m, 2H), 7.10 (s, 1H), 6.97 (s, 2H), 6.16 (dd, *J* = 27.2, 7.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.18-4.11 (m, 2H), 3.94 (s, 3H), 3.72-3.56 (m, 3H), 3.45-3.40 (m, 1H), 1.64-1.58 (m, 6H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.1 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.1 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 184.9 (d, *J* = 9 Hz), 166.1, 160.7 (t, *J* = 28 Hz), 157.9, 142.0 (d, *J* = 6 Hz), 136.1, 131.0, 129.4, 127.4, 122.5, 120.4, 118.0 (dd, *J* = 269 Hz, 254 Hz), 115.6, 64.4, 60.6, 55.2 (dd, *J* = 24, 17 Hz), 46.5 (t, *J* = 6 Hz), 44.5, 35.9, 26.2, 25.4, 24.1, 14.4, 14.1; HRMS (ESI) for $C_{24}H_{30}F_2N_3O_5$ $[M+H]^+$ calcd. 478.2148, found 478.2139.

(R)-3-(2,3-dihydrobenzofuran-5-yl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)butane-1,4-dione (**3r**) white solid, 87% yield, 35.1 mg (PE:EA = 1.5:1), mp = 70-72 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 97% (HPLC: IC-3, 260 nm, hexane/isopropanol = 50:50, flow rate 1.0 mL/min, 20°C, t_r (major) = 19.6 min, t_r (minor) = 11.7 min.) $[\alpha]_D^{20}$ = -98.607 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.07 (dd, *J* = 27.2, 7.6 Hz, 1H), 4.53 (t, *J* = 8.8 Hz, 2H), 3.95 (s, 3H), 3.77-3.54 (m, 3H), 3.41-3.36 (m, 1H), 3.25-3.12 (m, 2H), 1.66-1.58 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.3 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.6 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 186.0 (d, *J* = 9 Hz), 161.1 (t, *J* = 28 Hz), 160.2, 142.2 (d, *J* = 6 Hz), 130.8, 129.3, 127.3, 127.2, 127.1, 122.2, 118.1 (dd, *J* = 268 Hz, 254 Hz), 109.2, 71.3, 54.5 (dd, *J* = 25, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.5, 36.1, 29.5, 26.3, 25.5, 24.3; HRMS (ESI) for $C_{21}H_{24}F_2N_3O_3$ $[M+H]^+$ calcd. 404.1780, found 404.1772.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-(piperidin-1-yl)-3-(thiophen-3-yl)butane-1,4-dione (**3s**) white solid, 80% yield, 29.6 mg (PE:EA = 1.5:1), mp = 149-151 °C; Enantiomeric excess

established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 17.7 min, t_r (minor) = 9.0 min.) $[\alpha]_D^{20}$ = -94.898 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.30-7.28 (m, 2H), 7.14 (d, *J* = 0.4 Hz, 1H), 6.96 (s, 1H), 6.30 (dd, *J* = 26.8, 8.0 Hz, 1H), 3.95 (s, 3H), 3.77-3.56 (m, 3H), 3.42-3.36 (m, 1H), 1.67-1.57 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.1 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -102.8 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.3 (d, *J* = 10 Hz), 160.9 (t, *J* = 28 Hz), 142.2 (d, *J* = 5 Hz), 130.5, 129.4, 129.2, 127.3, 126.1, 125.3, 118.0 (dd, *J* = 268 Hz, 255 Hz), 50.9 (dd, *J* = 24, 17 Hz), 46.6 (t, *J* = 6 Hz), 44.5, 36.1, 26.3, 25.5, 24.3; HRMS (ESI) for $C_{17}H_{20}F_2N_3O_2S$ $[M+H]^+$ calcd. 368.1239, found 368.1233.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-3-phenyl-1-(pyrrolidin-1-yl)butane-1,4-dione (**3t**) white solid, 84% yield (PE:EA = 1.5:1), 29.2 mg, mp = 146-148 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 97% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 48.9 min, t_r (minor) = 16.6 min.) $[\alpha]_D^{20}$ = -149.00 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.37-7.29 (m, 3H), 7.09 (s, 1H), 6.92 (s, 1H), 6.17 (dd, *J* = 26.8, 8.8 Hz, 1H), 3.93 (s, 3H), 3.78-3.64 (m, 2H), 3.48 (t, *J* = 6.8 Hz, 2H), 1.99-1.88 (m, 2H), 1.86-1.77 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -99.1 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -107.0 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.9 (d, *J* = 10 Hz), 161.4 (t, *J* = 29 Hz), 142.2 (d, *J* = 5 Hz), 130.7, 129.4, 128.4, 128.2, 127.3, 117.3 (dd, *J* = 266 Hz, 252 Hz), 55.0 (dd, *J* = 24, 18 Hz), 47.2, 46.1 (t, *J* = 6 Hz), 36.1, 26.2, 23.2; HRMS (ESI) for $C_{18}H_{20}F_2N_3O_2$ $[M+H]^+$ calcd. 348.1518, found 348.1513.

(R)-1-(azepan-1-yl)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-3-phenylbutane-1,4-dione (**3u**) white solid, 80% yield, 30.0 mg (PE:EA = 1.5:1), mp = 146-148 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 17.1 min, t_r (minor) = 8.2 min.) $[\alpha]_D^{20}$ = -169.09 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.36-7.28 (m, 3H), 7.10 (s, 1H), 6.91 (s, 1H), 6.17 (dd, *J* = 27.2, 7.6 Hz, 1H), 3.93 (s, 3H), 3.78-3.72 (m, 1H), 3.64-3.53 (m, 2H), 3.43-3.36 (m, 1H), 1.75-1.69(m, 4H), 1.57-1.56 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.5 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.1 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.7 (d, *J* = 10 Hz), 162.5 (t, *J* = 28 Hz), 142.2 (d, *J* = 6 Hz), 130.8, 129.3 128.4, 128.2, 127.2, 118.1 (dd, *J* = 268 Hz, 254 Hz), 55.4 (dd, *J* = 25, 17 Hz), 48.2, 47.4 (t, *J* = 6 Hz), 36.0, 29.4, 27.3, 26.2, 25.8; HRMS (ESI) for $C_{20}H_{24}F_2N_3O_2$ $[M+H]^+$ calcd. 376.1831, found 376.1824.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-1-morpholino-3-phenylbutane-1,4-dione (**3v**) white solid, 94% yield, 34.0 mg (PE:EA = 1.5:1), mp = 132-134 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 30.7 min, t_r (minor) = 13.3 min.) $[\alpha]_D^{20}$ = -95.082 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.37-7.27 (m, 3H), 7.12 (s, 1H), 6.94 (s, 1H), 6.17 (dd, *J* = 26.8, 8.0 Hz, 1H), 3.94 (s, 3H), 3.76-3.60 (m, 7H), 3.55-3.49 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.2 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.3 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F);

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 185.5 (d, *J* = 10 Hz), 161.4 (t, *J* = 29 Hz), 142.1 (d, *J* = 5 Hz), 130.8, 130.4, 129.5, 128.4, 127.4, 117.8 (dd, *J* = 267 Hz, 253 Hz), 66.6, 66.5, 55.1 (dd, *J* = 24, 17 Hz), 46.2 (t, *J* = 6 Hz), 43.4, 36.1; HRMS (ESI) for $C_{18}H_{20}F_2N_3O_3$ $[M+H]^+$ calcd. 364.1467, found 364.1463.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-3-phenyl-1-thiomorpholinobutane-1,4-dione(**3w**) white solid, 92% yield, 35.0 mg (PE:EA = 1.5:1), mp = 190-192 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 20.5 min, t_r (minor) = 9.0 min.) $[\alpha]_D^{20}$ = -162.29 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 6.8 Hz, 2H), 7.36-7.32 (m, 3H), 7.12 (s, 1H), 6.95 (s, 1H), 6.16 (dd, *J* = 27.2, 7.6 Hz, 1H), 4.06-4.02 (m, 1H), 3.95-3.88 (m, 5H), 3.77-3.73 (m, 1H), 2.68-2.64 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.2 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.4 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 185.5 (d, *J* = 10 Hz), 161.5 (t, *J* = 29 Hz), 142.1 (d, *J* = 5 Hz), 130.8, 130.4, 129.5, 128.5, 128.3, 127.4, 117.9 (dd, *J* = 268 Hz, 253 Hz), 55.2 (dd, *J* = 24, 17 Hz), 48.4 (t, *J* = 6 Hz), 46.1, 36.1, 28.0, 27.2; HRMS (ESI) for $C_{18}H_{20}F_2N_3O_2S$ $[M+H]^+$ calcd. 380.1239, found 380.1232.

(R)-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-3-phenyl-1-(4-phenylpiperazin-1-yl)butane-1,4-dione (**3x**) white solid, 72% yield, 31.7 mg (PE:EA = 1.5:1), mp = 152-154 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 47.5 min, t_r (minor) = 16.7 min.) $[\alpha]_D^{20}$ = -169.09 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.38-7.31 (m, 3H), 7.29-7.24 (m, 2H), 7.11 (s, 1H), 6.92-6.88 (m, 2H), 6.19 (dd, *J* = 27.2, 8.0 Hz, 1H), 3.96-3.91 (m, 4H), 3.88-3.80 (m, 1H), 3.67-3.61 (m, 2H), 3.28-3.22 (m, 2H), 3.13-3.07 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -93.8 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -102.9 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 185.5 (d, *J* = 9 Hz), 161.3 (t, *J* = 29 Hz), 150.6, 142.1 (d, *J* = 5 Hz), 130.8, 130.5, 129.4, 129.1, 128.4, 128.3, 127.3, 120.6, 117.9 (dd, *J* = 268 Hz, 253 Hz), 55.1 (dd, *J* = 24, 17 Hz), 49.6, 49.1, 45.4 (t, *J* = 6 Hz), 43.1, 36.1; HRMS (ESI) for $C_{24}H_{25}F_2N_4O_2$ $[M+H]^+$ calcd. 439.1940, found 439.1932.

tert-butyl (R)-4-(2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-phenylbuta-noyl)piperazine-1-carboxylate (**3y**) white solid, 90% yield, 41.5 mg (PE:EA = 1.5:1), mp = 146-148 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 98% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 29.5 min, t_r (minor) = 18.6 min.) $[\alpha]_D^{20}$ = -94.00 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.38-7.32 (m, 3H), 7.12 (s, 1H), 6.94 (s, 1H), 6.17 (dd, *J* = 27.2, 8.0 Hz, 1H), 3.94 (s, 3H), 3.76-3.44 (m, 6H), 3.38-3.32 (m, 2H), 1.46 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.0 (d, *J* = 289.52 Hz, 1F), -103.1 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 185.5 (d, *J* = 9 Hz), 161.5 (t, *J* = 29 Hz), 154.3, 142.1 (d, *J* = 5 Hz), 130.8, 130.4, 129.4, 128.4, 128.3, 127.4, 117.8 (dd, *J* = 268 Hz, 253 Hz), 55.1 (dd, *J* = 24, 17 Hz), 45.4, 43.6, 36.5, 28.2; HRMS (ESI) for $C_{23}H_{29}F_2N_4O_4$ $[M+H]^+$ calcd. 463.2151, fo

und 463.2159.

(R)-N,N-diethyl-2,2-difluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-phenylbutanamide (**3z**) white solid, 87% yield, 30.5 mg (PE:EA = 1.5:1), mp = 114-116 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = 97% (HPLC: IC-3, 260 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 9.5 min, t_r (minor) = 6.5 min.) $[\alpha]_D^{20}$ = -170.53 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.36-7.28 (m, 3H), 7.08 (s, 1H), 6.89 (s, 1H), 6.16 (dd, *J* = 26.8, 8.0 Hz, 1H), 3.91 (s, 3H), 3.62-3.53 (m, 1H), 3.51-3.44 (m, 1H), 3.43-3.36 (m, 1H), 3.32-3.23 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.9 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.7 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.6 (d, *J* = 10 Hz), 162.1 (t, *J* = 29 Hz), 142.1 (d, *J* = 6 Hz), 130.8, 129.3, 128.3, 128.1, 127.2, 118.0 (dd, *J* = 268 Hz, 253 Hz), 55.3 (dd, *J* = 24, 18 Hz), 41.4 (t, *J* = 6 Hz), 36.0, 14.0, 12.1; HRMS (ESI) for $C_{18}H_{22}F_2N_3O_2$ $[M+H]^+$ calcd. 350.1675, found 350.1668.

(2S,3S)-2-fluoro-1-morpholino-3-phenyl-4-(1-phenyl-1H-imidazol-2-yl)butane-1,4-dione(**6**) white solid, 80% yield, 30.8 mg (PE:EA = 1.5:1), dr = 14:1, mp = 184-186 °C; Enantiomeric excess established by HPLC analysis using a Chiralpak IC-3 column, ee = >99% (HPLC: IC-3, 280 nm, hexane/isopropanol = 60:40, flow rate 1.0 mL/min, 20°C, t_r (major) = 35.5 min, t_r (minor) = 24.7 min.) $[\alpha]_D^{20}$ = 118.75 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.36-7.28 (m, 3H), 7.08 (s, 1H), 6.89 (s, 1H), 6.16 (dd, *J* = 26.8, 8.0 Hz, 1H), 3.91 (s, 3H), 3.62-3.53 (m, 1H), 3.51-3.44 (m, 1H), 3.43-3.36 (m, 1H), 3.32-3.23 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.9 (dd, *J* = 289.52 Hz, 7.52 Hz, 1F), -103.7 (dd, *J* = 289.52 Hz, 26.32 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 185.6 (d, *J* = 10 Hz), 162.1 (t, *J* = 29 Hz), 142.1 (d, *J* = 6 Hz), 130.8, 129.3, 128.3, 128.1, 127.2, 118.0 (dd, *J* = 268 Hz, 253 Hz), 55.3 (dd, *J* = 24, 18 Hz), 41.4 (t, *J* = 6 Hz), 36.0, 14.0, 12.1; HRMS (ESI) for $C_{18}H_{22}F_2N_3O_2$ $[M+H]^+$ calcd. 350.1675, found 350.1668.

General catalysis procedurefor the synthesis of product 8: A dried 10 mL reaction tube was charged with the catalyst *rac*-**RhS** (8 mol%, 7.0 mg), $Ru(bpy)_3(PF_6)_2$ (2 mol %, 1.7 mg) and the corresponding 2-acyl imidazole **1**(0.1 mmol, 1.0 equiv.).The tube was purged with nitrogen and then acetone (2.0 mL), ethyl bromodifluoroacetate **7** (0.2 mmol, 40.6 mg, 2.0 equiv.) and DIPEA (0.2 mmol, 25.9 mg, 2.0 equiv.)were added via a syringe. The reactionmixture was degassed by three cycles of freeze-pump-thaw. After the mixture was thoroughly degassed, the reaction was then irradiated under a 23W CFL. After completion of the reaction, the crude mixture was purified by flash chromatography (silica gel, mixtures of petroleum ether/ethyl acetate) to afford the pure product **8**.

General catalysis procedurefor the synthesis of product 8a at a 1 mmol scale: A dried reaction tube was charged with the catalyst *rac*-**RhS** (8 mol%, 70 mg), $Ru(bpy)_3(PF_6)_2$ (2 mol %, 17 mg) and the corresponding 2-acyl imidazole **1**(1 mmol, 200 mg).The tube was purged with nitrogen and then acetone (20 mL), ethyl bromodifluoroacetate **7** (2 mmol, 406 mg, 2.0 equiv.) and DIPEA (2 mmol, 259 mg, 2.0 equiv.)were added via a syringe. The reactionmixture was degassed by three cycles of freeze-pump-thaw. After the mixture was thoroughly degassed, the reaction was then irradiated under a 23W CFL. After completion of the reaction, the crude mixture was purified by flash chromatography

(silica gel, petroleum ether:ethyl acetate = 2:1) to afford the pure product **8a** (236 mg, 78% yield).

ethyl (E)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-phenylbut-2-enoate (**8a**) white solid, 79% yield, 24.0 mg, E/Z = >19:1, R_f = 0.22 (PE:EA = 2:1); mp=86-88°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J*=6.8 Hz, 2H), 7.41-7.33 (m, 3H), 7.14 (s, 1H), 7.05 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.10 (s, 3H); 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -127.65 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.4 (d, *J*=7 Hz), 160.8 (d, *J*=34 Hz), 144.8 (d, *J*=275 Hz), 143.2 (d, *J*=5 Hz), 131.5 (d, *J*=9 Hz), 130.7, 130.1, 129.4, 128.9 (d, *J*=5 Hz), 128.6, 126.9, 62.0, 35.9, 13.8; HRMS (ESI) for $C_{16}H_{16}FN_2O_3$ $[M+H]^+$ calcd. 303.1139, found 303.1136.

ethyl (E)-3-(4-chlorophenyl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8b**) colorless oil, 69% yield, 23.2 mg, E/Z = >19:1, R_f = 0.23 (PE:EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 7.14 (s, 1H), 7.07 (s, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 4.10 (s, 1H), 1.21 (d, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -126.67 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$):δ 182.0 (d, *J*=6 Hz), 160.5 (d, *J*=33 Hz), 145.0 (d, *J*=276 Hz), 143.0 (d, *J*=5 Hz), 135.6, 130.4 (d, *J*=8 Hz), 130.3, 130.2, 129.1, 128.9, 127.1, 62.1, 35.8, 13.8; HRMS (ESI) for $C_{16}H_{15}ClFN_2O_3$ $[M+H]^+$ calcd. 337.0750, found 337.0746;

ethyl (E)-3-(4-bromophenyl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8c**) yellow oil, 65% yield, 24.7 mg, E/Z = >19:1, R_f = 0.24 (PE:EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.51 (m, 2H), 7.48-7.45 (m, 2H), 7.13 (s, 1H), 7.06 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.09 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -126.54 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 181.9 (d, *J*=6 Hz), 160.5 (d, *J*=33 Hz), 145.0 (d, *J*=276 Hz), 143.0 (d, *J*=5 Hz), 131.9, 130.5, 130.4 (d, *J*=5 Hz), 129.6, 127.1, 124.0, 62.2, 35.9, 13.8; HRMS (ESI) for $C_{16}H_{15}BrFN_2O_3$ $[M+H]^+$ calcd. 381.0245, found 381.0239.

ethyl (E)-2-fluoro-3-(4-fluorophenyl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8d**) pale yellow oil, 79% yield, 25.3 mg, E/Z = 15:1, R_f = 0.24 (PE:EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.14 (d, *J*=0.8 Hz, 1H), 7.10-7.06 (m, 3H), 4.20 (q, *J*= 7.2 Hz, 3H), 4.10 (s, 3H), 1.21 (t, *J*= 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -110.57 - -110.64 (m, 1F), -127.73 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.2 (d, *J*=7 Hz), 163.1 (d, *J*=248 Hz), 160.6 (d, *J*=33 Hz), 144.8 (d, *J*=274 Hz), 143.1 (d, *J*=5 Hz), 131.0 (dd, *J*=8 Hz, *J*=5 Hz), 130.5 (d, *J*=8 Hz), 130.2, 127.1, 126.7 (d, *J*=3 Hz), 115.8 (d, *J*=22 Hz), 62.1, 35.9, 13.8; HRMS (ESI) for $C_{16}H_{15}F_2N_2O_3$ $[M+H]^+$ calcd. 321.1045, found 321.1039.

ethyl (E)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-(p-tolyl)but-2-enoate (**8e**) white solid, 65% yield, 20.5 mg, E/Z = 13:1, R_f = 0.23 (PE:EA = 2:1); mp=111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=8.0 Hz, 4H), 7.13 (d, *J*=0.8 Hz, 3H), 7.04 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.10 (s,3H), 2.34 (s, 3H), 1.20 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -128.37 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.6 (d, *J*=7 Hz), 160.8 (d, *J*=33 Hz), 144.4 (d, *J*=274 Hz), 143.2 (d, *J*=5 Hz), 139.7, 131.6 (d, *J*=9 Hz), 130.1, 129.4, 128.8 (d, *J*=6 Hz), 127.8, 126.8, 61.9, 35.9, 21.3, 13.8; HRMS (ESI) for $C_{17}H_{18}FN_2O_3$ $[M+H]^+$ calcd. 317.1296, found 317.1291.

ethyl (E)-3-(4-(tert-butyl)phenyl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8f**) white

solid, 74% yield, 26.5 mg, E/Z = 12:1; R_f = 0.24 (PE:EA = 2:1); mp= 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.52(m, 2H), 7.42-7.39 (m, 2H), 7.13 (d, *J*=0.4 Hz, 1H), 7.04 (m, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.10 (s, 3H), 1.29 (s, 9H), 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376MHz, $CDCl_3$): δ -128.35 (s 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.7 (d, *J*=7 Hz), 160.9 (d, *J*=33 Hz), 152.7, 144.4 (d, *J*=274 Hz), 143.2 (d, *J*=5 Hz), 131.5 (d, *J*=8 Hz), 130.1, 128.7 (d, *J*=5 Hz), 127.7, 126.8, 125.7, 61.9, 35.9, 34.7, 31.1, 13.8; HRMS (ESI) for $C_{20}H_{24}FN_2O_3$ $[M+H]^+$ calcd. 359.1765, found 359.1758.

ethyl (E)-2-fluoro-3-(4-methoxyphenyl)-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8g**) white solid, 74% yield, 24.5 mg, E/Z = >19:1, R_f = 0.18 (PE:EA = 2:1); mp = 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J*=8.8 Hz, 2H), 7.12 (d, *J*=0.4 Hz, 1H), 7.04 (s, 1H), 6.90 (d, *J*=8.8 Hz, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 4.11 (s, 3H), 3.80 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -129.53 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.8 (d, *J*=7 Hz), 160.9 (d, *J*=33 Hz), 160.4, 143.9 (d, *J*=273 Hz), 143.2 (d, *J*=5 Hz), 131.3 (d, *J*=7 Hz), 130.6 (d, *J*=6 Hz), 130.0, 126.8, 123.1, 114.2, 61.9, 55.2, 35.9, 13.8; HRMS (ESI) for $C_{17}H_{18}FN_2O_4$ $[M+H]^+$ calcd. 333.1245, found 333.1240.

ethyl (E)-3-(4-ethoxyphenyl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8h**) white solid, 68% yield, 20.5 mg, E/Z = 10:1, R_f = 0.20 (PE:EA = 2:1); mp = 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=8.8 Hz, 2H), 7.12 (s, 1H), 7.04 (s, 1H), 6.88 (d, *J*=9.2 Hz, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 4.10 (s, 3H), 4.03 (q, *J*=7.2 Hz, 2H), 1.39 (t, *J*=7.2 Hz, 3H), 1.20 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -129.64 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.9 (d, *J*=7 Hz), 161.0 (d, *J*=33 Hz), 159.8, 143.8 (d, *J*=273 Hz), 143.3 (d, *J*=5 Hz), 131.3 (d, *J*=8 Hz), 130.6 (d, *J*=6 Hz), 130.0, 126.8, 122.9 (d, *J*=2 Hz), 114.7, 63.4, 61.8, 35.9, 14.6, 13.8; HRMS (ESI) for $C_{18}H_{20}FN_2O_4$ $[M+H]^+$ calcd. 347.1402, found 347.1395.

ethyl (E)-3-([1,1'-biphenyl]-4-yl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8i**) white solid, 76% yield, 28.9 mg, E/Z = >19:1, R_f = 0.24 (PE:EA = 2:1); mp= 123-125°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.67 (m, 2H), 7.62-7.57 (m, 4H), 7.45-7.41 (m, 2H), 7.37-7.33 (m, 1H), 7.15 (d, *J*=0.4 Hz, 1H), 7.06 (s, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 4.12 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -127.37(s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.4 (d, *J*=6 Hz), 160.7 (d, *J*=33 Hz), 144.8 (d, *J*=275 Hz), 143.2 (d, *J*=5 Hz), 142.2, 131.0, 140.1, 131.2 (d, *J*=8 Hz), 130.1, 129.6, 129.4 (d, *J*=6 Hz), 128.8, 127.7, 127.3, 127.0 (d, *J*=6 Hz), 62.0, 35.9, 13.8; HRMS (ESI) for $C_{22}H_{20}FN_2O_3$ $[M+H]^+$ calcd. 379.1452, found 379.1448.

ethyl (E)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-3-(4-(methylthio)phenyl)-4-oxo-but-2-enoate (**8j**) yellow solid, 74% yield, 24.5 mg, E/Z = 12:1, R_f = 0.16 (PE:EA = 2:1); mp= 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50(d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.4 Hz, 2H), 7.12 (s, 1H), 7.05 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.10 (s, 3H), 2.46 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376MHz, $CDCl_3$): δ -128.35 (s 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.7 (d, *J*=7 Hz), 160.9 (d, *J*=33 Hz), 152.7, 144.4 (d, *J*=274 Hz), 143.2 (d, *J*=5 Hz), 131.5 (d, *J*=8 Hz), 130.1, 128.7 (d, *J*=5 Hz), 127.7, 126.8, 125.7, 61.9, 35.9, 34.7, 31.1, 13.8; HRMS (ESI) for $C_{17}H_{18}FN_2O_3S$ $[M+H]^+$ calcd. 349.1017, found 349.1010.

ethyl (E)-3-(3-chlorophenyl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8k**) colorless

oil, 62% yield, 20.8 mg, E/Z = 14:1, R_f = 0.22 (PE:EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.50-7.48 (m, 1H), 7.34-7.32 (m, 2H), 7.15 (s, 1H), 7.07 (s, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 4.10 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -125.84 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 181.7 (d, *J*=6 Hz), 160.4 (d, *J*=34 Hz), 145.3 (d, *J*=277 Hz), 143.0 (d, *J*=4 Hz), 134.6, 132.3, 130.2, 130.1 (d, *J*=9 Hz), 129.9, 129.5, 128.8 (d, *J*=5 Hz), 127.2, 127.1 (d, *J*=5 Hz), 62.2, 35.9, 13.8; HRMS (ESI) for $C_{16}H_{15}ClFN_2O_3$ $[M+H]^+$ calcd. 337.0750, found 337.0753.

ethyl (E)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-(m-tolyl)but-2-enoate (**8l**) white solid, 75% yield, 23.8 mg, E/Z = 15:1; Rf = 0.23 (PE:EA = 2:1); mp=160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (m, 2H), 7.29-7.25 (m, 1H), 7.17-7.15 (m, 1H); 7.14 (s, 1H), 7.04 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.10 (s, 3H), 2.34 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -127.74 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.4 (d, *J*=7 Hz), 160.8 (d, *J*=33 Hz), 144.7 (d, *J*=274 Hz), 143.1 (d, *J*=5 Hz), 138.3, 131.7 (d, *J*=9 Hz), 130.5, 130.3, 130.1, 129.3 (d, *J*=5 Hz), 128.5, 126.9, 126.0 (d, *J*=5 Hz), 62.0, 35.8, 21.4, 13.8; HRMS (ESI) for $C_{17}H_{18}FN_2O_3$ $[M+H]^+$ calcd. 317.1296, found 317.1291.

ethyl (E)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-(o-tolyl)but-2-enoate (**8n**) colorless oil, 53% yield, 16.7 mg, E/Z = 7:1, Rf = 0.36 (PE:EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=7.6 Hz, 2H), 7.28-7.22 (m, 2H), 7.19-7.15 (m, 2H), 7.04 (s, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 4.02 (s, 3H), 2.55 (s, 3H), 1.18 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -122.04 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.2 (d, *J*=7 Hz), 160.3 (d, *J*=35 Hz), 145.3 (d, *J*=270 Hz), 142.7 (d, *J*=5 Hz), 137.5, 131.0 (d, *J*=13 Hz), 130.6, 130.0, 129.0, 128.2(7), 128.2(6), 127.1, 125.4, 62.0, 35.8, 19.9 (d, *J*=3 Hz), 13.7; HRMS (ESI) for $C_{17}H_{18}FN_2O_3$ $[M+H]^+$ calcd. 317.1296, found 317.1289.

ethyl
(E)-3-(3-ethoxy-4-(propionyloxy)phenyl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8o**) yellow oil, 48% yield, 20.0 mg, E/Z = 8:1, R_f = 0.10 (PE:EA=2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74(m, 2H), 7.26 (d, *J*=0.8 Hz, 1H), 7.14-7.12 (m, 2H), 7.06 (s, 1H), 4.34 (q, *J*=7.2 Hz, 2H), 4.21 (q, *J*=7.2 Hz, 2H), 4.14-4.08 (m, 5H), 1.43 (t, *J*=7.2 Hz, 3H), 1.36 (t, *J*=7.2 Hz, 3H), 1.22 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376MHz, $CDCl_3$): δ -125.39 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 181.6, 165.95, 160.4 (d, *J*=33 Hz), 158.2, 142.3 (d, *J*=277 Hz), 142.9 (d, *J*=4 Hz), 135.1, 131.5, 130.8 (d, *J*=8 Hz), 130.2, 127.2, 121.7, 120.4 (d, *J*=4 Hz), 113.9 (d, *J*=6 Hz), 64.7, 62.2, 60.8, 35.8, 14.6, 14.2, 13.8; HRMS (ESI) for $C_{21}H_{24}FN_2O_6$ $[M+H]^+$ calcd.419.1613, found 419.1605.

ethyl (E)-3-(2,3-dihydrobenzofuran-5-yl)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8p**) white solid, 60% yield, 21.0 mg, E/Z = >19:1; R_f = 0.14 (PE:EA = 2:1); mp= 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.37-7.35 (m, 1H), 7.13 (s, 1H), 7.05 (s, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 4.58 (t, *J*=8.8 Hz, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 4.11 (s, 3H), 3.20 (t, *J*=8.8 Hz, 2H), 1.21 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -129.94 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 182.9 (d, *J*=7 Hz), 161.3 (d, *J*=1 Hz), 161.0 (d, *J*=33 Hz), 143.7 (d, *J*=273 Hz), 143.3 (d, *J*=5 Hz), 131.7 (d, *J*=8 Hz), 130.0, 129.6 (d, *J*=5 Hz), 127.8, 126.8, 125.9 (d, *J*=7 Hz), 122.8 (d, *J*=2 Hz), 109.6, 71.7, 61.8, 35.9, 29.4, 13.8; HRMS (ESI) for $C_{18}H_{18}FN_2O_4$ $[M+H]^+$ calcd. 345.1245, found 345.1238.

ethyl (E)-2-fluoro-4-(1-methyl-1H-imidazol-2-yl)-4-oxo-3-(thiophen-3-yl)but-2-enoate (**8q**) white solid, 60% yield, 22.6 mg, E/Z = >19:1; R_f = 0.15 (PE:EA = 2:1); mp= 104-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.62-7.61 (m, 1H), 7.35-7.34 (m, 2H), 7.13 (d, *J*=4.0 Hz , 1H), 7.08 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.14 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -125.33 (s, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ182.3 (d, *J*=7 Hz), 161.8 (d, *J*=33 Hz), 143.8 (d, *J*=275 Hz), 143.1 (d, *J*=4 Hz), 131.1 (d, *J*=3 Hz), 130.1, 128.4 (d, *J*=8 Hz), 127.7 (d, *J*=7 Hz), 127.0, 126.8 (d, *J*=8 Hz), 126.0, 62.0, 35.9, 13.8; HRMS (ESI) for $C_{14}H_{14}FN_2O_3S$ $[M+H]^+$ calcd. 309.0704, found 309.0698.

ethyl (E)-2-fluoro-3-methyl-4-(1-methyl-1H-imidazol-2-yl)-4-oxobut-2-enoate (**8r**) colorless oil, total 35% yield, 8.4 mg, E/Z = 1.7:1, R_f = 0.15 (PE:EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (s, 1H), 7.08 (s, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 4.06 (s, 3H), 2.16 (d, *J*=3.6 Hz, 2H), 1.16 (t, *J*=7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -127.84 (q,*J*=3.4 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 184.7 (d, *J*=7 Hz), 160.1 (d, *J*=34 Hz), 145.6 (d, *J*=266 Hz), 143.1 (d, *J*=4 Hz), 129.9, 129.5 (d, *J*=13 Hz), 127.0, 61.7, 35.8, 14.4 (d, *J*=5 Hz), 13.8; HRMS (ESI) for $C_{11}H_{14}FN_2O_3$ $[M+H]^+$ calcd. 241.0983, found 241.0977.

Trapping Experiments with TEMPO. The reactions were conducted as follows: 2-acyl imidazole **1a** (20.0 mg, 0.10 mmol) reacted with bromodifluoroacetamide **2a** (48.4 mg, 0.2 mmol) or ethyl bromodifluoroacetate **7** (40.6 mg, 0.2 mmol) and TEMPO (46.9 mg, 0.3 mmol), affording **9** in 90% yield and 72% yield. All spectroscopic data of **9**were in agreement with the literaturereport.[11e]

Trapping Experiments with 9. The reactions were conducted as follows: 2-acyl imidazole **1a** (20.0 mg, 0.10 mmol) reacted with bromodifluoroacetamide **2a** (48.4 mg, 0.2 mmol) or ethyl bromodifluoroacetate **7** (40.6 mg, 0.2 mmol) and **9** (51.6 mg, 0.2 mmol), affording **11** in 29% yieldor**12** in 10% yield. All spectroscopic data of **12**were in agreement with the literaturereport.[25]

2,2-difluoro-4-phenyl-1-(piperidin-1-yl)pent-4-en-1-one(**11**)colorless oil, 29% yield, 16 mg, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.35-7.31 (m, 2H), 7.29-7.26 (m, 1H), 5.56 (s, 1H), 5.32 (s, 1H), 3.57 (t, *J* = 5.2 Hz, 2H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.40 (t, *J* = 19.2 Hz, 2H), 1.68-1.52 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -98.3 (t, *J* = 18.8 Hz, 1F); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.6 (t, *J* = 28 Hz), 141.2, 139.5 (t, *J* = 3 Hz), 128.2, 127.5, 126.2, 119.1, 118.2 (t, *J* = 255 Hz), 46.8 (t, *J* = 7 Hz), 44.4, 39.7 (t, *J* = 23 Hz), 26.4, 25.5, 24.4; HRMS (ESI) for $C_{16}H_{20}F_2NO$ $[M+H]^+$ calcd. 280.1513, found 280.1508.

Competitive Experiment: Following the general procedure for the synthesis of product **3**, substrates with different substituent groups were both poured into the reaction mixture. After 14 h, the solvent was rapidly removed under reduced pressure to afford the crude products. The yield ratio (**3e**:**3h** = 3.6:1) was determined by ^{19}F NMR analysis.

Following the general procedure for the synthesis of product **8**, substrates with different substituent groups were both poured into the reaction mixture. After 30 h, the solvent was rapidly removed under reduced pressure and the residue was purified by silica gel chromatography to afford the mixed products. The yield ratio (**8b**:**8e** = 2.1:1) was determined by ^{19}F NMR analysis.

Light-Dark Interval Experiment: The light-dark interval experiments were performed according the general catalysis procedure. The conversion was determined by isolate yield of an aliquot from the reaction mixture. An aliquot was taken out of the reaction system via syringe for every 2 h. The whole process was performed under argon.

Kinetic Isotope Effect of the Difluoroalkylation of 2-acyl imidazole: A dried 10 mL reaction tube was charged with the catalyst *rac*-RhS (4 mol%, 3.5 mg), $Ir(ppy)_2(dtbbpy)(PF_6)_2$ (1 mol%, 0.9 mg) and the corresponding 2-acyl imidazole **1a** (0.1 mmol, 20.0 mg, 1.0 equiv.) and d_2-**1a** (0.1 mmol, 20.2 mg, 1.0 equiv.). The tube was purged with nitrogen and then CH_2Cl_2 (2.0 mL), Bromodifluoroacetamides **2a** (0.2 mmol, 48.4 mg, 2.0 equiv.) and DIPEA (0.2 mmol, 33μl, 2.0 equiv.) were added via a syringe. The reaction mixture was degassed by three cycles of freeze-pump-thaw. After the mixture was thoroughly degassed, the reaction was then irradiated under a 23W CFL. After 6 hours the mixture was removed to a round-bottom flask, and the solvent was removed under reduced pressure. Then the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate. The isolated product was investigated by ^{1}H NMR spectrum. The KIE value was determined by the ratios of the proton integral averaged over two experiments.

Stern-Volmer Quenching Experiments: Stern-Volmer fluorescence quenching experiments were run with freshly prepared solutions of 0.1 mM $Ir(ppy)_2(dtbbpy)PF_6$ in CH_2Cl_2 at room temperature. The solutions were irradiated at 345 nm and fluorescence was measured from 400 nm to 750 nm.

ASSOCIATED CONTENT

Supporting Information

The X-ray crystallographic data (CIF) for product **3l**, **6**, **8i** (CIF), copies of ^{1}H, ^{13}C and ^{19}F spectra for all products are 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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