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Palladium-Catalyzed Heck-Type Difluoroalkylation of Alkenes with Functionalized Difluoromethyl Bromides

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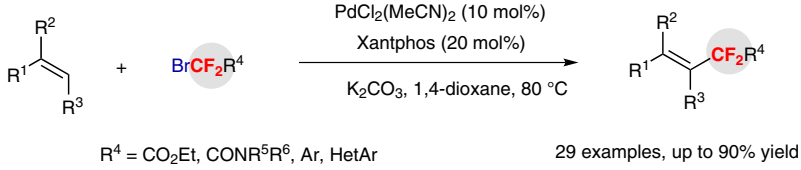

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Abstract An efficient method for the synthesis of difluoroalkylated alkenes through palladium-catalyzed Heck-type reaction with functionalized difluoromethyl bromides has been developed. The advantages of this protocol are its synthetic simplicity, excellent functional group compatibility, and efficient late-stage difluoroalkylation of biologically relevant molecules, thus paving a new way for application in drug discovery and development. Mechanistic studies revealed that the free difluoroalkyl radicals, initiated by a [Pd(0)L_n] via a single-electron-transfer (SET) pathway, were involved in the Heck-type catalytic cycle.

Key words alkenes, difluoroalkylation, functionalized difluoromethyl bromides, Heck-type reaction, palladium

Alkenes are an important structural motif in organic chemistry, and found in a wide range of natural products and functional materials.[1] Owning to the unique properties of difluoromethylene group CF_2, which can increase the dipole moments, enhance the acidity of its neighboring group, and change the molecular conformation,[2] the replacement of CH_2 with its difluorinated counterpart CF_2 at an allylic position could lead to the development of interesting molecules with applications in the life and material sciences. Although, considerable efforts have been devoted to the fluoroalkylation of aromatic compounds over the past few years,[3] efficient strategies for the synthesis of α,α-difluoromethylene alkenes are less studied.[4]

Usually, such difluoroalkylated alkenes can be prepared through cross-coupling of difluoroalkylmetal species with alkenyl halides. In 1986, Kobayashi reported the first example of the reaction of iododifluoroacetate-copper with alkenyl halides under mild reaction conditions, but stoichiometric amount of copper was required.[5] Later on, a copper-catalyzed coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide with alkenyl bromides was developed by Shibuya.[6] Recently, the copper-mediated difluoromethylation of iodoalkenes with nucleophilic difluoromethylated reagents (i.e., $TMSCF_2H$ or n-Bu_3SnCF_2H) were also reported by Hartwig and Prakash, respectively.[7] Despite the importance of these methods, such processes suffer from the use of stoichiometric amount of transition metal, and/or the requirement of multiple steps for the preparation of alkenyl halides. Using functionalized difluoroakyl halides as electrophiles to access α,α-difluoromethylene alkenes is an alternative strategy. In 2000, a nickel-catalyzed ethoxycarbonyldifluoromethylation of vinylzirconiums with bromodifluoroacetate was developed by Schwaebe.[8] However, the yields were low to moderate, and additional steps had to be used for the preparation of vinylzirconiums. Other strategies, including stepwise procedures of addition of free fluoroalkyl radicals to alkenes, followed by base-assisted elimination have also been demonstrated.[9]

From the point view of synthetic simplicity and environmentally benign processes, a transition-metal-catalyzed difluoroalkylation of alkenes through Heck-type reaction from readily and commercially available difluoroalkyl halides (RCF_2–X) would be an attractive and straightforward alternative. Although transition-metal-catalyzed Heck-type reactions between alkenes and alkyl halides are established,[10] similar fluoroalkylation of alkenes with RCF_2–X that are catalyzed by transition metal have remained underdeveloped, and represent a great challenge. Recently, a Pd-mediated Heck-type reaction of [(bromodifluoromethyl)sulfonyl]benzene was reported by Reutrakul.[11] However, the high loading of palladium salt (35 mol%) and low yields of this reaction significantly restrict its widespread synthetic applications. Therefore, it is highly desirable to develop new strategies and efficient catalytic system to address these crucial issues. Very recently, we reported the first example of Pd-catalyzed fluoroalkylation of alkenes with fluoroalkyl bromides.[12,13] As part of our continued efforts in this

area,[14] we herein describe a general and efficient method for the Pd-catalyzed Heck type difluoroalkylation of alkenes with functionalized difluoroalkyl bromides. The reaction proceeds under mild reaction conditions with excellent functional groups compatibility, and paves the way for efficient synthesis of a wide range of difluoroalkylated alkenes.

Our initial studies were focused on the palladium-catalyzed coupling reaction of ethyl bromodifluoroacetae (**1a**) with styrene (**2a**) (Table 1). To our delight, a 41% yield (determined by ^{19}F NMR analysis) of the desired product **3a** was observed when the reaction was conducted with $Pd(OAc)_2$ (10 mol%), Xantphos (20 mol%), and Cs_2CO_3 (2.0 equiv) in 1,4-dioxane at 80 °C (Table 1, entry 1). It was found that the reaction was very sensitive to the phosphine ligands. Among the tested ligands, only bidentate ligand Xantphos could promote the reaction.[15] The choice of the solvent is also crucial for the reaction efficiency. 1,4-Dioxane was the optimal reaction medium; polar solvents, such as DMSO and DMF, failed to provide **3a**. To improve the reaction efficiency further, different bases and palladium precatalysts were investigated (entries 2–8), and an optimal yield (75% upon isolation) was obtained when the reaction was carried out in the presence of $PdCl_2(MeCN)_2$ (10 mol%), Xantphos (20 mol%), and K_2CO_3 (2.0 equiv) (entry 6) while Pd(0) catalysts, such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ afforded lower yields (entries 7, 8). Diminished yields were also observed either by reducing the loading amount of Xantphos or $PdCl_2(MeCN)_2$ (entries 9, 10). However, neither product nor other by-products were observed without the base or the ligand, thus demonstrating the essential role of Pd(0)/Xantphos in the catalytic cycle (entries 11, 12).

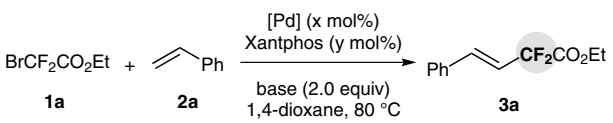
Biographical Sketches

Feng Zhang was born in Sichuan, China (1985). He received his B.S. degree from Southwest University in 2010, and obtained his Ph.D. degree in 2015 from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Science (CAS) under the supervision of Prof. Xingang Zhang. He is currently a research assistant at the Key Laboratory of Organofluorine Chemistry, SIOC, CAS. His research interest is focused on the transition-metal-catalyzed fluoroalkylation reactions.

Qiao-Qiao Min was born in Hubei, China (1984). He received his B.S. degree from Wuhan University in 2008, and obtained his M.S. degree as a joint student of Wuhan University and Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Science (CAS) in 2010 under the supervision of Prof. Haibing Zhou and Prof. Xingang Zhang. He is currently a research assistant of the Key Laboratory of Organofluorine Chemistry, SIOC, CAS. His research interest is focused on the transition-metal-catalyzed C–F/C–R_f (R_f, fluoroalkyl and polyfluoroaryl group) bond formation and mechanistic studies.

Xingang Zhang is a research professor in Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS). He was born in Xinjiang, China (1975). He graduated in 1998 from Sichuan University and received a Ph.D. in 2003 at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS). After his postdoctoral work at the University of Illinois at Urbana Champaign (UIUC) guided by Prof. Wilfred A. van der Donk, he joined the faculty team of SIOC as a research associate professor in 2008, and became research professor in 2012. His current research interests are focused on organofluorine chemistry and chemical biology. He received the Thieme Chemistry Journal Award 2014, the National Science Fund for Distinguished Young Scholars 2014, and the 2015 RSC Fluorine Chemistry Prize.

Table 1 Representative Results for Optimization of Pd-Catalyzed Heck-Type Reactions of Ethyl Bromodifluoroacetate (**1a**) with Styrene (**2a**)[a]



1a **2a** **3a**

Entry	[Pd] (x mol%)	Base	Xantphos (y mol%)	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	Cs_2CO_3	20	41
2	$Pd(OAc)_2$ (10)	K_2CO_3	20	64
3	$PdCl_2$ (10)	K_2CO_3	20	65
4	$PdCl_2(PPh_3)_2$ (10)	K_2CO_3	20	53
5	$PdCl_2$(dppf) (10)	K_2CO_3	20	61
6	$PdCl_2(MeCN)_2$ (10)	K_2CO_3	20	76 (75)
7	$Pd(PPh_3)_4$ (10)	K_2CO_3	20	31
8	$Pd_2(dba)_3$ (5)	K_2CO_3	20	36
9	$PdCl_2(MeCN)_2$ (10)	K_2CO_3	10	23
10	$PdCl_2(MeCN)_2$ (5)	K_2CO_3	10	49
11	$PdCl_2(MeCN)_2$ (10)	none	20	NR
12	$PdCl_2(MeCN)_2$ (10)	K_2CO_3	none	NR

[a] Reaction conditions: **1a** (0.6 mmol, 2.0 equiv), **2a** (0.3 mmol, 1.0 equiv), 1,4-dioxane (2 mL), 24 h. For details of the optimization, see the Supporting Information.
[b] Determined by ^{19}F NMR using fluorobenzene as internal standard. The isolated yield is shown in parentheses.

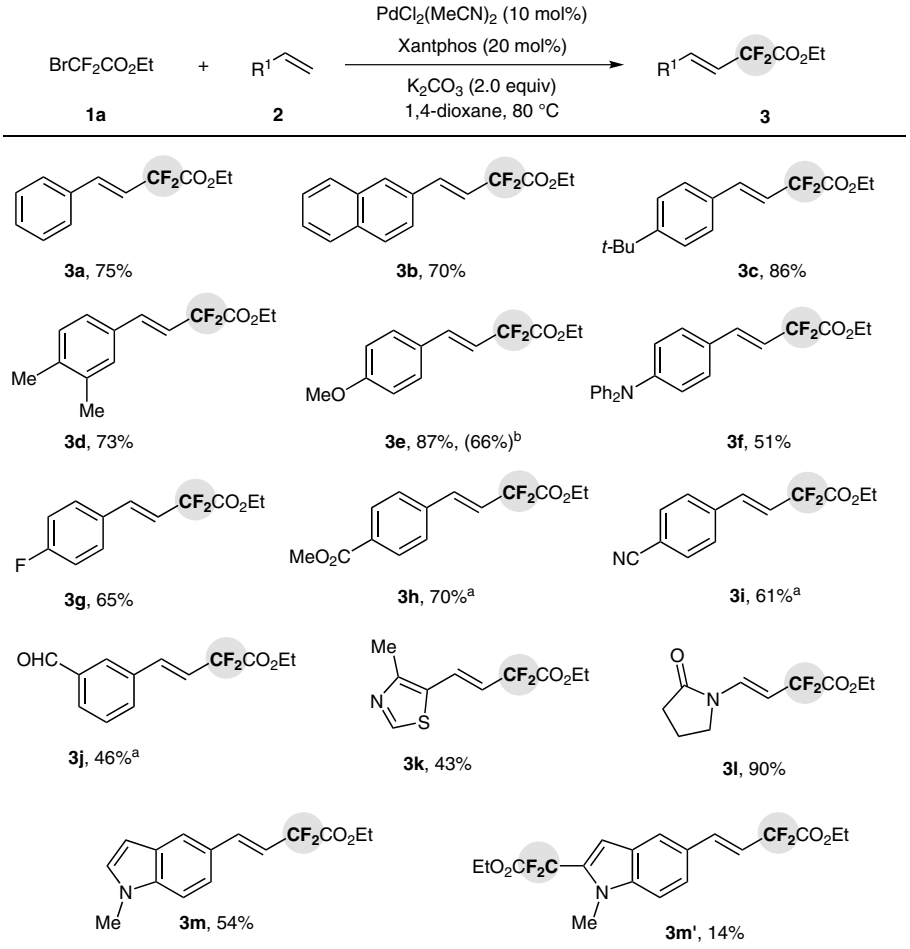
To ascertain the substrate scope of this method, a variety of styrene derivatives was examined with ethyl bromodifluoroacetate (**1a**) (Scheme 1). Many versatile functional groups, such as ester, aldehyde, and nitrile showed good tolerance to the reaction (**3h**–**j**). Importantly, the heterocycle thiazole, was also applicable and provided the corresponding product in a synthetic useful yield (**3k**). In the case of indole derivative **2m**, moderate yield of **3m** was obtained along with a small amount of **3m′** with second ethoxycarbonyldifluoromethyl group installed at C2 position (**3m** and **3m′**). We reasoned that the formation of **3m′** can be ascribed to the reaction of indole ring with free ethoxycarbonyldifluoromethyl radical that was generated by Pd/Xantphos/base with **1a**. Enamide was also a suitable substrate, and provided ethoxycarbonyldifluoromethylated alkene with even higher yield (**3l**). It should be mentioned that the 1-gram-scale reaction of **2e** also underwent smoothly and provided **3e** in good yield, thus highlighting the reliability of the current process.

It was also possible to carry out the reaction with branched alkenes (Scheme 2). Good yields were obtained, when 1,2-dihydronaphthalene (**2n**) and 1*H*-indene (**2o**) were examined (**3n** and **3o**). It is noteworthy that chromenone and quinolinone proceeded smoothly with difluoroacetyl group exclusively installed at the C3 position (**3p** and **3q**). In light of the importance of chromenone and quinolinone in the discovery of biologically interesting molecules,[16] this transformation may have potential applications in the drug discovery and development. Additionally, the successful ethoxycarbonyldifluoromethylation of dihydropyrane opens the possibility of the application of this method for the synthesis of glycomimetics for carbohydrate-based bioactive molecule studies (**3r**).[17] In the case of 1,1-diphenylethylene (**2s**), a mixture of adduct **3s** and reductive Heck-type product **3s′** was obtained. As for terminal branched alkenes bearing an alkyl group, the solely double bond migrated products **3t** and **3u** were obtained, thus providing an alternative strategy to prepare difluoroalkylated allylic compounds.

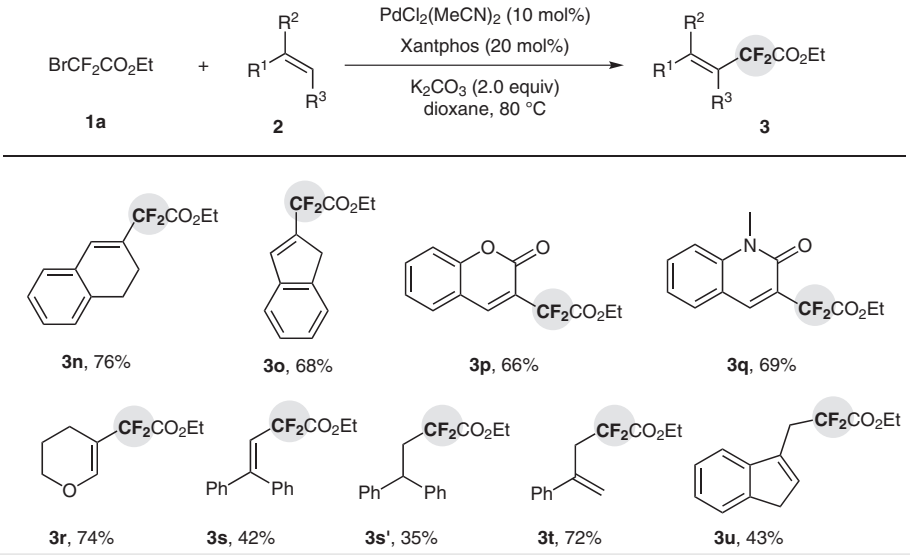
To further demonstrate the generality of this method, different functionalized difluoromethyl bromides were also explored (Scheme 3). High yields were obtained for bromodifluoroacetamide **1b** (**4a**–**c**). Phenylalanine derivative bromodifluoroamide **1c** also afforded the fluorinated alkene in good yield with an excellent functional group tolerance (**4d**). This is noteworthy as we can rapidly access such a valuable building block for fluorinated amino acids based biologically active peptides and protein engineering studies.[18] Furthermore, bromodifluoromethylarene and 2-bromodifluoromethylbenzooxazole were also suitable substrates, providing the corresponding Heck-type products **4e** and **4f** in good yields.

The usefulness of this protocol can also be featured by the late-stage difluoroalkylation of bioactive molecules. As illustrated in Scheme 4, difluoroalkylated alkenes **6** and **7** can be rapidly accessed by reaction of estrone derived alkene **5** with **1a** and **1c**, respectively, thus offering a useful instrument to prepare diversified fluorinated bioactive molecules from one key structure.

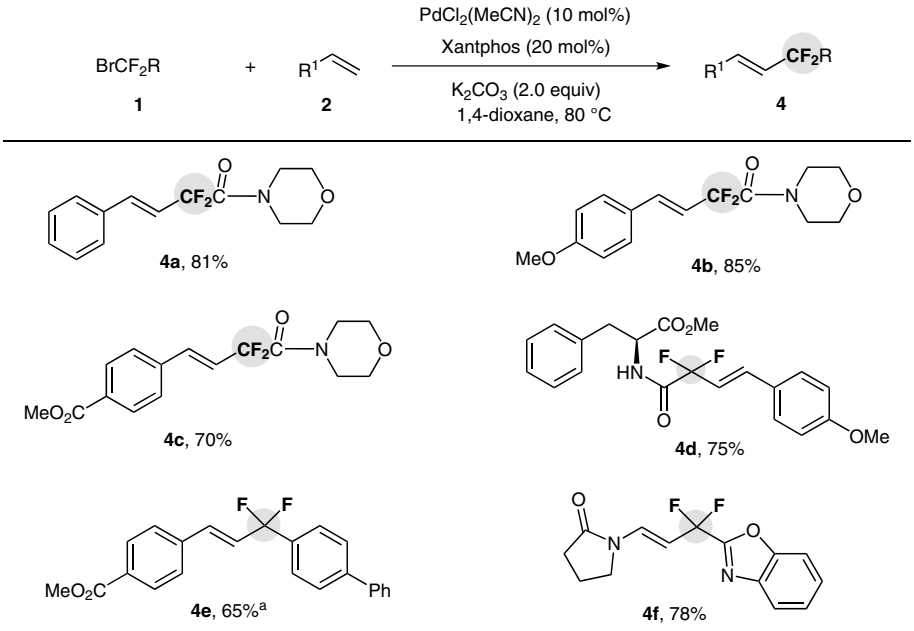
To gain some mechanistic insight into the present reaction, radical inhibition experiments were performed (Scheme 5). It was found that when a reaction mixture of **1a** and **2a** in the presence of $PdCl_2(MeCN)_2$ (10 mol%), Xantphos (20 mol%), and K_2CO_3 in 1,4-dioxane was treated with an ET scavenger 1,4-dinitrobenzene[19] or a radical inhibitor hydroquinone, the yield of **3a** was significantly decreased, thus implying that a SET pathway via an ethoxycarbonyldifluoromethyl radical, was involved in the catalytic cycle.



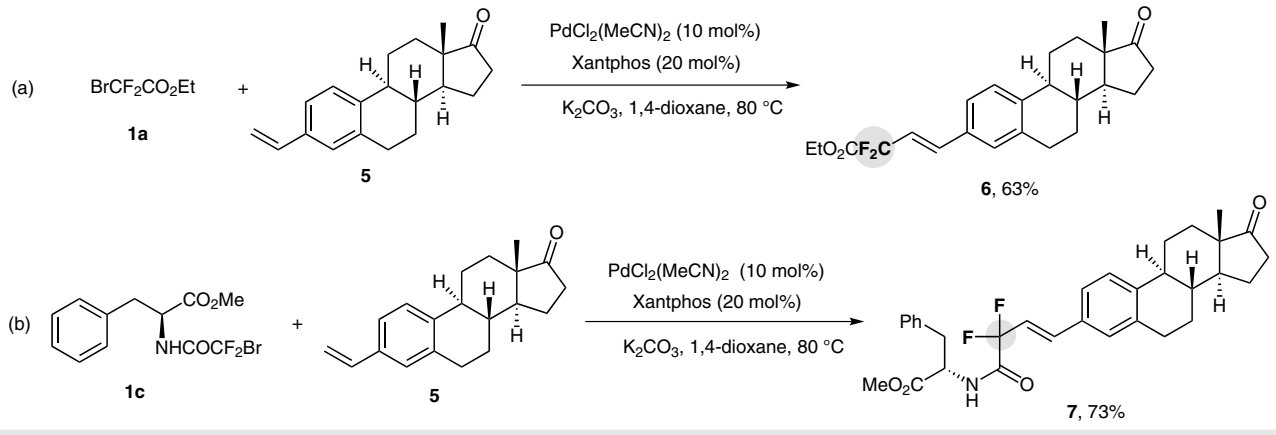
Scheme 1 Pd-catalyzed ethoxycarbonyldifluoromethylation of linear alkenes with ethyl bromodifluoroacetate (**1a**). *Reagents and conditions* (unless otherwise specified): **1a** (0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), 1,4-dioxane (2 mL), 24 h. All reported yields are isolated yields. [a] Molecular sieves (3Å) were used. [b] The reaction was carried out on a 1-gram-scale.



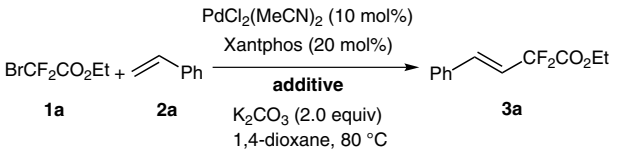
Scheme 2 Pd-catalyzed ethoxycarbonyldifluoromethylation of branched alkenes with ethyl bromodifluoroacetate (**1a**). *Reagents and conditions* (unless otherwise specified): **1a** (0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), 1,4-dioxane (2 mL), 24 h. All reported yields are isolated yields.



Scheme 3 Pd-catalyzed Heck-type reaction of functionalized difluoromethyl bromides with alkenes. *Reagents and conditions* (unless otherwise specified): **1** (0.6 mmol, 2.0 equiv), **2** (0.3 mmol, 1.0 equiv), 1,4-dioxane (2 mL), 24 h. All reported yields are isolated yields. [a] Molecular sieves (3 Å) were used.



Scheme 4 Synthesis of fluorinated biologically relevant active compounds



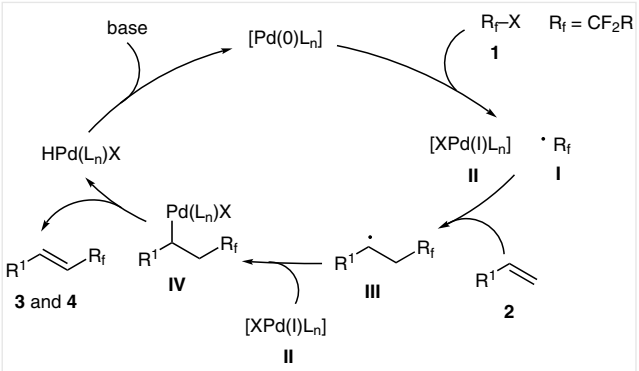
additive	3a, yield (%)
none	76
1,4-dinitrobenzene (0.2 equiv)	27
hydroquinone (0.2 equiv)	20

Scheme 5 Inhibition experiments for Pd-catalyzed cross-coupling of **1a** with **2a**

To further probe that a free fluoroalkyl radical existed in the reaction, a radical clock experiment was conducted. As illustrated in Scheme 6 (a), compound **9** (44% yield) instead of Heck-type product **10** was obtained when compound **8**[20] was treated with **1a** under the standard conditions. This finding suggested that a free ethoxycarbonyldifluoromethyl radical was produced in the reaction,[20] and the formation of the radical species **VI** from **V** was faster than the generation of key intermediate palladium complex **VIII**. Additionally, it has been demonstrated that the formation of iodine atom transfer fluoroalkylated adducts between the alkenes and fluoroalkyl iodides could be promoted by $Pd(PPh_3)_4$ without reformation of alkenes.[21] However, when styrene was treat-

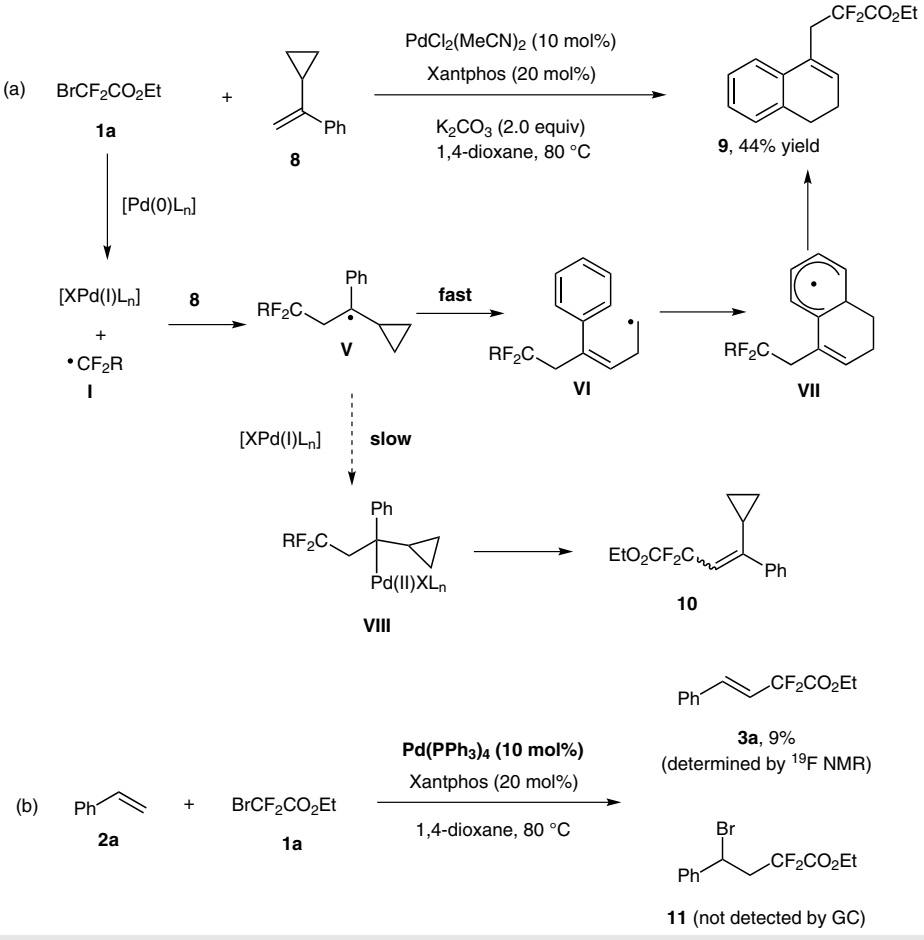
ed with **1a** in the presence of $Pd(PPh_3)_4$ and Xantphos without the base, no benzyl bromide **11** was detected by GC [Scheme 6 (b)]. Instead, fluorinated alkene **3a** was observed in 9% yield (determined by ^{19}F NMR). This finding is in sharp contrast to the result shown in Table 1 entry 7, because if the possibility that the formation of fluorinated alkenes via sequential bromine atom transfer radical addition to alkenes, followed by base-assisted elimination of the resulting benzyl bromides is feasible, some compound **11** should be observed in the absence of base. Thus, such a two-stepwise process for the formation of difluoroalkylated alkenes can be excluded.

On the basis of these preliminary studies, a plausible mechanism was proposed as shown in Scheme 7. The reaction was initiated by a single-electron-transfer (SET) pathway from $[Pd(0)L_n]$ to difluoroalkyl halides.[21] The resulting difluoroalkyl radicals **I** subsequently reacted with alkenes **2** to generate new radical intermediate **III**, which then recombined with $[XPd(I)L_n]$ **II** to form the key palladium species $[(alkyl)Pd(II)L_nX]$ **IV**. Finally, a β-hydride elimination afforded fluoroalkylated alkenes **3** and **4**.



Scheme 7 Proposed reaction mechanism

In conclusion, we have demonstrated an efficient method for the synthesis of difluoroalkylated alkenes through Pd-catalyzed Heck-type reaction with functionalized difluoromethyl bromides. The reaction allowed difluoroalkylation of a variety of alkenes under mild reaction conditions with excellent functional group compatibility. This protocol features synthetic simplicity and can be used for the late stage



Scheme 6 Experiments for mechanistic studies

difluoroalkylation in the synthesis of biologically relevant molecules, thus providing a facile route for application in drug discovery and development. Mechanistic studies revealed that the free fluoroalkyl radicals initiated by a [Pd(0)L_n] via SET pathway was involved in the Heck-type catalytic cycle, and the bidentate ligand Xantphos is essential for the reaction. We believe that such transition-metal-promoted SET pathway would prompt further research in the area of fluoroalkylation.

All reagents were used as received from commercial sources, unless specified otherwise. All reagents were weighed and handled in air, and refilled with an inert atmosphere of N_2 at r.t. Anhydrous K_2CO_3 and 3Å MS were purchased from Aldrich and Alfa, respectively. DMF and DMSO were distilled under reduced pressure from CaH_2. 1,4-Dioxane, toluene, and xylene were distilled from sodium and benzophenone immediately before use. Petroleum ether (PE) used refers to the hydrocarbon mixture with a boiling range of 60–90 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 and AM 500 spectrometer. ^{19}F NMR spectra were recorded on a Bruker AM 400 spectrometer ($CFCl_3$ as an external standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are given in hertz (Hz). Standard abbreviations were used to denote the multiplicities. NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before workup of the reaction.

Pd-Catalyzed Heck-Type Reaction of Functionalized Difluoromethyl Bromides with Alkenes; General Procedure

To a 25 mL Schlenk tube were added $PdCl_2(MeCN)_2$ (10 mol%) and Xantphos (20 mol%) under air, followed by anhydrous K_2CO_3 (powder, 2.0 equiv). The mixture was then evacuated and backfilled with N_2 (3 times). Functionalized difluoromethyl bromide **1** (2 equiv), alkene **2** (0.3 mmol), and freshly distilled 1,4-dioxane (2 mL) were added subsequently. The reaction mixture was heated to 80 °C (oil bath). After stirring for 24 h, the mixture was cooled to r.t., diluted with EtOAc, and filtered over a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel chromatography (PE–EtOAc, 10:1) to give the corresponding product.

Ethyl (*E*)-2,2-Difluoro-4-phenylbut-3-enoate (3a)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 51 mg (75%); colorless oil. This compound is known in the literature.[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H), 7.40–7.36 (m, 3 H), 7.08 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.31 (dt, *J* = 16.4, 11.2 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.9 (t, *J* = 34.8 Hz), 136.8 (t, *J* = 9.4 Hz), 134.1, 129.6, 128.8, 127.4, 118.9 (t, *J* = 25.0 Hz), 112.7 (t, *J* = 248.5 Hz), 63.1, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.3 (dd, *J* = 11.2, 2.2 Hz, 2 F).

Ethyl (*E*)-2,2-Difluoro-4-(naphthalen-2-yl)but-3-enoate (3b)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 58 mg (70%); colorless oil.

IR (film): 2984, 1766, 1653 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 4 H), 7.60 (d, *J* = 8.8 Hz, 1 H), 7.51–7.49 (m, 2 H), 7.25–7.22 (m, 1 H), 6.35 (dt, *J* = 16.4, 11.6 Hz, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.9 (t, *J* = 34.94 Hz), 136.9 (t, *J* = 9.4 Hz), 133.8, 133.2, 131.5 (t, *J* = 1.3 Hz), 128.7 (t, *J* = 1.2 Hz), 128.6, 128.3, 127.7, 126.9, 126.6, 123.2, 119.0 (t, *J* = 25.01 Hz), 112.8 (t, *J* = 248.7 Hz), 63.1, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.12 (dd, *J* = 11.2, 1.1 Hz, 2 F).

MS (EI): *m*/*z* (%) = 276 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{16}H_{14}F_2O_2$: 276.0962; found: 276.0966.

Ethyl (*E*)-4-(4-*tert*-Butylphenyl)-2,2-difluorobut-3-enoate (3c)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); 72 mg (86%); colorless oil.

IR (film): 2963, 1755, 1604, 1514 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 4 H), 6.98 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.19 (dt, *J* = 16.4, 11.6 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.33 (s, 9 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.0 (t, *J* = 35.1 Hz), 153.1, 136.6 (t, *J* = 9.4 Hz), 131.4, 127.2, 125.8, 118.0 (t, *J* = 25.3 Hz), 112.9 (t, *J* = 248.3 Hz), 63.0, 34.8, 31.2, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.2 (dd, *J* = 11.6, 2.2 Hz, 2 F).

MS (EI): *m*/*z* (%) = 282 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{16}H_{20}F_2O_2$: 282.1431; found: 282.1430.

Ethyl (*E*)-4-(3,4-Dimethylphenyl)-2,2-difluorobut-3-enoate (3d)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 56 mg (73%); colorless oil.

IR (film): 2923, 1759, 1593 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (s, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.02 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.24 (dt, *J* = 16.4, 11.6 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 2.27 (m, 6 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.0 (t, *J* = 35.3 Hz), 138.5, 137.0, 136.8 (t, *J* = 9.4 Hz), 131.7, 130.0, 128.6, 124.9, 117.5 (t, *J* = 25.01 Hz), 112.9 (t, *J* = 248.2 Hz), 63.0, 19.7, 19.6, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.0 (dd, *J* = 11.2, 1.9 Hz, 2 F).

MS (EI): *m*/*z* (%) = 254 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{16}F_2O_2$: 254.1118; found: 254.1121.

Ethyl (*E*)-2,2-Difluoro-4-(4-methoxyphenyl)but-3-enoate (3e)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 67 mg (87%); colorless oil.

IR (film): 2926, 1766, 1607, 1514 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 2 H), 7.01 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.15 (dt, *J* = 16.4, 11.2 Hz, 1 H), 4.34 (q, *J* = 7.6 Hz, 2 H), 3.82 (s, 3 H), 1.35 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.1 (t, *J* = 35.3 Hz), 160.7, 136.2 (t, *J* = 9.5 Hz), 128.8, 126.8, 116.3 (t, *J* = 25.0 Hz), 114.2, 112.9 (t, *J* = 248.2 Hz), 63.0, 55.3, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –102.7 (d, *J* = 10.8 Hz, 2 F).

MS (EI): *m*/*z* (%) = 256 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}F_2O_3$: 256.0911; found: 256.0912.

Ethyl (*E*)-4-[4-(Diphenylamino)phenyl]-2,2-difluorobut-3-enoate (3f)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 60 mg (51%); colorless oil.

IR (film): 3034, 1766, 1592, 1492 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 7 H), 7.04–6.99 (m, 6 H), 6.95–6.92 (m, 2 H), 6.90 (dt, *J* = 16.2, 2.4 Hz, 1 H), 6.07 (dt, *J* = 16.2, 11.4 Hz, 1 H), 4.26 (q, *J* = 6.9 Hz, 2 H), 1.28 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6 (t, *J* = 35.1 Hz), 148.7, 146.6, 135.7 (t, *J* = 9.4 Hz), 128.9, 127.9, 126.9, 124.5, 123.2, 121.8, 115.9 (t, *J* = 25.0 Hz), 112.5 (t, *J* = 246.7 Hz), 63.5, 13.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –103.1 (d, *J* = 11.8 Hz, 2 F).

MS (EI): *m*/*z* (%) = 393 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{24}H_{21}F_2NO_2$: 393.1540; found: 393.1538.

Ethyl (*E*)-2,2-Difluoro-4-(4-fluorophenyl)but-3-enoate (3g)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 48 mg (65%); colorless oil.

IR (film): 2927, 1762, 1606, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 2 H), 7.08–7.03 (m, 2 H), 7.02 (m, 1 H), 7.19 (dt, *J* = 16.0, 2.4 Hz, 1 H), 6.22 (dt, *J* = 16.0, 11.2 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.8 (t, *J* = 34.9 Hz), 163.4 (d, *J* = 250.0 Hz), 135.5 (t, *J* = 9.5 Hz), 130.3 (d, *J* = 3.4 Hz), 129.2 (d, *J* = 8.4 Hz), 118.6 (td, *J* = 25.0, 2.2 Hz), 115.9 (d, *J* = 21.8 Hz), 112.6 (t, *J* = 248.5 Hz), 63.1, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.2 (d, *J* = 11.2 Hz, 2 F), –110.92 (m, 1 F).

MS (EI): *m*/*z* (%) = 244 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_{11}F_3O_2$: 244.0711; found: 244.0712.

Methyl (*E*)-4-(4-Ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)benzoate (3h)

Molecular sieves 3 Å (100 mg) were used. The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 60 mg (70%); colorless oil.

IR (film): 2954, 1768, 1723, 1657 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.10 (dt, *J* = 16.8, 2.4 Hz, 1 H), 6.39 (dt, *J* = 16.8, 11.2 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.91 (s, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 166.4, 163.6 (t, *J* = 34.5 Hz), 138.3, 135.7 (t, *J* = 9.4 Hz), 130.9, 130.1, 127.3, 121.2 (t, *J* = 25.0 Hz), 112.3 (t, *J* = 249.0 Hz), 63.2, 52.2, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.7 (dd, *J* = 10.8, 2.6 Hz, 2 F).

MS (EI): *m*/*z* (%) = 284 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}F_2O_4$: 284.0860; found: 284.0863.

Ethyl (*E*)-4-(4-Cyanophenyl)-2,2-difluorobut-3-enoate (3i)

Molecular sieves 3 Å (100 mg) were used. The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 46 mg (61%); colorless oil.

IR (film): 2986, 2229, 1766, 1658 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.08 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.41 (dt, *J* = 16.4, 11.6 Hz, 1 H), 4.35 (q, *J* = 6.8 Hz, 2 H), 1.36 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.4 (t, *J* = 34.3 Hz), 138.4, 134.9 (t, *J* = 9.4 Hz), 132.6, 127.9, 122.5 (t, *J* = 25.1 Hz), 118.3, 113.0, 112.1 (t, *J* = 249.5 Hz), 63.4, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.9 (dd, *J* = 10.9, 2.2 Hz, 2 F).

MS (EI): *m*/*z* (%) = 251 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{11}F_2NO_2$: 251.0758; found: 251.0757.

Ethyl (*E*)-2,2-Difluoro-4-(3-formylphenyl)but-3-enoate (3j)

Molecular sieves 3 Å (100 mg) were used. The product was purified by silica gel chromatography (PE–EtOAc, 8:1); yield: 35 mg (46%); colorles oil.

IR (film): 2925, 2851, 1764, 1699, 1659 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.03 (s, 1 H), 7.96 (s, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.69 (d, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.13 (dt, *J* = 16.0, 2.4 Hz, 1 H), 6.41 (dt, *J* = 16.0, 11.6 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 163.6 (t, *J* = 34.3 Hz), 136.9, 135.4 (t, *J* = 9.3 Hz), 135.1, 133.1, 130.7, 129.6, 128.1, 120.8 (t, *J* = 25.0 Hz), 121.3 (t, *J* = 247.4 Hz), 63.2, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.6 (dd, *J* = 11.2, 2.3 Hz, 2 F).

MS (EI): *m*/*z* (%) = 254 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}F_2O_3$: 254.0755; found: 254.0758.

Ethyl (*E*)-2,2-Difluoro-4-(4-methylthiazol-5-yl)but-3-enoate (3k)

The product was purified by silica gel chromatography (PE–EtOAc, 3:1), yield: 32 mg (43%); colorless oil.

IR (film): 2919, 1732, 1463 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1 H), 7.19 (dt, *J* = 16.0, 2.0 Hz, 1 H), 6.02 (dt, *J* = 16.0, 11.2 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 2.50 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.5 (t, *J* = 34.6 Hz), 154.1, 151.9, 127.4, 126.4 (t, *J* = 10.1 Hz), 120.3 (t, *J* = 25.2 Hz), 112.1 (t, *J* = 249.2 Hz), 63.2, 15.4, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.2 (dd, *J* = 11.6, 1.1 Hz, 2 F).

MS (EI): *m*/*z* (%) = 247 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}F_2NO_2S$: 247.0479; found: 247.0483.

Ethyl (*E*)-2,2-Difluoro-4-(2-oxopyrrolidin-1-yl)but-3-enoate (3l)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 63 mg (90%); colorless oil.

IR (film): 2986, 1766, 1724, 1659 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (m, 1 H), 5.06 (dt, *J* = 14.4 Hz, *J* = 11.2 Hz, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 3.53 (t, *J* = 7.2 Hz, 2 H), 2.53 (t, *J* = 8.0 Hz, 2 H), 2.16 (m, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.9, 163.4 (t, *J* = 35.4 Hz), 130.3 (t, *J* = 10.4 Hz), 112.9 (d, *J* = 282.1 Hz), 101.1 (t, *J* = 26.2 Hz), 63.0, 44.8, 30.8, 17.3, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –100.0 (d, *J* = 10.9 Hz, 2 F).

MS (EI): *m*/*z* (%) = 233 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{10}H_{13}F_2NO_3$: 233.0863; found: 233.0860.

Ethyl (*E*)-2,2-Difluoro-4-(1-methyl-1*H*-indol-5-yl)but-3-enoate (3m) and Ethyl (*E*)-4-[3-(2-Ethoxy-1,1-difluoro-2-oxoethyl)-1-methyl-1*H*-indol-5-yl]-2,2-difluorobut-3-enoate (3m′)

A mixture of **3m** and **3m′** (52 mg) as a colorless oil was purified by silica gel chromatography (PE–EtOAc, 3:1); **3m**/**3m′** = 3.9:1, determined by ^{19}F NMR spectroscopy; **3m**, 54%; **3m′**, 14%. The mixture was further purified by preparative HPLC (column: ODS HYPERSIL (250 × 10 mm Φ 5 μm); flow rate: 4.5 mL/min; temperature: 25 °C; wavelength: UV 220 nm, MeCN–H_2O (v/v) = 70:30; time: 10 min) to give pure **3m** and **3m′**.

3m

IR (film): 2916, 1766, 1652, 1543 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.37 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.30 (d, *J* = 8.6 Hz, 1 H), 7.19 (dt, *J* = 16.0, 2.4 Hz, 1 H), 7.06 (d, *J* = 2.8 Hz, 1 H), 6.50 (dd, *J* = 3.2, 0.8 Hz, 1 H), 6.25 (dt, *J* = 16.0, 11.6 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.80 (s, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 35.1 Hz), 138.3 (t, *J* = 9.4 Hz), 137.4, 129.9, 128.6, 125.7, 121.4, 120.5, 115.4 (t, *J* = 24.9 Hz), 113.3 (t, *J* = 246.8 Hz), 109.7, 101.8, 63.0, 33.0, 14.0.

^{19}F NMR (375 MHz, $CDCl_3$): δ = –102.3 (dd, *J* = 11.3, 2.6 Hz, 2 F).

MS (EI): *m*/*z* (%) = 279 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}F_2O_2$: 279.1071; found: 279.1073.

3m′

IR (film): 2913, 1760, 1682, 1614 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 7.17 (dt, *J* = 16.0, 2.4 Hz, 1 H), 6.80 (s, 1 H), 6.26 (dt, *J* = 16.0, 11.6 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.88 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.2 (t, *J* = 35.1 Hz), 163.0 (t, *J* = 34.1 Hz), 139.4, 137.5 (t, *J* = 9.4 Hz), 130.5 (t, *J* = 29.0 Hz), 126.9, 126.2, 122.8, 122.3, 116.6 (t, *J* = 24.8 Hz), 113.0 (t, *J* = 248.3 Hz), 111.0 (t, *J* = 248.8 Hz), 110.3, 105.3 (t, *J* = 6.2 Hz), 63.7, 63.0, 31.4, 14.0, 13.9.

^{19}F NMR (375 MHz, $CDCl_3$): δ = –98.7 (s, 2 F), –102.6 (dd, *J* = 11.6, 2.2 Hz, 2 F).

MS (EI): *m*/*z* (%) = 401 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{19}F_4NO_4$: 401.1250; found: 401.1245.

Ethyl 2-(3,4-Dihydronaphthalen-2-yl)-2,2-difluoroacetate (3n)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 57 mg (76%); colorless oil.

IR (film): 2984, 1763, 1652, 1455 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 2 H), 7.15–7.13 (m, 2 H), 6.87 (s, 1 H), 4.35 (q, *J* = 6.8 Hz, 2 H), 2.88 (t, *J* = 8.4 Hz, 2 H), 2.44 (td, *J* = 8.4, 1.2 Hz, 2 H), 1.35 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.8 (t, *J* = 35.1 Hz), 135.4, 131.8, 130.5 (t, *J* = 23.6 Hz), 128.8, 128.6 (t, *J* = 9.1 Hz), 127.7, 127.5, 126.8, 113.6 (t, *J* = 249.7 Hz), 63.0, 27.3, 21.2 (t, *J* = 2.9 Hz), 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –107.2 (s, 2 F).

MS (EI): *m*/*z* (%) = 252 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}F_2O_2$: 252.0962; found: 252.0960.

Ethyl 2,2-Difluoro-2-(1*H*-inden-2-yl)acetate (3o)

The product was purified by silica gel chromatography (PE–EtOAc, 8:1); yield: 48 mg (68%); colorless oil.

IR (film): 2963, 1766, 1462 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 6.8 Hz, 1 H), 7.48 (d, *J* = 6.8 Hz, 1 H), 7.35–7.28 (m, 2 H), 7.23 (m, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.63 (s, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 34.8 Hz), 143.4, 142.3 (t, *J* = 0.9 Hz), 137.8 (t, *J* = 26.6 Hz), 134.3 (t, *J* = 7.5 Hz), 126.9, 126.7, 124.1, 122.6, 112.7 (t, *J* = 247.5 Hz), 63.2, 37.4 (t, *J* = 2.4 Hz), 14.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –100.58 (d, *J* = 1.5 Hz, 2 F).

MS (EI): *m*/*z* (%) = 238 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}F_2O_2$: 238.0805; found: 238.0802.

Ethyl 2,2-Difluoro-2-(2-oxo-2*H*-chromen-4-yl)acetate (3p)

The product was purified by silica gel chromatography (PE–EtOAc, 6:1); yield: 53 mg (66%); colorless oil.

IR (film): 2923, 1778, 1737, 1637, 1601 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.66–7.61 (m, 2 H), 7.39–7.35 (m, 2 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 162.2 (t, *J* = 32.6 Hz), 157.9 (t, *J* = 4.6 Hz), 154.2, 141.9 (t, *J* = 7.1 Hz), 133.7, 129.2, 125.2, 121.2 (t, *J* = 25.5 Hz), 117.5, 117.0, 110.5 (t, *J* = 250.8 Hz), 63.6, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.2 (s, 2 F).

MS (EI): *m*/*z* (%) = 268 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{10}F_2O_4$: 268.0547; found: 268.0545.

Ethyl 2,2-Difluoro-2-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)acetate (3q)

The product was purified by silica gel chromatography (PE–EtOAc, 2:1); yield: 58 mg (69%); colorless oil.

IR (film): 2988, 1777, 1659, 1598 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.67 (m, 2 H), 7.39 (d, *J* = 9.0 Hz, 1 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 3.70 (s, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7 (t, *J* = 32.6 Hz), 158.9 (t, *J* = 4.4 Hz), 140.0, 137.0 (t, *J* = 7.0 Hz), 131.9, 129.7, 124.5 (t, *J* = 24.3 Hz), 122.4, 118.5, 113.9, 110.9 (t, *J* = 247.6 Hz), 62.6, 28.9, 13.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –107.0 (s, 2 F).

MS (EI): *m*/*z* (%) = 281 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{13}F_2NO_3$: 281.0863; found: 281.0861.

Ethyl 2-(3,4-Dihydro-2*H*-pyran-5-yl)-2,2-difluoroacetate (3r)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 46 mg (74%); colorless oil. This compound is known in the literature.[9b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 4.31 (q, *J* = 6.8 Hz, 2 H), 3.99 (t, *J* = 5.2 Hz, 2 H), 2.12 (t, *J* = 5.2 Hz, 2 H), 1.88 (m, 2 H), 1.33 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.0 (t, *J* = 35.9 Hz), 146.3 (t, *J* = 11.0 Hz), 114.2 (t, *J* = 248.1 Hz), 105.8 (t, *J* = 0.3 Hz), 65.9, 62.7, 21.0, 17.8 (t, *J* = 2.5 Hz), 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –104.8 (d, *J* = 0.7 Hz, 2 F).

MS (EI): *m*/*z* (%) = 206 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_9H_{12}F_2O_3$: 206.0755; found: 206.0760.

Ethyl 2,2-Difluoro-4,4-diphenylbut-3-enoate (3s) and Ethyl 2,2-Difluoro-4,4-diphenylbutanoate (3s′)

A mixture of **3s** and **3s′** (70 mg, **3s**/**3s′** = 1.2:1, determined by ^{19}F NMR spectroscopy; **3s**, 42%; **3s′**, 35%) as a colorless oil was purified by silica gel chromatography (PE–EtOAc, 10:1). The mixture was further purified by preparative HPLC (column: ODS HYPERSIL (250 × 10 mm Φ 5 μm); flow rate: 4.0 mL/min; temperature: 25 °C; wavelength: UV 220 nm, MeCN–H_2O (v/v) = 70:30; time: 20 min) to give pure **3s** and **3s′**. The compounds **3s** and **3s′** are both known in the literature.[9b]

3s

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 6 H), 7.27–7.25 (m, 2 H), 7.21–7.19 (m, 2 H), 6.27 (t, *J* = 12.0 Hz, 1 H), 3.89 (q, *J* = 7.2 Hz, 2 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.4 (t, *J* = 34.1 Hz), 150.9 (t, *J* = 9.6 Hz), 140.4, 137.1, 129.8 (t, *J* = 2.0 Hz), 129.0, 128.5, 128.3, 127.9, 127.8, 119.4 (t, *J* = 28.4 Hz), 112.5 (t, *J* = 245.2 Hz), 62.7, 13.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –91.2 (d, *J* = 17.7 Hz, 2 F).

3s′

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 8 H), 7.27–7.17 (m, 2 H), 7.21–7.19 (m, 2 H), 4.27 (t, *J* = 7.2 Hz, 1 H), 3.82 (q, *J* = 7.2 Hz, 2 H), 2.94 (td, *J* = 15.2, 7.2 Hz, 2 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

^{19}F NMR (375 MHz, $CDCl_3$): δ = –103.5 (t, *J* = 15.3 Hz, 2 F).

Ethyl 2,2-Difluoro-4-phenylpent-4-enoate (3t)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); 52 mg (72%); colorless oil. This compound is known in the literature.[9b]

IR (film): 2963, 1770, 1625, 1493 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 5.50 (s, 1 H), 5.31 (s, 1 H), 4.04 (q, *J* = 7.2 Hz, 2 H), 2.50 (s, 3 H), 3.30 (t, *J* = 16.0 Hz, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 35.1 Hz), 140.1, 138.8 (t, *J* = 3.5 Hz), 128.3, 127.9, 126.3, 119.2, 115.1 (t, *J* = 252.3 Hz), 62.7, 40.3 (t, *J* = 24.1 Hz), 13.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.4 (t, *J* = 15.0 Hz, 2 F).

Ethyl 2,2-Difluoro-3-(1*H*-inden-3-yl)propanoate (3u)

The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 33 mg (43%); colorless oil.

IR (film): 2984, 1768, 1601, 1462 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.2 Hz, 1 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.22 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.48 (s, 1 H), 4.23 (q, *J* = 6.8 Hz, 2 H), 3.39 (t, *J* = 16.8 Hz, 2 H), 3.39 (s, 2 H), 1.23 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 163.9 (t, *J* = 36.5 Hz), 144.4, 143.7, 134.0, 133.9 (t, *J* = 4.4 Hz), 126.2, 125.0, 123.8, 119.1, 115.4 (t, *J* = 252.0 Hz), 62.8, 38.2, 33.1 (t, *J* = 24.8 Hz), 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.2 (t, *J* = 16.1 Hz, 2 F).

MS (EI): *m*/*z* (%) = 252 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}F_2O_2$: 252.0962; found: 252.0963.

(*E*)-2,2-Difluoro-1-morpholino-4-phenylbut-3-en-1-one (4a)

The product was purified by silica gel chromatography (PE–EtOAc, 5:1); yield: 65 mg (81%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H), 7.39–7.33 (m, 3 H), 7.10 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.44 (dt, *J* = 16.4, 11.2 Hz, 1 H), 3.74–3.98 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0 (t, *J* = 30.4 Hz), 135.7 (t, *J* = 9.8 Hz), 134.0 (t, *J* = 1.1 Hz), 129.5, 128.8, 127.4, 119.9 (t, *J* = 24.3 Hz), 115.2 (t, *J* = 249.3 Hz), 66.7, 66.6, 46.6 (t, *J* = 5.4 Hz), 43.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –95.1 (dd, *J* = 10.7, 2.2 Hz, 2 F).

MS (EI): *m*/*z* (%) = 267 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{15}F_2NO_2$: 267.1071; found: 267.1075.

(*E*)-2,2-Difluoro-4-(4-methoxyphenyl)-1-morpholinobut-3-en-1-one (4b)

The product was purified by silica gel chromatography (PE–EtOAc, 5:1); yield: 76 mg (85%); colorless oil.

IR (film): 2985, 1742, 1447, 1373 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 2 H), 6.93 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.29 (dt, *J* = 16.4, 10.8 Hz, 1 H), 3.82 (s, 3 H), 3.73–3.66 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2 (t, *J* = 30.4 Hz), 160.4, 135.3 (t, *J* = 9.7 Hz), 128.8, 126.8, 117.4 (t, *J* = 24.4 Hz), 115.5 (t, *J* = 247.0 Hz), 114.2, 66.7, 66.7, 55.3, 46.7 (t, *J* = 4.9 Hz), 43.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –94.3 (dd, *J* = 10.9, 1.5 Hz, 2 F).

MS (EI): *m*/*z* (%) = 297 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{17}F_2NO_3$: 297.1177; found: 297.1179.

Methyl (*E*)-4-(3,3-Difluoro-4-morpholino-4-oxobut-1-en-1-yl)benzoate (4c)

The product was purified by silica gel chromatography (PE–EtOAc, 5:1); yield: 68 mg (70%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.02 (m, 1 H), 6.56 (dt, *J* = 16.4, 11.2 Hz, 1 H), 3.91 (s, 3 H), 3.72–3.69 (m, 8 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 166.4, 161.7 (t, *J* = 31.04 Hz), 138.5, 134.2 (t, *J* = 9.8 Hz), 130.7, 130.0, 127.3, 122.4 (t, *J* = 23.8 Hz), 115.1 (t, *J* = 250.8 Hz), 66.7, 52.2, 46.5 (t, *J* = 5.0 Hz), 43.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –96.0 (d, *J* = 11.2 Hz, 2 F).

MS (EI): *m*/*z* (%) = 325 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{16}H_{17}F_2NO_4$: 325.1126; found: 325.1125.

Methyl (*S*,*E*)-2-[2,2-Difluoro-4-(4-methoxyphenyl)but-3-enamido]-3-phenylpropanoate (4d)

The product was purified by silica gel chromatography (PE–EtOAc, 3:1); yield: 87 mg (75%); colorless oil.

IR (film): 2955, 2925, 1748, 1740, 1604, 1514 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H), 7.15–7.14 (m, 3 H), 7.00–6.97 (m, 2 H), 6.86 (dt, *J* = 16.5, 2.1 Hz, 1 H), 6.80–6.78 (m, 3 H), 6.06 (dt, *J* = 16.5, 11.4 Hz, 1 H), 4.82 (dd, *J* = 13.5, 6.0 Hz, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H), 3.16 (dd, *J* = 14.1, 5.7 Hz, 1 H), 3.05 (dd, *J* = 14.1, 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 163.1 (t, *J* = 31.3 Hz), 160.3, 135.8 (t, *J* = 9.6 Hz), 134.7, 128.8, 128.5, 128.2, 126.9, 126.4, 115.9 (t, *J* = 25.0 Hz), 113.9 (t, *J* = 247.4 Hz), 113.7, 54.8, 52.7, 52.1, 37.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –102.89 (d, *J* = 11.5 Hz, 2 F).

MS (EI): *m*/*z* (%) = 389 (M^+).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{21}H_{21}F_2NO_4$: 389.1439; found: 389.1436.

Methyl (*E*)-4-[3-([1,1′-Biphenyl]-4-yl)-3,3-difluoroprop-1-en-1-yl]benzoate (4e)

Molecular sieves 3Å (100 mg) were used. The product was purified by silica gel chromatography (PE–EtOAc, 10:1); yield: 71 mg (65%); white solid; mp 81–84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 2 H), 7.65 (m, 6 H), 7.49 (m, 4 H), 7.40 (m, 1 H), 6.94 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.59 (dt, *J* = 16.4, 10.0 Hz, 1 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 143.1, 140.1, 139.1, 135.2 (t, *J* = 28.0 Hz), 133.2 (t, *J* = 9.2 Hz), 130.4, 130.1, 128.9, 127.9, 127.3, 127.2, 127.2, 126.7 (t, *J* = 29.7 Hz), 126.0 (t, *J* = 5.3 Hz), 119.7 (t, *J* = 237.1 Hz), 52.2.

^{19}F NMR (375 MHz, $CDCl_3$): δ = –91.2 (dd, *J* = 9.7, 0.8 Hz, 2 F).

MS (ESI): *m*/*z* (%) = 364 (M^+).

HRMS: *m*/*z* [M]$^+$calcd for $C_{23}H_{18}F_2O_2$: 364.1275; found: 364.1272.

(*E*)-1-[3-(Benzo[*d*]oxazol-2-yl)-3,3-difluoroprop-1-en-1-yl]pyrrolidin-2-one (4f)

The product was purified by silica gel chromatography (PE–EtOAc, 1:1); yield: 65 mg (78%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.6 Hz, 1 H), 7.68 (dt, *J* = 14.4, 2.0 Hz, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 7.45 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1 H), 5.41 (dt, *J* = 14.4, 10.4 Hz, 1 H), 3.61 (t, *J* = 7.2 Hz, 2 H), 2.53 (t, *J* = 8.4 Hz, 2 H), 2.16 (m, 2 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.9, 158.2 (t, *J* = 36.7 Hz), 150.7, 139.9, 130.4 (t, *J* = 10.0 Hz), 126.8, 125.3, 121.3, 113.8 (t, *J* = 238.9 Hz), 111.4, 101.8 (t, *J* = 26.0 Hz), 44.9, 30.9, 17.4.

^{19}F NMR (375 MHz, $CDCl_3$): δ = –90.7 (dd, *J* = 10.9, 1.9 Hz, 2 F).

MS (EI): *m*/*z* (%) = 278 (M^+).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{14}H_{12}F_2NO_2$: 278.0867; found: 278.0866.

Ethyl (*E*)-2,2-Difluoro-4-[(8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl]but-3-enoate (6)

The product was purified by silica gel chromatography (PE–EtOAc, 5:1); yield: 76 mg (63%); white solid, mp 150–154 °C.

IR (film): 2931, 1766, 1739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 7.18 (s, 1 H), 7.01 (dt, *J* = 16.4, 2.8 Hz, 1 H), 6.25 (dt, *J* = 16.4, 11.6 Hz, 1 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 2.92 (m, 2 H), 2.51 (dd, *J* = 14.1, 8.8 Hz, 1 H), 2.42–2.40 (m, 1 H), 2.31 (m, 1 H), 2.18–2.11 (m, 1 H), 2.09–2.01 (m, 2 H), 1.97–1.95 (m, 1 H), 1.65–1.58 (m, 2 H), 1.55–1.47 (m, 3 H), 1.43–1.42 (m, 1 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 0.91 (s, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 220.6, 164.0 (t, *J* = 35.1 Hz), 141.7, 137.1, 136.6 (t, *J* = 9.3 Hz), 131.7, 128.1, 125.9, 124.8, 118.1 (t, *J* = 25.01 Hz), 112.8 (t, *J* = 248.3 Hz), 63.1, 50.5, 47.9, 44.5, 38.0, 35.8, 31.6, 29.3, 26.3, 25.7, 21.6, 14.0, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.1 (d, *J* = 11.7 Hz, 2 F).

MS (EI): *m*/*z* (%) = 402 (M^+).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{24}H_{28}F_2O_3$: 402.2007; found: 402.2008.

Methyl (*R*)-2-{(*E*)-2,2-Difluoro-4-[(8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl]but-3-enamido}-3-phenylpropanoate (7)

The product was purified by silica gel chromatography (PE–EtOAc, 2:1); yield: 118 mg (73%); white solid; mp 104–108 °C.

IR (ATR, film): 2931, 2552, 1739, 1704, 1531 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 5 H), 7.16 (s, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.95 (dt, *J* = 16.4, 2.4 Hz, 1 H), 6.86 (br, 1 H), 6.24 (dt, *J* = 16.4, 11.6 Hz, 1 H), 4.90 (dd, *J* = 7.2, 6.0 Hz, 1 H), 3.76 (s, 3 H), 3.23 (dd, *J* = 14.4, 5.4 Hz, 1 H), 3.14 (dd, *J* = 14.4, 5.4 Hz, 1 H), 2.92 (dd, *J* = 8.8, 4.0 Hz, 2 H), 2.51 (m, 1 H), 2.43–2.41 (m, 1 H), 2.32–2.28 (m, 1 H), 2.19–2.11 (m, 1 H), 2.10–2.01 (m, 2 H), 1.98–1.95 (m, 1 H), 1.66–1.59 (m, 2 H), 1.56–1.47 (m, 3 H), 1.45–1.42 (m, 1 H), 0.91 (s, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 220.6, 170.9, 163.4 (t, *J* = 31.42 Hz), 141.6, 137.0, 136.5 (t, *J* = 9.4 Hz), 135.1, 131.7, 129.3, 128.7, 128.1, 127.4, 125.8, 124.9, 118.0 (t, *J* = 25.1 Hz), 114.2 (t, *J* = 249.3 Hz), 53.2, 52.6, 50.5, 47.9, 44.5, 38.0, 37.5, 35.8, 31.6, 29.3, 26.4, 25.6, 21.6, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.8 (d, *J* = 7.1 Hz, 2 F).

MS (EI): *m*/*z* (%) = 535 (M^+).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{32}H_{35}F_2NO_4$: 535.2534; found: 535.2538.

Ethyl 3-(3,4-Dihydronaphthalen-1-yl)-2,2-difluoropropanoate (9)

To a 25 mL Schlenk tube were added $PdCl_2(MeCN)_2$ (8 mg, 0.03 mmol, 10 mol%) and Xantphos (35 mg, 0.06 mmol, 20 mol%) under air, followed by anhydrous K_2CO_3 (powder, 2.0 equiv). The mixture was then evacuated and backfilled with N_2 (3 times). Ethyl bromodifluoroacetate (**1a**; 122 mg, 0.6 mmol, 2 equiv), alkene **8** (43 mg, 0.3 mmol) and fresh distilled 1,4-dioxane (2 mL) were added subsequently. The reaction mixture was heated to 80 °C (oil bath). After stirring for 24 h, the mixture was cooled to r.t. The mixture was diluted with EtOAc and filtered over a pad of Celite. The filtrate was concentrated, and the residue was purified by silica gel chromatography (PE–EtOAc, 10:1) to afford compound **9**; yield: 35 mg (44%); colorless oil.

IR (film): 2937, 1763, 1604, 1466 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 1 H), 7.21–7.18 (m, 1 H), 7.15–7.12 (m, 2 H), 6.08 (t, *J* = 4.4 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.24 (t, *J* = 8.4 Hz, 2 H), 2.74 (t, *J* = 8.4 Hz, 2 H), 2.28 (td, *J* = 8.4, 4.4 Hz, 2 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 164.1 (t, *J* = 32.4 Hz), 136.3, 133.8, 131.6, 127.6, 127.3 (t, *J* = 4.4 Hz), 127.1, 126.3, 122.8, 115.5 (t, *J* = 252.1 Hz), 62.7, 37.3 (t, *J* = 24.1 Hz), 28.0, 23.2, 13.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.3 (t, *J* = 15.7 Hz, 2 F).

MS (EI): *m*/*z* (%) = 266 (M^+).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{15}H_{16}F_2O_2$: 266.1118; found: 266.1116.

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Supporting Information

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