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Difluoroalkylation/C−H Annulation Cascade Reaction Induced by Visible-Light Photoredox Catalysis

Jin Li,[†] Jingzhi Chen,[†] Wei Jiao,[†] Guoqiang Wang,[‡] Ying Li,[†] Xu Cheng,*[,†] and Guigen Li[†,§]

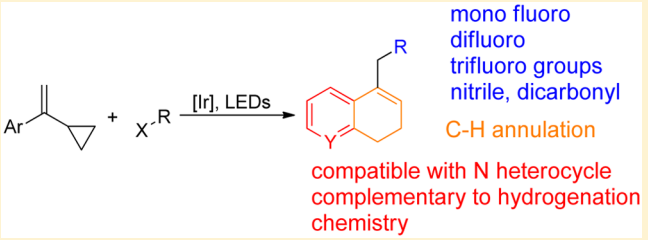
[†]Institute of Chemistry and Biomedical Science, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, China

[‡]Institute of Theoretical and Computational Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, China

[§]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409, United States

Supporting Information

ABSTRACT: We report the first example of difluoroalkylation/C−H annulation cascade reactions of cyclopropyl olefins induced by visible-light photoredox catalysis regioselectively affording partially hydrogenated naphthalenes and quinolines with a variety of difluorinated side chains. The alkylation reagent could be extended to monofluoro and trifluoro reagents, nitrile and malonate. The regioselectivity was investigated by means of density functional theory calculations.



Difluoroalkylation is a powerful strategy for introducing fluorine atoms into pharmaceuticals,[1] agricultural chemicals,[2] imaging agents,[3] and functional materials.[4] This reaction can be achieved with transition metal catalysis to form sp^3−sp^2 and sp^3−sp C−C bonds.[5] Recently, photoredox catalysis has emerged as a highly efficient method for facilitating difluoroalkylation reactions.[6] Difluoroacetate is a common, inexpensive, and easy to use reagent for such reactions. Photoredox reactions of difluoroacetate frequently involve a highly reactive radical species, and the difluoroacetate radical has been successfully integrated into alkenes,[7] alkynes, arenes,[8] and hydrazones.[9] We hypothesized that it might be advantageous to utilize the radical species for further transformation, resulting in a cascade reaction.

The cyclopropyl group is known for its reactivity toward α-radicals to give a linear carbon radical, and cyclopropyl compounds have been used as radical clocks.[10] For example, α-cyclopropylstyrene has been used as a radical clock for several transition-metal-catalyzed reactions that proceed via a radical pathway.[11] However, the potential of cyclopropyl ring-opening has not been thoroughly explored. We hypothesized that photoredox catalysis would facilitate annulation reactions of α-cyclopropylstyrene substrates, especially those with coordinative heterocyclic structures. Herein, we report our investigation of radical alkylation/C−H annulation cascade reactions of α-cyclopropylstyrene substrates, as well as pyridine substrates.

Our strategy is illustrated in Scheme 1. The reaction starts with oxidative quenching of an iridium photoredox catalyst to generate a difluoroacetate radical, which adds to the double bond of the α-cyclopropylstyrene substrate. Opening of the cyclopropyl ring generates a terminal radical. Subsequently, addition of the radical to the arene ring, oxidation of the resulting aryl radical by the catalyst, and deprotonation give the target molecule, which has two new C−C bonds and a new ring.

We began by investigating the reaction of α-cyclopropylstyrene (**1a**) and ethyl bromodifluoroacetate (**2a**) in the presence of various photocatalysts (Table 1). When the reaction was carried out in MeCN under nitrogen with $Ru(bpy)_3Cl_2$ or $Ir(ppy)_2(dtbbpy)PF_6$ as a catalyst and with illumination by blue LEDs (24 W), the target annulated compound (**3a**) was obtained as the major product (entries 1 and 3). Two other widely used iridium complexes failed to catalyze this conversion (entries 2 and 4). Little or none of the desired product was obtained when the reaction was carried out in DMF, DMSO, CH_2Cl_2, or ethanol (entries 5−8). Screening of various bases revealed that K_2HPO_4 gave the best results (entries 9−14). The reaction did not proceed in the absence of light (entry 16) or in the absence of a photocatalyst (entry 15). An inert atmosphere was necessary to ensure complete conversion of the starting material (entry 17).

With the optimized conditions in hand (Table 1, entry 3), we explored the substrate scope of the difluoroalkylation/C−H annulation cascade by using α-cyclopropylstyrenes **1** as substrates and **2a** as the radical donor (Table 2). We began by investigating styrenes with electron-withdrawing and electron-donating substituents at the *para* position of the phenyl ring and found that the corresponding products (**3b**−**3g**) could be obtained in acceptable yields.

Ortho-methoxy-substituted substrate **1h** afforded annulated product **3h** in moderate yield. We were interested to observe that *meta*-methoxy-substituted styrene **1i** underwent the sterically hindered *ortho*-annulation as the major reaction to afford **3i** in 48% yield, along with a 8% yield of *para*-annulation product **3i′**. Density functional theory calculations on the transition states for the two regioisomers were carried out at the UB3LYP/6-31G(d,p)

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Scheme 1. Plan for Difluoroalkylation/C−H Annulation Reaction

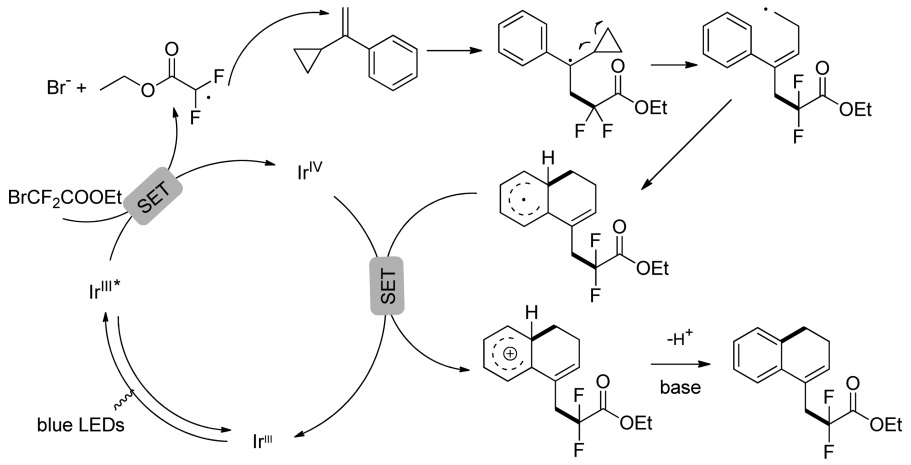
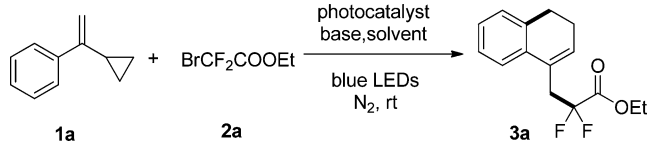


Table 1. Optimization of Conditions for Difluoroalkylation/C−H Annulation Cascade Reaction[a]



entry	photocatalyst	solvent	base	yield (%)[b]
1	$Ru(bpy)_3Cl_2$	CH_3CN	K_2HPO_4	35
2	$Ir(ppy)_3$	CH_3CN	K_2HPO_4	0
3	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	K_2HPO_4	63
4	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	CH_3CN	K_2HPO_4	0
5	$Ir(ppy)_2(dtbbpy)PF_6$	DMF	K_2HPO_4	17
6	$Ir(ppy)_2(dtbbpy)PF_6$	DMSO	K_2HPO_4	26
7	$Ir(ppy)_2(dtbbpy)PF_6$	CH_2Cl_2	K_2HPO_4	0
8	$Ir(ppy)_2(dtbbpy)PF_6$	EtOH	K_2HPO_4	0
9	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	Cs_2CO_3	33
10	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	Na_2CO_3	41
11	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	$NaHCO_3$	43
12	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	K_3PO_4	52
13	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	Na_2HPO_4	60
14	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	none	trace
15	none	CH_3CN	K_2HPO_4	0
16[c]	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	K_2HPO_4	0
17[d]	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	K_2HPO_4	trace

[a]Reaction conditions: **1a** (0.22 mmol), **2a** (0.2 mmol), base (0.24 mmol), photocatalyst (0.002 mmol, 1.0 mol %), anhydrous solvent (2.0 mL), 24 W blue LED strips, 12 h, rt. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide. [b]Isolated yields. [c]No light. [d]In air.

level to elucidate the reason for the regioselectivity (Scheme 2). The calculations revealed that the *ortho*-annulation transition state (**TS-3i**) was 2.3 kcal/mol lower in Gibbs free energy than the transition state for the *para*-annulation (**TS-3i′**). In addition, the calculated energy of intermediate **int-3i** was 1.9 kcal/mol lower than that of intermediate **int-3i**. The regioselectivity may have been due to the stabilizing effect of the heteroatom adjacent to the carbon radical.[12]

Substrates **1j** and **1k**, which have dimethoxy substitution, afforded the corresponding products in 61% and 50% yields, respectively. Substrate **1l**, with a tetrasubstituted double bond, was also compatible with the protocol; the corresponding product was obtained as the sole product in 61% yield. We next turned our attention to pyridine substrates. To our delight, pyridine substrates gave bicyclic compounds with different connectivity patterns; specifically, the reactions of **1m−1o** yielded quinoline and isoquinoline compounds **3m−3o** with an unsaturated phenyl ring, making this reaction complementary to the hydrogenation of quinolines, which affords benzopiperidine compounds for the first time. When substitutes were introduced to the cycloproyl moiety of substrates **1p** and **1q**, the annulation cascade reaction happened in the similar manner, offering products **3p** and **3q** respectively. The average moderate yield might rise from the step of ring-opening of cyclopropyl to both *Z* and *E* alkene radical speices, and only the *Z* intermediate underwent subsequent annulation reaction to give desired product **3**.

Subsequently, we evaluated various alternative *α*-bromo compounds as radical donors (Table 3). The radical addition/C−H annulation cascade could be carried out with bromodifluoroacetamides to afford aliphatic amine **3r** and aniline **3s**. Monofluoroacetate **3t** could also be obtained in an acceptable yield. The trifluoromethyl radical derived from Togni's reagent gave the corresponding product **3u** in 59% yield. *α*-Bromoacetonitrile

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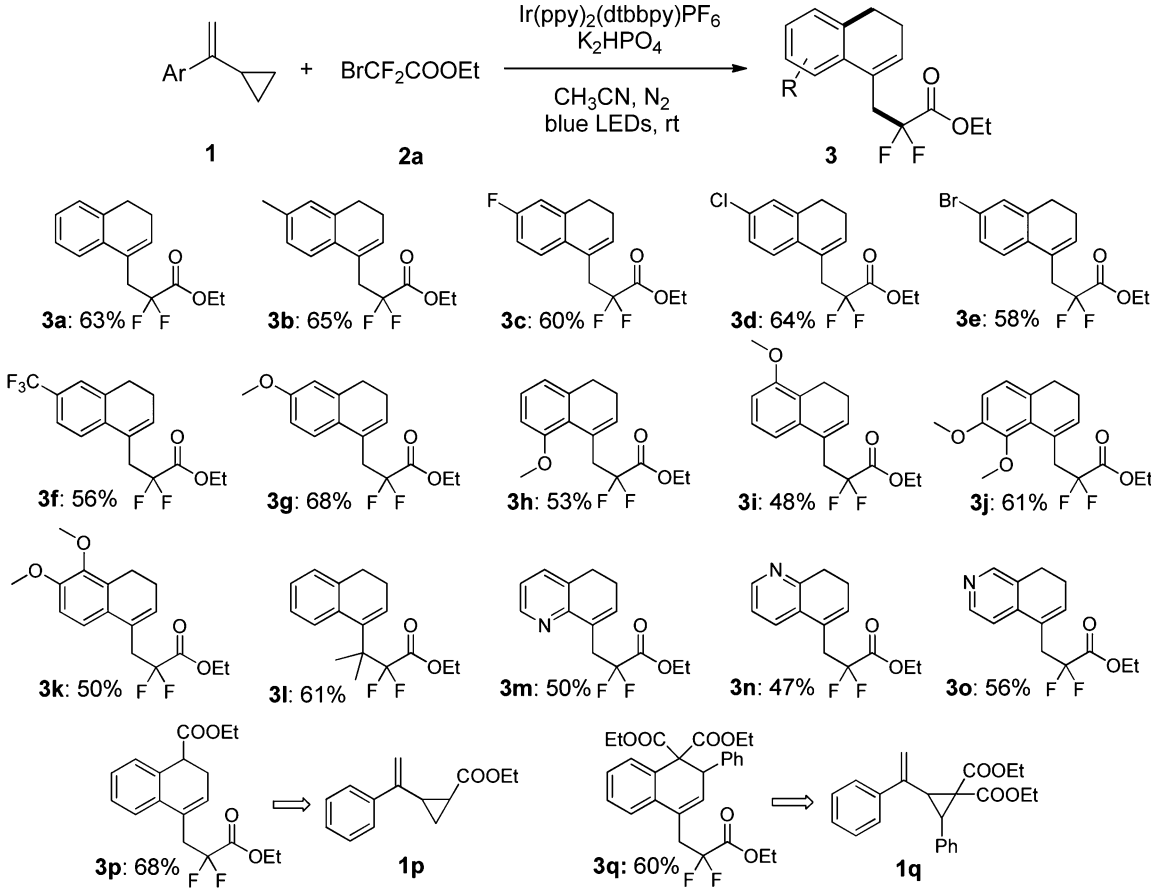
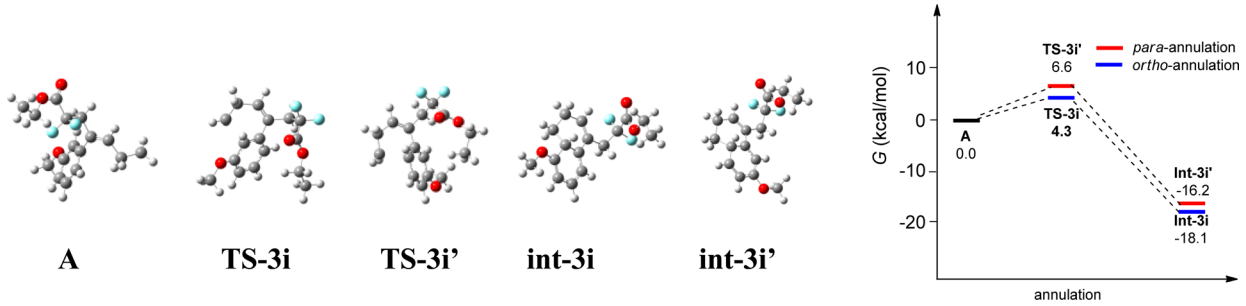
Table 2. Difluoroalkylation/C−H Annulation Cascade Reactions of Substrates 1[a]



[a]Reaction conditions: **1** (0.22 mmol), **2a** (0.2 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (0.002 mmol, 1.0 mol %), anhydrous CH_3CN (2.0 mL), 24 W blue LED strips, rt, 12−36 h. Yields of isolated products are reported.

Scheme 2. Density Functional Theory Calculations to Elucidate the Regioselectivity of the Reaction to Produce 3i



was converted to annulated product **3v**, along with unidentified decomposition products. Malonate **3w** was obtained in moderate yield. In addition to the terminal olefins, a substrate with an internal double bond, that is, a methylenecyclopropane group, was prepared and subjected to the standard conditions, which afforded expected annulation product **3x** in 63% yield (Scheme 3).

The reaction could be scaled up to 3.45 mmol of **1g**, which yielded 1 g of product **3g** (Scheme 4, eq 1). When the LED power was 24 W, which was the same as that used for the small-scale reactions, prolonged reaction time (24 h) was required to ensure full conversion. To demonstrate the potential synthetic applications of this reaction, we carried out several functional group manipulations. Specifically, ester **3g** could be hydrolyzed at room temperature to afford free acid **4g**, reduced to α-difluoroalcohol **5g** with $LiAlH_4$, or hydrogenated at 1 atm with Pd/C catalysis to give **6g**. All of these conversions were accomplished in excellent yields. Nitrile **3v** could be reduced to aldehyde **7v** in 80% yield, and epoxidation of **3u** with *m*-CPBA for 1.5 h afforded **8u** in 75% yield.

In summary, we developed a protocol for visible-light-induced photoredox difluoroalkylation/C−H annulation cascade reactions for the construction of substituted dihydronaphthalenes. The reaction could accommodate substrates bearing phenyl rings with various substitution patterns. Partially hydrogenated substituted quinolones could be prepared from pyridine substrates by means of this protocol. Various radical donors could be used for this transformation as well. Derivatization of the annulation products afforded a variety of functionalized bicyclic compounds.

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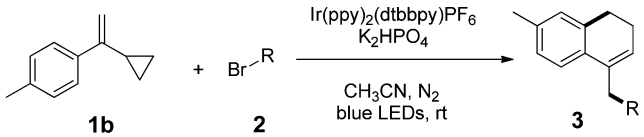
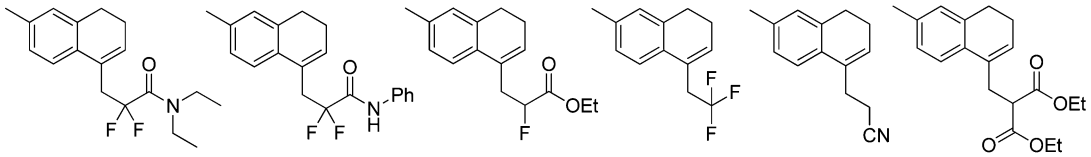
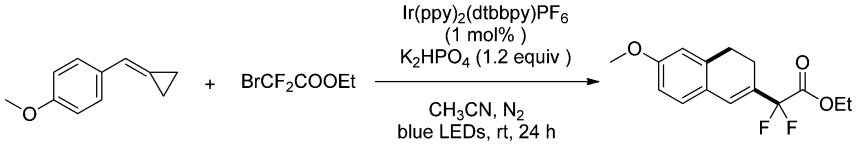
Table 3. Radical Addition/C−H Annulation Cascade Reactions of α-Cyclopropylstyrene 1b with Radical Donors 2[a]





[a]Reaction conditions: **1b** (0.22 mmol), **2** (0.2 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (0.002 mmol, 1.0 mol %), anhydrous CH_3CN (2.0 mL), 24 W blue LED strips, rt, 8−36 h. Yields are for products isolated by chromatography. [b]The reaction was carried out with Togni's reagent.

Scheme 3. Difluoroalkylation/C−H Annulation Cascade Reaction of an Internal Alkene



EXPERIMENTAL SECTION

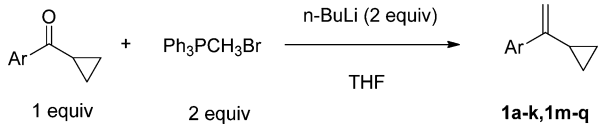
1. General Information. All reactions that required anhydrous conditions were carried out by standard procedures under a nitrogen atmosphere. Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. The solvents were dried by distillation over the appropriate drying reagents. Other chemicals were obtained from commercial sources and were used without further purification.

Column chromatography was generally performed on silica gel (300−400 mesh), and reactions were monitored by thin-layer chromatography (TLC) using 254 nm UV light to visualize the course of the reactions.

^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F (376 MHz) were measured on a 400 M spectrometer. Chemical shifts are expressed in parts per million (ppm) with respect to the residual solvent peak. Coupling constants are reported as hertz (Hz); signal shapes and splitting patterns are indicated as follows: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. IR spectra were recorded as a thin film on a KBr disk (2 cm diameter) using an FT-IR spectrometer and reported in wavenumbers (cm^{-1}).

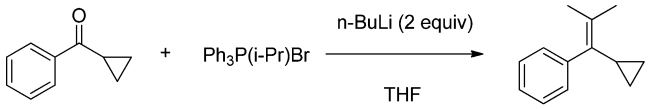
High-resolution mass spectra (HRMS) were equipped with an ESI, EI source, and a TOF detector mass spectrometer. The melting points were measured with a digital melting point detector.

2. General Procedure for Synthesis of Substrates. *General Procedure A.*[13]



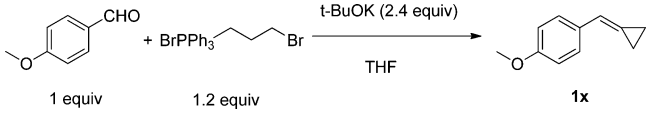
To a flask charged with methyltriphenylphosphonium bromide (3.57 g, 10 mmol, 2 equiv) and 30 mL of anhydrous THF at 0 °C was added *n*-butyllithium (4 mL, 2.5 M in hexanes, 10 mmol, 2 equiv). The reaction was allowed to warm to room temperature spontaneously and then stirred for 1 h. Cyclopropyl(aryl)methanone (5 mmol, 1 equiv) in anhydrous THF (3 mL) was added dropwise, and the reaction was stirred for 12 h at 40 °C. After being quenched with brine, the mixture was extracted with petroleum ether 3 times. The combined organic layers were washed with water three times, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography to afford the desired product.

General Procedure B.[14]



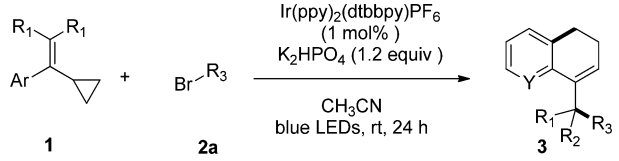
To a flask containing isopropyltriphenylphosphonium iodide (4.32 g, 10 mmol, 2 equiv) and 30 mL of anhydrous THF at 0 °C was added *n*-butyllithium (4 mL, 2.5 M in hexanes, 10 mmol, 2 equiv). The reaction was allowed to warm to room temperature spontaneously and then stirred for 1 h. Cyclopropyl(phenyl)methanone (5 mmol, 1 equiv) was added dropwise as a solution in dry THF (3 mL), and the reaction was allowed to stir for 12 h at 40 °C. After being quenched with brine, the mixture was extracted with petroleum ether 3 times. The combined organic layers were washed with water three times, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography to afford the desired product **1l**.

General Procedure C.[15]



To a solution of (3-bromopropyl)triphenylphosphonium bromide (2.87 g, 6 mmol, 1.2 equiv) in anhydrous THF (10 mL) was added *t*-BuOK (1.35 g, 12 mmol, 2.4 equiv) in anhydrous THF (10 mL) dropwise. The resulting suspension was heated at reflux for 10 min, and *p*-methoxybenzaldehyde (680 mg, 5 mmol, 1 equiv) was added as a solution in anhydrous THF (5 mL). The mixture was refluxed for 2 h. After cooling to room temperature, the mixture was layered with petroleum ether (20 mL) and the cloudy suspension was filtered through Celite. The residue was washed thoroughly with petroleum ether. The filtrate was concentrated and purified by chromatography on silica gel, affording the desired product **1x**.

3. General Procedure for the Synthesis of Products.



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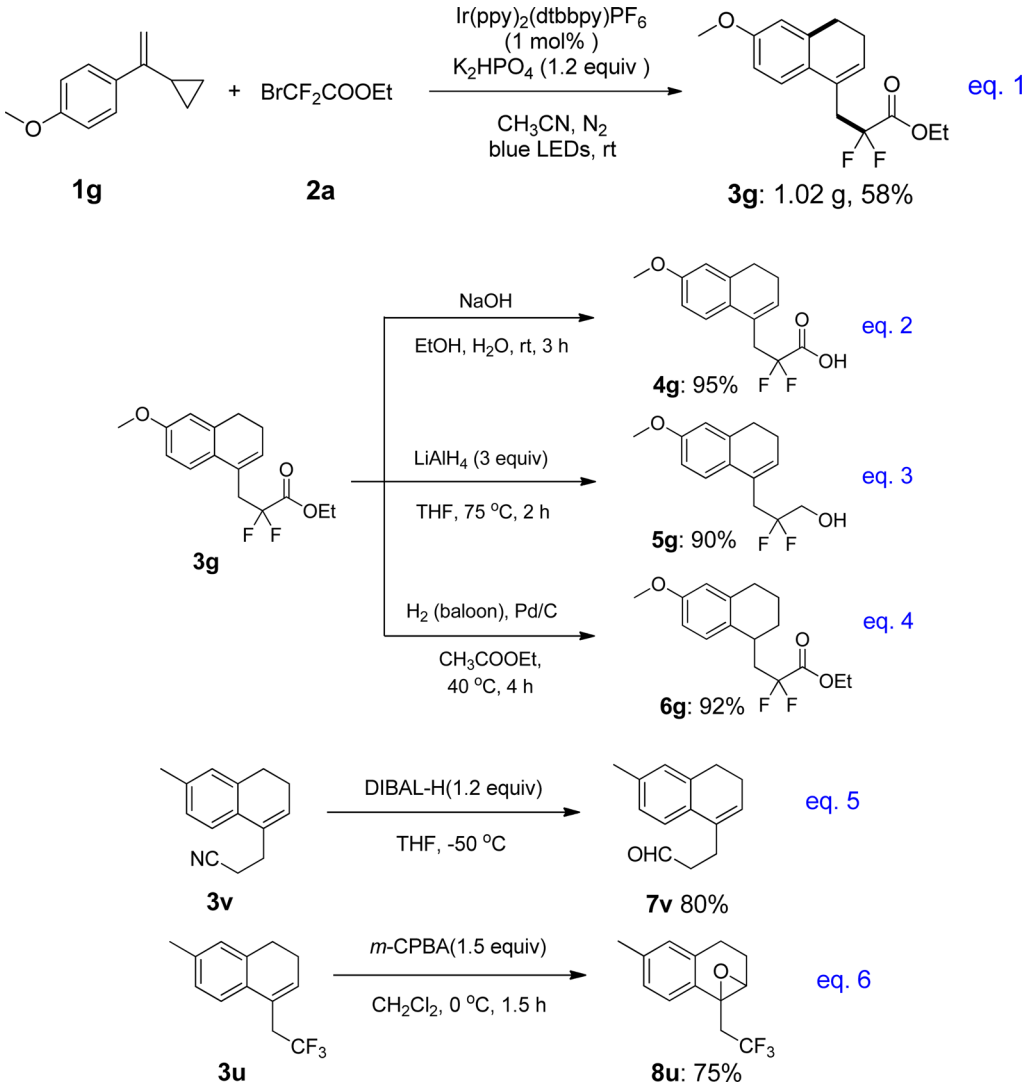
Scheme 4. Synthesis on a Gram Scale and Subsequent Functional Group Transformations



An oven-dried reaction vial was equipped with a magnetic stir bar, compound **1** (0.22 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (0.002 mmol), compound **2** (0.2 mmol), and K_2HPO_4 (0.24 mmol). The flask was evacuated and backfilled with nitrogen for 3 times. Anhydrous CH_3CN (2 mL) was added with a syringe. The vial was placed at a distance (app. 5 cm) from 24 W blue LEDs, and the resulting solution was stirred at ambient temperature. After the complete conversion of substrates as judged by TLC or GC−MS analysis, the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the **3a−x**.

4. Spectroscopic Data for the Substrates. *α-Cyclopropylstyrene* ***1a.*** This is a known compound[16] [CAS: 825-76-3] and prepared according to the general procedure A (684 mg, yield: 95%), column chromatography on silica gel (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63−7.60 (m, 2H), 7.39−7.33 (m, 2H), 7.33−7.27 (m, 1H), 5.30 (s, 1H), 4.95 (s, 1H), 1.72−1.61 (m, 1H), 0.88−0.83 (m, 2H), 0.64−0.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.3, 141.6, 128.1, 127.4, 126.0, 109.0, 15.6, 6.7. These data are consistent with the reported value.

α-Cyclopropyl-4-methylstyrene ***1b.*** This is prepared according to the general procedure A (735 mg, yield: 93%), chromatography on silica gel (petroleum ether). Colorless oil. IR (film) (cm^{-1}): 3084, 3050, 3007, 2866, 1625, 1512, 1427, 1021, 939, 888, 824, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 5.28 (s, 1H), 4.93 (s, 1H), 2.39 (s, 3H), 1.73−1.62 (m, 1H), 0.90−0.81 (m, 2H), 0.63−0.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.1, 138.7, 137.1, 128.8, 125.9, 108.2, 21.1, 15.6, 6.6. HRMS (EI) ($[M]^+$) Calcd For $C_{12}H_{14}$: 158.1096; found: 158.1093.

α-Cyclopropyl-4-fluorostyrene ***1c.*** This is a known compound[17] [CAS: 827-87-2] and prepared according to the general procedure A (786 mg, yield: 97%), chromatography on silica gel (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64−7.51 (m, 2H), 7.09−6.96 (m, 2H), 5.23 (s, 1H), 4.92 (s, 1H), 1.66−1.56 (m, 1H), 0.88−0.81 (m, 2H), 0.63−0.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6, 161.1, 148.3, 137.6 (d, J = 3.3 Hz), 127.4 (d, J = 7.9 Hz), 115.0 (d, J = 21 Hz), 114.8, 108.9 (d, J = 1.3 Hz), 15.7, 6.6. These data are consistent with the reported value.

α-Cyclopropyl-4-chlorostyrene ***1d.*** This is a known compound[18] [CAS: 1009-33-2] and prepared according to the general procedure A (881 mg, yield: 99%), chromatography on silica gel (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57−7.49 (m, 2H), 7.35−7.27 (m, 2H), 5.27 (s, 1H), 4.96 (s, 1H), 1.65−1.56 (m, 1H), 0.87−0.81 (m, 2H), 0.62−0.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.2, 140.0, 133.2, 128.2, 127.4, 109.6, 15.5, 6.6. These data are consistent with the reported value.

α-Cyclopropyl-4-bromostyrene ***1e.*** This is prepared according to the general procedure A (1.01 g, yield: 91%), chromatography on silica gel (petroleum ether). Colorless oil. IR (film) (cm^{-1}): 3083, 3003, 1623, 1587, 1487, 1390, 1086, 1008, 939, 895, 829, 731. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (s, 4H), 5.29 (s, 1H), 4.98 (s, 1H), 1.66−1.57 (m, 1H), 0.89−0.82 (m, 2H), 0.63−0.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$). δ = 148.2, 140.5, 131.2, 127.7, 121.4, 109.6, 15.5,

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6.6. HRMS (EI) ([M]$^+$) Calcd For $C_{11}H_{11}Br$: 222.0044; found: 222.0050.

α-Cyclopropyl-4-(trifluoromethyl)styrene ***1f***. This is prepared according to the general procedure A (996 mg, yield: 94%), chromatography on silica gel (petroleum ether). Colorless oil. IR (film) (cm^{-1}): 3088, 3007, 1617, 1405, 1328, 1167, 1125, 1066, 1016,901,850,716. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 5.35 (s, 1H), 5.05 (s, 1H), 1.70−1.60 (m, 1H), 0.92−0.84 (m, 2H), 0.65−0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3, 145.2, 129.4 (q, J = 32.4 Hz), 126.4, 125.09 (q, J = 3.8 Hz), 124.3 (q, J = 27 Hz), 111.1, 15.5, 6.7. HRMS (EI) ([M]$^+$) Calcd For $C_{12}H_{11}F_3$: 212.0813; found: 212.0809.

α-Cyclopropyl-4-methoxystyrene ***1g***. This is a known compound[17] [CAS: 829-17-4] and prepared according to the general procedure A (844 mg, yield: 97%), chromatography on silica gel (petroleum ether/EtOAc = 97:3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, J = 7.9 Hz, 2H), 6.92 (d, J = 7.9 Hz, 2H), 5.25 (s, 1H), 4.90 (s, 1H), 3.86 (s, 3H), 1.69−1.65 (m, 1H), 0.86 (d, J = 7.1 Hz, 2H), 0.63 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.1, 148.6, 134.2, 127.1, 113.5, 107.4, 55.3, 15.7, 6.5. These data are consistent with the reported value.

α-Cyclopropyl-2-methoxystyrene ***1h***. This is a known compound[19] [CAS: 1355988-71-4] and prepared according to the general procedure A (783 mg, yield: 90%), chromatography on silica gel (petroleum ether/EtOAc = 98:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (td, J = 8.0, 1.8 Hz, 1H), 7.14 (dd, J = 7.4, 1.7 Hz, 1H), 6.96−6.89 (m, 2H), 5.13 (dd, J = 1.5, 0.8 Hz, 1H), 4.97 (d, J = 1.7 Hz, 1H), 3.84 (s, 3H), 1.80−1.73 (m, 1H), 0.73−0.67 (m, 2H), 0.50−0.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.6, 149.3, 131.3, 130.1, 128.3, 120.2, 111.3, 110.7, 55.5, 16.7, 6.6. These data are consistent with the reported value.

α-Cyclopropyl-3-methoxystyrene ***1i***. This is a known compound[20] [CAS: 1883688-65-0] and prepared according to the general procedure A (792 mg, yield: 91%), chromatography on silica gel (petroleum ether/EtOAc = 98:2, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 5.34 (s, 1H), 5.00 (s, 1H), 3.89 (s, 3H), 1.77−1.64 (m, 1H), 0.90 (d, J = 7.6 Hz, 2H), 0.70−0.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.4, 149.2, 143.2, 129.0, 118.7, 112.6, 112.1, 109.2, 55.1, 15.6, 6.7. These data are consistent with the reported value.

α-Cyclopropyl-1,2-dimethoxystyrene ***1j***. This is prepared according to the general procedure A (1.04 g, yield: 92%), chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 3081, 3002, 2933, 2835, 1575, 1471, 1425, 1262, 1229, 1057, 1010, 894, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00 (t, J = 7.9 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 5.08 (s, 1H), 4.98 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 1.80−1.64 (m, 1H), 0.75−0.67 (m, 2H), 0.53−0.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.7, 148.9, 146.3, 136.9, 123.5, 122.1, 111.2, 111.2, 60.8, 55.8, 16.9, 6.8. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{13}H_{16}O_2Na$: 227.1042, found: 227.1043.

α-Cyclopropyl-3,4-dimethoxystyrene ***1k***. This is prepared according to the general procedure A (1.05 g, yield: 93%), chromatography on silica gel (petroleum ether/EtOAc = 5:1, v/v). White solid, mp. 55−57 °C. IR (film) (cm^{-1}): 2996, 2962, 2941, 2841, 1217, 1144, 1021, 867. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, J = 8.3 Hz, 1H), 7.14 (s, 1H), 6.85 (d, J = 8.3 Hz, 1H), 5.21 (s, 1H), 4.87 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 1.67−1.58 (m, 1H), 0.83 (q, J = 5.6 Hz, 2H), 0.59 (q, J = 5.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.8, 148.7, 148.5, 134.6, 118.5, 110.8, 109.5, 107.7, 55.9, 55.8, 15.7, 6.6. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{13}H_{16}O_2Na$: 227.1042, found: 227.1043.

α-Cyclopropyl-β,β-dimethylstyrene ***1l***. This is a known compound[21] [CAS: 34564-76-6] and prepared according to the general procedure B (645 mg, yield: 75%), chromatography on silica gel (petroleum ether/EtOAc = 97:3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (t, J = 7.3 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 6.97 (d, J = 7.3 Hz, 2H), 1.95 (s, 3H), 1.85−1.77 (m, 1H), 1.49 (s, 3H), 0.58 (d, J = 7.4 Hz, 2H), 0.14 (d, J = 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.0, 135.3, 129.8, 128.7, 127.6, 125.8, 22.7, 20.1, 13.6, 5.0. These data are consistent with the reported value.

α-Cyclopropyl-2-pyridylethylene ***1m***. This is prepared according to the general procedure A (620 mg, yield: 85%), chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 3080, 3003, 1770, 1584, 1563, 1468, 1430, 1245, 803, 746. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (d, J = 4.6 Hz, 1H), 7.66 (q, J = 7.9 Hz, 2H), 7.17 (t, J = 5.8 Hz, 1H), 5.89 (s, 1H), 5.12 (s, 1H), 1.88−1.80 (m, 1H), 0.91−0.83 (m, 2H), 0.63−0.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.2, 148.9, 148.5, 136.3, 122.2, 120.4, 112.5, 14.1, 6.9. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{10}H_{12}N$: 146.0964, found: 146.0966.

α-Cyclopropyl-3-pyridylethylene ***1n***. This is prepared according to the general procedure A (642 mg, yield: 88%), chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 3084, 3006, 1624, 1475, 1409, 1022, 897, 814, 718. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.83 (d, J = 1.9 Hz, 1H), 8.50 (dd, J = 4.8, 1.5 Hz, 1H), 7.87−7.84 (m, 1H), 7.27−7.24 (m, 1H), 5.32 (s, 1H), 5.03 (s, 1H), 1.66−1.57 (m, 1H), 0.89−0.83 (m, 2H), 0.62−0.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.5, 147.5, 146.4, 136.9, 133.3, 123.0, 110.8, 15.3, 6.5. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{10}H_{12}N$: 146.0964, found: 146.0965.

α-Cyclopropyl-4-pyridylethylene ***1o***. This is prepared according to the general procedure A (606 mg, yield: 83%), chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 3082, 3004, 1623, 1474, 1022, 897, 813, 718. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.83 (d, J = 1.9 Hz, 1H), 8.51 (dd, J = 4.8, 1.5 Hz, 1H), 7.87−7.85 (m, 1H), 7.27−7.24 (m, 1H), 5.32 (s, 1H), 5.03 (s, 1H), 1.65−1.56 (m, 1H), 0.88−0.84 (m, 2H), 0.62−0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.5, 147.5, 146.4, 136.9, 133.3, 123.0, 110.8, 15.3, 6.5. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{10}H_{12}N$: 146.0964, found: 146.0965.

α-Cyclopropanecarboxylate-styrene ***1p***. This is a known compound[22] [CAS: 54143-12-3] and prepared according to the general procedure A (930 mg, yield: 86%), chromatography on silica gel (petroleum ether/EtOAc = 98:2, v/v). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, J = 7.2 Hz, 2H), 7.37−7.28 (m, 3H), 5.38 (s, 1H), 5.03 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.31−2.26 (m, 1H), 1.81−1.76 (m, 1H), 1.51−1.46 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.23−1.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5 (s), 146.2 (s), 140.2 (s), 128.3 (s), 127.8 (s), 126.0 (s), 111.1 (s), 60.6 (s), 26.0 (s), 22.2 (s), 15.3 (s), 14.3 (s). These data are consistent with the reported value.

α-Cyclopropane-1,1-dicarboxylate-styrene ***1q***. This is a known compound[23] [CAS: 1943680-29-2] and prepared according to the general procedure A (1400 mg, yield: 77%), chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, J = 7.3 Hz, 2H), 7.40−7.27 (m, 8H), 5.73 (s, 1H), 5.32 (s, 1H), 4.02−3.94 (m, 3H), 3.92−3.86(m, 1H), 3.70−3.63 (m,, 2H), 0.97−0.97 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7 (s), 166.5 (s), 140.9 (s), 139.1 (s), 134.7 (s), 128.8 (s), 128.3 (s), 128.2 (s), 127.8 (s), 127.4 (s), 126.0 (s), 114. Eight (s), 61.4 (s), 61.4 (s), 44.9 (s), 34.8 (s), 34.4 (s), 13.8 (s), 13.8 (s). These data are consistent with the reported value.

1-(Cyclopropylidenemethyl)-4-methoxybenzene ***1x***. This a known compound[24] [CAS: 55088-84-1] and prepared according to the general procedure C (584 mg, yield: 73%), chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 4.0 Hz, 2H), 6.93−6.84 (m, 2H), 6.73−6.67 (m, 1H), 3.82 (s, 3H), 1.42−1.38 (m, 2H), 1.19−1.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.5, 131.2, 127.6, 121.7, 117.5, 113.9, 55.2, 4.0, 0.5. These data are consistent with the reported value.

5. Spectroscopic Data for Products. *Ethyl 3-(3,4-Dihydronaphthalen-1-yl)-2,2-difluoropropanoate* ***3a***.[5b] 33 mg, yield: 63%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2921, 2850, 1770, 1222, 1089. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26−7.13 (m, 4H), 6.09 (t, J = 4.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.25 (t, J = 15.9 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), 2.31−2.26 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1 (t, J = 32.6 Hz), 136.3, 133.9,

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131.6, 127.6, 127.3 (t, J = 4.4 Hz), 127.2, 126.3, 115.5 (t, J = 252.3 Hz), 62.7, 37.3 (t, J = 24.2 Hz), 28.0, 23.2, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.32. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{15}H_{16}F_2O_2Na$: 289.1010, found: 289.1010.

Ethyl 2,2-Difluoro-3-(6-methyl-3,4-dihydronaphthalen-1-yl)propanoate ***3b***. 36 mg, yield: 65%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2984, 2933, 2831.80, 1770, 1221, 1185, 1086, 828. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.95 (s, 1H), 6.01 (t, J = 4.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.22 (t, J = 15.9 Hz, 2H), 2.70 (t, J = 8.0 Hz, 2H), 2.31 (s, 3H), 2.28−2.23 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1 (t, J = 33 Hz), 136.9, 136.3, 131.3, 130.5, 128.5, 127.3 (t, J = 4.4 Hz), 126.8, 122.9, 115.6 (t, J = 251 Hz), 62.7, 37.4 (t, J = 24 Hz), 28.1, 23.3, 21.1, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.27. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{16}H_{18}F_2O_2Na$: 303.1167, found: 303.1169.

Ethyl 2,2-Difluoro-3-(6-fluoro-3,4-dihydronaphthalen-1-yl)propanoate ***3c***. 34 mg, yield: 34%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2935, 1769, 1497, 1245, 1086. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (dd, J = 8.4, 5.6 Hz, 1H), 6.90−6.83 (m, 2H), 6.03 (t, J = 4.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.21 (t, J = 15.9 Hz, 2H), 2.73 (t, J = 8.0 Hz, 2H), 2.29−2.24 (m, 2H), 1.24 (t, J = 7.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (t, J = 32 Hz), 161.7 (d, J = 245 Hz), 139.0 (d, J = 8 Hz), 130.8 (d, J = 1.9 Hz), 130.1 (d, J = 3 Hz), 126.7 (t, J = 4 Hz), 124.5 (d, J = 8.3 Hz), 115.4 (t, J = 251 Hz), 114.8 (d, J = 22 Hz), 112.7 (d, J = 21 Hz), 62.8, 37.5 (t, J = 36 Hz), 28.2 (d, J = 1.4 Hz), 22.9, 13.8. ^{19}F NMR (376 MHz, CDCl3) δ = −103.40, −115.09. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{15}H_{15}F_3O_2Na$: 307.0916, found: 307.0926.

Ethyl 3-(6-Chloro-3,4-dihydronaphthalen-1-yl)-2,2-difluoropropanoate ***3d***. 38 mg, yield: 64%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2984, 2939, 2385, 1769, 1487, 1221, 1186, 1102, 1084, 844. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (s, 2H), 7.12 (s, 1H), 6.08 (t, J = 4.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.21 (t, J = 15.9 Hz, 2H), 2.72 (t, J = 8.0 Hz, 2H), 2.30−2.25 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (t, J = 32.6 Hz), 138.2, 132.5, 132.4, 132.0, 127.7, 126.7 (t, J = 4.3 Hz), 126.3, 124.2, 115.4 (t, J = 251 Hz), 62.8, 37.3 (t, J = 24 Hz), 27.9, 23.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.41. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{15}H_{15}ClF_2O_2Na$: 323.0621, found: 323.0619.

Ethyl 3-(6-Bromo-3,4-dihydronaphthalen-1-yl)-2,2-difluoropropanoate ***3e***. 40 mg, yield: 58%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2984, 2937, 2832.65, 1768, 1488, 1221, 1185, 1094, 827. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (dd, J = 8.3, 2.0 Hz, 1H), 7.27 (s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.09 (t, J = 4.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.20 (t, J = 15.9 Hz, 2H), 2.72 (t, J = 8.0 Hz, 2H), 2.29−2.24 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (t, J = 32.6 Hz), 138.5, 132.9, 132.2, 130.5, 129.325, 126.8, 124.5, 120.7, 115.4 (t, J = 251 Hz), 62.8, 37.3 (t, J = 24 Hz), 27.8, 23.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.43. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{15}H_{15}BrF_2O_2Na$: 367.0115, found: 367.0113.

Ethyl 2,2-Difluoro-3-(6-(trifluoromethyl)-3,4-dihydronaphthalen-1-yl)propanoate ***3f***. 37 mg, yield: 56%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2984, 2941, 2837, 1770, 1324, 1168, 1122, 1093, 843. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 6.21 (t, J = 4.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.26 (t, J = 15.9 Hz, 2H), 2.80 (t, J = 8.0 Hz, 2H), 2.35−2.30 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.9 (t, J = 32.5 Hz), 137.2, 136.9, 134.3, 128.9 (q, J = 32 Hz), 126.8 (t, J = 4.0 Hz), 124.3 (q, J = 3.7 Hz), 124.1 (q, J = 270 Hz), 123.1 (q, J = 270 Hz), 123.1, 115.3 (t, J = 251 Hz), 62.9, 37.3 (t, J = 24 Hz), 27.8, 23.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −62.54, −103.56. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{16}H_{15}F_5O_2Na$: 357.0884, found: 357.0893.

Ethyl 2,2-Difluoro-3-(6-methoxy-3,4-dihydronaphthalen-1-yl)propanoate ***3g***. 40 mg, yield: 68%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2986, 2937, 2835, 1770, 1608, 1568, 1502, 1434, 1374, 1253, 1085, 1039. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 9.6 Hz, 2H), 5.94 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.21 (t, J = 15.9 Hz, 2H), 2.72 (t, J = 7.9 Hz, 2H), 2.28−2.23 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1 (t, J = 32.6 Hz), 158.6, 138.2, 129.0, 127.0, 126.9 (t, J = 5 Hz), 124.1, 115.6 (t, J = 251 Hz), 113.9, 110.7, 62.7, 55.2, 37.5 (t, J = 24 Hz), 28.6, 23.2, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.24. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{16}H_{18}F_2O_3Na$: 319.1116, found: 319.1120.

Ethyl 2,2-Difluoro-3-(8-methoxy-3,4-dihydronaphthalen-1-yl)-propanoate ***3h***. 31 mg, yield: 53%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2922, 2838, 1769, 1574, 1461, 1262, 1083. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (t, J = 8.0 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.09 (t, J = 4.6 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.23 (t, J = 15.9 Hz, 2H), 2.74 (t, J = 8.2 Hz, 2H), 2.27−2.21 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1 (t, J = 32 Hz), 156.0, 1345.0, 131.9, 127.2 (t, J = 4 Hz), 126.3, 124.3, 115.9, 115.5 (t, J = 251 Hz), 110.0, 77.3, 77.0, 76.7, 62.7, 55.6, 37.7 (t, J = 24 Hz), 22.6, 19.6, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.40. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{16}H_{19}F_2O_3$: 297.1297, found: 297.1298.

Ethyl 2,2-Difluoro-3-(5-methoxy-3,4-dihydronaphthalen-1-yl)-propanoate ***3i***. 28 mg, yield: 48%, chromatography on silica gel (petroleum ether/EtOAc = 9:51, v/v). Colorless oil. IR (film) (cm^{-1}): 2937, 2837, 1768, 1754, 1461, 1262, 1083. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (t, J = 8.1 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.09 (t, J = 4.6 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.23 (t, J = 15.9 Hz, 2H), 2.75 (t, J = 8.2 Hz, 2H), 2.27−2.21 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1 (t, J = 32.6 Hz), 156.0, 135.0, 131.9, 127.2 (t, J = 4.5 Hz), 126.3, 124.3, 115.9, 115.5 (t, J = 250 Hz), 109.9, 62.7, 55.6, 37.7 (t, J = 24.2 Hz), 37.7, 22.6, 19.6, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.39. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{16}H_{18}F_2O_3Na$: 319.1116, found: 319.1120.

Ethyl 3-(7,8-Dimethoxy-3,4-dihydronaphthalen-1-yl)-2,2-difluoropropanoate ***3j***. 40 mg, yield: 61%, chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2939, 2835, 1768.05, 1474, 1261, 1088, 1059, 1021, 803. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.85 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.14 (t, J = 4.8 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.62 (t, J = 16.3 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 2.14−2.09 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2 (t, J = 33 Hz), 151.8, 146.3, 134.2, 131.3, 127.3, 127.3 (t, J = 5 Hz), 122.2, 116.0 (t, J = 250 Hz), 110.7, 62.4, 60.5, 55.9, 39.3 (t, J = 24 Hz), 39.1, 38.8, 28.7, 23.5, 13.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.81. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{17}H_{20}F_2O_4Na$: 349.1222, found: 349.1226.

Ethyl 3-(5,6-Dimethoxy-3,4-dihydronaphthalen-1-yl)-2,2-difluoropropanoate ***3k***. 33 mg, yield: 50%, chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2936, 2837, 1770, 1490, 1270, 1225, 1089. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.98 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 5.96 (t, J = 4.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.20 (t, J = 15.9 Hz, 2H), 2.79 (t, J = 2 Hz, 2H), 2.26−2.21 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.1 (t, J = 32.6 Hz), 152.2, 145.7, 130.3, 129.5, 127.8, 126.9, 119.0, 115.6, 109.0, 62.7, 60.4, 55.6, 37.6 (t, J = 24 Hz), 22.7, 20.6, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.17. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{17}H_{20}F_2O_4Na$: 349.1222, found: 349.1226.

Ethyl 3-(3,4-Dihydronaphthalen-1-yl)-2,2-difluoro-3-methylbutanoate ***3l***. 36 mg, yield: 61%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2983, 2922, 2853, 1761, 1301, 1248, 1128, 1098, 1057, 705. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31−7.26 (m, 2H), 7.08 (d, J = 7.0 Hz, 2H), 5.84 (t, J = 7.0 Hz, 1H), 4.33 (d, J = 7.1 Hz, 2H), 3.25 (t, J = 6.8 Hz, 2H), 2.23 (q, J = 6.9 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (t, J = 34 Hz), 144.8, 138.8,

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129.6, 129.1, 127.8, 126.9, 118.4 (t, J = 257 Hz), 62.6, 45.3 (t, J = 21 Hz), 32.7, 32.3, 23.1 (t, J = 4 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −108.11. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{17}H_{20}F_2O_2Na$: 317.1323, found: 317.1312.

Ethyl 3-(5,6-Dihydroquinolin-8-yl)-2,2-difluoropropanoate ***3m***. 27 mg, yield: 50%, chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2987, 1938, 2835, 1768, 1443, 1223, 1197, 1088; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.03 (dd, J = 7.1, 5.2 Hz, 1H), 6.36 (t, J = 4.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.50 (t, J = 16.2 Hz, 2H), 2.81 (t, J = 8.1 Hz, 2H), 2.38−2.33 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2 (t, J = 33 Hz), 152.5, 146.4, 134.9, 134.7, 131.2, 129.9 (t, J = 4.8 Hz), 121.9, 115.4 (t, J = 249 Hz), 62.4, 35.6 (t, J = 25 Hz), 27.1, 22.8, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.37. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{16}F_2NO_2$: 268.1144, found: 268.1142.

Ethyl 3-(7,8-Dihydroquinolin-5-yl)-2,2-difluoropropanoate ***3n***. 25 mg, yield: 47%, chromatography on silica gel (petroleum ether/acetone = 4:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2986, 2940, 2833, 1766, 1442, 1225, 1185, 1092. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.9 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.12 (dd, J = 7.6, 5.1 Hz, 1H), 6.11 (t, J = 4.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.19 (t, J = 16.0 Hz, 2H), 2.95 (t, J = 8.2 Hz, 2H), 2.45−2.40 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.9 (t, J = 32 Hz), 157.0, 147.0, 132.9, 129.8, 129.4, 126.0 (t, J = 4.1 Hz), 121.6, 115.3 (t, J = 251 Hz), 62.9, 36.8 (t, J = 24 Hz), 30.4, 23.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.44. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{16}F_2NO_2$: 268.1144, found: 268.1141.

Ethyl 3-(7,8-Dihydroisoquinolin-5-yl)-2,2-difluoropropanoate ***3o***. 30 mg, yield: 56%, chromatography on silica gel (petroleum ether/EtOAc = 2:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2982, 2937, 2833, 1764, 1442, 1225, 1185, 1092. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 4.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 7.5, 5.1 Hz, 1H), 6.10 (t, J = 4.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.19 (t, J = 15.9 Hz, 2H), 2.95 (t, J = 8.2 Hz, 2H), 2.44−2.39 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8 (t, J = 32 Hz), 157.0, 147.0, 132.9, 129.8, 129.4, 126.0 (t, J = 4.1 Hz), 121.6, 115.3 (t, J = 251 Hz), 62.9, 36.7, 36.5, 30.4, 23.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.47. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{16}F_2NO_2$: 268.1144, found: 268.1141.

Ethyl 4-(3-Ethoxy-2,2-difluoro-3-oxopropyl)-1,2-dihydronaphthalene-1-carboxylate ***3p***. 46 mg, yield: 68%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2984, 2920, 2850, 1770, 1732, 1373, 1299, 1224, 1185, 1093, 1030, 759. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30−7.25 (m, 2H), 7.23−7.18 (m, 2H), 6.05 (t, J = 4.4 Hz, 1H), 4.23−4.10 (m, 4H), 3.70 (t, J = 6.6 Hz, 1H), 3.33−3.14 (m, 2H), 2.84−2.77 (m, 1H), 2.53−2.46 (m, 1H), 1.27−1.19 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.13 (s), 163.9 (t, J = 32 Hz), 133.4 (s), 133.0 (s), 129.6 (s), 128.3 (s), 127.5 (s), 127.5 (s), 127.2 (t, J = 4 Hz), 123.3 (s), 115.3 (t, J = 251 Hz), 62.8 (s), 60.9 (s), 43.9 (s), 37.1 (t, J = 24 Hz), 26.02 (s), 14.1 (s), 13.8 (s).^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.22. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{18}H_{20}F_2O_4Na$: 361.1222, found: 361.1231.

Diethyl 4-(3-Ethoxy-2,2-difluoro-3-oxopropyl)-2-phenylnaphthalene-1,1(2H)-dicarboxylate ***3q***. 58 mg, yield: 60%, chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2983, 2920, 2850, 1757, 1735, 1222, 1182, 1092, 1048, 757, 699. ^{1}H NMR (400 MHz, CDCl3) δ = 7.57 (d, J = 7.7 Hz, 1H), 7.39−7.33 (m, 2H), 7.31−7.28 (m, 1H), 7.17−7.11 (m, 3H), 7.01 (d, J = 6.6 Hz, 2H), 6.17 (d, J = 6.3 Hz, 1H), 4.50 (d, J = 6.2 Hz, 1H), 4.19−4.13 (m, 3H), 4.07−4.01 (m, 1H), 3.91 (q, J = 7.1 Hz, 2H), 3.40 (q, J = 15.4 Hz, 1H), 3.20 (q, J = 15.4 Hz, 1H), 1.22 (d, J = 7.2 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.2 (s), 168.8 (s), 163.8 (t, J = 32 Hz), 137.2 (s), 133.3 (s), 132.9 (s), 131.8 (s), 129.9 (s), 129.1 (s), 128.2 (s), 128.1 (s), 127.8 (s), 127.7 (s), 124.8 (t, J = 4 Hz), 123.3 (s), 115.4 (t, J = 251 Hz), 63.2 (s), 62.9 (s), 61.9 (s), 61.3 (s), 46.4 (s), 37.1 (t, J = 25 Hz), 13.8 (s), 13.7 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −102.36. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{27}H_{28}F_2O_6Na$: 509.1746, found: 509.1763.

N,N-Diethyl-2,2-difluoro-3-(6-methyl-3,4-dihydronaphthalen-1-yl)propanamide ***3r***. 41 mg, yield: 66%, chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2978, 2935, 1660, 1241, 1082, 1062, 824. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.95 (s, 1H), 6.02 (t, J = 4.5 Hz, 1H), 3.38 (m, 6H), 2.73 (t, J = 8.0 Hz, 2H), 2.32−2.24 (m, 5H), 1.13 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.1 (t, J = 29 Hz), 136.6, 136.1, 132.0, 130.7, 128.4, 127.9 (t, J = 2.9 Hz), 126.8, 123.3, 118.4 (t, J = 254 Hz), 41.9 (t, J = 7 Hz), 41.7, 37.2 (t, J = 24 Hz), 28.2, 23.4, 21.1, 14.3, 12.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −98.40. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{18}H_{23}F_2NONa$: 330.1640, found: 330.1635.

2,2-Difluoro-3-(6-methyl-3,4-dihydronaphthalen-1-yl)-N-phenylpropanamide ***3s***. 46 mg, yield: 71%, chromatography on silica gel (petroleum ether/EtOAc = 9:1, v/v). White solid, mp. 120−122 °C. IR (film) (cm^{-1}): 3325, 2928, 2829, 1697, 1602, 1541, 1447, 1240, 1073, 753, 690. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (s, 1H), 7.42 (dd, J = 8.5, 1.0 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.24 (d, J = 7.9 Hz, 1H), 7.18 (dd, J = 10.5, 4.2 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.95 (s, 1H), 6.07 (t, J = 4.6 Hz, 1H), 3.36 (t, J = 16.2 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H), 2.32 (s, 3H), 2.25−2.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.9 (t, J = 29 Hz), 137.0, 136.2, 135.8, 131.2, 131.2, 129.1, 128.6, 127.3 (t, J = 4.4 Hz), 126.9, 125.5, 123.2, 120.3, 117.8 (t, J = 255 Hz), 36.8 (t, J = 24 Hz), 28.1, 23.3, 21.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −103.48. HRMS (ESI) ([M-H]$^-$) Calcd For $C_{20}H_{18}F_2NO$: 326.1362, found: 326.1368.

Ethyl 2-Fluoro-3-(6-methyl-3,4-dihydronaphthalen-1-yl)propanoate ***3t***. 33 mg, yield: 62%, chromatography on silica gel (petroleum ether/acetone = 10:1, v/v). Colorless oil. IR (film) (cm^{-1}): 2982, 2931, 2831, 1761, 1739, 1285, 1195, 1078, 1029, 828. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.99 (s, 1H), 5.96 (t, J = 4.5 Hz, 1H), 5.12−4.96 (m, 1H), 4.25−4.20 (m, 2H), 3.18−3.02 (m, 1H), 2.9−2.86 (m, 1H), 2.79−2.66 (m, 2H), 2.32 (s, 3H), 2.29−2.24 (m, 2H), 1.29 (t, J = 8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.8 (d, J = 23 Hz), 136.8, 136.7, 131.1, 130.3 (d, J = 2.6 Hz), 128.7, 128.0, 126.9, 122.2, 87.8 (d, J = 185 Hz), 61.5, 35.9 (d, J = 22 Hz), 28.2, 23.2, 21.1, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −188.60. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{16}H_{19}FO_2Na$: 285.1261, found: 285.1267.

7-Methyl-4-(2,2,2-trifluoroethyl)-1,2-dihydronaphthalene ***3u***. 27 mg, yield: 59%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2932, 2833, 1353, 1270, 1258, 1132, 1097, 826. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.99 (s, 1H), 6.08 (t, J = 4.5 Hz, 1H), 3.22 (q, J = 10.7 Hz, 2H), 2.76 (t, J = 8.1 Hz, 2H), 2.35−2.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.1, 136.3, 131.0, 130.9, 129.2, 128.7, 126.9, 126.6 (q, J = 5.6, 2.7 Hz), 126.1 (q, J = 275, 175 Hz), 122.7, 77.3, 77.0, 76.7, 36.8 (q, J = 30, 29 Hz), 28.0, 23.3, 21.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −64.52. HRMS (EI) ([M]$^+$) Calcd For $C_{13}H_{13}F_3$: 226.0964; found: 226.0966.

3-(6-Methyl-3,4-dihydronaphthalen-1-yl)propanenitrile ***3v***. 15 mg, yield: 43%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2927, 2854, 2246, 1456, 1259, 1046.07, 825, 800, 668. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.02 (s, 2H), 7.00 (s, 1H), 5.94 (t, J = 4.5 Hz, 1H), 2.79 (t, J = 7.3 Hz, 2H), 2.72 (t, J = 8.0 Hz, 2H), 2.56 (t, J = 7.4 Hz, 2H), 2.33 (s, 3H), 2.30−2.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.1, 136.9, 133.0, 130.5, 128.9, 127.0, 126.4, 121.8, 119.4, 28.7, 28.1, 23.0, 211, 16.8. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{14}H_{15}NNa$: 220.1096, found: 220.1095.

Diethyl 2-((6-Methyl-3,4-dihydronaphthalen-1-yl)methyl)-malonate ***3w***. 37 mg, yield: 58%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2981, 2933, 2831, 1749, 1733, 1368, 1229, 1148, 1042, 828. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.96 (s, 1H), 5.86 (t, J = 4.5 Hz, 1H), 4.21−4.15 (m, 4H), 3.62 (t, J = 7.5 Hz, 1H), 3.05 (d, J = 7.5 Hz, 2H), 2.66 (t, J = 8.0 Hz, 2H), 2.31 (s, 3H), 2.23−2.20 (m, 2H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR

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(100 MHz, $CDCl_3$) δ = 169.2, 136.8, 136.7, 132.6, 131.1, 128.7, 127.0, 126.3, 122.2, 61.3, 51.1, 31.8, 28.3, 23.1, 21.1, 14.1. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{19}H_{24}O_4Na$: 339.1567, found: 339.1569.

Ethyl 2,2-Difluoro-2-(6-methoxy-3,4-dihydronaphthalen-2-yl)-acetate ***3x***. 36 mg, yield: 63%, chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v). Colorless oil. IR (film) (cm^{-1}): 2940, 2839, 1763, 1608, 1502, 1274, 1248, 1196, 1088, 1037. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (d, J = 8.0 Hz, 1H), 6.82 (s, 1H), 6.73−6.71 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 2.85 (t, J = 8.2 Hz, 2H), 2.44−2.40 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (t, J = 35 Hz), 160.1, 137.4, 129.0, 128.2 (t, J = 9.1 Hz), 127.7 (t, J = 23 Hz), 125.0, 113.8, 111.5, 62.9, 55.3, 27.9, 21.0 (t, J = 2.9 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −106.76. HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{15}H_{16}F_2O_3Na$: 305.0960, found: 305.0965.

6. Derivations of Annulation Product. *Hydrolysis of* ***3g***. To a solution of **3g** (30 mg, 0.1 mmol) in EtOH (2 mL) was added sodium hydroxide solution (80 mg, 2.0 mmol, 20 equiv in 2 mL of H_2O) at room temperature. The resulting suspension was stirred at room temperature for 3.5 h. After addition of H_2O (10 mL), the aqueous mixture was washed with EtOAc (3 × 5 mL). The organic layers were discarded. The aqueous solution was acidified to pH 1 with 2 M HCl solution. The suspension was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford oil product **4g** without further purification.

2,2-Difluoro-3-(6-methoxy-3,4-dihydronaphthalen-1-yl)propanoic Acid ***4g***. 26 mg, yield: 95%. Colorless oil. IR (film) (cm^{-1}): 2937, 2836, 1759, 1609, 1501, 1252, 1086, 1039. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, J = 8.0 Hz, 1H), 6.73−6.71 (m, 3H), 5.96 (s, 1H), 3.79 (s, 3H), 3.22 (t, J = 16.0 Hz, 2H), 2.71 (t, J = 7.9 Hz, 2H), 2.28−2.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 138.3, 129.4, 127.1, 126.7 (t, J = 3.7 Hz), 124.2, 114.0, 110.8, 77.3, 77.0, 76.7, 55.3, 37.3 (t, J = 24 Hz), 28.5, 23.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −104.07. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{15}F_2O_3$: 269.0984, found: 269.0988.

Reduction of ***3g***. To the solution of **3g** (30 mg, 0.1 mmol) in anhydrous THF (2 mL) was added $LiAlH_4$ (114 mg, 0.3 mmol). The mixture refluxed for 2 h and then cooled to room temperature. The mixture was cautiously quenched with H_2O (2 mL) and diluted with diethyl ether (10 mL) and 2 M HCl (2 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc = 5:1, v/v) to provide the desired oil product **5g**.

2,2-Difluoro-3-(6-methoxy-3,4-dihydronaphthalen-1-yl)propan-1-ol ***5g***. 23 mg, yield: 63%. Colorless oil. IR (film) (cm^{-1}): 2931, 2833, 1608, 1500, 1252, 1143.05, 1075, 1039. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (d, J = 8.0 Hz, 1H), 6.75−6.72 (m, 2H), 5.97 (t, J = 4.5 Hz, 1H), 3.80 (s, 3H), 3.72 (t, J = 12.6 Hz, 2H), 3.08 (t, J = 16.0 Hz, 2H), 2.74 (t, J = 8.0 Hz, 2H), 2.30−2.25 (m, 2H), 1.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 138.3, 128.8, 128.5 (t, J = 4.8 Hz), 127.5, 124.5, 122.6 (t, J = 243 Hz), 114.0, 110.8, 63.5 (t, J = 32 Hz), 55.2, 36.3 (t, J = 25 Hz), 28.7, 23.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −104.94. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{17}F_2O_2$: 255.1191, found: 255.1196.

Hydrogenation of ***3g***. A suspension of **3g** (44 mg, 0.15 mmol) and 10% Pd/C catalyst (35 mg, 0.016 mmol) on ethyl acetate (3 mL) was stirred vigorously under a hydrogen atmosphere (ballon) at 40 °C for 4 h. The filtered solution was concentrated, and the residue was purified by silica gel chromatography (petroleum ether/EtOAc = 95:5, v/v) to give the desired oil product **6g**.

Ethyl 2,2-Difluoro-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate ***6g***. 33 mg, yield: 63%. Colorless oil. IR (film) (cm^{-1}): 2936, 2867, 2838, 1768, 1609, 1502, 1316, 1279, 1255, 1231, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (d, J = 8.5 Hz, 1H), 6.72 (dd, J = 8.5, 2.5 Hz, 1H), 6.60 (d, J = 2.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 3.15−3.10 (m, 1H), 2.80−2.67 (m, 2H), 2.48−2.29 (m, 2H), 1.94−1.74 (m, 4H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.4 (t, J = 32 Hz), 157.7, 138.3, 131.4, 129.7, 116.3 (t, J = 250 Hz), 113.6, 112.4, 62.9, 55.2, 41.5 (t, J = 22 Hz), 31.2 (t, J = 3.5 Hz), 29.6, 28.3, 19.1, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −102.60 (t, J = 69 Hz), −105.32 (t, J = 69 Hz). HRMS (ESI) ([M + Na]$^+$) Calcd For $C_{16}H_{20}F_2O_3Na$: 321.1273, found: 321.1276.

Reduction of ***3v***. To a solution of **3v** (18 mg, 0.1 mmol) in anhydrous toluene (2 mL) was dropwise added DIBAL-H (1.0 M in hexane, 0.12 mL, 0.12 mmol, 1.2 equiv) at −50 °C. The reaction was stirred for 1 h at −40 °C under argon and then slowly warmed to room temperature. The reaction was quenched with 2 M HCl (2 mL) and was stirred for 0.5 h. The aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/DCM = 1:1, v/v) to afford oil product **7v**.

3-(6-Methyl-3,4-dihydronaphthalen-1-yl)propanal ***7v***. 16 mg, yield: 80%. Colorless oil. IR (film) (cm^{-1}): 2928, 2884, 2829, 2720, 1724, 1498, 1450, 1237, 1021, 827. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.82 (t, J = 1.5 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.98 (s, 1H), 5.82 (t, J = 4.6 Hz, 1H), 2.82−2.74 (m, 2H), 2.74−2.64 (m, 4H), 2.32 (s, 3H), 2.27−2.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.3, 136.7, 136.7, 134.5, 131.5, 128.65, 126.9, 124.6, 122.2, 42.5, 28.3, 25.0, 23.1, 21.1. HRMS (ESI) ([M − H]$^-$) Calcd For $C_{14}H_{15}O$: 199.1128, found: 199.1119.

Epoxidation of ***3u***. A solution of *m*-chloroperbenzoic acid (0.15 mmol, 1.5 equiv) in anhydrous DCM (1.0 mL) was added dropwise to a solution of product **3u** (0.1 mmol) in anhydrous DCM (0.5 mL) at 0 °C. The achieved solution was warmed to room temperature and then stirred for 1.5 h. The reaction mixture was washed with 2.5 M NaOH for 3 times. The organic layer was dried ($NaSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 95:5, v/v) to afford oil product **8u**.

5-Methyl-7b-(2,2,2-trifluoroethyl)-1a,2,3,7b-tetrahydronaphtho-[1,2-b]oxirene ***8u***. 18 mg, yield: 75%. Colorless oil. IR (film) (cm^{-1}): 2921, 2851, 1368, 1353, 1251, 1139, 1113, 1075, 812. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H), 6.95 (s, 1H), 3.73 (s, 1H), 3.59−3.48 (m, 2H), 2.82−2.73 (m, 1H), 2.56 (dd, J = 15.7, 5.4 Hz, 1H), 2.44−2.32 (m, 2H), 2.32 (s, 3H), 1.91 (td, J = 13.8, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.3, 136.9, 129.8, 128.9, 127.0, 126.7, 125.5 (q, J = 276 Hz), 60.5, 52.7, 38.5 (q, J = 276 Hz), 25.2, 21.6, 21.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −61.20 (s). HRMS (EI) ([M]$^+$) Calcd For $C_{13}H_{13}F_3O$: 242.0918; found: 242.0924.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01825.

Data of DFT calculations, and ^{1}H and ^{13}C NMR spectra for all pure products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chengxu@nju.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (b) Barnes-Seeman, D.; Beck, J.;

DOI: 10.1021/acs.joc.6b01825
J. Org. Chem. 2016, 81, 9992−10001

Springer, C. *Curr. Top. Med. Chem.* **2014**, *14*, 855−864. (c) Wang, J.; Sanchez-Rosello, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506. (d) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422−518.
(2) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16−29.
(3) (a) Marsh, E. N. G.; Suzuki, Y. *ACS Chem. Biol.* **2014**, *9*, 1242−1250. (b) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, *116*, 719−766.
(4) Gardiner, J. *Aust. J. Chem.* **2015**, *68*, 13−22.
(5) (a) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476−2536. (b) Zhang, F.; Min, Q.-Q.; Zhang, X. *Synthesis* **2015**, *47*, 2912−2923. (c) Belhomme, M. C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem.—Eur. J.* **2015**, *21*, 12836−12865. (d) Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. *ACS Catal.* **2016**, *6*, 1093−1096. (e) Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 1885−1889.
(6) (a) Douglas, J. J.; Albright, H.; Sevrin, M. J.; Cole, K. P.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14898−14902. (b) Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *Org. Biomol. Chem.* **2015**, *13*, 8740−8749. (c) Qu, C.; Xu, P.; Ma, W.; Cheng, Y.; Zhu, C. *Chem. Commun. (Cambridge, U. K.)* **2015**, *51*, 13508−13510. (d) Tang, X.-J.; Zhang, Z.; Dolbier, W. R., Jr. *Chem.—Eur. J.* **2015**, *21*, 18961−18965. (e) Zhang, Z.; Tang, X.; Dolbier, W. R., Jr. *Org. Lett.* **2015**, *17*, 4401−4403.
(7) (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160−4163. (b) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119−6122. (c) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144−4147. (d) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875−8884. (e) Yu, C.; Iqbal, N.; Park, S.; Cho, E. J. *Chem. Commun.* **2014**, *50*, 12884−12887. (f) Xu, P.; Hu, K.; Gu, Z.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2015**, *51*, 7222−7225. (g) Zhang, Z.; Tang, X.-J.; Dolbier, W. R. *Org. Lett.* **2016**, *18*, 1048−1051.
(8) (a) Lin, Q.; Chu, L.; Qing, F.-L. *Chin. J. Chem.* **2013**, *31*, 885−891. (b) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289−13292. (c) Straathof, N. J. W.; Gemoets, H. P. L.; Wang, X.; Schouten, J. C.; Hessel, V.; Noel, T. *ChemSusChem* **2014**, *7*, 1612−1617. (d) Jung, J.; Kim, E.; You, Y.; Cho, E. J. *Adv. Synth. Catal.* **2014**, *356*, 2741−2748. (e) Su, Y.-M.; Hou, Y.; Yin, F.; Xu, Y.-M.; Li, Y.; Zheng, X.; Wang, X.-S. *Org. Lett.* **2014**, *16*, 2958−2961. (f) Wang, L.; Wei, X.-J.; Jia, W.-L.; Zhong, J.-J.; Wu, L.-Z.; Liu, Q. *Org. Lett.* **2014**, *16*, 5842−5845.
(9) (a) Xie, J.; Zhang, T.; Chen, F.; Mehrkens, N.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 2934−2938. (b) Xu, P.; Wang, G.; Zhu, Y.; Li, W.; Cheng, Y.; Li, S.; Zhu, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2939−2943.
(10) Liu, K. E.; Johnson, C. C.; Newcomb, M.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 939−947.
(11) (a) Feng, Z.; Min, Q. Q.; Zhao, H. Y.; Gu, J. W.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1270−1274. (b) Gao, B.; Zhao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 638−642. (c) Gu, J.-W.; Zhang, X. *Org. Lett.* **2015**, *17*, 5384−5387. (d) Li, X.; Feng, Z.; Jiang, Z.-X.; Zhang, X. *Org. Lett.* **2015**, *17*, 5570−5573. (e) Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. *ACS Catal.* **2016**, *6*, 1093−1096.
(12) (a) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076. (b) Byers, J. H.; Whitehead, C. C.; Duff, M. E. *Tetrahedron Lett.* **1996**, *37*, 2743−2744.
(13) Fei, J.; Wang, Z.; Cai, Z.; Sun, H.; Cheng, X. *Adv. Synth. Catal.* **2015**, *357*, 4063.
(14) Varela, J. A.; Peña, D.; Goldfuss, B.; Denisenko, D.; Kulhanek, J.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2004**, *10*, 4252−4264.
(15) Wang, Y.; Muratore, M. E.; Rong, Z.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 14022−14026.
(16) Caldwell, R. A.; Zhou, L. *J. Am. Chem. Soc.* **1994**, *116*, 2271.
(17) Ketley, A. D.; McClanahan, J. L. *J. Org. Chem.* **1965**, *30*, 942.
(18) Quntar, A. A.-A.; Srebnik, M. *Synth. Commun.* **2002**, *32* (16), 2575−2579.
(19) Jiang, G.; Fu, X.; Li, Q.; Yu, Z. *Org. Lett.* **2012**, *14* (3), 692−695.
(20) Liu, C.; Zhuang, Z.; Bose, S.; Yu, Z. *Tetrahedron* **2016**, *72*, 2752−2755.
(21) Breuer, E.; Segall, E.; Stein, Y.; Sarel, S. *J. Org. Chem.* **1972**, *37*, 2242−2245.
(22) Davies, H. M. L.; Antoulinakis, E. G. In *Organic Reactions*; Wiley: Hoboken, NJ, 2001; Vol. *57*.
(23) Li, Z.-R.; Bao, X.-X.; Sun, J.; Shen, J.; Wu, D.-Q.; Liu, Y.-K.; Deng, Q.-H.; Liu, F. *Org. Chem. Front.* **2016**, *3*, 934−938.
(24) Zhu, Z.; Chen, K.; Yu, L.; Tang, X.; Shi, M. *Org. Lett.* **2015**, *17* (24), 5994−5997.

DOI: 10.1021/acs.joc.6b01825
J. Org. Chem. 2016, 81, 9992−10001