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An Easy Access to Difluoromethylene-Containing Arene Analogues via Palladium-Catalyzed C−H Olefination

Changdong Shao,[a,b] Guangfa Shi,[a] and Yanghui Zhang *[a,b,c]

Abstract: An efficient palladium-catalyzed *ortho* C−H olefination of α,α-difluorophenylacetic acid derivatives using 8-aminoquinoline as the bidentate directing group has been developed. A range of olefinated arenes can be synthesized in a concise way. This reaction provides an easy and straightforward access to a panel of difluoromethylated arene analogues in moderate to good yields with a satisfactory tolerance of common functional groups. Transformations of the products to a variety of other difluoromethylene-containing compounds demonstrated the utility of this method.

Introduction

Organofluorine compounds have found extensive applications in a wide range of fields owing to their novel and useful properties.[1] In particular, fluorine substituents are widely present in pharmaceutical molecules.[2] Currently, there are over 150 fluorinated drugs in the market, which make up 20~30% of all pharmaceuticals and agrochemicals.[3] As such, it is of great importance for chemists and pharmaceutists to develop facile and efficient methods for fluorine incorporation.[4] A large number of compounds usually need to be synthesized for high-throughput drug screening in drug discovery, and these compounds are often analogues. Currently, the approaches for

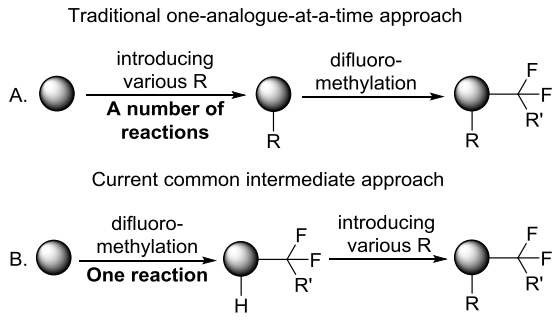

Figure 1. Approaches for the synthesis of difluoromethylated compounds.

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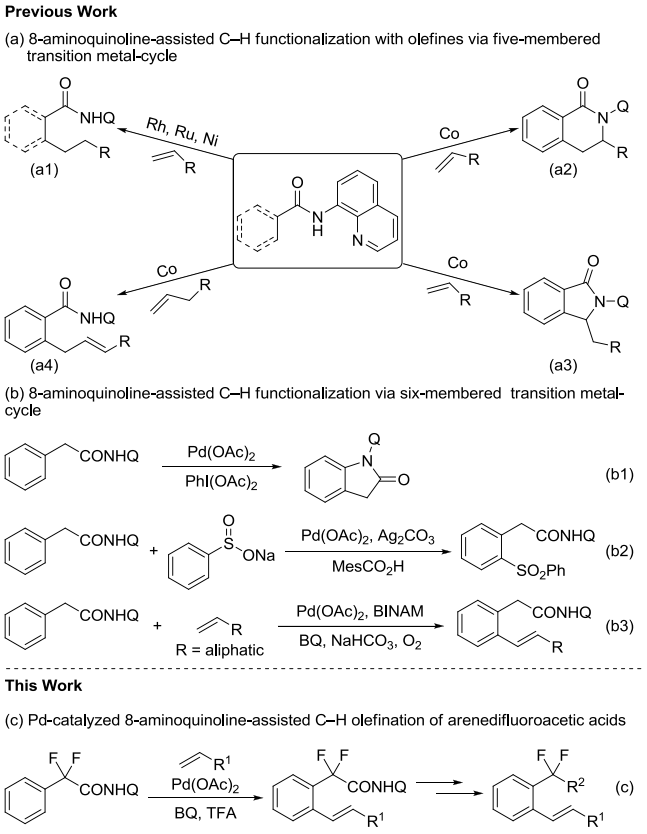


Scheme 1. TM-catalyzed 8-aminoquinoline assisted C-H functionalization reactions.

the synthesis of organofluorine compounds usually involve incorporating fluorine substituents into a precursor of each analogue, i.e. one-analogue-at-a-time approach (Figure 1, A). However, drug discovery requires a synthetic approach that offers a panel of analogues in a straightforward manner (Figure 1, B).

In the past few decades, C−H functionalization is emerging as a novel and valuable strategy in organic synthesis.[5] In particular, it provides an easy access to a wide range of analogues. Most of C−H functionalization reactions rely on the use of directing groups, because they can solve regioselectivity problems and accelerate C−H cleavage process.[6] Directed C−H functionalization allows for a range of substituents to be introduced into the substrates, and therefore a number of analogues can be obtained in a concise way. Thus, we envisaged that fluorine-containing directing groups would provide an easy access to a wide range of fluorinated analogues.

Recently, the difluoromethylene groups have attracted great attentions owing to their special biological properties, and

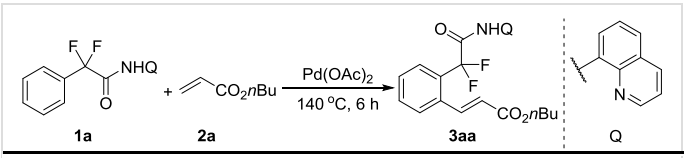
molecules containing these groups are particularly desirable building blocks for medicinal chemistry.[1c,1d,7]

On the other hand, among a variety of directing groups, the bidentate ones have proved to be particularly powerful, and successfully utilized to enable a range of novel organic transformations.[8] In this context, 8-minoquinoline[9] is particularly attractive. Chatani and Maiti reported several examples of Rh/Ru/Ni-catalyzed C−H alkylation reaction with olefines (Scheme 1, a1). [10a-c] Daugulis and Ackermann demonstrated Cobalt-catalyzed 8-aminoquinoline-directed annulation reactions with olefines via a C−H/N−H functionalization process (a2, a3). [10d-e] Cobalt-catalyzed *ortho* C−H allylation with unactivated olefines was also reported by Chatani and Maiti (a4). [10f-g] Palladium-catalyzed C−H functionalization reactions via a six-membered palladium-cycle using phenylacetyl aminoquinoline as the substrate have also been reported by Chen (b1), Shi (b2), and Maiti (b3) respectively. [10h-j]

Inspired by these great reactions, in particularl Maiti's impressive work (b3), [10j] and our persistent interests in organofluorine chemistry,[11] we present herein an efficient palladium-catalyzed Fujiwara-Moritani reaction of α,α-difluorophenylacetic acid derivatives using 8-aminoquinoline as the bidentate directing group. The directing group can be readily removed under mild conditions in the presence of the difluoromethylene group, affording diverse *ortho*-olefinated α,α-difluorophenylacetic acid derivatives (c). This reaction provides a new strategy for the synthesis of a range of difluoromethylene-containing arene analogues.

Results and Discussion

We initiated this research project by investigating the C−H olefination of 2,2-difluoro-2-phenyl-*N*-(quinolin-8-yl)acetamide (**1a**) with *n*-butyl acrylate (**2a**). After extensive condition survey, the reaction formed the desired alkenylated product (**3aa**) in 13% yield in the presence of 10 mol % $Pd(OAc)_2$ and 1.2 equivalent benzoquinone in 1,2-dichloroethane (Table 1, entry 1). The yield increased slightly to 21% when 1.5 equivalent HOAc was added (entry 2). Inspired by this result, we screened other acids. Methanesulfonic acid and pivalic acid enhanced the yield to 36% and 66% respectively (entries 3-4). It should be mentioned that diolefinated product was formed along with the desired monoolefinated one in these two reactions. Gratefully, the yield of monosubstituted product was improved to 79% in the presence of TFA along with 11% undesired disubstituted byproduct (entry 5). BQ proved to be the optimal oxidant, whereas other oxidants such as AgOAc, Ag_2CO_3, $Cu(OAc)_2$, $K_2S_2O_8$, and O_2 gave lower yields (entries 6-10), and the yield decreased dramatically in the absence of BQ (entry 11). The reaction still took place and formed the olefinated product in other solvents, including solvents with a higher boiling point, albeit in lower yields (entries 12-19). The yield decreased to 45% when 5 mol % $Pd(OAc)_2$ was used (entry 20) and no olefinated product was observed in the absence of $Pd(OAc)_2$ (entry 21). The yield was reduced to 61% or 31% when the reaction were carried out at 130 °C or 120 °C respectively

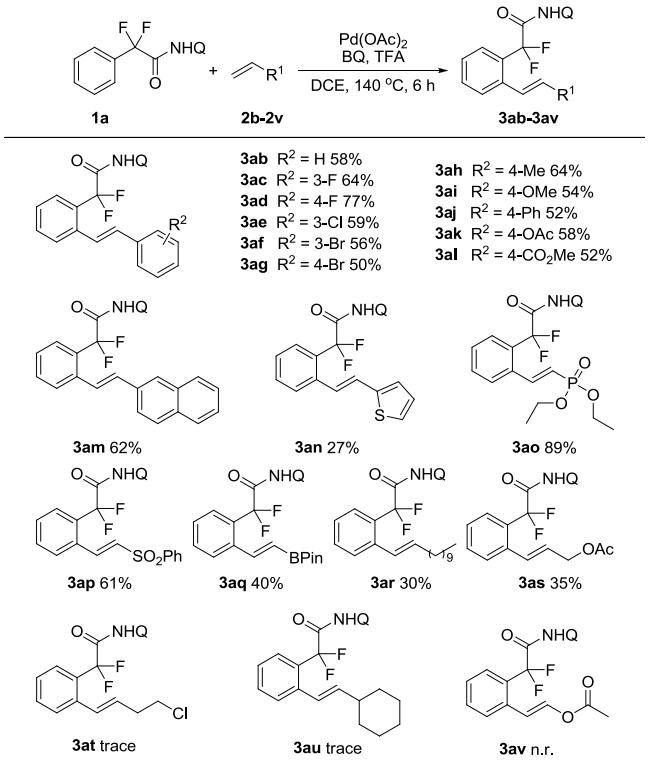


Entry	Additive	Oxidant	Solvent	Yield (%)[b, c]
1	—	BQ	DCE	13
2	HOAc	BQ	DCE	21
3	MsOH	BQ	DCE	36 (1)
4	PivOH	BQ	DCE	66 (2)
5	**TFA**	**BQ**	**DCE**	**79 (11) [76][d]**
6	TFA	AgOAc	DCE	41 (2)
7	TFA	Ag_2CO_3	DCE	51 (5)
8	TFA	$Cu(OAc)_2$	DCE	69 (5)
9	TFA	$K_2S_2O_8$	DCE	34 (1)
10	TFA	O_2	DCE	14
11	TFA	—	DCE	11
12	TFA	BQ	DMF	46 (6)
13	TFA	BQ	DMA	34 (9)
14	TFA	BQ	NMP	38
15	TFA	BQ	DMSO	60 (4)
16	TFA	BQ	mesitylene	10
17	TFA	BQ	dioxane	64 (10)
18	TFA	BQ	MeCN	22
19	TFA	BQ	THF	40 (2)
20	TFA	BQ	DCE	45 (2)[e]
21	TFA	BQ	DCE	—[f]
22	TFA	BQ	DCE	61 (5)[g]
23	TFA	BQ	DCE	31[h]
24	TFA	BQ	DCE	75 (4)[i]
25	TFA	BQ	DCE	73 (9)[j]

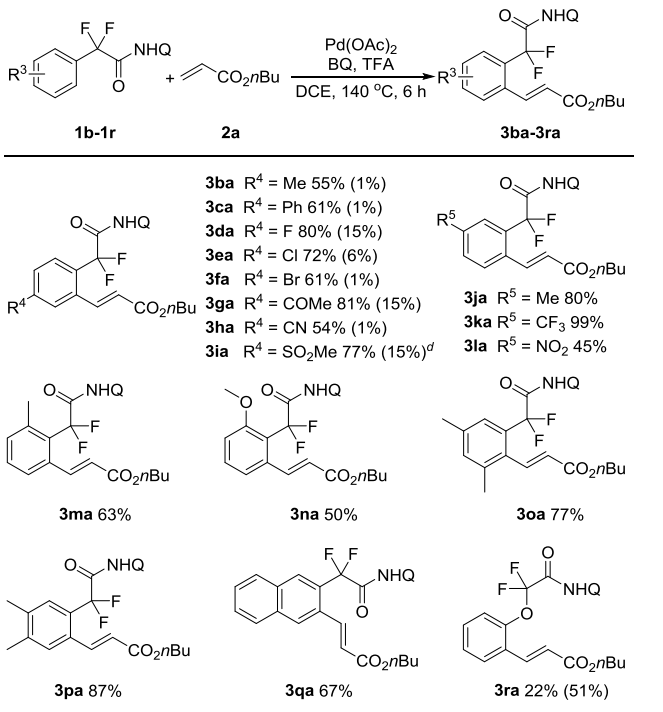
[a] Reactions conditions: **1a** (0.10 mmol), **2a** (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), additive (1.5 equiv.), oxidant (1.2 equiv.), solvent (1.0 mL), 140 °C, air, 6 h. [b] Yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. [c] Yields for disubstituted products were in parentheses. [d] Isolated yield was given in square brackets. [e] $Pd(OAc)_2$ (5 mol %). [f] Without $Pd(OAc)_2$. [g] 130 °C. [h] 120 °C. [i] Under N_2. [j] Under O_2.

Table 1. Optimization of the reaction conditions.[a]

Table 2. Substrate scope of olefines.[a,b]



[a] Reactions conditions: **1a** (0.10 mmol), **2** (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.2 equiv.), TFA (1.5 equiv.), DCE (1.0 mL), 140 °C, air, 6 h. [b] Isolated yield.



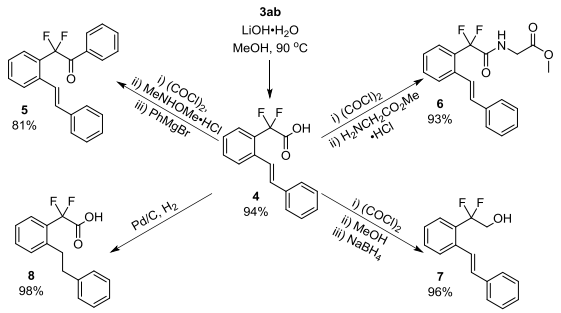
[a] Reactions conditions: **1** (0.10 mmol), **2a** (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.2 equiv.), TFA (1.5 equiv.), DCE (1.0 mL), 140 °C, air, 6 h. [b] Yields for disubstituted products showed in parentheses were determined by crude ^1H NMR using CH_2Br_2 as the internal standard. [c] Isolated yield. [d] 1.1 equiv. **2a** was used.

(entries 22-23). Furthermore, the reaction was insensitive to the atmosphere and proceeded smoothly under N_2, O_2, or air (entries 24-25).

With the optimal conditions in hand (Table 1, entry 5), we surveyed the substrate scope of this C–H olefination reaction. Firstly, we examined the performance of various alkenes under the optimized conditions. Thus, as shown in Table 2, a range of styrenes underwent the reaction to form the desired olefinated products. The halo groups, including F, Cl, and Br, were well tolerated (**2c-g**). Styrenes containing other common functional groups, including methoxy (**2i**), phenyl (**2j**), acetoxy (**2k**), and ester (**2l**) groups, were reactive, affording the olefinated products in moderate yields. 2-vinylnaphthalene was also suitable (**2m**), and 2-vinylthiophene (**2n**) underwent the olefination reaction successfully, albeit in a low yield (27%). Considering that the organophosphorus and organosulfur compounds are extensively exist in pharmaceuticals, agrochemicals, and functional materials,[12] we then examined two kinds of alkenes that containing phosphonate (**2o**) and sulfonyl (**2p**) group under the optimal reaction conditions. The reactions formed the desired products **3ao** (89%) and **3ap** (61%) in good yields. Intriguingly, vinylboronate (**2q**) selectively underwent the olefination reaction and the products derived from the reaction of the boronate moiety were not observed. Unactivated alkenes were also examined, and the reaction also occurred, albeit in low yields (**3ar** and **3as**). Other unactivated alkenes bearing a chloro or cyclohexyl group and vinyl acetate were almost unreactive (**2t-v**). It should be noted that diolefinated products were not observed for the substrates in Table 2.

Next, the arene scope was examined using *n*-butyl acrylate (**2a**) as the reaction partner. As shown in Table 3, arenes containing a variety of functional groups effectively underwent the olefination reaction under the standard conditions to form the corresponding olefinated products. Both electron-donating group, such as methyl (**1b**), and electron-withdrawing groups including carbonyl (**1g**), cyano (**1h**), and sulfonyl (**1i**) group at the *para*-position were well-tolerated in the reaction. Fluoro (**1d**), chloro (**1e**), and bromo (**1f**) groups were intact under the reaction conditions. It should be mentioned that a tiny or small amount of diolefinated products were formed for the substrate bearing *para*-substituents (**1b-i**). In the presence of *meta*-substituents (**1j-l**), the olefination reaction selectively took place at the less hindered positions, and diolefinated products were not observed. The substrates bearing an *ortho*-substituent, methyl (**1m**) or methoxyl (**1n**) group, were also suitable. The compatibility of disubstituted substrates was also examined. Thus, 3,5- or 3,4-disubstituted arene substrates could be efficiently transformed into the corresponding products **3oa-pa** in 77% and 87% yield respectively. Furthermore, the C−H bond of naphthalene was also compatible, and the alkenylation reaction occurred selectively at the less hindered position (**3qa**). Interestingly, when an oxygen atom was added between the phenyl group and the CF_2 group, the reaction still took place, forming mono- and

Table 3. Substrate scope of arenes.[a,b,c]



Scheme 2. Late stage transformations.

diolefinated products in 22% and 51% yield respectivley (**3ra**). Furthermore, some mechanistic studies were carried out, and the outcomes were consistent with the 8-aminoquinoline-directed C−H activation under palladium catalysis (see ESI).[13]

To demonstrate the synthetic utility of the products obtained via the C−H alkenylation reaction, compound **3ab** was converted to an aryl difluoroacetic acid. Gratefully, the hydrolysis of **3ab** could take place under mild conditions in the presence of the difluoromethylene group, providing (*E*)-2,2-difluoro-2-(2-styrylphenyl)acetic acid (**4**) in 94% yield. Compound **4** is a versatile intermediate, and can be transformed into a variety of products containing difluoromethylene groups (Scheme 2). First, **4** was converted to its acyl chloride derivative by reacting with $(COCl)_2$. The resulting acyl chloride was then allowed to react with *N,O*-dimethylhydroxylamine hydrochloride and PhMgBr, affording aryldifluoroketone derivative **5** as the final product in 81% total yield.[14] Second, the acyl chloride reacted with glycine methyl ester hydrochloride to form aryldifluoroamide derivative **6** in 93% yield. Third, the reduction of the ester, which was obtained by treating the acyl chloride with methanol, gave aryldifluoroethanol derivative **7** in 96% yield.[15] Finally, the double bond of **4** could be reduced via hydrogenation to give alkylated product **8** almost quantitatively (98%).[16]

Conclusions

In conclusion, we have successfully developed an efficient palladium-catalyzed *ortho* C−H olefination of α,α-difluorophenylacetic acid derivatives using 8-aminoquinoline as the bidentate directing group. The reaction provides an efficient and concise manner to gain access to a range of difluoromethylated arene analogues. The bidentate directing group can be removed under mild conditions. This strategy for synthesizing difluoromethylene group-containing compounds would have application potentials in drug discovery.

Experimental Section

General Information

High resolution mass spectra were measured on Bruker MicroTOF II ESI-TOF mass spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on Bruker ARX400 (400 MHz, 101 MHz and 376 MHz, respectively). The ^{1}H chemical shifts are reported in ppm and referenced to residual protium in the NMR solvent ($CDCl_3$: δ = 7.26 ppm, ^{6}d-DMSO: δ = 2.50 ppm, CD_3OD: δ = 3.31 ppm). The ^{13}C chemical shifts are reported in ppm and referenced to residual protium in the NMR solvent ($CDCl_3$: δ = 77.00 ppm, ^{6}d-DMSO: δ = 39.52 ppm, CD_3OD: δ = 49.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets. Substrates (**1a-1q)** were synthesized according to literatures and the rest commercial available chemicals were used without further purification.

Typical experimental procedure for 3

A 35 mL sealed tube equipped with a magnetic stir bar was charged with substrates **1** (0.10 mmol), palladium (II) acetate (10 mol %), 1,4-benzoquinone (1.2 equiv.), trifluoroacetic acid (1.5 equiv.), alkenes **2** (1.5 equiv.), and 1,2-dichloroethane (1.0 mL) under air. The reaction tube was sealed with a *Teflon*® high pressure valve and moved into a preheated oil bath. After stirring at 140 °C for 6 hours, the reaction mixture was allowed to cool down to room temperature and diluted with ethyl acetate (10 mL). The mixture was washed with saturated sodium sulfide (5 mL, once) and brine (5 mL, twice), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (PTLC) to give the corresponding compounds **3**.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)phenyl-)acrylate (3aa): White solid (32.2 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.86 (d, *J* = 3.9 Hz, 1H), 8.73 (d, *J* = 7.5 Hz, 1H), 8.27 (d, *J* = 15.8 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.45 (m, 4H), 6.33 (d, *J* = 15.8 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.35 – 1.19 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.10, 161.48 (t, *J* = 30.5 Hz), 148.74, 141.45 (t, *J* = 2.8 Hz), 138.58, 136.23, 134.14 (t, *J* = 2.5 Hz), 132.72, 131.33 (t, *J* = 23.8 Hz), 131.19, 129.47, 128.12, 127.83, 127.03, 126.94 (t, *J* = 8.5 Hz), 123.08, 122.30, 121.92, 117.07, 115.46 (t, *J* = 255.6 Hz), 64.33, 30.43, 18.96, 13.57. HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{22}F_2N_2NaO_3^+$: 447.1491 $(M + Na)^+$, found: 447.1501.

***(E)*-2,2-difluoro-*N*-(quinolin-8-yl)-2-(2-styrylphenyl)acetamide (3ab):** White solid (23.2 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.73 (dd, *J* = 7.4, 0.9 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.58 – 7.46 (m, 4H), 7.45 – 7.33 (m, 3H), 7.16 – 7.03 (m, 3H), 6.95 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.04 (t, *J* = 30.7 Hz), 148.67, 138.53, 136.85, 136.83 (t, *J* = 3.0 Hz), 136.25, 132.79, 132.60, 131.08, 130.25 (t, *J* = 23.4 Hz), 128.31, 127.82, 127.72, 127.44, 127.37, 127.07, 126.70, 126.65 (t, *J* = 8.8 Hz), 125.35 (t, *J* = 2.1 Hz), 122.98, 121.84, 117.05, 115.72 (t, *J* = 255.0 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{18}F_2N_2NaO^+$: 423.1279 $(M + Na)^+$, found: 423.1287.

***(E)*-2,2-difluoro-2-(2-(3-fluorostyryl)phenyl)-*N*-(quinolin-8-yl)acetamide (3ac):** White solid (26.7 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.82 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.72 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.57 – 7.40 (m, 5H), 7.13 – 6.99 (m, 3H), 6.87 (d, *J* = 16.0 Hz, 1H), 6.83 – 6.76 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.83 (d, *J* = 245.2 Hz), 161.95 (t, *J* = 30.6 Hz), 148.79, 139.16 (d, *J* = 7.7 Hz), 138.46, 136.35 (t, *J* = 3.0 Hz), 136.23, 132.67, 131.45 (d, *J* = 2.4 Hz), 131.12, 130.44 (t, *J* = 23.5 Hz), 129.69 (d, *J* = 8.4 Hz), 127.81, 127.77, 127.50, 126.99, 126.79

(d, *J* = 2.4 Hz), 126.69 (t, *J* = 8.8 Hz), 123.06, 122.68 (d, *J* = 2.7 Hz), 121.91, 116.98, 115.62 (t, *J* = 255.0 Hz), 114.50 (d, *J* = 21.5 Hz), 112.86 (d, *J* = 21.9 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{17}F_3N_2NaO^+$: 441.1185 (M + Na)$^+$, found: 441.1200.

***(E)*-2,2-difluoro-2-(2-(4-fluorostyryl)phenyl)-*N*-(quinolin-8-yl)acetamide (3ad):** White solid (32.2 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 7.5, 1.2 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.83 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.61 – 7.46 (m, 5H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.26 (m, 2H), 6.86 (d, *J* = 16.0 Hz, 1H), 6.77 – 6.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.25 (d, *J* = 247.7 Hz), 162.05 (t, *J* = 30.6 Hz), 148.65, 138.51, 136.71 (t, *J* = 3.1 Hz) 136.32, 133.03 (d, *J* = 3.3 Hz), 132.75, 131.47, 131.11, 130.32 (t, *J* = 23.4 Hz), 128.17 (d, *J* = 8.0 Hz), 127.84, 127.50, 127.36, 127.09, 126.60 (t, *J* = 8.8 Hz), 125.26 (d, *J* = 2.2 Hz), 123.01, 121.88, 117.04, 115.63 (t, *J* = 255.3 Hz), 115.17 (d, *J* = 21.7 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{17}F_3N_2NaO^+$: 441.1185 (M + Na)$^+$, found: 441.1180.

***(E)*-2-(2-(3-chlorostyryl)phenyl)-2,2-difluoro-*N*-(quinolin-8-yl)acetamide (3ae):** White solid (25.6 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.81 (d, *J* = 4.1 Hz, 1H), 8.71 (d, *J* = 7.5 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.58 – 7.39 (m, 5H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.98 (t, *J* = 30.5 Hz), 148.80, 138.73, 138.50, 136.43 (t, *J* = 3.0 Hz), 136.25, 134.33, 132.71, 131.36, 131.14, 130.52 (t, *J* = 23.6 Hz), 129.45, 127.86, 127.82, 127.63, 127.60, 127.05, 127.02, 126.69 (t, *J* = 8.7 Hz), 126.50, 124.81, 123.08, 121.92, 117.01, 115.60 (t, *J* = 255.0 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{17}ClF_2N_2NaO^+$: 457.0890 (M + Na)$^+$, found: 457.0897.

***(E)*-2-(2-(3-bromostyryl)phenyl)-2,2-difluoro-*N*-(quinolin-8-yl)acetamide (3af):** White solid (26.8 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.71 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.83 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.59 – 7.41 (m, 6H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.97 (t, *J* = 30.7 Hz), 148.80, 139.01, 138.50, 136.42 (t, *J* = 3.0 Hz), 136.25, 132.70, 131.26, 131.14, 130.53, 130.52 (t, *J* = 23.7Hz), 129.73, 129.50, 127.86, 127.82, 127.61, 127.07, 127.05, 126.67 (t, *J* = 8.7 Hz), 125.16, 123.08, 122.56, 121.93,117.00, 115.60 (t, *J* = 255.1 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{17}BrF_2N_2NaO^+$: 501.0385 (M + Na)$^+$, found: 501.0369.

***(E)*-2-(2-(4-bromostyryl)phenyl)-2,2-difluoro-*N*-(quinolin-8-yl)acetamide (3ag):** White solid (24.0 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.80 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.68 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.83 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.68 – 7.38 (m, 7H), 7.18 – 7.08 (m, 4H), 6.80 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.02 (t, *J* = 30.6 Hz), 148.64, 138.48, 136.57 (t, *J* = 2.8 Hz), 136.36, 135.74, 132.69, 131.54, 131.30, 131.13, 130.47 (t, *J* = 23.5 Hz), 128.03, 127.83, 127.69, 127.48, 127.06, 126.60 (t, *J* = 8.8 Hz), 126.33 (t, *J* = 1.8 Hz), 123.02, 121.89, 121.49, 117.00, 115.57 (t, *J* = 255.0 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{17}BrF_2N_2NaO^+$: 501.0385 (M + Na)$^+$, found: 501.0396.

***(E)*-2,2-difluoro-2-(2-(4-methylstyryl)phenyl)-*N*-(quinolin-8-yl)acetamide (3ah):** White solid (26.5 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.85 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.78 (d, *J* = 7.4 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.63 – 7.49 (m, 4H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.01 – 6.90 (m, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.07 (t, *J* = 30.7 Hz), 148.63, 138.52, 137.59, 137.03 (t, *J* = 3.0 Hz), 136.19, 134.09, 132.80, 132.59, 131.05, 130.13 (t, *J* = 23.4 Hz), 128.99, 127.80, 127.29, 127.23, 127.05, 126.60 (t, *J* = 8.8 Hz), 126.59, 124.32 (t, *J* = 2.1 Hz), 122.90, 121.78, 117.01, 115.73 (t, *J* = 254.7 Hz), 21.15. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{20}F_2N_2NaO^+$: 437.1436 (M + Na)$^+$, found: 437.1455.

***(E)*-2,2-difluoro-2-(2-(4-methoxystyryl)phenyl)-*N*-(quinolin-8-yl)acetamide (3ai):** White solid (23.2 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.71 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.57 – 7.46 (m, 5H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 16.0 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.14 (t, *J* = 30.8 Hz), 159.28, 148.66, 138.58, 137.14 (t, *J* = 2.9 Hz), 136.26, 132.86, 132.17, 131.05, 130.05, 129.74, 127.94, 127.85, 127.16, 127.14, 127.09, 126.61 (t, *J* = 8.9 Hz), 123.17 (t, *J* = 1.9 Hz), 122.93, 121.82, 117.08, 113.71, 113.23 (t, *J* = 229.5 Hz), 55.19. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{20}F_2N_2NaO_2^+$: 453.1385 (M + Na)$^+$, found: 453.1403.

***(E)*-2-(2-([1,1'-biphenyl]-4-yl)vinyl)phenyl)-2,2-difluoro-*N*-(quinolin-8-yl)acetamide (3aj):** White solid (24.7 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 8.81 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.73 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.12 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.59 – 7.27 (m, 14H), 6.96 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.07 (t, *J* = 30.6 Hz), 148.64, 140.51, 140.32, 138.54, 136.87 (t, *J* = 3.0 Hz), 136.23, 135.90, 132.79, 132.23, 131.10, 130.32 (t, *J* = 23.4 Hz), 128.73, 127.80, 127.46, 127.42, 127.29, 127.09, 126.90, 126.78, 126.63 (t, *J* = 8.8 Hz), 125.44, 122.95, 121.80, 117.04, 115.70 (t, *J* = 254.9 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{31}H_{22}F_2N_2NaO^+$: 499.1592 (M + Na)$^+$, found: 499.1606.

***(E)*-4-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)styryl)phenyl acetate (3ak):** White solid (31.1 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.72 (dd, *J* = 7.5, 1.2 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.57 – 7.34 (m, 7H), 6.91 (d, *J* = 16.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.20, 161.95 (t, *J* = 30.8 Hz), 150.11, 148.70, 138.44, 136.65 (t, *J* = 2.8 Hz), 136.23, 134.64, 132.68, 131.53, 131.08, 130.22 (t, *J* = 23.5 Hz), 127.78, 127.62, 127.51, 127.39, 127.00, 126.62 (t, *J* = 8.8 Hz), 125.64, 123.02, 121.86, 121.45, 116.98, 115.67 (t, *J* = 255.0 Hz), 21.06. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{20}F_2N_2NaO_3^+$: 481.1334 (M + Na)$^+$, found: 481.1341.

Methyl *(E)*-4-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)styryl-)benzoate (3al): White solid (23.8 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.80 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.69 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.80 – 7.65 (m, 4H), 7.57 – 7.41 (m, 5H), 7.38 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.70, 161.97 (t, *J* = 30.6 Hz), 148.71, 141.26, 138.49, 136.34, 136.29, 132.68, 131.58, 131.16, 130.62 (t, *J* = 23.5 Hz), 129.59, 128.94, 128.12 (t, *J* = 2.0 Hz), 127.96, 127.84, 127.54, 127.05, 126.68 (t, *J* = 8.7 Hz), 126.45, 123.09, 121.91, 117.03, 115.58 (t, *J* = 255.1 Hz), 52.02. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{20}F_2N_2NaO_3^+$: 481.1334 (M + Na)$^+$, found: 481.1347.

***(E)*-2,2-difluoro-2-(2-(2-(naphthalen-2-yl)vinyl)phenyl)-*N*-(quinolin-8-yl)acetamide (3am):** White solid (27.9 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.79 – 8.67 (m, 2H), 8.07 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.81 – 7.63 (m, 4H), 7.58 – 7.51 (m, 3H), 7.50 – 7.35 (m, 7H), 7.08 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.09 (t, *J* = 31.4 Hz), 148.62, 138.47, 136.92, 136.12, 134.39, 133.33, 132.96, 132.89, 132.76, 131.11, 130.37 (t, *J* = 24.1 Hz), 127.96, 127.85, 127.75, 127.47, 127.00, 126.85, 126.64 (t, *J* = 8.6 Hz), 126.05, 125.86, 125.79, 123.59, 122.95, 121.74, 116.98, 115.69 (t, *J* = 255.2 Hz).

HRMS (ESI-TOF) m/z: calcd. for $C_{29}H_{20}F_2N_2NaO^+$: 473.1436 (M + Na)$^+$, found: 473.1440.

***(E)*-2,2-difluoro-*N*-(quinolin-8-yl)-2-(2-(2-(thiophen-2-yl)vinyl)phenyl-)acetamide (3an):** claret viscous oil (11.0 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.73 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.43 (m, 5H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.11 – 7.00 (m, 2H), 6.98 (d, *J* = 3.4 Hz, 1H), 6.84 (dd, *J* = 5.0, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.97 (t, *J* = 30.8 Hz), 148.64, 142.36, 138.60, 136.45, 136.19, 132.90, 131.07, 130.09 (t, *J* = 23.5 Hz), 127.81, 127.40, 127.32, 127.13, 127.07, 126.75 (t, *J* = 8.7 Hz), 126.36, 125.42, 124.90, 124.85 (t, *J* = 2.4 Hz), 122.94, 121.84, 117.05, 115.72 (t, *J* = 254.9 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{23}H_{16}F_2N_2NaOS^+$: 429.0844 (M + Na)$^+$, found: 429.0835.

Diethyl *(E)*-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)styryl-)phosphonate (3ao): Clear viscous oil (41.0 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.85 (dd, *J* = 2.6, 1.6 Hz, 1H), 8.70 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.03 (td, *J* = 19.7, 1.7 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.43 (m, 6H), 6.20 (t, *J* = 17.9 Hz, 1H), 4.10 – 3.88 (m, 4H), 1.21 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.40 (t, *J* = 30.6 Hz), 148.78, 145.26 – 145.06 (m), 138.53, 136.25, 134.98 (d, *J* = 24.0 Hz), 132.72, 131.29, 130.89 (t, *J* = 23.9 Hz), 129.45, 128.05, 127.82, 126.97, 126.77 (t, *J* = 8.4 Hz), 123.12, 121.99, 118.96 (d, *J* = 188.7 Hz), 117.00, 115.46 (t, *J* = 255.5 Hz), 61.98 (d, *J* = 5.6 Hz), 16.16 (d, *J* = 6.4 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{23}H_{23}F_2N_2NaO_4P^+$: 483.1256 (M + Na)$^+$, found: 483.1267.

***(E)*-2,2-difluoro-2-(2-(2-(phenylsulfonyl)vinyl)phenyl)-*N*-(quinolin-8-yl)acetamide (3ap):** White solid (28.3 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.88 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.68 (d, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 15.2 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.81 – 7.74 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.46 (m, 6H), 7.40 (t, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 15.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.08 (t, *J* = 30.6 Hz), 148.85, 140.36 (t, *J* = 3.2 Hz), 140.11, 138.44, 136.25, 133.24, 132.53, 132.10, 131.64 (t, *J* = 24.1 Hz), 131.33, 131.13, 130.30, 129.06, 128.50, 127.79, 127.71, 126.96 (t, *J* = 8.6 Hz), 126.83, 123.27, 122.04, 116.97, 115.18 (t, *J* = 256.2 Hz). HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{18}F_2N_2NaO_3S^+$: 487.0898 (M + Na)$^+$, found: 487.0909.

***(E)*-2,2-difluoro-*N*-(quinolin-8-yl)-2-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)acetamide (3aq):** Clear viscous oil (18.0 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.88 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.75 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.86 (d, *J* = 18.0 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.61 – 7.38 (m, 5H), 6.05 (d, *J* = 18.0 Hz, 1H), 0.94 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.95 (t, *J* = 30.3 Hz), 148.66, 145.74, 138.74, 137.52 (t, *J* = 2.6 Hz), 136.18, 132.98, 131.08, 130.31 (t, *J* = 23.5 Hz), 128.27, 127.90, 127.63, 127.16, 126.40 (t, *J* = 8.7 Hz), 122.83, 121.86, 117.05, 115.50 (t, *J* = 254.7 Hz), 83.08, 24.33. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{25}BF_2N_2NaO_3^+$: 473.1823 (M + Na)$^+$, found: 473.1836.

***(E)*-2-(2-(dodec-1-en-1-yl)phenyl)-2,2-difluoro-*N*-(quinolin-8-yl)acetamide (3ar):** Clear oil (14.0 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.75 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.46 (m, 4H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 15.6 Hz, 1H), 6.04 (dt, *J* = 15.3, 6.8 Hz, 1H), 1.99 (dd, *J* = 13.8, 6.8 Hz, 2H), 1.37 – 0.96 (m, 16H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.10 (t, *J* = 30.6 Hz), 148.67, 138.65, 137.66 (t, *J* = 3.1 Hz), 136.25, 136.00, 132.91, 130.93, 129.49 (t, *J* = 23.3 Hz), 127.87, 127.77, 127.13, 126.74, 126.40, 126.31 (t, *J* = 8.9 Hz), 122.88, 121.88, 117.05, 115.68 (t, *J* = 254.3 Hz), 33.07, 31.89, 29.56, 29.49, 29.29, 29.09, 28.91, 22.67, 14.10. HRMS (ESI-TOF) m/z: calcd. for $C_{29}H_{34}F_2N_2NaO^+$: 487.2531 (M + Na)$^+$, found: 487.2514.

***(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)phenyl)allyl acetate (3as):** White solid (13.9 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.72 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.57 – 7.44 (m, 4H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.6, 6.1 Hz, 1H), 4.58 (dd, *J* = 6.1, 1.2 Hz, 2H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.51, 161.79 (t, *J* = 30.7 Hz), 148.78, 138.57, 136.29, 135.92 (t, *J* = 2.8 Hz), 132.73, 131.06, 130.49 (t, *J* = 2.4 Hz), 130.11 (t, *J* = 23.6 Hz), 127.98, 127.84, 127.82, 127.57, 127.06, 126.51 (t, *J* = 8.7 Hz), 123.04, 121.97, 117.05, 115.56 (t, *J* = 254.9 Hz), 64.57, 20.56. HRMS (ESI-TOF) m/z: calcd. for $C_{22}H_{18}F_2N_2NaO_3^+$: 419.1178 (M + Na)$^+$, found: 419.1189.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-5-methylphenyl)acrylate (3ba): White solid (24.1 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.73 (dd, *J* = 7.5, 1.2 Hz, 1H), 8.25 (dt, *J* = 15.8, 2.2 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.56 – 7.43 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 4.02 (t, *J* = 6.7 Hz, 2H), 2.40 (s, 3H), 1.52 – 1.37 (m, 2H), 1.35 – 1.19 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.19, 161.68 (t, *J* = 30.7 Hz), 148.73, 141.64 (t, *J* = 2.7 Hz), 141.44, 138.61, 136.24, 133.97 (t, *J* = 2.4 Hz), 132.81, 130.19, 128.78, 128.61 (t, *J* = 24.0 Hz), 127.85, 127.07, 126.98 (t, *J* = 8.4 Hz), 123.03, 122.00, 121.91, 117.08, 115.66 (t, *J* = 255.3 Hz), 64.31, 30.46, 21.21, 18.99, 13.60. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{24}F_2N_2NaO_3^+$: 461.1647 (M + Na)$^+$, found: 461.1648.

Butyl *(E)*-3-(4-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-[1,1'-biphenyl]-3-yl)acrylate (3ca): White solid (30.5 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.76 (dd, *J* = 7.4, 0.8 Hz, 1H), 8.33 (d, *J* = 15.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.91 – 7.81 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.64 – 7.38 (m, 8H), 6.41 (d, *J* = 15.7 Hz, 1H), 4.03 (t, *J* = 6.7 Hz, 2H), 1.52 – 1.42 (m, 2H), 1.33 – 1.22 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.10, 161.56 (t, *J* = 30.7 Hz), 148.79, 144.22, 141.57, 139.41, 138.66, 136.27, 134.64 (t, *J* = 2.3 Hz), 132.80, 130.10 (t, *J* = 24.0 Hz), 128.98, 128.26, 128.07, 127.89, 127.57 (t, *J* = 8.4 Hz), 127.21, 127.11, 126.95, 123.12, 122.58, 121.96, 117.16, 115.58 (t, *J* = 255.4 Hz), 64.41, 30.47, 19.00, 13.61. HRMS (ESI-TOF) m/z: calcd. for $C_{30}H_{26}F_2N_2NaO_3^+$: 523.1804 (M + Na)$^+$, found: 523.1826.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-5-fluorophenyl)acrylate (3da): White solid (35.4 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.71 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.25 – 8.15 (m, 2H), 7.78 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.64 – 7.45 (m, 3H), 7.34 (dd, *J* = 9.5, 2.2 Hz, 1H), 7.17 (td, *J* = 8.6, 2.4 Hz, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 1.50 – 1.40 (m, 2H), 1.32 – 1.20 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.74, 163.97 (d, *J* = 252.0 Hz), 161.28 (t, *J* = 30.6 Hz), 148.81, 140.23, 138.61, 136.93 (d, *J* = 8.4 Hz), 136.29, 132.66, 129.41 (q, *J* = 8.8 Hz), 127.88, 127.52 (dt, *J* = 24.2, 3.2 Hz), 127.07, 123.41, 123.21, 121.99, 117.14, 116.30 (d, *J* = 21.8 Hz), 115.15 (t, *J* = 256.6 Hz), 115.11 (d, *J* = 23.1 Hz), 64.52, 30.42, 18.97, 13.58. HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{21}F_3N_2NaO_3^+$: 465.1396 (M + Na)$^+$, found: 465.1406.

Butyl *(E)*-3-(5-chloro-2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)phenyl)acrylate (3ea): White solid (33.0 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.70 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.28 – 8.07 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.56 – 7.47 (m, 2H), 7.44 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.32 (d,

J = 15.7 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 1.49 – 1.40 (m, 2H), 1.32 – 1.20 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.68, 161.07 (t, *J* = 30.4 Hz), 148.78, 140.09 (t, *J* = 2.7 Hz), 138.55, 137.44, 136.26, 135.98 (t, *J* = 2.4 Hz), 132.58, 129.82 (t, *J* = 24.2 Hz), 129.32, 128.44 (t, *J* = 8.6 Hz), 128.13, 127.83, 127.02, 123.46, 123.21, 121.96, 117.11, 115.07 (t, *J* = 256.4 Hz), 64.48, 30.39, 18.95, 13.56. HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{21}ClF_2N_2NaO_3^+$: 481.1101 (M + Na)$^+$, found: 481.1092.

Butyl *(E)*-3-(5-bromo-2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)phenyl)acrylate (3fa): White solid (30.7 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.88 (d, *J* = 4.1 Hz, 1H), 8.70 (d, *J* = 7.5 Hz, 1H), 8.17 (dd, *J* = 20.6, 5.1 Hz, 2H), 7.77 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.57 – 7.48 (m, 2H), 6.32 (d, *J* = 15.7 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 1.50 – 1.39 (m, 2H), 1.33 – 1.19 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.69, 161.06 (t, *J* = 30.4 Hz), 148.79, 140.03 (t, *J* = 2.7 Hz), 138.55, 136.33, 136.15 (t, *J* = 2.3 Hz), 132.58, 132.33, 131.08, 130.32 (t, *J* = 24.2 Hz), 128.57 (t, *J* = 8.5 Hz), 127.87, 127.08, 125.73, 123.53, 123.25, 121.99, 117.20, 115.13 (t, *J* = 256.5 Hz), 64.51, 30.41, 18.97, 13.59. HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{21}BrF_2N_2NaO_3^+$: 525.0596 (M + Na)$^+$, found: 525.0617.

Butyl *(E)*-3-(5-acetyl-2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)phenyl)acrylate (3ga): White solid (37.7 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.88 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.69 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.30 – 8.14 (m, 3H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.57 – 7.47 (m, 2H), 6.41 (d, *J* = 15.7 Hz, 1H), 4.00 (t, *J* = 6.7 Hz, 2H), 2.65 (s, 3H), 1.49 – 1.38 (m, 2H), 1.32 – 1.19 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.68, 165.78, 160.94 (t, *J* = 30.0 Hz), 148.84, 140.55 (t, *J* = 2.6 Hz), 139.09, 138.60, 136.30, 135.30 (t, *J* = 23.9 Hz), 134.90 (t, *J* = 2.5 Hz), 132.58, 128.86, 127.87, 127.85, 127.55 (t, *J* = 8.5 Hz), 127.06, 123.59, 123.29, 122.01, 117.17, 115.00 (t, *J* = 256.7 Hz), 64.50, 30.42, 26.75, 18.97, 13.58. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{24}F_2N_2NaO_4^+$: 489.1596 (M + Na)$^+$, found: 489.1598.

Butyl *(E)*-3-(5-cyano-2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)phenyl)acrylate (3ha): White solid (24.2 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.66 (d, *J* = 7.6 Hz, 1H), 8.24 – 8.11 (m, 2H), 7.95 – 7.86 (m, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.57 – 7.49 (m, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 3.99 (t, *J* = 6.7 Hz, 2H), 1.48 – 1.37 (m, 2H), 1.31 – 1.18 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.30, 160.46 (t, *J* = 29.7 Hz), 148.87, 139.18 (t, *J* = 2.7 Hz), 138.53, 136.32, 135.76 (t, *J* = 2.3 Hz), 135.50 (t, *J* = 24.1 Hz), 132.37, 131.63, 128.04, 127.95, 127.86, 127.02, 124.68, 123.44, 122.06, 117.25, 117.19, 115.51, 114.50 (t, *J* = 257.6 Hz) 64.65, 30.34, 18.92, 13.54. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{21}F_2N_3NaO_3^+$: 472.1443 (M + Na)$^+$, found: 472.1441.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-5-(methylsulfonyl)phenyl)acrylate (3ia): White solid (38.6 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 7.6, 0.9 Hz, 1H), 8.25 – 8.17 (m, 3H), 8.07 – 7.99 (m, 2H), 7.62 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 6.43 (d, *J* = 15.7 Hz, 1H), 4.00 (t, *J* = 6.7 Hz, 2H), 3.09 (s, 3H), 1.49 – 1.39 (m, 2H), 1.32 – 1.18 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.37, 160.53 (t, *J* = 29.7 Hz), 148.89, 143.32, 139.37 (t, *J* = 2.7 Hz), 138.53, 136.54, 136.32, 136.05, 132.37, 128.36 (t, *J* = 8.5 Hz), 127.86, 127.80, 127.07, 127.00, 124.77, 123.46, 122.07, 117.17, 114.58 (t, *J* = 257.7 Hz), 64.62, 44.33, 30.35, 18.92, 13.54. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{24}F_2N_2NaO_5S^+$: 525.1266 (M + Na)$^+$, found: 525.1277.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-4-methylphenyl)acrylate (3ja): White solid (35.0 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.85 (d, *J* = 4.1 Hz, 1H), 8.72 (d, *J* = 7.3 Hz, 1H), 8.25 (d, *J* = 15.7 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.63 – 7.43 (m, 5H), 7.30 (d, *J* = 7.9 Hz, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 2.40 (s, 3H), 1.48 – 1.39 (m, 2H), 1.31 – 1.19 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.20, 161.50 (t, *J* = 30.6 Hz), 148.67, 141.28 (t, *J* = 2.7 Hz), 139.96, 138.50, 136.17, 132.67, 131.84, 131.12 (t, *J* = 23.6 Hz), 131.10 (t, *J* = 2.61 Hz), 127.98, 127.77, 127.47 (t, *J* = 8.4 Hz), 126.94, 123.02, 121.86, 121.23, 116.98, 115.48 (t, *J* = 255.7 Hz), 64.19, 30.39, 21.24, 18.90, 13.51. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{24}F_2N_2NaO_3^+$: 461.1647 (M + Na)$^+$, found: 461.1665.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-4-(trifluoromethyl)phenyl)acrylate (3ka): White solid (48.7 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.89 (d, *J* = 4.2 Hz, 1H), 8.68 (d, *J* = 7.5 Hz, 1H), 8.28 – 8.15 (m, 2H), 8.07 (s, 1H), 7.77 (q, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.57 – 7.48 (m, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 3.98 (t, *J* = 6.8 Hz, 2H), 1.49 – 1.33 (m, 2H), 1.30 – 1.16 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.49, 160.76 (t, *J* = 30.1 Hz), 148.82, 139.92, 138.54, 137.82, 136.26, 132.47, 132.25 (t, *J* = 24.2 Hz), 131.39 (q, *J* = 33.4 Hz), 128.78, 127.98 (d, *J* = 3.3 Hz), 127.84, 126.98 (d, *J* = 0.9 Hz), 124.45, 124.02 (td, *J* = 8.8, 4.4 Hz), 123.35 (q, *J* =273.7 Hz), 123.32, 122.00, 117.12, 114.68 (t, *J* = 257.1 Hz), 64.55, 30.33, 18.90, 13.50. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{21}F_5N_2NaO_3^+$: 515.1365 (M + Na)$^+$, found: 515.1382.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-4-nitrophenyl)acrylate (3la): White solid (21.1 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.91 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.73 – 8.60 (m, 2H), 8.37 (dd, *J* = 8.6, 2.0 Hz, 1H), 8.26 – 8.15 (m, 2H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.58 – 7.48 (m, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 3.99 (t, *J* = 6.7 Hz, 2H), 1.47 – 1.35 (m, 2H), 1.31 – 1.15 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.21, 160.41 (t, *J* = 29.9 Hz), 148.92, 147.90, 140.55, 139.17, 138.57, 136.33, 133.06 (t, *J* = 25.0 Hz), 132.39, 129.42, 127.88, 127.03, 125.89, 125.68, 123.48, 122.50 (t, *J* = 9.3 Hz), 122.09, 117.24, 114.27 (t, *J* = 258.2 Hz), 64.75, 30.34, 18.92, 13.54. HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{21}F_2N_3NaO_5^+$: 492.1341 (M + Na)$^+$, found: 492.1350.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-3-methylphenyl)acrylate (3ma): White solid (27.6 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.71 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.32 (dt, *J* = 15.7, 5.6 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.39 – 7.32 (m, 2H), 7.29 – 7.24 (m, 1H), 6.19 (d, *J* = 15.7 Hz, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 3.8 Hz, 3H), 1.57 – 1.46 (m, 2H), 1.36 – 1.24 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.31, 161.70 (t, *J* = 30.6 Hz), 148.77, 144.87 (t, *J* = 4.9 Hz), 138.61, 138.00 (t, *J* = 3.2 Hz), 136.23, 136.14 (t, *J* = 3.3 Hz), 133.34, 132.79, 130.45, 129.68 (t, *J* = 22.1 Hz), 127.85, 127.26, 127.03, 123.04, 121.93, 117.11 (t, *J* = 257.5 Hz), 117.02, 64.27, 30.51, 21.67 (t, *J* = 5.3 Hz), 19.02, 13.61. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{24}F_2N_2NaO_3^+$: 461.1647 (M + Na)$^+$, found: 461.1645.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-3-methoxyphenyl)acrylate (3na): White solid (22.7 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.76 (dd, *J* = 7.0, 1.8 Hz, 1H), 8.36 (dt, *J* = 15.7, 5.5 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.50 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.24 (d, *J* = 15.7 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.71 (s, 3H), 1.74 – 1.63 (m, 2H), 1.50 – 1.36 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.45, 162.67 (t, *J* = 29.2 Hz), 157.87 (t, *J* = 5.2 Hz), 148.66, 144.01 (t, *J* = 6.0 Hz), 138.75, 137.47, 136.26, 133.44, 132.00, 127.97, 127.19, 122.57, 122.17, 121.95, 121.86, 120.07 (t, *J* = 23.1 Hz), 116.87, 115.72 (t,

J = 255.5 Hz), 112.90, 64.46, 56.41, 30.71, 19.16, 13.72. HRMS (ESI-TOF) m/z: calcd. for $C_{25}H_{24}F_2N_2NaO_4^+$: 477.1596 (M + Na) $^+$, found: 477.1594.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-4,6-dimethylphenyl)acrylate (3oa): White solid (34.8 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.85 (d, *J* = 4.2 Hz, 1H), 8.70 (d, *J* = 7.3 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 16.3 Hz, 1H), 7.62 – 7.44 (m, 4H), 7.18 (s, 1H), 5.95 (d, *J* = 16.3 Hz, 1H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.38 (s, 3H), 2.25 (s, 3H), 1.18 – 0.96 (m, 4H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.40, 162.02 (t, *J* = 30.1 Hz), 148.64, 141.66, 138.53, 137.92, 136.75, 136.08, 133.55, 132.74, 131.06 (t, *J* = 3.5 Hz), 130.83 (t, *J* = 23.0 Hz), 127.74, 127.06, 126.21, 124.98 (t, *J* = 8.5 Hz), 122.83, 121.81, 116.87, 115.20 (t, *J* = 254.8 Hz), 64.00, 30.04, 21.09, 20.43, 18.78, 13.50. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{26}F_2N_2NaO_3^+$: 475.1804 (M + Na) $^+$, found: 475.1809.

Butyl *(E)*-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)-4,5-dimethylphenyl)acrylate (3pa): White solid (39.3 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.86 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.73 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.23 (d, *J* = 15.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.55 – 7.46 (m, 3H), 7.43 (s, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 1.50 – 1.40 (m, 2H), 1.32 – 1.20 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.32, 161.72 (t, *J* = 30.9 Hz), 148.68, 141.45 (t, *J* = 2.7 Hz), 139.99, 138.65, 138.54, 136.19, 132.76, 131.26, 129.20, 128.74 (t, *J* = 23.7 Hz), 128.05 (t, *J* = 8.2 Hz), 127.80, 127.00, 122.98, 121.87, 120.99, 117.01, 115.64 (t, *J* = 255.3 Hz), 64.20, 30.43, 19.65, 19.54, 18.95, 13.55. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{26}F_2N_2NaO_3^+$: 475.1804 (M + Na) $^+$, found: 475.1803.

Butyl *(E)*-3-(3-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl)naphthalen-2-yl)acrylate (3qa): White solid (31.7 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.76 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.35 (d, *J* = 15.7 Hz, 1H), 8.28 (s, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.11 (s, 1H), 7.95 – 7.84 (m, 2H), 7.63 – 7.52 (m, 4H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 4.01 (t, *J* = 6.7 Hz, 2H), 1.49 – 1.40 (m, 2H), 1.32 – 1.21 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.14, 161.51 (t, *J* = 30.4 Hz), 148.72, 141.87 (t, *J* = 2.5 Hz), 138.57, 136.20, 133.84, 132.74, 132.45, 130.77, 128.56, 128.39 (t, *J* = 23.2 Hz), 128.30, 128.17, 127.98, 127.82, 127.73 (t, *J* = 8.7 Hz), 127.70, 127.03, 123.08, 122.06, 121.90, 117.07, 115.72 (t, *J* = 255.1 Hz), 64.29, 30.43, 18.96, 13.57. HRMS (ESI-TOF) m/z: calcd. for $C_{28}H_{24}F_2N_2NaO_3^+$: 497.1647 (M + Na) $^+$, found: 497.1666.

Butyl (*E*)-3-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethoxy)phenyl)acrylate (3ra-mono): Clear oil (9.7 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.84 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.78 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.06 (d, *J* = 16.1 Hz, 1H), 7.71 – 7.55 (m, 3H), 7.54 – 7.39 (m, 3H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 1.54 – 1.40 (m, 2H), 1.34 – 1.17 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.49, 156.90 (t, *J* = 36.8 Hz), 148.87, 147.94, 138.55, 137.83, 136.28, 132.53, 131.06, 128.41, 127.94, 127.86, 127.08, 126.68, 123.31, 122.41, 121.99, 121.18, 117.37, 114.82 (t, *J* = 276.0 Hz), 64.38, 30.49, 19.02, 13.59. HRMS (ESI-TOF) m/z: calcd. for $C_{24}H_{22}F_2N_2NaO_4^+$: 463.1440 (M + Na) $^+$, found: 463.1437.

Dibutyl 3,3'-(2-(1,1-difluoro-2-oxo-2-(quinolin-8-ylamino)ethoxy)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (3ra-di): Yellow oil (29 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.85 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.80 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.09 (d, *J* = 16.1 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.67 – 7.56 (m, 2H), 7.51 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 16.1 Hz, 2H), 4.08 (t, *J* = 6.7 Hz, 4H), 1.59 – 1.48 (m, 4H), 1.38 – 1.26 (m, 4H), 0.84 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.26, 156.52 (t, *J* = 36.4 Hz), 148.87, 145.93, 138.59, 137.95, 136.28, 132.51, 131.06, 128.84, 127.86, 127.51, 127.10, 123.37, 122.01, 121.54, 117.45, 115.09 (t, *J* = 279.0 Hz), 64.53, 30.53, 19.06, 13.62. HRMS (ESI-TOF) m/z: calcd. for $C_{31}H_{32}F_2N_2NaO_6^+$: 589.2121 (M + Na) $^+$, found: 589.2116.

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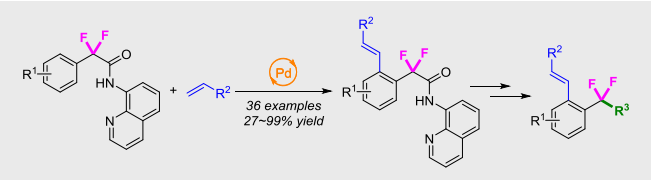

An efficient method for the synthesis of *ortho*-olefinated analogues of α,α-difluorophenylacetic acid via palladium-catalyzed C−H olefination using 8-aminoquinoline as the bidentate directing group has been developed. This reaction provides an easy and straightforward access to a panel of difluoromethylated arene analogues.

Synthetic Methods*

*Changdong Shao, Guangfa Shi, Yanghui Zhang **

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An Easy Access to Difluoromethylene-Containing Arene Analogues via Palladium-Catalyzed C−H Olefination