ChemPubSoc Europe

DOI: 10.1002/ejoc.201600954

EurJOC European Journal of Organic Chemistry

Full Paper

Synthetic Methods

Easy Access to Difluoromethylene-Containing Arene Analogues through Palladium-Catalysed C–H Olefination

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

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

Introduction

Organofluorine compounds have found extensive applications in a wide range of fields owing to their unusual and useful properties.[1] In particular, fluorine substituents are widely present in pharmaceutical molecules.[2] Currently, there are over 150 fluorinated drugs on the market, and fluorinated molecules make up 20–30 % of all pharmaceuticals and agrochemicals.[3] It is therefore very important for chemists to develop facile and efficient methods for the incorporation of fluorine into molecules.[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 available approaches for the synthesis of organofluorine compounds usually involve the incorporation of the fluorine substituents into a precursor of each analogue, in a 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 has been emerging as a new and valuable strategy for organic synthesis.[5] In particular, it provides easy access to a wide range of analogues. Most C–H functionalization reactions rely on the use of directing groups, which can solve regioselectivity problems and accelerate the C–H cleavage process.[6] Directed C–H functionalization allows 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 the use of fluorine-containing directing groups could provide an easy route to a wide range of fluorinated analogues.

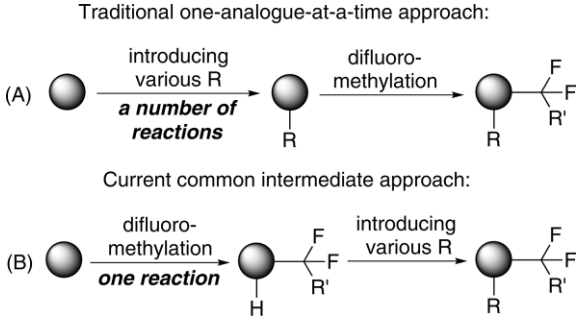


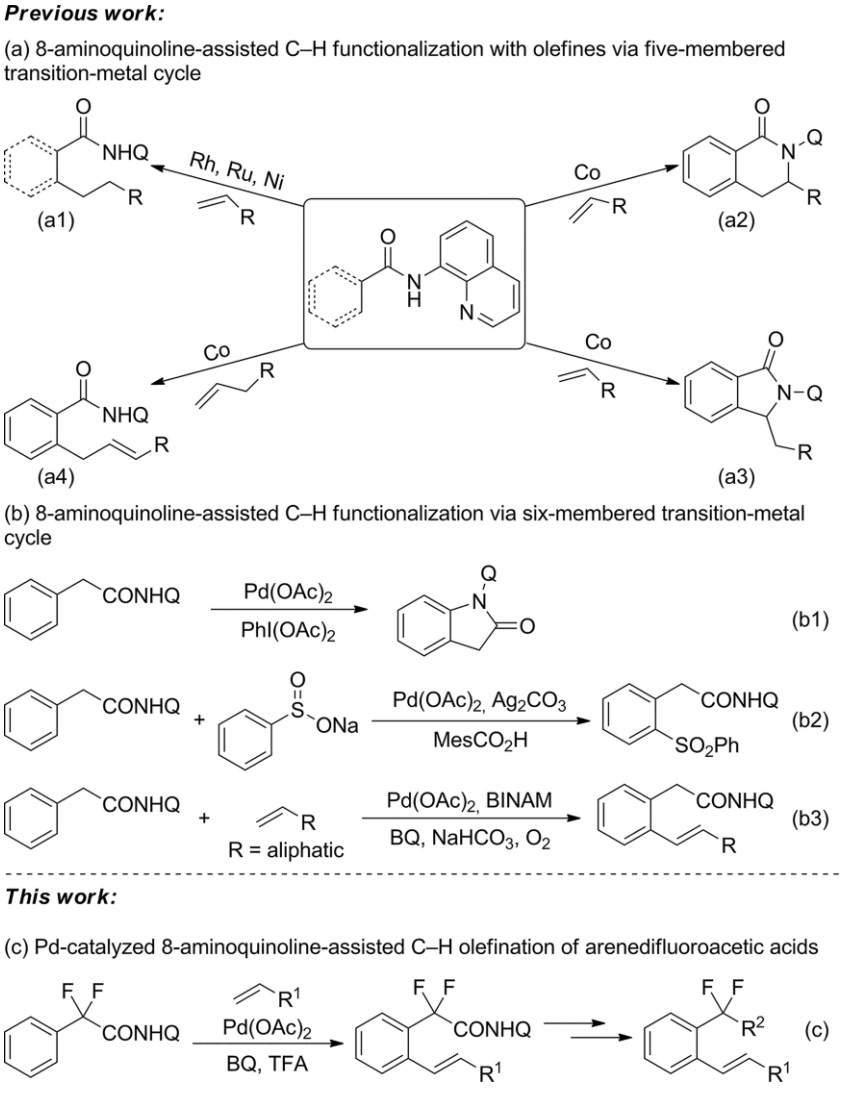
Figure 1. Approaches to the synthesis of difluoromethylated compounds.

Recently, difluoromethylene groups have attracted great attention owing to their unusual biological properties; 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, bidentate directing groups have proved to be particularly powerful, and they have been successfully used in a range of new organic transformations.[8] In this context, 8-aminoquinoline[9] is particularly attractive. Chatani and Maiti reported several examples of Rh/Ru/Ni-catalysed C–H alkylation reactions with olefins (Scheme 1, a1).[10a–10c] Daugulis and Ackermann demonstrated cobalt-catalysed 8-aminoquinoline-directed annulation reactions with olefins through a C–H/N–H functionalization process (Scheme 1, a2 and a3).[10d,10e] Cobalt-catalysed *ortho*-C–H allylation with unactivated olefins was also reported by Chatani and Maiti (Scheme 1, a4).[10f,10g] Palladium-catalysed C–H functionalization reactions via a six-membered palladacycle using phenylacetyl aminoquinoline as the substrate have also been reported by Chen, Shi, and Maiti (Scheme 1, b1, b2, and b3, respectively).[10h–10j]

Inspired by these great reactions, in particular by Maiti's impressive work (Scheme 1, b3),[10j] and by our ongoing interest in organofluorine chemistry,[11] we present in this paper an effi-

[a] *School of Chemical Science and Engineering, Tongji University, 1239 Siping Road, Shanghai 200092, P. R. China*
E-mail: zhangyanghui@tongji.edu.cn
http://zhangyhgroup.tongji.edu.cn
[b] *UNEP – Tongji Institute of Environment for Sustainable Development, Tongji University, 1239 Siping Road, Shanghai 200092, P. R. China*
[c] *Shanghai Key Laboratory of Chemical Assessment and Sustainability, 1239 Siping Road, Shanghai 200092, P. R. China*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600954.



Scheme 1. Transition-metal-catalysed 8-aminoquinoline-assisted C–H functionalization reactions. Q = quinolin-8-yl; Mes = mesityl; BINAM = 1,1′-binaphthyl-2,2′-diamine.

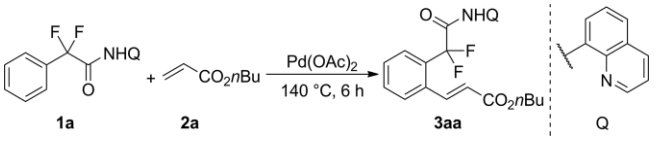
cient palladium-catalysed Fujiwara–Moritani reaction of α,α-difluorophenylacetic acid derivatives using 8-aminoquinoline as the bidentate directing group. The directing group can be readily removed under mild conditions in the presence of the difluoromethylene group to give diverse *ortho*-olefinated α,α-difluorophenylacetic acid derivatives (Scheme 1, c). This reaction provides a new strategy for the synthesis of a range of difluoromethylene-containing arene analogues.

Results and Discussion

We began 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 an extensive survey of reaction conditions, we found that the desired alkenylated product (i.e., **3aa**) was formed in 13 % yield in the presence of $Pd(OAc)_2$ (10 mol-%) and benzoquinone (BQ; 1.2 equiv.) in 1,2-dichloroethane (DCE; Table 1, Entry 1). The yield increased slightly to 21 % when 1.5 equiv. of HOAc was added (Table 1, Entry 2). Inspired by this result, we screened other acids. Methanesulfonic acid and pivalic acid increased the yield to 36 and 66 %, respectively (Table 1, Entries 3 and 4). It should be mentioned that diolefinated product was formed along with the desired monoolefinated product in these two reactions. Pleasingly, the yield of the monosubstituted product improved to 79 % when the reaction was run in the presence of TFA (trifluoroacetic acid); 11 % of the undesired disubstituted by-product was also formed (Table 1, Entry 5). BQ proved to be the optimal oxidant. Other oxidants such as AgOAc, Ag_2CO_3, $Cu(OAc)_2$, $K_2S_2O_8$, and O_2 gave lower yields (Table 1, Entries 6–10), and the yield decreased dramatically in the absence of BQ (Table 1, Entry 11). The reaction still took place to give the olefinated product in other solvents, including solvents with higher boiling points, although the yields were lower (Table 1, Entries 12–19). The yield decreased to 45 % when 5 mol-% $Pd(OAc)_2$ was used (Table 1, Entry 20), and none of the olefinated product was observed when the reaction was run in the absence of $Pd(OAc)_2$

(Table 1, Entry 21). The yield decreased to 61 or 31 % when the reaction were carried out at 130 or 120 °C, respectively (Table 1, Entries 22 and 23). Furthermore, the reaction was not affected by the atmosphere, and proceeded smoothly under N_2, O_2, or air (Table 1, Entries 24 and 25).

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

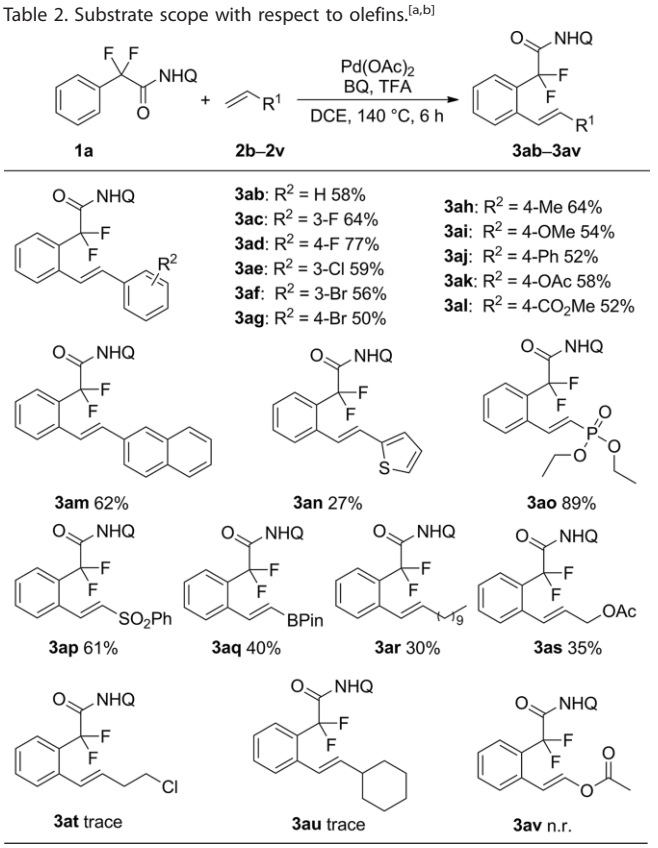


Entry	Additive	Oxidant	Solvent	Yield [%][b,c]
1	–	BQ	DCE	13
2	HOAc	BQ	DCE	21
3	MsOH	BQ	DCE	36 (1)
4	PivOH	BQ	DCE	66 (2)
5	TFA	BQ	DCE	79 (11) [76][d]
6	TFA	AgOAc	DCE	41 (2)
7	TFA	Ag_2CO_3	DCE	51 (5)
8	TFA	$Cu(OAc)_2$	DCE	69 (5)
9	TFA	$K_2S_2O_8$	DCE	34 (1)
10	TFA	O_2	DCE	14
11	TFA	–	DCE	11
12	TFA	BQ	DMF	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] Reaction 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. DMA = *N*,*N*-dimethylacetamide; NMP = *N*-methylpyrrolidine. [b] Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c] Yields of disubstituted products are given in parentheses. [d] Isolated yield is 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.

Having optimized the reaction conditions (Table 1, Entry 5), we surveyed the substrate scope of this C–H olefination reaction. First, 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. Halogen groups, including F, Cl, and Br, were well tolerated (**2c**–**2g**). Styrenes containing other common functional groups, including methoxy (**2i**), phenyl (**2j**), acetoxy (**2k**), and ester (**2l**) groups, were reactive, and the olefinated products were formed in moderate yields. 2-Vinylnaphthalene (**2m**) was also suitable, and 2-vinylthiophene (**2n**) underwent the olefination reaction successfully, although it gave a low yield (27 %). Considering that organophosphorus and organosulfur compounds are found extensively in pharmaceuticals, agrochemicals, and functional materials,[12] we then examined two kinds of alkenes containing a phosphonate (**2o**) or sulfonyl (**2p**) group under the optimal reaction conditions. The reactions

Table 2. Substrate scope with respect to olefins.[a,b]



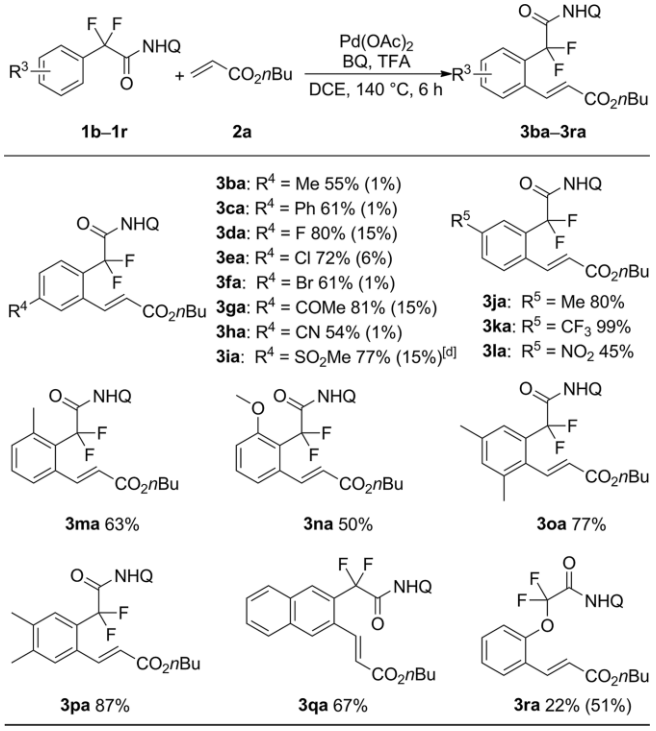
[a] Reaction conditions: **1a** (0.10 mmol), **2** (1.5 equiv.), $Pd(OAc)_2$ (10 mol-%), BQ (1.2 equiv.), TFA (1.5 equiv.), DCE (1.0 mL), 140 °C, air, 6 h. [b] Isolated yields.

formed the desired products [i.e., **3ao** (89 %) and **3ap** (61 %)] in good yields. Intriguingly, vinylboronate (**2q**) selectively underwent the olefination reaction, and products derived from the reaction of the boronate moiety were not observed. Unactivated alkenes were also examined, and the reaction also took place, albeit in low yield (**3ar** and **3as**). Other unactivated alkenes bearing a chloro or cyclohexyl group and vinyl acetate were almost completely unreactive (**2t**–**2v**). It should be noted that diolefinated products were not observed for the substrates in Table 2.

Next, the scope of the reaction in terms of arene substrates 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. An electron-donating group, i.e., methyl (**1b**), and also electron-withdrawing groups including carbonyl (**1g**), cyano (**1h**), and sulfonyl (**1i**) groups at the *para* position were well tolerated in the reaction. Fluoro (**1d**), chloro (**1e**), and bromo (**1f**) groups remained intact under the reaction conditions. It should be mentioned that small amounts of diolefinated products were formed for substrates bearing *para* substituents (**1b**–**1i**). In the presence of *meta* substituents (**1j**–**1l**), the olefination reaction took place selectively at the less hindered positions, and diolefinated products were not observed. Substrates bearing a methyl (**1m**) or methoxy (**1n**) group in the

ortho position were also suitable. The compatibility of disubstituted substrates was also examined. Thus, 3,5- or 3,4-disubstituted arene substrates were efficiently transformed into the corresponding products (i.e., **3oa** and **3pa**) in 77 and 87 % yields, 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 to give mono- and di-olefinated products in 22 and 51 % yields, respectively (**3ra**).

Table 3. Substrate scope with respect to arenes.[a,b,c]



[a] Reaction 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 of disubstituted products shown in parentheses were determined by ^1H NMR spectroscopic analysis of the crude product mixture, using CH_2Br_2 as an internal standard. [c] Isolated yields. [d] 1.1 equiv. of **2a** was used.

Furthermore, some mechanistic studies were carried out, and the results are consistent with 8-aminoquinoline-directed C–H activation under palladium catalysis (for details and the corresponding crystal structure of palladacycle **A**, see the Supporting Information).[13]

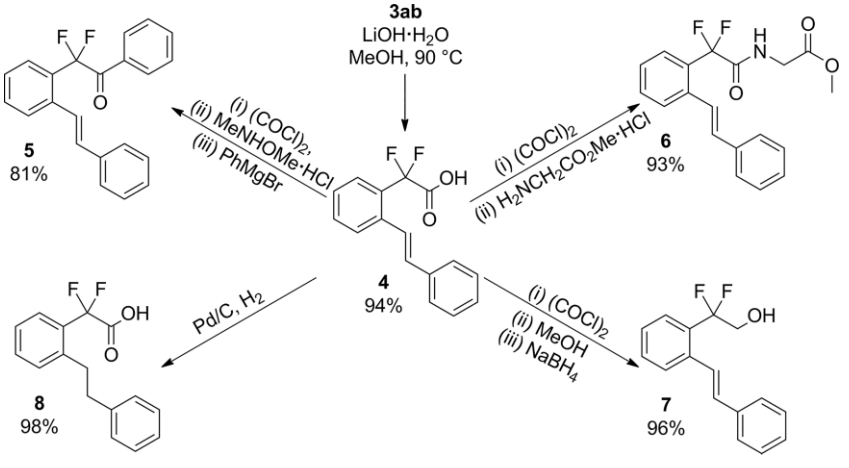
To demonstrate the synthetic utility of the products obtained by the C–H alkenylation reaction, compound **3ab** was converted into an aryl difluoroacetic acid. Pleasingly, hydrolysis of **3ab** took place under mild conditions in the presence of the difluoromethylene group to give (*E*)-2,2-difluoro-2-(2-styrylphenyl)acetic 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 into its acyl chloride derivative by treatment with $(COCl)_2$. The resulting acyl chloride was then treated with *N*,*O*-dimethylhydroxylamine hydrochloride and PhMgBr to give aryl difluoro ketone derivative **5** as the final product in 81 % overall yield.[14] Secondly, the acyl chloride reacted with glycine methyl ester hydrochloride to form aryl difluoro amide derivative **6** in 93 % yield. Thirdly, reduction of the ester obtained by treating the acyl chloride with methanol gave aryldifluoroethanol derivative **7** in 96 % yield.[15] Finally, the double bond of **4** was reduced by hydrogenation to give alkylated product **8** in almost quantitative yield (98 %).[16]

Conclusions

We have developed an efficient palladium-catalysed *ortho*-C–H olefination of α,α-difluorophenylacetic acid derivatives using 8-aminoquinoline as a bidentate directing group. This reaction provides an efficient and concise route 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 has potential applications in drug discovery.

Experimental Section

General Information: High-resolution mass spectra were measured with a Bruker MicroTOF II ESI-TOF mass spectrometer. ^1H and ^{13}C,



Scheme 2. Late-stage transformations.

and ^{19}F NMR spectra were recorded with Bruker ARX400 (400, 101, 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; [D_6]DMSO: δ = 2.50 ppm; CD_3OD: δ = 3.31 ppm). The ^{13}C chemical shifts are reported in ppm and referenced to the NMR solvent ($CDCl_3$: δ = 77.00 ppm; [D_6]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, br. s = 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 the literature; for details, see the Supporting Information. Commercially available chemicals were used without further purification.

Typical Experimental Procedure for the Synthesis of 3: Substrate **1** (0.10 mmol), palladium(II) acetate (10 mol-%), 1,4-benzoquinone (1.2 equiv.), trifluoroacetic acid (1.5 equiv.), alkene **2** (1.5 equiv.), and 1,2-dichloroethane (1.0 mL) were placed into a sealed tube (35 mL) equipped with a magnetic stirrer bar under air. The reaction tube was sealed with a Teflon® high-pressure valve, and placed into a preheated oil bath. The mixture was stirred at 140 °C for 6 h, then it was cooled to room temperature and diluted with ethyl acetate (10 mL). The mixture was washed with saturated sodium sulfide (5 mL) and brine (2 × 5 mL), dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (PTLC) to give the corresponding compound **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, 1 H), 8.86 (d, *J* = 3.9 Hz, 1 H), 8.73 (d, *J* = 7.5 Hz, 1 H), 8.27 (d, *J* = 15.8 Hz, 1 H), 8.18 (d, *J* = 8.2 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H), 7.56–7.45 (m, 4 H), 6.33 (d, *J* = 15.8 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 1.51–1.39 (m, 2 H), 1.35–1.19 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{22}F_2N_2NaO_3$ [M + Na]$^+$ 447.1491; 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, 1 H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1 H), 8.73 (dd, *J* = 7.4, 0.9 Hz, 1 H), 8.17 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.83 (d, *J* = 7.7 Hz, 1 H), 7.75–7.63 (m, 2 H), 7.58–7.46 (m, 4 H), 7.45–7.33 (m, 3 H), 7.16–7.03 (m, 3 H), 6.95 (d, *J* = 16.0 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{18}F_2N_2NaO$ [M + Na]$^+$ 423.1279; 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, 1 H), 8.82 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.72 (dd, *J* = 7.5, 1.1 Hz, 1 H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.84 (d, *J* = 7.7 Hz, 1 H), 7.71–7.64 (m, 2 H), 7.57–7.40 (m, 5 H), 7.13–6.99 (m, 3 H), 6.87 (d, *J* = 16.0 Hz, 1 H), 6.83–6.76 (m, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{17}F_3N_2NaO$ [M + Na]$^+$ 441.1185; 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, 1 H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.70 (dd, *J* = 7.5, 1.2 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.83 (dd, *J* = 7.8, 0.8 Hz, 1 H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.61–7.46 (m, 5 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.32–7.26 (m, 2 H), 6.86 (d, *J* = 16.0 Hz, 1 H), 6.77–6.68 (m, 2 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{17}F_3N_2NaO$ [M + Na]$^+$ 441.1185; 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, 1 H), 8.81 (d, *J* = 4.1 Hz, 1 H), 8.71 (d, *J* = 7.5 Hz, 1 H), 8.16 (d, *J* = 8.3 Hz, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.71–7.61 (m, 2 H), 7.58–7.39 (m, 5 H), 7.27 (d, *J* = 7.9 Hz, 1 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 7.9 Hz, 1 H), 6.99 (t, *J* = 7.7 Hz, 1 H), 6.83 (d, *J* = 16.1 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{17}ClF_2N_2NaO$ [M + Na]$^+$ 457.0890; 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, 1 H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.71 (dd, *J* = 7.5, 1.3 Hz, 1 H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.83 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.68–7.60 (m, 2 H), 7.59–7.41 (m, 6 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 6.92 (t, *J* = 7.9 Hz, 1 H), 6.81 (d, *J* = 16.0 Hz, 1 H) ppm. ^{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* = 23.7 Hz), 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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{17}BrF_2N_2NaO$ [M + Na]$^+$ 501.0385; 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, 1 H), 8.80 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.68 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.83 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.68–7.38 (m, 7 H), 7.18–7.08 (m, 4 H), 6.80 (d, *J* = 16.0 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{17}BrF_2N_2NaO$ [M + Na]$^+$ 501.0385; 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, 1 H), 8.85 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.78 (d, *J* = 7.4 Hz, 1 H), 8.20 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 7.7 Hz, 1 H), 7.68 (d, *J* = 16.0 Hz, 1 H), 7.63–7.49 (m, 4 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.01–6.90 (m, 3 H), 2.31 (s, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{20}F_2N_2NaO$ [M + Na]$^+$ 437.1436; 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, 1 H), 8.82 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.71 (dd, *J* = 7.4, 1.2 Hz, 1 H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.81 (d, *J* = 7.7 Hz, 1 H), 7.68 (d, *J* = 7.7 Hz, 1 H), 7.57–7.46 (m, 5 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 8.9 Hz, 2 H), 6.88 (d, *J* = 16.0 Hz, 1 H), 6.58 (d, *J* = 8.7 Hz, 2 H), 3.74 (s, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{20}F_2N_2NaO_2$ [M + Na]$^+$ 453.1385; found 453.1403.

(*E*)-2-{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, 1 H), 8.81 (dd, *J* = 4.1, 1.4 Hz, 1 H), 8.73 (dd, *J* = 7.3, 1.2 Hz, 1 H), 8.12 (dd, *J* = 8.2, 1.1 Hz, 1 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.75–7.66 (m, 2 H), 7.59–7.27 (m, 14 H), 6.96 (d, *J* = 16.0 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{31}H_{22}F_2N_2NaO$ [M + Na]$^+$ 499.1592; 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, 1 H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.72 (dd, *J* = 7.5, 1.2 Hz, 1 H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.83 (d, *J* = 7.2 Hz, 1 H), 7.71–7.61 (m, 2 H), 7.57–7.34 (m, 7 H), 6.91 (d, *J* = 16.0 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{27}H_{20}F_2N_2NaO_3$ [M + Na]$^+$ 481.1334; 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, 1 H), 8.80 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.69 (dd, *J* = 7.5, 1.1 Hz, 1 H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 1 H), 7.80–7.65 (m, 4 H), 7.57–7.41 (m, 5 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 6.92 (d, *J* = 16.0 Hz, 1 H), 3.90 (s, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{27}H_{20}F_2N_2NaO_3$ [M + Na]$^+$ 481.1334; 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, 1 H), 8.79–8.67 (m, 2 H), 8.07 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.81–7.63 (m, 4 H), 7.58–7.51 (m, 3 H), 7.50–7.35 (m, 7 H), 7.08 (d, *J* = 16.0 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{29}H_{20}F_2N_2NaO$ [M + Na]$^+$ 473.1436; found 473.1440.

(*E*)-2,2-Difluoro-*N*-(quinolin-8-yl)-2-{2-[2-(thiophen-2-yl)vinyl]-phenyl}acetamide (3an): Claret-coloured viscous oil (11.0 mg, 27 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.97 (s, 1 H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1 H), 8.73 (dd, *J* = 7.4, 1.1 Hz, 1 H), 8.16 (dd, *J* = 8.3, 1.1 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.60–7.43 (m, 5 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 7.11–7.00 (m, 2 H), 6.98 (d, *J* = 3.4 Hz, 1 H), 6.84 (dd, *J* = 5.0, 3.6 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{23}H_{16}F_2N_2NaOS$ [M + Na]$^+$ 429.0844; found 429.0835.

Diethyl (*E*)-{2-[1,1-Difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl]-styryl}phosphonate (3ao): Colourless viscous oil (41.0 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.93 (s, 1 H), 8.85 (dd, *J* = 2.6, 1.6 Hz, 1 H), 8.70 (d, *J* = 7.5 Hz, 1 H), 8.17 (d, *J* = 8.3 Hz, 1 H), 8.03 (td, *J* = 19.7, 1.7 Hz, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.66–7.43 (m, 6 H), 6.20 (t, *J* = 17.9 Hz, 1 H), 4.10–3.88 (m, 4 H), 1.21 (t, *J* = 7.0 Hz, 6 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{23}H_{23}F_2N_2NaO_4P$ [M + Na]$^+$ 483.1256; 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, 1 H), 8.88 (dd, *J* = 4.2, 1.4 Hz, 1 H), 8.68 (d, *J* = 7.6 Hz, 1 H), 8.39 (d, *J* = 15.2 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.88–7.83 (m, 2 H), 7.81–7.74 (m, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.58–7.46 (m, 6 H), 7.40 (t, *J* = 7.8 Hz, 2 H), 6.78 (d, *J* = 15.2 Hz, 1 H) ppm. ^{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) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{18}F_2N_2NaO_3S$ [M + Na]$^+$ 487.0898; 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): Colourless viscous oil (18.0 mg, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.03 (s, 1 H), 8.88 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.75 (dd, *J* = 7.4, 1.3 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.86 (d, *J* = 18.0 Hz, 1 H), 7.77 (d, *J* = 7.4 Hz, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.61–7.38 (m, 5 H), 6.05 (d, *J* = 18.0 Hz, 1 H), 0.94 (s, 12 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{25}BF_2N_2NaO_3$ [M + Na]$^+$ 473.1823; found 473.1836.

(*E*)-2-[2-(Dodec-1-en-1-yl)phenyl]-2,2-difluoro-*N*-(quinolin-8-yl)acetamide (3ar): Colourless oil (14.0 mg, 30 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.91 (s, 1 H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.75 (dd, *J* = 7.4, 1.4 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.63–7.46 (m, 4 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 6.87 (d, *J* = 15.6 Hz, 1 H), 6.04 (dt, *J* = 15.3, 6.8 Hz,

1 H), 1.99 (dd, *J* = 13.8, 6.8 Hz, 2 H), 1.37–0.96 (m, 16 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{29}H_{34}F_2N_2NaO$ $[M + Na]^+$ 487.2531; 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, 1 H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.72 (dd, *J* = 7.4, 1.2 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.77 (d, *J* = 7.6 Hz, 1 H), 7.59 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.57–7.44 (m, 4 H), 7.40 (t, *J* = 7.5 Hz, 1 H), 7.22 (d, *J* = 15.7 Hz, 1 H), 6.13 (dt, *J* = 15.6, 6.1 Hz, 1 H), 4.58 (dd, *J* = 6.1, 1.2 Hz, 2 H), 1.87 (s, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{22}H_{18}F_2N_2NaO_3$ $[M + Na]^+$ 419.1178; 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, 1 H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.73 (dd, *J* = 7.5, 1.2 Hz, 1 H), 8.25 (dt, *J* = 15.8, 2.2 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.59 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.56–7.43 (m, 3 H), 7.28 (d, *J* = 8.1 Hz, 1 H), 6.32 (d, *J* = 15.7 Hz, 1 H), 4.02 (t, *J* = 6.7 Hz, 2 H), 2.40 (s, 3 H), 1.52–1.37 (m, 2 H), 1.35–1.19 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{24}F_2N_2NaO_3$ $[M + Na]^+$ 461.1647; 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, 1 H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.76 (dd, *J* = 7.4, 0.8 Hz, 1 H), 8.33 (d, *J* = 15.8 Hz, 1 H), 8.20 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.91–7.81 (m, 2 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 7.64–7.38 (m, 8 H), 6.41 (d, *J* = 15.7 Hz, 1 H), 4.03 (t, *J* = 6.7 Hz, 2 H), 1.52–1.42 (m, 2 H), 1.33–1.22 (m, 2 H), 0.84 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{30}H_{26}F_2N_2NaO_3$ $[M + Na]^+$ 523.1804; 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, 1 H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.71 (dd, *J* = 7.5, 1.0 Hz, 1 H), 8.25–8.15 (m, 2 H), 7.78 (dd, *J* = 8.8, 5.5 Hz, 1 H), 7.64–7.45 (m, 3 H), 7.34 (dd, *J* = 9.5, 2.2 Hz, 1 H), 7.17 (td, *J* = 8.6, 2.4 Hz, 1 H), 6.31 (d, *J* = 15.7 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 1.50–1.40 (m, 2 H), 1.32–1.20 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{21}F_3N_2NaO_3$ $[M + Na]^+$ 465.1396; 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, 1 H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.70 (dd, *J* = 7.5, 0.9 Hz, 1 H), 8.28–8.07 (m, 2 H), 7.72 (d, *J* = 8.5 Hz, 1 H), 7.63–7.57 (m, 2 H), 7.56–7.47 (m, 2 H), 7.44 (dd, *J* = 8.4, 1.5 Hz, 1 H), 6.32 (d, *J* = 15.7 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 1.49–1.40 (m, 2 H), 1.32–1.20 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{21}ClF_2N_2NaO_3$ $[M + Na]^+$ 481.1101; 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, 1 H), 8.88 (d, *J* = 4.1 Hz, 1 H), 8.70 (d, *J* = 7.5 Hz, 1 H), 8.17 (dd, *J* = 20.6, 5.1 Hz, 2 H), 7.77 (s, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.61 (d, *J* = 8.1 Hz, 2 H), 7.57–7.48 (m, 2 H), 6.32 (d, *J* = 15.7 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 1.50–1.39 (m, 2 H), 1.33–1.19 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{21}BrF_2N_2NaO_3$ $[M + Na]^+$ 525.0596; 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, 1 H), 8.88 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.69 (dd, *J* = 7.5, 0.9 Hz, 1 H), 8.30–8.14 (m, 3 H), 8.03 (d, *J* = 8.2 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.61 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.57–7.47 (m, 2 H), 6.41 (d, *J* = 15.7 Hz, 1 H), 4.00 (t, *J* = 6.7 Hz, 2 H), 2.65 (s, 3 H), 1.49–1.38 (m, 2 H), 1.32–1.19 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{24}F_2N_2NaO_4$ $[M + Na]^+$ 489.1596; 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, 1 H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.66 (d, *J* = 7.6 Hz, 1 H), 8.24–8.11 (m, 2 H), 7.95–7.86 (m, 2 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 7.62 (d, *J* = 8.3 Hz, 1 H), 7.57–7.49 (m, 2 H), 6.34 (d, *J* = 15.8 Hz, 1 H), 3.99 (t, *J* = 6.7 Hz, 2 H), 1.48–1.37 (m, 2 H), 1.31–1.18 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{21}F_2N_3NaO_3$ $[M + Na]^+$ 472.1443; 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, 1 H), 8.89 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.67 (dd, *J* = 7.6, 0.9 Hz, 1 H), 8.25–8.17 (m, 3 H), 8.07–7.99 (m, 2 H), 7.62 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.57–7.49 (m, 2 H), 6.43 (d, *J* = 15.7 Hz, 1 H), 4.00 (t, *J* = 6.7 Hz, 2 H), 3.09 (s, 3 H), 1.49–

1.39 (m, 2 H), 1.32–1.18 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{24}F_2N_2NaO_5S$ [M + Na]$^+$ 525.1266; 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, 1 H), 8.85 (d, *J* = 4.1 Hz, 1 H), 8.72 (d, *J* = 7.3 Hz, 1 H), 8.25 (d, *J* = 15.7 Hz, 1 H), 8.16 (d, *J* = 8.3 Hz, 1 H), 7.63–7.43 (m, 5 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 6.31 (d, *J* = 15.7 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 2.40 (s, 3 H), 1.48–1.39 (m, 2 H), 1.31–1.19 (m, 2 H), 0.82 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{24}F_2N_2NaO_3$ [M + Na]$^+$ 461.1647; found 461.1665.

Butyl (*E*)-3-{2-[1,1-Difluoro-2-oxo-2-(quinolin-8-ylamino)ethyl]-4-(tri-fluoromethyl)phenyl}acrylate (3ka): White solid (48.7 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.04 (s, 1 H), 8.89 (d, *J* = 4.2 Hz, 1 H), 8.68 (d, *J* = 7.5 Hz, 1 H), 8.28–8.15 (m, 2 H), 8.07 (s, 1 H), 7.77 (q, *J* = 8.5 Hz, 2 H), 7.61 (d, *J* = 8.3 Hz, 1 H), 7.57–7.48 (m, 2 H), 6.37 (d, *J* = 15.8 Hz, 1 H), 3.98 (t, *J* = 6.8 Hz, 2 H), 1.49–1.33 (m, 2 H), 1.30–1.16 (m, 2 H), 0.81 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{21}F_5N_2NaO_3$ [M + Na]$^+$ 515.1365; 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, 1 H), 8.91 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.73–8.60 (m, 2 H), 8.37 (dd, *J* = 8.6, 2.0 Hz, 1 H), 8.26–8.15 (m, 2 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 7.63 (d, *J* = 7.4 Hz, 1 H), 7.58–7.48 (m, 2 H), 6.41 (d, *J* = 15.8 Hz, 1 H), 3.99 (t, *J* = 6.7 Hz, 2 H), 1.47–1.35 (m, 2 H), 1.31–1.15 (m, 2 H), 0.81 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{21}F_2N_3NaO_5$ [M + Na]$^+$ 492.1341; 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, 1 H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.71 (dd, *J* = 7.5, 1.0 Hz, 1 H), 8.32 (dt, *J* = 15.7, 5.6 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.59 (dd, *J* = 8.2, 1.1 Hz, 1 H), 7.57–7.47 (m, 2 H), 7.39–7.32 (m, 2 H), 7.29–7.24 (m, 1 H), 6.19 (d, *J* = 15.7 Hz, 1 H), 4.05 (t, *J* = 6.7 Hz, 2 H), 2.57 (t, *J* = 3.8 Hz, 3 H), 1.57–1.46 (m, 2 H), 1.36–1.24 (m, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{24}F_2N_2NaO_3$ [M + Na]$^+$ 461.1647; 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, 1 H), 8.88 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.76 (dd, *J* = 7.0, 1.8 Hz, 1 H), 8.36 (dt, *J* = 15.7, 5.5 Hz, 1 H), 8.20 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.62–7.53 (m, 2 H), 7.50 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.43 (t, *J* = 8.1 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.24 (d, *J* = 15.7 Hz, 1 H), 4.21 (t, *J* = 6.7 Hz, 2 H), 3.71 (s, 3 H), 1.74–1.63 (m, 2 H), 1.50–1.36 (m, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{24}F_2N_2NaO_4$ [M + Na]$^+$ 477.1596; 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, 1 H), 8.85 (d, *J* = 4.2 Hz, 1 H), 8.70 (d, *J* = 7.3 Hz, 1 H), 8.16 (d, *J* = 8.3 Hz, 1 H), 7.83 (d, *J* = 16.3 Hz, 1 H), 7.62–7.44 (m, 4 H), 7.18 (s, 1 H), 5.95 (d, *J* = 16.3 Hz, 1 H), 3.52 (t, *J* = 6.6 Hz, 2 H), 2.38 (s, 3 H), 2.25 (s, 3 H), 1.18–0.96 (m, 4 H), 0.74 (t, *J* = 7.1 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{26}F_2N_2NaO_3$ [M + Na]$^+$ 475.1804; 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, 1 H), 8.86 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.73 (dd, *J* = 7.5, 1.1 Hz, 1 H), 8.23 (d, *J* = 15.7 Hz, 1 H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.58 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.55–7.46 (m, 3 H), 7.43 (s, 1 H), 6.31 (d, *J* = 15.7 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 1.50–1.40 (m, 2 H), 1.32–1.20 (m, 2 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{26}H_{26}F_2N_2NaO_3$ [M + Na]$^+$ 475.1804; 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, 1 H), 8.86 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.76 (dd, *J* = 7.4, 1.3 Hz, 1 H), 8.35 (d, *J* = 15.7 Hz, 1 H), 8.28 (s, 1 H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1 H), 8.11 (s, 1 H), 7.95–7.84 (m, 2 H), 7.63–7.52 (m, 4 H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1 H), 6.45 (d, *J* = 15.6 Hz, 1 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 1.49–1.40 (m, 2 H), 1.32–1.21 (m, 2 H), 0.84 (t, *J* = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{28}H_{24}F_2N_2NaO_3$ [M + Na]$^+$ 497.1647; found 497.1666.

Butyl (*E*)-3-{2-[1,1-Difluoro-2-oxo-2-(quinolin-8-ylamino)-ethoxy]phenyl}acrylate (3ra-mono): Colourless oil (9.7 mg, 22 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.98 (s, 1 H), 8.84 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.78 (dd, *J* = 7.3, 1.3 Hz, 1 H), 8.20 (dd, *J* = 8.3, 1.4 Hz, 1 H), 8.06 (d, *J* = 16.1 Hz, 1 H), 7.71–7.55 (m, 3 H), 7.54–7.39 (m, 3 H),

7.31 (t, J = 7.3 Hz, 1 H), 6.51 (d, J = 16.1 Hz, 1 H), 4.05 (t, J = 6.7 Hz, 2 H), 1.54–1.40 (m, 2 H), 1.34–1.17 (m, 2 H), 0.80 (t, J = 7.4 Hz, 3 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{24}H_{22}F_2N_2NaO_4$ $[M + Na]^+$ 463.1440; 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, 1 H), 8.85 (dd, J = 4.2, 1.5 Hz, 1 H), 8.80 (dd, J = 7.3, 1.2 Hz, 1 H), 8.21 (dd, J = 8.3, 1.4 Hz, 1 H), 8.09 (d, J = 16.1 Hz, 2 H), 7.72 (d, J = 7.8 Hz, 2 H), 7.67–7.56 (m, 2 H), 7.51 (dd, J = 8.3, 4.2 Hz, 1 H), 7.39 (t, J = 7.8 Hz, 1 H), 6.48 (d, J = 16.1 Hz, 2 H), 4.08 (t, J = 6.7 Hz, 4 H), 1.59–1.48 (m, 4 H), 1.38–1.26 (m, 4 H), 0.84 (t, J = 7.4 Hz, 6 H) ppm. ^{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 ppm. HRMS (ESI-TOF): calcd. for $C_{31}H_{32}F_2N_2NaO_6$ $[M + Na]^+$ 589.2121; found 589.2116.

Acknowledgments

We gratefully acknowledge the National Natural Science Foundation of China (no. 21372176), the Tongji University 985 Phase III funds, the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning, and the Shanghai Science and Technology Commission (14DZ2261100) for financial support.

Keywords: Palladium · C-H activation · Olefination · Fluorine · Directing groups · Synthetic methods

[1] a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; c) H. Knust, G. Achermann, T. Ballard, B. Buettelmann, R. Gasser, H. Fischer, M.-C. Hernandez, F. Knoflach, A. Koblet, H. Stadler, A. W. Thomas, G. Trube, P. Waldmeier, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5940–5944; d) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626–1631; e) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, **2004**; f) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, **2006**; g) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.

[2] a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305–321; d) W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu, V. A. Soloshonok, *J. Fluorine Chem.* **2014**, *167*, 37–54; e) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**.

[3] K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[4] a) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; *Angew. Chem.* **2013**, *125*, 8372–8423; b) T. Besset, T. Poisson, X. Pannecoucke, *Chem. Eur. J.* **2014**, *20*, 16830–16845; c) Z. Jin, G. B. Hammond, B. Xu, *Aldrichim. Acta* **2012**, *45*, 67–83; d) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; e) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; f) P. Chen, G. Liu, *Synthesis* **2013**, *45*, 2919–2939; g) Y.-L. Liu, J.-S. Yu, J. Zhou, *Asian J. Org. Chem.* **2013**, *2*, 194–206; h) Y. Lu, C. Liu, Q.-Y. Chen, *Curr. Org. Chem.* **2015**, *19*, 1638–1650; i) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478; j) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612–633; k) C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929–2942; l) Y. Li, Y. Wu, G.-S. Li, X.-S. Wang, *Adv. Synth. Catal.* **2014**, *356*, 1412–1418; m) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786; n) S. Barata-Vallejo, A. Postigo, *Coord. Chem. Rev.* **2013**, *257*, 3051–3069; o) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764; p) C. Ni, M. Hu, J. Hu, *Chem. Rev.* **2015**, *115*, 765–825; q) L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513–1522; r) C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao, Y.-C. Gu, *Chem. Soc. Rev.* **2012**, *41*, 4536–4559; s) J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, *Chem. Commun.* **2013**, *49*, 7513–7515; t) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo, X. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233; u) X. Shao, C. Xu, L. Lu, Q. Shen, *Acc. Chem. Res.* **2015**, *48*, 1227–1236; v) Y.-M. Su, G.-S. Feng, Z.-Y. Wang, Q. Lan, X.-S. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 6003–6007; *Angew. Chem.* **2015**, *127*, 6101–6105.

[5] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; *Angew. Chem.* **2009**, *121*, 5196–5217; c) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; *Angew. Chem.* **2009**, *121*, 9976–10011; d) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761.

[6] a) J. P. Kleiman, M. Dubeck, *J. Am. Chem. Soc.* **1963**, *85*, 1544–1545; b) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802; c) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936–946; d) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814–825; e) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107–1295; f) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494; *Angew. Chem.* **2011**, *123*, 2498–2543.

[7] a) R. Aráoz, E. Anhalt, L. René, M.-A. Badet-Denisot, P. Courvalin, B. Badet, *Biochemistry* **2000**, *39*, 15971–15979; b) Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 3944–3947; *Angew. Chem.* **2012**, *124*, 4010–4013; c) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527; d) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99; e) G. Caillot, J. Dufour, M.-C. Belhomme, T. Poisson, L. Grimaud, X. Pannecoucke, I. Gillaizeau, *Chem. Commun.* **2014**, *50*, 5887–5890; f) C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984–5987; g) X. Sun, S. Yu, *Org. Lett.* **2014**, *16*, 2938–2941; h) L. Wang, X.-J. Wei, W.-L. Lei, H. Chen, L.-Z. Wu, Q. Liu, *Chem. Commun.* **2014**, *50*, 15916–15919; i) Y.-M. Su, Y. Hou, F. Yin, Y.-M. Xu, Y. Li, X. Zheng, X.-S. Wang, *Org. Lett.* **2014**, *16*, 2958–2961; j) Y. Gu, X. Leng, Q. Shen, *Nat. Commun.* **2014**, *5*, 5405; k) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1669–1673; *Angew. Chem.* **2014**, *126*, 1695–1699; l) P. Xu, K. Hu, Z. Gu, Y. Cheng, C. Zhu, *Chem. Commun.* **2015**, *51*, 7222–7225; m) S. Mishra, P. Mondal, M. Ghosh, S. Mondal, A. Hajra, *Org. Biomol. Chem.* **2016**, *14*, 1432–1436.

[8] a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; *Angew. Chem.* **2013**, *125*, 11942–11959; b) X. Yang, G. Shan, L. Wang, Y. Rao, *Tetrahedron Lett.* **2016**, *57*, 819–836; c) B. Zhang, H. Guan, B. Liu, B. Shi, *Chin. J. Org. Chem.* **2014**, *34*, 1487–1498; d) H. Tang, X.-R. Huang, J. Yao, H. Chen, *J. Org. Chem.* **2015**, *80*, 4672–4682; e) H. Tang, B. Zhou, X.-R. Huang, C. Wang, J. Yao, H. Chen, *ACS Catal.* **2014**, *4*, 649–656.

[9] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155; b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972; c) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; d) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064; e) M. Corbet, F. De Campo, *Angew. Chem. Int. Ed.* **2013**, *52*, 9896–9898; *Angew. Chem.* **2013**, *125*, 10080–10082; f) R. K. Rit, M. R. Yadav, K. Ghosh, A. K. Sahoo, *Tetrahedron* **2015**, *71*, 4450–4459.

[10] a) K. Shibata, N. Chatani, *Org. Lett.* **2014**, *16*, 5148–5151; b) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201–2208; c) S. Maity, S. Agasti, A. M. Earsad, A. Hazra, D. Maiti, *Chem. Eur. J.* **2015**, *21*, 11320–11324; d) L. Grigorjeva, O. Daugulis, *Org. Lett.* **2014**, *16*, 4684–4687; e) W. Ma, L. Ackermann, *ACS Catal.* **2015**, *5*, 2822–2825; f) T. Yamaguchi, Y. Kommagalla, Y. Aihara, N. Chatani, *Chem. Commun.* **2016**, *52*, 10129–10132; g) S. Maity, R. Kancherla, U. Dhawa, E. Hoque, S. Pimparkar, D. Maiti, *ACS Catal.* **2016**, *6*, 5493–5499; h) G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124–11128; *Angew. Chem.* **2013**, *125*, 11330–11334; i) W.-H. Rao, B.-B. Zhan, K. Chen, P.-X. Ling, Z.-Z. Zhang, B.-F. Shi, *Org. Lett.* **2015**, *17*, 3552–3555; j) A. Deb, S. Bag, R. Kancherla, D. Maiti, *J. Am. Chem. Soc.* **2014**, *136*, 13602–13605.

[11] a) C. Shao, G. Shi, Y. Zhang, S. Pan, X. Guan, *Org. Lett.* **2015**, *17*, 2652–2655; b) G. Shi, C. Shao, S. Pan, J. Yu, Y. Zhang, *Org. Lett.* **2015**, *17*, 38–41.

[12] a) K. A. Schug, W. Lindner, *Chem. Rev.* **2005**, *105*, 67–114; b) H.-H. Chou, C.-H. Cheng, *Adv. Mater.* **2010**, *22*, 2468–2471.
[13] CCDC 1455114 (for palladacycle **A**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[14] F. A. Davis, P. V. N. Kasu, *Tetrahedron Lett.* **1998**, *39*, 6135–6138.
[15] J. Jung, E. Kim, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2014**, *356*, 2741–2748.
[16] K. Motoshima, K. Sugita, Y. Hashimoto, M. Ishikawa, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3041–3045.

Received: August 2, 2016
Published Online: October 26, 2016

