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**PAPER**

# A cascade process for the synthesis of *gem*-difluoromethylene compounds†

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An efficient strategy for the synthesis of 2,2-difluoro-2,3-dihydrofuran derivatives from β-fluoroalkyl-β-enaminoketones is described. The reaction occurred *via* an intramolecular halophilic attack-initiated cascade process. A series of 2,3-dihydrofurans were prepared in high yields. And an intermolecular domino process achieved providing polysubstituted furans. The mechanism of the reaction is discussed.

## Introduction

Halophilic reactions were observed many years ago,[1] and substrates such as halogenated aliphatic nitro-compounds,[2] perhaloalkanes,[3] *N*-halo-acetanlides,[4] and succinimides,[5] and α-halosulfones[6] could be attacked directly by nucleophiles on their halogen atoms rather than halogen-bound carbon atoms, followed by the formation of reactive carbanion intermediates, which diversify into many products (Scheme 1). A lot of nitrogen, oxygen, sulfur and carbon based nucleophiles can be employed in this interesting transformation.


**Scheme 1** General equation for halophilic reactions.

Different from carbophilic reactions ($S_NC$) which have a significant impact in organic chemistry, the halophilic reaction is observed only when the reactant **1** contains one or more electron-withdrawing groups at the α-C atom, thus providing the necessary stabilization of the active carbanion **3**.[7] Various fluorinated halides with structures that satisfy the requirements are particularly suitable for this type of reaction. A series of fluorinated compounds ($R_f$-OR, $R_f$-SR, $R_f$-NR, *etc.*) are synthesized conveniently through this halophilic attack-initiated nucleophilic substitution protocol.[8]

The selective introduction of a *gem*-difluoromethylene moiety into organic compounds has attracted a lot of attention in recent years due to the unique properties of this group. *gem*-Difluorination is often used on biologically active compounds in order to improve their pharmacological properties. The $CF_2/CH_2$ transposition has been recognized as a valuable tool in the blockage of metabolic processes,[9] as fluorine is the smallest replacement for hydrogen in the C–H bond,[10] and its substitution introduces only small steric and geometric perturbations which are generally recognized by macromolecular recognition sites. Moreover, the difluoromethylene group has also been regarded as an isopolar–isosteric replacement for oxygen and extensively used to modify nucleoside and phosphate analogues.[11] In addition, using this subunit as a surrogate for a carbonyl group was also reported recently.[12]

Due to the ongoing interest in the synthesis of fluorinated compounds,[13] our group has communicated a convenient method for the synthesis of a useful fluorine-containing building block, β-fluoroalkyl-β-enaminoketones.[14] While we tried to investigate the cyclization reaction of this synthon under conditions involving a transition-metal, a 2,2-difluoro-2,3-dihydrofuran product was formed through a halophilic attack initiated cascade process. As dihydrofuran and furan derivatives are important heterocyclic compounds commonly found in natural products and biologically relevant compounds,[15] and methods for the synthesis of their fluoro-analogs are limited, the importance of this strategy becomes self-explanatory. Herein we wish to report a detailed investigation of the scope and limitations of this strategy, and the reaction mechanism is also discussed.

## Results and discussion

Initially, we chose 4-bromo-4,4-difluoro-3-((4-methoxyphenyl)-amino)-1-phenylbut-2-en-1-one **1a** as the model substrate to optimize the reaction conditions (Table 1).[14] As previously communicated, the cyclization took place when DMF was used as the solvent, however, the temperature could be reduced to 60 °C. Common inorganic bases such as $K_3PO_4$ and $K_2CO_3$ could afford the product in good yields, while $Na_2CO_3$ was inefficient probably due to its poor solubility compared with sylvites. An organic base which was screened but this only led to recovery of the material. Among the other solvents evaluated, only $CH_3CN$ could give moderate yield. Further attempts to decrease the amount of

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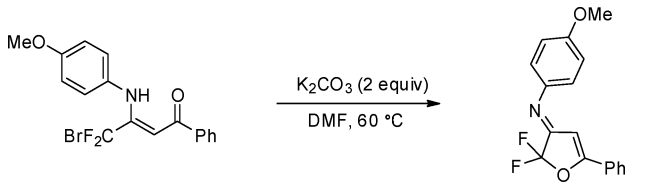
**Table 1** Optimization of reaction conditions[a]




1a 2a

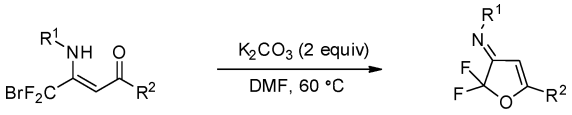
| Entry | Base | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | $K_3PO_4$ | DMF | 84 |
| 2 | $K_2CO_3$ | DMF | 84 |
| 3 | $Na_2CO_3$ | DMF | 15 |
| 4 | $Et_3N$ | DMF | — |
| 5 | $K_2CO_3$ | $CH_3CN$ | 40 |
| 6 | $K_2CO_3$ | Toluene | — |
| 7 | $K_2CO_3$ | THF | — |
| 8 | $K_2CO_3$ | DMF | 67[c] |

[a] Reactions were carried out on a 0.2 mmol scale with $K_2CO_3$ (2.0 eq.) and solvent (2 mL) at 60 °C unless otherwise stated. [b] Isolated yields. [c] $K_2CO_3$ (1.2 eq.) was used.

base used under the ascertained conditions led to a decrease in yield.

Having established suitable reaction conditions, we explored the scope and generality of the methodology starting with β-fluoroalkyl-β-enaminoketones, which could be prepared from the condensation of methyl ketones with fluoroalkylimidoyl chlorides.[16] As displayed in Table 2, when the $CF_2Cl$ group was used in place of $CF_2Br$ (Table 2, entry 1), the corresponding product was formed only in moderate yield due to the inertness of the C–Cl bond.[3c] Next, the substituents of the enaminoketones were investigated. When $R^1$ was an aromatic ring with an electron-donating group, the products were isolated in good yields (Table 2, entries 3–5), while electron-withdrawing groups led to a decline in yields (Table 2, entries 6–8), especially the $NO_2$ group. Substrates

**Table 2** Cyclization of β-fluoroalkyl-β-enaminoketones[a]

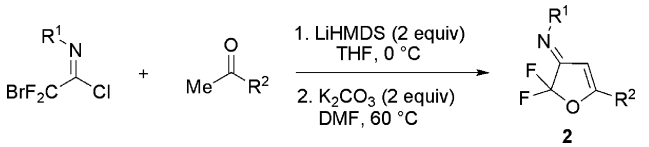



1 2

| Entry | $R^1$ | $R^2$ | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | Ph | **2a** | 52[c] |
| 2 | Ph | Ph | **2b** | 82 |
| 3 | 4-$MeC_6H_4$ | Ph | **2c** | 84 |
| 4 | 3-$MeC_6H_4$ | Ph | **2d** | 90 |
| 5 | 2-$MeC_6H_4$ | Ph | **2e** | 99 |
| 6 | 4-$ClC_6H_4$ | Ph | **2f** | 87 |
| 7 | 3-$ClC_6H_4$ | Ph | **2g** | 83 |
| 8 | 4-$NO_2C_6H_4$ | Ph | **2h** | 46 |
| 9 | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | **2i** | 71 |
| 10 | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | **2j** | 73 |
| 11 | 4-$MeOC_6H_4$ | 4-$ClC_6H_4$ | **2k** | 83 |
| 12 | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | **2l** | 81 |
| 13 | 4-$MeOC_6H_4$ | 2-Naphthyl | **2m** | 79 |
| 14 | 4-$ClC_6H_4$ | 2-Naphthyl | **2n** | 80 |

[a] Reactions were carried out on a 0.5 mmol scale with $K_2CO_3$ (2.0 eq.) and DMF (4 mL) at 60 °C unless otherwise stated. [b] Isolated yields.

**Table 3** One-pot synthesis of dihydrofurans[a]




2

| Entry | $R^1$ | $R^2$ | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 4-$MeC_6H_4$ | Ph | **2c** | 81 |
| 2 | 3-$MeC_6H_4$ | Ph | **2d** | 82 |
| 3 | 2-$MeC_6H_4$ | Ph | **2e** | 89 |
| 4 | 4-$CF_3C_6H_4$ | Ph | **2o** | 70 |
| 5 | 2-$CF_3C_6H_4$ | Ph | **2p** | 66 |
| 6 | 4-$COOEtC_6H_4$ | Ph | **2q** | 70 |
| 7 | Ph | 4-$MeC_6H_4$ | **2r** | 81 |
| 8 | Ph | 3-$MeOC_6H_4$ | **2s** | 60 |
| 9 | Ph | 4-$FC_6H_4$ | **2t** | 74 |
| 10 | Ph | 4-$BrC_6H_4$ | **2u** | 54 |

[a] Reactions were carried out on a 0.5 mmol scale with LiHMDS (2.0 eq.) and methyl ketones (1.0 eq.), then $K_2CO_3$ (2.0 eq.) and DMF (4 mL) at 60 °C unless otherwise stated. [b] Isolated yields.

with substituents *meta* or *ortho* to the nitrogen both proceeded well. Modifying the $R^2$ group revealed that both electron-rich and electron-poor aryl rings could give favourable yields (Table 2, entries 9–14).

The high efficiency of this cyclization reaction under mild conditions motivated us to explorer the feasibility of forming the products through a one-pot process from fluoroalkylimidoyl chlorides and methyl ketones. However, we soon realized that these two steps could not be carried out under the same reaction medium, and a sequential process was established finally based on the addition of DMF and $K_2CO_3$ to the crude mixture derived from the condensation of methyl ketones with fluoroalkylimidoyl chlorides in THF after evaporation of the volatile materials. Then the scope and generality of the consecutive process was studied. Changing the $R^1$ group still indicated that the reactivity was affected by the electronic effects of the substituents, as shown by comparing the results of the electron donating groups (Table 3, entries 1–3) with the electron withdrawing groups (Table 3, entries 4–6). However, different from the stepwise procedure, the electron-poor $R^2$ group afforded the products in moderate yields (Table 3, entries 9–10). This may result from the low conversion of the prior (condensation) step.

Surprisingly, novel 3,3-difluoroindoline compounds were obtained as the only detectable products (Fig. 1), while expanding the reaction scope with β-enaminoalkylketone **1v** and β-enamino ester **1w** (Scheme 2). However, attempts to improve the yields for these types of heterocycles were unsuccessful.[17]

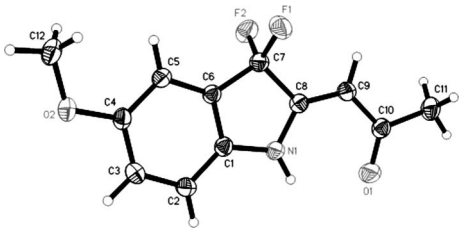
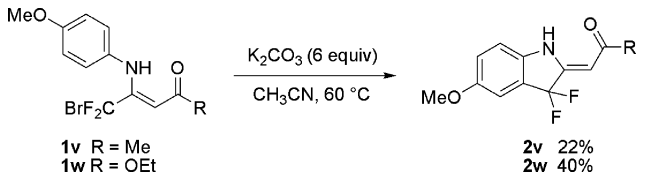
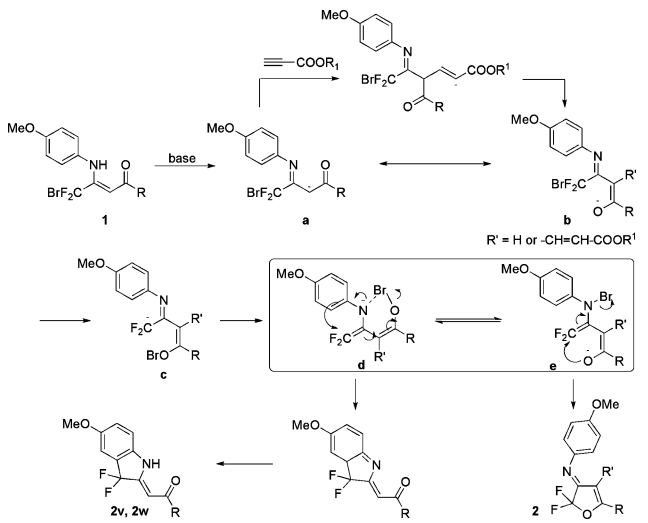



**Fig. 1** X-Ray structure of **2v**.



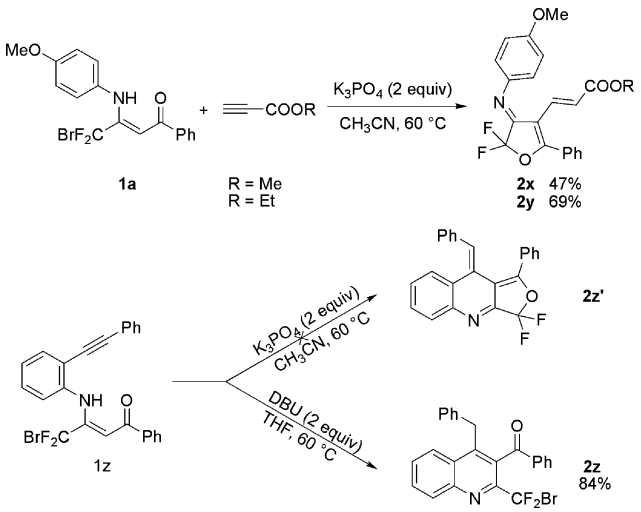

**Scheme 2** Synthesis of indolines.

Based on the above observations, a possible mechanism of this transformation is proposed in Scheme 3. As the 1,4-dinitrobenzene added could not inhibit the reaction, a single electron transfer (SET) course can be excluded. The β-enaminoketone is initially deprotonated by base, and subsequent intramolecular halophilic attack occurred after the generation of the enolate anion. The generated active carbanion **c** is rapidly transformed into vinyl amide **d**, forming a six-membered ring to stabilize the Br–O bond. Then the oxygen anion might be regenerated (**e**) which generated dihydrofuran products **2** by nucleophilic addition to the *gem*-difluorovinyl.[18] In the case of β-enaminoalkylketone and β-enamino ester, the indoline product **2v/2w** may be formed through nucleophilic addition of the carbanion to the *gem*-difluorovinyl, isomerised from the initially formed amide. And the formation of these products can also exclude the simple intramolecular nucleophilic substitution pathway, as the $CF_2Br$ group is hard to undergo such a reaction by a carbanion due to its unique property.[19]



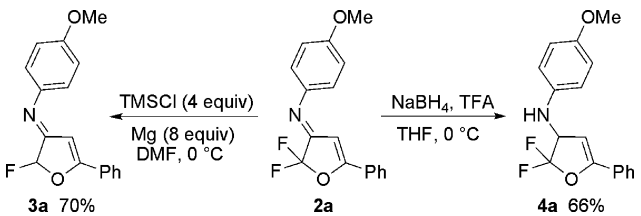

**Scheme 3** Proposed mechanism.

We also interested in whether the resonance structure **a** (Scheme 3) could react with some electrophilic reagents as reported in the literature (Scheme 4).[20] As expected, an intermolecular reaction with ethyl propiolate and methyl propiolate was accomplished forming the fully substituted dihydrofurans as the major products besides the intramolecular products. However, when we introduce the alkynyl moiety into the *N*-aryl ring of the substrate in order to synthesis a polycyclic compound, a quinoline product **2z** was obtained through a quick aromatization process which inhibited the formation of the oxygen anion, which complements our previously reported fluorinated quinoline synthesis.[13c] The condition for synthesis of this 2-fluoroalkylquinoline was also optimized delivering an 84% yield (DBU 2 eq., THF, 60 °C).




**Scheme 4** Cascade strategy.

With these dihydrofurans in hand and the expectation to diversify the variety of fluoro-furan compounds, some derivation reactions were developed (Scheme 5). While we used a standard Mg participated defluorination reaction to synthesize the aromatized furan ring,[21] a mono fluorine dihydrofuran **3a** was produced without aromatization. And reduction of the 2,2-difluoro-2,3-dihydrofuran with $NaBH_4$ in the presence of trifluoroacetic acid (TFA) at 0 °C yielded the 2,2-difluoro-3-amino-dihydrofuran **4a**.[22]




**Scheme 5** Product derivation.

## Conclusions

In conclusion, an efficient strategy for the synthesis of fluoro-furan derivates by the cascade reaction of fluoroalkylimidoyl chlorides and methyl ketones was developed. A wide variety of functionalized 2,2-difluoro-2,3-dihydrofurans can be synthesized in good yields under mild conditions, and several fully substituted 2,3-dihydrofurans were also obtained according to the proposed mechanism, rendering this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

## Experimental section

### General experimental

Melting points were measured on a Melt-Temp apparatus and uncorrected. $^1$HNMR spectra were recorded in $CDCl_3$ and *d*-DMSO on a Bruker AM-300 spectrometer (300 MHz) with TMS as the internal standard. $^{19}$F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as the external

standard. $^{13}C$ NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Elemental analysis was performed by the Analytical Laboratory of Shanghai Institute of Organic Chemistry. Mass spectra were recorded by EI and ESI methods, HRMS (ESI) was measured on a Bruker Daltonics APEXIII 7.0 TESLA FTMS. Solvents and reagents were purchased from commercial sources and used as received. THF was distilled from sodium. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure and petroleum ether/ethyl acetate combination was used as the eluent

**Representative procedure for the synthesis of 2**

β-fluoroalkyl-β-enaminoketones **1** (0.5 mmol) was added to a solution of $K_2CO_3$ (2.0 eq.) in DMF (4.0 mL). The solution was then stirred at 60 °C until completion of the reaction as indicated by TLC, then partitioned between ethyl acetate and water; the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to provide **2**.

***N*-(2,2-Difluoro-5-phenylfuran-3(2H)-ylidene)-4-methoxyaniline (2a)**

Yellow solid, mp 70–71 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.79–7.72 (m, 2H), 7.57–7.42 (m, 3H), 7.10 (d, $J$ = 9.1 Hz, 2H), 6.94 (d, $J$ = 8.7 Hz, 2H), 6.37 (t, $J$ = 1.4 Hz, 1H), 3.84 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −78.44; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 170.0, 158.4, 156.3 (q, $J$ = 24.0 Hz), 141.8, 133.3, 129.6, 127.2, 127.1, 124.2, 122.4 (q, $J$ = 263.3 Hz), 115.0, 95.5, 55.8; LRMS-EI $m/z$ (relative intensity) 301 (100) [$M^+$], 286 (72), 133 (35), 102 (41), 77 (30); Anal. calcd for $C_{17}H_{13}F_2NO_2$: C, 67.77; H, 4.35; N, 4.65. Found: C, 67.70; H, 4.36; N, 4.49; IR (KBr): 3290, 2914, 2836, 1650, 1606, 1570, 1504, 1247, 1153, 1122, 1021, 840, 771 $cm^{-1}$.

***N*-(2,2-Difluoro-5-phenylfuran-3(2*H*)-ylidene)aniline (2b)**

Yellow solid, mp 89–90 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.80–7.70 (m, 2H), 7.59–7.36 (m, 5H), 7.22 (t, $J$ = 7.8 Hz, 1H), 7.08 (d, $J$ = 7.8 Hz, 2H), 6.26 (s, 1H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −79.11; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 171.1, 158.8 (t, $J$ = 23.5 Hz), 149.2, 133.8, 130.0, 129.8, 127.6, 127.1, 126.7, 122.3 (t, $J$ = 264.9 Hz), 122.1, 95.3; LRMS-EI $m/z$ (relative intensity) 271 (56) [$M^+$], 102 (100); Anal. calcd for $C_{16}H_{11}F_2NO$: C, 70.84; H, 4.09; N, 5.16. Found: C, 70.73; H, 4.36; N, 4.94; IR (KBr): 1662, 1606, 1589, 1572, 1490, 1279, 1155, 1129, 1019, 765, 698 $cm^{-1}$.

***N*-(2,2-Difluoro-5-phenylfuran-3(2*H*)-ylidene)-4-methylaniline (2c)**

Yellow solid, mp 102–104 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.7 Hz, 2H), 7.57–7.41 (m, 3H), 7.21 (d, $J$ = 8.2 Hz, 2H), 7.00 (d, $J$ = 8.2 Hz, 2H), 6.31 (s, 1H), 2.38 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −78.80; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 170.0, 157.3 (t, $J$ = 23.4 Hz), 146.0, 135.6, 133.0, 129.8, 129.1, 126.8, 126.5, 121.7 (t, $J$ = 264.8 Hz), 121.6, 94.8, 20.5; LRMS-EI $m/z$ (relative intensity) 285 (63) [$M^+$], 102 (100); Anal. calcd for $C_{17}H_{13}F_2NO$: C, 71.57; H, 4.59; N, 4.91. Found: C, 71.41; H, 4.75; N, 4.55; IR (KBr): 1651, 1608, 1589, 1449, 1277, 1144, 1119, 1017, 761, 678 $cm^{-1}$.

***N*-(2,2-Difluoro-5-phenylfuran-3(2*H*)-ylidene)-3-methylaniline (2d)**

Yellow solid, mp 74–76 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.77–7.64 (m, 2H), 7.54–7.37 (m, 3H), 7.27 (t, $J$ = 7.8 Hz, 1H), 7.02 (d, $J$ = 7.3 Hz, 1H), 6.91–6.80 (m, 2H), 6.23 (s, 1H), 2.37 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −78.86; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 170.9, 158.6 (t, $J$ = 24.2 Hz), 149.3, 139.5, 133.8, 129.9, 129.8, 127.6, 127.4, 127.2, 122.5, 122.3 (t, $J$ = 264.5 Hz), 119.1, 95.4, 21.6; LRMS-EI $m/z$ (relative intensity) 285 (54) [$M^+$], 102 (100); Anal. calcd for $C_{17}H_{13}F_2NO$: C, 71.57; H, 4.59; N, 4.91. Found: C, 71.56; H, 4.88; N, 4.83; IR (KBr): 3111, 1659, 1597, 1570, 1491, 1449, 1319, 1279, 1149, 1121, 1020, 765 $cm^{-1}$.

***N*-(2,2-Difluoro-5-phenylfuran-3(2*H*)-ylidene)-2-methylaniline (2e)**

Yellow solid, mp 70–72 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.80–7.70 (m, 2H), 7.58–7.41 (m, 3H), 7.29–7.07 (m, 3H), 6.83 (d, $J$ = 7.3 Hz, 1H), 6.12 (s, 1H), 2.25 (s, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −79.10; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 170.2, 158.0 (t, $J$ = 24.2 Hz), 147.5, 133.1, 130.5, 129.7, 129.2, 126.9, 126.7, 126.4, 125.7, 121.3 (t, $J$ = 264.4 Hz), 119.0, 94.6, 17.2; LRMS-EI $m/z$ (relative intensity) 285 (66) [$M^+$], 102 (100); HRMS-EI ($m/z$) calcd for $C_{17}H_{13}F_2NO$ 285.0965; found 285.0962. IR (KBr): 3123, 1665, 1607, 1593, 1573, 1483, 1451, 1321, 1277, 1150, 1128, 1017, 768 $cm^{-1}$.

**4-Chloro-*N*-(2,2-difluoro-5-phenylfuran-3(2*H*)-ylidene)aniline (2f)**

Yellow solid, mp 116–118 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.81–7.71 (m, 2H), 7.61–7.42 (m, 3H), 7.37 (d, $J$ = 8.7 Hz, 2H), 7.02 (d, $J$ = 8.7 Hz, 2H), 6.23 (s, 1H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −79.30; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 170.8, 158.9 (t, $J$ = 24.0 Hz), 147.4, 133.2, 130.3, 129.2, 129.2, 127.0, 126.4, 123.2, 121.5 (t, $J$ = 265.0 Hz), 94.7; LRMS-EI $m/z$ (relative intensity) 305 (44) [$M^+$], 102 (100); Anal. calcd for $C_{16}H_{10}ClF_2NO$: C, 62.86; H, 3.30; N, 4.58. Found: C, 62.97; H, 3.49; N, 4.44; IR (KBr): 1657, 1604, 1571, 1483, 1281, 1175, 1150, 1088, 1017, 849, 677 $cm^{-1}$.

**3-Chloro-*N*-(2,2-difluoro-5-phenylfuran-3(2*H*)-ylidene)aniline (2g)**

Yellow solid, mp 60–61 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.81–7.73 (m, 2H), 7.61–7.43 (m, 3H), 7.33 (t, $J$ = 8.0 Hz, 1H), 7.22–7.16 (m, 1H), 7.07 (t, $J$ = 1.8 Hz, 1H), 6.95 (d, $J$ = 7.8 Hz, 1H), 6.21 (t, $J$ = 1.4 Hz, 1H); $^{19}F$ NMR (282 MHz, $CDCl_3$) $\delta$ −79.48; $^{13}C$ NMR (100 MHz, *d*-DMSO) $\delta$ 171.8, 160.2 (t, $J$ = 24.2 Hz), 150.8, 134.5, 134.0, 131.7, 129.9, 127.8, 127.0, 126.3, 122.1 (t, $J$ = 264.8 Hz), 121.6, 120.6, 95.3; LRMS-EI $m/z$ (relative intensity) 305 (41) [$M^+$], 102 (100); Anal. calcd for $C_{16}H_{10}ClF_2NO$: C, 62.86; H, 3.30; N, 4.58. Found: C, 62.59; H, 3.40; N, 4.40; IR (KBr): 1665, 1605, 1584, 1571, 1492, 1470, 1320, 1280, 1156, 1020, 766 $cm^{-1}$.

***N*-(2,2-Difluoro-5-phenylfuran-3(2*H*)-ylidene)-4-nitroaniline (2h)**

Yellow solid, mp 199–202 °C; $^1H$ NMR (300 MHz, *d*-DMSO) $\delta$ 8.32 (d, $J$ = 9.1 Hz, 2H), 7.99 (d, $J$ = 7.3 Hz, 2H), 7.74–7.53 (m, 3H), 7.36 (d, $J$ = 9.1 Hz, 2H), 6.99 (s, 1H); $^{19}F$ NMR (282 MHz,

*d*-DMSO) $\delta$ −75.71; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 171.9, 160.6 (t, $J$ = 24.0 Hz), 154.7, 144.7, 133.7, 129.3, 127.2, 126.1, 125.1, 121.9, 121.2 (t, $J$ = 264.9 Hz), 94.6; LRMS-EI *m/z* (relative intensity) 316 (63) [M$^+$], 102 (100); Anal. calcd for $C_{16}H_{10}F_2N_2O_3$: C, 60.76; H, 3.19; N, 8.86. Found: C, 60.72; H, 3.12; N, 8.56; IR (KBr): 1652, 1596, 1581, 1568, 1509, 1485, 1450, 1338, 1320, 1155, 1126, 1108, 1016, 768 cm$^{-1}$.

**_N_-(2,2-Difluoro-5-(4-methoxyphenyl)furan-3(2_H_)-ylidene)-4-methoxyaniline (2i)**

Yellow solid, mp 119–120 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 8.6 Hz, 2H), 7.09 (d, $J$ = 8.7 Hz, 2H), 7.00–6.90 (m, 4H), 6.23 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −79.58; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 169.6, 163.0, 157.7, 156.0 (t, $J$ = 23.9 Hz), 141.6, 128.9, 123.6, 122.1 (t, $J$ = 263.3 Hz), 118.9, 114.7, 114.4, 92.9, 55.6, 55.3; LRMS-EI *m/z* (relative intensity) 331 (100) [M$^+$], 316 (86), 132 (57); Anal. calcd for $C_{18}H_{15}F_2NO_3$: C, 65.25; H, 4.56; N, 4.23. Found: C, 65.28; H, 4.59; N, 4.02; IR (KBr): 2944, 2838, 1606, 1502, 1264, 1245, 1151, 1117, 1024, 839 cm$^{-1}$.

**4-Chloro-_N_-(2,2-difluoro-5-(4-methoxyphenyl)furan-3(2H)-ylidene)aniline (2j)**

Yellow solid, mp 138–140 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.94 (d, $J$ = 9.2 Hz, 2H), 7.49 (d, $J$ = 8.7 Hz, 2H), 7.17 (d, $J$ = 8.7 Hz, 2H), 7.11 (d, $J$ = 9.1 Hz, 2H), 6.84 (s, 1H), 3.87 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −78.52; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 170.8, 163.3, 159.0 (t, $J$ = 24.7 Hz), 147.7, 129.9, 129.2, 123.2, 121.7 (t, $J$ = 264.1 Hz), 118.6, 114.8, 92.5, 55.6; LRMS-EI *m/z* (relative intensity) 335 (71) [M$^+$], 132 (100); HRMS-EI (*m/z*) calcd for $C_{17}H_{12}ClF_2NO_2$ 335.0525; found 335.0527; IR (KBr): 1603, 1506, 1485, 1320, 1257, 1150, 1111, 1024, 837, 800 cm$^{-1}$.

**_N_-(5-(4-Chlorophenyl)-2,2-difluorofuran-3(2_H_)-ylidene)-4-methoxyaniline (2k)**

Yellow solid, mp 125–127 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 8.7 Hz, 2H), 7.45 (d, $J$ = 8.3 Hz, 2H), 7.10 (d, $J$ = 8.7 Hz, 2H), 6.95 (d, $J$ = 9.1 Hz, 2H), 6.37 (s,1H), 3.84 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −78.15; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 168.3, 158.0, 155.5 (t, $J$ = 23.9 Hz), 141.3, 137.5, 129.3, 128.4, 125.5, 123.8, 121.9 (t, $J$ = 264.0 Hz), 114.5, 95.7, 55.3; LRMS-EI *m/z* (relative intensity) 335 (100) [M$^+$], 320 (71), 133 (42); Anal. calcd for $C_{17}H_{12}ClF_2NO_2$: C, 60.82; H, 3.60; N, 4.17. Found: C, 60.69; H, 3.96; N, 4.09; IR (KBr): 1606, 1592, 1503, 1292, 1248, 1153, 1091, 1025, 1009, 836 cm$^{-1}$.

**4-Chloro-_N_-(5-(4-chlorophenyl)-2,2-difluorofuran-3(2_H_)-ylidene)aniline (2l)**

Yellow solid, mp 144–146 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 8.7 Hz, 2H), 7.46 (d, $J$ = 8.7 Hz, 2H), 7.37 (d, $J$ = 8.7 Hz, 2H), 7.01 (d, $J$ = 8.6 Hz, 2H), 6.22 (s, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −78.99; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 170.2, 159.5 (t, $J$ = 24.2 Hz), 148.0, 138.7, 131.1, 130.1, 130.0, 129.4, 125.9, 123.9, 122.2 (t, $J$ = 265.2 Hz), 96.0; LRMS-EI *m/z* (relative intensity) 339 (54) [M$^+$], 136 (100); Anal. calcd for $C_{16}H_9Cl_2F_2NO$: C, 56.50; H, 2.67; N, 4.12. Found: C, 56.38; H, 2.79; N, 3.82; IR (KBr): 1590, 1483, 1406, 1279, 1152, 1104, 1089, 1008, 836, 802 cm$^{-1}$.

**_N_-(2,2-Difluoro-5-(naphthalen-2-yl)furan-3(2_H_)-ylidene)-4-methoxyaniline (2m)**

Yellow solid, mp 153–155 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 8.58 (s, 1H), 8.17–7.95 (m, 4H), 7.72–7.59 (m, 2H), 7.32–7.20 (m, 3H), 7.06 (d, $J$ = 8.7 Hz, 2H), 3.83 (s, 3H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −77.15; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 169.4, 158.0, 155.8 (t, $J$ = 23.6 Hz), 141.5, 134.6, 132.3, 129.2, 128.8, 128.7, 127.8, 127.3, 127.2, 124.0, 123.8, 123.0, 122.1 (t, $J$ = 264.2 Hz), 114.5, 95.6, 55.3; LRMS-EI *m/z* (relative intensity) 351 (100) [M$^+$], 336 (59), 152 (78); Anal. calcd for $C_{21}H_{15}F_2NO_2$: C, 71.79; H, 4.30; N, 3.99. Found: C, 71.73; H, 4.64; N, 3.81; IR (KBr): 2838, 1605, 1561, 1503, 1296, 1245, 1145, 1129, 1030, 792 cm$^{-1}$.

**4-Chloro-_N_-(2,2-difluoro-5-(naphthalen-2-yl)furan-3(2_H_)-ylidene)aniline (2n)**

Yellow solid, mp 146–147 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 8.60 (s, 1H), 8.20–7.96 (m, 4H), 7.74–7.60 (m, 2H), 7.54 (d, $J$ = 8.7 Hz, 2H), 7.23 (d, $J$ = 8.6 Hz, 2H), 7.13 (s, 1H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −78.31; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 166.0, 154.3 (t, $J$ = 24.1 Hz), 142.8, 130.1, 127.5, 125.6, 124.6, 124.6, 124.2, 123.1, 122.9, 122.6, 119.0, 118.6, 118.3, 116.9 (t, $J$ = 265.0 Hz), 90.4; LRMS-EI *m/z* (relative intensity) 355 (63) [M$^+$], 152 (100); Anal. calcd for $C_{20}H_{12}ClF_2NO$: C, 67.52; H, 3.40; N, 3.94. Found: C, 67.53; H, 3.48; N, 3.78; IR (KBr): 1604, 1590, 1562, 1483, 1294, 1145, 1113, 1032, 790 cm$^{-1}$.

**Representative procedure for the one-pot synthesis of 2**

Fluoroalkylimidoyl chlorides (0.5 mmol) and methyl ketones (1.0 eq.) were added to 2.0 mL anhydrous THF. Then LiHMDS (2.0 eq. in THF) was added dropwise at 0 °C, the solution was stirred for a further 20 min, then concentrated *in vacuo*. The residue was next dissolved with 4 mL DMF, and $K_2CO_3$ (2.0 eq.) was added. The mixture was then stirred at 60 °C until completion of reaction as indicated by TLC, then partitioned between ethyl acetate and water, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to provide **2**.

**_N_-(2,2-Difluoro-5-phenylfuran-3(2_H_)-ylidene)-4-(trifluoromethyl)aniline (2o)**

Yellow solid, mp 105–108 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 8.00 (d, $J$ = 8.7 Hz, 2H), 7.81 (d, $J$ = 8.7 Hz, 2H), 7.71–7.52 (m, 3H), 7.32 (d, $J$ = 8.2 Hz, 2H), 6.99 (s, 1H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −62.78 (s, 3F), −81.18 (s, 2F); $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 172.0, 160.6 (t, $J$ = 24.2 Hz), 152.7, 133.9, 129.7, 127.6, 127.0 (t, $J$ = 3.6 Hz), 126.8, 126.5 (t, $J$ = 32.2 Hz), 124.8 (t, $J$ = 272.2 Hz), 122.1, 121.8 (t, $J$ = 264.8 Hz), 95.0; LRMS-EI *m/z* (relative intensity) 339 (81) [M$^+$], 338 (47), 102 (100); Anal. calcd for $C_{17}H_{10}F_5NO$: C, 60.18; H, 2.97; N, 4.13. Found: C, 60.06; H, 3.05; N, 3.89; IR (KBr): 1657, 1594, 1572, 1491, 1320, 1282, 1163, 1107, 1065, 1012, 861, 766 cm$^{-1}$.

**N-(2,2-Difluoro-5-phenylfuran-3(2*H*)-ylidene)-2-(trifluoromethyl)aniline (2p)**

Yellow solid, mp 88–91 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 7.99 (d, $J$ = 8.6 Hz, 2H), 7.84–7.52 (m, 5H), 7.46 (t, $J$ = 7.8 Hz, 1H), 7.21 (d, $J$ = 8.7 Hz, 1H), 6.88 (s, 1H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −59.66 (s, 3F), −79.94 (s, 2F); $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 172.2, 160.8 (t, $J$ = 24.2 Hz), 147.7, 134.3, 134.0, 129.7, 126.9 (t, $J$ = 5.2 Hz), 126.7, 126.1, 124.2 (t, $J$ = 272.9 Hz), 121.6 (t, $J$ = 264.8 Hz), 121.3, 120.9, 118.9, 95.0; LRMS-EI *m/z* (relative intensity) 339 (83) [M$^+$], 102 (100); Anal. calcd for $C_{17}H_{10}F_5NO$: C, 60.18; H, 2.97; N, 4.13. Found: C, 60.23; H, 3.10; N, 4.00; IR (KBr): 1670, 1597, 1572, 1487, 1451, 1319, 1280, 1160, 1131, 1035, 762 cm$^{-1}$.

**Ethyl 4-((2,2-difluoro-5-phenylfuran-3(2*H*)-ylidene)amino)benzoate (2q)**

Yellow solid, mp 95–97 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 8.05 (d, $J$ = 8.2 Hz, 2H), 7.99 (d, $J$ = 7.3 Hz, 2H), 7.67 (t, $J$ = 7.3 Hz, 1H), 7.57 (t, $J$ = 7.3 Hz, 2H), 7.25 (d, $J$ = 8.7 Hz, 2H), 6.96 (s, 1H), 4.35 (q, $J$ = 6.9 Hz, 2H), 1.35 (t, $J$ = 6.9 Hz, 3H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −79.11; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 171.8, 165.8, 160.2 (t, $J$ = 24.2 Hz), 153.4, 133.9, 131.0, 129.7, 127.6, 127.5, 126.8, 121.9 (t, $J$ = 264.9 Hz), 121.7, 95.1, 61.2, 14.7; LRMS-EI *m/z* (relative intensity) 343 (100) [M$^+$], 298 (50), 102 (74); Anal. calcd for $C_{19}H_{15}F_2NO_3$: C, 66.47; H, 4.40; N, 4.08. Found: C, 66.48; H, 4.58; N, 4.05; IR (KBr): 3104, 2979, 1698, 1673, 1591, 1570, 1492, 1451, 1411, 1369, 1279, 1157, 1125, 1021, 869, 771 cm$^{-1}$.

**N-(2,2-Difluoro-5-(p-tolyl)furan-3(2*H*)-ylidene)aniline (2r)**

Yellow solid, mp 86–87 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 7.85 (d, $J$ = 8.2 Hz, 2H), 7.48 (t, $J$ = 7.7 Hz, 2H), 7.39–7.25 (m, 3H), 7.17 (d, $J$ = 7.3 Hz, 2H), 6.88 (s, 1H), 2.38 (s, 3H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −78.66; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 171.0, 158.6 (t, $J$ = 24.0 Hz), 149.1, 144.1, 130.2, 129.7, 127.3, 126.3, 124.2, 122.1 (t, $J$ = 264.3 Hz), 121.8, 94.2, 21.6; LRMS-EI *m/z* (relative intensity) 285 (100) [M$^+$], 116 (70); Anal. calcd for $C_{17}H_{13}F_2NO$: C, 71.57; H, 4.59; N, 4.91. Found: C, 71.56; H, 4.80; N, 4.92; IR (KBr): 1649, 1607, 1483, 1452, 1317, 1282, 1149, 1012, 795, 693 cm$^{-1}$.

**N-(2,2-Difluoro-5-(3-methoxyphenyl)furan-3(2*H*)-ylidene)aniline (2s)**

Yellow oil. $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 7.57–7.43 (m, 5H), 7.29 (t, $J$ = 7.3 Hz, 1H), 7.23–7.14 (m, 3H), 7.05 (s, 1H), 3.83 (s, 3H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −78.29; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 171.2, 160.6, 159.1 (t, $J$ = 24.0 Hz), 149.5, 131.3, 130.3, 128.7, 127.0, 122.5 (t, $J$ = 264.3 Hz), 122.3, 120.6, 120.1, 112.3, 96.0, 56.5; LRMS-EI *m/z* (relative intensity) 301 (100) [M$^+$], 132 (59); Anal. calcd for $C_{17}H_{13}F_2NO_2$: C, 67.77; H, 4.35; N, 4.65. Found: C, 67.32; H, 4.72; N, 4.42. IR (KBr): 1666, 1606, 1575, 1486, 1299, 1223, 1155, 1128, 1028, 783 cm$^{-1}$.

**N-(2,2-Difluoro-5-(4-fluorophenyl)furan-3(2*H*)-ylidene)aniline (2t)**

Yellow solid, mp 88–90 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 8.13–8.00 (m, 2H), 7.54–7.25 (m, 5H), 7.18 (d, $J$ = 7.3 Hz, 2H), 6.99 (s, 1H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −78.31 (s, 3F), −105.11 (m, 1F). $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 169.8, 165.1 (d, $J$ = 252.8 Hz), 158.4 (t, $J$ = 24.0 Hz), 148.9, 130.1 (d, $J$ = 9.3 Hz), 129.7, 126.4, 123.5, 122.0 (t, $J$ = 264.8 Hz), 121.8, 116.8 (d, $J$ = 22.3 Hz), 94.9; LRMS-EI *m/z* (relative intensity) 289 (84) [M$^+$], 120 (100); Anal. calcd for $C_{16}H_{10}F_3NO$: C, 66.44; H, 3.48; N, 4.84. Found: C, 66.52; H, 3.48; N, 4.78; IR (KBr): 3100, 3073, 1658, 1605, 1579, 1504, 1483, 1416, 1242, 1146, 1119, 812, 755, 700 cm$^{-1}$.

**N-(5-(4-Bromophenyl)-2,2-difluorofuran-3(2*H*)-ylidene)aniline (2u)**

Yellow solid, mp 57–60 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 7.90 (d, $J$ = 8.7 Hz, 2H), 7.75 (d, $J$ = 8.7 Hz, 2H), 7.49 (t, $J$ = 7.3 Hz, 2H), 7.30 (t, $J$ = 7.3 Hz, 1H), 7.18 (d, $J$ = 8.2 Hz, 2H), 7.06 (s, 1H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ −78.19; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 169.8, 158.4 (t, $J$ = 24.2 Hz), 149.0, 132.8, 129.9, 129.2, 127.4, 126.7, 126.2, 122.0 (t, $J$ = 264.9 Hz), 121.9, 95.9; LRMS-EI *m/z* (relative intensity) 349 (100) [M$^+$], 351 (100), 182 (77), 180 (76); Anal. calcd for $C_{16}H_{10}BrF_2NO$: C, 54.88; H, 2.88; N, 4.00. Found: C, 54.99; H, 3.16; N, 3.78; IR (KBr): 1604, 1588, 1483, 1404, 1272, 1155, 1070, 1008 cm$^{-1}$.

**Procedure for the synthesis of 2v/2w**

β-Enaminoalkylketone **1v** or β-enamino ester **1w** (0.5 mmol) was added to a solution of $K_2CO_3$ (6.0 eq.) in $CH_3CN$ (4.0 mL). The solution was then stirred at 60 °C. After completion of reaction as indicated by TLC, the reaction crude was filtered and the filtrate evaporated. The residue was purified by flash chromatography on silica gel to provide the desired product **2v/2w**.

**(*Z*)-1-(3,3-Difluoro-6-methoxyindolin-2-ylidene)propan-2-one (2v)**

Yellow solid, mp 124–126 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.98 (br, 1H), 7.10 (s, 1H), 6.96–6.89 (m, 1H), 6.79 (d, $J$ = 8.5 Hz, 1H), 5.84 (t, $J$ = 3.0 Hz, 1H), 3.80 (s, 3H), 2.26 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ -95.71; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.2, 155.8, 152.3 (t, $J$ = 27.2 Hz), 137.9 (t, $J$ = 7.4 Hz), 121.9 (t, $J$ = 23.5 Hz), 120.6 (t, $J$ = 245.0 Hz), 119.2, 111.6, 110.2, 95.4, 56.0, 29.7; LRMS-EI *m/z* (relative intensity) 239 (100) [M$^+$], 224 (33), 204 (46); HRMS-EI (*m/z*) calcd for $C_{12}H_{11}F_2NO_2$ 239.0758; found 239.0759.

**(*Z*)-Ethyl 2-(3,3-difluoro-6-methoxyindolin-2-ylidene)acetate (2w)**

Yellow solid, mp 79–80 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.80 (br, 1H), 7.10 (s, 1H), 6.94 (d, $J$ = 8.2 Hz, 1H), 6.76 (d, $J$ = 8.5 Hz, 1H), 5.44 (d, $J$ = 3.5 Hz, 1H), 4.22 (q, $J$ = 7.0 Hz, 2H), 3.80 (s, 3H), 1.32 (d, $J$ = 7.0 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ.–93.53; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.1, 155.3, 153.3 (t, $J$ = 27.2 Hz), 138.0 (t, $J$ = 6.6 Hz), 121.8 (t, $J$ = 23.5 Hz), 120.1 (t, $J$ = 245.0 Hz), 119.5, 111.1, 110.0, 87.9, 60.1, 56.0, 14.3; LRMS-EI *m/z* (relative intensity) 269 (29) [M$^+$], 223 (100), 208 (37); HRMS-EI (*m/z*) calcd for $C_{13}H_{13}F_2NO_3$ 269.0864; found 269.0869.

**Procedure for the synthesis of 2x/2y**

Ethyl propiolate or methyl propiolate (2.0 eq.) was added to a solution of $K_3PO_4$ (2.0 eq.) in $CH_3CN$ (4.0 mL), and **1a** (0.5 mmol)

was added after the temperature was raised to 60 °C. After completion of reaction as indicated by TLC, the reaction crude was filtered and the filtrate evaporated. The residue was purified by flash chromatography on silica gel to provide the desired product **2x**/**2y**.

**(*E*)-Methyl 3-(5,5-difluoro-4-((4-methoxyphenyl)imino)-2-phenyl-4,5-dihydrofuran-3-yl)acrylate (2x)**

Yellow solid, mp 153–154 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 7.83–7.64 (m, 5H), 7.49 (d, $J$ = 15.6 Hz, 1H), 7.17 (d, $J$ = 15.6 Hz, 1H), 7.08–6.97 (m, 4H), 3.79 (s, 3H), 3.71 (s, 3H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ -72.61; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 169.4, 167.0, 157.9, 154.8 (t, $J$ = 22.0 Hz), 140.4, 133.8, 131.4, 130.0, 129.2, 126.8, 122.4, 121.9, 118.1 (t, $J$ = 272.9 Hz), 114.6, 109.9, 55.8, 52.1; LRMS-EI *m*/*z* (relative intensity) 385 (26) [M$^+$], 326 (100), 306 (44); HRMS-EI (*m*/*z*) calcd for $C_{21}H_{17}F_2NO_4$ 385.1126; found 385.1121; IR (KBr): 1720, 1631, 1505, 1453, 1310, 1291, 1251, 1172, 1108, 1063, 836 cm$^{-1}$.

**(*E*)-Ethyl 3-(5,5-difluoro-4-((4-methoxyphenyl)imino)-2-phenyl-4,5-dihydrofuran-3-yl)acrylate (2y)**

Yellow solid, mp 105–108 °C; $^1$H NMR (300 MHz, *d*-DMSO) $\delta$ 7.84–7.63 (m, 5H), 7.48 (d, $J$ = 15.5 Hz, 1H), 7.15 (d, $J$ = 15.5 Hz, 1H), 7.06–6.95 (m, 4H), 4.17 (q, $J$ = 7.0 Hz, 2H), 3.78 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H); $^{19}$F NMR (282 MHz, *d*-DMSO) $\delta$ –72.58; $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 169.3, 166.6, 157.8, 154.9 (t, $J$ = 21.3 Hz), 140.5, 133.7, 131.3, 130.0, 129.2, 126.8, 122.8, 121.8, 118.1 (t, $J$ = 272.9 Hz), 114.6, 109.9, 60.7, 55.8, 14.6; LRMS-EI *m*/*z* (relative intensity) 399(6) [M$^+$], 326 (39), 301 (100), 286 (72); HRMS-EI (*m*/*z*) calcd for $C_{22}H_{19}F_2NO_4$ 399.1282; found 399.1285; IR (KBr): 2922, 1715, 1633, 1604, 1504, 1290, 1261, 1251, 1178, 1107, 1063, 1028, 839 cm$^{-1}$.

**Procedure for the synthesis of 2z**

**1z** (0.5 mmol) and DBU (2.0 eq.) was added to 2.0 mL THF, the mixture was then stirred at 60 °C. After completion of reaction as indicated by TLC, the reaction crude was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to provide the desired product **2z**

**(4-Benzyl-2-(bromodifluoromethyl)quinolin-3-yl)(phenyl)methanone (2z)**

Yellow solid, mp 115–118 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.28 (d, $J$ = 8.5 Hz, 1H), 8.01 (d, $J$ = 8.5 Hz, 1H), 7.82 (t, $J$ = 7.8 Hz, 1H), 7.75 (d, $J$ = 7.0 Hz, 2H), 7.61 (t, $J$ = 7.8 Hz, 1H), 7.55 (t, $J$ = 7.5 Hz, 1H), 7.38 (t, $J$ = 7.8 Hz, 2H), 7.20–7.06 (m, 3H), 7.01 (d, $J$ = 7.0 Hz, 2H), 4.30 (AB, $J$ = 16.1 Hz, 2H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ –46.98 (AB, $J$ = 160.8 Hz, 2H); $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 194.8, 149.5 (t, $J$ = 24.9 Hz), 146.9, 145.8, 137.8, 137.1, 134.1, 131.0, 131.0, 129.6, 129.4, 129.0, 128.7, 128.7, 128.3, 127.7, 126.7, 124.9, 116.9 (t, $J$ = 307.4 Hz), 35.6; LRMS-EI *m*/*z* (relative intensity) 451 (3) [M$^+$], 279 (28), 193 (88), 55 (100); HRMS-EI (*m*/*z*) calcd for $C_{24}H_{16}BrF_2NO$ 451.0383; found 451.0387; IR (KBr): 3059, 2921, 2850, 1672, 1596, 1563, 1494, 1450, 1409, 1254, 1144, 1127, 1070, 960, 918, 761 cm$^{-1}$.

**Procedure for the synthesis of 3a**

A schlenk tube was charged with **2a** (0.3 mmol), and Mg (8.0 eq.), evacuated and back-filled with nitrogen. DMF (2 ml) and TMSCl (4 eq.) was successively added at 0 °C. Then the reaction mixture was stirred at 0 °C for 0.5 h. The mixture was partitioned between ethyl acetate and water, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to provide **3a** as a yellow oil.

***N*-(2-Fluoro-5-phenylfuran-3(2*H*)-ylidene)-4-methoxyaniline (3a)**

Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.75 (dd, $J$ = 8.0, 1.6 Hz, 2H), 7.53–7.39 (m, 3H), 7.04 (d, $J$ = 8.7 Hz, 2H), 6.93 (d, $J$ = 8.7 Hz, 2H), 6.36 (d, $J$ = 61.7 Hz, 1H), 6.27 (s, 1H), 3.83 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ –122.92 (d, $J$ = 61.9 Hz, 1F); $^{13}$C NMR (100 MHz, *d*-DMSO) $\delta$ 173.7 (d, $J$ = 5.1 Hz), 165.5 (d, $J$ = 10.3 Hz), 157.5, 143.5 (d, $J$ = 4.4 Hz), 132.7, 129.5, 128.3, 127.2, 123.3 (d, $J$ = 2.9 Hz), 114.9, 107.9 (d, $J$ = 230.3 Hz), 94.5, 55.8; LRMS-EI *m*/*z* (relative intensity) 283 (29) [M$^+$], 178 (34), 102 (100); HRMS-EI (*m*/*z*) calcd for $C_{17}H_{14}FNO_2$ 283.1009; found 283.1010; IR (KBr): 2925, 1648, 1608, 1593, 1571, 1503, 1491, 1449, 1285, 1245, 1031, 1008 cm$^{-1}$.

**Procedure for the reduction of 2a**

$NaBH_4$ (2 mmol) was slowly added to a solution of the corresponding **2a** (0.3 mmol) and TFA (0.1 mL) in THF (2 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h, and was then quenched with an aqueous saturated solution of $NaHCO_3$ (5 mL), extracted with ethyl acetate (3 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide **4a** as a yellow solid.

**2,2-Difluoro-*N*-(4-methoxyphenyl)-5-phenyl-2,3-dihydrofuran-3-amine (4a)**

Yellow solid, mp 90–91 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ.7.66–7.58 (m, 2H), 7.47–7.37 (m, 3H), 6.84 (d, $J$ = 9.1 Hz, 2H), 6.72 (d, $J$ = 8.9 Hz, 2H),5.62 (t, $J$ = 2.0 Hz, 1H), 4.94 (ddd, $J$ = 12.4, 6.0, 2.6 Hz, 1H), 3.78 (s, 3H), 3.12 (br, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ –68.20 (dd, $J$ = 148.6, 12.4 Hz, 1F), –82.55 (dd, $J$ = 148.6, 5.9 Hz, 1F); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.4 (d, $J$ = 3.0 Hz), 153.3, 140.0, 130.3, 130.2 (t, $J$ = 269.2 Hz), 128.7, 128.1, 125.5, 115.1, 115.1, 97.8 (d, $J$ = 3.0 Hz), 62.1 (dd, $J$ = 37.0, 22.3 Hz), 55.8; LRMS-EI *m*/*z* (relative intensity) 303 (31) [M$^+$], 181 (100), 133 (39), 122 (51); HRMS-EI (*m*/*z*) calcd for $C_{12}H_{11}F_2NO_2$ 303.1071; found 303.1060; IR (KBr): 3391, 2997, 2936, 1655, 1512, 1493, 1449, 1260, 1243, 1114, 1090, 1021, 744 cm$^{-1}$.

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## Notes and references

1 N. S. Zefirov and D. I. Makhon'kov, *Chem. Rev.*, 1982, **82**, 615–624.
2 (*a*) W. R. Bowman, *Chem. Soc. Rev.*, 1988, **17**, 283–316 and references cited therein; (*b*) B. R. Fishwick, D. K. Rowles and C. J. M. Stifling, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1171–1179.

 

3 (*a*) X. Y. Li, X. K. Jiang and X. J. Zhang, *Chin. J. Chem.*, 1992, **10**, 186–188; (*b*) X. Y. Li, H. Q. Pan and X. K. Jiang, *Tetrahedron Lett.*, 1984, **25**, 4937–4940; (*c*) X. Y. Li, H. Q. Pan, X. K. Jiang and Z. Y. Zhan, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 871–872; (*d*) X. Y. Li, H. Q. Pan and X. K. Jiang, *Tetrahedron Lett.*, 1987, **28**, 3699–3702; (*e*) I. Rico, D. Cantacuzene and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1063–1065; (*f*) A. Jonczyk and P. Balcerzak, *Tetrahedron Lett.*, 1989, **30**, 4697–4700; (*g*) Y. Migron, J. Blum and J. Bartana, *Tetrahedron*, 1987, **43**, 361–364; (*h*) K. I. Petko, T. M. Sokolenko, A. V. Bezdudny and L. M. Yagupolskii, *J. Fluorine Chem.*, 2005, **126**, 1342–1346; (*i*) K. I. Petko, S. Y. Kot and L. M. Yagupolskii, *J. Fluorine Chem.*, 2008, **129**, 1119–1123.

4 G. R. Underwood and P. E. Dietze, *J. Org. Chem.*, 1984, **49**, 5225–5229.

5 L. Eberson, M. Finkelstein, B. Folkesson, G. A. Hutchins, L. Jonsson, R. Larsson, W. M. Moore and S. D. Ross, *J. Org. Chem.*, 1986, **51**, 4400–4403.

6 (*a*) M. Galvagni, F. Kelleher, C. Paradisi and G. Scorrano, *J. Org. Chem.*, 1990, **55**, 4454–4456; (*b*) J. S. Grossert, P. K. Dubey and T. Elwood, *Can. J. Chem.*, 1985, **63**, 1263–1267.

7 J. Tatar, M. Baranac-Stojanovic, M. Stojanovic and R. Markovic, *Tetrahedron Lett.*, 2009, **50**, 700–703.

8 X. Y. Li, X. K. Jiang, H. Q. Pan, J. S. Hu and W. M. Fu, *Pure Appl. Chem.*, 1987, **59**, 1015–1020.

9 C. S. Burgey, K. A. Robinson, T. A. Lyle, P. E. J. Sanderson, S. D. Lewis, B. J. Lucas, J. A. Krueger, R. Singh, C. Miller-Stein, R. B. White, B. Wong, E. A. Lyle, P. D. Williams, C. A. Coburn, B. D. Dorsey, J. C. Barrow, M. T. Stranieri, M. A. Holahan, G. R. Sitko, J. J. Cook, D. R. McMasters, C. M. McDonough, W. M. Sanders, A. A. Wallace, F. C. Clayton, D. Bohn, Y. M. Leonard, T. J. Detwiler, J. J. Lynch, Y. Yan, Z. Chen, L. Kuo, S. J. Gardell, J. A. Shafer and J. P. Vacca, *J. Med. Chem.*, 2003, **46**, 461–473.

10 B. E. Smart, In *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum, New York, 1994; p 57–88.

11 R. J. Cox, A. T. Hadfield and M. B. Mayo-Martin, *Chem. Commun.*, 2001, 1710–1711 and references cited therein.

12 G. M. Dubowchik, V. M. Vrudhula, B. Dasgupta, J. Ditta, T. Chen, S. Sheriff, K. Sipman, M. Witmer, J. Tredup, D. M. Vyas, T. A. Verdoorn, S. Bollini and A. Vinitsky, *Org. Lett.*, 2001, **3**, 3987–3990.

13 (*a*) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu and Y. Gong, *Org. Lett.*, 2010, **12**, 4376–4379; (*b*) Z. X. Chen, J. T. Zhu, H. B. Xie, S. Li, Y. M. Wu and Y. F. Gong, *Adv. Synth. Catal.*, 2010, **352**, 1296–1300; (*c*) Z. X. Chen, J. T. Zhu, H. B. Xie, S. Li, Y. M. Wu and Y. F. Gong, *Chem. Commun.*, 2010, **46**, 2145–2147; (*d*) Z. X. Chen, J. T. Zhu, H. B. Xie, S. A. Li, Y. M. Wu and Y. F. Gong, *Synlett*, 2010, 1418–1420; (*e*) S. Li, Y. Yuan, J. Zhu, H. Xie, Z. Chen and Y. Wu, *Adv. Synth. Catal.*, 2010, **352**, 1582–1586; (*f*) J. T. Zhu, Z. X. Chen, H. B. Xie, S. Li and Y. M. Wu, *Org. Lett.*, 2010, **12**, 2434–2436; (*g*) J. T. Zhu, H. B. Xie, Z. X. Chen, S. Li and Y. M. Wu, *Chem. Commun.*, 2009, 2338–2340; (*h*) J. T. Zhu, H. B. Xie, Z. X. Chen, S. Li and Y. M. Wu, *Synlett*, 2009, 3299–3302.

14 Y. M. Wu, Y. Li and J. Deng, *Tetrahedron Lett.*, 2005, **46**, 5357–5360.

15 Y. Shang, K. Ju, X. He, J. Hu, S. Yu, M. Zhang, K. Liao, L. Wang and P. Zhang, *J. Org. Chem.*, 2010, **75**, 5743–5745.

16 (*a*) K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem.*, 1993, **58**, 32–35; (*b*) Y. M. Wu, Y. Li and J. Deng, *J. Fluorine Chem.*, 2005, **126**, 791–795.

17 CCDC 806367 contains the supplementary crystallographic data for **2v**.† These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/products/csd/request/.

18 J. Ichikawa, Y. Wada, M. Fujiwara and K. Sakoda, *Synthesis*, 2002, 1917–1936.

19 R. A. Rossi, A. B. Pierini and A. B. Peñéñory, *Chem. Rev.*, 2002, **103**, 71–168.

20 (*a*) J. J. Neumann, M. Suri and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 7790–7794; (*b*) R. Bernini, S. Cacchi, G. Fabrizi, E. Filisti and A. Sferrazza, *Synlett*, 2009, 1245–1250; (*c*) R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, *Angew. Chem., Int. Ed.*, 2009, **48**, 8078–8081; (*d*) S. Würtz, S. Rakshit, J. Neumann, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230–7233.

21 T. Kobayashi, T. Nakagawa, H. Amii and K. Uneyama, *Org. Lett.*, 2003, **5**, 4297–4300.

22 F. Palacios, J. Vicario and D. Aparicio, *J. Org. Chem.*, 2006, **71**, 7690–7696.