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Synthesis of tri(di)fluoroethylanilines *via* copper-catalyzed coupling reaction of tri(di) fluoroethylamine with (hetero)aromatic bromides†

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We have realized the first Ullmann type coupling reaction of tri(di)fluoroethylamine with (hetero)aromatic bromides, employing 5–20 mol% Cu_2O and an oxalamide ligand [*N*-(2,4,6-trimethoxyphenyl)acetamide]. This efficient and practical method has the following features: (i) avoids the use of an expensive catalyst; (ii) does not require anhydrous solvent and strict air extrusion; (iii) uses bench stable and inexpensive (hetero)aromatic bromides; (iv) is suitable for the synthesis of fluoroalkylated hetero-aromatic substrates; (v) is suitable for gram-scale synthesis. This work also shows the "negative fluorine effect" for the alkylamines in the copper catalysed coupling reactions.

Introduction

The introduction of fluoroalkyl groups can usually impart the parent molecules with better pharmacokinetic and pharmacodynamic properties.[1,2] In particular, the incorporation of a 2,2,2-trifluoroethyl group onto the nitrogen atom of anilines can significantly increase their metabolic stability as the P450-mediated oxidation could be inhibited by a fluoroalkyl group.[3] Selected pharmaceutically important *N*-trifluoroethylanilines, such as T0901317,[4] quazepam[5] and 6-*N*,*N*-bis(2,2,2-trifluoroethyl)amino-trifluoromethylquinolin-2(1*H*)-ones,[6] are shown in Fig. 1. As a result, it is highly desirable to develop novel methods for the easy access of trifluoroethylated anilines.

Traditionally, trifluoroethylated anilines can be synthesized from a trifluoroethyl chloride or hypervalent-iodine reagent by nucleophilic substitution,[7] from trifluoroethylamine by S_NAr reactions[8] and from trifluoroacetaldehyde by reductive aminations.[9] Recently, the transition-metal catalysed coupling reaction has gained success in the synthesis of trifluoroethylated anilines. For example, in 2015, Hartwig *et al.* reported a general, palladium-catalysed synthesis of trifluoromethylated anilines from aryl bromides and aryl chlorides (1a).[10] In the same year, Wang *et al.* reported a silver-catalysed insertion reaction for the same purpose (1b).[11] However, these two methods all require the use of expensive and moisture-sensitive catalysts. Other catalytic methods were reported, but the generality needs to be tested.[12,13] In 2018, we achieved a successful Chan–Lam type coupling for the synthesis of fluoroalkylated anilines, utilizing an inexpensive copper catalyst/promoter.[14a] However, the reaction is not suitable for medicinally relevant, hetero-aromatic substrates; moreover, some boronic acids used are expensive and not stable.

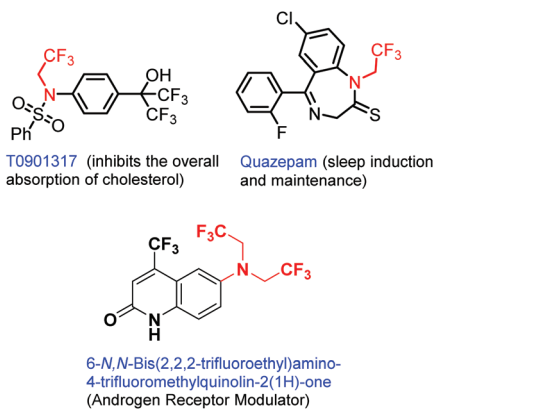

Fig. 1 Selected examples of drugs and drug candidates bearing $ArNHCH_2CF_3$.

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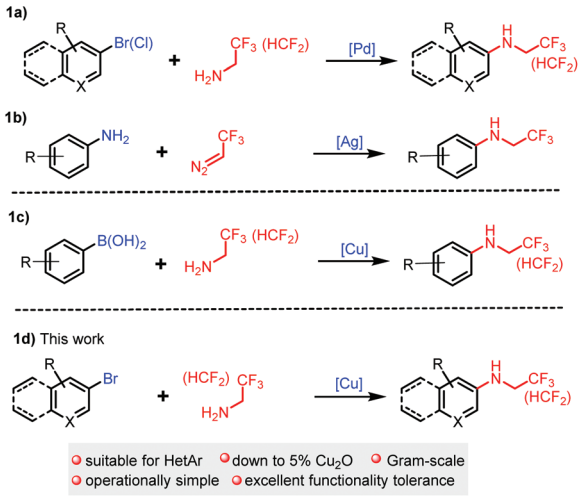


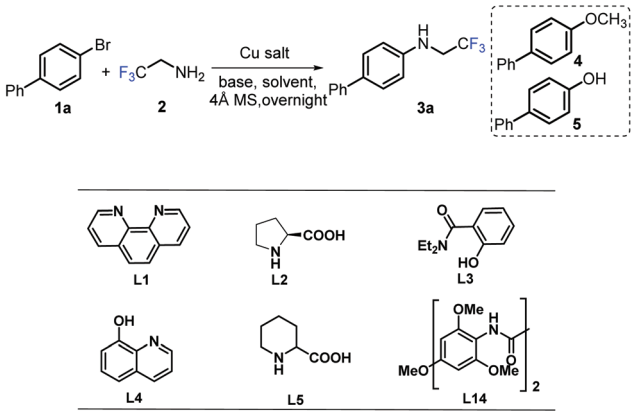
Inspired by the recent success[15–18] of the bidentate ligand enabled copper catalysed Ullmann reaction, we envisioned that the aforementioned shortcomings of the transition-metal catalysed synthesis of trifluoroethylanilines could be addressed if a Ullmann type coupling between aryl bromides and trifluoroethylamine could be developed. Challenges, however, exist: (1) compared to other alkylamines, trifluoroethylamine shows lower reactivity in the copper-catalysed coupling reaction, presumably due to strong negativity of fluorine.[14a,19] (2) Fluoroalkylanilines are not stable under forcing conditions (*e.g.*, strong bases).[10]

In continuation of our interest in using fluoroalkylamines for the synthesis of highly valued compounds,[14] we report the realization of the aforementioned goal by developing a practical and efficient synthesis of trifluoroethylanilines from inexpensive, bench-stable aryl bromides and trifluoroethylamine, which employs 5–20% copper catalyst and does not need anhydrous solvent and air extrusion. This reaction can be applied to the heteroaromatic substrates and is also suitable for difluoroethylamine. To our knowledge, this method represents the first example of the Ullmann-type coupling reaction employing fluoroalkylamines.

Results and discussion

Initially, we selected 4-bromobiphenyl **1a** and 2,2,2-trifluoroethylamine **2** as the model substrates to explore the optimal reaction conditions. We first tested various reported conditions employing ligands such as 1,10-phenanthroline **L1**,[21] L-proline **L2**,[22] *N*,*N*-diethylsalicylamide **L3**,[23] quinolin-8-ol **L4**,[24] and pipecolinic acid **L5**,[25] however, none of them yielded the desired products (Table 1, entries 1–5 and Table S1†). We next turned our attention to the oxalamide ligands developed by Ma *et al.*[18] To our delight, the conditions utilizing *N*-(2,4,6-trimethoxyphenyl)acetamide **L14** in DMSO at 120 °C could give the product, albeit in 10% yield (Table 1, entry 6).[26–28] Next, solvents such as DMF, THF, MeCN, MeOH, and EtOH were screened, and the results showed that MeOH was the best solvent for this procedure (Table 1, entries 7–11 and Table S2†). An extensive screening of the oxalamide ligands demonstrated that **L14** is the most suitable one (Table 1, entries 12 and 13 and Table S3†). Then, different inorganic bases were tested (Table 1, entries 14–17 and Table S4†), and a 75% yield of the target product was obtained with K_2CO_3 as the base (Table 1, entry 14). With these encouraging results in hand, a number of copper salts[29,30] were also screened (Table 1, entries 18–21 and Table S5†). It is noted that the

Table 1 Reaction optimization



Entry	Cu salt/ligand	Solvent	Base	Yield[a] (%)
1[b,c]	CuI/**L1**	Toluene	^{t}BuOK	0
2[c,d]	CuI/**L2**	DMSO	K_2CO_3	0
3[c,e]	CuI/**L3**	DMF	K_3PO_4	0
4[c,f]	CuI/**L4**	^{t}BuOH	Cs_2CO_3	0
5[c,g]	CuI/**L5**	DMF	K_2CO_3	0
6	CuI/**L14**	DMSO	K_3PO_4	10
7	CuI/**L14**	DMF	K_3PO_4	Trace
8	CuI/**L14**	THF	K_3PO_4	0
9	CuI/**L14**	MeCN	K_3PO_4	0
10	CuI/**L14**	MeOH	K_3PO_4	57
11	CuI/**L14**	EtOH	K_3PO_4	8
12	CuI/**L6**	MeOH	K_3PO_4	28
13	CuI/**L15**	MeOH	K_3PO_4	27
14	CuI/**L14**	MeOH	K_2CO_3	75
15	CuI/**L14**	MeOH	Cs_2CO_3	70
16	CuI/**L14**	MeOH	Na_2CO_3	48
17	CuI/**L14**	MeOH	NaOAc	0
18	CuCl/**L14**	MeOH	K_2CO_3	78
19	Cu_2O/**L14**	MeOH	K_2CO_3	90
20	$CuCl_2$/**L14**	MeOH	K_2CO_3	53
21	$Cu(OAc)_2$/**L14**	MeOH	K_2CO_3	42
22[h]	Cu_2O/**L14**	MeOH	K_2CO_3	0
23[i]	Cu_2O/**L14**	MeOH	K_2CO_3	3
24[c]	Cu_2O/**L14**	MeOH	K_2CO_3	93
25[j]	Cu_2O/**L14**	MeOH	K_2CO_3	91
26[k]	Cu_2O/**L14**	MeOH	K_2CO_3	95
27[c,l]	**Cu_2O/L14**	**MeOH**	**K_2CO_3**	**92**

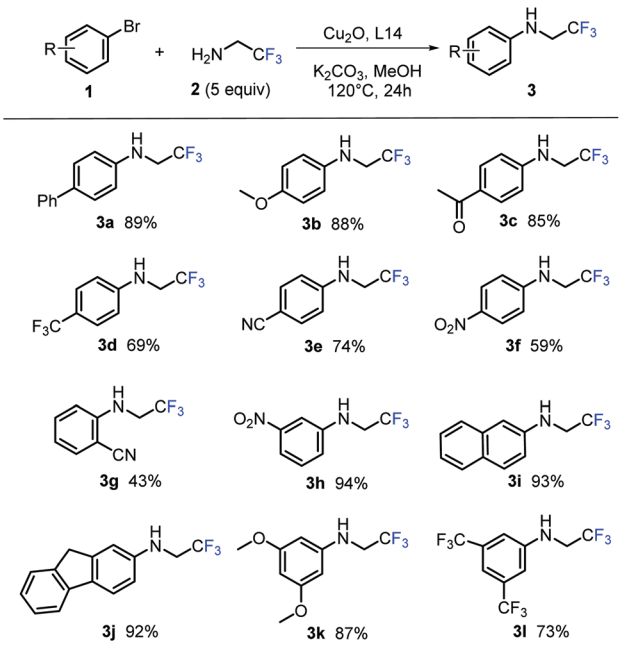
Reaction conditions: **1a** (0.25 mmol, 1 equiv.), **2** (1.25 mmol, 5 equiv.), Cu salts (0.05 mmol, 20 mol%), **L** (0.05 mmol, 20 mol%), base (0.38 mmol, 1.5 equiv.), 4 Å MS, solvents (1.0 mL), 120 °C, 24 h. [a] Yields were determined by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard. [b] 115 °C, 3.5 h. [c] No 4 Å MS. [d] rt, 17 h. [e] 90 °C, 22 h. [f] 100 °C, 16 h. [g] 110 °C, 24 h. [h] 80 °C. [i] 100 °C. [j] 2 equiv. H_2O. [k] Analytical grade MeOH. [l] Cu_2O (0.025 mmol, 10 mol%), **L** (0.025 mmol, 10 mol%).

target product was obtained in 90% yield with Cu_2O as the catalyst (Table 1, entry 19). Comparison experiments showed that the yield is slightly higher in the absence of activated 4 Å molecular sieves (93%) compared to that in the presence of this water scavenger (90%) (Table 1, entry 24). Furthermore, the addition of two equivalents of water did not affect the reaction efficacy (91%) (Table 1, entry 25). These experiments indicated that the reaction is not sensitive to moisture. For the reason of simplicity, we used commercially available MeOH as the solvent and the yield was 95% (Table 1, entry 26). Furthermore, we could obtain the desired product in 92% yield when using 10 mol% copper salt and ligand (Table 1, entry 27). Under these optimized conditions, possible side products **4** and **5** could not be observed (Table 1, entry 27).

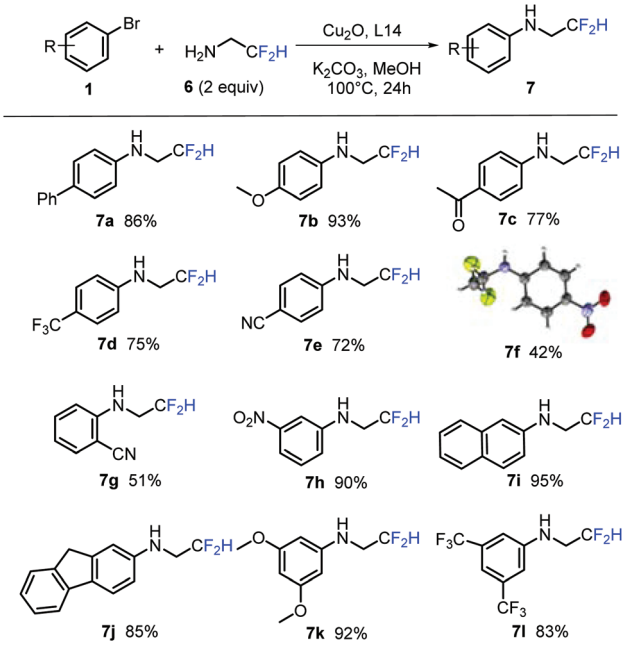
Having established the optimal conditions, we commenced to investigate the generality with various aryl bromides (Scheme 1). To our delight, aryl bromides bearing either electron-donating groups (**1a–1b**, **1k**) or electron-withdrawing groups (**1c–1h**, **1l**) were both compatible with standard conditions, furnishing the desired products in good yields. The only exception is **1f** carrying a *para*-nitro group, which only yielded **3f** in 59% yield. Notably, substrates bearing a pharmaceutically relevant trifluoromethyl group (**1d**, **1l**) underwent the transformation smoothly. The sensitive carbonyl group is tolerated and **3c** was obtained in 85% yield. The influence of the substituent pattern [*para*-(**1a–1f**), *ortho*-(**1g**), *meta*-(**1h**)] on the phenyl ring was evaluated, which indicates that the *ortho*-substituent (**1g**) has a negative effect on this reaction.[28] The substrates like naphthalene and fluorene also worked satisfactorily to give **3i** and **3j** in 93% and 92% yields, respectively. Furthermore, 3,5-disubstituted aryl bromides (**3k, 3l**) are viable substrates as well, and good yields of the corresponding products can be isolated.

Considering the pharmaceutical importance of the CF_2H moiety (the slightly acidic C–H bond of CF_2H can be utilized as a lipophilic hydrogen-bond donor and a bioisostere for hydroxyl and thiol groups),[31,32] we became interested in investigating if a similar strategy could be applied to synthesize difluoroethylanilines. To test this hypothesis, the reaction of difluoroethylamine **6** with 4-bromobiphenyl **1a** was investigated briefly (Table S7†). Gratifyingly, as observed in our previous work,[14a] difluoroethylamine showed better reactivity than trifluoroethylamine, and the transformation could proceed successfully at lower temperature (100 °C) and less equivalents (2 equiv.) compared with trifluoroethylamine, giving the desired product **7a** in 86% yields. Generally, the reaction exhibited a similar reactivity trend to that observed for trifluoroethylamine. For example, substrates with electron-rich groups gave high yields compared to those with an electron-withdrawing group at the *para*-position; *ortho*-substitution is not good for the desired coupling. The structure of **7f** was confirmed by X-ray crystallographic analysis (Scheme 2).[33]

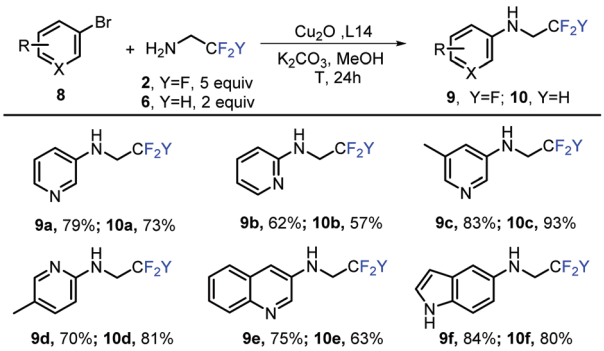
One significant limitation of our previous method[14a] is that it is not suitable for the synthesis of pharmaceutically important fluoroalkylated heteroaromatic compounds. Bearing this in mind, we started to study the possibility of utilizing heterocyclic bromides for this coupling reaction (Scheme 3). As shown in Scheme 3, the reactions occurred smoothly and pro-



Scheme 1 Reaction of **2** with different aryl bromides. Reaction conditions: Aryl bromides (0.5 mmol, 1 equiv.), **2** (2.5 mmol, 5 equiv.), Cu_2O (0.05 mmol, 10 mol%), **L14** (0.05 mmol, 10 mol%), MeOH (2.0 mL), 120 °C, K_2CO_3 (0.75 mmol, 1.5 equiv.), 24 h.



Scheme 2 Reaction of **6** with different aryl bromides. Reaction conditions: Aryl bromides (0.5 mmol, 1 equiv.), **6** (1.0 mmol, 2 equiv.), Cu_2O (0.05 mmol, 10 mol%), **L14** (0.05 mmol, 10 mol%), MeOH (2.0 mL), 100 °C, K_2CO_3 (0.75 mmol, 1.5 equiv.), 24 h.



Scheme 3 Reaction of **2** and **6** with heterocyclic aryl bromides. Reaction conditions: Aryl bromides (0.25 mmol, 1 equiv.), **2** (1.25 mmol, 5 equiv.), **6** (0.5 mmol, 2 equiv.), Cu_2O (0.05 mmol, 20 mol%), L14 (0.05 mmol, 20 mol%), MeOH (1.0 mL), 120 °C or 100 °C, K_2CO_3 (0.38 mmol, 1.5 equiv.), 24 h.

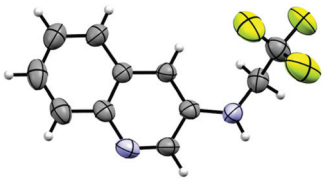
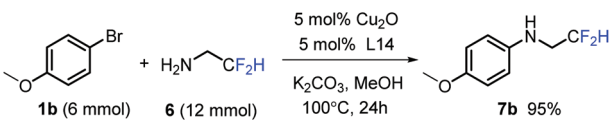


Fig. 2 X-Ray crystal structures of **9e**.

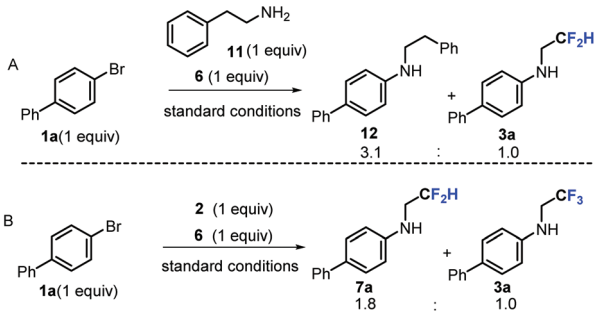
ducts **9a–9f** and **10a–10f** were obtained in good to high yields, although 20 mol% of catalyst and ligand were required. Among heterocyclic substrates tested, the "privileged" indole gave the highest yields (**9f–10f**). More attractively, no protection of N–H was needed. The structure of **9e** was confirmed by X-ray crystallographic analysis (Fig. 2).[33]

To demonstrate the synthetic utility of this transformation, we next performed a scale-up reaction of **7b**. As shown in Scheme 4, a gram scale reaction of 1-bromo-4-methoxybenzene **1a** with difluoroethylamine **6** proceeded to give **7b** in 95% yield. Importantly, the copper catalyst and the oxalamide ligand could be lowered to 5 mol%.

Our previous work[14a] shows that the increase in fluorine atom in the alkylamine decreases the reactivity in the Chan–Lam type coupling reaction. We also noticed in this work that difluoroethylamine was more reactive than trifluoroethylamine. On the basis of these results, we became interested in evaluating the reactivity of tri(di)fluoroethylamine relative to other alkylamines. To this end, we selected 2-phenylethan-1-amine **11** for a competitive reaction. As shown in Scheme 5,



Scheme 4 Gram-scale synthesis of **7b** with 5 mol% of catalyst and ligand.



Scheme 5 Comparison of the reactivity of different amines. Reaction conditions: **1a** (0.5 mmol, 1 equiv.), **2** (0.5 mmol, 1 equiv.), **6** (0.5 mmol, 1 equiv.), Cu_2O (0.05 mmol, 10 mol%), **L14** (0.05 mmol, 10 mol%), MeOH (2.0 mL), 120 °C, K_2CO_3 (0.75 mmol, 1.5 equiv.), 24 h; the ratio of different products is determined by the ^1H NMR.

this series of competitive reactions indicates that amines exhibit the following reactivity: **11** > **6** > **2**. Overall, this work further demonstrates the "negative fluorine effect"[14a,20] on the reactivity of alkylamines in the copper-catalyzed cross coupling reaction.

Conclusions

In conclusion, we have realized the first Ullmann type coupling reaction of tri(di)fluoroethylamine with (hetero)aromatic bromides, employing 5–20 mol% Cu_2O and *N*-(2,4,6-trimethoxyphenyl)acetamide (an oxalamide ligand). This efficient and practical method has the following features: (i) avoids the use of an expensive catalyst; (ii) does not require anhydrous solvent and strict air extrusion; (iii) uses bench stable and inexpensive (hetero)aromatic bromides; (iv) is suitable for the synthesis of fluoroalkylated hetero-aromatic substrates and gram-scale synthesis. This work also shows the "negative fluorine effect" for the alkylamines in the copper catalysed coupling reactions. In addition to the synthetic utility for the synthesis of pharmaceutically important fluorinated building blocks, this reaction also showcases the powerfulness of bidentate ligands, particularly the oxalamide ligands developed by Ma *et al.* enabled the Ullmann reaction in the synthesis of high-value compounds.

Experimental

General information

All reagents were used as received from commercial sources without further purification. All solvents were dried over 4 Å molecular sieves before use unless otherwise stated. The reaction mixtures were stirred using Teflon-coated magnetic stirring bars. Analytical TLC was performed with 0.20 mm silica gel 60F plates with a 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O} or a

solution of 0.5% ninhydrin in *n*-butanol. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230–400 mesh). Melting points were determined using a WRX-4 visual melting point apparatus. NMR spectra were recorded in $CDCl_3$ (with TMS as the internal standard) or D_2O or MeOD on a Bruker AV400 (^1H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The HRMS were recorded using an ESI model (specified in the section of characterization data). All the reactions were conducted in high pressure bottles with PTFE thread (resist 6 atm pressure) under the protection of a safety shield. In all the experiments, the solvent should never exceed the half volume of the high pressure bottle.

The general procedure for the reaction of 2(6) with different aryl bromides

A 10 mL high pressure bottle equipped with a magnetic stir bar was charged with aryl bromides (0.5 mmol, 1 equiv.), Cu_2O (7.1 mg, 0.05 mmol, 10 mol%), **L14** (21.0 mg, 0.05 mmol, 10 mol%), K_2CO_3 (103.6 mg, 0.75 mmol, 1.50 equiv.), **2** (200 μL, 2.5 mmol, 5 equiv.) [**6**, (70 μL, 1.0 mmol, 2 equiv.)] and MeOH (2.0 mL). The reaction mixture was heated at 120 °C (**6**, 100 °C) for 24 h under vigorous stirring. After the removal of the solvent under vacuum, the residue was purified by column chromatography.

N-(2,2,2-Trifluoroethyl)-[1,1′-biphenyl]-4-amine (3a)[11]

Purified by flash column chromatography (petroleum ether/AcOEt = 100 : 1), white solid (111.8 mg, 89% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.56 (m, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.40–7.30 (m, 1H), 6.92–6.67 (m, 2H), 3.85 (s, 1H), 3.82 (q, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 140.9, 132.1, 128.8, 128.2, 126.56, 126.53, 125.2 (q, J = 280.2 Hz), 113.5, 46.0 (q, J = 33.8 Hz).

4-Methoxy-*N*-(2,2,2-trifluoroethyl)aniline (3b)[11]

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), pale yellow liquid (90.3 mg, 88% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.71 (q, J = 9.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 140.4, 125.3 (q, J = 279.9 Hz), 115.0, 114.8, 55.7, 47.1 (q, J = 33.0 Hz).

1-(4-((2,2,2-Trifluoroethyl)amino)phenyl)ethan-1-one (3c)[10]

Purified by flash column chromatography (petroleum ether/AcOEt = 10 : 1), white solid (93.1 mg, 85% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 4.76 (s, 1H), 3.94–3.68 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 150.5, 130.9, 128.5, 124.8 (q, J = 280.2 Hz), 112.1, 45.3 (q, J = 34.1 Hz), 26.3.

N-(2,2,2-Trifluoroethyl)-4-(trifluoromethyl)aniline (3d)[11]

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), colorless and transparent liquid (84 mg, 69% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 4.21 (s, 1H), 3.81 (q, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 126.9 (q, J = 3.8 Hz), 124.9 (q, J = 280.4 Hz), 124.8 (q, J = 270.0 Hz), 121.0 (q, J = 32.7 Hz), 112.5, 45.5 (q, J = 34.0 Hz).

4-((2,2,2-Trifluoroethyl)amino)benzonitrile (3e)[10]

Purified by flash column chromatography (petroleum ether/AcOEt = 10 : 1), white solid (74 mg, 74% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 4.64 (s, 1H), 3.82 (dq, J = 8.0, 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 133.9, 124.7 (q, J = 280.3 Hz), 120.0, 112.9, 101.0, 45.1 (q, J = 34.3 Hz).

4-Nitro-*N*-(2,2,2-trifluoroethyl)aniline (3f)

Purified by flash column chromatography (petroleum ether/AcOEt = 5 : 1), yellow solid (64.9 mg, 59% yield), m.p. 113–114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 9.2 Hz, 2H), 6.69 (d, J = 9.2 Hz, 2H), 4.84 (s, 1H), 4.04–3.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 139.8, 126.4, 124.5 (q, J = 280.3 Hz), 112.0, 45.2 (q, J = 34.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.05 (t, J = 8.7 Hz); ^{19}F {^1H} NMR (376 MHz, $CDCl_3$) δ −72.05(s); HRMS (ESI): calcd for $C_8H_8F_3N_2O_2^+$ $[M + H]^+$ 221.0532, found 221.0524.

2-((2,2,2-Trifluoroethyl)amino)benzonitrile (3g)[10]

Purified by flash column chromatography (petroleum ether/AcOEt = 10 : 1), white solid (42.8 mg, 43% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (ddd, J = 7.4, 4.4, 2.6 Hz, 2H), 6.87–6.75 (m, 2H), 4.94 (s, 1H), 3.88 (qd, J = 8.7, 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 134.5, 133.0, 124.6 (q, J = 280.3 Hz), 118.7, 117.4, 111.0 (q, J = 1.6 Hz), 97.3, 45.2 (q, J = 34.6 Hz).

3-Nitro-*N*-(2,2,2-trifluoroethyl)aniline (3h)[11]

Purified by flash column chromatography (petroleum ether/dichloromethane = 5 : 1), yellow solid (103.6 mg, 94% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 8.1, 2.1 Hz, 1H), 7.51 (t, J = 2.3 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 6.98 (dd, J = 8.2, 2.5 Hz, 1H), 4.36 (s, 1H), 3.85 (q, J = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 147.2, 130.2, 124.8 (q, J = 280.1 Hz), 119.1, 113.9, 107.1, 45.7 (q, J = 34.2 Hz).

N-(2,2,2-Trifluoroethyl)naphthalen-2-amine (3i)

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), white solid (105.4 mg, 93% yield), m.p. 96–97 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.62 (m, 3H), 7.45 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.31 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 6.99–6.87 (m, 2H), 4.00 (s, 1H), 3.87 (q, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 134.9, 129.4, 128.3, 127.8, 126.7, 126.3, 125.2 (q, J = 280.4 Hz), 123.0, 117.5, 105.7, 46.1 (q, J = 33.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.97 (t,

J = 8.9 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.97(s); HRMS (ESI): calcd for $C_{12}H_{11}F_3N^+$ $[M + H]^+$ 226.0838, found 226.0832.

N-(2,2,2-Trifluoroethyl)-9*H*-fluoren-2-amine (3j)

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), white solid (131.6 mg, 92% yield), m.p. 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 19.3, 7.9 Hz, 2H), 7.49 (d, J = 7.4 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.23 (td, J = 7.4, 1.2 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.71 (dd, J = 8.3, 2.2 Hz, 1H), 3.99 (s, 1H), 3.89–3.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 145.4, 142.4, 142.0, 133.7, 126.8, 125.4, 125.2 (q, J = 280.1 Hz), 124.9, 120.8, 118.9, 112.5, 109.9, 46.5 (q, J = 33.4 Hz), 37.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.19 (t, J = 8.8 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −72.19(s); HRMS (ESI): calcd for $C_{15}H_{13}F_3N^+$ $[M + H]^+$ 264.0995, found 264.0988.

3,5-Dimethoxy-*N*-(2,2,2-trifluoroethyl)aniline (3k)

Purified by flash column chromatography (petroleum ether/AcOEt = 20 : 1), colorless liquid (102.3 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.86 (d, J = 2.0 Hz, 2H), 3.76 (s, 6H), 3.75–3.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 148.4, 125.0 (q, J = 279.9 Hz), 92.2, 91.2, 55.3, 46.1 (q, J = 33.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.28 (t, J = 8.9 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −72.28(s); HRMS (ESI): calcd for $C_{10}H_{13}F_3NO_2^+$ $[M + H]^+$ 236.0893, found 236.0888.

N-(2,2,2-Trifluoroethyl)-3,5-bis(trifluoromethyl)aniline (3l)

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), pale yellow liquid (113.4 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.06 (s, 2H), 4.40 (s, 1H), 3.85 (q, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 131.9 (q, J = 33.0 Hz), 123.7 (q, J = 280.5 Hz), 122.5 (q, J = 272.7 Hz), 111.6 (d, J = 4.1 Hz), 111.52–111.27 (m), 44.57 (q, J = 34.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.30(s), −72.22 (t, J = 8.8 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −63.30(s), −72.22(s); HRMS (ESI): calcd for $C_{10}H_7F_9N^+$ $[M + H]^+$ 312.0429, found 312.0426.

N-(2,2-Difluoroethyl)-[1,1′-biphenyl]-4-amine (7a)[14a]

Purified by flash column chromatography (petroleum ether/AcOEt = 100 : 1), white solid (100.3 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.51 (m, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.33–7.23 (m, 1H), 6.79 (d, J = 8.2 Hz, 2H), 5.98 (tt, J = 56.0, 4.1 Hz, 1H), 3.60 (td, J = 14.3, 4.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 140.9, 132.3, 128.9, 128.2, 126.58, 126.56, 114.5 (t, J = 240.8 Hz), 113.9, 46.8 (t, J = 26.1 Hz).

N-(2,2-Difluoroethyl)-4-methoxyaniline (7b)[10]

Purified by flash column chromatography (petroleum ether/EtOAc = 50 : 1), pale yellow liquid (87.8 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 8.9 Hz, 2H), 5.91 (tt, J = 56.2, 4.3 Hz, 1H), 3.76 (s, 3H), 3.48 (td, J = 14.4, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 140.9, 115.2, 114.9 (t, J = 240.5 Hz), 114.8, 55.9, 47.7 (t, J = 25.7 Hz).

1-(4-((2,2-Difluoroethyl)amino)phenyl)ethan-1-one (7c)[14a]

Purified by flash column chromatography (petroleum ether/EtOAc = 5 : 1), white solid (77.1 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 5.92 (tt, J = 55.8, 4.0 Hz, 1H), 4.39 (s, 1H), 3.61 (td, J = 14.5, 4.0 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 151.2, 130.9, 127.9, 114.2 (t, J = 241.0 Hz), 111.9, 45.7 (t, J = 26.0 Hz), 26.1.

N-(2,2-Difluoroethyl)-4-(trifluoromethyl)aniline (7d)

Purified by flash column chromatography (petroleum ether/EtOAc = 50 : 1), tawny liquid (85 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.92 (tt, J = 55.8, 4.0 Hz, 1H), 4.21 (s, 1H), 3.59 (tdd, J = 14.5, 6.7, 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 127.0 (q, J = 3.8 Hz), 124.9 (q, J = 270.4 Hz), 120.4 (q, J = 32.8 Hz), 114.3 (t, J = 242.3 Hz), 112.4, 46.0 (t, J = 26.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.27(s), −122.67 (dt, J = 55.8, 14.5 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −61.27(s), −122.67(s); HRMS (ESI): calcd for $C_9H_9F_5N^+$ $[M + H]^+$ 226.0650, found 226.0643.

4-((2,2-Difluoroethyl)amino)benzonitrile (7e)[10]

Purified by flash column chromatography (petroleum ether/EtOAc = 8 : 1), white solid (66 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 5.92 (tt, J = 55.6, 3.9 Hz, 1H), 4.36 (s, 1H), 3.60 (td, J = 14.5, 3.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 134.0, 120.0, 114.0 (t, J = 241.2 Hz), 112.7, 100.8, 45.6 (t, J = 25.8 Hz).

N-(2,2-Difluoroethyl)-4-nitroaniline (7f)

Purified by flash column chromatography (petroleum ether/EtOAc = 5 : 1), yellow solid (42.4 mg, 42% yield), m.p. 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9.2 Hz, 2H), 6.64 (d, J = 9.2 Hz, 2H), 5.95 (tt, J = 55.5, 3.8 Hz, 1H), 4.80 (t, J = 6.7 Hz, 1H), 3.66 (tdd, J = 14.6, 6.6, 3.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 139.2, 126.5, 114.0 (t, J = 242.8 Hz), 111.7, 45.7 (t, J = 25.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.51 (dt, J = 55.7, 14.6 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.51(s); HRMS (ESI): calcd for $C_8H_9F_2N_2O_2^+$ $[M + H]^+$ 203.0627, found 203.0626.

2-((2,2-Difluoroethyl)amino)benzonitrile (7g)

Purified by flash column chromatography (petroleum ether/AcOEt = 10 : 1), colorless and transparent liquid (47.2 mg, 51% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (ddd, J = 8.1, 6.7, 1.7 Hz, 2H), 6.88–6.63 (m, 2H), 5.93 (tt, J = 55.6, 4.0 Hz, 1H), 4.78 (s, 1H), 3.66 (td, J = 14.2, 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 134.5, 133.2, 118.2, 114.2 (t, J = 243.0 Hz), 110.8, 97.1, 45.8 (t, J = 26.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.17 (dt, J = 55.5, 14.2 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.17(s); HRMS (ESI): calcd for $C_9H_9F_2N_2^+$ $[M + H]^+$ 183.0728, found 183.0727.

***N*-(2,2-Difluoroethyl)-3-nitroaniline (7h)[14a]**

Purified by flash column chromatography (petroleum ether/EtOAc = 10 : 1), yellow solid (92.4 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.55 (m, 1H), 7.48 (t, J = 2.3 Hz, 1H), 7.33 (t, J = 8.2 Hz, 1H), 6.95 (dd, J = 8.0, 2.4 Hz, 1H), 5.95 (tt, J = 55.7, 3.9 Hz, 1H), 4.25 (s, 1H), 3.63 (dddd, J = 14.6, 10.7, 6.7, 3.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 147.9, 130.2, 119.2, 114.2 (t, J = 242.4 Hz), 113.5, 106.8, 46.2 (t, J = 25.8 Hz).

***N*-(2,2-Difluoroethyl)naphthalen-2-amine (7i)**

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), white solid (99.1 mg, 95% yield), m.p. 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.58 (m, 3H), 7.39 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.28–7.18 (m, 1H), 6.91–6.83 (m, 2H), 5.97 (tt, J = 56.1, 4.2 Hz, 1H), 3.93 (s, 1H), 3.61 (td, J = 14.4, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 135.0, 129.5, 128.15, 127.8, 126.78, 126.2, 122.8, 117.8, 117.49–110.91 (m), 105.1, 46.5 (t, J = 26.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.42 (dt, J = 56.0, 14.4 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.42(s); HRMS (ESI): calcd for $C_{12}H_{12}F_2N^+$ $[M + H]^+$ 208.0932, found 208.0933.

***N*-(2,2-Difluoroethyl)-9*H*-fluoren-2-amine (7j)**

Purified by flash column chromatography (petroleum ether/AcOEt = 50 : 1), white solid (104.6 mg, 85% yield), m.p. 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 17.3, 7.9 Hz, 2H), 7.48 (d, J = 7.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.21 (td, J = 7.5, 1.2 Hz, 1H), 6.89–6.82 (m, 1H), 6.69 (dd, J = 8.2, 2.2 Hz, 1H), 5.97 (tt, J = 56.1, 4.3 Hz, 1H), 3.96 (s, 1H), 3.83 (s, 2H), 3.60 (td, J = 14.4, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 145.4, 142.4, 142.1, 133.3, 126.8, 125.4, 124.9, 120.9, 118.8, 114.7 (t, J = 240.8 Hz), 112.4, 109.7, 46.9 (t, J = 26.0 Hz), 37.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.57 (dt, J = 56.3, 14.3 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.57(s); HRMS (ESI): calcd for $C_{15}H_{14}F_2N^+$ $[M + H]^+$ 246.1089, found 246.1082.

***N*-(2,2-Difluoroethyl)-3,5-dimethoxyaniline (7k)**

Purified by flash column chromatography (petroleum ether/EtOAc = 20 : 1), colorless liquid (99.8 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (tt, J = 56.2, 2.1 Hz, 1H), 5.91 (t, J = 4.2 Hz, 1H), 5.84 (d, J = 2.1 Hz, 2H), 3.76 (s, 6H), 3.49 (td, J = 14.4, 4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 148.8, 120.2–109.6 (m), 92.1, 90.8, 55.24, 55.19, 46.45 (t, J = 26.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.60 (dt, J = 56.0, 14.4 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.60(s); HRMS (ESI): calcd for $C_{10}H_{14}F_2NO_2^+$ $[M + H]^+$ 218.0987, found 218.0985.

***N*-(2,2-Difluoroethyl)-3,5-bis(trifluoromethyl)aniline (7l)**

Purified by flash column chromatography (petroleum ether/EtOAc = 30 : 1), pale yellow liquid (120.8 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.02 (s, 2H), 5.95 (tt, J = 55.5, 3.8 Hz, 1H), 4.32 (s, 1H), 3.62 (td, J = 14.6, 3.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 132.9 (q, J = 32.9 Hz), 123.5 (q, J = 272.8 Hz), 114.1 (q, J = 242.5 Hz), 112.4 (d, J = 4.2 Hz), 112.0–111.8 (m), 46.0 (t, J = 25.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.26(s), −122.73 (dt, J = 55.6, 14.4 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −63.26(s), −122.73(s); HRMS (ESI): calcd for $C_{10}H_8F_8N^+$ $[M + H]^+$ 294.0524, found 294.0527.

***N*-(2,2,2-Trifluoroethyl)pyridin-3-amine (9a)[10]**

Purified by flash column chromatography (petroleum ether/EtOAc = 1 : 1), white solid (35.7 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 2.9 Hz, 1H), 8.06 (d, J = 4.7 Hz, 1H), 7.14 (dd, J = 8.3, 4.6 Hz, 1H), 6.99 (ddd, J = 8.4, 3.0, 1.3 Hz, 1H), 4.21 (s, 1H), 3.78 (qd, J = 8.8, 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.5, 136.4, 124.9 (q, J = 280.0 Hz), 123.9, 119.1, 45.7 (q, J = 34.0 Hz).

***N*-(2,2,2-Trifluoroethyl)pyridin-2-amine (9b)[10]**

Purified by flash column chromatography (petroleum ether/EtOAc = 20 : 1), white solid (27.4 mg, 62% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 5.1, 1.8 Hz, 1H), 7.45 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 6.68 (ddd, J = 7.3, 5.0, 1.0 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 4.62 (s, 1H), 4.11 (qd, J = 9.2, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 148.0, 137.8, 125.1 (q, J = 279.3 Hz), 114.7, 108.3, 43.0 (q, J = 33.8 Hz).

5-Methyl-*N*-(2,2,2-trifluoroethyl)pyridin-3-amine (9c)

Purified by flash column chromatography (petroleum ether/EtOAc = 1 : 1), white solid (39.6 mg, 83% yield), m.p. 46–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 23.4 Hz, 2H), 6.82 (s, 1H), 4.22 (s, 1H), 3.89–3.63 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 133.4, 125.0 (q, J = 280.0 Hz), 120.1, 45.7 (q, J = 33.9 Hz), 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.28 (t, J = 8.8 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −72.28(s); HRMS (ESI): calcd for $C_8H_{10}F_3N_2^+$ $[M + H]^+$ 191.0791, found 191.0787.

5-Methyl-*N*-(2,2,2-trifluoroethyl)pyridin-2-amine (9d)

Purified by flash column chromatography (petroleum ether/EtOAc = 5 : 1), white solid (33.6 mg, 70% yield), m.p. 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.30 (dd, J = 8.4, 2.3 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 4.66 (s, 1H), 4.06 (qd, J = 9.1, 6.8 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 147.1, 139.2, 125.1 (q, J = 279.5 Hz), 123.6, 108.0, 43.3 (q, J = 34.0 Hz), 17.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.67 (t, J = 9.1 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −72.67(s); HRMS (ESI): calcd for $C_8H_{10}F_3N_2^+$ $[M + H]^+$ 191.0791, found 191.0785.

***N*-(2,2,2-Trifluoroethyl)quinolin-3-amine (9e)**

Purified by flash column chromatography (petroleum ether/EtOAc = 3 : 1), white solid (42.6 mg, 75% yield), m.p. 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.9 Hz, 1H), 8.02–7.94 (m, 1H), 7.71–7.59 (m, 1H), 7.54–7.40 (m, 2H), 7.18 (d, J = 2.8 Hz, 1H), 4.54 (s, 1H), 3.88 (qd, J = 8.8, 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 142.7, 139.8, 129.04, 128.98, 127.4, 126.3, 126.1, 125.0 (q, J = 281.1 Hz), 111.7, 45.7 (q, J = 34.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.87 (t, J = 8.8 Hz);

^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −71.87(s); HRMS (ESI): calcd for $C_{11}H_{10}F_3N_2^+$ $[M + H]^+$ 227.0791, found 227.0784.

***N*-(2,2,2-Trifluoroethyl)-1*H*-indol-5-amine (9f)**

Purified by flash column chromatography (petroleum ether/AcOEt = 5 : 1), white solid (45.0 mg, 84% yield), m.p. 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.29–7.21 (m, 1H), 7.15 (t, J = 2.8 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.68 (dd, J = 8.6, 2.3 Hz, 1H), 6.52–6.36 (m, 1H), 3.79 (q, J = 9.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 130.9, 128.8, 125.5 (q, J = 279.8 Hz), 125.0, 112.2, 111.9, 103.5, 102.0, 47.9 (q, J = 33.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.10 (t, J = 8.9 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −72.10(s); HRMS (ESI): calcd for $C_{10}H_{10}F_3N_2^+$ $[M + H]^+$ 215.0791, found 215.0783.

***N*-(2,2-Difluoroethyl)pyridin-3-amine (10a)[10]**

Purified by flash column chromatography (petroleum ether/EtOAc = 2 : 3), brown liquid (33.2 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–7.89 (m, 2H), 7.12 (dd, J = 8.3, 4.6 Hz, 1H), 6.95 (ddd, J = 8.3, 3.0, 1.3 Hz, 1H), 5.92 (tt, J = 55.8, 4.0 Hz, 1H), 4.09 (s, 1H), 3.55 (tdd, J = 14.5, 6.7, 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 140.1, 136.3, 123.9, 119.1, 114.4 (t, J = 242.2 Hz), 46.1 (t, J = 26.0 Hz).

***N*-(2,2-Difluoroethyl)pyridin-2-amine (10b)**

Purified by flash column chromatography (petroleum ether/EtOAc = 20 : 1), colorless and transparent liquid (22.5 mg, 57% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 4.4 Hz, 1H), 7.42 (ddd, J = 8.7, 7.1, 1.9 Hz, 1H), 6.64 (ddd, J = 7.2, 5.1, 1.0 Hz, 1H), 6.46 (dd, J = 8.3, 1.0 Hz, 1H), 5.97 (tt, J = 56.6, 4.3 Hz, 1H), 4.66 (s, 1H), 3.78 (tdd, J = 14.6, 6.5, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 148.0, 137.6, 114.6 (t, J = 241.7 Hz), 114.1, 108.4, 44.1 (t, J = 26.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.14 (dt, J = 56.5, 14.7 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −123.14(s); HRMS (ESI): calcd for $C_7H_9F_2N_2^+$ $[M + H]^+$ 159.0728, found 159.0726.

***N*-(2,2-Difluoroethyl)-5-methylpyridin-3-amine (10c)**

Purified by flash column chromatography (petroleum ether/EtOAc = 1 : 1), white solid (40.2 mg, 93% yield), m.p. 43–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.80 (m, 2H), 6.76 (t, J = 2.1 Hz, 1H), 5.91 (tt, J = 55.8, 4.1 Hz, 1H), 4.08 (s, 1H), 3.53 (tdd, J = 14.5, 6.5, 4.1 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.7, 133.7, 133.5, 119.9, 114.5 (t, J = 242.1 Hz), 46.1 (t, J = 26.0 Hz), 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.65 (dt, J = 55.6, 14.2 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.65(s); HRMS (ESI): calcd for $C_8H_{11}F_2N_2^+$ $[M + H]^+$ 173.0885, found 173.0884.

***N*-(2,2-Difluoroethyl)-5-methylpyridin-2-amine (10d)**

Purified by flash column chromatography (petroleum ether/EtOAc = 5 : 1), pale yellow liquid (34.8 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.25 (dd, J = 8.3, 2.4 Hz, 1H), 6.39 (d, J = 8.4 Hz, 1H), 5.95 (tt, J = 56.6, 4.3 Hz, 1H), 4.60 (s, 1H), 3.73 (tdd, J = 14.6, 6.5, 4.3 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 147.3, 138.7, 122.9, 114.7 (t, J = 241.2 Hz), 108.1, 44.3 (t, J = 26.5 Hz), 17.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.11 (dt, J = 56.6, 14.7 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −123.11(s); HRMS (ESI): calcd for $C_8H_{11}F_2N_2^+$ $[M + H]^+$ 173.0885, found 173.0882.

***N*-(2,2-Difluoroethyl)quinolin-3-amine (10e)**

Purified by flash column chromatography (petroleum ether/EtOAc = 3 : 1), white solid (40.5 mg, 77% yield), m.p. 73–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 2.9 Hz, 1H), 7.96 (dd, J = 6.2, 3.4 Hz, 1H), 7.62 (dd, J = 6.2, 3.4 Hz, 1H), 7.45 (dt, J = 6.3, 3.5 Hz, 2H), 7.10 (d, J = 2.8 Hz, 1H), 5.98 (tt, J = 55.8, 4.1 Hz, 1H), 4.42 (s, 1H), 3.62 (tdd, J = 14.5, 6.6, 4.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 142.7, 140.4, 129.1, 129.1, 126.2, 125.8, 114.4 (t, J = 242.3 Hz), 111.0, 46.1 (t, J = 26.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.23 (dt, J = 55.8, 14.5 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.23(s); HRMS (ESI): calcd for $C_{11}H_{11}F_2N_2^+$ $[M + H]^+$ 209.0885, found 209.0879.

***N*-(2,2-Difluoroethyl)-1*H*-indol-5-amine (10f)**

Purified by flash column chromatography (petroleum ether/EtOAc = 5 : 1), brown solid (39.4 mg, 80% yield), m.p. 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.15 (t, J = 2.8 Hz, 1H), 6.92 (d, J = 2.3 Hz, 1H), 6.67 (dd, J = 8.6, 2.3 Hz, 1H), 6.43 (t, J = 2.8 Hz, 1H), 5.98 (tt, J = 56.4, 4.3 Hz, 1H), 3.57 (td, J = 14.4, 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 130.8, 128.8, 125.0, 115.0 (t, J = 241.3 Hz), 112.4, 112.0, 103.1, 102.0, 48.1 (t, J = 25.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.70 (dt, J = 56.3, 14.4 Hz); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ −122.70(s); HRMS (ESI): calcd for $C_{10}H_{11}F_2N_2^+$ $[M + H]^+$ 197.0885, found 197.0881.

Conflicts of interest

There are no conflicts to declare.

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