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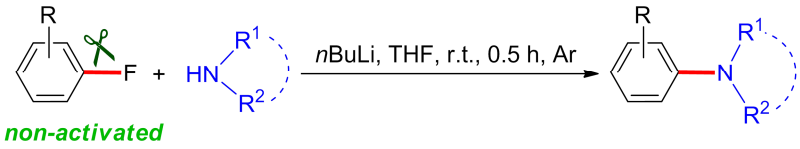

• Performed at r.t. • Reacted rapidly • Good yields

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ABSTRACT

A simple and facile method for the synthesis of aromatic tertiary amines by amination of fluoroarenes with secondary amines in the presence of *n*-butyllithium at room temperature was reported.

1. Introduction

The carbon−nitrogen bond formation has been one of the important themes in organic chemistry. The aromatic tertiary amine moiety is frequently found in many biologically active compounds and pharmaceutical agents (Figure 1).[1] Therefore, the efficient synthesis of aromatic tertiary amines continues to attract significant attention from synthetic chemists.[2] To date, many methods have been developed for the synthesis of *N*-aryl tertiary amines.[3] The most general and commonly used methods for the synthesis of arylamines are palladium-catalyzed Buchwald–Hartwig amination (Scheme 1 a)[4] and copper-mediated/catalyzed Ullmann coupling.[5] The transition-metal-free amination of aryl halides provides a promising alternative route for preparation of arylamines.[6] However, this protocol suffers from drawbacks, such as the use of strong base (e. g., *t*BuOK, KHMDS), higher reaction temperature (e.g., 150 °C), and long reaction time.[7] Typically, aryl chlorides, bromides or iodides could be served as coupling partners in Pd- or Cu-catalyzed amination reactions,[8] whereas unreactive aryl fluorides are seldom used as coupling partners. Although metal-free S_NAr substitutions of aryl fluorides with amines are well documented, the applicable substrates were limited to electron-poor aryl fluorides.[9] Examples of amination of electron-rich aryl fluorides are very rare.[10] In 2010, Shibata et al. reported Ru-catalyzed S_NAr reaction of non-activated fluoroarenes with amines and a variety of aromatic tertiary amines were obtained in moderate yields (Scheme 1 b).[11] More recently, Wang et al. reported an efficient method for the synthesis of aromatic tertiary amines by the Ni-catalyzed coupling of activated, unactivated and deactivated fluoroarenes with various secondary amines in the presence of $Ni(COD)_2$, IPr•HCl and *t*BuONa (Scheme 1 c).[12] Zhou et al. developed a transition-metal-free amination of fluorobenzene with 1-methylpiperazine under microwave irradiation (Scheme 1 d).[13a]

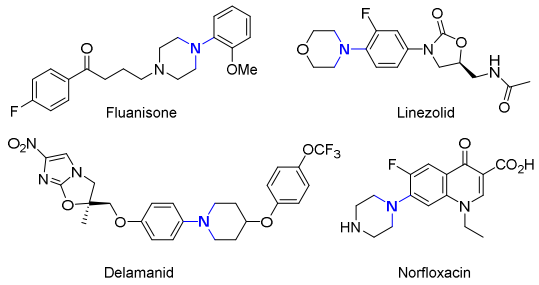
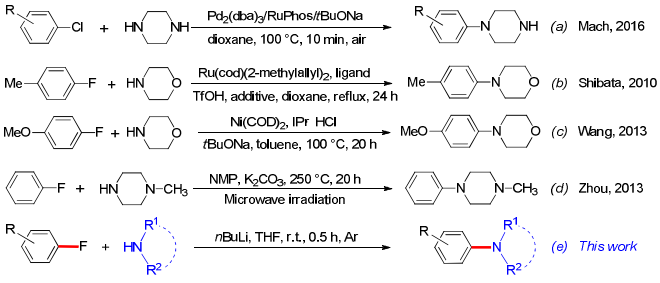


Figure 1. Examples of aromatic tertiary amine-containing drugs.



Scheme 1. Amination of aryl chlorides and non-activated aryl fluorides.

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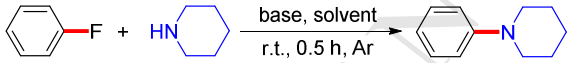
The cleavage, activation and functionalization of the robust carbon−fluorine bonds is one of the most challenging topics in organic synthesis and fluorine chemistry.[14] The nucleophilic aromatic substitution (S_NAr) reaction of fluoroarenes is a classic method for the functionalization of carbon−fluorine bond.[15] However, the substrate scope is mostly limited to highly electron-deficient aryl fluorides.[16] Alternatively, in recent years, transition-metal-catalyzed cross-coupling of fluoroarenes with organometallics represents an attractive protocol to derivatize fluoroarenes.[17] The cleavage of aromatic C−F bond by defluorination reaction in presence of organolithium has previously been reported in the literature.[18] However, functionalization of the carbon−fluorine bond via the formation benzyne-tethered organolithiums remains a largely unexplored area and only a few examples have been reported.[19] The major drawback of this process is the use of very low reaction temperature (e.g., −78 °C),[20] which limits the synthetic utility of this reaction. In continuation of our research on the cleavage and functionalization of carbon−fluorine bonds,[21] we herein report an efficient and mild method for the synthesis of aromatic tertiary amines by reactions of fluoroarenes with secondary amines in the presence of *n*-butyllithium at room temperature (Scheme 1 e).

2. Results and discussion

Initially, fluorobenzene **1a** and piperidine **2a** were used as model reactants for the optimization of the amination reaction conditions, and the results are shown in Table 1. Screening of several bases revealed that *n*BuLi was the most suitable (entry 8), affording the desired product **3aa** in excellent yield. The replacement of *n*BuLi with LDA (lithium diisopropylamide) or *t*BuLi led to decreased yields (entries 6–7). While other bases such as LiHMDS, NaHMDS, KHMDS, *t*BuOLi and *t*BuOK proved to be completely ineffective, providing essentially no expected product (entries 1−5). Among the solvents examined, THF was found to be superior to other solvents such as CH_3CN, toluene, hexane and Et_2O (entries 8 and 11−14). Upon using DMF or 1,4-dioxane as solvent, none of the desired product was observed (entries 9−10). Finally, the effect of the amount of piperidine **2a** and *n*BuLi on the yield of the reaction was studied. The results indicated that 1.5 equivalents of piperidine **2a** and 3.0 equivalents of *n*BuLi (based on **1a**) were enough to afford the corresponding amination product in satisfactory yield (entry 8), while increasing or decreasing the amount of piperidine **2a** and *n*BuLi would diminish the yield of **3aa** obviously (entries 15–18). Remarkably, reaction of fluorobenzene **1a** with piperidine **2a** in the presence of *n*BuLi occurs rapidly in THF at room temperature and provided **3aa** in excellent yield within 0.5 h.

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



1a **2a** **3aa**

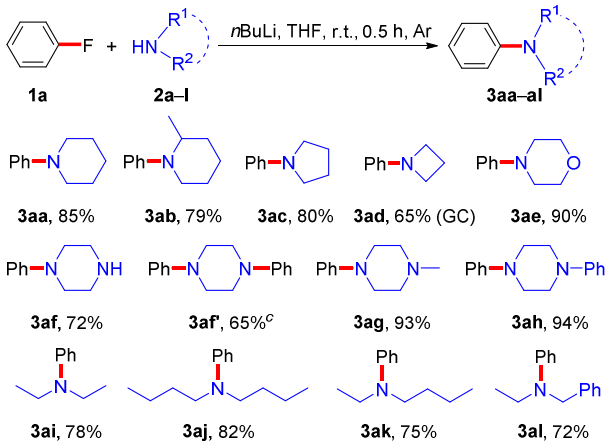
Entry	**2a** (equiv.)	Base (equiv.)	Solvent	Yield **3aa** (%)[b]
1	1.5	LiHMDS (3.0)	THF	0
2	1.5	NaHMDS (3.0)	THF	0
3	1.5	KHMDS (3.0)	THF	0
4	1.5	*t*BuOLi (3.0)	THF	0
5	1.5	*t*BuOK (3.0)	THF	0
6	1.5	LDA (3.0)	THF	57
7	1.5	*t*BuLi (3.0)	THF	83
8	1.5	*n*BuLi (3.0)	THF	96
9	1.5	*n*BuLi (3.0)	DMF	0
10	1.5	*n*BuLi (3.0)	1,4-dioxane	0
11	1.5	*n*BuLi (3.0)	CH_3CN	25
12	1.5	*n*BuLi (3.0)	toluene	58
13	1.5	*n*BuLi (3.0)	hexane	61
14	1.5	*n*BuLi (3.0)	Et_2O	81
15	1.5	*n*BuLi (2.5)	THF	69
16	1.5	*n*BuLi (3.5)	THF	58
17	1.2	*n*BuLi (3.0)	THF	85
18	1.7	*n*BuLi (3.0)	THF	76

[a] Reaction conditions: **1a** (1.0 mmol), solvent (2 mL), 0.5 h, r.t., Ar.

[b] Yields determined by GC analysis and based on **1a**.

Having identified optimized conditions (Table 1 entry 8), we next examined the scope and limitations of the novel amination reaction. Firstly, we applied this new protocol to the reaction of fluorobenzene **1a** with a range of secondary amines, as shown in Scheme 2. The results indicated that both cyclic and acyclic secondary amines could provide aromatic tertiary amines in good to excellent yields. Piperidine **2a**, 2-Methylpiperidine **2b** and tetrahydropyrrole **2c** proved to be good substrates for this amination, affording the expected products **3aa**−**ac** in good yields, while azetidine **2d** gave a slightly lower yield (**3ad**, GC,

the isolation of **3ad** was difficult owing to its low boiling point, b.p.: 77 °C). The amination reaction of fluorobenzene **1a** with morpholine **2e**, 1-methylpiperazine **2g** and 1-phenylpiperazine **2h** proceeded very well and the desired products were obtained in excellent yields (**3ae**, **3ag** and **3ah**). When piperazine **2f** (1.5 mmol) was reacted with 1.0 mmol or 3.75 mmol of fluorobenzene **1a**, monoamination product **3af** and diamination product **3af'** were obtained in 72% and 65% yields, respectively. Aliphatic symmetrical and unsymmetrical secondary amines (**2i**–**l**) were also found to be suitable substrates, the corresponding amination products being afforded in good yields (**3ai**–**al**). Unfortunately, primary amines such as $EtNH_2$, primary and secondary anilines failed to give the desired products.

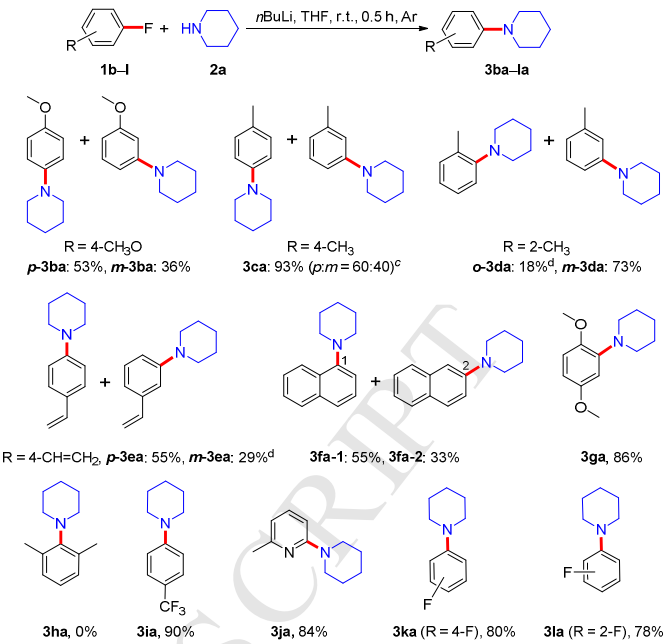


[a] Reaction conditions: **1a** (1.0 mmol), **2a**–**l** (1.5 mmol), *n*BuLi (3.0 mmol), THF (2 mL), r.t., 0.5 h, Ar. [b] Isolated yield. [c] Reaction conditions: **1a** (3.75 mmol), **2f** (1.5 mmol), *n*BuLi (6.0 mmol), THF (2 mL), r.t., 0.5 h, Ar.

Scheme 2 Reactions of **1a** with various secondary amines.[a,b]

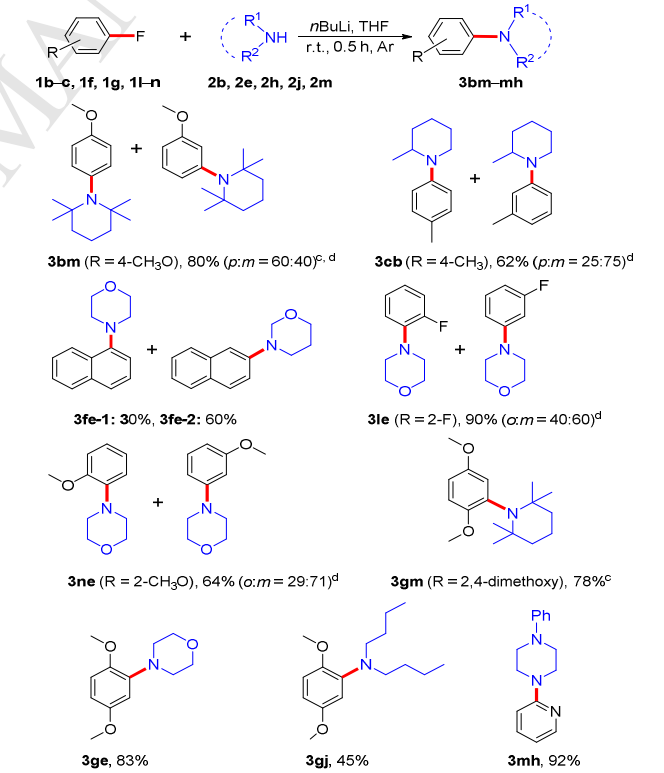
Subsequently, the scope of fluoroarenes was investigated (Scheme 3). The reactions of piperidine **2a** with a variety of fluoroarenes were conducted under the optimized reaction conditions. Generally, non-activated fluoroarenes, which bear electron-donating or neutral group, gave a mixture of two regioisomeric products (**3ba**–**fa**) in high yields. The tolerance of vinyl group is particularly useful (**3ea**), thus providing an excellent starting point for further derivatization. Fortunately, in some cases, regioisomeric products could be separated by column chromatography on silica gel (**3ba**, **3da**–**fa**). Substrate containing two strong electron-donating group such as 2-fluoro-1,4-dimethoxybenzene **1g** also worked well and exclusively afforded the corresponding amination product in 86% yield (**3ga**). However, no reaction occurred when 2-fluoro-1,3-dimethylbenzene **1h** was applied as starting material. This may be because two methyl groups blocked the formation of the aryne intermediate. As expected, treatment of highly electron-poor fluoroarenes (**1i** and **1j**) with piperidine **2a** under the optimized conditions gave nucleophilic aromatic substitution products (**3ia** and **3ja**) in high yields. These results are consistent with the nucleophilic aromatic substitution (S_NAr) mechanism.[22] Fluoroarene bearing relatively weaker electron-withdrawing groups such as fluorine atom (**1k** and **1l**) could yielded a mixture of two isomers (**3ka** and **3la**), indicating that aryne mechanism might be involved in this process. Finally, no reaction took place when the fluoroarenes bearing ester or ketone groups was employed.

To further elucidate the generality of this practical approach, a number of fluoroarenes and secondary amines were investigated in this amination reaction (Scheme 4). In most cases, the desired



[a] Reaction conditions: **1b**–**l** (1.0 mmol), **2a** (1.5 mmol), *n*BuLi (3.0 mmol), THF (2 mL), r.t., 0.5 h, Ar. [b] Isolated yield. [c] The ratio of two isomers was determined by ^{1}H NMR spectroscopy. [d] GC-MS yield.

Scheme 3 Reactions of piperidine **2a** with fluoroarenes.[a, b]



[a] Reaction conditions: **1b**–**c**, **1f**, **1g**, **1l**–**n** (1.0 mmol), **2b**, **2e**, **2h**, **2j** and **2m** (1.5 mmol), *n*BuLi (3.0 mmol), THF (2 mL), r.t., 0.5 h, Ar. [b] Isolated yield. [c] −78 °C (0.5 h) and then rt (0.5 h). [d] The ratio of two isomers was determined by ^{1}H NMR spectroscopy and GC-MS.

Scheme 4 Reactions of various fluoroarenes with secondary amines.[a, b]

aminated products were obtained in good yields. With regard to 2,2,6,6-tetramethylpiperidine (**2m**, TMP), a hindered secondary amine, no amination product was detected under the standard conditions. To address this problem, the reactions of **2m** with **1b** or **1g** was subsequently conducted at –78 °C for 30 minutes, and

then warmed to room temperature for another 30 minutes Thus, the expected products **3bm** and **3gm** were obtained via this slight modification of optimized conditions. Unfortunately, only small amount of amination products was observed when chlorobenzene and bromobenzene reacted with piperidine **2a**.[23]

3. Conclusions

In summary, we have developed a gilfacile method for the synthesis of aromatic tertiary amines by amination of fluoroarenes with secondary amines in the presence of *n*-butyllithium at room temperature. Both electron-rich aryl fluorides and electron-poor aryl fluorides proceeded efficiently and afforded a variety of aromatic tertiary amines in good yields. The amination of electron-rich aryl fluorides with secondary amines proceeded via aryne intermediates, whereas electron-poor aryl fluorides proceed via a classical S_NAr pathway. Although the regioselectivity of this protocol is low, we anticipated that the regioselectivity might be controlled by tuning the position, steric and electronic properties of the substituents on the aryl ring and some special substrates could be aminated regioselectively. Noticeably, important chemical raw material fluorobenzene could be easily transformed into various useful aromatic tertiary amines by this protocol. Therefore, this methodology provides an alternative approach to valuable aromatic tertiary amines from simple and readily available starting materials.

4. Experimental

4.1. General information

All reagents were of analytical grade, and obtained from commercial suppliers and used without further purification. THF was dried by standard method prior to use and degassed. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS as internal standard, The ^{19}F NMR spectra were obtained using a 400 spectrometer (376 MHz). $CDCl_3$ was used as the NMR solvent in all cases. The GC and GC-MS were calibrated by authentic standards. High-resolution mass spectra (HRMS) were acquired in the electron-impact mode (EI) using a TOF mass analyzer.

4.2 General procedure for the synthesis of target compounds 3

To an oven-dried round-bottom flask with a stir bar were charged with a solution of secondary amines **2** (1.5 mmol) in 1 mL dry THF at room temperature under an argon atmosphere. To this solution was slowly added 1.2 mL *n*BuLi (2.5 mol/L in *n*-hexane, 3.0 mmol) via syringe. After stirring at 25 °C for 10 min, a solution of fluoroarene **1** (1.0 mmol) in 1 mL dry THF was added to the reaction flask. The reaction mixture was stirred for 0.5 h at 25 °C, and then quenched with 2 mL saturated aqueous solution of NaCl and extracted with H_2O (20 mL) and ethyl acetate (3 × 20 mL). The organic layer was separated and dried with anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel using a petroleum ether/ethyl acetate mixture as eluent to afford the pure target compounds **3**.

*4.2.1. 1-Phenylpiperidine (**3aa**, CAS: 4096-20-2).*[24] Yellow liquid. Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.81 (t, J = 7.4 Hz, 1H), 3.13 (t, J = 5.6 Hz, 4H), 1.72–1.66 (m, 4H), 1.57–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 129.1, 119.3, 116.6, 50.8, 26.0, 24.4.

4.2.2. 2-Methyl-1-phenylpiperidine (***3ab***, *CAS: 14142-16-6).*[24] Yellow liquid. Yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.22 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.81 (t, J = 7.2 Hz, 1H), 3.91–3.88 (m, 1H), 3.22–3.18 (m, 1H), 2.98–2.93 (m, 1H), 1.86–1.56 (m, 6H), 0.99 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 129.0, 119.2, 117.7, 51.5, 45.1, 31.9, 26.2, 19.8, 13.9.

*4.2.3. 1-Phenylpyrrolidine (**3ac**, CAS: 4096-21-3).*[25] Colorless oil. Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.19 (m, 2H), 6.64 (t, J = 7.2 Hz, 1H), 6.54 (d, J = 8.0 Hz, 2H), 3.24 (t, J = 6.4 Hz, 4H), 1.97–1.94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 129.2, 115.5, 111.8, 47.7, 25.6.

*4.2.4. 4-Phenylmorpholine (**3ae**, CAS: 92-53-5).*[24] Yellow liquid. Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 6.91–6.85 (m, 3H), 3.84 (t, J = 4.8 Hz, 4H), 3.13 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.2, 120.1, 115.8, 67.0, 49.4.

*4.2.5. 1-Phenylpiperazine (**3af**, CAS: 92-54-6).*[26] Colorless oil. Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2H), 6.92 (d, J = 7.6 Hz, 2H), 6.85 (t, J = 7.2 Hz, 1H), 3.13–3.10 (m, 4H), 3.01–2.99 (m, 4H), 1.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 129.1, 119.7, 116.1, 50.4, 46.2.

*4.2.6. 1,4-Diphenylpiperazine (**3af'**, **3ah**, CAS:613-39-8).*[24] White solid. Mp 159.7–161.3 ºC. **3af'**, yield 72%; **3ah**, yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 4H), 6.97 (d, J = 8.0 Hz, 4H), 6.88 (t, J = 7.2 Hz, 2H), 3.32 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.3, 120.1, 116.4, 49.5.

*4.2.7. 1-Methyl-4-phenylpiperazine (**3ag**, CAS: 3074-43-9).*[3b] Yellow liquid. Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.85 (t, J = 7.2 Hz, 1H), 3.20 (t, J = 5.0 Hz, 4H), 2.56 (t, J = 5.0 Hz, 4H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.1, 119.7, 116.1, 55.2, 49.1, 46.2.

*4.2.8. N,N-Diethylaniline (**3ai**, CAS:91-66-7).*[27] Yellow liquid. Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 2H), 6.70–6.64 (m, 3H), 3.37–3.34 (m, 4H), 1.53–1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 129.3, 115.4, 111.9, 44.4, 12.6.

*4.2.9. N,N-Dibutylaniline (**3aj**, CAS: 613-29-6).*[26] Yellow liquid. Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2H), 6.65–6.59 (m, 3H), 3.25 (t, J = 7.6 Hz, 4H), 1.60–1.52 (m, 4H), 1.39–1.30 (m, 4H), 0.95 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 129.2, 115.1, 111.7, 50.8, 29.5, 20.4, 14.1.

*4.2.10. N-Butyl-N-ethylaniline (**3ak**, CAS:13206-64-9).*[28] Yellow oil. Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.18 (m, 2H), 6.67–6.61 (m, 3H), 3.35 (q, J = 6.9 Hz, 2H), 3.24 (t, J = 7.4 Hz, 2H), 1.61–1.53 (m, 2H), 1.40–1.33 (m, 2H), 1.14 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 129.2, 115.2, 111.8, 50.2, 44.9, 29.7, 20.4, 14.1, 12.3.

*4.2.11. N-Benzyl-N-ethylaniline (**3al**, CAS: 92-59-1).*[29] Light yellow liquid. Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.16 (m, 7H), 6.70–6.64 (m, 3H), 4.51 (s, 2H), 3.46 (q, J = 6.8 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 139.3, 129.3, 128.6, 126.8, 126.6, 116.1, 112.2, 54.0, 45.2, 12.2.

*4.2.12. 1-(4-Methoxyphenyl)piperidine (**p-3ba**, CAS: 5097-25-6).*[26] Yellow liquid. Yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93（d, J = 9.2 Hz, 2H）, 6.83 (d, J = 9.2 Hz, 2H), 3.76 (s, 3H), 3.03 (t, J = 5.4 Hz, 4H), 1.76–1.70 (m, 4H), 1.57–1.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 146.7, 118.9, 114.4, 55.6, 52.4, 26.1, 24.2.

*4.2.13. 1-(3-Methoxyphenyl)piperidine (**m-3ba**, CAS: 32040-06-5).*[5e] Yellow liquid. Yield 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.17–7.13 (m, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.15 (t, *J* = 5.4 Hz, 4H), 1.72–1.67 (m, 4H), 1.60–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 153.6, 129.7, 109.4, 104.0, 102.8, 55.2, 50.6, 25.8, 24.4.

*4.2.14. 1-(p- and m-Tolyl)piperidine (**3ca**, CAS: 31053-03-9; 71982-24-6).*[4a] Yellow liquid. Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.6 Hz, 0.40 × 1H, *m*-isomer), 7.05 (d, *J* = 8.0 Hz, 0.60 × 2H, *p*-isomer), 6.85 (d, *J* = 7.6 Hz, 0.60 × 2H, *p*-isomer), 6.74 (d, *J* = 7.6 Hz, 0.40 × 2H, *m*-isomer), 6.64 (d, *J* = 7.2 Hz, 0.40 × 1H, *m*-isomer), 3.12 (t, *J* = 5.0 Hz, 0.40 × 4H, *m*-isomer), 3.08 (t, *J* = 5.0 Hz, 0.60 × 4H, *p*-isomer), 2.30 (s, 0.40 × 3H, *m*-isomer), 2.25 (s, 0.60 × 3H, *p*-isomer), 1.70 (s, 4H), 1.57–1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 150.4, 138.6, 129.6, 128.9, 128.8, 120.2, 117.5, 117.0, 113.8, 51.4, 50.9, 26.1, 26.0, 24.4, 24.3, 21.9, 20.5.

*4.2.15. 1-(m-Tolyl)piperidine (**m-3da**, CAS: 31053-03-9).*[4a] Yellow liquid. Yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.13 (t, *J* = 5.2 Hz, 4H), 2.30 (s, 3H), 1.72–1.67 (m, 4H), 1.59–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 138.6, 128.8, 120.2, 117.5, 113.7, 50.8, 26.0, 24.4, 21.8.

*4.2.16. 1-(4-Vinylphenyl)piperidine (**p-3ea**, CAS: 40377-61-5).*[11] Yellow liquid. Yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.63 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.57 (d, *J* = 17.6 Hz, 1H), 5.06 (d, *J* = 11.2 Hz, 1H), 3.17 (t, *J* = 5.4 Hz, 4H), 1.72–1.67 (m, 4H), 1.60–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 136.5, 128.6, 127.0, 116.1, 110.5, 50.4, 25.7, 24.3.

*4.2.17. 1-(Naphthalen-1-yl)piperidine (**3fa-1**, CAS: 62062-39-9).*[4d] White crystal. Mp 142.8–143.5 °C. Yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.80–7.78 (m, 1H), 7.51–7.35 (m, 4H), 7.03 (d, *J* = 8.0 Hz, 1H), 3.03 (s, 4H), 1.84–1.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 134.8, 129.2, 128.4, 125.9, 125.7, 125.2, 123.9, 123.0, 114.5, 54.7, 26.7, 24.7.

*4.2.18. 1-(Naphthalen-2-yl)piperidine (**3fa-2**, CAS: 5465-85-0).*[30] Yellow crystal. Mp 53.5–54.4 °C. Yield 33%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 3H), 7.38–7.34 (m, 1H), 7.27–7.23 (m, 2H), 7.10 (s, 1H), 3.22 (t, *J* = 5.4 Hz, 4H), 1.76–1.70 (m, 4H), 1.61–1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 134.8, 128.6, 128.4, 127.5, 126.8, 126.2, 123.2, 120.3, 110.4, 51.1, 26.0, 24.5.

*4.2.19. 1-(2,5-Dimethoxyphenyl)piperidine (**3ga**, CAS: 92197-33-6).*[6a] Yellow liquid. Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 6.45 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.97 (t, *J* = 5.2 Hz, 4H), 1.76–1.71 (m, 4H), 1.58–1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 146.8, 143.9, 111.8, 106.5, 104.8, 55.9, 55.5, 52.2, 26.3, 24.4; HRMS (EI) calcd for $C_{13}H_{19}NO_2$ $[M]^+$ 221.1416, found 221.1417.

*4.2.20. 1-(4-(Trifluoromethyl)phenyl)piperidine (**3ia**, CAS: 10338-55-3).*[31] Yellow liquid. Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 3.23 (t, *J* = 4.0 Hz, 4H), 1.66–1.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 126.4 (q, $^3J_{CF}$ = 3.7 Hz,), 125.0 (q, $^1J_{CF}$ = 266.8 Hz,) 119.5 (q, $^2J_{CF}$ = 32.3 Hz), 114.6, 49.3, 25.4, 24.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.1 (s, 3F).

*4.2.21. 2-Methyl-6-(piperidin-1-yl)pyridine (**3ja**, CAS: 924862-37-3).* Yellow liquid. Yield 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.31 (m, 1H), 6.44–6.41 (m, 2H), 3.50–3.49 (m, 4H), 2.38 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 156.7, 137.6, 111.8, 103.7, 46.4, 25.6, 24.8, 24.7; HRMS (EI) calcd for $C_{11}H_{16}N_2$ $[M]^+$ 176.1313, found 176.1311.

*4.2.22. 1-(3- and 4-Fluorophenyl)piperidine (**3ka**, CAS: 64287-25-8; 4280-36-8).* Yellow liquid. Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.22 (m, 0.20 × 2H), 6.96–6.86 (m, 3.4H), 6.83–6.80 (m, 0.20 × 1H), 3,15 (t, *J* = 5.6 Hz, 0.20 × 4H), 3.05 (t, *J* = 5.4 Hz, 0.80 × 4H), 1.74–1.68 (m, 4H), 1.60–1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (d, $^1J_{CF}$ = 236.7 Hz), 152.3, 149.1 (d, $^4J_{CF}$ = 2.2 Hz), 129.0, 119.2, 118.4 (d, $^3J_{CF}$ = 7.5 Hz), 116.6, 115.4 (d, $^2J_{CF}$ = 21.8 Hz), 51.8, 50.7, 26.0, 25.9, 24.3, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –125.1 to –125.1 (m, 1F); HRMS (EI) calcd for $C_{11}H_{14}FN$ $[M]^+$ 179.1110, found 179.1109.

*4.2.23. 1-(2- and 3-Fluorophenyl)piperidine (**3la**, CAS: 64287-24-7; 64287-25-8).* Yellow liquid. Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06–6.87 (m, 4H), 3.02 (t, *J* = 5.4 Hz, 4H), 1.78–1.72 (m, 4H), 1.60–1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (d, $^1J_{CF}$ = 244.2 Hz), 141.4 (d, $^3J_{CF}$ = 8.5 Hz), 124.3 (d, $^4J_{CF}$ = 3.6 Hz), 122.0 (d, $^3J_{CF}$ = 7.9 Hz), 119.2 (d, $^4J_{CF}$ = 3.1 Hz), 116.0 (d, $^2J_{CF}$ = 20.8 Hz), 52.2, 52.1, 26.2, 24.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –122.7 to –122.8 (m, 1F), HRMS (EI) calcd for $C_{11}H_{14}FN$ $[M]^+$ 179.1110, found 179.1109.

*4.2.24. 1-(3- and 4-Methoxyphenyl)-2,2,6,6-tetramethylpiperidine (**3bm**, CAS: 72835-06-4; 1391766-38-3).* Yellow liquid. Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.4 Hz, 0.50 × 1H, *m*-isomer）, 7.10 (d, *J* = 8.8 Hz, 0.50 × 2H, *p*-isomer), 6.81 (d, 0.50 × 1H, *m*-isomer), 6.75–6.70 (m, 2H), 3.79–3.78 (m, 3H), 1.73–1.70 (m, 2H), 1.56–1.53 (m, 4H), 1.02 (s, 6H), 1.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.1, 148.1, 139.5, 134.7, 127.7, 126.6, 120.2, 112.6, 110.1, 55.2, 55.1, 54.1, 54.0, 42.4, 42.3, 28.7, 18.4; HRMS (EI) calcd for $C_{16}H_{25}NO$ $[M]^+$ 247.1936, found 247.1936.

*4.2.25. 2-Methyl-1-(m- and p-tolyl)piperidine (**3cb**, CAS: 1843260-04-7).* Yellow liquid. Yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.8 Hz, 0.75 × 1H, *m*-isomer); 7.05 (d, *J* = 8.4 Hz, 0.25 × 2H, *p*-isomer), 6.88 (d, *J* = 8.4 Hz, 0.25 × 2H, *p*-isomer), 6.76–6.74 (m, 0.75 × 2H, *m*-isomer), 6.65 (d, *J* = 7.6 Hz, 0.75 × 1H, *m*-isomer), 3.88–3.84 (m, 0.75 × 1H, *m*-isomer), 3.72–3.65 (m, 0.25 × 1H, *p*-isomer), 3.21–3.16 (m, 0.75 × 1H, *m*-isomer) 3.09–3.04 (m, 0.25 × 1H, *p*-isomer), 2.99–2.93 (m, 1H), 2.30 (s, 0.75 × 3H, *m*-isomer), 2.27 (s, 0.25 × 3H, *p*-isomer), 1.88–1.55 (m, 6H), 0.98 (d, *J* = 6.8 Hz, 0.75 × 3H, *m*-isomer), 0.95 (d, *J* = 6.4 Hz, 0.25 × 3H, *p*-isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 138.6, 129.5, 128.8, 120.2, 119.0, 118.7, 114.9, 52.5, 51.6, 47.2, 45.4, 32.4, 31.9, 29.7, 26.3, 26.2, 20.6, 20.5, 20.0, 14.8, 14.1.

*4.2.26. 4-(Naphthalen-1-yl)morpholine (**3fe-1**, CAS:98223-72-4).*[2a] White solid. Mp 82.6–83.6 °C. Yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.47–7.40 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 3.91 (t, *J* = 4.4 Hz, 4H), 3.03 (t, *J* = 4.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 134.9, 128.9, 128.6, 126.0, 125.9, 125.6, 123.9, 123.5, 114.8, 67.5, 53.6.

*4.2.27. 4-(Naphthalen-2-yl)morpholine (**3fe-2**, CAS:7508-21-6).*[2a] Yellow solid. Mp 89.3–90.2 °C. Yield 30%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.68 (m, 3H), 7.42–7.38 (m, 1H), 7.32–7.28 (m, 1H), 7.25–7.22 (m, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 3.90 (t, *J* = 4.8 Hz, 4H), 3.24 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 134.6, 128.8, 128.7, 127.5, 126.8, 126.4, 123.6, 118.9, 110.2, 67.0, 49.8.

*4.2.28. 4-(2- and 3-Fluorophenyl)morpholine (**3le**, CAS: 353743-42-7; CAS: 384344-17-6).*[8b] Yellow liquid. Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.00 (m, 2H), 6.98–6.92 (m, 2H), 3.88

(t, J = 4.6 Hz, 4H), 3.09 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (d, $^1J_{CF}$ = 244.5 Hz), 140.0 (d, $^3J_{CF}$ = 8.4 Hz), 139.3, 124.5 (d, $^4J_{CF}$ = 3.6 Hz), 122.7 (d, $^3J_{CF}$ = 7.9 Hz), 118.7 (d, $^4J_{CF}$ = 2.9 Hz), 116.2 (d, $^2J_{CF}$ = 20.6 Hz), 114.1, 67.0, 51.0, 50.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –122.9 to –123.0 (m, 1F).

*4.2.29. 4-(2- and 3-Methoxyphenyl)morpholine (**3ne**, CAS: 27347-13-3: CAS: 32040-09-8).*[2a] Yellow liquid. Yield 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 8.0 Hz, 0.29 × 1H, *m*-isomer), 7.02–6.97 (m, 0.71 × 1H, *o*-isomer), 6.92 (d, J = 4.0 Hz, 0.71 × 2H, *o*-isomer), 6.86 (d, J = 8.0 Hz, 0.71 × 1H, *o*-isomer), 6.52–6.50 (m, 0.29 × 1H, *m*-isomer), 6.44–6.41 (m, 0.29 × 2H, *m*-isomer), 3.87 (t, J = 4.6 Hz, 0.71 × 4H, *o*-isomer), 3.84 (s, 0.71 × 3H, *o*-isomer), 3.82 (t, J = 5.0 Hz, 0.29 × 4H, *m*-isomer), 3.75 (s, 0.29 × 3H, *m*-isomer), 3.12 (t, J = 4.8 Hz, 0.29 × 4H, *m*-isomer), 3.05 (t, J = 4.6 Hz, 0.71 × 4H, *o*-isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 152.7, 152.3, 141.2, 129.9, 123.2, 121.1, 118.0, 111.4, 108.5, 104.7, 102.2, 67.2, 66.9, 55.4, 55.2, 51.2, 49.3.

*4.2.30. 1-(2,5-Dimethoxyphenyl)-2,2,6,6-tetramethylpiperidine (**3gm**).* White crystal. Mp 77.2–77.7 °C. Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, J = 3.2 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.72–6.69 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 1.86–1.80 (m, 1H), 1.62–1.51 (m, 5H), 1.24 (s, 6H), 0.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 152.4, 136.7, 121.1, 110.8, 110.0, 55.6, 55.4, 54.3, 41.7, 31.4, 25.8, 18.5; HRMS (EI) calcd for $C_{17}H_{27}NO_2$ $[M]^+$ 277.2042, found 277.2043.

*4.2.31. 4-(2,5-Dimethoxyphenyl)morpholine (**3ge**, CAS: 154519-06-9).*[6a] Yellow liquid. Yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.49（dd, J = 8.6, 3.0 Hz, 1H）, 3.87 (t, J = 4.6 Hz, 4H), 3.81 (s, 3H), 3.76 (s, 3H), 3.06 (t, J = 4.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 146.6, 142.2, 112.1, 106.1, 105.5, 67.1, 55.9, 55.6, 51.0.

*4.2.32. N,N-Dibutyl-2,5-dimethoxyaniline (**3gj**, CAS: 84311-83-1).*[6a] Yellow liquid. Yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, J = 8.8 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.44 (dd, J = 8.8, 2.8 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.08 (t, J = 7.6 Hz, 4H), 1.48–1.41 (m, 4H), 1.30–1.24 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 148.0, 141.4, 112.8, 108.7, 104.7, 56.2, 55.5, 52.4, 29.1, 20.6, 14.0.

*4.2.33. 1-Phenyl-4-(pyridin-2-yl)piperazine (**3mh**, CAS: 682773-53-1).*[2a] Yellow solid. Mp 108.3–109.5°C. Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 4.8, 1.6 Hz, 1H), 7.51–7.46 (m, 1H), 7.28 (dd, J = 8.6, 7.4 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 7.4 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H), 6.64 (dd, J = 7.2 Hz, 5.2 Hz, 1H), 3.69 (t, J = 5.2 Hz, 4H), 3.29 (t, J = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 151.3, 148.0, 137.6, 129.2, 120.1, 116.4, 113.6, 107.3, 49.2, 45.3.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.