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Synthesis of Tetrahydro[1,3,4]triazepines via Redox-Neutral α-C(sp^3)−H Amination of Cyclic Amines

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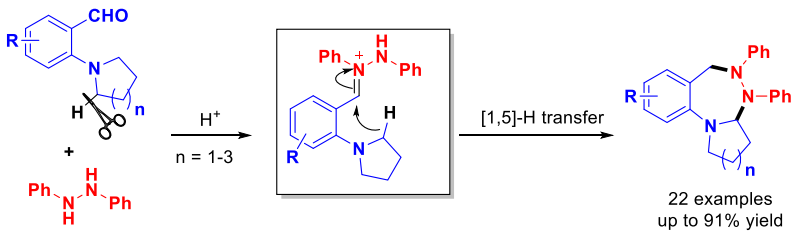
Graphic Abstract



Abstract: A Brønsted acid-catalyzed α-C(sp^3)-H amination of cyclic amines using hydrazines as coupling partners has been reported. This methodology provides an unique protocol to the one-step assembly of tetrahydro[1,3,4]triazepines via [1,5]-hydride transfer-initiated C(sp^3)-H amination. This reaction features mild conditions, good yields and high atom-economy.

INTRODUCTION

The ring-fused azepine structural motifs are cores of several natural alkaloids and pharmaceuticals,[1, 2] such as stenine[1c-e, 2a, 2b] (*stemona* alkaloid, with a pyrrolo[1,2-*a*]azepine ring system), cephalotaxine[2c-e] (*cephalotaxu*, with a pyrrolo[1,2-*a*]azepine ring system),

cochinchistemonine[2f-h] (*stemona* alkaloid, with a pyrido[1,2-*a*]azepine ring system) and amtramycin[2i] (*Streptomyces*, with pyrrolo[2,1-*c*][1,4]diazepine ring system) (Figure 1). Among them, pyrrolo[2,1-*c*][1,4]benzodiazepine scaffold can be used as sequence-selective DNA-binding agent, owing to the presence of polynitrogen-containing azepine geometry.[2i, 3] Given that the average number of nitrogen atoms per drug is 2.3 for all the small-molecule drugs,[4] the polynitrogen-containing azepines would be ideal motifs for new drug discovery.[5] In comparison to the substantial achievements that have been made to access ring-fused azepines,[6] little effort has been devoted to the construction of polynitrogen-containing azepines.

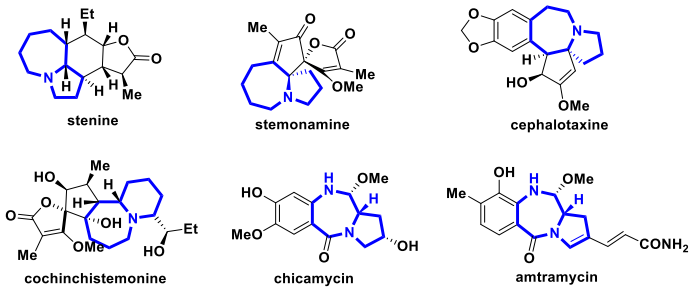
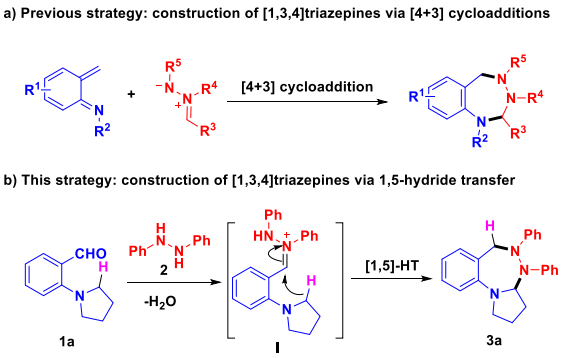


Figure 1. Natural products and pharmaceuticals containing ring-fused azepine moieties.

Until now, approaches toward polynitrogen-containing azepines heavily relied on 1,3-dipole involved [4 + 3] cycloadditions (Scheme 1a).[7] However, the requirement of specialized 1,3-dipolar synthons for the cycloaddition largely limits the generality and application of these reactions. Therefore, the exploration of new methodologies to construct polynitrogen-containing azepines derivatives is in great demand. In recent years, [1,5]-hydride transfer (HT) initiated C(sp^3)-H functionalization has emerged as a powerful tool for the rapid construction of heterocycles with high efficiency and high step/atom economy.[8-10] As our continuing interest in [1,5]-HT initiated C(sp^3)-H functionalizations,[11] we intend to develop an organocatalytic α-C(sp^3)−H amination of cyclic amines to access polynitrogen-containing azepines. As shown in Scheme 1b, condensation of aldehyde **1a** with hydrazines **2** would afford iminium ion **I** [12], which would induce the [1,5]-HT to give access to the cyclization product **3a**.

Scheme 1. α-C(sp^3)−H Amination of Cyclic Amines to Access [1,3,4]Triazepines.

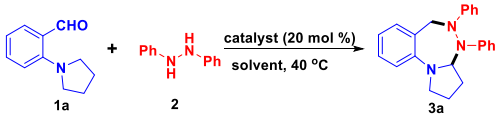


Herein, we report a Brønsted acid-catalyzed direct α-C(sp^3)-H amination reaction of cyclic amines using hydrazines as coupling partners. This methodology provided access to ring-fused [1,3,4]triazepine derivatives in good yields.

RESULTS AND DISCUSSION

At the outset, *ortho*-pyrrolidinylbenzaldehdyde **1a** and 1, 2-diphenylhydrazine **2** were selected as model substrates to test this reaction. Initially, a range of Brønsted acids catalysts were evaluated for this reaction at 20 mol % catalyst loadings in EtOH. To our delight, when (-)-10-camphorsulfonic acid ((-)-CSA) was used as a catalyst, the desired product **3a** was isolated in 80% yield (Table 1, entry 1). Although the yields were not improved by 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (PA) and trifluoroacetic acid (TFA), *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) could afford the desired product in 91% yield (Table 1, entries 2-5). Further screening of Lewis acids such as $BF_3{\cdot}Et_2O$, $Mg(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_3$ and $FeCl_3$ led to inferior results (Table 1, entries 6-10). Therefore, $TsOH{\cdot}H_2O$ was chosen as the best catalyst for further evaluation. The subsequent investigation of solvents showed EtOH was the best reaction media (Table 1, entries 11-16). Finally, a diminished yield was observed when 1.5 equiv of **2** was used (Table 1, entry 17). Consequently, the most effective condition to carry out the reaction was indicated as in entry 5.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]
1	(−)-CSA	EtOH	80
2	PA	EtOH	80
3	TFA	EtOH	70
4	TfOH	EtOH	82
5	$TsOH{\cdot}H_2O$	EtOH	91
6	$BF_3{\cdot}Et_2O$	EtOH	80
7	$Mg(OTf)_2$	EtOH	23

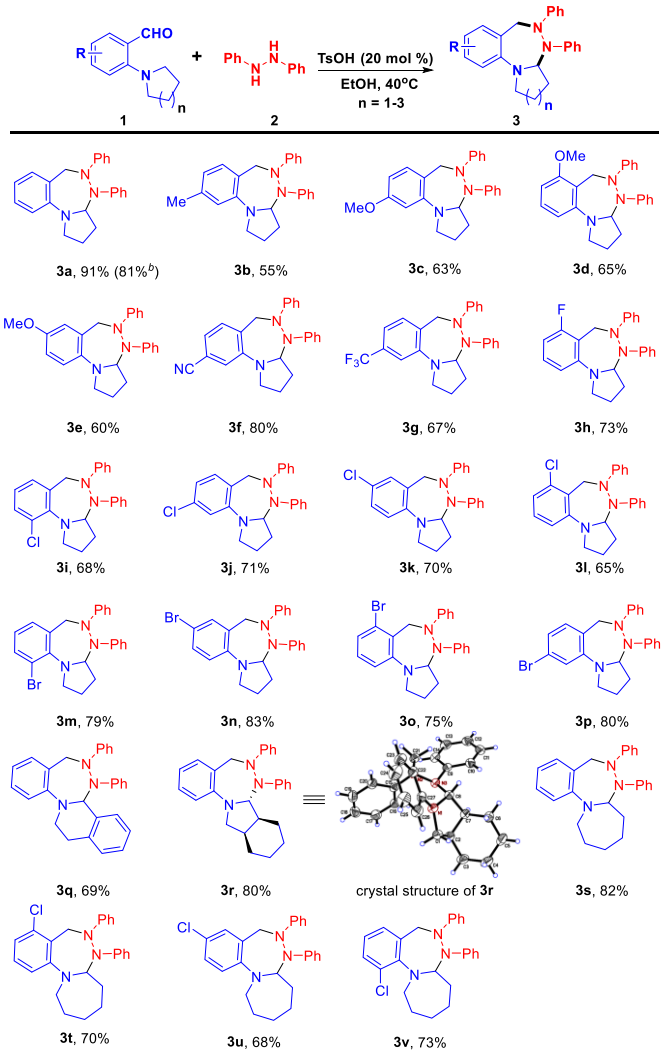
8	$Cu(OTf)_2$	EtOH	< 10
9	$Sc(OTf)_3$	EtOH	86
10	$FeCl_3$	EtOH	21
11	$TsOH{\cdot}H_2O$	DCE	65
12	$TsOH{\cdot}H_2O$	DCM	60
13	$TsOH{\cdot}H_2O$	TFE	80
14	$TsOH{\cdot}H_2O$	toluene	trace
15	$TsOH{\cdot}H_2O$	THF	trace
16	$TsOH{\cdot}H_2O$	H_2O	trace
17[c]	$TsOH{\cdot}H_2O$	EtOH	82

[a]Reaction conditions (unless otherwise noted): a solution of **1a** (0.1 mmol), **2** (0.1 mmol) and catalyst (0.02 mmol) in the indicated solvent (1.0 mL) was stirred at 40 °C for 5h. [b]**3a** was isolated in pure form by simple filtration. [c]1.5 equiv of **2** (0.2 mmol) was used. (−)-CSA = (−)-10-camphorsulfonic acid. PA = 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate.

With the optimized reaction conditions in hand, the substrate scope was investigated to examine the generality of the protocol (Table 2). Generally, a series of *ortho*-dialkylaminobenzaldehdydes **1** were employed in the reaction, affording the corresponding products **3** in moderate to excellent yields. With regard to the phenyl portion of **1**, to our delight, *ortho*-pyrrolidinylbenzaldehdyde substrates bearing electron-donating or electron-withdrawing substituents were both compatible with the reaction conditions, providing products **3b**-**3p** in 55-83% yields. The electron-donating methoxy group at different positions had negligible influence on the reactivity, giving the expected products **3c**-**3e** in 60-65% yields. Moreover, the electron-withdrawing group such as trifluoromethyl and fluoro groups were well tolerated and furnished the desired products **3g** and **3h** in 67% and 73% yields, respectively. Notably, the success of the fluorine-substituted products indicated the potential application of this method in drug discovery. Besides, the desired triazepine adducts with chloro and bromo groups at various positions of benzene were all obtained in high yields (65-83%), which held great potential for further manipulations. Encouragingly, the transformation of the *ortho*-tetrahydroisoquinoline substituted benzaldehdyde were successful as well, giving pyrido[2,1-*c*]triazepine ring system **3q** in 69% yield. Octahydro-isoindole could also engage in this α-C(sp^3)-H amination to furnish the corresponding azepine **3r** in 80% yield. The relative configuration of the product **3r** has been unambiguously confirmed by X-ray crystallographic analysis. Remarkably, when dialkylamine substrates were used, the corresponding products azepino[2,1-*c*]]triazepines **3s**-**3v** were fully accessible via this methodology, which characterized by the challenging fused [7,7] polynitrogen-containing ring system. To further demonstrate the practicability of this established methodology, the gram-scale synthesis of **3a** was conducted in a 3 mmol scale. The reaction

proceeded efficiently and delivered the corresponding product in 81% yield, indicating the promising prospect in the medical industry.

Table 2. Substrate Scope of the Ring-fused [1,3,4]Triazepines [a]

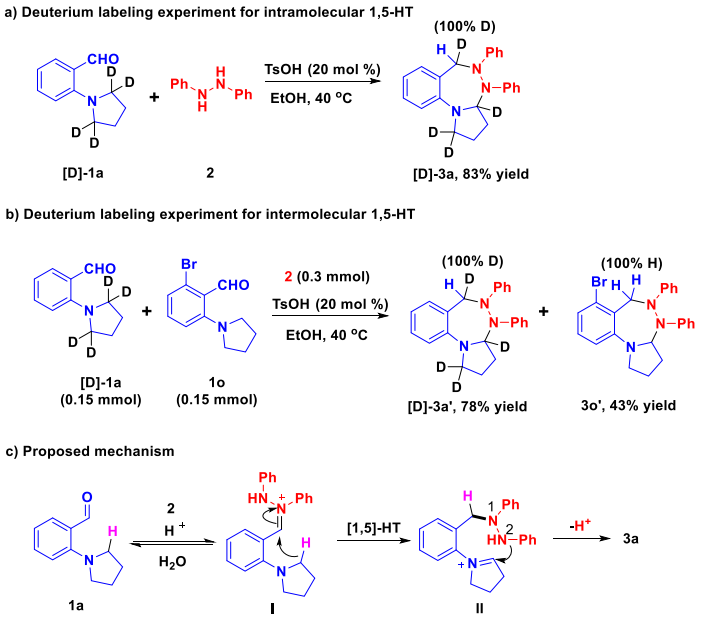


[a]Reaction conditions: a solution of **1** (0.1 mmol), **2** (0.1 mmol) and TsOH (0.02 mmol) in EtOH (1.0 mL) was stirred at 40 °C for 5h. The yields are for the isolated products after column chromatography. [b]The reaction was performed on a 3.0 mmol scale. [c]The pure solid product was obtained after filtration and washed with EtOH.

In order to further investigate the mechanism of this reaction, a deuterium labeling experiment was carried out as shown in Scheme 2. The deuteration at the benzylic position of **[D]-3a** fully corroborated the occurrence of intramolecular [1,5]-HT process (Scheme 2a). Moreover, the cross-over deuterium labeling experiment was conducted with **[D]-1a** and **1o** as the starting materials, leading to 100% deuterated **[D]-3a′** and non-deuterated **3o′**, correspondingly. This result indicated the nonexistence of intermolecular 1,5-HT in this reaction (Scheme 2b). On the basis of these

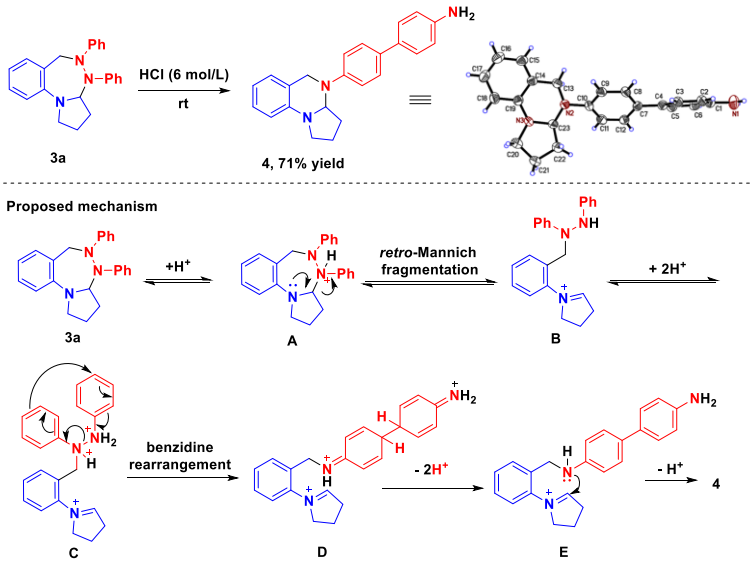
experimental results, we proposed a mechanism as shown in Scheme 2c. The condensation product **I** served as the key precursor for this intramolecular [1,5]-HT. The subsequent nucleophilic attack of nitrogen atom N2 toward the resultant iminium ion II furnished the cyclization product **3a**.

Scheme 2. Mechanistic Details



A late-stage derivatization of **3a** was carried out in hydrochloric acid, as depicted in Scheme 3. Intriguingly, the six-membered diaza-heterocycle **4** was obtained in 71% yield, accompanied by the emergence of benzidine motif. Plausible mechanistic pathway was proposed in Scheme 3. The triazepine adducts **3a** might undergo an acid-promoted retro-Mannich fragmentation to generate iminium ion B. Assisted by the highly acidic condition, the benzidine rearrangement[13] occurred to furnish the dearomative intermediate **D,** which followed by deprotonation to give the rearomatic intermediate **E**. Finally, the subsequent 6-*endo-trig* cyclization of **E** gave rise to the compound **4**. The structure of **4** has been confirmed by X-ray crystallographic analysis (Scheme 3).

Scheme 3. Conversion of 3a to Diaza-heterocycle 4



CONCLUSION

In conclusion, a Brønsted acid-catalyzed α-C(sp^3)-H amination of cyclic amines using hydrazines as coupling partners has been developed. This methodology enabled the one-step assembly of ring-fused tetrahydro[1,3,4]triazepines via [1,5]-HT initiated C(sp^3)-H amination. Various [1,3,4]triazepines could be synthesized in good yields. The mild and easy handling conditions, good yields and high atom-economy make it an appealing method for future applications in medicinal chemistry.

Experimental Section

All commercially available reagents, unless otherwise indicated, were used without further purification. All solvents were purified and dried according to standard methods prior to use. Reactions were monitored by thin layer chromatography (TLC) with 0.2 mm silica gel-coated HSGF 254 plates, visualized by UV light at 254 or 365 nm. Products were isolated and purified by column chromatography on 200-300 mesh silica gel. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker AMX 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer at room temperature. The chemical shifts (δ) were reported in ppm with respect to an internal standard, tetramethylsilane (0 ppm), and the solvent ($CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm). Coupling constants (J) are given in Hertz. Splitting patterns of apparent multiplets associated with an averaged coupling constants were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets) and br (broadened). All ^{13}C spectra were recorded with broadband proton decoupling. HRMS were

performed on a Waters XEVO QTOF mass spectrometer. Starting material **1** were synthesized according to the literature.[11b, 11e, 12a] For new compounds **1d**, **1m** and **1t-v**, they were synthesized and characterized as follows.

General procedure for the synthesis of 1

To a 100-mL round bottom flask equipped with a magnetic stir bar were charged with 2-fluorobenzaldehydes (5.0 mmol), cyclamines (5.0 mmol), K_2CO_3 (10.0 mmol) and DMF (30 mL). The mixture was stirred at 150 ºC in heating blocks for 5-6 h. After the consumption of starting material, the mixture was poured into a separatory funnel containing 20 mL of saturated NaCl and 40 mL of EtOAc. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. Further column chromatography on silica gel (EtOAc: hexane = 1:500-1:800) afforded **1** as oil.

2-methoxy-6-(pyrrolidin-1-yl)benzaldehyde (1d). Yellow oil; 0.84 g, 82% yield; column chromatography eluent, petroleum ether/ethyl acetate = 500:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 8.7 Hz, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 3.33 – 2.91 (m, 4H), 2.13 – 1.66 (m, 4H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 188.9, 163.9, 150.3, 134.3, 112.3, 107.3, 98.0, 55.8, 52.4, 25.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1176; found 206.1182.

3-bromo-2-(pyrrolidin-1-yl)benzaldehyde (1m). Yellow oil; 0.93 g, 73% yield; column chromatography eluent, petroleum ether/ethyl acetate = 500:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 7.80 (d, *J* = 7.9, 1H), 7.77 (d, *J* = 7.6, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 3.77 – 2.92 (m, 4H), 2.47 – 1.73 (m, 4H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 150.5, 139.8, 138.0, 127.5, 126.8, 124.7, 52.3, 26.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{13}BrNO$ 254.0175; found 254.0177.

2-(azepan-1-yl)-6-chlorobenzaldehyde (1t). Yellow oil; 0.89 g, 75% yield; column chromatography

eluent, petroleum ether/ethyl acetate = 500:1; ^{1}H NMR (500 MHz, $CDCl_3$)δ 10.31 (s, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 3.35 – 3.23 (t, *J* = 5.5 Hz, 4H), 1.78 (s, 4H), 1.62 (s, 4H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 189.3, 155.4, 137.2, 133.1, 121.6, 119.8, 116.4, 54.9, 28.3, 28.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$ 238.0993; found 238.0999.

2-(azepan-1-yl)-5-chlorobenzaldehyde (1u). Yellow oil; 0.92 g, 77% yield; column chromatography eluent, petroleum ether/ethyl acetate = 500:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.67 (d, *J* = 2.8 Hz, 1H), 7.33 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 3.37 (t, *J* = 6.7Hz, 4H), 1.90 – 1.74 (m, 4H), 1.73 – 1.60 (m, 4H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 189.9, 154.6, 133.9, 129.6, 129.6, 127.4, 124.9, 120.1, 56.0, 28.6, 27.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$ 238.0993; found 238.0995.

2-(azepan-1-yl)-3-chlorobenzaldehyde (1v). Yellow oil; 0.93 g, 78% yield; column chromatography eluent, petroleum ether/ethyl acetate = 600:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 3.28 (s, 4H), 1.80-1.68 (m, 8H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 192.7, 153.8, 136.5, 136.3, 135.5, 126.7, 126.2, 54.6, 30.5, 28.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$ 238.0993; found 238.0998.

General Procedure for the Synthesis of 3

An oven-dried reaction tube was charged with *ortho*-pyrrolidinylbenzaldehdyde **1** (1.0 equiv, 0.1 mmol), 1,2-diphenylhydrazine **2** (1.0 equiv, 0.1 mmol), $TsOH{\cdot}H_2O$ (20 mol %) and EtOH (1 mL). The reaction mixture was stirred at 40 ºC in heating blocks and monitored by TLC. After the consumption of **1**, the solvent was removed under reduced pressure, and the residue was purified by

flash column chromatography (column chromatography eluent, petroleum ether/ethyl acetate = 100:1) to afford products **3**.

General Procedure for Gram-Scale Synthesis of 3a

An oven-dried round-bottomed flask was charged with *ortho*-pyrrolidinylbenzaldehdyde **1a** (3 mmol, 525 mg), 1,2-diphenylhydrazine **2a** (3 mmol, 552 mg), $TsOH{\cdot}H_2O$ (0.6 mmol, 114 mg) and EtOH (30 mL). The reaction mixture was stirred at 40 °C in heating blocks and monitored by TLC. After the consumption of **1a**, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (column chromatography eluent, petroleum ether/ethyl acetate = 100:1) to afford product **3a** as a white solid in 81% yield (0.87 g).

General Procedure for the Synthesis of diaza-heterocycle 4

An oven-dried reaction tube was charged with product **3a** (0.2 mmol, 68.3 mg) and 6M HCl (2 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After the consumption of **3a**, the reaction was quenched with Et_3N and extracted with ethyl acetate. The organic layers were dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (column chromatography eluent, petroleum ether/ethyl acetate = 10:1) to afford product **4** as a white solid in 70% yield (47.8 mg).

4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3a). White solid; 31.1 mg, 91% yield; mp 153–155 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 13.2, 5.9 Hz, 2H), 7.10 (s, 4H), 7.05 – 6.92 (m, 3H), 6.91 – 6.73 (m, 3H), 6.68 (t, *J* = 6.6 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 4.99 (d, *J* = 4.0 Hz, 1H), 4.67 (q, *J* = 17.9 Hz, 2H), 3.26 (s, 1H), 2.85 (d, *J* = 7.0 Hz, 1H), 2.24 (d, *J* = 5.7 Hz, 1H), 2.22 – 2.04 (m, 2H), 1.91 (d, *J* = 5.1 Hz, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 150.6, 149.0,

145.8, 128.9, 128.9, 128.6, 127.3, 123.7, 121.1, 119.9, 117.6, 116.6, 114.4, 79.9, 49.8, 49.2, 34.0, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}N_3$ 342.1965; found 342.1971.

9-methyl-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3b). White solid; 19.6 mg, 55% yield; mp 88–89 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.10 (t, *J* = 7.9 Hz, 2H), 7.03 – 6.92 (m, 4H), 6.84 (s, 2H), 6.72 – 6.63 (m, 2H), 6.43 (s, 1H), 4.96 (d, *J* = 5.6 Hz, 1H), 4.63 (q, *J* = 17.8 Hz, 2H), 3.27 (ddd, *J* = 10.9, 8.1, 5.7 Hz, 1H), 2.83 (t, *J* = 7.4 Hz, 1H), 2.32 – 2.21 (m, 4H), 2.19-2.05 (m, 2H), 1.96 – 1.86 (m, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 150.6, 149.0, 145.7, 137.0, 128.9, 128.8, 128.6, 121.0, 120.7, 117.5, 116.6, 115.2, 79.9, 49.5, 49.2, 34.0, 23.1, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{26}N_3$ 356.2121; found 356.2121.

9-methoxy-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3c). Light pink solid; 23.4 mg, 63% yield; mp 115–117 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 14.8, 7.2 Hz, 2H), 7.10 (t, *J* = 7.9 Hz, 2H), 6.97 (dt, *J* = 14.7, 6.8 Hz, 4H), 6.83 (s, 2H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.41 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.17 (d, *J* = 2.2 Hz, 1H), 4.98 (d, *J* = 5.5 Hz, 1H), 4.60 (q, *J* = 17.7 Hz, 2H), 3.74 (s, 3H), 3.30 – 3.17 (m, 1H), 2.84 (t, *J* = 7.4 Hz, 1H), 2.24 (dd, *J* = 11.6, 6.3 Hz, 1H), 2.21 – 2.06 (m, 2H), 1.94 – 1.86 (m, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 159.2, 150.6, 149.0, 147.0, 129.6, 128.9, 128.60, 121.1, 117.5, 116.8, 116.2, 104.5, 101.0, 79.7, 55.2, 49.3, 49.2, 34.0, 23.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{26}N_3O$ 372.2070; found 372.2072.

7-methoxy-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3d). White solid; 24.1 mg, 65% yield; mp 175–176 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 9.3, 6.6 Hz, 3H), 7.10 (t, *J* = 7.9 Hz, 2H), 7.05 (t, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.77 (s, 2H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 8.1 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 5.02 (d, *J* = 18.4 Hz, 1H), 4.96 (d, *J* = 5.4 Hz, 1H), 4.29 (d, *J* = 18.4 Hz, 1H), 3.83 (s, 3H), 3.25 (ddd, *J* = 10.6, 8.1, 5.9 Hz, 1H), 2.81 (t, *J* = 7.2 Hz, 1H), 2.23 (dd, *J* = 11.5, 6.2 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.88 (dd, *J* = 11.1, 5.8 Hz, 1H), -0.00 (s, 1H); ^{13}C{^{1}H}NMR (126 MHz, CDCl3) δ 158.2, 150.7, 149.0, 147.1,

128.9, 128.6, 127.5, 120.9, 117.3, 116.5, 110.8, 107.4, 102.1, 80.3, 55.5, 49.3, 43.3, 33.8, 23.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{25}N_3ONa$ 394.1890; found 394.1899.

8-methoxy-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3e). White solid; 22.3 mg, 60% yield; mp 151–153 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dt, *J* = 17.3, 8.8 Hz, 2H), 7.10 (t, *J* = 7.9 Hz, 2H), 7.03 – 6.91 (m, 3H), 6.84 (s, 2H), 6.74 – 6.63 (m, 3H), 6.57 (d, *J* = 8.7 Hz, 1H), 4.87 (d, *J* = 5.7 Hz, 1H), 4.62 (q, *J* = 17.9 Hz, 2H), 3.75 (s, 3H), 3.23 (ddd, *J* = 11.1, 7.8, 5.7 Hz, 1H), 2.77 (t, *J* = 7.3 Hz, 1H), 2.25 – 2.11 (m, 2H), 2.11 – 2.01 (m, 1H), 1.87 (dt, *J* = 11.5, 5.8 Hz, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 153.5, 150.7, 148.8, 139.8, 129.0, 128.6, 125.4, 120.9, 117.6, 116.3, 115.4, 114.4, 112.3, 80.4, 55.7, 49.9, 49.4, 34.2, 23.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{25}N_3ONa$ 394.1890; found 394.1893.

4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine-9-carbonitrile (3f). White solid; 29.3 mg, 80% yield; mp 171–173 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.17 (m, 3H), 7.07 (t, *J* = 7.9 Hz, 2H), 6.99 – 6.91 (m, 4H), 6.81 (s, 2H), 6.62 (t, *J* = 7.2 Hz, 1H), 5.11 (d, *J* = 6.2 Hz, 1H), 4.81 (d, *J* = 18.4 Hz, 1H), 4.59 (d, *J* = 18.2 Hz, 1H), 3.30 – 3.17 (m, 1H), 2.75 (t, *J* = 7.6 Hz, 1H), 2.34 – 2.15 (m, 1H), 2.03 (ddd, *J* = 18.6, 14.7, 6.3 Hz, 2H), 1.97 – 1.86 (m, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 150.0, 148.6, 146.4, 129.8, 129.2, 129.0, 128.8, 123.4, 121.7, 119.3, 118.3, 117.5, 116.8, 111.2, 111.0, 79.7, 49.7, 49.4, 34.0, 23.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}N_4$ 367.1917; found 367.1924.

4,5-diphenyl-9-(trifluoromethyl)-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4] triazepine (3g). White solid; 32.7 mg, 80% yield; mp 158–160 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.22 – 7.16 (m, 1H), 7.10 (dd, *J* = 14.8, 7.1 Hz, 3H), 7.04 – 6.92 (m, 3H), 6.81 (s, 3H), 6.71 (t, *J* = 7.3 Hz, 1H), 5.00 (d, *J* = 5.5 Hz, 1H), 4.76 – 4.61 (m, 2H), 3.35 – 3.24 (m, 1H), 2.88 (t, *J* = 7.4 Hz, 1H), 2.27 (dd, *J* = 11.5, 6.2 Hz, 1H), 2.18 (tdd, *J* = 11.4, 9.6, 5.4 Hz, 2H), 1.95 (dd, *J* = 10.8, 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.2, 148.7, 146.1, 129.7 (q, *J* = 32.0 Hz), 129.3, 129.0, 128.8, 127.5, 124.3 (q, *J* = 272.2 Hz), 121.5, 118.1, 116.7, 116.5 (q, *J* = 3.7 Hz), 111.1 (q, *J* = 3.6Hz), 79.9,

49.5, 49.4, 34.1, 23.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.44 (s); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}F_3N_3$ 410.1839; found 410.1839.

7-fluoro-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3h). White solid; 26.2 mg, 73% yield; mp 189–191 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 2H), 7.07 – 6.92 (m, 4H), 6.82 (s, 2H), 6.70 (t, *J* = 6.9 Hz, 1H), 6.58 (t, *J* = 8.6 Hz, 1H), 6.36 (d, *J* = 8.0 Hz, 1H), 5.00 (dd, *J* = 22.2, 11.2 Hz, 2H), 4.42 (d, *J* = 18.3 Hz, 1H), 3.32 – 3.19 (m, 1H), 2.83 (t, *J* = 6.7 Hz, 1H), 2.24 (d, *J* = 5.1 Hz, 1H), 2.23 – 2.08 (m, 2H), 1.92 (d, *J* = 4.6 Hz, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 161.85 (d, *J* = 239.4 Hz), 150.2, 148.7, 147.8 (d, *J* = 6.8 Hz), 128.9, 128.7, 128.1 (d, *J* = 10.6 Hz), 121.3, 117.8, 116.7, 110.3 (d, *J* = 17.0 Hz), 109.8 (d, *J* = 2.3 Hz), 106.4 (d, *J* = 22.4 Hz), 79.9, 49.5, 42.3 (d, *J* = 7.1 Hz), 33.9, 23.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -117.21 (s); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}FN_3$ 360.1871; found 360.1880.

10-chloro-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3i). White solid; 25.5 mg, 68% yield; mp 135–137 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.07 (s, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 3H), 6.87 – 6.79 (m, 2H), 6.70 (t, *J* = 7.1 Hz, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 4.95 (d, *J* = 5.3 Hz, 1H), 4.61 (q, *J* = 18.0 Hz, 2H), 3.23 (dt, *J* = 11.5, 6.8 Hz, 1H), 2.81 (t, *J* = 7.3 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.22-2.07 (m, 2H), 1.97 – 1.83 (m, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 149.0, 148.5, 141.5, 133.7, 130.6, 129.5, 129.2, 129.0, 126.6, 124.7, 120.2, 118.1, 114.6, 81.3, 50.9, 48.3, 34.1, 22.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}ClN_3$ 376.1575; found 376.1582.

9-chloro-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3j). Light pink solid; 26.3 mg, 70% yield; mp 114–116 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.11 (t, *J* = 7.9 Hz, 2H), 6.99 (dt, *J* = 11.2, 7.7 Hz, 4H), 6.82 (dd, *J* = 8.0, 1.8 Hz, 3H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 1.6 Hz, 1H), 4.99 (d, *J* = 5.6 Hz, 1H), 4.62 (q, *J* = 17.9 Hz, 2H), 3.27 – 3.19 (m, 1H), 2.83 (t, *J* = 7.4 Hz, 1H), 2.25 (dd, *J* = 11.6, 6.3 Hz, 1H), 2.22 – 2.07 (m, 2H), 1.96 – 1.88 (m, 1H). ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 150.3, 148.8, 146.9, 132.9, 129.9, 128.9, 128.7, 122.1, 121.4,

119.7, 117.9, 116.7, 114.6, 79.7, 49.3, 49.3, 34.0, 23.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}ClN_3$ 376.1575; found 376.1581.

8-chloro-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3k). White solid; 26.3 mg, 70% yield; mp 186–188 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 13.7, 6.1 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.07 (s, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.97 (t, *J* = 8.5 Hz, 3H), 6.83 (d, *J* = 4.4 Hz, 2H), 6.70 (t, *J* = 7.1 Hz, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 4.95 (d, *J* = 5.3 Hz, 1H), 4.61 (q, *J* = 18.0 Hz, 2H), 3.31 – 3.16 (m, 1H), 2.81 (t, *J* = 7.3 Hz, 1H), 2.24 (dt, *J* = 12.7, 6.5 Hz, 1H), 2.22 – 2.05 (m, 2H), 1.91 (dd, *J* = 11.2, 5.9 Hz, 1H); $^{13}C\{^1H\}$NMR (126 MHz, $CDCl_3$) δ 150.3, 148.7, 144.5, 129.0, 128.7, 128.4, 127.2, 125.4, 124.5, 121.3, 117.9, 116.6, 115.6, 79.9, 49.4, 49.4, 34.0, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}ClN_3$ 376.1575; found 376.1579.

7-chloro-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3l). White solid; 24.4 mg, 65% yield; mp 193–195 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.4 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 2H), 6.99 (t, *J* = 8.5 Hz, 4H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.71 (dd, *J* = 24.2, 17.0 Hz, 3H), 6.49 (d, *J* = 8.1 Hz, 1H), 5.07 (d, *J* = 18.4 Hz, 1H), 4.98 (d, *J* = 4.2 Hz, 1H), 4.45 (d, *J* = 18.4 Hz, 1H), 3.30 – 3.18 (m, 1H), 2.79 (t, *J* = 6.8 Hz, 1H), 2.24 (d, *J* = 5.3 Hz, 1H), 2.20 – 2.05 (m, 2H), 1.98 – 1.84 (m, 1H); $^{13}C\{^1H\}$NMR (126 MHz, $CDCl_3$) δ 150.3, 148.7, 147.5, 134.5, 129.0, 128.8, 128.0, 121.4, 120.8, 120.4, 117.9, 116.7, 112.8, 80.0, 49.5, 47.0, 33.9, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}ClN_3$ 376.1575; found 376.1577.

10-bromo-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3m). White solid; 33.2 mg, 79% yield; mp 132–134 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 9.7, 6.2 Hz, 3H), 7.18 (t, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.95 – 6.78 (m, 5H), 6.75 (t, *J* = 7.3 Hz, 1H), 5.13 (d, *J* = 2.3 Hz, 1H), 4.77 (d, *J* = 17.0 Hz, 1H), 4.61 (d, *J* = 17.0 Hz, 1H), 3.98 (dd,

J = 14.1, 8.3 Hz, 1H), 2.45 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.29-2.22 (m, 1H), 2.21-2.15 (m, 1H), 2.05 – 1.90 (m, 2H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 149.0, 148.4, 142.90, 134.8, 132.8, 129.2, 129.1, 127.3, 125.5, 122.0, 119.9, 118.1, 114.3, 80.9, 51.3, 48.6, 34.0, 22.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{22}BrN_3Na$ 442.0889; found 442.0899.

8-bromo-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3n). White solid; 34.7 mg, 83% yield; mp 199–200 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.8 Hz, 2H), 7.21 (s, 1H), 7.18 – 7.07 (m, 3H), 6.97 (t, *J* = 7.6 Hz, 3H), 6.82 (s, 2H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 4.94 (d, *J* = 5.4 Hz, 1H), 4.61 (dd, *J* = 42.3, 18.0 Hz, 2H), 3.29 – 3.16 (m, 1H), 2.80 (t, *J* = 7.3 Hz, 1H), 2.24 (dt, *J* = 13.1, 6.6 Hz, 1H), 2.21 – 2.07 (m, 2H), 1.95 – 1.87 (m, 1H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 150.2, 148.7, 144.9, 131.2, 130.2, 129.0, 128.7, 125.9, 121.4, 117.9, 116.6, 116.1, 111.8, 79.9, 49.3, 49.3, 34.0, 23.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{22}BrN_3Na$ 442.0889; found 442.0896.

7-bromo-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3o). White solid; 31.5 mg, 75% yield; mp 189–191 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.6 Hz, 2H), 7.10 (dd, *J* = 16.9, 8.0 Hz, 3H), 6.98 (dd, *J* = 14.4, 7.6 Hz, 3H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.71 (dd, *J* = 20.5, 13.3 Hz, 3H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.02 (d, *J* = 18.3 Hz, 1H), 4.98 (d, *J* = 4.6 Hz, 1H), 4.44 (d, *J* = 18.3 Hz, 1H), 3.24 (dd, *J* = 14.3, 9.8 Hz, 1H), 2.78 (t, *J* = 6.9 Hz, 1H), 2.24 (d, *J* = 5.4 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.94 – 1.85 (m, 1H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 150.2, 148.7, 147.5, 129.0, 128.8, 128.3, 124.8, 124.1, 121.7, 121.4, 117.9, 116.7, 113.5, 79.9, 50.0, 49.5, 33.9, 23.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{22}BrN_3Na$ 442.0889; found 442.0907.

9-bromo-4,5-diphenyl-2,3,3a,4,5,6-hexahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]triazepine (3p). Light orange solid; 33.6 mg, 80% yield; mp 158–160 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.11 (t, *J* = 7.6 Hz,

2H), 7.03 – 6.94 (m, 5H), 6.82 (s, 2H), 6.74 – 6.67 (m, 2H), 4.98 (d, *J* = 5.0 Hz, 1H), 4.68 – 4.52 (m, 2H), 3.28 – 3.17 (m, 1H), 2.83 (t, *J* = 7.1 Hz, 1H), 2.25 (dd, *J* = 11.3, 6.1 Hz, 1H), 2.22 – 2.08 (m, 2H), 1.92 (dd, *J* = 10.9, 5.7 Hz, 1H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 150.2, 148.7, 147.1, 130.2, 128.9, 128.7, 122.7, 122.6, 121.4, 121.0, 117.9, 117.5, 116.7, 79.8, 49.3, 34.0, 23.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}BrN_3$ 420.1070; found 420.1068.

1,2-diphenyl-1,2,3,9,10,14b-hexahydrobenzo[5,6][1,2,4]triazepino[3,4-a]isoquinoline (3q). White solid; 27.8 mg, 69% yield; mp 180–182 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 3.2 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.30 – 7.24 (m, 4H), 7.23 – 7.19 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.10 – 7.05 (m, 3H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.91 (t, *J* = 7.0 Hz, 1H), 6.82 – 6.75 (m, 2H), 5.46 (s, 1H), 4.70 (s, 2H), 4.06 – 4.00 (m, 1H), 3.68 (t, *J* = 12.7 Hz, 1H), 3.13 (t, *J* = 13.2 Hz, 1H), 2.98 (d, *J* = 15.1 Hz, 1H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 152.9, 148.6, 146.1, 135.9, 134.8, 131.5, 129.3, 129.1, 128.7, 128.6, 128.3, 127.3, 127.2, 127.1, 121.2, 120.1, 119.1, 117.5, 117.3, 114.3, 77.2, 52.6, 46.9, 30.4; HRMS (ESI-TOF) m/z: $[M +H]^+$ calcd for $C_{28}H_{26}N_3$ 404.2121; found 404.2131.

6,7-diphenyl-6,7,7a,7b,8,9,10,11,11a,12-decahydro-5H-benzo[5,6][1,2,4]triazepino[3,4-a]isoindole (3r). White solid; 31.6 mg, 80% yield; mp 217–218 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.10 (d, *J* = 6.9 Hz, 4H), 6.97 (t, *J* = 8.6 Hz, 3H), 6.84 (t, *J* = 7.2 Hz, 3H), 6.67 (t, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.69 (d, *J* = 17.8 Hz, 1H), 4.62 (s, 1H), 4.58 (d, *J* = 17.9 Hz, 1H), 3.58 – 3.47 (m, 1H), 2.79 (d, *J* = 4.4 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 1H), 2.30 – 2.22 (m, 1H), 1.91 (d, *J* = 10.0 Hz, 1H), 1.75 (dd, *J* = 22.0, 12.4 Hz, 2H), 1.58 (d, *J* = 12.8 Hz, 2H), 1.41 (d, *J* = 11.3 Hz, 1H), 1.23 (dt, *J* = 21.9, 10.9 Hz, 2H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 150.3, 149.5, 146.2, 128.9, 128.6, 127.3, 123.4, 121.2, 119.6, 117.5, 116.6, 114.2, 86.5, 49.8, 49.1, 44.2, 33.7, 25.1, 24.8, 24.2, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{30}N_3$ 396.2434; found 396.2434.

6,7-diphenyl-6,7,7a,8,9,10,11,12-octahydro-5H-azepino[2,1-c]benzo[e][1,2,4]triazepine (3s). White solid; 30.3 mg, 82% yield; mp 83–85 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dt, *J* = 9.5, 4.8 Hz, 2H), 7.22 – 7.16 (m, 3H), 7.15 – 7.10 (m, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 8.3 Hz, 4H), 6.87 (t, *J* = 7.3 Hz, 1H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.71 (t, *J* = 7.3 Hz, 1H), 5.41 (dd, *J* = 8.2, 6.6 Hz, 1H), 4.55 (d, *J* =

7.5 Hz, 2H), 3.68 (dt, *J* = 15.1, 5.3 Hz, 1H), 3.35 (ddd, *J* = 14.8, 9.2, 5.3 Hz, 1H), 2.12 (ddd, *J* = 13.7, 9.3, 4.3 Hz, 1H), 1.91 – 1.81 (m, 3H), 1.75 – 1.65 (m, 2H), 1.52 – 1.43 (m, 1H), 1.40 – 1.32 (m, 1H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 150.0, 149.3, 148.3, 129. 6, 129.3, 129.1, 128.0, 127.2, 120.5, 119.9, 117.7, 117.5, 116.2, 75.9, 52.0, 51.6, 32.1, 30.3, 25. 6, 24.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{28}N_3$ 370.2278; found 370.2281.

4-chloro-6,7-diphenyl-6,7,7a,8,9,10,11,12-octahydro-5H-azepino[2,1-c]benzo[e][1,2,4]triazepine (3t). White solid; 28.3 mg, 70% yield; mp 220–222 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.17 (t, *J* = 7.8 Hz, 2H), 7.07 – 6.83 (m, 8H), 6.71 (t, *J* = 7.2 Hz, 1H), 5.18 (dd, *J* = 10.7, 4.3 Hz, 1H), 4.97 (d, *J* = 17.0 Hz, 1H), 4.56 (d, *J* = 17.0 Hz, 1H), 3.49 (ddd, *J* = 15.4, 7.8, 4.1 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.30 – 2.20 (m, 1H), 1.91 – 1.72 (m, 4H), 1.58 (dd, *J* = 12.7, 7.5 Hz, 1H), 1.54 – 1.42 (m, 2H).$^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 152.0, 149.8, 148.7, 134.2, 129.0, 128.9, 127.9, 123.6, 121.7, 121.5, 118.2, 117.7, 116.6, 50.5, 47.1, 32.9, 30.0, 27.3, 23.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{27}ClN_3$ 404.1888; found 404.1889.

3-chloro-6,7-diphenyl-6,7,7a,8,9,10,11,12-octahydro-5H-azepino[2,1-c]benzo[e][1,2,4] triazepine (3u). White solid; 27.4 mg, 68% yield; mp 144–146 °C; column chromatography eluent, petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.20 (dd, *J* = 9.6, 5.4 Hz, 3H), 7.08 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.98 – 6.87 (m, 6H), 6.74 (t, *J* = 7.3 Hz, 1H), 5.39 (dd, *J* = 9.9, 5.0 Hz, 1H), 4.56 – 4.46 (m, 2H), 3.63 (dt, *J* = 15.1, 5.2 Hz, 1H), 3.38 – 3.29 (m, 1H), 2.10 (ddd, *J* = 13.5, 9.2, 4.4 Hz, 1H), 1.85 (dt, *J* = 11.5, 5.4 Hz, 3H), 1.75 – 1.66 (m, 2H), 1.49 (dd, *J* = 10.1, 4.1 Hz, 1H), 1.38 – 1.30 (m, 1H); $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$) δ 149.7, 148.0, 147.9, 129.4, 129.2, 129.0, 128.8, 127.7, 124.5, 120.8, 118.8, 117.7, 116.3, 75.9, 51.8, 51.6, 31.9, 30.1, 25.4, 23.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{27}ClN_3$ 404.1888; found 404.1895.

1-chloro-6,7-diphenyl-6,7,7a,8,9,10,11,12-octahydro-5H-azepino[2,1-c]benzo[e][1,2,4] triazepine (3v). White solid; 29.5 mg, 73% yield; mp 140–142 °C; column chromatography eluent,

petroleum ether/ethyl acetate = 100:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 3H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.97 (t, *J* = 7.9 Hz, 2H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.54 (t, *J* = 7.2 Hz, 1H), 6.36 (d, *J* = 8.1 Hz, 2H), 5.10 (dd, *J* = 15.0, 5.0 Hz, 2H), 4.55 (d, *J* = 12.9 Hz, 1H), 3.72 (dd, *J* = 13.8, 11.3 Hz, 1H), 2.91 (dd, *J* = 14.2, 3.1 Hz, 1H), 2.33 – 2.23 (m, 1H), 2.00 (dd, *J* = 25.2, 10.9 Hz, 1H), 1.88 (dd, *J* = 19.0, 12.9 Hz, 3H), 1.74 (t, *J* = 11.4 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.37 – 1.25 (m, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 148.6, 148.2, 146.1, 138.1, 134.5, 129.5, 129.3, 129.0, 127.9, 127.1, 117.8, 117.6, 111.4, 78.4, 54.1, 49.2, 33.5, 31.9, 30.2, 24.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{27}ClN_3$ 404.1888; found 404.1889.

4'-(1,2,3,3a-tetrahydropyrrolo[1,2-a]quinazolin-4(5H)-yl)-[1,1'-biphenyl]-4-amine (4)

White solid; 47.8 mg, 70% yield; mp 90–92 °C; column chromatography eluent, petroleum ether/ethyl acetate = 10:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.17 (dt, *J* = 14.4, 9.1 Hz, 3H), 6.96 (d, *J* = 6.8 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 2H), 6.65 (t, *J* = 6.9 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.70 – 4.59 (m, 1H), 4.39 (d, *J* = 14.8 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.63 (s, 2H), 3.44 (d, *J* = 7.0 Hz, 1H), 3.41 – 3.26 (m, 1H), 2.09 (d, *J* = 5.0 Hz, 1H), 1.92 (dd, *J* = 24.2, 14.7 Hz, 2H), 1.77 (dd, *J* = 18.6, 9.0 Hz, 1H); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ 148.5, 145.8, 143.5, 137.7, 131.0, 127.9, 127.8, 126.8, 126.0, 125.4, 120.9, 116.3, 115.5, 111.4, 57.4, 47.2, 32.0, 22.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}N_3$ 342.1965; found 342.1971.

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org. Structural proofs and NMR spectra of products. List of the substrates and deuterium labeling experiments. X-ray crystallography data and CIF file of compounds **3r** and **4** (CIF).

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Notes

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