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Domino Assembly of Trifluoromethylated N,O-Heterocycles by the Reaction of Fluorinated α-Bromoenones with Amino Alcohols

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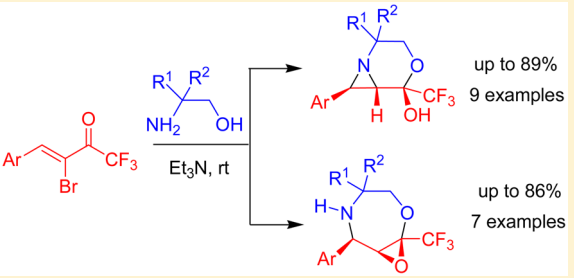
Supporting Information

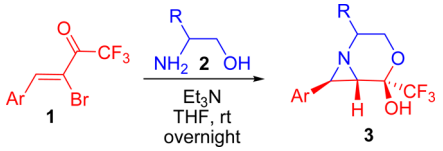
ABSTRACT: A highly efficient method for the selective synthesis of trifluoromethylated morpholines (4-oxa-1-azabicyclo[4.1.0]heptanes) and so far unknown 1,4-oxazepanes (2,8-dioxa-5-azabicyclo[5.1.0]-octanes) based on a domino reaction of fluorinated α-bromoenones with β-amino alcohols was elaborated. The assembly of both heterocyclic systems is initiated by an aza-Michael reaction followed by intramolecular cyclization. The conditions for total control of selectivity of the reaction were found.



Morpholine is an important scaffold of many bioactive compounds, exhibiting a wide range of biological activity. This heterocyclic fragment can be frequently found in the structure of natural products, pharmaceuticals, and agrochemicals.[1] Despite the importance of morpholine in drug discovery, its application in medicinal chemistry is so far limited, possibly due to the lack of efficient methods to prepare substituted morpholines.[2] Although several synthetic approaches have been developed for the preparation of these heterocycles, some of them suffer from serious disadvantages such as multistep procedure, low yield, or selectivity and harsh reaction conditions.[1] On the other hand, fluorinated heterocycles attract significant attention worldwide. Approximately 25% of modern drugs and agrochemicals contains at least one fluorine atom.[3] As a rule, the incorporation of fluorine into a molecule of organic compounds dramatically effects their physical, chemical, and biological properties, often in surprising and unpredictable ways.[4] To the best of our knowledge, only a very few trifluoromethylated morpholines are known to date.[1] Recently, we demonstrated that an unusual 1,2-migration of trifluoromethyl group completed a cascade of transformations initiated by the reaction of CF_3-bromoenones with symmetrically substituted 1,2-diamines giving a very rare type of piperazine derivatives.[5] These nontrivial results motivated us to investigate the reaction of fluorinated α-bromoenones with β-amino alcohols as 1,4-binucleophiles. We assumed that this transformation can open a new way to fluorinated morpholine derivatives and probably some other heterocycles.

We started our investigation from the reaction of α-bromoenones **1a**–**d**[4] with parent 2-aminoethanol **2a**. It was found that this transformation leads to regio- and diastereoselective formation of trifluoromethylated morpholines condensed with aziridine ring (4-oxa-1-azabicyclo[4.1.0]heptanes). For example, enone **1a** reacts smoothly with amino ethanol **2a** in the presence of triethylamine in THF or diethyl ether to give the corresponding bicycle **3a** in excellent yield at room temperature overnight (Table 1). It should be noted that our attempts to use similar nonfluorinated enones in this reaction failed. These results demonstrate the unique effect of CF_3CO moiety in this transformation. The studied reaction was found to be general, and morpholinols **3b**–**d** were obtained in good to excellent yields and very high diastereoselectivity in the case of enones **1b**–**d**.

Table 1. Reaction of Bromoenones 1 with Amino Alcohols 2



1 2 3

entry	enone	Ar	amino alcohol	R	isolated yield (%)	ratio of diastereomers
1	**1a**	Ph	**2a**	H	**3a** (86)	84:16
2	**1b**	3-MeC_6H_4	**2a**	H	**3b** (81)	77:23
3	**1c**	3-$MeOC_6H_4$	**2a**	H	**3c** (88)	82:18
4	**1d**	3-$O_2NC_6H_4$	**2a**	H	**3d** (89)	73:27
5	**1c**	3-$MeOC_6H_4$	**2b**	Et	**3e** (77)	55:25:20

The nature of substituent at the aryl moiety has no significant effect on the reaction result. In most cases, compounds **3** were isolated as a mixture of diastereomers according to NMR data (Table 1). The configuration of major isomer was determined by ^{1}H NMR spectroscopy. Thus, the vicinal coupling constant of

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aziridine protons (J < 1 Hz) allowed us to conclude that they have a *trans*-position.[6] Finally, X-ray data for heterocycles **3c,d** permit to determine the configuration unambiguously (Figure 1,

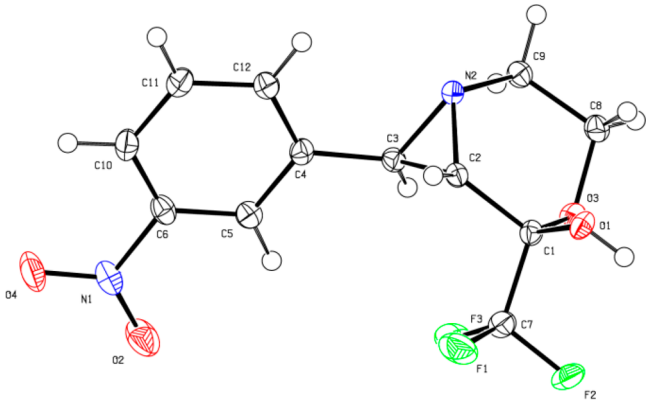
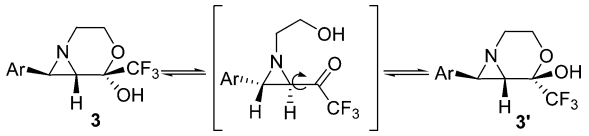


Figure 1. X-ray crystal structure of **3d**. Thermal ellipsoids set at 50% probability.

for compound **3c** see SI). Next, we examined the reaction with amino alcohol **2b** having an additional substituent. To our delight, in this case the reaction of enone **1c** with amino alcohol **2b** gave the target morpholinol **3e** in 77% yield (mixture of diastereomers in ratio 55:25:20) (Table 1, entry 5).

It is very interesting to note that heterocycles **3** exist as a single diastereomer in the solid state but slowly undergo spontaneous epimerization in solution. According to NMR data, the epimerization of pure **3c** took place in CD_3CN to reach a 3:1 ratio of two isomers after a week at rt. Apparently, this isomerization at the hemiketal carbon occurs via an equilibrium formation of the corresponding ketone as an opened form (Scheme 1). We showed that epimerization is reversible. Thus,

Scheme 1. Epimerization of Bicycles 3

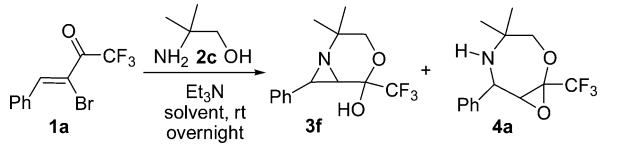


when a solution of a mixture of epimers was evaporated and NMR spectrum of the residue was registered immediately, only one isomer **3c** was detected. Quantum chemical calculations carried out for **3a** as a model heterocycle suggest that the epimer **3a′** is slightly less stable (by 0.6 kcal/mol, see SI).

Next, the reaction with 2-methyl-2-aminopropanol **2c**, having amino group at the tertiary carbon atom, was investigated. Surprisingly, the reaction of **1a** with **2c** led to the mixture of morpholine **3f** and unexpected heterocycle **4a** in 1:4 ratio and 88% total yield (Table 2). The structure of **4a** was ascertained unambiguously by means of NMR spectroscopy. Finally, the X-ray diffraction data for single crystal **4d** confirmed the proposed structure (Figure 2). Compounds **4** have a skeleton of 2,8-dioxa-5-azabicyclo[5.1.0]octane. It should be noted that these heterocycles are the first representatives of a new, previously unknown heterocyclic system.

Various solvents of different nature were screened to find conditions for the selective formation either six- or seven-membered heterocycles **3f** and **4a** (Table 2). Out of these, triethylamine and chloroform appeared to be the solvents of

Table 2. Effect of Solvent on the Reaction of Enone 1a with Amino Alcohol 2c[a]



solvent	3f:4a[b]	total yield (%)[b]	solvent	3f:4a[b]	total yield (%)[b]
neat	48:52	–	dioxane	25:75	–
NEt_3	2:98	–	EtOH[c]	25:75	75
CCl_4	6:94	–	EtOH	32:68	–
$CHCl_3$[c]	4:96	92 (76)[e]	*t*-BuOH	29:71	88
$CHCl_3$[d]	3:97	84	*i*-PrOH	29:71	–
$CHCl_3$	13:87	–	EtOAc	29:71	–
CH_2Cl_2	15:85	92	MeCN	35:65	–
$ClCH_2CH_2Cl$	11:89	–	DMF[c]	38:62	80
Toluene	7:93	87[e]	TFE	75:25	–
Benzene	20:80	–	DMSO	74:26	85
THF	19:81	91 (88)[e]	DMSO[f]	98:2	47
Et_2O	25:75	91	DMSO[g]	97:3	56 (51)[e]

[a]Complete conversion of **1a** was observed in all cases. [b]According to ^{19}F NMR data ($PhCF_3$ was used as standard). [c]Reaction was carried out at +7 °C. [d]Reaction was carried out at −18 °C. [e]Isolated yield. [f]DBU was used as a base. [g]DBU was added after 14 h.

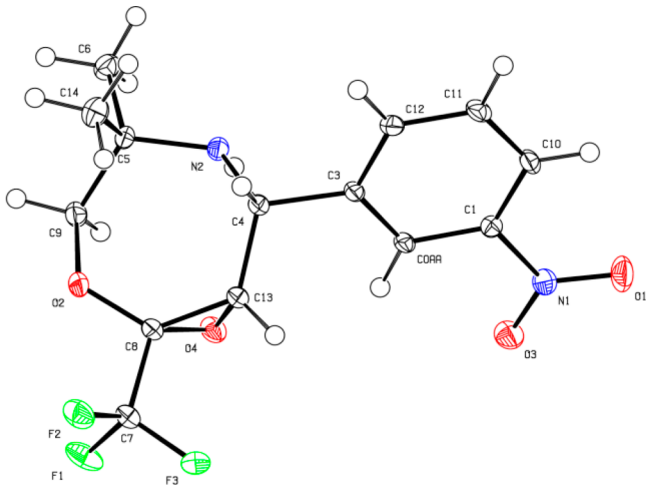


Figure 2. X-ray crystal structure of **4d**. Thermal ellipsoids set at 50% probability.

choice for the synthesis of oxazepane **4a**. In this case, the observed admixture of morpholine **3f** is <5%. In contrast, DMSO favors the assembly of morpholine **3f**. When DBU was used as a base instead of Et_3N, the ratio **3**:**4** reached 98:2. However, the overall yield in this case is quite moderate, which seems to be due to fragmentation of oxazepane **4** under the treatment with a strong base.

Having found the conditions for the chemoselective synthesis of both heterocyclic systems, we carried out reactions of bromoenones **1a**−**f** with amino alcohol **2c** in $CHCl_3$ and DMSO. As a result, a series of morpholines **3** and oxazepanes **4** was selectively prepared in good to high yields. It was shown that there is no significant influence of the aromatic moiety on the reaction direction: the enones having electron-withdrawing or electron-donating groups on the benzene ring give the corresponding oxazepane **4** in $CHCl_3$, whereas morpholines **3**

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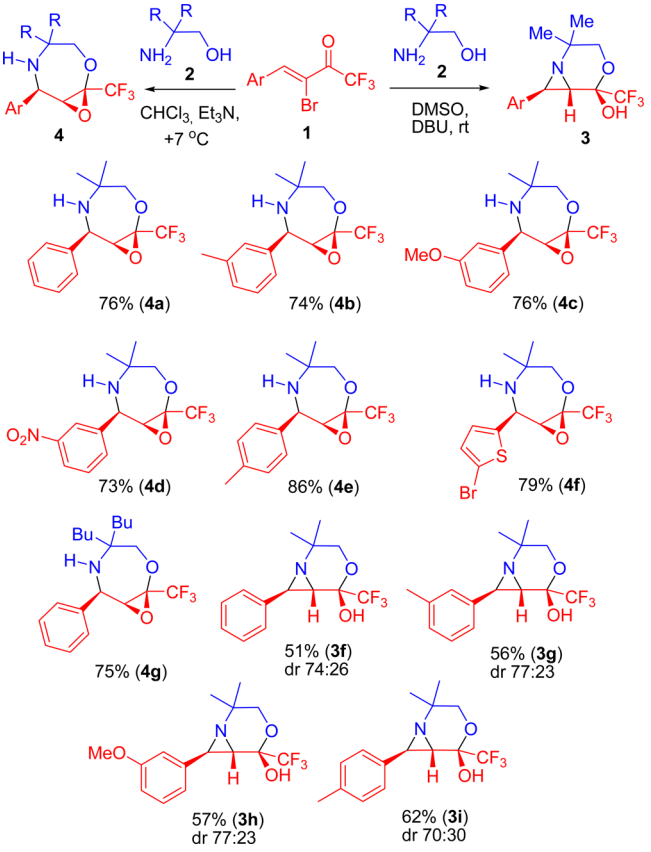
are formed in DMSO selectively (Scheme 2). The reaction of **1** with dibutyl-substituted amino ethanol **2d** proceeds in a similar

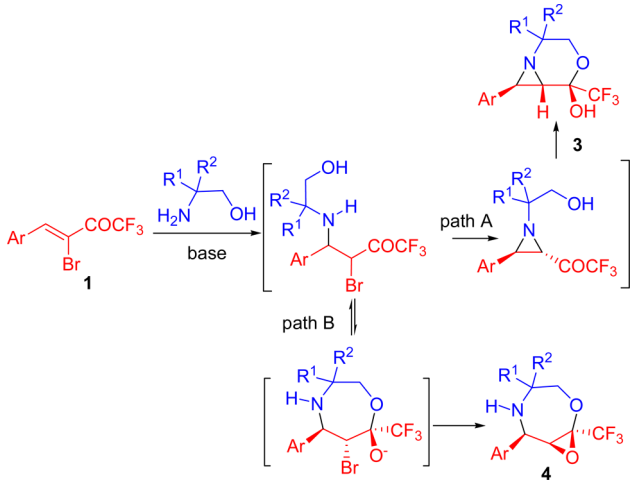
Scheme 2. Reaction of Bromoenones 1 with Amino Alcohols 2c and 2d



manner. Due to steric hindrance of amino group, in this case **4g** is formed highly selectively. It is very important to note that all oxazepanes **4** were formed in high yield and diastereoselectivity. The results obtained can be easily explained by a Thorpe−Ingold effect of two methyl groups at the carbon atom bonded to the nucleophilic center.[7]

A possible mechanism for the assembly of six- (**3**) and seven-membered heterocycles **4** from bromoenones **1** is outlined in Scheme 3. Obviously, both domino transformations are initiated by aza-Michael addition (aza-MIRC reactions).[8] The amino group, as a more nucleophilic center, adds to the β-carbon atom of the double bond of initial ketone **1**. In the first case, the Michael adduct undergoes intramolecular nucleophilic substitution to form the aziridine intermediate (pathway **A**). Subsequent cyclization via nucleophilic attack of the hydroxy group on the carbonyl group leads to bicyclic derivatives **3**. Alternatively, nucleophilic cyclization with participation of hydroxy group of amino alcohol moiety in the Michael adduct and carbonyl group takes place to form oxazepane **4** (pathway **B**) via a domino substitution of bromine. The key step in the proposed mechanism is the ring closure. In principle, both directions are competitive reaction paths. The nucleophilicity of nitrogen plays the most important role to switch the reaction into formation of **3** or **4**. Highly nucleophilic nitrogen favors the aziridine ring closure (pathway **A**). If the nitrogen is sterically hindered, then the oxygen becomes more a prominent reaction center. As a result, the nucleophilic substitution of bromine in a

Scheme 3. Possible Reaction Mechanism



seven-membered intermediate to give an oxirane ring completes the formation of bicycle **4**.[9] The observed stereochemistry of the reaction can be also explained in terms of this mechanism. The stereochemistry of ring fusion in the case of **3** is explained by the formation of thermodynamically favorable *trans*-aziridine. Subsequent cyclization leads to the structure having an equatorially arranged group CF_3 (A value 2.1 kcal/mol) and an axial hydroxyl more favorable due to anomeric effect. On the other hand, the stereochemical result in the case of formation of **4** can be explained by the preferable formation of the most stable intermediate having an aryl group and bromine *trans*-arranged. This configuration will determine the configuration of third stereocenter because the oxirane ring closure is possible only as a S_N2 process with *trans* configurated bromine and negatively charged oxygen participating in the final step of cyclization. We attempted to study the reaction mechanism by NMR, however, the reaction proceeds rapidly, and no intermediates were observed even at lower temperatures.

In summary, new approaches to trifluoromethylated morpholines (4-oxa-1-azabicyclo[4.1.0]heptanes) and 1,4-oxazepanes (2,8-dioxa-5-azabicyclo[5.1.0]octanes) were found via reactions of fluorinated α-bromoenones with 1,2-amino alcohols. The target compounds were isolated in high yield and excellent chemo- and stereoselectivity. It should be noted that prepared 2,8-dioxa-5-azabicyclo[5.1.0]octanes are the first representatives of a new, previously unknown heterocyclic system. All these heterocycles are of particular interest in medicinal chemistry.

EXPERIMENTAL SECTION

General Remarks. ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectra were at 400.1, 100.6, 40.6, and 375.6 MHz, respectively, from solutions in $CDCl_3$, MeCN-d_3, and DMSO-d_6. Chemical shifts (δ) in ppm are reported with the use of the residual chloroform (7.24 for ^{1}H and 77.2 for ^{13}C), acetonitrile (1.94 for ^{1}H; 1.4 and 118.7 for ^{13}C), and dimethyl sulfoxide (2.50 for ^{1}H and 39.5 for ^{13}C) as internal references. The coupling constants (J) are given in Hertz (Hz). The assignment of signals in the ^{1}H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ^{1}H−^{13}C HSQC and ^{1}H−^{13}C HMBC experiments. The values of the δ ^{15}N were measured through the 2D ^{1}H−^{15}N HMBC experiment. Here 2D NMR spectra are shown for **3e** and **4f** only. The ^{15}N and ^{19}F chemical shifts were referenced to CH_3NO_2 and $CFCl_3$, respectively. The IR spectra were recorded with an ATR/FT-IR spectrometer. The films of solid products for IR spectra are prepared by vaporization of corresponding solutions. The GC/MS analyses were performed with a GCMS

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instrument (EI, 70 eV). The silica gel used for flash chromatography was 230−400 mesh. All reagents were of reagent grade and were either used as such or distilled prior to use. All solvents were dried by standard procedures and freshly distilled prior to use.

Synthesis of Initial Bromoenones 1. The α-bromoenones **1a−f** were prepared as reported previously.[10]

*3-Bromo-1,1,1-trifluoro-4-(3-nitrophenyl)but-3-ene-2-one (**1d**).* Yellow solid, mp 67−69 °C, yield 775 mg (80%). ^{1}H NMR ($CDCl_3$): 7.70 (t, J = 7.5 Hz, 1H, Ar); 8.19 (d, J = 7.5 Hz, 1H, Ar), 8.22 (s, 1H, Ar); 8.34 (d, J = 7.5 Hz, 1H, Ar); 8.78 (s, 1H, C^4H). ^{13}C NMR ($CDCl_3$): 115.7 (q, J = 291.6 Hz, CF_3); 119.8 (C^3); 125.4 (C-2′, Ar); 126.1 (C-4′, Ar); 130.1 (C-5′, Ar); 134.6 (C-6′, Ar); 136.4 (C-1′, Ar); 144.2 (q, J = 3.6 Hz, C^4); 148.5 (C-3′, Ar); 175.8 (q, J = 36.0 Hz, C═O). ^{19}F NMR ($CDCl_3$): −68.5. IR (KBr, cm^{-1}): 1596 (C═C), 1716 (C═O). MS (EI), m/z (relative intensity, %): 325 (M^+ + 1, 11), 323 (M^+-1, 11), 256, 254 (57), 101 (100). Calcd for $C_{10}H_5BrF_3NO_3$: C 37.07; H 1.56; N 4.32. Found: C 37.47; H 1.76; N 4.08.

General Procedure for Synthesis of Morpholines (3a−e) and Oxazepanes (4a−g). A mixture of appropriate bromoenone **1** (1 mmol), amino alcohol **2** (1.2−1.8 mmol), and Et_3N (1.3−1.5 mmol) in corresponding solvent (3−5 mL, THF (**3a−e**), $CHCl_3$ (**4a−g**)) was maintained at room temperature (THF) or +7 °C ($CHCl_3$) for 16−24 h. The sediment (salt Et_3N·HBr) was filtered off, and the solvent was evaporated in vacuo. The residue was purified by column chromatography [silica gel, CH_2Cl_2, $CHCl_3$/methanol (90:10 or 95:5)] to give target products **3−4**.

General Procedure for Synthesis of Morpholines (3f−i). A mixture of appropriate bromoenone **1** (1 mmol), amino alcohol **2c** (1.2 mmol), and DBU (1.5 mmol) in DMSO was maintained at room temperature for 24 h. Reaction mixture was poured into 50 mL of water, extracted with CH_2Cl_2 (3 × 15 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography [silica gel, CH_2Cl_2, $CHCl_3$/methanol (90:10 or 95:5)] to give target products **3f−i**.

*7-Phenyl-5-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-ol (**3a**).* Pale yellow solid, mixture of two diastereomers in ratio 84:16, mp 124−125 °C (for pure major isomer), yield 224 mg (86%). ^{1}H NMR (MeCN-d_3): major: 2.09 (s, 1H, C^6H), 2.98 (ddd, J = 5.9, 11.3, 13.3 Hz, 1H, C^2H_2), 3.12 (s, 1H, C^7H), 3.36 (ddd, J = 2.1, 4.9, 13.3 Hz, 1H, C^2H_2), 3.73 (ddd, J = 2.1, 5.9, 12.0 Hz, 1H, C^3H_2), 4.00 (ddd, J = 4.9, 11.3, 12.0 Hz, 1H, C^3H_2), 5.49 (b.s., 1H, OH), 7.19−7.35 (m, 5H, Ph); minor: 2.41 (s, 1H, C^6H), 2.87−3.04 (m, 1H, C^2H_2), 3.13−3.21 (m, 1H, C^2H_2), 3.38 (s, 1H, C^7H), 3.61−3.67 (m, 1H, C^3H_2), 3.86−3.95 (m, 1H, C^3H_2), 5.49 (b.s., 1H, OH), 7.19−7.35 (m, 5H, Ph). ^{13}C NMR (MeCN-d_3): major: 41.1 (C^7), 46.3 (C^6), 46.9 (C^2), 58.1 (C^3), 92.7 (q, J = 32.4 Hz, C^5), 124.3 (q, J = 285.6 Hz, CF_3), 127.3, 128.8, 129.8, 140.1 (Ar); minor: 38.3 (C^7), 42.5 (C^6), 44.1 (C^2), 56.5 (C^3), 92.7 (q, J = 32.4 Hz, C^5), 124.3 (q, J = 285.6 Hz, CF_3), 127.7, 128.8, 129.8, 140.1 (Ar). ^{19}F NMR (MeCN-d_3): major: −85.2; minor: −87.0. IR (film, cm^{-1}): 1186 (C−F), 1606 (Ph). MS (EI), m/z (relative intensity, %): 259 (4, M^+), 258 (18), 161 (100), 160 (52), 132 (32), 123 (49), 118 (14), 105 (62), 104 (91), 91 (55), 77 (66), 69 (13), 51 (46). Calcd for $C_{12}H_{12}F_3NO_2$: C 55.60; H 4.67; N 5.40. Found: C 55.27; H 4.97; N 5.34.

*7-m-Tolyl-5-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-ol (**3b**).* Pale yellow solid, mixture of diastereomers in ratio 77:23, mp 136−138 °C (for pure major isomer), yield 221 mg (81%). ^{1}H NMR (MeCN-d_3): major: 2.08 (d, J = 2.3 Hz, 1H, C^6H), 2.33 (s, 3H, CH_3), 2.96 (ddd, J = 5.9, 11.3, 13.6 Hz, 1H, C^2H_2), 3.08 (b.s., 1H, C^7H), 3.36 (ddd, J = 2.3, 4.4, 13.6 Hz, 1H, C^2H_2), 3.73 (ddd, J = 2.6, 5.9, 12.3 Hz, 1H, C^3H_2), 4.01 (ddd, J = 4.6, 11.3, 12.3 Hz, 1H, C^3H_2), 5.33 (b.s., 1H, OH), 6.90−7.00 (m, 2H, Ar), 7.05 (d, J = 7.4 Hz, 1H, Ar), 7.18 (t, J = 7.7 Hz, 1H, Ar). ^{13}C NMR (MeCN-d_3): major: 21.8 (CH_3), 41.1 (C^7), 46.3 (C^6), 47.0 (C^2), 58.1 (C^3), 92.7 (q, J = 32.4 Hz, C^5), 124.3 (q, J = 285.2 Hz, CF_3), 124.5, 127.9, 129.5, 129.8, 139.6, 140.2 (Ar). ^{19}F NMR (MeCN-d_3): major: −84.5; minor: −86.1. IR (film, cm^{-1}): 1180 (C−F), 1608 (Ar). MS (EI), m/z (relative intensity, %): 273 (4, M^+), 272 (15), 175 (100), 174 (24), 160 (47), 146 (27), 132 (57), 123 (41), 119 (52), 118 (59), 105 (37), 104 (20), 91 (76), 77 (24), 65 (44), 51 (21). Calcd for $C_{13}H_{14}F_3NO_2$: C 57.14; H 5.16; N 5.13. Found: C 57.52; H 5.48; N 5.34.

*7-(3-Methoxyphenyl)-5-trifluoromethyl-4-oxa-1-azabicyclo-[4.1.0]heptan-5-ol (**3c**).* White solid, mixture of diastereomers in ratio 82:18, mp 130−131 °C (for pure major isomer), yield 254 mg (88%). ^{1}H NMR (MeCN-d_3): major: 2.09 (d, J = 2.7 Hz, C^6H), 2.94 (ddd, J = 6.1, 11.7, 13.5 Hz, 1H, C^2H_2), 3.09 (b.s., 1H, C^7H), 3.32 (ddd, J = 2.5, 4.6, 13.5 Hz, 1H, C^2H_2), 3.69 (ddd, J = 2.1, 5.9, 12.1 Hz, 1H, C^3H_2), 3.78 (s, 3H, CH_3), 3.97 (ddd, J = 4.5, 11.7, 12.1 Hz, 1H, C^3H_2), 5.48 (b.s., 1H, OH), 6.72−6.95 (m, 3H, Ar), 7.22 (t, J = 8.0 Hz, 1H, Ar); minor: 2.41 (d, J = 2.5 Hz, 1H, C^6H), 2.85−3.05 (m, 1H, C^2H_2), 3.13−3.21 (m, 1H, C^2H_2), 3.35 (d, J = 2.5 Hz, 1H, C^7H), 3.61−3.67 (m, 1H, C^3H_2), 3.78 (s, 3H, CH_3), 3.86−3.95 (m, 1H, C^3H_2), 5.48 (b.s., 1H, OH), 6.72−6.95 (m, 3H, Ar), 7.44 (t, J = 8.0 Hz, 1H, Ar). ^{13}C NMR (MeCN-d_3): major: 41.1 (C^7), 46.2 (C^6), 46.9 (C^2), 56.2 (C^3), 58.1 (CH_3), 92.6 (q, J = 32.3 Hz, C^5), 124.3 (q, J = 285.6 Hz, CF_3), 112.5, 114.4, 119.7, 130.9, 141.9, 161.4 (Ar). ^{19}F NMR (MeCN-d_3): major: −85.1; minor: −86.9. IR (film, cm^{-1}): 1185 (C−F), 1609 (Ar), 3369 (OH). MS (EI), m/z (relative intensity, %): 289 (21, M^+), 288 (21), 191 (100), 182 (15), 160 (38), 136 (51), 135 (58), 134 (47), 121 (40), 105 (27), 105 (27), 91 (29), 77 (52), 63 (21), 56 (32), 51 (29). Calcd for $C_{13}H_{14}F_3NO_3$: C 53.98; H 4.88; N 4.84. Found: C 54.09; H 4.96; N 4.52.

*7-(3-Nitrophenyl)-5-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0]-heptan-5-ol (**3d**).* Light-yellow solid, mixture of diastereomers in ratio 73:27, mp 159−160 °C (for pure major isomer), yield 257 mg (89%). ^{1}H NMR (MeCN-d_3): major: 2.16 (d, J = 2.7 Hz, C^6H), 3.02 (ddd, J = 6.0, 10.9, 13.3 Hz, 1H, C^2H_2), 3.29 (b.s., 1H, C^7H), 3.40 (ddd, J = 2.5, 4.5, 13.3 Hz, 1H, C^2H_2), 3.76 (ddd, J = 2.5, 6.0, 12.1 Hz, 1H, C^3H_2), 4.03 (ddd, J = 4.5, 10.9, 12.1 Hz, 1H, C^3H_2), 5.43 (b.s., 1H, OH), 7.51−7.66 (m, 2H, Ar), 8.00−8.05 (m, 1H, Ar), 8.07−8.15 (m, 1H, Ar); minor: 2.50 (d, J = 2.6 Hz, 1H, C^6H), 3.03−3.10 (m, 1H, C^2H_2), 3.15−3.25 (m, 1H, C^2H_2), 3.58 (d, J = 2.6 Hz, 1H, C^7H), 3.69 (ddd, J = 1.7, 4.7, 12.8 Hz, 1H, C^3H_2), 3.93 (ddd, J = 3.2, 11.3, 12.5 Hz, 1H, C^3H_2), 5.16 (b.s., 1H, OH), 7.51−7.66 (m, 2H, Ar), 8.10−8.15 (m, 2H, Ar). ^{13}C NMR (MeCN-d_3): major: 41.7 (C^7), 45.0 (C^6), 46.7 (C^2), 58.1 (C^3), 92.7 (q, J = 32.4 Hz, C^5), 122.0, 123.7 (Ar), 124.2 (q, J = 286.0 Hz, CF_3), 131.1, 133.8, 142.7, 150.0 (Ar); minor: 37.5 (C^7), 43.1 (C^6), 44.0 (C^2), 56.5 (C^3), 90.9 (q, J = 31.6 Hz, C^5), 122.5, 123.6 (Ar), 124.4 (q, J = 285.6 Hz, CF_3), 142.8, 150.0 (Ar). ^{19}F NMR (MeCN-d_3): major: −84.4; minor: −86.2. IR (CH_2Cl_2, cm^{-1}): 1193 (C−F), 1352, 1533 (NO_2), 1606 (Ar), 3550 (OH). MS (EI), m/z (relative intensity, %): 304 (<1, M^+), 303 (3), 257 (4), 206 (100), 189 (29), 177 (10), 159 (26), 149 (18), 131 (10), 123 (51), 104 (67), 89 (23), 77 (31). Calcd for $C_{12}H_{11}F_3N_2O_4$: C 47.38; H 3.64; N 9.21. Found: C 47.55; H 3.62; N 9.08.

*2-Ethyl-7-(3-methoxyphenyl)-5-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-ol (**3e**).* Light-yellow oil, mixture of three diastereomers in ratio 55:25:20, yield 243 mg (77%). ^{1}H NMR ($CDCl_3$): major: 1.08 (t, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.48−1.60 (m, 2H, $C\underline{H}_2CH_3$), 2.17 (s, 1H, C^6H), 2.67−2.72 (m, 1H, C^2H), 3.09 (s, 1H, C^7H), 3.64−3.67 (m, 2H, C^3H_2), 3.83 (s, 3H, OCH_3), 4.30 (b.s., 1H. OH), 6.83−6.98 (m, 3H, Ar), 7.24−7.28 (m, 1H, Ar); minor: 1.06 (t, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.48−1.60 [1.38−1.53] (m, 2H, $C\underline{H}_2CH_3$), 2.47 [2.64] (s, 1H, C^6H), 3.36 [3.27] (s, 1H, C^7H), 3.45−3.48 [3.20−3.24] (m, 1H, C^2H), 3.54−3.57 [3.38−3.42] (m, 1H, C^3H_2), 3.83 [3.82] (s, 3H, OCH_3), 3.87−3.90 [3.56−3.60] (m, 1H, C^3H_2), 4.30 (b.s., 1H. OH), 6.78−6.94 (m, 3H, Ar), 7.20−7.24 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$): major: 10.4 ($CH_2\underline{C}H_3$), 26.8 ($\underline{C}H_2CH_3$), 39.7 (C^6), 46.0 (C^7), 58.9 (C^2), 61.6 (C^3), 91.9 (q, J = 32.6 Hz, C^5), 111.5, 111.8, 113.3 (Ar), 122.8 (q, J = 286.8 Hz, CF_3), 129.5, 140.1, 159.8 (Ar); minor: 10.4 [10.4] ($CH_2\underline{C}H_3$), 25.8 [24.2] ($\underline{C}H_2CH_3$), 36.8 [34.8] (C^7), 41.1 [41.6] (C^6), 51.3 [52.0] (C^2), 61.8 [58.8] (C^3), 90.1 [89.6] (q, J = 32.6 Hz, C^5), 111.5, 111.8, 119.3 (Ar), 122.8 (q, J = 286.8 Hz, CF_3), 129.6, 139.2 [139.7], 159.9 (Ar). ^{19}F NMR ($CDCl_3$): major: −84.2; minor: −84.8 [−86.4]. ^{15}N NMR ($CDCl_3$): major: −339.9; minor: −343.6 [−338.5]. IR (film, cm^{-1}): 1063, 1112, 1187, 1603, 2968, 3363 (OH). MS (EI), m/z (relative intensity, %): 317 (7, M^+), 219 (100), 188 (35), 163 (83), 151 (18), 136 (49), 131 (32), 105 (19), 82 (28), 77 (28), 55 (31). Calcd for $C_{15}H_{18}F_3NO_3$: C 56.78; H 5.72; N 4.41. Found: C 56.49; H 5.57; N 4.32.

*2,2-Dimethyl-7-phenyl-5-trifluoromethyl-4-oxa-1-azabicyclo-[4.1.0]heptan-5-ol (**3f**).* Pale yellow solid, mixture of two diastereomers in ratio 74:26, mp 111−113 °C (for pure major isomer), yield 71 mg

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(25%). ^{1}H NMR ($CDCl_3$): major: 1.10 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.58 (d J = 2.7 Hz, 1H, C^6H), 3.18 (d, J = 2.7 Hz, 1H, C^7H), 3.28 (d, J = 12.3 Hz, 1H, C^3H_2), 3.48 (d, J = 12.3 Hz, 1H, C^3H_2), 3.50 (b.s., 1H, OH), 7.21−7.38 (m, 5H, Ar); minor: 1.19 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.35 (d, J = 2.5 Hz, 1H, C^6H), 3.27 (d, J = 2.5 Hz,, 1H, C^7H), 3.43 (d, J = 12.2 Hz, 1H, C^3H_2), 3.50 (b.s., 1H, OH), 3.64 (d, J = 12.2 Hz, 1H, C^3H_2), 7.21−7.38 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): major: 24.4 (CH_3), 26.4 (CH_3), 36.7 (C^7), 41.3 (C^6), 48.4 (C^2), 63.4 (C^3), 89.5 (q, J = 32.4 Hz, C^5), 122.9 (q, J = 286.0 Hz, CF_3), 126.7, 127.6, 128.6, 138.8 (Ar); minor: 25.5 (CH_3), 28.6 (CH_3), 37.6 (C^7), 40.6 (C^6), 49.2 (C^2), 66.9 (C^3), 90.1 (q, J = 32.8 Hz, C^5), 122.9 (q, J = 286.9 Hz, CF_3), 126.7, 127.6, 128.6, 138.8 (Ar). ^{19}F NMR ($CDCl_3$): major: −86.5; minor: −84.4. ^{15}N NMR ($CDCl_3$): major: −326.8; minor: −329.7. IR (film, cm^{-1}): 1184 (C−F), 1607 (Ph). MS (EI), m/z (relative intensity, %): 287 (2, M^+), 259 (38), 231 (28), 213 (25), 201 (13), 185 (29), 165 (17), 153 (18), 133 (17), 119 (14), 115 (28), 103 (21), 91 (100), 77 (32), 69 (24). Calcd for $C_{14}H_{16}F_3NO_2$: C 58.53; H 5.61; N 4.88. Found: C 58.92; H 5.59; N 4.95.

*2,2-Dimethyl-7-m-tolyl-5-trifluoromethyl-4-oxa-1-azabicyclo-[4.1.0]heptan-5-ol (**3g**).* Pale yellow solid, mixture of two diastereomers in ratio 77:23, mp 130−132 °C (for pure major isomer), yield 170 mg (56%). ^{1}H NMR ($CDCl_3$): major: 1.10 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.33 (s, 3H, $ArCH_3$), 2.56 (d, J = 2.5 Hz, 1H, C^6H), 3.14 (d, J = 2.5 Hz, 1H, C^7H), 3.28 (d, J = 12.3 Hz, 1H, C^3H_2), 3.50 (b.s., 1H, OH), 3.52 (d, J = 12.3 Hz, 1H, C^3H_2), 7.00−7.25 (m, 4H, Ar); minor: 1.17 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.33 (s, 3H, $ArCH_3$), 2.33 (d, J = 2.3 Hz, 1H, C^6H), 3.21 (d, J = 2.3 Hz, 1H, C^7H), 3.45 (d, J = 12.0 Hz, 1H, C^3H_2), 3.50 (b.s., 1H, OH), 3.65 (d, J = 12.0 Hz, 1H, C^3H_2), 7.00−7.25 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$): major: 21.5 ($ArCH_3$), 24.3 (CH_3), 25.5 (CH_3), 36.7 (C^7), 41.3 (C^6), 48.4 (C^2), 63.3 (C^3), 89.7 (q, J = 32.4 Hz, C^5), 123.0 (q, J = 286.0 Hz, CF_3), 121.7, 123.8, 124.4, 124.4, 138.5, 138.6 (Ar); minor: 25.5 (CH_3), 25.7 ($ArCH_3$), 28.5 (CH_3), 37.7 (C^7), 40.6 (C^6), 49.2 (C^2), 68.1 (C^3), 90.5 (q, J = 32.8 Hz, C^5), 123.1 (q, J = 286.8 Hz, CF_3), 121.7, 123.9, 124.4, 124.4, 138.5, 138.6 (Ar). ^{19}F NMR ($CDCl_3$): major: −87.3; minor: −85.6. IR (film, cm^{-1}): 1180 (C−F), 1610 (Ar). MS (EI), m/z (relative intensity, %): major: 301 (7, M^+), 204 (33), 181 (31), 174 (14), 166 (13), 152 (14), 138 (30), 121 (20), 119 (86), 91 (67), 84 (42), 77 (18), 56 (100); minor: 301 (12, M^+), 203 (88), 166 (15), 151 (56), 148 (88), 136 (69), 132 (24), 120 (43), 119 (100), 105 (29), 91 (88), 77 (24), 65 (36), 57 (27). Calcd for $C_{15}H_{18}F_3NO_2$: C 59.79; H 6.02; N 4.65. Found: C 59.36; H 5.98; N 4.54.

*2,2-Dimethyl-7-(3-methoxyphenyl)-5-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-ol (**3h**).* White solid, mixture of diastereomers in ratio 77:23, mp 114−115 °C (for pure major isomer), yield 181 mg (57%) ^{1}H NMR ($CDCl_3$): major: 1.10 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.55 (d, J = 2.6 Hz, 1H, C^6H), 3.16 (d, J = 2.6 Hz, 1H, C^7H), 3.24 (b.s. 1H, OH), 3.29 (d, J = 12.3 Hz, 1H, C^3H_2), 3.50 (d, J = 12.3 Hz, 1H, C^3H_2), 3.80 (s, 3H, OCH_3), 6.78−6.81 (m, 1H, Ar), 6.86−6.88 (m, 1H, Ar), 6.91−6.94 (m, 1H, Ar), 7.20−7.24 (m, 1H, Ar); minor: 1.18 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.32 (d, J = 2.3 Hz, 1H, C^6H), 3.23 (d, J = 2.3 Hz, 1H, C^7H), 3.30 (b.s. 1H, OH), 3.45 (d, J = 12.0 Hz, 1H, C^3H_2), 3.65 (d, J = 12.0 Hz, 1H, C^3H_2), 3.80 (s, 3H, OCH_3), 6.77−6.90 (m, 3H, Ar), 7.20−7.24 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$): major: 24.2 (CH_3), 26.1 (CH_3), 36.7 (C^7), 41.3 (C^6), 48.4 (C^2), 55.4 (OCH_3), 63.2 (C^3), 89.5 (q, J = 32.1 Hz, C^5), 112.4, 113.1, 119.4, 123.0 (q, J = 286.1 Hz, CF_3), 129.55, 140.3, 159.9 (Ar); minor: 25.5 (CH_3), 28.3 (CH_3), 37.8 (C^7), 40.6 (C^6), 49.1 (C^2), 55.3 (OCH_3), 66.7 (C^3), 90.4 (q, J = 32.3 Hz, C^5), 112.3, 113.0, 119.3, 123.1 (q, J = 286.9 Hz, CF_3), 129.58, 140.2, 159.9 (Ar). ^{19}F NMR ($CDCl_3$): major: −87.3; minor: −85.5. IR (film, cm^{-1}): 1181, 1195 (C−F, C−O−C), 1586, 1604 (Ar), 2973 (CH), 3357 (OH). MS (EI, Direct input), m/z (relative intensity, %): 317 (100, M^+), 299 (17), 248 (38), 230 (14), 188 (18), 176 (35), 161 (26), 147 (87), 132 (54), 77 (32). Calcd for $C_{15}H_{18}F_3NO_3$: C 56.78; H 5.72; N 4.41. Found: C 56.45; H 5.59; N 4.23.

*2,2-Dimethyl-7-(4-methylphenyl)-5-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0]heptan-5-ol (**3i**).* Colorless solid, mixture of diastereomers in ratio 70:30, mp 132−133 °C (for pure major isomer), yield 187 mg (62%). ^{1}H NMR ($CDCl_3$): major: 1.09 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.32 (s, 3H, $ArCH_3$), 2.53 (d, J = 2.3 Hz, 1H, C^6H), 2.99 (b.s., 1H, OH), 3.15 (d, J = 2.3 Hz, 1H, C^7H), 3.30 (d, J = 12.3 Hz, 1H, C^3H_2), 3.53 (d, J = 12.3 Hz, 1H, C^3H_2), 7.12 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H); minor:1.17 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.31 (s, 3H, $ArCH_3$), 2.54 (d, J = 2.6 Hz, 1H, C^6H), 3.14 (d, J = 2.6 Hz, 1H, C^7H), 3.22 (b.s., 1H, OH), 3.44 (d, J = 12.0 Hz, 1H, C^3H_2), 3.64 (d, J = 12.0 Hz, 1H, C^3H_2), 7.12 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): major: 22.0 ($ArCH_3$), 24.3 (CH_3), 26.4 (CH_3), 36.4 (C^7), 41.4 (C^6), 48.3 (C^2), 63.3 (C^3), 89.7 (q, J = 40.0 Hz, C^5), 122.8 (q, J = 286.0 Hz, CF_3), 126.5, 129.2, 135.9, 137.2 (Ar); minor: 22.0 ($ArCH_3$), 25.3 (CH_3), 28.3 (CH_3), 37.3 (C^7), 40.3 (C^6), 48.2 (C^2), 66.6 (C^3), 89.4 (q, J = 32.4 Hz, C^5), 122.7 (q, J = 286.0 Hz, CF_3), 126.4, 129.1, 135.5, 137.1 (Ar); ^{19}F NMR ($CDCl_3$): major: −86.4; minor: −84.7. IR (film, cm^{-1}): 1181, 1195 (C−F, C−O−C), 1586, 1604 (Ar), 2973 (CH), 3357 (OH). Calcd for $C_{15}H_{18}F_3NO_2$: C 59.79; H 6.02; N 4.65. Found: C 59.45; H 5.98; N 4.53.

*4,4-Dimethyl-6-phenyl-1-trifluoromethyl-2,8-dioxa-5-azabicyclo-[5.1.0]octane (**4a**).* Pale yellow oil, yield 219 mg (76%). ^{1}H NMR ($CDCl_3$): 1.06 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.88 (b.s., 1H, NH), 3.60 (s, 1H, C^7H), 3.74 (d, J = 12.6 Hz, 1H, C^3H_2), 3.85 (d, J = 12.6 Hz, 1H, C^3H_2), 4.29 (s, 1H, C^6H), 7.25−7.41 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): 21.9 (CH_3), 27.3 (CH_3), 53.5 (C^6), 53.5 (C^4), 62.8 (C^7), 79.0 (C^3), 84.7 (q, J = 40.5 Hz, C^1), 121.5 (q, J = 279.3 Hz, CF_3), 127.1, 127.9, 129.2, 141.3 (Ph). ^{19}F NMR ($CDCl_3$): −80.3. ^{15}N NMR ($CDCl_3$): −326.7. IR (film, cm^{-1}): 1152, 1170, 1197 (C−F, C−O−C), 1604 (Ph), 3336 (NH). MS (EI), m/z (relative intensity, %): 287 (2, M^+), 272 (20), 218 (64), 186 (100), 160 (45), 146 (23), 131 (81), 117 (14), 106 (87), 91 (53), 84 (21), 77 (66), 51 (32). Calcd for $C_{14}H_{16}F_3NO_2$: C 58.53; H 5.61; N 4.88. Found: C 58.52; H 5.87; N 4.59.

*4,4-Dimethyl-6-(m-tolyl)-1-trifluoromethyl-2,8-dioxa-5-azabicyclo[5.1.0]octane (**4b**).* Pale brown oil, yield 223 mg (74%). ^{1}H NMR ($CDCl_3$): 1.05 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.87 (b.s., 1H, NH), 2.34 (s, 3H, $ArCH_3$), 3.58 (s, 1H, C^7H), 3.73 (d, J = 12.5 Hz, 1H, C^3H_2), 3.83 (d, J = 12.5 Hz, 1H, C^3H_2), 4.23 (s, 1H, C^6H), 7.07−7.28 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$): 21.8 (CH_3), 21.9 ($ArCH_3$), 27.3 (CH_3), 53.5 (C^6), 53.5 (C^4), 62.9 (C^7), 79.0 (C^3), 84.7 (q, J = 39.9 Hz, C^1), 121.5 (q, J = 279.6 Hz, CF_3), 124.1, 127.8, 128.8, 129.1, 139.0, 141.2 (Ar). ^{19}F NMR ($CDCl_3$): −80.3. IR (film, cm^{-1}): 1173 (C−F, C−O−C), 1609 (Ar), 3337 (NH). MS (EI), m/z (relative intensity, %): 301 (2, M^+), 286 (17), 232 (57), 200 (100), 174 (44), 160 (34), 145 (66), 118 (95), 105 (74), 91 (78), 84 (18), 77 (29), 65 (38), 58 (52). Calcd for $C_{15}H_{18}F_3NO_2$: C 59.79; H 6.02; N 4.65. Found: C 59.71; H 5.95; N 4.38.

*4,4-Dimethyl-6-(3-methoxyphenyl)-1-trifluoromethyl-2,8-dioxa-5-azabicyclo[5.1.0]octane (**4c**).* Light-yellow oil, yield 240 mg (76%). ^{1}H NMR ($CDCl_3$): 1.06 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.90 (b.s., 1H, NH), 3.59 (s, 1H, C^7H), 3.74 (d, J = 12.6 Hz, 1H, C^3H_2), 3.81 (s, 3H, OCH_3), 3.85 (d, J = 12.6 Hz, 1H, C^3H_2), 4.25 (s, 1H, C^6H), 6.80−6.85 (m, 1H, Ar), 6.90−6.97 (m, 2H, Ar), 7.26−7.30 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$): 21.9 (CH_3), 27.3 (CH_3), 53.3 (C^4), 53.4 (C^6), 55.4 (OCH_3), 62.8 (C^7), 79.0 (C^3), 84.7 (q, J = 40.2 Hz, C^1), 113.0, 113.4, 119.4, 121.4 (q, J = 279.7 Hz, CF_3), 130.3, 142.8, 160.3. ^{19}F NMR ($CDCl_3$): −80.3. ^{15}N NMR ($CDCl_3$): −328.3. IR (film, cm^{-1}): 1167, 1195 (C−F, C−O−C), 1602 (Ar), 2970 (CH), 3334 (NH). MS (EI), m/z (relative intensity, %): 317 (5, M^+), 302 (15), 248 (49), 216 (100), 199 (24), 190 (44), 161 (82), 134 (96), 118 (33), 105 (39), 91 (44), 77 (53), 55 (58), 42 (60). Calcd for $C_{15}H_{18}F_3NO_3$: C 56.78; H 5.72; N 4.41. Found: C 56.61; H 5.63; N 4.20.

*4,4-Dimethyl-6-(3-nitrophenyl)-1-trifluoromethyl-2,8-dioxa-5-azabicyclo[5.1.0]octane (**4d**).* Pale yellow solid, mp 98 °C, yield 241 mg (73%). ^{1}H NMR ($CDCl_3$): 1.07 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.90 (b.s., 1H, NH), 3.62 (s, 1H, C^7H), 3.74 (d, J = 12.5 Hz, 1H, C^3H_2), 3.88 (d, J = 12.5 Hz, 1H, C^3H_2), 4.42 (s, 1H, C^6H), 7.55 (t, J = 7.7, 8.4 Hz, 1H, Ar), 7.75 (d, J = 7.7 Hz, 1H, Ar), 8.15 (d, J = 8.4 Hz, 1H, Ar), 8.26 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$): 21.9 (CH_3), 27.2 (CH_3), 52.9 (C^6), 53.7 (C^4), 62.1 (C^7), 77.5 (C^3), 84.7 (q, J = 40.3 Hz, C^1), 120.9 (q, J = 279.3 Hz, CF_3), 122.5, 122.6, 130.2, 133.3, 143.2, 148.7 (Ar). ^{19}F NMR ($CDCl_3$): −80.3. ^{15}N NMR ($CDCl_3$): −329.7. IR (film, cm^{-1}): 1150, 1179, 1195 (C−F, C−O−C), 1348, 1532 (NO_2), 3337 (NH). MS (EI), m/z (relative intensity, %): 332 (1, M^+), 317 (18), 263 (36), 231

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(63), 205 (17), 151 (31), 102 (25), 89 (13), 76 (15), 69 (22), 56 (30), 42 (100). Calcd for $C_{14}H_{15}F_3N_2O_4$: C 50.61; H 4.55; N 8.43. Found: C 50.46; H 4.54; N 8.40.

*4,4-Dimethyl-6-(p-tolyl)-1-trifluoromethyl-2,8-dioxa-5-azabicyclo[5.1.0]octane (**4e**).* Light-brown oil, yield 259 mg (86%). ^{1}H NMR ($CDCl_3$): 1.07 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.85 (b.s., 1H, NH), 2.34 (s, 3H, Ar$C\underline{H}_3$), 3.60 (s, 1H, C^7H), 3.73 (d, J = 12.5 Hz, 1H, C^3H_2), 3.84 (d, J = 12.5 Hz, 1H, C^3H_2), 4.27 (s, 1H, C^6H), 7.14−7.30 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$): 21.2 (Ar$\underline{C}H_3$), 21.9 (CH_3), 27.3 (CH_3), 53.2 (C^6), 53.4 (C^4), 63.0 (C^7), 79.0 (C^3), 84.7 (q, J = 40.3 Hz, C^1), 121.5 (q, J = 279.5 Hz, CF_3), 127.1, 129.8, 137.7, 138.5 (Ar). ^{19}F NMR ($CDCl_3$):-80.3. ^{15}N NMR ($CDCl_3$): −325.8. IR (film, cm^{-1}): 1168, 1195 (C−F, C−O−C), 1606 (Ar), 3336 (NH). MS (EI), m/z (relative intensity, %): 301 (8, M^+), 286 (27), 232 (58), 200 (100), 199 (28), 175 (36), 160 (68), 145 (71), 120 (76), 119 (82), 118 (100), 117 (56), 115 (53), 105 (33), 91 (49), 84 (20), 58 (44). Calcd for $C_{15}H_{18}F_3NO_2$: C 59.79; H 6.02; N 4.65. Found: C 59.61; H 5.97; N 4.66.

*6-(5-Bromothiophen-2-yl)-4,4-dimethyl-1-trifluoromethyl-2,8-dioxa-5-azabicyclo[5.1.0]octane (**4f**).* Yellow solid, mp 85−86 °C, yield 294 mg (79%). ^{1}H NMR ($CDCl_3$): major: 1.02 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.93 (b.s., 1H, NH), 3.63 (d, J = 12.5 Hz, 1H, C^3H_2), 3.71 (s, 1H, C^7H), 3.83 (d, J = 12.5 Hz, 1H, C^3H_2), 4.48 (s, 1H, C^6H), 6.77 (d, J = 3.9 Hz, 1H, thienyl), 6.91 (d, J = 3.9 Hz, 1H, thienyl). ^{13}C NMR ($CDCl_3$): 21.8 (CH_3), 27.2 (CH_3), 49.7 (C^7), 53.6 (C^4), 61.7 (C^6), 79.3 (C^3), 85.2 (q, J = 40.4 Hz, C^1), 112.4 (C−Br), 121.2 (q, J = 279.7 Hz, CF_3), 124.2, 129.9, 147.0 (thienyl). ^{19}F NMR ($CDCl_3$): major: −80.3. ^{15}N NMR ($CDCl_3$): −323.4. IR (film, cm^{-1}): 1171, 1197 (C−F, C−O−C), 1539, 1590 (thienyl), 3329 (NH). MS (EI), m/z (relative intensity, %): 373 (17, M^+ + 1), 371 (14, M^+-1), 358 (19), 356 (19), 304 (39), 302 (36), 272 (88), 270 (78), 247 (40), 245 (42), 217 (47), 215 (50), 205 (69), 196 (24), 192 (24), 191 (88), 190 (79), 189 (100), 188 (64), 187 (19), 177 (23), 175 (22), 166 (54), 136 (21), 124 (16), 123 (19), 122 (22), 110 (73), 109 (26), 108 (86), 96 (22), 95 (25), 84 (38), 83 (15), 82 (29), 73 (17), 70 (18), 69 (43), 63 (16), 58 (68), 55 (35). Calcd for $C_{12}H_{13}BrF_3NO_2S$: C 38.72; H 3.52; N 3.76. Found: C 38.82; H 3.57; N 3.95.

*4,4-Di(n-butyl)-6-phenyl-1-trifluoromethyl-2,8-dioxa-5-azabicyclo[5.1.0]octane (**4g**).* Colorless oil, yield 277 mg (75%). ^{1}H NMR ($CDCl_3$): 0.91 (t, J = 7.2 Hz, 3H, CH_3), 0.92 (t, J = 7.2 Hz, 3H, CH_3), 1.10−1.44 (m, 12H, $6CH_2$), 1.59 (b.s., 1H, NH), 3.63 (s, 1H, C^7H), 3.64 (d, J = 12.6 Hz, 1H, C^3H_2), 4.01 (d, J = 12.6 Hz, 1H, C^3H_2), 4.34 (s, 1H, C^6H), 7.29−7.31 (m, 1H, Ph), 7.36−7.43 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): 13.98 (CH_3), 14.03 (CH_3), 23.2 (CH_2), 23.3 (CH_2), 24.9 (CH_2), 25.4 (CH_2), 30.7 (CH_2), 35.4 (CH_2), 52.6 (C^6), 57.7 (C^4), 62.8 (C^7), 76.9 (C^3), 84.4 (q, J = 40.0 Hz, C^1), 121.4 (q, J = 279.8 Hz, CF_3), 127.1, 127.7, 128.9, 141.4 (Ph). ^{19}F NMR ($CDCl_3$): −81.1. IR (film, cm^{-1}): 1150, 1171, 1197 (C−F, C−O−C), 1603 (Ph), 3340 (NH). HRMS (ESI): m/z calcd for $C_{20}H_{28}F_3NO_2H^+$ [M + H^+]: 372.21449; found: 372.21548.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01927.

Crystallographic data **3d** (CIF)
Crystallographic data **4d** (CIF)
Copies of NMR spectra, quantum chemical calculations and X-ray data (PDF)
Crystallographic data **3c** (CIF)

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Notes

The authors declare no competing financial interest.

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