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Nitrogen Heterocycles

Multichannel Reaction of α-Bromoenones with 1,2-Diamines: Synthesis of 1,4-Diazabicyclo[4.1.0]hept-4-enes by Reaction with *N*-Unsubstituted 1,2-Diamines

Vasily M. Muzalevskiy,[a] Alexander Yu. Rulev,*[b] Evgeniy V. Kondrashov,[b] Alexey R. Romanov,[b] Igor A. Ushakov,[b] Vyacheslav A. Chertkov,[a] and Valentine G. Nenajdenko*[a]

Abstract: The reaction of 2-bromoenones with *N*-unsubstituted 1,2-diamines was studied. An easy access to 1,4-diazabicyclo[4.1.0]hept-4-enes was developed. The multistep mechanism of the reaction is discussed. Final conclusions on the influence of the structure of the starting 2-bromoenones and 1,2-diamines on the direction of the reaction are established.

Introduction

The piperazine moiety is a very important structural unit for medicinal chemistry. Analysis of the structures of drugs approved by the US FDA showed that the piperazine core is found as a substructure of 59 marketed drugs [in third place after pyridine (62) and piperidine (72) in the list of the most frequently found nitrogen heterocycles in the structures of approved drugs].[1] One can also find 13 piperazine derivatives among the 200 best-selling small-molecule drugs of 2012 (for examples, see Figure 1).[2] A very diverse spectrum of physiological activities has been demonstrated for piperazine derivatives, which include antineoplastics [Gleevec (Imatinib)], DPP-IV inhibitors [diabetes treatment, Januvia (Sitagliptin)], drugs for erectile dysfunction treatment [Viagra (Sildenafil)], antibiotics (fluoroquinolone family of antibiotics, for example Ciprobay), and angiogen-II antagonists [Ranexa (Ranolizine)]. The worldwide sales of three piperazine-derived antipsychotics [Abilify (Aripiprazole), Seroquel (Quetiapine), and Zyprexa (Olanzapine)] alone were worth nearly 15 billion dollars in 2011 (Figure 1).

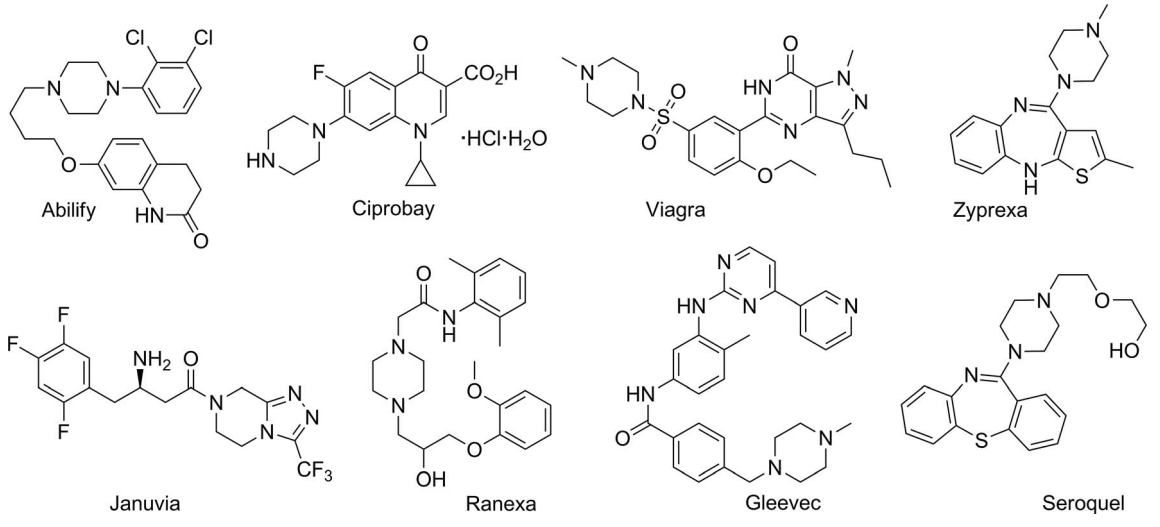

Figure 1. Examples of piperazine-containing drugs from the 200 best-selling small-molecule drugs in 2012.

Another important trend in modern drug design is the incorporation of fluorine or trifluoromethyl groups into target molecules. The current medicinal chemistry literature shows that the combination of two structural moieties — a nitrogen heterocycle and a fluorine-containing group — is the trend in

[a] *Department of Chemistry, Moscow State University, Leninskie Gory, Moscow 119992, Russia*
E-mail: nenajdenko@org.chem.msu.ru
[b] *A. E. Favorsky Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1, Favorsky Str., Irkutsk 664033, Russia*
E-mail: rulev@irioch.irk.ru

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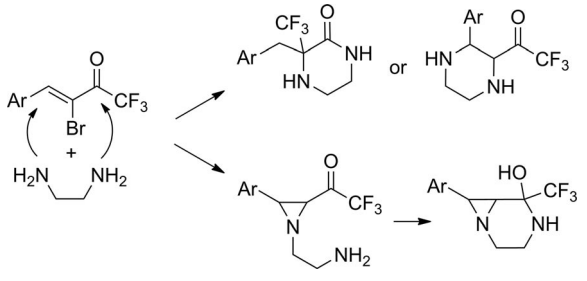
drug development.[3] In fact, it is well known that the introduction of a fluorine atom or an organofluorine moiety into a biologically active molecule has a dramatic influence on its reactivity, as well as its biological properties, such as membrane permeability, and binding to target receptors; it can also have a blocking effect on metabolic decomposition. Thus, it is not surprising that about 225 fluorinated drugs have been approved by the FDA since 1955,[4a] and that nearly 25 % of newly synthesized drugs and agrochemicals contain fluorine in their structure.[3,4]

Readily available CF_3-bromoenones are attractive building blocks for the construction of fluorinated heterocycles. These compounds have at least two electrophilic sites (Scheme 1), which opens up the number of possible reaction mechanisms, and makes the outcome of reactions rather unpredictable. Their reactions with binucleophiles can proceed as complex domino sequences beginning with an aza-Michael addition as a first reaction step. These transformations are known as aza-Michael-initiated ring-closure processes (aza-MIRC), and they play a key role in the multistep syntheses of biologically active N-heterocycles and of analogues of natural products.[5]

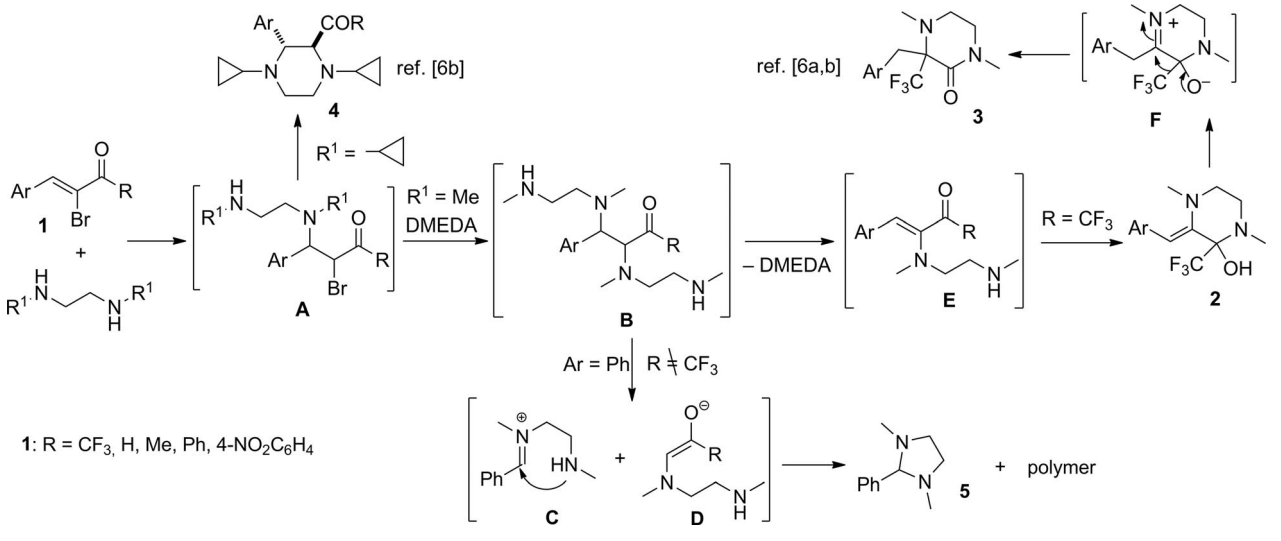


Scheme 1. Possible reaction directions.

Recently we found an unusual reaction of CF_3-bromoenones with symmetrically substituted ethylenediamines, which leads to trifluoromethylated piperazinones rather than trifluoroacetylated piperazines.[6] To gain more detailed information about the scope and the mechanism of this reaction, we decided to study the reaction of bromoenones with other 1,2-diamines.[7] Using this approach, we expected to be able to prepare other types of piperazine-derived heterocycles bearing fluorinated fragments (Scheme 1).

We have previously shown that the reaction of CF_3-bromoenones **1** with secondary amines represents an easy access to indenol derivatives, and proceeds through an aza-Michael addition–substitution–elimination–intramolecular cyclization sequence.[7] However, if the same substrates are treated with diamines such as *N*,*N*′-dimethylethylenediamine (DMEDA), the second amine group attacks the carbonyl carbon to give intermediate **2**. The latter then undergoes a 1,2-shift of the CF_3 group to finally give piperazinones **3**.[6] In the case of *N*,*N*′-dicyclopropyl ethylenediamine, an alternative sequence is preferable, as confirmed by calculations.[6b] Instead of intermolecular nucleophilic substitution to form intermediate **B** with a second molecule of diamine, cyclization takes place through intramolecular nucleophilic substitution of bromine (Scheme 2).

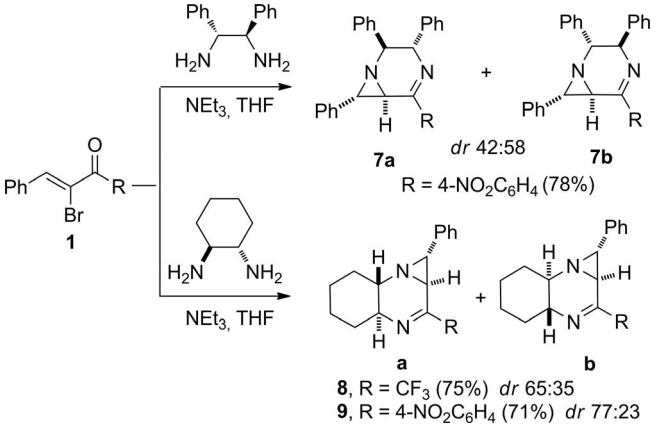
We have demonstrated the unique nature of fluorinated bromoenones in this reaction. The reaction of nonfluorinated bromoenones **1c**–**1f** resulted in the destructive cleavage of the double bond to form cyclic aminal **5** as the principal reaction product. This fragmentation is a rare example of C–C bond cleavage under mild nucleophilic conditions.[8,9] A possible mechanism for the formation of benzaldehyde derivative **5** is shown in Scheme 2. The key step of the sequence is a retro-Mannich reaction giving aminoketone derivative **D** and iminium salt **C**, which are then transformed into aminal **5** by cyclization. Detailed GC–MS analysis of the reaction mixtures for the reactions with CF_3 enones **1a** and **1b** showed that fragmentation is a minor side reaction in these cases. The principal reaction pathway is the formation of piperazinone **3**. This shift of reactivity can be explained in terms of the much higher electrophilicity of the carbonyl group in fluorinated enones, which directs the attack of the amine onto the carbonyl moiety preferentially (Scheme 2).



Scheme 2. Reactions of bromoenones with *N*,*N*′-substituted ethylenediamines.

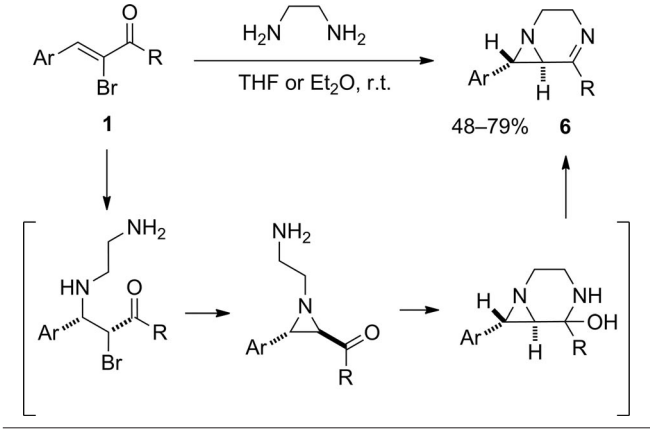
Results and Discussion

To conclude our investigation of the reactions of 2-bromoenones with 1,2-diamines, we examined the reaction with *N*-unsubstituted 1,2-diamines. In contrast to the behaviour of substituted derivatives, unsubstituted ethylenediamine reacts with α-bromo α,β-unsaturated carbonyl compounds by a different pathway to form bicyclic piperazine derivatives **6**. Three key steps of this sequence of transformations are: aza-Michael addition, intramolecular S_N2 nucleophilic substitution resulting in aziridine ring construction, and finally carbonyl condensation. The corresponding 1,4-diazabicyclo[4.1.0]hept-4-ene derivatives **6** were isolated in good yields for both fluorinated and non-fluorinated bromoenones (Scheme 3, Table 1). The reaction is highly stereoselective, and all the heterocyclic products were isolated as single diastereomers. This means that all the steps of this cascade reaction are stereoselective.



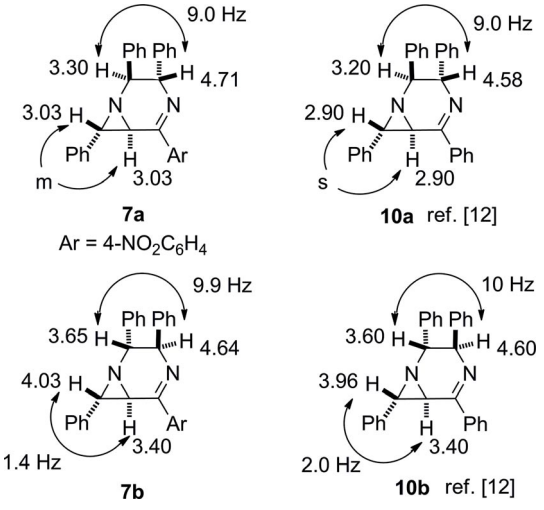
Scheme 3. The reaction of **1** with chiral diamines.

Table 1. Synthesis of 1,4-diazabicyclo[4.1.0]hept-4-enes.



Entry	Enone	Ar	R	**6**, Yield [%]
1	**1a**	Ph	CF_3	**6a**, 49
2	**1b**	4-MeC_6H_4	CF_3	**6b**, 53
3	**1c**	Ph	H	**6c**, 48
4	**1d**	Ph	Me	**6d**, 79
5	**1e**	Ph	Ph	**6e**, 77
6	**1f**	Ph	4-$NO_2C_6H_4$	**6f**, 72

The more sterically hindered chiral (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and *trans*-1,2-diaminocyclohexane were also successfully used in the reaction, and gave compounds **7**–**9** in high yields. The reaction of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine gave a 42:58 mixture of diastereomers **7a** and **7b**, while the reactions with *trans*-1,2-diaminocyclohexane were more stereoselective, and gave 2:1 (for **8**) and 3:1 (for **9**) mixtures of diastereomeric heterocycles. The relative configurations of the substituents in the aziridine ring in **7** were determined by comparison of the ^{1}H NMR spectroscopic data with literature data (Scheme 4). The coupling constants of the aziridine ring protons of **7** are 1.6–2.4 Hz, which indicates their *trans* configuration.[10,11]



Scheme 4. Assignment of the configuration of compounds **7a** and **7b**.

For diastereomeric compounds **7a** and **7b**, a careful comparison with their close analogues **10a** and **10b**[12] was carried out. This allowed us to assign the configurations of **7a** and **7b** (Scheme 4). By comparing the ^{1}H NMR spectra of these diastereomeric pairs, it is possible to see similar multiplicities, chemical shifts, and coupling constants for corresponding protons.

The structures of isomeric compounds **8a** (major diastereomer) and **8b** (minor diastereomer) were assigned through elucidation of ^{1}H, ^{13}C, and ^{19}F NMR spectra, and cross-peak positions and multiplicities in two-dimensional COSY, HSQC, and HMBC experiments. The starting points for the structural assignments were the characteristic multiplets of the monosubstituted benzene and methyne moieties in the ^{1}H and ^{13}C NMR spectra. Analysis of the multiplets was based on vicinal and geminal $^nJ_{H,H}$ couplings (see, e.g., ref.[13]), as well as heteronuclear $^nJ_{C,H}$ couplings (see, e.g., ref.[14]) in the parent cyclic systems. The complete NMR spectroscopic data set allows us to conclude that the products under investigation are diastereomeric (Figure 2).

The characteristic values of the vicinal $^3J_{3a\text{-}H,7a\text{-}H}$ coupling constants [i.e., 9.2 Hz for **8a** (major) and 9.6 Hz for **8b** minor diastereomers] show that the nitrogens retain their *trans*-diequatorial configuration on the cyclohexane ring. The low values of the vicinal $^3J_{1\text{-}H,1a\text{-}H}$ coupling constants, and high values of the vicinal $^3J_{1\text{-}H,C\text{-}7a}$ coupling constants (measured according to ref.[15]) indicate that the 1-H proton is in a *trans* position relative to 1a-H, and a *cis* position relative to C-7a. A 2D NOESY

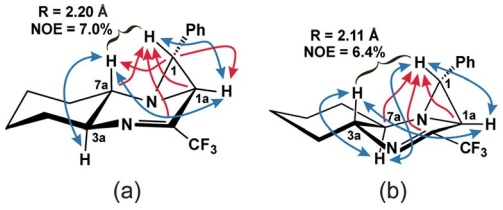
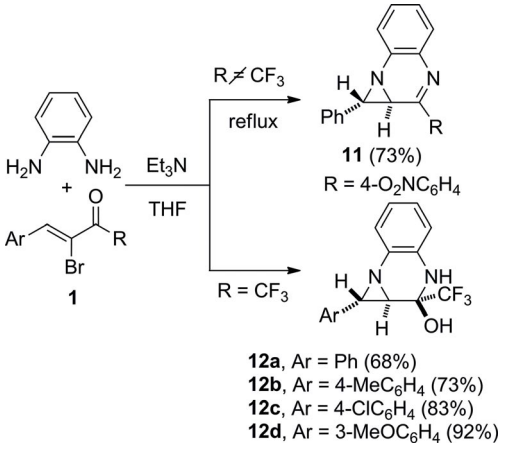


Figure 2. Structure and atom numbering for compounds **8a** (major) and **8b** (minor). Arrows indicate selected long-range connectivities $^{n}J_{H,H}$ (blue) and $^{n}J_{C,H}$ (red).

experiment provided the final point in the assignment of the structures, revealing strong NOE factors of 7.0 % between the 1-H and 7a-H protons for the major diastereomer, and of 6.4 % between the 1-H and 3a-H protons for the minor diastereomer. DFT optimized structures [B3LYP/6-311G(d,p)] support the closeness of these proton pairs, see Figure 2.

The less nucleophilic *ortho*-phenylenediamine can also be involved in this reaction. Thus, 1,1a-dihydroazirino[1,2-*a*]quinoxaline **11** was prepared in 73 % yield by the reaction with bromoenone **1f** at reflux in THF. In contrast, when fluorinated enones **1a** and **1b** were treated with the same binucleophile, the reaction could be stopped at the stage of hemiaminals **12**, which were isolated in high yield (Scheme 5). The presence of the CF_3 group stabilizes these compounds.[16] The isolation of **12** confirms that the reactions of enones **1** with diamines bearing primary amino groups follow the classical sequence, including aza-Michael addition, intramolecular nucleophilic substitution, and attack of the second NH_2 group of the diamine onto the carbonyl group.[5a,17,18]



Scheme 5. Reaction with *o*-phenylenediamine.

The configurations of **12c** and the whole series of compounds **12** were determined by NMR spectroscopy, supported by DFT calculations. DFT-optimized structures [B3LYP/6-311G(d,p)] revealed that in contrast to diastereomers **8**, the spatial structure of the six-membered heterocyclic moiety in compounds **12** is strongly flattened, with only C-2 going noticeably out of the C-1a–N-1–C-7a–C-3a–N-3 plane (Figure 3). The hydroxy group at C-2 thus becomes effectively axial, with the proton orientated away from C-1a (torsion angle H–O–C-2–C-1a 173°). This configuration is supported by the observation of a vicinal $^{3}J_{C\text{-}1a,OH}$ coupling of 7.3 Hz (DMSO solution, high-resolution HMBC), and an unexpectedly large long-range coupling of the hydroxyl proton to 1a-H ($^{4}J_{1a\text{-}H,OH}$ = 2.7 Hz). In our opinion, this latter value can be rationalised only for a W-configuration of the coupling path. So, the relative configuration of the stereocenters at C-1, C-1a, and C-2 is *rel*-(1*R*,1a*S*,2*S*).

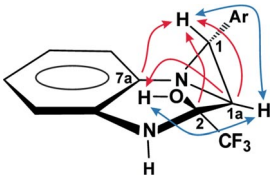
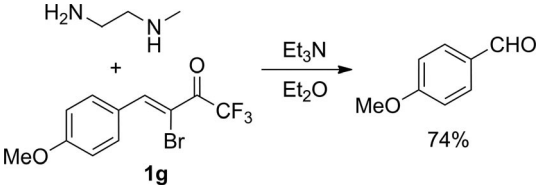


Figure 3. Structure and atom numbering of compound **12c**. Arrows indicate selected long-range connectivities $^{n}J_{H,H}$ (blue) and $^{n}J_{C,H}$ (red).

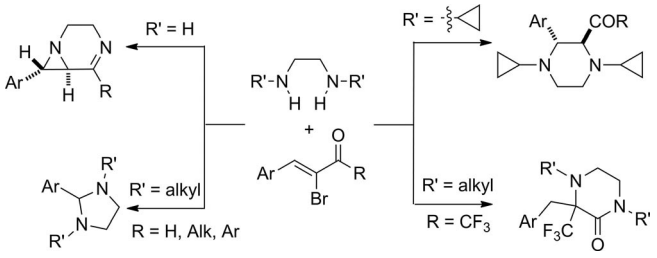
Finally, we examined the reaction of CF_3-bromoenone **1g** with *N*-methylethylenediamine as a binucleophile bearing both a primary and a secondary amino group. Unlike the reaction with ethylenediamine and its derivatives bearing two NH_2 groups, in this case, fragmentation of the starting enone took place. Thus, after the treatment of ketone **1g** with *N*-methylethylenediamine under the standard reaction conditions, only 4-methoxybenzaldehyde was isolated in 74 % yield after column chromatography (Scheme 6). Its formation seems to be similar to that described for non-fluorinated bromoenones (see Scheme 2). The isolation of the aldehyde instead of its aminal can be explained by hydrolysis of the aminal during chromatography.



Scheme 6. Degradation of **1g** with *N*-methylethylenediamine.

Conclusions

In conclusion, we have found that the reaction of fluorinated and non-fluorinated α-bromoenones with 1,2-diamines is extremely sensitive to the structure of both electrophile and nucleophile. As a result, the reaction can go in four different directions to form various nitrogen heterocycles (Scheme 7). The reaction with *N*-unsubstituted ethylenediamines gives 1,4-diazabicyclo[4.1.0]hept-4-enes. 3-Trifluoromethylated piperazine-2-ones are formed in the reaction with *N*,*N*′-dialkylethylenediamines through an unusual rearrangement, involving an intramolecular 1,2-migration of a CF_3 group as a key step.[6] The unique role of the perfluoroalkyl groups in this rearrangement was established. In contrast, the reaction of non-fluorinated bromoenones with *N*,*N*′-dialkylethylenediamines results in the destructive cleavage of the C=C double bond. Finally, reaction of bromoenones with *N*,*N*′-dicyclopropylethylenediamine leads to the formation of piperazin-2-yl ketones.[6b]



Scheme 7. Four directions of the reaction of bromoenones with diamines.

Experimental Section

General Remarks: ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectra were recorded with Bruker ARX 300, Bruker AMX 400, Bruker AVANCE 400, and Bruker AV 600 spectrometers with solutions in $CDCl_3$. Chemical shifts (δ) in ppm are reported with the use of the residual chloroform (δ = 7.25 ppm for ^{1}H, and δ = 77.20 ppm for ^{13}C) as internal references. Coupling constants (J) are given in Hertz (Hz). IR spectra were recorded with a Bruker Vertex 70 FTIR spectrometer, and with a portable Varian 3100 diamond ATR/FTIR spectrometer. GC/MS analyses were carried out with a Shimadzu GC–MS-QP5050A instrument (EI, 70 eV). ESI-MS spectra were measured with a MicroTof Bruker Daltonics instrument. The silica gel used for flash chromatography was 230–400 mesh. All reagents were of reagent grade, and were either used as supplied or distilled before use. All solvents were dried by standard procedures, and were freshly distilled before use. Diastereomers **7a** and **7b** as well as **8a** and **8b** were separated. Diastereomers **9a** and **9b** were obtained as a mixture, which was not separated.

General Procedure for the Reactions of α-Bromoenones 1 with Diamines: The appropriate enone (1 equiv.), diamine (1.1 equiv.), and triethylamine (1.5 equiv.) were mixed in THF (2 mL for 1 mmol). The mixture was kept at room temperature for 48 h, or at reflux for 4 h (compound **11**). After this time, the volatiles were evaporated in vacuo. The residue was purified by column chromatography (silica gel; CH_2Cl_2 for **7**; CH_2Cl_2/MeOH, 30:1 for **6**, **8**, **11**, and **12**) to give the target heterocycles. The following compounds were obtained according to this procedure.

(6*R,7*S**)-7-Phenyl-5-trifluoromethyl-1,4-diazabicyclo[4.1.0]-hept-4-ene (6a):** Pale yellow oil (117 mg, 49 %). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.73–2.83 (m, 1 H, 2-H_2), 2.79 (m, 1 H, 6-H_2), 3.37 (dd, J = 6.8, J = 13.7 Hz, 1 H, 2-H_2), 3.48 (d, J = 1.6 Hz, 1 H, 7-H), 3.52–3.65 (m, 1 H, 3-H_2), 4.04 (dd, J = 4.4, J = 17.6 Hz, 1 H, 3-H_2), 7.28–7.41 (m, 5 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 36.6 (C-6), 39.6 (C-2), 40.7 (C-7), 43.6 (C-3), 119.5 (q, $J_{C,F}$ = 277.6 Hz, CF_3), 126.5 (C^o), 128.3 (C^p), 128.8 (C^m), 136.8 (C^i), 157.9 (q, $J_{C,F}$ = 34.7 Hz, C-5) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –73.2 (d, $J_{H,F}$ = 2.6 Hz) ppm. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ = –59.9 (N-4), –345.8 (N-1) ppm. IR: $\tilde{\nu}$ = 1091, 1135, 1195 (C–F), 1662 (C=N) cm^{-1}. MS (EI): m/z (%) = 240 (60) $[M]^+$, 117 (100). 91 (46). $C_{12}H_{11}F_3N_2$ (240.23): calcd. C 60.00, H 4.62, N 11.66; found C 59.85, H 4.61, N 11.56.

(6*R,7*S**)-7-*p*-Tolyl-5-trifluoromethyl-1,4-diazabicyclo[4.1.0]-hept-4-ene (6b):** Pale yellow oil (134 mg, 53 %). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, ArCH_3), 2.59–2.68 (m, 1 H, 2-H_2), 2.66 (m, 1 H, 6-H), 3.23 (dd, J = 6.8, J = 13.8 Hz, 1 H, 2-H_2), 3.33 (d, J = 2.0 Hz, 1 H, 7-H), 3.39–3.50 (m, 1 H, 3-H_2), 3.93 (dd, J = 4.6, J = 17.8 Hz, 1 H, 3-H_2), 7.02–7.11 (m, 4 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.2 (ArCH_3), 36.6 (C-6), 39.6 (C-2), 40.5 (C-7), 43.6 (C-3), 119.5 (q, $J_{C,F}$ = 277.6 Hz, CF_3), 126.3 (Ar-C-2,6), 129.5 (Ar-C-3,5), 133.7 (Ar-C-1), 138.1 (Ar-C-4), 158.0 (q, $J_{C,F}$ = 34.6 Hz, C-5) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –73.4 (d, $J_{H,F}$ = 2.5 Hz) ppm. IR: $\tilde{\nu}$ = 1089, 1135, 1195 (C–F), 1661 (C=N) cm^{-1}. $C_{13}H_{13}F_3N_2$ (254.25): calcd. C 61.41, H 5.15, N 11.02; found C 60.95, H 5.17, N 10.68.

(6*R,7*S**)-7-Phenyl-3,6-diazabicyclo[4.1.0]hept-2-ene (6c):** Brownish viscous oil (84 mg, 48 %). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.51 (br. s, 1 H, CH), 2.75–2.82 (m, 1 H, CH_2), 2.99–3.11 (m, 1 H, CH_2), 3.25–3.30 (m, 1 H, CH_2), 3.46 (d, J = 2.1 Hz, 1 H, CH), 3.75–3.80 (m, 1 H, CH_2), 7.23–7.32 (m, 5 H, Ph), 8.24 (br. s, 1 H, CH=N) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 39.5 (CH), 39.8 (CH), 40.5 (CH_2), 43.7 (CH_2), 126.0 (Ph), 127.6 (Ph), 128.4 (Ph), 137.7 (Ph), 160.9 (CH=N) ppm. IR: $\tilde{\nu}$ = 1609 (C=N) cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}N_2H^+$ $[M + H]^+$ 173.1073; found 173.1077.

(6*R,7*S**)-5-Methyl-7-phenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (6d):** Brownish powder (147 mg, 79 %), m.p. 186–188 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.14 (d, J = 2.4 Hz, 3 H, CH_3), 2.44 (d, J = 2.1 Hz, 1 H, CH), 2.66.50–2.74 (m, 1 H, CH_2), 3.15 (dd, J = 13.1, J = 5.7 Hz, 1 H, CH_2), 3.34 (d, J = 2.1 Hz, 1 H, CH), 3.36–3.43 (m, 1 H, CH_2), 3.64 (dd, J = 16.8, J = 4.6 Hz, 1 H, CH_2), 7.20–7.30 (m, 5 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.0 (CH_3), 38.9 (CH_2), 39.7 (CH), 41.1 (CH_2), 42.5 (CH), 125.9 (Ph), 127.3 (Ph), 128.2 (Ph), 137.9 (Ph), 166.1 (C=N) ppm. IR: $\tilde{\nu}$ = 1660 (C=N) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{14}N_2H^+$ $[M + H]^+$ 187.1230; found 187.1222.

(6*R,7*S**)-5,7-Diphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (6e):** Brownish powder (191 mg, 77 %), m.p. 70–72 °C (Lit.[19] 71–73 °C). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.91–2.99 (m, 1 H, CH_2), 3.07 (d, J = 2.4 Hz, 1 H, CH), 3.24 (ddd, J = 13.3, J = 6.1, J = 1.9 Hz, 1 H, CH_2), 3.47 (d, J = 2.4 Hz, 1 H, CH), 3.64–3.73 (m, 1 H, CH_2), 3.94–4.00 (m, 1 H, CH_2), 7.30–7.35 (m, 1 H, Ph), 7.36–7.43 (m, 7 H, Ph), 7.78–7.81 (m, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 39.2 (CH), 40.5 (CH_2), 40.7 (CH), 43.3 (CH_2), 125.8 (Ph), 125.9 (Ph), 127.4 (Ph), 128.2 (Ph), 128.3 (Ph), 129.8 (Ph), 137.9 (Ph), 138.7 (Ph), 164.4 (C=N) ppm.

(6*R,7*S**)-5-(4-Nitrophenyl)-7-phenyl-1,4-diazabicyclo[4.1.0]-hept-4-ene (6f):** Brown-yellow powder (212 mg, 72 %), m.p. 121–122 °C (Lit.[20] 124 °C). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.86–2.93 (m, 1 H, CH_2), 2.99 (d, J = 2.4 Hz, 1 H, CH), 3.29 (ddd, J = 13.4, J = 6.4, J = 1.5 Hz, 1 H, CH_2), 3.50 (d, J = 2.4 Hz, 1 H, CH), 3.66–3.74 (m, 1 H, CH_2), 3.99–4.03 (m, 1 H, CH_2), 7.26–7.30 (m, 1 H, Ph), 7.31–7.37 (m, 4 H, Ph), 7.87 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$), 8.16 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 39.0 (CH), 40.1 (CH_2), 40.9 (CH), 43.8 (CH_2), 123.6 (Ar), 125.9 (Ar), 126.9 (Ar), 127.1 (Ar), 128.5 (Ar), 137.4 (Ar), 144.1 (Ar), 148.4 (Ar), 162.9 (C=N) ppm.

5-(4-Nitrophenyl)-2,3,7-triphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (7): Obtained as a mixture of diastereomers (42:58; 276 mg, 78 %).

***rel*-(2*S*,3*S*,6*R*,7*R*)-5-(4-Nitrophenyl)-2,3,7-triphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (7a):** a brownish viscous oil: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.02–3.04 (m 2 H, CH), 3.30 (d, J = 9.0 Hz, 1 H, C*H*Ph), 4.71 (d, J = 9.0 Hz, 1 H, C*H*Ph), 6.96–7.02 (m, 2 H, Ph), 7.16–7.24 (m, 8 H, Ph), 7.28–7.42 (m, 5 H, Ph), 8.18 (d, J = 9.0 Hz, 2 H, 4-$NO_2C_6H_4$), 8.29 (d, J = 9.0 Hz, 2 H, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 41.6 (CH), 52.4 (CH), 68.5 (CHPh), 73.2 (CHPh), 123.8 (Ar), 125.9 (Ar), 127.0 (Ar), 127.1 (Ar), 127.4 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.1 (Ar), 128.3 (Ar), 128.7 (Ar), 138.2 (Ar), 140.7 (Ar), 140.8 (Ar), 142.0 (Ar), 149.2 (Ar), 164.2 (C=N) ppm. HRMS (ESI): calcd. for $C_{29}H_{23}N_3O_2H^+$ $[M + H]^+$ 446.1863; found 446.1852.

***rel*-(2*R*,3*R*,6*R*,7*R*)-5-(4-Nitrophenyl)-2,3,7-triphenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (7b):** brown-yellow crystals: m.p. 123–

124 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.40 (d, J = 1.4 Hz, 1 H, CH), 3.65 (d, J = 9.9 Hz, 1 H, C*H*Ph), 4.03 (d, J = 1.4 Hz, 1 H, CH), 4.64 (d, J = 9.9 Hz, 1 H, C*H*Ph), 6.88–6.94 (m, 2 H, Ph), 6.96–7.01 (m, 2 H, Ph), 7.15–7.29 (m, 6 H, Ph), 7.34–7.49 (m, 5 H, Ph), 8.11 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$), 8.29 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 40.3 (CH), 42.4 (CH), 61.6 (*C*HPh), 62.0 (*C*HPh), 126.6 (Ar), 127.1 (Ar), 127.5 (Ar), 127.6 (Ar), 127.9 (Ar), 128.1 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 128.8 (Ar), 137.0 (Ar), 139.7 (Ar), 141.3 (Ar), 143.9 (Ar), 148.9 (Ar), 162.9 (C=N) ppm. HRMS (ESI): calcd. for $C_{29}H_{23}N_3O_2H^+$ [M + H]$^+$ 446.1863; found 446.1851.

1-Phenyl-2-(trifluoromethyl)-1,1a,3a,4,5,6,7,7a-octahydroazireno[1,2-*a*]quinoxaline (8): Obtained as a mixture of diastereomers (65:35; 221 mg, 75 %).

Major diastereomer, *rel*-(1*R*,1a*S*,3a*S*,7a*S*)-1-Phenyl-2-(trifluoromethyl)-1,1a,3a,4,5,6,7,7a-octahydroazireno[1,2-*a*]quinoxaline (8a): a pale yellow viscous oil: ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 1.25–1.36 (m, 1 H, 4-H^{ax} and 6-H^{ax}), 1.39–1.48 (m, 1 H, 5-H^{ax}), 1.59–1.68 (m, 1 H, 7-H^{ax}), 1.78–1.82 (m, 1 H, 6-H^{eq}), 1.83–1.87 (m, 1 H, 5-H^{eq}), 1.92 (ddd, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 4.2, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.2, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 11.5 Hz, 1 H, 7a-H), 2.17–2.21 (m, 1 H, 7-H^{eq}), 2.40–2.48 (m, 1 H, 4-H^{eq}), 2.50 (dd, $^3J_{1\text{-}H,1a\text{-}H}$ = 3.1, $^5J_{1a\text{-}H,3a\text{-}H}$ = 1.3 Hz, 1 H, 1a-H), 2.79 (d, $^3J_{1\text{-}H,1a\text{-}H}$ = 3.1 Hz, 1 H, 1-H), 3.19–3.29 (m, 1 H, 3a-H), 7.24–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 24.8 (C-6), 25.2 (C-5), 33.0 (C-4), 34.04 (C-7), 37.3 (C-1a), 52.7 (C-1), 60.7 (C-3a), 67.1 (C-7a), 119.2 (q, $^1J_{C,F}$ = 277.2 Hz, CF_3), 126.1 (Ph-C^o), 127.8 (Ph- C^p), 128.5 (Ph-C^m), 137.7 (Ph-C^i), 158.9 (q, $^2J_{C,F}$ = 35.1 Hz, C-2) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –73.4 ppm.

Minor diastereomer, *rel*-(1*R*,1a*S*,3a*R*,7a*R*)-1-Phenyl-2-(trifluoromethyl)-1,1a,3a,4,5,6,7,7a-octahydroazireno[1,2-*a*]quinoxaline (8b): a pale yellow viscous oil: ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 1.20–1.27 (m, 1 H, 7-H^{ax}), 1.32–1.49 (m, 3 H, 4-H^{ax}, 5-H^{ax}, 6-H^{ax}), 1.85–1.91 (m, 2 H, 6-H^{eq}, 5-H^{eq}), 2.23 (ddd, $^3J_{7a\text{-}H,7\text{-}Heq}$ = 3.4, $^3J_{3a\text{-}H,7a\text{-}H}$ = 9.6, $^3J_{7a\text{-}H,7\text{-}Hax}$ = 11.8 Hz, 1 H, 7a-H), 2.35–2.40 (m, 1 H, 7-H^{eq}), 2.43–2.48 (m, 1 H, 4-H^{eq}), 2.87 (dd, $^3J_{1\text{-}H,1a\text{-}H}$ = 3.1, $^5J_{1a\text{-}H,3a\text{-}H}$ = 1.3 Hz, 1 H, 1a-H), 2.91–2.98 (m, 1 H, 3a-H), 3.49 (d, $^3J_{1\text{-}H,1a\text{-}H}$ = 2.4 Hz, 1 H, 1-H), 7.27–7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 25.5 (C-5), 25.9 (C-6), 31.6 (C-7), 33.62 (C-4), 38.4 (C-1a), 39.0 (C-1), 55.3 (C-7a), 56.4 (C-3a), 119.4 (q, $^1J_{C,F}$ = 277.9 Hz, CF_3), 126.5 (Ph-C^o), 128.1 (Ph-C^m), 128.6 (Ph-C^p), 137.1 (Ph-C^i), 156.6 (q, $^2J_{C,F}$ = 34.3 Hz, C-2) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –73.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}F_3N_2H^+$ [M + H]$^+$ 295.1417; found 295.1408.

2-(4-Nitrophenyl)-1-phenyl-1,1a,3a,4,5,6,7,7a-octahydroazireno[1,2-*a*]quinoxaline (9): Brown-yellow crystals, obtained as a mixture of diastereomers (23:77; 246 mg, 71 %), m.p. 162–164 °C.

Major diastereomer, *rel*-(1*R*,1a*S*,3a*S*,7a*S*)-2-(4-Nitrophenyl)-1-phenyl-1,1a,3a,4,5,6,7,7a-octahydroazireno[1,2-*a*]quinoxaline (9a): ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.29–1.56 (m, 3 H, CH_2), 1.66–1.73 (m, 1 H, CH_2), 1.80–1.99 (m, 3 H, CH_2), 2.19–2.22 (m, 1 H, CH_2), 2.47–2.51 (m, 1 H, CH), 2.64 (d, J = 3.1 Hz, 1 H, CH), 2.75 (d, J = 3.1 Hz, 1 H, CH), 3.27–3.34 (m, 1 H, CH), 7.31–7.41 (m, 5 H, Ph), 8.02 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$), 8.20 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.8 (CH_2), 25.2 (CH_2), 33.7 (CH_2), 34.1 (CH_2), 40.5 (CH), 52.1 (CH), 60.9 (CH), 67.0 (CH), 123.5 (Ar), 125.8 (Ar), 126.9 (Ar), 127.6 (Ar), 128.6 (Ar), 138.4 (Ar), 142.1 (Ar), 148.8 (Ar), 163.2 (C=N) ppm.

Minor diastereomer, *rel*-(1*R*,1a*S*,3a*R*,7a*R*)-2-(4-Nitrophenyl)-1-phenyl-1,1a,3a,4,5,6,7,7a-octahydroazireno[1,2-*a*]quinoxaline (9b): ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.28–2.39 (m, 2 H, CH_2), 2.99–3.07 (m, 1 H, CH), 3.14 (d, J = 1.8 Hz, 1 H, CH), 3.62 (d, J = 1.8 Hz, 1 H, CH), 7.93 (d, J = 8.9 Hz, 2 H, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.5 (CH_2), 26.0 (CH_2), 31.6 (CH_2), 34.3 (CH_2), 38.7 (CH), 41.2 (CH), 55.1 (CH), 56.3 (CH), 123.5 (Ar), 126.2 (Ar), 127.3 (Ar), 127.7 (Ar), 128.5 (Ar), 138.0 (Ar), 144.5 (Ar), 148.4 (Ar), 162.1 (C=N) ppm. IR: $\tilde{\nu}$ = 1350, 1525 (NO_2), 1600 (C=O) cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{21}N_3O_2H^+$ [M + H]$^+$ 348.1707; found 348.1703.

(1*S,1a*S**)-2-(4-Nitrophenyl)-1-phenyl-1,1a-dihydroazirino[1,2-*a*]quinoxaline (11):** Orange-yellow crystals (250 mg, 73 %), m.p. 139–140 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.04 (s, 1 H, CH), 3.43 (s, 1 H, CH), 7.23–7.51 (m, 10 H, Ph), 8.11 (d, J = 8.6 Hz, 2 H, 4-$NO_2C_6H_4$), 8.28 (d, J = 8.6 Hz, 2 H, 4-$NO_2C_6H_4$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 39.5 (CH), 43.6 (CH), 123.7, 125.6, 126.2, 126.5, 127.7, 128.0, 128.8, 129.8, 130.1, 136.1, 137.0, 137.7, 142.3, 149.1 (Ar), 158.0 (C=N) ppm. HRMS (ESI): calcd. for $C_{21}H_{15}N_3O_2H^+$ [M + H]$^+$ 342.1237; found 342.1234.

***rel*-(1*S*,1a*R*,2*R*)-1-Phenyl-2-(trifluoromethyl)-1,1a,2,3-tetrahydroazireno[1,2-*a*]quinoxalin-2-ol (12a):** Pale yellow solid (208 mg, 68 %), m.p. 135–136 °C. ^{1}H NMR (400.1 MHz, [D$_6$]acetone): δ = 3.04 (m, 1 H, 1a-H), 3.57 (m, 1 H, 1-H), 5.90 (br. s, 1 H, NH), 6.45 (s, 1 H, OH), 6.73–6.80 (m, 1 H, 6-H), 6.87–6.92 (m, 1 H, 4-H), 6.96–7.02 (m, 1 H, 5-H), 7.27–7.31 (m, 2 H, 7-H, Ar-4-H), 7.34–7.40 (m, 4 H, Ar-2,6-H, Ar-3,5-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 45.4 (C-1a), 50.1 (C-1), 79.7 (q, $J_{C,F}$ = 30.8 Hz, C-2), 117.2 (C-4), 120.6 (C-6), 125.1 (q, $J_{C,F}$ = 285.3 Hz, CF_3), 126.4 (C-5), 126.7 (Ar-C-2,6), 127.0 (C-7), 128.0 (Ar-C-4), 128.9 (Ar-C-3,5), 135.1 (C-8), 135.6 (C-9), 138.5 (Ar-C-1) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –84.2 ppm. IR (KBr): $\tilde{\nu}$ = 1113, 1132, 1151 (C–F), 3161 (N–H), 3407 (O–H) cm^{-1}. MS (EI): *m/z* (%) = 306 (35) [M]$^+$, 207 (100), 129 (22). HRMS (ESI): calcd. for $C_{16}H_{13}BrF_3N_2OH^+$ [M + H]$^+$ 307.1053; found 307.1047. $C_{16}H_{13}F_3N_2O$ (306.29): calcd. C 62.74, H 4.28, N 9.15; found C 62.86, H 4.57, N 8.75.

***rel*-(1*S*,1a*R*,2*R*)-1-*p*-Tolyl-2-trifluoromethyl-1,1a,2,3-tetrahydroazireno[1,2-*a*]quinoxalin-2-ol (12b):** Pale yellow solid (233 mg, 73 %), m.p. 145–146 °C. ^{1}H NMR (400.1 MHz, [D$_6$]acetone): δ = 2.30 (s, 3 H, Ar*CH*$_3$), 2.97 (m, 1 H, 1a-H), 3.49 (m, 1 H, 1-H), 5.90 (br. s, 1 H, NH), 6.49 (s, 1 H, OH), 6.74–6.79 (m, 1 H, 6-H), 6.88–6.92 (m, 1 H, 4-H), 6.96–7.02 (m, 1 H, 5-H), 7.14–7.19 (m, 2 H, Ar-3,5-H), 7.23–7.27 (m, 3 H, 7-H, Ar-2,6-H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 20.8 ($ArCH_3$), 45.3 (C-1), 50.0 (C-1a), 79.7 (q, $J_{C,F}$ = 30.9 Hz, C-2), 117.1 (C-4), 120.5 (C-6), 125.3 (q, $J_{C,F}$ = 285.1 Hz, CF_3), 126.3 (C-5), 126.6 (Ar-C-2,6), 126.9 (C-7), 129.6 (Ar-C-3,5), 135.1 (C-8), 135.4 (Ar-C-1), 135.6 (C-9), 137.6 (Ar-C-4) ppm. ^{19}F NMR (376.5 MHz, [D$_6$]acetone): δ = –84.1 ppm. ^{15}N NMR (40.6 MHz, [D$_6$]acetone): δ = –310.1 (N-4), –333.9 (N-1) ppm. MS (EI): *m/z* (%) = 198 (100), 129 (46). IR (KBr): $\tilde{\nu}$ = 1182, 1195, 1221 (C–F), 3326 (O–H) cm^{-1}. $C_{17}H_{15}F_3N_2O$ (320.31): calcd. C 63.75, H 4.72, N 8.75; found C 63.76, H 4.75, N 8.54.

***rel*-(1*S*,1a*R*,2*R*)-1-(4-Chlorophenyl)-2-(trifluoromethyl)-1,1a,2,3-tetrahydroazireno[1,2-*a*]quinoxalin-2-ol (12c):** Pale yellow solid (284 mg, 83 %), m.p. 195–197 °C. ^{1}H NMR (600.1 MHz, [D$_6$]DMSO): δ = 2.88 (dd, $^3J_{1\text{-}H,1a\text{-}H}$ = 3.2, $^4J_{1a\text{-}H,OH}$ = 2.7 Hz, 1 H, 1a-H), 3.47 (d, $^3J_{1\text{-}H,1a\text{-}H}$ = 3.2 Hz, 1 H, 1-H), 6.63 (d, $^4J_{1a\text{-}H,OH}$ = 2.7 Hz, 1 H, OH), 6.69 (ddd, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.5 Hz, 1 H, 6-H), 6.90 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.5 Hz, 1 H, 4-H), 6.96 (ddd, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.5 Hz, 1 H, 5-H), 7.16 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.5 Hz, 1 H, 7-H), 7.32–7.34 (m, 1 H, H^o), 7.39–7.42 (m, 1 H, H^m) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 43.6 (C-1), 49.2 (C-1a), 79.7 (q, $^2J_{C,F}$ = 30.2 Hz, C-2), 116.5 (CH, C-4), 119.2 (CH, C-6), 124.0 (q, $J_{C,F}$ = 287.9 Hz, CF_3), 125.7 (CH, C-5), 126.0 (CH, C-7), 127.9 (2 CH, C^o), 128.4 (2 CH, C^m), 132.1 (C^p), 133.5 (C-7a), 135.4 (C-3a), 136.8 (C^i) ppm. ^{19}F NMR (376.5 MHz, [D$_6$]DMSO): δ = –82.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}ClF_3N_2OH^+$ [M + H]$^+$ 341.0663; found 341.0668.

***rel*-(1*S*,1a*R*,2*R*)-1-(3-Methoxyphenyl)-2-(trifluoromethyl)-1,1a,2,3-tetrahydroazireno[1,2-*a*]quinoxalin-2-ol (12d):** Pale yel-

low solid (308 mg, 92 %), m.p. 176–177 °C. ^{1}H NMR (400.1 MHz, [D$_6$]acetone): δ = 3.02 (m, 1 H, CH), 3.53 (m, 1 H, CH), 3.78 (s, 3 H, MeO), 5.90 (br. s, 1 H, NH), 6.76–6.79 (m, 1 H), 6.84–6.86 (m, 1 H), 6.90 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 6.94–7.02 (m, 3 H, Ar), 7.24–7.29 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 45.7 (CH), 50.3 (CH), 55.4 (MeO), 79.9 (q, $^2J_{C,F}$ = 31.0 Hz, CCF_3), 112.3 (CH, Ar), 113.9 (CH, Ar), 117.4 (CH, Ar), 119.3 (CH, Ar), 120.8 (CH, Ar), 124.9 (q, $J_{C,F}$ = 285.3 Hz, CF_3), 126.7 (CH, Ar), 127.2 (CH, Ar), 130.3 (CH, Ar), 135.1 (Ar), 135.8 (Ar), 140.2 (Ar), 160.8 (Ar) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –84.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}F_3N_2O_2H^+$ [M + H]$^+$ 337.1158; found 337.1151.

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[1] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274; b) A slightly lower number (51 drugs) was found in: R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.

[2] a) The poster containing structural formulas of the top 200 selling drugs can be downloaded from: http://cbc.arizona.edu/njardarson/group; b) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348–1349.

[3] For recent reviews, see: a) *Fluorine Chemistry*, *Chem. Rev.* **2015**, *115*, 563–1306; b) V. G. Nenajdenko (Ed.), *Fluorine in Heterocyclic Chemistry*, Springer, Cham, **2014**, vol. 1, p. 681, vol. 2, p. 760; c) V. A. Petrov (Ed.), *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Wiley, New Jersey, **2009**, p. 515; d) A. A. Gakh, K. L. Kirk (Eds.), *Fluorinated Heterocycles*, ACS Symposium Series, Oxford University Press/American Chemical Society, Washington, DC, **2009**, p. 360.

[4] For reviews, see: a) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359; c) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081; d) P. V. Ramachandran, *Future Med. Chem.* **2009**, *1*, 771–772; e) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 771–791; f) I. Ojima (Ed.), *Fluorine in Medicinal Chemistry and Chemical Biology*, John Wiley & Sons, Chichester, UK, UK, **2009**, p. 640; g) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; h) W. L. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; i) J. P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, **2008**; j) A. Tressaud, G. Haufe (Eds.), *Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals*, Elsevier, Amsterdam, **2008**, p. 553–778; k) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; l) S. V. Druzhinin, E. S. Balenkova, V. G. Nenajdenko, *Tetrahedron* **2007**, *63*, 7753–7808; m) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1039; n) G. Theodoridis, *Fluorine-Containing Agrochemicals: An Overview of Recent Developments*, in: *Advances in Fluorine Science*, vol. 2 (Ed.: A. Tressaud), Elsevier, Amsterdam, **2006**, p. 121–175; o) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; *Angew. Chem.* **2005**, *117*, 218–234; p) V. G. Nenajdenko, A. V. Sanin, E. S. Balenkova, *Russ. Chem. Rev.* **1999**, 483–505; q) V. G. Nenajdenko, A. V. Sanin, E. S. Balenkova, *Molecules* **1997**, *2*, 186–232.

[5] a) For reviews, see: A. Yu. Rulev, *Russ. Chem. Rev.* **1998**, *67*, 279–293; b) A. Yu. Rulev, *Russ. Chem. Rev.* **2011**, *80*, 197–218; c) L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881–7929. For recent examples, see: d) A. Yu. Rulev, S. Azad, H. Kotsuki, J. Maddaluno, *Eur. J. Org. Chem.* **2010**, 6423–6429; e) M. Görmen, R. Le Goff, A. M. Lawson, A. Daïch, S. Comesse, *Tetrahedron Lett.* **2013**, *54*, 2174–2176; f) Z. Amara, E. Drge, C. Troufflard, P. Retailleau, M.-E. Tran Huu-Dau, D. Joseph, *Chem. Eur. J.* **2014**, *20*, 15840–15848.

[6] a) A. Yu. Rulev, V. M. Muzalevskiy, E. V. Kondrashov, I. A. Ushakov, A. R. Romanov, V. N. Khrustalev, V. G. Nenajdenko, *Org. Lett.* **2013**, *15*, 2726–2729; b) V. M. Muzalevskiy, Yu. A. Ustynyuk, I. P. Gloriosov, V. A. Chertkov, A. Yu. Rulev, E. V. Kondrashov, I. A. Ushakov, A. R. Romanov, V. G. Nenajdenko, *Chem. Eur. J.* **2015**, *21*, 16982–16989.

[7] a) A. Yu. Rulev, I. A. Ushakov, V. G. Nenajdenko, E. S. Balenkova, M. G. Voronkov, *Eur. J. Org. Chem.* **2007**, 6039–6045; b) A. Yu. Rulev, I. A. Ushakov, V. G. Nenajdenko, *Tetrahedron* **2008**, *64*, 8073–8077.

[8] a) V. M. Muzalevskiy, V. G. Nenajdenko, A. Yu. Rulev, I. A. Ushakov, G. V. Romanenko, A. V. Shastin, E. S. Balenkova, G. Haufe, *Tetrahedron* **2009**, *65*, 6991–7000; b) A. Yu. Rulev, V. M. Muzalevskiy, E. V. Kondrashov, I. A. Ushakov, A. V. Shastin, E. S. Balenkova, G. Haufe, V. G. Nenajdenko, *Eur. J. Org. Chem.* **2010**, 300–310; c) V. G. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, E. S. Balenkova, E. V. Kondrashov, I. A. Ushakov, A. Yu. Rulev, *J. Org. Chem.* **2010**, *75*, 5679–5688; d) A. Yu. Rulev, I. A. Ushakov, E. V. Kondrashov, V. M. Muzalevskiy, A. V. Shastin, V. G. Nenajdenko, *J. Fluorine Chem.* **2011**, *132*, 945–950.

[9] S. Roy, M. P. Davydova, R. Pal, K. Gilmore, G. A. Tolstikov, S. F. Vasilevsky, I. V. Alabugin, *J. Org. Chem.* **2011**, *76*, 7482–7490.

[10] E. Pretsch, P. Bühlmann, M. Badertscher, *Structure Determination of Organic Compounds*, Springer-Verlag, Berlin/Heidelberg, Germany, **2009**, p. 433.

[11] A. I. Zbruyev, V. V. Vashchenko, A. A. Andryushchenko, S. M. Desenko, V. I. Musatov, I. V. Knyazeva, V. A. Chebanov, *Tetrahedron* **2007**, *63*, 4297–4303.

[12] A. Padwa, L. Gehrlein, R. B. Kinnel, *J. Org. Chem.* **1975**, *40*, 1683–1688.

[13] a) A. V. Samoshin, I. S. Veselov, V. A. Chertkov, A. A. Yaroslavov, G. V. Grishina, N. M. Samoshina, V. V. Samoshin, *Tetrahedron Lett.* **2013**, *54*, 5600–5604; b) Y. Zheng, X. Liu, N. M. Samoshina, V. A. Chertkov, A. Franz, X. Guo, V. V. Samoshin, *Natural Product Commun.* **2012**, *7*, 353–358.

[14] V. A. Chertkov, N. M. Sergeyev, *J. Am. Chem. Soc.* **1977**, *99*, 6750–6752.

[15] V. A. Chertkov, A. K. Shestakova, D. V. Davydov, *Chem. Heterocycl. Compd.* **2011**, *47*, 45–54.

[16] A. V. Fokin, A. F. Kolomiets, N. V. Vasil'ev, *Russ. Chem. Rev.* **1984**, *53*, 238–255.

[17] A. Yu. Rulev, N. Yenil, A. Pesquet, H. Oulyadi, J. Maddaluno, *Tetrahedron* **2006**, *62*, 5411–5416.

[18] A. Yu. Rulev, J. Maddaluno, *J. Phys. Org. Chem.* **2002**, *15*, 590–598.

[19] H. W. Heine, R. P. Henzel, *J. Org. Chem.* **1969**, *34*, 171–175.

[20] V. D. Orlov, Z. Kaluski, N. P. Borob'eva, E. Figas, A. A. Tishchenko, F. G. Yaremko, *Chem. Heterocycl. Compd.* **1994**, *30*, 964–971.

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