EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201725

Highly β-Regioselective Friedel–Crafts Aminoalkylation of Pyrroles with Cyclic Perfluoroalkylated Imines

Olga I. Shmatova,[a] Nikolay E. Shevchenko,[a] Elisabeth S. Balenkova,[a] Gerd-Volker Röschenthaler,*[b] and Valentine G. Nenajdenko*[a]

Keywords: Nitrogen heterocycles / Electrophilic substitution / Lewis acids / Fluorine / Amines / Regioselectivity

A Friedel–Crafts-type alkylation reaction was studied between various pyrroles and α-polyfluoroalkylated cyclic imines that were activated by Lewis acids. The reaction proceeded under mild conditions and provided a high yielding synthesis of α-CF_3-substituted pyrrolidines and piperidines as well as seven-membered analogues that contained a pyrrole ring. The unpredictably high β-selectivity for the aminoalkylation of both 1*H*-pyrrole and *N*-substituted pyrrole was observed as a result of a thermodynamically-controlled electrophilic substitution reaction. The computational data are in full agreement with the experimental results, which confirmed the observed regioselectivity as a result of the lower energy of the β-substituted pyrroles that contain α-trifluoromethyl-substituted pyrrolidine, piperidine, and azepane rings.

1. Introduction

The importance of fluoroorganic substances is well-known with regard to the chemistry of biologically active compounds and in modern material science. For instance, about 25% of currently used drugs contain at least one fluorine atom.[1] The improvement of the metabolic stability and the changes in the physicochemical properties and biological activity when fluorine atoms or perfluoroalkyl groups are incorporated into bioactive molecules explains this percentage.[2] At the same time, organofluorine compounds rarely occur in nature, and procedures that use reagents to introduce fluorine or fluorine-containing groups directly are limited in spite of significant progress in this field.[3] Therefore, the employment of fluorine-containing building blocks is the most widely used tool to synthesize compounds with the necessary fluorinated fragment in the appropriate position of the molecule.

Fluorine-containing amines are of great importance to medicinal chemistry. Such fragments are essential tools for modern drug discovery because they can modulate lipophilicity and steric effects, bring about a change to a preferred conformation (gauche effect), and improve metabolic stability and binding affinity. β-Trifluoromethylated amines are much less basic compounds in comparison to their non-fluorinated analogues, and the pK_a value changes significantly to make CF_3-substituted amines only a little more basic than anilines. The basicity of such amines is shifted to pK_a = 5–6, which is similar to the basicity of aniline (pK_a = 4.6) and *p*-anisidine (pK_a = 5.6). All of these changes can improve the bioavailability and increase the blood-brain barrier penetration of derivatives, creating an extreme demand for fluorinated amines for drug discovery.[1]

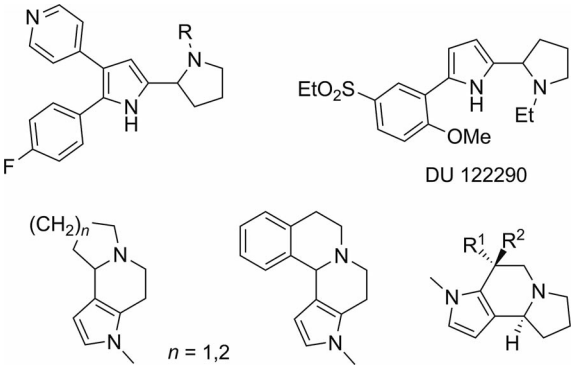
Recently we elaborated the synthesis of cyclic imines that contained a polyfluoroalkylated (CF_3 or C_2F_5) group at the α-position[4] and started an investigation into their chemical applications.[5] These imines are valuable building blocks for simultaneously incorporating an alkaloid-like cyclic amine fragment (i.e., pyrrolidine, piperidine, azepane) and a trifluoromethyl or pentafluoroethyl group attached at the α-position to the nitrogen. Because of the electron-withdrawing character of perfluoroalkyl group, it is typical for such fluorinated imines to be more reactive towards nucleophiles. For example, there are rare publications devoted to Friedel–Crafts-type aminoalkylations of electron-rich aromatics and heteroaromatics with acyclic CF_3-substituted imines.[6,7] We propose that perfluoroalkylated cyclic imines can also participate in an aminoalkylation reaction to create direct access to pyrrolidine, piperidine, and azepane compounds that have a perfluorinated fragment and an aryl (heteroaryl) group at the α-position to the amine nitrogen. Recently, we elaborated an efficient synthesis of corresponding indole derivatives connected to saturated five-, six-, and seven-membered cyclic amines that contained CF_3 and C_2F_5 groups at the α-position. This was accomplished

[a] Department of Chemistry, Lomonosov Moscow State University,
Moscow 119991, Russia
Fax: +7-495-9328846
E-mail: nen@acylium.chem.msu.ru
Homepage: www.msu.ru
[b] School of Engineering and Science, Jacobs University Bremen GmbH,
Campus Ring 1, 28759 Bremen, Germany
Fax: +49-421-200-3229
E-mail: g.roeschenthaler@jacobs-university.de
Homepage: www.jacobs-university.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201725.

through the alkylation of cyclic imines that contained a polyfluoroalkylated (CF_3 or C_2F_5) group. These compounds are very attractive for subsequent biological studies.[8]

Herein, we report the results of our investigation of the aminoalkylation of pyrroles with cyclic imines that contain a trifluoromethyl or pentafluorophenyl group. Because they are very nucleophilic, aromatics pyrroles are efficient partners in reactions with various electrophiles. Furthermore, the pyrrole structural fragment is a key unit in many natural and biologically active compounds.[9] We expect that a Friedel–Crafts-type reaction of activated CF_3-substututed cyclic imines with pyrroles can open a simple and straightforward route to attractive alkaloid-like derivatives that contain a CF_3 group. Many substituted pyrroles connected to a cyclic amine fragment have been used in medicinal chemistry research.[10] For example, such substituted pyrroles were found to be Et-PKG inhibitors, anticoccidial agents, antipsychotics, inhibitors of D1, and 5-HT_{2A} receptors, and some were investigated for use as potent antidepressants (see Scheme 1).

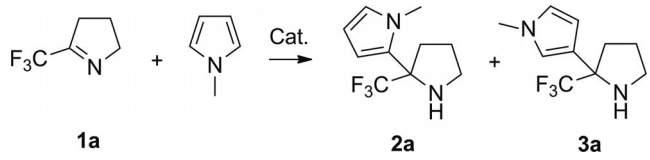


Scheme 1. Examples of biologically active pyrroles that contain a cyclic amine group.

2. Results and Discussion

The literature reveals only rare examples of Friedel–Crafts alkylations with noncyclic CF_3-substituted imines. The highly reactive imines of hexafluoroacetone or methyl trifluoropyruvate, which are activated additionally by electron-withdrawing groups attached to the imine nitrogen, can react with electron-rich aromatics such as pyrroles, indoles, furans, thiophenes, and some benzene derivatives without any activators.[6] However, Brnsted or Lewis acid activation was required in case of NH imines or imines with an aryl or alkyl group.[7] The reaction with cyclic imines occurs only with the corresponding nonfluorinated aldimines (i.e., pyrroline and tetrahydropyridine), as ketimines that have an additional α-substituent are much less reactive. Until now, no literature examples are known for similar reactions of ketimines without additional activation by electron-withdrawing groups.[11]

Thus, we commenced our work to screen the reaction conditions for aminoalkylation. The reaction of 2-trifluoromethylpyrroline (**1a**) with *N*-methylpyrrole (see Scheme 2) in dichloromethane was chosen as a model reaction. We used equimolar amounts of triflic acid (TfOH) and several Lewis acids [i.e., $AlCl_3$, $TiCl_4$, $Ti(OiPr)_4$, $BF_3{\cdot}Et_2O$, $Zn(OTf)_2$, $ZnCl_2$, $MgCl_2$] to activate imine **1a**, as no reaction occurs without an additive.



Scheme 2. Reaction of α-trifluoromethylpyrroline with *N*-methylpyrrole.

The reaction did not proceed in the presence of $Ti(OiPr)_4$ or triflic acid (see Table 1, Entries 4 and 8). In the presence of other activators, we observed that the desired transformation formed two major products. According to NMR spectroscopic data, two regioisomeric derivatives were formed. These compounds were isolated easily in pure form by using column chromatography. The ratio of the isomers and the reaction rate depended significantly on the nature of the employed Lewis acid. In the cases of $ZnCl_2$, $Zn(OTf)_2$, and $MgCl_2$, the reaction required 8 d, but $MgCl_2$ afforded a low selectivity to form the two regioisomers **2a** and **3a** in approximately a 1:1 ratio (see Table 1, Entry 7). The reaction with $ZnCl_2$ and $Zn(OTf)_2$ was more selective to give product **3a** preferentially (see Table 1, Entries 5 and 6). In presence of $BF_3{\cdot}Et_2O$ and in 5 d, the reaction smoothly gave **3a** and a small amount of **2a** in an almost quantitative total yield (see Table 1, Entry 3). In contrast, the transformation with $AlCl_3$ and $TiCl_4$ required a shorter reaction time (2 and 4 h, respectively). In these cases, the selectivity was not so high, and a significant amount of **2a** was isolated. Therefore, $BF_3{\cdot}Et_2O$ was the best activator for **1a**, as it provided the highest yield and selectivity. Changing the solvent (i.e., THF, ether, toluene) and varying the amount of Lewis acid did not provide any improvement. In the presence of $BF_3{\cdot}Et_2O$, using an elevated reaction temperature led only to decomposition of the Lewis acid-imine complex and resulted in subsequent tarring.

Table 1. Screening of catalysts for the reaction between imine **1a** and *N*-methylpyrrole.[a]

Entry	Catalyst and conditions	Isolated yield [%] **2a**	**3a**	Time
1	$AlCl_3$, –40 °C	26[b]	70[b]	2 h
2	$TiCl_4$, –40 °C	22[b]	69[b]	4 h
3	$BF_3{\cdot}Et_2O$, 0 °C	9[c]	87[c]	5 d
4	$Ti(OiPr)_4$, room temp.	0	0	8 d
5	$ZnCl_2$, room temp.	6[b]	66[b]	8 d
6	$Zn(OTf)_2$, room temp.	16[b]	61[b]	8 d
7	$MgCl_2$, room temp.	32[b]	37[b]	8 d
8	TfOH, room temp.	0	0	–

[a] Reagents and conditions: catalyst (1 equiv.), and CH_2Cl_2 as a solvent. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture. [c] Isolated yield.

We made the preliminary regiochemical assignments of isomers **3a** and **2a** by using only ^{1}H and ^{13}C NMR spectroscopic data (see Table 1). To our surprise, unpredictable regiochemical outcomes were observed. The major product **3a**, which was formed in all of the reactions, was not the α isomer, but the β isomer instead. The preference for electrophilic attack to occur at the α-position is a well-known standard of pyrrole chemistry. Earlier electrophilic substitution reactions of *N*-methylpyrrole with acyclic CF_3-substituted imines in presence of Lewis or Brønsted acids yielded only 2-substituted products.[6,7] Other CF_3-substituted electrophiles underwent reaction with pyrroles to form α-substituted products as well.[12] On the other hand, the bromination of *N*-methylpyrrole proceeded by a similar mechanism, but its course could change under acidic conditions from the preferable formation of the α isomer to the β isomer.[13]

To clarify the point, the 2D NMR spectroscopic data of both regioisomers were recorded. A gHMBC experiment of **3a** showed a three-bond proton-carbon correlation between the hydrogen of methyl group attached to the pyrrole nitrogen and two aromatic CH carbons of the pyrrole ring (see Figure 1). Isomeric molecule **2a** displayed a three-bond proton-carbon correlation between the same hydrogen and both the quaternary carbon and CH carbon of the pyrrole ring (see Figure 1).

Finally, we were also able to obtain a single crystal of the main isomer **3a** as a tetrafluoroborate salt and confirm unambiguously the structure by X-ray crystal structure analysis. The crystal structure of the tetrafluoroborate salt of **3a** with the shortest contact between the BF_4 anion and the pyrrolidinium cycle (dotted line) is shown in Figure 1. Interestingly, the tetrafluoroborate anion is located on the same side of the pyrrolidinium ring as the trifluoromethyl group. Thus, the aminoalkyaltion of *N*-methylpyrrole with **1a**, which is activated by various Lewis acids, preferentially gave the β isomer as the product. Examples for the β-substitution of a pyrrole ring could be found in several reviews.[14] However, there are very few methods for the direct incorporation of an alkyl group into the 3-position of a pyrrole.

To study the scope of the reaction and its general character, we also examined the aminoalkylation of *N*-methylpyrrole with other cyclic imines **1b**–**1e** that consisted of five-, six-, and seven-membered rings as well as contained trifluoromethyl and pentafluoroethyl groups at the imine carbon (see Scheme 3) in the presence of $BF_3{\cdot}Et_2O$.

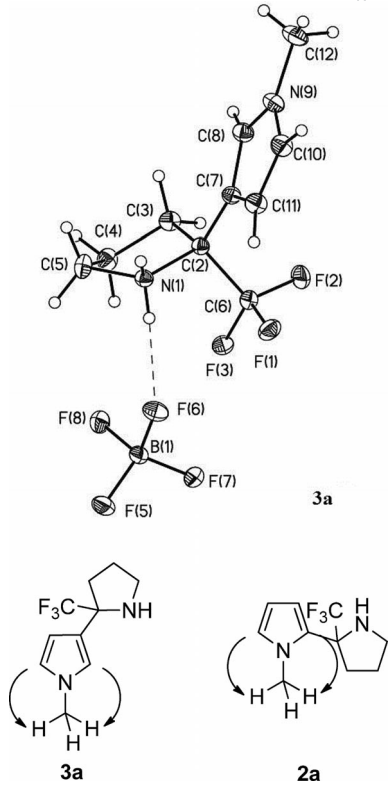
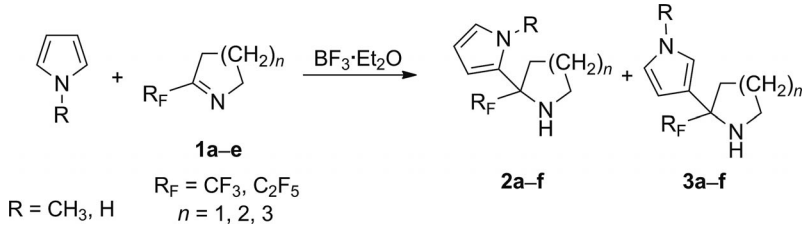


Figure 1. HMBC assignments for **3a** and **2a** and molecular structure of tetrafluoroborate salt of **3a**.

All reactions with trifluoromethylated imines **1a**, **1c**, and **1e** proceeded smoothly to afford β isomers **3a**, **3b**, and **3c** selectively in good yields (see Table 2). Pentafluoroethylated imines **1b** and **1d** were much less reactive and gave no products. Employing Lewis acids such as $TiCl_4$ or $AlCl_3$ as well as varying the reaction temperature and the amount of catalyst also did not lead to the desirable products. The trifluoromethyl and pentafluoroethyl groups have similar electron-withdrawing character, but the C_2F_5 fragment is more bulky [conformational energy *A* value of 2.67 kcal/mol].[15] Therefore, we believe that higher steric demand of this fragment resulted in a significant decrease in the electrophilicity of the Lewis acid-imine complex to block the desired reaction.

The reaction between imine **1a** and *N*-methylpyrrole produced a mixture of 2- and 3-substituted pyrroles in a ratio of 1:10. We believe the β isomer is the thermodynamically



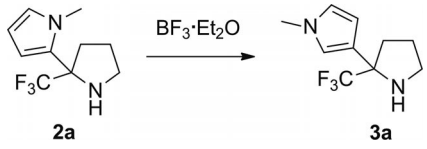
Scheme 3. Reaction of α-perfluoroalkylated cyclic imines with 1*H*-pyrrole and *N*-methylpyrrole.

Table 2. Reaction of α-perfluoroalkylated cyclic imines with *N*-methylpyrroles.[a]

Imine			Product, % yield		Pyrrole
Compound	R_F	*n*	2-Isomer	3-Isomer	^{1}H NMR signals [δ, ppm]
1a	CF_3	1	**2a**, 9	**3a**, 87	2-isomer; 6.09, 6.31, 6.63 3-isomer; 6.16, 6.58, 6.63
1b	C_2F_5	1	0	0	–
1c	CF_3	2	–	**3b**, 83	3-isomer; 6.10, 6.61, 6.61
1d	C_2F_5	2	0	0	–
1e	CF_3	3	–	**3c**, 87	3-isomer; 6.16, 6.57, 6.65

[a] Reagents and conditions: CH_2Cl_2 as a solvent and $BF_3{\cdot}Et_2O$ (1 equiv.) were combined with imine at 0 °C, and then *N*-methylpyrrole was added.

controlled product and, therefore, is formed preferentially. To confirm this, we performed a model experiment with a pure sample of α isomer **2a**. By combining this compound with an excess amount of BF_3 in an NMR tube, we observed its isomerization into β isomer **3a** (see Scheme 4). Similar isomerizations of pyrrole derivatives have been previously demonstrated with pyrrole 2-aldehydes and ketones, but these reactions required highly acidic or harsh conditions [heating with triflic acid or polyphosphoric acid (PPA)].[16] A possible mechanism for such an isomerization includes protonation (coordination of Lewis acid) followed by an intramolecular migration to the adjacent position. The transformation is similar to the stabilization of the *ipso* intermediate that is formed during an electrophilic substitution reaction. Several examples of acid-catalyzed and other rearrangements are described in review.[14a]



Scheme 4. Isomerization isomer **2a** into **3a** in the presence of $BF_3{\cdot}Et_2O$.

The unsubstituted pyrrole was also examined in the reactions with imines **1a**–**1e** (see Scheme 3). The 2-pentafluoroethylated cyclic imines did not undergo a reaction with pyrrole in the presence of $BF_3{\cdot}Et_2O$. When $TiCl_4$ was employed as the activator, tar formed in the reaction mixture. In contrast to the reaction with *N*-methylpyrrole, the aminoalkylation of 1*H*-pyrrole with CF_3-substituted imines **1a**, **1c**, and **1e** under the same conditions required a shorter reaction time (i.e., 12 h) that depended on the ring size of the imine (see Table 3). We observed quite an important influence on the reaction from the structure of the imine. Five- and seven-membered imines **1a** and **1e** led to a mixture of regioisomers **2** and **3** in approximately a 1:1 ratio, but six-membered imine **1c** selectively gave α-isomer **2e**. It is interesting to note that the same imine **1c** had undergone a reaction with *N*-methylpyrrole to form the β isomer exclusively (see Table 2). Such a difference can likely be explained in terms of the peculiarities of the conformations of these cyclic imines as well as the influence of the substituent on the pyrrole nitrogen.[17] Alkylation proceeded at the 2- or 3-position depending on the steric volume of the substituent at the nitrogen atom.

Table 3. Reaction of α-perfluoroalkylated cyclic imines with 1*H*-pyrrole.[a]

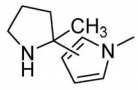
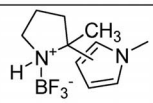
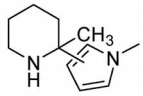
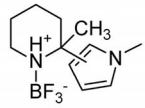
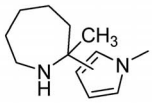
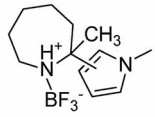
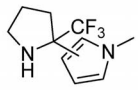
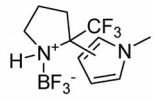
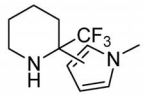
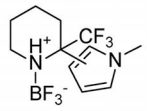
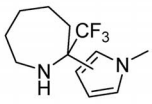
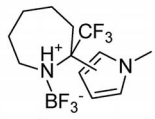
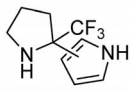
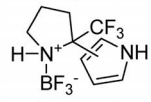
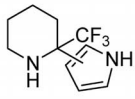
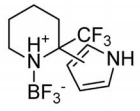
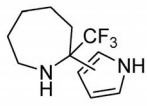
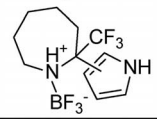
Imine	Product, % yield		Pyrrole
	2-Isomer	3-Isomer	^{1}H NMR signals [δ, ppm]
1a	**2d**, 43	**3d**, 37	2-isomer; 6.19, 6.19, 6.76 3-isomer; 6.26, 6.76, 6.80
1b	0	0	–
1c	**2e**, 67	–	2-isomer; 6.21, 6.25, 6.84
1d	0	0	–
1e	**2f**, 22	**3f**, 30	2-isomer; 6.17, 6.23, 6.76 3-isomer; 6.29, 6.77, 6.82

[a] Reagents and conditions: CH_2Cl_2 as a solvent and $BF_3{\cdot}Et_2O$ (1 equiv.) were combined with imine at 0 °C, and then 1*H*-pyrrole was added.

To gain further insight into the regioselectivity of the reaction, we decided to perform quantum chemical calculations. We estimated the Gibbs free energy of formation for the α- and β-substituted products as well as the corresponding BF_3 complexes for the reaction between imines **1** and pyrrole and *N*-methylpyrrole. We also performed a computational study of model nonfluorinated compounds that have a methyl group instead of a trifluoromethyl moiety to obtain additional data regarding the influence of a fluorinated substituent in such amines. The data that was obtained by using DFT PBE/L22 basis are summarized in Table 4.[18]

Almost all of the β-substituted *N*-methylpyrroles, independent of the size of the saturated cycle, are more energetically favorable in comparison to the α-substituted products. The same is especially true for the corresponding complexes with BF_3, which are primary reaction products. Many of the complexes with boron trifluoride resulted in a larger energy difference between the α and β isomers with a preference for the β isomers. This data clearly indicates that the β isomers are the thermodynamically controlled products of the reaction. The presence of the CF_3 group has a significant influence on the reaction and is an important reason for the observed β-regioselectivity. To minimize the steric interaction between the methyl group at the pyrrole nitrogen and the bulky saturated amine residue, the β-isomeric derivatives are formed. As a lower regioselectivity was observed for the reactions with 1*H*-pyrrole, we also obtained computation data for the derivatives. The results of the cal-

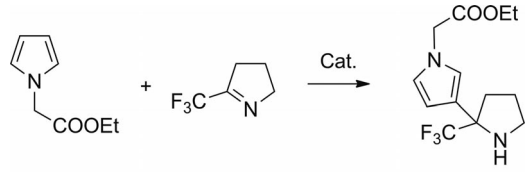
Table 4. Calculated ΔG_f° and the difference in energies for α- and β-substituted pyrrole derivatives.

Structure	α-Isomer Δ_fG° [kcal/mol]	β-Isomer Δ_fG° [kcal/mol]	α Δ_fG°-β Δ_fG°	Structure	α-Isomer Δ_fG° [kcal/mol]	β-Isomer Δ_fG° [kcal/mol]	α Δ_fG°-β Δ_fG°
	128.02	126.88	1.14		134.53	133.48	1.05
	144.96	144.27	0.69		152.25	150.88	1.37
	161.85	160.57	1.28		168.62	167.42	1.20
	111.49	110.50	0.99		117.88	116.49	1.39
	129.07	128.68	0.39		136.07	133.33	2.74
	145.78	144.45	1.33		153.05	150.80	2.25
	95.11	95.21	-0.10		102.33	101.85	0.47
	113.01	112.90	0.11		119.37	119.09	0.27
	129.22	129.19	0.03		136.40	135.91	0.49

culations are in good agreement with experiment, and in these cases, they exhibit smaller energy difference between the α and β isomers.

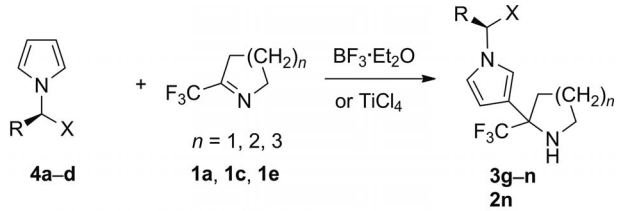
Such unusual regiochemical results led us to a deeper study of the aminoalkylation of other *N*-substituted pyrroles. Because some Lewis acids are able to coordinate to an oxygen-containing group, we propose that such a chelation could preferentially provide the α-substituted product in the reaction with imines **1**. With these considerations in mind, we investigated the regiochemical outcome of the reaction between pyrroles that contain either ester, alcohol, or carboxylic functionalities and imines **1a**, **1c**, and **1e** (see Schemes 5 and 6). The starting pyrroles **4a**–**4d** were synthesized from natural amino acids by using literature procedures.[19–21]

Using glycine-derived pyrrole **4a** and 2-(trifluoromethyl)-pyrroline (**1a**, Scheme 5), we varied the Lewis acids to study the regiochemical outcomes (see Table 5). In a typical experiment, imine **1a** was combined with 1 equiv. of catalyst in dichloromethane at 0 °C. Pyrrole **4a** was then added, and the progress of the reaction was monitored by TLC.



4a **1a** **3g**

Scheme 5. The reaction between **1a** and glycine-derived pyrrole.



4a–d **1a**, **1c**, **1e** **3g–n** **2n**

R = CH_3, H; X = COOEt, COOH, CH_2OH

Scheme 6. Aminoalkylation reaction of pyrroles derivatives **4a**–**4d** with imines **1a**, **1c**, and **1e**.

Table 5. Screening of the Lewis acids in the reaction of **1a** with **4a**.[a]

Entry	Catalyst, conditions	% Yield	Time
1	$AlCl_3$, –40 °C	68[b]	2 h
2	$TiCl_4$, –40 °C	81[c]	2 h
3	$BF_3{\cdot}Et_2O$, 0 °C	75[c]	5 d
4	$ZnCl_2$, room temp.	53[b]	10 d
5	$Zn(OTf)_2$, room temp.	50[b]	10 d
6	$MgCl_2$, room temp.	38[b]	10 d

[a] Reagents and conditions: CH_2Cl_2 as the solvent and a catalyst (1 equiv.). [b] Determined by ^{19}F NMR analysis of the crude reaction mixture. [c] Isolated yield.

In the case of $AlCl_3$ and $TiCl_4$, the reaction was complete within 2 h to give only the β-substituted product **3g** in 68 and 81% yields, respectively (see Table 5, Entries 1 and 2). The reaction promoted by $BF_3{\cdot}Et_2O$ required a longer but reasonable reaction time of 5 d and furnished the same product **3g** in a slightly lower 75% yield (see Table 5, Entry 3). Other activators afforded β-alkylation as well (see Table 5), but a cleaner reaction with an easier isolation was achieved by using $BF_3{\cdot}Et_2O$ and $TiCl_4$ as catalysts.

The reactions between the other functionalized pyrrole derivatives **4b**–**4d** and imines **1a**, **1c**, and **1e** that were activated by $BF_3{\cdot}Et_2O$ or $TiCl_4$ afforded again the corresponding β-substituted products (see Scheme 6). The reaction of pyrrole derivatives **4a** and **4b** with imines **1a**, **1c**, and **1e** gave compounds **3g**–**3l** (see Table 6, Entries 1–6). In the case of chiral pyrroles **4b** and **4c**, the diastereomers **3j**–**3m** were formed in a 1:1 ratio according to the NMR spectroscopic data. This occurred because the newly formed stereocenter is distant from the chiral center in the starting material.

Table 6. Aminoalkylation reaction of pyrroles **4** with imines **1**.[a]

Entry	Imine			Pyrrole		Product, % yield	
	n	Compd.	R	X	Compd.	2-Isomer	3-Isomer
1	1	**1a**	H	COOEt	**4a**	–	**3g**, 75 (81)[b]
2	2	**1c**	H	COOEt	**4a**	–	**3h**, 62
3	3	**1e**	H	COOEt	**4a**	–	**3i**, 65
4	1	**1a**	CH_3	COOEt	**4b**	–	**3j**, 69 (73)[b]
5	2	**1c**	CH_3	COOEt	**4b**	–	**3k**, 75
6	3	**1e**	CH_3	COOEt	**4b**	–	**3l**, 60
7	1	**1a**	CH_3	COOH	**4c**	–	**3m**, 73
8	1	**1a**	H	CH_2OH	**4d**	**2n**, 14	**3n**, 64

[a] Reagents and conditions: CH_2Cl_2 as the solvent, 1 equiv. of $BF_3{\cdot}Et_2O$ ($TiCl_4$), combined with imine at 0 °C (–40 °C), and then *N*-substituted pyrrole was added. [b] Yields with $TiCl_4$ are given in parentheses.

Only by using pyrrole **4d**, which contained a CH_2OH moiety, did we isolate a small amount of the α isomer **2n** (14%) and the β isomer **3n**, again, as the major product (see Table 6, Entry 8). Thus, the reaction of various pyrroles that contained groups capable of coordinating with Lewis acids did not result in a change in the regiochemistry of the aminoalkylation with **1**. This reaction was highly regioselective and provided the β isomer, which again confirmed the specificity of these fluorinated imines. Therefore, we believe that the steric interactions between the N-substituent and the cyclic amine are quite significant as a result of the bulkiness of the trifluoromethyl group and its specific nature. To minimize these interactions, the β isomers are formed. The only observed case of the selective formation of an α-substituted product involved the less sterically demanding *N*-unsubstituted pyrrole.

3. Conclusion

The aminoalkylation of pyrrole derivatives with trifluoromethylated cyclic imines was studied. For this reaction, it was necessary to activate the imines with a Lewis acid, and boron trifluoride provided the best results. The Friedel–Crafts-type reaction afforded α-CF_3-substituted pyrrolidines, piperidines, and azepanes in high yields. An unpredictable β-selectivity was observed for this aminoalkylation of pyrroles. The regioselectivity of the reaction was explained in terms of the thermodynamic stability of the β-isomeric derivatives, which was confirmed by computational data.

4. Experimental Section

4.1. General Methods: The 1D NMR (^1H, ^{19}F, and ^{13}C NMR) spectroscopic data were recorded with a Jeol ECX-400, a Bruker VRX-400, or a Bruker AM-300 spectrometer. The chemical shifts for the ^1H NMR spectroscopic data are referenced internally to tetramethylsilane (0.0 ppm). The chemical shifts for the ^{13}C NMR spectroscopic data are referenced to $CDCl_3$ (77.2 ppm), and for the ^{19}F NMR spectroscopic data, the chemical shirts are referenced to $CFCl_3$ (0.0 ppm) or $PhCF_3$ (–63.90 ppm). The 2D HMBC NMR spectroscopic data were recorded with a Bruker AV 600 spectrometer. High resolution mass spectra were recorded with a Bruker Daltonics (MicroTOF-Q). Electrospray ionization (ESI) mass spectra (MS) were obtained with a methanol or acetonitrile solution. TLC was carried out on precoated silica plates (Merck $60F_{254}$), and the results were visualized by using UV light. Flash chromatography was performed with MP Silica 60 (320–630 mesh) and the indicated solvents. All reactions were conducted with oven-dried glassware under nitrogen. All reagents were purchased from Aldrich, unless otherwise stated. The starting trifluoromethyl imines **1a**, **1c**, and **1e** were prepared by the reaction of ethyl trifluoroacetate and *N*-vinylpyrrolidin-2-one, *N*-(diethoxymethyl)piperidin-2-one, or *N*-vinylcaprolactam, respectively, according to the described procedure.[4a] Pentafluoroethyl imines **1b** and **1d** were obtained by the reaction of pentafluoroethyllithium and the appropriate lactim ethers in the presence of boron trifluoride.[4b] The lactim ethers were prepared from the corresponding lactams through a reaction with dimethyl sulfate.[22]

4.2. General Procedure for the Reaction of 1 with Pyrroles: Freshly distilled boron trifluoride–diethyl ether (0.25 mL, 0.28 g, 2 mmol) was added slowly to a solution of imine **1** [0.27 g (**1a**), 0.37 g (**1b**), 0.30 g (**1c**), 0.40 g (**1d**), 0.33 g (**1e**); 2 mmol] in dichloromethane (20 mL) under vigorous stirring and cooling with an ice-bath. After stirring the reaction mixture for 5 min, a solution of the corresponding pyrrole (2 mmol) in a small amount of dichloromethane (5 mL) was added dropwise. The cooling bath was removed, and the reaction mixture was stirred for the required time at room temp. to complete the transformation (5 d for *N*-methylpyrrole, 1 d for pyrrole). After that the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL), the resulting mixture

was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to afford the target product.

1-Methyl-3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1,*H*-pyrrole (3a): Colorless oil (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83–1.89 (m, 1 H), 1.97–2.02 (m, 1 H), 2.08 (br. s, 1 H, NH), 2.15–2.21 (m, 1 H), 2.34–2.41 (m, 1 H), 3.07–3.20 (m, 2 H), 3.63 (s, 3 H, CH_3N), 6.15–6.17 (m, 1 H, Ar), 6.56–6.59 (m, 1 H, Ar), 6.54–6.56 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 34.0 (s, CH_3N), 36.0 (br. s, *C*H_2-C_q), 47.2 (CH_2N), 66.2 (q, $J_{C,F}$ = 27.0 Hz, *C*-CF_3), 106.8 (Ar), 119.5 (Ar), 121.9 (Ar), 123.7 (C_q, Ar), 127.8 (q, $J_{C,F}$ = 288.2 Hz, CF_3) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –77.6 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3363, 1149 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}F_3N_2$ [M + H] 219.1104; found 219.1108.

1-Methyl-2-[2-(trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrole (2a): Yellow oil (9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93–2.00 (m, 1 H), 2.04–2.11 (m, 1 H), 2.41–2.49 (m, 1 H), 2.54–2.61 (m, 1 H), 3.28–3.32 (m, 2 H), 3.81 (s, 3 H, CH_3N), 4.75 (br. s, 1 H, NH), 6.08–6.10 (m, 1 H, Ar), 6.30–6.32 (m, 1 H, Ar), 6.63–6.64 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 34.3 (s, CH_3N), 36.0 (q, $J_{C,F}$ = 2.6 Hz, *C*H_2-C_q), 47.2 (CH_2N), 68.2 (q, $J_{C,F}$ = 28.8 Hz, *C*-CF_3), 107.0 (Ar), 111.0 (Ar), 126.3 (q, $J_{C,F}$ = 284.9 Hz, CF_3), 126.3 (Ar), 127.1 (C_q, Ar) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –76.7 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3360, 1154 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}F_3N_2$ [M + H] 219.1104; found 219.1119.

1-Methyl-3-[2-(trifluoromethyl)piperidine-2-yl]-1*H*-pyrrole (3b): White crystalline solid (83%); m.p. 57–59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.57 (m, 3 H), 1.68–1.73 (m, 1 H), 1.87–1.94 (m, 1 H), 2.03 (br. s, 1 H, NH), 2.10–2.14 (m, 1 H), 2.80–2.93 (m, 2 H, CH_2N), 3.65 (s, 3 H, CH_3N), 6.10 (d, *J* = 1.8 Hz, 1 H, Ar), 6.59–6.62 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 25.6, 28.5 (br. s, *C*H_2-C_q), 36.2 (s, CH_3N), 41.1 (CH_2N), 59.4 (q, $J_{C,F}$ = 26.0 Hz, *C*-CF_3), 108.1 (Ar), 119.1 (C_q, Ar), 121.5 (Ar), 121.9 (Ar), 126.1 (q, $J_{C,F}$ = 282.3 Hz, CF_3) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –81.1 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3352, 1171, 1159 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{16}F_3N_2$ [M + H] 233.1260; found 233.1257.

2-(1-Methyl-1*H*-pyrrol-3-yl)-2-(trifluoromethyl)azepane (3c): Yellow oil (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.53 (m, 3 H), 1.69–1.83 (m, 4 H), 2.09–2.15 (m, 1 H), 2.23–2.29 (m, 1 H), 2.95–2.98 (m, 2 H, CH_2N), 3.65 (s, 3 H, CH_3N), 6.15–6.17 (m, 1 H, Ar), 6.57–6.58 (m, 1 H, Ar), 6.64–6.65 (m, 1 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.9, 30.0, 33.3, 34.1 (*C*H_2-C_q), 36.2 (s, CH_3N), 43.7 (CH_2N), 62.5 (q, $J_{C,F}$ = 30.7 Hz, *C*-CF_3), 107.4 (Ar), 120.6 (Ar), 121.6 (Ar), 124.0 (C_q, Ar), 128.0 (q, $J_{C,F}$ = 286.5 Hz, CF_3) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –79.6 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3390, 1170, 1150 cm^{-1}. $C_{12}H_{17}F_3N_2$ (246.27): calcd. C 58.52, H 6.96, N 11.38; found C 58.45, H 6.80, N 11.24.

3-[(2-Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrole (3d): White crystalline solid (37%); m.p. 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83–1.92 (m, 1 H), 1.96–2.04 (m, 1 H), 2.19–2.25 (m, 2 H), 2.37–2.44 (m, 1 H), 3.06–3.12 (m, 1 H), 3.16–3.21 (m, 1 H), 6.25–6.27 (m, 1 H, Ar), 6.75–6.77 (m, 1 H, Ar), 6.79–6.81 (m, 1 H, Ar), 8.9 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 34.0 (*C*H_2-C_q), 47.3 (CH_2N), 66.4 (q, $J_{C,F}$ = 27.7 Hz, *C*-CF_3), 106.9 (Ar), 115.7 (Ar), 118.4 (Ar), 123.5 (C_q, Ar), 127.6 (q, $J_{C,F}$ = 282.3 Hz, CF_3) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –78.5 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3335, 1155, 1100 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{12}F_3N_2$ [M + H] 205.0947; found 205.0951.

2-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrole (2d): White crystalline solid (43%); m.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82–1.87 (m, 2 H), 1.91–1.96 (m, 1 H), 2.18–2.25 (m, 1 H), 2.31–2.39 (m, 1 H), 3.05–3.18 (m, 2 H), 6.17–6.21 (m, 2 H, Ar), 6.75–6.77 (m, 1 H, Ar), 8.73 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 34.3 (*C*H_2-C_q), 47.3 (CH_2N), 66.7 (q, $J_{C,F}$ = 27.6 Hz, *C*-CF_3), 106.3 (Ar), 108.8 (Ar), 117.6 (Ar), 127.0 (q, $J_{C,F}$ = 283.4 Hz, CF_3), 129.8 (C_q, Ar) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –77.8 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3353, 1170, 1120 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{11}F_3N_2$ [M + H] 205.0947; found 205.0948.

2-(1*H*-Pyrrol-2-yl)-2-(trifluoromethyl)piperidine (2e): White crystalline solid (67%); m.p. 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28–1.40 (m, 1 H), 1.48–1.54 (m, 1 H), 1.61–1.85 (m, 4 H), 2.26–2.31 (m, 1 H), 2.51–2.58 (m, 1 H, CH_2N), 2.93–2.98 (m, 1 H, CH_2N), 6.19–6.21 (m, 1 H, Ar), 6.23–6.25 (m, 1 H, Ar), 6.83–6.85 (m, 1 H, Ar), 8.81 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 26.2, 28.0 (*C*H_2-C_q), 41.6 (CH_2N), 59.8 (q, $J_{C,F}$ = 26.5 Hz, *C*-CF_3), 108.6 (Ar), 108.9 (Ar), 118.1 (Ar), 125.6 (Ar), 125.9 (q, $J_{C,F}$ = 283.8 Hz, CF_3) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –81.7 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3471, 1194, 1180, 1140 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}F_3N_2$ [M + H] 219.1104; found 219.1111.

2-(1*H*-Pyrrol-3-yl)-2-(trifluoromethyl)azepane (3f): White crystalline solid (30%); m.p. 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31–1.54 (m, 3 H), 1.70–1.84 (m, 4 H), 2.13–2.19 (m, 1 H), 2.29–2.35 (m, 1 H), 2.98–3.00 (m, 2 H, CH_2N), 6.28–6.30 (m, 1 H, Ar), 6.75–6.78 (m, 1 H, Ar), 6.81–6.83 (m, 1 H, Ar), 8.56 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 29.9, 33.2, 34.0 (*C*H_2-C_q), 43.7 (CH_2N), 62.5 (q, $J_{C,F}$ = 25.1 Hz, *C*-CF_3), 107.4 (Ar), 116.7 (Ar), 118.0 (Ar), 123.8 (C_q, Ar), 128.0 (q, $J_{C,F}$ = 286.4 Hz, CF_3) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –79.4 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3475, 1189 cm^{-1}. $C_{11}H_{15}F_3N_2$ (232.25): calcd. C 56.89, H 6.51; found C 56.86, H 6.61.

2-(1*H*-Pyrrol-2-yl)-2-(trifluoromethyl)azepane (2f): White crystalline solid (22%); m.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.52 (m, 3 H), 1.67–1.78 (m, 3 H), 1.88 (br. s, 1 H, NH), 2.16–2.31 (m, 2 H), 2.86–2.91 (m, 1 H, CH_2N), 3.02–3.08 (m, 1 H, CH_2N), 6.17–6.23 (m, 2 H, Ar), 6.75–6.77 (m, 1 H, Ar), 8.87 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 29.8, 33.6, 34.2 (*C*H_2-C_q), 43.6 (CH_2N), 63.2 (q, $J_{C,F}$ = 25.1 Hz, *C*-CF_3), 106.5 (Ar), 108.9 (Ar), 117.0 (Ar), 127.5 (q, $J_{C,F}$ = 287.1 Hz, CF_3), 130.3 (C_q, Ar) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –79.2 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3477, 1183 cm^{-1}. $C_{11}H_{15}F_3N_2$ (232.25): calcd. C 56.89, H 6.51; found C 56.81, H 6.86.

4.3. General Procedure for the Reaction of 2-Perfluoroalkyl Cyclic Imines with Ethyl *N*-Pyrrolylacetates: Freshly distilled boron trifluoride–diethyl ether (0.25 mL, 0.28 g, 2 mmol) or titanium tetrachloride (0.22 mL, 2 mmol) was added slowly under vigorous stirring and cooling to a solution of imine **1** [0.27 g (**1a**), 0.37 g (**1b**), 0.30 g (**1c**), 0.40 g (**1d**), 0.33 g (**1e**); 2 mmol] in dry dichloromethane (20 mL). After 5 min, a solution of the corresponding pyrrole (2 mmol) in dichloromethane (5 mL) was added dropwise. The reaction mixture was stirred for 4 h at 0 °C when titanium tetrachloride was employed and for 5 d at room temp. when boron trifluoride–diethyl ether was employed. The reaction mixture was then quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL), and the resulting solution was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford the target products.

Ethyl {2-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrol-1-yl}acetate (3g): Yellow oil [75% (BF_3·Et_2O), 81% ($TiCl_4$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.13 Hz, 3 H, CH_2CH_3), 1.81–1.99 (m, 3 H), 2.12–2.19 (m, 1 H), 2.32–2.39 (m, 1 H), 3.04–3.17 (m, 2 H, CH_2N), 4.23 (q, J = 7.13 Hz, 2 H, $COOCH_2CH_3$), 4.58 (s, 2 H, CH_2COOEt), 6.19–6.22 (m, 1 H, Ar), 6.62–6.63 (t, J = 2.52 Hz, 1 H, Ar), 6.68–6.69 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 26.0, 34.0 (CH_2-C_q), 47.3 (CH_2N), 50.8 (CH_2COOEt), 61.6 ($COOCH_2CH_3$), 66.3 (q, $J_{C,F}$ = 27.3 Hz, C-CF_3), 107.8 (Ar), 119.7 (Ar), 122.1 (Ar), 124.4 (C_q, Ar), 127.5 (q, $J_{C,F}$ = 282.7 Hz, CF_3), 168.4 (CO) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –78.6 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3367, 1753, 1155 cm^{-1}. $C_{13}H_{17}F_3N_2O_2$ (290.28): calcd. C 53.79, H 5.90, N 9.65; found C 53.85, H 5.99, N 9.58.

Ethyl {2-[2-(Trifluoromethyl)piperidin-2-yl]-1*H*-pyrrol-1-yl}acetate (3h): Yellow oil (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.13 Hz, 3 H, CH_2CH_3), 1.41–1.57 (m, 3 H), 1.65–1.72 (m, 1 H), 1.85–1.92 (m, 1 H), 1.96 (br. s, 1 H, NH), 2.08–2.13 (m, 1 H), 2.77–2.84 (m, 1 H, CH_2N), 2.87–2.92 (m, 1 H, CH_2N), 4.21 (q, J = 7.13 Hz, 2 H, $COOCH_2CH_3$), 4.59 (s, 2 H, CH_2COOEt), 6.13–6.15 (m, 1 H, Ar), 6.63–6.66 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.9, 25.6, 28.5 (br. s, CH_2-C_q), 41.2 (CH_2N), 50.9 (CH_2COOEt), 59.4 (q, $J_{C,F}$ = 26.4 Hz, C-CF_3), 61.5 ($COOCH_2CH_3$), 108.9 (Ar), 120.0 (C_q, Ar), 121.9 (Ar), 122.0 (Ar), 126.5 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 168.4 (CO) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –81.9 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3345, 1755, 1160 cm^{-1}. $C_{14}H_{19}F_3N_2O_2$ (304.31): calcd. C 55.26, H 6.29, N 9.21; found C 55.26, H 6.35, N 9.10.

Ethyl {2-[2-(Trifluoromethyl)azepan-2-yl]-1*H*-pyrrol-1-yl}acetate (3i): Yellow oil (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.13 Hz, 3 H, CH_2CH_3), 1.31–1.52 (m, 3 H), 1.67–1.80 (m, 4 H), 2.04–2.12 (m, 1 H), 2.20–2.26 (m, 1 H), 2.93–2.95 (m, 2 H, CH_2N), 4.21 (q, J = 7.13 Hz, 2 H, $COOCH_2CH_3$), 4.56 (s, 2 H, CH_2COOEt), 6.19–6.21 (t, J = 2.52 Hz, 1 H, Ar), 6.60–6.62 (t, J = 1.97 Hz, 1 H, Ar), 6.68–6.70 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.7, 29.9, 33.2, 33.9, (CH_2-C_q), 43.6 (CH_2N), 50.8 (CH_2COOEt), 61.5 ($COOCH_2CH_3$), 62.4 (q, $J_{C,F}$ = 25.3 Hz, C-CF_3), 108.1 (Ar), 120.8 (Ar), 121.8 (Ar), 124.6 (C_q, Ar), 127.9 (q, $J_{C,F}$ = 286.5 Hz, CF_3), 168.4 (CO) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –78.7 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3390, 1755, 1145, 1149 cm^{-1}. $C_{15}H_{21}F_3N_2O_2$ (318.34): calcd. C 56.59, H 6.65, N 8.80; found C 56.30, H 6.50, N 8.83.

Ethyl 2-{2-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrol-1-yl}propanoate (3j): Yellow oil [69% (BF_3·Et_2O), 73% ($TiCl_4$), diastereomer mixture (1:1)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.12 Hz, 3 H, CH_2CH_3), 1.71 (d, J = 7.23 Hz, 3 H, $CHCH_3$), 1.82–1.89 (m, 2 H), 1.93–2.01 (m, 1 H), 2.12–2.18 (m, 1 H), 2.32–2.39 (m, 1 H), 3.04–3.10 (m, 1 H, CH_2N), 3.13–3.19 (m, 1 H, CH_2N), 4.18 (q, J = 7.12 Hz, 2 H, $COOCH_2CH_3$), 4.69 (q, J = 7.23 Hz, 1 H, $CHCOOEt$), 6.18–6.20 (m, 1 H, Ar), 6.70–6.72 (m, 1 H, Ar), 6.75–6.77 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 18.1 ($CHCH_3$), 25.6, 33.9 and 34.0 (CH_2-C_q), 42.3 (CH_2N), 57.1 ($CHCOOEt$), 61.5 ($COOCH_2CH_3$), 66.4 (q, $J_{C,F}$ = 27.3 Hz, C-CF_3), 107.3 (Ar), 117.7 (Ar), 119.9 and 120.0 (Ar), 123.9 (C_q, Ar), 127.5 (q, $J_{C,F}$ = 283.1 Hz, CF_3), 170.9 (CO) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –77.8 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3373, 1741, 1190, 1151 cm^{-1}. $C_{14}H_{19}F_3N_2O_2$ (304.31): calcd. C 55.26, H 6.29, N 9.21; found C 55.36, H 6.33, N 9.17. $[\alpha]_D^{25}$ = +13.2 (c = 1.0, CH_2Cl_2).

Ethyl 2-{2-[2-(Trifluoromethyl)piperidin-2-yl]-1*H*-pyrrol-1-yl}propanoate (3k): Yellow solid [75%, diastereomeric mixture (1:1)]; m.p. 46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.13 Hz, 3 H, CH_2CH_3), 1.44–1.56 (m, 3 H), 1.67–1.74 [m including 1.73 (d, J = 7.23 Hz, 4 H, 3 H, $CHCH_3$)], 1.84–1.98 (m, 2 H), 2.09–2.14 (m, 1 H), 2.78–2.85 (m, 1 H, CH_2N), 2.89–2.94 (m, 1 H, CH_2N), 4.17 (q, J = 7.13 Hz, 2 H, $COOCH_2CH_3$), 4.71 (q, J = 7.23 Hz, 1 H, $CHCOOEt$), 6.11–6.15 (m, 1 H, Ar), 6.72–6.76 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 17.9 and 18.0 ($CHCH_3$), 19.9, 25.6, 28.4 and 28.5 (br. s, CH_2-C_q), 41.2 (CH_2N), 57.1 ($CHCOOEt$), 59.4 (q, $J_{C,F}$ = 26.4 Hz, C-CF_3), 61.4 ($COOCH_2CH_3$), 108.4 (Ar), 119.4 and 119.5 (C_q, Ar), 119.7 and 119.8 (Ar), 119.9 and 120.0 (Ar), 126.5 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 171.0 (CO) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –81.1 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3338, 1728, 1167, 1149 cm^{-1}. $C_{15}H_{21}F_3N_2O_2$ (318.34): calcd. C 56.59, H 6.65, N 8.80; found C 56.60, H 6.55, N 8.89. $[\alpha]_D^{17}$ = +11.6 (c = 1.0, CH_2Cl_2).

Ethyl 2-{2-[2-(Trifluoromethyl)azepan-2-yl]-1*H*-pyrrol-1-yl}propanoate (3l): Yellow oil [60%, diastereomeric mixture (1:1)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.13 Hz, 3 H, CH_2CH_3), 1.29–1.48 (m, 3 H), 1.64–1.78 [m including 1.68 (d, J = 7.34 Hz, 7 H, 3 H, $CHCH_3$)], 2.04–2.10 (m, 1 H), 2.18–2.24 (m, 1 H), 2.91–2.93 (m, 2 H, CH_2N), 4.14 (q, J = 7.13 Hz, 2 H, $COOCH_2CH_3$), 4.66 (q, J = 7.34 Hz, 1 H, $CHCOOEt$), 6.14–6.16 (m, 1 H, Ar), 6.66–6.68 (m, 1 H, Ar), 6.74–6.76 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 18.0 and 18.1 ($CHCH_3$), 22.8 and 22.9, 30.0, 33.2 and 33.3, 34.0 (CH_2-C_q), 43.7 (CH_2N), 57.1 and 57.2 ($CHCOOEt$), 61.5 ($COOCH_2CH_3$), 62.5 (q, $J_{C,F}$ = 24.9 Hz, C-CF_3), 107.7 (Ar), 118.9 (Ar), 119.7 and 119.8 (Ar), 123.8 (C_q, Ar), 128.0 (q, $J_{C,F}$ = 286.5 Hz, CF_3), 171.1 (CO) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –78.75 and 78.76 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3395, 1745, 1205, 1165, 1145 cm^{-1}. $C_{16}H_{23}F_3N_2O_2$ (332.36): calcd. C 57.82, H 6.98, N 8.43; found C 57.94, H 7.00, N 8.30. $[\alpha]_D^{25}$ = +10.8 (c = 1.0, CH_2Cl_2).

2-{2-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrol-1-yl}propanoic Acid (3m): Yellow liquid [73%, diastereomeric mixture (1:1)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63 (t, J = 5.92 Hz, 3 H, $CHCH_3$), 1.84–2.03 (m, 2 H), 2.23–2.41 (m, 2 H), 3.07–3.17 (m, 2 H, CH_2N), 4.59 (m, 1 H, $CHCOOH$), 6.09–6.14 (m, 1 H, Ar), 6.65–6.70 (m, 1 H, Ar), 6.84–6.87 (m, 1 H, Ar), 8.36 (br. s, 2 H, NH_2^+) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 and 18.5 ppm ($CHCH_3$), 24.6 and 24.7, 32.0 (CH_2-C_q), 46.4 and 46.5 (CH_2N), 58.3 and 58.5 ($CHCOOH$), 67.4 (q, $J_{C,F}$ = 29.1 Hz, C-CF_3), 106.9 (Ar), 118.9 (Ar), 119.2 and 119.3 (C_q, Ar), 120.4 and 120.5 (Ar), 126.2 and 126.3 (q, $J_{C,F}$ = 282.0 Hz, $J_{C,F}$ = 283.1 Hz, CF_3), 175.7 (br. s, COOH) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –77.25 and 77.29 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3381 (br. s), 1714, 1155 cm^{-1}. $C_{12}H_{15}F_3N_2O_2$·H_2O (276.26): calcd. C 48.98, H 5.82, N 9.52; found C 48.97, H 5.67, N 9.18. $[\alpha]_D^{17}$ = +12.0 (c = 0.5, CH_2Cl_2).

2-{3-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrol-1-yl}ethanol (3n): Yellow oil (64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75–1.82 (m, 1 H), 1.89–1.96 (m, 1 H), 2.09–2.14 (m, 1 H), 2.28–2.33 (m, 1 H), 2.83 (br. s, 2 H, NH and OH), 2.93–2.97 (m, 1 H, CH_2N), 3.02–3.06 (m, 1 H, CH_2N), 3.76 (t, J = 5.23 Hz, 2 H, CH_2CH_2), 3.90 (t, J = 5.23 Hz, 2 H, CH_2CH_2), 6.11–6.12 (m, 1 H, Ar), 6.63–6.64 (m, 1 H, Ar), 6.68 (t, J = 2.02 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 33.8 (CH_2-C_q), 47.3 (CH_2N), 52.2 (CH_2CH_2), 62.16 (CH_2CH_2), 66.3 (q, $J_{C,F}$ = 27.3 Hz, C-CF_3), 107.0 (Ar), 118.8 (Ar), 121.4 (Ar), 123.3 (C_q, Ar), 127.4 (q, $J_{C,F}$ = 283.1 Hz, CF_3) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –77.4 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3325, 1151, 1082, 783, 731 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}F_3N_2O$ [M + H] 249.1209; found 249.1221.

2-{2-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-pyrrol-1-yl}ethanol (2n): Yellow solid (14%); m.p. 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84–1.91 (m, 1 H), 1.92–1.99 (m, 1 H), 2.45–2.53 (m,

2 H), 3.00–3.19 (m, 4 H, CH_2N, NH, and OH), 3.83–3.92 (m, 2 H, CH_2CH_2), 4.08 (dt, J = 15.04 Hz, J = 3.44 Hz, 1 H, CH_2CH_2), 4.53–4.58 (m, 1 H, CH_2CH_2), 6.14–6.15 (m, 1 H, Ar), 6.18–6.19 (m, 1 H, Ar), 6.74–6.75 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 35.7 (CH_2-C_q), 47.8 (CH_2N), 50.0 (CH_2CH_2), 63.6 (CH_2CH_2), 67.8 (q, $J_{C,F}$ = 27.3 Hz, C-CF_3), 107.7 (Ar), 110.2 (Ar), 123.7 (Ar), 126.9 (q, $J_{C,F}$ = 284.9 Hz, CF_3), 129.7 (C_q, Ar) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –76.1 (CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3276 (br. s), 1282, 1169, 1157, 1144, 1068, 723 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}F_3N_2O$ [M + H] 249.1209; found 249.1211.

Supporting Information (see footnote on the first page of this article): ^1H and ^{19}F NMR spectroscopic data for iminium salts and isomerization of pyrrole **2a** into **3b**. Full sets of 1D (^1H, ^{13}C, and ^{19}F) NMR spectra for synthesized products, 2D (HMBC) NMR spectra of **2a** and **3b**, crystallographic data for **3a**, computation results (optimized geometries, Cartesian coordinates and energies).

Acknowledgments

The authors thank the Deutsche Forschungsgemeinschaft (DFG) (RO 362/42-1) and the Russian Foundation for Basic Research (RFBR) (grant number 11-03-01167-a) for their financial support of this work. The authors thank L. Kulikov for the DFT calculations.

[1] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[2] For selected publications, see: a) R. Filler, Y. Kobayashi, L. M. Yagulpolskii, in: *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, **1993**; b) V. P. Kukhar, V. A. Soloshonok (Eds.), *Fluorine-containing Amino Acids: Synthesis and Properties*, John Wiley & Sons, Chichester, **1995**; c) V. A. Hiyama, in: *Organofluorine Compounds: Chemistry and Properties*, Springer-Verlag, Berlin, **2000**, chapter 5, pp. 137–182; d) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11; e) V. M. Muzalevskiy, V. G. Nenajdenko, A. V. Shastin, E. S. Balenkova, G. Haufe, *Synthesis* **2009**, 3905–3929.

[3] For selected publications, see: a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, 4475–4521; b) N. Shibata, A. Matsnev, D. Cahard, *Beilstein J. Org. Chem.* **2010**, *6*, 65; c) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; d) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909–1911; e) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, 757–786.

[4] a) N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synthesis* **2010**, 120–126; b) N. E. Shevchenko, V. G. Nenajdenko, G.-V. Röschenthaler, *J. Fluorine Chem.* **2008**, *129*, 390–396.

[5] a) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synlett* **2009**, 403–406; b) I. L. Odinets, O. I. Artyushin, K. A. Lyssenko, N. E. Shevchenko, V. E. Nenaidenko, G.-V. Röschenthaler, *J. Fluorine Chem.* **2009**, *130*, 662–666.

[6] a) H. Skarpos, D. V. Vorob'eva, S. N. Osipov, I. L. Odinets, E. Breuer, G. V. Roeschenthaler, *Org. Biomol. Chem.* **2006**, *4*, 3669–3674; b) N. D. Chkanikov, V. L. Vershinin, M. V. Galakhov, A. F. Kolomiets, A. V. Fokin, *Russ. Chem. Bull.* **1989**, *38*, 113–129.

[7] a) D. M. Gale, C. G. Krespan, *J. Org. Chem.* **1968**, *33*, 1002–1008; b) M. Abid, L. Teixeira, B. Török, *Org. Lett.* **2008**, *10*, 933–935; c) R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping, C. Bolm, *Org. Lett.* **2011**, *13*, 1044–1047; d) Y. Gong, K. Kato, H. Kimoto, *Synlett* **2000**, 1058–1060; e) Y. Gong, K. Kato, *Tetrahedron: Asymmetry* **2001**, *12*, 2121–2127.

[8] a) N. E. Shevchenko, O. I. Shmatova, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko *Eur. J. Org. Chem.* **2013**, accepted; b) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Mendeleev Commun.* **2013**, *23*, 92–93.

[9] For selected publications, see: a) S. Thirumalairajan, B. M. Pearce, A. Thompson, *Chem. Commun.* **2010**, *46*, 1797–1812; b) P. M. Dewick, in: *Medicinal Natural Products: A Biosynthesic Approach*, John Wiley & Sons, Chichester, UK, **2009**; c) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264–287; d) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **1999**, *20*, 2849–2866; e) A. S. Demir, N. T. Subasi, E. Sahin, *Tetrahedron: Asymmetry* **2006**, *17*, 2625–2631.

[10] For selected publications, see: a) X. Qian, G. B. Liang, D. Feng, M. Fisher, T. Crumley, S. Rattray, P. M. Dulski, A. Gurnett, P. S. Leavitt, P. A. Liberator, A. S. Misura, S. Samaras, T. Tamas, D. M. Schmatz, M. Wyvratt, T. Biftu, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2817–2821; b) I. Boyfield, M. C. Coldwell, M. S. Hadley, M. A. M. Healy, C. N. Johnson, D. J. Nash, G. J. Riley, E. E. Scott, S. A. Smith, G. Stemp, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 327–330; c) I. van Wijngaarden, C. G. Kruse, R. van Hes, J. A. M. van der Heyden, M. T. M. Tulp, *J. Med. Chem.* **1987**, *30*, 2099–2104; d) S. A. F. Rostom, A. M. Farghaly, F. S. G. Soliman, M. M. El-Semary, S. Elz, J. Lehmann, *Arch. Pharm.* **2001**, *334*, 241–247; e) S. A. F. Rostom, *Arch. Pharm.* **2010**, *343*, 73–80, f) D. Bolton, I. Boyfield, M. C. Coldwell, M. S. Hadley, M. A. M. Healy, C. N. Johnson, R. E. Markwell, D. J. Nash, G. J. Riley, G. Stemp, H. J. Wadsworth, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1233–1236; g) B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, P. E. Setler, *J. Med. Chem.* **1987**, *30*, 1433–1454.

[11] a) E. Aranzamendi, N. Sotomayor, E. Lete, *J. Org. Chem.* **2012**, *77*, 2986–2991; b) L. Ollero, G. Mentink, F. P. J. T. Rutjes, W. N. Speckamp, H. Hiemstra, *Org. Lett.* **1999**, *1*, 1331–1334; c) M. Rueping, B. J. Nachtsheim, *Synlett* **2010**, 119–122; d) X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou, C. Tang, *Eur. J. Org. Chem.* **2011**, 3060–3066.

[12] For selected publications, see: a) Y. Huang, S. Suzuki, G. Liu, E. Tokunaga, M. Shiro, N. Shibata, *New J. Chem.* **2011**, *35*, 2614–2621; b) Y. Huang, E. Tokunaga, S. Suzuki, M. Shiro, N. Shibata, *Org. Lett.* **2010**, *12*, 1136–1138.

[13] A representative example is the bromination of *N*-methylpyrrole with *N*-bromosuccinimide (NBS) in the presence of base, which produces only 2-bromopyrrole, whereas the addition of PBr_3 or HBr affords 3-bromopyrrole exclusively. For details, see: E. Dvornikova, K. Kamienska-Trela, *Synlett* **2002**, 1152–1154.

[14] a) H. J. Anderson, C. E. Loader, *Synthesis* **1985**, 353–364; b) N. J. L. Guernion, W. Hayes, *Curr. Org. Chem.* **2004**, *8*, 637–651; c) C. Schmuck, D. Ruprecht, *Synthesis* **2007**, *20*, 3095–3110; d) T. Tsuchimoto, *Chem. Eur. J.* **2011**, *17*, 4064–4075; e) L. I. Belen'kii, T. G. Kim, I. A. Suslov, N. D. Chuvylkin, *Russ. Chem. Bull.* **2005**, *54*, 853–863.

[15] Y. Carcenac, M. Tordeux, C. Wakselman, P. Diter, *New J. Chem.* **2006**, *30*, 447–457.

[16] a) P. Dallemagne, S. Rault, F. Fabis, H. Dumoulin, M. Robba, *Synth. Commun.* **1994**, *24*, 1855–1857; b) J. R. Carson, N. M. Davis, *J. Org. Chem.* **1981**, *46*, 839–843; c) M. C. Pina, V. A. Budilin, M. Rodrigues, Yu. G. Bundel, *Chem. Heterocycl. Compd.* **1989**, *25*, 180–184; d) K. Hrncarikova, D. Vegh, *Molecules* **2003**, *8*, 536–540; e) H. M. Gilow, D. E. Burton, *J. Org. Chem.* **1981**, *46*, 2221–2225.

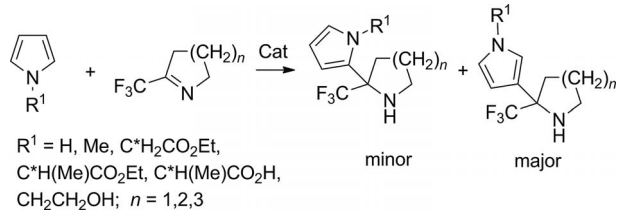
[17] I. T. Raheem, P. S. Thiara, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 1577–1580.

[18] a) D. N. Laikov, *Chem. Phys. Lett.* **1997**, *281*, 151–156; b) D. N. Laikov, Yu. A. Ustynyuk, *Russ. Chem. Bull.* **2005**, *54*, 820–826; c) F. Neese, U. Becker, D. Bykov, D. Ganyushin, A. Hansen, R. Izsak, D. G. Liakos, C. Kollmar, S. Kossmann, D. A. Pantazis, T. Petrenko, C. Reimann, C. Riplinger, M. Roemelt, B. Sandhöfer, I. Schapiro, K. Sivalingam, F. Wennmohs, B. Wez-

isla, M. Kállay, S. Grimme, E. Valeev, *ORCA program package*, release 2.9.0, **2012**.
[19] V. G. Nenajdenko, A. L. Reznichenko, E. S. Balenkova, *Tetrahedron* **2007**, *63*, 3031–3041.
[20] C. W. Jefford, F. V. Naide, K. Sienkiewicz, *Tetrahedron: Asymmetry* **1996**, *7*, 1069–1076.
[21] C. Kashima, T. Maruyama, Y. Fujioka, K. Harada, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1041–1046.
[22] a) A. Etienne, Y. Correia, *Bull. Soc. Chim. Fr.* **1969**, 3704–3712; b) C. Benson, in: *Org. Synth., Coll.*, **1963**, vol. 4, pp. 588.

Received: December 21, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry



R^1 = H, Me, C*H_2CO_2Et, C*H(Me)CO_2Et, C*H(Me)CO_2H, CH_2CH_2OH; n = 1,2,3

Trifluoromethyl-substituted cyclic imines were activated by various Lewis acids and underwent a reaction with pyrrole derivatives. An unpredictable β-selectivity was observed. The regioselectivity of the aminoalkylation was explained by computation data, which also confirmed the isomerization of the α isomer into the β isomer.

Keywords: Nitrogen heterocycles / Electrophilic substitution / Lewis acids / Fluorine / Amines / Regioselectivity

