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Intra–Intermolecular Criss-cross Cycloaddition of Nonsymmetrical Allenylazines with Fluorinated Enones as an Initial Step in the Synthesis of 4*H*-Pyrrolo[1,2-*b*]pyrazoles

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Nonsymmetrical allenylazines undergo, in boiling xylene, intramolecular cycloaddition by forming an unstable 1,3-dipole that reacts with an added dipolarophile. In this paper we report the first intra–intermolecular criss-cross cycloaddition with a fluorinated enone. Although the expected products with three fused heterocycles were not isolated, new bicyclic products were found and characterized. These compounds are formed by a spontaneous transformation involving fluorine atom migration and hydrogen fluoride elimination. A mechanism of the reaction is discussed to explain the formation of these new heterocycles.

Introduction

Criss-cross cycloadditions[1] belong to the rather rich group of [3+2] dipolar cycloadditions.[2] The first reaction of this type between two equivalents of PhNCO and benzaldazine afforded a new compound with two fused five-membered heterocycles.[3] In the first step of the reaction, a 1,3-dipole is formed. Although the mechanism[4] of the reaction was proposed in 1963, it was proved eleven years later when a stable 1,3-dipole intermediate was isolated.[5,6]

On the basis of our knowledge, we can divide criss-cross cycloadditions into three basic groups. The first group is an intermolecular criss-cross cycloaddition. The heterodiene and the dipolarophile entering the reaction are individual molecules.[3,7,8] The second group may be considered as an intramolecular cycloaddition. Depending upon the regioselectivity of the reaction, we can observe formation of laterally[9,10] or centrally[11,12] fused heterocyclic compounds. The third group is a combination of the first and the second approaches: a combined intra–intermolecular cycloaddition.[13–15] The first step of this combined cycloaddition is an intramolecular attack resulting in the formation of a 1,3-dipole, as predicted by ab initio calculations[16] and proved by the isolation of a bicyclic product,[13] which is a result of a proton transfer in the intermediate, formed in the absence of a dipolarophile, to stabilize the product of the first intramolecular reaction step. Compounds of this structure, pyrrolidino[1,2-b]pyrazoles, are known as biologically active structures. They are used in the traditional Indian system of medicine in the form of extracts from *Withania somnifera* Dun., commonly known as "Indian ginseng".[17–19] The structure was identified by Schröter.[20]

This paper deals with the study of a combined intra–intermolecular cycloaddition reaction of nonsymmetrical homoallenylaldazines **1** with a new dipolarophile, perfluorinated enone **2**.[21] The reaction is accompanied by an unexpected fluoride anion migration. Fluorinated enone **2**, a good dienophile,[22] was chosen as an interesting dipolarophile with the expectation that new fluorinated fused heterocycles would be formed.

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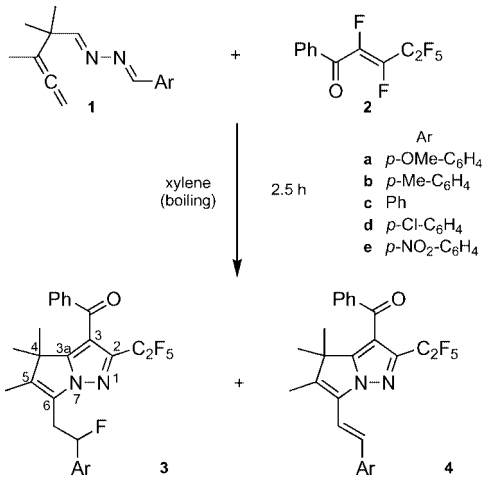
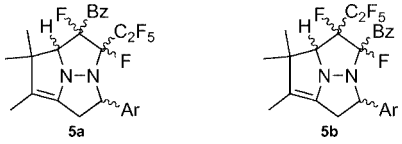
Results and Discussion

Compound **1** was treated with enone **2** in boiling xylene. In analogy with the previous paper,[11] we expected the formation of a heterocyclic compound with three fused five-membered rings. Instead of criss-cross adducts **5a**,**b** (regio- and stereoisomers), we found new bicyclic compounds **3** as single regioisomers alongside small amounts of compounds **4a**–**d** (Scheme 1).



Scheme 1. General scheme of the reaction.



Only derivative **4a** was isolated and fully identified by NMR and X-ray analysis. Compounds **4b**–**d** were identified by ^{1}H NMR spectroscopy as traces in the crude reaction mixtures. Product **4e** was not found at all.

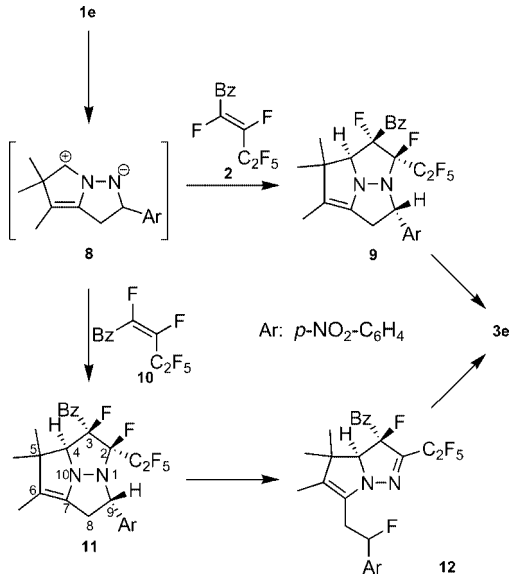
Allenylazine **1e** and enone **2** were shown to undergo the reaction to afford compound **3e** in the highest yield and purity. Products **3a**–**d** were formed in a lower purity, and their purification was rather difficult (Table 1). The lower yields of products **3a**–**d** could be explained by the fact that the formation of the corresponding 1,3-dipole intermediate in these cases is slower. This means that while azine **1e** is completely transformed to the criss-cross adduct within 20 min, in the cases of azines **1a**–**d**, the criss-cross adducts are formed much more slowly but they immediately undergo further transformations leading to final products **3** and **4**. As a consequence, the starting unreacted allenylazine is decomposed by the released HF. Alternatively, cycloadduct **9** from azine **1e** (Scheme 2) is transformed relatively slowly to final product **3e** and can be monitored in the reaction mixture by ^{19}F NMR spectroscopy.

Table 1. Yields of products **3** and **4** [%].

Compound	3	4
a	[a]	40
b	58	[b]
c	46	[b]
d	64	[b]
e	69	0[c]

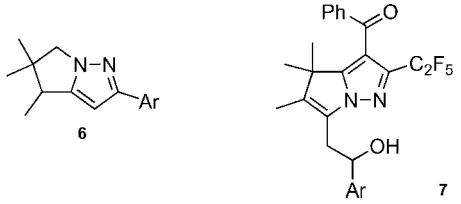
[a] Product **3a** was not isolated. [b] Only trace amounts appeared in the crude reaction mixture. [c] The formation of product **4** was not observed.

In addition to the new products **3** and **4**, compound **6** was identified as a product of the reaction of azine **1** with enone **2**, which has already been observed when **1** was refluxed in xylene without any dipolarophile.[13] We must



Scheme 2. Transformations of azine **1e** in reaction with fluorinated enones **2** and **10**.

state here a rather poor reproducibility of the ratio of compounds **3a** and **4a** in the reaction. Product **3a** could be identified only by ^{1}H- and ^{19}F NMR spectroscopy of the crude reaction mixture. Its transformation to alcohol **7** was observed by TLC. In order to isolate alcohol **7** in a sufficient quantity, the crude reaction mixture was stirred overnight in a suspension of silica gel in dichloromethane. Although the transformation was not studied in detail, a similar substitution by water was observed in the case where two Ph groups were bound to the carbon atom bearing a fluorine atom.[23] In that case the fluorine atom was substituted even without any silica gel.



Isolated products **3b**–**e** and **7** underwent crystallization only with difficulty. However, we succeeded in preparing suitable crystals of compounds **3d** and **4a** for X-ray diffraction analysis (Figure 1 and Figure 2), which made possible the unambiguous assignment of the regioselectivity of the reaction.

Chemical shifts and coupling constants in the ^{1}H NMR spectra of the CH_2–CHF and CH_2CHOH groups support the structure of compounds **3a**–**e** and **7** (see Supporting Information, Table S1). Because a stereogenic centre is present in compounds **3**, the methyl groups at the C4-carbon are diastereotopic. Therefore, one can find two distinct signals of methyl groups differing by about 0.06 ppm in the ^{1}H NMR spectra and differing by about 0.1 ppm in the ^{13}C NMR spectra. Although compound **7** also bears a stereogenic centre (CH–OH) the signals of the two diastereotopic methyl groups overlap each other.

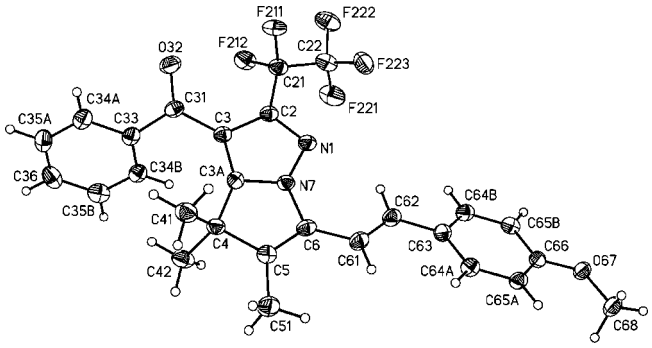


Figure 1. X-ray structure of compound **4a**.

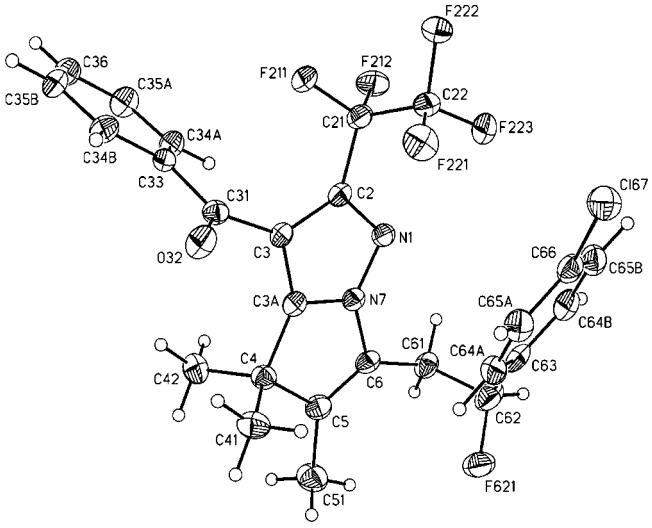


Figure 2. X-ray structure of compound **3d**.

Comparison of the ^{13}C NMR spectra of compounds **3b**–**e**, **4a** and **7** with the results of X-ray analyses enabled us to prove the structure. The carbon atom at the C2-position neighbouring the C_2F_5 substitution (Scheme 1) showed a triplet with a chemical shift close to 140 ppm and a coupling constant $^2J_{C,F} \approx 30$ Hz. Other carbon atoms of the heterocyclic system appeared at similar chemical shifts (see Supporting Information, Table S2).

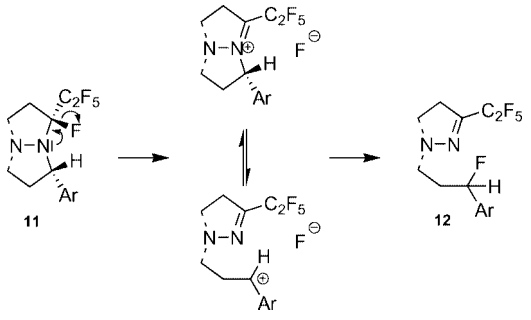
The ^{19}F NMR spectra of compounds **3a**–**e** are similar (see Supporting Information, Table S3). The chemical shifts corresponding to the fluorine atoms of the CF_3 and CF_2 groups appeared at the same values. The chemical shifts of the fluorine atom in the CHF group correlate with the substitution on the aromatic system in all products **3a**–**e**. Their chemical shifts increase from electron-donating (**3a**) to electron-withdrawing substituents (**3e**) on the aromatic ring.

The mechanism of the transformation of allenylazine **1e** was studied: the electron-withdrawing substitution on the aromatic ring (*p*-NO_2) accelerates the initial intramolecular attack. The resulting 1,3-dipole intermediate **8** (Scheme 2) reacts consequently with fluorinated enone **2** [(*E*) isomer]. When the reaction was stopped after the mixture had been heated for 20–25 min, the unstable adduct **9** was identified. Storage at room temperature or any attempts to isolate compound **9** led to its decomposition.

Reaction of enone **10** [(*Z*) isomer] leads to compound **11**, which shows the same instability. Longer heating in both cases afforded the final product **3e**. In the procedure with derivative **11**, we succeeded in identifying another unstable product **12**. Heating of **12**, or attempts to isolate it on silica gel again gave product **3e**. Records of ^1H- and ^{19}F NMR spectra of the crude reaction mixtures are given in the Supporting Information.

^1H- and ^{19}F NMR spectra and our knowledge of intra–intermolecular criss-cross cycloadditions with various dipolarophiles (especially with *N*-methylmaleinimide)[24] allowed us to establish the configuration of the stereogenic centres of products **9**, **11** and **12** as shown in Scheme 2. The tricyclic skeleton has the shape of a shallow bowl.[13,24] The bulky substituents (Ph–C=O and C_2F_5) in compound **11** are *exo* oriented, as we have already observed in the cycloadduct with *N*-methylmaleinimide.[24] The situation is more complex with compound **9**, whose bulky substituents have *anti* orientation. NMR analysis, especially examination of the ^{19}F NMR spectra, showed the formation of one product that was only slightly different from compound **11**. Considering its behaviour in the subsequent step, we concluded that the two compounds differ only in the configuration at the C3-carbon atom. The estimated dihedral angle[25] (F–C3–C4–H) of approximately 10° in compound **9** appeared to be more suitable for HF elimination (formation of **3e**) than the angle (F–C3–C4–H) of approximately 130° estimated for HF elimination in compound **11** (formation of **3e** via compound **12**). This could explain why intermediate **12** was observed only in the reaction of **1e** with the (*Z*) isomer of enone **10**.

A possible mechanism for fluorine atom migration that leads to the formation of a new double bond in compound **12** could be explained by the following reaction pathway (Scheme 3): In the first step, fluoride anion elimination and the subsequent formation of an iminium salt could take place. Nucleophilic substitution at the benzylic carbon, either concerted with C–N^+ bond cleavage, or after a predissociation of this bond (S_N1 type) affords **12**.



Scheme 3. Proposed mechanism of the observed fluorine atom migration.

The S_N1-type process may be favoured by both the destabilizing effect of the perfluoroalkyl group on the iminium charge and the stabilizing delocalization at the benzylic cat-

ion level. The process is reminiscent of the proposed mechanism of the fluorinating activity of the so-called Jarovenko reagent.[26–28]

Conclusions

A new reaction of nonsymmetrical allenylazines with fluorinated enones was studied. It was found that the expected intermediate formed by intramolecular criss-cross cycloaddition undergoes rapid transformations. Migration of the fluorine atom and hydrogen fluoride elimination proceed in high yield. Compounds **3b**–**e**, **4a** and **7**, fluorinated substituted derivatives of *4H*-pyrrolo[1,2-b]pyrazole, were isolated and identified. In the case of allenylazine **1e**, intermediates **9**, **11** and **12** were characterized by ^{1}H and ^{19}F NMR spectra of the crude reaction mixture. An unusually facile substitution of a fluorine atom by a hydroxy group was observed when compound **3a** was passed through silica gel. Because of their close similarity to the central skeleton of the biologically active alkaloid withasomnine, compounds **3**, **4** and **7** might have a practical application.

Experimental Section

General Remarks: Melting points are uncorrected. FTIR spectra were recorded with a MIDAC Corporation Spectrafile IR apparatus. ^{1}H- , ^{13}C- and ^{19}F NMR spectra were recorded with a Bruker AC-250 or AC-500 spectrometer. Tetramethylsilane (δ = 0.00 ppm) or $CHCl_3$ (δ = 7.27 ppm) were used as internal standards for ^{1}H NMR spectra, $CDCl_3$ (δ = 77.23 ppm) for ^{13}C NMR spectra and $CFCl_3$ (δ = 0.0 ppm) for ^{19}F NMR spectra. The ^{13}C NMR spectra signals of CF_3 as (tq) and CF_2 as (qt) appeared at about 120 ppm. The signals were very low in intensity and were often overlapped by a noise signal, and therefore they are not listed in the overview of the spectra. Only the most important signals are listed for the ^{1}H NMR spectra. Supporting Information includes the most important spectra for the structure resolution of compounds **3a**, **3e**, **9**, **11** and **12**. MS data were obtained with a Trace MS Thermoquest apparatus (GC–MS) at 70 eV in the electron impact mode and an MS TRIO 1000 (Fisons) apparatus (MS) at 70 eV in the electron impact mode and by thermal desorption. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. High Resolution Mass Spectra (HRMS) were recorded with a Q-TOF Micro micromass instrument in the positive ESI (CV = 30 V) mode. All reactions were carried out under a dry argon atmosphere and were monitored by TLC (Merck F254 silica gel). Products were separated by preparative TLC. Xylene (mixture of isomers) was dried and distilled from sodium/benzophenone and stored over dry 4-Å molecular sieves. Fluorinated enone **2** was prepared according to the literature.[21] Nonsymmetrical azines **1a**–**e** were prepared according to the general method.[29,30] Diffraction data were collected with a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by using a SHELXTL program package.[31] The hydrogen atoms were placed in calculated idealized positions and refined as riding. Both compounds crystallize in centrosymmetric space groups; the chiral molecules of **3d** thus form a crystalline racemate. In the 2-(*p*-chlorophenyl)-2-fluoroethyl moiety of **3d**, the fluorine and hydrogen atoms were found to exchange their positions in the ratio 85:15 approximately. CCDC-268500 (**3d**) and CCDC-268501 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Cycloaddition Reactions

Nonsymmetrical azine **1a**–**e** (0.25 mmol) was mixed with fluorinated enone **2** (0.28 mmol) in dry xylene (10 mL). The mixture was heated at reflux for 2.5 h, and then xylene was removed under vacuum. All products were purified by preparative TLC.

3-Benzoyl-6-[2-fluoroethyl-2-(*p*-methoxyphenyl)]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (3a): The product was not separated. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.6 (m, 3 F, CF_3), –107.6 (m, 2 F, CF_2), –171.4 (ddd, $^{2}J_{F,H}$ = 46.7 Hz, $^{3}J_{F,H}$ = 24.2 Hz, $^{3}J_{F,H}$ = 13.5 Hz, 1 F, C*F*–CH_2) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, H_3C–C–CH_3), 1.10 (s, 3 H, H_3C–C–CH_3), 1.59 (s, 3 H, H_3C–C=), 3.15 (m, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 5.79 (dd, $^{2}J_{H,F}$ = 46.7 Hz, $^{3}J_{H,H}$ = 7.4 Hz, $^{3}J_{H,H}$ = 5.6 Hz, 1 H, C*H*F–CH_2) ppm.

3-Benzoyl-6-[2-fluoroethyl-2-(*p*-methylphenyl)]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (3b): Repeated chromatographic separations [(1) AcOEt/petroleum ether = 10:90; (2) CH_2Cl_2/petroleum ether = 50:50] afforded 74 mg (58%). Oil. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.6 (t, $^{3}J_{F,F}$ = 2.2 Hz, 3 F, CF_3), –107.7 (q, $^{3}J_{F,F}$ = 2.2 Hz, 2 F, CF_2), –174.6 (ddd, $^{2}J_{H,F}$ = 46.9 Hz, $^{3}J_{H,F}$ = 25.4 Hz, $^{3}J_{H,F}$ = 14.1 Hz, 1 F, CFH) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, H_3C–C–CH_3), 1.22 (s, 3 H, H_3C–C–CH_3), 1.70 (s, 3 H, H_3C–C=), 2.35 (s, 3 H, CH=C–CH_3), 3.24 (m, 2 H, CH_2), 5.90 (ddd, $^{2}J_{H,F}$ = 47.0 Hz, $^{3}J_{H,H}$ = 7.6 Hz, $^{3}J_{H,H}$ = 5.2 Hz, 1 H, CFH), 7.16 (d, $^{3}J_{H,H}$ = 8.3 Hz, 2 H, C*H*=C–CH_3), 7.22 (d, $^{3}J_{H,H}$ = 8.3 Hz, 2 H, CFH–C=C*H*), 7.46 (tm, $^{3}J_{H,H}$ = 7.6 Hz, 1 H, C*H*=CH–CH=C–C=O), 7.60 (tm, $^{3}J_{H,H}$ = 7.4 Hz, 2 H, C*H*–CH=C–C=O), 7.79 (dm, $^{3}J_{H,H}$ = 7.0 Hz, 2 H, CH=C–C=O) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.4 (d, $^{5}J_{C,F}$ = 1.1 Hz, H_3C–C=), 21.4 (s, CH=C–*C*H_3), 22.8 (s, H_3C–C–CH_3), 22.9 (s, H_3C–C–*C*H_3), 32.2 (d, $^{2}J_{C,F}$ = 28.0 Hz, CH_2), 45.8 (s, H_3C–*C*–CH_3), 91.4 (d, $^{1}J_{C,F}$ = 174.6 Hz, CFH), 116.3 (m, *C*–C–CF_2), 125.5 (d, $^{3}J_{C,F}$ = 6.4 Hz, CFH–C=*C*H), 128.3 (d, $^{3}J_{C,F}$ = 5.5 Hz, N–*C*–CH_2), 128.5 (s, *C*H–CH=C–C=O), 129.3 (s, *C*H=C–CH_3), 129.7 (s, *C*H=C–C=O), 133.7 (s, *C*H=CH–CH=C–C=O), 136.2 (d, $^{2}J_{C,F}$ = 19.8 Hz, CFH–*C*), 138.7 (d, $^{5}J_{C,F}$ = 2.3 Hz, CH=*C*–CH_3), 138.9 (t, $^{5}J_{C,F}$ = 1.4 Hz, CH=*C*–C=O), 139.1 (s, H_3C–*C*=), 140.0 (t, $^{2}J_{C,F}$ = 30.6 Hz, *C*–CF_2), 153.3 [s, N–*C*–C–$(CH_3)_2$], 191.3 (s, C=O) ppm. IR (film): $\tilde{\nu}$ = 1008, 1092, 1166, 1217, 1329, 1451, 1667 (C=O), 2868, 2929, 2971, 3031, 3060 cm^{-1}. GC–MS: *m*/*z* (%) = 486 (52) $[M–HF]^+$, 471 (31), 204 (16), 105 (100). HRMS: calcd. for $C_{27}H_{24}F_6N_2ONa^+$ 529.1691; found 529.1707.

3-Benzoyl-6-(2-fluoroethyl-2-phenyl)-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (3c): Repeated chromatographic separations [(1). AcOEt/petroleum ether = 10:90; (2). CH_2Cl_2/petroleum ether = 20:80] afforded 56 mg (46%). Oil. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.6 (m, 3 F, CF_3), –107.7 (m, 2 F, CF_2), –176.2 (ddd, $^{2}J_{H,F}$ = 46.9 Hz, $^{3}J_{H,F}$ = 25.4 Hz, $^{3}J_{H,F}$ = 14.1 Hz, 1 F, CFH) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, H_3C–C–CH_3), 1.23 (s, 3 H, H_3C–C–CH_3), 1.69 (s, 3 H, H_3C–C=), 3.27 (m, 2 H, CH_2), 5.97 (ddd, $^{2}J_{H,F}$ = 47.0 Hz, $^{3}J_{H,H}$ = 7.5 Hz, $^{3}J_{H,H}$ = 5.5 Hz, 1 H, CFH), 7.35 (m, 5 H, CH), 7.47 (tm, $^{3}J_{H,H}$ = 7.6 Hz, 2 H, CH), 7.61 (tm, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, CH), 7.81 (dm, $^{3}J_{H,H}$ = 7.5 Hz, 2 H, CH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.3 (d, $^{5}J_{C,F}$ = 0.9 Hz, H_3C–C=), 22.7 (s, H_3C–C–CH_3), 22.9 (s, H_3C–C–*C*H_3), 32.3 (d, $^{2}J_{C,F}$ = 27.7 Hz, CH_2), 45.9 (s, H_3C–*C*–CH_3), 91.3 (d, $^{1}J_{C,F}$ = 175.6 Hz, CFH), 116.3 (m, *C*–C–CF_2), 125.5 (d, $^{3}J_{C,F}$ = 6.8 Hz, CFH–C=*C*H), 128.2 (d, $^{3}J_{C,F}$ = 6.0 Hz, N–*C*–CH_2),

128.5 (s, *C*H–CH=C–C=O), 128.7 (s, CH), 128.9 (s, CH), 129.7 (s, *C*H=C–C=O), 133.7 (s, *C*H=CH–CH=C–C=O), 138.9 (t, $^5J_{C,F}$ = 1.3 Hz, CH=*C*–C=O), 139.18 (s, d, $^2J_{C,F}$ = 20.0 Hz, CFH–*C*), 139.24 (s, H_3C–*C*=), 140.1 (t, $^2J_{C,F}$ = 30.3 Hz, *C*–CF_2), 153.3 [s, N–*C*–C–$(CH_3)_2$], 191.2 (s, C=O) ppm. IR (film): $\tilde{\nu}$ = 1006, 1101, 1223, 1329, 1450, 1666 (C=O), 2868, 2931, 2972, 3035, 3065 cm^{-1}. GC–MS: *m*/*z* (%) = 492 (3) $[M]^+$, 472 (14), 457 (5), 370 (7), 109 (65), 105 (100). HRMS: calcd. for $C_{26}H_{22}F_6N_2ONa^+$ 515.1534; found 515.1529.

3-Benzoyl-6-[2-(*p*-chlorophenyl)-2-fluoroethyl]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (3d): Chromatographic separation using CH_2Cl_2/petroleum ether = 50:50 afforded 84 mg (64%) of a slowly crystallizing liquid sample. Crystallization from methanol afforded an appropriate crystal for X-ray analysis. M.p. 93–99 °C. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.6 (t, $^3J_{F,F}$ = 2.2 Hz, 3 F, CF_3), –107.7 (q, $^3J_{F,F}$ = 2.2 Hz, 2 F, CF_2), –176.5 (ddd, $^2J_{H,F}$ = 46.9 Hz, $^3J_{H,F}$ = 24.9 Hz, $^3J_{H,F}$ = 15.9 Hz, 1 F, CFH) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, H_3C–C–CH_3), 1.22 (s, 3 H, H_3C–C–CH_3), 1.72 (s, 3 H, H_3C–C=), 3.04–3.42 (m, 2 H, CH_2), 5.92 (ddd, $^2J_{H,F}$ = 48.8 Hz, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 5.5 Hz, 1 H, CFH), 7.25 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, CFH–C=*C*H), 7.33 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *C*H=C–Cl), 7.45 (tm, $^3J_{H,H}$ = 8.0 Hz, 1 H, C*H*=CH–CH=C–C=O), 7.59 (tm, $^3J_{H,H}$ = 7.2 Hz, 2 H, C*H*–CH=C–C=O), 7.77 (dm, $^3J_{H,H}$ = 8.3 Hz, 2 H, CH=C–C=O) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.4 (d, $^5J_{C,F}$ = 0.9 Hz, H_3C–C=), 22.8 (s, H_3C–C–CH_3), 22.9 (s, H_3C–C–*C*H_3), 32.1 (d, $^2J_{C,F}$ = 27.1 Hz, CH_2), 45.9 (s, H_3C–*C*–CH_3), 90.8 (d, $^1J_{C,F}$ = 176.5 Hz, CFH), 116.4 (m, *C*–C–CF_2), 126.9 (d, $^3J_{C,F}$ = 6.9 Hz, CFH–C=*C*H), 127.9 (d, $^3J_{C,F}$ = 5.5 Hz, N–*C*–CH_2), 128.5 (s, *C*H–CH=C–C=O), 128.8 (s, *C*H=C–Cl), 129.7 (s, *C*H=C–C=O), 133.7 (s, *C*H=CH–CH=C–C=O), 134.7 (d, $^5J_{C,F}$ = 1.8 Hz, C–Cl), 137.6 (d, $^2J_{C,F}$ = 20.7 Hz, CFH–*C*), 138.8 (t, $^5J_{C,F}$ = 1.4 Hz, CH=*C*–C=O), 139.5 (s, H_3C–*C*=), 140.1 (t, $^2J_{C,F}$ = 30.3 Hz, *C*–CF_2), 153.3 [s, N–*C*–C–$(CH_3)_2$], 191.2 (s, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 1012, 1143, 1193, 1219, 1660 (C=O), 2867, 2935, 2976, 3067 cm^{-1}. GC–MS: *m*/*z* (%) = 526 (2) $[M]^+$, 506 (38), 491 (18), 214 (12), 143 (15), 105 (100). HRMS: calcd. for $C_{26}H_{21}ClF_6N_2ONa^+$ 549.1144; found 549.1130.

3-Benzoyl-6-[2-fluoroethyl-2-(*p*-nitrophenyl)]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (3e): Repeated chromatographic separations [(1) AcOEt/petroleum ether = 10:90; (2) CH_2Cl_2/petroleum ether = 20:80] afforded 93 mg (69%) of a slowly crystallizing liquid sample. M.p. 96–100 °C. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.6 (m, 3 F, CF_3), –107.6 (m, 2 F, CF_2), –180.3 (ddd, $^2J_{H,F}$ = 46.7 Hz, $^3J_{H,F}$ = 25.1 Hz, $^3J_{H,F}$ = 18.7 Hz, 1 F, CFH) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (s, 3 H, H_3C–C–CH_3), 1.26 (s, 3 H, H_3C–C–CH_3), 1.79 (s, 3 H, H_3C–C=), 3.19–3.42 (m, 2 H, CH_2), 6.07 (ddd, $^2J_{H,F}$ = 46.8 Hz, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,H}$ = 4.7 Hz, 1 H, CFH), 7.47 (tm, $^3J_{H,H}$ = 7.8 Hz, 2 H, C*H*–CH=C–C=O), 7.52 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, CFH–C=*C*H), 7.60 (tm, $^3J_{H,H}$ = 7.5 Hz, 1 H, C*H*=CH–CH=C–C=O), 7.76 (dm, $^3J_{H,H}$ = 7.3 Hz, 2 H, CH=C–C=O), 8.23 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, C*H*=C–NO_2) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.5 (d, $^5J_{C,F}$ = 0.9 Hz, H_3C–C=), 22.8 (s, H_3C–C–CH_3), 22.9 (s, H_3C–C–*C*H_3), 31.9 (d, $^2J_{C,F}$ = 26.3 Hz, CH_2), 46.0 (s, H_3C–*C*–CH_3), 90.3 (d, $^1J_{C,F}$ = 178.9 Hz, CFH), 116.4 (m, *C*–C–CF_2), 123.8 (s, *C*H–C–NO_2), 126.2 (d, $^3J_{C,F}$ = 7.7 Hz, CFH–C=*C*H), 127.3 (d, $^3J_{C,F}$ = 5.1 Hz, N–*C*–CH_2), 128.5 (s, *C*H–CH=C–C=O), 129.6 (s, *C*H=C–C=O), 133.8 (s, *C*H=CH–CH=C–C=O), 138.7 (t, $^5J_{C,F}$ = 1.1 Hz, CH=*C*–C=O), 140.06 (t, $^2J_{C,F}$ = 29.7 Hz, *C*–CF_2), 140.12 (s, H_3C–*C*=), 146.1 (d, $^2J_{C,F}$ = 20.3 Hz, CFH–*C*), 148.1 (d, $^5J_{C,F}$ = 0.9 Hz, C–NO_2), 153.2 [s, N–*C*–C–$(CH_3)_2$], 191.0 (s, C=O) ppm. IR (film): $\tilde{\nu}$ = 1009, 1100, 1165, 1217, 1348, 1527, 1662 (C=O), 2866, 2931, 2973, 3082 cm^{-1}. GC–MS: *m*/*z* (%) = 537 (29) $[M]^+$, 370 (70), 291 (30), 105 (100). $C_{26}H_{21}F_6N_3O_3$ (537.45): calcd. C 58.10, H 3.94, N 7.82; found C 57.86, H 4.14, N 7.49.

3-Benzoyl-6-[2-(*p*-methoxyphenyl)ethenyl]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (4a): The crude reaction mixture contained compound **4a** as the main product (^{1}H- and ^{19}F NMR measurements). After removal of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and mixed with silica gel (2 g). The reaction mixture was stirred overnight, filtered and then washed with another portion of CH_2Cl_2 (100 mL). Chromatographic separation using CH_2Cl_2/petroleum ether = 50:50 afforded 50 mg (40%) of a solid. Crystallization from ether afforded an appropriate crystal for X-ray analysis. M.p. 123–129 °C. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.5 (t, $^3J_{F,F}$ = 2.4 Hz, 3 F, CF_3), –107.3 (q, $^3J_{F,F}$ = 2.4 Hz, 2 F, CF_2) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (s, 6 H, H_3C–C–CH_3), 2.04 (s, 3 H, H_3C–C=), 3.85 (s, 3 H, OCH_3), 6.84 (d, $^3J_{H,H}$ = 16.3 Hz, 1 H, C*H*–C–N), 6.93 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, *C*H=C–OCH_3), 7.49 (m, 4 H, C*H*–CH=C–C=O and H_3C–O–C=CH–C*H*), 7.61 (tm, $^3J_{H,H}$ = 7.3 Hz, 1 H, C*H*=CH–CH=C–C=O), 7.83 (dm, $^3J_{H,H}$ = 7.0 Hz, 2 H, C*H*=C–C=O), 8.11 (d, $^3J_{H,H}$ = 16.3 Hz, 1 H, C*H*=CH–C–N) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 9.2 (s, H_3C–C=), 23.1 (s, H_3C–C–*C*H_3), 45.1 (s, H_3C–*C*–CH_3), 55.6 (s, OCH_3), 111.0 (s, N–C–*C*H), 114.5 (s, *C*H=C–OCH_3), 115.5 (m, *C*–C–CF_2), 128.4 (s, *C*H–CH=C–OCH_3), 128.5 (s, *C*H–CH=C–C=O), 129.7 (s, *C*H=C–C=O), 129.9 (s, *C*=CH–CH=C–OCH_3), 131.3 (s, N–*C*=C–CH_3), 133.1 (s, N–C–CH=*C*H), 133.7 (s, *C*H=CH–CH=C–C=O), 137.8 (s, H_3C–*C*=), 139.0 (t, $^5J_{C,F}$ = 1.3 Hz, CH=*C*–C=O), 140.1 (t, $^2J_{C,F}$ = 29.8 Hz, *C*–CF_2), 154.4 [s, N–*C*–C–$(CH_3)_2$], 160.2 (s, *C*–OCH_3), 191.4 (s, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 1013, 1171, 1217, 1511, 1603, 1666 (C=O), 2840, 2933, 2969, 3031, 3062 cm^{-1}. GC–MS: *m*/*z* (%) 502 (44) $[M]^+$, 487 (41), 480 (16), 212 (36), 205 (24), 105 (100). $C_{27}H_{23}F_5N_2O_2$ (502.48): calcd. C 64.54, H 4.61, N 5.58; found C 64.57, H 4.66, N 5.42.

3-Benzoyl-6-[2-hydroxyethyl-2-(*p*-methoxyphenyl)]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-pyrrolo[1,2-*b*]pyrazole (7): The crude reaction mixture contained compound **3a** as the main product (^{1}H- and ^{19}F NMR measurements). After removal of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and mixed with silica gel (2 g). The reaction mixture was stirred overnight and filtered. After removal of the solvent, the crude product was extracted with diethyl ether (100 mL). Chromatographic separation using CH_2Cl_2 afforded 44 mg (34%). Oil. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.6 (m, 3 F, CF_3), –107.8 (m, 2 F, CF_2) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (s, 6 H, H_3C–C–CH_3), 1.56 (s, 3 H, H_3C–C=), 3.09 (dd, $^2J_{H,H}$ = 14.7 Hz, $^3J_{H,H}$ = 5.5 Hz, 1 H, CH_2), 3.18 (dd, $^2J_{H,H}$ = 14.7 Hz, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH_2), 3.33 (broad s, 1 H, OH), 3.79 (s, 3 H, OCH_3), 5.20 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, HO–C*H*), 6.84 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, C*H*=C–OCH_3), 7.20 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, HO–CH–C=C*H*), 7.46 (tm, $^3J_{H,H}$ = 7.8 Hz, 2 H, C*H*–CH=C–C=O), 7.61 (tm, $^3J_{H,H}$ = 7.5 Hz, 1 H, C*H*=CH–CH=C–C=O), 7.79 (dm, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH=C–C=O) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.2 (s, H_3C–C=), 22.8 (s, H_3C–C–*C*H_3), 34.1 (s, CH_2), 45.8 (s, H_3C–*C*–CH_3), 55.5 (s, OCH_3), 71.7 (s, HO–CH), 113.8 (s, *C*H=C–OCH_3), 116.3 (m, *C*–C–CF_2), 126.9 (s, HO–CH–C=*C*H), 128.5 (s, *C*H–CH=C–C=O), 129.7 (s, *C*H=C–C=O), 130.0 (s, N–*C*–CH_2), 133.7 (s, *C*H=CH–CH=C–C=O), 135.5 (s, HO–CH–*C*), 138.4 (s, H_3C–*C*=), 138.8 (t, $^5J_{C,F}$ = 1.4 Hz, CH=*C*–C=O), 139.7 (t, $^2J_{C,F}$ = 30.1 Hz, *C*–CF_2), 153.4 [s, N–*C*–C–$(CH_3)_2$], 159.3 (s, *C*–OCH_3), 191.1 (s, C=O) ppm. IR (film): $\tilde{\nu}$ = 1032, 1101, 1169, 1219, 1248, 1328, 1514, 1664 (C=O), 2842, 2870, 2931, 2970, 3064, 3433 (broad, OH) cm^{-1}. MS: *m*/*z* (%) 520 (2) $[M]^+$, 502 (17), 384 (73), 369 (60), 137 (100), 105 (60). HRMS: calcd. for $C_{27}H_{25}F_5N_2O_3Na^+$ 543.1683; found 543.1670.

(2*S*,3*S*,4*S*,9*S*)-3-Benzoyl-2,3-difluoro-2-pentafluoroethyl-5,5,6-trimethyl-9-(*p*-nitrophenyl)-1,10-diazatricyclo[5.2.1.0^{4,10}]dec-6-ene (9): Nonsymmetrical azine **1e** (0.25 mmol) was mixed with fluorinated enone **2** (0.28 mmol) in dry xylene (10 mL). The mixture was heated at reflux for 20 min. and then xylene was removed under vacuum. The product was not separated. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –80.2 (t, $^3J_{F,F}$ = 11.2 Hz, 3 F, CF_3), –114.2 (ddm, $^2J_{F,F}$ = 291.5 Hz, $J_{F,F}$ = 23.8 Hz, 1 F, CF_2), –115.7 (dt, $^2J_{F,F}$ = 291.5 Hz, $^3J_{F,F}$ = 10.8 Hz, 1 F, CF_2), –134.9 (m, CF), –141.6 (m, CF) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, H_3C–C–CH_3), 1.17 (s, 3 H, H_3C–C–CH_3), 1.40 (m, 3 H, H_3C–C=), 2.32 (dm, $^2J_{H,H}$ = 14.7 Hz, 1 H, CH_2), 3.15 (dd, $^2J_{H,H}$ = 14.7 Hz, $^3J_{H,F}$ = 8.9 Hz, 1 H, CH_2), 4.31 (d, $^3J_{H,F}$ = 36.1 Hz, 1 H, CH–CF), 5.15 (dd, $^3J_{H,H}$ = 8.9 Hz, $^3J_{H,H}$ = 4.0 Hz, 1 H, C*H*–CH_2) ppm.

(2*S*,3*R*,4*S*,9*S*)-3-Benzoyl-2,3-difluoro-2-pentafluoroethyl-5,5,6-trimethyl-9-(*p*-nitrophenyl)-1,10-diazatricyclo[5.2.1.0^{4,10}]dec-6-ene (11): Nonsymmetrical azine **1e** (0.25 mmol) was mixed with fluorinated enone **10** (0.28 mmol) in dry xylene (10 mL). The mixture was heated at reflux for 20 min. and then xylene was removed under vacuum. The product was not separated. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –78.6 (dm, $^3J_{F,F}$ = 13.5 Hz, 3 F, CF_3), –117.9 (dd, $^2J_{F,F}$ = 287.9 Hz, $J_{F,F}$ = 13.9 Hz, 1 F, CF_2), –123.9 (dm, $^2J_{F,F}$ = 287.9 Hz, 1 F, CF_2), –158.7 (sextet m, $J_{F,F}$ = 13.5 Hz, 1 F, C*F*–CF_2), –163.1 (dd, $^3J_{F,H}$ = 33.7 Hz, $^3J_{F,F}$ = 16.6 Hz, 1 F, C*F*–CH) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95 (m, 3 H, H_3C–C–CH_3), 1.27 (s, 3 H, H_3C–C–CH_3), 1.44 (m, 3 H, H_3C–C=), 2.44 (m, 1 H, CH_2), 2.95 (dd, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,F}$ = 7.5 Hz, 1 H, CH_2), 4.55 (dd, $^3J_{H,F}$ = 33.5 Hz, $^4J_{H,F}$ = 3.5 Hz, 1 H, CH–CF), 5.15 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H, C*H*–CH_2) ppm.

3-Benzoyl-6-[2-fluoroethyl-2-(*p*-nitrophenyl)]-2-pentafluoroethyl-4,4,5-trimethyl-4*H*-3,3a-dihydropyrrolo[1,2-*b*]pyrazole (12): Nonsymmetrical azine **1e** (0.25 mmol) was mixed with fluorinated enone **10** (0.28 mmol) in dry xylene (10 mL). The mixture was heated at reflux for 2–3 h and then xylene was removed under vacuum. The product was not separated. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –83.7 (m, 3 F, CF_3), –110.7 (dm, $^2J_{F,F}$ = 293.8 Hz, 1 F, CF_2), –113.0 (dm, $^2J_{F,F}$ = 293.8 Hz, 1 F, CF_2), –155.4 (dm, $^3J_{F,F}$ = 18.0 Hz, 1 F, N–CH–C*F*), –179.6 (ddd, $^2J_{F,H}$ = 46.9 Hz, $^3J_{F,H}$ = 20.9 Hz, $^3J_{F,H}$ = 15.0 Hz, 1 F, C*F*–CH_2) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.11 and 1.12 (s and s, 6 H, H_3C–C–CH_3), 1.29 (s, 3 H, H_3C–C=), 2.72 (dtd, $^3J_{H,F}$ = 22.5 Hz, $^2J_{H,H}$ = 14.4 Hz, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH_2), 3.11 (td, $^2J_{H,H}$ = 14.4 Hz, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH_2), 4.16 (d, $^3J_{H,F}$ = 20.0 Hz, 1 H, CH–CF), 5.83 (dt, $^2J_{H,F}$ = 46.7 Hz, $^3J_{H,H}$ = 6.7 Hz, 1 H, C*H*F–CH_2) ppm.

Supporting Information (see footnote on the first page of this article): NMR data of compounds **3**, **4**, **7**, **9**, **11** and **12**.

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