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New Synthesis of 3-Fluoropyrroles

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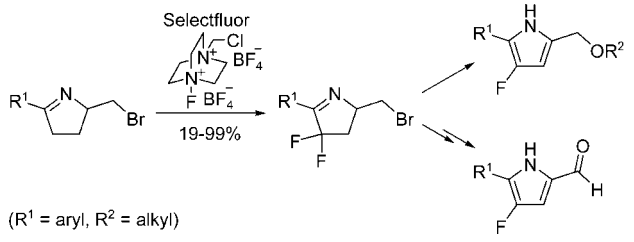

5-Alkoxymethyl-2-aryl-3-fluoro-1*H*-pyrroles and 2-aryl-3-fluoro-1*H*-pyrrole-5-carbaldehydes were efficiently prepared from the corresponding 2-aryl-5-(bromomethyl)-1-pyrrolines via electrophilic α,α-difluorination of the imino bond, using Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bistetrafluoroborate) and subsequent aromatization by dehydrofluorination. This methodology provides a new and easy entry toward various new 3-fluorinated pyrroles.

Fluorinated pyrroles have already proven to be important building blocks for the preparation of potent pharmaceutical and agrochemical compounds, such as drugs against cytokine mediated diseases,[1] fungicides and bactericides,[2] porphyrines,[3] and antithrombosis[4] agents. However, the selective synthesis of fluoropyrroles remains a difficult task,[5] especially to access 3-fluoropyrroles. Only a limited number of papers reported a direct fluorination toward 3-fluoropyrroles via photolysis of pyrrole-3-diazonium tetrafluoroborates,[3] or via bromine−lithium exchange of 3-bromo-1-(triisopropylsilyl)pyrroles followed by treatment with *N*-fluorobenzenesulfonimide (NFSI).[6] The use of difluorine gas in He and chloroform at −60 °C to fluorinate 1-methylpyrrole resulted in a mixture of 2- and 3-fluoro-1-methylpyrroles (1:4).[7] Cyclization strategies starting from acyclic precursors toward 3-fluoropyrroles included a cyclocondensation reaction of γ-iodo-α,α-difluorocarbonyl compounds with ammonia,[8,9] cyclization and dehydrofluorination of α,α-difluoro-γ-iodo-γ-trimethylsilanyl ketones with ammonium hydroxide[9] or primary amines,[10] dehydrofluorination and dehydration of 3,3-difluoro-5-hydroxypyrrolidines,[11] and a rhodium(II) acetate-catalyzed intramolecular N−H insertion of 5-amino-4,4-difluoro-2-diazo-3-ketoesters followed by dehydrofluorination.[12]

Rhodium complexes also catalyze the reaction between isonitriles and 2-fluoro-1,3-diketones to give α,β-unsaturated formamides that undergo cyclocondensation after decarbonylation to yield 3-fluoropyrroles.[13] Synthetically less important routes to 3-fluoropyrroles include the thermal isomerization of *N*-[(2,2-difluoro-1-arylcyclopropyl)methylidene]amines,[14] the ring contraction of 1-azidocyclobutenes followed by nucleophilic attack of arenes,[15] and the ring contraction of fluorinated dihydrooxazines with Zn.[16]

Finally, 4-fluoro-1*H*-pyrrole-2-carboxylates can be synthesized by oxidation of 4,4-difluoropyrrolidine-2-carboxylates which were prepared from proline derivatives with use of diethylaminosulfur trifluoride (DAST).[6b] It is clear that no general method to synthesize functionalized 3-fluoropyrroles is available. Although the above-mentioned methodologies each have their benefits, the use of not readily available fluorinated starting materials, expensive or difficult to handle fluorinating agents (DAST, F_2-gas), or the need for photolysis clearly is a disadvantage when a multigram scale synthesis of 3-fluoropyrroles is envisaged. Moreover, arylated 3-fluoropyrroles bearing an aldehyde or alkoxymethyl function at the C-5 position have not been synthesized before, despite the interest of the pharmaceutical industry in such compounds. Because of the fact that we recently disclosed a methodology to synthesize α,α-difluoroimines,[17] it was proposed to use 1-pyrrolines as precursors for polyfunctionalized 3-fluoropyrroles. Although α-fluorinated imines can hardly be compared to α-chlorinated imines in terms of synthesis and reactivity, the above-mentioned synthetic strategy resulted previously in the synthesis of

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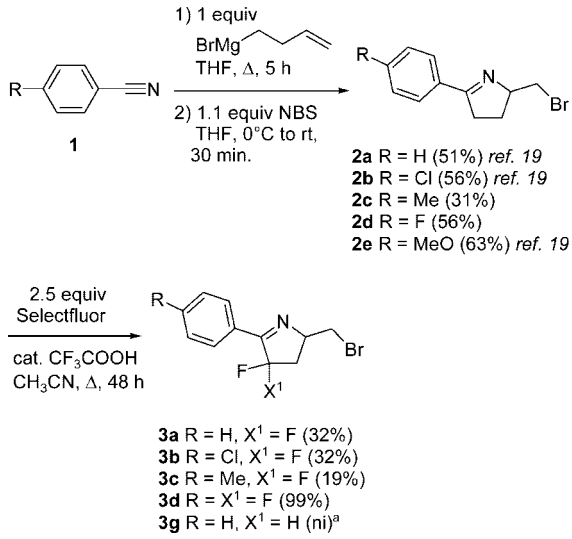
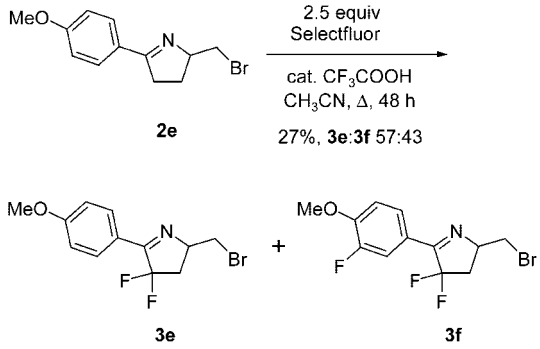
SCHEME 1. Synthesis of α(,α)-(Di)fluoro-1-pyrroline Derivatives 3[a]



[a] Not Isolated, See Table 1.

SCHEME 2. Fluorination of 2-(4-Methoxyphenyl)-1-pyrroline 2e



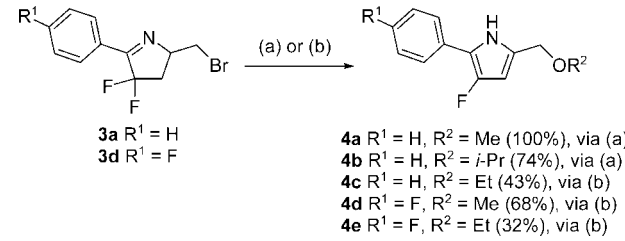
3-chloropyrroles starting from the corresponding 3,3-dichloro-1-pyrrolines.[18]

2-Aryl-5-(bromomethyl)-1-pyrrolines **2** were used as starting materials because of the interesting bromomethyl group at the 5-position, which allows further transformations. These functionalized 1-pyrrolines were prepared from benzonitriles **1** by reaction with 3-butenylmagnesium bromide and subsequently with *N*-bromosuccinimide, both in THF as solvent.[19] In a first attempt to fluorinate pyrroline **2a**, *N*-fluorobenzenesulfonimide (NFSI) was used as an electrophilic fluorination reagent (Scheme 1). In contrast to the fluorination of acyclic *N*-alkylimines, 1-pyrroline **2a** could not be fluorinated under the same mild conditions, using NFSI in acetonitrile with dimethylformamide as a cosolvent (5/2) at 0 °C for 2.5 h or room temperature for 15 h (Table 1), probably due to the more difficult enamine formation. Increasing the temperature (50 °C to reflux temperature) and the reaction time (until 15 h) in acetonitrile without cosolvent resulted in a mixture of starting material **2a** and monofluorinated 1-pyrroline **3g** (a **2a**:**3g** ratio of 95:5 to 75:25, see Table 1); however, the reaction mixture became more complex due to the presence of numerous unidentified compounds. Analogously, when 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor, 1.2 equiv) was used as a fluorination agent in acetonitrile at reflux temperature for 48 h, monofluorination of pyrroline **2a** could not be driven to completion. However, the use of a catalytic amount of trifluoroacetic acid to facilitate enamine formation indeed accelerated the reaction of **2a** with Selectfluor. Reacting 5-(bromomethyl)-2-phenyl-1-pyrroline **2a** with 2.5 equiv of Selectfluor in acetonitrile at reflux temperature for 2 days finally led to complete conversion and yielded 32% of 3,3-difluoro-1-pyrroline **3a** after flash chromatography. This synthetic methodology also afforded other derivatives with a different substitution pattern of the aryl group, which proves the generality of the method. It should be noted that the α,α-difluorination of 2-(4-fluorophenyl)-1-pyrroline **2d** resulted in an exceptionally clean reaction mixture, giving rise to a high yield of difluoropyrroline **3d** (purity >95%, determined via ^{1}H NMR).

On the other hand, the fluorination of 2-(4-methoxyphenyl)-1-pyrroline **2e** by using an excess of Selectfluor resulted in a fluorination of the 3′-position of the phenyl group and led to a mixture of di- and trifluorinated pyrroline **3e** and **3f** (57:43 ratio), which could not be separated via flash chromatography (Scheme 2).

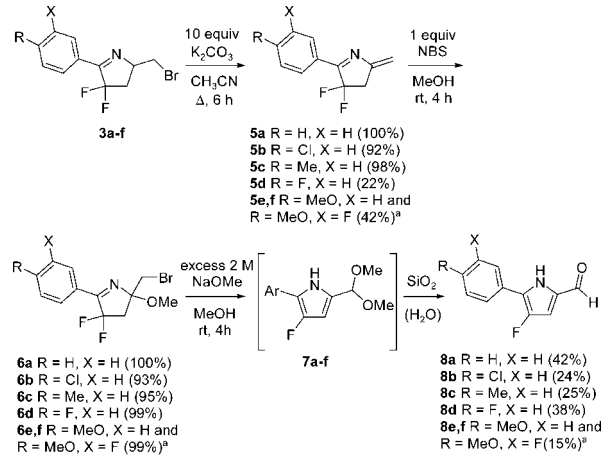
A simultaneous nucleophilic substitution on the brominated carbon atom and dehydrofluorination of 2-aryl-5-(bromomethyl)-3,3-difluoro-1-pyrrolines **3a** and **3d** could be accomplished by heating these compounds in a mixture of 2 M aqueous sodium

SCHEME 3. Synthesis of 5-(Alkoxymethyl)-3-fluoro-1*H*-pyrroles 4[a]



[a] Conditions: (a) 5 equiv of 2 M aq NaOH, R^2OH, Δ, 1 h; (b) excess 1 M $NaOR^2$ in R^2OH, Δ, 1 h.

SCHEME 4. Synthesis of 3-Fluoro-1*H*-pyrrole-5-carbaldehydes 8[a]



[a] **5e** and **5f** (ratio 56:44); **6e** and **6f** (ratio 49:51); **8e** and **8f** (ratio 57:43) could not be separated via flash chromatography.

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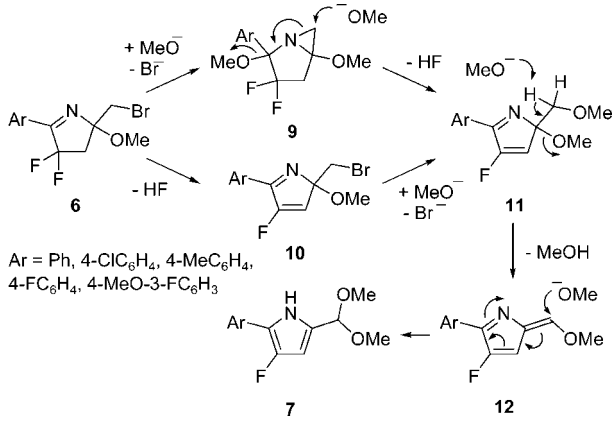
TABLE 1. Fluorination of Pyrroline 2a, Using NFSI or Selectfluor

reaction conditions	ratio **2a**:**3g**:**3a**[a]
1.2 equiv of NFSI, 3 equiv of K_2CO_3, CH_3CN/DMF 5/2, 0 °C, 2.5 h	no reaction
1.2 equiv of NFSI, 3 equiv of K_2CO_3, CH_3CN/DMF 5/2, rt, 15 h	no reaction
1.2 equiv of NFSI, 3 equiv of K_2CO_3, CH_3CN, 50 °C, 6.5 h	no reaction
1.2 equiv of NFSI, 3 equiv of K_2CO_3, CH_3CN, Δ, 3.5 h	95:5:0
1.2 equiv of NFSI, 3 equiv of K_2CO_3, CH_3CN, Δ, 15 h	75:25:0
1.2 equiv of Selectfluor, CH_3CN, Δ, 48 h	40:60:0
2.5 equiv of Selectfluor, cat. TFA, CH_3CN, Δ, 48 h	0:0:100

[a] Ratio determined by ^{1}H NMR analysis.

SCHEME 5. Possible Mechanisms for the Synthesis of 3-Fluoro-1*H*-pyrrole-5-carbaldehydes 8

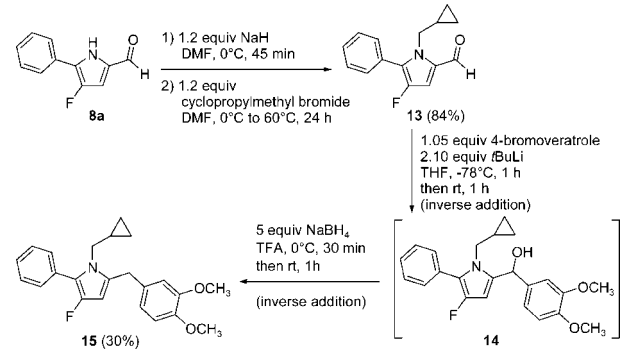


hydroxide in a suitable alcoholic solvent or in a mixture of 1 M sodium alkoxide in the corresponding alcohol (Scheme 3). Both methods led to new fluorinated 5-(alkoxymethyl)-1*H*-pyrroles **4** in comparable yields.

It was observed that during the α,α-difluorination of pyrroline **2a** for 48 h, a trace amount of 5-methylene-1-pyrroline **5a** was formed via dehydrobromination of difluoropyrroline **3a**. The latter conversion could be optimized by using potassium carbonate as base and yielded almost quantitatively the new 2-aryl-3,3-difluoro-5-methylene-1-pyrrolines **5**, which are interesting building blocks for further transformations (Scheme 4). The reactivity of these cyclic azadienes was investigated by using *N*-bromosuccinimide in methanol. Reaction of 2-aryl-3,3-difluoro-5-methylene-1-pyrrolines **5** with *N*-bromosuccinimide in methanol at room temperature for 4 h provided a vicinal bromomethoxylation of the exocyclic double bond, affording 5-(bromomethyl)-3,3-difluoro-5-methoxy-1-pyrrolines **6** in excellent yields (93−100%). The relatively unstable hemiaminal-type compounds **6** were not purified by flash chromatography to avoid decomposition, but were treated directly with an excess of 2 M sodium methoxide in methanol at room temperature to target fluorinated azaheterocyclic compounds. Surprisingly, these mild conditions gave access to new fluorinated 5-(dimethoxymethyl)-1*H*-pyrroles **7** in good yields. A mild hydrolysis of the dimethoxymethyl group of pyrroles **7** could be established through flash chromatography on wet silica gel, resulting in new 3-fluoro-1*H*-pyrrole-5-carbaldehydes **8** directly.

The conversion of 5-(bromomethyl)-3,3-difluoro-5-methoxy-1-pyrrolines **6** into 2-aryl-5-(dimethoxymethyl)-3-fluoro-1*H*-pyrroles **7** can be rationalized via an initial addition of methoxide across the imino bond of the starting material **6** (Scheme 5) and expulsion of bromide resulting in bicyclic aziridine intermediate **9**, which is attacked by methoxide at the less hindered carbon atom to form azafulvene **12** after dehydrofluorination and elimination of methanol. An alternative mechanistic explanation is an initial dehydrofluorination of pyrroline **6** followed by substitution of the bromomethyl group by methoxide and elimination of methanol to give compound **12**. Most probably, the resulting reactive azafulvene intermediate **12** is immediately attacked by methoxide giving rise to pyrroles **7**.

SCHEME 6. Synthesis of 5-(3,4-dimethoxybenzyl)-1*H*-pyrrole 15



Finally 3-fluoro-1*H*-pyrrole-5-carbaldehyde **8a** was further derivatized to demonstrate the versatility of this building block in the field of organic and medicinal chemistry (Scheme 6). Direct *N*-alkylation of pyrrole carbaldehyde **8a** with cyclopropylmethyl bromide with use of sodium hydride in dimethylformamide at 60 °C gave *N*-(cyclopropylmethyl)pyrrole carbaldehyde **13** in good yield. Treatment of aldehyde **13** with (3,4-dimethoxyphenyl)lithium (prepared in situ from 4-bromoveratrole with *tert*-butyllithium at −78 °C in THF) resulted in (pyrrol-5-yl)methanol **14**. This unstable carbinol **14** was not purified but directly reduced by using sodium borohydride in trifluoroacetic acid leading to the new fluorinated 5-(3,4-dimethoxybenzyl)pyrrole **15**.

In conclusion, a convenient synthetic route to new fluorinated pyrroles was developed, which are interesting building blocks for the preparation of physiological active compounds in medicinal chemistry and agrochemistry. The common precursors, i.e., 3,3-difluoro-1-pyrrolines **3**, were prepared via electrophilic fluorination of the corresponding 1-pyrrolines by Selectfluor. Reaction of these difluoropyrrolines **3** with sodium alkoxides yielded new fluorinated 5-(alkoxymethyl)pyrroles in good yields. In addition, a new synthesis of new fluorinated pyrrole-5-carbaldehydes via intermediate fluorinated 5-methylene-1-pyrrolines was accomplished.

Experimental Section

Synthesis of 2-Aryl-5-(bromomethyl)-1-pyrrolines 2. Compounds **2a**, **2b**, and **2e** were synthesized according to literature procedures in 38%, 29%, and 28% yield, respectively (lit. yields: **2a**, 51%; **2b**, 56%; **2e**, 63%).[19] New compounds **2c** and **2d** were synthesized analogously.

Difluorination of Pyrrolines 2. In a dry 250 mL flask equipped with a reflux condenser and $CaCl_2$-tube, 4.23 g (17.78 mmol) of 5-(bromomethyl)-2-phenyl-1-pyrroline **2a** was dissolved in 150 mL of dry acetonitrile (dest. from CaH_2). Under stirring at room temperature was added 15.75 g (44.46 mmol, 2.5 equiv) of Selectfluor and 0.5 mL of trifluoroacetic acid. The solution was heated under reflux for 2 days. After cooling, the heterogeneous mixture was filtered over Celite, and the filtrate was poured into 150 mL of aq 0.5 M NaOH followed by extraction with 3 × 100 mL of diethyl ether. The combined organic phases were dried over $MgSO_4$, and after filtration, the solvent was evaporated in vacuo. The crude product (dark brown) was purified by flash chromatography to yield 1.56 g (5.70 mmol) of pure **5-(bromomethyl)-3,3-difluoro-2-phenyl-1-pyrroline 3a**: flash chromatography (hexane/EtOAc 98:2, R_f 0.10). Yield 32%. Mp 57.3 °C. White crystals. ^{1}H NMR ($CDCl_3$) δ 2.34−2.55 (1H, m, CH_aH$_b$CF$_2$), 2.61−2.80 (1H, m, CH$_a$$H_bCF_2$), 3.62 (1H, dd, J = 10.5, 6.6 Hz, CH_aH$_b$Br), 3.75 (1H, dd, J = 10.5, 3.9 Hz, CH$_a$$H_b$Br), 4.50−4.62 (1H, m, CHN), 7.39−7.53 (3H, m, 3 × CH$_{ar}$), 7.99−8.05 (2H, m, 2 × CH$_{ar}$). ^{19}F NMR ($CDCl_3$) δ −91.1 (1F, ddt, J = 269.7, 17.5, 9.2 Hz), −92.0 (1F, ddt, J = 269.7, 17.1, 2.6 Hz). ^{13}C NMR ($CDCl_3$) δ 35.8 (d, J = 2.3 Hz), 38.7 (t, J = 24.8 Hz), 66.4 (t, J = 6.8 Hz), 128.3, 128.7, 128.9, 129.8 (dd, J = 256.1, 253.8 Hz), 131.8, 167.0 (t, J = 26.0 Hz). IR (KBr, cm^{-1}) ν 1626 (C═N). MS (ES+) m/z (%) 274/276 (M + H$^+$, 100). Anal. Calcd for $C_{11}H_{10}BrF_2N$: C, 48.20; H, 3.68; N, 5.11. Found: C, 48.61; H, 4.01; N, 4.62.

Synthesis of 2-(Alkoxymethyl)-1*H*-pyrroles 4 (Method 1). In a flame-dried 10 mL flask, 0.10 g (0.36 mmol) of 5-(bromomethyl)-3,3-difluoro-2-phenyl-1-pyrroline **3a** was dissolved in a mixture of 3 mL of methanol and 3 mL of aq 2 M NaOH. The solution was heated under reflux for 1 h. After cooling, the mixture was poured in 30 mL of water and the aqueous phase was extracted with 3 × 15 mL of diethyl ether. The combined organic phases were dried over $MgSO_4$, and after filtration, the solvent was evaporated in vacuo to yield 0.07 g (0.36 mmol) of pure and crystalline **3-fluoro-5-(methoxymethyl)-2-phenyl-1*H*-pyrrole 4a**. Yield 100%. Mp 115.7 °C. Orange crystals. ^{1}H NMR ($CDCl_3$) δ 3.37 (3H, s, MeO), 4.39 (2H, s, CH$_2$), 6.00 (1H, d, J = 3.0 Hz, CHCF), 7.17−7.23 (1H, m, CH$_{ar}$), 7.35−7.42 (2H, m, 2 × CH$_{ar}$), 7.48−7.53 (2H, m, 2 × CH$_{ar}$), 7.96−8.16 (1H, s (broad), NH). ^{19}F NMR ($CDCl_3$) δ −161.7 (1F, s). ^{13}C NMR ($CDCl_3$) δ 57.4, 67.2, 98.7 (d, J = 16.5 Hz), 115.0 (d, J = 19.6 Hz), 123.8 (d, J = 4.6 Hz), 124.9 (d, J = 5.8 Hz), 125.9, 128.8, 130.4 (d, J = 4.6 Hz), 148.7 (d, J = 244.6 Hz). IR (KBr, cm^{-1}) ν 3228 (NH), 1609. MS (ES−) m/z (%) 204 (M − H$^+$, 100). Anal. Calcd for $C_{12}H_{12}FNO$: C, 70.23; H, 5.89; N, 6.82. Found: C, 70.29; H, 5.72; N, 6.73.

Synthesis of 1*H*-Pyrrole-5-carbaldehydes 8. In a dry 50 mL flask containing 25 mL of 2 M sodium methoxide in methanol (50 mmol; freshly prepared from Na and MeOH) was added 0.33 g (1.09 mmol) of 5-(bromomethyl)-3,3-difluoro-5-methoxy-2-phenyl-1-pyrroline **6a** (for the synthesis of compounds **6** refer to the Supporting Information). The solution was stirred at room temperature for 4 h and subsequently poured in 25 mL of water and extracted with 3 × 30 mL of dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo to yield 0.19 g (0.81 mmol) of **5-(dimethoxymethyl)-3-fluoro-2-phenyl-1*H*-pyrrole 7a**. Yield 74%. Red oil. ^{1}H NMR ($CDCl_3$) δ 3.34 (6H, s, 2 × MeO), 5.46 (1H, s, CH(OMe)$_2$), 6.06 (1H, d, J = 2.8 Hz, CHCF), 7.16−7.25 (1H, m, CH$_{ar}$), 7.34−7.41 (2H, m, 2 × CH$_{ar}$), 7.49−7.55 (2H, m, 2 × CH$_{ar}$), 8.20−8.43 (1H, s (broad), NH). ^{19}F NMR ($CDCl_3$) δ −160.9 (1F, s). ^{13}C NMR ($CDCl_3$) δ 52.5, 97.4 (d, J = 17.3 Hz), 98.1 (d, J = 2.3 Hz), 114.2 (d, J = 19.6 Hz), 123.9 (d, J = 4.6 Hz), 125.2 (d, J = 5.8 Hz), 126.0, 128.9, 130.4 (d, J = 3.5 Hz), 149.1 (d, J = 244.6 Hz). IR (NaCl, cm^{-1}) ν 3280 (NH), 1614. MS (ES−) m/z (%) 188 (M − Me − OMe − H$^+$, 100).

3-Fluoro-2-phenyl-1*H*-pyrrole-5-carbaldehyde 8a. During chromatography (hexane/EtOAc 9:1, R_f 0.17), 5-(dimethoxymethyl)-1*H*-pyrrole **7a** was converted to 1*H*-pyrrole-5-carbaldehyde **8a**. Yield 42%. Mp 157.6 °C. Pink crystals. ^{1}H NMR ($CDCl_3$) δ 6.74 (1H, d, J = 0.6 Hz, CHCF), 7.32−7.39 (1H, m, CH$_{ar}$), 7.41−7.49 (2H, m, 2 × CH$_{ar}$), 7.70−7.76 (2H, m, 2 × CH$_{ar}$), 9.44 (1H, s, CHO). ^{19}F NMR ($CDCl_3$) δ −157.4 (1F, s). ^{13}C NMR ($CDCl_3$) δ 107.9 (d, J = 16.2 Hz), 124.3 (d, J = 18.5 Hz), 125.6 (d, J = 4.6 Hz), 127.0 (d, J = 4.6 Hz), 128.4 (d, J = 4.6 Hz), 128.6, 129.1, 149.5 (d, J = 249.2 Hz), 178.8 (d, J = 3.5 Hz). IR (KBr, cm^{-1}) ν 3117 (NH), 1638 (C═O). MS (ES+) m/z (%) 190 (M + H$^+$, 100). Anal. Calcd for $C_{11}H_8FNO$: C, 69.83; H, 4.26; N, 7.40. Found: C, 69.68; H, 4.33; N, 7.44.

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Supporting Information Available: General experimental methods and ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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