Organic Process Research & Development

Article

pubs.acs.org/OPRD

A New Synthesis and Process Development of Bis(fluoroalkyl)pyrazoles As Novel Agrophores

Florence Giornal,[†] Grégory Landelle,[†] Norbert Lui,[‡] Jean-Pierre Vors,[§] Sergiy Pazenok,[‡] and Frédéric R. Leroux*,[†]

[†]CNRS-Université de Strasbourg, UMR 7509, SynCat, 25 Rue Becquerel, 67087 Strasbourg Cedex 02, France

[‡]Bayer CropScience AG, Alfred-Nobel-Strasse 50, 40789 Monheim, Germany

[§]Bayer S.A.S, 14 Impasse Pierre Baizet, BP99163, 69263 Lyon Cedex 09, France

Supporting Information

ABSTRACT: The synthesis of 3,5-bis(fluoroalkyl)-pyrazoles as novel agrophores is described. Commercially available fluoroacetoacetates are treated with BF_3-activated TFEDMA affording in a straightforward one-pot sequence pyrazole carboxylates in good yields and with excellent regioselectivity. The carboxylate intermediates have been converted into the corresponding pyrazolic acids and submitted to decarboxylation, affording valuable building blocks for the design of novel bioactive ingredients. The found process is suitable for scale up and preparation of compounds in kilogram quantity.

INTRODUCTION

Fluorine introduction into lead structures allows optimizing the physicochemical and biological properties of agricultural products.[1] A significant increase of the number of fluorinated active ingredients has been observed over the last decades,[2] and a recent survey estimated that as many as 18% of the pesticides on the market were fluorinated compounds.[3] Among the vast array of fluorine-containing functionalities the synthesis of fluoroalkyl pyrazoles has attracted considerable interest during the last decades.[4] Indeed, their potential enhanced biological properties make them very attractive for the preparation of pharmaceutical and agrochemical ingredients. In particular, 3,5-bis(haloalkyl)pyrazole derivatives,[5] polyfluoroalkyl pyrazolyl carboxylic acid derivatives and 3,5-bis(fluoroalkyl)pyrazoles are important building blocks for the preparation of crop protection chemicals.[6]

Nevertheless, the preparation of pyrazoles bearing two fluorinated groups remains scarcely depicted in the literature.[5n,7]

Pyrazole carboxylic acid derivatives are typically prepared by reacting acrylic acid derivatives having two leaving groups with hydrazines.[8] In turn, 2,2-dihaloacyl-3-aminoacrylic esters can be obtained by reacting acid halides with dialkylaminoacrylic esters.[9] 3-Dihalomethylpyrazole-4-carboxylic acid derivatives are obtained when α,α-difluoroamines are reacted in the presence of Lewis acids with acrylic acid derivatives and subsequent reaction with alkyl hydrazines.[10]

3,5-Bis(fluoroalkyl)pyrazoles are prepared by reacting bisperfluoroalkyl diketones (e.g., 1,1,1,5,5,5-hexafluoroacetylacetone) with hydrazines, the yields being only 27−40%.[7a] The synthesis, isolation and purification of the polyfluoroalkyl diketones are very complex since the compounds are generally very volatile and highly toxic.

Another access towards 3,5-bis(fluoroalkyl)pyrazoles might be based on the decarboxylation reactions of 4-pyrazole carboxylic acids. However, this kind of reaction in the presence of one haloalkyl substituent has only poorly been developed: only two references can be found in the literature. Indeed, the resulting products are generally very volatile, thus very difficult to isolate. 5-Methyl-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid was transformed into 5-methyl-1-phenyl-3-trifluoromethyl pyrazole by reaction with copper powder in quinoline,[11] but the yield merely reached 32%. Maggio et al. described the decarboxylation of 5-amino-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid by heating it neat at its melting point for 1 h with a low yield of 30%.[12] No method was reported for the decarboxylation of a 4-pyrazole carboxylic acids bearing more than one haloalkyl substituent. Guillou et al. describe a copper-catalyzed protodecarboxylation on pyrazoles using Cu_2O in the presence of 1,10-phenanthroline and cesium carbonate.[13] The reaction is carried out in DMF and under harsh conditions (microwave irradiation for 2 h at 200 °C). Metal-catalyzed protodecarboxylation reactions are described by Goossen et al. using copper and silver catalysts.[14] These reactions have been performed on aromatic and heteroaromatic carboxylic acids; however, no substrates having bis(haloalkyl)-substituents have been reported as they could significantly influence the reaction in a negative way.

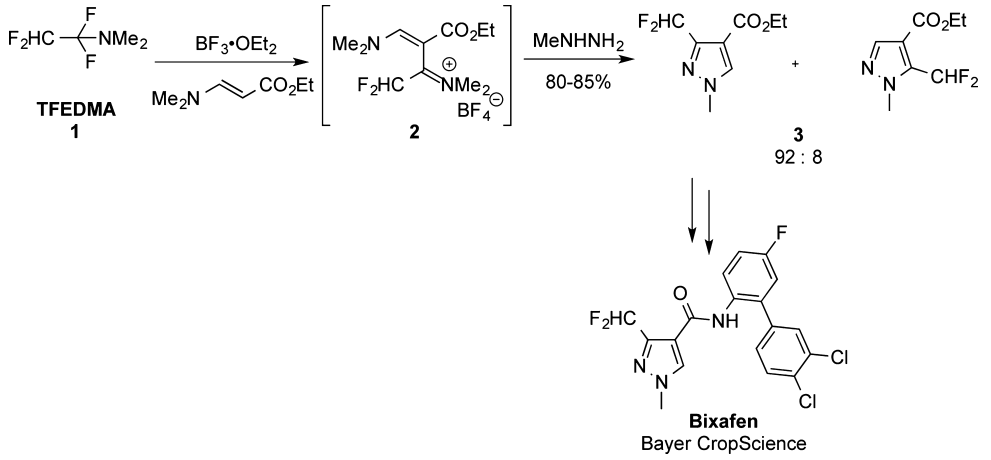
Herein we report a scalable and operationally convenient method that does not have the aforementioned disadvantages and hence provides a route for the regioselective preparation of 3,5-bis(fluoroalkyl)pyrazoles. Starting from commercially available fluoroacetoacetates and by using TFEDMA as a convenient $(CF_2H)C$-transfer reagent, a straightforward one-pot sequence affords highly substituted pyrazoles in good yields and excellent regioselectivity (>97:3). Furthermore, these carboxylate intermediates have been converted into the

Special Issue: Fluorine Chemistry 14

Received: March 24, 2014

   dx.doi.org/10.1021/op500102h | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

Scheme 1. Utilization of FAR for the synthesis of a key intermediate (3) of Bixafen



corresponding pyrazolic acids, valuable building blocks for the design of novel bioactive ingredients.

RESULTS AND DISCUSSION

Synthesis of Bis(perfluoroalkyl)pyrazole Carboxylates. α,α-Fluoroalkyl amino reagents (FAR) have been so far employed for the selective fluorination of alcohols and activated carbonyls.[15] Tetrafluoroethyl dimethylamine (TFEDMA, **1**), prepared at low cost from tetrafluoroethylene and thus a reagent of choice for industrial applications, reacts as a difluoroacetyl-transfer reagent after activation with a Lewis acid.[16] Some of us showed its use in the preparation of difluoromethyl pyrazoles. Activation with BF_3−OEt_2 followed by reaction with dimethylamino acrylate afforded the intermediate **2** which undergoes cyclization with methyl hydrazine towards mono(fluoroalkyl)pyrazole **3** in a 92:8 regioselectivity (Scheme 1).[10]

During the present process research and development study, TFEDMA (**1**) was activated with one equivalent of $BF_3(OEt_2)$ in dichloromethane or acetonitrile at 20 °C affording an intermediate iminium salt **A**, which has been submitted to the reaction with various β-keto esters. When ethyl trifluoroacetoacetate was added in the presence of pyridine as organic base, the desired 3-(difluoromethyl)-5-(trifluoromethyl)pyrazole **4a** was obtained in a fair 63% yield. In contrast, inorganic bases such as Cs_2CO_3 and KF led to no reaction or very poor yields. The addition of azaphilic Lewis acids like iron(III), titanium(IV) and copper(II) chlorides, ytterbium(III) and copper(II) triflates showed no beneficial influence on the outcome of the reaction.

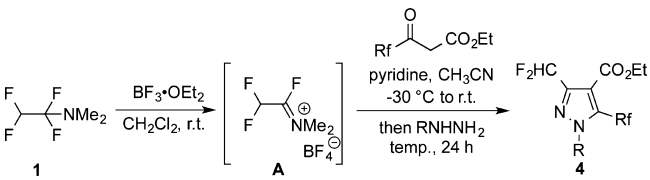
Various commercially available ethyl difluoro-, trifluoro- and pentafluoroethyl acetoacetates, as well as ethyl chlorodifluoroacetoacetate, synthesized by Claisen condensation,[17] were submitted to the reaction with activated TFEDMA and cyclized with different hydrazines (Table 1).[18]

Moderate to good yields were obtained for 3,5-bis(fluoroalkyl)pyrazoles **4a**−**o** depending on the fluoroalkyl group at the β-keto ester and the hydrazine. Ethyl trifluoroacetoacetate led to yields ranging between 53% and 75%. In all cases 3,5-bis(fluoroalkyl)pyrazoles **4** were formed as single regioisomers.

Saponification of Bis(perfluoroalkyl)pyrazole Carboxylates. The saponification of the ester group in these products would allow access to attractive difluoromethyl pyrazolecarboxamides. Thus, the carboxyesters **4** were reacted with aqueous sodium hydroxide in ethanol at 20 °C. These conditions provided the desired carboxylic acids in very high yields (Table 2). All saponification yields were almost quantitative, and all the obtained products are crystalline and did not need any further purification, which makes this method very practical and adaptable to scale-up.

In spite of numerous efforts, the saponification of the free *N*-H pyrazoles (**4b**, **4f**, **4j**, **4n**) did not occur, and in every case the starting material was completely recovered. Therefore, *tert*-butyl pyrazoles were employed as an access towards the desired free NH-derivatives, since the *N*-*t*Bu group can be readily deprotected under strong acidic conditions. Developing an access to 3,5-difluoroalkyl pyrazoles having a free nitrogen atom is a very important aspect as this provides further options for functionalisation of the pyrazole nitrogen on demand.

Table 1. Reaction of activated TFEDMA with β-keto esters and hydrazines

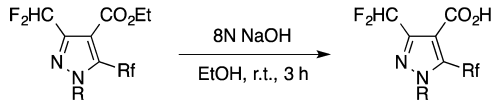


entry	Rf	R	cmpd	yield (%)[a]
1	CF_3	CH_3	**4a**	73
2		H	**4b**[b]	75
3		Ph	**4c**	67
4		*t*Bu	**4d**[c]	53
5	CF_2H	CH_3	**4e**	69
6		H	**4f**[b]	56
7		Ph	**4g**	43
8		*t*Bu	**4h**[c]	30
9	C_2F_5	CH_3	**4i**	75
10		H	**4j**[b]	67
11		Ph	**4k**	85
12		*t*Bu	**4l**[c]	33
13	CF_2Cl	CH_3	**4m**	72
14		H	**4n**[b]	72
15		Ph	**4o**	53

[a]Isolated yield. [b]Hydrazine hydrate was used for the cyclocondensation step. [c]*t*BuNHNH$_2$·HCl was used for the cyclocondensation step.

dx.doi.org/10.1021/op500102h | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 2. Saponification of 3,5-bis(fluoroalkyl)pyrazoles 4



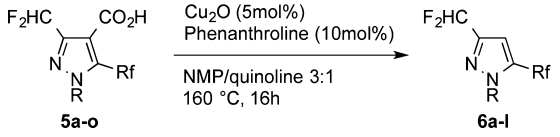
entry	Rf	R	cmpd	yield (%)[a]
1	CF_3	CH_3	**5a**	98
2		Ph	**5c**	94
3		*t*Bu	**5d**	94
4	CF_2H	CH_3	**5e**	97
5		Ph	**5g**	98
6		*t*Bu	**5h**	97
7	C_2F_5	CH_3	**5i**	97
8		Ph	**5k**	98
9		*t*Bu	**5l**	99
10	CF_2Cl	CH_3	**5m**	80
11		Ph	**5o**	99

[a]Isolated yield.

Decarboxylation of Bis(perfluoroalkyl)pyrazole Carboxylic Acids. The obtention of the free 4-position could lead to worthwhile synthons functionalizable by means of halogenation reactions[19] or organometallic reagents.[20] However, the decarboxylation of these compounds, expected to occur readily due to the presence of two electron-withdrawing groups in the pyrazole moiety, revealed being a challenging task. After numerous unsuccessful attempts employing classical methods such as heating to its melting point, Krapcho conditions and use of transition metals, the decarboxylation was performed with a copper(I) oxide/phenanthroline catalytic system in NMP/quinoline (3:1) as solvent, as recently reported by Goossen et al.[21] The pyrazolic acids were stirred in this solvent mixture with 5 mol % of Cu_2O and 10 mol % of phenanthroline at 160 °C for 14 h. The above approach finally offers an efficient way to obtain the desired products in moderate to good yields (Table 3).[22]

Product **5l** was deprotected during decarboxylation, but the other free *N*-H-pyrazoles can be obtained by deprotection of the *tert*-butyl derivative, as exemplified for **6d**. Heating to reflux in TFA for 14 h in the presence of anisole afforded the desired compound **7a** (Scheme 2).

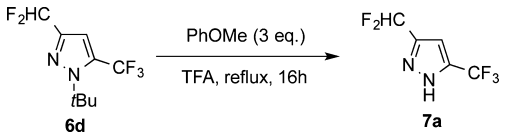
Table 3. Decarboxylation of 3,5-bis(fluoroalkyl)pyrazoles 5



entry	Rf	R	cmpd	yield (%)[a]
1	CF_3	CH_3	**6a**	50
2		Ph	**6c**	84
3		*t*Bu	**6d**	83
4	CF_2H	CH_3	**6e**	78
5		Ph	**6g**	87
6		*t*Bu	**6h**	64
7	C_2F_5	CH_3	**6i**	63
8		Ph	**6k**	88
9		*t*Bu	**6l**	46[b]

[a]Isolated yield. [b]Yield for the isolated *N*-H pyrazole.

Scheme 2. Access to *N*-H pyrazoles



CONCLUSION

We developed and optimized a scalable route for the synthesis of unsymmetrical 3,5-bis(fluoroalkyl)-pyrazoles. Our process utilizes commercially available β-keto esters and hydrazines using TFEDMA as a $(CF_2H)C$ transfer reagent. Experiments have been done even in 100 g quantity without any scale up problems related to exothermicity or stirring problems. This robust and operationally convenient process is therefore suitable for scalability. An important class of pyrazole-carboxamides after optimized saponification conditions starting from pyrazolic acids becomes accessible. The decarboxylation leads then to 4-unsubstituted and thus functionalizable pyrazole scaffolds as promising agrophores.

EXPERIMENTAL SECTION

General. All air- and moisture-sensitive manipulations were conducted under inert gas atmosphere. All substrates, reagents, and solvents were used from suppliers without further purification. In some samples, all the solvent could not be removed due to volatility issues. In those cases, yields have been calculated according to NMR ratios.

General Procedure for the Preparation of Pyrazole Carboxylates 4a–o. $BF_3(OEt_2)$ (0.1 mol, 1 equiv) was added to a solution of TFEDMA (0.1 mol, 1 equiv) in dry CH_2Cl_2 (100 mL) under argon in a Teflon flask. The solution was stirred for 15 min at 20 °C, and CH_2Cl_2 was removed under reduced pressure. The solid was taken up in dry CH_3CN (150 mL). In another Teflon flask, the fluoroacetoacetate (0.1 mmol, 1 equiv) was added to a solution of pyridine (0,3 mol, 3 equiv) in dry CH_3CN (100 mL) and stirred at 20 °C for 15 min. At −30 °C, the content of the first flask was added dropwise, and the reaction mixture was stirred at −30 °C for 2 h and allowed to reach 20 °C over 14 h. The desired hydrazine (0.15 mol, 1.5 equiv) was added dropwise at 20 °C, and the reaction mixture was stirred for 12 h at 30 °C. The solution was concentrated under reduced pressure and taken up in methyl *tert*-butylether (200 mL). The organic phase was washed with HCl 1 M (3 × 50 mL) and brine (50 mL), dried over sodium sulfate, and evaporated at atmospheric pressure. The crude material was purified by crystallization from a toluene/methylcyclohexane mixture or by column chromatography (pentane/Et_2O mixture) on silica gel to afford the expected 3,5-bis-(fluoroalkyl)pyrazole carboxylate.

*Ethyl 1-Methyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylate (**4a**).* Yellow oil; 73%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.00 (t, $^2J_{H-F}$ = 54 Hz, 1H, CHF_2), 4.37 (q, J = 7.2 Hz, 2H, CH_2), 4.12 (s, 3H, N−CH_3), 1.37 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.2 (CO), 145.7 (t, $^2J_{C-F}$ = 25.6 Hz, C_{IV}arom), 133.2 (q, $^2J_{C-F}$ = 40.3 Hz, C_{IV}arom), 119.0 (q, J_{C-F} = 271.2 Hz, CF_3), 114.4 (C_{IV}arom), 109.0 (t, J_{C-F} = 237.9 Hz, CHF_2), 61.9 (CH_2), 40.8 (q, $^4J_{C-F}$ = 3.2 Hz, N−CH_3), 13.8 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −57.6 (CF_3), −116.4 (CHF_2) ; elemental analysis: calcd (%) C 39.72, H 3.33, N 10.29; found C 39.03, H 3.33, N 10.26.

dx.doi.org/10.1021/op500102h | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

*Ethyl 3-Difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylate (**4b**).* Colorless solid; 75%; mp 63−64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.07 (br s, 1H, NH), 7.22 (t, J_{H-F} = 53.5 Hz, 1H, CHF_2), 4.39 (q, J = 6.9 Hz, 2H, CH_2), 1.38 (t, J = 6.9 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.4 (CO), 142.2 (t, $^2J_{C-F}$ = 18.3 Hz, C_{IV}arom), 142.2 (q, $^2J_{C-F}$ = 32.0 Hz, C_{IV}arom), 119.7 (q, J_{C-F} = 268.1 Hz, CF_3), 111.7 (C_{IV}arom), 107.4 (t, J_{C-F} = 237.5 Hz, CHF_2), 62.0 (CH_2), 13.7 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −62.5 (CF_3), −117.1 (d, J_{F-H} = 53.5 Hz, CHF_2) ; elemental analysis: calcd (%) C 37.22, H 2.73, N 10.85; found C 37.27, H 2.91, N 10.61.

*Ethyl 1-Phenyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylate (**4c**).* Colorless solid; 67%; mp 58−59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.55−7.42 (m, 5H, N-Ph), 7.05 (t, J_{H-F} = 53.7 Hz, 1H, CHF_2), 4.42 (q, J = 7.1 Hz, 2H, CH_2), 1.40 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.3 (CO), 146.7 (t, $^2J_{C-F}$ = 26.2 Hz, C_{IV}arom), 138.8 (N−C_{IV} Phenyl), 133.8 (q, $^2J_{C-F}$ = 40.1 Hz, C_{IV}arom), 130.4 (CH Phenyl), 129.3 (CH Phenyl), 125.9 (CH Phenyl), 118.6 (q, J_{C-F} = 271.9 Hz, CF_3), 115.0 (C_{IV}arom), 109.2 (t, J_{C-F} = 238.4 Hz, CHF_2), 62.0 (CH_2), 13.8 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −56.8 (CF_3), −117.3 (CHF_2) ; elemental analysis: calcd (%) C 50.31, H 3.32, N 8.38; found C 50.34, H 3.40, N 8.51.

*Ethyl 1-tert-Butyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylate (**4d**).* Yellow oil; 53%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.80 (t, J_{H-F} = 54.0 Hz, 1H, CHF_2), 4.37 (q, J = 7.1 Hz, 2H, CH_2), 1.70 (s, 9H, *t*Bu), 1.36 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.5 (CO), 141.9 (t, $^2J_{C-F}$ = 27.8 Hz, C_{IV}arom), 131.5 (q, $^2J_{C-F}$ = 40.6 Hz, C_{IV}arom), 119.3 (q, J_{C-F} = 270.7 Hz, CF_3), 116.9 (C_{IV}arom), 109.9 (t, J_{C-F} = 236.7 Hz, CHF_2), 66.0 (N−C_{IV} *t*Bu), 62.0 (CH_2), 29.9 (q, $^5J_{C-F}$ = 2.4 Hz, *t*Bu CH_3), 13.8 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −53.3 (CF_3), −114.4 (d, J_{F-H} = 54.0 Hz, CHF_2) ; HRMS (ESI positive) for $C_{12}H_{15}F_5N_2NaO_2$ [M + Na]: calcd 337.095; found 337.097.

*Ethyl 1-Methyl-3,5-bis(difluoromethyl)-1H-pyrazole-4-carboxylate (**4e**).* Colorless solid; 69%; mp 53−54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.48 (t, J_{H-F} = 52.6 Hz, 1H, CHF_2), 7.04 (t, J_{H-F} = 53.8 Hz, 1H, CHF_2), 4.38 (q, J = 7.1 Hz, 2H, CH_2), 4.12 (s, 3H, N−CH_3), 1.39 (t, J = 7.2 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.1 (CO), 145.3 (t, $^2J_{C-F}$ = 24.9 Hz, C_{IV}arom), 138.2 (t, $^2J_{C-F}$ = 24.1 Hz, C_{IV}arom), 112.9 (m, C_{IV}arom), 109.1 (t, J_{C-F} = 237.6 Hz, CHF_2), 107.2 (t, J_{C-F} = 236.3 Hz, CHF_2), 61.5 (CH_2), 39.6 (t, $^4J_{C-F}$ = 3.1 Hz, N−CH_3), 13.9 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −117.00 (d, J_{F-H} = 53.8 Hz, CHF_2), −117.04 (d, J_{F-H} = 52.6 Hz, CHF_2) ; elemental analysis: calcd (%) C 42.53, H 3.97, N 11.02; found C 42.50, H 4.05, N 11.18.

*Ethyl 3,5-Bis(difluoromethyl)-1H-pyrazole-4-carboxylate (**4f**).* Colorless solid; 56%; mp 88−89 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.15 (t, J_{H-F} = 53.6 Hz, 2H, CHF_2), 4.39 (q, J = 7.1 Hz, 2H, CH_2), 1.39 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.1 (CO), 143.8 (t, $^2J_{C-F}$ = 23.1 Hz, C_{IV}arom), 111.6 (C_{IV}arom), 108.2 (t, J_{C-F} = 238.4 Hz, CHF_2), 61.7 (CH_2), 13.9 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −117.3 (d, J_{F-H} = 53.6 Hz, CHF_2) ; HRMS (ESI positive) for $C_8H_8F_4N_2NaO_2$ [M + Na]: calcd 263.041; found 263.043.

*Ethyl 1-Phenyl-3,5-bis(difluoromethyl)-1H-pyrazole-4-carboxylate (**4g**).* Colorless solid; 43%; mp 54−55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.57−7.51 (m, 5H, N-Ph), 7.44 (t, J_{H-F} = 52.5 Hz, 1H, CHF_2), 7.13 (t, J_{H-F} = 53.7 Hz, 1H, CHF_2), 4.43 (q, J = 7.1 Hz, 2H, CH_2), 1.43 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.2 (CO), 146.6 (t, $^2J_{C-F}$ = 25.3 Hz, C_{IV}arom), 139.0 (N−C_{IV} Phenyl), 138.9 (t, $^2J_{C-F}$ = 24.8 Hz, C_{IV}arom), 130.1 (CH Phenyl), 129.1 (CH Phenyl), 125.9 (CH Phenyl), 113.8 (C_{IV}arom), 109.4 (t, J_{C-F} = 238.2 Hz, CF_2H), 106.9 (t, J_{C-F} = 238.4 Hz, CHF_2), 61.8 (CH_2), 14.0 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −114.3 (d, J_{F-H} = 52.5 Hz, CHF_2), −117.7 (d, J_{F-H} = 53.7 Hz, CHF_2) ; HRMS (ESI positive) for $C_{14}H_{12}F_4N_2NaO_2$ [M + Na]: calcd339.073; found 339.075.

*Ethyl 1-tert-Butyl-3,5-bis(difluoromethyl)-1H-pyrazole-4-carboxylate (**4h**).* Orange oil; 30%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.71 (t, J_{H-F} = 52.9 Hz, 1H, CHF_2), 6.97 (t, J_{H-F} = 54.0 Hz, 1H, CHF_2), 4.37 (q, J = 7.1 Hz, 2H, CH_2), 1.71 (s, 9H, *t*Bu), 1.39 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.9 (CO), 143.4 (t, $^2J_{C-F}$ = 25.5 Hz, C_{IV}arom), 137.9 (t, $^2J_{C-F}$ = 24.8 Hz, C_{IV}arom), 114.5 (C_{IV}arom), 109.9 (t, J_{C-F} = 237.3 Hz, CHF_2), 106.8 (t, J_{C-F} = 238.3 Hz, CHF_2), 65.3 (N−C_{IV} *t*Bu), 61.5 (CH_2), 30.0 (t, $^5J_{C-F}$ = 3.4 Hz, *t*Bu CH_3), 14.0 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −111.5 (CHF_2), −116.0 (CHF_2) ; HRMS (ESI positive) for $C_{12}H_{16}F_4N_2NaO_2$ [M + Na]: calcd 319.104; found 319.104.

*Ethyl 1-Methyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylate (**4i**).* Colorless oil; 75%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.00 (t, $^2J_{H-F}$ = 53.9 Hz, 1H, CHF_2), 4.35 (q, J = 7.1 Hz, 2H, CH_2), 4.10 (t, $^5J_{H-F}$ = 2.2 Hz, 3H, N−CH_3), 1.35 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.2 (CO), 146.1 (t, $^2J_{C-F}$ = 25.6 Hz, C_{IV}arom), 131.1 (t, $^2J_{C-F}$ = 29.6 Hz, C_{IV}arom), 118.6 (qt, $^1J_{C-F}$ = 287.1 Hz, $^2J_{C-F}$ = 37.7 Hz, $CF_2\underline{CF_3}$), 116.3 (C_{IV}arom), 109.98 (tq, $^1J_{C-F}$ = 192.0 Hz, $^2J_{C-F}$ = 41.7 Hz, $\underline{CF_2}CF_3$), 109.1 (t, J_{C-F} = 238.1 Hz, CHF_2), 61.9 (CH_2), 41.0 (t, $^4J_{C-F}$ = 4.3 Hz, N−CH_3), 13.8 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −83.7 ($CF_2\underline{CF_3}$), −109.5 ($\underline{CF_2}CF_3$), −116.8 (d, J_{F-H} = 53.9 Hz, CHF_2) ; HRMS (ESI positive) for $C_{10}H_9F_7N_2NaO_2$ [M + Na]: calcd345.044; found 345.046.

*Ethyl 3-Difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylate (**4j**).* Colorless oil; 67%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.69 (br s, 1H, N−H), 7.26 (t, J_{H-F} = 53.5 Hz, 1H, CHF_2), 4.40 (q, J = 7.1 Hz, 2H, CH_2), 1.39 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.6 (CO), 141.8 (t, $^2J_{C-F}$ = 25.9 Hz, C_{IV}arom), 141.1 (t, $^2J_{C-F}$ = 31.7 Hz, C_{IV}arom), 118.7 (qt, $^1J_{C-F}$ = 286.6 Hz, $^2J_{C-F}$ = 36.3 Hz, $CF_2\underline{CF_3}$), 113.2 (C_{IV}arom), 110.1 (tq, $^1J_{C-F}$ = 252.9 Hz, $^2J_{C-F}$ = 39.5 Hz, $\underline{CF_2}CF_3$), 107.5 (t, J_{C-F} = 238.8 Hz, CHF_2), 62.0 (CH_2), 13.6 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −83.2 ($CF_2\underline{CF_3}$), −110.1 ($\underline{CF_2}CF_3$), −117.2 (d, J_{F-H} = 53.5 Hz, CHF_2) ; HRMS (ESI positive) for $C_9H_7F_7N_2NaO_2$ [M + Na]: calcd 331.029; found 331.031.

*Ethyl 1-Phenyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylate (**4k**).* Beige solid; 85%; mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.58−7.35 (m, 5H, N-Ph), 7.04 (t, J_{H-F} = 53.8 Hz, 1H, CHF_2), 4.40 (q, J = 7.1 Hz, 2H, CH_2), 1.38 (t, J = 7.2 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8 (CO), 147.6 (t, $^2J_{C-F}$ = 25.8 Hz, C_{IV}arom), 138.7 (N−C_{IV} Phenyl), 135.1 (q, $^2J_{C-F}$ = 40.4 Hz, C_{IV}arom), 130.6 (CH Phenyl), 129.4 (CH Phenyl), 125.9 (CH Phenyl), 118.4 (qt, $^1J_{C-F}$ = 287.5 Hz, $^2J_{C-F}$ = 37.5

dx.doi.org/10.1021/op500102h | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

Hz, $CF_2\underline{CF_3}$), 116.4 (C_{IV}arom), 109.6 (tq, $^1J_{C-F}$ = 255.3 Hz, $^2J_{C-F}$ = 41.6 Hz, $\underline{CF_2}CF_3$), 109.4 (t, J_{C-F} = 238.6 Hz, CHF_2), 62.1 (CH_2), 13.7 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −83.6 ($CF_2\underline{CF_3}$), −107.1 ($\underline{CF_2}CF_3$), −117.3 (CHF_2) ; elemental analysis: calcd (%) C 46.88, H 2.88, N 7.29; found (%) C 46.84, H 3.00, N 7.11.

*Ethyl 1-tert-Butyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylate (**4l**).* Colorless oil; 33%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.83 (t, J_{H-F} = 54.1 Hz, 1H, CHF_2), 4.35 (q, J = 7.1 Hz, 2H, CH_2), 1.69 (s, 9H, *t*Bu), 1.34 (t, J = 7.2 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 161.2 (CO), 142.8 (t, $^2J_{C-F}$ = 27.3 Hz, C_{IV}arom), 130.0 (q, $^2J_{C-F}$ = 31.0 Hz, C_{IV}arom), 118.6 (qt, $^1J_{C-F}$ = 287.8 Hz, $^2J_{C-F}$ = 38.3 Hz, $CF_2\underline{CF_3}$), 118.5 (C_{IV}arom), 110.8 (tq, $^1J_{C-F}$ = 258.1 Hz, $^2J_{C-F}$ = 41.0 Hz, $\underline{CF_2}CF_3$), 110.0 (t, J_{C-F} = 237.2 Hz, CHF_2), 67.6 (N−C_{IV} *t*Bu), 62.0 (CH_2), 30.5 (t, $^5J_{C-F}$ = 3.6 Hz, CH_3 *t*Bu), 13.7 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −80.7 ($CF_2\underline{CF_3}$), −100.8 ($\underline{CF_2}CF_3$), −115.5 (d, J_{F-H} = 54.1 Hz, CHF_2) ; HRMS (ESI positive) for $C_{13}H_{15}F_7N_2NaO_2$ [M + Na]: calcd 387.091; found 387.091.

*Ethyl 1-Methyl-3-difluoromethyl-5-chlorodifluoromethyl-1H-pyrazole-4-carboxylate (**4m**).* Colorless oil; 72%; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.97 (t, J_{H-F} = 53.9 Hz, 1H, CHF_2), 4.37 (q, J = 7.1 Hz, 2H, CH_2), 4.10 (t, $^5J_{H-F}$ = 2.2 Hz, 3H, N−CH_3), 1.38 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.3 (CO), 145.3 (t, $^2J_{C-F}$ = 25.7 Hz, C_{IV}arom), 137.5 (t, $^2J_{C-F}$ = 33.3 Hz, C_{IV}arom), 119.9 (t, J_{C-F} = 288.8 Hz, CF_2Cl), 112.7 (C_{IV}arom), 109.1 (t, J_{C-F} = 237.8 Hz, CHF_2), 61.8 (CH_2), 40.6 (t, $^4J_{C-F}$ = 4.6 Hz, N−CH_3), 13.7 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −47.9 (CF_2Cl), −116.7 (d, J_{F-H} = 53.9 Hz, CHF_2) ; HRMS (ESI positive) for $C_9H_9ClF_4N_2NaO_2$ [M + Na]: calcd 311.018; found 311.018.

*Ethyl 3-Difluoromethyl-5-chlorodifluoromethyl-1H-pyrazole-4-carboxylate (**4n**).* Colorless solid; 72%; mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.62 (br s, 1H, NH), 7.25 (t, J_{H-F} = 53.5 Hz, 2H, CHF_2), 4.41 (q, J = 7.1 Hz, 2H, CH_2), 1.41 (t, J = 7.1 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.6 (CO), 146.3 (t, $^2J_{C-F}$ = 32.3 Hz, C_{IV}arom), 142.7 (t, $^2J_{C-F}$ = 29.3 Hz, CHF_2), 121.3 (t, J_{C-F} = 287.3 Hz, CF_2Cl), 110.8 (C_{IV}arom), 109.1 (t, J_{C-F} = 240.2 Hz, CHF_2), 62.0 (CH_2), 13.6 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −49.6 (CF_2Cl), −116.8 (d, J_{F-H} = 53.5 Hz, CHF_2) ; elemental analysis: calcd (%) C 35.00, H 2.57, N 10.20; found C 35.22, H 2.67, N 9.95.

*Ethyl 1-Phenyl-3-difluoromethyl-5-chlorodifluoromethyl-1H-pyrazole-4-carboxylate (**4o**).* Colorless solid; 53%; mp 70−71 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.55−7.45 (m, 5H, N-Ph), 7.03 (t, J_{H-F} = 53.7 Hz, 1H, CHF_2), 4.42 (q, J = 7.1 Hz, 2H, CH_2), 1.41 (t, J = 7.2 Hz, 3H, CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 160.5 (CO), 146.5 (t, $^2J_{C-F}$ = 26.3 Hz, C_{IV}arom), 138.9 (N−C_{IV} Phenyl), 138.3 (t, $^2J_{C-F}$ = 32.7 Hz, C_{IV}arom), 130.3 (CH Phenyl), 129.2 (CH Phenyl), 126.2 (CH Phenyl), 119.5 (t, J_{C-F} = 290.0 Hz, CF_2Cl), 115.6 (C_{IV}arom), 109.3 (t, J_{C-F} = 238.4 Hz, CHF_2), 62.0 (CH_2), 13.9 (CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −46.6 (CF_2Cl), −117.3 (CHF_2) ; elemental analysis: calcd (%) C 47.95, H 3.16, N 7.99; found (%) C 47.86, H 3.20, N 7.73.

General Procedure for the Saponification of Pyrazole Carboxylates 4a−o. To a pyrazole-4-carboxylate **4** (1.8 mmol, 1 equiv) in ethanol (3 mL) was slowly added an 8 M aqueous solution of NaOH (0.70 mL, 3 equiv). The reaction mixture was stirred at 20 °C for 3 h until completion of the reaction. The solvents were evaporated, and the crude solid obtained was taken up in water (10 mL). The aqueous layer was extracted with Et_2O (10 mL) and acidified to pH = 1 with 1 M HCl before being extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford pure pyrazole-4-carboxylic acid **5**.

*1-Methyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylic Acid (**5a**).* Yellow solid; 98%; mp 116−117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.08 (t, J_{H-F} = 53.5 Hz, 1H, CHF_2), 4.16 (s, 3H, N−CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.5 (CO), 146.7 (t, $^2J_{C-F}$ = 18.8 Hz, C_{IV}arom), 134.4 (q, $^2J_{C-F}$ = 30.8 Hz, C_{IV}arom), 118.8 (q, J_{C-F} = 202.5 Hz, CF_3), 112.9 (C_{IV}arom), 108.7 (t, J_{C-F} = 177.0 Hz, CHF_2), 41.1 (q, $^4J_{C-F}$ = 2.3 Hz, N−CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −57.9 (CF_3), −117.3 (d, J_{F-H} = 53.5 Hz, CHF_2) ; elemental analysis: calcd (%) C 34.44, H 2.06, N 11.48; found (%) C 34.44, H 2.19, N 11.13.

*1-Phenyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylic Acid (**5c**).* Colorless solid; 94%; mp 154−155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.53 (br s, 1H, COOH), 7.58−7.44 (m, 5H, *N*-Phenyl), 7.15 (t, J_{H-F} = 53.5 Hz, 1H, CHF_2) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8 (CO), 147.6 (t, $^2J_{C-F}$ = 25.8 Hz, C_{IV}arom), 138.7 (N−C_{IV} Phenyl), 135.1 (q, $^2J_{C-F}$ = 40.4 Hz, C_{IV}arom), 130.6 (CH Phenyl), 129.4 (CH Phenyl), 125.9 (CH Phenyl), 118.4 (q, J_{C-F} = 272.3 Hz, CF_3), 114.3 (C_{IV}arom), 108.9 (t, J_{C-F} = 239.0 Hz, CHF_2) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −56.8 (CF_3), −117.8 (CHF_2) ; elemental analysis: calcd (%) C 47.07, H 2.30, N 9.15; found C 47.24, H 2.40, N 8.89.

*1-tert-Butyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole-4-carboxylic Acid (**5d**).* Yellow solid; 94%; mp 126−127 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.92 (t, J_{H-F} = 53.8 Hz, 1H, CHF_2), 1.74 (s, 9H, *t*Bu) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.8 (CO), 142.9 (t, $^2J_{C-F}$ = 26.9 Hz, C_{IV}arom), 132.9 (q, $^2J_{C-F}$ = 41.1 Hz, C_{IV}arom), 119.1 (q, J_{C-F} = 271.1 Hz, CF_3), 115.1 (C_{IV}arom), 109.5 (t, J_{C-F} = 237.5 Hz, CHF_2), 66.7 (N−C_{IV} *t*Bu), 29.9 (q, $^5J_{C-F}$ = 2.5 Hz, CH_3 *t*Bu) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −54.0 (CF_3), −116.0 (CHF_2) ; HRMS (ESI negative) for $C_{10}H_{10}F_5N_2O_2$ [M-H]: calcd 285.066; found 285.067.

*1-Methyl-3,5-bis(difluoromethyl)-1H-pyrazole-4-carboxylic acid (**5e**).* Colorless solid; 97%; mp 131−132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.16 (br s, 1H, COOH), 7.48 (t, J_{H-F} = 52.4 Hz, 1H, CHF_2), 7.08 (t, J_{H-F} = 53.6 Hz, 1H, CHF_2), 4.16 (s, 3H, N−CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.9 (CO), 146.4 (t, $^2J_{C-F}$ = 25.1 Hz, C_{IV}arom), 139.2 (t, $^2J_{C-F}$ = 24.4 Hz, C_{IV}arom), 111.5 (C_{IV}arom), 108.8 (t, J_{C-F} = 238.1 Hz, CHF_2), 106.9 (t, J_{C-F} = 237.0 Hz, CHF_2), 39.9 (t, $^4J_{C-F}$ = 3.1 Hz, N−CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −117.1 (d, J_{F-H} = 52.6 Hz, CHF_2), −117.3 (d, J_{F-H} = 53.7 Hz, CHF_2) ; elemental analysis: calcd (%) C 37.18, H 2.67, N 12.39; found C 37.19, H 2.84, N 12.00.

*1-Phenyl-3,5-bis(difluoromethyl)-1H-pyrazole-4-carboxylic Acid (**5g**).* Colorless solid; 98%; mp 169−170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.59−7.49 (m, 5H, *N*-Phenyl), 7.43 (t, J_{H-F} = 52.3 Hz, 1H, CHF_2), 7.16 (t, J_{H-F} = 53.5 Hz, 1H, CHF_2) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.3 (CO), 147.4 (t, $^2J_{C-F}$ = 25.5 Hz, C_{IV}arom), 139.8 (t, $^2J_{C-F}$ = 24.9 Hz, C_{IV}arom), 138.8 (N−C_{IV} Phenyl), 130.3 (CH Phenyl), 129.2 (CH Phenyl), 125.9 (CH Phenyl), 112.3 (t, $^3J_{C-F}$ = 3.5 Hz, C_{IV}arom), 109.0 (t, J_{C-F} = 238.7 Hz, CHF_2), 106.6 (t, J_{C-F} =

dx.doi.org/10.1021/op500102h | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

239.2 Hz, CHF_2) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −113.4 (CHF_2), −117.0 (CHF_2) ; elemental analysis: calcd (%) C 50.01, H 2.80, N 9.72; found C 50.28, H 3.04, N 9.59.

*1-tert-Butyl-3,5-bis(difluoromethyl)-1H-pyrazole-4-carboxylic Acid (**5h**).* Pink solid; 97%; mp 159−160 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.72 (t, J_{H-F} = 52.7 Hz, 1H, CHF_2), 7.06 (t, J_{H-F} = 53.7 Hz, 1H, CHF_2), 1.75 (s, 9H, *t*Bu) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 167.3 (CO), 144.5 (t, $^2J_{C-F}$ = 25.3 Hz, C_{IV}arom), 138.8 (q, $^2J_{C-F}$ = 25.1 Hz, C_{IV}arom), 113.0 (C_{IV}arom), 109.4 (t, J_{C-F} = 237.7 Hz, CF_2H), 106.5 (t, J_{C-F} = 238.8 Hz, CHF_2), 65.9 (N−C_{IV} *t*Bu), 30.0 (t, $^5J_{C-F}$ = 3.5 Hz, CH_3 *t*Bu) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −112.5 (CHF_2), −117.4 (CHF_2) ; HRMS (ESI negative) for $C_{10}H_{11}F_4N_2O_2$ [M-H]: calcd 267.076; found 267.076.

*1-Methyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylic Acid (**5i**).* Colorless solid; 97%; mp 138−139 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.16 (br s, 1H, COOH), 7.09 (t, J_{H-F} = 53.6 Hz, 1H, CHF_2), 4.15 (t, $^5J_{H-F}$ = 2.4 Hz, 3H, N−CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.2 (CO), 147.2 (t, $^2J_{C-F}$ = 25.2 Hz, C_{IV}arom), 132.5 (t, $^2J_{C-F}$ = 29.8 Hz, C_{IV}arom), 118.5 (qt, $^1J_{C-F}$ = 287.0 Hz, $^2J_{C-F}$ = 37.5 Hz, $CF_2\underline{CF_3}$), 114.6 (C_{IV}arom), 109.9 (tq, $^1J_{C-F}$ = 258.0 Hz, $^2J_{C-F}$ = 41.7 Hz, $\underline{CF_2}CF_3$), 108.8 (t, J_{C-F} = 238.6 Hz, CHF_2), 41.4 (t, $^4J_{C-F}$ = 4.8 Hz, N−CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −83.2 ($CF_2\underline{CF_3}$), −108.9 ($\underline{CF_2}CF_3$), −116.8 (d, J_{F-H} = 53.6 Hz, CHF_2) ; elemental analysis: calcd (%) C 32.67, H 1.71, N 9.52; found C 32.82, H 1.86, N 9.30.

*1-Phenyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylic Acid (**5k**).* Colorless solid; 98%; mp 187−188 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.60−7.37 (m, 5H, *N*-Phenyl), 7.14 (t, J_{H-F} = 53.6 Hz, 1H, CHF_2) ; ^{13}C NMR (CD_3OD, 75 MHz, 25 °C): δ = 164.0 (CO), 148.6 (t, $^2J_{C-F}$ = 25.6 Hz, C_{IV}arom), 141.4 (N−C_{IV} Phenyl), 133.4 (CH Phenyl), 133.1 (t, $^2J_{C-F}$ = 29.1 Hz, C_{IV}arom), 131.7 (CH Phenyl), 130.0 (CH Phenyl), 120.6 (qt, $^1J_{C-F}$ = 287.6 Hz, $^2J_{C-F}$ = 37.9 Hz, $CF_2\underline{CF_3}$), 120.1 (C_{IV}arom), 112.3 (t, J_{C-F} = 236.4 Hz, CHF_2), 112.1 (tq, $^1J_{C-F}$ = 262.5 Hz, $^2J_{C-F}$ = 40.5 Hz, $\underline{CF_2}CF_3$) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −83.5 ($CF_2\underline{CF_3}$), −107.1 ($\underline{CF_2}CF_3$), −117.9 (CHF_2) ; elemental analysis: calcd (%) C 43.84, H 1.98, N 7.86; found C 44.02, H 2.10, N 7.62.

*1-tert-Butyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole-4-carboxylic Acid (**5l**).* Yellow solid; 99%; mp 97−98 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.4 (br s, 1H, COOH), 7.01 (t, J_{H-F} = 53.9 Hz, 1H, CHF_2), 1.78 (s, 9H, *t*Bu) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.5 (CO), 143.9 (t, $^2J_{C-F}$ = 26.3 Hz, C_{IV}arom), 131.5 (q, $^2J_{C-F}$ = 31.0 Hz, C_{IV}arom), 120.0 (qt, $^1J_{C-F}$ = 288.1 Hz, $^2J_{C-F}$ = 38.1 Hz, $CF_2\underline{CF_3}$), 117.4 (C_{IV}arom), 110.6 (tq, $^1J_{C-F}$ = 258.7 Hz, $^2J_{C-F}$ = 41.2 Hz, $\underline{CF_2}CF_3$), 109.5 (t, J_{C-F} = 237.9 Hz, CHF_2), 68.3 (N−C_{IV} *t*Bu), 30.6 (t, $^5J_{C-F}$ = 3.7 Hz, CH_3 *t*Bu) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −80.3 ($CF_2\underline{CF_3}$), −100.4 ($\underline{CF_2}CF_3$), −116.3 (d, J_{F-H} = 53.9 Hz, CHF_2) ; HRMS (ESI negative) for $C_{11}H_{10}F_7N_2O_2$ [M-H]: calcd 335.064; found 335.065.

*1-Methyl-3-difluoromethyl-5-chlorodifluoromethyl-1H-pyrazole-4-carboxylic Acid (**5m**).* Colorless solid; 80%; mp 111−112 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 12.15 (br s, 1H, COOH), 7.07 (t, J_{H-F} = 53.6 Hz, 1H, CHF_2), 4.15 (t, $^5J_{H-F}$ = 2.1 Hz, 3H, N−CH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8 (CO), 146.4 (t, $^2J_{C-F}$ = 25.3 Hz, C_{IV}arom), 138.9 (t, $^2J_{C-F}$ = 33.6 Hz, C_{IV}arom), 119.6 (t, J_{C-F} = 289.4 Hz, CF_2Cl), 111.15 (C_{IV}arom), 108.8 (t, J_{C-F} = 238.4 Hz, CHF_2), 41.0 (t, $^4J_{C-F}$ = 4.9 Hz, N−CH_3) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −48.1 (CF_2Cl), −117.2 (d, J_{F-H} = 53.6 Hz, CHF_2) ; elemental analysis: calcd (%) C 32.27, H 1.93, N 10.75; found C 32.53, H 2.13, N 10.38.

*1-Phenyl-3-difluoromethyl-5-chlorodifluoromethyl-1H-pyrazole-4-carboxylic Acid (**5o**).* Colorless solid; 99%; mp 155−156 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.57−7.47 (m, 5H, *N*-Phenyl), 7.12 (t, J_{H-F} = 53.5 Hz, 1H, CHF_2) ; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.9 (CO), 147.4 (t, $^2J_{C-F}$ = 25.8 Hz, C_{IV}arom), 139.8 (t, $^2J_{C-F}$ = 33.0 Hz, C_{IV}arom), 138.9 (N−C_{IV} Phenyl), 130.5 (CH Phenyl), 129.3 (CH Phenyl), 126.2 (CH Phenyl), 119.2 (t, J_{C-F} = 290.6 Hz, CF_2Cl), 112.1 (C_{IV}arom), 108.9 (t, J_{C-F} = 239.0 Hz, CHF_2) ; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −46.9 (CF_2Cl), −117.8 (CHF_2) ; elemental analysis: calcd (%) C 44.67, H 2.19, N 8.68; found C 44.83, H 2.34, N 8.32.

General Procedure for the Decarboxylation of Pyrazole Carboxylic Acids 5. The carboxylic acid **5** (2.1 g, 8.6 mmol, 1 equiv), Cu_2O (65 mg, 0.45 mmol, 5 mol %), and 1,10-phenanthroline hydrate (176 mg, 0.90 mmol, 10 mol %), NMP (15 mL), quinoline (5 mL), and H_2O (2 drops) were heated at 160 °C for 14 h. The reaction mixture was then diluted with Et_2O (30 mL) and water (30 mL). The organic layer was washed with 1 M HCl (4 × 30 mL) and brine (30 mL), and dried over Na_2SO_4, and the solvent was distilled off through a Vigreux column at atmospheric pressure. The crude material obtained was purified by distillation under reduced pressure.

*1-Methyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole (**6a**).* Colorless liquid (bp = 45−46 °C, 27 mbar); 50%. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.84 (s, 1H, Harom), 6.66 (t, 1H, J_{H-F} = 55 Hz, CHF_2), 4.02 (s, 3H, N−CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 145.6 (t, $^2J_{C-F}$ = 30 Hz, C_{IV}arom), 133.3 (q, $^2J_{C-F}$ = 39.6 Hz, C_{IV}arom), 119.5 (q, J_{C-F} = 267.2 Hz, CF_3), 110.3 (t, J_{C-F} = 233.2 Hz, CHF_2), 105.2 (q, $^3J_{C-F}$ = 2.0 Hz, CHarom), 38.3 (q, $^4J_{C-F}$ = 1.6 Hz, N−CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −61.5 (CF_3), −113.0 (CHF_2) ppm. HRMS (ESI positive) for $C_6H_6F_5N_2$ [M + H]: calcd 201.045 found 201.045.

*1-Methyl-3,5-bis(difluoromethyl)-1H-pyrazole (**6e**).* Colorless liquid (bp = 78−80 °C, 28 mbar); 78%. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.73 (t, 1H, CHF_2, J_{H-F} = 53.4 Hz), 6.69 (s, 1H, Harom), 6.66 (t, 1H, CHF_2, J_{H-F} = 54.9 Hz), 4.01 (s, 3H, N−CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 145.6 (t, C_{IV}arom, $^2J_{C-F}$ = 30.0 Hz), 136.5 (t, C_{IV}arom, $^2J_{C-F}$ = 26.6 Hz), 110.6 (t, CHF_2, J_{C-F} = 234.1 Hz), 108.2 (t, CHF_2, J_{C-F} = 236.5 Hz), 104.7 (m, CHarom), 38.1 (s, N−CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −112.5 (CHF_2, J_{F-H} = 54.9 Hz), −113.7 (d, J_{F-H} = 53.3 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_6H_7F_4N_2$ [M + H]: calcd 183.054 found 183.055.

*1-Methyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole (**6i**).* Colorless liquid (bp = 53−54 °C, 28 mbar); 63%. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.84 (s, 1H, Harom), 6.67 (t, 1H, J_{H-F} = 54.8 Hz, CHF_2), 4.05 (s, 3H, N−CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.0 (t, $^2J_{C-F}$ = 30.1 Hz, C_{IV}arom), 131.2 (t, $^2J_{C-F}$ = 28.9 Hz, C_{IV}arom), 118.5 (qt, $^1J_{C-F}$ = 285.7 Hz, $^2J_{C-F}$ = 37.3 Hz, $CF_2\underline{CF_3}$), 110.2 (t, J_{C-F} = 234.8 Hz, CHF_2), 109.8 (tq, $^1J_{C-F}$ = 252.7 Hz, $^2J_{C-F}$ = 40.6 Hz, $\underline{CF_2}CF_3$), 106.9 (br s, CHarom), 39.2 (br s, N−CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −84.4 ($CF_2\underline{CF_3}$), −111.1

dx.doi.org/10.1021/op500102h | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

($\underline{CF_2}CF_3$), −113.0 (d, J_{F-H} = 54.8 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_7H_6F_7N_2$ [M + H]: calcd 251.042; found 251.042.

*1-Phenyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole (**6c**).* Colorless oil; 84%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.55−7.48 (m, 5H, phenylH), 7.07 (br s, 1H, Hpyrazole), 6.78 (t, 1H, J_{H-F} = 54.6 Hz, CHF_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 146.9 (t, $^2J_{C-F}$ = 30.5 Hz, C_{IV}pyrazole), 138.4 (s, N−C_{IV}phenyl), 134.2 (q, $^2J_{C-F}$ = 40.0 Hz, C_{IV}pyrazole), 130.0 (s, CHphenyl), 129.3 (s, CHphenyl), 125.7 (s, CHphenyl), 119.2 (q, J_{C-F} = 269.4 Hz, CF_3), 110.4 (t, J_{C-F} = 235.1 Hz, CHF_2), 106.4 (br s, CHpyrazole) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −58.4 (CF_3), −112.9 (d, J_{F-H} = 54.6 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_{11}H_8F_5N_2$ [M + H]: calcd 263.061; found 263.060.

*1-Phenyl-3,5-bis(difluoromethyl)-1H-pyrazole (**6g**).* Colorless oil; 87%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.54−7.46 (m, 5H, *N*-Phenyl), 6.97 (s, 1H, CHarom), 6.76 (t, 1H, J_{H-F} = 54.8 Hz, CHF_2), 6.61 (t, 1H, J_{H-F} = 53.4 Hz, CHF_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (t, $^2J_{C-F}$ = 30.2 Hz, C_{IV}arom), 138.2 (N−C_{IV} Phenyl), 137.8 (t, $^2J_{C-F}$ = 30.3 Hz, C_{IV}arom), 129.62 (CH Phenyl), 129.60 (CH Phenyl), 125.1 (CH Phenyl), 110.7 (t, J_{C-F} = 234.8 Hz, CHF_2), 107.9 (t, J_{C-F} = 236.6 Hz, CHF_2), 104.8 (s, CHarom)ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −110.6 (CHF_2), −112.2 (CHF_2) ppm. HRMS (ESI positive) for $C_{11}H_9F_4N_2$ [M + H]: calcd 245.070; found 245.070.

*1-Phenyl-3-difluoromethyl-5-pentafluoroethyl-1H-pyrazole (**6k**).* Colorless oil; 88%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.54−7.43 (m, 5H, phenylH), 7.03 (br s, 1H, Hpyrazole), 6.76 (t, 1H, J_{H-F} = 54.6 Hz, CHF_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 147.4 (t, $^2J_{C-F}$ = 30.4 Hz, C_{IV}pyrazole), 139.1 (s, N−C_{IV}phenyl), 132.4 (t, $^2J_{C-F}$ = 28.1 Hz, C_{IV}pyrazole), 130.2 (s, CHphenyl), 129.1 (s, CHphenyl), 126.7 (s, CHphenyl), 118.5 (qt, $^1J_{C-F}$ = 286.3 Hz, $^2J_{C-F}$ = 36.8 Hz, $CF_2\underline{CF_3}$), 110.4 (t, J_{C-F} = 235.3 Hz, CHF_2), 109.5 (tq, $^1J_{C-F}$ = 252.0 Hz, $^2J_{C-F}$ = 40.4 Hz, $\underline{CF_2}CF_3$), 107.5 (br s, CHpyrazole) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −83.9 ($CF_2\underline{CF_3}$), −107.1 ($\underline{CF_2}CF_3$), −113.0 (d, J_{F-H} = 54.6 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_{12}H_8F_7N_2$ [M + H]: calcd 313.058; found 313.058.

*1-tert-Butyl-3-difluoromethyl-5-trifluoromethyl-1H-pyrazole (**6d**).* Colorless liquid (bp = 68−69 °C, 32 mbar); 83%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.94 (br s, 1H, Harom), 6.68 (t, 1H, J_{H-F} = 54.8 Hz, CHF_2), 1.69 (s, 9H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 143.5 (t, $^2J_{C-F}$ = 30.4 Hz, C_{IV}arom), 132.7 (q, $^2J_{C-F}$ = 40.1 Hz, C_{IV}arom), 119.9 (q, J_{C-F} = 268.9 Hz, CF_3), 110.8 (t, J_{C-F} = 233.9 Hz, CHF_2), 108.0 (q, $^3J_{C-F}$ = 3.8 Hz, CHarom), 64.2 (s, C_{IV}*t*Bu), 29.8 (q, $^5J_{C-F}$ = 2.1 Hz, *t*Bu CH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = = −55.6 (CF_3), −112.3 (d, J_{F-H} = 54.9 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_9H_{12}F_5N_2$ [M + H]: calcd 243.092 found 243.094.

*1-tert-Butyl-3,5-bis(difluoromethyl)-1H-pyrazole (**6h**).* Colorless liquid (bp = 90−91 °C, 24 mbar); 64%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.96 (t, 1H, J_{H-F} = 54.4 Hz, CHF_2), 6.82 (br s, 1H, Harom), 6.68 (t, 1H, J_{H-F} = 55.0 Hz, CHF_2), 1.67 (s, 9H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 143.9 (t, $^2J_{C-F}$ = 30.1 Hz, C_{IV}arom), 137.2 (t, $^2J_{C-F}$ = 29.7 Hz, C_{IV}arom), 111.1 (t, J_{C-F} = 233.5 Hz, CF_2H), 108.4 (t, J_{C-F} = 236.9 Hz, CHF_2), 105.5 (t, $^3J_{C-F}$ = 4.5 Hz, CHarom), 62.6 (s, C_{IV}*t*Bu), 30.0 (s, *t*BuCH_3) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −110.2 (d, J_{F-H} = 54.5 Hz, CHF_2), −112.5 (d, J_{F-H} = 55.0 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_9H_{13}F_4N_2$ [M + H]: calcd 225.102; found 225.101.

Protocol for the Deprotection of *tert*-Bu-*N*-pyrazoles and Access to *N*-H-Pyrazoles. A mixture of 1-*tert*-butyl-1*H*-pyrazole **6d** (0.41 mmol, 1 equiv), anisole (0.13 g, 0.14 mL, 1.2 mmol, 3 equiv) and trifluoroacetic acid (2 mL) was stirred and heated to 90 °C for 16 h. The reaction mixture was cooled to 20 °C and neutralised by the addition of a solution of sodium hydroxide (8.4 g, 0.21 mol) in water (30 mL) until pH = 8. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate, and the solvent was evaporated under atmospheric pressure. The crude material was purified by column chromatography on silica gel.

*3-Difluoromethyl-5-trifluoromethyl-1H-pyrazole (**7a**).* Colorless solid, mp 72−73 °C; 76%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 13.38 (br s, 1H, N−H), 6.84 (s, 1H, Harom), 6.79 (t, 1H, J_{H-F} = 54.7 Hz, CHF_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 141.1 (br s, C_{IV}arom, C-1 and C-3), 120.1 (q, J_{C-F} = 268.8 Hz, CF_3), 108.3 (t, J_{C-F} = 238.2 Hz, CHF_2), 103.6 (d, $^3J_{C-F}$ = 1.6 Hz, CHarom) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −62.3 (CF_3), −114.2 (CHF_2) ppm. HRMS (ESI positive) for $C_5H_4F_5N_2$ [M + H]: calcd 187.029; found 187.029.

*3-Difluoromethyl-5-pentafluoroethyl-1H-pyrazole (**6l**).* Colorless solid (bp = 63−65 °C, 55 mbar); 46%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 11.87 (br s, 1H, NH), 6.87 (br s, 1H, Harom), 6.80 (t, 1H, J_{H-F} = 54.7 Hz, CHF_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 141.5 (br s, C_{IV}arom), 139.5 (br s, C_{IV}arom), 118.4 (qt, $^1J_{C-F}$ = 285.4 Hz, $^2J_{C-F}$ = 37.3 Hz, $CF_2\underline{CF_3}$), 109.9 (tq, $^1J_{C-F}$ = 252.2 Hz, $^2J_{C-F}$ = 40.1 Hz, $\underline{CF_2}CF_3$), 108.4 (t, J_{C-F} = 238.2 Hz, CHF_2), 104.9 (br s, CHpyrazole) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ = −85.1 ($CF_2\underline{CF_3}$), −113.5 ($\underline{CF_2}CF_3$), −113.8 (d, J_{F-H} = 54.7 Hz, CHF_2) ppm. HRMS (ESI positive) for $C_6H_4F_7N_2$ [M + H]: calcd 237.026 found 237.026.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: frederic.leroux@unistra.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the CNRS France and are very much grateful to Bayer S.A.S. for giving grants to F.G. and G.L. The French Fluorine Network (GIS Fluor) is also acknowledged.

■ REFERENCES

(1) (a) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Application*; Springer: New York, 2000 (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3−11. (c) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013−1029. (d) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992−1012. (e) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publications: Ames, IA, 2006. (f) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (g) Jeschke, P.; Baston, E.; Leroux, F. R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1027−1034. (h) Purser, S.; Moore, P. R.;

Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (i) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071−1081. (j) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140−158.
(2) (a) Jeschke, P. *ChemBioChem.* **2004**, *5*, 571−589. (b) Jeschke, P. *Pest Manag. Sci.* **2010**, *66*, 10−27.
(3) MacBean, C. *The Pesticide Manual: A World Compendium*, 16th ed.; British Crop Protection Council: Alton, 2012.
(4) Uneyama, K.; Sasaki, K. In *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry and Applications*; Petrov, V. A., Ed.; John Wiley & Sons: Hoboken, 2009; pp 419−492.
(5) (a) Cristau, P.; Hoffmann, S.; Kluth, J.; Tsuchiya, T.; Wasnaire, P.; Benting, J.; Portz, D.; Wachendorff-Neumann, U. WO/2011/076699A1, 2011. *Chem. Abstr.* **2011**, *155*, 123398. (b) Liepa, A. J.; Pasteris, R. J.; Stevenson, T. M. WO/2011/085170A1, 2011. *Chem. Abstr.* **2011**, *155*, 200034. (c) Cristau, P.; Tsuchiya, T.; Wachendorff-Neumann, U.; Dahmen, P., WO/2011/051243A1, 2011. *Chem. Abstr.* **2011**, *154*, 532493. (d) Hanagan, M. A.; Oberholzer, M. R.; Pasteris, R. J.; Shapiro, R., WO/2010/123791A1, 2010. *Chem. Abstr.* **2010**, *153*, 573289. (e) Cristau, P.; Rahn, N.; Tsuchiya, T.; Wachendorff-Neumann, U.; Voerste, A.; Benting, J. WO/2010/066353A1, 2010. *Chem. Abstr.* **2010**, *153*, 62249. (f) Pasteris, R. J. WO/2010/065579A2, 2010. *Chem. Abstr.* **2010**, *153*, 75907. (g) Cristau, P.; Rahn, N.; Herrmann, S.; Tsuchiya, T.; Wachendorf-Neumann, U.; Voerste, A.; Benting, J.; Wasnaire, P.; Hoffmann, S. WO/2010/037479A1, 2010. *Chem. Abstr.* **2010**, *152*, 454087. (h) Cristau, P.; Herrmann, S.; Rahn, N.; Voerste, A.; Wachendorff-Neumann, U. WO/2009/132785A1, 2009. *Chem. Abstr.* **2009**, *151*, 491110 (i) Kamireddy, B.; Pasteris, R. J.; Hanagan, M. A. WO/2009/094445A2, 2009. *Chem. Abstr.* **2009**, *151*, 173451. (j) Hanagan, M. A.; Pasteris, R. J. WO/2009/094407A2, 2009. *Chem. Abstr.* **2009**, *151*, 234956. (k) Gregory, V.; Pasteris, R. J. WO/2009/055514A2, 2009. *Chem. Abstr.* **2009**, *150*, 578441. (l) Pasteris, R. J.; Lahm, G. P. WO/2008/091580A2, 2008. *Chem. Abstr.* **2008**, *149*, 200904. (m) Bruhn, J. A.; Pasteris, R. J. WO/2008/091594A2, 2008. *Chem. Abstr.* **2008**, *149*, 193346. (n) Pasteris, R. J.; Hanagan, M. A.; Shapiro, R. WO/2008/013925A2, 2008. *Chem. Abstr.* **2008**, *148*, 185135. (o) Bisaha, J. J.; Kovacs, P. R.; Lett, R. M.; Long, J. K.; Pasteris, R. J.; Finkelstein, B. L.; Smith, B. T.; Klyashchitsky, B. A. WO/2007/014290A2, 2007. *Chem. Abstr.* **2007**, *146*, 206290.
(6) Dunkel, R.; Rieck, H.; Elbe, H.-L.; Wachendorff-Neumann, U.; Kuck, K.-H. WO/2003/070705A1, 2003. *Chem. Abstr.* **2003**, *139*, 180060
(7) (a) Pashkevich, K. I.; Saloutin, V. I.; Fomin, A. N.; Berenblit, V. V.; Plashkin, V. S.; Postovskii, I. Y. *Zh. Vses. Khim. Ova. im D. I. Mendeleeva* **1981**, *26*, 105−107. (b) Claire, P. P. K.; Coe, P. L.; Jones, C. J.; McCleverty, J. A. *J. Fluorine Chem.* **1991**, *51*, 283−289. (c) Threadgill, M. D.; Heer, A. K.; Jones, B. G. *J. Fluorine Chem.* **1993**, *65*, 21−23. (d) Sloop, J. C.; Bumgardner, C. L.; Loehle, W. D. *J. Fluorine Chem.* **2002**, *118*, 135−147. (e) Obermayer, D.; Glasnov, T. N.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 6657−6669. (f) Maspero, A.; Giovenzana, G. B.; Monticelli, D.; Tagliapietra, S.; Palmisano, G.; Penoni, A. *J. Fluorine Chem.* **2012**, *139*, 53−57.
(8) (a) Pazenok, S.; Lui, N.; Heinrich, J.-D.; Wollner, T. WO/2009/106230, 2009. *Chem. Abstr.* **2009**, *151*, 337180. (b) Pazenok, S. WO/2009/112157A1, 2009. *Chem. Abstr.* **2009**, *151*, 358746.
(9) Lantzsch, R.; Joerges, W.; Pazenok, S. WO/2005/042468A1, 2005. *Chem. Abstr.* **2005**, *142*, 463718.
(10) Pazenok, S.; Norbert, L.; Neeff, A. WO/2008/022777A2, 2008. *Chem. Abstr.* **2008**, *148*, 308336.
(11) Tanaka, K.; Kishida, M.; Maeno, S.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2631−2632.
(12) Maggio, B.; Raffa, D.; Raimondi, M. V.; Cascioferro, S.; Plescia, F.; Tolomeo, M.; Barbusca, E.; Cannizzo, G.; Mancuso, S.; Daidone, G. *Eur. J. Med. Chem.* **2008**, *43*, 2386−2394.
(13) Guillou, S.; Bonhomme, F. J.; Chahine, D. B.; Nesme, O.; Janin, Y. L. *Tetrahedron* **2010**, *66*, 2654−2663.
(14) Rudzki, M.; Alcalde-Aragones, A.; Dzik, W. I.; Rodriguez, N.; Goossen, L. J. *Synthesis* **2012**, *44*, 184−193.
(15) (a) Yarovenko, N. N.; Raksha, M. A. *Zh. Obshch. Khim.* **1959**, *29*, 2159−2163. (b) England, D. C.; Melby, L. R.; Dietrich, M. A.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 5116−5122. (c) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377−3380. (d) Petrov, V. A. *Adv. Org. Synth.* **2006**, *2*, 269−290.
(16) (a) Wakselman, C.; Tordeux, M. *Chem. Commun.* **1975**, 956−956. (b) Pazenok, S.; Lui, N.WO/2008/092583A2, 2008. *Chem. Abstr.* **2008**, *149*, 223826. (c) Grieco, L. M.; Halliday, G. A.; Junk, C. P.; Lustig, S. R.; Marshall, W. J.; Petrov, V. A. *J. Fluorine Chem.* **2011**, *132*, 1198−1206.
(17) Kitazume, T.; Asai, M.; Tsukamoto, T.; Yamazaki, T. *J. Fluorine Chem.* **1992**, *56*, 271−284.
(18) (a) Giornal, F. *Novel Access to Heteroaromatic Building Blocks Bearing Diversely Fluorinated Substituents*; University of Strasbourg: Strasbourg, France, 2012. (b) Pazenok, S.; Lui, N.; Vors, J.-P.; Leroux, J.-P.; Giornal, F. WO/2013/113829A1, 2013. (c) Pazenok, S.; Giornal, F.; Landelle, G.; Lui, N.; Vors, J.-P.; Leroux, F. R. *Eur. J. Org. Chem.* **2013**, 4249−4253.
(19) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924−3958.
(20) (a) Schlosser, M.; Volle, J. N.; Leroux, F.; Schenk, K. *Eur. J. Org. Chem.* **2002**, 2913−2920. (b) Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, *11*, 3326−3329.
(21) Goossen, L. J.; Manjolinho, F.; Khan, B. A.; Rodriguez, N. *J. Org. Chem.* **2009**, *74*, 2620−2623.
(22) Pazenok, S.; Vors, J.-P.; Leroux, F. R.; Giornal, F. WO/2014/033164A1, 2014. *Chem. Abstr.* **2014**, *160*, 399096.