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2,4-Bis(fluoroalkyl)quinoline-3-carboxylates as tools for the development of potential agrochemical ingredients

Fallia Aribi,^[a,b] Armen Panossian,^[a,b] Jean-Pierre Vors,^[b,c] Sergii Pazenok,^[b,d] and Frédéric R. Leroux*^[a,b]

Abstract: From an easy and scalable synthetic access to quinoline derivatives substituted by fluorinated groups in both C2- and C4-positions developed in our laboratory, we devised the synthesis of a new series of unprecedented 2,4-bis(fluoroalkyl)quinoline-3-carboxylates in two steps only. After standard saponification, the latter afforded their corresponding 2,4-bis(fluoroalkyl)quinoline-3-carboxylic acids, which served as pivotal intermediates for post-functionalization reactions. Indeed, the carboxylic function could then be derived according to known procedures and allowed the introduction of chemical diversity in C3-position of these unprecedented structures. The resulting highly functionalized quinolines will then serve as platform in the development of ingredients with strong potential for agrochemical research.

Introduction

Introduction of fluoroalkyl groups into organic molecules in a selective and efficient way has piqued the interest of chemists, not only because of its synthetic challenge, but also because fluoro-organic compounds, when compared to their non-fluorinated analogues, often show unique biological properties useful in medicinal and agrochemical chemistry, as well as in materials science.^[1] Indeed, because of the strong electronic perturbation induced by fluorine atoms and fluorinated groups, organic molecules are subjected to drastic changes of their physico-chemical properties. For that reason, general methodologies for the synthesis of fluoroalkylated compounds are highly demanded.^[2]

Recently, bis-fluorinated quinolines have been increasingly investigated in literature.^[2f, 3] This sudden interest for such compounds is caused by the fact that, on the one hand, the quinoline moiety is frequently found among active ingredients, especially therapeutic drugs,^[4] and, on the other hand, fluoroalkyl

groups appended to heteroaromatics may enhance the lipophilicity and oxidative stability of bioactive molecules.^[5] Despite this interest, only few series of quinolines substituted in C2- and C4-positions by fluorinated groups have been reported,^[3c, 3e, 6] and even fewer of them bear substituents in C3-position.^[3a, 7] However, it seems that such substitution in C3-position of quinolines already stands out as potentially attractive.^[3a]

We had already reported on the easy and modular access to 2,4-bis(fluoroalkylated) quinoline derivatives with various substitution on the benzo ring.^[6] Their synthesis (**Scheme 1**) relied on 1) the condensation of *N*-aryl α -fluoroacetimines onto highly reactive acyl fluoride equivalents, namely 1-fluoro-1-(fluoroalkyl)-*N,N*-dialkyliminium salts obtained by treatment of FluoroalkylAmino Reagents (FARs, **Figure 1**) by a Lewis acid; and 2) on the subsequent cyclization of the resulting vinamidinium in a Combes-like reaction. In fact, apart from quinolines, FARs allow the access to various types of new fluorinated heterocycles, as we had also demonstrated.^[6, 8] Three of these reagents are commercially available: 1,1,2,2-tetrafluoro-*N,N*-dimethylethan-1-amine (**1A**; TFEDMA, Petrov reagent),^[9] 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine (**1B**; Yarovenko reagent),^[10] and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (**1C**; Ishikawa reagent).^[11] Additionally, we developed a new FAR **1D**, which showed similar reactivity to TFEDMA **1A** and allowed the introduction of the –CHFOCF₃ group (**Figure 1**).^[8d, 8f]

Herein, we wish to describe the synthesis of new 2,4-bis(fluoroalkyl)quinolines substituted in the aforementioned interesting C3-position, with an effort to introduce chemical diversity. Indeed, the purpose was to design molecules which will serve as platform for further functionalization towards active agrochemical ingredients.

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Supporting information for this article is given via a link at the end of the document.

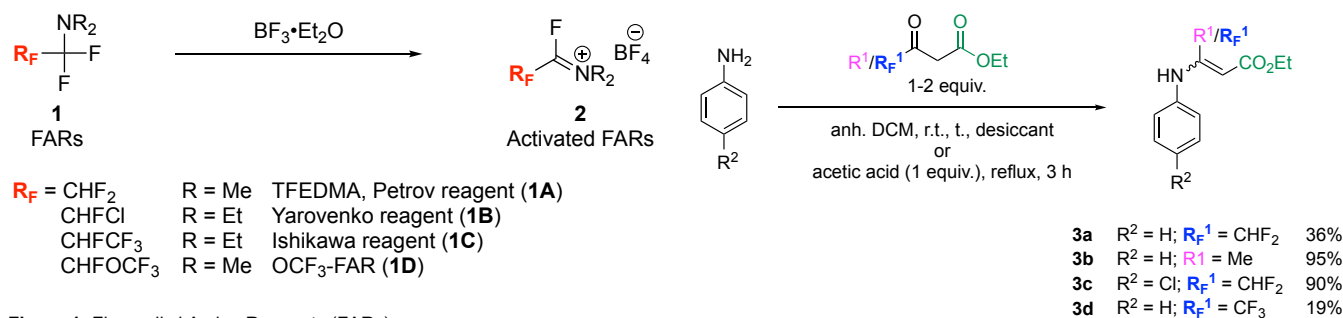
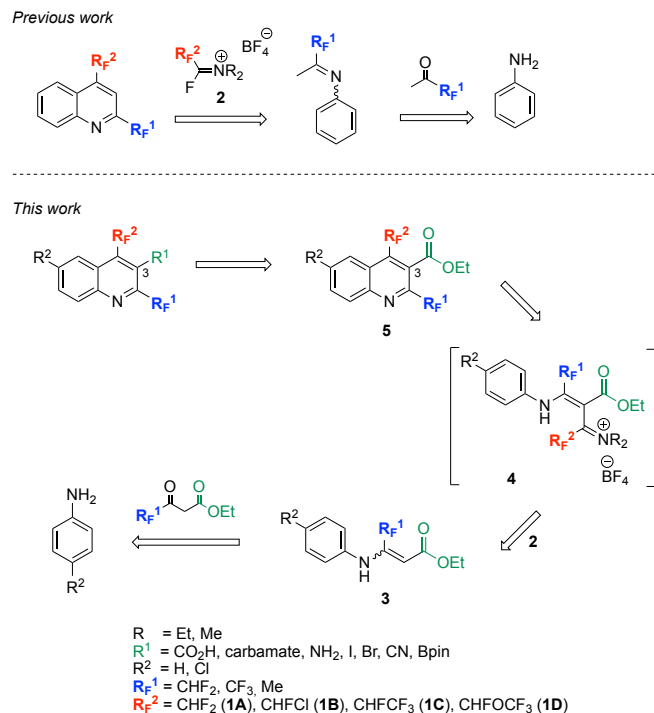


Figure 1: Fluoroalkyl Amino Reagents (FARs)

Scheme 2: Synthesis of fluorinated enamines **3**

Results and Discussion

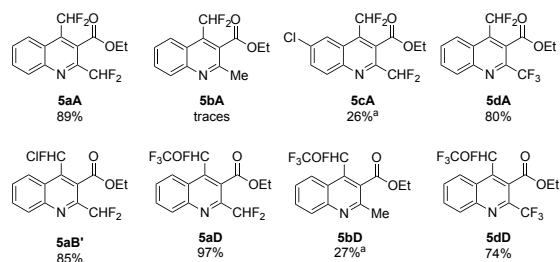
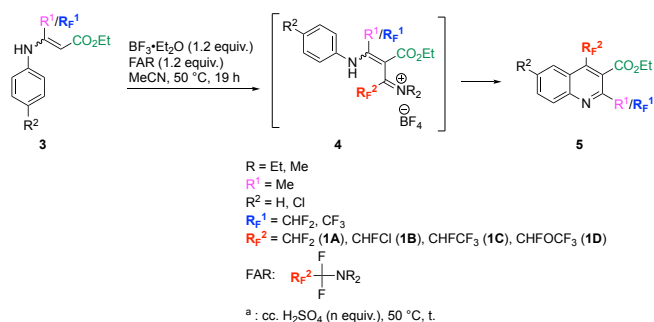
To access the desired quinolines with diverse functionalization in C3-position, we first performed the synthesis of the corresponding quinoline-3-carboxylates **5**. Towards this aim, we followed a strategy similar to the previous one, but starting from fluorinated ethyl acetoacetates (**Scheme 1**). Their condensation with aniline derivatives provided the expected enamines **3** (**Scheme 2**).



Scheme 1: Retrosynthetic scheme of 2,4-bis(fluoroalkyl)-3-substituted quinoline derivatives

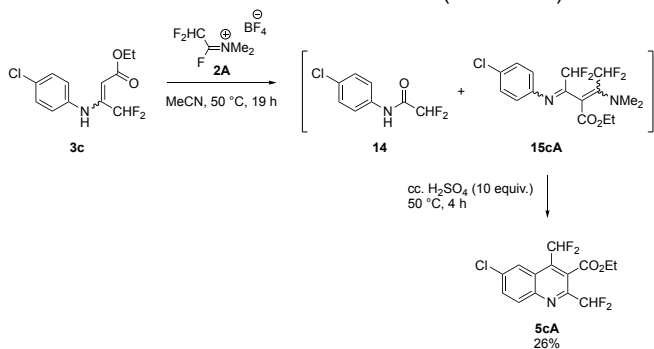
Enamines **3b** and **3c** were obtained in almost quantitative yields. These molecules appeared sensitive to moisture and silica, undergoing degradation in certain cases accompanied by the recovery of unknown fluorinated species; consequently, they were used without being further purified. The synthesis of 4,4-difluoro-*N*-phenylaminobutanoate **3a** was carried out according to the conditions developed by Perrone *et al.*^[12] A mixture of the desired compound and unidentified fluorinated species was recovered even after purification by distillation of the starting fluoroacetoacetate. We also attempted to purify the reactional mixture by column chromatography; however, even though compound **3a** was collected pure, a non-negligible amount of degraded product was also recovered, which considerably decreased the yield of the reaction. Following the same procedure, **3d** was obtained in only negligible amount. The starting aniline, ethyl α',α',α' -trifluoroacetoacetate and degradation products were often recovered. To account for these results, we assume that the latter trifluoroacetoacetate predominantly exists under its enol form, which can impede aniline condensation. On the other hand, we could obtain compound **3d** in refluxing acetic acid according to the procedure of Sharada *et al.*^[13] However, in our hands, only 19% yield of product was obtained compared to the 63% of literature. Analysis of **3d** by ¹H-NMR showed an imine-enamine equilibrium, which rapidly shifted towards the enamine form only.

The second step was the nucleophilic attack of activated FARs **2** by enamines **3** to afford quinoline derivatives **5** (**Scheme 3**). Good yields, ranging from 74 to 97% were obtained for compounds **5aA**, **5dA**, **5aD**, **5dD**. These molecules bear either a -CHF₂ or a -CHFOCF₃ moiety in C4-position and they were obtained after *in situ* cyclization of the vinamidinium intermediate **4** and purification by column chromatography.



Scheme 3: Synthesis of quinoline derivatives **5** bearing a carboxylate group in position 3

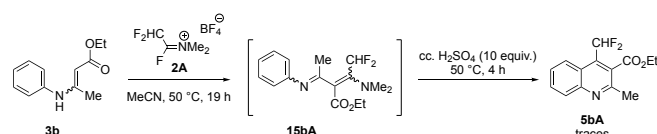
Conversely, according to GCMS and $^1\text{H-NMR}$ analysis, the attempted synthesis of **5cA** led to a mixture of acetamide **14** — which results from the reaction of activated TFEDMA **2A** with *p*-chloroaniline, released by the cleavage of enamine **3c**— and vinamide **15cA** —which corresponds to the hydrolysed vinamidinium intermediate—, with only traces of the targeted quinoline. After acidic treatment with 10 equiv. of concentrated sulfuric acid, we difficultly managed to reach 26% yield of the desired product. Indeed, despite the excess of acid, a substantial amount of **14** and **15cA** was still recovered (**Scheme 4**).



Scheme 4: Synthesis of ethyl 6-chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate **5cA**

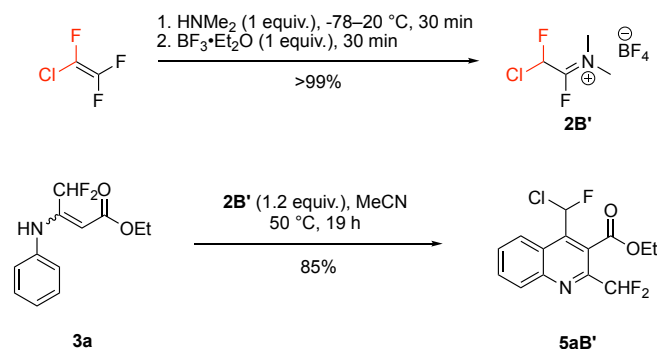
On the other hand, the synthesis of **5bA**, starting from a non-fluorinated acetoacetate remained unsuccessful despite the addition of 20 equiv. of concentrated H_2SO_4 in the reaction mixture. Although we observed by $^1\text{H-NMR}$ the formation of the vinamide intermediate **15bA**, the addition of acid did not alter sensibly the unsuccessful outcome of the cyclization process

(**Scheme 5**). This result contrasts dramatically with the good yield (89%) of the closely related compound **5aA**, bearing a second difluoromethyl group instead of the methyl one. A partial explanation would incriminate the inductively electron-donating terminal methyl group, which may decrease the electrophilic character of the distal carbon being attacked by the phenyl ring; however, unlike the CHF_2 group, the methyl group should also enrich the aniline nitrogen, hence the nucleophilicity of the arene. Thus, as we had described previously,^[6] counter-operating effects of a same substituent makes rationalization of the cyclization of vinamides or vinamidiniums into the desired quinolines quite difficult. Similarly, one can only speculate on the reasons for which quinoline **5bD** could be obtained in 27% yield, by using activated OCF_3 -FAR **2D**, while **5bA** failed to be produced.



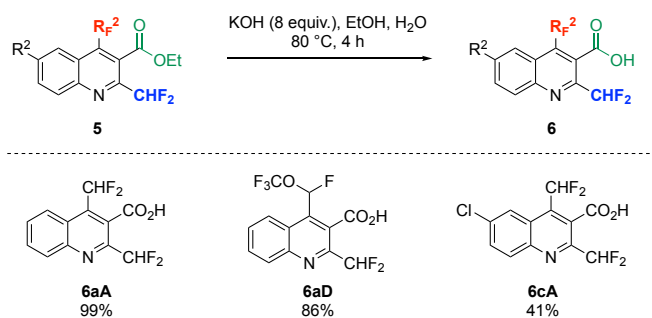
Scheme 5: Attempt to synthesize compound **5bA**

Finally, when starting from the Yarovenko reagent **1B**, the reaction with **3a** led mostly to the degradation of the latter starting material and to the recovery of the hydrolysed FAR. Suspecting that the presence of less bulky substituents on the nitrogen atom of the FAR could enhance the reactivity of the corresponding iminium,^[8] we freshly prepared the *N,N*-dimethyl analogue **1B'** of Yarovenko's reagent **1B**, which, upon reaction with **3a**, successfully afforded **5aB'** in 85% yield (**Scheme 6**).



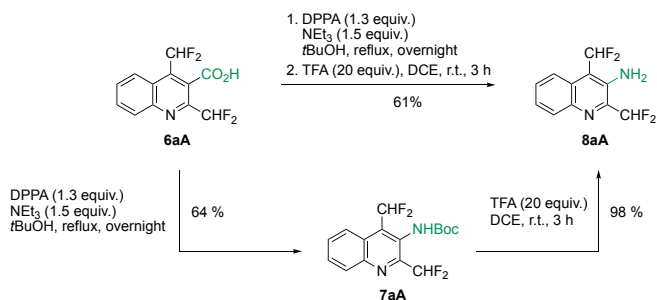
Scheme 6: Synthesis of **5aB'** from the *N,N*-dimethyl analogue of the activated Yarovenko reagent **B.2**

The next part of this work was the functionalization of the synthesized quinolines in C3-position. First, we saponified selected compounds **5aA**, **5aD** and **5cA** using potassium hydroxide in ethanol and water (60:40) at 80 °C (**Scheme 7**). The reaction afforded carboxylic acids **6aA** and **6aD** efficiently, while **6cA** was obtained in moderate yield only.



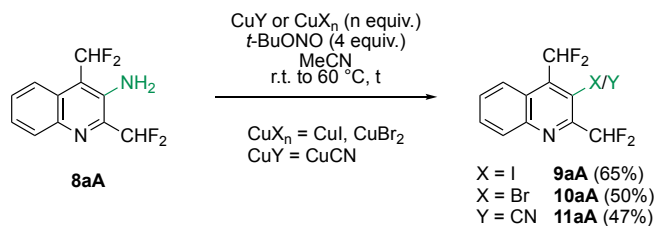
Scheme 7: Saponification of selected esters

Second, we investigated on the conversion of the carboxylic acid function into other functional groups. 2,4-Bis(difluoromethyl)quinoline-3-carboxylic acid **6aA** was used as a model compound to undergo a Curtius rearrangement in presence of diphenylphosphoryl azide (DPPA). The resulting isocyanate intermediate was trapped by *t*-BuOH to provide the corresponding *t*-butyl (2,4-bis(difluoromethyl)quinolin-3-yl)carbamate **7aA** in 64% yield. The amine moiety was then deprotected in acidic medium using TFA and 2,4-bis(difluoromethyl)quinolin-3-amine **8aA** was obtained in quantitative yield. This 2-step sequence (63% yield) was also performed in one pot following the procedure of Miller *et al.*^[14] in 61% yield (**Scheme 8**).



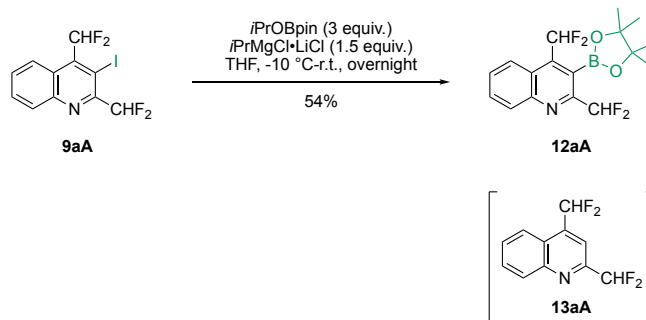
Scheme 8: Curtius rearrangement of compound **6aA**

Having installed an amino group in C3-position, we envisaged its transformation to several other groups by means of Sandmeyer reactions. In a first attempt, following the procedure of Bui *et al.*^[15] using sodium nitrite, a mixture of copper bromide and hydrobromic acid, only the starting material was recovered. When using *t*-butyl nitrite instead, following the work of Boezio *et al.*,^[16] and several copper sources, we accessed 2,4-bis(difluoromethyl)-3-iodoquinoline **9aA**, 3-bromo-2,4-bis(difluoromethyl)quinoline **10aA** and 2,4-bis(difluoromethyl)quinoline-3-carbonitrile **11aA** with moderate yields (**Scheme 9**).



Scheme 9: Sandmeyer reactions of aminoquinoline **8aA**

Last but not least, we used in turn the iodo derivative **9aA** to access the corresponding pinacolboronic ester. Thus, **9aA** underwent halogen/metal exchange using *i*PrMgCl•LiCl and *in situ* trapping with isopropoxy pinacolborane following the procedure of Chavant *et al.*^[17] 2,4-Bis(difluoromethyl)-3-(pinacolboranyl)quinoline **12aA** was obtained in 54% yield, along with the hydrolysed compound **13aA**, which we had already described,^[6] as sole remnant of the starting material (**Scheme 10**).



Scheme 10: Halogen/metal interconversion-borylation sequence

Thus, thanks to model substrate **5aA**, we showed that we could access several key 2,4-bis(fluoroalkyl)quinoline building blocks, with diverse substitution in C3-position by synthetically useful functional groups. These compounds could be obtained from FARs, anilines and fluorinated acetoacetates in two to seven steps, with an overall yield comprised between 7 and 13%, by means of generally easy-to-implement reactions.

Conclusions

We developed an access to a series of unprecedented ethyl 2,4-bis(fluoroalkyl)quinoline-3-carboxylates, whose fluoroalkyl groups are either identical or not, in two steps starting from available or easily accessible reagents. Most carboxylates were formed in good yields. Interestingly, when the intermediate *N*-aryl- β -aminoacrylates were non-fluorinated, the expected quinoline-3-carboxylates bearing only one fluoroalkyl group in C4-position could not be obtained. We also demonstrated that, using known methodologies, the resulting ethyl quinoline-3-carboxylates can serve as platform towards various highly useful 2,4-bis(fluoroalkyl)quinoline building blocks, bearing versatile

carboxylic acid, amino, halogeno, cyano or pinacolboranyl groups in C3-position. These key compounds open avenues to further derivation. Finally, it would be of great interest to develop new FARs, as already attempted by Maslennikov *et al.*,^[18] in order to access quinoline derivatives bearing other fluorinated moieties in C4-position.

Experimental Section

General remarks: All reactions were performed in flame-dried glassware using Schlenk techniques for reactions needing anhydrous conditions. Liquids and solutions were transferred with syringes. Air- and moisture-sensitive materials were stored and handled under an atmosphere of argon. Solvents were purified and dried following standard procedures: Dichloromethane (DCM) and Tetrahydrofuran (THF) were respectively distilled from CaH₂ or sodium + benzophenone prior to use. Desiccants (4 Å molecular sieves (4 Å MS) were previously activated in an oven. Technical grade solvents for extraction and chromatography (cyclohexane, dichloromethane, *n*-pentane, ether, toluene, and ethyl acetate) were used without purification. Starting materials, if commercial, were purchased from standard suppliers (Sigma-Aldrich, Acros, Alfa Aesar and Apollo scientific) and used as such, provided that adequate checks (NMR) had confirmed the claimed purity. Analytical thin-layer chromatography (TLC) was carried out on 0.25 mm Merck silica-gel (60-F254). Flash column chromatography was performed on silica gel 60 (40–63 μm, 230–400 mesh, ASTM) by Merck using the indicated solvents. ¹H, ¹³C, and ¹⁹F-NMR spectra were recorded in CDCl₃, acetone-d₆ and DMSO-d₆ on Bruker AV 400 instruments (¹H: 400 MHz, ¹⁹F: 376 MHz, ¹³C: 101 MHz). Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard (chloroform (δ [¹H] = 7.26 and accordingly δ [¹³C] = 77.16 ppm). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, qd = quadruplet of doublets, td = triplet of doublets, dd = doublet of doublets, dq = doublet of quadruplets), coupling constant (Hz) and integration. Spectra were processed with the program MestReNova (Version 6.0.2-5475). Melting points (MP) were determined for crystalline compounds with a Büchi Melting Point Apparatus M-560 and are not corrected. IR spectra were measured with a Perkin Elmer Spectrum UATR two (diamond detection). HRMS analysis (measurement accuracy ≤ 15 ppm) and EA were performed by the analytical facility at the University of Strasbourg. Crystal X-ray diffraction analysis was carried out by the Radiocrystallography Service of the University of Strasbourg.

SYNTHESIS OF FLUOROALKYL AMINO REAGENT-DERIVED FLUOROIMINIUM SALTS

N-(2-Chloro-1,2-difluoroethylidene)-*N*-methylmethanaminium tetrafluoroborate **2B'**

1-Chloro-1,2,2-trifluoroethene (1 equiv., 0.195 mL, 2.58 mmol) was liquefied in a Schlenk apparatus under argon at -78 °C.

Dimethylamine (1 equiv., 2 M in THF, 1.29 mL, 2.58 mmol) was added slowly via syringe at -78 °C. After 5 min, the cold bath was replaced by a water bath and the mixture was stirred for 15 min. Boron trifluoride diethyl etherate (BF₃•Et₂O) (1 equiv., 0.328 mL, 2.59 mmol) was added via syringe and the reaction mixture was stirred for 30 min. Anhydrous DCM was then added to precipitate the desired salts, and the supernatant was removed; in case of polymerization, addition of anhydrous acetonitrile solubilized the mixture which was then used as such. Yield of **2B'** was estimated to be of 99% according to ¹H NMR analysis. ¹H NMR (400 MHz, DMSO) δ_H = 7.16 (d, ²J_{H-F} = 48.8 Hz, 1H, CHFCl), 2.97 and 2.87 (2 * s, 6H, N(CH₃)₂⁺) ppm. ¹⁹F NMR (376 MHz, DMSO) δ_F = -144.34 (d, ²J_{F-H} = 48.8 Hz, CHFCl), -148.03 (s, N=CF), -148.08 (s, BF₄⁻) ppm.

¹³C NMR analysis was carried out on the corresponding amide after hydrolysis.

¹³C NMR (126 MHz, DMSO) δ_C = 163.20 (d, ²J_{C-F} = 23.9 Hz, CO), 91.52 (d, ¹J_{C-F} = 244.8 Hz, CHFCl), 36.26 and 35.70 (2 * s, CH₃) ppm.

N-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate **2D**

1,1,2-Trifluoro-2-(trifluoromethoxy)ethene (1 equiv., 0.8 mL, 7.23 mmol) was liquefied in a Schlenk apparatus under argon at -78 °C. Dimethylamine (1 equiv., 2 M in THF, 3.62 mL, 7.24 mmol) was added slowly via syringe at -78 °C. After 5 min, the cold bath was replaced by a water bath and the mixture was stirred for 15 min. BF₃•Et₂O (1 equiv., 0.92 mL, 7.26 mmol) was added via syringe and the reaction mixture was stirred for 30 min. The yield of the desired *N*-(1,2-difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate (**2D**) was estimated to be of 85% by ¹H NMR analysis and the compound was used directly in the next step.

SYNTHESIS OF ENAMINES FROM FLUORINATED ACETOACETATES

Typical procedure A for the synthesis of enamines derivatives (3)

Under argon atmosphere, an excess of cold fluorinated ethyl acetoacetate (1 equiv.) was added to the aniline derivative (1 equiv.) in anhydrous DCM (2 mL/1 mmol) in presence of desiccant (e.g. 4 Å MS). The reaction mixture was stirred for the indicated time at room temperature. The desiccant was then filtered off on a Celite® pad, which was washed with ether. The filtrate was concentrated under reduced pressure to provide the desired product.

The following experiments were carried out according to *Typical Procedure A*, and specific details are reported as: a) commercially available perfluoroacetoacetate; b) aniline derivative; c) desiccant and time; and d) yield and aspect. Individual analysis for each compound **3** is given below. Atoms are numbered in the description of NMR spectra according to the Supporting Information.

Ethyl 4,4-difluoro-3-(phenylamino)but-2-enoate **3a**

a) Ethyl 4,4-difluoroacetoacetate (1 equiv., 8.43 mL, 64.4 mmol); b) Aniline (1 equiv., 5.87 mL, 64.4 mmol); c) 4 Å MS, for 4 h; d) Ethyl 4,4-difluoro-3-(phenylamino)but-2-enoate **3a** was obtained in 36% yield (5.63 g) as a colourless oil after purification by column chromatography using a gradient of AcOEt in pentane (2-98%). Compound **3a** was used directly without any further purification to avoid its degradation on silica gel column. ¹H NMR (400 MHz, CDCl₃) δ_H = 9.93 (s, 1H, NH), 7.36 (t, ³J_{H-H} = 7.8 Hz, 2H, C_{3,5}H), 7.22 (t, ³J_{H-H} = 7.4 Hz, 1H, C₄H), 7.15 (d, ³J_{H-H} = 7.6 Hz, 2H, C_{2,6}H), 6.21 (t, ²J_{H-F} = 53.3 Hz, 1H, C₇CHF₂), 5.26 (s, 1H, C₈H), 4.20 (q, ³J_{H-H} = 7.1 Hz, 2H, C₉OCH₂CH₃), 1.31 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -117.33 (dd, ²J_{F-H} = 53.3, ⁴J_{F-H} = 1.8 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 170.31 (s, C₉), 151.37 (t, ²J_{C-F} = 23.2 Hz, C₇), 138.00 (s, C₁), 129.61 (s, C_{3,5}), 126.19 (s, C₄), 124.83 (s, C_{2,6}), 109.51 (t, ¹J_{C-F} = 241.5 Hz, C₇CHF₂), 86.73 (t, ³J_{C-F} = 7.0 Hz, C₈), 59.88 (s, C₉OCH₂CH₃), 14.49 (s, C₉OCH₂CH₃). HRMS (ESI positive) for C₁₂H₁₄F₂NO₂ [M⁺]: calcd 242.0987, found 242.0972.

Ethyl 3-(phenylamino)but-2-enoate **3b**

a) Ethyl 3-oxobutanoate (1 equiv., 8.14 mL, 64.4 mmol); b) Aniline (1 equiv., 5.87 mL, 64.4 mmol); c) 4 Å MS, for 24 h; d) Ethyl 3-(phenylamino)but-2-enoate **3b** was obtained in 95% yield (12.6 g) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ_H = 10.38 (s, 1H, NH), 7.36 – 7.28 (m, 2H, C_{3,5}H), 7.19 – 7.12 (m, 1H, C₄H), 7.11 – 7.06 (m, 2H, C_{2,6}H), 4.69 (m, 1H, C₈H), 4.15 (q, ³J_{H-H} = 7.1 Hz, 2H, C₉OCH₂CH₃), 2.00 (m, 3H, C₇CH₃), 1.29 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 170.35 (s, C₉), 158.85 and 158.83 (d, iso¹ - iso², C₇), 139.34 (s, C₁), 129.03 (s, C_{3,5}), 124.86 (s, C₄), 124.34 and 124.32 (d, iso¹ - iso², C_{2,6}), 86.10 (s, C₈), 58.69 (s, C₉OCH₂CH₃), 20.25 and 20.24 (d, iso¹ - iso², C₇CH₃), 14.57 (s, C₉OCH₂CH₃) ppm.

Ethyl 3-[(4-chlorophenyl)amino]-4,4-difluorobut-2-enoate **3c**

a) Ethyl 4,4-difluoroacetoacetate (2 equiv., 10.4 g, 8.16 mL, 62.3 mmol); b) *p*-Chloroaniline (1 equiv., 3.98 g, 31.2 mmol); c) 4 Å MS, for 21 h; d) Ethyl 3-[(4-chlorophenyl)amino]-4,4-difluorobut-2-enoate **3c** was obtained in 90% yield (7.76 g) as a brown oil with an estimated purity around 75%. ¹H NMR (400 MHz, CDCl₃) δ_H = 9.85 (s, 1H, NH), 7.31 (d, ³J_{H-H} = 8.7 Hz, 2H, C_{3,5}H), 7.09 (d, ³J_{H-H} = 8.6 Hz, 2H, C_{2,6}H), 6.15 (t, ²J_{H-F} = 53.3 Hz, 1H, C₇CHF₂), 5.25 (s, 1H, C₈H), 4.20 (q, ³J_{H-H} = 7.1 Hz, 2H, C₉OCH₂CH₃), 1.31 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -116.93 (dd, ²J_{F-H} = 53.3, ⁴J_{F-H} = 1.2 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 170.22 (s, C₉), 150.88 (t, ²J_{C-F} = 22.9 Hz, C₇), 136.71 (s, C₄), 131.80 (s, C₁), 129.70 (s, C_{3,5}), 126.15 (s, C_{2,6}), 109.81 (t, ¹J_{C-F} = 242.0 Hz, C₇CHF₂), 87.87 (t, ³J_{C-F} = 7.2 Hz, C₈), 60.06 (s, C₉OCH₂CH₃), 14.47 (s, C₉OCH₂CH₃) ppm. HRMS (ESI positive) for C₁₂H₁₃ClF₂NO₂ [M⁺]: calcd 276.0597, found 276.0605.

Ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **3d**^[13]

A mixture of ethyl 4,4,4-trifluoroacetoacetate (1 equiv., 1.58 mL, 10.7 mmol) and aniline (1 equiv., 0.98 mL, 10.7 mmol) was heated at reflux in acetic acid (1 equiv., 0.615 mL, 10.7 mmol) for 3 h. The reaction mixture was quenched by addition of a saturated

solution of sodium bicarbonate (NaHCO₃), extracted with ether, dried over Na₂SO₄, and concentrated under vacuum. The crude mixture was purified by column chromatography, using a gradient of AcOEt in pentane (2-98%) to provide ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **3d** as a colourless oil in 19% yield (530 mg). Both imine and enamine forms of the product were observed by NMR analysis, however the imine form rapidly evolved into the enamine form. **Enamine form** ¹H NMR (400 MHz, CDCl₃) δ_H = 9.84 (s, 1H, NH), 7.37 – 7.30 (m, 2H, C_{3,5}H), 7.28 – 7.22 (m, 1H, C₄H), 7.21 – 7.17 (m, 2H, C_{2,6}H), 5.35 (s, 1H, C₈H), 4.22 (q, ³J_{H-H} = 7.1 Hz, 2H, C₉OCH₂CH₃), 1.32 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -63.33 (s, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 169.81 (s, C₉), 147.29 (q, ²J_{C-F} = 31.4 Hz, C₇), 138.50 (s, C₁), 129.08 (s, C_{3,5}), 126.76 (s, C₄), 126.13 (q, ⁵J_{C-F} = 1.5 Hz, C_{2,6}), 120.37 (q, ¹J_{C-F} = 277.4 Hz, C₇CF₃), 88.67 (q, ³J_{C-F} = 5.4 Hz, C₈), 60.26 (s, C₉OCH₂CH₃), 14.44 (s, C₉OCH₂CH₃) ppm. **Imine form** ¹H NMR (400 MHz, CDCl₃) δ_H = 7.40 – 7.32 (m, 2H, C_{3,5}H), 7.20 – 7.14 (m, 1H, C₄H), 6.88 – 6.82 (m, 2H, C_{2,6}H), 4.15 (q, ³J_{H-H} = 7.0 Hz, 2H, C₉OCH₂CH₃), 3.41 (s, 2H, C₈H), 1.24 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -72.64 (s, C₇CF₃) ppm.

QUINOLINE SYNTHESIS

Typical procedure B for the synthesis of quinoline derivatives (5)

Under an argon atmosphere, a solution of the desired FAR (1,1,2,2-tetrafluoro-*N,N*-dimethylethan-1-amine (**1A**; TFEDMA), 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine (**1B**; Yarovenko reagent), and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (**1C**; Ishikawa reagent) (1.2 equiv.) was activated by adding boron trifluoride diethyl etherate (BF₃•Et₂O) (1.2 equiv.) in dry MeCN (3.6 mmol/5 mL) and stirred for 15 min. Then a solution of the desired enamine derivative (**3**) (1 equiv.) in dry MeCN (3 mmol/5 mL) was slowly syringed into this mixture. After 15 min at room temperature, the mixture was heated at 50 °C for 19 h. MeCN was removed under reduced pressure and the crude material was purified by flash chromatography using a gradient of AcOEt in cyclohexane to provide the final compound (**5**).

The following experiments were carried out according to **Typical Procedure B**, and specific details are reported as: a) FAR (**1**) and BF₃•Et₂O, or activated FAR (**2**); b) Enamine (**3**); and c) yield and aspect. Individual analysis for each compound (**5**) is given below. Atoms are numbered in the description of NMR spectra according to the Supporting Information.

Ethyl 2,4-bis(difluoromethyl)quinoline-3-carboxylate **5aA**

a) TFEDMA **1A** (1.2 equiv., 3.26 mL, 27.9 mmol), BF₃•Et₂O (1.2 equiv., 3.53 mL, 27.9 mmol); b) Ethyl 4,4-difluoro-3-(phenylamino)but-2-enoate **3a** (1 equiv., 5.6 g, 23.2 mmol); c) After purification by flash chromatography using a gradient of AcOEt in cyclohexane (0-5%), ethyl 2,4-bis(difluoromethyl)quinoline-3-carboxylate **5aA** was obtained as a colourless solid in 89% yield (6.54 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.40 (dd, ³J_{H-H} = 8.6, ⁵J_{H-F} = 1.4 Hz, 1H, C₅H), 8.23 (d, ³J_{H-H} = 8.4 Hz, 1H, C₈H), 7.88 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 7.0, ⁴J_{H-H2} = 1.2

H_z, 1H, C₆H), 7.76 (ddd, ³J_{H-H2} = 8.3, ³J_{H-H3} = 7.0, ⁴J_{H-H1} = 1.0 Hz, 1H, C₇H), 7.19 (t, ²J_{H-F} = 52.9 Hz, 1H, C₄CHF₂), 6.93 (t, ²J_{H-F} = 54.6 Hz, 1H, C₂CHF₂), 4.53 (q, ³J_{H-H} = 7.2 Hz, 2H, C₃OCH₂CH₃), 1.44 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -109.64 (dd, ²J_{F-H} = 53.0, ⁵J_{F-H} = 2.0 Hz, C₄CHF₂), -115.25 (d, ²J_{F-H} = 54.6 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.32 (s, C₃CO), 148.26 (t, ²J_{C-F} = 25.3 Hz, C₂), 147.56 (s, C₁₀), 137.17 (t, ²J_{C-F} = 23.3 Hz, C₄), 131.84 (s, C₆), 130.80 (s, C₈), 129.99 (s, C₇), 125.43 (t, ⁴J_{C-F} = 3.7 Hz, C₅), 124.21 (t, ³J_{C-F} = 6.6 Hz, C₃), 123.57 (s, C₉), 114.08 (t, ¹J_{C-F} = 242.4 Hz, C₂CHF₂), 112.93 (t, ¹J_{C-F} = 241.4 Hz, C₄CHF₂), 63.30 (s, C₃OCH₂CH₃), 14.03 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2988-2901 (C_{sp3}H), 1721 (C=O_{ester}). C₁₄H₁₁F₄NO₂ (301): calcd (%) N 4.65, C 55.82, H 3.68, found N 4.63, C 55.86, H 3.78. MP: 65.5 – 66.7 °C.

Ethyl 4-(chlorofluoromethyl)-2-(difluoromethyl)quinoline-3-carboxylate 5aB'

The required FAR **1B'** was freshly prepared and activated by BF₃•Et₂O, in order to be used as the corresponding fluoroiminium salt **2B'**.

a) *N*-(2-Chloro-1,2-difluoroethylidene)-*N*-methylmethanaminium tetrafluoroborate **2B'** (1.30 equiv., 1.19 g, 5.20 mmol); b) Ethyl 4,4-difluoro-3-(phenylamino)but-2-enoate **3a** (1 equiv., 1.56 g, 3.87 mmol); c) After purification by flash chromatography using a gradient of AcOEt in cyclohexane (0-5%), ethyl 4-(chlorofluoromethyl)-2-(difluoromethyl)quinoline-3-carboxylate **5aB'** was obtained as a yellow oil in 85% yield (1.04 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.48 (d, ³J_{H-H} = 8.6 Hz, 1H, C₅H), 8.23 (d, ³J_{H-H} = 7.9 Hz, 1H, C₈H), 7.88 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.77 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.62 (d, ²J_{H-F} = 48.6 Hz, 1H, C₄CHFCl), 6.93 (t, ²J_{H-F} = 54.6 Hz, 1H, C₂CHF₂), 4.61 – 4.44 (m, 2H, C₃OCH₂CH₃), 1.45 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -115.30 (d, ²J_{F-H} = 54.6 Hz, C₂CHF₂), -133.91 (d, ²J_{F-H} = 48.6 Hz, C₄CHFCl) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.40 (s, C₃CO), 148.30 (t, ²J_{C-F} = 25.2 Hz, C₂), 147.71 (s, C₁₀), 140.20 (d, ²J_{C-F} = 21.2 Hz, C₄), 131.77 (s, C₆), 131.02 (s, C₈), 129.71 (s, C₇), 125.43 (d, ⁴J_{C-F} = 5.7 Hz, C₅), 123.07 (s, C₉), 122.10 (d, ³J_{C-F} = 5.3 Hz, C₃), 114.03 (t, ¹J_{C-F} = 244.1 Hz, C₂CHF₂), 96.76 (d, ¹J_{C-F} = 244.6 Hz, C₄CHFCl), 63.26 (s, C₃OCH₂CH₃), 14.04 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2987-2907 (C_{sp3}H), 1727 (C=O_{ester}). C₁₄H₁₁F₃ClNO₂ (317): calcd (%) N 4.41, C 52.93, H 3.49, found N 4.32, C 52.63, H 3.59.

Ethyl 2-(difluoromethyl)-4-(fluoro(trifluoromethoxy)methyl)quinoline-3-carboxylate 5aD

a) *N*-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate **2D** (1.57 equiv., 1.7 g, 6.1 mmol); b) Ethyl 4,4-difluoro-3-(phenylamino)but-2-enoate **3a** (1 equiv., 1.56 g, 3.87 mmol); c) After purification by flash chromatography using a gradient of AcOEt in cyclohexane (0-20%), ethyl 2-(difluoromethyl)-4-(fluoro(trifluoromethoxy)methyl)quinoline-3-carboxylate **5aD** was obtained as a colourless solid in 97% yield (1.38 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.41 (d, ³J_{H-H} = 8.6 Hz, 1H, C₅H), 8.23 (d, ³J_{H-H} = 8.4 Hz, 1H, C₈H), 7.93 – 7.82 (m, 1H, C₇H), 7.82 – 7.67 (m, 1H,

C₆H), 7.28 (d, ²J_{H-F} = 54.8 Hz, 1H, C₄CHFOCF₃), 6.95 (t, ²J_{H-F} = 54.6 Hz, 1H, C₂CHF₂), 4.61 – 4.45 (m, 2H, C₃OCH₂CH₃), 1.44 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -59.39 (d, ⁴J_{F-F} = 4.9 Hz, C₄CHFOCF₃), -114.33 – -116.46 (m, A₂B₂, Δν = 485.13 Hz, C₂CHF₂), -120.55 (dq, ²J_{F-H} = 54.9, ⁴J_{F-F} = 4.8, ⁵J_{F-H} = 2.1 Hz, C₄CHFOCF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.28 (s, C₃CO), 148.35 (t, ²J_{C-F} = 25.3 Hz, C₂), 147.68 (s, C₉), 136.42 (d, ²J_{C-F} = 24.1 Hz, C₄), 131.91 (s, C₇), 130.87 (s, C₈), 130.02 (s, C₆), 125.63 (d, ⁴J_{C-F} = 4.9 Hz, C₅), 123.97 (d, ³J_{C-F} = 6.2 Hz, C₃), 123.46 (s, C₁₀), 121.08 (qd, ¹J_{C-F} = 262.6, ³J_{C-F} = 1.7 Hz, C₄CHFOCF₃), 114.05 (t, ¹J_{C-F} = 244.1 Hz, C₂CHF₂), 103.11 (dq, ¹J_{C-F} = 232.2, ³J_{C-F} = 3.9 Hz, C₄CHFOCF₃), 63.42 (s, C₃OCH₂CH₃), 13.90 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2991-2943 (C_{sp3}H), 1727 (C=O_{ester}). C₁₅H₁₁F₆NO₃ (367): calcd (%) N 3.81, C 49.06, H 3.02, found N 3.74, C 49.23, H 3.18. MP: 43.3 - 44.8 °C.

Ethyl 4-(difluoromethyl)-2-methylquinoline-3-carboxylate 5bA

Deviation from the general procedure: H₂SO₄ was added after formation of the vinamidine.

a) TFEDMA **1A** (1.2 equiv., 0.207 mL, 1.77 mmol), BF₃•Et₂O (1.2 equiv., 0.224 mL, 1.77 mmol); b) Ethyl 3-(phenylamino)but-2-enoate **3b** (1 equiv., 0.466 g, 1.47 mmol), followed by addition of H₂SO₄ (20 equiv., 18 M, 1.64 mL, 29.5 mmol) after 19 h and stirring for an additional 12 h; c) Traces of ethyl 4-(difluoromethyl)-2-methylquinoline-3-carboxylate **5bA** were obtained after purification using a gradient of AcOEt in cyclohexane (0-80%) as a clear yellow oil. ¹H NMR (500 MHz, CDCl₃) δ_H = 8.25 (dd, ³J_{H-H} = 8.5, ⁵J_{H-F} = 1.6 Hz, 1H, C₅H), 8.09 (d, ³J_{H-H} = 8.4 Hz, 1H, C₈H), 7.79 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.63 (ddd, ³J_{H-H1} = 8.3, ³J_{H-H3} = 6.9, ⁴J_{H-H2} = 1.2 Hz, 1H, C₆H), 7.10 (t, ²J_{H-F} = 53.3 Hz, 1H, C₄CHF₂), 4.51 (q, ³J_{H-H} = 7.2 Hz, 2H, C₃OCH₂CH₃), 2.77 (s, 3H, C₂CH₃), 1.45 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -110.31 (dd, ²J_{F-H} = 53.2, ⁵J_{F-H} = 1.9 Hz, C₄CHF₂) ppm. ¹³C NMR (126 MHz, CDCl₃) δ_C = 167.51 (s, C₃CO), 154.78 (s, C₂), 148.29 (s, C₁₀), 134.78 (t, ²J_{C-F} = 22.6 Hz, C₄), 130.97 (s, C₇), 129.72 (s, C₈), 127.73 (s, C₆), 126.54 (t, ³J_{C-F} = 6.0 Hz, C₃), 124.79 (t, ⁴J_{C-F} = 2.9 Hz, C₅), 121.72 (s, C₉), 113.38 (t, ¹J_{C-F} = 241.2 Hz, C₄CHF₂), 62.67 (s, C₃OCH₂CH₃), 23.83 (s, C₂CH₃), 14.26 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2986-2929 (C_{sp3}H), 1726 (C=O_{ester}). C₁₄H₁₃F₂NO₂ (265): calcd (%) N 5.28, C 63.39, H 4.94, found N 4.89, C 63.62, H 5.21.

Ethyl 4-[fluoro(trifluoromethoxy)methyl]-2-methylquinoline-3-carboxylate 5bD

Deviation from the general procedure: H₂SO₄ was added after formation of the vinamidine.

The required FAR **1D** was freshly prepared and activated by BF₃•Et₂O, in order to be used as the corresponding fluoroiminium salt **2D**.

a) *N*-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate **2D** (1.59 equiv., 1.7 g, 6.1 mmol); b) Ethyl 3-(phenylamino)but-2-enoate **3b** (1 equiv., 1.21 g, 3.82 mmol), followed by addition of H₂SO₄ (10 equiv., 18 M, 2.12 mL, 38.2 mmol) after 19 h and stirring for an additional 4 h; c) Ethyl 4-[fluoro(trifluoromethoxy)methyl]-2-methylquinoline-3-carboxylate **5bD** was obtained after purification using a gradient

of AcOEt in cyclohexane (0-20%) in 27% yield (346 mg) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ_H = 8.25 (d, ³J_{H-H} = 8.6 Hz, ⁵J_{H-F} = 1.5, 1H, C₅H), 8.09 (dd, ³J_{H-H} = 8.5, ⁶J_{H-F} = 0.6 Hz, 1H, C₈H), 7.79 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.63 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.16 (d, ²J_{H-F} = 55.1 Hz, 1H, C₄CHFOCF₃), 4.58 – 4.44 (m, 2H, C₃OCH₂CH₃), 2.77 (s, 3H, C₂CH₃), 1.44 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -59.28 (d, ⁴J_{F-F} = 5.2 Hz, C₄CHFOCF₃), -121.02 (dq, ²J_{F-H} = 55.1, ⁴J_{F-F} = 5.0, ⁵J_{F-H} = 1.9 Hz, C₄CHFOCF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 167.32 (s, C₃CO), 154.81 (s, C₂), 148.41 (s, C₁₀), 134.01 (d, ²J_{C-F} = 23.4 Hz, C₄), 131.04 (s, C₇), 129.79 (s, C₈), 127.77 (s, C₆), 126.45 (d, ³J_{C-F} = 5.7 Hz, C₃), 124.90 (d, ⁴J_{C-F} = 3.9 Hz, C₅), 121.52 (s, C₉), 121.11 (qd, ¹J_{C-F} = 262.2, ³J_{C-F} = 1.7 Hz, C₄CHFOCF₃), 103.55 (dq, ¹J_{C-F} = 232.2, ³J_{C-F} = 3.9 Hz, C₄CHFOCF₃), 62.76 (s, C₃OCH₂CH₃), 23.96 (s, C₂CH₃), 14.12 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2987 (C_{sp3}H), 1727 (C=O_{ester}). HRMS (ESI positive) for C₁₅H₁₄F₄NO₃ [M⁺]: calcd 332.0904, found 332.0898.

Ethyl 6-chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate 5cA

Deviation from the general procedure: H₂SO₄ was added after formation of the vinamidine.

a) TFEDMA **1A** (1.2 equiv., 0.58 mL, 4.96 mmol), BF₃•Et₂O (1.2 equiv., 0.628 mL, 4.96 mmol); b) Ethyl 3-[(4-chlorophenyl)amino]-4,4-difluorobut-2-enoate **3c** (1 equiv., 1.52 g, 4.13 mmol), followed by addition of H₂SO₄ (10 equiv., 18 M, 2.29 mL, 41.3 mmol) after 19 h and stirring for an additional 4 h; c) Ethyl 6-chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate **5cA** was obtained after purification using a gradient of AcOEt in cyclohexane (0-5%) as a beige solid in 26% yield (358 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.39 (dd, ⁴J_{H-H} = 3.7, ⁵J_{H-F} = 1.8 Hz, 1H, C₅H), 8.17 (d, ³J_{H-H} = 9.0 Hz, 1H, C₈H), 7.83 (dd, ³J_{H-H} = 9.0, ⁴J_{H-H} = 2.2 Hz, 1H, C₇H), 7.12 (t, ²J_{H-F} = 52.0 Hz, 1H, C₄CHF₂), 6.91 (t, ²J_{H-F} = 54.5 Hz, 1H, C₂CHF₂), 4.53 (q, ³J_{H-H} = 7.2 Hz, 1H, C₃OCH₂CH₃), 1.45 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -109.66 (dd, ²J_{F-H} = 52.8, ⁵J_{F-H} = 1.7 Hz, C₄CHF₂), -115.46 (d, ²J_{F-H} = 54.5 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.91 (s, C₃CO), 148.53 (t, ²J_{C-F} = 25.5 Hz, C₂), 145.99 (s, C₆), 137.61 – 135.84 (m, C₄ + C₁₀), 132.99 (s, C₇), 132.22 (s, C₈), 125.09 (t, ³J_{C-F} = 6.7 Hz, C₃), 124.63 (t, ⁴J_{C-F} = 4.2 Hz, C₅), 124.18 (s, C₉), 113.86 (t, ¹J_{C-F} = 245.4 Hz, C₂CHF₂), 112.69 (t, ¹J_{C-F} = 241.5 Hz, C₄CHF₂), 63.53 (s, C₃OCH₂CH₃), 14.04 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2990-2941 (C_{sp3}H), 1721 (C=O_{ester}). C₁₄H₁₀F₄NCIO₂ (335): calcd (%) N 4.17, C 50.09, H 3.00, found N 3.98, C 49.59, H 3.19. MP: 71.9 - 74.3 °C.

Ethyl 4-(difluoromethyl)-2-(trifluoromethyl)quinoline-3-carboxylate 5dA

a) TFEDMA **1A** (1.2 equiv., 0.176 mL, 1.51 mmol), BF₃•Et₂O (1.2 equiv., 0.191 mL, 1.51 mmol); b) Ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **3d** (1 equiv., 406 mg, 1.26 mmol); c) Ethyl 4-(difluoromethyl)-2-(trifluoromethyl)quinoline-3-carboxylate **5dA** was obtained after purification using a gradient of AcOEt in cyclohexane (0-5%) as colourless solid in 80% yield (316 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.44 (dd, ³J_{H-H} = 8.6, ⁵J_{H-F} = 2.0 Hz, 1H, C₅H), 8.31 (dd, ³J_{H-H} = 8.5, ⁶J_{H-F} = 0.6 Hz, 1H,

C₈H), 7.95 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.83 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.13 (t, ²J_{H-F} = 52.8 Hz, 1H, C₄CHF₂), 4.52 (q, ³J_{H-H} = 7.2 Hz, 2H, C₃OCH₂CH₃), 1.44 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -64.17 (s, C₂CF₃), -109.48 (dd, ²J_{F-H} = 52.7, ⁵J_{F-H} = 2.0 Hz, C₄CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.90 (s, C₃CO), 147.30 (s, C₁₀), 143.72 (q, ²J_{C-F} = 35.0 Hz, C₂), 137.33 (t, ²J_{C-F} = 23.5 Hz, C₄), 132.19 (s, C₆), 131.17 (s, C₈), 130.75 (s, C₇), 125.37 (t, ⁴J_{C-F} = 3.7 Hz, C₅), 124.04 (s, C₉), 123.97 (s, C₃), 121.03 (q, ¹J_{C-F} = 276.7 Hz, C₂CF₃), 112.86 (t, ¹J_{C-F} = 241.8 Hz, C₄CHF₂), 63.56 (s, C₃OCH₂CH₃), 13.99 (s, C₃OCH₂CH₃). IR ν (cm⁻¹): 2987-2901 (C_{sp3}H), 1731 (C=O_{ester}). C₁₄H₁₀F₅NO₂ (319): calcd (%) N 4.39, C 52.67, H 3.16, found N 4.39, C 52.80, H 3.27. MP: 79.8 - 80.8 °C.

Ethyl 4-[fluoro(trifluoromethoxy)methyl]-2-(trifluoromethyl)quinoline-3-carboxylate 5dD

The required FAR **1D** was freshly prepared and activated by BF₃•Et₂O, in order to be used as the corresponding fluoroiminium salt **2D**.

a) *N*-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate **2D** (1.57 equiv., 852 mg, 3.06 mmol); b) Ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **3d** (1 equiv., 503 mg, 1.94 mmol); c) Ethyl 4-[fluoro(trifluoromethoxy)methyl]-2-(trifluoromethyl)quinoline-3-carboxylate **5dD** was obtained after purification using a gradient of AcOEt in cyclohexane (0-20%) as colourless solid in 74% yield (551 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.45 (d, ³J_{H-H} = 8.6 Hz, 1H, C₅H), 8.31 (dd, ³J_{H-H} = 8.5, ⁶J_{H-F} = 0.6 Hz, 1H, C₈H), 7.95 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.84 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.21 (d, ²J_{H-F} = 54.6 Hz, 1H, C₄CHFOCF₃), 4.62 – 4.43 (m, 2H, C₃OCH₂CH₃), 1.43 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -59.40 (d, ⁴J_{F-F} = 4.8 Hz, C₄CHFOCF₃), -64.17 (s, C₂CF₃), -120.38 (dq, ²J_{F-H} = 54.5, ⁴J_{F-F} = 4.9, ⁵J_{F-H} = 2.1 Hz, C₄CHFOCF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.87 (s, C₃CO), 147.43 (s, C₁₀), 143.76 (q, ²J_{C-F} = 35.2 Hz, C₂), 136.59 (d, ²J_{C-F} = 24.4 Hz, C₄), 132.27 (s, C₆), 131.22 (s, C₈), 130.79 (s, C₇), 125.59 (d, ⁴J_{C-F} = 4.9 Hz, C₅), 123.86 (s, C₉), 123.80 (s, C₃), 121.04 (qd, ¹J_{C-F} = 262.9, ³J_{C-F} = 1.6 Hz, C₄CHFOCF₃), 121.01 (q, ¹J_{C-F} = 276.7 Hz, C₂CF₃), 103.06 (dq, ¹J_{C-F} = 232.7, ³J_{C-F} = 3.9 Hz, C₄CHFOCF₃), 63.69 (s, C₃OCH₂CH₃), 13.88 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2987-2901 (C_{sp3}H), 1728 (C=O_{ester}). C₁₅H₁₀F₇NO₃ (385): calcd (%) N 3.64, C 46.77, H 2.62, found N 3.58, C 47.10, H 2.71. MP: 57.8 - 59.5 °C.

POST-FUNCTIONALIZATION IN POSITION 3 OF QUINOLINE DERIVATIVES

Typical procedure C for the saponification reaction

To a stirred solution of potassium hydroxide in ethanol/water 60:40 was added quinoline **5**. The reaction mixture was stirred under reflux for 4 h, then quenched with concentrated hydrochloric acid until pH reached 1. EtOH was removed under vacuum and organic compounds were extracted with AcOEt. The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated under reduced pressure.

The following experiments were carried out according to **Typical Procedure C**, and specific details are reported as: a) KOH and ethanol/water mixture; b) quinoline **5**; c) yield and aspect.

Individual analysis for each compound (**6**) is given below. Atoms are numbered in the description of NMR spectra according to the Supporting Information.

2,4-Bis(difluoromethyl)quinoline-3-carboxylic acid **6aA**

a) KOH (8 equiv., 10.6 g, 189 mmol), ethanol/water 60:40 (187 ml); b) Ethyl 2,4-bis(difluoromethyl)quinoline-3-carboxylate **5aA** (1 equiv., 7.14 g, 23.7 mmol); c) 2,4-Bis(difluoromethyl)quinoline-3-carboxylic acid **6aA** was obtained as a colourless solid in 99% yield (6.44 g). ¹H NMR (400 MHz, DMSO) $\delta_{\text{H}} = 8.39$ (d, ³*J*_{H-H} = 7.7 Hz, 1H, C₅H), 8.27 (d, ³*J*_{H-H} = 7.8 Hz, 1H, C₈H), 8.07 – 7.99 (m, 1H, C₆H), 7.97 – 7.88 (m, 1H, C₇H), 7.70 (t, ²*J*_{H-F} = 52.1 Hz, 1H, C₄CHF₂), 7.27 (t, ²*J*_{H-F} = 53.7 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, DMSO) $\delta_{\text{F}} = -106.25$ (dd, ²*J*_{F-H} = 52.0, ⁵*J*_{F-H} = 1.7 Hz, C₄CHF₂), -110.60 (d, ²*J*_{F-H} = 53.7 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, DMSO) $\delta_{\text{C}} = 166.11$ (s, C₃CO), 147.73 (t, ²*J*_{C-F} = 24.2 Hz, C₂), 146.40 (s, C₁₀), 135.53 (t, ²*J*_{C-F} = 22.7 Hz, C₄), 132.02 (s, C₆), 130.33 (s, C₇), 130.20 (s, C₈), 125.21 (t, ³*J*_{C-F} = 6.1 Hz, C₃), 124.74 (s, C₅), 123.07 (s, C₉), 113.02 (t, ¹*J*_{C-F} = 241.7 Hz, C₂CHF₂), 112.87 (t, ¹*J*_{C-F} = 240.4 Hz, C₄CHF₂) ppm. IR ν (cm⁻¹): 3418 (OH), 1696 (C=O_{acid}). C₁₂H₇F₄NO₂ (273): calcd (%) N 5.13, C 52.76, H 2.58, found N 5.03, C 52.80, H 2.75. MP: 183.1 – 184 °C.

2-(Difluoromethyl)-4-

[fluoro(trifluoromethoxy)methyl]quinoline-3-carboxylic acid **6aD**

a) KOH (8 equiv., 305 mg, 5.45 mmol), ethanol/water 60:40 (5.40 ml); b) Ethyl 2-(difluoromethyl)-4-[fluoro(trifluoromethoxy)methyl]quinoline-3-carboxylate **5aD** (1 equiv., 250 mg, 0.681 mmol); c) 2-(Difluoromethyl)-4-[fluoro(trifluoromethoxy)methyl]quinoline-3-carboxylic acid **6aD** was obtained as a light beige solid in 86% yield (197 mg). ¹H NMR (400 MHz, DMSO) $\delta_{\text{H}} = 8.38$ (d, ³*J*_{H-H} = 8.5 Hz, 1H, C₅H), 8.28 (d, ³*J*_{H-H} = 8.4 Hz, 1H, C₈H), 8.04 (t, ³*J*_{H-H} = 7.7 Hz, 1H, C₆H), 7.96 (t, ³*J*_{H-H} = 7.5 Hz, 1H, C₇H), 7.88 (d, ²*J*_{H-F} = 54.0 Hz, 1H, C₄CHFOCF₃), 7.30 (t, ²*J*_{H-F} = 53.7 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, DMSO) $\delta_{\text{F}} = -57.85$ (d, ⁴*J*_{F-F} = 4.8 Hz, C₄CHFOCF₃), -114.57 – -116.64 (m, A₂B₂, $\Delta\nu = 459.45$ Hz, C₂CHF₂), -122.18 – -122.61 (m, C₄CHFOCF₃) ppm. ¹³C NMR (101 MHz, DMSO) $\delta_{\text{C}} = 166.04$ (s, C₃CO), 147.96 (t, ²*J*_{C-F} = 23.8 Hz, C₂), 146.51 (s, C₉), 134.67 (d, ²*J*_{C-F} = 23.3 Hz, C₄), 132.12 (s, C₇), 130.43 (s, C₆), 130.34 (s, C₈), 125.59 – 125.22 (m, C₃), 124.71 (d, ⁴*J*_{C-F} = 3.9 Hz, C₅), 122.86 (s, C₁₀), 120.55 (qd, ¹*J*_{C-F} = 261.6, ³*J*_{C-F} = 1.2 Hz, C₄CHFOCF₃), 112.80 (t, ¹*J*_{C-F} = 241.5 Hz, C₂CHF₂), 103.06 (dq, ¹*J*_{C-F} = 230.2, ³*J*_{C-F} = 3.8 Hz, C₄CHFOCF₃) ppm. IR ν (cm⁻¹): 2920 (C_{sp3}H), 1714 (C=O_{acid}). C₁₃H₇F₆NO₃ (339): calcd (%) N 4.13, C 46.03, H 2.08, found N 4.02, C 46.87, H 2.39. MP: 183.3 – 185.5 °C.

6-Chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylic acid **6cA**

a) KOH (8 equiv., 0.585 g, 10.4 mmol), ethanol/water 60:40 (10.30 ml); b) Ethyl 6-chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate **5cA** (1 equiv., 0.583 g, 1.3 mmol); c) 6-Chloro-2,4-

bis(difluoromethyl)quinoline-3-carboxylic acid **6cA** was obtained as a light beige solid in 41% yield (531 mg). ¹H NMR (400 MHz, Acetone^{d6}) $\delta_{\text{H}} = 8.45$ (dd, ⁴*J*_{H-H} = 3.7, ⁵*J*_{H-F} = 1.8 Hz, 1H, C₅H), 8.30 (d, ³*J*_{H-H} = 9.0 Hz, 1H, C₈H), 8.04 (dd, ³*J*_{H-H} = 9.0, ⁴*J*_{H-H} = 2.2 Hz, 1H, C₇H), 7.63 (t, ²*J*_{H-F} = 52.3 Hz, 1H, C₄CHF₂), 7.20 (t, ²*J*_{H-F} = 54.1 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, Acetone^{d6}) $\delta_{\text{F}} = -111.47$ (d, ²*J*_{F-H} = 52.2 Hz, C₄CHF₂), -116.87 (d, ²*J*_{F-H} = 54.1 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, Acetone^{d6}) $\delta_{\text{C}} = 166.01$ (s, C₃CO), 149.66 (t, ²*J*_{C-F} = 24.7 Hz, C₂), 146.77 (s, C₆), 136.89 (t, ²*J*_{C-F} = 23.4 Hz, C₄), 136.61 (s, C₁₀), 133.57 (s, C₇), 133.43 (s, C₈), 126.53 (t, ³*J*_{C-F} = 6.4 Hz, C₃), 125.03 (s, C₉), 124.94 (t, ⁴*J*_{C-F} = 3.7 Hz, C₅), 114.20 (t, ¹*J*_{C-F} = 242.1 Hz, C₂CHF₂), 114.05 (t, ¹*J*_{C-F} = 240.4 Hz, C₄CHF₂) ppm. IR ν (cm⁻¹): 2918 (C_{sp3}H), 1725-1706 (C=O_{acid}). C₁₂H₆F₄ClNO₂ (307): calcd (%) N 4.55, C 46.85, H 1.97, found N 4.43, C 47.22, H 2.27. MP: 236.2 – 237.2 °C.

Carbamate synthesis: *t*-Butyl *N*-[2,4-bis(difluoromethyl)quinolin-3-yl]carbamate **7aA**

To a solution of 2,4-bis(difluoromethyl)quinoline-3-carboxylic acid **6aA** (1 equiv., 802 mg, 2.56 mmol) in *tert*-butyl alcohol (10 mL) were added NEt₃ (1.6 equiv., 0.552 mL, 4.09 mmol) and DPPA (1.3 equiv., 0.718 mL, 3.32 mmol). The reactor was not totally sealed in order to allow gas evacuation and the mixture was stirred at 100 °C overnight. The reaction mixture was cooled down and diluted with water. The organic layer was extracted with AcOEt, washed with a solution of NaHCO₃ followed by brine, dried over Na₂SO₄ and concentrated under vacuum. The product was purified by flash chromatography using a gradient of AcOEt in cyclohexane (0-20%). *t*-Butyl *N*-[2,4-bis(difluoromethyl)quinolin-3-yl]carbamate **7aA** was obtained as a beige solid in 64% yield (0.567 g). ¹H NMR (400 MHz, CDCl₃) $\delta_{\text{H}} = 8.47$ (d, ³*J*_{H-H} = 7.9 Hz, 1H, C₅H), 8.16 (d, ³*J*_{H-H} = 8.5 Hz, 1H, C₈H), 7.82 (t, ³*J*_{H-H} = 7.4 Hz, 1H, C₇H), 7.73 (t, ³*J*_{H-H} = 7.5 Hz, 1H, C₆H), 7.21 (t, ²*J*_{H-F} = 53.7 Hz, 1H, C₄CHF₂), 6.85 (t, ²*J*_{H-F} = 54.2 Hz, 1H, C₂CHF₂), 6.65 (s, 1H, NH), 1.69 – 1.20 (m, 9H, *t*-Bu) ppm. ¹⁹F NMR (376 MHz, CDCl₃) $\delta_{\text{F}} = -112.09$ (s, C₄CHF₂), -113.57 (d, ²*J*_{F-H} = 52.5 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) $\delta_{\text{C}} = 154.31$ (s, C₁₁), 149.51 – 146.66 (m, C₂), 146.01 (s, C₁₀), 137.39 – 134.67 (m, C₄), 130.46 (s, C_{7,8}), 129.61 (s, C₆), 127.05 (s, C₉), 125.59 (t, ⁴*J*_{C-F} = 3.9 Hz, C₅), 125.13 (s, C₃), 116.89 (t, ¹*J*_{C-F} = 240.1 Hz, C₂CHF₂), 112.55 (t, ¹*J*_{C-F} = 238.5 Hz, C₄CHF₂), 82.57 (s, C₁₂), 28.14 (s, *t*-Bu) ppm. IR ν (cm⁻¹): 3675 (NH), 2978-2901 (C_{sp3}H), 1704 (C=O_{ester}). C₁₆H₁₆F₄N₂O₂ (344): calcd (%) N 8.14, C 55.81, H 4.68, found N 8.01, C 56.22, H 4.79. MP: 135.6 – 136.5 °C.

2,4-Bis(difluoromethyl)quinolin-3-amine **8aA**

t-Butyl *N*-[2,4-bis(difluoromethyl)quinolin-3-yl]carbamate **7aA** (1 equiv., 566 mg, 1.32 mmol) was dissolved in DCE (4.53 mL) and treated with TFA (20.9 equiv., 2.04 mL, 27.5 mmol). After being stirred for 4 h at room temperature, the mixture was quenched with water and a solution of NaHCO₃ until neutral pH was reached. The organic layer was extracted with DCM, washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. 2,4-Bis(difluoromethyl)quinolin-3-amine **8aA** was obtained as a yellow solid in 98% yield (315 mg). ¹H NMR (400 MHz, CDCl₃) $\delta_{\text{H}} = 8.00$ (dd, ³*J*_{H-H} = 8.3, ⁴*J*_{H-H} = 1.1 Hz, 1H, C₅H), 7.83 (d, ³*J*_{H-H} = 8.6 Hz, 1H, C₈H), 7.62 – 7.57 (m, 1H, C₆H), 7.51 (ddd, ³*J*_{H-H} = 8.2,

$^3J_{H-H3} = 6.9$, $^4J_{H-H1} = 1.3$ Hz, 1H, C₇H), 7.43 (t, $^2J_{H-F} = 53.7$ Hz, 1H, C₄CHF₂), 6.84 (t, $^2J_{H-F} = 54.2$ Hz, 1H, C₂CHF₂), 5.08 (s, 2H, NH₂) ppm. ^{19}F NMR (376 MHz, CDCl₃) $\delta_{\text{F}} = -116.50$ (d, $^2J_{F-H} = 56.4$ Hz, C₄CHF₂), -116.63 (d, $^2J_{F-H} = 52.6$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl₃) $\delta_{\text{C}} = 141.95$ (t, $^2J_{C-F} = 26.1$ Hz, C₂), 140.35 (s, C₉), 137.10 (s, C₃), 130.85 (s, C₅), 129.93 (s, C₆), 126.92 (t, $^3J_{C-F} = 4.9$ Hz, C₁₀), 126.21 (s, C₇), 119.97 (s, C₈), 118.65 (t, $^1J_{C-F} = 239.4$ Hz, C₂CHF₂), 114.58 (t, $^2J_{C-F} = 20.4$ Hz, C₄), 113.90 (t, $^1J_{C-F} = 234.9$ Hz, C₄CHF₂) ppm. IR ν (cm⁻¹): 3533-3238 (NH + C_{sp}2H), 1635-1591 (C=C). C₁₁H₈F₄N₂ (244): calcd (%) N 11.37, C 54.11, H 3.30, found N 11.34, C 54.19, H 3.39. MP: 68.3 - 70.3 °C.

Typical procedure D for the Sandmeyer reaction

To a solution of 2,4-bis(difluoromethyl)quinolin-3-amine **8aA** (1 equiv.) in dry MeCN under argon was added the copper precursor (1 equiv.). The suspension was stirred for 10 min and *tert*-butyl nitrite (4 equiv.) was added. The mixture was stirred for 20 min at room temperature. Then the flask was fitted with a reflux condenser and heated at 60 °C for 4 h. After cooling to room temperature, the mixture was diluted with saturated aqueous NaHCO₃ and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure.

The following experiments were carried out according to **Typical Procedure D**, and specific details are reported as: a) Amine; b) MeCN; c) Copper precursor; d) *t*-BuONO; and e) yield and aspect. Individual analysis for each compound (**9aA**, **10aA** and **11aA**) is given below. Atoms are numbered in the description of NMR spectra according to the Supporting Information.

2,4-Bis(difluoromethyl)-3-iodoquinoline 9aA

a) 2,4-Bis(difluoromethyl)quinolin-3-amine **8aA** (1 equiv., 231 mg, 0.475 mmol); b) MeCN (4.97 mL); c) Copper (I) iodide (1 equiv., 90.4 mg, 0.475 mmol); d) *t*-BuONO (4 equiv., 0.228 mL, 1.9 mmol); e) 2,4-Bis(difluoromethyl)-3-iodoquinoline **9aA** was obtained as a colourless solid after purification on flash chromatography using a gradient of AcOEt in cyclohexane (0-20%) in 65% yield (109 mg). ^1H NMR (400 MHz, CDCl₃) $\delta_{\text{H}} = 8.44$ (d, $^3J_{H-H} = 8.1$ Hz, 1H, C₅H), 8.23 (d, $^3J_{H-H} = 8.4$ Hz, 1H, C₈H), 7.87 (ddd, $^3J_{H-H1} = 8.4$, $^3J_{H-H4} = 6.9$, $^4J_{H-H2} = 1.3$ Hz, 1H, C₆H), 7.75 (ddd, $^3J_{H-H2} = 8.4$, $^3J_{H-H3} = 6.9$, $^4J_{H-H1} = 1.3$ Hz, 1H, C₇H), 7.51 (t, $^2J_{H-F} = 52.7$ Hz, 1H, C₄CHF₂), 7.06 (t, $^2J_{H-F} = 54.0$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl₃) $\delta_{\text{F}} = -109.46$ (dd, $^2J_{F-H} = 52.7$, $^5J_{F-H} = 2.4$ Hz, C₄CHF₂), -115.42 (d, $^2J_{F-H} = 54.0$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl₃) $\delta_{\text{C}} = 150.58$ (t, $^2J_{C-F} = 23.4$ Hz, C₂), 147.13 (s, C₁₀), 141.31 (t, $^2J_{C-F} = 24.0$ Hz, C₄), 131.38 (s, C₆), 130.66 (s, C₈), 129.87 (s, C₇), 126.04 (s, C₉), 124.51 (t, $^4J_{C-F} = 5.2$ Hz, C₅), 121.69 (t, $^1J_{C-F} = 242.4$ Hz, C₄CHF₂), 115.50 (t, $^1J_{C-F} = 244.5$ Hz, C₂CHF₂), 89.31 (t, $^3J_{C-F} = 8.1$ Hz, C₃) ppm. C₁₁H₆F₄N (355): calcd (%) N 3.94, C 37.21, H 1.70, found N 3.96, C 37.33, H 1.78. MP: 87.1-87.9 °C.

3-Bromo-2,4-bis(difluoromethyl)quinoline 10aA

a) 2,4-Bis(difluoromethyl)quinolin-3-amine **8aA** (1 equiv., 245 mg, 1 mmol); b) MeCN (10.5 mL); c) Copper (II) bromide (0.5 equiv., 112 mg, 0.502 mmol); d) *t*-BuONO (4 equiv., 0.481 mL, 4.01 mmol); e) 3-Bromo-2,4-bis(difluoromethyl)quinoline **10aA** was

obtained as a colourless solid after purification on flash chromatography using a gradient of AcOEt in cyclohexane (0-5%) in 50% yield (153 mg). ^1H NMR (400 MHz, CDCl₃) $\delta_{\text{H}} = 8.45$ (dd, $^3J_{H-H} = 8.6$, $^5J_{H-F} = 2.0$ Hz, 1H, C₅H), 8.24 (d, $^3J_{H-H} = 8.2$ Hz, 1H, C₈H), 7.87 (ddd, $^3J_{H-H2} = 8.4$, $^3J_{H-H4} = 6.9$, $^4J_{H-H1} = 1.3$ Hz, 1H, C₇H), 7.77 (ddd, $^3J_{H-H1} = 8.5$, $^3J_{H-H3} = 6.9$, $^4J_{H-H2} = 1.3$ Hz, 1H, C₆H), 7.59 (t, $^2J_{H-F} = 52.9$ Hz, 1H, C₄CHF₂), 7.06 (t, $^2J_{H-F} = 53.8$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl₃) $\delta_{\text{F}} = -111.19$ (dd, $^2J_{F-H} = 52.9$, $^5J_{F-H} = 2.3$ Hz, C₄CHF₂), -116.95 (d, $^2J_{F-H} = 53.8$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl₃) $\delta_{\text{C}} = 148.80$ (t, $^2J_{C-F} = 23.7$ Hz, C₂), 146.53 (s, C₁₀), 137.87 (t, $^2J_{C-F} = 24.4$ Hz, C₄), 131.20 (s, C₇), 146.53 (s, C₈), 130.19 (s, C₆), 125.97 (s, C₉), 124.78 (t, $^4J_{C-F} = 4.8$ Hz, C₅), 115.80 (t, $^1J_{C-F} = 193.9$ Hz, C₄CHF₂), 114.95 (t, $^3J_{C-F} = 7.7$ Hz, C₃), 113.88 (t, $^1J_{C-F} = 196.9$ Hz, C₂CHF₂) ppm. C₁₁H₆BrF₄N (308): calcd (%) N 4.55, C 42.89, H 1.96, found N 4.47, C 43.05, H 2.13. MP: 68.8 - 70 °C.

2,4-Bis(difluoromethyl)quinoline-3-carbonitrile 11aA

a) 2,4-Bis(difluoromethyl)quinolin-3-amine **8aA** (1 equiv., 247 mg, 1.01 mmol); b) MeCN (5 mL); c) Copper (I) cyanide (1 equiv., 90.6 mg, 1.01 mmol); d) *t*-BuONO (4 equiv., 0.485 mL, 4.05 mmol); e) 2,4-Bis(difluoromethyl)quinoline-3-carbonitrile **11aA** was obtained as a colourless solid after purification on flash chromatography using a gradient of AcOEt in cyclohexane (0-5%) in 47% yield (121 mg). ^1H NMR (400 MHz, CDCl₃) $\delta_{\text{H}} = 8.51$ (dd, $^3J_{H-H} = 8.6$, $^5J_{H-F} = 1.7$ Hz, 1H, C₅H), 8.30 (d, $^3J_{H-H} = 8.4$ Hz, 1H, C₈H), 8.04 (ddd, $^3J_{H-H2} = 8.4$, $^3J_{H-H4} = 7.0$, $^4J_{H-H1} = 1.3$ Hz, 1H, C₇H), 7.89 (ddd, $^3J_{H-H1} = 8.4$, $^3J_{H-H3} = 7.0$, $^4J_{H-H2} = 1.2$ Hz, 1H, C₆H), 7.47 (t, $^2J_{H-F} = 52.4$ Hz, 1H, C₄CHF₂), 6.93 (t, $^2J_{H-F} = 53.6$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl₃) $\delta_{\text{F}} = -109.07$ (dd, $^2J_{F-H} = 52.4$, $^5J_{F-H} = 2.0$ Hz, C₄CHF₂), -113.13 (d, $^2J_{F-H} = 53.7$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl₃) $\delta_{\text{C}} = 150.64$ (t, $^2J_{C-F} = 26.9$ Hz, C₂), 148.16 (s, C₉), 144.60 (t, $^2J_{C-F} = 24.6$ Hz, C₄), 134.07 (s, C₇), 131.14 and (2 * s, C₆, ₈), 125.70 (t, $^4J_{C-F} = 3.8$ Hz, C₅), 123.07 (s, C₁₀), 114.09 (t, $^1J_{C-F} = 243.4$ Hz, C₂CHF₂), 113.23 (t, $^1J_{C-F} = 242.7$ Hz, C₄CHF₂), 112.20 (s, C₃CN), 102.62 (t, $^3J_{C-F} = 6.6$ Hz, C₃) ppm. IR ν (cm⁻¹): 2988-2901 (C_{sp}3H), 2234 (CN). C₁₂H₆F₄N₂ (254): calcd (%) N 11.02, C 56.70, H 2.38, found N 10.96, C 56.28, H 2.43. MP: 130.6 - 132.3 °C.

2,4-Bis(difluoromethyl)-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline 12aA

To a solution of 2,4-bis(difluoromethyl)-3-iodoquinoline **9aA** (1 equiv., 2.42 g, 6.82 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equiv., 4.17 mL, 20.4 mmol) in anhydrous THF (10 ml) at -10 °C was added dropwise *i*PrMgCl.LiCl (1.5 equiv., 1.3 M in THF, 7.86 mL, 10.2 mmol). The reaction mixture was allowed to warm up to r.t. overnight. It was quenched with a saturated aqueous solution of ammonium chloride (NH₄Cl) and the aqueous phase was extracted with Et₂O. The combined organic layers were washed with saturated aqueous NH₄Cl then brine, dried over Na₂SO₄ and concentrated under reduced pressure.

2,4-Bis(difluoromethyl)-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline **12aA** was obtained after purification on column chromatography using a gradient of AcOEt in cyclohexane (0-5%) as a colourless solid in 54% yield (1.31 g). ^1H NMR (400 MHz, CDCl₃) $\delta_{\text{H}} = 8.30$ (d, $^3J_{H-H} = 8.5$ Hz, 1H, C₅H),

8.21 (d, $^3J_{H-H} = 8.4$ Hz, 1H, C₈H), 7.86 – 7.80 (m, 1H, C₇H), 7.71 (t, $^3J_{H-H} = 7.2$ Hz, 1H, C₆H), 7.34 (t, $^2J_{H-F} = 53.9$ Hz, 1H, C₄CHF₂), 6.98 (t, $^2J_{H-F} = 55.2$ Hz, 1H, C₂CHF₂), 1.45 (s, 12H, Bpin) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -108.94 (d, $^2J_{F-H} = 53.8$ Hz, C₄CHF₂), -112.64 (d, $^2J_{F-H} = 55.2$ Hz, C₂CHF₂) ppm. ¹¹B NMR (128 MHz, CDCl₃) δ_B = 31.01 (s, Bpin) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 154.17 (t, $^2J_{C-F} = 24.8$ Hz, C₂), 147.70 (s, C₉), 144.29 (t, $^2J_{C-F} = 21.9$ Hz, C₄), 131.15 (s, C₇), 130.67 (s, C₈), 129.12 (s, C₆), 124.57 (t, $^4J_{C-F} = 2.9$ Hz, C₅), 124.07 (s, C₁₀), 114.83 (t, $^1J_{C-F} = 242.4$ Hz, C₄CHF₂), 114.57 (t, $^1J_{C-F} = 241.4$ Hz, C₂CHF₂), 85.62 (s, C₁₁), 25.19 (s, C₁₁CH₃) ppm. C₁₇H₁₈F₄NBO₂ (355): calcd (%) N 3.94, C 57.49, H 5.11, found N 4.01, C 57.68, H 5.20. MP: 82.6-83.5 °C.

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