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A new approach toward the synthesis of 2,4-bis(fluoroalkyl)-substituted quinoline derivatives using Fluoroalkyl Amino Reagent chemistry

Fallia Aribi,^{a,d} Etienne Schmitt,^{a,d} Armen Panossian,^{a,d} Jean-Pierre Vors,^{b,d} Sergiy Pazenok,^{c,d} and Frédéric R. Leroux^{*a,d}

The present work describes the unprecedented use of Fluoroalkyl Amino Reagents (FARs) to afford 2,4-bis(fluoroalkyl)-substituted quinoline derivatives in two steps. In contrast to the Combes reaction, this approach allows for the synthesis of numerous quinoline derivatives bearing two identical or different fluoroalkyl substituents in 2 and 4 positions, under mild reaction conditions, in good yields and with a very good regioselectivity. This reaction is easily scalable and suitable for an industrial process.

Introduction

Since the last decade, fluorine is starting to become an alternative solution to many issues in agrochemistry, medicinal chemistry and material science. Indeed, its specific properties such as its high electronegativity, the strength of the C-F bond due to its low polarizability, and its size comparable to that of a hydrogen atom gives it a special appeal. Introduction of fluorine into a lead molecule may considerably improve its physicochemical properties. For example, the metabolic stability of C-F bonds toward oxidative degradation is well-known, and the acidity or basicity of adjacent functional groups can be modified. Likewise, the lipophilicity of molecules can be enhanced by introducing fluorine atoms in order to facilitate transport through membranes.¹⁻¹⁸ Therefore, the interest in fluorine chemistry encounters a swift rise and developing new strategies for the introduction of emergent fluorinated groups remains a challenge to overcome. A recent survey has shown that 20% of pharmaceuticals and 40% of agrochemicals (*e.g.* Fluazinam (fungicide), (Fluoxetine (anti-depressant)) are F-containing compounds (Figure 1). Among the 155 F-containing compounds listed as agrochemicals, 43% bear a trifluoromethyl group, 32% a single fluorine atom and around 11% are difluoromethyl derivatives.^{19, 20} On the other hand, the quinoline motif is present in many natural products and drugs already commercialized (*e.g.* Mefloquine, used as antimalarial drug). For example, they are used in the treatment of cancer, inflammatory diseases, bacterial or viral infections, etc. Quinoline-derived molecules are known for their various biological activities which make them important pharmaceutical and agrochemical precursors.²¹⁻²⁷ The combination of an aza-heterocycle and various fluorinated substituents may enhance the properties of previously known compounds and make them highly attractive as agrochemical ingredients.^{15, 28-31}

In this paper, we report on a new method to synthesize unprecedented 2,4-bis(fluoroalkyl)-substituted quinoline derivatives, based on the reaction of Fluoroalkyl Amino Reagents (FARs) (Scheme 1) with *N*-aryl imines **1**. FARs represent a powerful tool for the introduction of various

fluorinated substituents. In literature, three different FARs were used: 1,1,2,2-tetrafluoro-*N,N*-dimethylethan-1-amine (**4a**; TFEDMA), 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine (**4b**; Yarovenko reagent), and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (**4c**; Ishikawa reagent). FARs are prepared from commercially available fluoroolefins and dimethyl- or diethylamine, and were initially used as fluorinating agents in order to convert hydroxyl or carbonyl groups into fluoroalkyl substituents under mild conditions.³²⁻³⁶

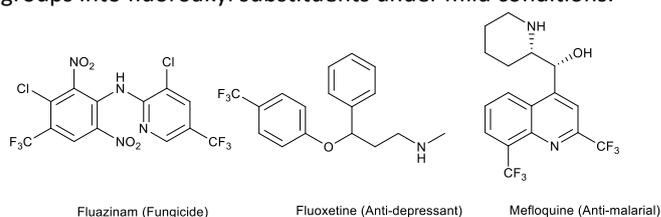
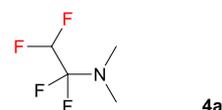
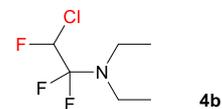


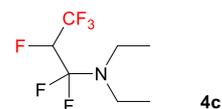
Figure 1: Bioactive compounds containing fluorinated groups.



1,1,2,2-Tetrafluoro-*N,N*-dimethylethan-1-amine
Petrov: TFEDMA (2001)



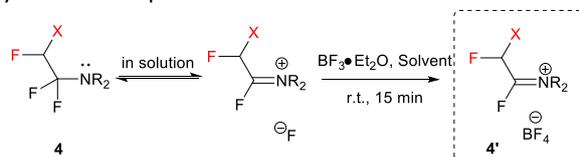
2-Chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine
Yarovenko reagent (1959)



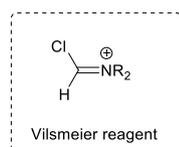
N,N-Diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine
Ishikawa reagent (1979)

Scheme 1: Commercially available Fluoroalkyl Amino Reagents (FARs)

A key feature of FARs is their activation by Lewis acids (e.g. $\text{BF}_3 \cdot \text{Et}_2\text{O}$), preferentially in an aprotic solvent, to provide highly reactive Vilsmeier-like iminium salts (Scheme 2).³⁷⁻³⁹ After activation, the electrophilic character of FARs is enhanced, and the iminium salts can undergo nucleophilic attack by various compounds.



R= CH₃, C₂H₅
X= F, Cl, CF₃
Solvent: DCM, MeCN

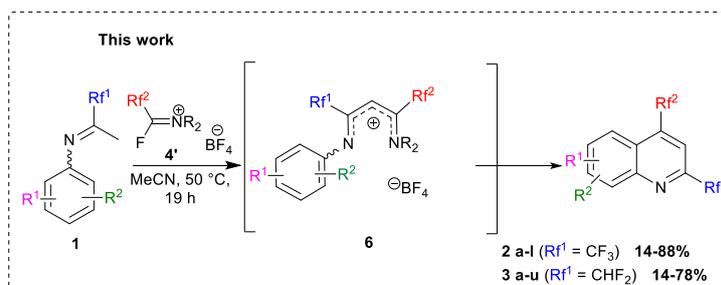
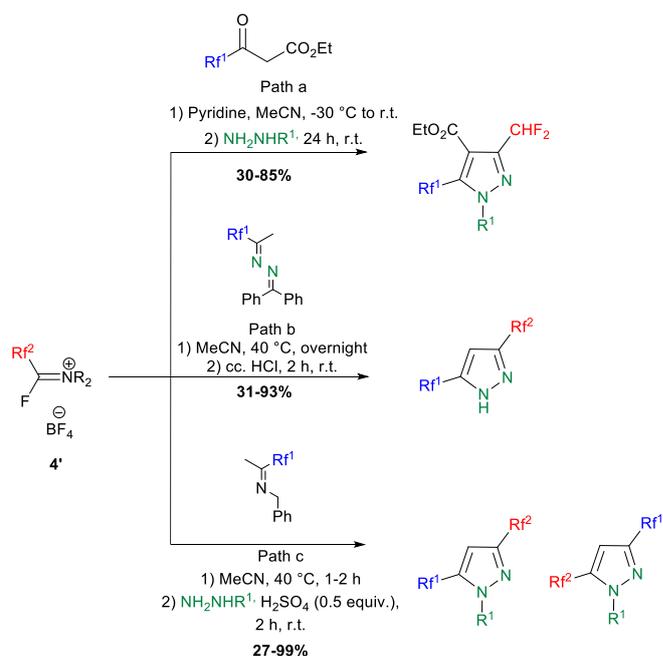


Scheme 2: Activation of FARs by Lewis acids converting them into their corresponding iminium salts.

Of the three existing FARs, TFEDMA is the most stable at ambient temperature, the purer after activation and it is also the most reactive one, due to the presence of the dimethyl moiety that makes it less hindered and thus more prone to nucleophilic attack.

In 1979, Ishikawa employed the Yarovenko reagent (**4b**) in cyclization reactions with 2-amino-anilines, -phenols and -thiophenols to provide various benzazoles.⁴⁰ More recently, we further demonstrated the ability of FARs to behave as α -fluoroacyl equivalents for the introduction of fluorinated substituents (CHF_2 , CHFC and CHFCF_3) in the preparation of a new family of compounds for agrochemistry.⁴¹⁻⁴⁶ We were able to synthesize fluorinated heterocycles, especially 3,5-bis(fluoroalkyl) pyrazoles following 3 strategies (Scheme 3). In Path a, pyrazoles carboxylates were formed by reaction of FARs with fluorinated acetoacetates, followed by cyclization with hydrazines.^{42, 43} The limited availability of fluorinated acetoacetates encouraged us to turn towards other strategies. NH-pyrazoles could also be obtained from the condensation of benzophenone-derived fluorinated azines with activated FARs, followed by cyclization under acidic conditions (Path b). However, a major drawback of this reaction was residual benzophenone, which proved difficult to remove even after several purifications.^{44, 45} This method was then improved in terms of yield, reaction time and waste by the use of fluorinated *N*-benzyl imines (Path c).^{46, 47}

Previous work



R: Me, Et
R¹: H, Me, Ph, tBu, aryl, benzyl, quinoline, ect
R²: H, F, OMe, Cl, NMe₂, OCF₃, CF₃, Ph, SPh, fused phenol
R¹: CHF₂, CH₂F, CF₃, C₂F₅, CF₂Cl
R²: CHF₂, CHFCI, CHFCF₃, CHFOCF₃

Scheme 3: Previous work: Formation of fluorinated pyrazoles involving activated FARs: a) from fluorinated acetoacetates, b) from fluorinated azines and c) from fluorinated imines. This work: Formation of fluorinated quinoline derivatives involving activated FARs.

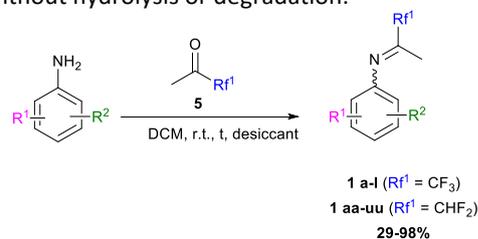
To further exploit the reactivity of FARs, we decided to use *N*-aryl fluoroketimines. The reactions afforded bis-fluorinated quinolines **2** and **3** (Scheme 3). Such fluorinated quinolines are commonly prepared by first constructing the quinoline core (via the Skraup, Döbner-von Miller, Pfitzinger, Conrad-Limpach, Friedlander or Combes syntheses, to cite a few),^{21, 48, 49} mostly under harsh conditions, and sometimes with low yields. Then, fluorine might be introduced by means of fluorinating agents, Balz-Schiemann reaction, Halex process or HF-mediated. Nevertheless, such fluorinations often require multi-step reactions and particular equipment.^{31, 50-59} Among the existing syntheses of fluorinated quinolines, none combines short synthetic pathway, mild reaction conditions, the possibility to introduce different fluorinated substituents in

the same molecule and industrially suitable conditions. In particular, the synthesis of quinoline derivatives bearing two fluorinated groups in both positions 2 and 4 is scarcely described in the literature; only a few bis(trifluoromethylated)quinolines can be found.^{57, 58, 60, 61} Some examples reported on the use of anilines and fluorinated β -diketones, which are difficultly accessible. The products were formed in low yields and their isolation proved to be tricky because of their volatility. Moreover, the cyclization step is usually performed under harsh conditions in polyphosphoric acid, which produces P-containing waste in large amounts, and the use of unsymmetrical β -diketones leads to mixtures of regioisomers.⁶²⁻⁶⁴ In the present work, we describe the access to quinolines substituted in positions 2 and 4 with different fluoroalkyl groups, under mild conditions and with complete regioselectivity.

Results and discussion

Synthesis of quinoline derivatives

Substituted anilines were condensed onto di- or trifluoroacetone **5** at room temperature in anhydrous dichloromethane (DCM) in presence of a desiccant (*e.g.* 4 Å MS, MgSO₄) following the publication of Perrone *et al.* (Scheme 4).⁶⁵ The desired fluorinated imines **1** were obtained in moderate to excellent yields (Tables 1 and 2). Ketimines obtained from 1,1-difluoroacetone gave better results than from trifluoroacetone. This can be explained by the weaker destabilization of the carbocation - due to the less intense electron-withdrawing effect of the CHF₂ moiety compared to CF₃ - during the hemi-aminal dehydration step. In some cases, the purity of the ketimine was low, either because of incomplete conversion - even after introduction of additional ketone or prolonged reaction time - or side reactions, *e.g.* self-condensation of the ketone. This can be avoided by performing the reaction at 0 °C; however, under these conditions, the condensation between anilines and the ketones is either very slow or totally ineffective. Ketimines cannot be purified due to their sensitivity to moisture or silica. Nonetheless, the presence of side products in **1** did not seem to affect the next step. The stability of the ketimines is acceptable and they can be stored under argon for a few weeks without hydrolysis or degradation.



Scheme 4: Synthesis of fluorinated ketimines.

Table 1: Trifluoromethylated ketimines.

Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
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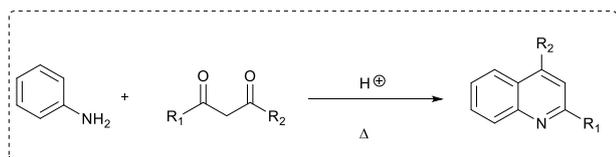
1		87	7		93
2		90	8		82
3		92	9		93
4		93	10		80
5		70	11		57
6		62	12		50

Table 2: Difluoromethylated ketimines.

Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1		96	12		94
2		98	13		90
3		98	14		91
4		98	15		a
5		78	16		29
6		91	17		93
7		83	18		40
8		75	19		a
9		93	20		a
10		91	21		91
11		a			

[a]: Mixture (SM, Impurities).

Next, ketimines **1** were reacted with activated FARs. In practice, FARs were treated beforehand with BF₃•Et₂O in MeCN for 15 min and directly mixed with fluorinated imines. Upon nucleophilic attack of the enamine tautomer of **1** onto the iminium salt, the resulting vinamidinium intermediate **6** undergoes electrophilic aromatic substitution yielding quinolines **2** and **3**, following a Combes-like rearrangement (Schemes 3, 5 and figure 2).⁶⁶



Scheme 5: Combes reaction.

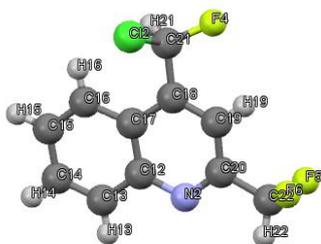
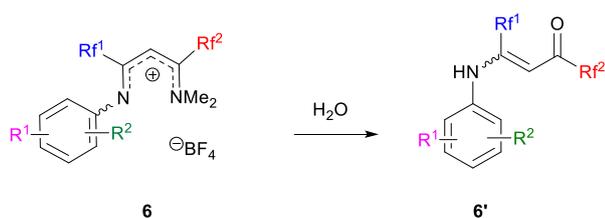


Figure 2: Crystal structure of 4-[chloro(fluoro)methyl]-2-(difluoromethyl)quinoline **3a**.⁶⁷

In certain cases, the transformation was not complete and hydrolysis of the reaction mixture provided vinamidines **6'**, thus confirming the mechanistic pathway (Scheme 6).



Scheme 6: Vinamidinium hydrolysis.

The desired quinolines were obtained in moderate to good yields. All results are summarized below (Tables 3 and 4, figures 3 and 4).

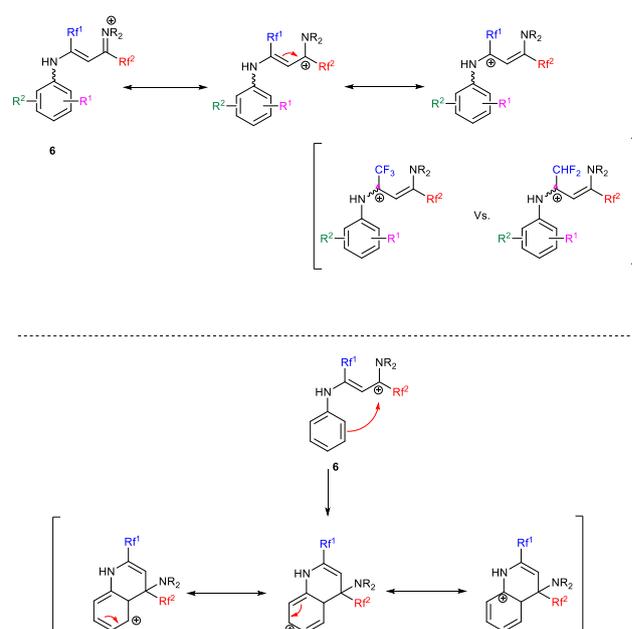
In general, quinoline derivatives obtained from either the Yarovenko **4b** or Ishikawa **4c** reagents (Table 3: entries 2, 3, 10 and 11; Table 4: entries 2 and 9) were formed in lower yields than those obtained from the reaction with TFEDMA **4a**. This confirms the higher reactivity of the latter reagent.

The synthesis of quinolines derived from CF₃ substituted anilines (Table 4: entries 18-20) was performed, however the yields were not satisfying due to the high volatility of these compounds.

Starting from imines bearing a 3-substituent on the arene (Table 3: entries 5, 8 and 12; Table 4: entries 4, 7, 11, 13 and 19), only one regioisomer was observed after purification, namely 7-substituted quinolines. Indeed, the cyclisation of the vinamidinium intermediate **6** occurs at the less hindered position, *i.e.* *para* to the 3-substituent of the imine.

Overall, the relative yields of quinolines in Tables 3 and 4 can be rationalized in part by an interplay of destabilizing and stabilizing effects operating on the vinamidinium intermediate

on the one hand, and on the Wheland intermediate obtained during cyclisation on the other hand (Scheme 7).



Scheme 7: Stabilization/destabilization of intermediate **6** during the cyclization process.

Table 3: Synthesis of quinolines from 1,1,1-trifluoroacetone-derived imines **1a**–**l**.

Entry	Substrate	FAR	Product	Yield (%) ^a
1		4a	2ai	62
2	1a	4b	2aii	57
3		4c	2aiii	14
4	1b		2b	88
5	1c		2c	64
6	1d	4a	2d	85
7	1e		2e	70
8	1f		2f	62
9		4a	2gi	67
10	1g	4b	2gii	35 ^b
11		4c	2giii	1:3 ^c
12	1h		2h	36
13	1i		2i	49
14	1j	4a	2j	37
15	1k		2k	38
16	1l		2l	38

[a]: Isolated yield except indicated otherwise; [b]:¹⁹F NMR yield by using fluorobenzene as internal standard. [c]: ¹H NMR ratio (**2:6'**), not isolated.

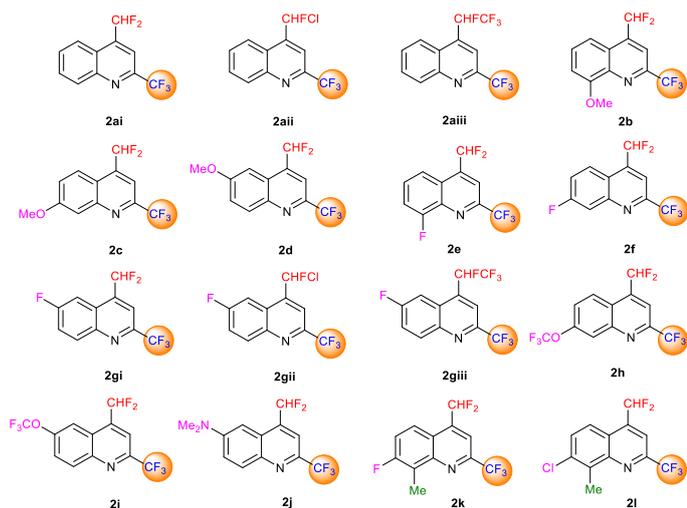


Figure 3: 4-(Difluoromethyl)-2-(trifluoromethyl)-substituted quinoline derivatives **2ai-l**.

In the case where Rf¹ is a CF₃ group, the withdrawing effect of CF₃ destabilizes the vinamidinium intermediate **6**. The addition of mesomeric donor substituents on **6** might stabilize it. We indeed obtained similar or better results than starting from the corresponding *N*-phenyl substrate (Table 3, entries 1, 4–9). A notable exception is the dimethylamino-substituted substrate (entry 14). When Rf¹ is a CF₃ group, the best results in terms of yields were obtained when mesomeric donor substituents are in position 2 and 4 (Table 3, entries 4 and 6 vs. entry 5, entries 7 and 9 vs. entry 8). The introduction of electron-withdrawing substituents destabilizes the vinamidinium even further and the cyclization is less efficient (Table 3, entries 1, 12–13).

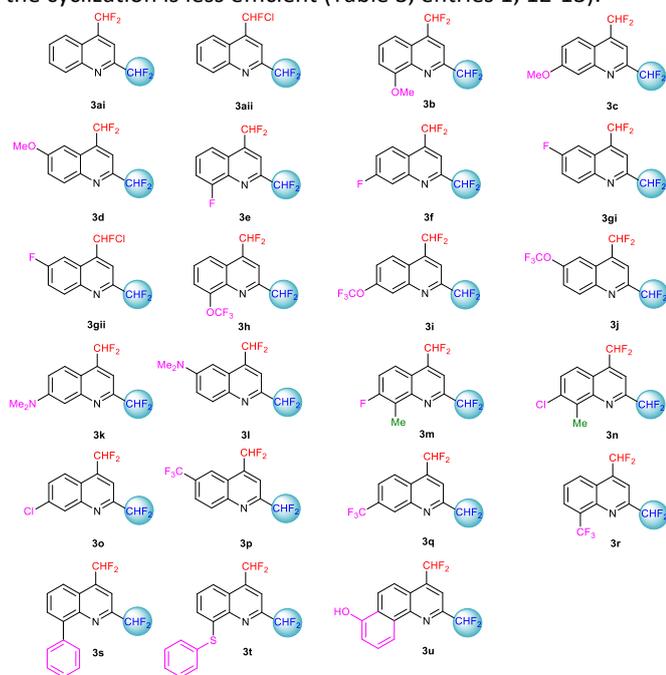


Figure 4: 2,4-Bis(difluoromethyl)-substituted quinoline derivatives **3ai-u**.

Table 4: Synthesis of quinolines from 1,1-difluoroacetone-derived imines **1aa-uu**.

Entry	Substrate	FAR	Product	Yield (%) ^a
1		4a	3ai	77
2	1aa	4b	3aii	78
3	1bb		3b	72
4	1cc		3c	78
5	1dd	4a	3d	71
6	1ee		3e	39 (3:1) ^b
7	1ff		3f	70
8			3gi	39
9	1gg	4b	3gii	traces
10	1hh		3h	39
11	1ii		3i	71
12	1jj		3j	58
13	1kk		3k	15
14	1ll		3l	14
15	1mm		3m	76
16	1nn	4a	3n	75
17	1oo		3o	45
18	1pp		3p	23
19	1qq		3q	28
20	1rr		3r	traces
21	1ss		3s	28
22	1tt		3t	52
23	1uu		3u	51

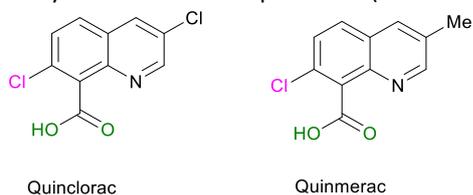
[a]: Isolated yield except indicated otherwise; [b]: ¹H NMR ratio (**3:6'**), not isolated.

When Rf¹ is a CHF₂, the vinamidinium intermediate **6** is less destabilized. Cyclization would therefore be facilitated by mesomeric donor substituents (Table 4, entries 1, 3–5, 7 vs. 10, 12, 18–20). As expected quinoline derivatives which possess mesomeric donor substituents in position 7 gave the best results. Indeed the carbocation is stabilized during the cyclization process (Table 4, entry 4 vs. entries 3 and 5, entry 7 vs. entries 6 and 8). However, once again the dimethylamino group fails to obey this rule (entry 13), and a 3-OCF₃ substituent leads to a surprisingly high yield of 71% (entry 11).

Clearly, other subtle effects have yet to be invoked to account for the observed reactivities. In general, higher yields are obtained for 7-substituted quinolines compared to 6- or 8-substituted ones with Rf¹ = CHF₂ (Table 4, entry 4 vs. entries 3 and 5; entry 7 vs. entries 6 and 8), while the opposite applies when Rf¹ is a CF₃ (Table 3, entry 5 vs. entries 4 and 6; entry 8 vs. entries 7 and 9).

Introduction of new functionalities in position 8 by oxidation

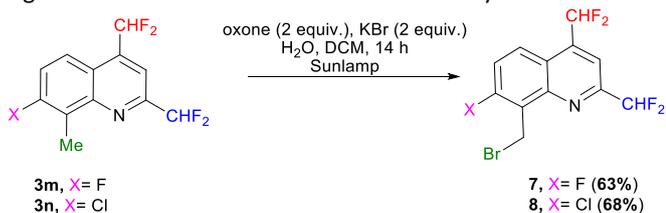
Commercially available quinolines named Quinmerac and Quinclorac, developed by BASF, have shown some activities as selective herbicides and are used on cereals to control weeds growth.^{68, 69} The particularity of these molecules is that they bear a carboxylic acid function in position 8 (Scheme 8).



Scheme 8: Molecular structures of Quinclorac and Quinmerac.

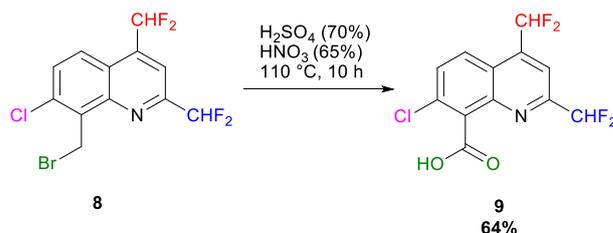
Thus, we were interested in the introduction of a carboxylic acid function in the same position on our fluorinated quinoline derivatives. Bis-substituted quinolines **3n** and **3m** were chosen as precursors for the synthesis of bis(fluoroalkyl) analogues of Quinmerac and Quinclorac in order to test their potential activity as phytosanitary ingredients.

We first attempted to oxidize the methyl group of quinolines **3m–n** under photochemical conditions, following the procedure of Togo *et al.*, which should afford the desired carboxylic acids in presence of oxone and potassium bromide in a mixture of water and dichloromethane.⁷⁰ Nevertheless, the reaction did not allow the access to the desired compounds but to the 8-(bromomethyl)-2,4-bis(difluoromethyl)-7-halo-quinolines **7** (X = F) and **8** (X = Cl) (Scheme 9). Alternately, the oxidation conditions of Sudalai *et al.* (aqueous sulfuric acid, sodium periodate and lithium bromide in the absence of solvent)⁷¹ provided the same 8-(bromomethyl)quinoline derivatives **7** and **8** in 50 and 55% yields, respectively. Although it requires a slightly longer reaction time, the photochemical procedure was preferred as it gave better results and is also easier to carry out.



Scheme 9: Methyl group oxidation by photochemistry.

In 1984, H. Hagen and coworkers described the oxidation of a bromomethyl quinoline derivative into its corresponding carboxylic acid (Quinmerac) thanks to a mixture of concentrated acids at 110 °C.⁶⁹ Following this procedure, 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid **9** was obtained in 64% yield (Scheme 10).



Scheme 10: Oxidation of 8-(bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **8** into its corresponding carboxylic acid **9**.

The structure of the desired compound was confirmed by X-Ray diffraction crystallography, which allowed us to observe the presence of a reciprocal intermolecular hydrogen bonding between the hydroxyl group of one molecule and the nitrogen of the other (Figure 5).

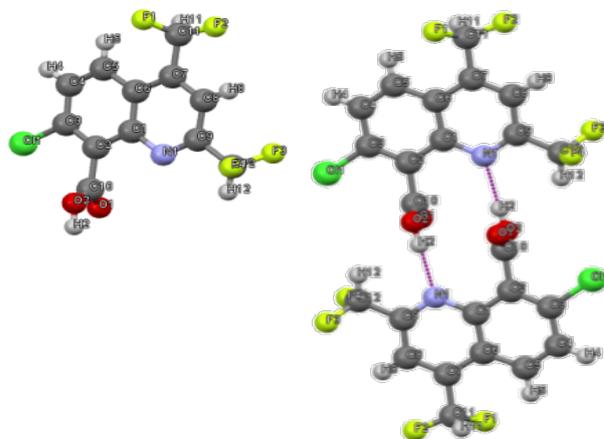
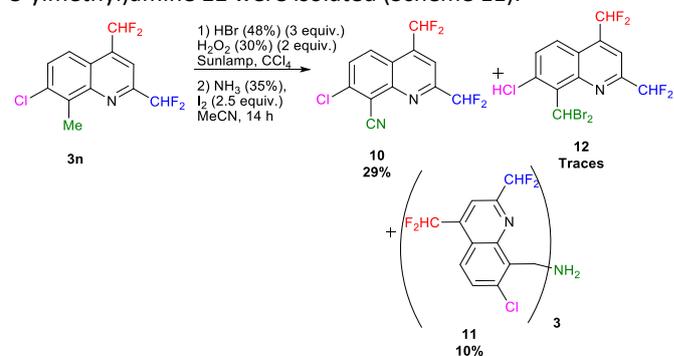


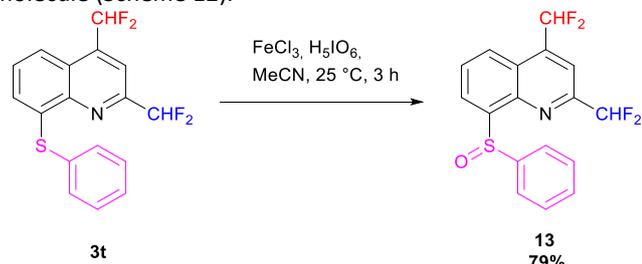
Figure 5: Single crystal X-ray diffraction structure of **9**.⁶⁷

In parallel, we attempted the transformation of the methyl in position 8 into a nitrile according to Togo *et al.*, employing aq. HBr, aq. H₂O₂ in CCl₄ followed by the addition of aq. NH₃ and I₂ in MeCN.⁷² After 14 hours of reaction under sunlamp irradiation at 60 °C, 29% of the desired 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carbonitrile **10** was obtained. After purification, traces of 8-(dibromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **12** and 10% of the tris(quinoline-8-ylmethyl)amine **11** were isolated (Scheme 11).



Scheme 11: One-pot transformation of 8-methylquinoline **3n** into the corresponding quinoline-8-carbonitrile **10**.

Then, oxidation of the 2,4-bis(difluoromethyl)-8-(phenylsulfanyl)quinoline **3t** was performed following the procedure of Kim *et al.* using iron(III) chloride and periodic acid.⁷³ The desired sulfoxide **13** was obtained in 79% yield in racemic form. The diastereotopic fluorine atoms observed in ¹⁹F NMR confirm the presence of the stereocenter on the molecule (Scheme 12).



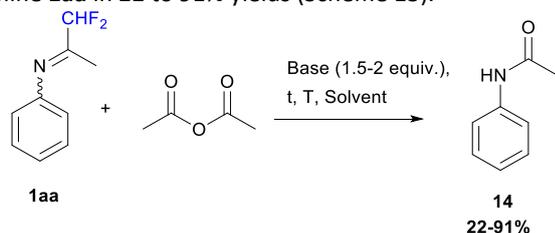
Scheme 12: Oxidation of **3t** into sulfoxide **13**.

Several other oxidation protocols were attempted in order to functionalize the position 8 of quinolines **7** and **8** but all failed. The low electron-density of these bis(fluoroalkyl)quinolines render them difficult to oxidize, as attested by the need of really harsh conditions, even at high temperature, to afford the desired compounds in moderate yields only.

Comparison between the use of FARs and carboxylic anhydrides or oxalate derivatives in the synthesis of quinolines

Furthermore, we studied the reaction of ketimine **1aa** with carboxylic anhydrides and acyl chloride. Indeed, various anhydrides or acyl chlorides are commercially available and could enlarge the scope of the approach. The purpose was to study the possibility to access to new quinoline derivatives by using this abundant starting material.

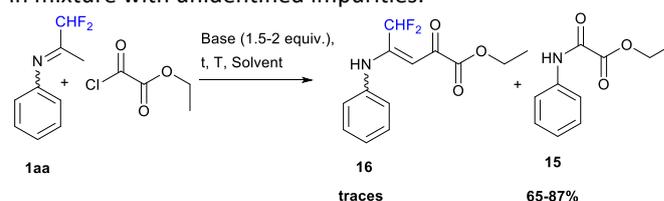
Our first attempt used acetic anhydride (1 equiv.) in either dichloromethane or acetonitrile, from -5 to 50 °C, in presence of bases such as pyridine or DIPEA (1.5 to 2 equiv.) or without. At the end of the reaction, the *N*-phenylacetamide **14** was always obtained after *N*-acylation and hydrolysis of the ketimine **1aa** in 22 to 91% yields (Scheme 13).



Scheme 13: Reaction between ketimine **1aa** and acetic anhydride.

When ketimine **1aa** was reacted with ethyl oxalyl monochloride (1 equiv.) under the same series of conditions as for acetic anhydride, the corresponding ethyl-2-oxo-2-(phenylamino)acetate **15** was obtained in 65 to 87% yields (Scheme 14). However, when **1aa** was dissolved in acetonitrile in presence of pyridine (1.5 equiv.) at room temperature, a

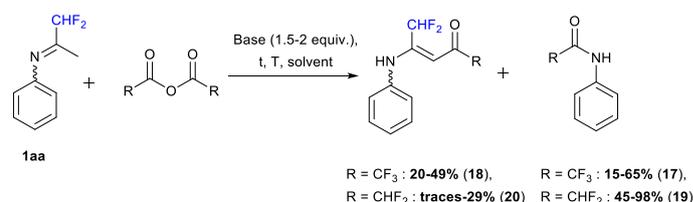
small amount of vinamide **16** was obtained as a minor fraction in mixture with unidentified impurities.



Scheme 14: Reaction between ketimine **1aa** and ethyl oxalyl monochloride.

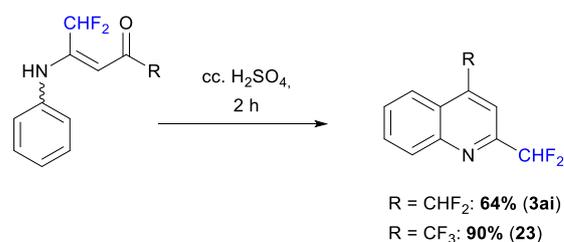
In a second part, we decided to study the reactivity of ketimine **1aa** in presence of fluorinated acetic anhydrides (1 equiv.). First, when trifluoroacetic anhydride was used, the corresponding 2,2,2-trifluoro-*N*-phenylacetamide **17** was obtained. In dichloromethane in presence of pyridine (1.5 equiv.) at -5 to 50 °C and in acetonitrile in presence of DIPEA (2 equiv.) at room temperature, only the compound **17** was formed in respectively 65 and 35% yield. However, in acetonitrile in presence of pyridine (1.5 equiv.) or without base, at room temperature or at 50 °C, the desired vinamide **18** was obtained in 20 to 49% yields (Scheme 15).

Next, difluoroacetic anhydride was reacted with ketimine **1aa** under the same reaction conditions (Scheme 15). In dichloromethane in presence of pyridine (1.5 equiv.) at -5 to 50 °C, 45% yield of 2,2-difluoro-*N*-phenylacetamide **19** was obtained. Vinamide **20** was observed in a small amount in mixture with degradation products and isolated in 29% yield after purification by column chromatography. DIPEA, used instead of pyridine also led to the formation of amide **19** as a major product in 47% yield and only traces of vinamide **20** were isolated.



Scheme 15: Reaction between ketimine **1aa** and fluorinated anhydrides.

The vinamides **18** and **20** were finally involved in a cyclization reaction in presence of concentrated H₂SO₄ (10 equiv.) at 50 °C for 2 h. The corresponding quinoline derivatives **3ai** and **23** were obtained in 64 and 90% yield, respectively (Scheme 16).



Scheme 16: Cyclization reaction of vinamide.

These results confirm the superiority of FARs in the synthesis of quinoline derivatives in one step with overall good yields. Although the use of anhydrides or acyl chlorides was a synthetic asset, they have not allowed to access the desired quinoline derivatives in one step, as they afforded first the intermediate vinamides which had to be converted into the quinolines under harsh conditions.

Conclusions

In summary, this work describes a new and efficient way to access quinolines bearing two different or identical fluoroalkyl groups in positions 2 and 4. FARs proved to be highly useful tools in the synthesis of these fluorinated heterocycles and afforded them in moderate to high yield (14-88%) under mild conditions.

Experimental section

Materials and methods.

All reactions were performed in flame-dried glassware using Schlenk techniques. 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 distilled from CaH₂ or sodium + benzophenone prior to use. Desiccants (4 Å molecular sieves (4 Å MS) or magnesium sulphate (MgSO₄) 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 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, td = triplet of doublets, dd = doublet of doublets), coupling constant (Hz) and integration. The 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.

General procedure for the synthesis of ketimines derivatives 1

Under argon atmosphere, an excess of cold perfluoroacetone (2 equiv.) was added to aniline derivatives (1 equiv.) in anhydrous DCM (2 mL/1 mmol) in presence of desiccant (e.g. (4 Å MS) or MgSO₄). Then the reaction mixture was stirred for the indicated time at room temperature. The desiccant was then filtered off on celite and washed with ether. The filtrate was concentrated under reduced pressure to provide the desired product. Ketimines cannot be purified due to their sensitivity to moisture or silica so the compound was used without any further purification.

***N*-(1,1,1-Trifluoropropan-2-ylidene)aniline 1a.** The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.92 mL, 21.4 mmol) and aniline (1 equiv., 0.98 mL, 10.7 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 3 h at room temperature. *N*-(1,1,1-Trifluoropropan-2-ylidene)aniline **1a** was provided as a brown oil (1.74 g, 87%, estimated). ¹H NMR δH = 7.38 (2 H, t, ³J_{H-H} = 7.9 Hz, C(3,5)H), 7.18 (1 H, t, ³J_{H-H} = 7.5 Hz, C(4)H), 6.82 – 6.74 (2 H, m, C(2,6)H), 2.02 (3 H, s, Me) ppm. ¹⁹F NMR δF = -74.68 (3 F, s, CF₃) ppm. ¹³C NMR δC = 157.41 (q, ²J_{C-F} = 33.9 Hz, CCF₃), 147.72 (s, C-1), 129.33 (2 C, s, C-3,5), 125.29 (s, C-4), 119.87 (q, ¹J_{C-F} = 278.4 Hz, CF₃) 118.87 (2 C, s, C-2,6), 14.50 (s, Me) ppm.

2-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1b. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.46 mL, 16.2 mmol) and 2-methoxyaniline (1 equiv., 0.92 mL, 8.12 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 21 h at room temperature. 2-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1b** was provided as a brown oil (1.59 g, 90%). ¹H NMR δH = 7.16 – 7.12 (1 H, m, C(4)H), 7.00 – 6.90 (2 H, m, C(5,6)H), 6.78 – 6.75 (1 H, m, C(3)H), 3.78 (3 H, s, OMe), 1.95 (3 H, s, Me) ppm. ¹⁹F NMR δF = -74.33 – -74.42 (3 F, m, CF₃) ppm. ¹³C NMR δC = 158.86 (q, ²J_{C-F} = 33.7 Hz, CCF₃), 148.19 (s, C-2), 136.43 (s, C-1), 126.15 (s, C-4), 120.90 (s, C-5), 120.14 (s, C-3), 119.77 (q, ¹J_{C-F} = 278.4 Hz, CF₃), 111.78 (s, C-6), 55.51 (s, OMe), 14.90 (s, Me) ppm. HRMS (ESI +) for C₁₀H₁₁F₃NO [M + H]: calcd 218.0787, found 218.0773.

3-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1c. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.47 mL, 16.4 mmol) and 3-methoxyaniline (1 equiv., 0.91 mL, 8.12 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 24 h at room temperature. 3-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1c** was provided as a brown oil (1.62 g, 92%, estimated). ¹H NMR δH = 7.35 – 7.22 (1 H, m, C(5)H), 6.79 – 6.70 (1 H, m, C(4)H), 6.44 – 6.32 (2 H, m, C(2,6)H), 3.79 (3 H, s, OMe), 2.05 (3 H, s, Me) ppm. ¹⁹F NMR δF = -74.81 (3 F, s, CF₃), -74.91 (3 F, s, CF₃) ppm. ¹³C NMR δC = 160.50 (s, C-3), 157.56 (q, ²J_{C-F} = 33.9 Hz, CCF₃), 148.95 (s, C-1), 130.08 (s, C-5), 119.78 (q, ¹J_{C-F} = 278.2 Hz, CF₃), 110.60 (2 C, s, C-4,6), 104.49 (s, C-2),

54.91 (s, OMe), 14.01 (s, Me) ppm. HRMS (ESI +) for $C_{10}H_{11}F_3NO$ [M + H]: calcd 218.0787, found 218.0818.

4-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1d. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.47 mL, 16.4 mmol) and 4-methoxyaniline (1 equiv., 1.01 g, 8.2 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 20 h at room temperature. 4-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1d** was provided as a brown oil (1.65 g, 93%). 1H NMR δ_H = 6.86 (2 H, m, **AA'**, C(2,6)H), 6.73 (2 H, m, **BB'**, C(3,5)H), 3.75 – 3.71 (3 H, m, OMe), 2.03 – 2.00 (3 H, m, Me) ppm. ^{19}F NMR δ_F = -74.58 – -74.63 (3 F, m, CF_3) ppm. ^{13}C NMR δ_C = 157.51 (s, C-4), 156.53 (q, $^2J_{C-F}$ = 33.5 Hz, CCF_3), 140.36 (s, C-1), 120.85 (2 C, s, C-3,5), 119.96 (q, $^1J_{C-F}$ = 278.1 Hz, CF_3), 114.31 (2 C, s, C-2,6), 55.09 (s, OMe), 13.99 (s, Me) ppm. HRMS (ESI +) for $C_{10}H_{11}F_3NO$ [M + H]: calcd 218.0787, found 218.0815.

2-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1e. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 3.23 mL, 36 mmol) and 2-fluoroaniline (1 equiv., 1.74 mL, 18 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 16 h at room temperature. 2-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1e** was provided as a brown oil (2.58 g, 70%). 1H NMR δ_H = 7.21 – 7.07 (3 H, m, C(4,5,6)H), 6.93 – 6.86 (1 H, m, C(3)H), 2.02 (3 H, s, Me) ppm. ^{19}F NMR δ_F = -74.65 (3 F, s, CF_3), -126.51 – -126.58 (1 F, m, F) ppm. ^{13}C NMR δ_C = 160.40 (qd, $^2J_{C-F}$ = 34.1, $^4J_{C-F}$ = 0.5 Hz, CCF_3), 151.01 (d, $^1J_{C-F}$ = 246.3 Hz, C-2), 134.91 (d, $^2J_{C-F}$ = 12.8 Hz, C-3), 126.57 (d, $^3J_{C-F}$ = 7.3 Hz, C-4), 124.59 (d, $^4J_{C-F}$ = 3.8 Hz, C-5), 121.68 (d, $^3J_{C-F}$ = 1.1 Hz, C-6), 119.53 (q, $^1J_{C-F}$ = 278.2 Hz, CF_3), 116.18 (d, $^2J_{C-F}$ = 19.7 Hz, C-3), 15.01 (s, Me) ppm. HRMS (ESI +) for $C_9H_8F_4N$ [M + H]: calcd 206.0587, found 206.0590.

3-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1f. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.61 mL, 18 mmol) and 3-fluoroaniline (1 equiv., 0.87 mL, 9 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 48 h at room temperature. 3-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1f** was provided as a brown oil (1.14 g, 62%). 1H NMR δ_H = 7.36 – 7.28 (1 H, m, C(5)H), 6.90 – 6.82 (1 H, m, C(4)H), 6.57 – 6.49 (2 H, m, C(2,6)H), 2.02 (3 H, s, Me) ppm. ^{19}F NMR δ_F = -73.12 – -77.79 (3 F, m, CF_3), -109.19 – -115.09 (1 F, m, F) ppm. ^{13}C NMR δ_C = 163.44 (d, $^1J_{C-F}$ = 247.2 Hz, C-3), 158.64 (q, $^2J_{C-F}$ = 34.3 Hz, CCF_3), 149.33 (d, $^3J_{C-F}$ = 9.1 Hz, C-1), 130.70 (d, $^3J_{C-F}$ = 9.2 Hz, C-5), 119.56 (q, $^1J_{C-F}$ = 278.3 Hz, CF_3), 114.45 (d, $^4J_{C-F}$ = 2.9 Hz, C-6), 112 (d, $^2J_{C-F}$ = 21.3 Hz, C-4), 106.38 (d, $^2J_{C-F}$ = 24.1 Hz, C-2), 14.36 (s, Me) ppm. HRMS (ESI +) for $C_9H_8F_4N$ [M + H]: calcd 206.0587, found 206.0572.

4-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1g. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.87 mL, 20.8 mmol) and 4-fluoroaniline (1 equiv., 1 mL, 10.4 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 13 h at room temperature. 4-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1g** was provided as a brown oil (1.97 g, 93%). 1H NMR δ_H = 7.10 – 7.03 (2 H, m, C(3,5)H), 6.79 – 6.73 (2 H, m,

C(2,6)H), 2.03 (3 H, s, Me) ppm. ^{19}F NMR δ_F = -74.77 – -74.79 (3 F, m, CF_3), -117.79 – -118.66 (1 F, m, F) ppm. ^{13}C NMR δ_C = 160.39 (d, $^1J_{C-F}$ = 244.1 Hz, C-4), 158.01 (qd, $^2J_{C-F}$ = 33.9, $^6J_{C-F}$ = 1.1 Hz, CCF_3), 143.59 (d, $^4J_{C-F}$ = 2.7 Hz, C-1), 120.68 (2 C, d, $^3J_{C-F}$ = 8.2 Hz, C-2,6), 119.68 (q, $^1J_{C-F}$ = 278.2 Hz, CF_3), 115.98 (2 C, d, $^2J_{C-F}$ = 22.8 Hz, C-3,5), 14.38 (s, Me) ppm. LCMS (ESI -) for $C_9H_6F_4N$ [M - H] m/z 223 (M+ H₂O, 100%), 153 (15).

3-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1h. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.01 mL, 11.3 mmol) and 3-(trifluoromethoxy)aniline (1 equiv., 0.76 mL, 5.65 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 48 h at room temperature. 3-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1h** was provided as a brown oil (1.25 g, 82%, estimated). 1H NMR δ_H = 7.40 (1 H, t, $^3J_{H-H}$ = 8.1 Hz, C(5)H), 7.04 (1 H, d, $^3J_{H-H}$ = 8.3 Hz, C(4)H), 6.71 (1 H, d, $^3J_{H-H}$ = 7.9 Hz, C(6)H), 6.68 (1 H, s, C(2)H), 2.03 (s, Me) ppm. ^{19}F NMR δ_F = -58.08 (3 F, s, OCF_3), -74.91 (3 F, s, CF_3) ppm. ^{13}C NMR δ_C = 158.85 (q, $^2J_{C-F}$ = 34.3 Hz, CCF_3), 150.05 (q, $^3J_{C-F}$ = 2.02 Hz, C-3), 149.12 (s, C-1), 130.75 (s, C-5), 120.41 (q, $^1J_{C-F}$ = 258.2 Hz, OCF_3), 119.49 (q, $^1J_{C-F}$ = 278.3 Hz, CF_3), 117.27 (s, C-4), 116.96 (s, C-6), 111.58 (s, C-2), 14.52 (s, Me) ppm. HRMS (ESI +) for $C_{10}H_8F_6NO$ [M + H]: calcd 272.0505, found 272.0488.

4-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline 1i. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 2.02 mL, 22.6 mmol) and 4-(trifluoromethoxy)aniline (1 equiv., 1.53 mL, 11.3 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 48 h at room temperature. 4-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1i** was provided as a brown oil (2.85 g, 93%, estimated), isomer ratio 87:13. 1H NMR δ_H = 7.17 (2 H, d, $^3J_{H-H}$ = 8.8 Hz, C(2,6)H), 6.95 (2 H, d, $^3J_{H-H}$ = 8.8 Hz, C(2',6')H), 6.73 (2 H, d, $^3J_{H-H}$ = 8.8 Hz, C(3,5)H), 6.61 (2 H, d, $^3J_{H-H}$ = 8.8 Hz, C(3',5')H), 1.96 (3 H, s, Me), 1.96 (3 H, s, Me') ppm. ^{19}F NMR δ_F = -58.40 – -58.67 (3 F, m, OCF_3), -74.89 – -75.12 (3 F, m, CF_3) ppm. ^{13}C NMR δ_C = 158.94 (q, $^2J_{C-F}$ = 34.3 Hz, CCF_3), 146.84 (q, $^3J_{C-F}$ = 2.02 Hz, C-4), 146.15 (s, C-1), 122.26 (2 C, s, C-2,6), 120.31 (2 C, s, C-3,5), 120.76 (q, $^1J_{C-F}$ = 256.8 Hz, OCF_3), 119.79 (q, $^1J_{C-F}$ = 278.2 Hz, CF_3), 14.46 (s, Me) ppm. HRMS (ESI +) for $C_{10}H_8F_6NO$ [M + H]: calcd 272.0505, found 272.0496.

1-*N,N*-Dimethyl-4-*N*-(1,1,1-trifluoropropan-2-ylidene)benzene-1,4-diamine 1j. The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 1.32 mL, 14.8 mmol) and *N,N*-dimethyl-1,4-benzenediamine (1 equiv., 0.92 mL, 7.39 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 24 h at room temperature. 1-*N,N*-Dimethyl-4-*N*-(1,1,1-trifluoropropan-2-ylidene)benzene-1,4-diamine **1j** was provided as a brown oil (1.36 g, 80%). 1H NMR δ_H = 6.83 (2 H, m, **AA'**, C(2,6)H), 6.74 (2 H, m, **BB'**, C(3,5)H), 2.96 (6 H, s, NMe_2), 2.11 (3 H, s, Me) ppm. ^{19}F NMR δ_F = -74.19 (3 F, s, CF_3) ppm. ^{13}C NMR δ_C = 154.86 (q, $^2J_{C-F}$ = 33.3 Hz, CCF_3), 148.94 (s, C-4), 136.65 (s, C-1), 121.94 (2 C, s, C-2,6), 120.15 (q, $^1J_{C-F}$ = 278.0 Hz, CF_3), 112.86 (2 C, s, C-3,5), 40.84 (2 C, s, NMe_2),

14.67 (s, Me) ppm. HRMS (ESI +) for C₁₁H₁₄F₃N₂ [M + H]: calcd 231.1104, found 231.1125.

3-Fluoro-2-methyl-N-(1,1,1-trifluoropropan-2-ylidene)aniline 1k.

The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 2.87 mL, 32 mmol) and 3-fluoro-2-methylaniline (1 equiv., 1.82 mL, 16 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 26 h at room temperature. 3-Fluoro-2-methyl-N-(1,1,1-trifluoropropan-2-ylidene)aniline **1k** was provided as a brown oil (2.01 g, 57%, estimated). ¹H NMR δH = 7.17 (1 H, dd, ³J_{H-F} = 14.3, ³J_{H-H} = 7.8 Hz, C(4)H), 6.97 (1 H, dd, ⁴J_{H-F} = 14.8, ³J_{H-H} = 7.8 Hz, C(5)H), 6.43 (1 H, d, ³J_{H-H} = 7.9 Hz, C(6)H), 2.01 (3 H, s, C(2)HMe), 1.99 (3 H, s, Me) ppm. ¹⁹F NMR δF = -74.56 (3 F, s, CF₃), -115.94 (1 F, s, F) ppm. HRMS (ESI +) for C₁₀H₁₀F₄N [M + H]: calcd 220.0744, found 220.0746.

3-Chloro-2-methyl-N-(1,1,1-trifluoropropan-2-ylidene)aniline 1l.

The product was prepared according to the general procedure and starting from 1,1,1-trifluoroacetone (2 equiv., 2.53 mL, 28.2 mmol) and 3-chloro-2-methylaniline (1 equiv., 1.71 mL, 14.1 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 26 h at room temperature. 3-Chloro-2-methyl-N-(1,1,1-trifluoropropan-2-ylidene)aniline **1l** was provided as a brown oil (1.67 g, 50%, estimated). ¹H NMR δH = 7.22 (1 H, dd, ³J_{H-H} = 8.0, ⁴J_{H-H} = 1.0 Hz, C(4)H), 7.14 (1 H, t, ³J_{H-H} = 7.9 Hz, C(5)H), 6.53 (1 H, dd, ³J_{H-H} = 7.8, ⁴J_{H-H} = 0.8 Hz, C(6)H), 2.14 (3 H, s, C(2)HMe), 1.98 (3 H, s, Me) ppm. ¹⁹F NMR δF = -74.51 (3 F, s, CF₃) ppm. HRMS (ESI +) for C₁₀H₁₀F₃NCl [M + H]: calcd 236.0448, found 236.0462.

N-(1,1-Difluoropropan-2-ylidene)aniline 1aa. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (1.07 equiv., 5 mL, 58.2 mmol) and aniline (1 equiv., 5 mL, 54.6 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 3 h at room temperature. N-(1,1-Difluoropropan-2-ylidene)aniline **1aa** was provided as a brown oil (8.72 g, 96%). ¹H NMR δH = 7.37 (2 H, t, ³J_{H-H} = 7.8 Hz, C(3,5)H), 7.16 (1 H, t, ³J_{H-H} = 7.2 Hz, C(4)H), 6.78 (2 H, d, ³J_{H-H} = 7.4 Hz, C(2,6)H), 6.07 (1 H, t, ²J_{H-F} = 55.6 Hz, CHF₂), 1.95 (3 H, s, Me) ppm. ¹⁹F NMR δF = -121.27 (2 F, d, ²J_{F-H} = 55.5 Hz, CHF₂) ppm. ¹³C NMR δC = 163.54 (t, ²J_{C-F} = 28.8 Hz, CCHF₂), 148.47 (s, C-1), 129.12 (2 C, s, C-3,5), 124.86 (s, C-4), 119.01 (2 C, s, C-2,6), 114.96 (t, ¹J_{C-F} = 243.0 Hz, CHF₂), 12.65 (s, Me) ppm. HRMS (ESI +) for C₉H₁₀F₂N [M + H]: calcd 170.0774, found 170.0776.

N-(1,1-Difluoropropan-2-ylidene)-2-methoxyaniline 1bb. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.32 mL, 16.2 mmol) and 2-methoxyaniline (1 equiv., 0.92 mL, 8.12 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 5 h at room temperature. N-(1,1-Difluoropropan-2-ylidene)-2-methoxyaniline **1bb** was provided as a brown oil (1.59 g, 98%). ¹H NMR δH = 7.14 (1 H, td, ³J_{H-H} = 7.8, ⁴J_{H-H} = 1.6 Hz, C(4)H), 6.99 – 6.92 (2 H, m, C(5,6)H), 6.74 (1 H, dd, ³J_{H-H} = 7.6, ⁴J_{H-H} = 1.6 Hz, C(3)H), 6.12 (1 H, t, ²J_{H-F} = 55.6 Hz, CHF₂), 3.80 (3 H, s, OMe), 1.89 (3 H, s, Me) ppm. ¹⁹F NMR δF = -120.86 (2 F, d, ²J_{F-H} = 55.5 Hz, CHF₂) ppm. ¹³C NMR δC = 164.88 (t, ²J_{C-F} = 28.6 Hz, CCHF₂), 148.64 (s, C-2), 137.30 (s, C-1), 125.75 (s, C-4), 120.87 (s, C-5), 120.17 (s, C-3), 114.83 (t, ¹J_{C-F} = 242.8 Hz, CHF₂),

111.65 (s, C-6), 55.56 (s, OMe), 13.11 (s, Me) ppm. HRMS (ESI +) for C₁₀H₁₂F₂NO [M + H]: calcd 200.0881, found 200.0875.

N-(1,1-Difluoropropan-2-ylidene)-3-methoxyaniline 1cc. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.32 mL, 16.2 mmol) and 3-methoxyaniline (1 equiv., 0.91 mL, 8.12 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 4 h at room temperature. N-(1,1-Difluoropropan-2-ylidene)-3-methoxyaniline **1cc** was provided as a brown oil (1.58 g, 98%). ¹H NMR (δH = 7.30 – 7.26 (1 H, m, C(5)H), 6.75 – 6.73 (1 H, m, C(4)H), 6.39 – 6.38 (2 H, m, C(2,6)H), 6.10 (1 H, t, ²J_{H-F} = 55.6 Hz, CHF₂), 3.83 – 3.80 (3 H, m, OMe), 1.99 – 1.97 (3 H, m, Me) ppm. ¹⁹F NMR δF = -121.26 – -121.44 (2 F, m, ²J_{F-H} = 55.6 Hz, CHF₂) ppm. ¹³C NMR δC = 163.41 (t, ²J_{C-F} = 28.7 Hz, CCHF₂), 160.41 (s, C-3), 149.81 (s, C-1), 129.95 (s, C-5), 114.89 (t, ¹J_{C-F} = 242.9 Hz, CHF₂), 110.92 (s, C-6), 110.25 (s, C-4), 104.65 (s, C-2), 55.01 (s, OMe), 12.35 (s, Me) ppm. HRMS (ESI +) for C₁₀H₁₂F₂NO [M + H]: calcd 200.0881, found 200.0884.

N-(1,1-Difluoropropan-2-ylidene)-4-methoxyaniline 1dd. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.44 mL, 17.8 mmol) and 4-methoxyaniline (1 equiv., 8.91 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 5 h at room temperature.

N-(1,1-Difluoropropan-2-ylidene)-4-methoxyaniline **1dd** was provided as a brown oil (1.74 g, 98%, estimated). ¹H NMR δH = 6.87 (2 H, m, **AA'**, C(2,6)H), 6.73 (2 H, m, **BB'**, C(3,5)H), 6.02 (1 H, t, ²J_{H-F} = 55.7 Hz, CHF₂), 3.77 – 3.69 (3 H, m, OMe), 1.94 – 1.93 (3 H, m, Me) ppm. ¹⁹F NMR δF = -121.11 (2 F, dd, ²J_{F-H} = 55.8, ⁴J_{F-H} = 4.0 Hz, CHF₂) ppm. ¹³C NMR δC = 162.77 (t, ²J_{C-F} = 29.4 Hz, CCHF₂), 157.11 (s, C-4), 141.22 (s, C-1), 120.80 (2 C, s, C-3,5), 115.23 (t, ¹J_{C-F} = 242.7 Hz, CHF₂), 114.21 (2 C, s, C-2,6), 55.11 (s, OMe), 12.26 (s, Me) ppm. HRMS (ESI +) for C₁₀H₁₂F₂NO [M + H]: calcd 200.0881, found 200.0893.

N-(1,1-Difluoropropan-2-ylidene)-2-fluoroaniline 1ee. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 2.92 mL, 36 mmol) and 2-fluoroaniline (1 equiv., 1.74 mL, 18 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 4 h at room temperature. N-(1,1-Difluoropropan-2-ylidene)-2-fluoroaniline **1ee** was provided as a brown oil (2.62 g, 78%, estimated). ¹H NMR δH = 7.19 – 7.08 (3 H, m, C(4,5,6)H), 6.90 – 6.82 (1 H, m, C(3)H), 6.10 (1 H, t, ²J_{H-F} = 55.5 Hz, CHF₂), 1.99 – 1.91 (3 H, m, Me) ppm. ¹⁹F NMR δF = -121.24 (2 F, d, ²J_{F-H} = 55.5 Hz, CHF₂), -126.63 (1 F, s, F) ppm. ¹³C NMR δC = 166.37 (t, ²J_{C-F} = 28.9 Hz, CCHF₂), 151.51 (d, ¹J_{C-F} = 245.8 Hz, C-2), 135.82 (d, ²J_{C-F} = 13.0 Hz, C-1), 126.07 (d, ³J_{C-F} = 7.3 Hz, C-4), 124.48 (d, ⁴J_{C-F} = 3.8 Hz, C-5), 121.72 (s, C-6), 116.11 (d, ²J_{C-F} = 19.8 Hz, C-3), 114.49 (t, ¹J_{C-F} = 243.0 Hz, CHF₂), 13.14 (s, Me) ppm. HRMS (ESI +) for C₉H₉F₃N [M + H]: calcd 188.0682, found 188.0687.

N-(1,1-Difluoropropan-2-ylidene)-3-fluoroaniline 1ff. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.46 mL, 18 mmol) and 3-fluoroaniline (1 equiv., 0.87 mL, 9 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 5 h at room temperature. N-(1,1-difluoropropan-2-ylidene)-3-fluoroaniline **1ff** was provided as a brown oil (1.53 g, 91%). ¹H NMR δH =

7.33 – 7.28 (1 H, m, C(5)H), 6.84 (1 H, td, $^3J_{H-H} = 8.5$, $^4J_{H-H} = 2.5$ Hz, C(4)H), 6.55 – 6.49 (2 H, m, C(2,6)H), 6.03 (1 H, t, $^2J_{H-F} = 55.5$ Hz, CHF₂), 1.94 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -111.96 - -112.07$ (1 F, m, F), -121.51 (2 F, d, $^2J_{F-H} = 55.4$ Hz, CHF₂) ppm. ¹³C NMR $\delta C = 164.38$ (t, $^2J_{C-F} = 28.9$ Hz, CCHF₂), 163.35 (d, $^1J_{C-F} = 247.45$ Hz, C-3), 150.28 (d, $^3J_{C-F} = 9.2$ Hz, C-1), 130.63 (d, $^3J_{C-F} = 9.2$ Hz, C-5), 114.57 (t, $^1J_{C-F} = 242.4$ Hz, CHF₂), 114.48 (d, $^4J_{C-F} = 2.9$ Hz, C-6), 111.38 (d, $^2J_{C-F} = 21.3$ Hz, C-4), 106.36 (d, $^2J_{C-F} = 23.7$ Hz, C-2), 12.65 (s, Me) ppm. HRMS (ESI +) for C₉H₉F₃N [M + H]: calcd 188.0682, found 188.0672.

***N*-(1,1-Difluoropropan-2-ylidene)-4-fluoroaniline 1gg.** The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.35 mL, 16.7 mmol) and 4-fluoroaniline (1 equiv., 0.8 mL, 8.33 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 3 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-4-fluoroaniline 1gg was provided as a brown oil (1.29 g, 83%). ¹H NMR $\delta H = 7.04$ (2 H, t, $^3J_{H-H} = 8.7$ Hz, C(2,6)H), 6.75 – 6.72 (2 H, m, C(3,5)H), 6.02 (1 H, t, $^2J_{H-F} = 55.6$ Hz, CHF₂), 1.94 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -118.69 - -119.06$ (1 F, m, F), -121.38 (2 F, dd, $^2J_{F-H} = 55.6$, $^4J_{F-H} = 2.6$ Hz, CHF₂) ppm. ¹³C NMR $\delta C = 164.10$ (t, $^2J_{C-F} = 28.2$ Hz, CCHF₂), 160.27 (d, $^1J_{C-F} = 243.3$ Hz, C-4), 144.44 (d, $^4J_{C-F} = 1.2$, C-1), 120.60 (2 C, d, $^3J_{C-F} = 8.1$ Hz, C-2,6), 115.86 (2 C, d, $^2J_{C-F} = 22.6$ Hz, C-3,5), 114.82 (t, $^1J_{C-F} = 243.0$ Hz, CHF₂), 12.57 (s, Me) ppm. HRMS (ESI -) for C₉H₇F₃N [M - H]: calcd 186.0525, found 186.0544.

***N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethoxy)aniline 1hh.** The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.83 mL, 22.6 mmol) and 2-(trifluoromethoxy)aniline (1 equiv., 1.54 mL, 11.3 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 5 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethoxy)aniline 1hh was provided as a brown oil (2.13 g, 75%). ¹H NMR $\delta H = 7.27 - 7.18$ (2 H, m, C(4,6)H), 7.12 – 7.06 (1 H, m, C(5)H), 6.78 – 6.73 (1 H, m, C(3)H), 6.03 (1 H, t, $^2J_{H-F} = 55.5$ Hz, CHF₂), 1.85 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -58.46$ (3 F, s, OCF₃), -121.95 (2 F, d, $^2J_{F-H} = 55.4$ Hz, CHF₂) ppm. ¹³C NMR $\delta C = 166.44$ (t, $^2J_{C-F} = 29.1$ Hz, CCHF₂), 141.52 (s, C-2), 138.31 (s, C-1), 127.75 (s, C-4), 125.82 (s, C-5), 122.38 (s, C-6), 122.14 (q, $^1J_{C-F} = 234.3$ Hz, OCF₃), 120.96 (s, C-3), 114.62 (t, $^1J_{C-F} = 242.9$ Hz, CHF₂), 12.96 (s, Me) ppm. HRMS (ESI positive) for C₁₀H₉F₅NO [M + H]: calcd 254.0599, found 254.0622.

***N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethoxy)aniline 1ii.** The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 0.92 mL, 11.3 mmol) and 3-(trifluoromethoxy)aniline (1 equiv., 0.76 mL, 5.65 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 7 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethoxy)aniline 1ii was provided as a brown oil (1.32 g, 93%). ¹H NMR $\delta H = 7.37$ (1 H, t, $^3J_{H-H} = 8.1$ Hz, C(5)H), 7.04 – 6.99 (1 H, m, C(4)H), 6.69 (1 H, d, $^3J_{H-H} = 7.9$ Hz, C(6)H), 6.66 (1 H, s, C(2)H), 6.03 (1 H, t, $^2J_{H-F} = 55.5$ Hz, CHF₂), 1.94 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -58.10$ (3 F, s, OCF₃), -121.65 (2 F, d, $^2J_{F-H} = 55.6$ Hz, CHF₂). ¹³C NMR $\delta C = 164.80$ (t, $^2J_{C-F} = 29.0$ Hz, CCHF₂), 150.07 – 150.02 (2 C, m, C-1,3), 130.57 (s, C-5), 121.72 (q, $^1J_{C-F} = 258.6$ Hz, OCF₃), 117.37

(s, C-4), 117.00 (s, C-6), 114.68 (t, $^1J_{C-F} = 243.2$ Hz, CHF₂), 111.92 (s, C-2), 12.74 (s, Me) ppm. HRMS (ESI +) for C₁₀H₉F₅NO [M + H]: calcd 254.0599, found 254.0583.

***N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethoxy)aniline 1jj.** The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.83 mL, 22.6 mmol) and 4-(trifluoromethoxy)aniline (1 equiv., 1.53 mL, 11.3 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 3 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethoxy)aniline 1jj was provided as a brown oil (2.59 g, 91%). ¹H NMR $\delta H = 7.22$ (2 H, d, $^3J_{H-H} = 8.6$ Hz, C(2,6)H), 6.78 (2 H, d, $^3J_{H-H} = 8.8$ Hz, C(3,5)H), 6.03 (1 H, t, $^2J_{H-F} = 55.6$ Hz, CHF₂), 1.94 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -58.44$ (3 F, s, OCF₃), -121.67 (2 F, dd, $^2J_{F-H} = 55.6$, $^4J_{F-H} = 2$ Hz, CHF₂) ppm. ¹³C NMR $\delta C = 164.54$ (t, $^2J_{C-F} = 28.9$ Hz, CCHF₂), 147.21 (s, C-1), 146.39 (q, $^3J_{C-F} = 2$ Hz, C-4), 122.10 (2 C, s, C-2,6), 120.76 (q, $^1J_{C-F} = 256.7$ Hz, OCF₃), 120.34 (2 C, s, C-3,5), 114.84 (t, $^1J_{C-F} = 244.4$ Hz, CHF₂), 12.38 (s, Me) ppm. HRMS (ESI +) for C₁₀H₉F₅NO [M + H]: calcd 254.0599, found 254.0622.

3-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,3-diamine 1kk. Under argon atmosphere, an excess of cold 1,1-difluoroacetone (2 equiv., 0.83 mL, 10.2 mmol) was added to 1-*N,N*-dimethyl-1,3-phenylenediamine dihydrochloride (1 equiv., 695 mg, 5.1 mmol) and sodium hydride (2.1 equiv., 257.2 mg, 10.72 mmol) in anhydrous DCM (15 mL) in presence of (4 Å MS). Then the reaction mixture was stirred for 24 h at room temperature. (4 Å MS) was then filtered off on celite and washed with ether. The filtrate was concentrated under reduced pressure to give the 3-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,3-diamine 1kk as a black paste (1.26 g). ¹H NMR $\delta H = 7.21$ (1 H, t, $^3J_{H-H} = 8.2$ Hz, C(5)H), 6.56 – 6.51 (1 H, m, C(4)H), 6.13 – 6.08 (2 H, m, C(2,6)H), 6.06 (1 H, t, $^2J_{H-F} = 55.5$ Hz, CHF₂), 2.95 (6 H, s, NMe₂), 1.96 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -121.31$ (2 F, d, $^2J_{F-H} = 55.5$ Hz, CHF₂) ppm. HRMS (ESI +) for C₁₁H₁₅F₂N₂ [M + H]: calcd 213.1198, found 213.1209.

4-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,4-diamine 1ll. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.19 mL, 14.7 mmol) and *N,N*-dimethyl-1,4-benzenediamine (1 equiv., 0.92 mL, 7.35 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 20 h at room temperature. 4-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,4-diamine 1ll was provided as a yellow solid (1.46 g, 94%). ¹H NMR $\delta H = 6.77$ (4 H, **A₂B₂**, $^3J_{H-H} = 8.9$ Hz, $\Delta v = 27.76$ Hz, C(2,6/3,5)H), 6.05 (1 H, t, $^2J_{H-F} = 55.9$ Hz, CHF₂), 2.96 (6 H, s, NMe₂), 2.03 (3 H, s, Me) ppm. ¹⁹F NMR $\delta F = -120.62$ (2 F, d, $^2J_{F-H} = 55.9$ Hz, CHF₂) ppm. ¹³C NMR $\delta C = 161.26$ (t, $^2J_{C-F} = 28.4$ Hz, CCHF₂), 148.61 (s, C-2), 137.60 (s, C-1), 121.72 (2 C, s, C-2,6), 115.70 (t, $^1J_{C-F} = 242.6$ Hz, CHF₂), 112.84 (2 C, s, C-3,5), 40.83 (2 C, s, NMe₂), 12.74 (s, Me) ppm. HRMS (ESI +) for C₁₁H₁₅F₂N₂ [M + H]: calcd 213.1198, found 213.1214. C₁₁H₁₄F₂N₂ (212): calcd (%) N 13.19, C 62.19, H 6.60, found N 13.22, C 61.99, H 6.68. MP : 80.5 – 82 °C.

***N*-(1,1-Difluoropropan-2-ylidene)-3-fluoro-2-methylaniline 1mm.** The product was prepared according to the general

procedure and starting from 1,1-difluoroacetone (2 equiv., 2.59 mL, 32 mmol) and 3-fluoro-2-methylaniline (1 equiv., 1.82 mL, 16 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 18 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-3-fluoro-2-methylaniline **1mm** was provided as a brown oil (2.88 g, 90%, estimated). ¹H NMR δH = 7.16 – 7.13 (1 H, m, C(4)H), 6.83 (1 H, t, ³J_{H-H} = 8.8 Hz, C(5)H), 6.41 (1 H, d, ³J_{H-H} = 7.9 Hz, C(6)H), 6.10 (1 H, t, ²J_{H-F} = 55.5 Hz, CHF₂), 1.99 (3 H, d, ⁴J_{H-F} = 2.0 Hz, C(2Me)H), 1.89 (3 H, s, Me) ppm. ¹⁹F NMR δF = -116.18 - -116.24 (1 F, m, F), -121.21 (2 F, dd, ²J_{F-H} = 55.5, ⁴J_{F-H} = 2.4 Hz, CHF₂) ppm. ¹³C NMR δC = 164.50 (t, ²J_{C-F} = 29.0 Hz, CCHF₂), 161.79 (d, ¹J_{C-F} = 244.3 Hz, C-3), 148.91 (d, ³J_{C-F} = 7.8 Hz, C-1), 126.98 (d, ²J_{C-F} = 9.8 Hz, C-4), 114.68 (s, C-2), 114.55 (t, ¹J_{C-F} = 243.0 Hz, CHF₂), 113.50 (d, ⁴J_{C-F} = 3.1 Hz, C-6), 111.17 (d, ³J_{C-F} = 23.0 Hz, C-5), 12.83 (s, Me), 9.02 (d, ³J_{C-F} = 4.8 Hz, C(2)Me) ppm. HRMS (ESI +) for C₁₀H₁₁F₃N [M + H]: calcd 202.0838, found 202.0866.

3-Chloro-*N*-(1,1-difluoropropan-2-ylidene)-2-methylaniline

1nn. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 2.29 mL, 28.2 mmol) and 3-chloro-2-methylaniline (1 equiv., 1.71 mL, 14.1 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 18 h at room temperature. 3-Chloro-*N*-(1,1-difluoropropan-2-ylidene)-2-methylaniline **1nn** was provided as a brown oil (2.79 g, 91%, estimated). ¹H NMR δH = 7.17 (1 H, dd, ³J_{H-H} = 8.0, ⁴J_{H-H} = 1.1 Hz, C(4)H), 7.10 (1 H, t, ³J_{H-H} = 7.7 Hz, C(5)H), 6.52 (1 H, dd, ³J_{H-H} = 7.7, ⁴J_{H-H} = 0.9 Hz, C(6)H), 6.11 (1 H, t, ²J_{H-F} = 55.5 Hz, CHF₂), 2.12 (3 H, s, C(2Me)H), 1.88 (3 H, s, Me) ppm. ¹⁹F NMR δF = -121.15 (2 F, d, ²J_{F-H} = 55.5 Hz, CHF₂) ppm. ¹³C NMR δC = 164.43 (t, ²J_{C-F} = 28.9 Hz, CCHF₂), 148.44 (s, C-1), 135.57 (s, C-3), 127.06 (s, C-5), 125.48 (s, C-4), 116.39 (s, C-6), 114.63 (t, ¹J_{C-F} = 243.1 Hz, CHF₂), 113.56 (s, C-2), 14.26 (s, C(2)Me), 12.89 (s, Me) ppm. HRMS (ESI +) for C₁₀H₁₁F₂NCl [M + H]: calcd 218.0543, found 218.0557.

3-Chloro-*N*-(1,1-difluoropropan-2-ylidene)aniline **1oo**. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 5.08 mL, 62.7 mmol) and 3-chloroaniline (1 equiv., 3.33 mL, 31.4 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 18 h at room temperature. 3-Chloro-*N*-(1,1-difluoropropan-2-ylidene)aniline **1oo** was provided as a brown oil (9.68 g). ¹H NMR δH = 7.31 (1 H, t, ³J_{H-H} = 8.0 Hz, C(5)H), 7.16 (1 H, d, ³J_{H-H} = 8.1 Hz, C(4)H), 6.81 (1 H, t, ⁴J_{H-H} = 1.9 Hz, C(2)H), 6.68 (1 H, d, ³J_{H-H} = 7.9 Hz, C(6)H), 6.06 (1 H, t, ²J_{H-F} = 55.4 Hz, CHF₂), 1.97 (3 H, s, Me) ppm. ¹⁹F NMR δF = -121.46 (2 F, d, ²J_{F-H} = 55.4 Hz, CHF₂) ppm. ¹³C NMR δC = 164.76 (t, ²J_{C-F} = 29.0 Hz, CCHF₂), 149.64 (s, C-1), 134.99 (s, C-3), 130.44 (s, C-5), 124.96 (s, C-4), 119.18 (s, C-2), 117.24 (s, C-6), 114.55 (t, ¹J_{C-F} = 243.2 Hz, CHF₂), 12.87 (s, Me) ppm. HRMS (ESI +) for C₉H₉F₂NCl [M + H]: calcd 204.0386, found 204.0367.

N-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethyl)aniline

1pp. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 0.503 mL, 6.21 mmol) and 4-(trifluoromethyl)aniline (1 equiv., 0.386 mL, 3.1 mmol) in presence of anhydrous MgSO₄. The reaction mixture was stirred for 16 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethyl)aniline **1pp**

was provided as a brown oil (212 mg, 29%, estimated). ¹H δH = 7.63 (2 H, d, ³J_{H-H} = 8.3 Hz, C(3,5)H), 6.85 (2 H, d, ³J_{H-H} = 8.2 Hz, C(2,6)H), 6.05 (1 H, t, ²J_{H-F} = 55.4 Hz, CHF₂), 1.93 (3 H, s, Me) ppm. ¹⁹F NMR δF = -62.13 (3 F, s, CF₃), -121.34 – -121.59 (2 F, m, CHF₂) ppm. ¹³C NMR δC = 164.59 (t, ²J_{C-F} = 29.0 Hz, CCHF₂), 151.64 (s, C-1), 126.64 (2 C, q, ³J_{C-F} = 3.8 Hz, C-3,5), 124.30 (q, ¹J_{C-F} = 271.6 Hz, CF₃), 120.30 (q, ²J_{C-F} = 32.6 Hz, C-4), 119.03 (2 C, s, C-2,6), 114.49 (t, ¹J_{C-F} = 243.3 Hz, CHF₂), 12.97 (s, Me) ppm. HRMS (ESI +) for C₁₀H₉F₅N [M + H]: calcd 238.0650, found 238.0658.

N-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethyl)aniline

1qq. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 1.01 mL, 12.4 mmol) and 3-(trifluoromethyl)aniline (1 equiv., 0.767 mL, 6.21 mmol) in presence of (4 Å MS). The reaction mixture was stirred for 5 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethyl)aniline **1qq** was provided as a brown oil (1.47 g, 93%, estimated). ¹H NMR δH = 7.49 (1 H, t, ³J_{H-H} = 7.8 Hz, C(5)H), 7.42 (1 H, d, ³J_{H-H} = 7.8 Hz, C(4)H), 7.03 (1 H, s, C(2)H), 6.94 (1 H, d, ³J_{H-H} = 7.2 Hz, C(4)H), 6.05 (1 H, t, ²J_{H-F} = 55.5 Hz, CHF₂), 1.95 (3 H, s, Me) ppm. ¹⁹F NMR δF = -62.80 (3 F, s, CF₃), -121.44 (2 F, d, ²J_{F-H} = 55.4 Hz, CHF₂) ppm. ¹³C NMR δC = 165.21 (t, ²J_{C-F} = 28.9 Hz, CCHF₂), 148.91 (s, C-1), 131.84 (q, ²J_{C-F} = 32.5 Hz, C-3), 129.96 (s, C-5), 124.03 (q, ¹J_{C-F} = 272.3 Hz, CF₃), 122.38 (s, C-6), 121.68 (q, ³J_{C-F} = 3.8 Hz, C-4), 116.01 (q, ³J_{C-F} = 4.0 Hz, C-2), 114.53 (t, ¹J_{C-F} = 243.2 Hz, CHF₂), 12.78 (s, Me) ppm. HRMS (ESI +) for C₁₀H₉F₅N [M + H]: calcd 238.0650, found 238.0660.

N-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethyl)aniline

1rr. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 0.503 mL, 6.21 mmol) and 2-(trifluoromethyl)aniline (1 equiv., 0.386 mL, 3.1 mmol) in presence of anhydrous MgSO₄. The reaction mixture was stirred for 16 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethyl)aniline **1rr** was provided as a brown oil (291.5 mg, 40%, estimated). ¹H NMR δH = 7.67 (1 H, d, ³J_{H-H} = 7.9 Hz, C(3)H), 7.52 (1 H, t, ³J_{H-H} = 7.7 Hz, C(5)H), 7.23 (1 H, t, ³J_{H-H} = 7.7 Hz, C(5)H), 6.72 (1 H, d, ³J_{H-H} = 7.9 Hz, C(6)H), 6.08 (1 H, t, ²J_{H-F} = 55.4 Hz, CHF₂), 1.90 (3 H, s, Me) ppm. ¹⁹F NMR δF = -61.85 (3 F, s, CF₃), -121.82 (2 F, d, ²J_{F-H} = 55.4 Hz, CHF₂) ppm. ¹³C NMR δC = 165.58 (t, ²J_{C-F} = 29.4 Hz, CCHF₂), 146.98 (q, ³J_{C-F} = 2.02 Hz, C-1), 132.87 (s, C-5), 126.77 (q, ³J_{C-F} = 5.05 Hz, C-3), 124.50 (s, C-4), 123.67 (q, ¹J_{C-F} = 273.0 Hz, CF₃), 119.65 (q, ²J_{C-F} = 31.3 Hz, C-2), 119.18 (s, C-6), 114.27 (t, ¹J_{C-F} = 243.3 Hz, CHF₂), 13.42 (s, Me) ppm. HRMS (ESI +) for C₁₀H₉F₅N [M + H]: calcd 238.0650, found 238.0654.

N-(1,1-Difluoropropan-2-ylidene)-2-phenylaniline

1ss. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 0.485 mL, 5.98 mmol) and 2-aminodiphenyl (1 equiv., 505 mg, 2.99 mmol) in presence of anhydrous MgSO₄. The reaction mixture was stirred for 14 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-2-phenylaniline **1ss** was provided as a brown oil (953.7 mg). ¹H NMR δH = 7.42 – 7.23 (8 H, m, C(3,4,5,2',3',4',5',6')H), 6.71 (1 H, dd, ³J_{H-H} = 7.8, ⁴J_{H-H} = 1.0 Hz, C(6)H), 5.88 (1 H, t, ²J_{H-F} = 55.6 Hz, CHF₂), 1.64 (3 H, s, Me) ppm. ¹⁹F NMR δF = -121.61 (2 F, d, ²J_{F-H} = 55.5 Hz, CHF₂) ppm.

^{13}C NMR δC = 163.53 (t, $^2J_{\text{C-F}}$ = 28.8 Hz, CCHF₂), 146.07 (s, C-1), 139.00 (s, C-1'), 132.02 (s, C-2), 131.44 – 123.83 (8 C, m, C-3,4,5,2',3',4',5',6'), 119.16 (s, C-6), 114.67 (t, $^1J_{\text{C-F}}$ = 243.2 Hz, CHF₂), 13.40 (s, Me) ppm. HRMS (ESI positive) for C₁₅H₁₄F₂N [M + H]: calcd 246.1089, found 246.1112.

***N*-(1,1-Difluoropropan-2-ylidene)-2-(phenylsulfanyl)aniline**

1tt. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 0.422 mL, 5.2 mmol) and 2-(phenylsulfanyl)aniline (1 equiv., 523 mg, 2.6 mmol) in presence of anhydrous MgSO₄. The reaction mixture was stirred for 12 h at room temperature. *N*-(1,1-Difluoropropan-2-ylidene)-2-(phenylsulfanyl)aniline **1tt** was provided as a brown oil (796.1 mg). ^1H NMR δH = 7.34 – 7.20 (6 H, m, C(3,2',3',4',5',6')H), 7.09 (2 H, td, $^3J_{\text{H-H}}$ = 7.65, $^4J_{\text{H-H}}$ = 1.3 Hz, C(4,5)H), 6.69 (1 H, dd, $^3J_{\text{H-H}}$ = 7.8, $^4J_{\text{H-H}}$ = 1.1 Hz, C(6)H), 6.01 (1 H, t, $^2J_{\text{H-F}}$ = 55.5 Hz, CHF₂), 1.78 (3 H, s, Me) ppm. ^{19}F NMR δF = -121.06 (2 F, d, $^2J_{\text{F-H}}$ = 55.4 Hz, CHF₂) ppm. ^{13}C NMR δC = 164.78 (t, $^2J_{\text{C-F}}$ = 28.9 Hz, CCHF₂), 148.85 (s, C-1), 136.88 (s, C-1'), 134.64 (s, C-2), 132.37 - 127.42 (6 C, m, C-3,2',3',4',5',6'), 126.57 (s, C-5), 125.43 (s, C-4), 118.87 (s, C-6), 114.45 (t, $^1J_{\text{C-F}}$ = 243.3 Hz, CHF₂), 13.04 (s, Me) ppm. HRMS (ESI +) for C₁₅H₁₄F₂NS [M + H]: calcd 278.0810, found 278.0781.

5-[(1,1-Difluoropropan-2-ylidene)amino]-1-naphthol 1uu. The product was prepared according to the general procedure and starting from 1,1-difluoroacetone (2 equiv., 0.509 mL, 6.28 mmol) and 5-amino-1-naphthol (1 equiv., 500 mg, 3.14 mmol) in presence of anhydrous MgSO₄. The reaction mixture was stirred for 14 h at room temperature. 5-[(1,1-Difluoropropan-2-ylidene)amino]-1-naphthol **1uu** was provided as a purple solid (670 mg, 91%, estimated). ^1H NMR δH = 8.01 (1 H, d, $^3J_{\text{H-H}}$ = 8.5 Hz, C(8)H), 7.45 (1 H, t, $^3J_{\text{H-H}}$ = 8.0 Hz, C(7)H), 7.35 – 7.17 (2 H, m, C(3,4)H), 6.84 (1 H, d, $^3J_{\text{H-H}}$ = 7.3 Hz, C(2)H), 6.78 (1 H, d, $^3J_{\text{H-H}}$ = 7.2 Hz, C(6)H), 6.24 (1 H, t, $^2J_{\text{H-F}}$ = 55.6 Hz, CHF₂), 5.45 (1 H, br s, OH), 1.91 (3 H, s, Me) ppm. ^{19}F NMR δF = -120.84 (2 F, d, $^2J_{\text{F-H}}$ = 55.5 Hz, CHF₂) ppm. ^{13}C NMR δC = 165.18 (t, $^2J_{\text{C-F}}$ = 28.9 Hz, CCHF₂), 151.81 (s, C-1), 144.46 (s, C-5), 126.46 (s, C-1-C-8), 126.24 (s, C-3), 125.23 (s, C-4-C-5), 125.00 (s, C-7), 118.80 (s, C-8), 115.48 (s, C-4), 114.83 (t, $^1J_{\text{C-F}}$ = 243.3 Hz, CHF₂), 114.07 (s, C-6), 109.46 (s, C-2), 13.18 (s, Me) ppm. HRMS (ESI +) for C₁₃H₁₂F₂NO [M + H]: calcd 236.0881, found 236.0909.

General procedure for the synthesis of quinoline derivatives 2 and 3

Under argon atmosphere, a solution of the desired FAR (1,1,2,2-tetrafluoro-*N,N*-dimethylethan-1-amine (**4a**; TFEDMA), 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine (**4b**; Yarovenko reagent), and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (**4c**; Ishikawa reagent)) (1.2 equiv.) was activated by adding boron trifluoride diethyl etherate (BF₃•Et₂O) (1.2 equiv.) in dry acetonitrile (3.6 mmol/5 mL) and stirred for 15 min. Then a solution of the desired ketimine derivative **1** (1 equiv.) in dry acetonitrile (3 mmol/5 mL) was slowly added to this mixture via syringe. After 15 min at room temperature, the mixture was heated at 50 °C for 19 h. Acetonitrile was removed under reduced pressure and the reaction mixture was purified by flash chromatography using a

gradient of ethyl acetate in pentane to provide the final compound **2** or **3**.

4-(Difluoromethyl)-2-(trifluoromethyl)quinoline 2ai. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.42 mL, 3.61 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.46 mL, 3.61 mmol) and *N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1** (1 equiv., 562 mg, 3.01 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-2-(trifluoromethyl)quinoline **2ai** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (458 mg, 62%). ^1H NMR δH = 8.33 (1 H, d, $^3J_{\text{H-H}}$ = 8.5 Hz, C(8)H), 8.16 (1 H, d, $^3J_{\text{H-H}}$ = 8.5 Hz, C(5)H), 7.93 (1 H, s, C(3)H), 7.92 – 7.87 (1 H, m, C(7)H), 7.80 (1 H, t, $^3J_{\text{H-H}}$ = 7.7 Hz, C(6)H), 7.22 (1 H, t, $^2J_{\text{H-F}}$ = 54.2 Hz, C(4-CHF₂)H) ppm. ^{19}F NMR δF = -67.66 (3 F, s, CF₃), -115.53 (2 F, d, $^2J_{\text{F-H}}$ = 54.1 Hz, CHF₂) ppm. ^{13}C NMR δC = 147.94 (q, $^2J_{\text{C-F}}$ = 35.3 Hz, C-2), 147.87 (t, C-8-C-N), 140.33 (t, $^2J_{\text{C-F}}$ = 22.3 Hz, C-4), 131.39 (s, C-7), 131.29 (s, C-8), 130.06 (s, C-6), 125.09 (s, C-5-C-4), 123.44 (s, C-5), 121.33 (q, $^1J_{\text{C-F}}$ = 275.73 Hz, C(2)CF₃), 114.14 (td, $^3J_{\text{C-F}}$ = 7.9, $^3J_{\text{C-F}}$ = 2.1 Hz, C-3), 112.74 (t, $^1J_{\text{C-F}}$ = 241.5 Hz, C(4)CHF₂) ppm. HRMS (ESI +) for C₁₁H₇F₅N [M + H]: calcd 248.0493, found 248.0520. C₁₁H₆F₅N (247): calcd (%) N 5.66, C 53.40, H 2.43, found N 5.73, C 53.83, H 2.58. MP: 64 – 65.1 °C.

4-[Chloro(fluoro)methyl]-2-(trifluoromethyl)quinoline 2aii. The product was prepared according to the general procedure and starting from an activated solution of Yarovenko's reagent **4b** (1.2 equiv., 0.73 mL, 3.21 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.41 mL, 3.21 mmol) and *N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1a** (1 equiv., 500 mg, 2.67 mmol) in presence of anhydrous acetonitrile. 4-[Chloro(fluoro)methyl]-2-(trifluoromethyl)quinoline **2aii** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a light yellow solid (402 mg, 57%). ^1H NMR δH = 8.32 (1 H, d, $^3J_{\text{H-H}}$ = 8.4 Hz, C(8)H), 8.13 (1 H, d, $^3J_{\text{H-H}}$ = 8.5 Hz, C(5)H), 7.95 (1 H, s, C(3)H), 7.92 – 7.88 (1 H, m, C(7)H), 7.81 – 7.77 (1 H, m, C(3)H), 7.66 (1 H, d, $^2J_{\text{H-F}}$ = 48.9 Hz, C(4-CHFCI)H) ppm. ^{19}F NMR δF = -67.65 (3 F, s, CF₃), -138.75 (1 F, d, $^2J_{\text{F-H}}$ = 48.9 Hz, C4-CHFCI) ppm. ^{13}C NMR δC = 148.02 (q, $^2J_{\text{C-F}}$ = 35.4 Hz, C-2), 147.88 (s, C-8-C-N), 143.82 (d, $^2J_{\text{C-F}}$ = 21.1 Hz, C-4), 131.40 (s, C-7), 131.31 (s, C-8), 129.82 (s, C-6), 124.03 (d, $^2J_{\text{C-F}}$ = 3.6 Hz, C-5-C-4), 123.08 (s, C-5), 121.34 (q, $^1J_{\text{C-F}}$ = 275.4 Hz, C(2)CF₃), 113.04 (dq, $^3J_{\text{C-F}}$ = 9.9, $^3J_{\text{C-F}}$ = 2.0 Hz, C-3), 96.75 (d, $^1J_{\text{C-F}}$ = 244.6 Hz, C(4)CHFCI) ppm. C₁₁H₆F₄NCl (263): calcd (%) N 5.31, C 50.07, H 2.27, found N 5.11, C 50.19, H 2.65. HRMS (ESI +) for C₁₁H₇F₄NCl [M + H]: calcd 264.0198, found 264.0231. MP: 49.4 – 50.4 °C.

4-(1,2,2,2-Tetrafluoroethyl)-2-(trifluoromethyl)quinoline 2aiii. The product was prepared according to the general procedure and starting from an activated solution of Ishikawa's reagent **4c** (1.2 equiv., 0.95 mL, 3.26 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.41 mL, 3.26 mmol) and *N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1a** (1 equiv., 508 mg, 2.71 mmol) in presence of anhydrous acetonitrile. 4-(1,2,2,2-Tetrafluoroethyl)-2-(trifluoromethyl)quinoline **2aiii** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a light brown solid (112 mg, 14%, estimated). ^1H NMR δH = 8.32 (1 H,

d, $^3J_{H-H} = 8.4$ Hz, C(8)H), 7.99 - 7.97 (2 H, m, C(3,5)H), 7.89 (1 H, t, $^3J_{H-H} = 8.4$ Hz, C(7)H), 7.78 (1 H, t, $^3J_{H-H} = 8.3$ Hz, C(6)H), 6.46 (dq, $^2J_{H-F} = 43.9$, $^3J_{H-F} = 5.5$ Hz, C(4-CHFCF₃)H) ppm. ^{19}F NMR $\delta\text{F} = -67.72$ (3 F, s, C2-CF₃), -77.25 (3 F, dd, $^3J_{F-F} = 13.1$, $^3J_{F-H} = 5.8$ Hz, C4-CHFCF₃), -198.87 (1 F, dq, $^2J_{F-H} = 44.3$, $^3J_{F-F} = 12.8$ Hz, C4-CHFCF₃). ppm. ^{13}C NMR $\delta\text{C} = 147.72$ (q, $^2J_{C-F} = 35.4$ Hz, C-2), 147.51 (s, C-8-C-N), 137.94 (d, $^2J_{C-F} = 19.1$ Hz, C-4), 131.34 (s, C-7), 131.16 (s, C-8), 130.06 (s, C-6), 125.89 (d, C-5-C-C-4, $^2J_{C-F} = 3.7$ Hz), 122.72 (s, C-5), 121.91 (q, $^1J_{C-F} = 282.6$ Hz, C(4)CHCF₃), 121.68 (q, $^1J_{C-F} = 282.6$ Hz, C(2)CF₃), 115.77 (d, $^3J_{C-F} = 10.4$ Hz, C-3), 85.41 (dq, $^1J_{C-F} = 189.9$, $^2J_{C-F} = 36.1$ Hz, C(4)CHFCF₃) ppm. C₁₂H₆F₇N (297): calcd (%) N 4.71, C 48.45, H 2.02, found N 4.71, C 48.80, H 2.32. HRMS (ESI +) for C₁₁H₇F₇N [M + H]: calcd 298.0461, found 298.0462. MP: 58 – 58.8 °C.

4-(Difluoromethyl)-8-methoxy-2-(trifluoromethyl)quinoline

2b. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.33 mL, 2.82 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.357 mL, 2.82 mmol) and 2-methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1b** (1 equiv., 510 mg, 2.35 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-8-methoxy-2-(trifluoromethyl)quinoline **2b** was provided after purification using a gradient of ethyl acetate in pentane (10-25%) as a yellow solid (575 mg, 88%). ^1H NMR $\delta\text{H} = 7.97$ (1 H, s, C(5)H), 7.74 – 7.63 (2 H, m, C(6,7)H), 7.21 (1 H, d, $^4J_{H-F} = 7.8$ Hz, C(3)H), 7.20 (1 H, t, $^2J_{H-F} = 54.3$ Hz, C(4-CHF₂)H), 4.12 (3 H, s, Me) ppm. ^{19}F NMR $\delta\text{F} = -67.16$ (3 F, s, CF₃), -116.17 (2 F, d, $^2J_{F-H} = 54.4$ Hz, CHF₂) ppm. ^{13}C NMR $\delta\text{C} = 156.58$ (s, C-8), 146.50 (q, $^2J_{C-F} = 35.7$ Hz, C-2), 140.11 (t, $^2J_{C-F} = 22.2$ Hz, C-4), 139.95 (s, C-8-C-N), 130.74 (s, C-6), 126.43 (s, C-5-C-C-4), 121.40 (q, $^1J_{C-F} = 275.2$ Hz, C(2)CF₃), 114.70 – 114.16 (2 C, m, C-5, 7), 112.55 (t, $^1J_{C-F} = 241.5$ Hz, C(4)CHF₂), 109.56 (s, C-3), 56.58 (s, Me) ppm. C₁₂H₈F₅NO (277): calcd (%) N 5.05, C 51.95, H 2.88, found N 5.16, C 51.92, H 2.74. MP: 72.5 – 76.8 °C.

4-(Difluoromethyl)-7-methoxy-2-(trifluoromethyl)quinoline

2c. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.324 mL, 2.77 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.35 mL, 2.77 mmol) and 3-methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1c** (1 equiv., 500 mg, 2.3 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-7-methoxy-2-(trifluoromethyl)quinoline **2c** was provided after purification using a gradient of ethyl acetate in pentane (10-25%) as a light brown solid (407 mg, 64%). ^1H NMR $\delta\text{H} = 8.00$ (1 H, d, $^3J_{H-H} = 9.3$ Hz, C(5)H), 7.76 (1 H, s, C(3)H), 7.57 (1 H, d, $^4J_{H-H} = 2.6$ Hz, C(8)H), 7.39 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-H} = 2.6$ Hz, C(6)H), 7.14 (1 H, t, $^2J_{H-F} = 54.3$ Hz, C(4-CHF₂)H), 3.97 (3 H, s, Me) ppm. ^{19}F NMR $\delta\text{F} = -67.74$ (3 F, s, CF₃), -115.04 (2 F, d, $^2J_{F-H} = 54.4$ Hz, C4-CHF₂) ppm. ^{13}C NMR $\delta\text{C} = 161.92$ (s, C-7), 150.09 (s, C-8-C-N), 148.04 (q, $^2J_{C-F} = 35.2$ Hz, C-2), 140.01 (t, $^2J_{C-F} = 22.4$ Hz, C-4), 124.36 (s, C-5), 123.61 (s, C-6), 121.26 (q, $^1J_{C-F} = 275.2$ Hz, C(2)CF₃), 120.32 (t, $^3J_{C-F} = 2.8$ Hz, C-5-C-C-4), 112.86 (t, $^1J_{C-F} = 241.4$ Hz, C(4)CHF₂), 111.81 (td, $^3J_{C-F} = 8.0$, $^3J_{C-F} = 2.3$ Hz, C-3), 108.56 (s, C-8), 55.91 (s, Me) ppm. C₁₂H₈F₅NO (277): calcd (%) N 5.05, C

51.95, H 2.88, found N 5.14, C 51.71, H 2.87. MP: 83.4 – 87.2 °C.

4-(Difluoromethyl)-6-methoxy-2-(trifluoromethyl)quinoline

2d. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.325 mL, 2.78 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.352 mL, 2.78 mmol) and 4-methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1d** (1 equiv., 502 mg, 2.31 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-6-methoxy-2-(trifluoromethyl)quinoline **2d** was provided after purification using a gradient of ethyl acetate in pentane (10-25%) as a brown solid (543 mg, 85%). ^1H NMR $\delta\text{H} = 8.16$ (1 H, d, $^3J_{H-H} = 9.3$ Hz, C(8)H), 7.85 (1 H, s, C(3)H), 7.50 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-H} = 2.6$ Hz, C(7)H), 7.29 (1 H, s, C(5)H), 7.11 (1 H, t, $^2J_{H-F} = 54.3$ Hz, C(4-CHF₂)H), 3.97 (3 H, s, Me) ppm. ^{19}F NMR $\delta\text{F} = -67.30$ (3 F, s, CF₃), -115.95 (2 F, d, $^2J_{F-H} = 54.4$ Hz, C4-CHF₂) ppm. ^{13}C NMR $\delta\text{C} = 160.35$ (s, C-6), 144.95 (q, $^2J_{C-F} = 35.4$ Hz, C-2), 144.11 (s, C-8-C-N), 138.21 (t, $^2J_{C-F} = 22.1$ Hz, C-4), 132.56 (s, C-8), 126.63 (s, C-5-C-C-4), 124.40 (s, C-7), 121.43 (q, $^1J_{C-F} = 274.7$ Hz, C(2)CF₃), 114.59 (td, $^3J_{C-F} = 8.1$, $^3J_{C-F} = 2.3$ Hz, C-3), 113.17 (t, $^1J_{C-F} = 241.1$ Hz, C(4)CHF₂), 101.06 (s, C-3), 55.88 (s, Me) ppm. C₁₂H₈F₅NO (277): calcd (%) N 5.05, C 51.95, H 2.88, found N 5.03, C 51.64, H 2.80. MP: 105.9 – 108.2 °C.

4-(Difluoromethyl)-8-fluoro-2-(trifluoromethyl)quinoline

2e. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.347 mL, 2.97 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.376 mL, 2.97 mmol) and 2-fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1e** (1 equiv., 507 mg, 2.47 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-8-fluoro-2-(trifluoromethyl)quinoline **2e** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as an orange solid (466 mg, 70%). ^1H NMR $\delta\text{H} = 7.99$ (1 H, s, C(3)H), 7.94 (1 H, d, $^3J_{H-H} = 8.6$ Hz, C(5)H), 7.76 (1 H, td, $^3J_{H-H} = 8.2$, $^4J_{H-F} = 5.0$ Hz, C(6)H), 7.63 – 7.55 (1 H, m, C(7)H), 7.20 (1 H, t, $^2J_{H-F} = 54.1$ Hz, C(4-CHF₂)H) ppm. ^{19}F NMR $\delta\text{F} = -67.64$ (3 F, s, CF₃), -115.74 (2 F, d, $^2J_{F-H} = 54.2$ Hz, C4-CHF₂), -119.97 (1 F, dd, $^3J_{F-H} = 10.5$, $^4J_{F-H} = 5.4$ Hz, F) ppm. ^{13}C NMR $\delta\text{C} = 158.51$ (d, $^1J_{C-F} = 261.9$ Hz, C-8), 147.96 (qd, $^2J_{C-F} = 34.4$ Hz, $^4J_{C-F} = 1.7$ Hz, C-2), 140.33 (td, $^2J_{C-F} = 22.6$, $^4J_{C-F} = 2.9$ Hz, C-4), 138.40 (d, $^2J_{C-F} = 12.2$ Hz, C-8-C-N), 130.35 (d, $^3J_{C-F} = 8.1$ Hz, C-6), 126.50 (s, C-5-C-C-4), 120.95 (q, $^1J_{C-F} = 275.5$ Hz, C(2)CF₃), 119.25 (d, $^4J_{C-F} = 5.3$ Hz, C-5), 115.90 (d, $^2J_{C-F} = 18.6$ Hz, C-7), 115.20 (t, $^3J_{C-F} = 7.5$ Hz, C-3), 112.48 (t, $^1J_{C-F} = 241.9$ Hz, C(4)CHF₂) ppm. C₁₁H₅F₆N (265): calcd (%) N 5.28, C 49.78, H 1.88, found N 5.44, C 50.00, H 1.95. MP: 49.7 – 51.3 °C.

4-(Difluoromethyl)-7-fluoro-2-(trifluoromethyl)quinoline

2f. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.349 mL, 2.98 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.378 mL, 2.98 mmol) and 3-fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1f** (1 equiv., 509 mg, 2.48 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-7-fluoro-2-(trifluoromethyl)quinoline **2f** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (405 mg, 62%) ^1H NMR $\delta = 8.19$ (1 H, dd, $^4J_{H-H} = 9.2$, $^3J_{H-F} =$

5.7 Hz, C(8)H), 7.93 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-F} = 2.3$ Hz, C(5)H), 7.88 (1 H, s, C(3)H), 7.61 – 7.54 (1 H, m, C(6)H), 7.17 (1 H, $^2J_{H-F} = 54.1$ Hz, C(4-CHF₂)H) ppm. ¹⁹F NMR $\delta F = -67.89$ (3 F, s, CF₃), -105.57 – -105.66 (1 F, m, F), -114.89 (2 F, d, $^2J_{F-H} = 54.0$ Hz, C4-CHF₂) ppm. ¹³C NMR $\delta C = 163.84$ (d, $^1J_{C-F} = 254.8$ Hz, C-7), 149.36 (d, $^3J_{C-F} = 13.1$ Hz, C 8-C-N), 149.09 (q, $^2J_{C-F} = 35.6$ Hz, C-2), 140.60 (td, $^2J_{C-F} = 22.5$, $^5J_{C-F} = 1.4$ Hz, C-4), 125.92 (d, $^3J_{C-F} = 9.8$ Hz, C-5), 122.08 (s, C-5-C-C-4), 121.04 (q, $^1J_{C-F} = 275.4$ Hz, C(2)CF₃), 120.77 (d, $^2J_{C-F} = 25.6$ Hz, C-6), 114.89 (d, $^2J_{C-F} = 20.7$ Hz, C-8), 113.92 – 113.16 (m, C-3), 112.81 (t, $^1J_{C-F} = 241.8$ Hz, C(4)CHF₂) ppm. C₁₁H₅F₆N (265): calcd (%) N 5.28, C 49.78, H 1.88, found N 5.36, C 49.88, H 1.77. MP: 61.6 – 62.8 °C.

4-(Difluoromethyl)-6-fluoro-2-(trifluoromethyl)quinoline 2gi. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.346 mL, 2.96 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.374 mL, 2.96 mmol) and 4-fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1g** (1 equiv., 505 mg, 2.46 mmol) in presence of anhydrous acetonitrile. 4-(Difluoromethyl)-6-fluoro-2-(trifluoromethyl)quinoline **2gi** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (434 mg, 67%). ¹H NMR $\delta H = 8.32$ (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-F} = 5.5$ Hz, C(8)H), 7.93 (1 H, s, C(3)H), 7.81 – 7.73 (1 H, m, C(5)H), 7.67 – 7.66 (1 H, m, C(7)H), 7.12 (1 H, t, $^2J_{H-F} = 54.1$ Hz, C(4-CHF₂)H) ppm. ¹⁹F NMR $\delta F = -67.69$ (3 F, s, CF₃), -105.84 – -105.77 (1 F, m, F), -115.61 (2 F, d, $^2J_{F-H} = 54.1$ Hz, C4-CHF₂) ppm. ¹³C NMR $\delta C = 162.40$ (d, $^1J_{C-F} = 254.3$ Hz, C-6), 147.31 (qd, $^2J_{C-F} = 35.7$, $^6J_{C-F} = 3.2$ Hz, C-2), 145.05 (s, C-8-C-N), 139.92 (td, $^2J_{C-F} = 22.5$, $^4J_{C-F} = 6.2$ Hz, C-4), 133.96 (d, $^3J_{C-F} = 9.8$ Hz, C-8), 126.06 (d, $^3J_{C-F} = 10.7$ Hz, C-5-C-C-4), 122.01 (d, $^2J_{C-F} = 26.0$ Hz, C-7), 121.24 (q, $^1J_{C-F} = 275.1$ Hz, C(2)CF₃), 115.17 – 115.02 (m, C-3), 112.74 (t, $^1J_{C-F} = 237.4$ Hz, C(4)CHF₂), 107.68 (d, $^2J_{C-F} = 24.1$ Hz, C-5) ppm. HRMS (ESI +) for C₁₁H₆F₆N [M + H]: calcd 266.0399, found 266.0387. MP: 68.2 – 69.8 °C.

4-[Chloro(fluoro)methyl]-6-fluoro-2-(trifluoromethyl)quinoline 2gii. The product was prepared according to the general procedure and starting from an activated solution of Yarovenko's reagent **4b** (1.2 equiv., 0.675 mL, 2.97 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.376 mL, 2.97 mmol) and 4-fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1g** (1 equiv., 507 mg, 2.47 mmol) in presence of anhydrous acetonitrile. 4-[Chloro(fluoro)methyl]-6-fluoro-2-(trifluoromethyl)quinoline **2gii** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) in mixture with the non-cyclised compound, the 1-chloro-1,5,5,5-tetrafluoro-4-((4-fluorophenyl)amino)pent-3-en-2-one (**6'g**) with a ratio of 7:1 (35% by ¹⁹F NMR). ¹H $\delta H = 8.32$ (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-F} = 5.5$ Hz, C(8)H), 7.94 (1 H, s, C(3)H), 7.75 (1 H, dd, $^3J_{H-F} = 9.4$, $^4J_{H-H} = 2.7$ Hz, C(5)H), 7.65 (1 H, ddd, $^3J_{H-F} = 9.4$, $^4J_{H-F} = 7.9$, $^4J_{H-H} = 2.7$ Hz, C(7)H), 7.54 (1 H, d, $^2J_{H-F} = 48.7$ Hz, C(4-CHFCI)H) ppm.

6-Fluoro-4-(1,2,2,2-tetrafluoroethyl)-2-(trifluoromethyl)quinoline 2giii. The product was prepared according to the general procedure and starting from an activated solution of Ishikawa's reagent **4c** (1.2 equiv., 0.854 mL, 2.92 mmol) by (BF₃•Et₂O) (1.21 equiv., 0.372 mL, 2.93 mmol) and 4-fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline

1g (1 equiv., 498 mg, 2.43 mmol) in presence of anhydrous acetonitrile.

6-Fluoro-4-(1,2,2,2-tetrafluoroethyl)-2-(trifluoromethyl)quinoline **2giii** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) in mixture with the non-cyclized compound, the 1,1,1,2,6,6,6-heptafluoro-5-((4-fluorophenyl)amino)hex-4-en-3-one (**6'giii**) with a ratio of 1:3. as a brown oil (64.7 mg). ¹H NMR $\delta H = 8.35$ (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-F} = 5.5$ Hz, C(8)H), 7.97 (1 H, s, C(3)H), 7.72 – 7.65 (1 H, m, C(5)H), 7.64 - 7.62 (1 H, m, C(7)H), 6.33 (1 H, dq, $^2J_{H-F} = 43.8$, $^3J_{H-F} = 5.4$ Hz, C(4-CHFCF₃)H) ppm. HRMS (ESI +) for C₁₂H₆F₈N [M + H]: calcd 316.0367, found 316.0375.

4-(Difluoromethyl)-7-(trifluoromethoxy)-2-(trifluoromethyl)quinoline 2h. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.259 mL, 2.21 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.28 mL, 2.21 mmol) and 3-(trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1h** (1 equiv., 500 mg, 1.84 mmol) in presence of anhydrous acetonitrile.

4-(Difluoromethyl)-7-(trifluoromethoxy)-2-(trifluoromethyl)quinoline **2h** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (219 mg, 36%). ¹H NMR $\delta H = 8.24$ (1 H, d, $^3J_{H-H} = 9.3$ Hz, C(5)H), 8.16 (1 H, s, C(8)H), 7.94 (1 H, s, C(3)H), 7.65 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-H} = 2.4$ Hz, C(6)H), 7.18 (1 H, t, $^2J_{H-F} = 54.1$ Hz, C(4-CHF₂)H) ppm. ¹⁹F NMR $\delta F = -57.88$ (3 F, s, OCF₃), -67.89 (3 F, s, CF₃), -114.87 (2 F, d, $^2J_{F-H} = 54.1$ Hz, C4-CHF₂) ppm. ¹³C NMR $\delta C = 151$ (s, C-7), 149.37 (q, $^2J_{C-F} = 35.8$ Hz, C-2), 148.63 (s, C-8-C-N), 140.65 (t, $^2J_{C-F} = 22.6$ Hz, C-4), 125.80 (s, C-5), 123.99 (s, C-6), 123.23 – 123.19 (m, C-5-C-C-4), 121.07 (q, $^1J_{C-F} = 276.7$ Hz, C(2)CF₃), 120.55 (q, $^1J_{C-F} = 260.0$ Hz, OCF₃), 120.25 (s, C-8), 114.60 (td, $^3J_{C-F} = 8.0$, $^3J_{C-F} = 2.0$ Hz, C-3), 112.72 (t, $^1J_{C-F} = 242.0$ Hz, C(4)CHF₂) ppm. C₁₂H₅F₈NO (331): calcd (%) N 4.23, C 43.48, H 1.51, found N 4.28, C 43.94, H 1.35. MP: 36.3 – 37.8 °C.

4-(Difluoromethyl)-6-(trifluoromethoxy)-2-(trifluoromethyl)quinoline 2i. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.278 mL, 2.38 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.282 mL, 2.22 mmol) and of 4-(trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1i** (1 equiv., 584 mg, 1.85 mmol) in presence of anhydrous acetonitrile.

4-(Difluoromethyl)-6-(trifluoromethoxy)-2-(trifluoromethyl)quinoline **2i** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (300.3 mg, 49%). ¹H NMR $\delta H = 8.39$ (1 H, d, $^3J_{H-H} = 9.3$ Hz, C(8)H), 7.97 (2 H, s, C(3,5)H), 7.77 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-H} = 1.9$ Hz, C(7)H), 7.15 (1 H, t, $^2J_{H-F} = 54.0$ Hz, C(4-CHF₂)H) ppm. ¹⁹F NMR $\delta F = -57.72$ (3 F, s, OCF₃), -67.79 (3 F, s, CF₃), -115.31 (2 F, d, $^2J_{F-H} = 53.9$ Hz, C4-CHF₂) ppm. ¹³C NMR $\delta C = 149.50$ (s, C-6), 148.41 (q, $^2J_{C-F} = 35.9$ Hz, C-2), 146.02 (s, C-8-C-N), 140.46 (t, $^2J_{C-F} = 22.6$ Hz, C-4), 133.66 (s, C-8), 125.52 (s, C-5-C-C-4), 125.35 (s, C-7), 121.12 (q, $^1J_{C-F} = 276.4$ Hz, C(2)CF₃), 120.74 (q, $^1J_{C-F} = 260.6$ Hz, OCF₃), 115.36 (td, $^3J_{C-F} = 8.0$, $^3J_{C-F} = 2.1$ Hz, C-3), 113.97 (s, C-5), 112.67 (t, $^1J_{C-F} = 242.0$ Hz, C(4)CHF₂) ppm. C₁₂H₅F₈NO (331): calcd (%) N 4.23, C 43.48, H 1.51, found N 4.20, C 43.77, H 1.83. MP: 42.2 – 43.8 °C.

4-(Difluoromethyl)-N,N-dimethyl-2-(trifluoromethyl)quinolin-6-amine 2j. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.305 mL, 2.61 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.33 mL, 2.61 mmol) and of 1-*N,N*-dimethyl-4-*N*-(1,1,1-trifluoropropan-2-ylidene)benzene-1,4-diamine **1j** (1 equiv., 500 mg, 2.17 mmol) in presence of anhydrous acetonitrile.

4-(Difluoromethyl)-*N,N*-dimethyl-2-(trifluoromethyl)quinolin-6-amine **2j** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (235 mg, 37%). ¹H NMR δH = 8.07 (1 H, d, ³J_{H-H} = 9.5 Hz, C(8)H), 7.75 (1 H, s, C(3)H), 7.43 (1 H, dd, ³J_{H-H} = 9.5, ⁴J_{H-H} = 2.8 Hz, C(7)H), 7.07 (1 H, t, ²J_{H-F} = 54.5 Hz, C(4-CHF₂)H), 6.84 (1 H, s, C(5)H), 3.14 (1 H, s, NMe₂) ppm. ¹⁹F NMR δF = -66.90 (3 F, s, CF₃), -117.13 (2 F, d, ²J_{F-H} = 54.7 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 150.28 (s, C-6), 143.01 – 141.69 (2 C, m, C-2/C-8-C-N), 136.12 (t, ²J_{C-F} = 21.6 Hz, C-4), 131.80 (s, C-8), 127.25 (t, ³J_{C-F} = 2.5 Hz, C-5-C-C-4), 121.98 (q, ¹J_{C-F} = 274.0 Hz, C(2)CF₃), 120.46 (s, C-7), 114.48 (td, ³J_{C-F} = 8.2, ³J_{C-F} = 2.3 Hz, C-3), 113.29 (t, ¹J_{C-F} = 240.4 Hz, C(4)CHF₂), 98.92 (s, C-5), 40.46 (2 C, s, NMe₂) ppm. C₁₃H₁₁F₅N₂ (290): calcd (%) N 9.65, C 53.75, H 3.79, found N 9.42, C 53.55, H 3.81. MP: 107.5 – 108.4 °C.

4-(Difluoromethyl)-7-fluoro-8-methyl-2-(trifluoromethyl)quinoline 2k. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.644 mL, 5.5 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.698 mL, 5.5 mmol) and 3-fluoro-2-methyl-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1k** (1 equiv., 1.76 g, 4.59 mmol) in presence of anhydrous acetonitrile.

4-(Difluoromethyl)-7-fluoro-8-methyl-2-(trifluoromethyl)quinoline **2k** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (488.4 mg, 38%). ¹H NMR δH = 7.99 (1 H, dd, ³J_{H-H} = 9.0, ⁴J_{H-F} = 5.9 Hz, C(5)H), 7.88 (1 H, s, C(3)H), 7.54 (1 H, t, ³J_{H-H} = 9.0 Hz, C(6)H), 7.17 (1 H, t, ²J_{H-F} = 54.2 Hz, C(4-CHF₂)H), 2.75 (3 H, d, ⁴J_{H-F} = 2.6 Hz, Me) ppm. ¹⁹F NMR δF = -67.78 (3 F, s, CF₃), -108.31 – -108.46 (1 F, m, F), -114.94 (2 F, d, ²J_{F-H} = 54.2 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 161.60 (d, ¹J_{C-F} = 250.2 Hz, C-7), 148.47 – 147.14 (2 C, m, C-2/C-8-C-N), 140.54 (td, ²J_{C-F} = 22.3, ⁵J_{C-F} = 1.8 Hz, C-4), 123.79 (d, ²J_{C-F} = 16.2 Hz, C-8), 122.26 (2 C, d, ³J_{C-F} = 10.3 Hz, C-5/C-5-C-C-4), 121.32 (q, ¹J_{C-F} = 275.3 Hz, C(2)CF₃), 120.25 (d, ²J_{C-F} = 27.2 Hz, C-6), 113.49 – 112.94 (m, C-3), 112.84 (t, ¹J_{C-F} = 241.6 Hz, C(4)CHF₂), 9.38 (d, ³J_{C-F} = 3.7 Hz, Me) ppm. HRMS (ESI +) for C₁₂H₈F₆N [M + H]: calcd 280.0555, found 280.0570. MP: 78.7 – 79.4 °C.

7-Chloro-4-(difluoromethyl)-8-methyl-2-(trifluoromethyl)quinoline 2l. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.599 mL, 5.12 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.648 mL, 5.12 mmol) and 3-chloro-2-methyl-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **1l** (1 equiv., 2.01 g, 4.26 mmol) in presence of anhydrous acetonitrile.

7-Chloro-4-(difluoromethyl)-8-methyl-2-(trifluoromethyl)quinoline **2l** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a beige amorphous solid (485 mg, 38%). ¹H NMR δH = 7.93 – 7.91 (2 H, m, C(3,5)H), 7.74 (1 H, d, ³J_{H-H} = 9.1 Hz, C(6)H), 7.17 (1 H, t, ²J_{H-F}

= 54.2 Hz, C(4-CHF₂)H), 2.93 (3 H, s, Me) ppm. ¹⁹F δF = -67.78 (3 F, s, CF₃), -115.12 (2 F, d, ²J_{F-H} = 54.1 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 147.53 (q, ²J_{C-F} = 35.8 Hz, C-2), 147.44 (s, C-8-C-N), 140.63 (t, ²J_{C-F} = 22.3 Hz, C-4), 137.44 (s, C-7), 137.10 (s, C-8), 131.35 (s, C-6), 121.50 (s, C-5), 121.27 (q, ¹J_{C-F} = 275.3 Hz, C(2)CF₃), 119.32 (s, C-5-C-C-4), 113.93 – 113.73 (m, C-3), 112.70 (t, ¹J_{C-F} = 241.7 Hz, C(4)CHF₂), 14.91 (s, Me) ppm. C₁₂H₇F₅NCl (295): calcd (%) N 4.73, C 48.70, H 2.36, found N 4.62, C 48.82, H 2.55.

2,4-Bis(difluoromethyl)quinoline 3ai. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.427 mL, 3.65 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.463 mL, 3.65 mmol) and *N*-(1,1-difluoropropan-2-ylidene)aniline **1aa** (1 equiv., 515 mg, 3.04 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)quinoline **3ai** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (537 mg, 77%). ¹H NMR δH = 8.23 (1 H, d, ³J_{H-H} = 8.5 Hz, C(8)H), 8.14 (1 H, d, ³J_{H-H} = 8.5 Hz, C(5)H), 7.92 (1 H, s, C(3)H), 7.86 (1 H, t, ³J_{H-H} = 7.7 Hz, C(7)H), 7.74 (1 H, t, ³J_{H-H} = 7.7 Hz, C(6)H), 7.19 (1 H, t, ²J_{H-F} = 54.3 Hz, C(4-CHF₂)H), 6.81 (1 H, t, ²J_{H-F} = 55.1 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -114.46 (2 F, d, ²J_{F-H} = 55.1 Hz, C2-CHF₂), -115.16 (2 F, d, ²J_{F-H} = 54.3 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 152.70 (t, ²J_{C-F} = 27.1 Hz, C-2), 147.80 (s, C-8-C-N), 139.93 (t, ²J_{C-F} = 22.2 Hz, C-4), 130.91 (s, C-7), 130.83 (s, C-8), 129.33 (s, C-6), 124.84 (s, C-5-C-C-4), 123.55 (s, C-5), 114.37 (t, ¹J_{C-F} = 242.0 Hz, C(4)CHF₂), 114.32 – 114.17 (m, C-3), 113.13 (t, ¹J_{C-F} = 241.2 Hz, C(2)CHF₂) ppm. C₁₁H₇F₄N (229): calcd (%) N 6.10, C 57.60, H 3.05, found N 6.20, C 57.56, H 2.96. MP: 48.2 – 49.7 °C.

4-[Chloro(fluoro)methyl]-2-(difluoromethyl)quinoline 3aii. The product was prepared according to the general procedure and starting from an activated solution of Yarovenko's reagent **4b** (1.2 equiv., 0.56 mL, 3.55 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.45 mL, 3.55 mmol) and *N*-(1,1-difluoropropan-2-ylidene)aniline **1aa** (1 equiv., 500 mg, 2.96 mmol) in presence of anhydrous acetonitrile. 4-[Chloro(fluoro)methyl]-2-(difluoromethyl)quinoline **3aii** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a brown solid (567 mg, 78%). ¹H NMR δH = 8.02 (1 H, d, ³J_{H-H} = 8.5 Hz, C(8)H), 7.88 (1 H, d, ³J_{H-H} = 8.5 Hz, C(5)H), 7.75 (1 H, s, C(3)H), 7.62 (1 H, t, ³J_{H-H} = 7.7 Hz, C(7)H), 7.51 – 7.42 (2 H, m, C(7)H/C(4-CHFCI)H), 6.65 (1 H, t, ²J_{H-F} = 55.1 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -114.5 (2 F, dd, ²J_{F-H} = 55.2 Hz, ⁴J_{F-H} = 3 Hz, C2-CHF₂), -138.0 (1 F, d, ²J_{F-H} = 49 Hz, C4-CHFCI) ppm. ¹³C NMR δC = 152.63 (t, ²J_{C-F} = 27 Hz, C-2), 147.69 (s, C-8-C-N), 143.25 (d, ²J_{C-F} = 21 Hz, C-4), 130.80 (s, C-7), 130.70 (s, C-8), 128.96 (s, C-6), 123.68 (d, ³J_{C-F} = 3.6 Hz, C-5-C-C-4), 123.06 (s, C-5), 114.33 (t, ¹J_{C-F} = 241.3 Hz, C(2)CHF₂), 113.0 (dt, ³J_{C-F} = 9.6, ³J_{C-F} = 1.9 Hz, C-3), 97.08 (d, ¹J_{C-F} = 244.3 Hz, C(4)CHFCI) ppm. HRMS (ESI +) for C₁₁H₈F₃NCl [M + H]: calcd 246.0292, found 246.0312.

2,4-Bis(difluoromethyl)-8-methoxyquinoline 3b. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.354 mL, 3.02 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.383 mL, 3.02 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-2-methoxyaniline **1bb** (1 equiv., 502 mg, 2.52 mmol) in presence of anhydrous

acetonitrile. 2,4-Bis(difluoromethyl)-8-methoxyquinoline **3b** was provided after purification using a gradient of ethyl acetate in pentane (10-25%) as a yellow solid (473 mg, 72%). ¹H NMR δH = 7.94 (1 H, s, C(5)H), 7.62 (2 H, d, ³J_{H-H} = 4.2 Hz, C(6,7)H), 7.31 – 7.02 (2 H, m, C(3)H/ C(4-CHF₂)H), 6.88 (1 H, t, ²J_{H-F} = 51.4 Hz, C(2-CHF₂)H), 4.09 (3 H, s, Me) ppm. ¹⁹F NMR δF = -113.42 (2 F, d, ²J_{F-H} = 54.9 Hz, C2-CHF₂), -115.88 (d, ²J_{F-H} = 54.3 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 156.17 (s, C-8), 151.14 (t, ²J_{C-F} = 27.7 Hz, C-2), 140.04 – 139.19 (2 C, m, C-4/C-8-C-N), 129.84 (s, C-6), 126.13 (s, C-5-C-C-4), 114.92 (s, C-5), 114.72 (t, J = 7.9 Hz, C-7), 114.48 (t, ¹J_{C-F} = 241.9 Hz, C(2)CHF₂), 112.85 (t, ¹J_{C-F} = 241.1 Hz, C(4)CHF₂), 109.17 (s, C-3), 56.41 (s, Me) ppm. C₁₂H₉F₄NO (259): calcd (%) N 5.40, C 55.55, H 3.47, found N 5.35, C 55.30, H 3.51. MP: 96.8 – 98.6 °C.

2,4-Bis(difluoromethyl)-7-methoxyquinoline 3c. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.356 mL, 3.04 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.386 mL, 3.04 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-3-methoxyaniline **1cc** (1 equiv., 505 mg, 2.54 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-7-methoxyquinoline **3c** was provided after purification using a gradient of ethyl acetate in pentane (10-25%) as a yellow solid (515 mg, 78%). ¹H NMR δH = 7.79 (1 H, d, ³J_{H-H} = 9.3 Hz, C(5)H), 7.57 (1 H, s, C(3)H), 7.30 (1 H, d, ⁴J_{H-H} = 2.6 Hz, C(8)H), 7.14 (1 H, dd, ³J_{H-H} = 9.3, ⁴J_{H-H} = 2.6 Hz, C(6)H), 6.94 (1 H, t, ²J_{H-F} = 54.4 Hz, C(4-CHF₂)H), 6.62 (1 H, t, ²J_{H-F} = 55.2 Hz, C(2-CHF₂)H), 3.79 (3 H, s, Me) ppm. ¹⁹F NMR δF = -114.79 (2 F, d, ²J_{F-H} = 54.4 Hz, C2-CHF₂), -114.95 (2 F, d, ²J_{F-H} = 55.3 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 161.45 (s, C-7), 152.86 (t, ²J_{C-F} = 26.7 Hz, C-2), 149.83 (s, C-8-C-N), 139.56 (t, ²J_{C-F} = 22.2 Hz, C-4), 124.33 (s, C-5), 122.45 (s, C-6), 119.77 (t, ³J_{C-F} = 2.8 Hz, C-5-C-C-4), 114.25 (t, ¹J_{C-F} = 242.4 Hz, C(2)CHF₂), 113.18 (t, ¹J_{C-F} = 241.0 Hz, C(4)CHF₂), 111.89 – 111.70 (m, C-3), 108.24 (s, C-8), 55.60 (s, Me) ppm. C₁₂H₉F₄NO (259): calcd (%) N 5.40, C 55.55, H 3.47, found N 5.55, C 55.57, H 3.67. MP: 55.4 – 56.9 °C.

2,4-Bis(difluoromethyl)-6-methoxyquinoline 3d. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.357 mL, 3.05 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.386 mL, 3.05 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-4-methoxyaniline **1dd** (1 equiv., 506 mg, 2.54 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-6-methoxyquinoline **3d** was provided after purification using a gradient of ethyl acetate in pentane (10-25%) as an orange solid (468 mg, 71%). ¹H NMR δH = 8.15 (1 H, d, ³J_{H-H} = 9.3 Hz, C(8)H), 7.90 (1 H, s, C(3)H), 7.53 (1 H, dd, ³J_{H-H} = 9.3, ⁴J_{H-H} = 2.5 Hz, C(7)H), 7.36 (1 H, s, C(5)H), 7.16 (1 H, t, ²J_{H-F} = 54.4 Hz, C(4-CHF₂)H), 6.85 (1 H, t, ²J_{H-F} = 55.2 Hz, C(2-CHF₂)H), 4.03 (3 H, s, Me) ppm. ¹⁹F NMR δF = -113.99 (2 F, d, ²J_{F-H} = 55.3 Hz, C2-CHF₂), -115.52 (2 F, d, ²J_{F-H} = 54.4 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 159.77 (s, C-6), 149.93 (t, ²J_{C-F} = 27.0 Hz, C-2), 143.966 (s, C-8-C-N), 138.02 (t, ²J_{C-F} = 22.0 Hz, C-4), 132.11 (s, C-8), 126.21 (s, C-5-C-C-4), 123.71 (s, C-7), 114.70 (tt, ³J_{C-F} = 8.0, ³J_{C-F} = 1.8 Hz, C-3), 114.51 (t, C(2)CHF₂, ¹J_{C-F} = 241.9 Hz), 113.57 (t, C(4)CHF₂, ¹J_{C-F} = 240.8 Hz), 101.35 (s, C-5), 55.79 (s, Me) ppm. C₁₂H₉F₄NO (259): calcd

(%) N 5.40, C 55.55, H 3.47, found N 5.43, C 55.24, H 3.30. MP: 93.5 – 97.2 °C.

2,4-Bis(difluoromethyl)-8-fluoroquinoline 3e. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.377 mL, 3.22 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.408 mL, 3.22 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-2-fluoroaniline **1ee** (1 equiv., 502 mg, 2.68 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-8-fluoroquinoline **3e** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (466 mg, 39%) in mixture (3:1) with the 1,1,5,5-tetrafluoro-4-((2-fluorophenyl)amino)pent-3-en-2-one after purification (**6'e**). ¹H NMR δH = 8.00 (1 H, s, C(3)H), 7.93 (1 H, d, ³J_{H-H} = 8.6 Hz, C(5)H), 7.73 – 7.68 (1 H, m, C(6)H), 7.60 – 7.52 (1 H, m, C(7)H), 7.17 (1 H, t, ²J_{H-F} = 54.2 Hz, C(4-CHF₂)H), 6.86 (1 H, t, ²J_{H-F} = 54.8 Hz, C(2-CHF₂)H) ppm. HRMS (ESI +) for C₁₁H₇F₅N [M + H]: calcd 248.0493, found 248.0499.

2,4-Bis(difluoromethyl)-7-fluoroquinoline 3f. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.376 mL, 3.22 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.408 mL, 3.22 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-3-fluoroaniline **1ff** (1 equiv., 501 mg, 2.68 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-7-fluoroquinoline **3f** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (464 mg, 70%). ¹H NMR δH = 8.17 (1 H, dd, ⁴J_{H-H} = 9.3, ³J_{H-F} = 5.7 Hz, C(8)H), 7.86 (1 H, s, C(3)H), 7.84 (1 H, s, C(5)H), 7.57 – 7.49 (1 H, m, C(6)H), 7.14 (1 H, t, ²J_{H-F} = 54.2 Hz, C(4-CHF₂)H), 6.78 (1 H, t, ²J_{H-F} = 55.0 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -106.41 – -106.96 (1 F, m, F), -114.43 (2 F, d, ²J_{F-H} = 54.2 Hz, C2-CHF₂), -114.83 (2 F, d, ²J_{F-H} = 55.0 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 163.60 (d, ¹J_{C-F} = 253.6 Hz, C-7), 153.93 (t, ²J_{C-F} = 27.3 Hz, C-2), 149.21 (d, ³J_{C-F} = 12.7 Hz, C-8-C-N), 140.17 (td, ²J_{C-F} = 22.4, ⁵J_{C-F} = 1.1 Hz, C-4), 126.00 (d, ³J_{C-F} = 9.8 Hz, C-5), 121.79 (d, ⁴J_{C-F} = 1.0 Hz, C-5-C-C-4), 119.91 (d, ²J_{C-F} = 25.39 Hz, C-6), 114.54 (d, ²J_{C-F} = 20.56 Hz, C-8), 114.12 (t, ¹J_{C-F} = 242.9 Hz, C(2)CHF₂), 113.86 (m, C-3), 113.23 (t, ¹J_{C-F} = 241.5 Hz, C(4)CHF₂) ppm. C₁₁H₆F₅N (247): calcd (%) N 5.66, C 53.41, H 2.43, found N 5.79, C 53.54, H 2.69. MP: 73.2 – 74.6 °C.

2,4-Bis(difluoromethyl)-6-fluoroquinoline 3gi. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.5 equiv., 0.375 mL, 3.2 mmol) by (BF₃•Et₂O) (1.51 equiv., 0.408 mL, 3.22 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-4-fluoroaniline **1gg** (1 equiv., 400 mg, 2.14 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-6-fluoroquinoline **3gi** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (205 mg, 39%). ¹H NMR δH = 8.24 (1 H, dd, ³J_{H-H} = 9.3, ⁴J_{H-F} = 5.5 Hz, C(8)H), 7.92 (1 H, s, C(3)H), 7.80 – 7.74 (1 H, m, C(5)H), 7.65 – 7.60 (1 H, m, C(7)H), 7.09 (1 H, t, ²J_{H-F} = 54.2 Hz, C(4-CHF₂)H), 6.79 (1 H, t, ²J_{H-F} = 55.0 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -107.18 – -107.24 (1 F, m, F), -114.45 (2 F, d, ²J_{F-H} = 55.0 Hz, C2-CHF₂), -115.17 (2 F, d, ²J_{F-H} = 54.2 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 162.01 (d, ¹J_{C-F} = 252.9 Hz, C-6), 152.09 (td, ²J_{C-F} = 27.3, ⁶J_{C-F} = 3.1 Hz, C-2), 144.98 (s, C-8-C-N), 139.56 (td, ²J_{C-F} = 22.4, ⁴J_{C-F} = 6.1 Hz, C-4), 133.46 (d, ³J_C

$f = 9.6$ Hz, C-8), 125.76 (d, $^3J_{C-F} = 10.4$ Hz, C-5-C-C-4), 121.43 (d, $^2J_{C-F} = 25.8$ Hz, C-7), 115.28 (t, $^3J_{C-F} = 7.8$ Hz, C-3), 114.21 (t, $^1J_{C-F} = 241.3$ Hz, C(2)CHF₂), 110.78 (t, $^1J_{C-F} = 242.0$ Hz, C(4)CHF₂), 107.84 (d, $^2J_{C-F} = 24.0$ Hz, C-5) ppm. C₁₁H₆F₅N (247): calcd (%) N 5.66, C 53.41, H 2.43, found N 5.67, C 53.42, H 2.57. HRMS (ESI +) for C₁₁H₇F₅N [M + H]: calcd 248.0493, found 248.0497. MP: 68.7 – 71.2 °C.

4-[Chloro(fluoro)methyl]-2-(difluoromethyl)-6-

fluoroquinoline 3gii. The product was prepared according to the general procedure and starting from an activated solution of Yarovenko's reagent **4b** (1.2 equiv., 0.597 mL, 2.62 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.332 mL, 2.62 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-4-fluoroaniline **1gg** (1 equiv., 409 mg, 2.19 mmol) in presence of anhydrous acetonitrile. 4-[Chloro(fluoro)methyl]-2-(difluoromethyl)-6-fluoroquinoline

3gii was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a brown liquid (17 mg, 3% estimated). ¹H NMR δH = 8.26 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-F} = 5.5$ Hz, C(8)H), 7.94 (1 H, s, C(3)H), 7.77 (1 H, dd, $^3J_{H-H} = 9.6$, $^4J_{H-H} = 2.7$ Hz, C(5)H), 7.63 (1 H, ddd, $^3J_{H-H} = 9.3$, $^4J_{H-F} = 8.0$, $^4J_{H-H} = 2.7$ Hz, C(7)H), 7.53 (1 H, d, $^2J_{H-F} = 48.9$ Hz, C(4-CHFCI)H), 6.80 (1 H, t, $^2J_{H-F} = 55.0$ Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -106.78 - -106.84 (1 F, m, F), -114.49 (2 F, dd, $^2J_{F-H} = 55.0$, $^4J_{F-H} = 2.9$ Hz, C2-CHF₂), -137.65 (1 F, d, $^2J_{F-H} = 48.7$ Hz, C4-CHFCI) ppm. ¹³C NMR δC = 161.61 (d, $^1J_{C-F} = 253.2$ Hz, C-6), 152.11 (t, $^2J_{C-F} = 27.1$ Hz, C-2), 144.94 (s, C-8-C-N), 143.01 (dd, $^2J_{C-F} = 20.9$, $^4J_{C-F} = 6.2$ Hz, C-4), 133.56 (d, $^3J_{C-F} = 9.7$ Hz, C-8), 128.42 (s, C-5-C-C-4), 121.43 (d, $^2J_{C-F} = 25.8$ Hz, C-7), 114.11 (t, $^1J_{C-F} = 241.0$ Hz, C(2)CHF₂), 114.10 (d, $^3J_{C-F} = 8.8$ Hz, C-3), 107.65 (d, $^2J_{C-F} = 24.1$ Hz, C-5), 97.09 (d, $^1J_{C-F} = 244.8$ Hz, C(4)CHFCI) ppm. HRMS (ESI positive) for C₁₁H₇F₄NCl [M + H]: calcd 264.0198, found 264.0198.

2,4-Bis(difluoromethyl)-8-(trifluoromethoxy)quinoline 3h.

The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.44 equiv., 0.34 mL, 2.91 mmol) by (BF₃•Et₂O) (1.44 equiv., 0.37 mL, 2.92 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-2-(trifluoromethoxy)aniline **1hh** (1 equiv., 512 mg, 2.02 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-8-(trifluoromethoxy)quinoline **3h** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (244 mg, 39%). ¹H NMR δH = 8.11 (1 H, dd, $^3J_{H-H} = 8.1$, $^4J_{H-H} = 1.4$ Hz, C(7)H), 8.01 (1 H, s, C(3)H), 7.76 – 7.75 (2 H, m, C(5,6)H), 7.18 (1 H, t, $^2J_{H-F} = 54.1$ Hz, C(4-CHF₂)H), 6.85 (1 H, t, $^2J_{H-F} = 54.8$ Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -57.55 (3 F, s, OCF₃), -114.12 (2 F, d, $^2J_{F-H} = 54.9$ Hz, C2-CHF₂), -114.91 (2 F, d, $^2J_{F-H} = 54.3$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 153.55 (t, $^2J_{C-F} = 28.0$ Hz, C-2), 146.06 (s, C-8), 141.11 (s, C-8-C-N), 140.23 (t, $^2J_{C-F} = 22.5$ Hz, C-4), 128.98 (s, C-5), 126.25 (s, C-5-C-C-4), 122.56 (s, C-7), 122.14 (s, C-6), 120.47 (q, $^1J_{C-F} = 259.6$ Hz, OCF₃), 115.59 (t, $^3J_{C-F} = 7.9$ Hz, C-3), 114.29 (t, $^1J_{C-F} = 242.4$ Hz, C(2)CHF₂), 112.98 (t, $^1J_{C-F} = 241.7$ Hz, C(4)CHF₂) ppm. C₁₂H₆F₇NO (313): calcd (%) N 4.47, C 45.98, H 1.92, found N 4.57, C 46.23, H 1.98. MP: 59.4 - 60 °C.

2,4-Bis(difluoromethyl)-7-(trifluoromethoxy)quinoline 3i. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv.,

0.278 mL, 2.38 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.301 mL, 2.38 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-3-(trifluoromethoxy)aniline **1ii** (1 equiv., 501 mg, 1.98 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-7-(trifluoromethoxy)quinoline **3i** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a light brown liquid (440 mg, 71%). ¹H NMR δH = 8.08 (1 H, d, $^3J_{H-H} = 9.2$ Hz, C(5)H), 7.93 (1 H, s, C(8)H), 7.79 (1 H, s, C(3)H), 7.46 (1 H, d, $^3J_{H-H} = 9.2$ Hz, C(6)H), 7.03 (1 H, t, $^2J_{H-F} = 54.2$ Hz, C(4-CHF₂)H), 6.69 (1 H, t, $^2J_{H-F} = 55.0$ Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -58.14 (3 F, s, OCF₃), -114.72 (2 F, d, $^2J_{F-H} = 54.1$ Hz, C2-CHF₂), -115.17 (2 F, d, $^2J_{F-H} = 54.9$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 154.12 (t, $^2J_{C-F} = 27.3$ Hz, C-2), 150.58 (s, C-7), 148.46 (s, C-8-C-N), 140.14 (t, $^2J_{C-F} = 22.5$ Hz, C-4), 125.76 (s, C-5), 123.13 (s, C-6), 122.95 (s, C-5-C-C-4), 120.58 (q, $^1J_{C-F} = 259.4$ Hz, OCF₃), 120.02 (s, C-8), 114.72 (tt, $^3J_{C-F} = 8$, $^3J_{C-F} = 1.8$ Hz, C-3), 114.04 (t, $^1J_{C-F} = 242.4$ Hz, C(2)CHF₂), 113.12 (t, $^1J_{C-F} = 241.4$ Hz, C(4)CHF₂) ppm. C₁₂H₆F₇NO (313): calcd (%) N 4.47, C 45.98, H 1.92, found N 4.49, C 46.13, H 2.15.

2,4-Bis(difluoromethyl)-6-(trifluoromethoxy)quinoline 3j. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.5 equiv., 0.347 mL, 2.96 mmol) by (BF₃•Et₂O) (1.51 equiv., 0.378 mL, 2.98 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-4-(trifluoromethoxy)aniline **1jj** (1 equiv., 500 mg, 1.98 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-6-(trifluoromethoxy)quinoline **3j** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (361 mg, 58%). ¹H NMR δH = 8.30 (1 H, d, $^3J_{H-H} = 9.3$ Hz, C(8)H), 7.96 – 7.95 (2 H, m, C(3,5)H), 7.73 (1 H, dd, $^3J_{H-H} = 9.3$, $^4J_{H-H} = 1.8$ Hz, C(7)H), 7.13 (1 H, t, $^2J_{H-F} = 56.0$ Hz, C(4-CHF₂)H), 6.80 (1 H, t, $^2J_{H-F} = 55.0$ Hz, C(2-CHF₂)H) ppm. ¹⁹F δF = -57.71 (3 F, s, OCF₃), -114.67 (2 F, d, $^2J_{F-H} = 55.0$ Hz, C2-CHF₂), -114.88 (2 F, d, $^2J_{F-H} = 54.1$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 153.23 (t, $^2J_{C-F} = 27.5$ Hz, C-2), 148.97 (s, C-6), 146.01 (s, C-8-C-N), 140.06 (t, $^2J_{C-F} = 22.5$ Hz, C-4), 133.17 (s, C-8), 125.23 (s, C-5-C-C-4), 124.89 (s, C-7), 120.59 (q, $^1J_{C-F} = 259.2$ Hz, OCF₃), 115.64 – 115.49 (m, C-3), 114.32 (s, C-5), 114.08 (t, $^1J_{C-F} = 241.6$ Hz, C(2)CHF₂), 113.09 (t, $^1J_{C-F} = 240.0$ Hz, C(4)CHF₂) ppm. C₁₂H₆F₇NO (313): calcd (%) N 4.47, C 45.98, H 1.92, found N 4.49, C 46.35, H 2.07. MP: 47.5 – 48.2 °C.

2,4-Bis(difluoromethyl)-N,N-dimethylquinolin-7-amine 3k.

The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.331 mL, 2.83 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.358 mL, 2.83 mmol) and 3-*N*-(1,1-difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,3-diamine **1kk** (1 equiv., 500 mg, 2.36 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-*N,N*-dimethylquinolin-7-amine **3k** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a brown solid (98.2 mg, 15%). ¹H NMR δH = 7.94 (1 H, d, $^3J_{H-H} = 9.4$ Hz, C(5)H), 7.55 (1 H, s, C(8)H), 7.29 (1 H, dd, $^3J_{H-H} = 9.4$, $^4J_{H-H} = 2.7$ Hz, C(6)H), 7.21 (1 H, d, $J = 2.7$ Hz, C(3)H), 7.08 (1 H, t, $^2J_{H-F} = 54.6$ Hz, C(4-CHF₂)H), 6.72 (1 H, t, $^2J_{H-F} = 55.4$ Hz, C(2-CHF₂)H), 3.13 (6 H, s, NMe₂) ppm. ¹⁹F NMR δF = -114.59 (2 F, d, $^2J_{F-H} = 54.6$ Hz, C2-CHF₂), -114.89 (2 F, d, $^2J_{F-H} = 55.4$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 152.95 (t, $^2J_{C-F} = 26.5$ Hz,

C-2), 151.69 (s, C-7), 150.03 (s, C-8-C-N), 139.30 (t, $^2J_{C-F} = 23.9$ Hz, C-4), 124.08 (s, C-5), 118.49 (s, C-8), 116.98 (s, C-5-C-C-4), 114.56 (t, $^1J_{C-F} = 264.0$ Hz, C(2)CHF₂), 113.54 (t, $^1J_{C-F} = 240.8$ Hz, C(4)CHF₂), 109.73 (tt, $^3J_{C-F} = 8.0$, $^3J_{C-F} = 2.2$ Hz, C-3), 107.26 (s, C-6), 40.38 (2 C, s, NMe₂) ppm. C₁₃H₁₂F₄N₂ (272): calcd (%) N 10.20, C 57.30, H 4.41, found N 10.06, C 57.26, H 4.41. MP: 83.7 – 84.7 °C.

2,4-Bis(difluoromethyl)-N,N-dimethylquinolin-6-amine 3l. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.331 mL, 2.83 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.358 mL, 2.83 mmol) and 4-*N*-(1,1-difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,4-diamine **1ll** (1 equiv., 500 mg, 2.36 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-*N,N*-dimethylquinolin-6-amine **3l** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as an orange solid (91.9 mg, 14%). ¹H NMR δH = 8.01 (1 H, d, $^3J_{H-H} = 9.4$ Hz, C(8)H), 7.76 (1 H, s, C(3)H), 7.42 (1 H, dd, $^3J_{H-H} = 9.5$, $^4J_{H-H} = 2.7$ Hz, C(7)H), 7.07 (1 H, t, $^2J_{H-F} = 54.6$ Hz, C(4-CHF₂)H), 6.90 (1 H, s, C(5)H), 6.75 (1 H, t, $^2J_{H-F} = 55.5$ Hz, C(2-CHF₂)H), 3.14 (1 H, s, NMe₂) ppm. ¹⁹F NMR δF = -113.38 (2 F, d, $^2J_{F-H} = 55.5$ Hz, C2-CHF₂), -116.67 (2 F, d, $^2J_{F-H} = 54.6$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 149.96 (s, C-6), 147.42 (t, $^2J_{C-F} = 26.8$ Hz, C-2), 141.73 (s, C-8-C-N), 136.29 (t, $^2J_{C-F} = 21.5$ Hz, C-4), 131.36 (s, C-8), 126.89 (s, C-5-C-C-4), 120.03 (s, C-7), 114.90 (t, $^1J_{C-F} = 239.9$ Hz, C(2)CHF₂), 114.64 (t, $^3J_{C-F} = 8.1$ Hz, C-3), 113.69 (t, $^1J_{C-F} = 241.4$ Hz, C(4)CHF₂), 99.55 (s, C-5), 40.53 (s, NMe₂) ppm. C₁₃H₁₂F₄N₂ (272): calcd (%) N 10.20, C 57.30, H 4.41, found N 10.09, C 56.86, H 4.40. MP: 115.6 – 116.9 °C.

2,4-Bis(difluoromethyl)-7-fluoro-8-methylquinoline 3m. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.698 mL, 5.96 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.756 mL, 5.96 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-3-fluoro-2-methylaniline **1mm** (1 equiv., 1 g, 4.97 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-7-fluoro-8-methylquinoline **3m** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a yellow solid (990 mg, 76%). ¹H NMR δH = 7.96 (1 H, dd, $^3J_{H-H} = 9.0$, $^4J_{H-F} = 5.9$ Hz, C(5)H), 7.86 (1 H, s, C(3)H), 7.47 (1 H, t, $^3J_{H-H} = 9.0$ Hz, C(6)H), 7.13 (1 H, t, $^2J_{H-F} = 54.3$ Hz, C(4-CHF₂)H), 6.81 (1 H, t, $^2J_{H-F} = 55.1$ Hz, C(2-CHF₂)H), 2.71 (3 H, d, $^4J_{H-F} = 2.5$ Hz, Me) ppm. ¹⁹F NMR δF = -109.41 (1 F, ddd, $^3J_{H-F} = 8.4$, $^4J_{H-F} = 5.6$, $^4J_{CH3-F} = 2.7$ Hz, F), -114.20 (2 F, d, $^2J_{H-F} = 55.1$ Hz, C2-CHF₂), -114.56 (2 F, d, $^2J_{H-F} = 54.3$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 161.37 (d, $^1J_{C-F} = 249.1$ Hz, C-7), 152.53 (t, $^2J_{C-F} = 27.5$ Hz, C-2), 148.08 (d, $^3J_{C-F} = 10.1$ Hz, C-8-C-N), 140.19 (t, $^2J_{C-F} = 21.5$ Hz, C-4), 123.23 (d, $^2J_{C-F} = 16.1$ Hz, C-8), 122.36 (d, $^3J_{C-F} = 10.2$ Hz, C-5), 121.85 (s, C-5-C-C-4), 119.38 (d, $^2J_{C-F} = 27.0$ Hz, C-6), 114.58 (t, $^1J_{C-F} = 241.2$ Hz, C(2)CHF₂), 113.12 (t, $^1J_{C-F} = 242.4$ Hz, C(4)CHF₂), 113.12 (s, C-3), 9.34 (d, $^4J_{H-F} = 3.8$ Hz, Me) ppm. C₁₂H₈F₅N (261): calcd (%) N 5.36, C 55.13, H 3.06, found N 5.26, C 55.13, H 3.22. MP: 87.7 – 89 °C.

7-Chloro-2,4-bis(difluoromethyl)-8-methylquinoline 3n. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.662 mL, 5.66 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.717 mL, 5.66

mmol) and 3-chloro-*N*-(1,1-difluoropropan-2-ylidene)-2-methylaniline **1nn** (1 equiv., 1.03 g, 4.72 mmol) in presence of anhydrous acetonitrile. 7-Chloro-2,4-bis(difluoromethyl)-8-methylquinoline **3n** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a colourless solid (977 mg, 75%). ¹H NMR δH = 7.89 – 7.88 (2 H, m, C(3,5)H), 7.67 (1 H, d, $^3J_{H-H} = 9.1$ Hz, C(6)H), 7.13 (1 H, t, $^2J_{H-F} = 54.3$ Hz, C(4-CHF₂)H), 6.80 (1 H, t, $^2J_{H-F} = 55.1$ Hz, C(2-CHF₂)H), 2.88 (3 H, s, Me) ppm. ¹⁹F NMR δF = -114.17 (2 F, d, $^2J_{F-H} = 55.1$ Hz, C2-CHF₂), -114.75 (2 F, d, $^2J_{F-H} = 54.3$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 152.34 (t, $^2J_{C-F} = 27.6$ Hz, C-2), 147.27 (s, C-8-C-N), 140.27 (t, $^2J_{C-F} = 22.2$ Hz, C-4), 136.83 (s, C-7), 136.57 (s, C-8), 130.56 (s, C-6), 123.48 (s, C-5-C-C-4), 121.65 (s, C-5), 114.52 (t, $^1J_{C-F} = 241.3$ Hz, C(2)CHF₂), 113.97 (t, $^3J_{C-F} = 7.9$ Hz, C-3), 113.08 (t, $^1J_{C-F} = 242.4$ Hz, C(4)CHF₂), 14.84 (s, Me) ppm. C₁₂H₈F₄NCl (277): calcd (%) N 5.04, C 51.86, H 2.88, found N 4.92, C 52.02, H 3.03. MP: 58.9 – 59.5 °C.

7-Chloro-2,4-bis(difluoromethyl)quinoline 3o. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 3.45 mL, 29.5 mmol) by (BF₃•Et₂O) (1.2 equiv., 3.73 mL, 29.5 mmol) and 3-chloro-*N*-(1,1-difluoropropan-2-ylidene)aniline **1oo** (1 equiv., 5 g, 24.6 mmol) in presence of anhydrous acetonitrile. 7-Chloro-2,4-bis(difluoromethyl)quinoline **3o** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a colourless solid (2.93 g, 45%). ¹H NMR δH = 8.20 (1 H, d, $^4J_{H-H} = 2.1$ Hz, C(8)H), 8.07 (1 H, d, $^3J_{H-H} = 9.0$ Hz, C(5)H), 7.88 (1 H, s, C(3)H), 7.67 (1 H, dd, $^3J_{H-H} = 9.0$, $^4J_{H-H} = 2.1$ Hz, C(6)H), 7.12 (1 H, t, $^2J_{H-F} = 54.2$ Hz, C(4-CHF₂)H), 6.77 (1 H, t, $^2J_{H-F} = 55.0$ Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -114.73 (4 F, t, $^2J_{F-H} = 54.4$ Hz, C2-CHF₂/C4-CHF₂) ppm. ¹³C NMR δC = 153.83 (t, $^2J_{C-F} = 27.3$ Hz, C-2), 148.27 (s, C8-C-N), 140.12 (t, $^2J_{C-F} = 22.4$ Hz, C-4), 137.12 (s, C-7), 130.33 (s, C-6), 129.71 (s, C-8), 124.95 (s, C-5), 123.13 (s, C-5-C-C-4), 114.58 (tt, $^3J_{C-F} = 8$, $^3J_{C-F} = 1.8$ Hz, C-3), 114.09 (t, $^1J_{C-F} = 242.9$ Hz, C(2)CHF₂), 113.08 (t, $^1J_{C-F} = 241.5$ Hz, C(4)CHF₂) ppm. C₁₁H₆F₄NCl (263): calcd (%) N 5.31, C 50.12, H 2.29, found N 5.23, C 50.00, H 2.29. MP: 90.2 – 91 °C.

2,4-Bis(difluoromethyl)-6-(trifluoromethyl)quinoline 3p. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.195 mL, 1.66 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.211 mL, 1.66 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-4-(trifluoromethyl)aniline **1pp** (1 equiv., 328 mg, 1.39 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-6-(trifluoromethyl)quinoline **3p** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a grey solid (93.9 mg, 23%). ¹H NMR δH = 8.46 (1 H, s, C(5)H), 8.37 (1 H, d, $^3J_{H-H} = 8.9$ Hz, C(8)H), 8.04 (1 H, dd, $^3J_{H-H} = 8.9$, $^4J_{H-H} = 1.8$ Hz, C(7)H), 8.00 (1 H, s, C(3)H), 7.20 (1 H, t, $^2J_{H-F} = 54.0$ Hz, C(4-CHF₂)H), 6.82 (1 H, t, $^2J_{H-F} = 54.9$ Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -62.70 (3 F, s, CF₃), -114.48 (2 F, d, $^2J_{F-H} = 54.0$ Hz, C2-CHF₂), -114.98 (2 F, d, $^2J_{F-H} = 54.9$ Hz, C4-CHF₂) ppm. ¹³C NMR δC = 154.90 (t, $^2J_{C-F} = 27.4$ Hz, C-2), 148.77 (s, C-8-C-N), 141.09 (t, $^2J_{C-F} = 22.5$ Hz, C-4), 132.14 (s, C-8), 131.11 (q, $^2J_{C-F} = 33.1$ Hz, C-6), 126.76 (q, $^3J_{C-F} = 2.9$ Hz, C-7), 123.95 (t, $^3J_{C-F} = 2.5$ Hz, C-5-C-C-4), 123.65 (q, $^1J_{C-F} = 272.9$ Hz, CF₃), 121.81 (s, C-5), 115.71 (tt, $^3J_{C-F} = 7.6$, $^3J_{C-F} = 2.2$ Hz, C-3), 113.94 (t, $^1J_{C-F} = 243.4$ Hz,

C(2)CHF₂), 112.93 (t, ¹J_{C-F} = 241.9 Hz, C(4)CHF₂) ppm. C₁₂H₆F₇N (297): calcd (%) N 4.71, C 48.50, H 2.04, found N 4.78, C 48.51, H 2.17. MP: 57.7 – 58.3 °C.

2,4-Bis(difluoromethyl)-7-(trifluoromethyl)quinoline 3q. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.56 mL, 4.79 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.606 mL, 4.79 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-3-(trifluoromethyl)aniline **1qq** (1 equiv., 0.946 g, 3.99 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-7-(trifluoromethyl)quinoline **3q** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a colourless solid (328.5 mg, 28%). ¹H NMR δH = 8.56 (1 H, s, C(8)H), 8.31 (1 H, d, ³J_{H-H} = 8.9 Hz, C(5)H), 8.02 (1 H, s, C(3)H), 7.93 (1 H, d, ³J_{H-H} = 8.7 Hz, C(6)H), 7.19 (1 H, t, ²J_{H-F} = 54.1 Hz, C(4-CHF₂)H), 6.82 (1 H, t, ²J_{H-F} = 54.9 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -63.10 (3 F, s, CF₃), -114.71 (2 F, d, ²J_{F-H} = 56.4 Hz, C2-CHF₂), -114.81 (2 F, d, ²J_{F-H} = 54.8 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 154.19 (t, ²J_{C-F} = 27.5 Hz, C-2), 146.86 (s, C-8-C-N), 140.20 (t, ²J_{C-F} = 22.6 Hz, C-4), 132.69 (q, ²J_{C-F} = 33.7 Hz, C-7), 128.43 (s, C-8), 126.15 (s, C-5-C-C-4), 125.08 (s, C-5), 124.85 (s, C-6), 123.54 (q, ¹J_{C-F} = 272.4 Hz, CF₃), 116.20 (t, ³J_{C-F} = 7.6 Hz, C-3), 114.02 (t, ¹J_{C-F} = 242.3 Hz, C(2)CHF₂), 112.98 (t, ¹J_{C-F} = 241.5 Hz, C(4)CHF₂) ppm. C₁₂H₆F₇N (297): calcd (%) N 4.71, C 48.50, H 2.04, found N 4.74, C 48.35, H 2.10. MP: 39.7 - 40 °C.

2,4-Bis(difluoromethyl)-8-(trifluoromethyl)quinoline 3r. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.178 mL, 1.52 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.192 mL, 1.52 mmol) and *N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethyl)aniline **1rr** (1 equiv., 0.5 g, 1.26 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-8-(trifluoromethyl)quinoline **3r** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a colourless solid (traces). ¹H NMR δH = 8.37 (1 H, d, ²J_{H-H} = 8.4 Hz, C(7)H), 8.22 (1 H, d, ²J_{H-H} = 7.3 Hz, C(5)H), 8.02 (1 H, s, C(3)H), 7.81 (1 H, t, ³J_{H-H} = 7.9 Hz, C(6)H), 7.18 (1 H, t, ²J_{H-F} = 54.1 Hz, C(4-CHF₂)H), 6.84 (1H, t, ²J_{H-F} = 54.9 Hz, C(2-CHF₂)H). ¹⁹F NMR δF = -60.17 (3 F, s, CF₃), -114.25 (2 F, d, ²J_{F-H} = 56.4 Hz, C2-CHF₂), -114.36 (2 F, d, ²J_{F-H} = 54.8 Hz, C4-CHF₂) ppm.

2,4-Bis(difluoromethyl)-8-phenylquinoline 3s. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.403 mL, 3.45 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.437 mL, 3.45 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-2-phenylaniline **1ss** (1 equiv., 704 mg, 2.87 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-8-phenylquinoline **3s** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a colour less solid (248.9 mg, 28%). ¹H NMR δH = 8.16 (1 H, dd, ³J_{H-H} = 8.5, ⁴J_{H-H} = 1.5 Hz, C(5)H), 8.00 (1 H, s, C(3)H), 7.92 (1 H, dd, ³J_{H-H} = 7.2, ⁴J_{H-H} = 1.3 Hz, C(7)H), 7.85 – 7.77 (1 H, m, C(6)H), 7.76 – 7.70 (2 H, m, C(5')H), 7.58 – 7.45 (3 H, m, C(6')H), 7.24 (1 H, t, ²J_{H-F} = 54.3 Hz, C(4-CHF₂)H), 6.74 (1 H, t, ²J_{H-F} = 55.1 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -113.70 (2 F, d, ²J_{F-H} = 55.1 Hz, C2-CHF₂), -114.97 (2 F, d, ²J_{F-H} = 54.3 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 152.18 (t, ²J_{C-F} = 27.8 Hz, C-2), 145.30 (s, C-8-C-N), 142.28 (s, C-1'), 140.04 (t, ²J_{C-F} = 22.0 Hz, C-

4), 138.65 (s, C-8), 131.61 (s, C-7), 131.02 (2 C, s, C-3',5'), 129.09 (s, C-6), 128.06 (2 C, s, C-2',6'), 127.84 (s, C-4'), 125.29 (s, C-5-C-C-4), 122.83 (s, C-5), 114.68 (t, ¹J_{C-F} = 240.9 Hz, C(2)CHF₂), 114.17 (t, ³J_{C-F} = 8.0 Hz, C-3), 113.25 (t, ¹J_{C-F} = 242.4 Hz, C(4)CHF₂) ppm. C₁₁H₁₁F₄N (305): calcd (%) N 4.59, C 66.89, H 3.63, found N 4.71, C 66.99, H 3.70. MP: 58.6 – 59.5 °C.

2,4-Bis(difluoromethyl)-8-(phenylsulfanyl)quinoline 3t. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.253 mL, 2.16 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.274 mL, 2.16 mmol) and *N*-(1,1-difluoropropan-2-ylidene)-2-(phenylsulfanyl)aniline **1tt** (1 equiv., 500 mg, 1.8 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)-8-(phenylsulfanyl)quinoline **3t** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a colour less solid (308.7 mg, 52%). ¹H NMR δH = 7.99 (1 H, s, C(3)H), 7.82 (1 H, d, ³J_{H-H} = 8.4 Hz, C(5)H), 7.66 (2 H, dd, ³J_{H-H} = 6.4, ⁴J_{H-H} = 3.0 Hz, C(2',6')H), 7.53 – 7.49 (3 H, m, C(3',4',5')H), 7.47 (1 H, t, ³J_{H-H} = 8.0 Hz, C(6)H), 7.17 (1 H, t, ²J_{H-F} = 54.3 Hz, C(4-CHF₂)H), 7.06 (1 H, d, ³J_{H-H} = 7.6 Hz, C(7)H), 6.89 (1 H, t, ²J_{H-F} = 54.9 Hz, C(2-CHF₂)H) ppm. ¹⁹F NMR δF = -113.66 (2 F, d, ²J_{F-H} = 55.0 Hz, C2-CHF₂), -115.22 (2 F, d, ²J_{F-H} = 54.2 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 151.47 (t, ²J_{C-F} = 27.7 Hz, C-2), 143.85 (s, C-8-C-N), 143.02 (s, C-8), 140.20 (t, ²J_{C-F} = 22.2 Hz, C-4), 136.16 (2 C, s, C-2',6'), 130.89 (s, C-1'), 130.11 (2 C, s, C-3',5'), 129.64 (s, C-4'), 129.33 (s, C-6), 126.16 (s, C-7), 125.13 (s, C-5-C-C-4), 119.37 (s, C-5), 114.86 (t, ³J_{C-F} = 7.9 Hz, C-3), 114.31 (t, ¹J_{C-F} = 242.4 Hz, C(2)CHF₂), 112.87 (t, ¹J_{C-F} = 241.4 Hz, C(4)CHF₂). C₁₇H₁₁F₄NS (337): calcd (%) N 4.15, C 60.53, H 3.29, found N 4.22, C 60.60, H 3.36. MP: 109.9 – 110.7 °C.

2,4-Bis(difluoromethyl)benzo[h]quinolin-7-ol 3u. The product was prepared according to the general procedure and starting from an activated solution of TFEDMA **4a** (1.2 equiv., 0.298 mL, 2.55 mmol) by (BF₃•Et₂O) (1.2 equiv., 0.323 mL, 2.55 mmol) and 5-[(1,1-difluoropropan-2-ylidene)amino]-1-naphthol **1uu** (1 equiv., 500 mg, 2.13 mmol) in presence of anhydrous acetonitrile. 2,4-Bis(difluoromethyl)benzo[h]quinolin-7-ol **3u** was provided after purification using a gradient of ethyl acetate in pentane (0-5%) as a brown solid (321.7 mg, 51%). ¹H NMR δH = 8.90 (1 H, d, ³J_{H-H} = 8.3 Hz, C(10)H), 8.39 (1 H, d, ³J_{H-H} = 9.4 Hz, C(5)H), 8.04 (1 H, s, C(3)H), 7.93 (1 H, d, ³J_{H-H} = 9.4 Hz, C(6)H), 7.61 (1 H, t, ³J_{H-H} = 8.0 Hz, C(9)H), 7.25 (1 H, t, ²J_{H-F} = 54.4 Hz, C(4-CHF₂)H), 7.11 (1 H, d, ³J_{H-H} = 7.6 Hz, C(8)H), 6.92 (1 H, t, ²J_{H-F} = 55.3 Hz, C(2-CHF₂)H), 5.43 (1 H, br s, OH) ppm. ¹⁹F NMR δF = -113.93 (2 F, d, ²J_{F-H} = 55.3 Hz, C2-CHF₂), -114.96 (2 F, d, ²J_{F-H} = 54.4 Hz, C4-CHF₂) ppm. ¹³C NMR δC = 151.71 (s, C-7), 151.27 (t, ²J_{C-F} = 27.2 Hz, C-2), 146.29 (s, C-10-C-C-N), 139.47 (t, ²J_{C-F} = 22.2 Hz, C-4), 132.81 (2 C, s, C-5-C-C-4/C-10-C-CN), 128.23 (s, C-9), 124.51 (s, C-5), 123.57 (s, C-7-C-C-6), 118.94 (s, C-6), 117.77 (s, C-10), 114.73 (tt, ³J_{C-F} = 7.6, ³J_{C-F} = 2.2 Hz, C-3), 114.60 (t, ¹J_{C-F} = 241.0 Hz, C(2)CHF₂), 113.24 (s, C-5), 113.06 (t, ¹J_{C-F} = 242.4 Hz, C(4)CHF₂) ppm. C₁₅H₉F₄NO (295): calcd (%) N 4.74, C 61.02, H 3.07, found N 4.82, C 60.87, H 3.14. MP: 139.5 – 141.2 °C.

Functionalization in position 8 of quinoline derivatives

8-(Bromomethyl)-2,4-bis(difluoromethyl)-7-fluoroquinoline 7.

Method A: To a solution of 2,4-bis(difluoromethyl)-7-fluoro-8-methylquinoline **3m** (1 equiv., 300 mg, 1.15 mmol) and oxone (2 equiv., 349 mg, 2.3 mmol) in a mixture of DCM (2.7 mL) and H₂O (0.3 mL) (9:1) was added KBr (2 equiv., 273 mg, 2.3 mmol) at room temperature, and stirred under visible light irradiation for 14 h. Upon addition of KBr the reaction mixture became brown, then turned into a colourless suspension after 10 min under light. Saturated aq. solution Na₂S₂O₃ was added to the reaction mixture, and the product was extracted with ethyl acetate. The combined extracts were washed with brine and dried over Na₂SO₄. The organic phase was concentrated under reduced pressure.

Method B: To a mixture of 2,4-bis(difluoromethyl)-7-fluoro-8-methylquinoline **3m** (1 equiv., 300 mg, 1.15 mmol), NaIO₄ (1.5 equiv., 368 mg, 1.72 mmol) and LiBr (1.5 equiv., 149 mg, 1.72 mmol) was added aq. H₂SO₄ (2%) (6 mL). The reaction mixture was heated at 95°C for 6 h. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate. The combined organic layers were washed with saturated aq. solution Na₂S₂O₃ then water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. In both cases the crude reaction mixture was purified by column chromatography using a gradient of ethyl acetate in cyclohexane (0-15%).

8-(bromomethyl)-2,4-bis(difluoromethyl)-7-fluoroquinoline **7** was obtained as a colourless solid 194 mg (**Method A:** 63% / **Method B:** 50%). ¹H NMR δH = 8.17 (1H, dd, ³J_{H-H} = 9.4, ⁴J_{H-F} = 5.7 Hz, C(5)H), 7.93 (1 H, s, C(3)H), 7.55 (1 H, t, ³J_{H-H} = 9.1 Hz, C(6)H), 7.14 (1 H, t, ²J_{H-F} = 54.1 Hz, C(4-CHF₂)H), 6.86 (1 H, t, ²J_{H-F} = 55.0 Hz, C(2-CHF₂)H), 5.22 (2 H, d, ⁴J_{H-F} = 1.6 Hz, C(8-CH₂Br)H). ¹⁹F NMR δF = -106.81 - -106.85 (1 F, m, F), -114.12 (2 F, d, ²J_{H-F} = 54.1 Hz, C2-CHF₂), -114.52 (2 F, d, ²J_{H-F} = 55.0 Hz, C4-CHF₂). ¹³C NMR δC = 161.55 (d, ¹J_{C-F} = 257.1 Hz, C-7), 153.60 (t, ²J_{C-F} = 27.7 Hz, C-2), 146.39 (d, ³J_{C-F} = 8.3 Hz, C-8-C-N), 140.59 (td, ²J_{C-F} = 22.5, ⁵J_{C-F} = 1.5 Hz, C-4), 125.95 (d, ²J_{C-F} = 10.7 Hz, C-8), 122.95 (d, ³J_{C-F} = 13.7 Hz, C-5), 122.14 (s, C-5-C-C-4), 119.74 (d, ²J_{C-F} = 25.7 Hz, C-6), 114.26 (t, ¹J_{C-F} = 242.4 Hz, C(2)CHF₂), 114.36 - 114.18 (m, C-3), 113.20 (t, ¹J_{C-F} = 241.7 Hz, C(4)CHF₂), 20.07 (d, ³J_{C-F} = 4.6 Hz, C(8)CH₂Br). C₁₂H₇F₅NBr (340): calcd (%) N 4.12, C 42.38, H 2.07 found N 4.22, C 42.33, H 2.68.

8-(Bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline 8

Method A: The same previous procedure was used on the 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **3n** (1 equiv., 300 mg, 1.08 mmol)

Method B: The same previous procedure was used on the 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **3n** (1 equiv., 302 mg, 1.09 mmol). In both cases the crude reaction mixture was purified by column chromatography using a gradient of ethyl acetate in cyclohexane (0-15%).

8-(Bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **8** was obtained as a colourless solid 263 mg (**Method A:** 68% / **Method B:** 55%). ¹H NMR δH = 8.08 (1 H, d, ³J_{H-H} = 9.1 Hz, C(5)H), 7.96 (1 H, s, C(3)H), 7.75 (1 H, d, ³J_{H-H} = 9.1 Hz, C(6)H), 7.14 (1 H, t, ²J_{H-F} = 54.1 Hz, C(4-CHF₂)H), 6.85 (1 H, t, ²J_{H-F} = 54.9 Hz, C(2-CHF₂)H), 5.36 (1 H, s, C(8-CH₂Br)H). ¹⁹F NMR δF = -114.27 - -114.56 (4 F, m, C2-CHF₂/C4-CHF₂). ¹³C NMR δC = 153.37 (t, ²J_{C-F} = 27.8 Hz, C-2), 145.97 (s, C-8-C-N), 140.63 (t, ²J_{C-F} = 22.4 Hz, C-4), 137.78 (s, C-7), 135.37 (s, C-8), 131.05 (s, C-6),

124.80 (s, C-5), 123.76 (s, C-5-C-C-4), 115.04 - 114.85 (m, C-3), 114.21 (t, ¹J_{C-F} = 242.4 Hz, C(2)CHF₂), 113.05 (t, ¹J_{C-F} = 241.8 Hz, C(4)CHF₂), 25.08 (s, C(8)CH₂Br). C₁₂H₇F₄NBrCl (356): calcd (%) N 3.93, C 40.42, H 1.98 found N 3.78, C 40.78, H 2.18. MP: 113.3-114 °C.

7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid 9.

To a solution of 8-(bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **8** (1 equiv., 370 mg, 1.04 mmol) in aq. H₂SO₄ (70%) (3962 mg) at 110°C was added aq. HNO₃ (65%) (321 mg) dropwise. CAUTION: a release of Brown toxic gaz was observed. The reaction mixture was stirred for 17 h, then the reaction mixture was cooled down and poured into ice. The precipitate was filtered off, washed with water and dried under vacuum. The crude was triturated into pentane to remove all impurities. 7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid **9** was obtained as a beige solid (77.7 mg, 64%). ¹H NMR δH = 9.55 (1 H, br s, OH), 8.22 (1 H, d, ³J_{H-H} = 9.0 Hz, C(5)H), 8.00 (1 H, s, C(3)H), 7.84 (1 H, d, ³J_{H-H} = 9.1 Hz, C(6)H), 7.18 (1 H, t, ²J_{H-F} = 53.9 Hz, C(4-CHF₂)H), 6.84 (1 H, t, ²J_{H-F} = 54.7 Hz, C(2-CHF₂)H). ¹⁹F NMR δF = -114.47 (2 F, d, ²J_{H-F} = 53.9 Hz, C2-CHF₂), -115.22 (2 F, d, ²J_{H-F} = 54.7 Hz, C4-CHF₂). ¹³C NMR δC = 167.41 (s, C(8)CO₂H), 153.70 (t, ²J_{C-F} = 27.8 Hz, C-2), 145.41 (s, C-8-C-N), 141.30 (t, ²J_{C-F} = 22.7 Hz, C-4), 137.17 (s, C-7), 131.93 (s, C-6), 130.18 (s, C-8), 126.57 (s, C-5), 123.41 (s, C-5-C-C-4), 115.48 (t, ³J_{C-F} = 7.9 Hz, C-3), 113.30 (t, ¹J_{C-F} = 243.4 Hz, C(2)CHF₂), 112.74 (t, ¹J_{C-F} = 242.3 Hz, C(4)CHF₂). C₁₂H₇F₄NBrCl (356): calcd (%) N 4.55, C 46.80, H 1.95 found N 4.56, C 46.41, H 2.06. MP: 158-159 °C.

7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carbonitrile 10 and Tris([7-chloro-2,4-bis(difluoromethyl)quinolin-8-yl]methyl)amine 11.

To a solution of 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **3n** (1 equiv., 300 mg, 1.08 mmol) and aq. HBr (48%) (3 equiv., 0.368 mL, 3.24 mmol) in CCl₄ (4.5 mL) was added dropwise aq. H₂O₂ (30%) (2 equiv., 0.17 mL, 2.16 mmol) at room temperature. The suspension became red and the reaction mixture was stirred under sunlamp for 1h. Then, acetonitrile (2 mL), aq. NH₃ (35%) (50.2 equiv., 3 mL, 54.3 mmol), and I₂ (2.5 equiv., 685 mg, 2.7 mmol) were added to the mixture at room temperature, and stirred overnight at 60 °C. The reaction mixture was cooled down to room temperature and quenched by saturated aq. Solution Na₂S₂O₃. The mixture was extracted with DCM and the combined organic layers were washed with water and brine, then dried over Na₂SO₄ and concentrated under vacuum. 7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carbonitrile **10** was isolated after purification using ethyl acetate in cyclohexane (0-15%) as a yellow solid (91 mg, 29%). ¹H NMR δH = 8.36 (1 H, d, ³J_{H-H} = 9.1 Hz, C(5)H), 8.03 (1 H, s, C(3)H), 7.85 (1 H, d, ³J_{H-H} = 9.1 Hz, C(6)H), 7.14 (1 H, t, ²J_{H-F} = 51.0 Hz, C(4-CHF₂)H), 6.88 (1 H, t, ²J_{H-F} = 51.7 Hz, C(2-CHF₂)H). ¹⁹F NMR δF = -113.56 (2 F, d, ²J_{H-F} = 53.8 Hz, C2-CHF₂), -114.48 (2 F, d, ²J_{H-F} = 54.6 Hz, C4-CHF₂). ¹³C NMR δC = 155.77 (t, ²J_{C-F} = 28.3 Hz, C-2), 147.88 (s, C-8-C-N), 142.63 (s, C-7), 141.07 (t, ²J_{C-F} = 22.9 Hz, C-4), 130.33 (s, C-6), 129.10 (s, C-5), 123.23 (s, C-5-C-C-4), 116.48 (t, ³J_{C-F} = 7.9 Hz, C-3), 114.62 (s, C(8)CN), 113.66 (t, ¹J_{C-F} = 242.9 Hz, C(2)CHF₂), 113.55 (s C-8), 112.89 (t, ¹J_{C-F} = 242.3 Hz, C(4)CHF₂).

HRMS (ESI +) for C₁₂H₆F₄N₂Cl [M + H]: calcd 289.0150 found 289.0164. MP: 116-116.5 °C.

Tris([7-chloro-2,4-bis(difluoromethyl)quinolin-8-yl]methyl)amine **11** was isolated during the purification of **10** as a yellow solid (94.5 mg, 10%). ¹H NMR δH = 7.95 (3 H, d, ³J_{H-H} = 9.1 Hz, C(5)H), 7.82 (3 H, s, C(3)H), 7.57 (3 H, d, ³J_{H-H} = 9.1 Hz, C(6)H), 7.11 (3 H, t, ²J_{H-F} = 54.2 Hz, C(4-CHF₂)H), 6.39 (3 H, t, ²J_{H-F} = 55.1 Hz, C(2-CHF₂)H), 4.49 (6 H, s, C(8-CH₂)H). ¹⁹F NMR δF = -114.15 (6 F, d, ²J_{H-F} = 55.1 Hz, C2-CHF₂), -114.67 (6 F, d, ²J_{H-F} = 54.2 Hz, C4-CHF₂). ¹³C NMR δC = 152.45 (3 C, t, ²J_{C-F} = 27.7 Hz, C-2), 147.95 (3 C, s, C-8-C-N), 140.13 (3 C, t, ²J_{C-F} = 22.3 Hz, C-4), 139.25 (3 C, s, C-7), 136.72 (3 C, s, C-8), 130.92 (3C, s, C-6), 123.33 (3 C, s, C-5), 123.01 (3 C, s, C-5-C-C-4), 114.28 (3 C, t, ¹J_{C-F} = 242.4 Hz, C(2)CHF₂), 113.96 (3 C, t, ³J_{C-F} = 7.9 Hz, C-3), 113.08 (3 C, t, ¹J_{C-F} = 241.4 Hz, C(4)CHF₂), 50.30 (3 C, s, C(8)CH₂). HRMS (ESI +) for C₃₆H₂₂F₁₂N₄Cl₃ [M + H]: calcd 843.0713 found 843.0716. MP: 120-121°C.

8-(Benzenesulfinyl)-2,4-bis(difluoromethyl)quinoline 13. FeCl₃ (0.03 equiv., 1.59 mg, 0.00979 mmol) and 2,4-bis(difluoromethyl)-8-(phenylsulfanyl)quinoline **3t** (1 equiv., 110 mg, 0.326 mmol) were dissolved in acetonitrile (1 mL) and stirred for 5 min. To this solution was added H₂SO₆ (1.1 equiv., 81.8 mg, 0.359 mmol) at once. The yellow suspension, was stirred at room temperature for 3 h. The reaction was quenched by the addition of a saturated aq. solution of Na₂S₂O₃ and extracted with DCM. Organic layers were dried over Na₂SO₄ and concentrated under vacuum. **8-(Benzenesulfinyl)-2,4-bis(difluoromethyl)quinoline 13** was obtained as a sticky brown solid (91.2 mg, 79%). ¹H NMR δH = 8.61 (1 H, dd, ³J_{H-H} = 7.3, ⁴J_{H-H} = 1.2 Hz, C(7)H), 8.22 (1 H, dd, ³J_{H-H} = 8.5, ⁴J_{H-H} = 1.3 Hz, C(6)H), 7.96 (1 H, d, ³J_{H-H} = 7.5 Hz, C(5)H), 7.93 (1 H, s, C(3)H), 7.91 – 7.87 (2 H, m, C(2',6')H), 7.41 – 7.31 (3 H, m, C(3',4',5')H), 7.14 (1 H, t, ²J_{H-F} = 54.1 Hz, C(4-CHF₂)H), 6.81 (1 H, t, ²J_{H-F} = 55.0 Hz, C(2-CHF₂)H). ¹⁹F NMR δF = -113.77 – -115.99 (2 F, m, C4-CHF₂), -113.36 – -117.48 (2 F, m, C4-CHF₂). ¹³C NMR δC = 152.39 (dd, ²J_{C-F} = 28.2, 26.2 Hz, C-2), 145.60 (s, C-8-C-N), 145.42 (s, C-1'), 143.42 (s, C-8), 140.52 (t, ²J_{C-F} = 22.5 Hz, C-4), 131.28 (s, C-4'), 129.60 (s, C-5), 129.09 (2 C, s, C-3',5'), 126.66 (s, C-7), 125.93 (2 C, s, C-2',6'), 124.93 (s, C-5-C-C-4), 115.39 – 115.08 (m, C-3), 113.45 (t, ¹J_{C-F} = 243.4 Hz, C(4)CHF₂), 112.79 (t, ¹J_{C-F} = 241.9 Hz, C(2)CHF₂). C₁₇H₁₁F₄NOS (353): calcd (%) N 3.96, C 57.79, H 3.14, found N 3.94, C 57.64, H 3.32.

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Notes and references

1 J. P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, New Jersey, 2008.

- I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell 2009.
- P. Jeschke, in *Modern Methods in Crop Protection Research*, eds. P. Jeschke, W. Krämer, U. Schirmer and M. Witschel, Wiley-VCH, Weinheim, Germany, 2012, ch. 4, pp. 73-128.
- P. Jeschke, *ChemBioChem*, 2004, **5**, 571-589.
- P. Jeschke, E. Baston and F. R. Leroux, *Mini-Rev. Med. Chem.*, 2007, **7**, 1027-1034.
- K. L. Kirk, *Org. Proc. Res. Dev.*, 2008, **12**, 305-321.
- K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881-1886.
- J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506.
- D. O'Hagan and D. B. Harper, *J. Fluorine Chem.*, 1999, **100**, 127-133.
- K. Uneyama, *Fundamentals in Organic Fluorine Chemistry*, Blackwell, Oxford, 2006.
- W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359-4369.
- P. Jeschke, *Pest. Manag. Sci.*, 2010, **66**, 10-27.
- G. Theodoridis, in *Advances in Fluorine Science*, ed. A. Tressaud, Elsevier B.V, 2006, vol. 2, ch. 4, pp. 120-175.
- J.-P. Bégué, in *Chimie bioorganique et médicinale du fluor*, ed. E. C. ÉDITIONS, 2005, p. 384.
- M. M. Ghorab, F. A. Ragab, H. I. Heiba, R. K. Arafa and E. M. El-Hossary, *Med. Chem. Res.*, 2010, **20**, 388-400.
- F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827-856.
- P. V. Reddy, in *Organofluorine Compounds in Biology and Medicine*, Elsevier, 2015, pp. 1-27.
- S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320-330.
- A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15-24.
- The Pesticide Manual: A World Compendium*, British Crop Protection Council, Alton edn., 2012.
- S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal and H. D. Patel, *RSC Adv.*, 2014, **4**, 24463-24476.
- Y. Li and W. Gao, *Beilstein J. Org. Chem.*, 2010, **6**, 966-972.
- H. Kumar, A. Chattopadhyay, R. Prasath, V. Devaraji, R. Joshi, P. Bhavana, P. Saini and S. K. Ghosh, *J. Phys. Chem. B*, 2014, **118**, 7257-7266.
- G. Shan, X. Sun, Q. Xia and Y. Rao, *Org. Lett.*, 2011, **13**, 5770-5773.
- R. E. Lutz, C. J. Ohnmacht and A. R. Patel, *J. Med. Chem.*, 1971, **14**, 926-928.
- J. Mulero, G. Martinez, J. Oliva, S. Cermeno, J. M. Cayuela, P. Zafrilla, A. Martinez-Cacha and A. Barba, *Food Chem.*, 2015, **180**, 25-31.
- M. Kidwai, K. R. Bhushan, P. Sapra, R. K. Saxena and R. Gupta, *Bioorg. Med. Chem.*, 2000, **8**, 69-72.
- Y.-M. Wu, Y. Li and J. Deng, *J. Fluorine Chem.*, 2006, **127**, 223-228.
- A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, 1946, **68**, 113-116.
- W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, 1952, **74**, 4513-4516.
- V. Nenajdenko, in *Fluorine in Heterocyclic Chemistry Volume 2*, ed. V. Nenajdenko, Springer International Publishing, 2014.
- V. A. Petrov, S. Swearingen, W. Hong and W. Chris Petersen, *J. Fluorine Chem.*, 2001, **109**, 25-31.
- N. N. Yarovenko and M. A. Raksha, *Zh. Obshch. Khim.*, 1959, **29**, 2159-2163.
- N. N. Yarovenko and M. A. Raksha, *J. Gen. Chem. USSR (Engl. Transl.)*, 1959, **29**, 2125-2128.
- A. Takaoka, H. Iwakiri and N. Ishikawa, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3377-3380.
- V. A. Petrov, *Adv. Org. Synth.*, 2006, **2**, 269-290.

- 37 A. Vilsmeier and A. Haack, *Ber. Dtsch. Chem. Ges.*, 1927, **60**, 119-122.
- 38 C. Wakselman and M. Tordeux, *J.C.S. Chem. Comm*, 1975, 956-956.
- 39 *WO Pat.*, 2008022777, 2008.
- 40 A. Takaoka, K. Iwamoto, T. Kitazume and N. Ishikawa, *J. Fluorine Chem.*, 1979, **14**, 421-428.
- 41 E. Schmitt, B. Rugeri, A. Panossian, J.-P. Vors, S. Pazenok and F. R. Leroux, *Org. Lett.*, 2015, **17**, 4510-4513.
- 42 F. Giornal, G. Landelle, N. Lui, J.-P. Vors, S. Pazenok and F. R. Leroux, *Org. Proc. Res. Dev.*, 2014, **18**, 1002-1009.
- 43 F. Giornal, S. Pazenok, L. Rodefied, N. Lui, J.-P. Vors and F. R. Leroux, *J. Fluorine Chem.*, 2013, **152**, 2-11.
- 44 *WO Pat.*, 2014187773 2014.
- 45 E. Schmitt, G. Landelle, J.-P. Vors, N. Lui, S. Pazenok and F. R. Leroux, *Eur. J. Org. Chem.*, 2015, 6052-6060.
- 46 *WO Pat.*, 2015144578 2015.
- 47 E. Schmitt, A. Panossian, J.-P. Vors, C. Funke, N. Lui, S. Pazenok and F. R. Leroux, *Chem. Eur. J.*, 2016, in press.
- 48 K. T. Finley, in *Kirk-Othmer Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc., 2000, p. 32.
- 49 T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2491-2515.
- 50 A. Roe and G. F. Hawkins, *J. Am. Chem. Soc.*, 1949, **71**, 1785-1786.
- 51 J. Hamer, W. J. Link, A. Jurjevich and T. L. Vigo, *Recl. Trav. Chim. Pays-Bas*, 1962, **81**, 1058-1060.
- 52 R. D. Chambers, D. Holling, G. Sandford, H. Puschmann and J. A. K. Howard, *J. Fluorine Chem.*, 2002, **117**, 99-101.
- 53 R. D. Chambers, D. Holling, G. Sandford, A. S. Batsanov and J. A. K. Howard, *J. Fluorine Chem.*, 2004, **125**, 661-671.
- 54 M. Oishi, H. Kondo and H. Amii, *Chem. Commun.*, 2009, 1909-1911.
- 55 H. Yanai, H. Mimura, K. Kawada and T. Taguchi, *Tetrahedron*, 2007, **63**, 2153-2160.
- 56 H. Keller and M. Schlosser, *Tetrahedron*, 1996, **52**, 4637-4644.
- 57 D. M. Volochnyuk, A. O. Pushechnikov, D. G. Krotko, D. A. Sibgatulin, S. A. Kovalyova and A. A. Tolmachev, *Synthesis*, 2003, 1531-1540.
- 58 N. S. Boltacheva, V. I. Filyakova and V. N. Charushin, *Russ. J. Org. Chem.*, **41**, 1452-1457.
- 59 K. Uneyama, *J. Fluorine Chem.*, 1999, **97**, 11-25.
- 60 M. G. Mormino, P. S. Fier and J. F. Hartwig, *Org. Lett.*, 2014, **16**, 1744-1747.
- 61 B. Duda, S. N. Tverdomed, B. S. Bassil and G.-V. Rösenthaller, *Tetrahedron*, 2014, **70**, 8084-8096.
- 62 J. C. Sloop, C. L. Bumgardner and W. D. Loehle, *J. Fluorine Chem.*, 2002, **118**, 135-147.
- 63 J. C. Sloop, *J. Phys. Org. Chem.*, 2009, **22**, 110-117.
- 64 F. Zhao, X. Yang and J. Liu, *Tetrahedron*, 2004, **60**, 9945-9951.
- 65 S. Perrone, F. Rosato, A. Salomone and L. Troisi, *Tetrahedron*, 2013, **69**, 3878-3884.
- 66 A. Combes, *Bull. Soc. Chim. Fr.*, 1888, **49**, 89-92.
- 67 CCDC 1487974 (**3a**iii) and 1487975 (**9**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- 68 B. Wuerzer and R. Berghaus, presented in part at the 10th Asian-Pacific Weed Science Society Conference, Part. 1, Thailand 1985.
- 69 *DE Pat.*, 3233089, 1984.
- 70 K. Moriyama, M. Takemura and H. Togo, *Org. Lett.*, 2012, **14**, 2414-2417.
- 71 T. M. A. Shaikh, L. Emmanuel and A. Sudalai, *J. Org. Chem.*, 2006, **71**, 5043-5046.
- 72 Y. Kawagoe, K. Moriyama and H. Togo, *Eur. J. Org. Chem.*, 2014, 4115-4122.
- 73 S. Kim, K. Nehru, S. S. Kim, D. W. Kim and H. C. Jung, *Synthesis*, 2002, 2484-2486.